TECNOLOGIE PER L'ADROTERAPIA (TADR)

Two projects:

- **Imaging Dosimetrico per Adroterapia (IMDO)** **Vincenzo Patera**
- **Monitor for Neutron Dose in Hadrontherapy (MONDO)** **Michela Marafini**

Participants (only CF associates) :

- **Michela Marafini**, *CF, RTD (02/2016 => 23/03/2019);*
- Valentina Giacometti Centro Fermi, Assegno di Ricerca fromn SIR (01/02/2017->31/07/2017)
- Eliana Gioscio , Centro Fermi, Assegno di Ricerca from SIR(01/10/2017->30/09/2018
- **Vincenzo Patera**, Universita' di Roma "Sapienza", Dipartimento SBAI, Professore Associato;
- Alessio Sarti , Universita' di Roma "Sapienza", Dipartimento SBAI, Professore Associato;
- Adalberto Sciubba, Universita' di Roma "Sapienza", Dipartimento SBAI, Professore Ordinario;

Institutions & Collaborations:

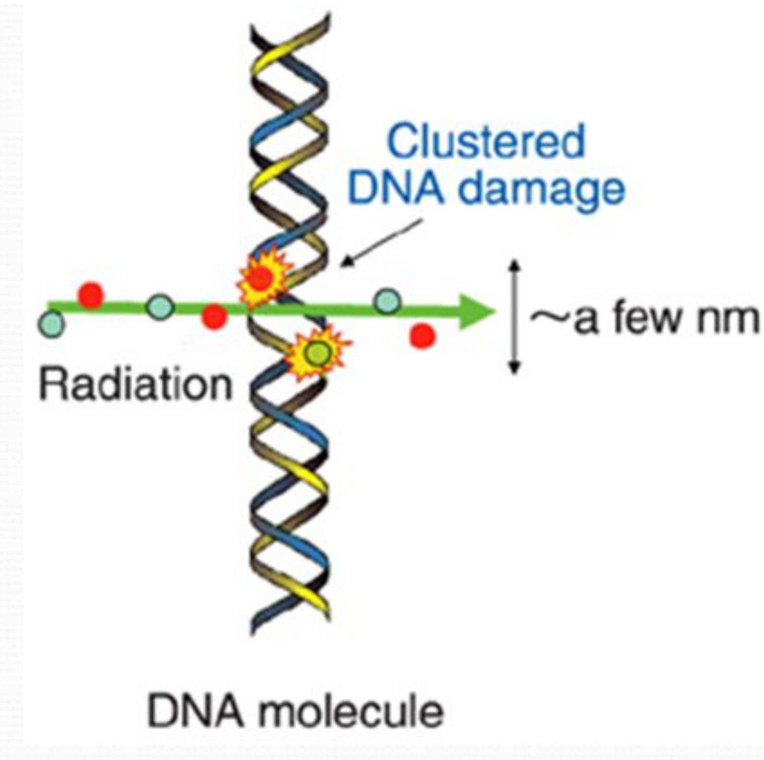
Main laboratory: SBAI – Universita' di Roma "Sapienza"

Collaborations:

•TIFPA - Proton Therapy Centre, Trento
•CNAO - Centro Nazionale di Adroterapia Oncologica, Pavia
•FBK – Fondazione Bruno Kessler, Trento
•INFN – Sezione di Roma1, LNF, Milano

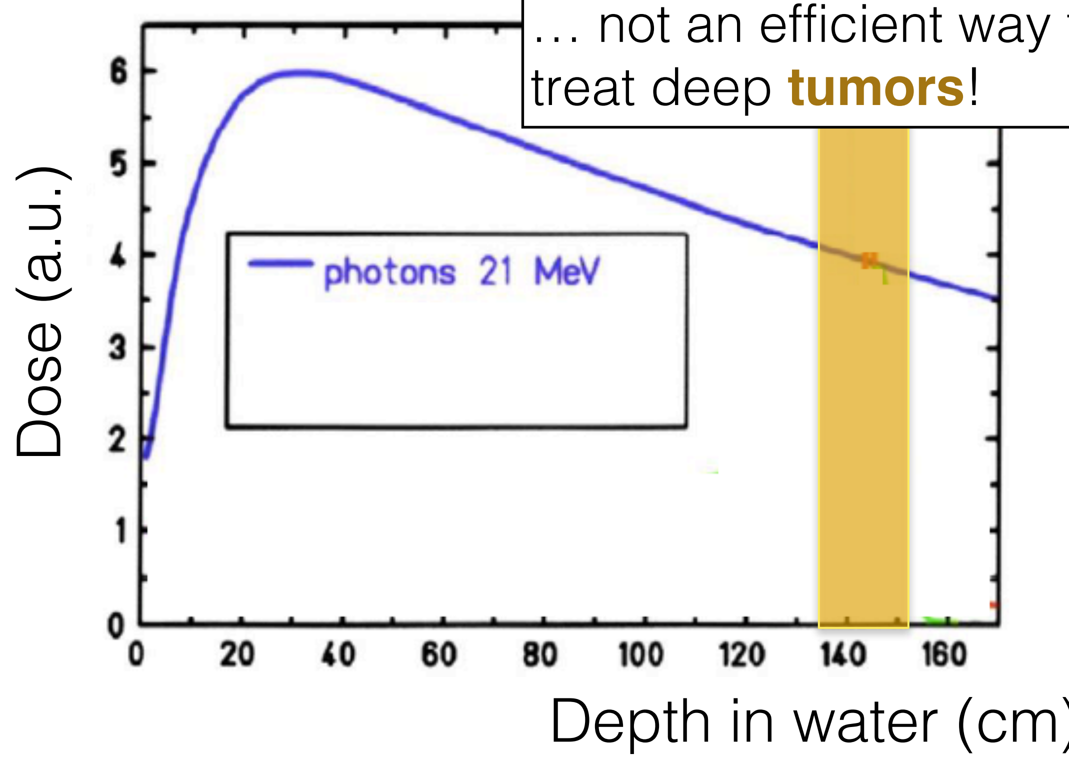
•***INFN*** = Instituto Nazionale di Fisica Nucleare
•***SBAI*** = Dipartimento di Scienze di Base e Applicate per l'Ingegneria - Università degli Studi di Roma *La Sapienza*
•**LNF** = Laboratori Nazionali di Frascati

Radiotherapy



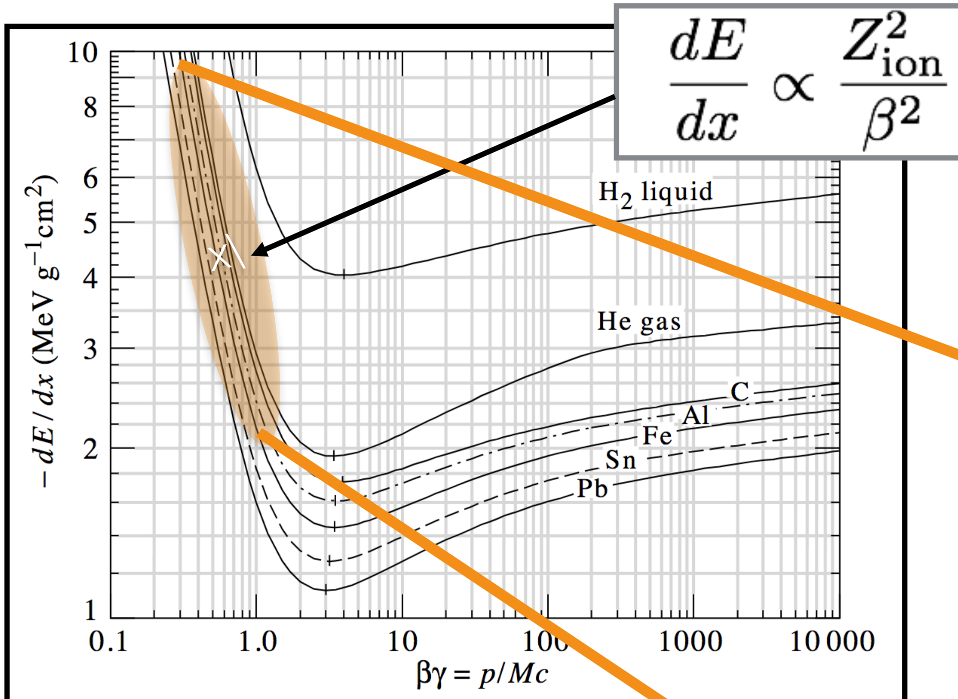
$$\text{Dose [Gy]} = \frac{dE}{dm}$$

- **Goal**: deliver energy on tumor cells to damage them in an irreparable way
- **Conventional radiotherapy**: photon or e⁻ beams

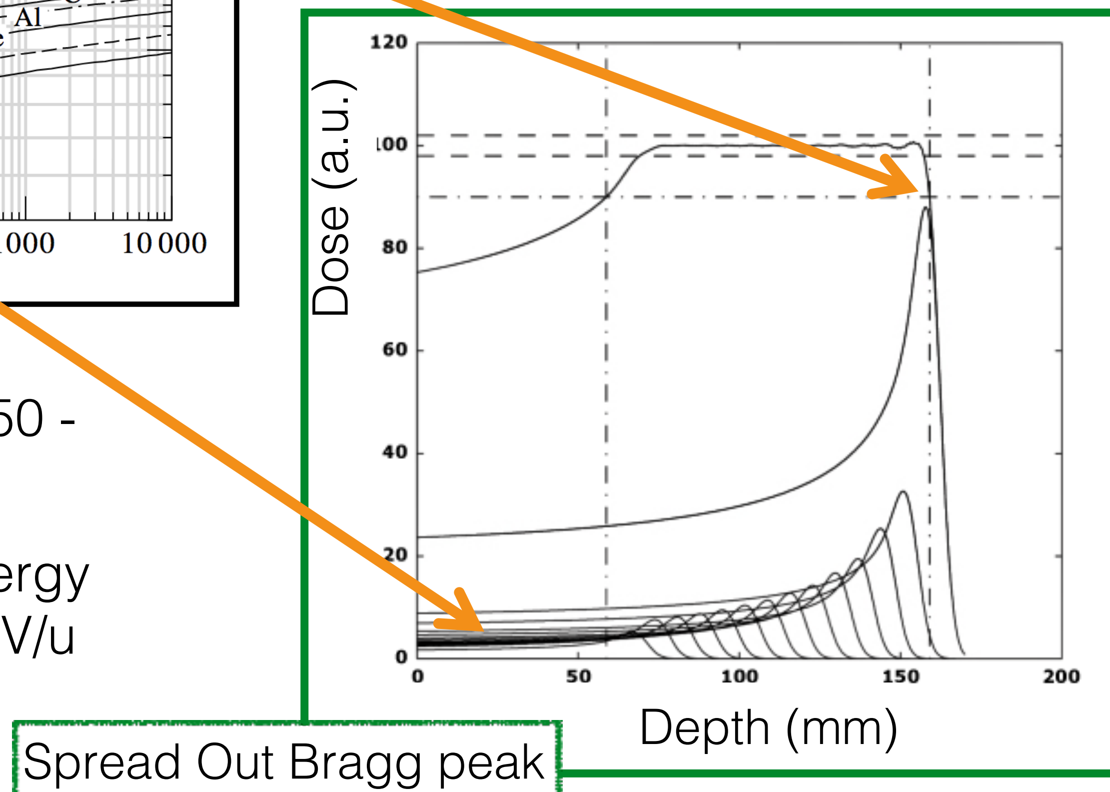


… not an efficient way to treat deep **tumors**!

A different approach: Particle therapy



- Using charged ions, It is possible to reach a **high precision** in the dose release, minimising the dose deposited outside the tumor region

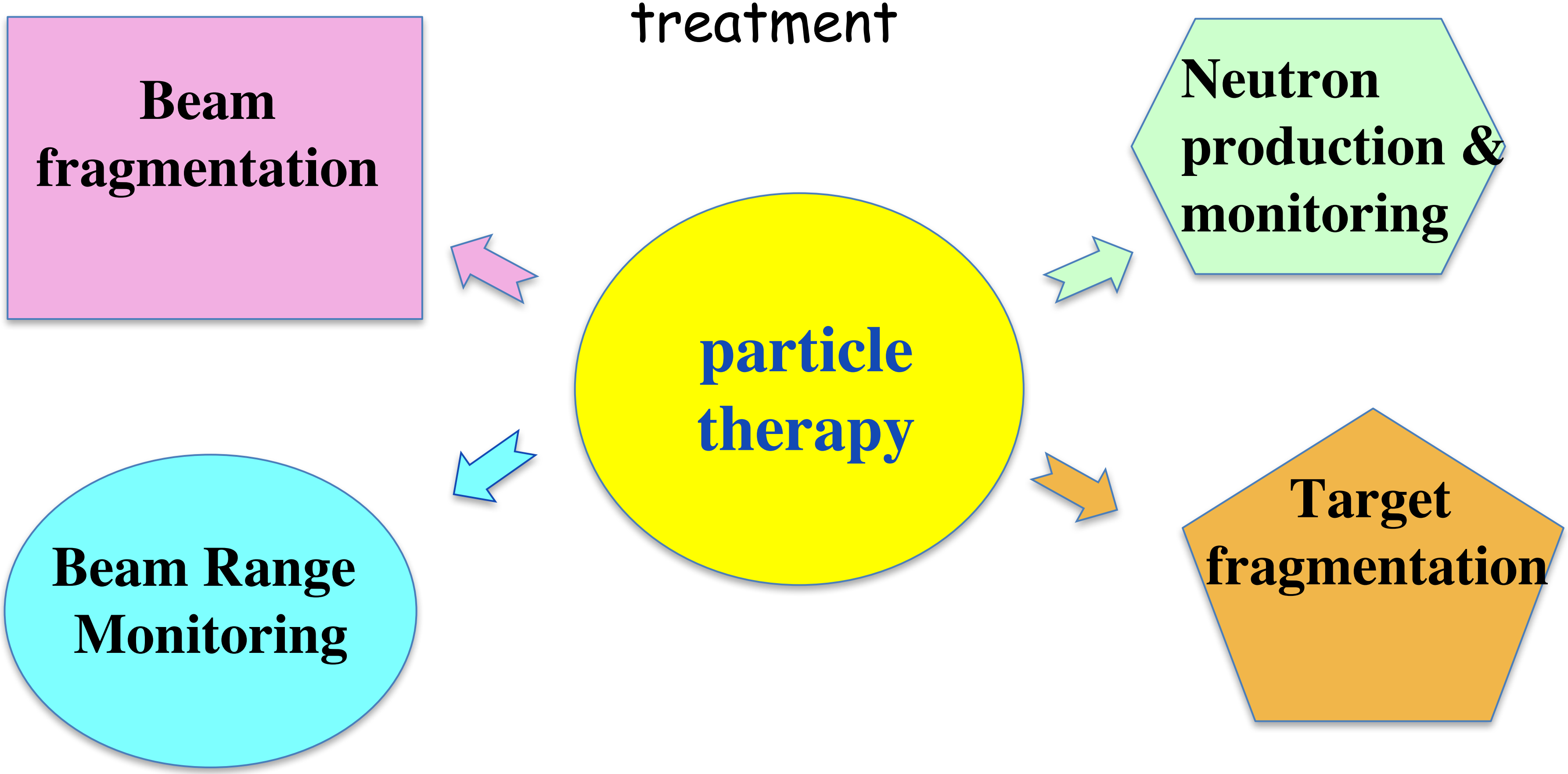


- **Protons**: kinetic energy 50 - 250 MeV
- **Carbon ions**: kinetic energy per nucleon 60 - 400 MeV/u

