Application to society: Imaging in particle therapy

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National Institute of Nuclear Physics, Section of Pisa, Italy

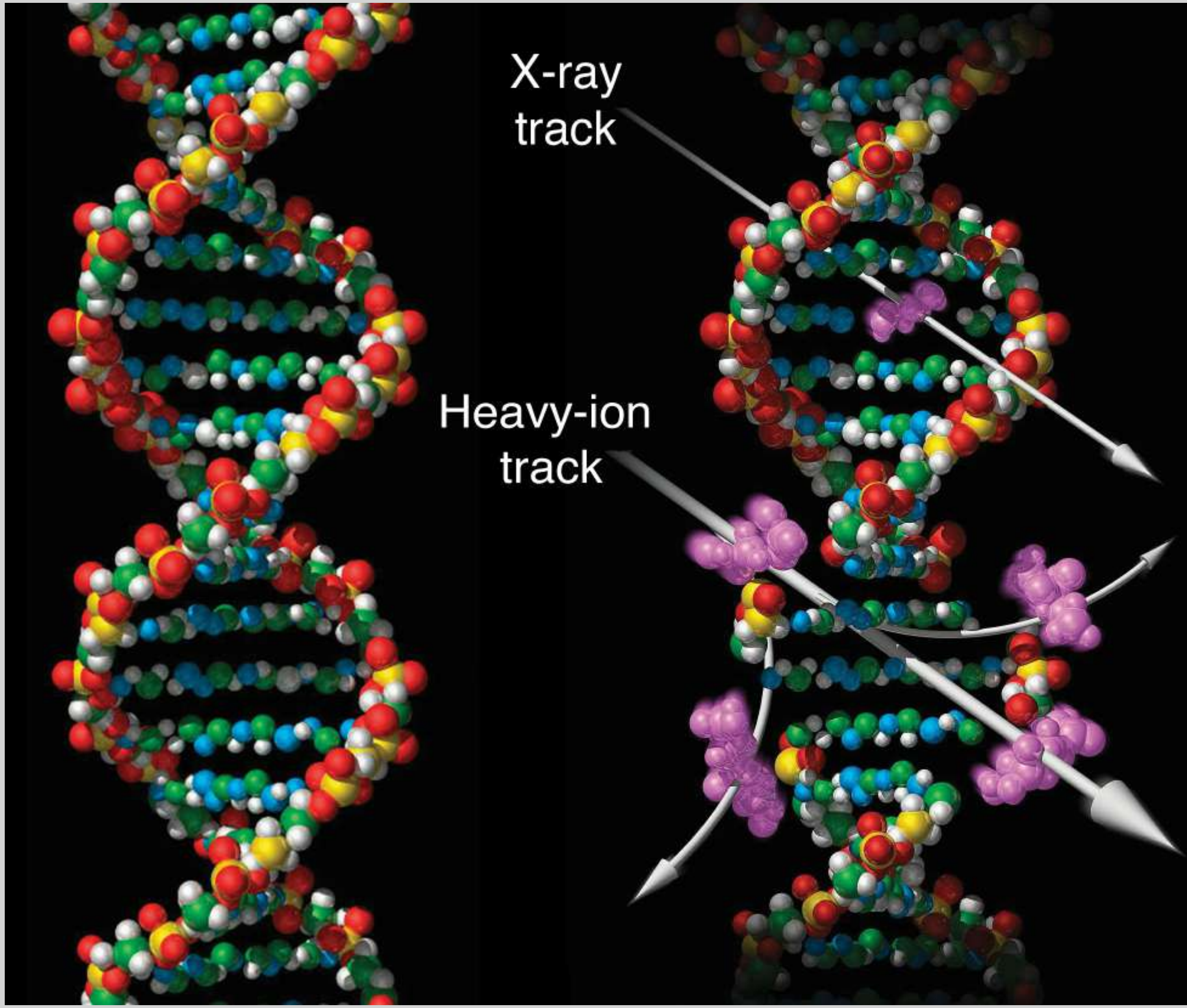
Outline

- Introduction to particle therapy
- Imaging in particle therapy
- Imaging methods taking advantage of nuclear interactions
- Proton radiography and proton tomography
- Conclusions

Particle therapy

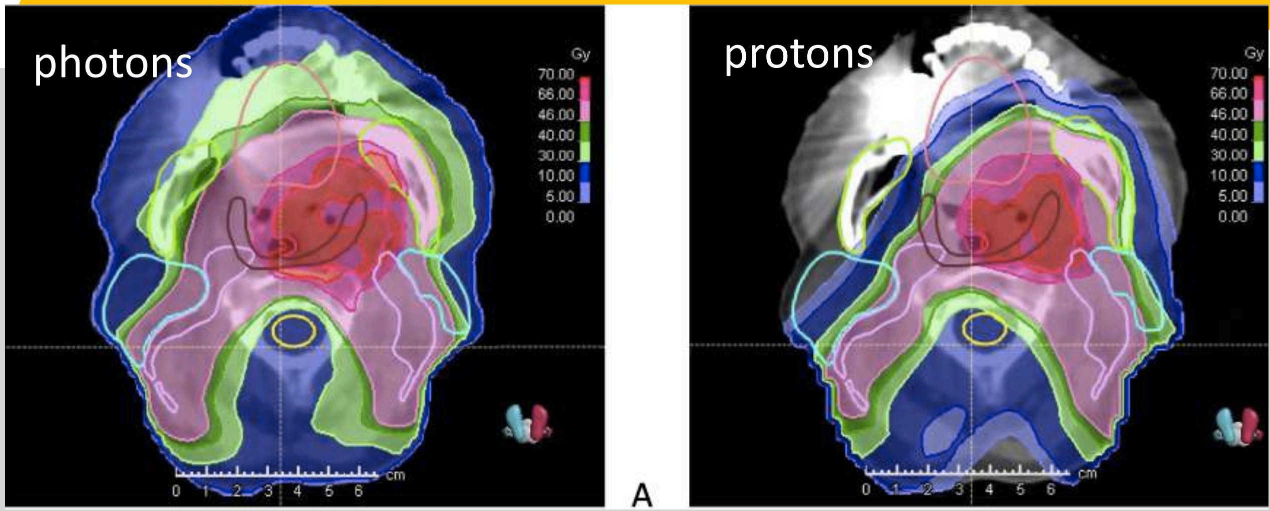
- Radiotherapy=usage of radiation to kill tumorous cells
- Conventional radiotherapy: mostly photons (x-ray)
- Particle therapy=special kind of radiotherapy
- What particles?
  - Protons : up to 250 MeV
  - Carbon : up to 400 MeV/u
  - Others: Helium, Oxygen, ...
- Particle beams can deliver energy to small volume, penetrate in depth (different from lasers), interact with cells, molecules, and atoms (electrons and nuclei)

