**ENLIGHT Meeting, Kraków**
**18-20 September 2015**

# *The current status and challenges of detection and imaging in radiation therapy.*

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- Rationale for imaging in hadrontherapy
- First attempts in the late '70s
- Proton radiography and proton tomography
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  - Positron emitters and PET imaging
  - Prompt neutral particles → gammas
  - Prompt charged particles → protons
  - Combined systems
- Conclusions

# Rationale for imaging in hadrontherapy: critical issues

Physics related

- CT HU (e.g.calibration apparatus)
- conversion to proton stopping power
- dose calculation uncertainties

Patient related

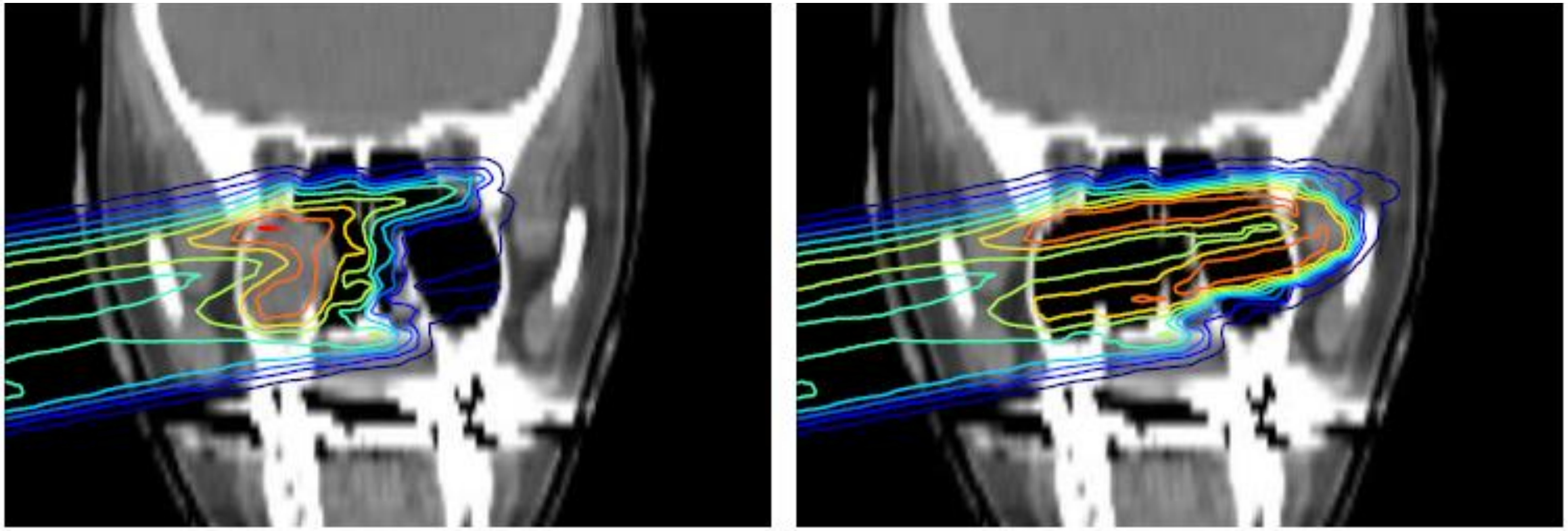
- daily positioning on the couch
- internal organ motion
- changes in air cavities
- tumour regression
- weight loss

Other sources

- RBE values
- Tumor heterogeneity
- Contouring uncertainties
- Reconstruction artifacts in CT
- Machine related

**Dose/Bragg Peak Monitoring is advisable!**

# Rationale for imaging in hadrontherapy



Planned .. but there was a tissues variation !!

➔Dose/Bragg Peak monitoring➔ 2 major techniques

- **1 - Based on X-ray CT- analogous: pCT (only for Protons)**
- **2 - Based on Nuclear Reactions of Hadrons in Tissue**
  - **Off-line & On-line PET**
  - **Prompt gamma's and neutrons**
  - **Prompt charged particles (only for Ions)**

# The BEVALAC experience @Berkeley with radioactive beams (late'70s)

**"Physical Measurements with High-Energy Radioactive Beams"**
**A. Chatterjee, W. Saunders, E. L. Alpen, J. Alonso, J. Scherer and J. Llacer**
**Radiation Research, Vol. 92, No. 2 (Nov 1982), pp. 230-244**


**Abstract**

**"**Physical measurements were made with **high-energy radioactive beams (positron emitters) produced as secondary particles from a heavy-particle accelerator**. **Data are presented for water-equivalent thickness of a silicon diode,a comparison of Bragg peak ionization depth vs stopping depth,and differential stopping depths when a beam is intercepted by heterogeneous materials in the orthogonal direction. A special positron-emitting beam analyzing (PEBA) system was used to form images of the stopped radioactive beam. These measurements will have direct impact on charged-particle radiotherapy,since the precise range of beams of charged particles to targets within patients can be measured and used for treatment planning. Also, during the treatments the stopping point of the beam can be monitored** to verify that the treatment is being delivered as planned.

# The PEBA detector

**IEEE Transactions on Nuclear Science, Vol. NS-26, No. 1, February 1979, Jorge Llacer, et al.**

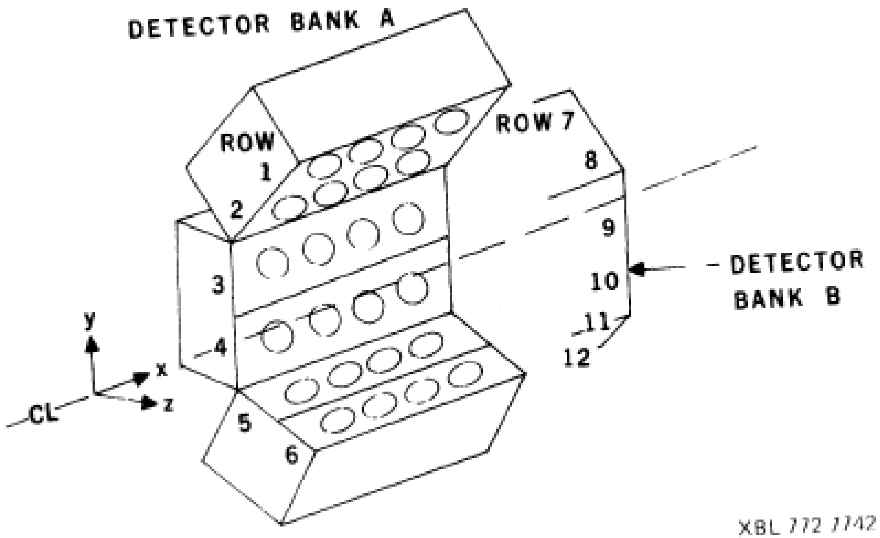
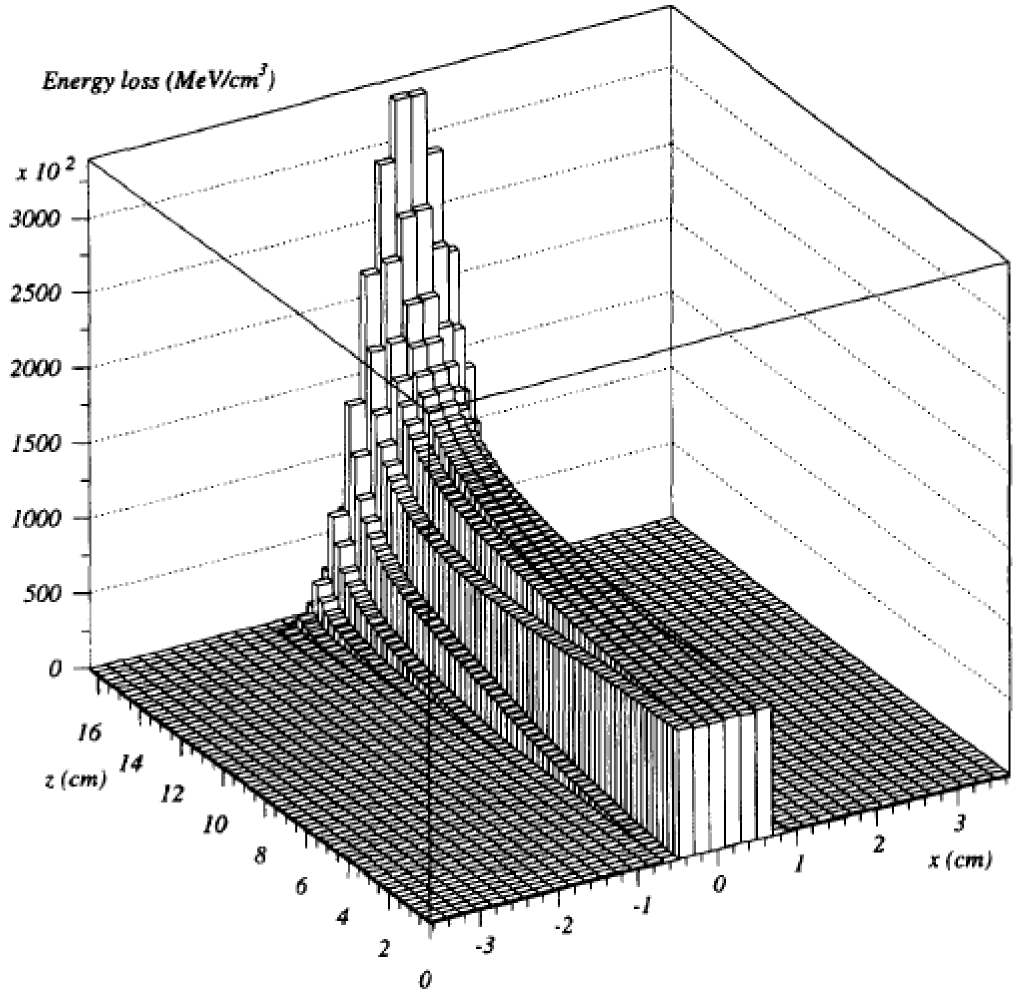



Fig. 1 Conceptual design of PEBA, showing two banks of 24 detectors each defining a volume along the path of a heavy-ion beam (x direction).

Fig. 4 Layout of PEBA, showing the 24 tubes of one detector bank arranged in modules of four detectors each.

**NaI(TI) 3” long for the inner; 2” for the outer ones.**
**In-house electronics+ CAMAC+ and microprocessors**
**Results: 1 mm resolution – Limited 3-D reconstruction**

# Energy loss distribution with a proton beam of 140.5 MeV in water, using the code PTRAN (one-dimensional/pencil beam) [1997]




**A.Del Guerra et al., "PET Dosimetry in Proton Radiotherapy:a Monte Carlo Study",** ***Appl. Radiat. Isot. Vol. 48, No. 10-12, pp. 1617-1624, 1997***

# Proton radiography and proton tomography (*)

**Using the same particles (i.e. protons) but with a higher energy, so that they pass through the target:**

- Measure the position with a **tracker** before (**upstream**) and after the target (**downstream**)
- Measure the residual enery with an energy detector (**calorimeter**) downstream
- Make **one planar view** to obtain a proton-radiography (pR)
- Make **many projections** to obtain a proton-CT (pCT)

**(*)The idea was originally proposed by Allan Cormack in 1963**

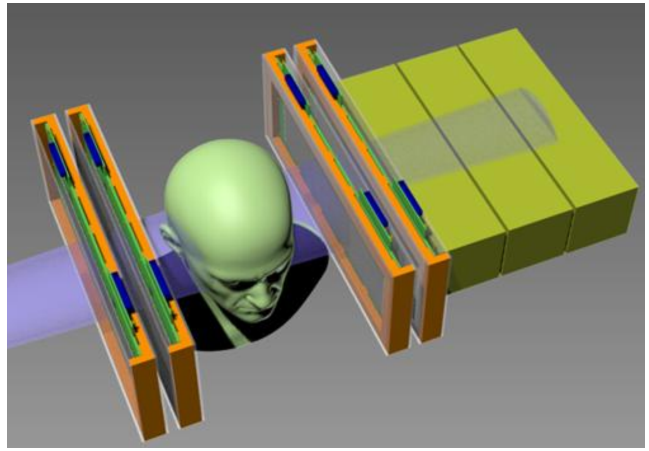
( J.Appl. Phys.1963,34, p.2722)

# Status of the pCT Project

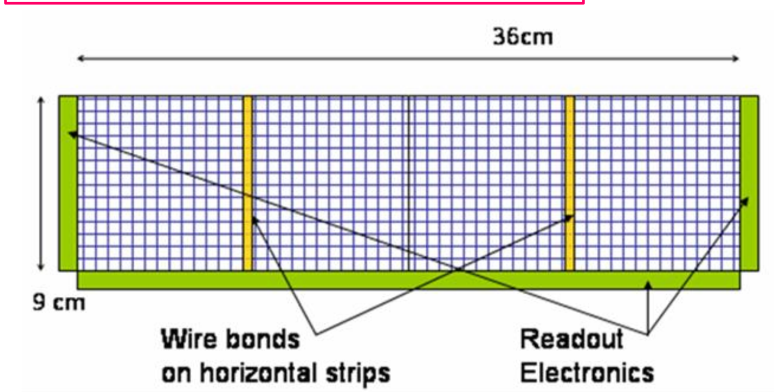
## UC Santa Cruz, Loma Linda U., Baylor U., Wollongong U.



**Tracker:**
Extrapolates protons into the phantom.
4 x-y planes of Silicon strip detectors with "slim edges" to avoid image artifacts.