Focus on Particle Therapy

The TADR project activity ranges from fundamental physics to applied physics, with particular focus on nuclear fragmentation effect in PT

The aim is to increase the quality assurance of the clinical treatment



Focus on Particle Therapy

The TADR project activity ranges from fundamental physics to applied physics, with particular focus on nuclear fragmentation effect in PT

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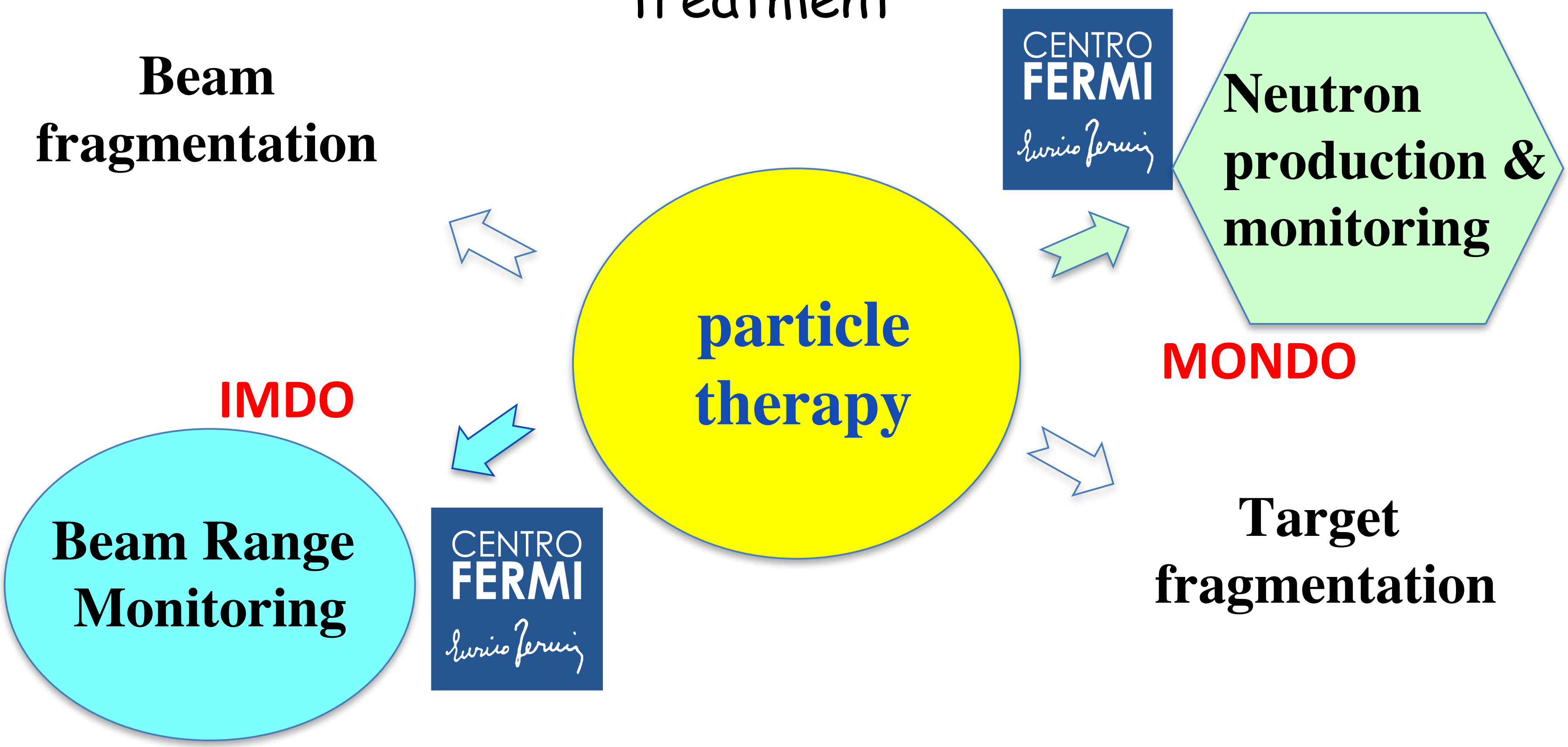
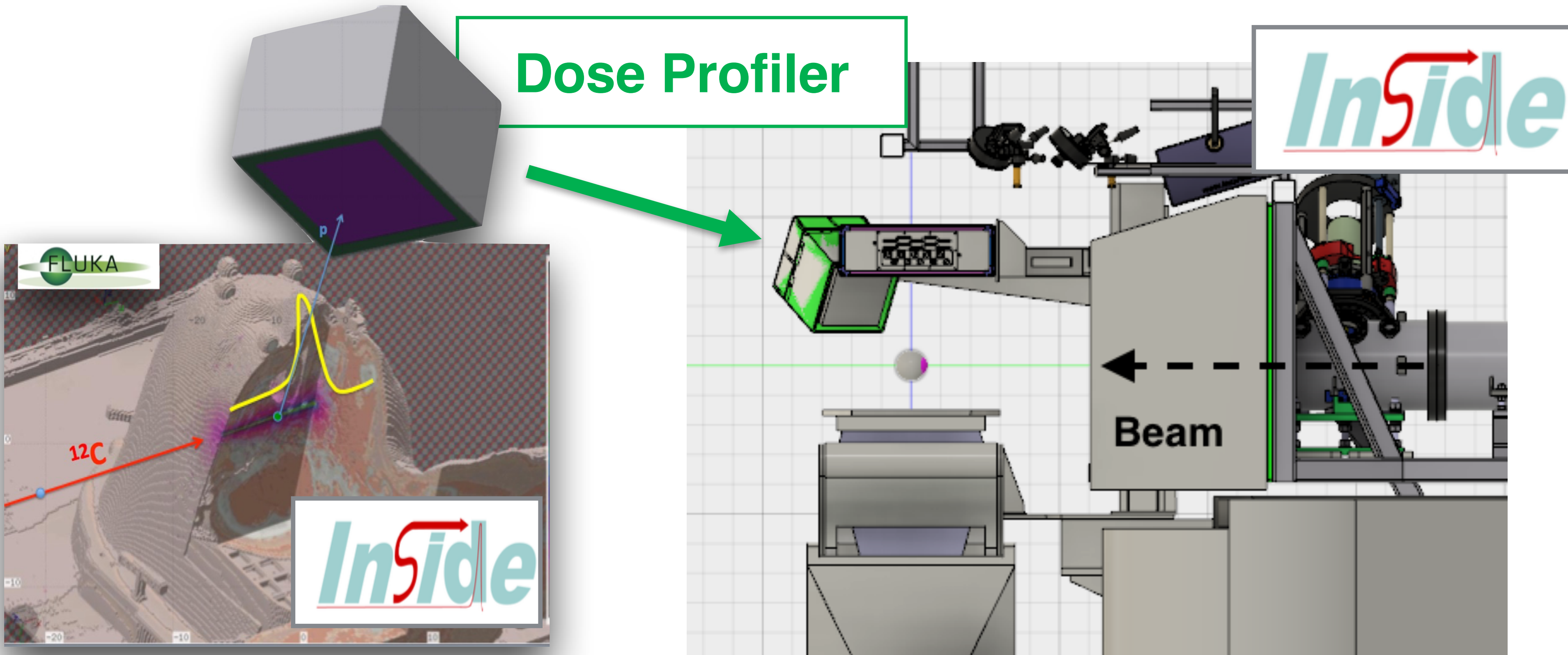
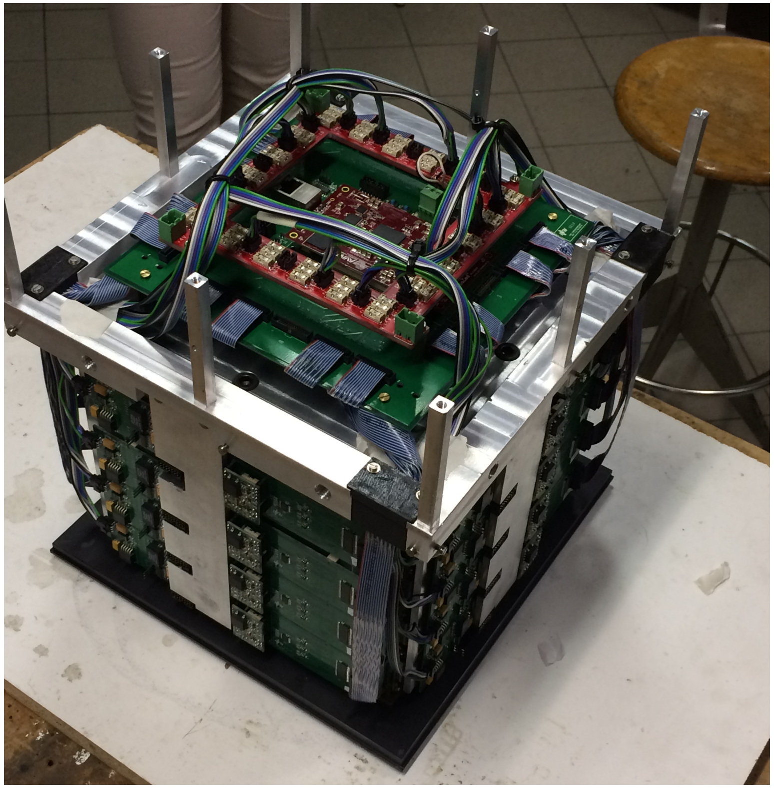


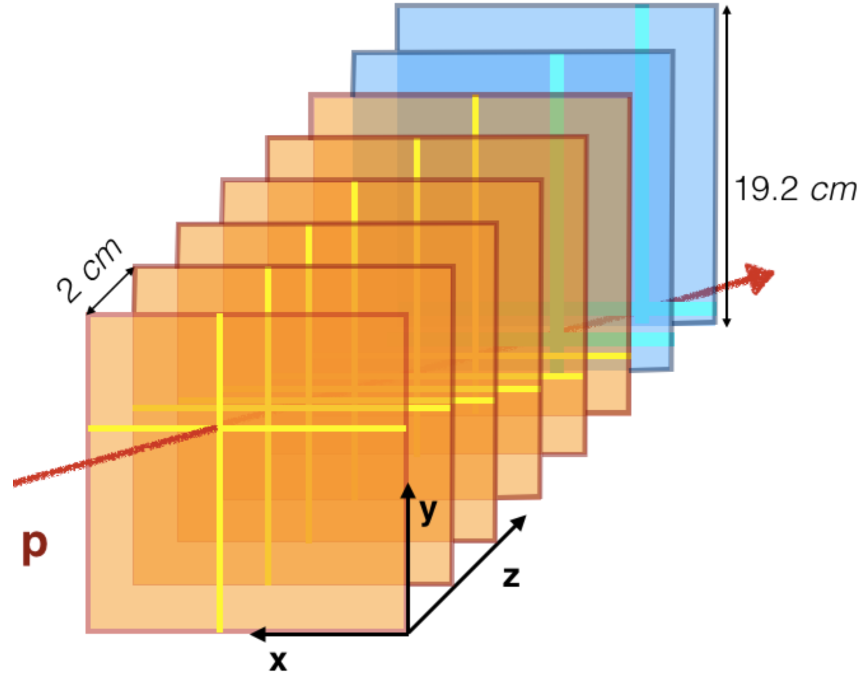
Imaging Dosimetrico per Adroterapia

- Development of a range monitor for on-line feedback to the beam control during Charge Particle Therapy treatments.
- The device exploits the charged particles (protons) produced by the interaction of the beam with the patient tissue



Dose Profiler layout





- **Tracker**: 6 xy planes with 2 cm spacing. Each plane is made of 2 stereo layers of 192 0.5x0.5 mm^2 square scintillating fibres.