→ destroy cancerous cells



Particle therapy

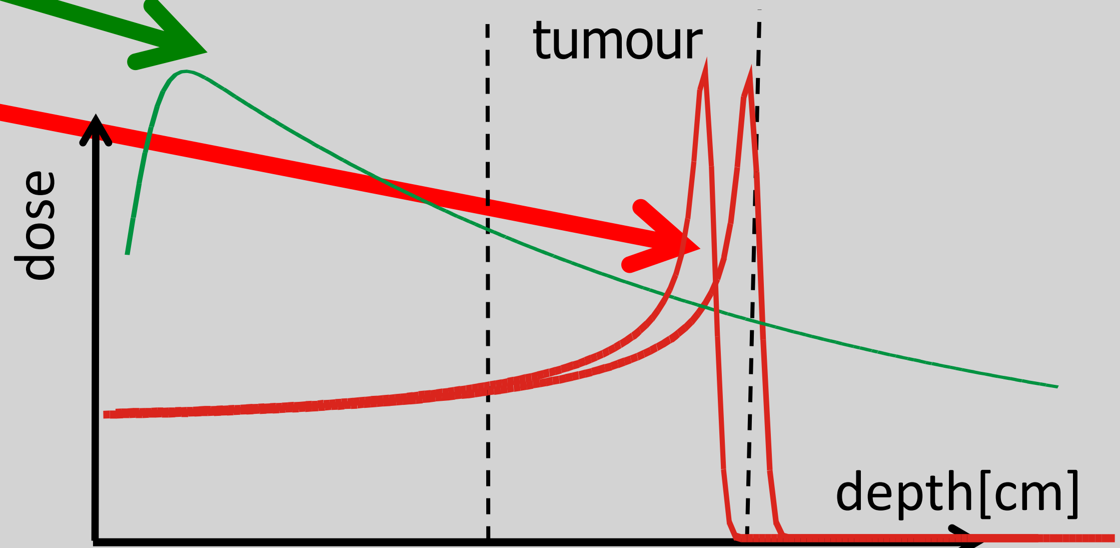
From: A. Beddok et. al., Radiotherapy and Oncology 147 (2020) 30–39



- Compared to photons, charge particles have a more selective energy deposition
  - Photons: high dose delivered in front and behind tumor
  - Charged particles: Bragg Peak: Dose spot
    - Energy ~ depth
    - Nr. particles ~ height

$$-\frac{dE}{dx}=\frac{4\pi}{m_e c^2}\cdot\frac{nz^2}{\beta^2}\cdot\left(\frac{e^2}{4\pi\varepsilon_0}\right)^2\cdot\left[\ln\left(\frac{2m_e c^2\beta^2}{I.(1-\beta^2)}\right)-\beta^2\right]$$

Bethe-bloch



Reminder: dose [Gy]=Energy [J]/mass [kg]

Particle therapy

End of 2020, more than 290'000 patients have been treated worldwide with Particle Therapy

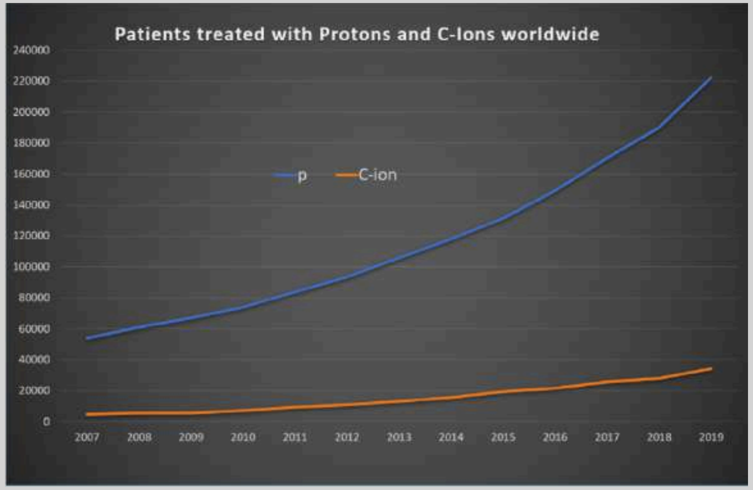
- about 250'000 with protons
- about 40'000 with C-ions
- 3'500 with He, pions and with other ions.

India: 

The Apollo Proton Cancer Centre was inaugurated on **January 25, 2019** in Chennai

South East Asia's first Proton Therapy Centre

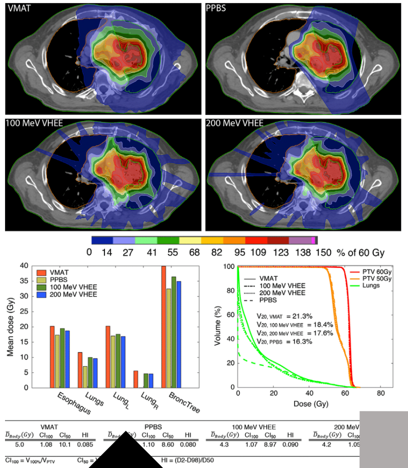
From: https://www.ptcog.ch/index.php/ptcog-patient-statistics

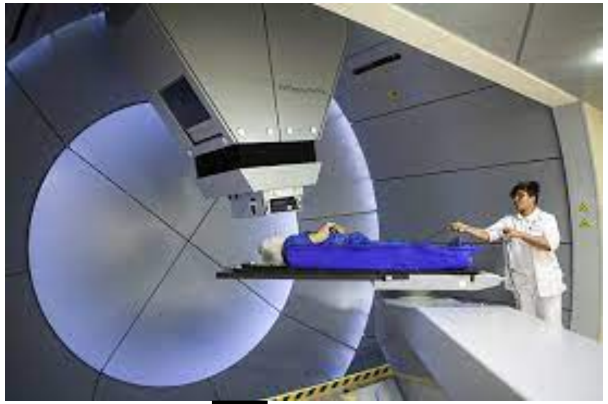


Idea by Robert Wilson, 1946

Particle therapy

Consultation → Treatment planning → Treatment delivery (few weeks) → Follow-up





CT scan
Structures
Dose prescription

Usually after N weeks:
CT scan with structures

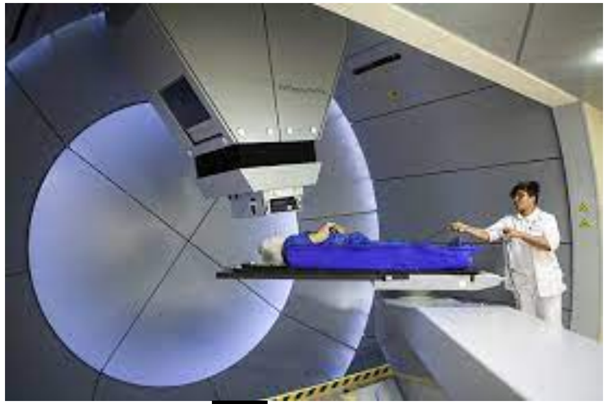
Imaging in particle therapy

Pre-treatment: for diagnosis, contouring and treatment planning

- Computed Tomography
  - Single Energy CT
  - Dual Energy CT
- MRI: Magnetic Resonance Imaging
- SPECT: Single-photon emission computed tomography
- PET: Positron-Emission-Tomography

Treatment delivery (few weeks)

Follow-up



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Treatment: for patient daily positioning, dose delivery and evaluation of anatomical changes

- In-room image guidance
  - X-ray
  - Cone –beam CT
  - Future: proton CT (pCT) or proton radiography
- During treatment:
  - PET;
  - prompt gamma;
  - charged fragments
  - Implantable dosimeters for direct Bragg peak evaluation.

Follow-up

s

Imaging in particle therapy

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Post-treatment: patient follow-up and post-treatment assessment

- MRI
- CT

Imaging in particle therapy

See also J. Seco, M.F. Spadea, Imaging in particle therapy: State of the art and future perspective, Acta Oncologica 54, 9, 1254-1258, 2015

See also A. Del Guerra, Ionizing Radiation Detectors for Medical Imaging

Pre-treatment: for diagnosis, contouring and treatment planning

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  - **positron emission tomography (PET);**
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TODAY

Post-treatment: patient follow-up and post-treatment assessment

- MRI
- CT

Imaging in particle therapy: uncertainties

Patient related

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

Physics related

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

Other sources

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

Dose/Bragg Peak
Monitoring is advisable!

