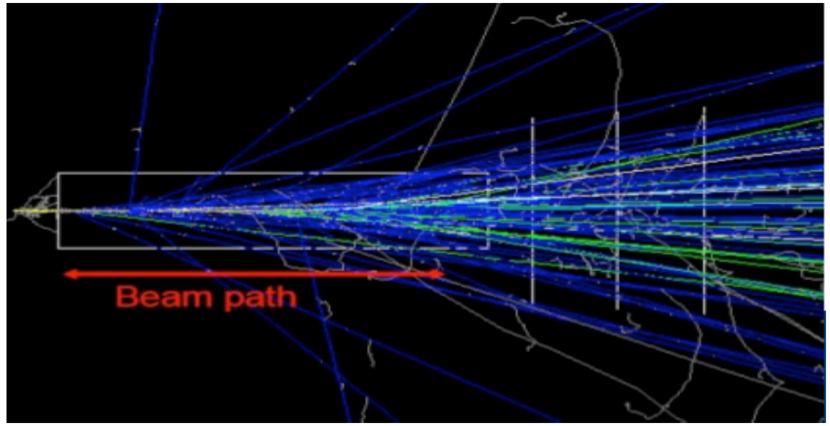

Nuclear physics in particle therapy: the role of the fragmentation

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Roma, 16 December 2019

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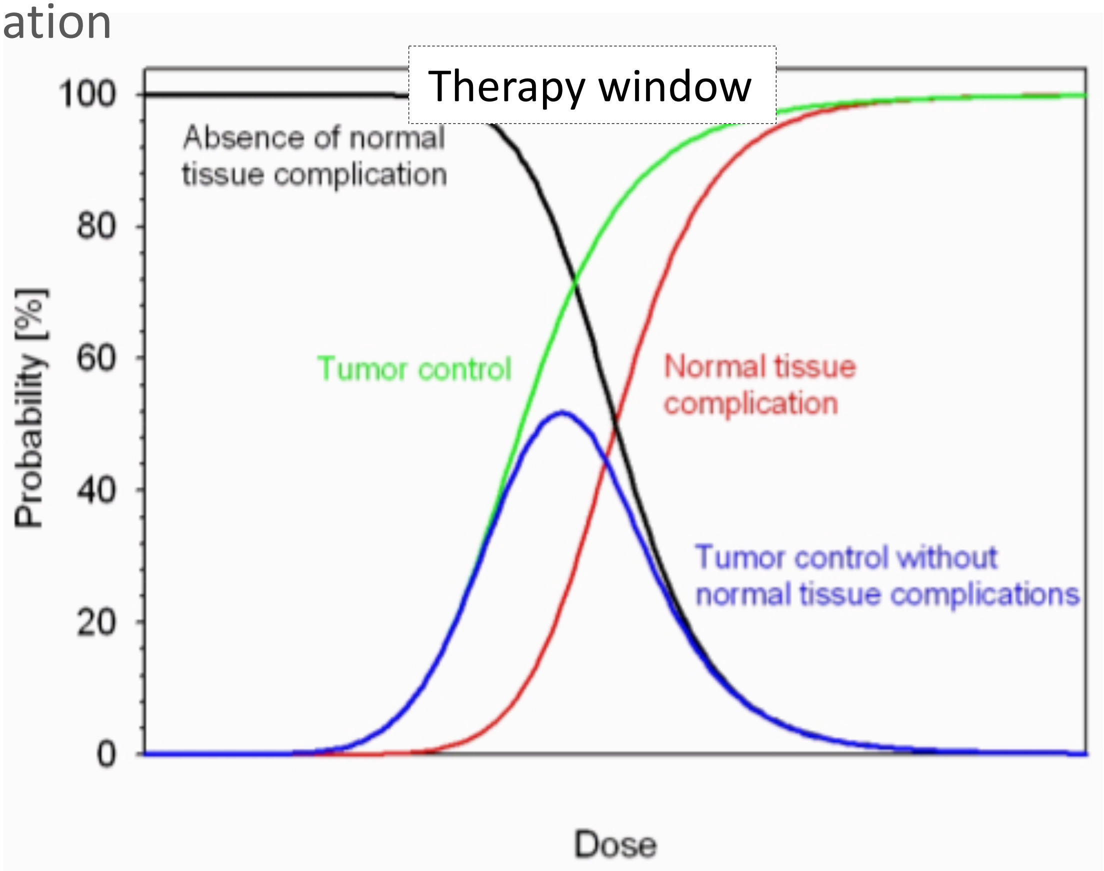
Cancer therapy with radiations

- Part of multi-disciplinary approach to cancer cure
- Useful for 50-60% of all cancer treatment (with or without surgery)
- Can be given for cure or palliation

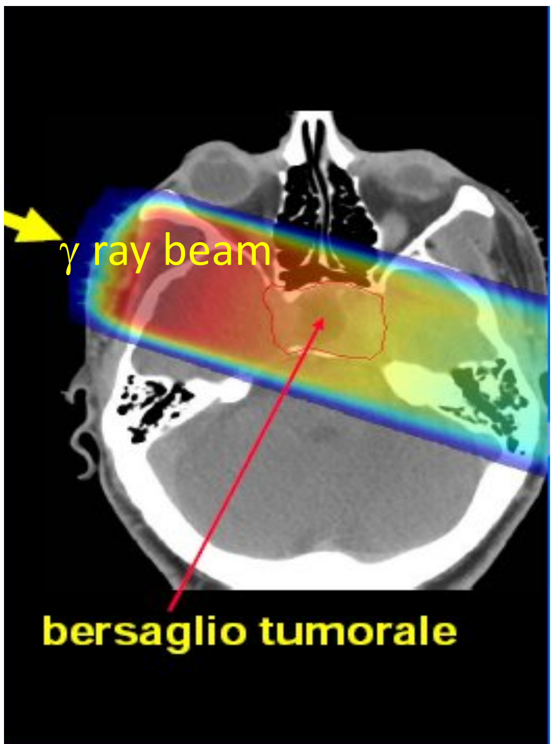


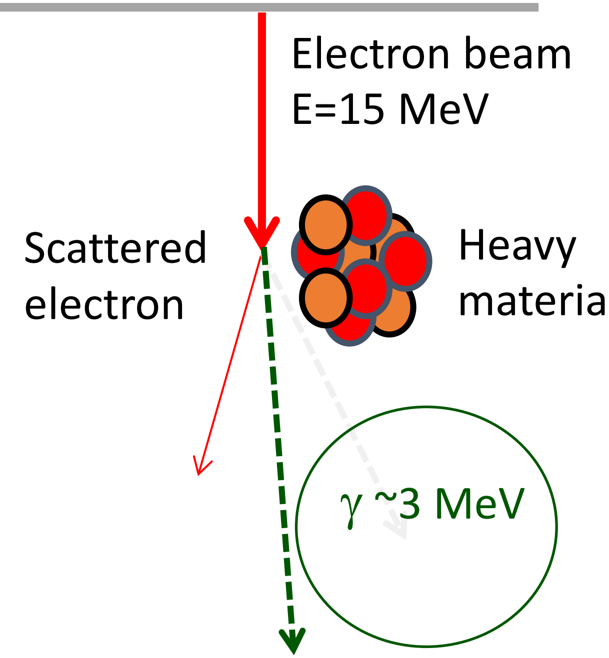
- Goal: kill the cancer cell damaging their DNA
- Mainly used for loco-regional treatment

$$Dose = \frac{dE_{abs}}{dm} (Gray)$$

Conventional Radiotherapy

- Conventional RT uses **γ rays**, both emitted from nuclear decays or from electron interaction.
- Electron are accelerated in a LINAC before interacting and producing photon beam.

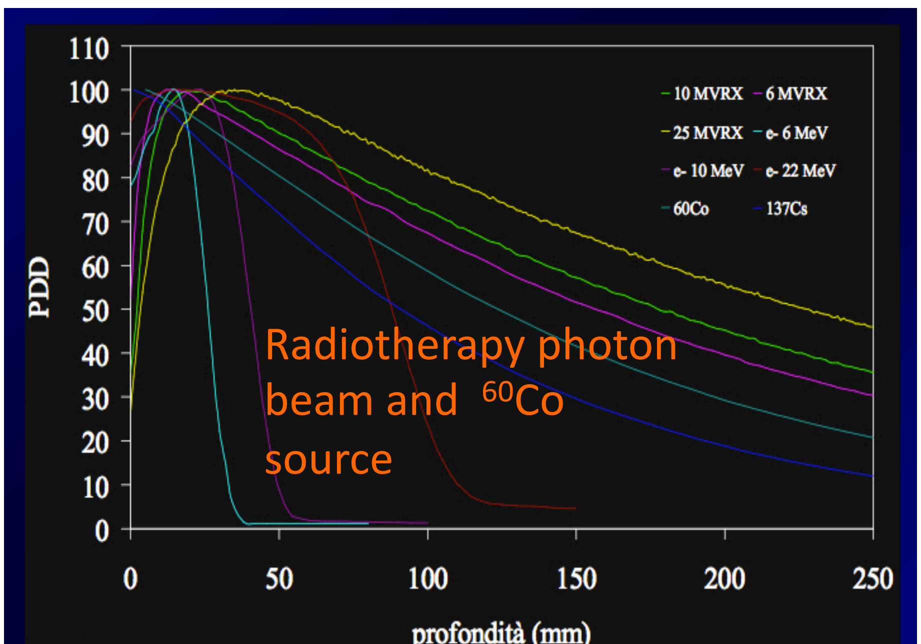




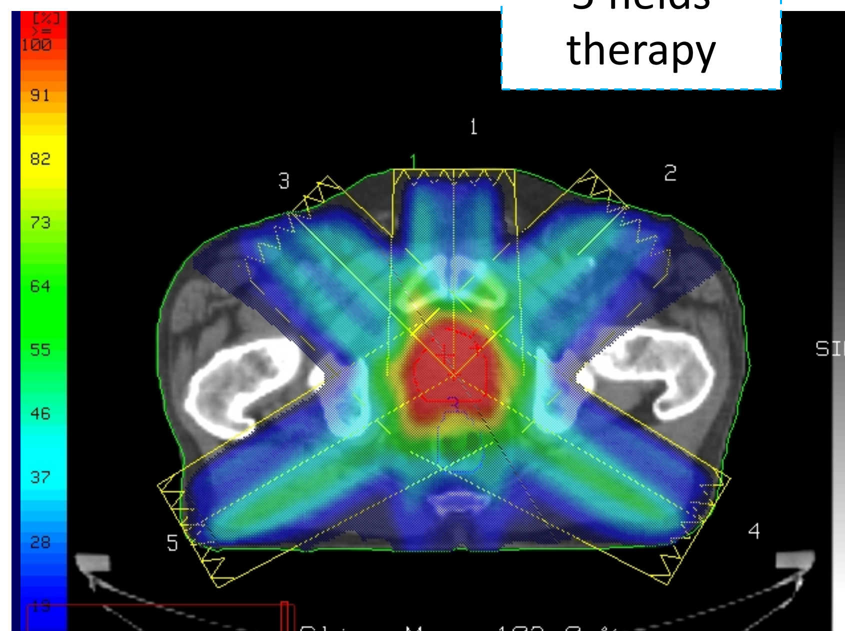
Approximatively half of the tumor are treated with γ RT.
In Italy ~ 200000 patients/year

Dose released by photons in RT

- More than 50 years of R&D made photon RT a very optimized, compact, effective technology (IMRT, radio surgery, etc)
- However, the photon beam has an exponential energy release with the depth inside the patient: **not optimal to treat deep tumors**
- Concentrating more beams with the aid of imaging and complex software (TPS), the dose given on the tumor is maximized with respect to that given to healthy tissues.

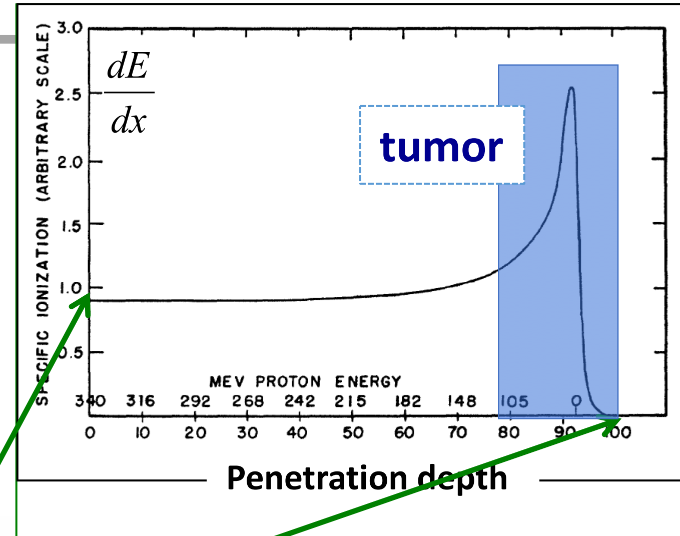


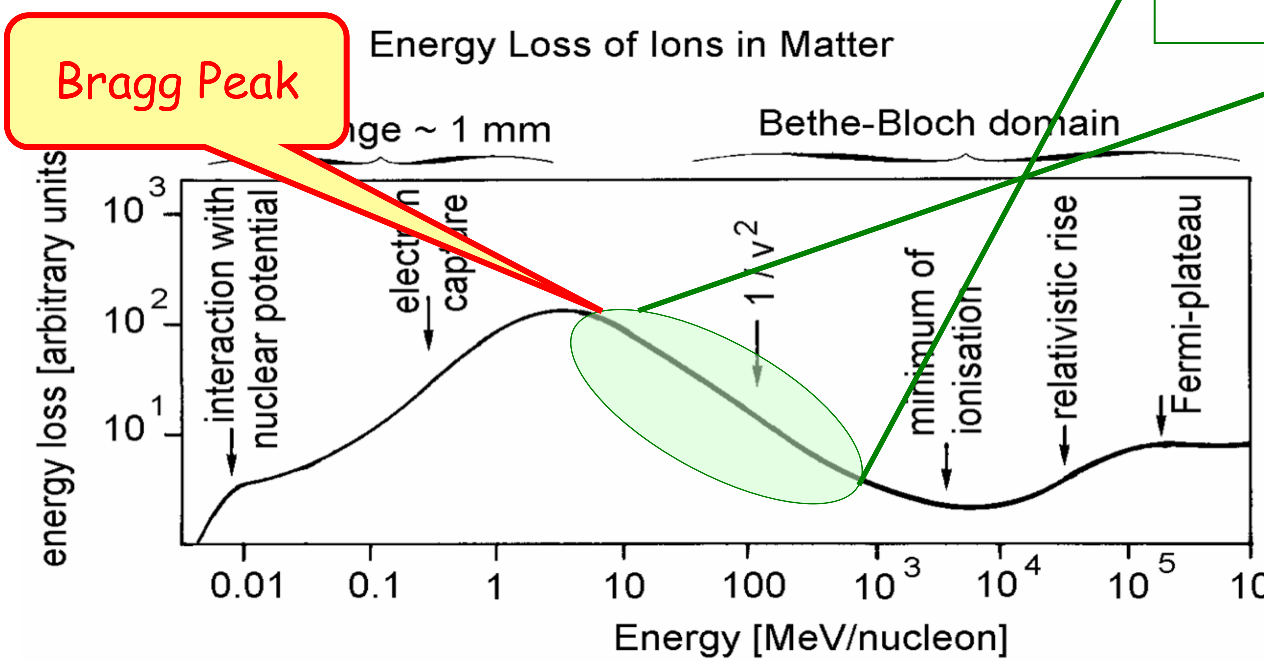
5 fields therapy



The particle therapy rationale

- On the other hand, the release of energy by **charged particles** has very different, and attractive, features… why not to use them?
- Perfect to release energy (dose) in a tumor buried inside the patient, **like a depth bomb…**
- BTW: quite and old idea: 1946!!



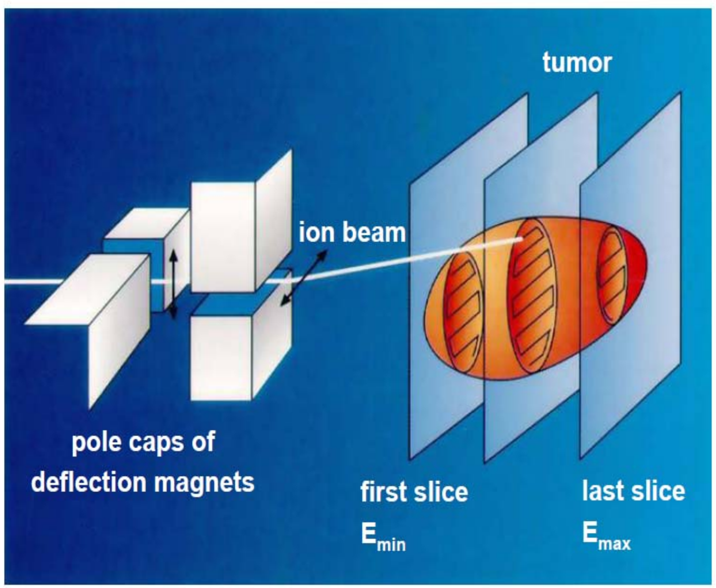


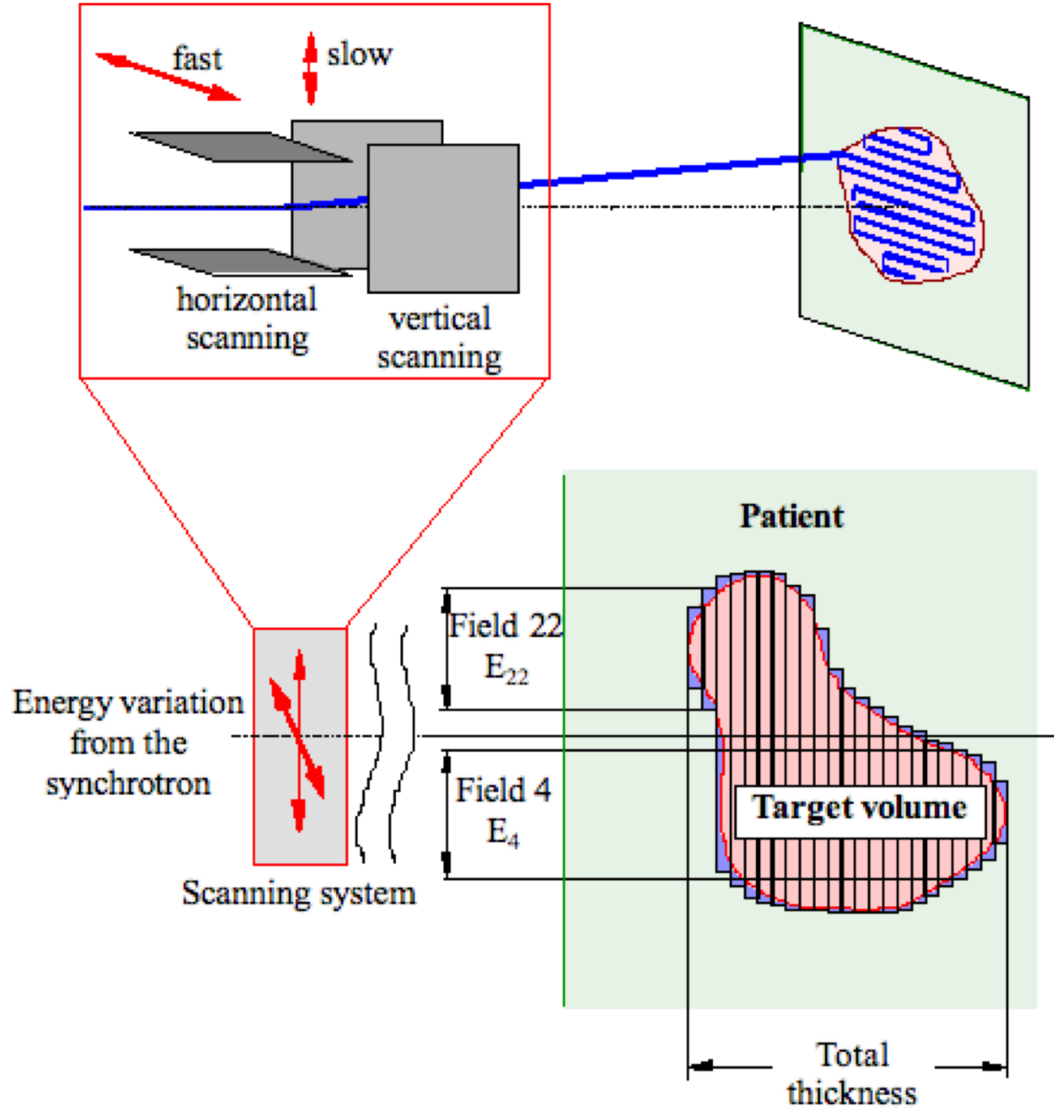
Mostly proton, few ^{12}C beams.