- **Absorber**: 2 planes made of segmented plastic scintillator 6 mm thick for dE/dx measurements and trigger

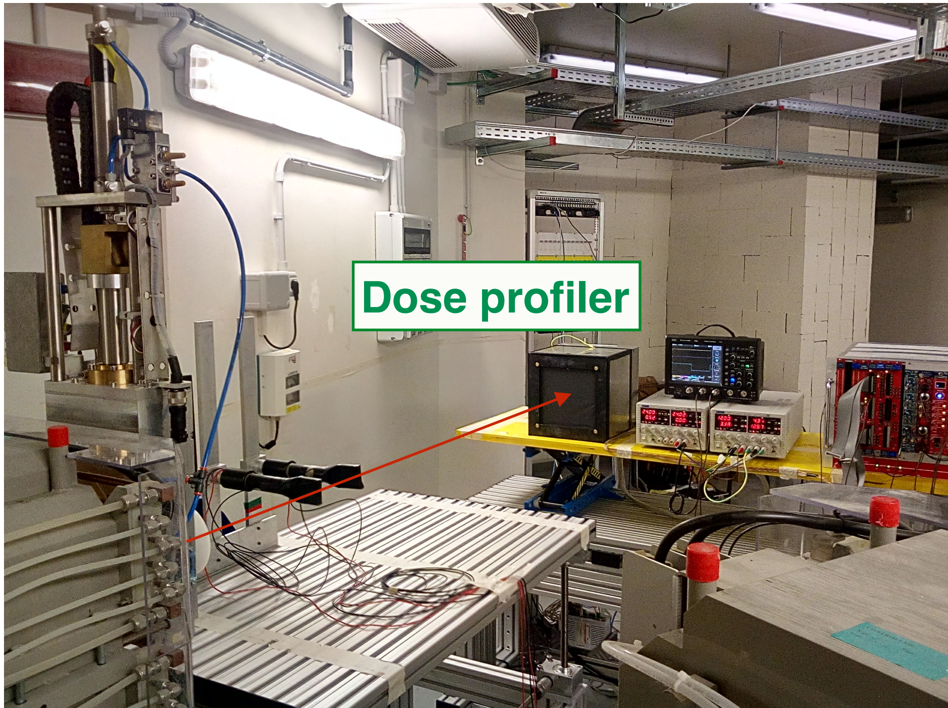
- The fibers and absorber are read-out by Hamamatsu 1mm^2 SiPM S12571-050P

- SiPM are interfaced with dedicated ASIC that are read out by FPGA system

2017 hardware activity highlights

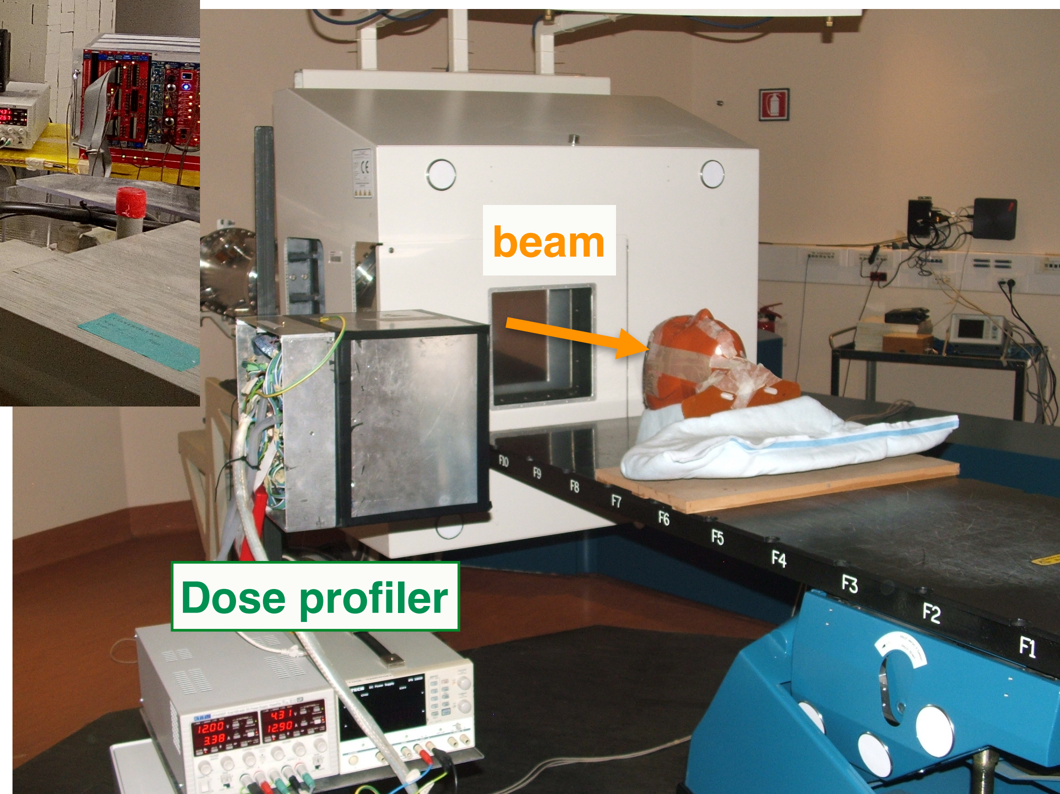
- Cosmic ray acquisition and system characterization @SBAI
  - Test of reconstruction code, cooling system, FEE
- First test using protons @ Trento Proton Therapy center
  - Hardware check performed → Improved mechanical assembly of boards, alignment of SiPMs with fibres
- July: operation condition test @ Trento and CNAO Centers:
  - HW and SW development to address some issues spotted in the July data taking
- November: additional data taken @CNAO
  - large amount of data is currently being digested to assess efficiency/resolutions/reliability etc etc

Data taking conditions

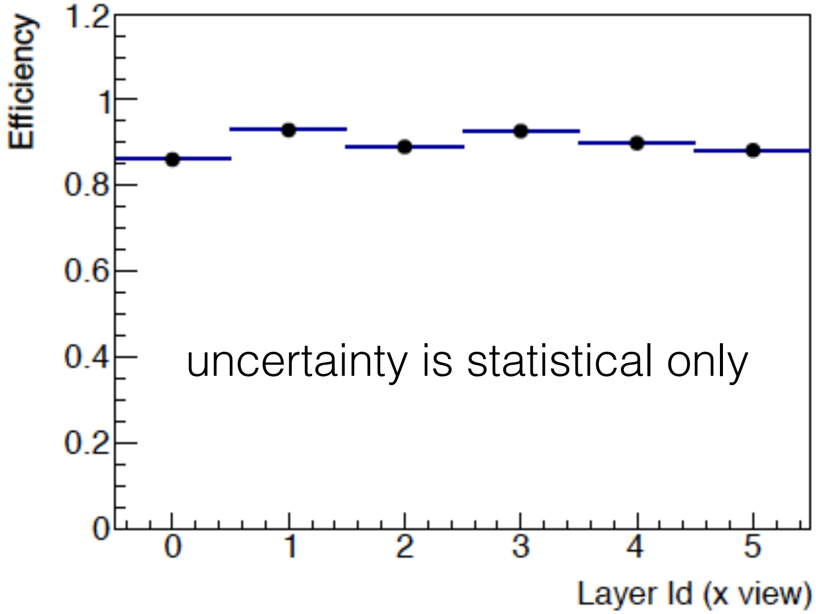


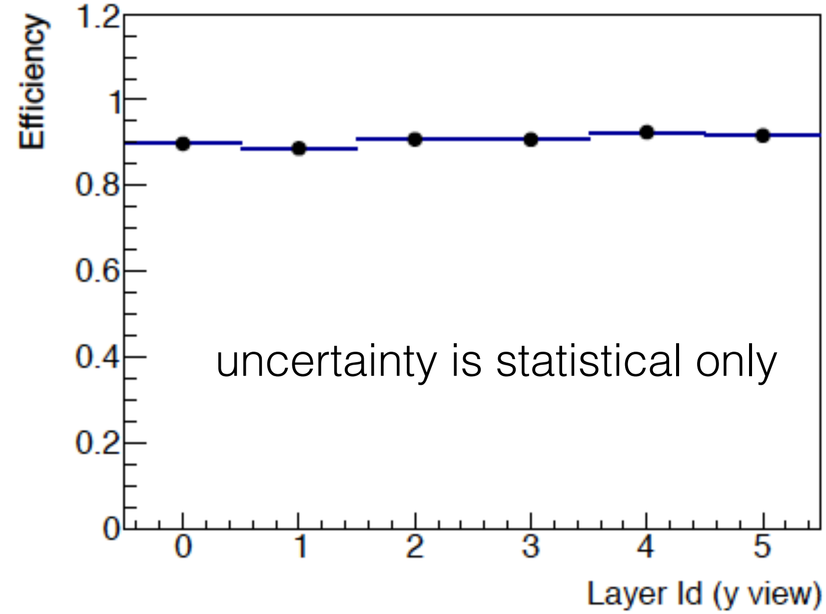
Trento APSS center
experimental room

Cnao treatment room



Detection efficiency

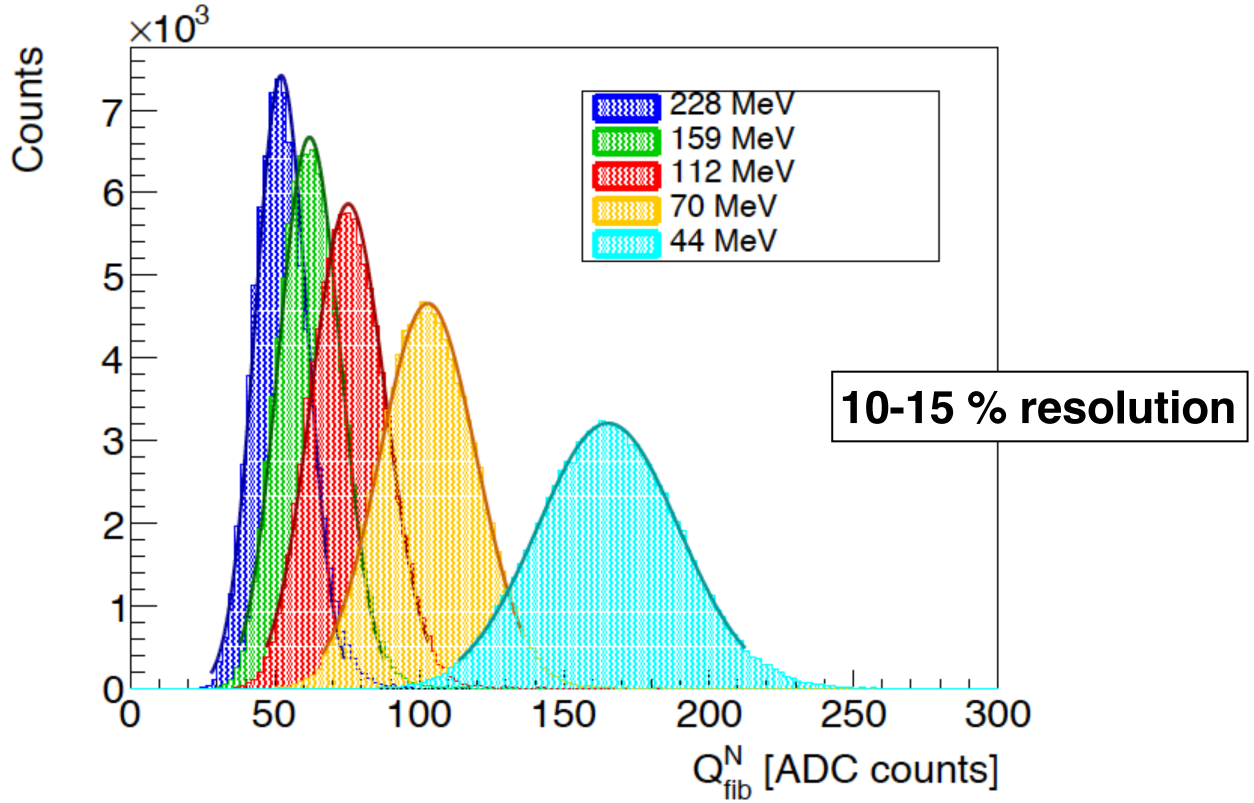




$$\varepsilon_{\mathrm{l}} = \frac{N^{\mathrm{l}}_{\mathrm{rec}}}{N^{\mathrm{l}}_{\mathrm{tot}}}$$

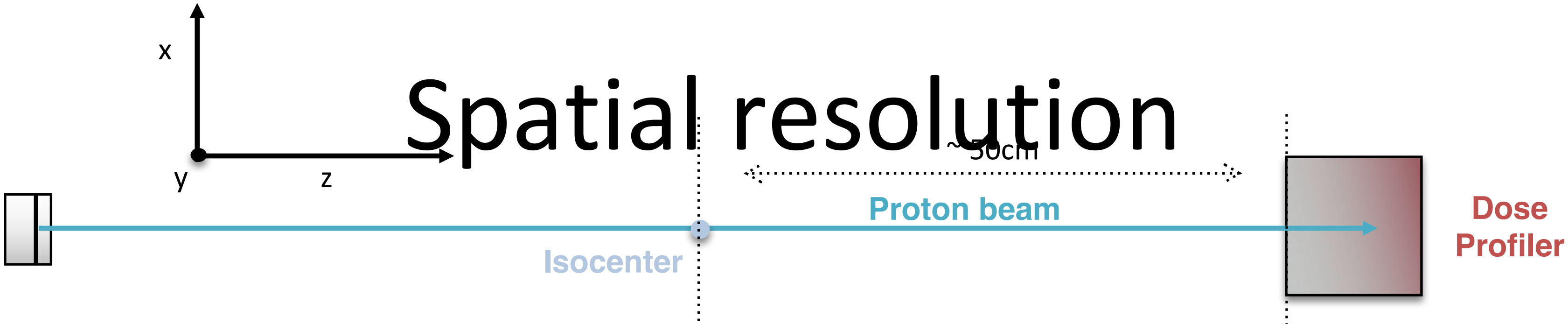
- Unbiased efficiency definition
- N^{l}_{rec}: number of tracks in which a cluster is present in the l-th layer
- N^{l}_{tot}: number of reconstructed tracks not considering the l-th plane
- **~90% efficiency**: compatible with the fibre cladding (4%) and the dead space due to the assembling