**Energy Detector:**
Provides measurement of the Water Equivalent Path Length (WEPL) of the phantom.
5-stage scintillator with PMT readout.




http://dx.doi.org/10.1016/j.nima.2015.07.066

(Courtesy of H.Sadrozinski, 2015)

# Radiography with pCT Scanner

pCT Collaboration (UC Santa Cruz, Loma Linda, Baylor, Wollongong)

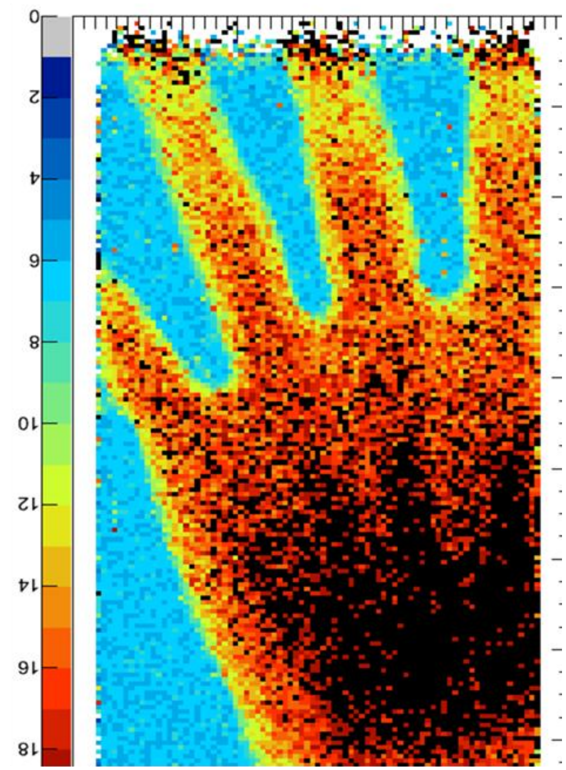
## X-Rays


Wilhelm Roentgen,
Laboratory Radiology (1895)

## 200 MeV Protons

### Stopping Power

### Multiple Scattering



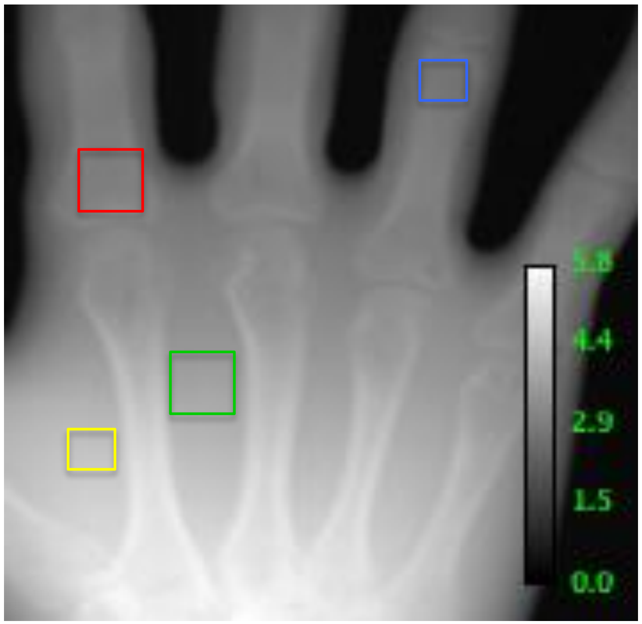

UCSC-LLU-CSUSB 2012, T. Plautz et al., 2012 IEEE NSS-MIC

N.B . Berta's hand, Hand Phantom!

# Radiography Relative Stopping Power from X-rays & Protons



X-ray radiograph transformed from Hounsfield Units to RSP

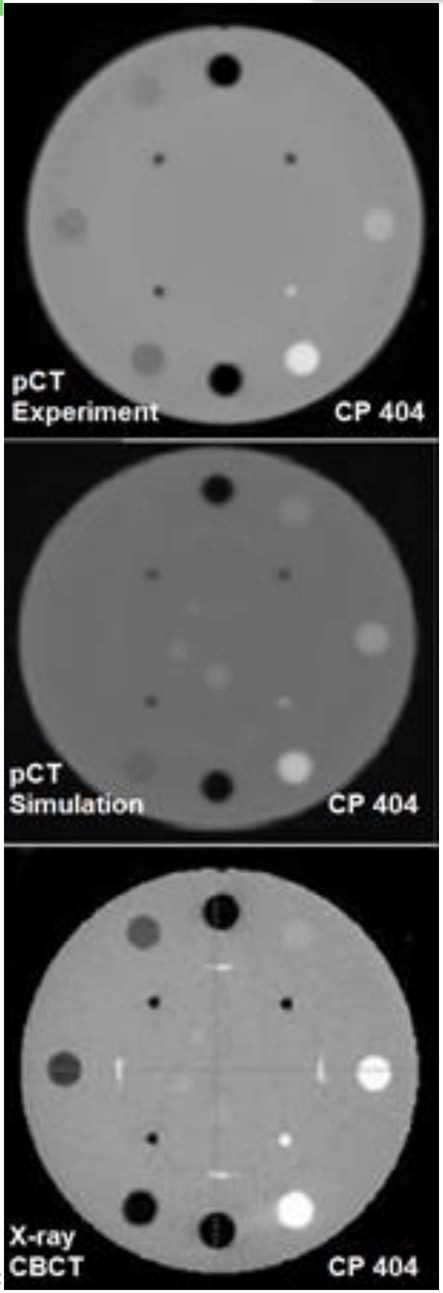



Proton Radiograph (directly in RSP) with 0.5x0.5 mm pixels


**About 3%-7% difference between X-ray R and pR**

| ROI | $RSP_{xray}$ (cm) | $RSP_{proton}$ (cm) | % difference (2*diff/sum) | Relative Error |
|---|---|---|---|---|
| a. | 3.618±0.130 | 3.527±0.125 | **2.55%** | 0.505σ |
| b. | 2.892±0.070 | 3.015±0.076 | **4.16%** | 1.190σ |
| c. | 4.236±0.119 | 4.561±0.153 | **7.39%** | 1.677σ |
| d. | 2.548±0.082 | 2.539±0.041 | **3.54%** | 0.0981σ |

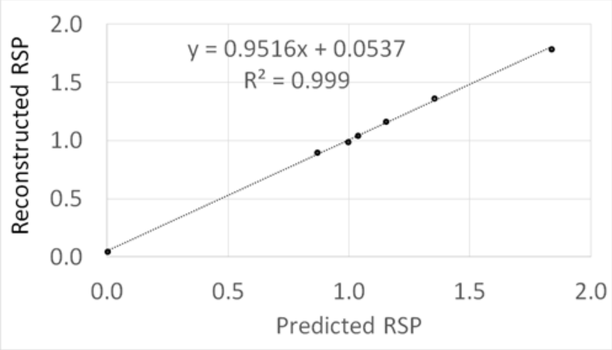
# Testing the RSP Resolution & Dose: CTP 404




The Catphan CTP 404 contains inserts of relative stopping power varying from 0.001 to 1.85.
This permits a comparison of a proton scan with Geant4 simulation and X-ray scan.

| Insert | Predicted | Reconstr Exp/Sim | Stdnd dev Exp/Sim | Abs Diff \|Rec-Pred\| Exp/Sim |
|---|---|---|---|---|
| Teflon | 1.84 | 1.78/1.82 | 0.002/0.02 | 0.06 |
| Delrin | 1.35 | 1.36/1.35 | 0.001/0.02 | 0.01 |
| Acrylic | 1.16 | 1.16/1.16 | 0.002/0.02 | 0.01 |
| Air | 0.001 | 0.04/0.02 | 0.004/0.02 | 0.04 |
| PMP | 0.87 | 0.90/0.88 | 0.004/0.03 | 0.03 |
| Polystyrene | 1.04 | 1.04/1.04 | 0.007/0.02 | 0.00 |
| LDPE | 1.00 | 0.99/1.00 | 0.005/0.02 | 0.01 |

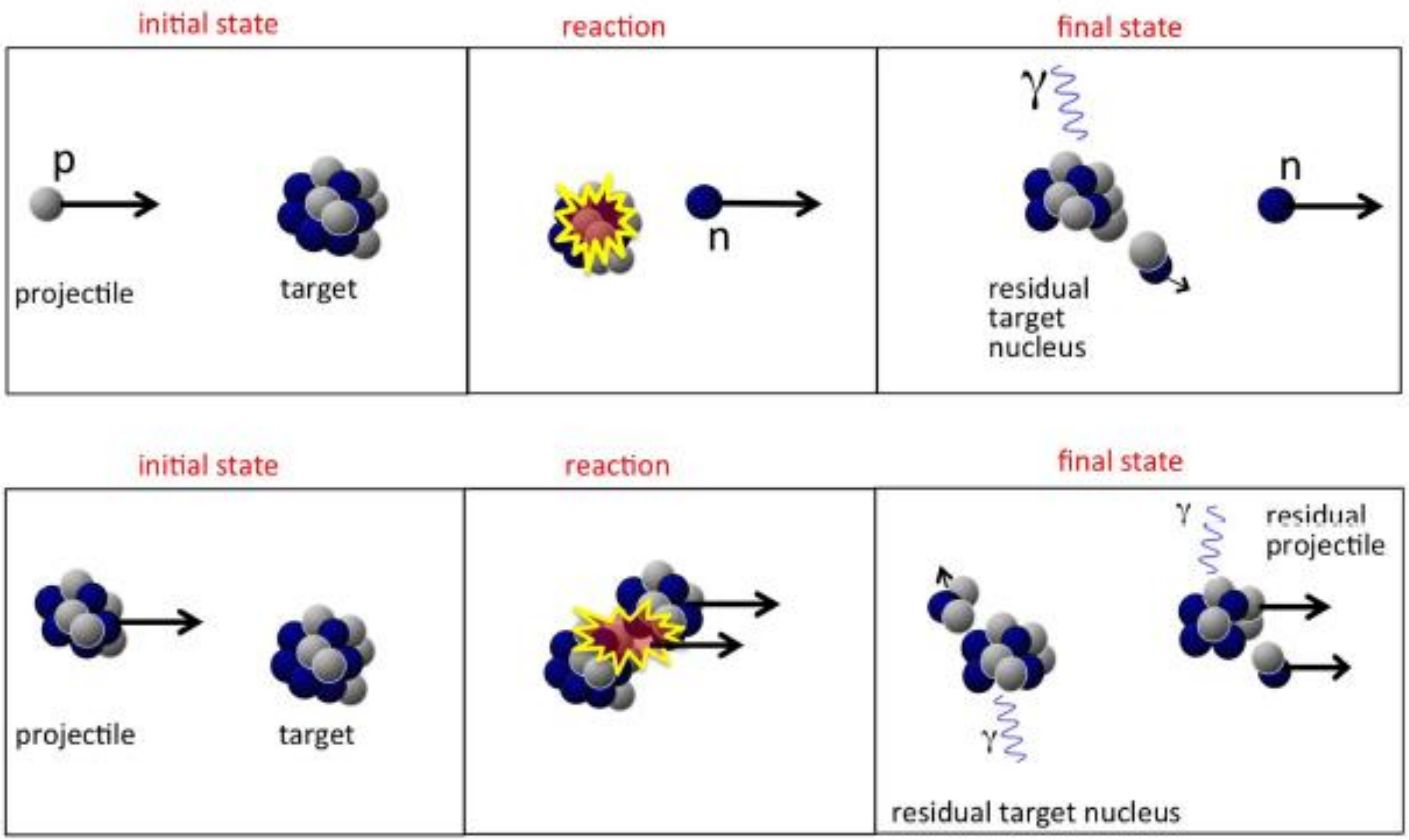
**Table 1.** Comparison of predicted versus reconstructed mean RSP of sensitometry inserts for experimental and simulated pCT data. The experimental data had better statistics (2.5M histories per projection), which explains their smaller standard deviation.




The reconstructed map of the **relative stopping power RSP** in the CTP 404 phantom reproduces RSP values of all inserts with accuracy required by clinical specifications.

**Dose comparison of proton vs. X-ray CT scans:**
Using weighted CT Dose Index (CTDI)
**Proton CT (2 M histories): CTDI = 0.61 mGy X-ray eq**
**CBCT: CTDI = 2.53 mGy**