Future ^{4}He, ^{16}O ?

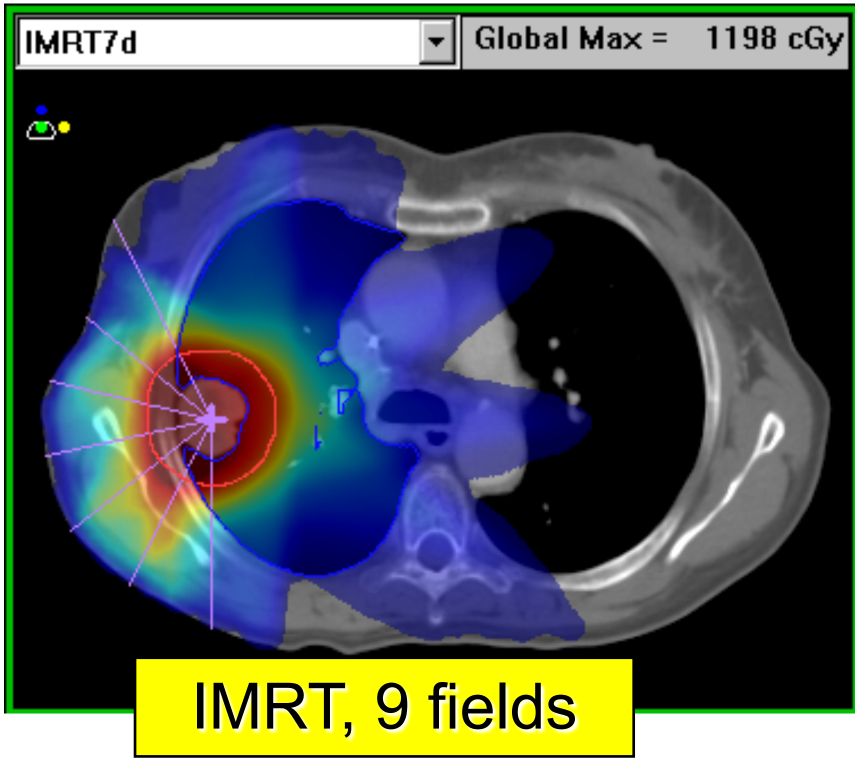
Painting the tumor

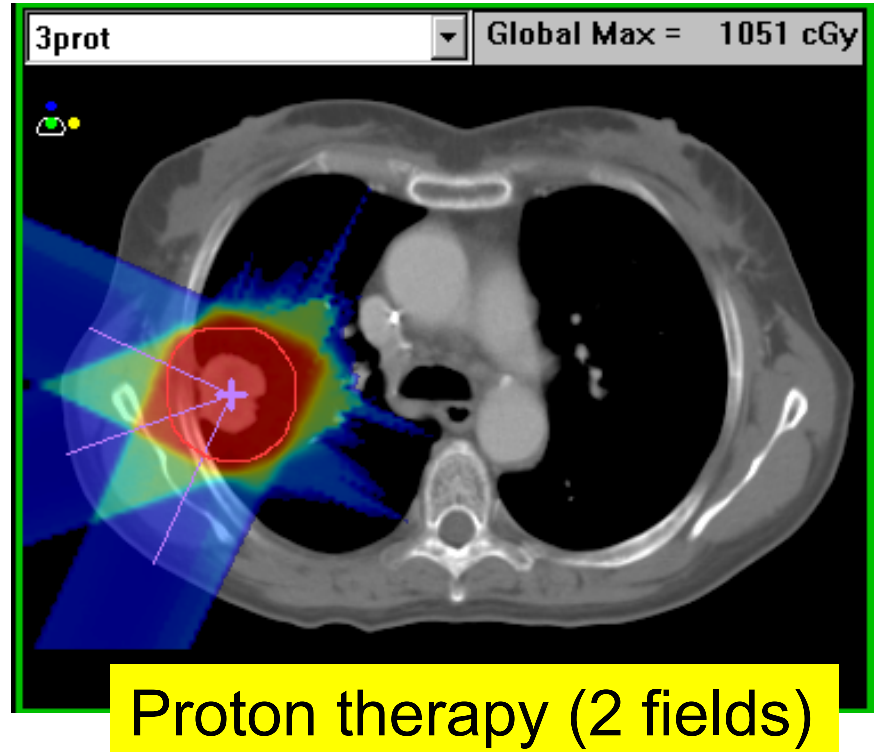
- A charged beam can be easily deflected by means of electric or magnetic fields, and changing also the beam energy (and so the depth) you can paint with energy all the tumor volume





Radiotherapy vs particle therapy

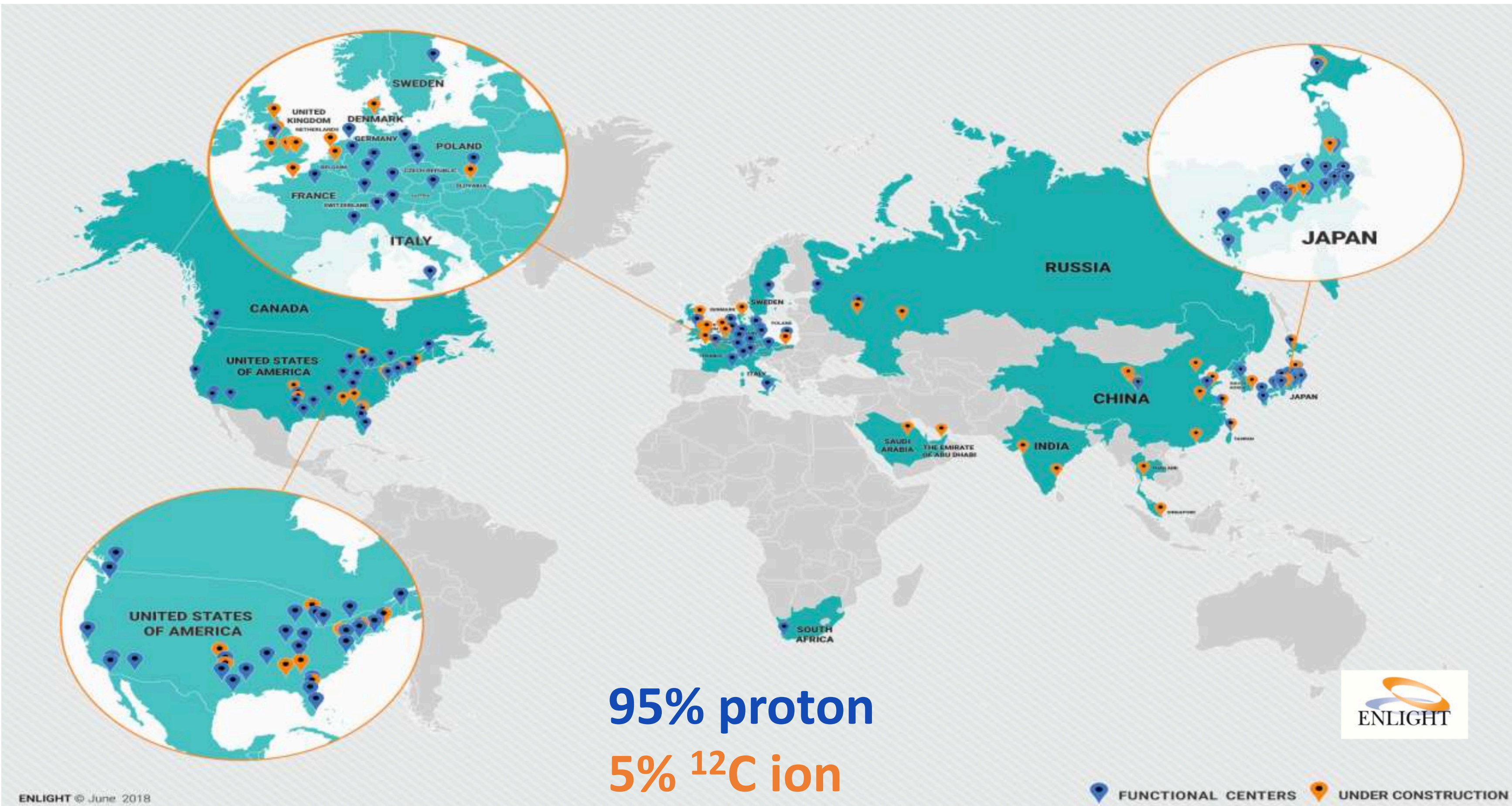




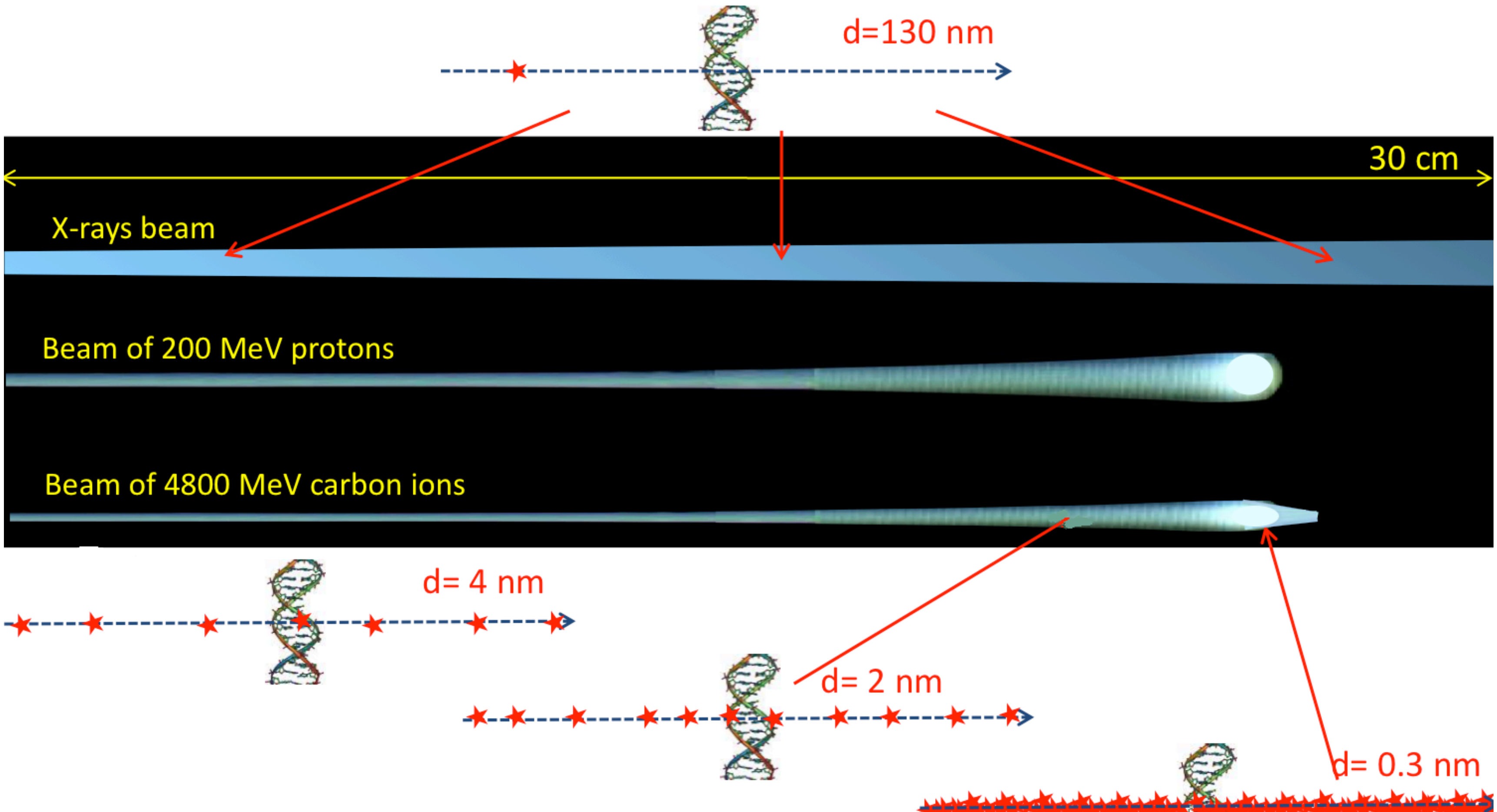
Comparison between Radiotherapy and proton-therapy for a tumor located at the skull base. Particle therapy can show **better selectivity** with respect to photon techniques, helping to **spare the organs at risk**

Particle therapy in the world

- 95 facilities currently in clinical operation in the world (25 in Europe, 3 in Italy → **CNAO, APSS Trento, LNS**) , ~40 under construction



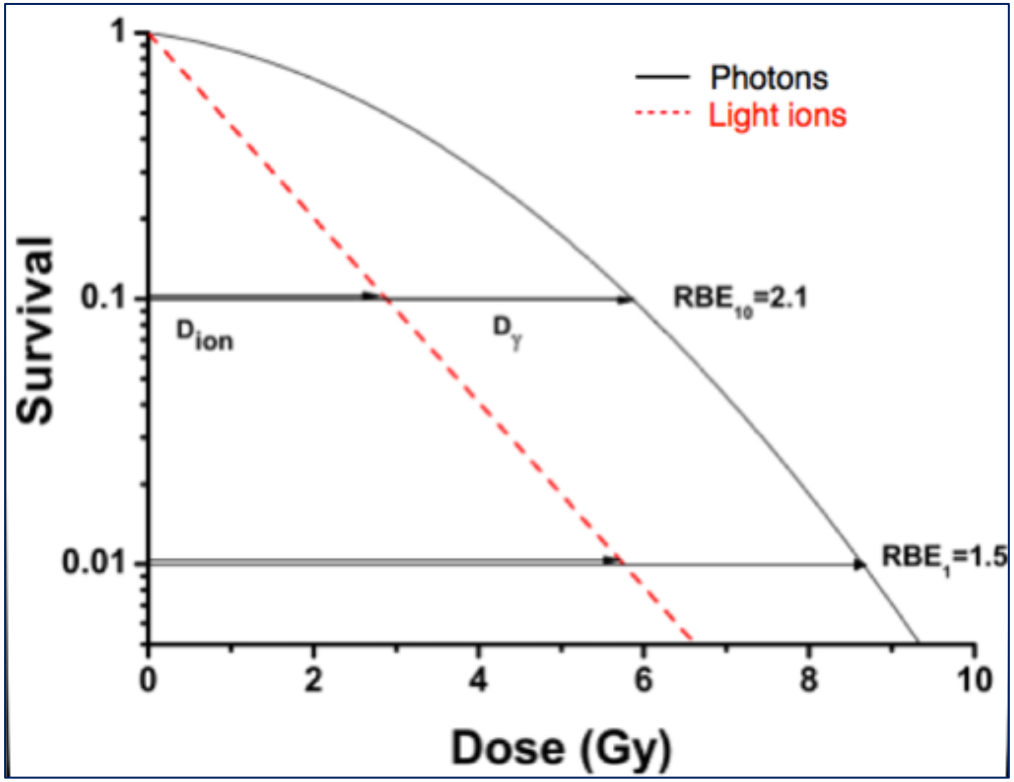
Different bullet, different effects



Carbon ions are DENSELY IONIZING
(higher biological effectiveness)

Radiobiological Effectiveness (RBE)

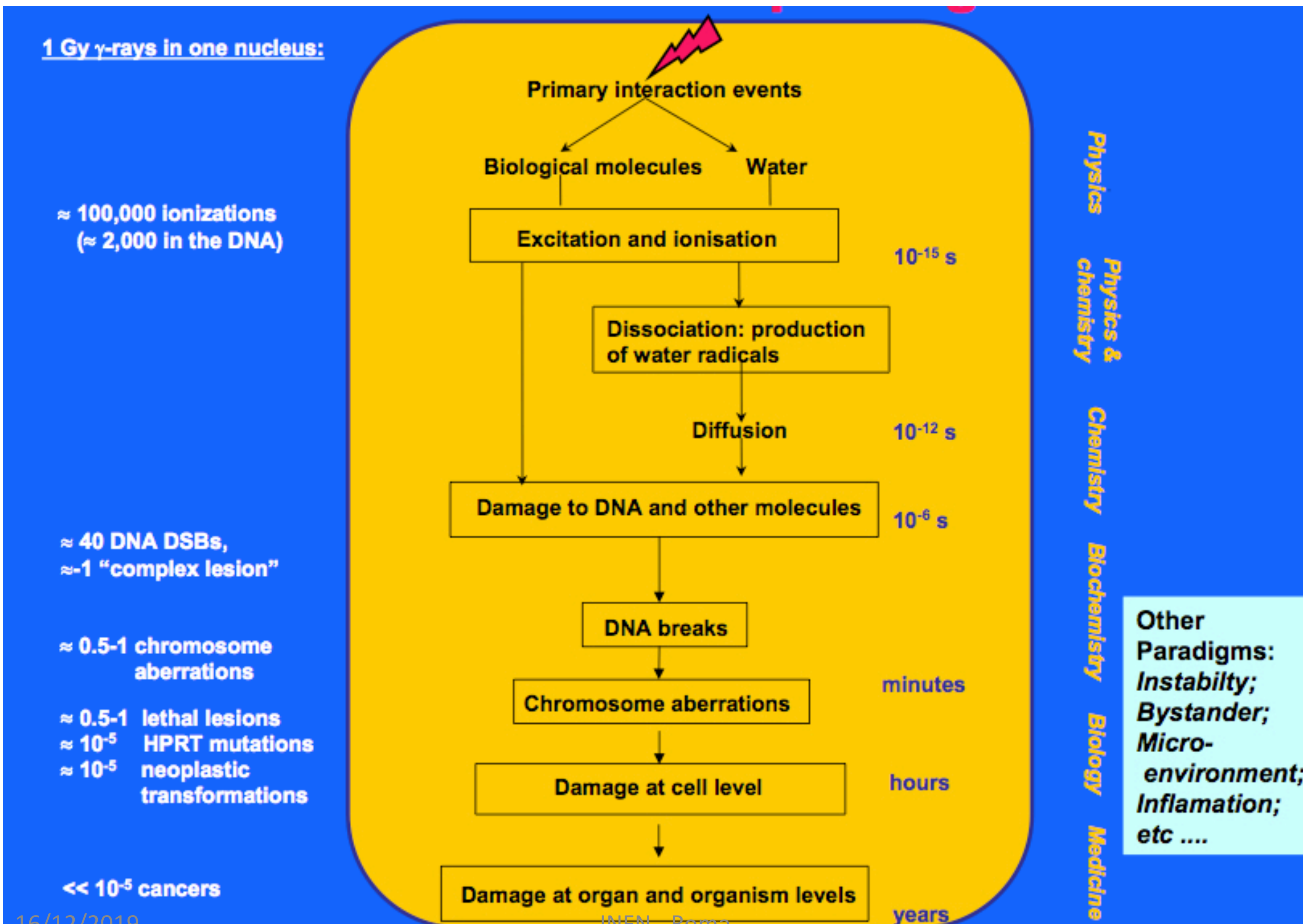
- The **heavier ions are much better at killing the tumor cells** with respect to the X rays (and p) for a given ➔high RBE
- RBE is typically measured evaluating cell survival