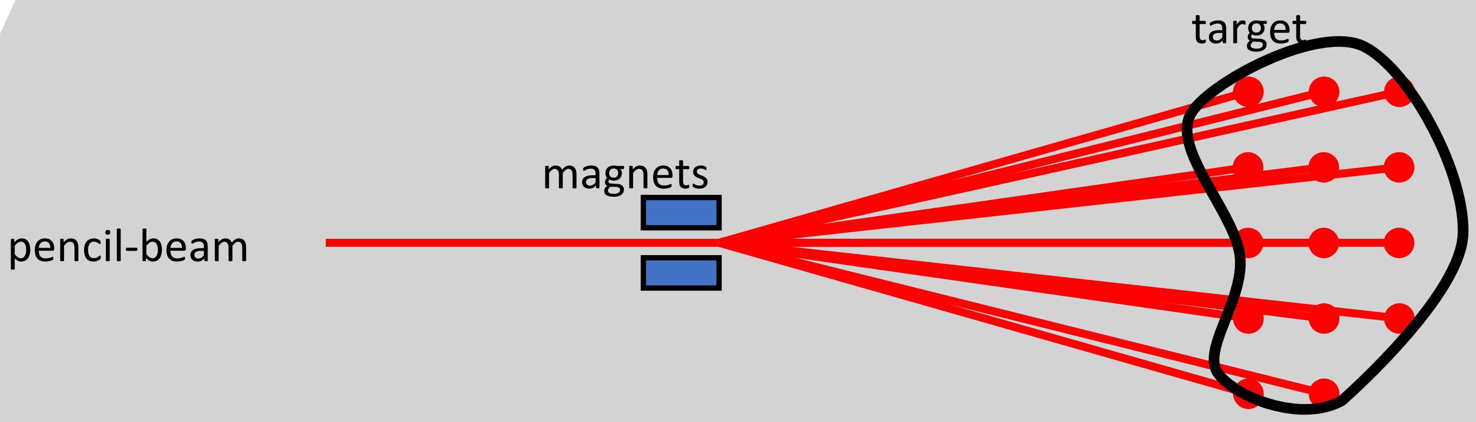
Courtesy of A. Del Guerra. Krakow 2015

Particle therapy

One of **the most** impactful developments since the advent of proton therapy has been **pencil beam scanning** (PBS)

(applied widely worldwide, also at Apollo Proton Cancer Centre)

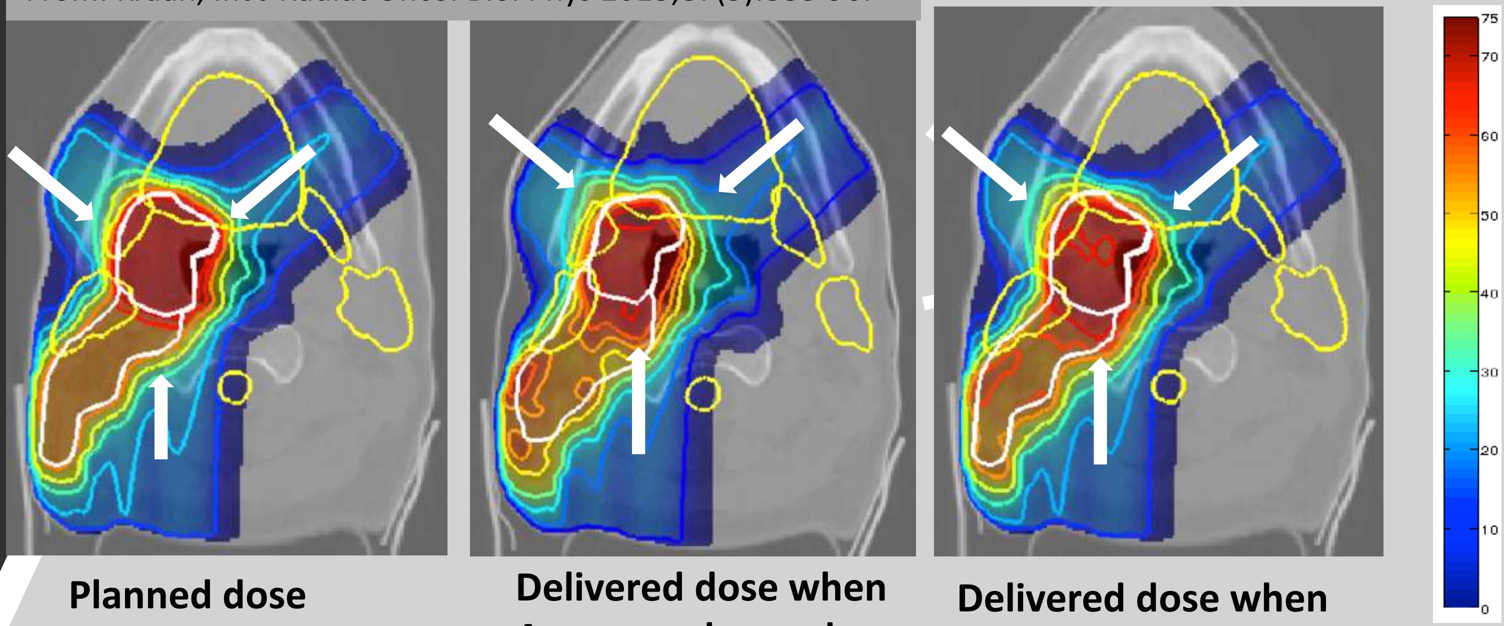
Small currents: 10 nA for a typical dose of 1 Gy to 1 liter in 1 minute.



Dose impact of uncertainties

- Very precise…
- But different uncertainties can lead to dose distortions…

From: Kraan, Int J Radiat Oncol Biol Phys 2013;87(5):888-96.



Planned dose

Delivered dose when Anatomy changed

Delivered dose when patient misaligned

Dose/Bragg Peak Monitoring is advisable!

Treatment monitoring

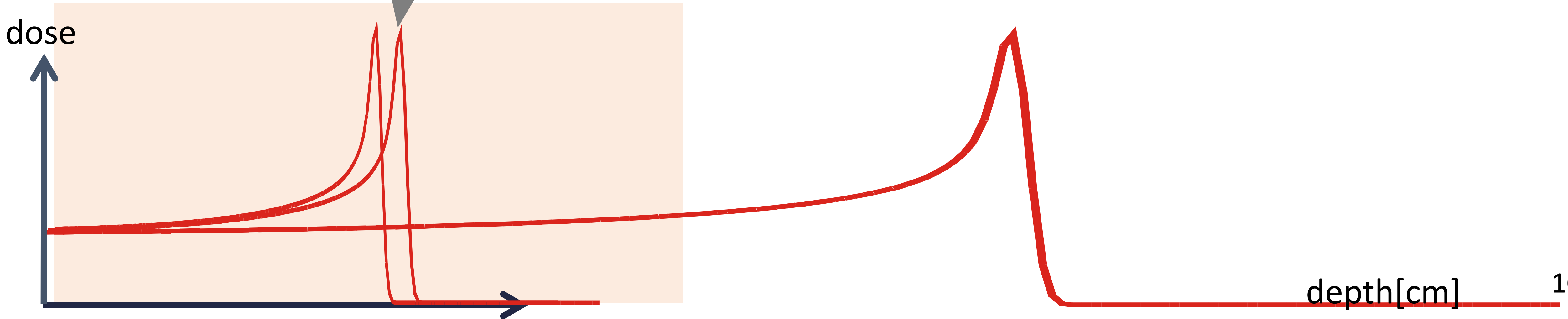
Based on Nuclear Reactions of Hadrons in Tissue