# Taking advantage of nuclear interactions




**Top: proton-nucleus interaction;Bottom:nucleus-nucleus interaction**

Ref.: Aafke Kraan, Frontiers in Oncology, 07 July 2015 doi: 10.3389

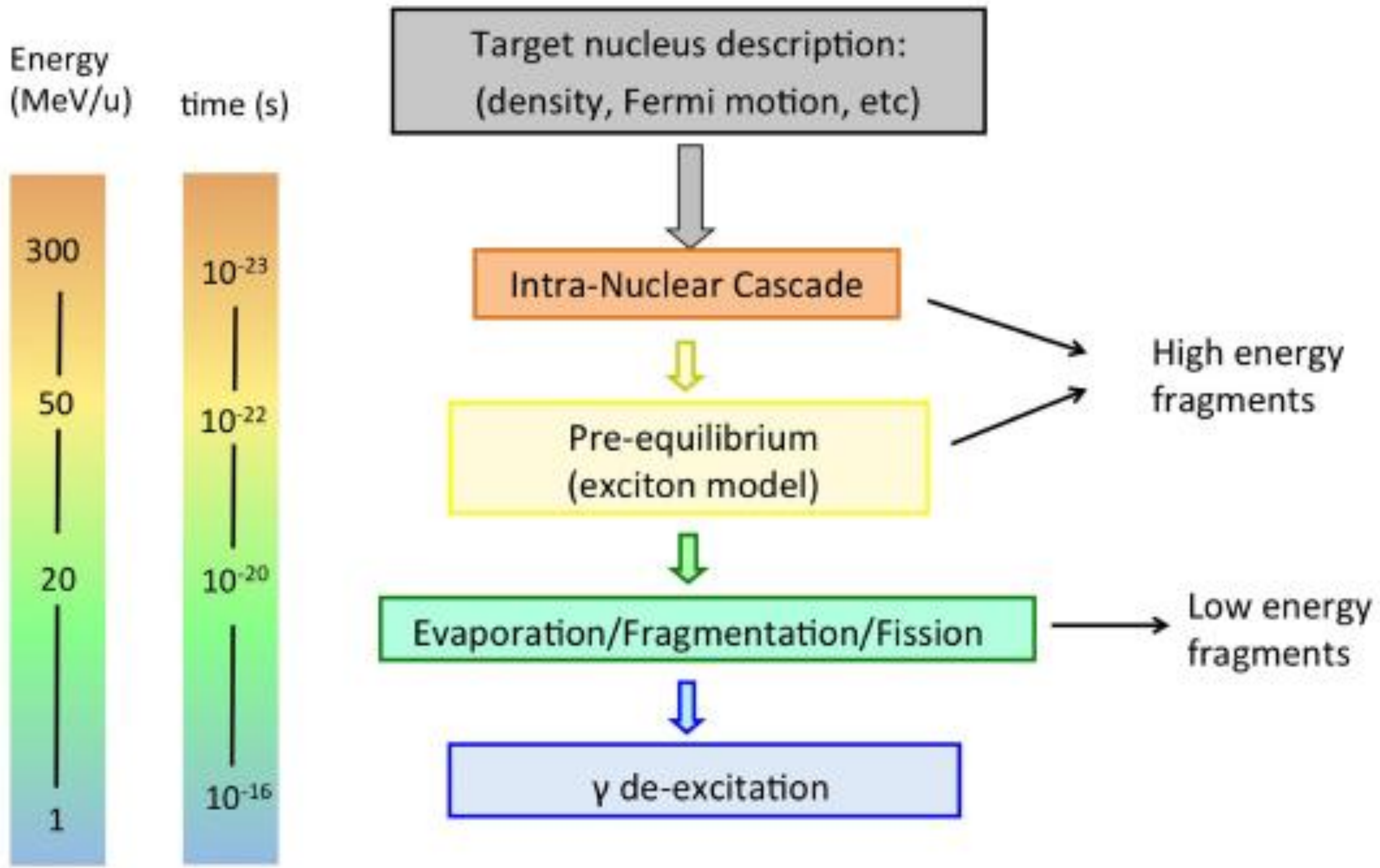
# Modelling

## A “pletora” of Monte Carlo Codes(*)

**FLUKA** - <www.fluka.org>
**GEANT4** – S.Agostinelli et al. NIM-A, 2003,506(6),250-303
**MCNPX/6** -T.Gorley et al. Nucl Techol,2012,180(3),298-315
**PHITS** -T.Sato et al. Nucl Sci.Techol,2013,50(9),913-923
**HIBRAC** - L.Silver et al.,Radiat. Meas, 2009,44(1),38-46
**SHIELD-HIT** – DC Hansen et al.Phys. Med. Biol 2012,57, 2393-409
**VMCpro** – M.Fippel et al. Med. Phys. 2004,31(8),2263-73
**PENELOPE➔PENH** – E.Sterpin et al. Med.Phys. 2013,40.
**... and more**

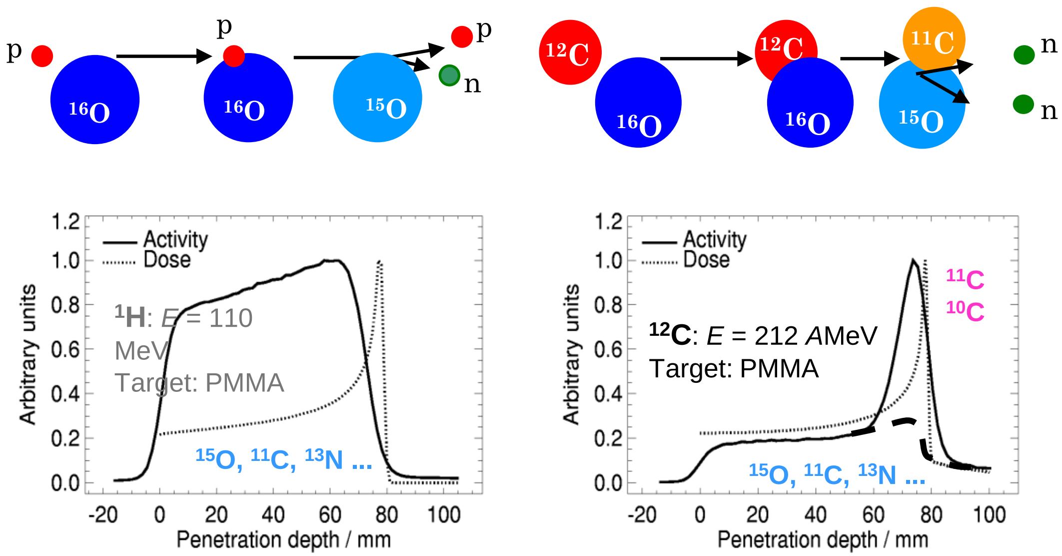
**(*) -** For a thorough discussion see Ref.: Aafke Kraan, “Range verification methods in particle therapy: underlying physics and Monte Carlo modeling “, Frontiers in Oncology, 7 July 2015, open access; doi: 10.3389/fonc.2015.00150

# Display of stages in nucleon-nucleus interaction relevant for radiotherapy




Ref.: Aafke Kraan, Frontiers in Oncology, 7 July 2015 doi: 10.3389

# Positron Emitters and PET imaging




- A possible method for the control of the geometrical accuracy of the treatment (TPS) is PET imaging of the activity generated in the nuclear interactions in tissue

- Small amounts of $\beta^{+}$ emitting radioisotopes are produced with short half-lives
  - $^{11}C$ (20.3 min)
  - $^{13}N$ (9.97 min)
  - $^{15}0$ (2.03 min)

# TERMINOLOGY
# (Both for Protons and Carbon)

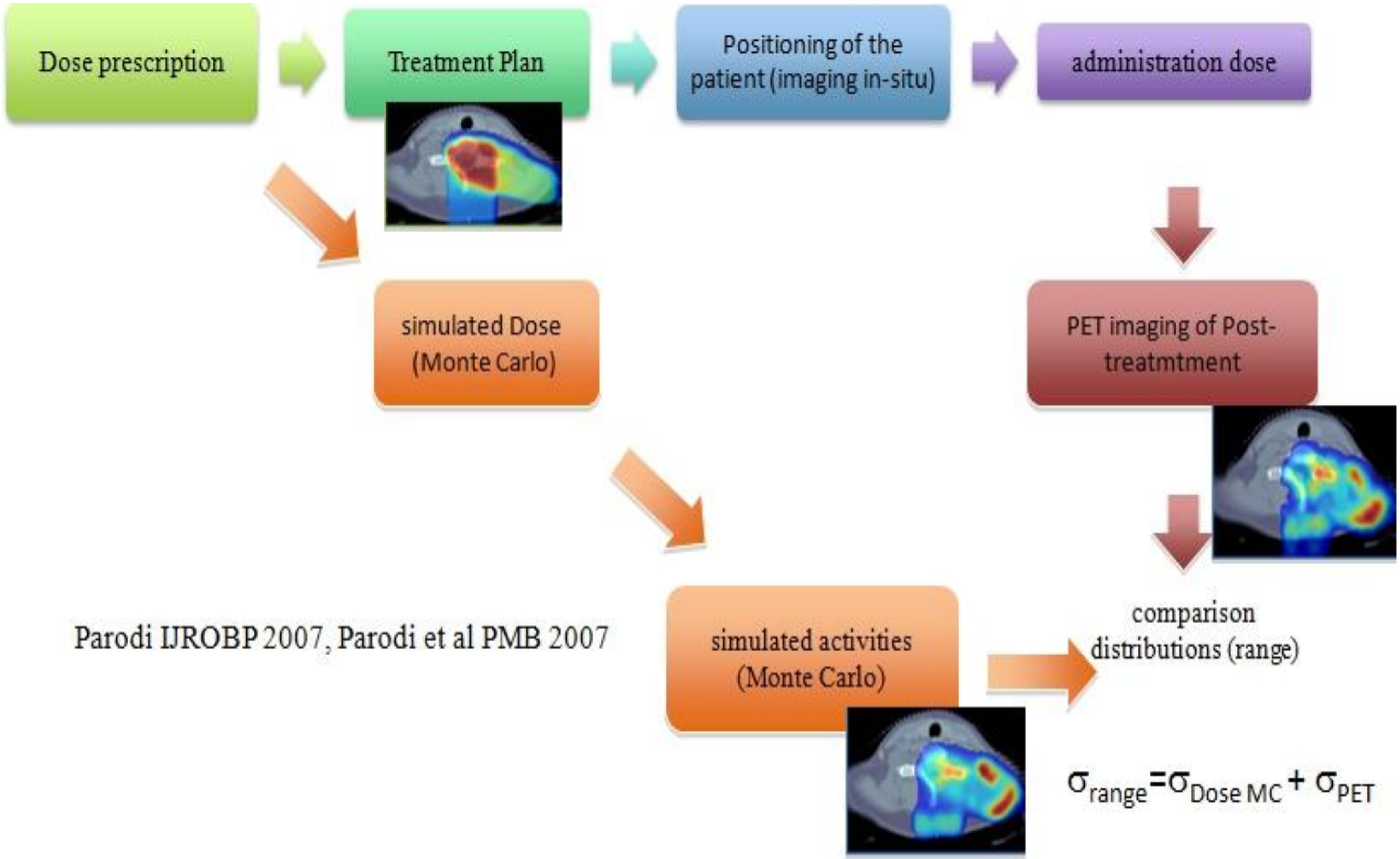
***First pioneer work by W. Enghardt et al. in the '90 with Carbon Ions (GSI/Bastei tomograph)***

- **Off-line PET (e.g.) (MGH/Heidelberg/CHIBA)**

*However ➔In-beam/In-room dedicated instruments are needed to:*
*1- Avoid patient re-positioning*
*2- Avoid data loss of very short living isotopes (e.g. $^{15}O$ )*
*3- Avoid radioisotope wash-out*

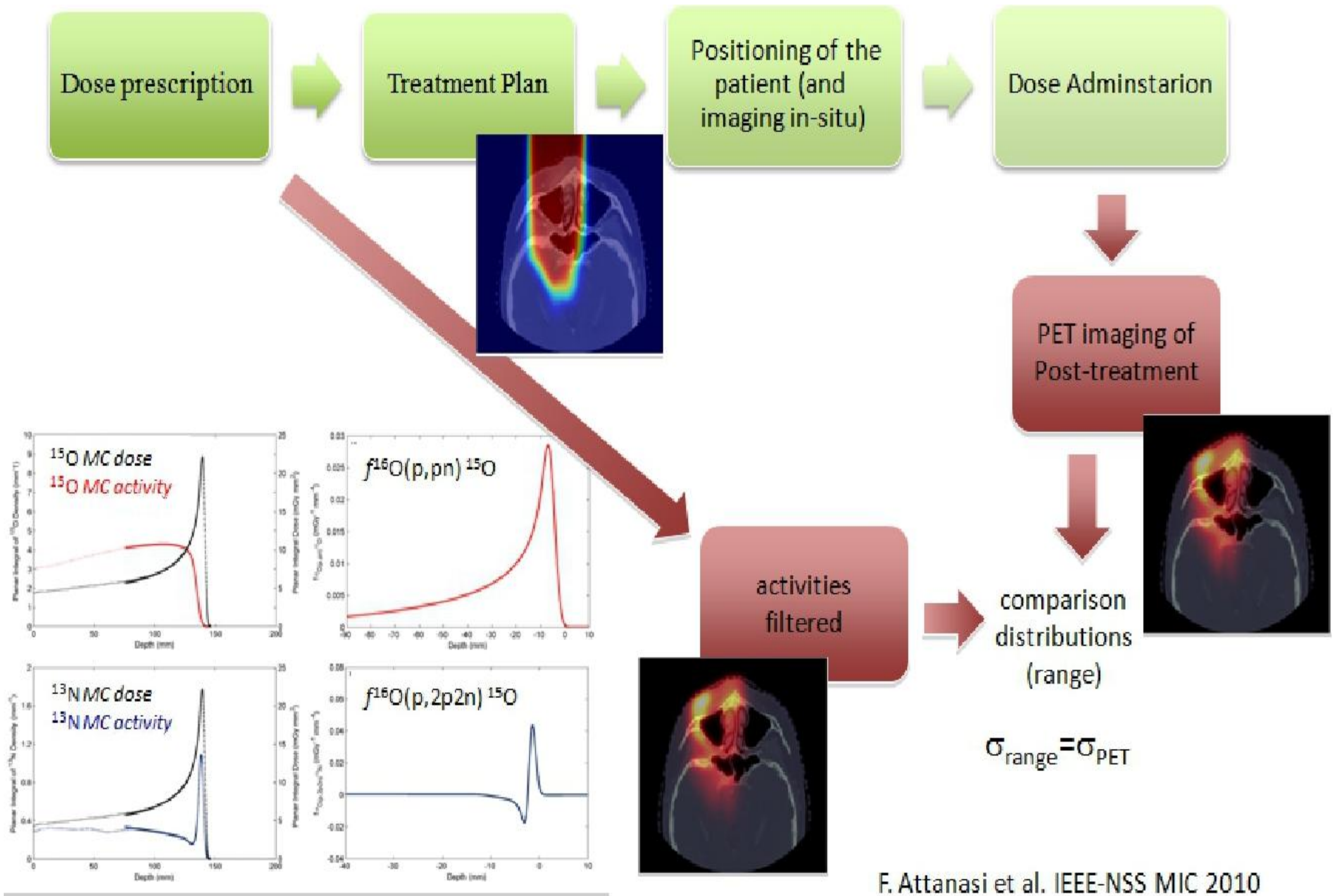
- **On-line PET** (only on phantoms up until now)
  - **➔In Room-PET, but off-Beam**
    **(GSI/PISA-CNAO/CHIBA/MGH/HEIDELBERG)**
  - **➔In Beam-PET, but with beam-on**
    **(PISA-CNAO/CHIBA-openPET)**