$$\mathrm{RBE} = \frac{D_\gamma}{D_{\mathrm{ion}}}$$

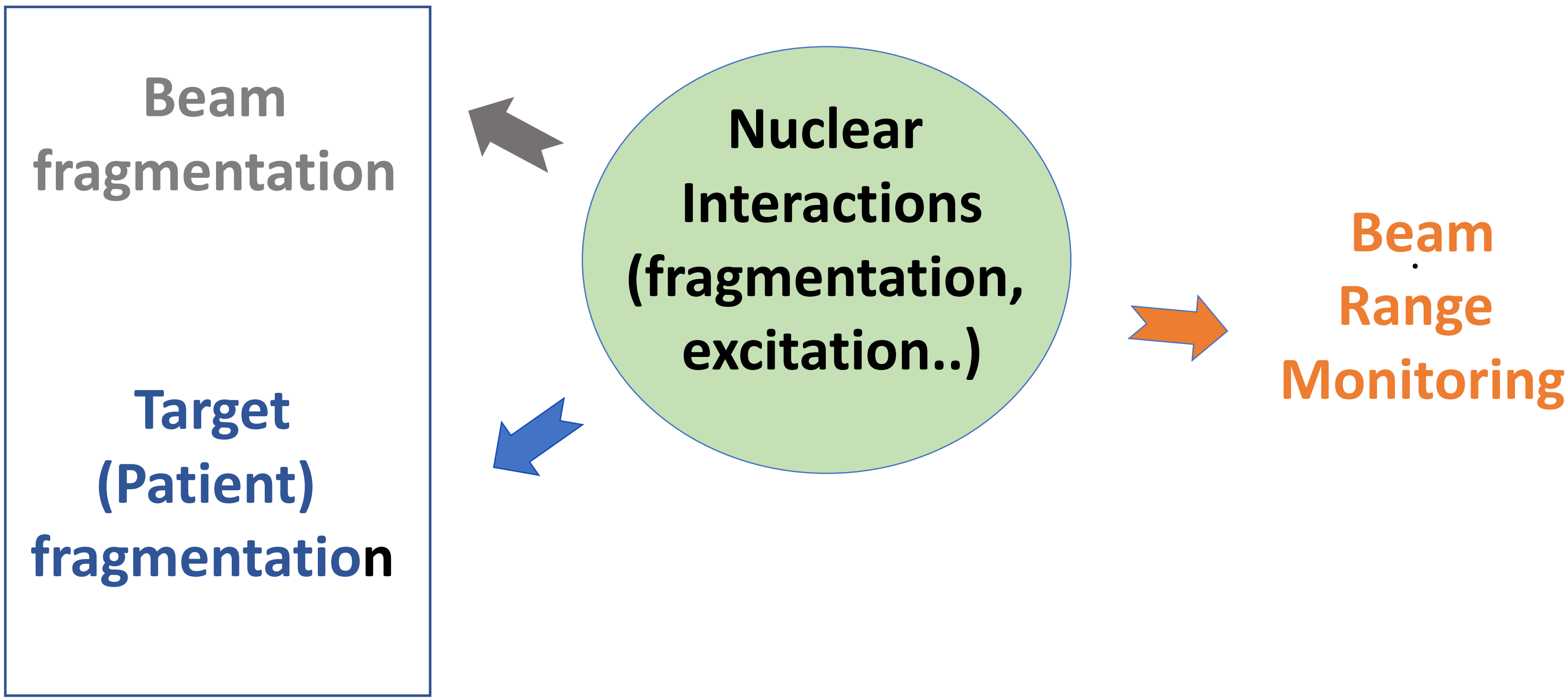
$$\text{(eq. damage)}$$

Time scale of events



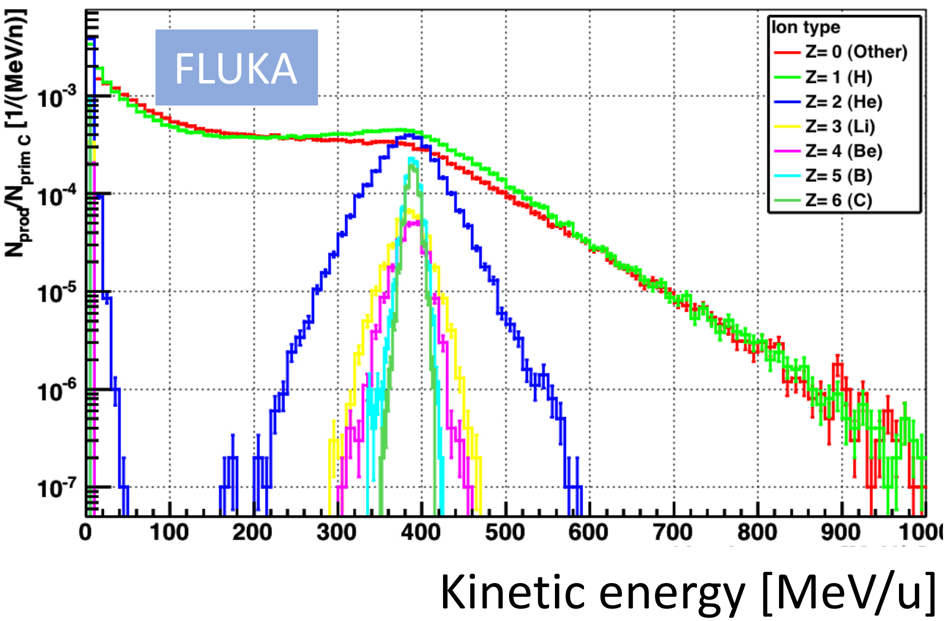
Nuclear fragmentation in particle therapy

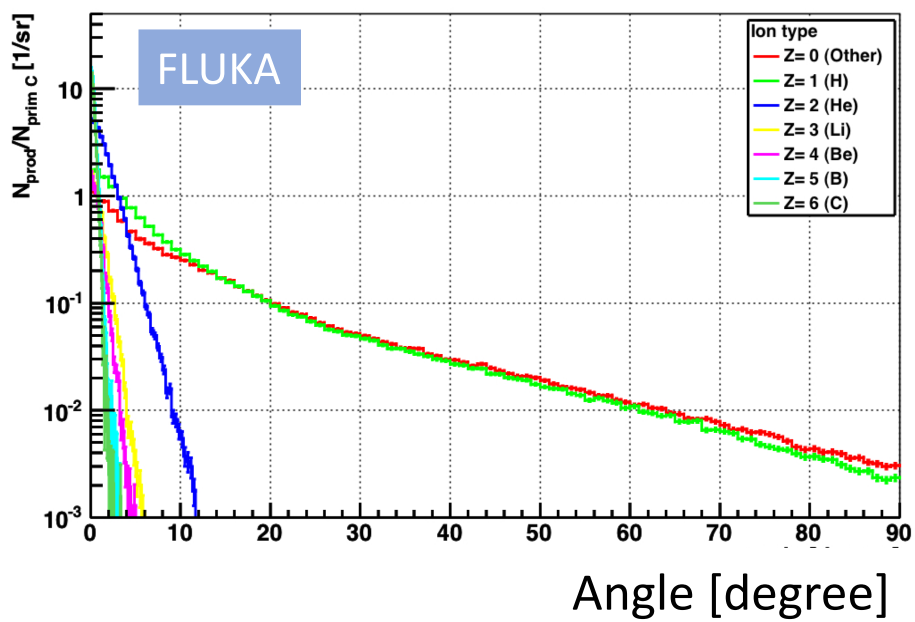
- The total deposited dose is essentially due electromagnetic interactions. However the projectiles commonly used in PT are almost energetic to overcome the Coulomb barrier of nuclei → **fragmentation**



Fragments from ^{12}C beam on graphite target

- The Z>2 produced fragments approximately have the same velocity of the ^{12}C beam and are collimated in the forward direction
- The protons are the most abundant fragments with a wide b spectrum $0<\beta<0.6$ and with a wide angular distribution with long tail
- The Z<=2 fragment are all emitted within 20^0 of angular aperture.

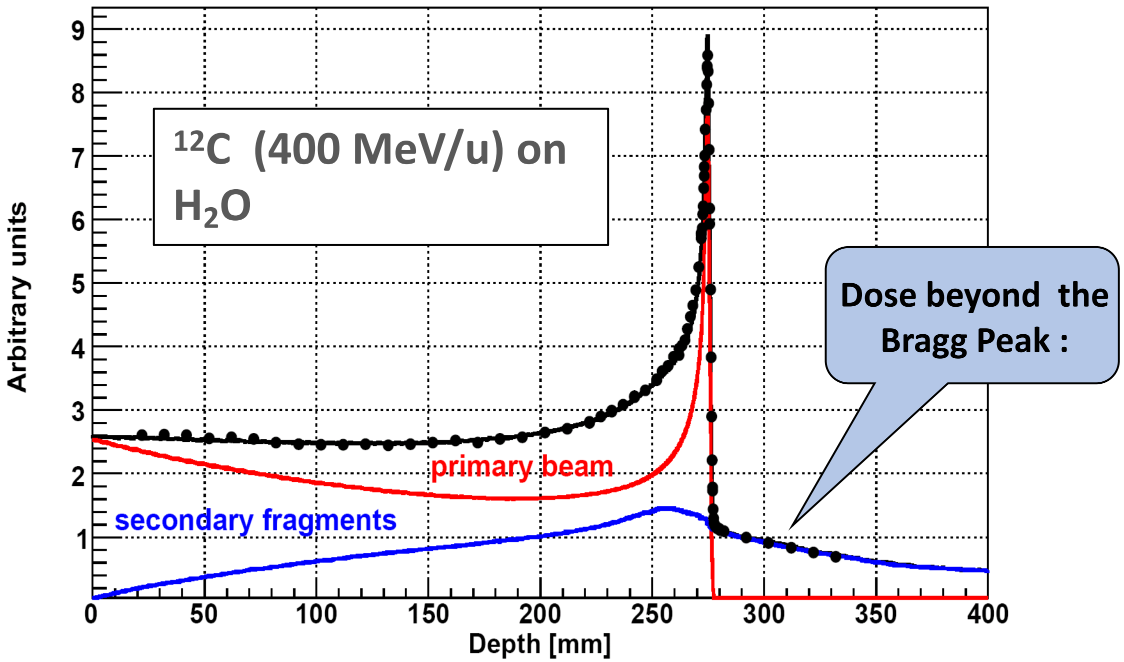




Do not trust MC too much!

The effect on the dose

- Production of fragments with **higher range** and **different direction** vs primary ions
- Mitigation and attenuation of the primary beam
- **Different biological effectiveness** of the fragments wrt the beam

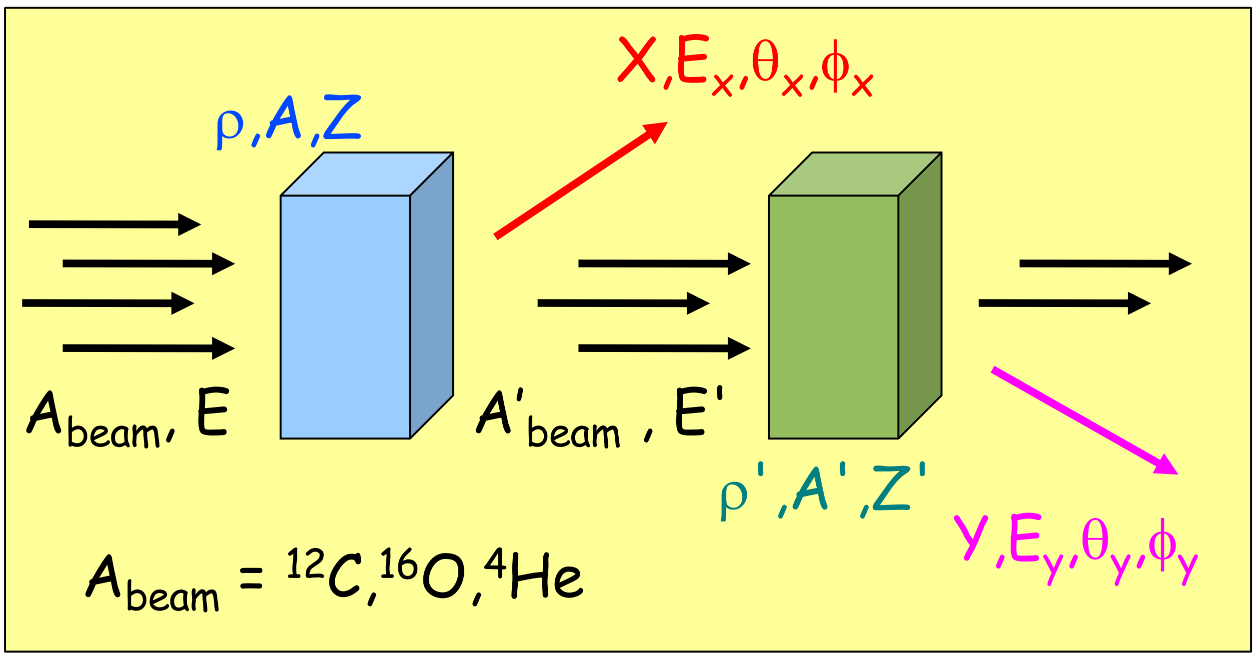


Exp. Data (points) from Haettner et al, Rad. Prot. Dos. 2006
Simulation: A. Mairani PhD Thesis, 2007, Nuovo Cimento C, 31, 2008

Dose release in healthy tissues with possible long term side effects, in particular in treatment of young patients → **must be carefully taken into account in the Treatment Planning System**

What we still miss to know about light ions fragmentation in 2019?

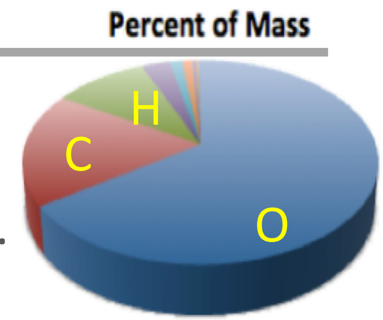
- Production yields of all $Z \leq Z_{beam}$ fragments, if possible of all $A \leq A_{beam}$
- $d^2\sigma/d\Omega dE$ wrt angle and energy, with large angular acceptance
- For any beam energy of interest (100-300 AMeV)
- Thin target measurement of all materials crossed by beam



Not possible a complete DB of measurements

We need to train a nuclear interaction model with the measurements!!

Fragments from proton beam on ^{16}O target



- The elastic interaction and the forward Z=1,2 fragment production are quite well known. Uncertainties on large angle Z=1,2 fragments**. Missing data on heavier fragments production**.
- **Highly ionizing heavier fragment not included in dose evaluation in treatment planning**: possible impact on the RBE?

Very low energy-short range fragments, almost isotropic.

MCs confirm this picture but.....

Nuclear model & MC not reliable at the needed level

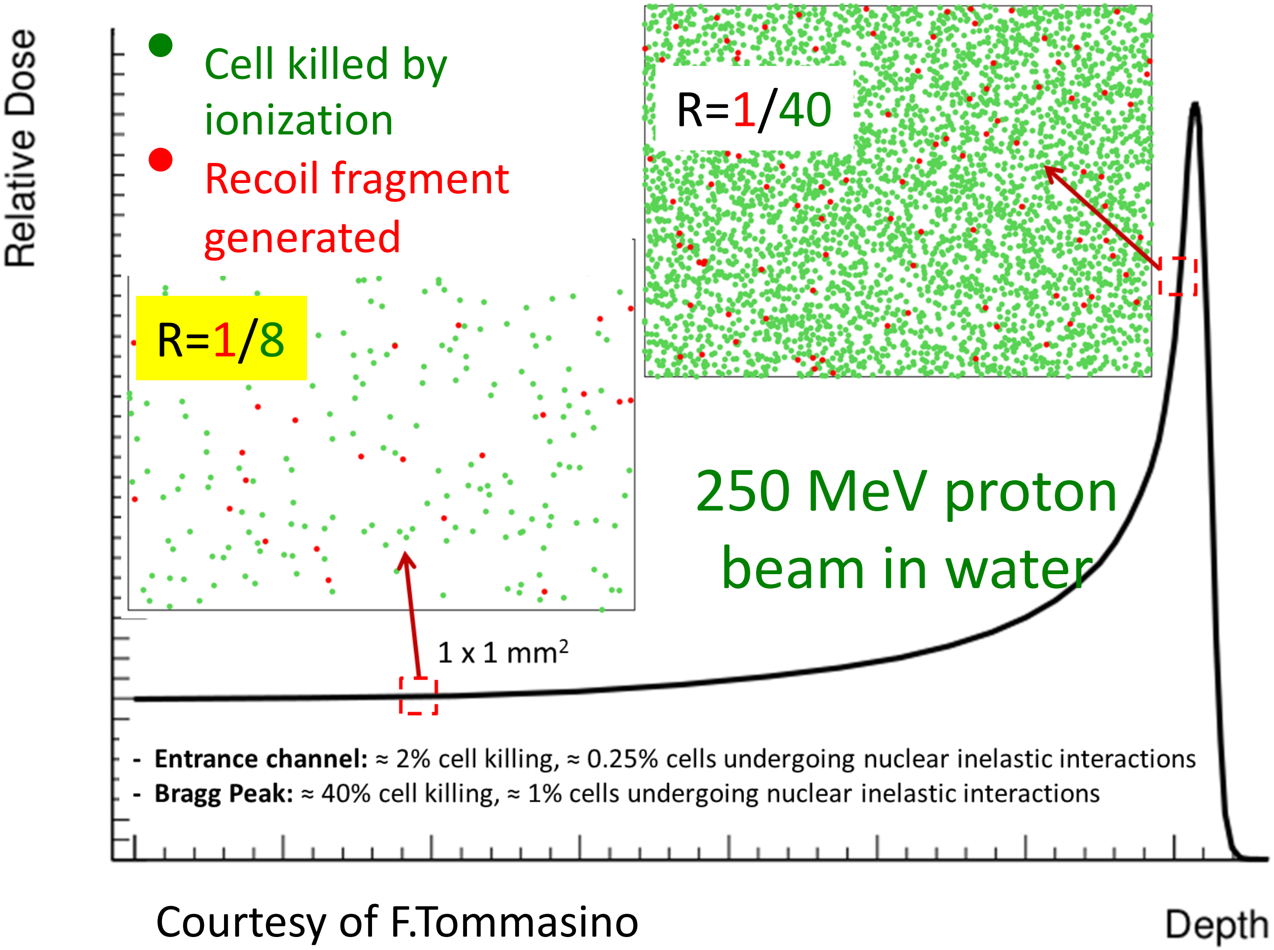
Needed Z>2 fragment yields and emission energy

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

Target fragmentation & RBE

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



Courtesy of F.Tommasino

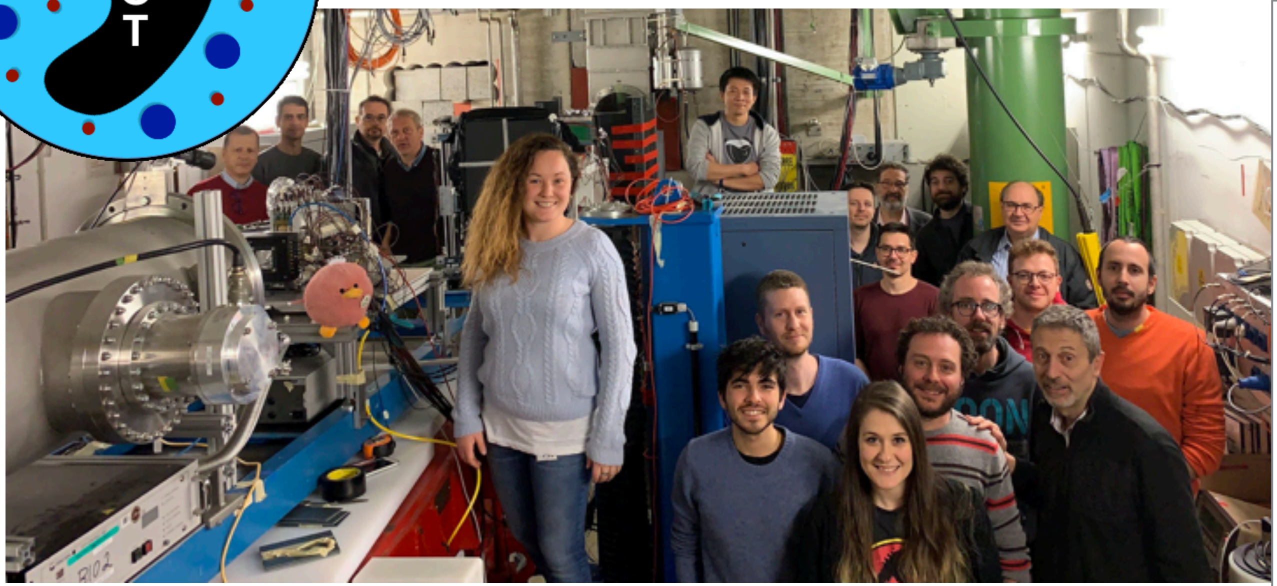
About 10% of biological effect in the entrance channel due to secondary fragments

Largest contributions of recoil fragments expected from He, C, Be, O, N

See also dedicated MC studies:
- Paganetti 2002 PMB
- Grassberger 2011 PMB

The FOOT experiment

The FOOT collaboration wants to tackle the issues of PT and RPS related to light **nuclei fragmentation in the energy region 200 MeV/u - 1 GeV/u**



Nagoya University (**Japan**), GSI (**Germany**), Aachen University (**Germany**), IPHC Strasbourg (**France**), CNAO (**Italy**)

10 Italian University/**INFN sections**

Main issue is the ^{16}O, ^{12}C beams availability. In Europe are not easy to find in laboratory (GSI, ??) but can be available in treatment center (HIT, CNAO,…) -> **the detector must have limited size and be movable**

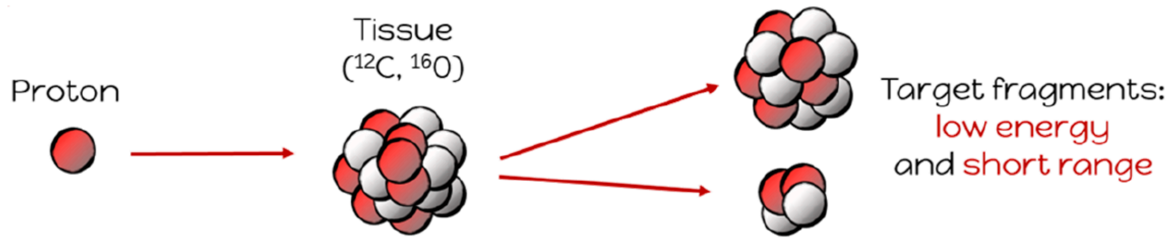
https://web.infn.it/f00t/index.php/en/

Radiobiology requests & detector constraints

To implement Normal Tissue Complication Probability models requirements are very strict. Lorentz boost in the patient frame asks for good energy and angular accuracy in the lab frame

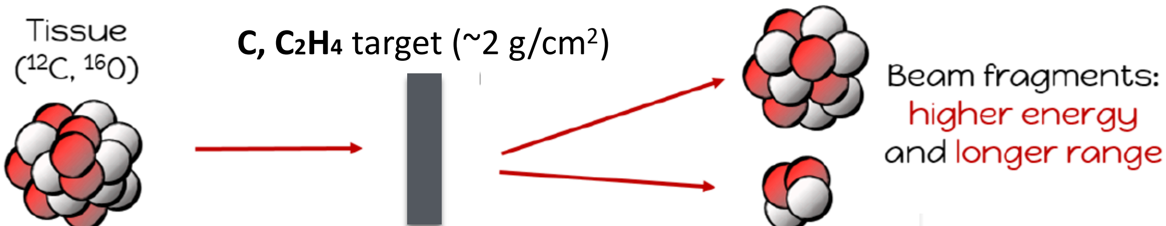
- Heavy fragment (Z>2) production cross section with uncertainty **of 5%**
- Relative accuracy on fragment energy of the order of **few %**
- Charge and isotopic identification capability of fragments **< 10%**
- Accuracy on light ions production also at large angle
- Angular resolution on the beam-fragment emission angle at **mr** level

Target fragmentation measurement strategy



Fragments remain in the target!