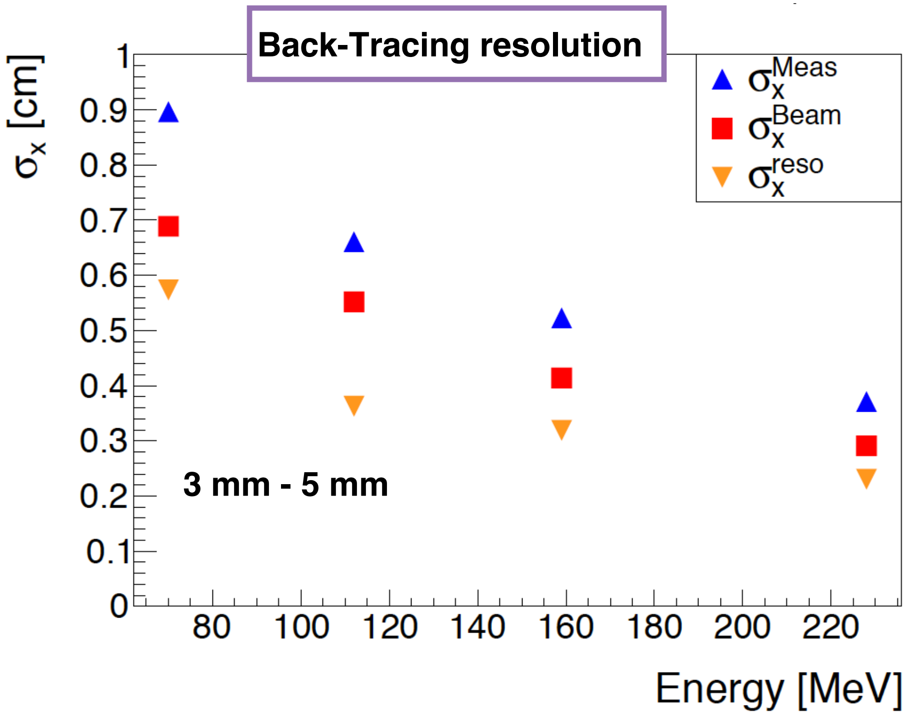
Charge response

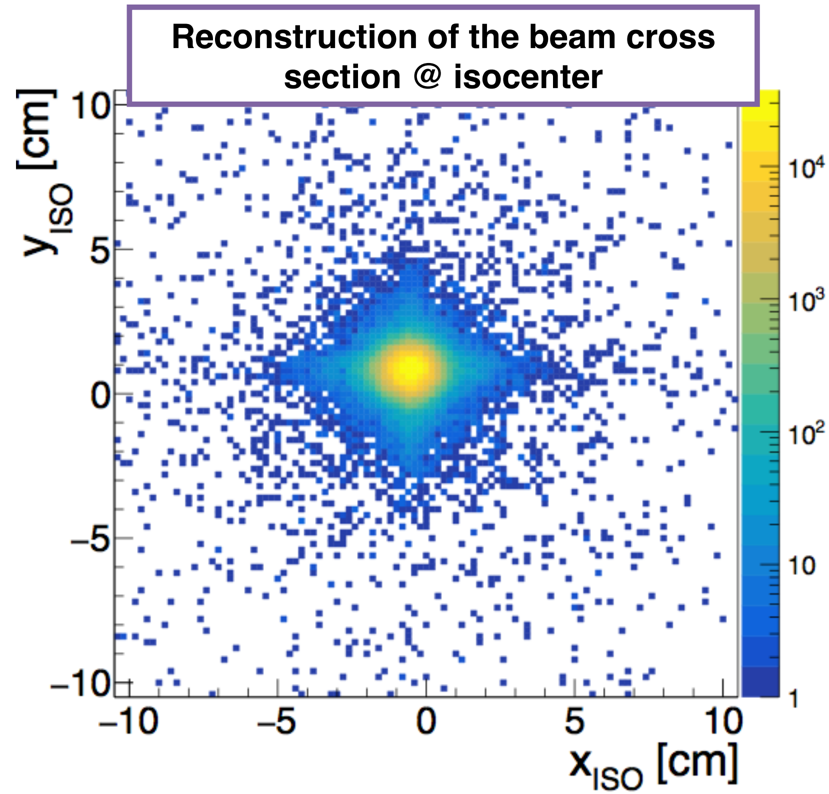


- Total amount of charge of SiPM associated to a track, normalised to the number of fired layers.

Spatial resolution







$$\sigma_{DP} = \sqrt{\sigma^2_{Meas} - \sigma^2_{Beam}}$$

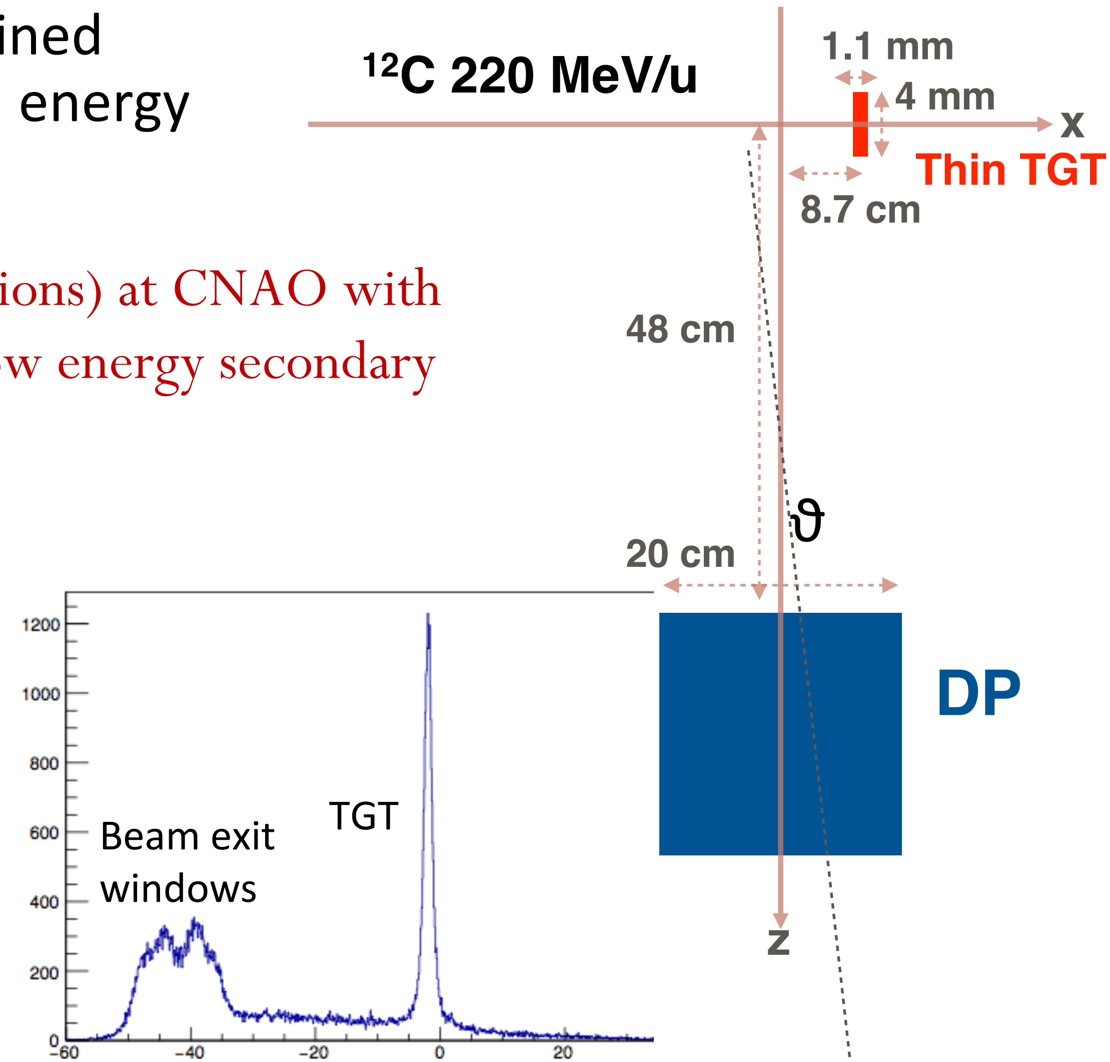
Resolution: secondary protons

- Trento results were obtained shooting protons of fixed energy inside our detector.

➡ Same results (3-5 mm resolutions) at CNAO with broad energy spectrum and low energy secondary protons

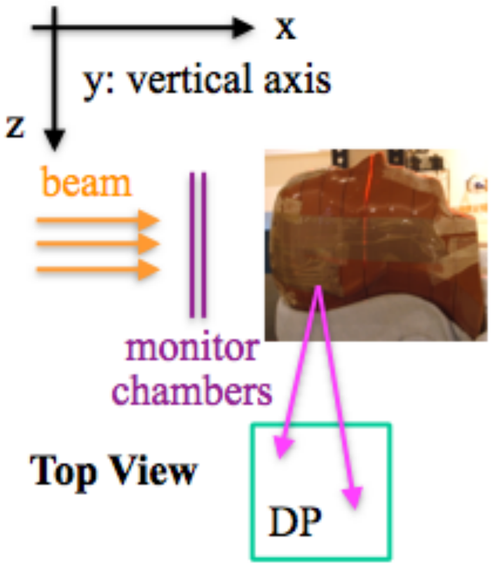
➡ To assess the DP resolution in clinical conditions:

  – Ultra thin targets have been chosen (1.1 mm ‘wire’ plastic, 2mm ‘wire’ aluminum, 4mm ‘sphere’ plastic thickness/diameter)
  – Distance from TGT as in clinical conditions (~50 cm)
  – Different angles (90°, 60°)

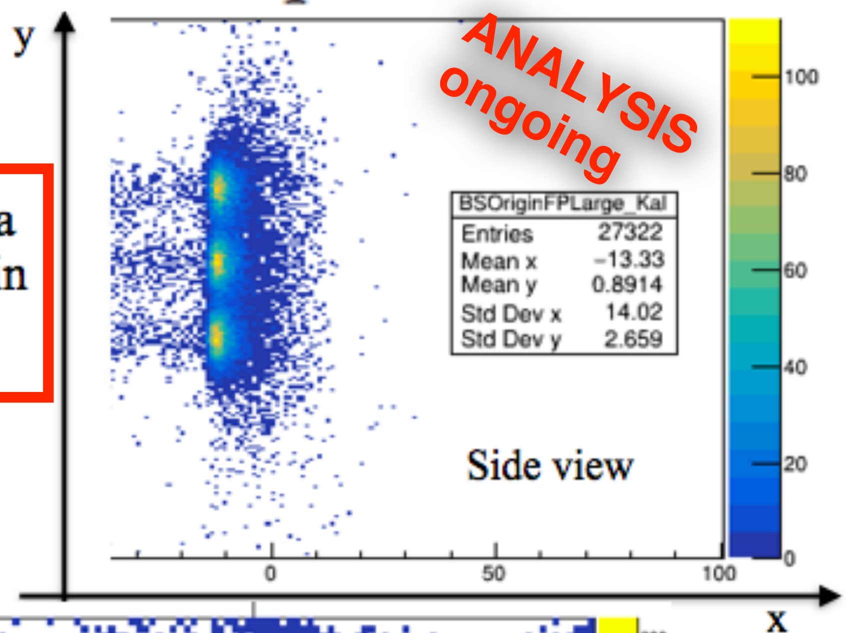


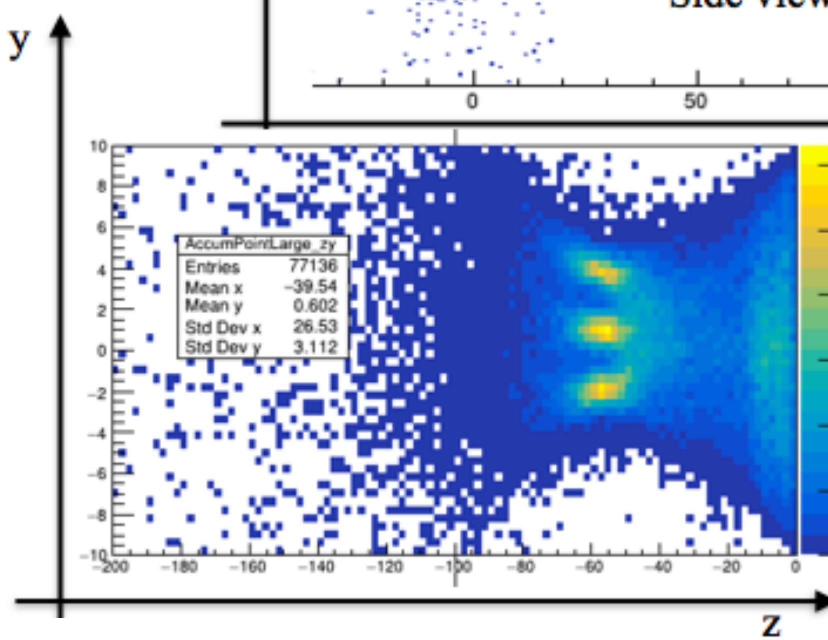
Preliminary Results

Only quick online checks performed



Treatment plan, a grid of 9 points, in x,y @ 220MeV

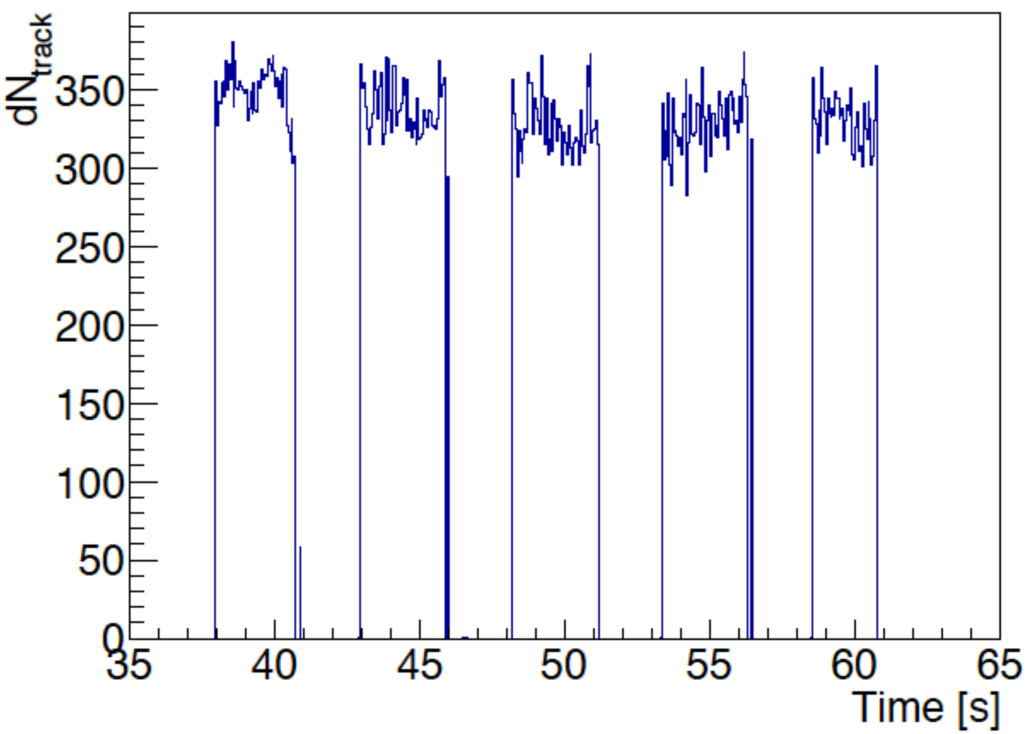




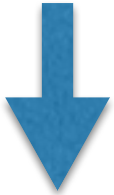
Preliminary (rough) attempt of pencil beam standalone reconstruction using POCA of tracks from consecutive events.