# PET monitoring (Dose → Activity: Standard Approach)




- **Comparison between simulated and measured activity with PET**

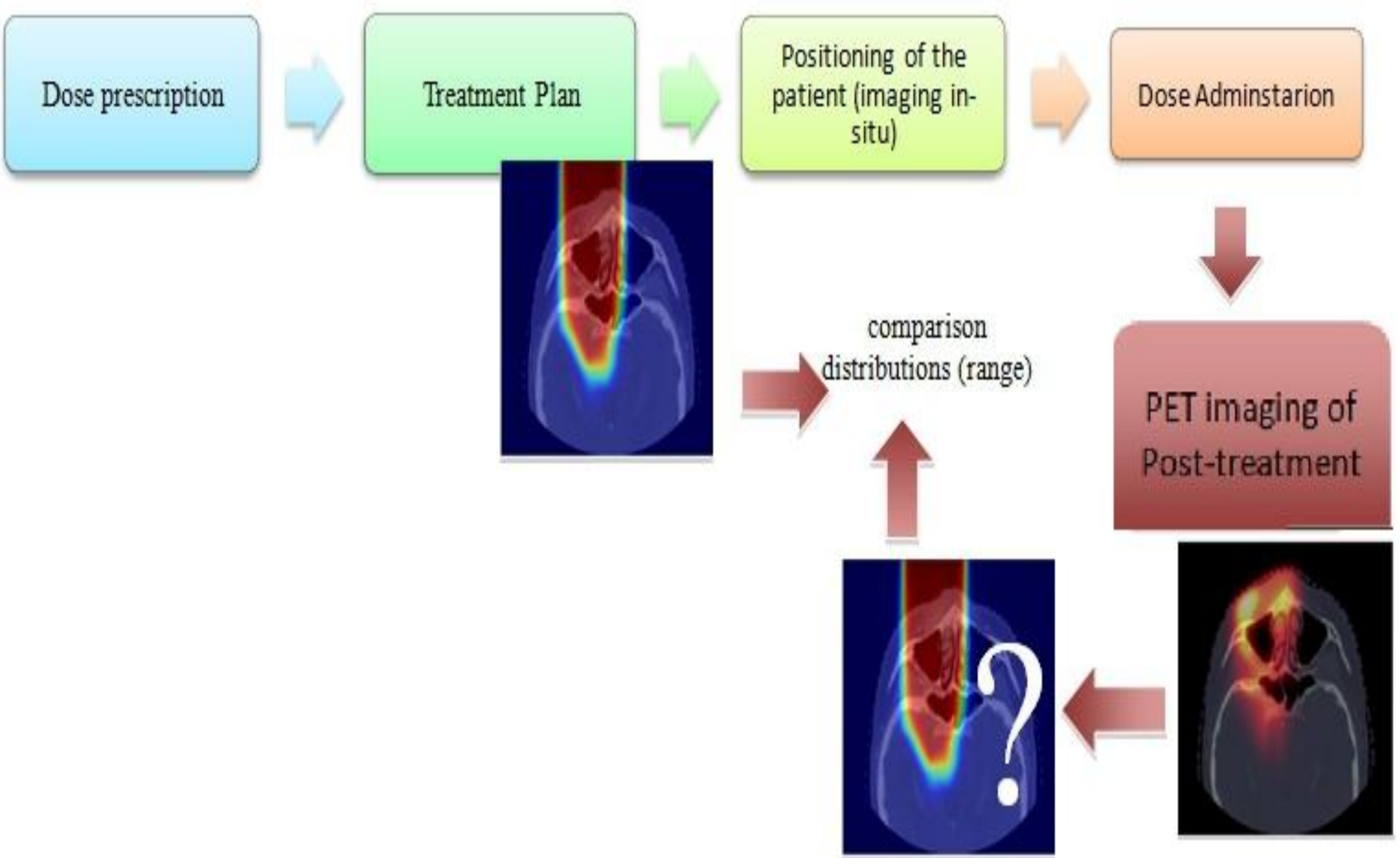
# PET monitoring (Dose → Activity: The "Filtering")




The filter is independent of E!

- **From the planned dose the simulated activity profile is obtained by using the filter approach (ref.:F.Attanasi, et al. Phys. Med. Biol, 2011, 56, 5079-5098).**

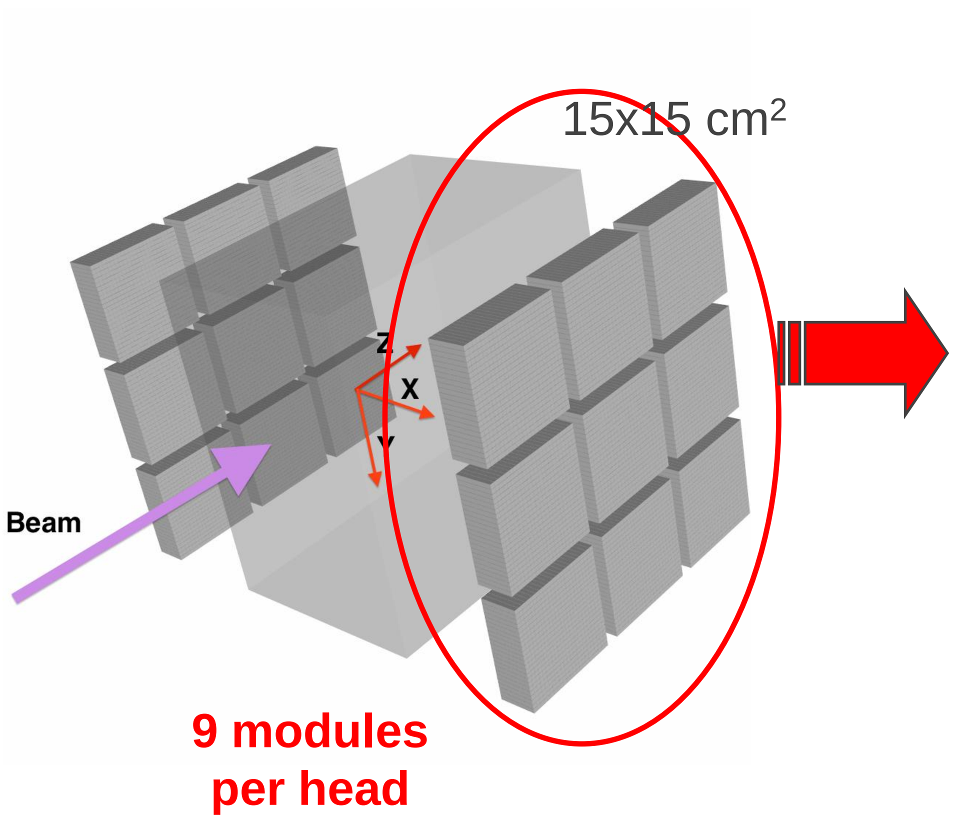
# PET monitoring : The dream

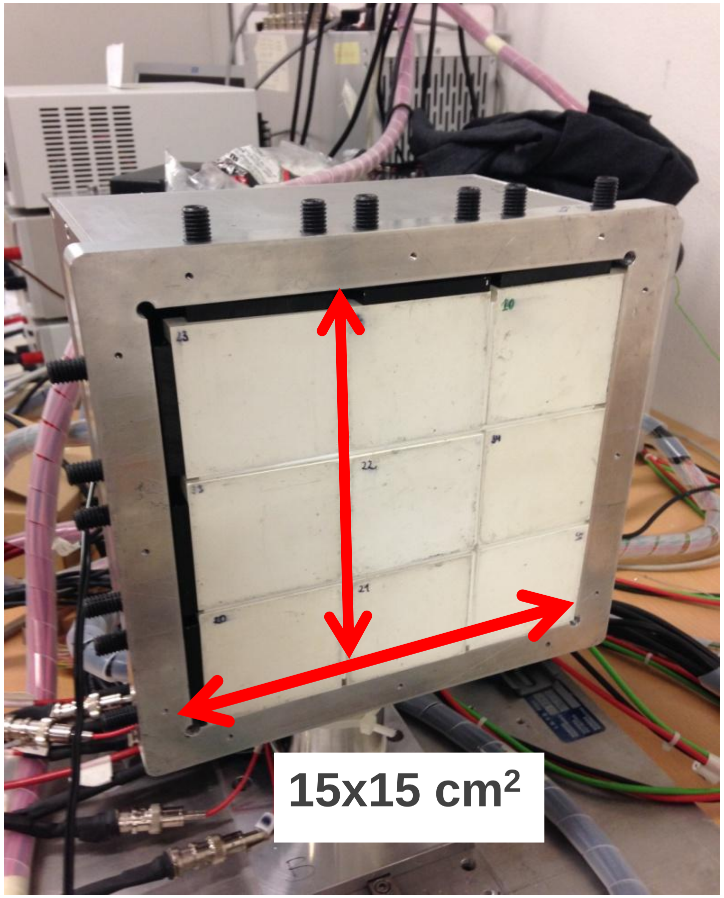



- The delivered dose is measured from the measured activity of PET by using an inverse filtering .The planned dose can then be compared with the measured dose

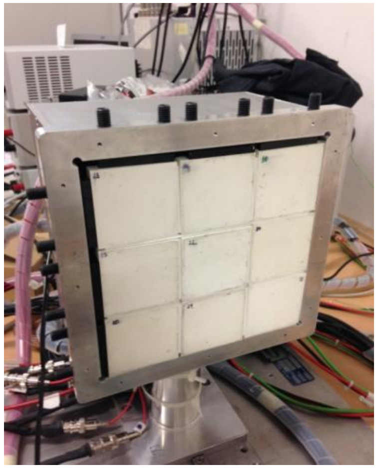
# DoPET(University of PISA & INFN

**DoPET is a stationary 2 heads tomograph**
- **gantry compatibility**
- **in-beam acquisition**



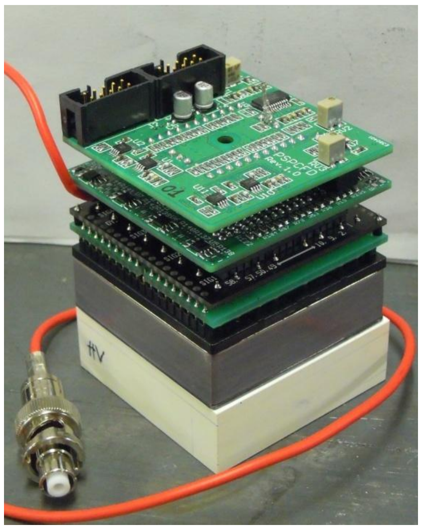



# DoPET (9 vs 9 modules)



***The current prototype is an upgrade of a previous 4x4 system***

**S,Vecchio, IEEE Trans. Nucl. Science, 56 (1), (2009)**
**G.Sportelli, IEEE Trans. Nucl. Science 58 (3) (2011)**



- **Hardware (9x9 modules)**
  *- Each detecting module made of*
  *one LYSO matrix (23 x 23 crystals, 2mm pitch)*
  *one PS-PMT 8500 Hamamatsu*
  *Dedicated front-end electronics*
  *- FPGA based acquisition and coincidence processing*
  *(Coincidence time window ~5 ns).*

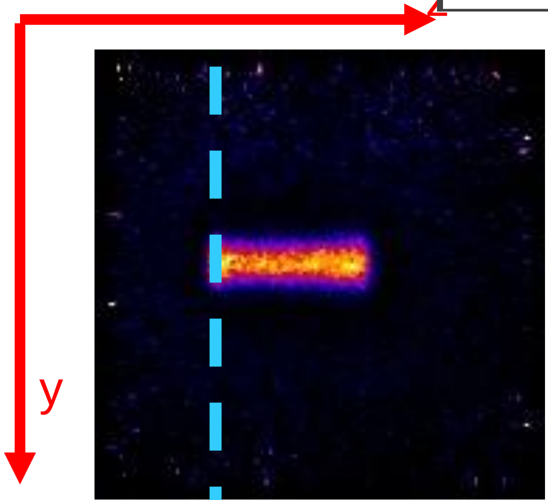
- **Software:** Activity reconstruction algorithm:
  - Maximum Likelihood Estimation Maximization (MLEM)
  - The reconstruction is performed in few minutes➔
  We are working on implementing GPU for bringing down the time to 30s

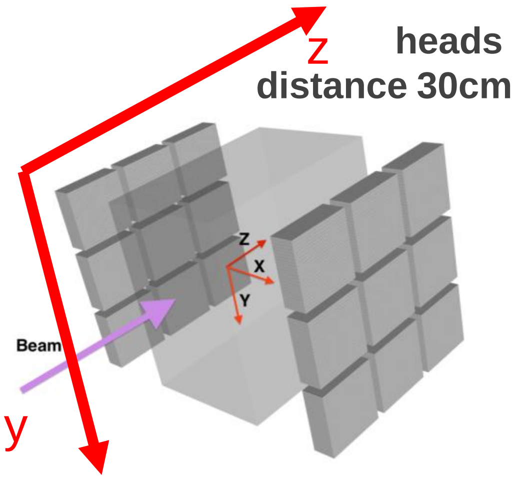
# Protons and Carbon ions onto PMMA phantoms: Imaging of the produced activity