Inverse kinematic approach



fragmentation probability ~ 10^{-3}

Fragment	E (MeV)	Range (μm)
^{15}O	1.0	2.3
^{15}N	1.0	2.5
^{14}N	2.0	3.6
^{13}C	3.0	5.4
^{12}C	3.8	6.2
^{11}C	4.6	7.0
^{10}B	5.4	9.9
^{8}Be	6.4	15.7
^{6}Li	6.8	26.7
^{4}He	6.0	48.5
^{3}He	4.7	38.8
^{2}H	2.5	68.9

$$\Lambda\left(\underline{P}_{\text{beam}}\right)$$

Lab. Frame ⟷ Patient Frame

$$\frac{d\sigma}{dE}(H) = \frac{1}{4}\left(\frac{d\sigma}{dE}(C_2H_4) - 2\frac{d\sigma}{dE}(C)\right)$$

By applying a **Lorentz transformation** we switch from the laboratory frame to the "patient frame"

The **cross section** on ^1H is computed by **subtraction**

The FOOT physics program

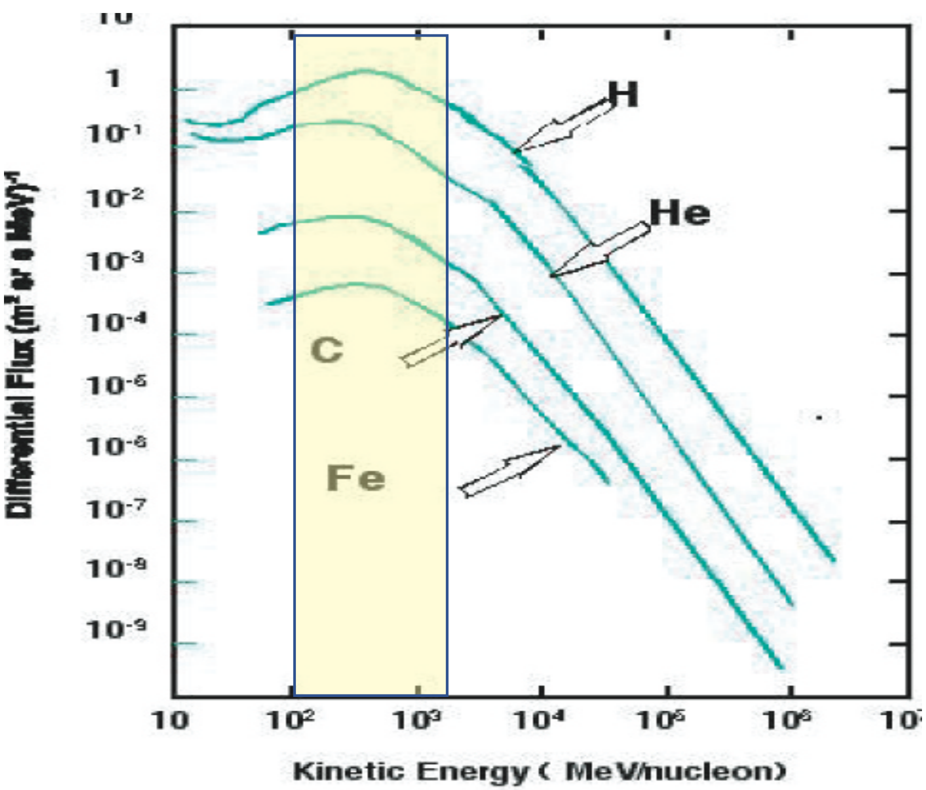
Method of cross section difference is crucial to obtain X section on pure elements:

- Using C, C_2H_4 → cross sections on C and H
- Using C, C_2H_4, PMMA → cross sections on C, O and H

Phys	Beam	Target	Energy (MeV/u)	Inv/direct
Target Frag. PT	^{12}C	C, C_2H_4	200	inv
Target Frag. PT	^{16}O	C, C_2H_4	200	inv
Beam Frag. PT	^{12}C	C, C_2H_4, PMMA	350	dir
Beam Frag. PT	^{16}O	C, C_2H_4, PMMA	400	dir
Beam Frag. PT	^{4}He	C, C_2H_4, PMMA	250	dir
Rad. Prot.space	^{4}He	C, C_2H_4, PMMA	700	dir
Rad. Prot.space	^{12}C	C, C_2H_4, PMMA	700	dir
Rad. Prot.space	^{16}O	C, C_2H_4, PMMA	700	dir

From treatment room to space

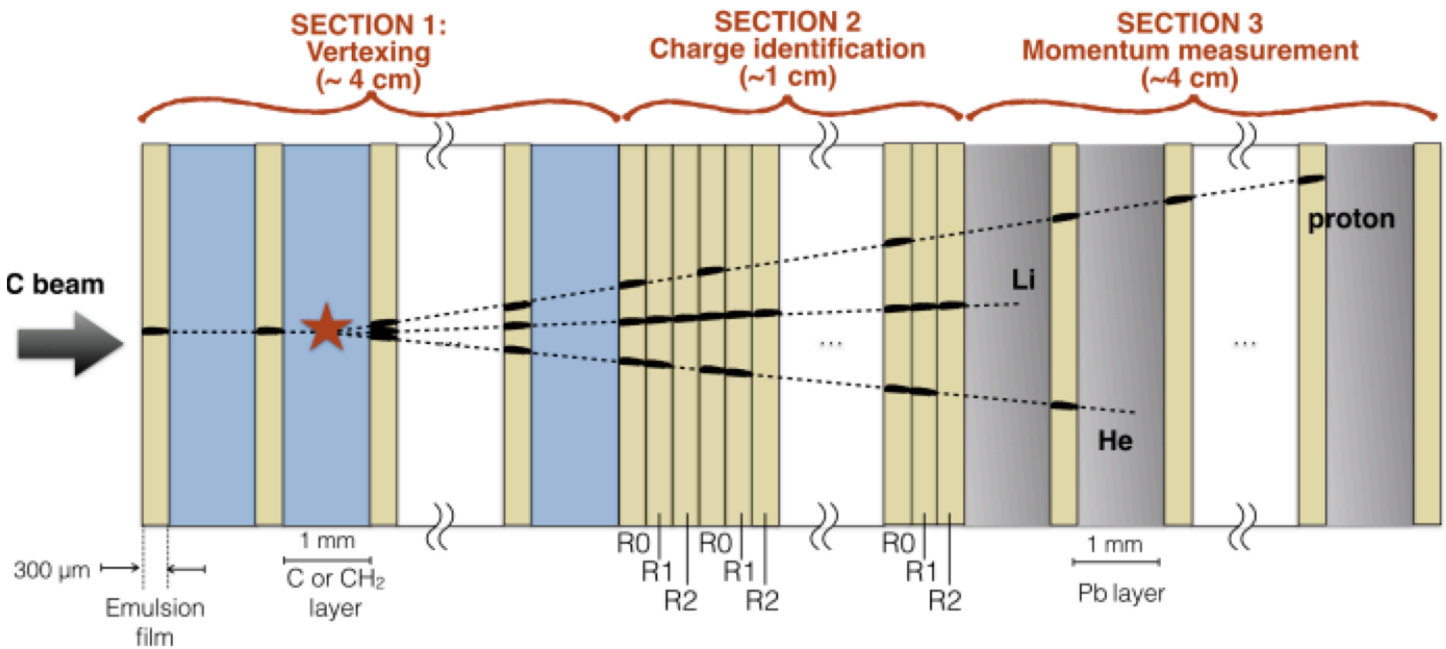
- Long term mission ()Mars) : the astronauths will be exposed to Galactic Cosmi Ray for year(s) with daily equivalent dose of ~ 1 mSv/day
- Threat also from Solar Particle Events: rare (~10 years) but with lethal dose: order of Sv from low energy protons

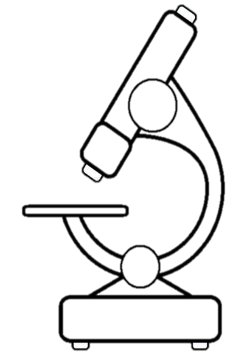


spectrum: 87% protons, 12% He ions and 1% heavier ions (mainly O,C,N) with peaks at 0,7- 1 GeV/n

flux: 4 particles/(cm^2 s) at solar min.

The FOOT emulsion setup

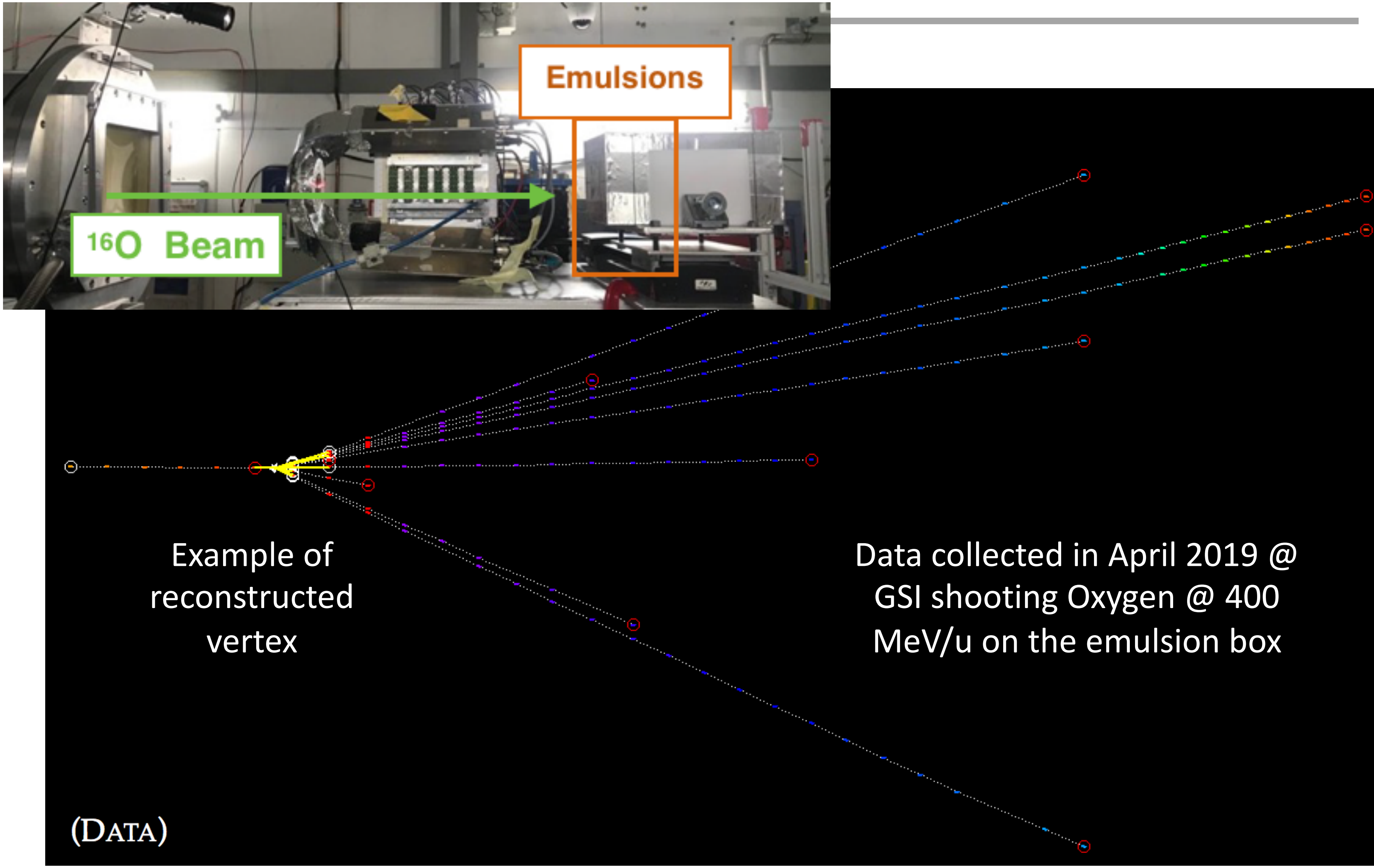




Optimised for Z<3 fragments, covering a wide angular region (75°)

- **Section1**: target plates (C/C_2H_4) interspersed with emulsion films —> vertex detector
- **Section2**: emulsion films only —> charge identification for low Z fragments
- **Section3**: lead planes interspersed by emulsion films: momentum measurement and isotopic ID

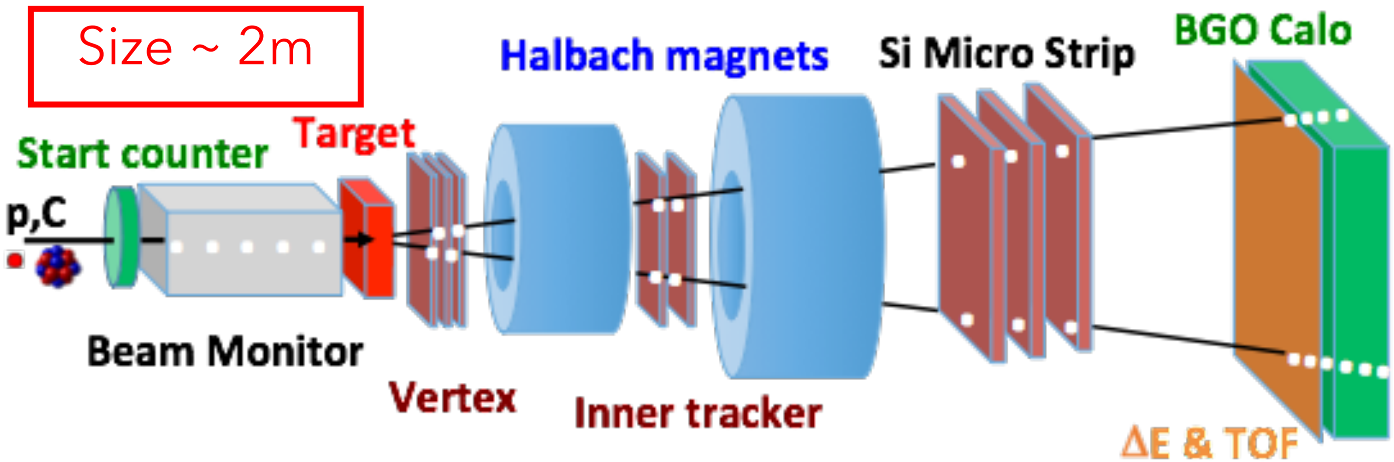
GSI data-taking



Example of reconstructed vertex

Data collected in April 2019 @ GSI shooting Oxygen @ 400 MeV/u on the emulsion box

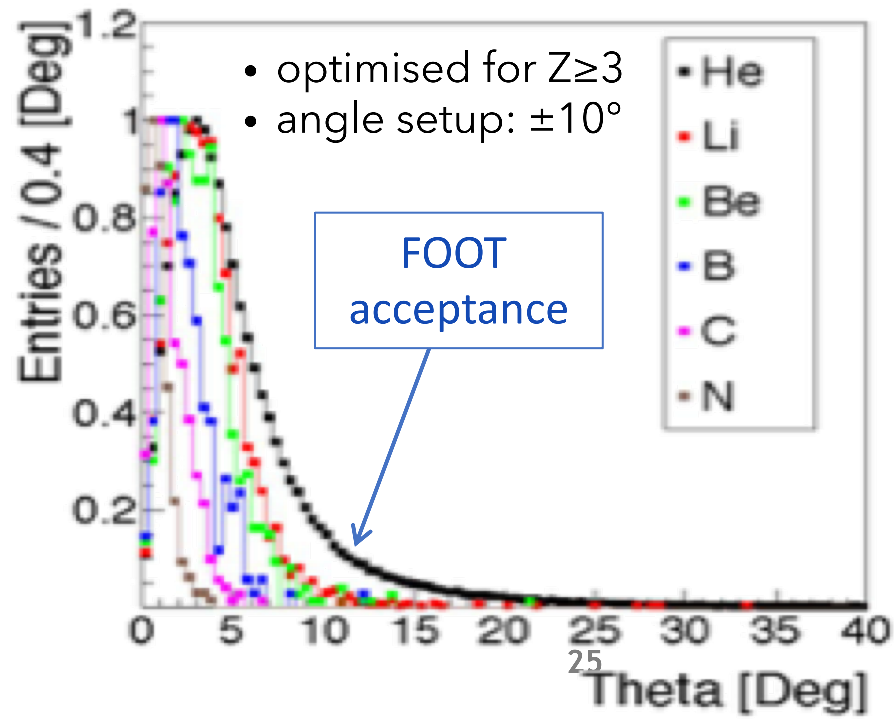
The FOOT electronic setup



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)
Calorimeter	360 BGO crystals (2x2x14 µm)



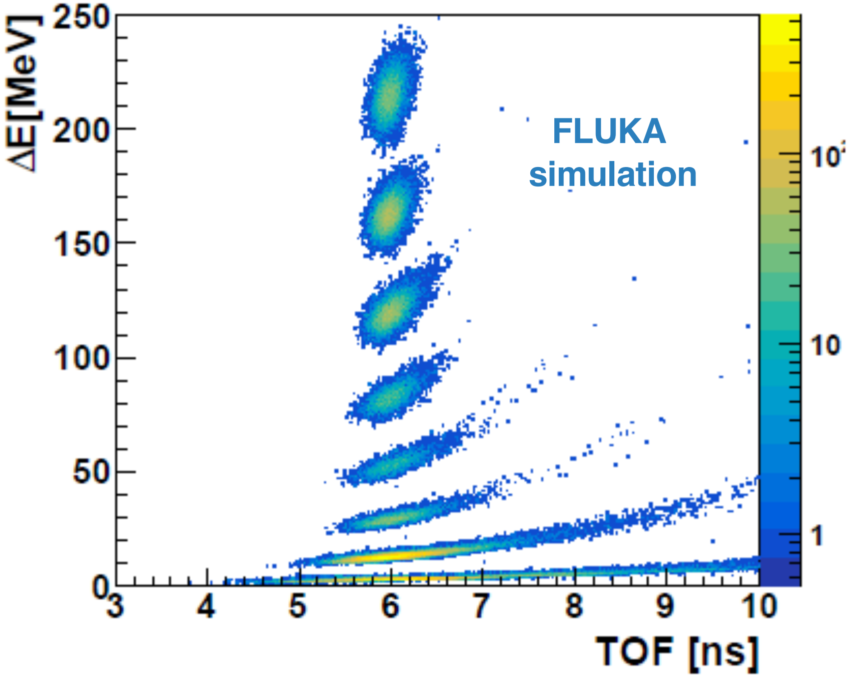
Fragment identification: Z

ΔE in SCN

$$-\frac{dE}{dx} = \frac{\rho \cdot Z}{A} \frac{4\pi N_A m_e c^2}{M_U} \left(\frac{e^2}{4\pi\epsilon_0 m_e c^2}\right)^2 \frac{z^2}{\beta^2} \left[\ln\left(\frac{2 m_e c^2 \beta^2}{I \cdot (1-\beta^2)}\right) - \beta^2\right]$$