- Off-line & On-line PET
- Prompt gamma’s and neutrons
- Prompt charged particles (only for Ions)

Beam stopping inside patient

Based on X-ray CT- analogous: pCT (only for Protons)

Beam going through



Treatment monitoring

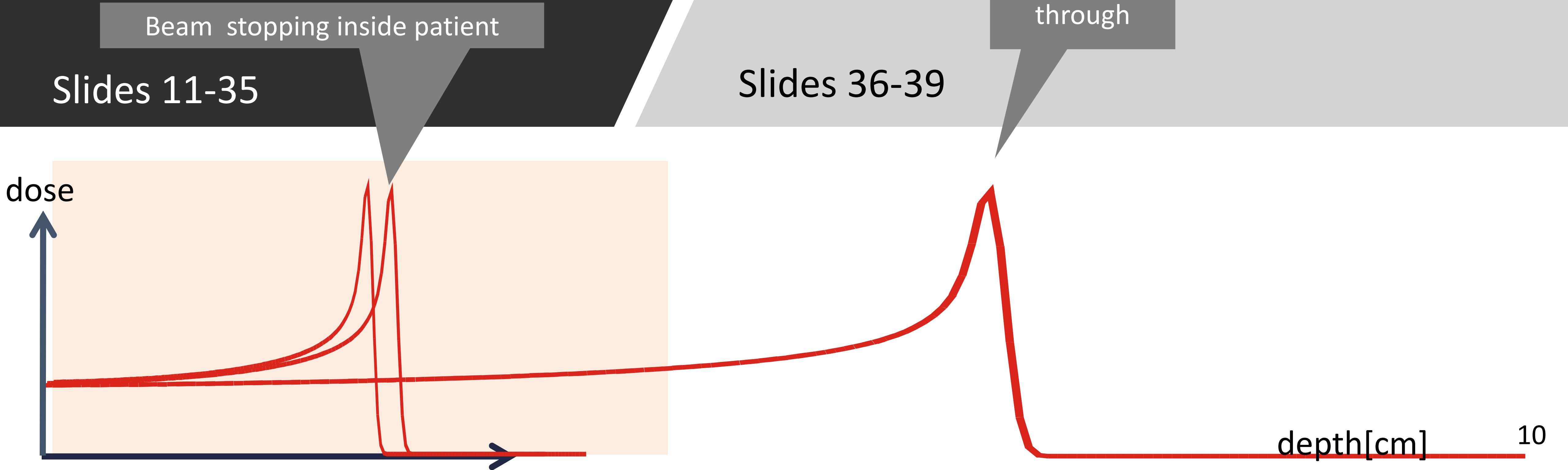
Based on Nuclear Reactions of Hadrons in Tissue

- Off-line & On-line PET
- Prompt gamma's and neutrons
- Prompt charged particles (only for Ions)

Slides 11-35

Based on X-ray CT- analogous: pCT (only for Protons)