The dead time issue

- At therapeutical intensities, **60°** angle, and **50cm** distance the expected fragment rate in the dose profiler is ~**150kHZ**
- **The dead time becomes a crucial parameter:** with the initial dead time of the profiler (~80 μs) only the **8%** of the event are acquired!



Bottle-neck: ethernet transmission (contribution of ~80%)



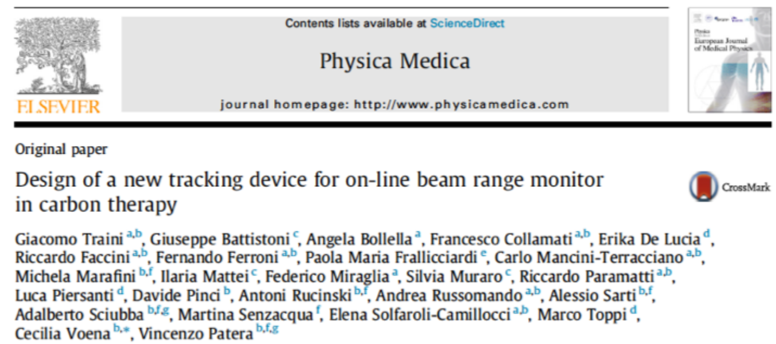
Solution: the data are sent to the workstation when the beam is off!

Obtained dead time: **7 μs**, corresponding to a event loss fraction of ~ **40% (daq rate 80 kHz)**

Next improvement: modify the trigger condition to reduce data size

How to use the DP in a real case scenario

- Using the **MC simulation** and a **back-filtering algorithm** we reconstructed the emission profile from a **heterogeneous phantom**



Contents lists available at ScienceDirect
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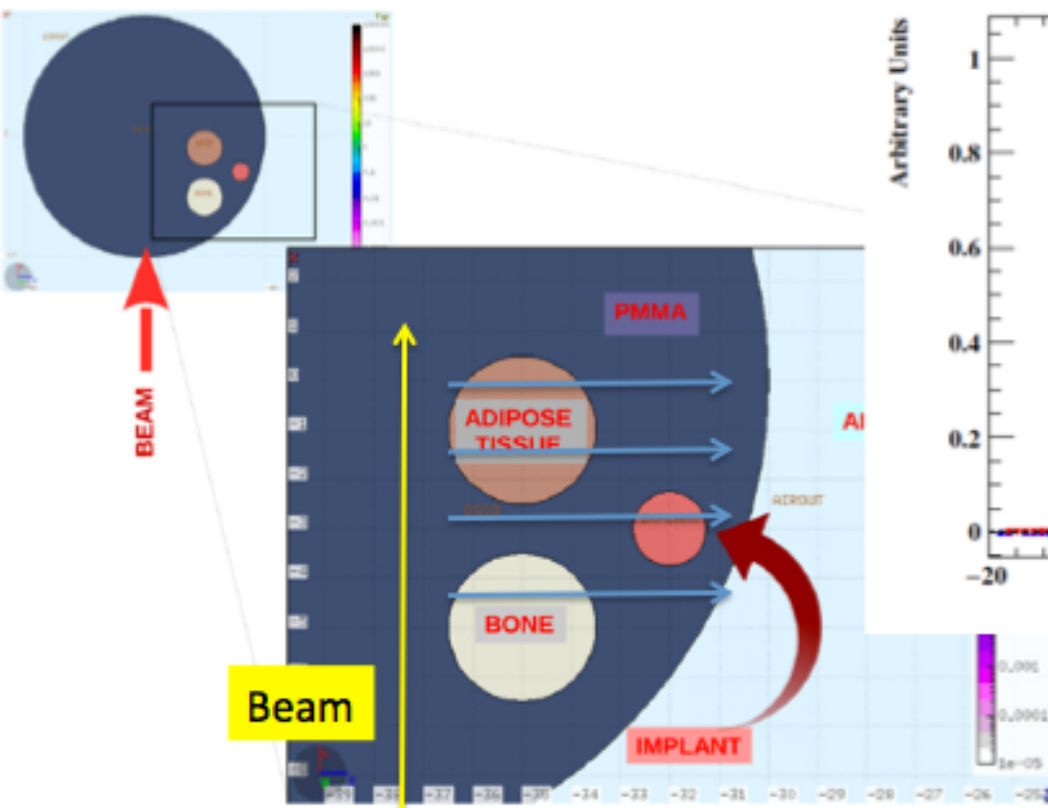
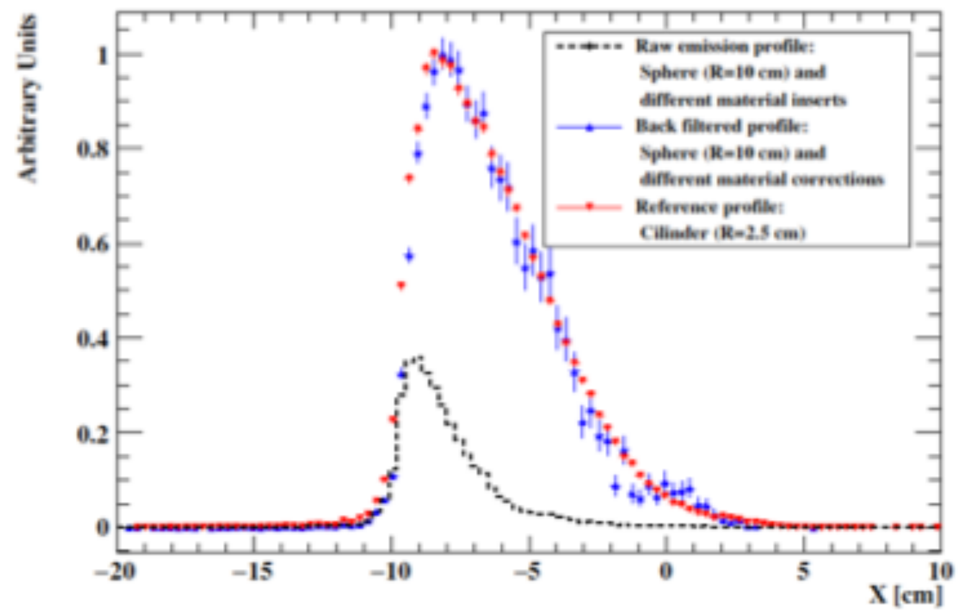
Original paper

Design of a new tracking device for on-line beam range monitor in carbon therapy

Giacomo Traini [a,b], Giuseppe Battistoni [c], Angela Bollella [a], Francesco Collamati [a,b], Erika De Lucia [d], Riccardo Faccini [a,b], Fernando Ferroni [a,b], Paola Maria Frallicciardi [e], Carlo Mancini-Terracciano [a,b], Michela Marafini [b,f], Ilaria Mattei [c], Federico Miraglia [a], Silvia Muraro [c], Riccardo Paramatti [a,b], Luca Piersanti [d], Davide Pinci [b], Antoni Rucinski [b,f], Andrea Russomando [a,b], Alessio Sarti [b,f], Adalberto Sciubba [b,f,g], Martina Senzacqua [f], Elena Solfaroli-Camillocci [a,b], Marco Toppi [d], Cecilia Voena [b,*], Vincenzo Patera [b,f,g]





IMDO activities 2018

1. Finalize the reconstruction code that compensate the absoption in the patient of the secondary protons

2. Implement comunication between Dose profiler and the Dose Delivery System of the CNAO treatment room. Needed to:
   - Include the beam direction info in the reconstruction
   - Obtain the start signal for the data transfer when the spill is off

3. Test of the Dose profiler data taking with a patient

IMDO Plan of activities 2019/20

2019

1) Development of a PET like reconstruction code that provide the beam range and take care of proton absoption using the M-LEM iterative technique
2) Porting of the on-line reconstruction code on GPU system. Needed to achieve the needed CPU power to keep up with data production
3) Optimization of the operation conditions: distance from patient, angle with respect to the beam

- **2020**

1) Evaluation of the performance on selected patients and pathologies;
2) Development of a clinical protocol that foresees the use of the profiler feedback in standard treatment ;

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IMDO expected funding in the next 3 year

Request of funding by Centro Fermi

- *Specific Consumables/inventory per year. In 2018 we will upgrade of the Main FPGA + motherboard to improve the data transfer (20 kEuro)*
- *Grant contract in 2019-2020*

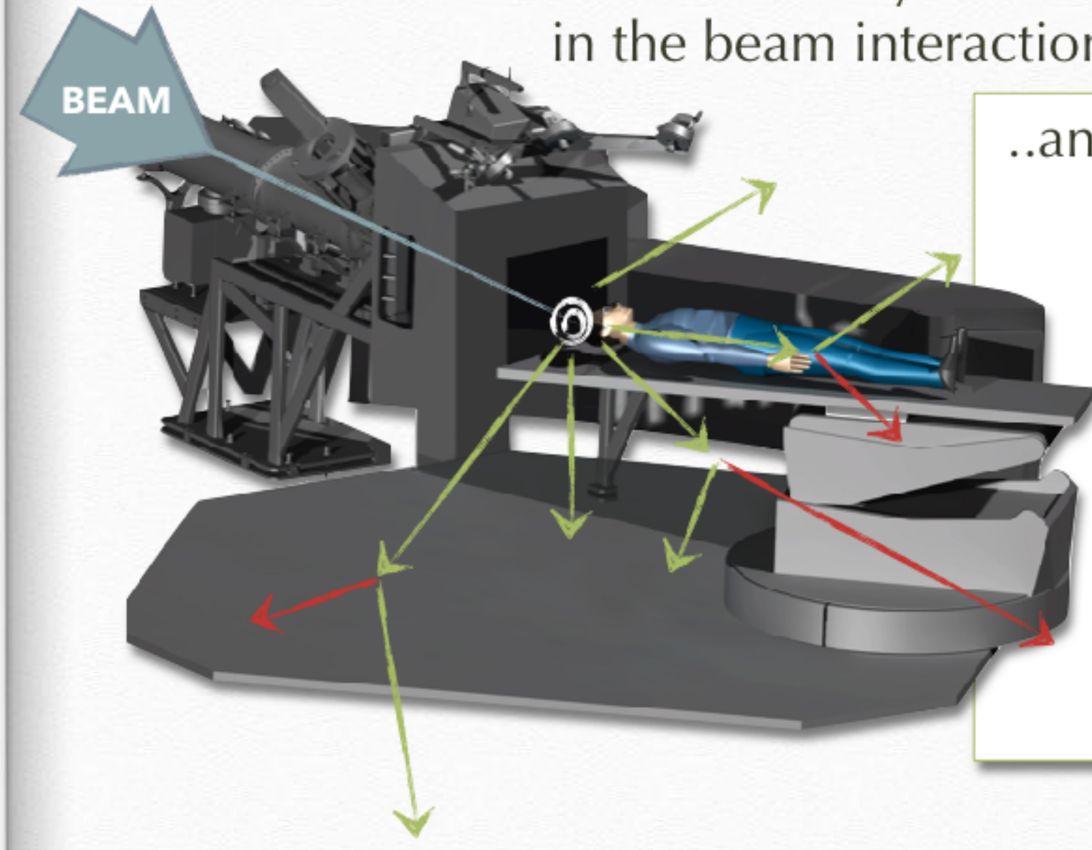
EXTERNAL funding:

- *Part of the travel expense will be covered by CNAO in 2018.*

Neutrons in PT

In a Particle Therapy (PT) treatment the patient is irradiated with a charged light ion (proton, carbon, ecc..) beam. Most of the dose is released on the tumour or in its proximity.

However many secondary particles are produced in the beam interactions with the patient..



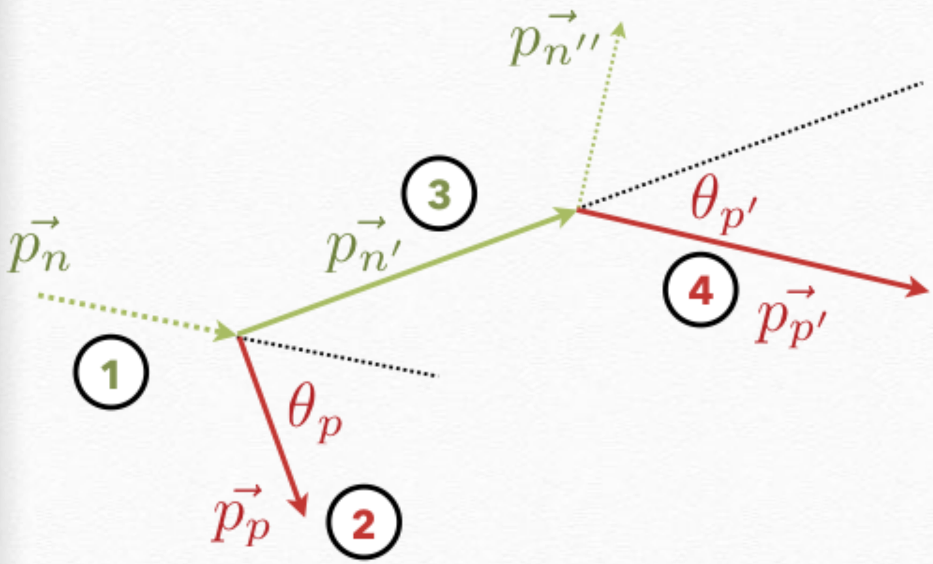
..and a large fraction of them.. are neutrons!

The **neutron interactions** with the patient are responsible of **additional dose** far away from the treated volume.

Tracking is more than detecting

In hydrogenated target the most probable neutron interactions are scattering on the nucleons (H). We want to **exploit elastic scattering**.