ToF

Energy deposited ΔE vs ToF



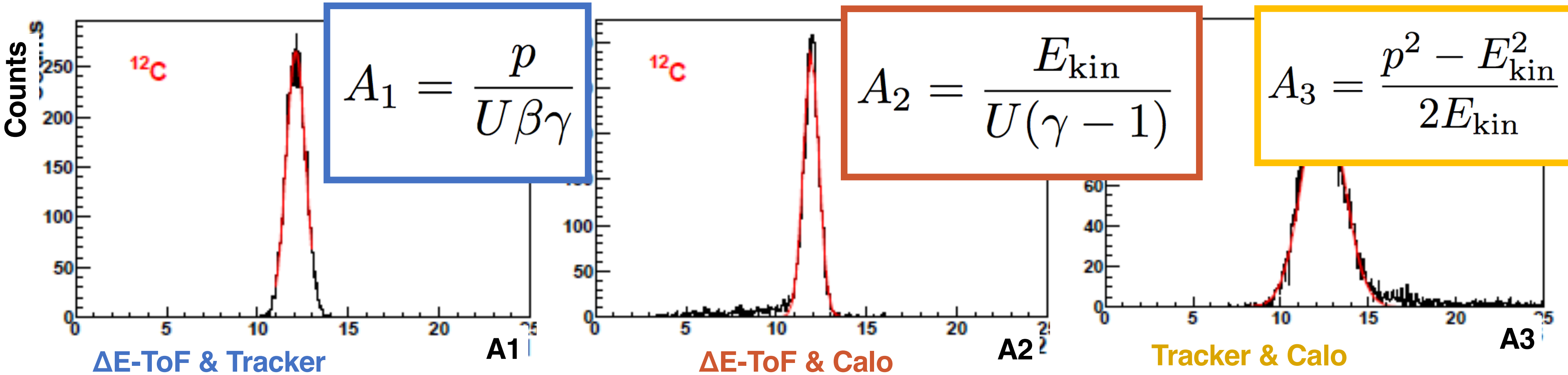
^{16}O (200 MeV/u) —> C_2H_4

Reconstructed Z

Fragment	Z	$\sigma(Z)$ [%]
H	1.01±0.06	6.26
He	2.02±0.06	3.06
Li	3.03±0.07	2.46
Be	4.05±0.09	2.20
B	5.07±0.10	2.06
C	6.09±0.12	1.97
N	7.12±0.14	1.91
O	8.17±0.15	1.86

The Z resolution ranges between **2% (^{16}O)** and **6% (H)**

Fragment identification: A



$$A_1 = \frac{p}{U\beta\gamma}$$

$$A_2 = \frac{E_{\mathrm{kin}}}{U(\gamma - 1)}$$

$$A_3 = \frac{p^2 - E_{\mathrm{kin}}^2}{2E_{\mathrm{kin}}}$$

Redundant Detector: different ways to determine A

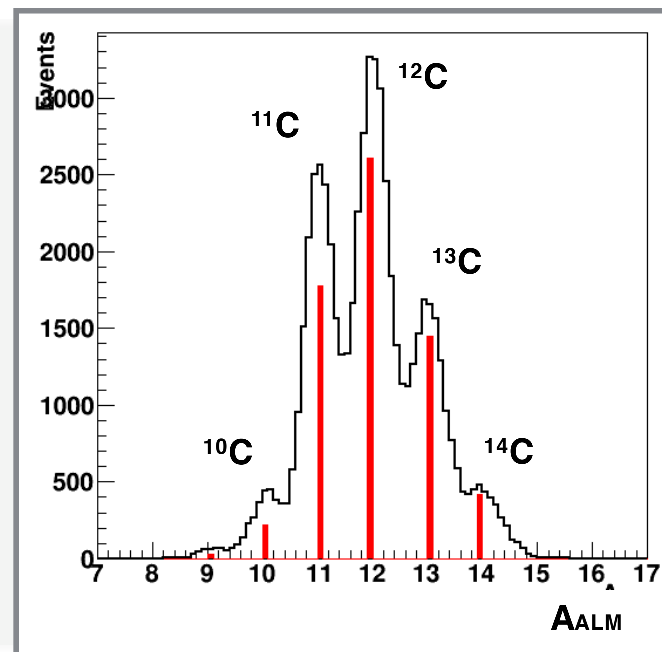
FLUKA simulation

^{16}O (200 MeV/u) —> C_2H_4

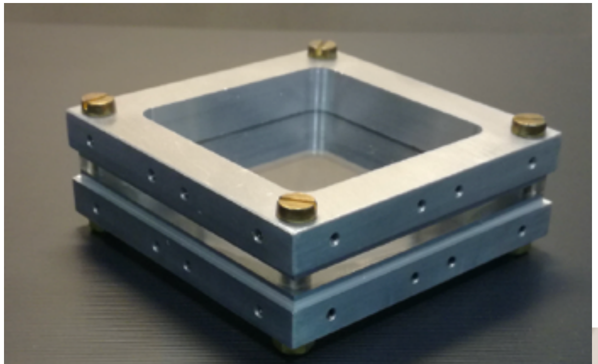
Expected resolution on the atomic mass A ranging between **3% and 6%**, with the required detector resolution

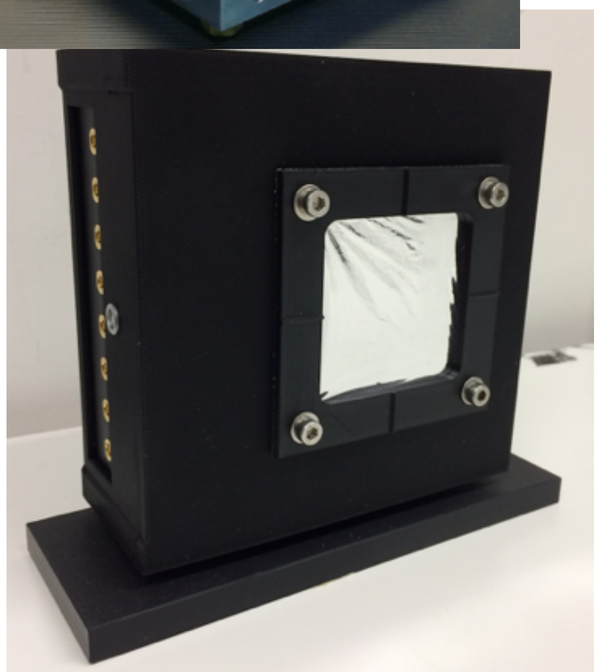
Resolutions:

- σ(p)/p = 4%
- σ(Ekin)/Ekin = 1.5%
- σ(ToF) = 100ps
- σ(ΔE)/ΔE = 3-10%



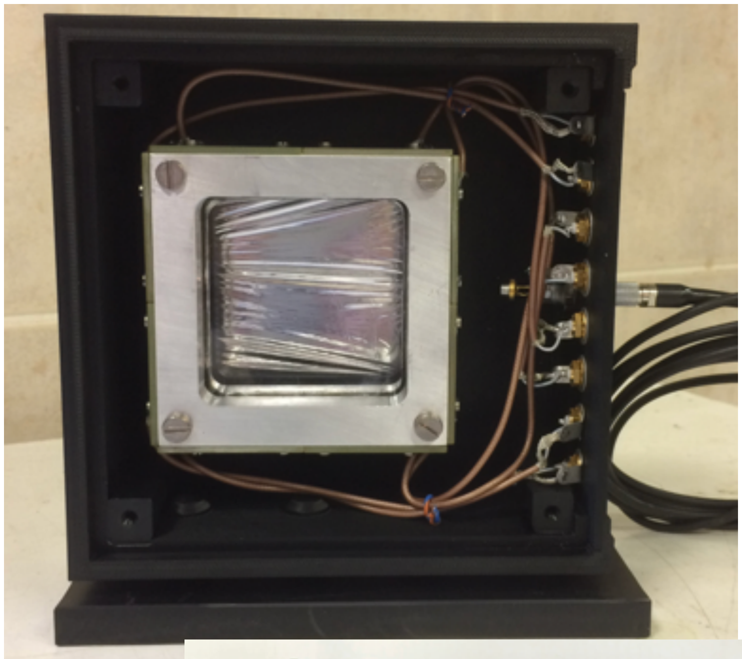
ST detector



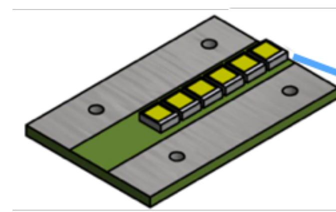


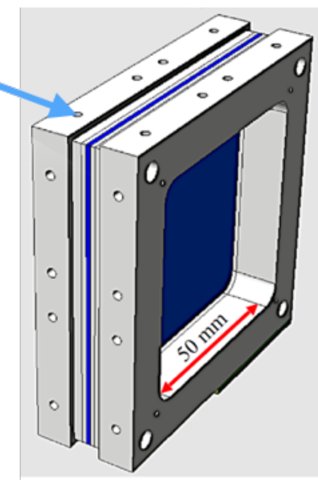
- **Goals**:
  - Incoming ions counter
  - Trigger
  - ToF start
- **Requirements**:
  - Minimise the fragmentation probability inside the detector active medium
  - ToF resolution below 100 ps
- **Active mean:**
  - Plastic **scintillator EJ-228**, 5 x 5 cm^2, **250μm** thick, incapsulated in an aluminum frame
  - Enclosed in a tight-light box with 2 thin aluminum (0.4 μm)+mylar windows (4μm)

ST read-out



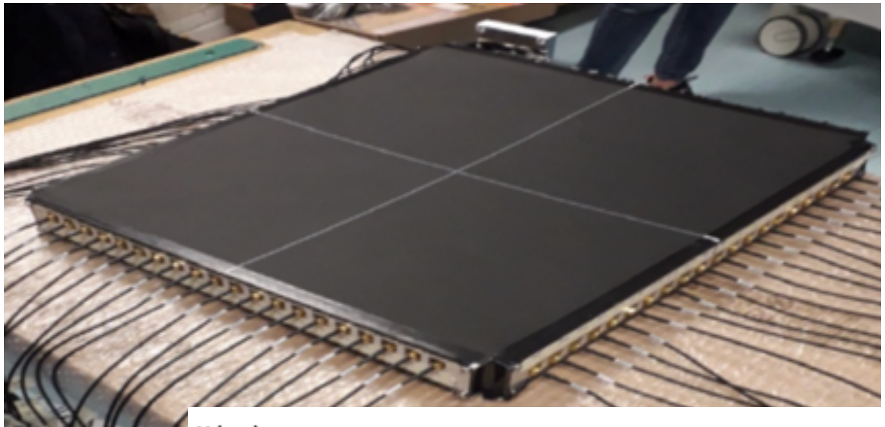
- Read-out performed by **48 SiPM ASD-NUV3S-P**, (8 boards of 6 SiPM connected in series)
- The SiPMs are side-coupled to the scintillator, instrumenting 3.6/5 cm per side

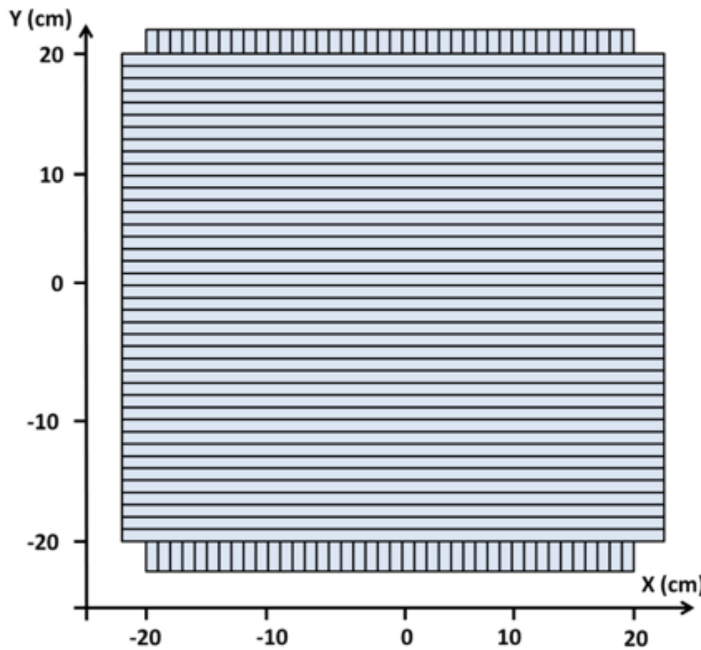




- The power supply and the ead-out of the SiPMs is provided by the **WaveDream** digitizer **(up to 5 GS/s)**

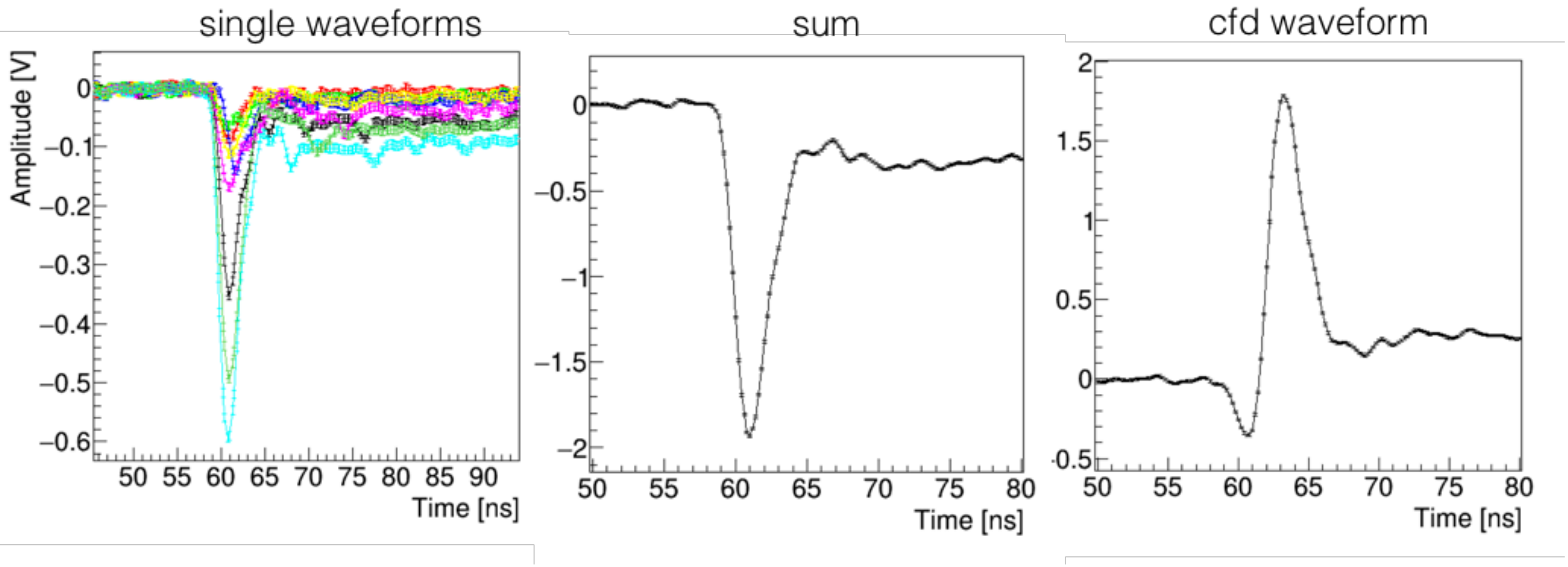
Tof Wall detector





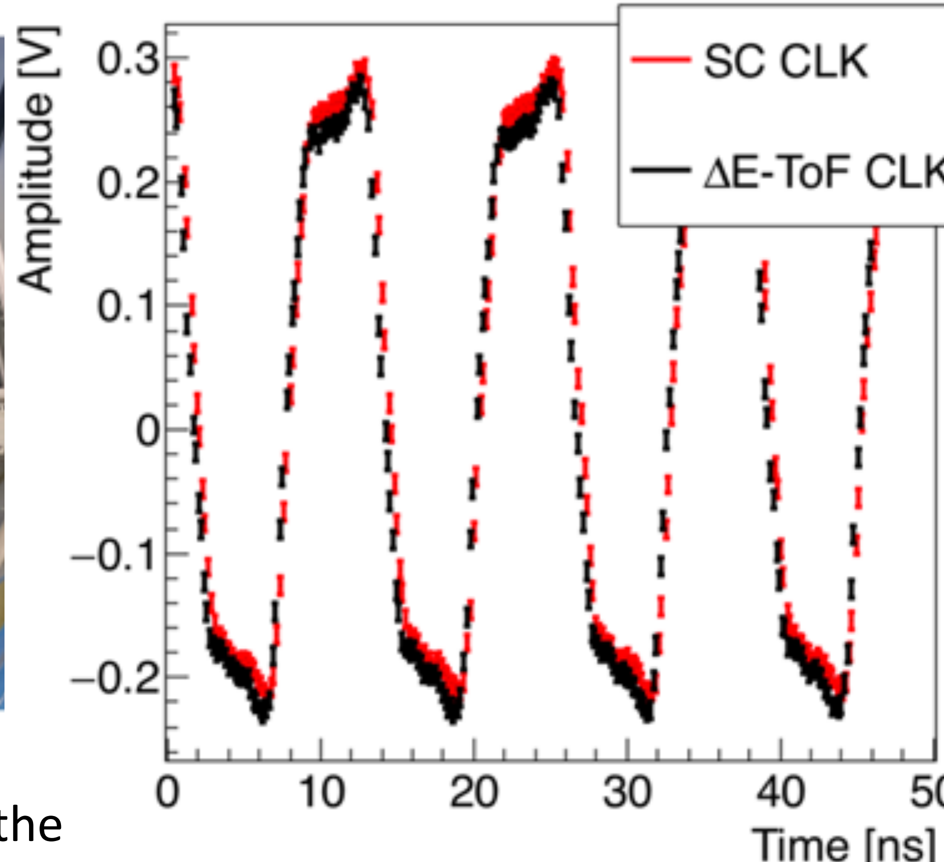
- **Goals**:
  - ΔE measurements for fragment Z identification
  - Trigger (?)
  - ToF end
- **Active mean:**
  - 20x20 bars of plastic **scintillator EJ-200**, 2x44x0.3 cm^3**,** hold by an aluminum frame
  - Each bar is wrapped with and ESR specular reflector
  - Read-out:2 SiPM (**MPPC by Hamamatsu**) with 3x3 mm^2 active area, biased and read-out by a single channel

Time extraction



- The waveform are summed up (linear interpolation bewteen adjacent samplings), then a **digital Constant Fraction Discriminator** (CFD) is applied to assess the event timestamp
- The CFD parameters (delay and fraction) are optimized to minimize the time resolution

Sampling clock jitter correction

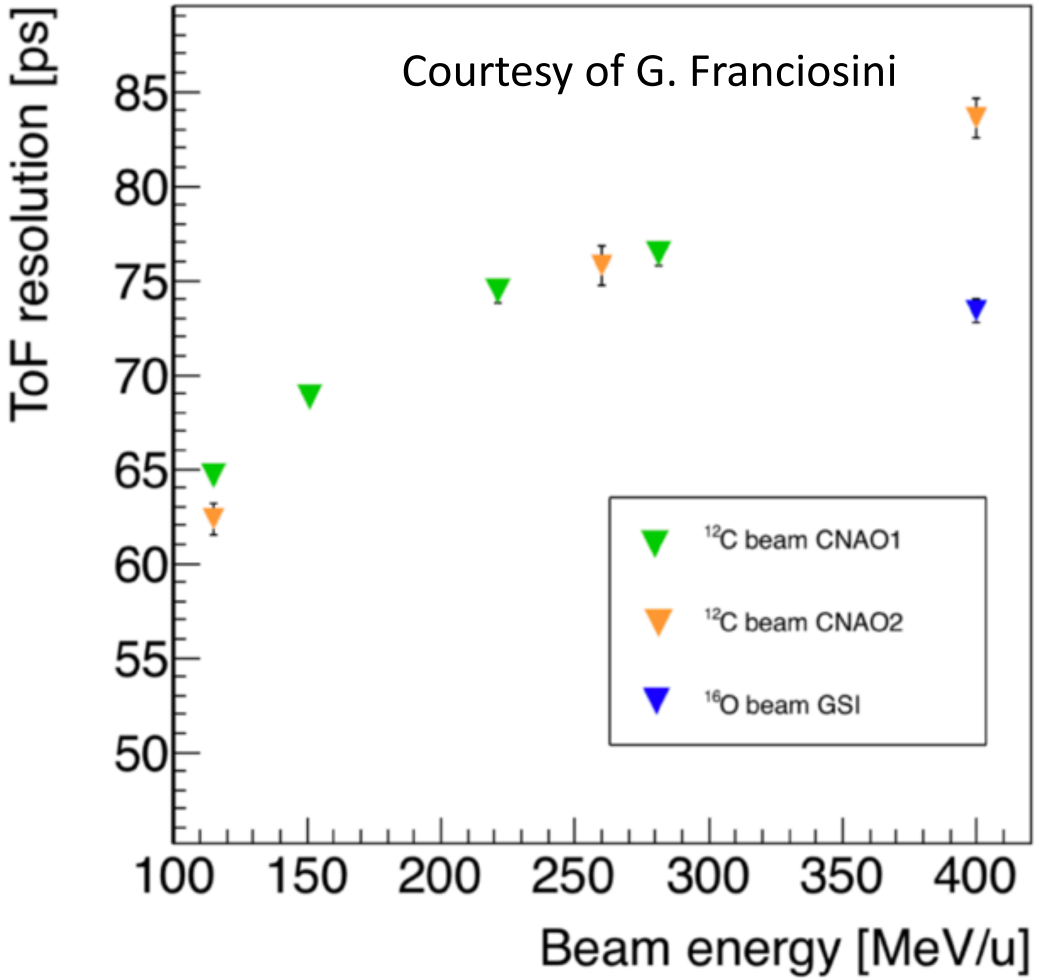


The ST and the TW detector share the same read-out system. However, The **time jitter between the sampling clock** (due to the internal WaveDream routing) has to be taken into account and subctracted when evaluating the signal time!