Slides 36-39



Nuclear interactions in particle therapy

1940-2009

"*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

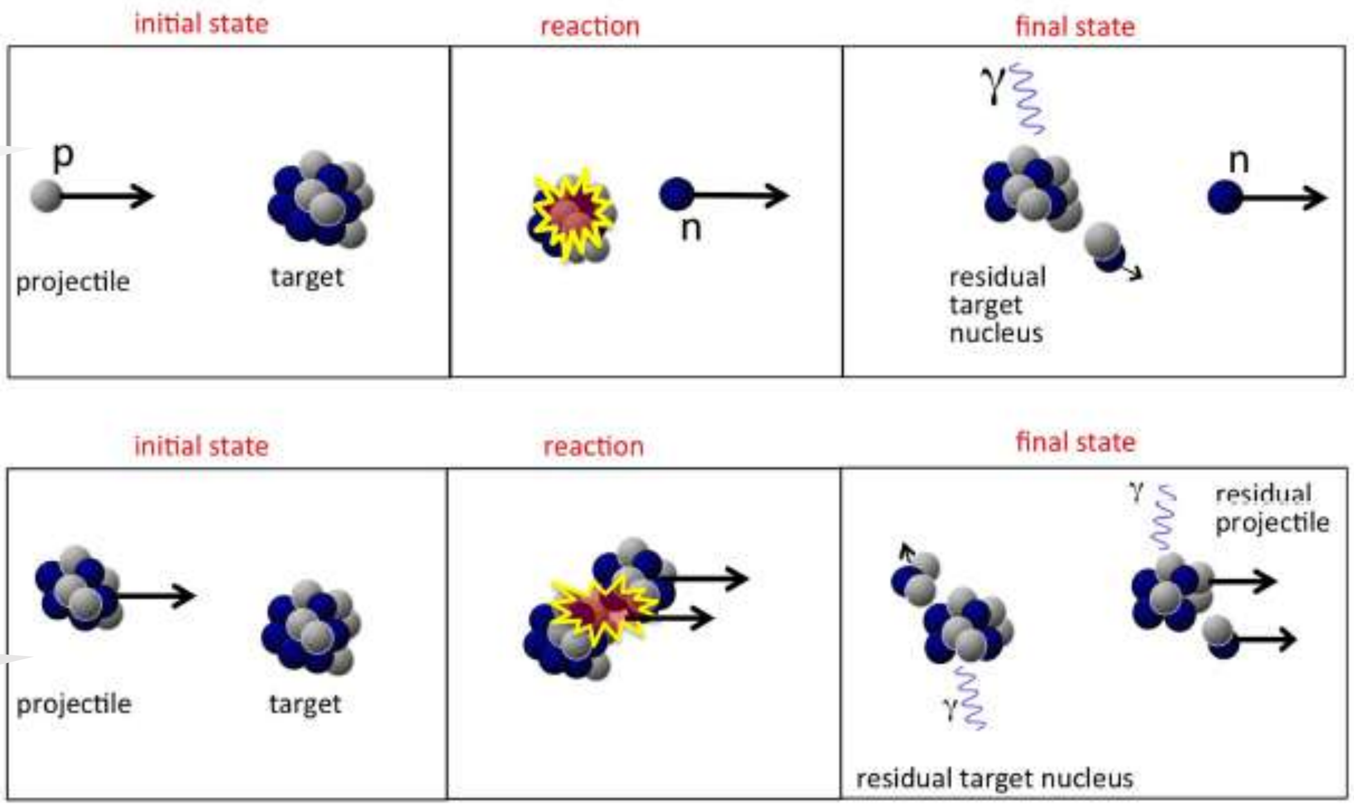
Abstract

"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.***

Nuclear interactions in particle therapy

Proton therapy: Example of proton nucleus interaction

Carbon therapy: Example of nucleus nucleus interaction

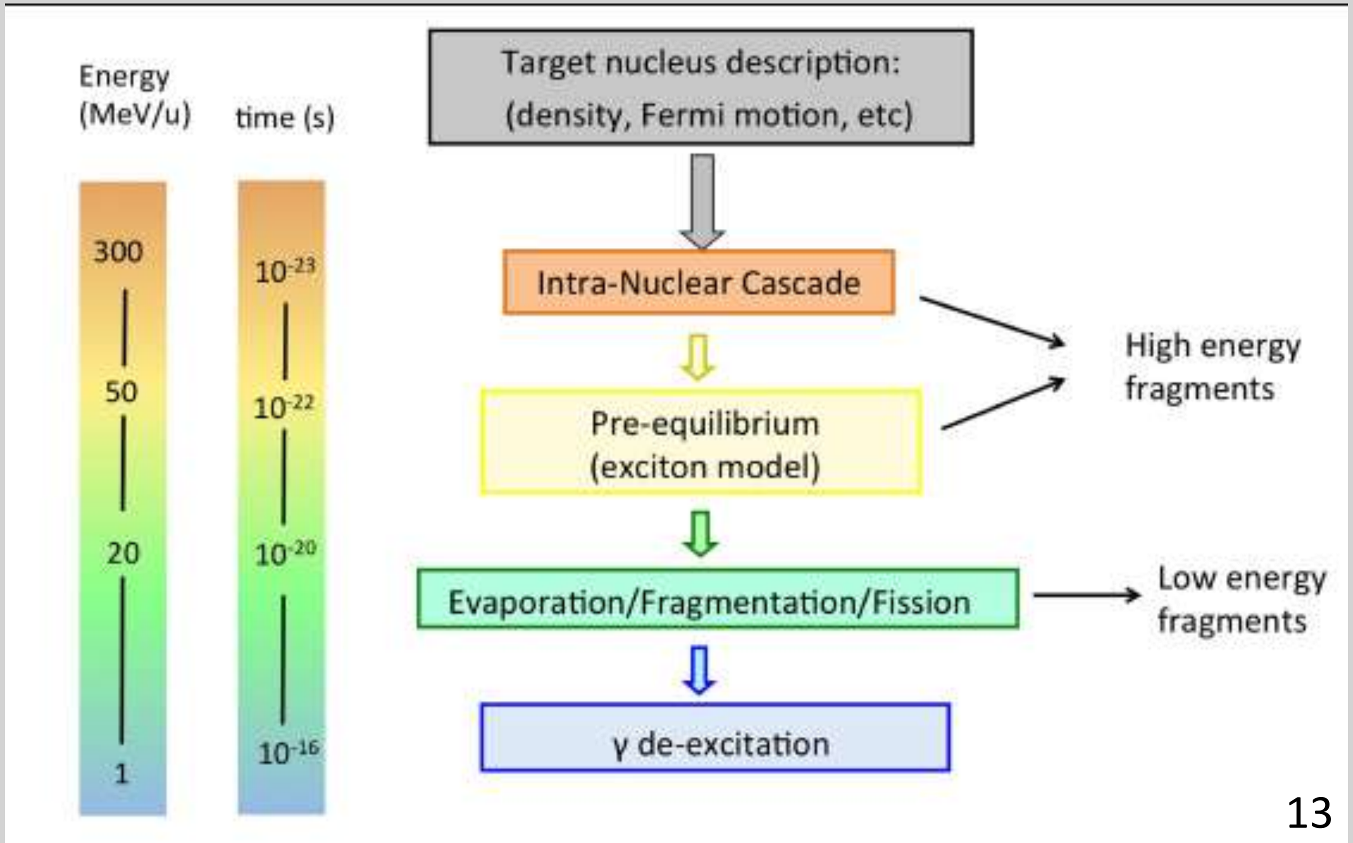


Ref.:AK, Frontiers in Oncology, 07 July 2015 doi: 10.3389

Nuclear interactions in particle therapy

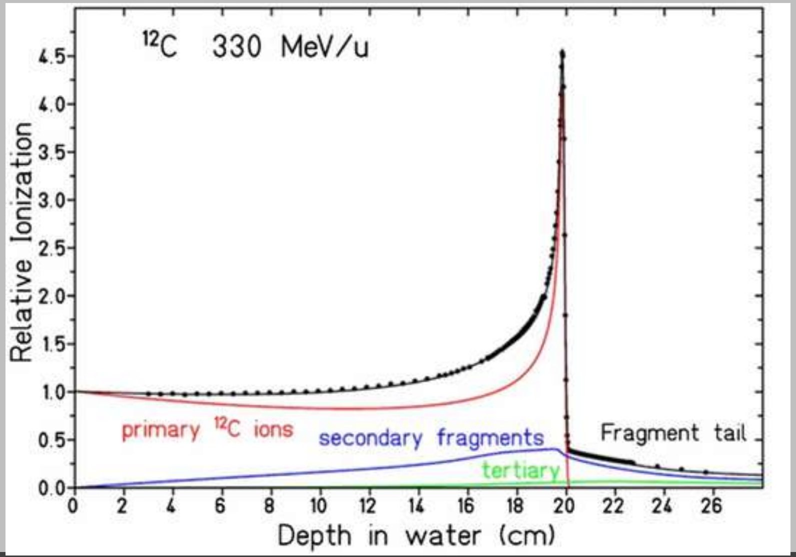
- Many stages in nuclear reaction…

Ref.: AK, Frontiers in Oncology, 07 July 2015 doi: 10.3389, adapted from A. Ferrari ‘s presentations



Battistoni G, Bauer J, Böhlen T, Cerutti F, Chin M, et al. The FLUKA code: an accurate simulation tool for particle therapy. *Fron Oncol.* (2016). **6**:116. doi:10.3389/fonc.2016.00116

Nuclear interactions in particle therapy

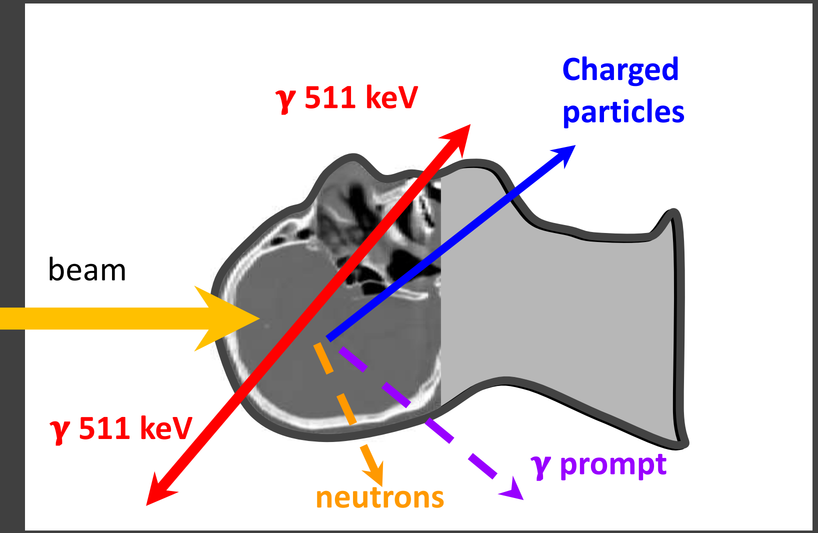


Consequences

Loss of beam fluence. For 290 MeV/u carbons: 50% of ions have nuclear reaction

The dose distributions are modified:

- Build-up region of Bragg curve
- Height of the Bragg peak.
- Carbon therapy: dose beyond the Bragg peak.
- Low energetic secondary particles --> “low dose envelope”



- Various types of secondary particles are produced. Kinematics depend on stage during nuclear reaction
  - β+ emitting isotopes → PET
  - Prompt gammas
  - Charged fragments are produced

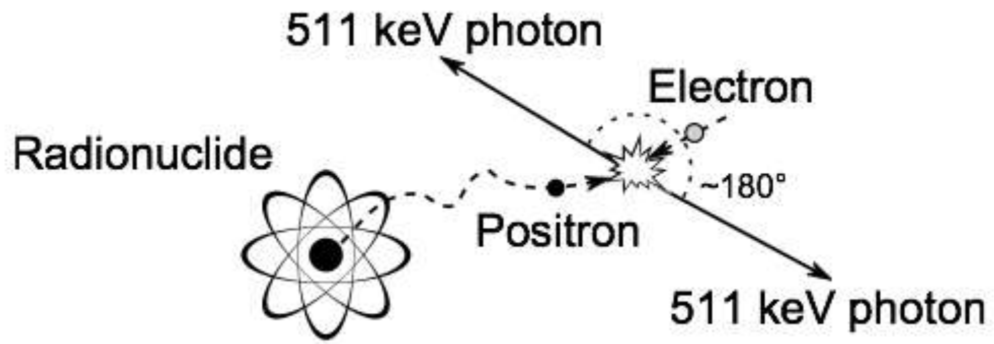
Nuclear interactions in particle therapy