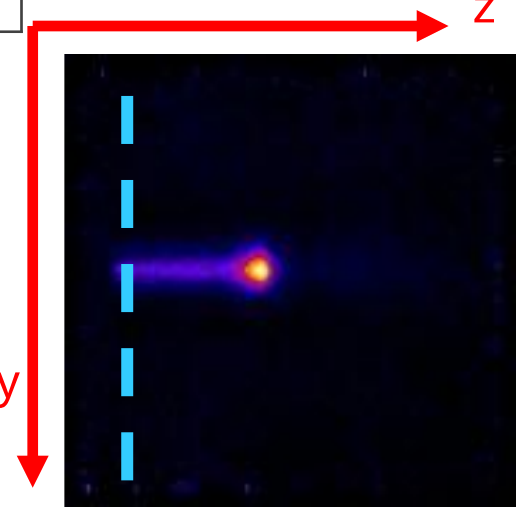
Proton beam
98 MeV

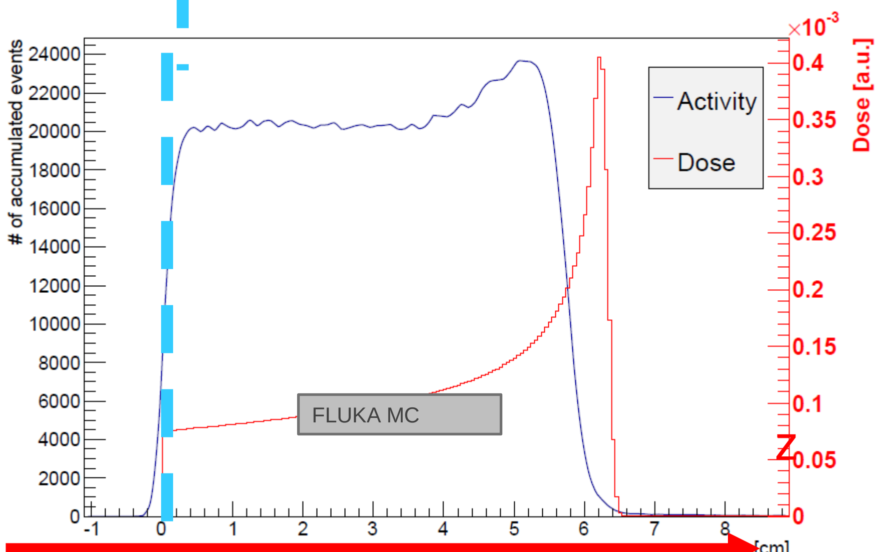
| | ρ(g/cm**3) | H(%) | C (%) | O (%) |
|---|---|---|---|---|
| PMMA | 1.18 | 8 | 60 | 32 |
| H2O | 1.0 | 11.19 | | 88.81 |

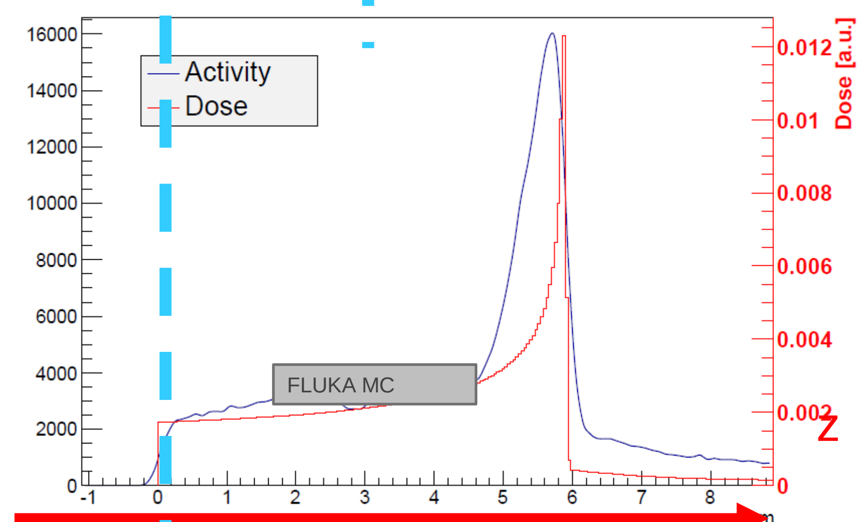
Carbon beam
178 MeV/u



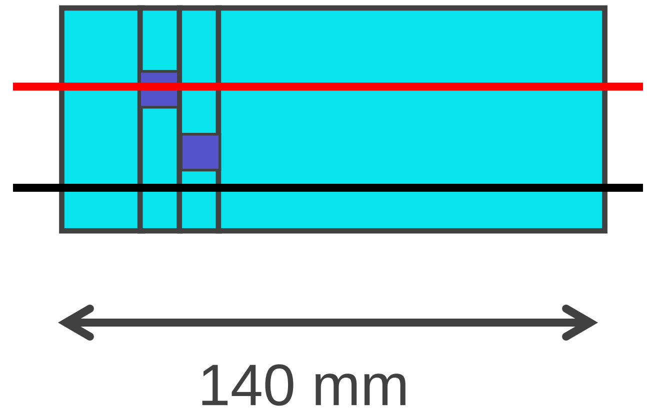



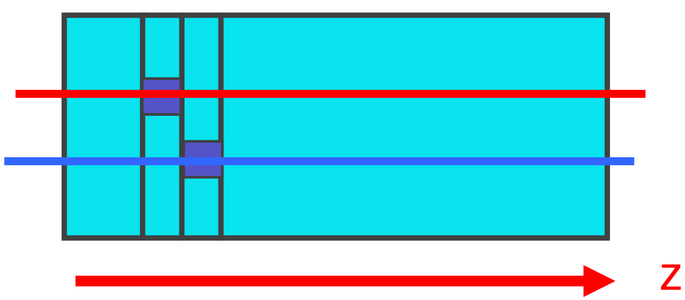



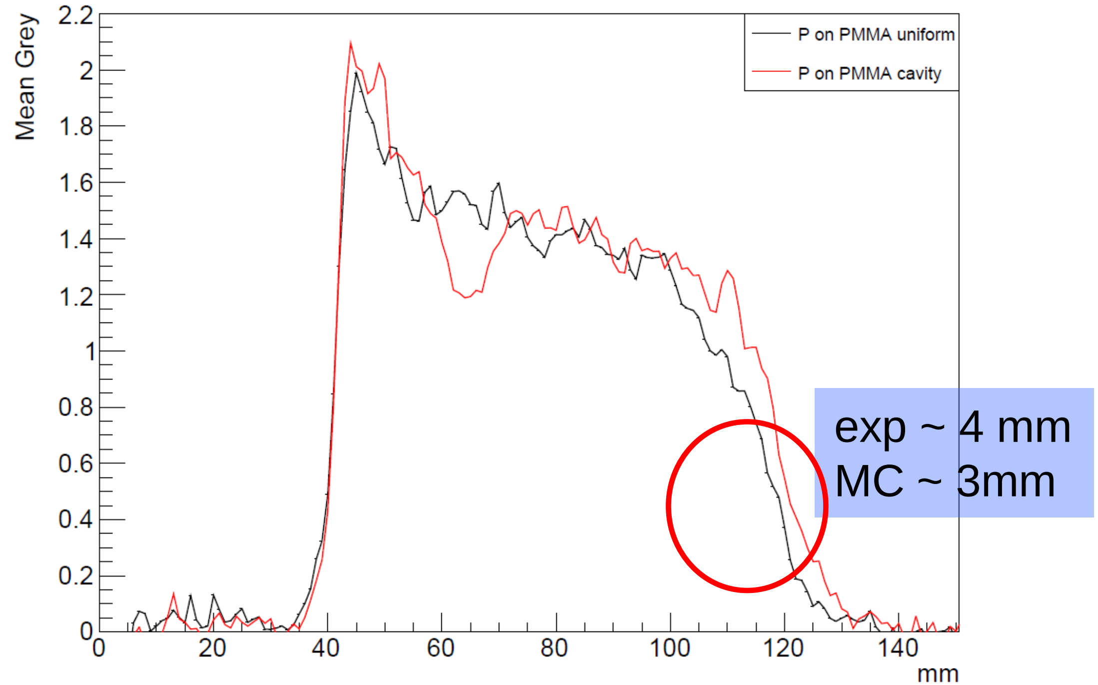
**Protons 2Gy**
(TPS-Single fraction)
Two cavities z-profiles
Acquisition time:0-600 s

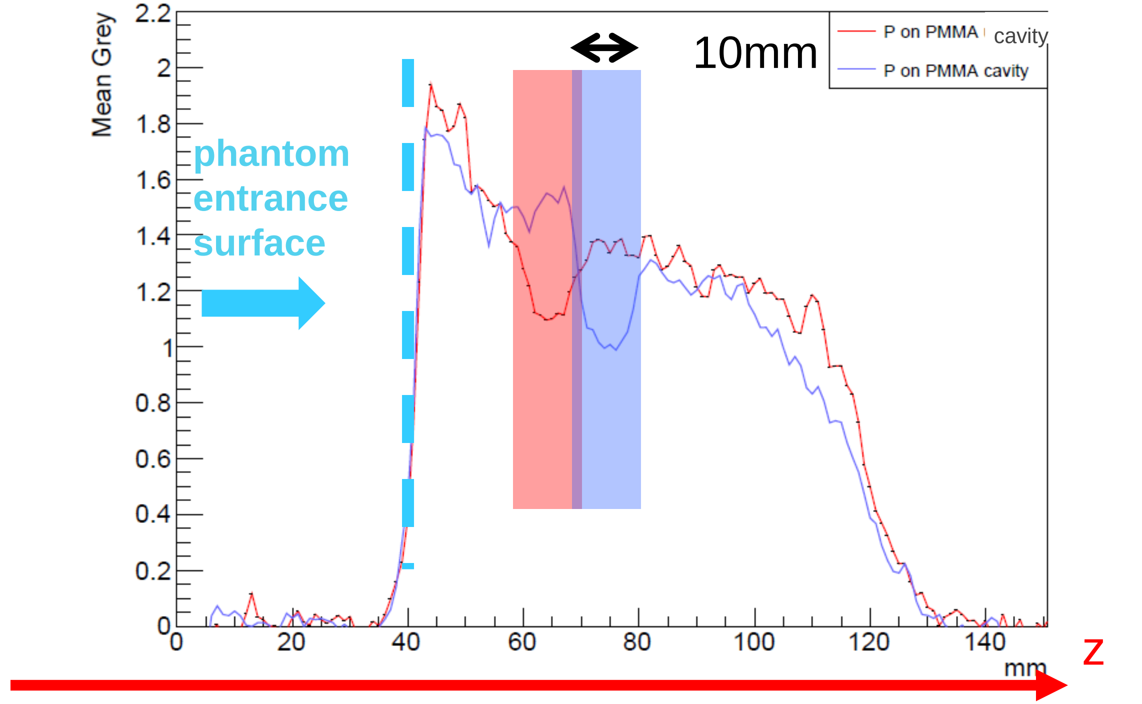
**Difference: full vs. void**




**Reproducibility:  void vs. void**

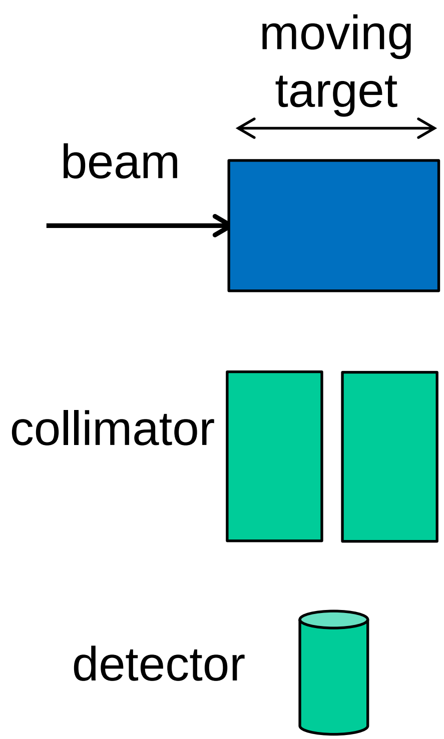


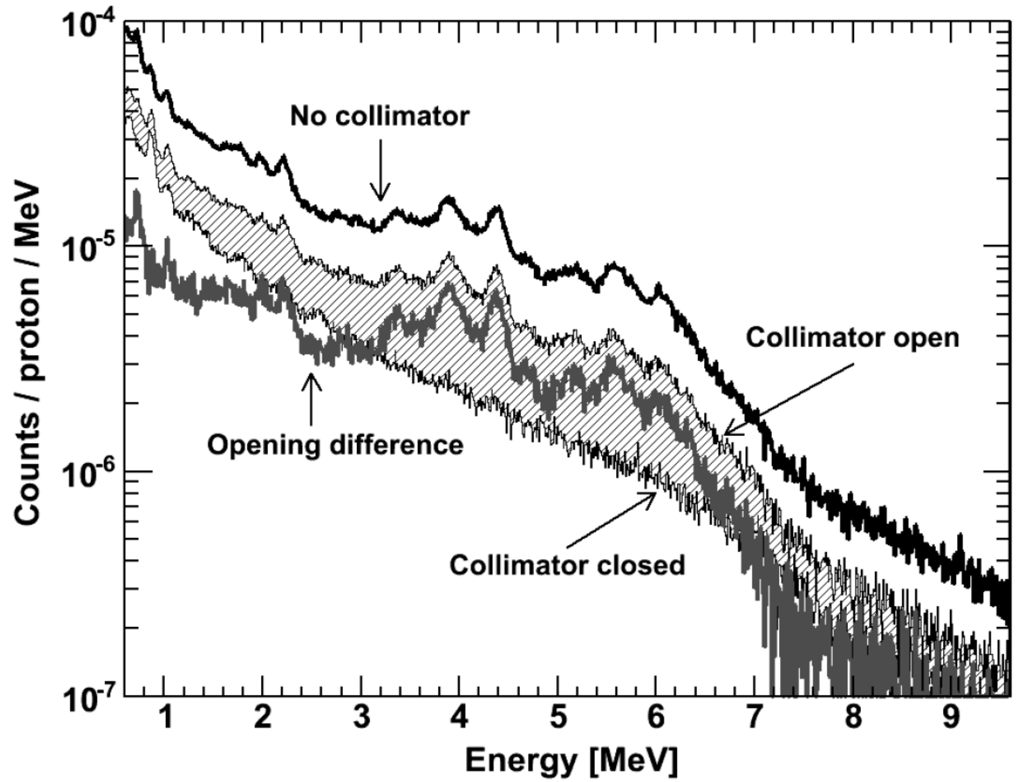



# Prompt gamma's w/protons

## Measurements with collimated detectors




Energy spectrum 160 MeV protons in PMMA, NaI(Tl) detector




*Smeets PMB 2012*

**Energy: <1 MeV to 10 MeV**
**A small fraction is measured as discrete lines**
**Low energy gammas: larger scattered fraction**
**Synchronization with accelerator RF or monitor and Time of Flight**