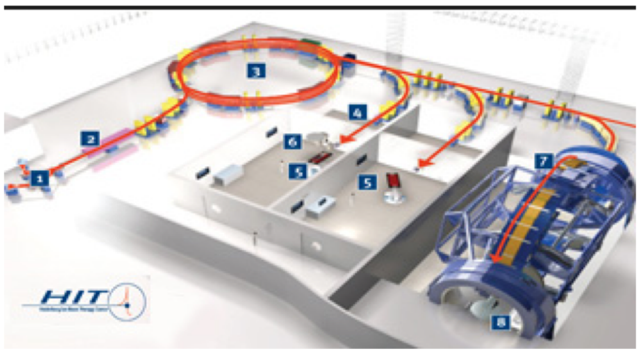
ToF resolution

- The ToF system has been tested @ CNAO and @ GSI using **^{12}C ion** and **^{16}O beams** exploring different energies.

- **ST time resolution between 55 ps and 75 ps**
- **TW resolution between 30 and 40 ps**



Future: beams, data taking & schedule



We need facilities providing ^{4}He, ^{12}C, ^{16}O ions in the 200-700 MeV/u energy range. Possible (affordable-> no BNL, Japan) choices are

GSI : all beams

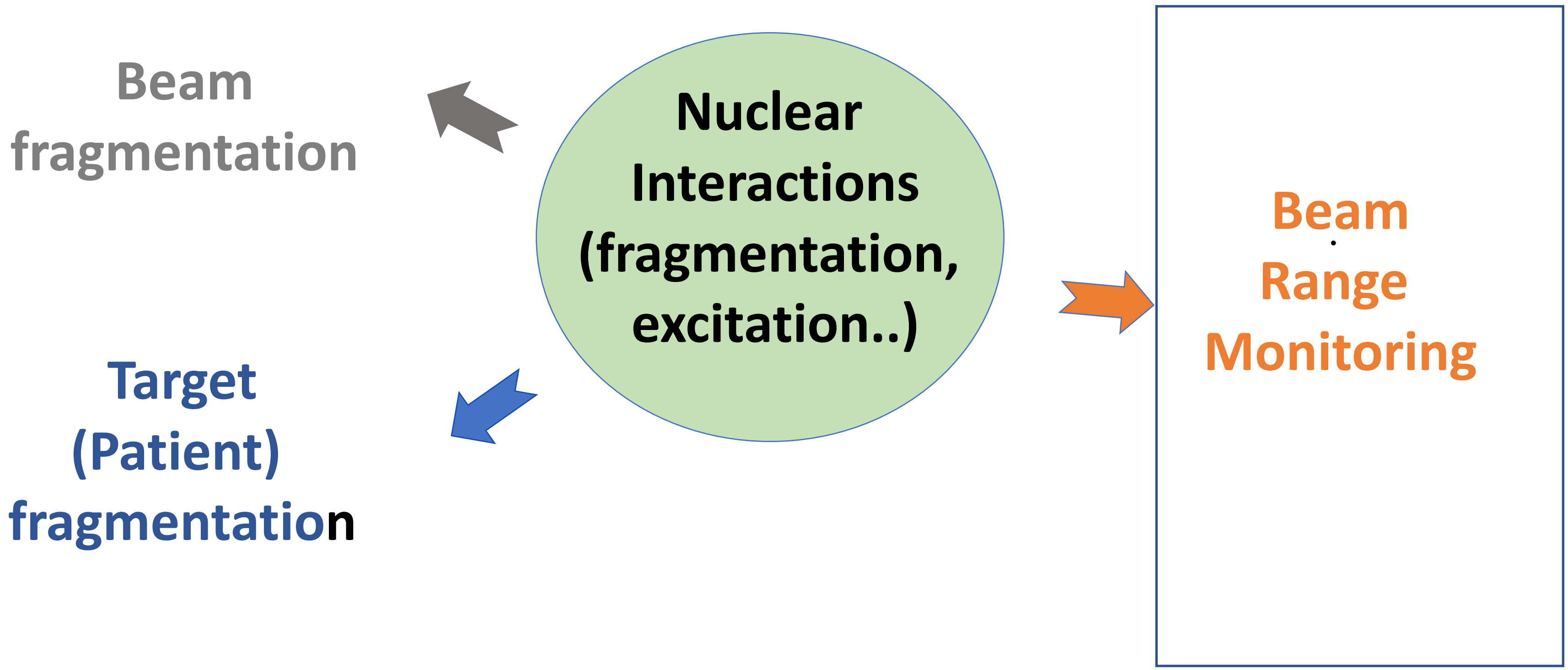
HIT : all beams only up to 400 MeV/u

CNAO : only ^{12}C, p beams up to 400 MeV/u (since late 2019)

- The electronic setup will be completed mid 2020. Engineering data taking April 2019 at GSI
- Electronic setup data taking campaign will start late 2020. It is already funded till 2022
- Next data-taking @ GSI with ^{12}C beam, dedicated to the emulsions stup

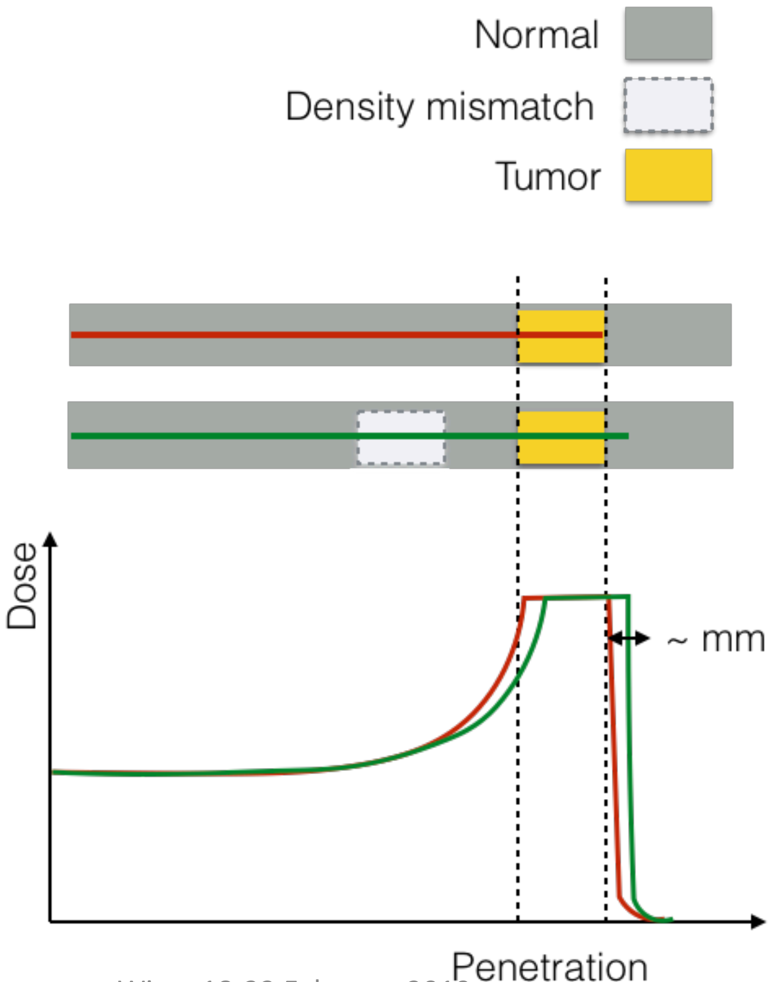
Nuclear fragmentation in particle therapy

- The total deposited dose is essentially due electromagnetic interactions. However the projectiles commonly used in PT are almost energetic to overcome the Coulomb barrier of nuclei → **fragmentation**



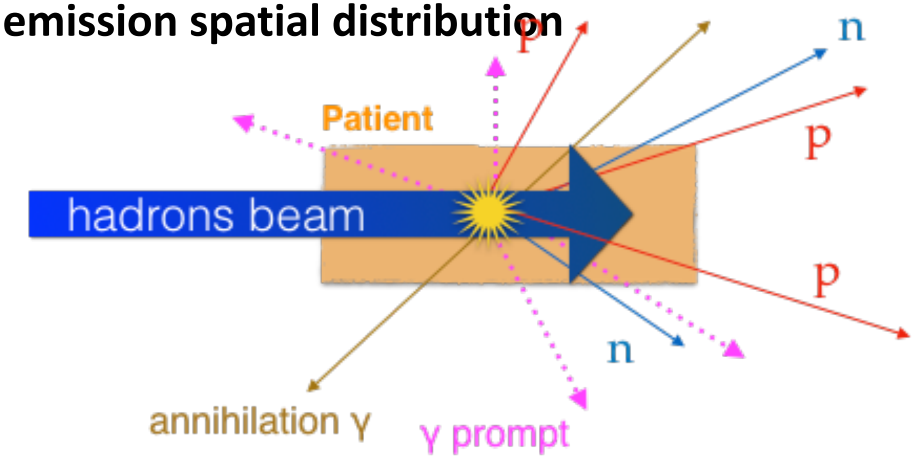
Exploiting the projectile fragments for range monitoring(?)

PT is highly sensible to range variations (patient mispositioning, uncertainties on the CT Hounsfield number conversion, anatomical density variation...)



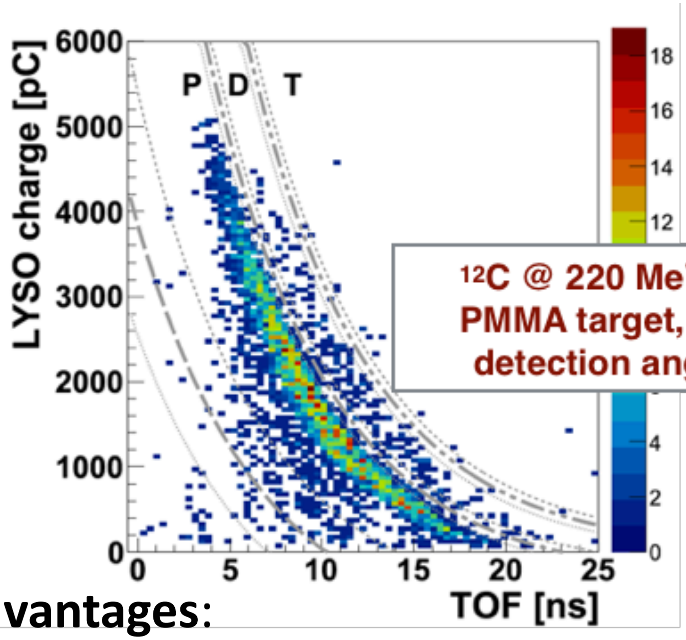
-A range monitor must rely on **secondary particles produced in nuclear interactions** and coming out from the patient, giving a feedback during the treatment (possibly online)

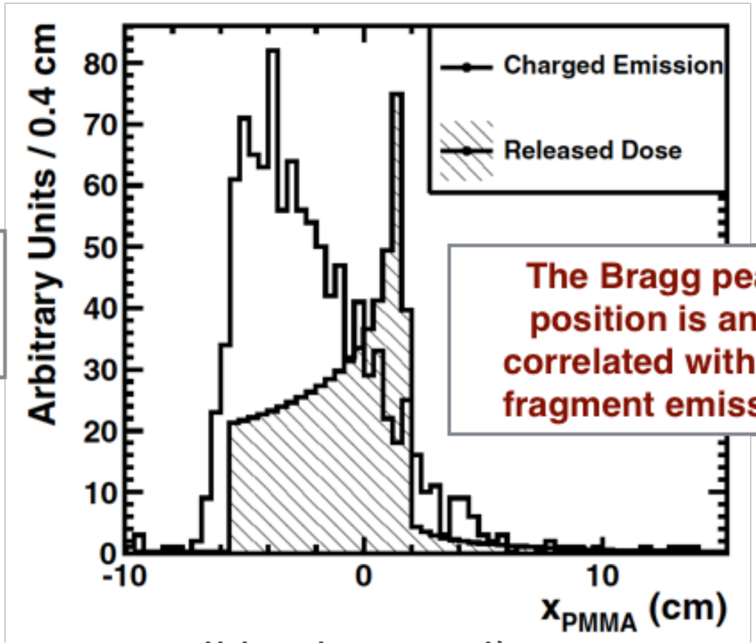
- Generally the Bragg peak position can be correlated with the secondary particles **emission spatial distribution**



Fragments @ large angle

A **significant emission of secondary charged fragments** occurs when using **Z>1** ions also @ large angles with respect to the beam direction)!





Advantages:

Easy to detect (high detection efficiency, small background)

Easy reconstruction of the production vertex with tracking devices

Drawbacks:

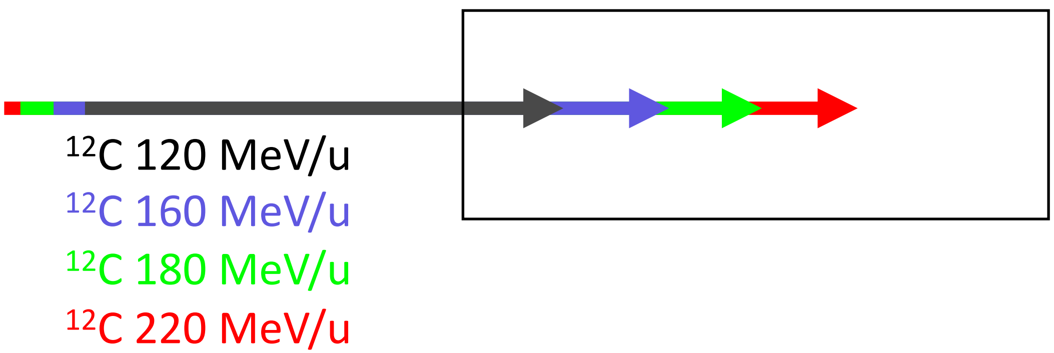
Patient-dependent fragment absorption —> non trivial correlation with the Bragg peak

Resolution limited by the multiple scattering

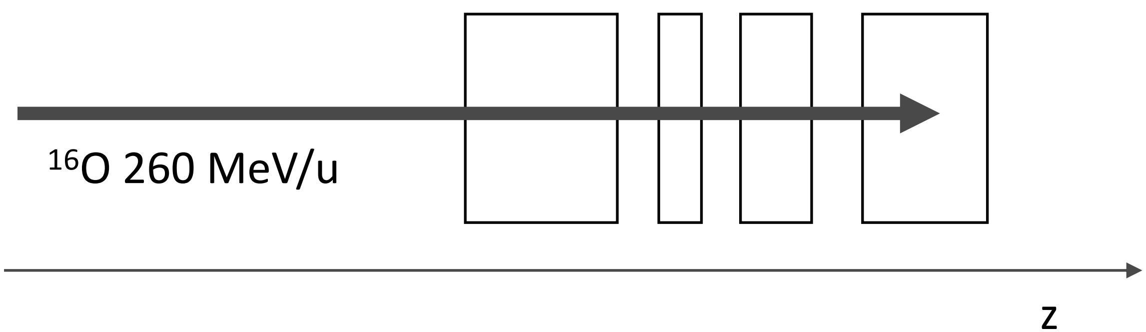
Proof of concept

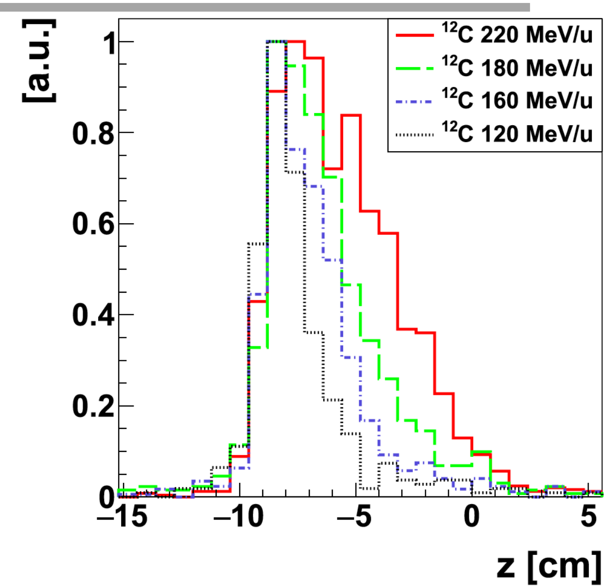
The emission shape is sensitive to density variations!