- One of the ways to verify the delivered dose is by means of PET (Positron-Emission-Tomography)
- Therapeutic hadron beams produce β^+ emitters in the body

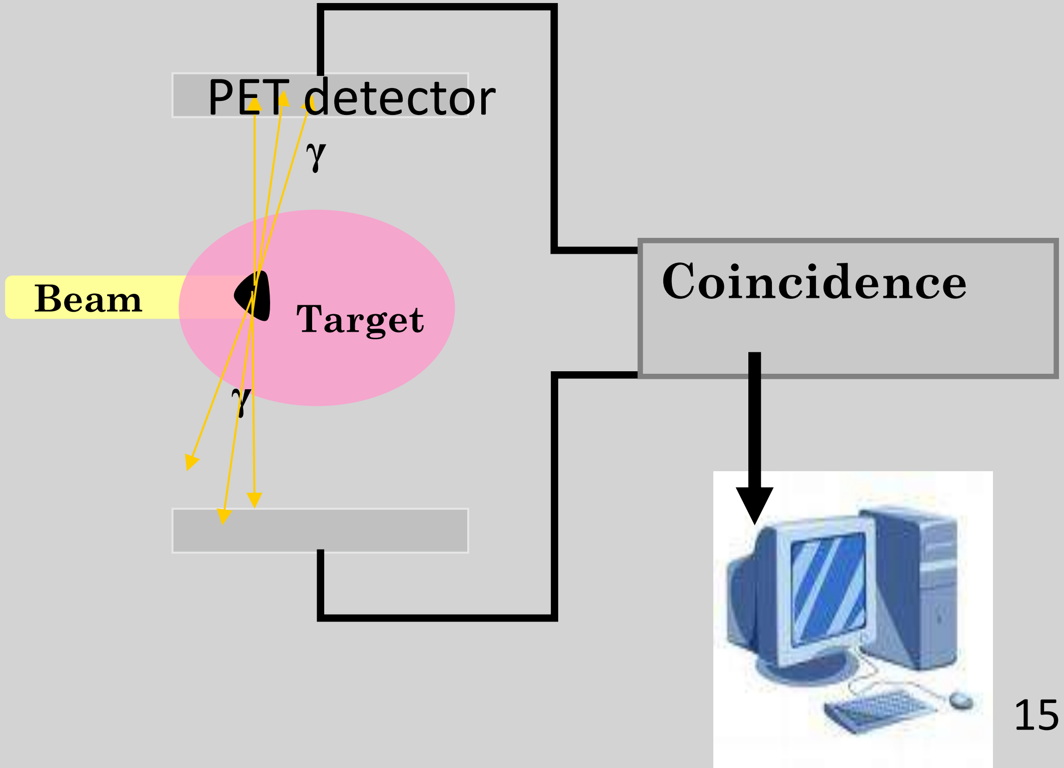
E.g. proton beam:

$p + {}^{16}O \rightarrow (p,n) + {}^{15}O \rightarrow {}^{15}N + \beta^+ + \nu \quad \tau_{15\text{-}O}=121.8$ s (2 min)

$p + {}^{12}C \rightarrow (p,n) + {}^{11}C \rightarrow {}^{11}B + \beta^+ + \nu \quad \tau_{11\text{-}C}=1222.8$ s (20 min)



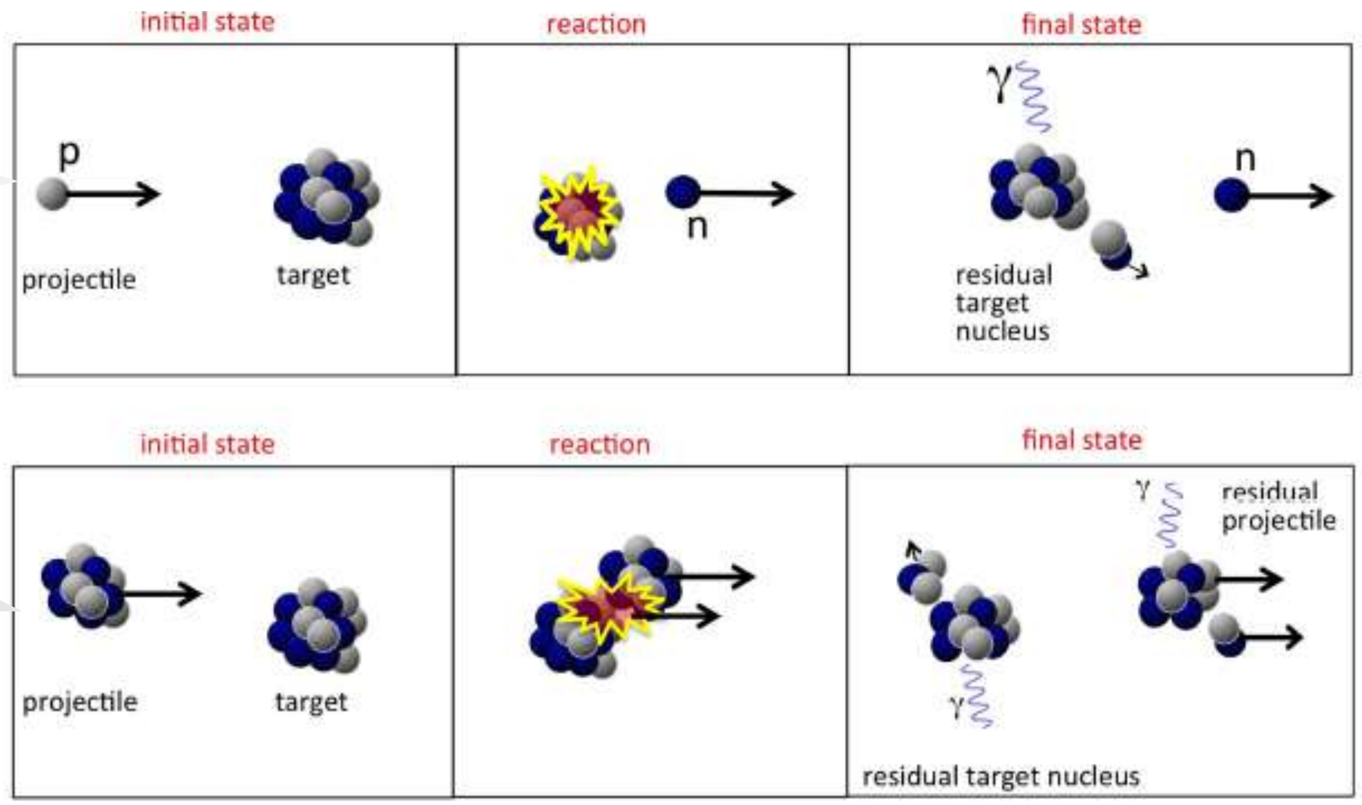
PET activity=
nr of radioactive decays per time-interval