TRACKING THE NEUTRONS WITH HIGH EFFICIENCY



1. First neutron interaction: elastic scattering (ES)
2. Proton recoil

$$\vec{p_n} = \frac{p_p}{\cos\theta_p}\hat{n}$$

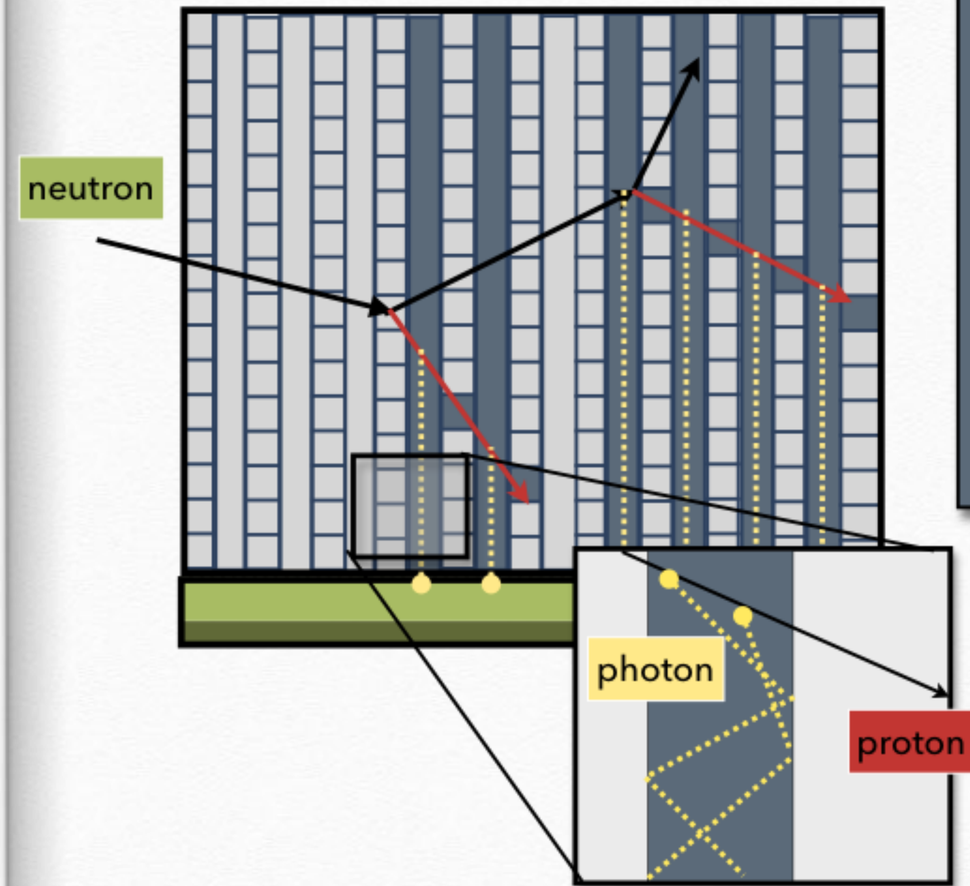
3. The diffused neutron interacts again via ES
4. Second proton recoil

$$\vec{p_{n'}} = \frac{p_{p'}}{\cos\theta_{p'}}\hat{n}'$$

M.Marafini

Tracking neutrons

SCINTILLATING PLASTIC FIBRES



1. squared 250 μm (maximise the resolution on for proton range)

2. plastic (maximise the interaction probability for the n on H reaction)

3. "easy" to manipulate

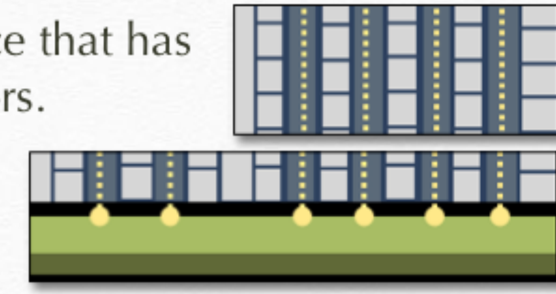
4. "cheap" 1€/m

target and tracker

Final tracker size
10 x 10 x 20 cm³

Readout system

The large number of channels and the large surface that has to be readout call for a customised silicon detectors.

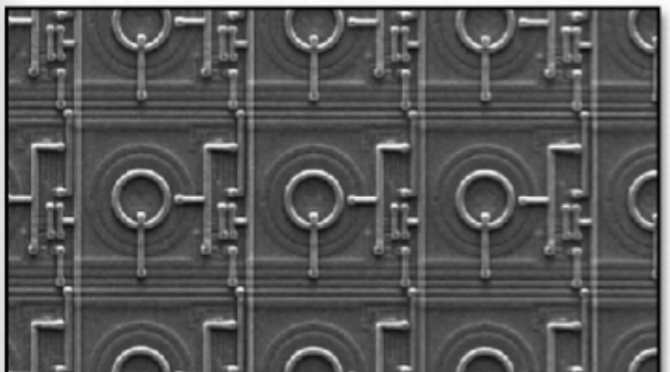


SPAD: Silicon Photon Avalanche Diode

1. Need to preserve the space granularity of the fibres

2. Few photons/ph.electrons 3. Fast signals: typically ~ 5ns

Digital silicon diode (SPAD) allows to build a sensor with customised pixel size. **An internal smart trigger logic allows to discriminate the scintillation light signals** from the background due to the dark count rate.



We choose to develop a new SPAD array sensor in collaboration with FBK **SBAM sensor** tailored for the MONDO needs.

Fondazione Bruno Kessler

Readout system

The large number of channel[...] to be readout call for a c[...]

SPAD: Silicon Phot[...]

1. Need to preserve the sp[...] granularity of the fibres

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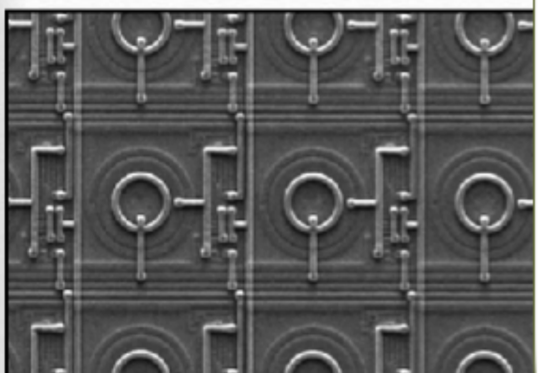
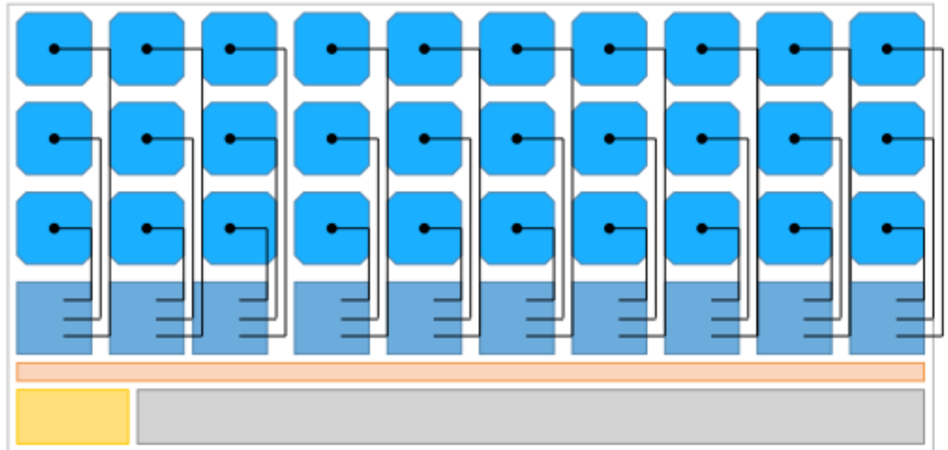




SPAD
19×19µm² active area
25×25µm² incl. GR and spacing

SRAM, front-end and quenching ×3
25×25µm²

Merging of SPAD signals (OR tree, monostables, …)

5-bit Digital counter
5bit×6×16µm²

Space left for discriminator

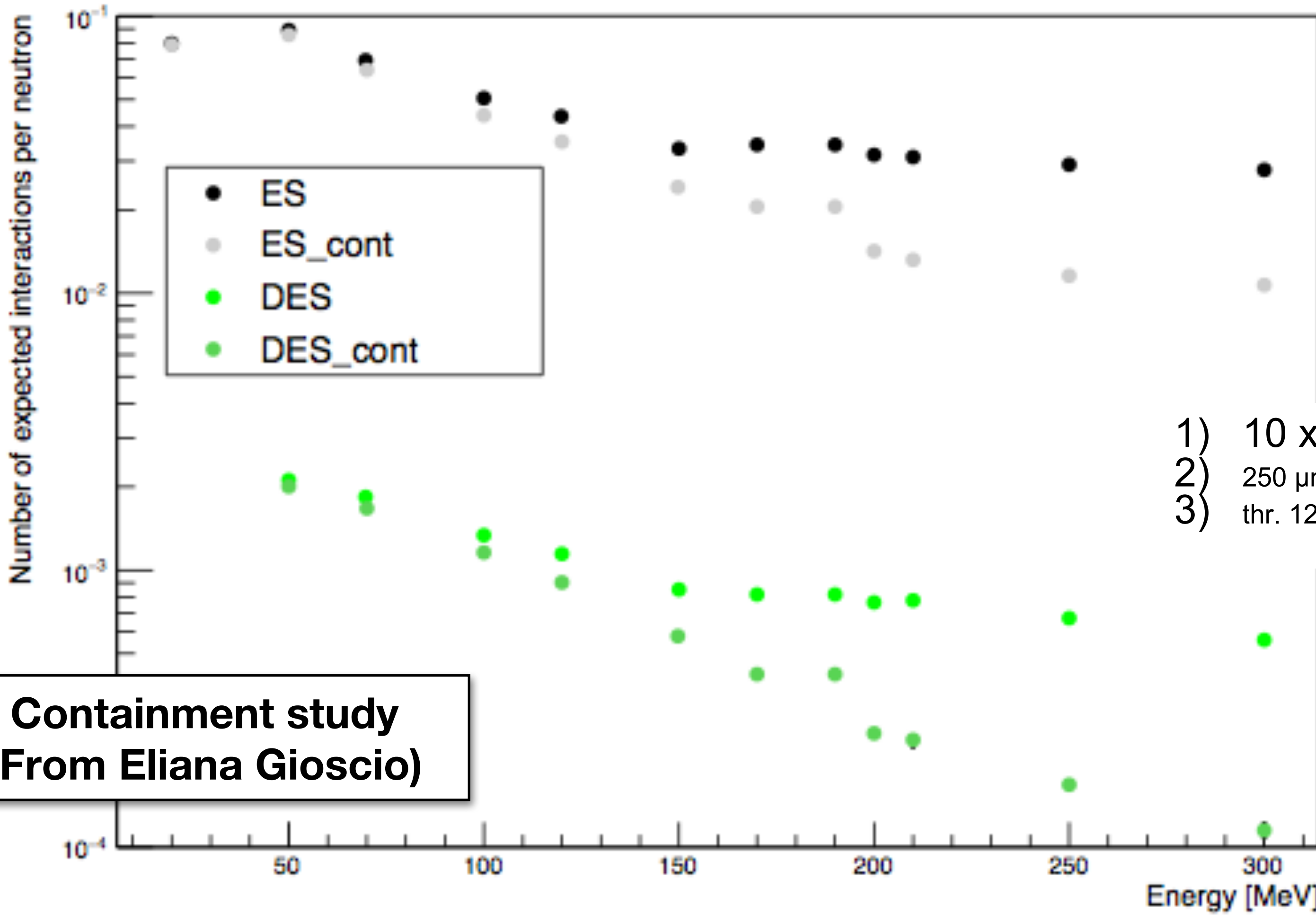
Fondazione Bruno Kess[...]

MONDO

Project main goals and results achieved in 2017

The MONDO detector description in MC FLUKA simulation has been implemented now and the readout system has been simulated as well.

Detection probability



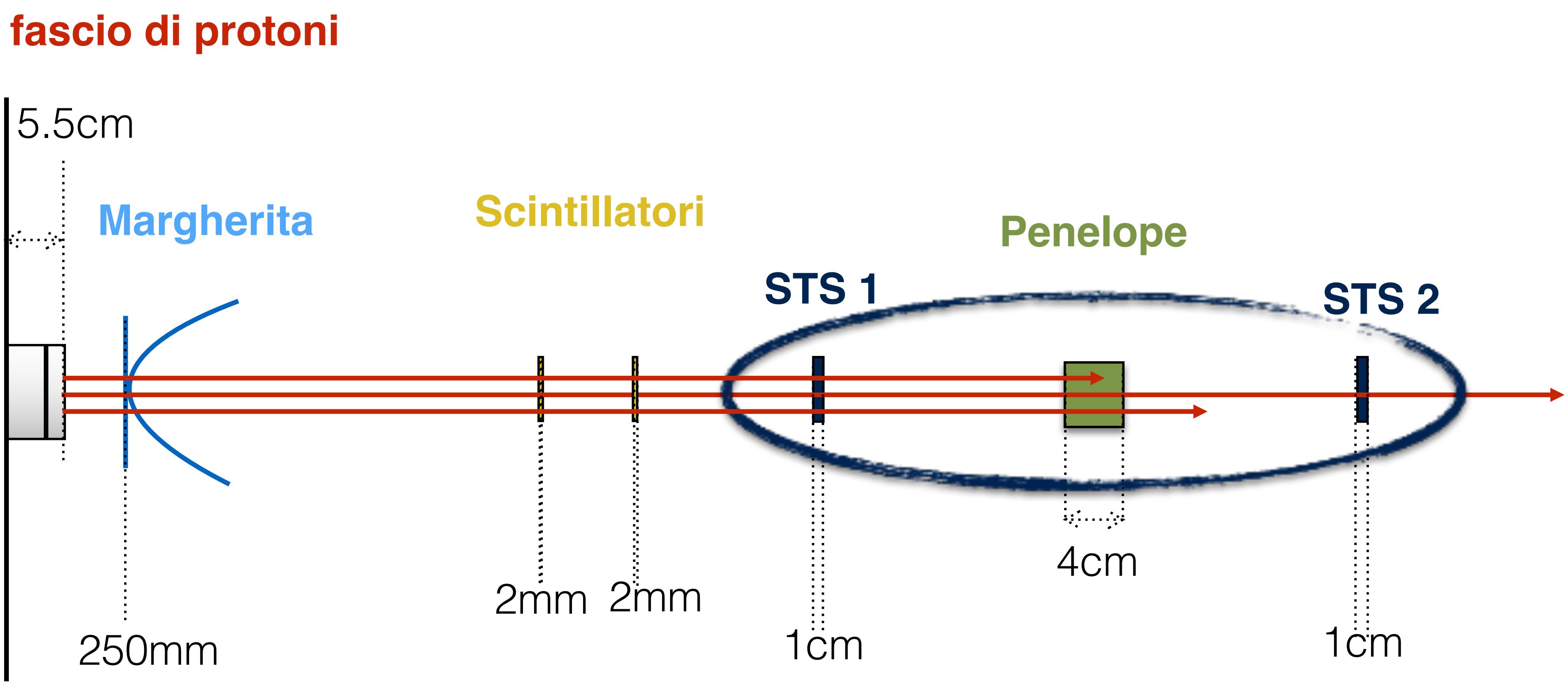
1) 10 x 10 x 20 cm^3
2) 250 μm fibres
3) thr. 12 MeV on protons