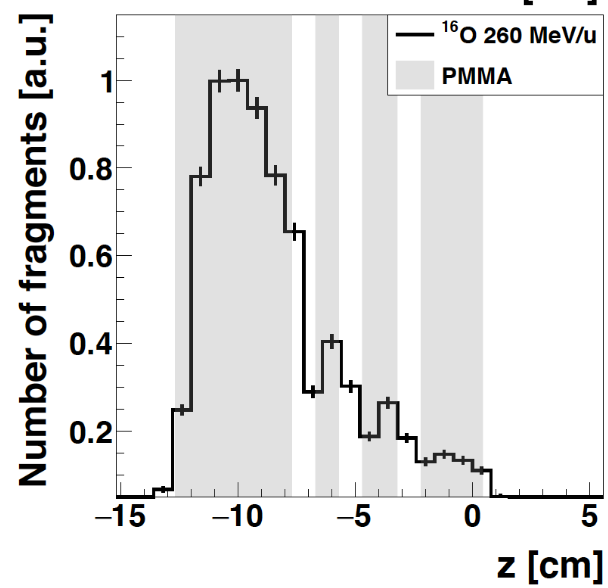
Homogeneous PMMA target



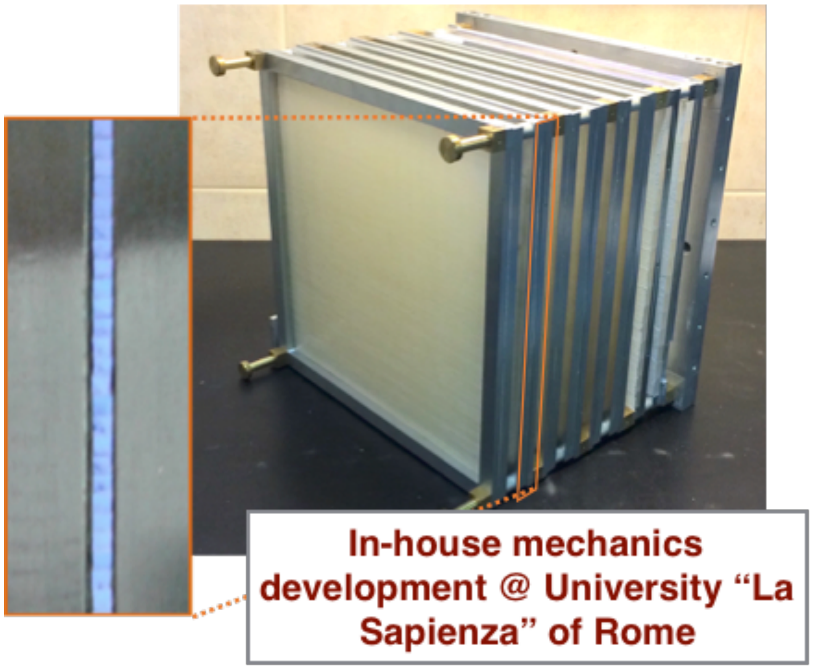
PMMA target
with air gaps





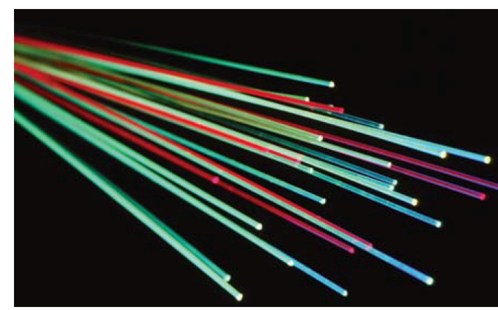


The Dose Profiler



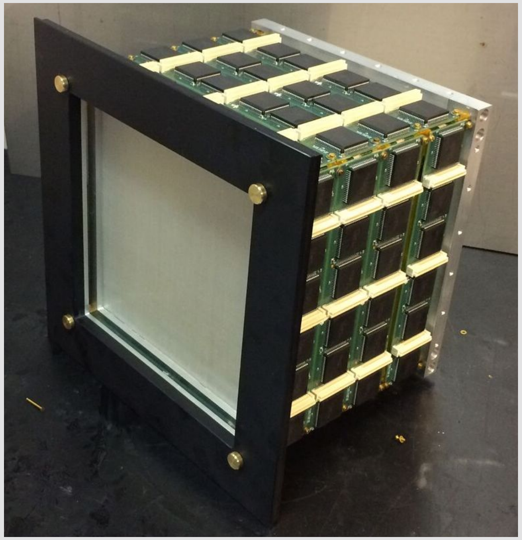
- 8 planes each one composed of 2 orthogonally oriented layers of **plastic scintillating fibres** (squared 500 µm, double cladding) are used to track the incoming particles
- **Custom read-out system** based on ASIC and FPGAs
- Interface with the Dose Delivery system of CNAO

Fiber	Color	Peak, nm	Time, ns	m*	per MeV**
BCF-12	Blue	435	3.2	2.7	~8000

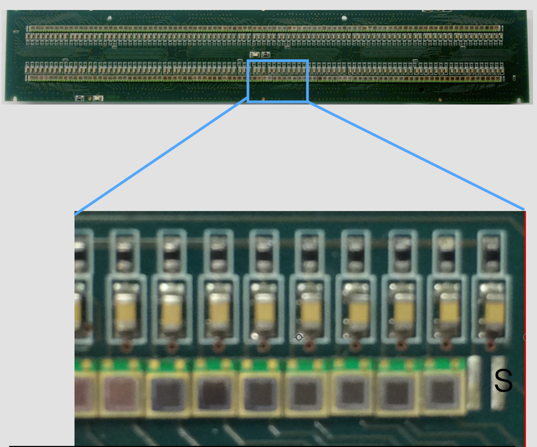


Design criteria: **compactness**, **easy of maintenance**, **high detection efficiency** and **DAQ rate capability** (up to 100kHz)

Read-out system



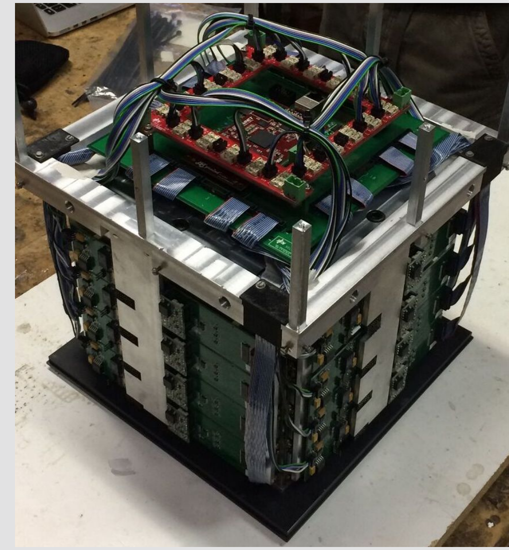
SiPM boards



Hamamatsu SiPM 1 mm^2

FPGAs boards

- 3072 channels
- 16 FPGA used for ASIC configuration and readout

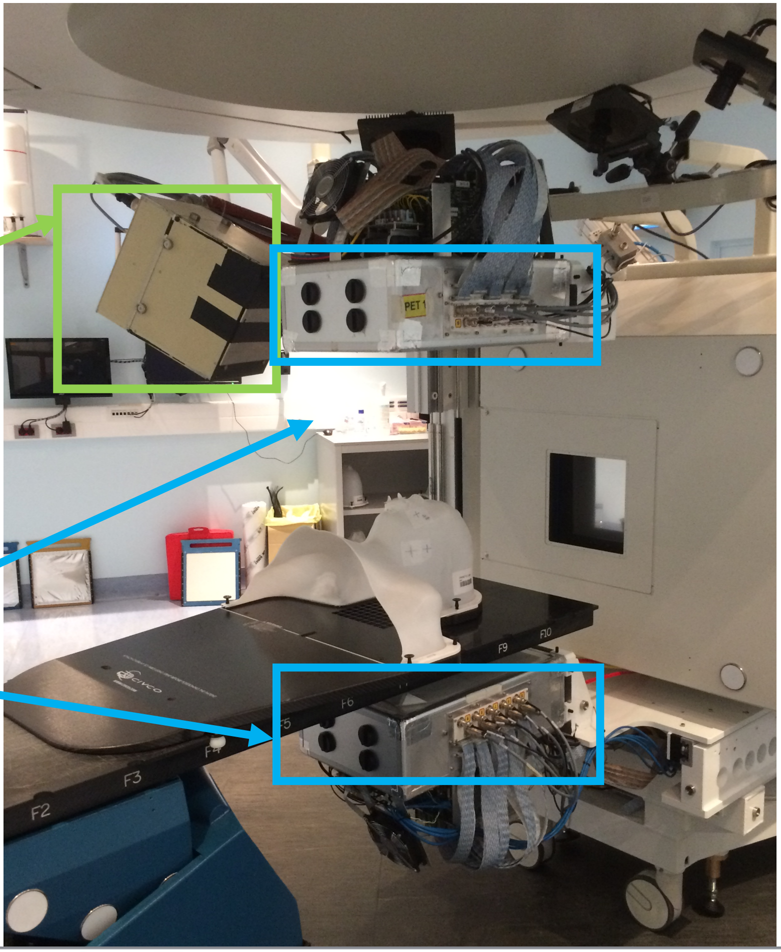


Concentrator board

- Data collection and event building
- Trigger (sustainable rate > 100KHz)
- Data transfer via ethernet link (TCP/IP)
- Dose Delivery system interface

The INSIDE project

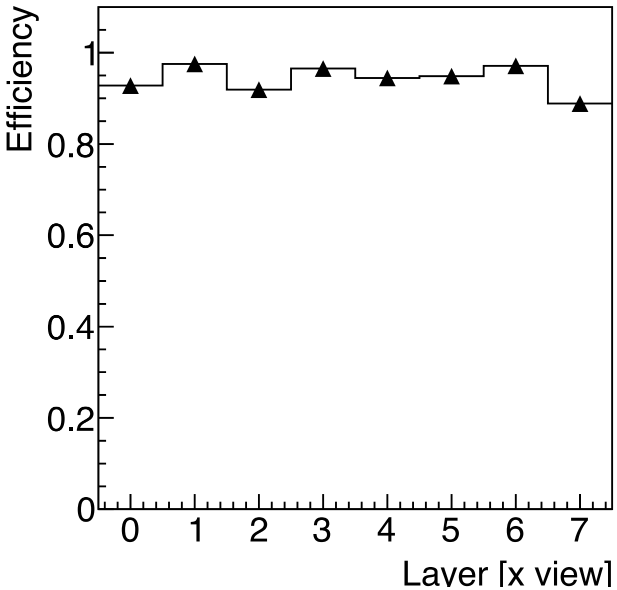
- Inside pioneered since 2013 the **bi-modal approach** with synergistic combination of PET and charged fragment detection.
- In beam PET exploits the β+ emitters activated by the beam inside the patient (^{11}C, ^{10}C, ^{14}O, ^{15}O, ^{13}N…). It's more suitable for proton treatment monitoring
- Charged fragments emission significanlty occurs only in ^{12}C treatment.



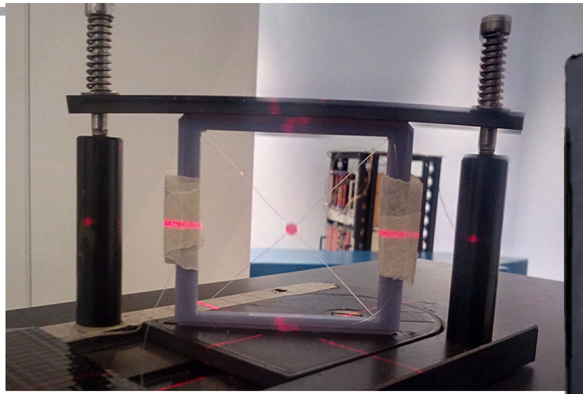
Fragment tracker

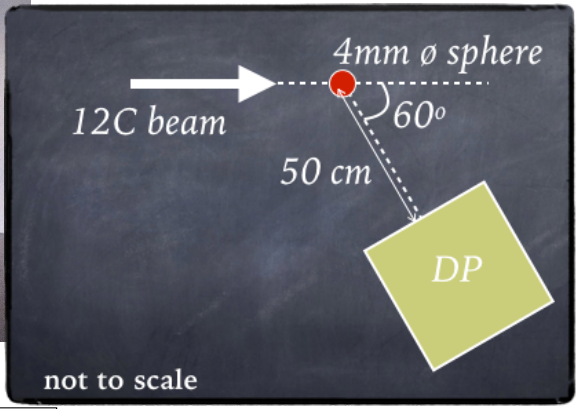
PET heads

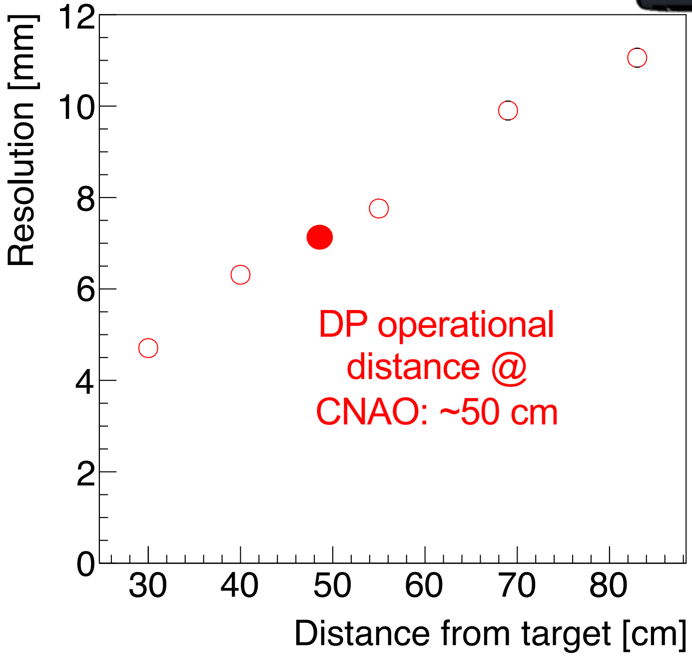
DP characterization



The **detection efficiency (~90%)** matches what was expected from detector calibration when properly taking into account the fibre cladding and inter-layer alignment

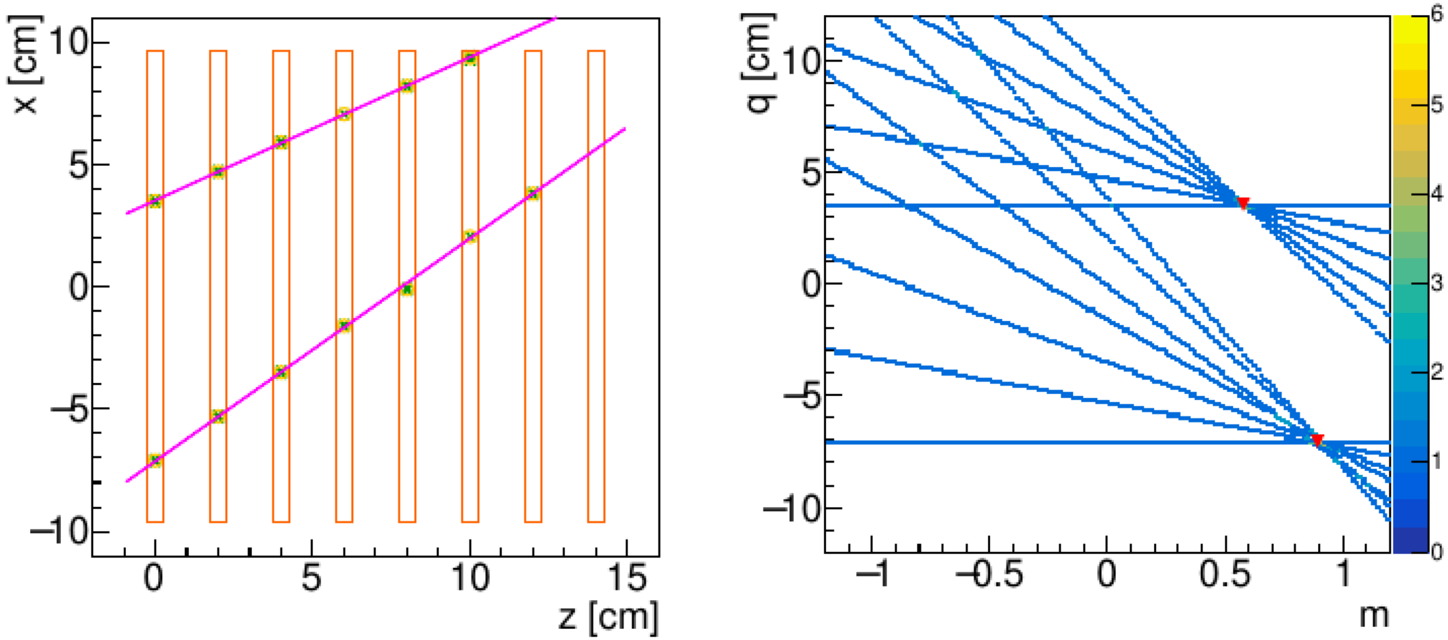






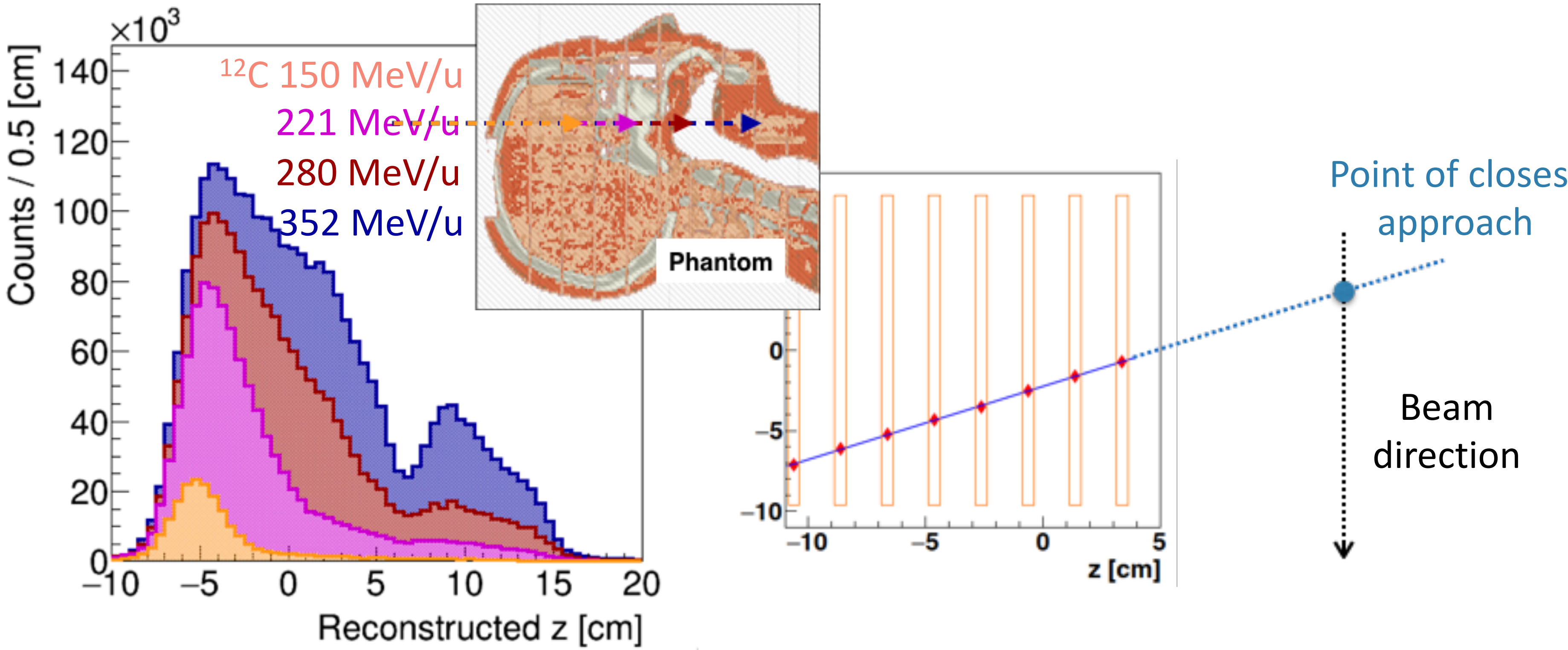
The **'per-track' back-traking resolution** has been evaluated using a small (4mm diam.) plastic spherical target

Track reconstruction



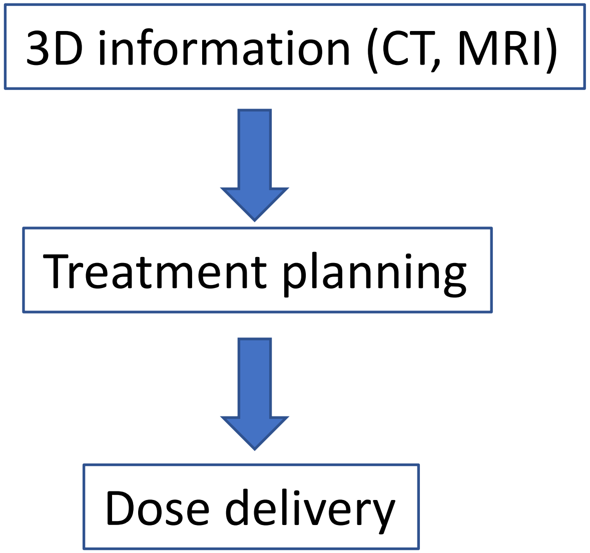
- **Clustering**: channels over threshold are grouped with proximity criteria (average cluster size 1.5-2 depending on the energy)
- **Cluster selection**: Hough transform is used to recognise the track pattern. **4 "aligned" cluster** are requested to identify a track.
- **Fit**: chi square fit is performed to evaluate the trajectory parameters.