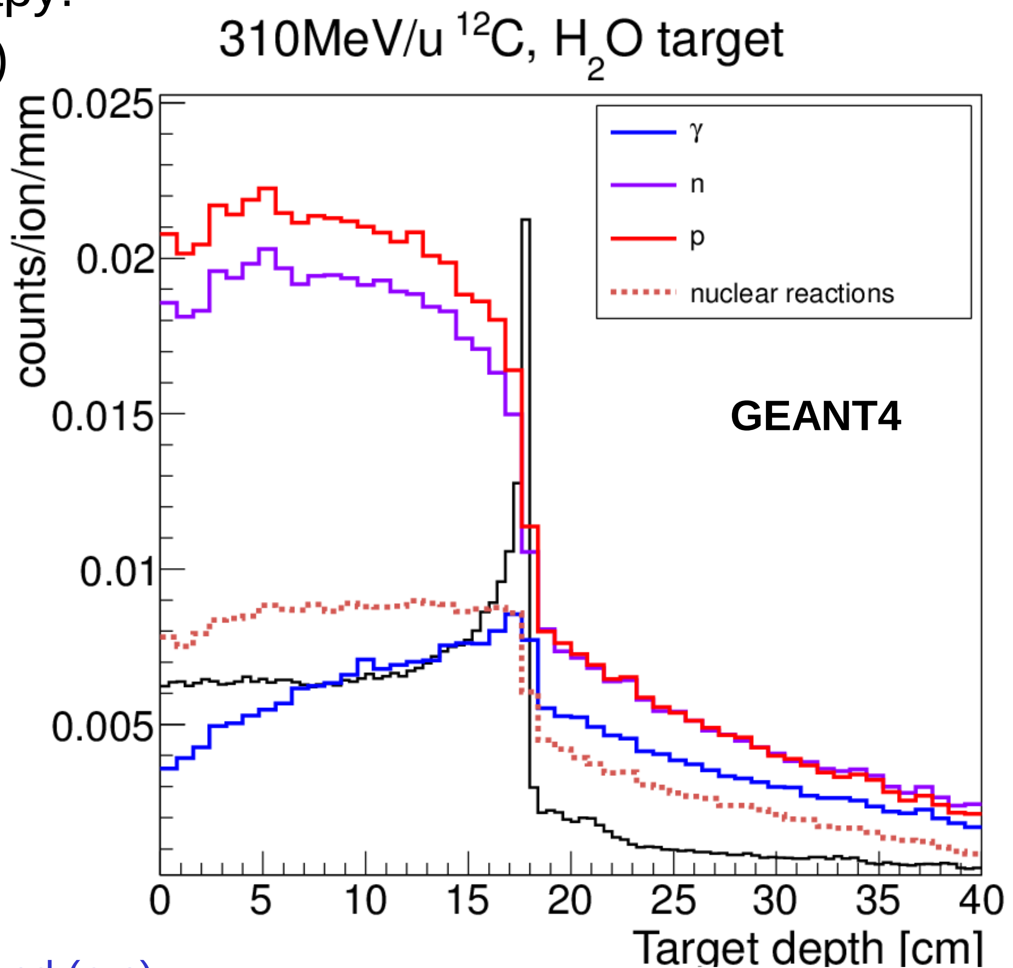
# Nuclear fragmentation w/C-12 Ions

- Dose deposition during radiotherapy:
  - Ionization (in black on the plot)
- Hadrontherapy:
  - Nuclear fragmentation
    - High probability
    - Influence on dose deposition
    - Secondary particles
      - $\gamma$, *n*, *p*, fragments
      - Radioactive Isotopes ($\beta^+$)
  - Range control by means of nuclear reaction products:
    - **Prompt gamma's**

      ≤ 1 per nuclear reaction

      ~ isotropic emission

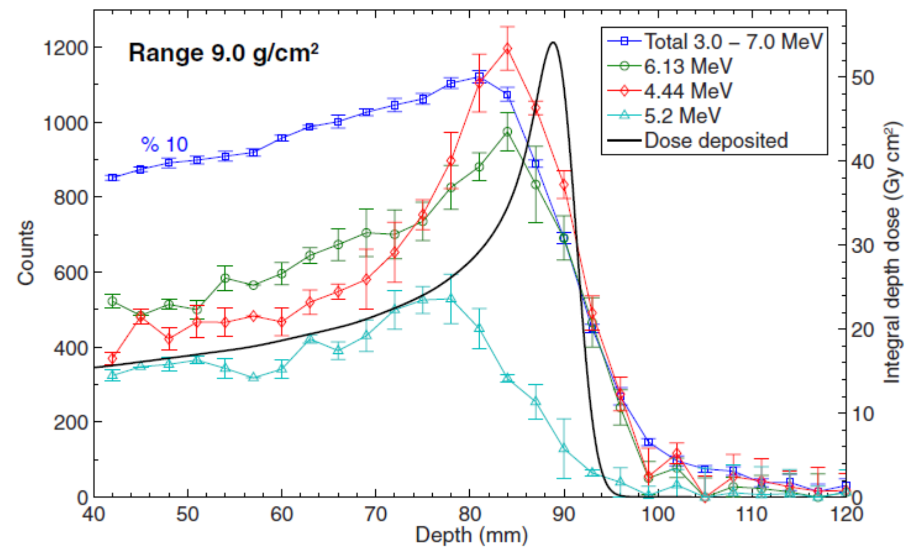
      Massive particle background (p,n)



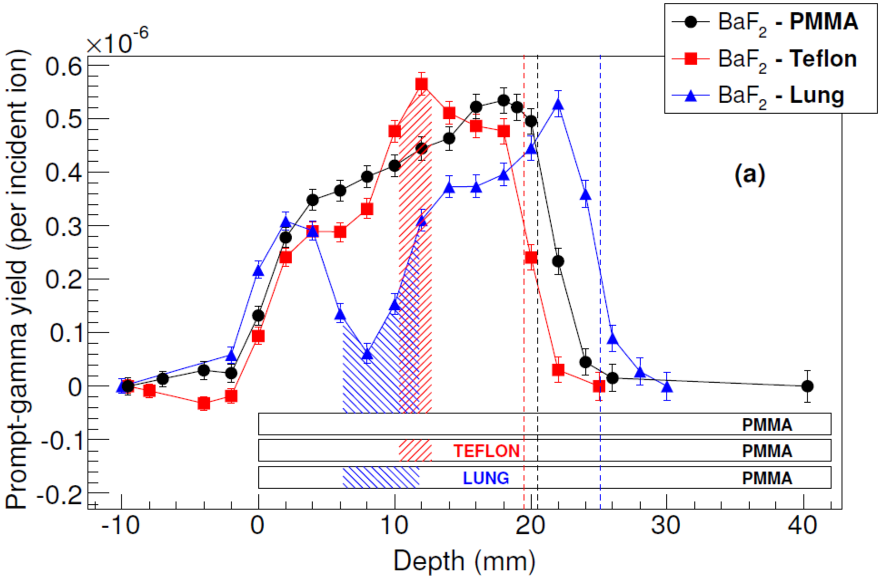
# Prompt gamma's measurements

***110 MeV protons in water***

***95 MeV/u carbon ions in PMMA***




*J.Verburg, PMB 2013*




*M. Pinto et al, Med Phys 2015*

PG yield above 1 MeV

~ 0.3% /cm per proton

~ 2% /cm per carbon

High resolution profiles: influence of heterogeneities close to the Bragg peak

# Detectors for Prompt gamma's

## Collimated cameras

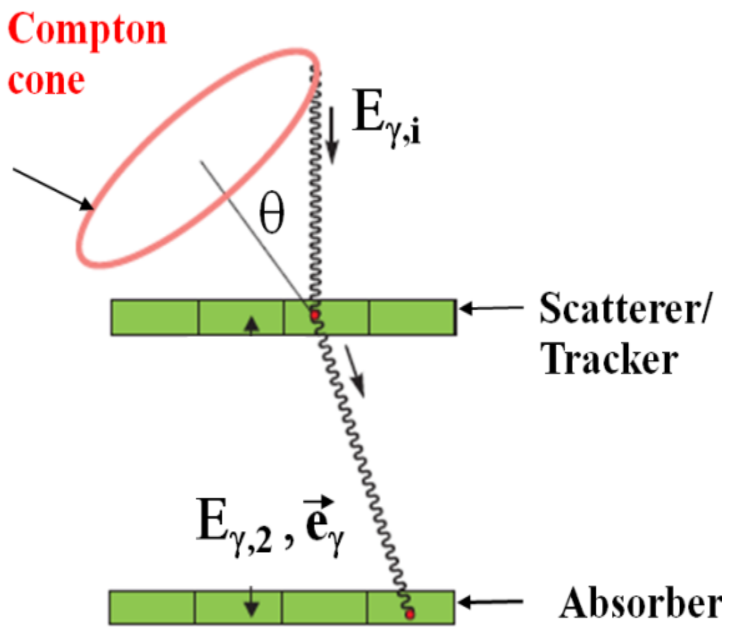
- Multi-slit cameras
  - **Seoul**
  - **Lyon** ~1mm at pencil beam scale ($10^8$ protons)
  - **Delft** - Multislit with TOF (project)
  - **MGH**: TOPAS Simulation of collimated camera for passive delivery: Synchronization with range modulator wheel *(M. Testa, PMB 2014, J. Verburg, PMB 2015)*
- Knife edge
  - **Seoul** *(D. Kim, JKPS 2009)*
  - **Delft** : Simulation *(Bom, PMB 2012, Cambraia Lopes, PMB 2015)*
  - **IBA** : Operational prototype *(Perali, PMB 2014, Preignitz, PMB 2015)*

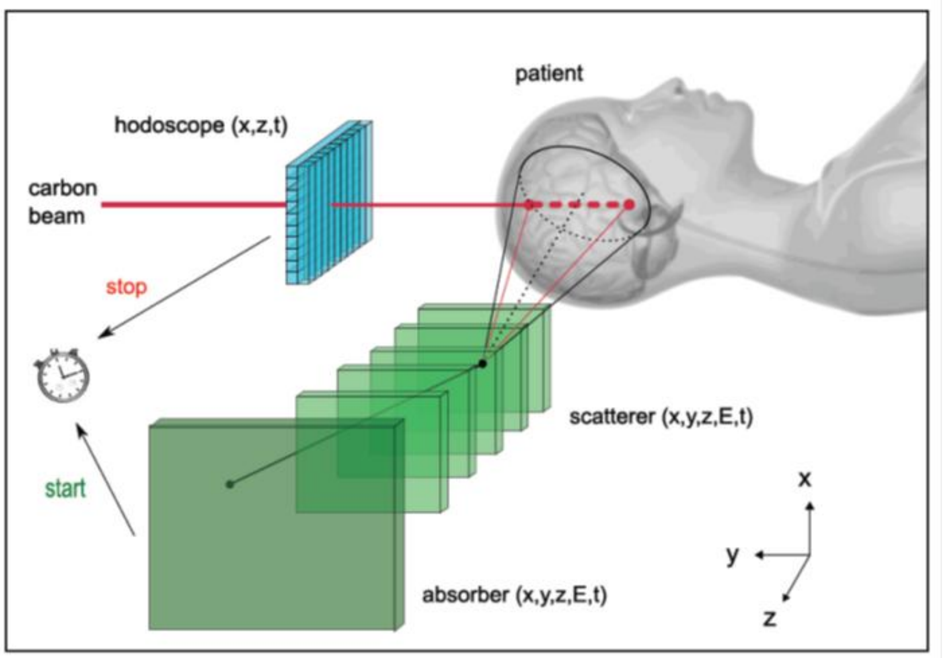
## Compton cameras

- No collimation: potentially higher efficiency
- Potentially better spatial resolution (< 1cm PSF)
- If beam position known → simplified reconstruction
- 3D-potential imaging (several cameras)

# Compton camera

## Lyon project: TOF and beam position with hodoscope




**Count rate issue**

Simulation: line-cone reconstruction for Lyon prototype

1 distal spot ($10^8$ incident protons) incident on PMMA target, 160 MeV

Continuous beam (IBA C230)

**Clinical intensity: 200 protons/bunch ➔S/N=1/10**

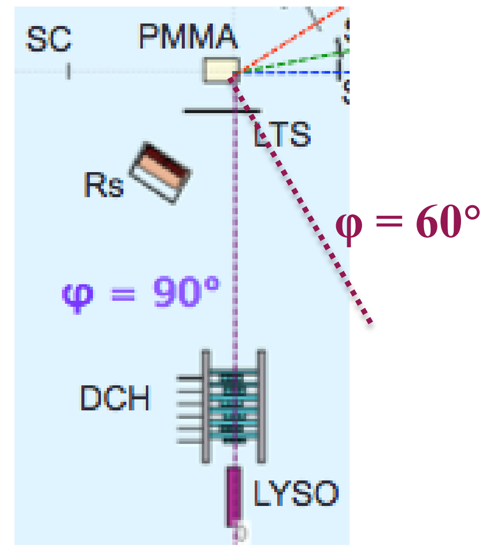
**Reduced intensity: 1 proton/bunch ➔S/N=5/1**

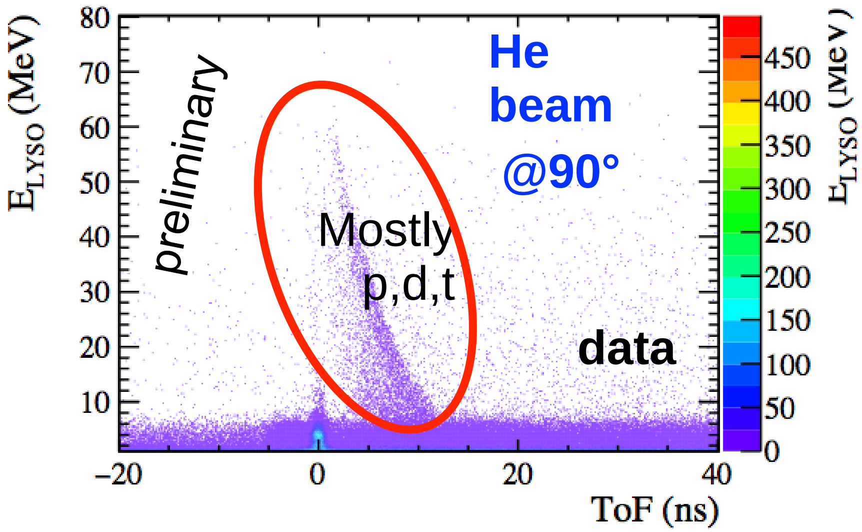
(J.Krimmer, NIMA 2015)