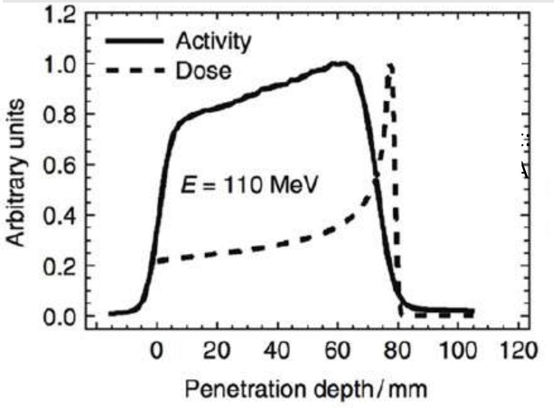
Nuclear interactions in particle therapy

Proton therapy: Example of proton nucleus interaction

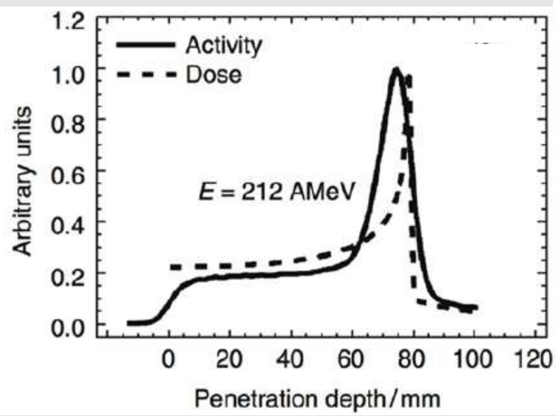
Carbon therapy: Example of nucleus nucleus interaction



Beam: proton   Target: PMMA



Beam: ^{12}C Target: PMMA

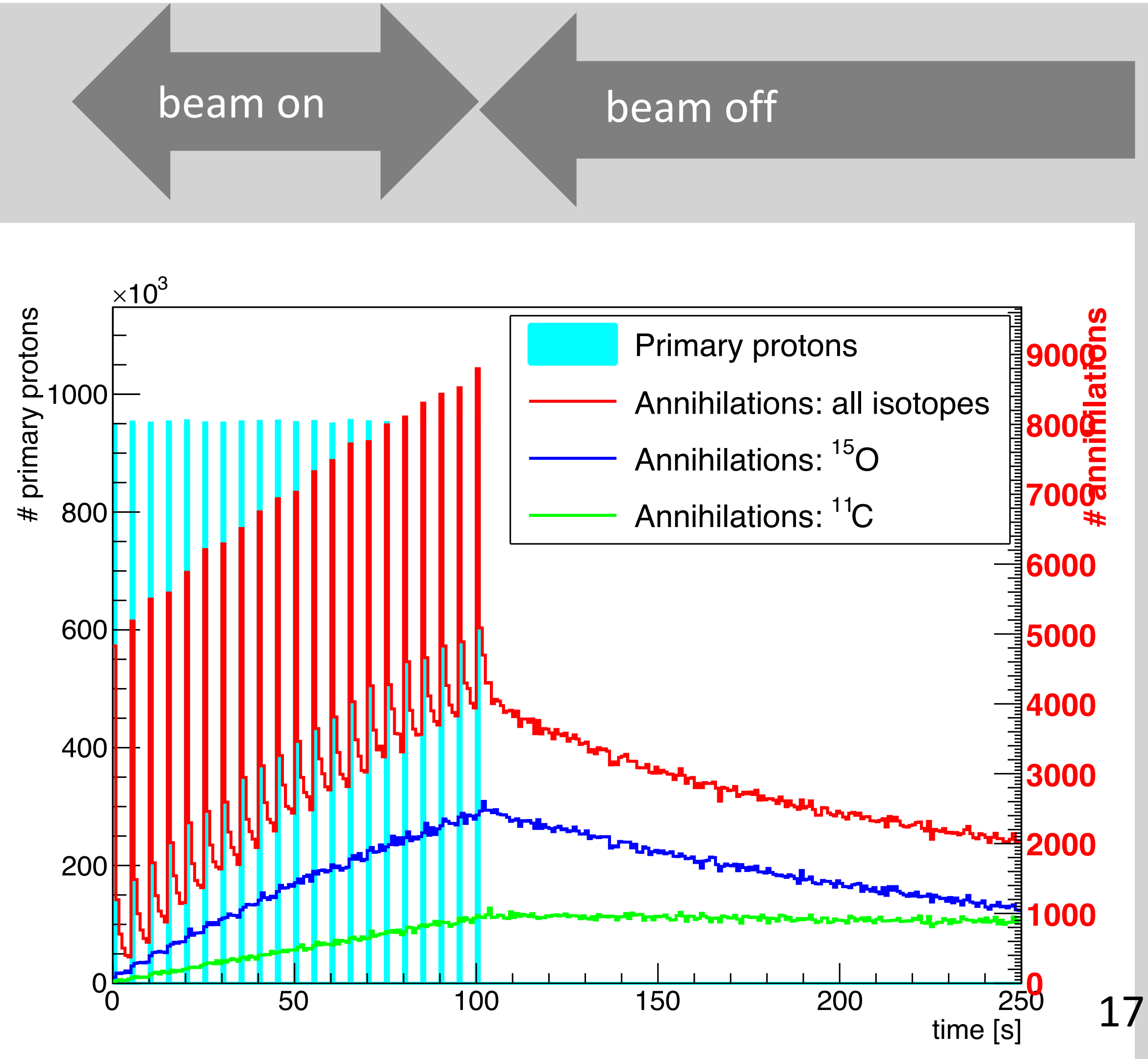


Beta+ activity indirectly related with Bragg peak position!

Fiedler F, et al, *Ion Beam Therapy Fundamentals, Technology, Clinical Applications*. Berlin: Springer-Verlag (2012). p. 527–43.

Nuclear interactions in particle therapy

FLUKA simulation of beta+ annihilation in phantom for a proton beam



PET monitoring in particle therapy

K. Parodi and J. Polf. "In vivo range verification in particle therapy", Medical Physics 45, 2018

A.C. Knopf and A Lomax. "In vivo proton range verification: a review". In:Phys Med. Biol.58.15 (2013), R131–160.

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

Off-line PET = dose delivery and PET in different locations *(MGH/Heidelberg/CHIBA)*

- Advantages
  - Commercial PET scanner 360 degrees (no image artefacts)
- Disadvantages:
  - Patient re-positioning
  - Data loss of very short living isotopes (e.g. ^{15}O)
  - Radio-isotope wash-out

Room

dose delivery

Other room/building

PET

On-line PET = dose delivery and PET in same room

➔In Room-PET: data when beam is off *(GSI/PISA-CNAO/CHIBA/MGH/HEIDELBERG)*

Dose delivery

PET

➔In-beam-PET: data when beam on *(PISA-Torino-CNAO/CHIBA-openPET)*

- Disadvantages:
  - Image artefacts
  - Small statistics (not much ^{11}C)

Dose delivery + PET

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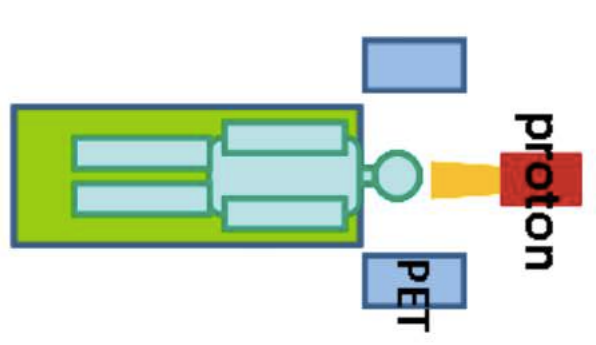
COVERED TODAY