Containment study (From Eliana Gioscio)

MONDO

Project main goals and results achieved in 2017

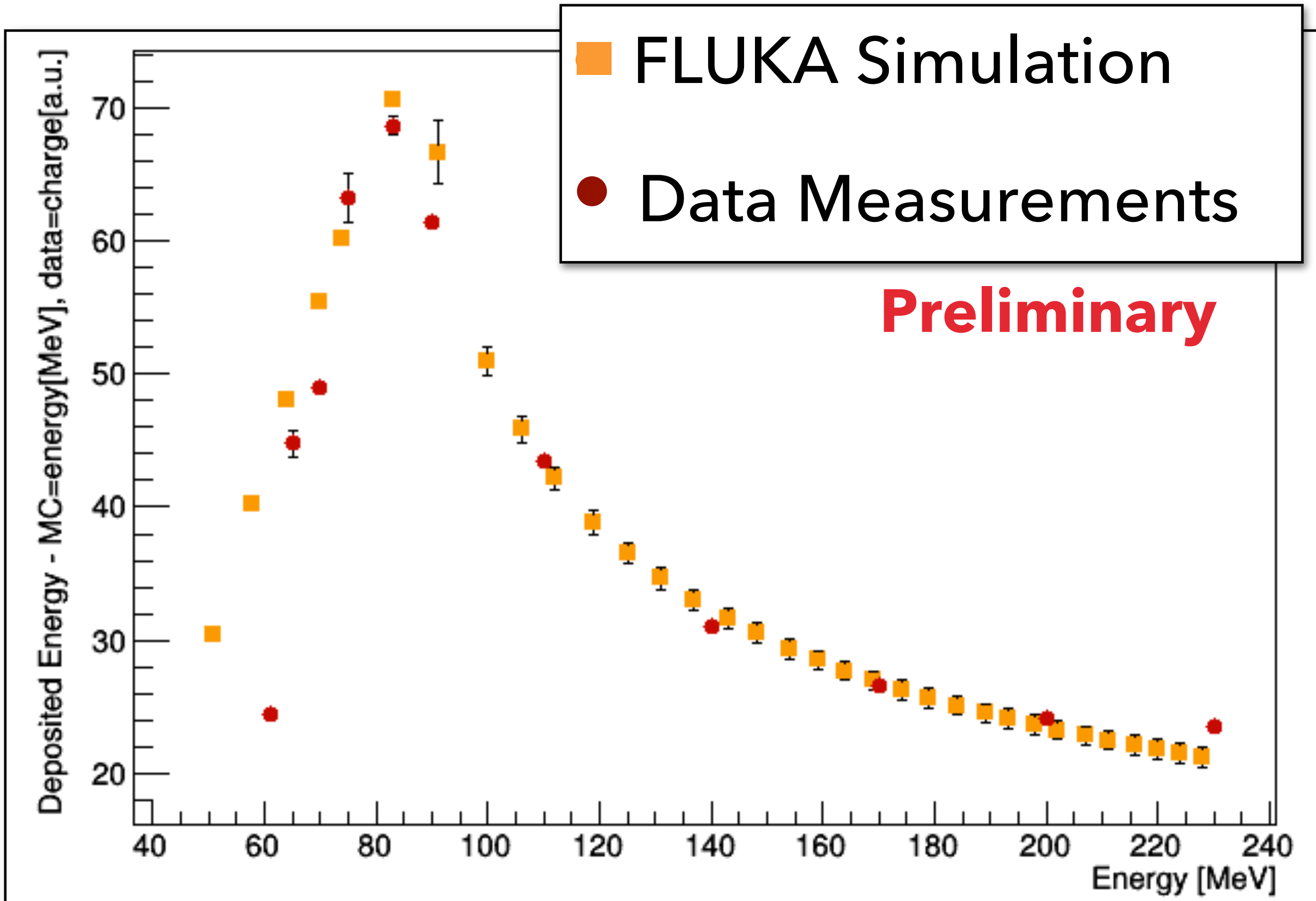
The MONDO detector prototype – PENELOPE – has been tested at the experimental ASSP facility of Trento with proton beams ad different energies.

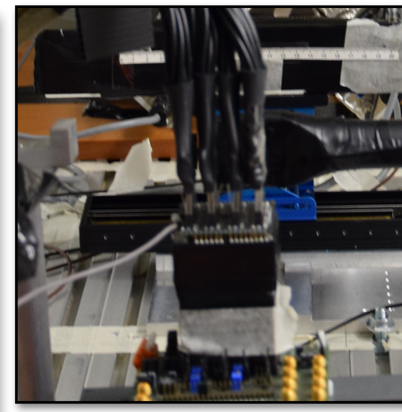


MONDO

Project main goals and results achieved in 2017

2° PENELOPE readout: HAMAMATSU Multianode (64 ch., 6mm per pixel)

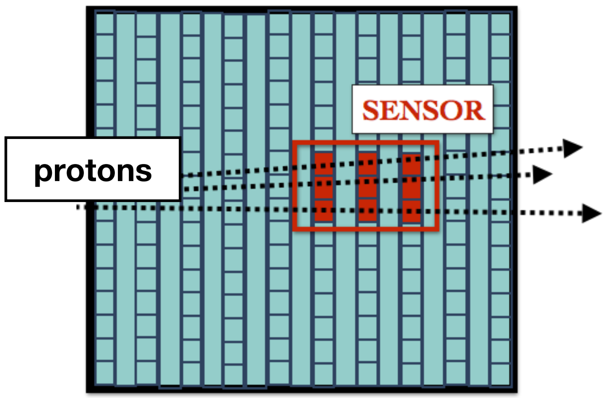


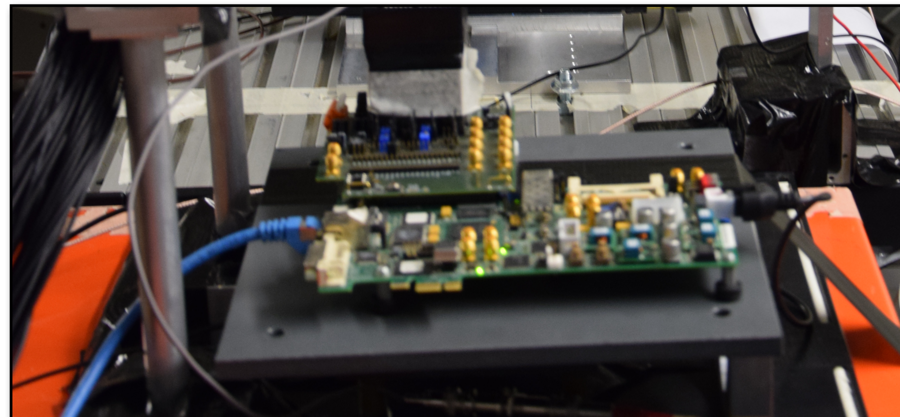


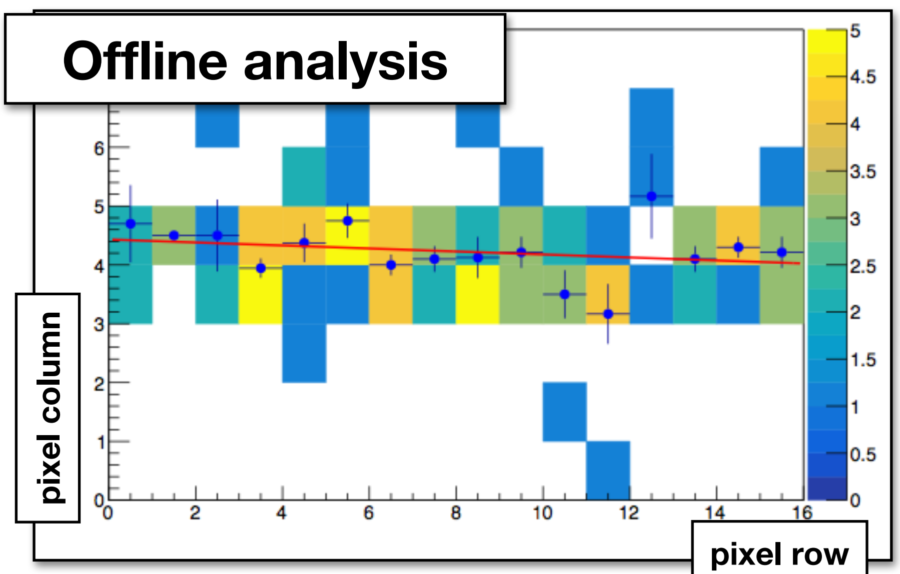
- Data charge normalised to peak
- Only average total charge
- Only statistical errors

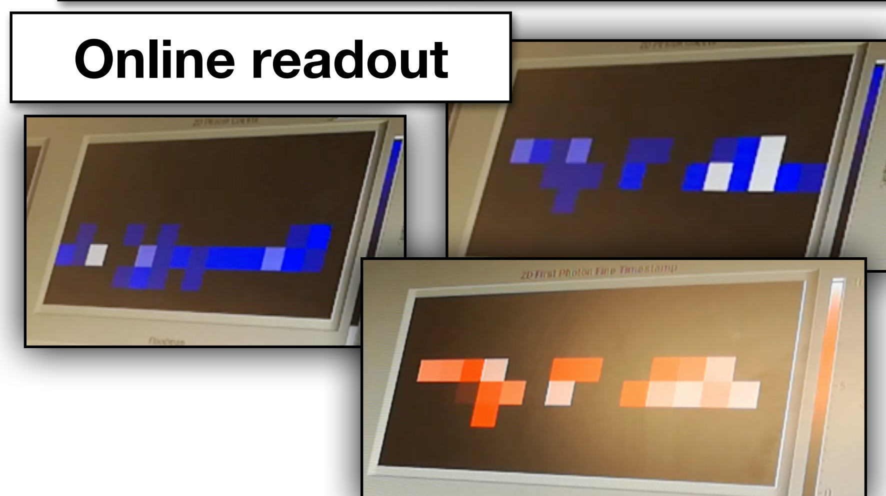
Project main goals and results achieved in 2017

1° PENELOPE readout: FBK spadnet sensor (128 ch., 600µm per pixel)



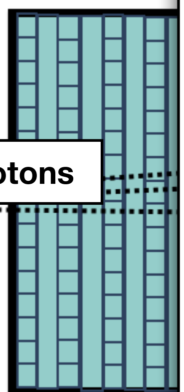




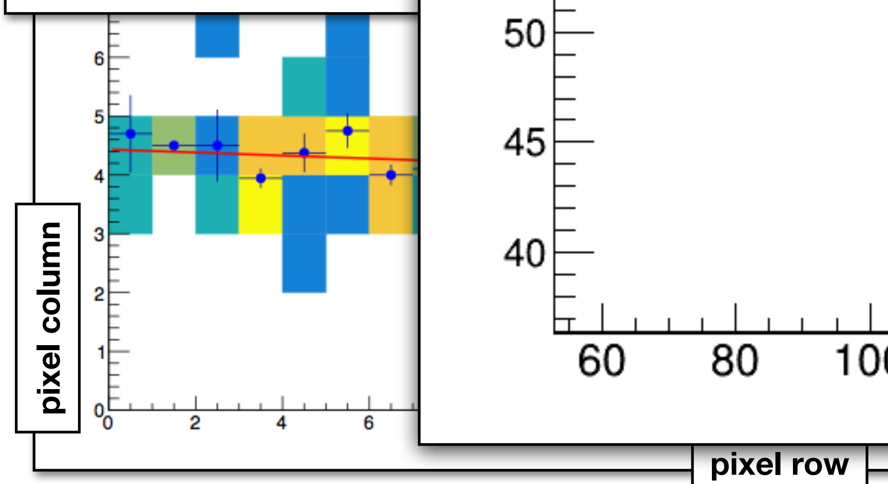


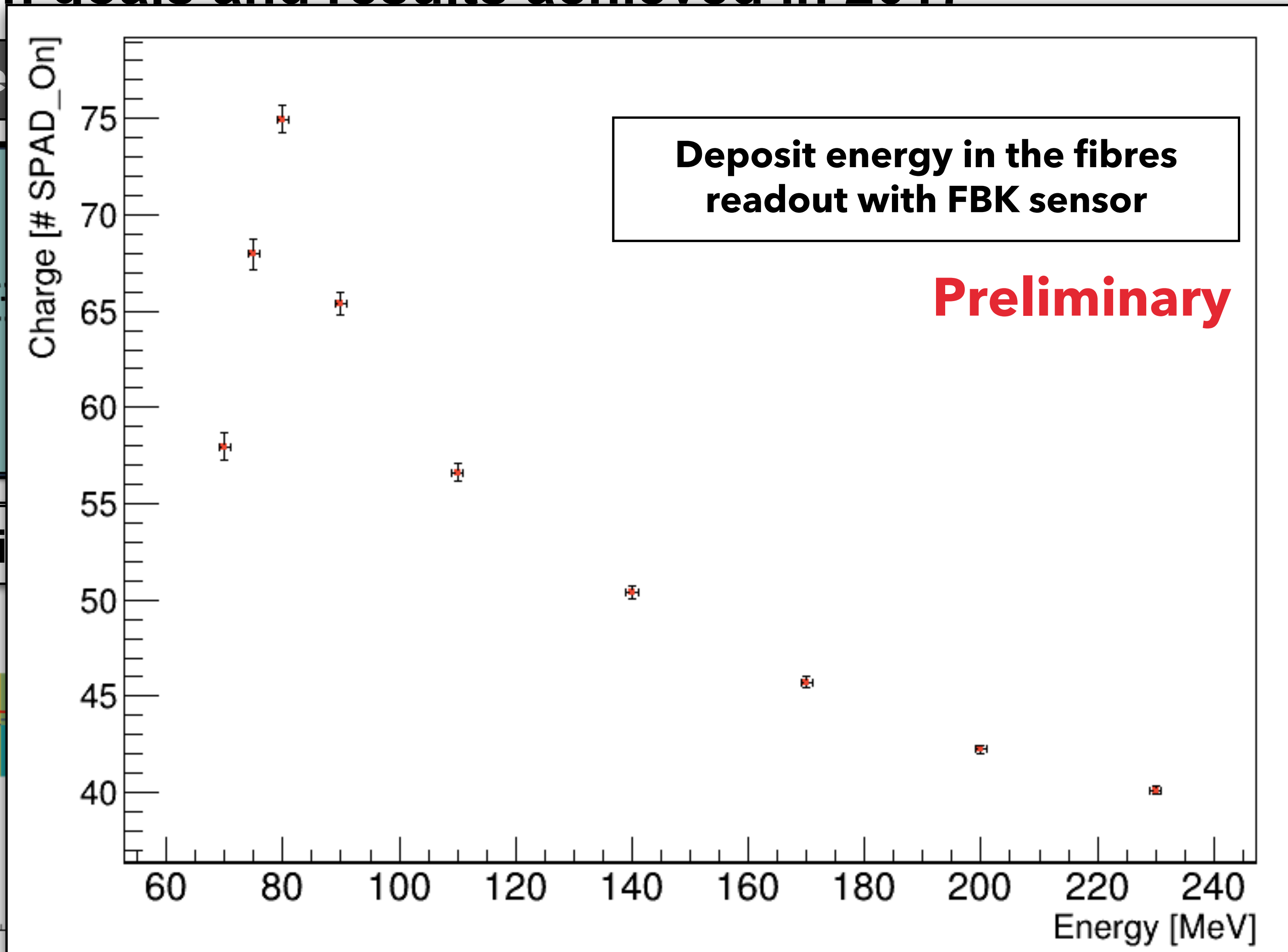
Project main goals and results achieved in 2017