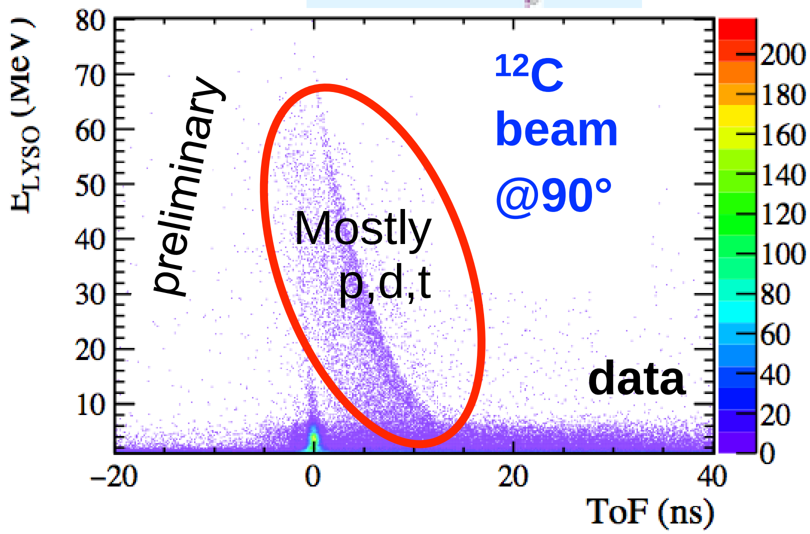
# Prompt protons
# Charged fragments - large angles

- Tracks reconstructed by the Dose CHarged particle profile (DCH)
  - ➡ Detector alignment done with aluminum table fixed positions (± 1mm)
  - ➡ DCH center aligned with fixed BP positions ($x_{PMMA}$ = 0, ~1.5 cm before exit window)
  - ➡ $\Omega \sim 6 \cdot 10^{-5}$ sr, $\varepsilon_{det} > 90\%$
  - ➡ DCH trk resolution @ emission point **~ 1mm**

beam direction



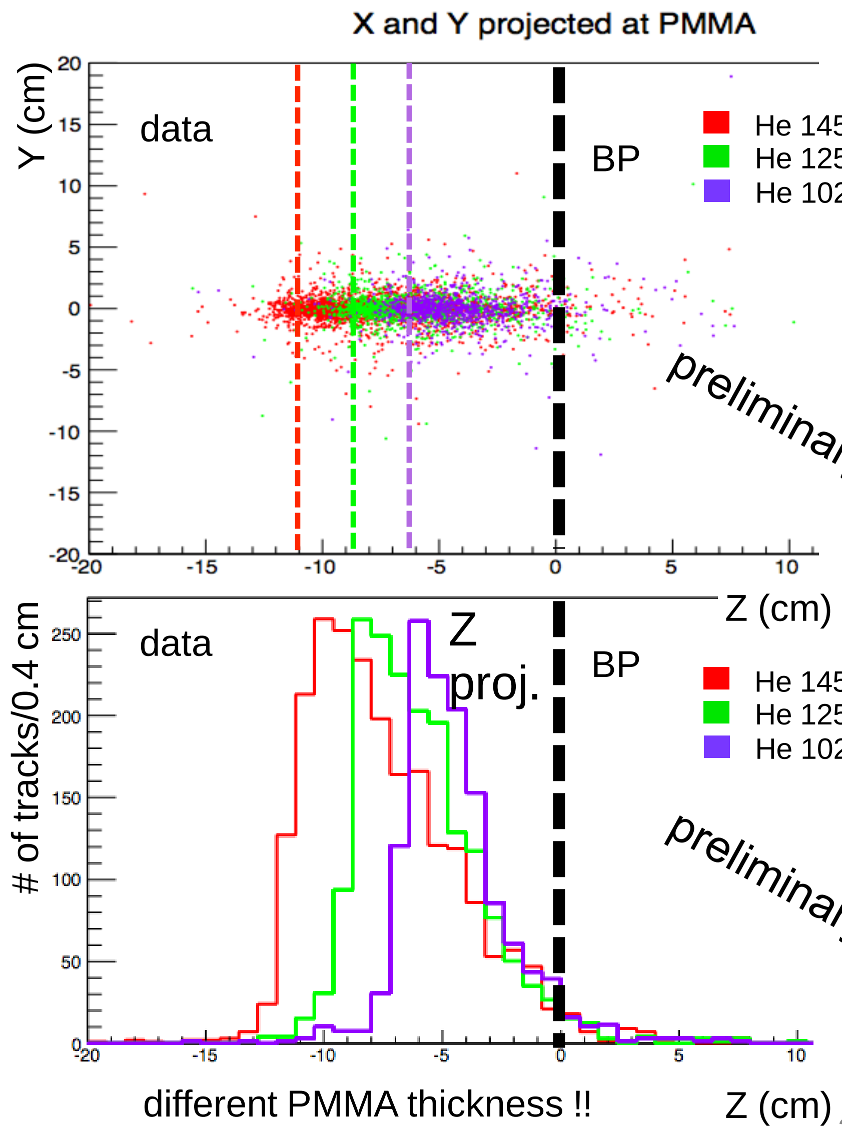

**(Courtesy of V.Patera, 2015)**

# Bragg Peak monitoring on He beams

- A non negligible production of charged particles at large angles is observed for all beam types
- The emission shape is correlated to the beam entrance window and BP position as already measured with $^{12}C$
- $\varphi = dN_{all}/(N_{ions}\, d\Omega)$

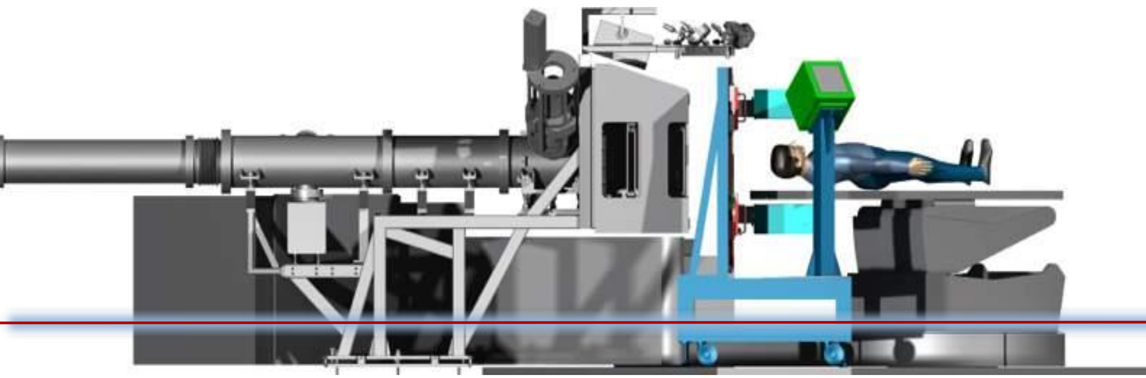
| Beam type/E | φ 90° ($10^{-3}$) |
|---|---|
| He 102 | 0.6 |
| He 125 | 0.7 |
| He 145 | 1 |
| C 160 | 1 |
| C 180 | 2 |
| C 220 | 3 |
| O 210 | 3 |
| O 260 | 5 |
| O 300 | 10 |

preliminary




different PMMA thickness !!

(Courtesy of V.Patera, 2015)



# INnovative Solutions for In-beam DosimEtry in Hadrontherapy

Pisa,Torino,Roma"La Sapienza",Bari,INFN

## INSIDE coordinator: M. G. Bisogni (Pisa)

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partners: CNAO

# The InSide Project

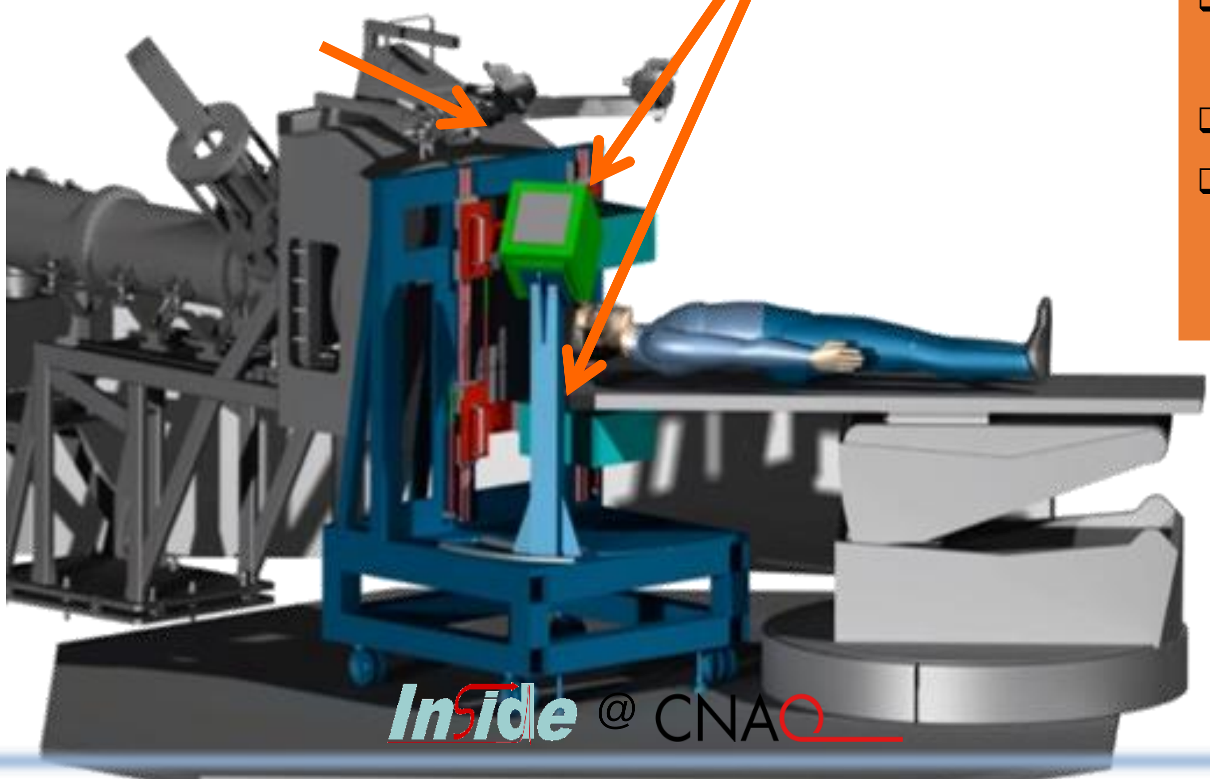
**Prompt secondary particles emission**
**DOSE PROFILER**

**Tracker + Calorimeter =**

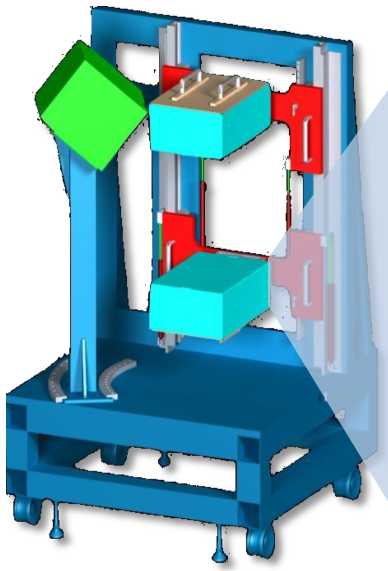
**$\beta^+$ activity distribution**
**IN-BEAM PET HEADS**

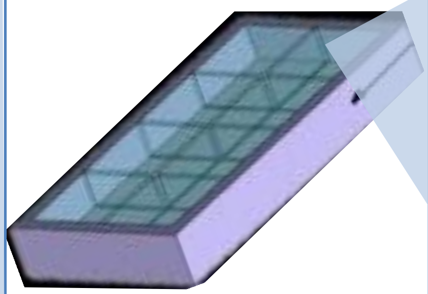
**BI-MODAL MONITORING SYSTEM**

Goals:
- To be integrated in the gantry
- To be operated in-beam
- **To provide an IMMEDIATE feedback on the particle range**