Fragment production in a head phantom



- The emission profiles along the beam axis is sensible to the **density variations** during the projectile travel inside the patient
- The fragment path travelled inside the patient depends on the treatment topology. To extrapolate the beam range from the emission shape we need a robust and reliable unfolding…

A different approach: interfractional monitoring



Get info about the tumour localisation inside the body, and **the human tissues density map**

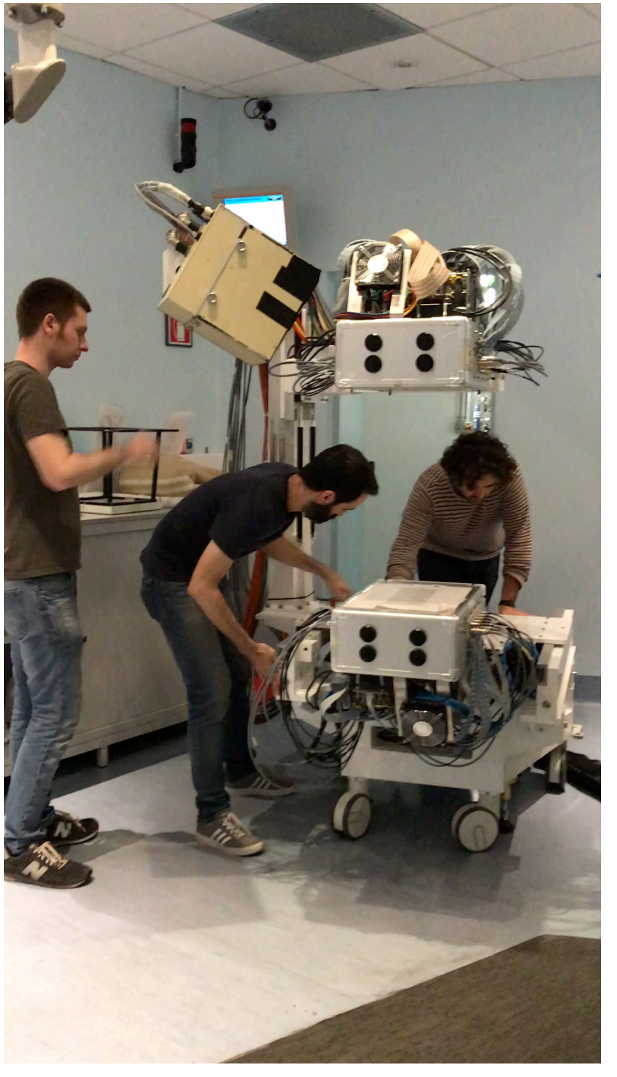
A software tool produces as output the instructions for the accelerator to deliver the prescribed dose in the patient (E, θ, N)

The total dose is delivered within few weeks **(~15-30 fractions),** each one lasting **few minutes**

- A replanning CT is done only when evident external morphological variations are expected, to avoid additional dose to the patient.
- Dis-homogeneities onset could be spotted **comparing the reconstructed emission map of the secondary charged particles in different fractions of the treatment.**

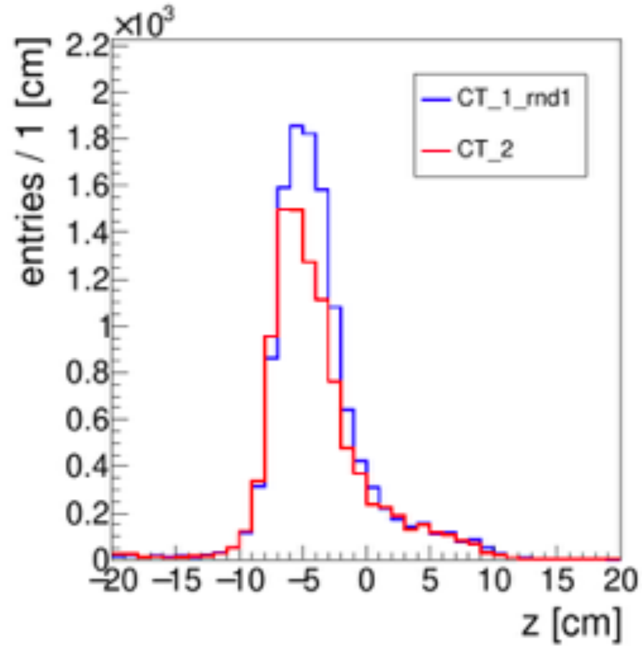
Clinical trial @ CNAO

- A **clinical trial @ CNAO** started in july 2019 to evaluate the detector sensitivity to range variation and morphological changes inside the patient in the context on the INSIDE project
- Four selected pathologies have been identified: meningioma and nasopharynx cancer treated with proton beams, Adenoid Cystic Carcinoma (ACC) and clival chordoma treated with carbon ion beams
- The system can be used with minimum impact in the treatment time workflow in the clinical routine



Comparison strategy

- Secondary particles crossed the detector are tracked
- The 3D coordinates of the production vertex are estimated using the point of closest approach of the reconstructed track with respect to the incoming beam direction
- The 1D emission spatial distribution along the beam axis (z in the reference frame) is built for each PB delivered in the treatment
- A statistical comparison between spectra single PB would be too sensible to fluctuations (~**300 tracks per PB**). **PBs belonging from the same target volume of 1cm x 1cm x 0.6 cm have been summed up in order to create Super Pencil Beams (SPB).**



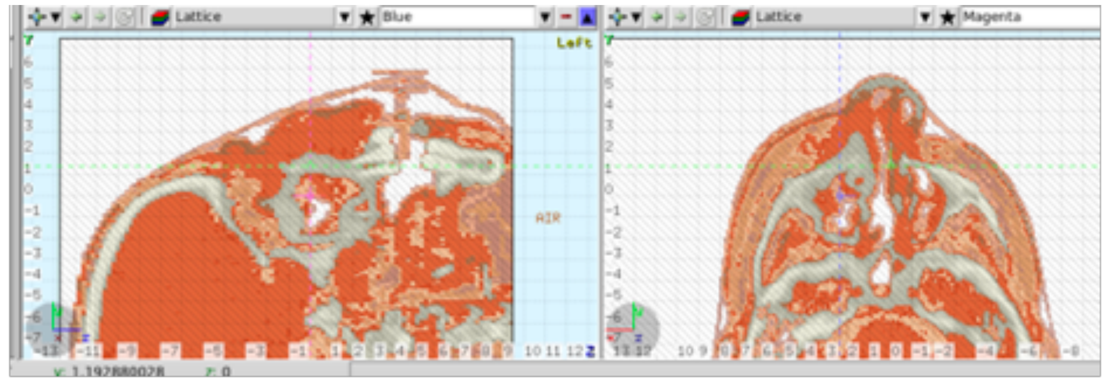
A treatment can be composed by 10k PB!

MC preliminary study

- Two CT scan of a patient affected by an **Adenoid Cystic Carcinoma** (ACC), for which internal and external toxicities are expected during the treatment (inflammation, swelling and filling of nasal cavities), have been acquired.

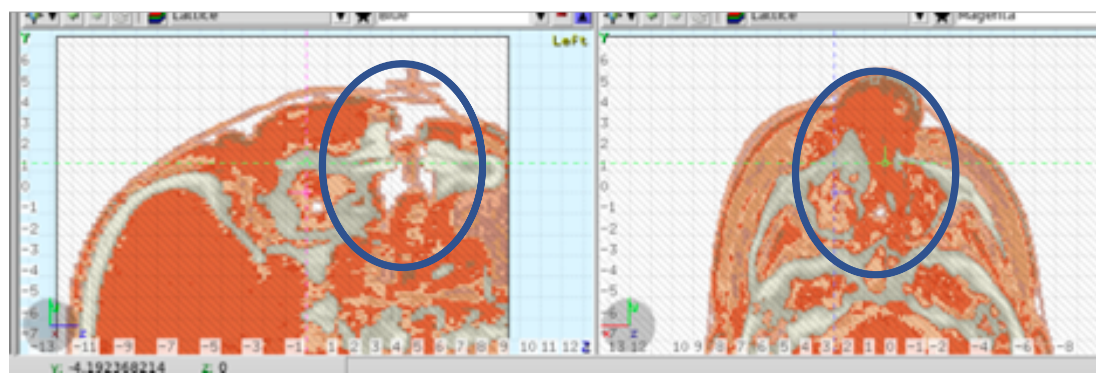
- In the simulation the same treatment plan has been delivered->accurate alignment of the skull's bones of the 2 CT images has been done

CT scan performed before the treatment start



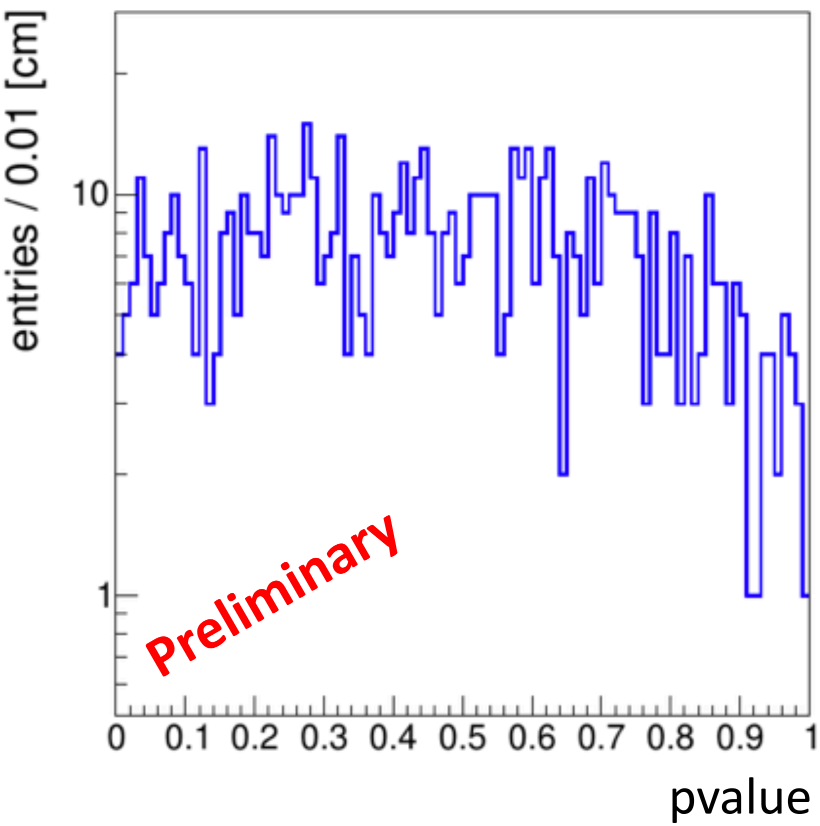
FLUKA

CT scan performed after 3 weeks

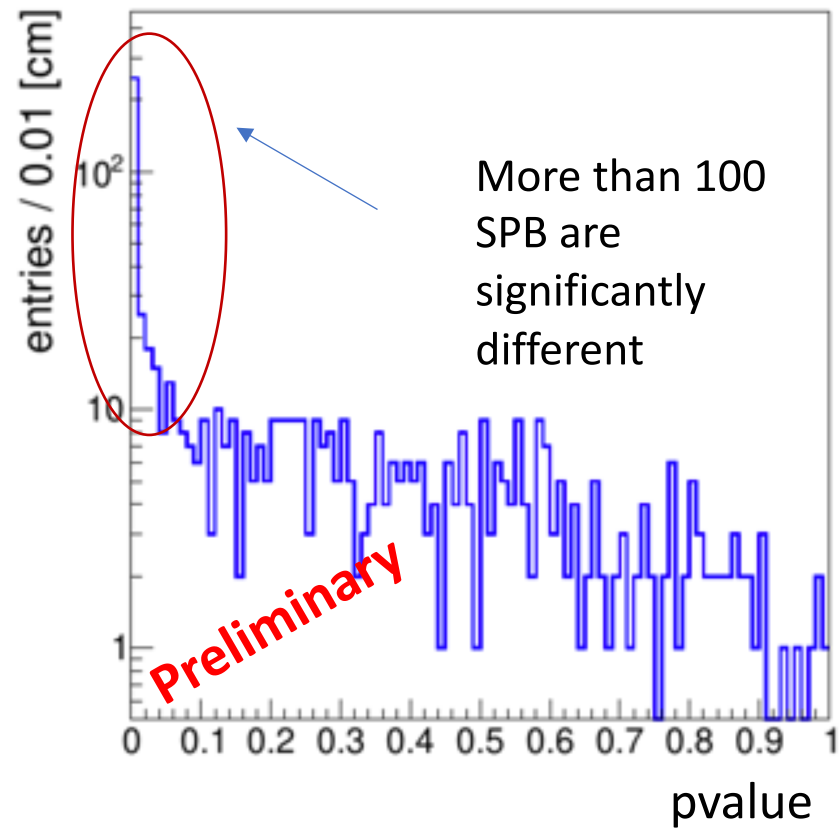


Results

Comparison bewteen the emission maps obtained delivering the same treatment plan on the **same CT1** scan with **different random seed**



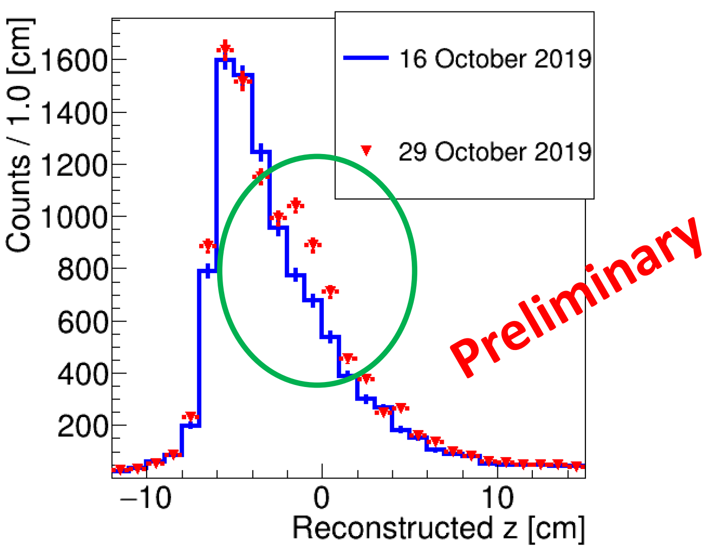
Comparison bewteen the emission maps obtained delivering the same treatment plan on the **two different CT scans**

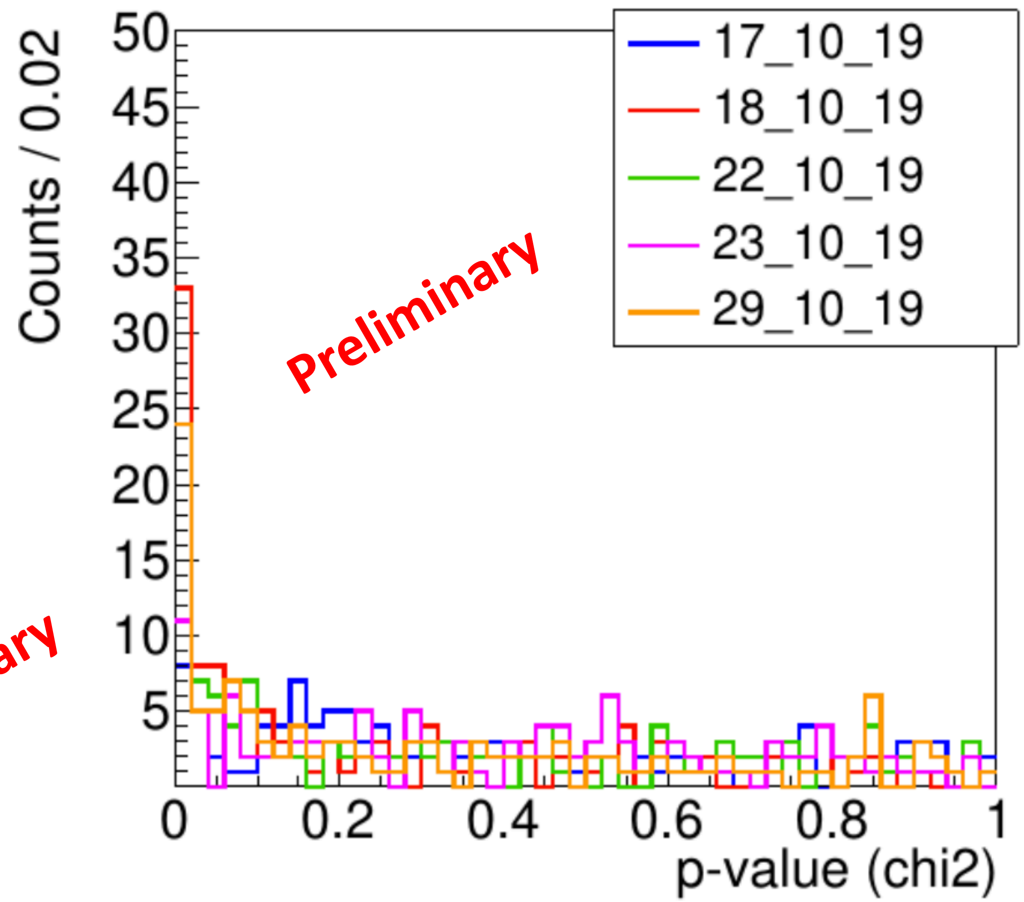


…let’s go to real patient

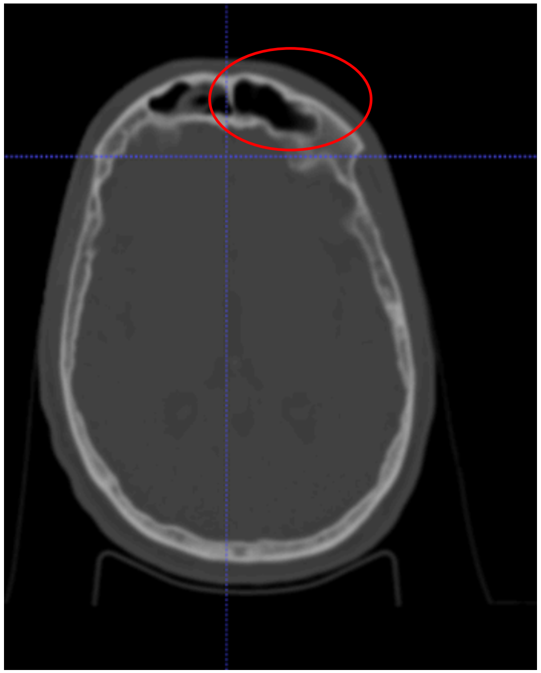
- Patient affected by an ACC, 16 fractions in 4 weeks. Three fields treatment
- Control CT after 8 fractions.

CAVEAT: when dealing with data, we have to take into account the detector **inter-fraction possible misalignment** and the **beam intensity fluctuations**!

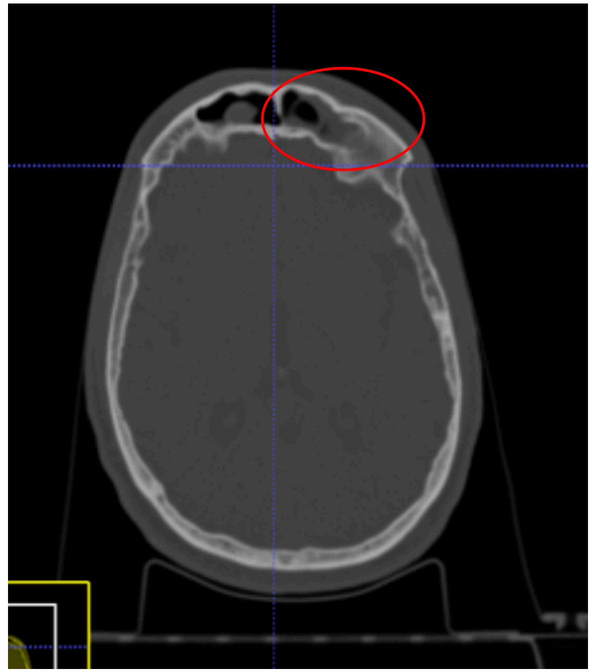




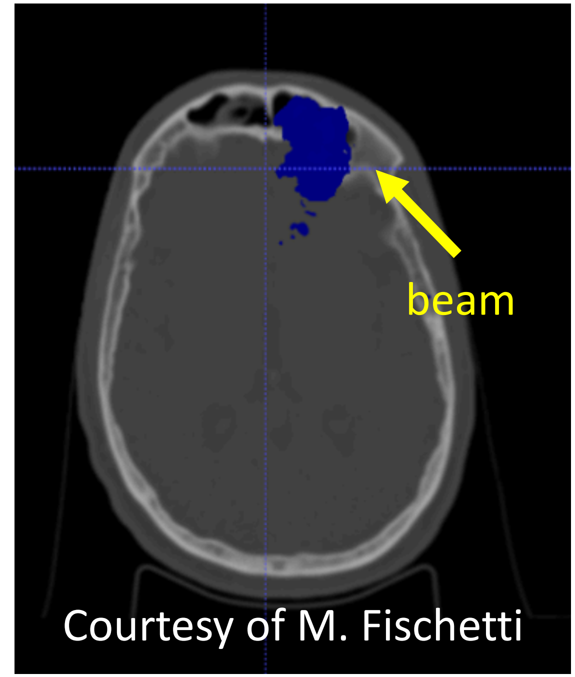
Spotting the morphological change



CT
16 October



CT
28 October



CT and **data collected**
28 October

Drawing the emission map image selecting the fragments belonging to SPB with pvalue<0.02 we are able to spot the morphological change!

Conclusions

- The inter-fractional monitoring capability of the DP has been tested in the case of an ACC replanning patient and MC results seems to be promising
- Other MC studies on patients with less obvious morphological changes are ongoing to assess the inter-fractional monitoring sensitivity
- ~10 patients have been monitored during the clinical trial, the analysis is ongoing to study the sensitivity of the technique, taking into account of the sources of systematic uncertainty
- Clinical trial will help us in understanding which is the best method to "pack" the PB in a real treatment