1° PENELOPE re



Offline analysi





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MONDO

Milestones 2018

1. Realisation of the full size detector with scintillating fibres organised in x-y oriented layers: 10 x 10 x 20 cm3;
2. Production of the first SBAM sensor test chip. Realisation of a prototype tile sensor.;
3. Fiber coupling test - SBAM sensor;
4. Implementation in the readout simulation of the trigger system. Realisation of the traces reconstruction system.

Plan of activities :MONDO

2018

1) Scintillating Matrix construction: => 10 x 10 x 20 cm^3;
2) Neutron production cross-section measurements at CNAO with ToF technique;
3) SBAM sensor test chips realization (2 FPGA evaluation board 2 x 0.5 cm^2):
    1) test of the sensors in FBK
    2) evaluation of the sensor as fibers readout at SBAI
4) Test measurements with proton beam (Trento) with SBAM sensor test chips
5) Reconstruction Software: event display and event reconstruction;
6) Simulation:
    1) Evaluation of the intrinsic background (impact on resolution);
    2) Other applications of MONDO detector will be investigated: Neutron in space, neutron beam monitor.

- **2019**

1) New SBAM sensors (full run);
2) Full detector instrumentation;
3) Preliminary measurements of neutrons produced in PMMA during Carbon ion (CNAO) and proton (TIFPA) irradiation;

- **2020**

SIR will be closed in March (6 month extension has already been approved)

- **Our group has interest in finalising the project:**

=> Neutron in paediatric Particle Therapy
=> Characterisation of PT European Centres

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Funding request for MONDO

- Request of funding by Centro Fermi

- *M. Marafini RTD extension;*
- *Specific Consumables/inventory per year*

Potential external funding

- **SPARE (**Space Radiation Shielding) project has been funded (Premiale INFN + CF+ASI) and the MONDO detector will be also employed for space radioprotection application;

- An **ERC StG2017** has been proposed (CF as HI):
  - COSMOs (**C**hasing neutr**O**ns to understand **S**econdary **M**alignant ne**O**plasm**s** in particle therapy): double differential cross section production of neutrons in body compounds and development of a new Effective Nuclear Model with Fast MC (ENM-Fred);

- A **PRIN Under40** is going to be submitted with CF as RU:
  - 19F4: Monitoring in PT exploiting Oxygen (and Fluorine) prompt gamma production;

- An **AIRC MFAG2018** has been proposed (CF as HI):
  - MARE (**M**onitoring in **A**dro-**R**adio-th**E**rapy)

IMDO/MONDO

Impact of the research and outreach initiatives

- The beam range monitoring will improve quality assurance of the PT treatment
- The measurement of the secondary neutron flux and spectra would improves the Treatments Planning Systems

According to the new upgrade of the L.E.A. the Particle Therapy is going to be offered by Italian national sanitary service for 10 different type of tumours (for example, paediatric solid tumours and brainstem cancers) and the interest in this technique is growing up exponentially.*

* LEA [Definizione e aggiornamento dei livelli essenziali di assistenza (LEA) - Novembre 2016 - Atti del Governo n. 351: http://www.senato.it/service/PDF/PDFServer/BGT/00994183.pdf]

Outreach initiatives

- Presentation of the results to international conference (5/year);
- Several papers (5/year) are expected to be published on refereed journals in the next few years:

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TADR publications in 2017

1) Battistoni G.et al. “Design of a tracking device for on-line dose monitoring in hadrontherapy” (2017) NIM A 845, pp. 679-683.
2) Traini G. et al. “Design of a new tracking device for on-line beam range monitor in carbon therapy” (2017) Physica Medica, 34, pp. 18-27
3) Mattei I. et al. “Secondary radiation measurements for particle therapy applications: Prompt photons produced by 4He, 12C and 16O ion beams in a PMMA target” (2017) Physics in Medicine and Biology, 62 (4), pp. 1438-1455
4) Marafini M. et al. “Secondary radiation measurements for particle therapy applications: Nuclear fragmentation produced by 4He ion beams in a PMMA target “(2017) Physics in Medicine and Biology, 62 (4), pp. 1291-1309
5) Marafini M et al. *“MONDO: a neutron tracker for Particle Therapy secondary emission characterization” PMB 62 (2017) 32993312 doi: 10.1088/1361-6560/aa623a*
6) Mirabelli R et al. *“The MONDO detector prototype development and test: steps towards a SPAD-CMOS based integrated readout (SBAM sensor)”* TNS PP (2017) 99 1-1 doi: 10.1109/TNS.2017.2785768
7) S.Valle, et al. *‘’The MONDO project: A secondary neutron tracker detector for particle therapy*" NIMA 845, 556–559 (2017) DOI: 10.1016/j.nima.2016.05.001

- The FBK and CF signed a collaboration (*Convenzione Quadro*) for the development of the SBAM sensor. The **intellectual property of the sensor** is now shared by the two parts.

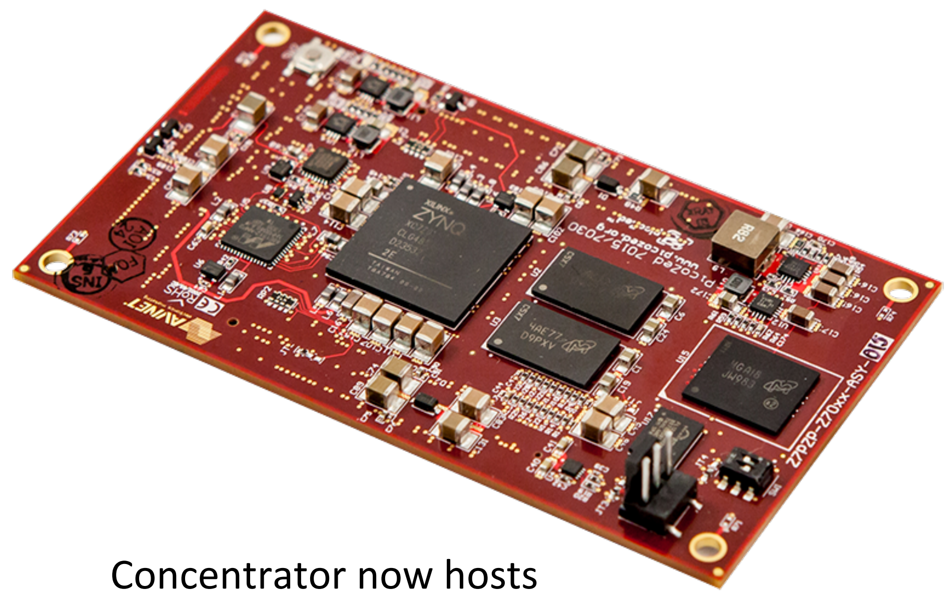
TADR Conferences in 2017

1) *M.Marafini 6/2017 MLZ: Neutrons for Health - Bad Reichenhall, Germany. "Characterisation of the secondary fast and ultrafast neutrons emitted in Particle Therapy with the MONDO experiment".*
2) R.Mirabelli 5/2017 YRM – Cagliari, Italy *''MONDO: A tracker for the characterization of secondary fast and ultrafast neutrons emitted in Particle Therapy''* - contribution on proceeding.
3) I.Mattei 6/2017 MEDAMI *''Characterisation of the secondary fast and ultrafast neutrons emitted in Particle Therapy with the MONDO experiment''.*
4) G.Traini 7/2017 IWORID -Krakow, Poland *''Characterisation of a tracker for secondary fast and ultrafast neutrons: the MONDO project"* - Proceeding JINST accepted.
5) V.Giacometti 8/2017 ICTR – Strasbourge, France *"Characterization of secondary neutrons for the MONDO experiment by means of FLUKA simulations"* – Accepted by Rad.Meas.
6) R.Mirabelli 9/2017 SIF – Trento, Italy "MONDO neutron tracker characterisation by means of proton therapeutic beams and MonteCarlo simulation studies".
7) M.Marafini 11/2017 PRESS: PRoton thErapy research SeminarS – Krakow, Poland *"Secondary neutrons in particle therapy: the Mondo project"- Invited talk.*
8) G.Battistoni 11/2017 PRESS: PRoton thErapy research SeminarS – Krakow, Poland Range Monitoring in particle therapy: the INSIDE project and the case for charged particles
9) S.Muraro 10/2017 MCMA-Naples, MC codes and Range Monitoring in Particle Therapy: the case of secondary charged particles
10) S.M.Valle, 9/2017 *ICNTRM 2017, Strasbourg Study of the radiation produced by therapeutic He, C and O ion beams impinging on a PMMA target for beam range monitoring purpose in Particle Therapy*

Thanks for the attention

Data transfer strategies

- Protocols smarter than TCP-IP will be investigated (UDP is claimed to perform much better)
- The possibility to store the data on a local memory and to transfer them when the spill/beam is off, is also on the table and is being studied. Requires
  - Proper study of the memory dimensions needed to store interactions from 2x10^8 primary ions (maximum that can be provided in a single spill). If larger memory is needed → new concentrator will be needed
  - Implementation of a data transfer driven from the DDS (next slide).



Concentrator now hosts
4 GB eMMC memory

DP resolution: summary

- Extensive data and MC effort to assess the DP resolution. Preliminary summary:
  - MC + Al wire + Plastic sphere are ~ in agreement: σx,σy of ~9,7 mm are observed
  - Plastic wire runs are being scrutinised to understand the discrepancy source

Preliminary

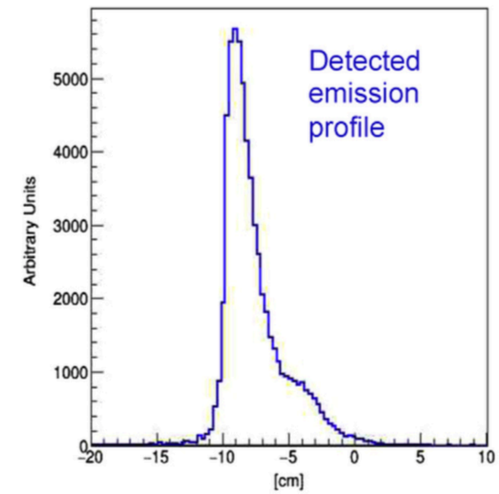
	220 MeV/u	σ^X	σ^Y
90°	MC Pl wire	8.3mm	7.9mm
90°	Pl wire	1.4cm	8.4mm
60°	Sphere	8.8mm	6.5mm
60°	Al wire	8.6mm	7.4mm

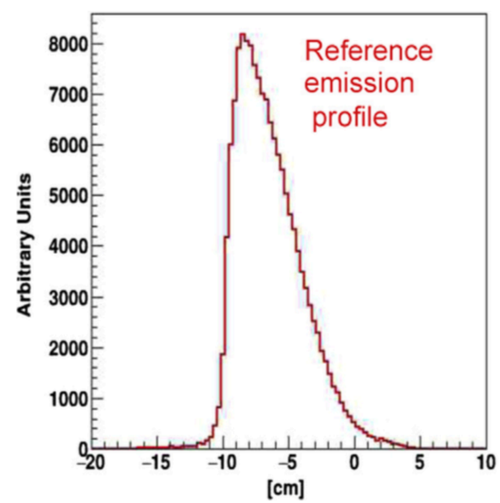
Huge ongoing work

The 5mm from Trento become 8-9mm after: a) **softer E_{kin} spectra**, b) different angular distribution

Matter effect: going on-line

- If we divide the path of the beam in the patient in N bins, then the emission distribution is a vector where the i-th component gives the number of secondary truly emitted in the bin i of the path
- A charged emitted at bin i (x_i) can be reconstructed in bin j (y_j). The relation between the true emission point x and the reconstructed point y can be written as y = S(x)
- The system operator S include multiple scattering, detection resolution, absorption in matter. It can be represented by a system matrix A with A_{ij}: Probability that emission in bin i results in a detection in bin j. So $y_j = S_i A_{ij} x_i$
- We need to solve the inverse problem: $x = A^{-1}y$. Typical deconvolution problem: is fundamental to evaluate the system matrix S





Strategy: use FRED & M-LEM

From MC+
Patient CT

- Initial guess for emission distribution: $x_i^{(0)}$
- Estimate measurements from system matrix (forward proj.):

$$y_j^{est} = \sum_k A_{kj} x_j^{(0)}$$

- Compare this to actual measurements: $R_j = \dfrac{y_j}{y_j^{est}}$
- Improve iteratively image estimation (backw. projection):

ML-EM

$$x_i^{(n+1)} = x_i^{(n)} \cdot \frac{1}{\sum_j A_{ij}} \cdot \sum_j A_{ij} \frac{y_j}{\sum_k A_{kj} x_k^{(n)}}$$