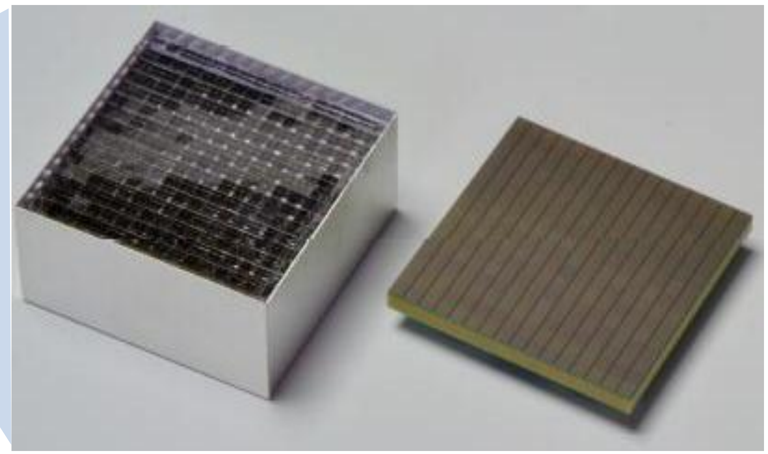


# In-beam PET heads



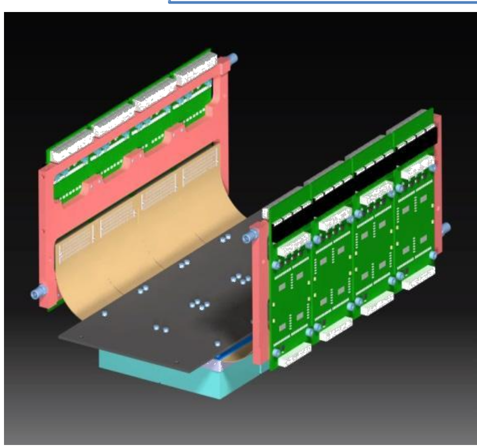


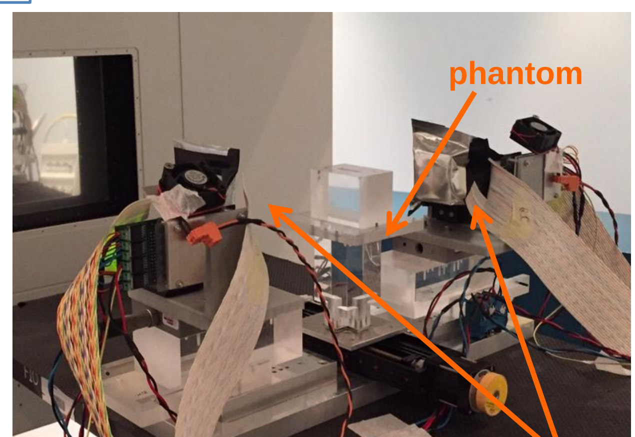
10x 20 x 5 cm$^3$
Distance from the isocenter=25 cm



256 LFS pixel crystals (3x3x20mm$^3$) coupled one to one to MPPCs (Multi Pixel Photon Counters, SiPMs).

Solid model Of the PET head

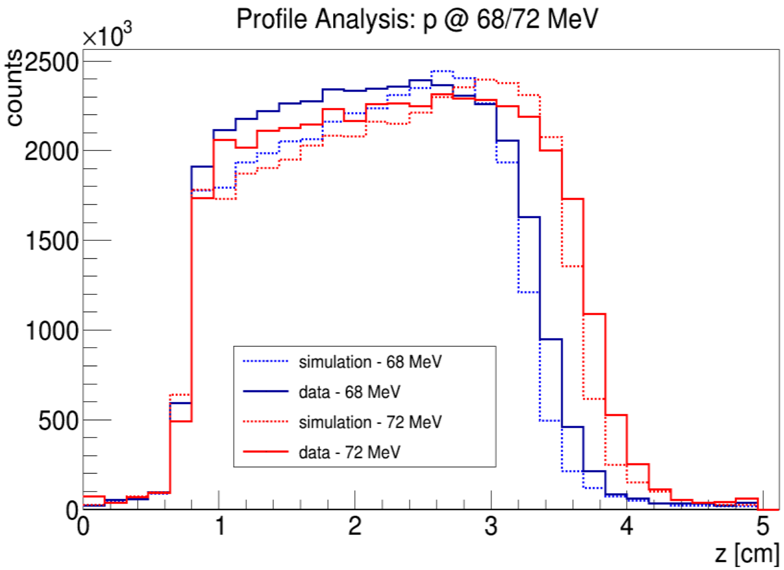




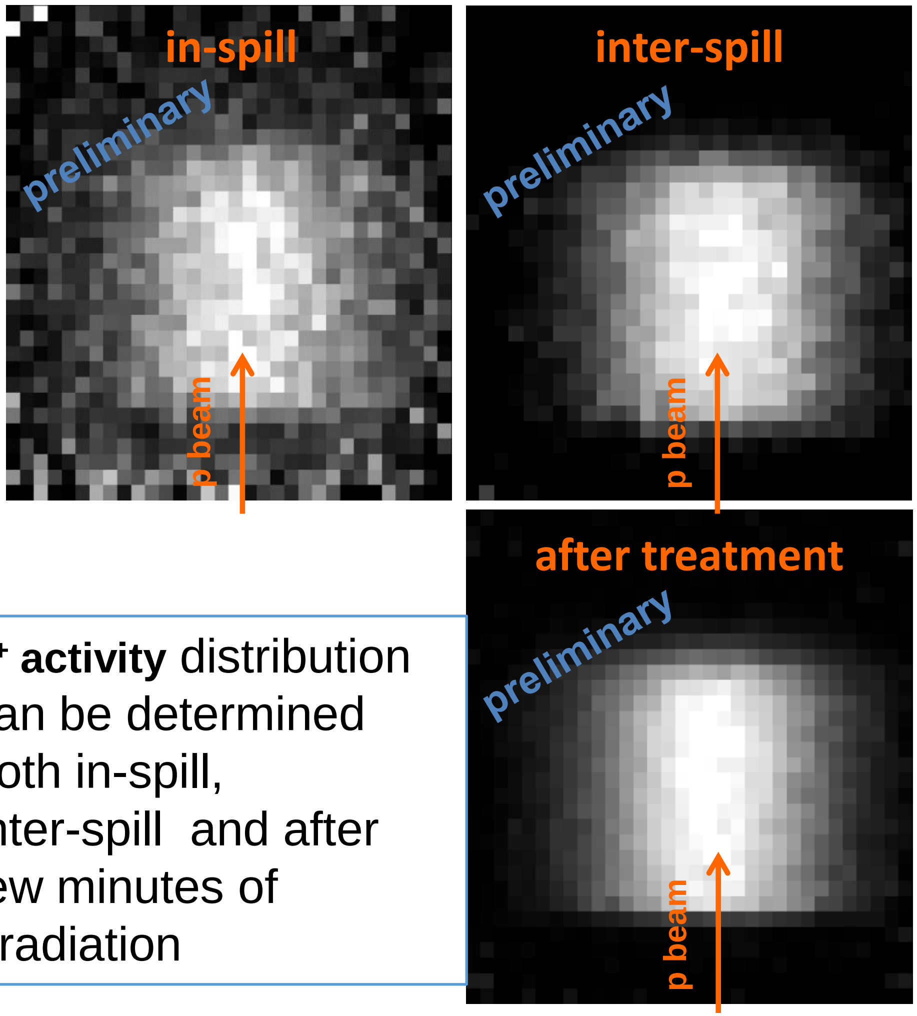

Demonstrator
1 vs 1 module
Tested at CNAO
On May 5 2015

Work partly supportedd by the European Union EndoTOFPET-US project and by a Marie Curie Early Initial Training Network Fellowship of the European Union 7th Framework Program (PITN-GA-2011-289355-PicoSEC-MCNet).

# Mono-energetic proton beams CNAO




PET reconstructed activity

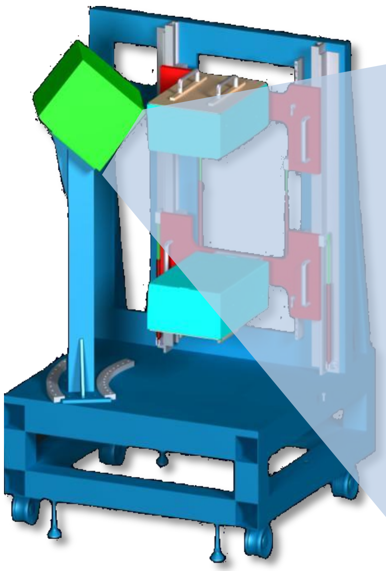


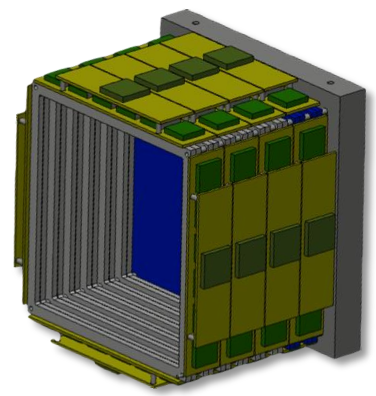

The MC simulation is a reliable tool to evaluate the performance of the full in-beam PET system.

$\beta^+$ **activity** distribution can be determined both in-spill, Inter-spill and after few minutes of Irradiation

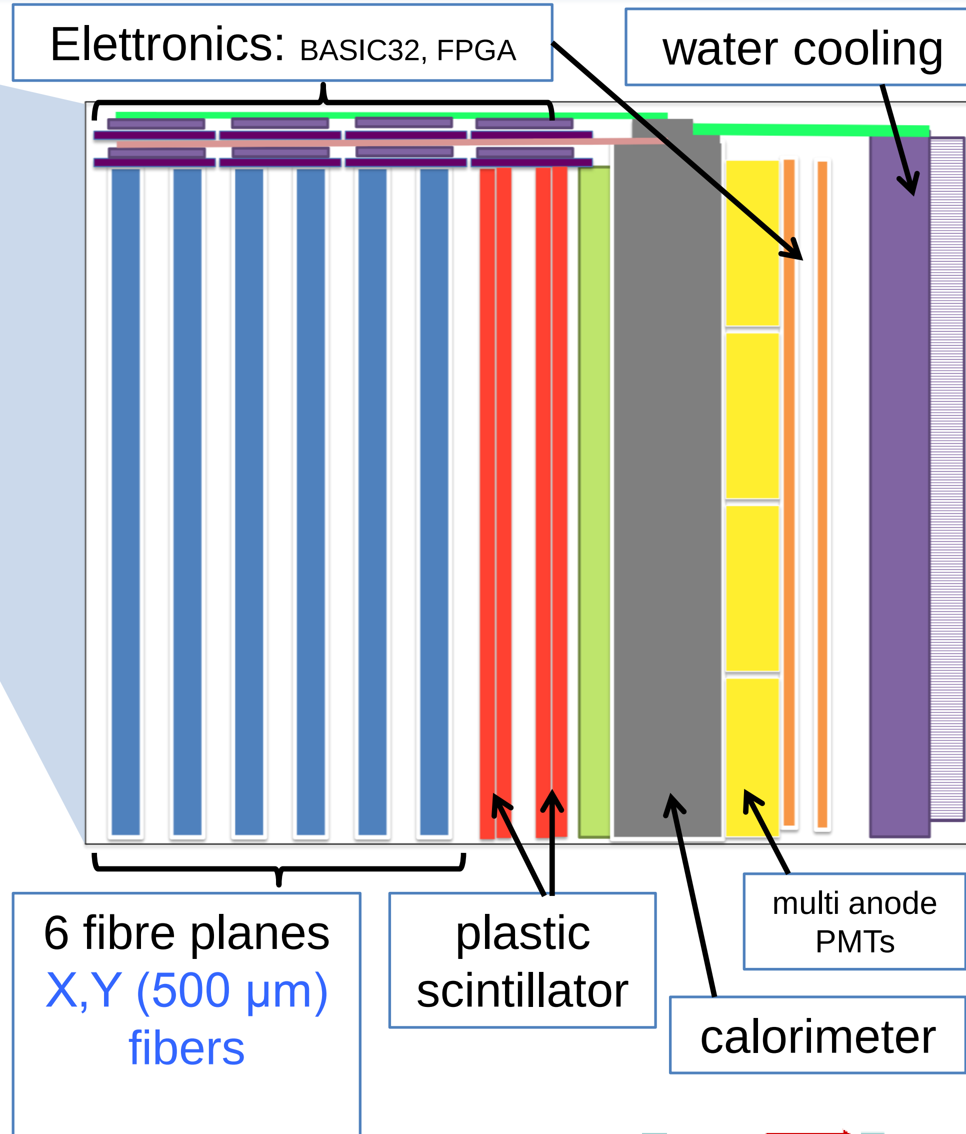
InSide

# Dose Profiler

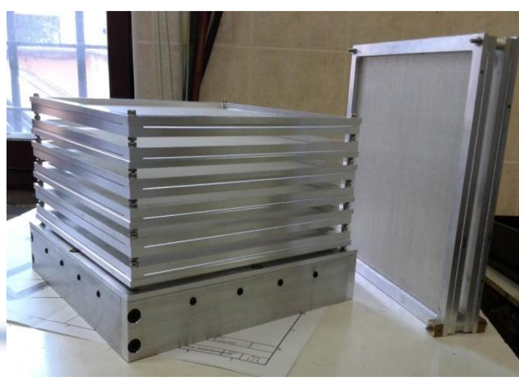




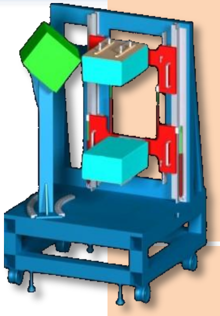
28 x 28 x 35 $cm^3$




- 6 planes of orthogonal squared scintillating fibers coupled to SiPMs
- an electromagnetic calorimeter coupled to Position Sensitive PMTs.



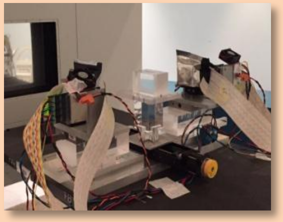
# INSIDE: a combined system x protons and x Ions



- ❑ $\beta^+$ activity detection: **IN-BEAM PET HEADS**
- ❑ secondary particle tracking: **DOSE PROFILER**

to provide 3D real-time monitoring in hadrontherapy

**MC simulation** is essential for system design, development and operation
**In-beam PET**: two-steps technique reduces the simulation time (70x), **validated on real data**
**Dose Profiler**: secondary particle signal quantification with $^{12}$C beam



In-beam PET first modules (tested at CNAO, May 2015):

- ❑ very satisfactory results
- ❑ both in-spill and inter-spill and off beam. PET imaes
- ❑ adequate coincidence time resolution

**The commissioning of the INSIDE system at CNAO is planned by early 2016.**

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**Denis Dauvergne (in2p3, France )**
**Vincenzo Patera (University of Roma "La Sapienza")**
**... and more**

**... and the members of the Fiig Group (Pisa University), and in particular:**
**Valeria Rosso**
**Maria Giuseppina Bisogni**

# THANK YOU!