Dose delivery + PET

PET monitoring in particle therapy

- Main problem in in-beam PET: difficult to integrate with dose delivery system, position systems, etc …

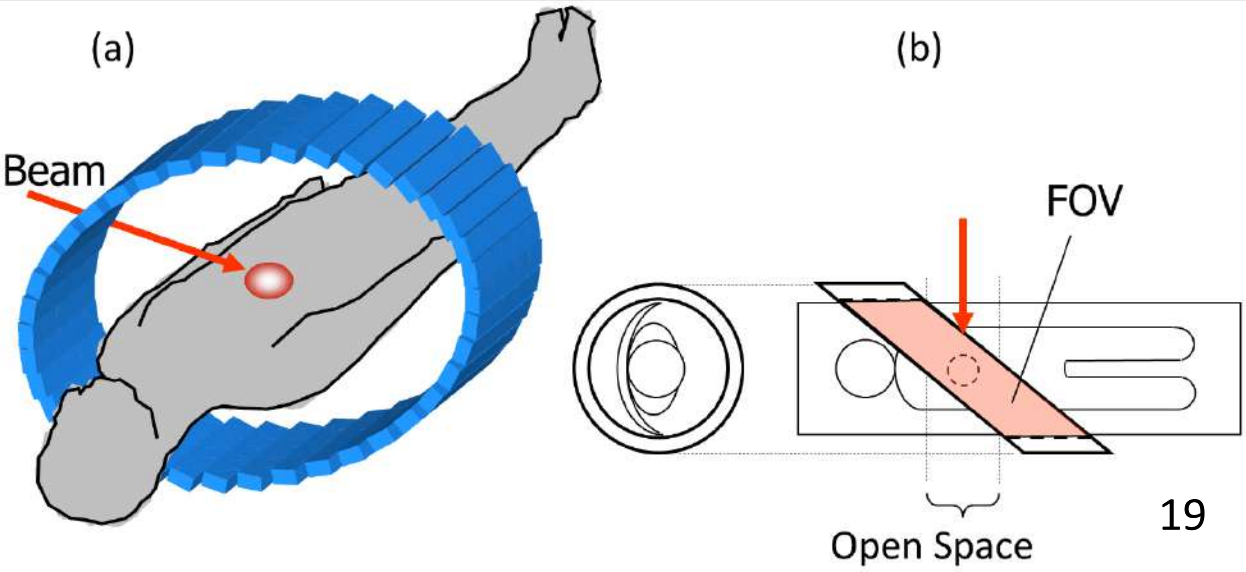
- Solutions
  - Two planes (see next)
  - Particular geometries
    - Example: Open PET system @ CHIBA, Japan



V. Rosso et al, DoPET: an in-treatment monitoring system for particle therapy, Radiotherapy and Oncology 118:S92

G.M. Bisogni et al.:Journal of Medical Imaging4 (Dec. 2016), p. 011005

Tashima et al 2016 Phys. Med. Biol. 61 1795



PET monitoring in particle therapy

INnovative **S**olutions for **I**n-beam **D**osim**E**try in Hadrontherapy

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

INSIDE coordinator: M. G. Bisogni (Pisa)

This project has been supported by Italian MIUR under the program PRIN 2010-2011 project nr. 2010P98A75 and by EU FP7 for research, technological development and demonstration under grant agreement no 317446 (INFIERI)

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F. Ciciriello
F. Corsi
F. Licciulli
C. Marzocca
G. Matarrese

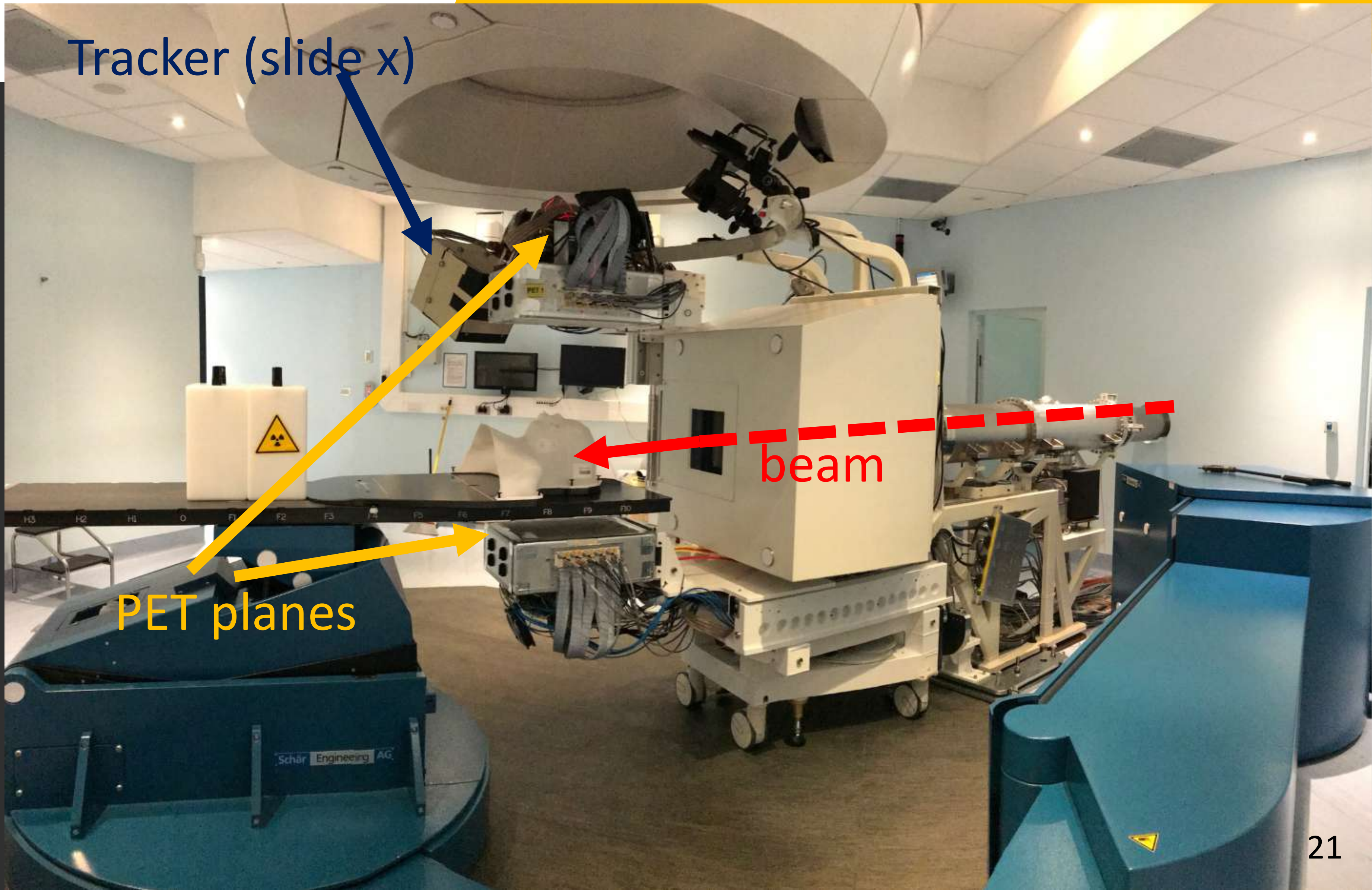
G. Battistoni
M. Cecchetti
F. Cappucci
S. Muraro
P. Sala

partners: CNAO

INSIDE

INSIDE detector :

- Designed in 2010-2013
- Constructed 2014-2016
- Installed at CNAO since 2016
  - Close to nozzle
  - Operated during beam delivery and up to about 30 seconds after

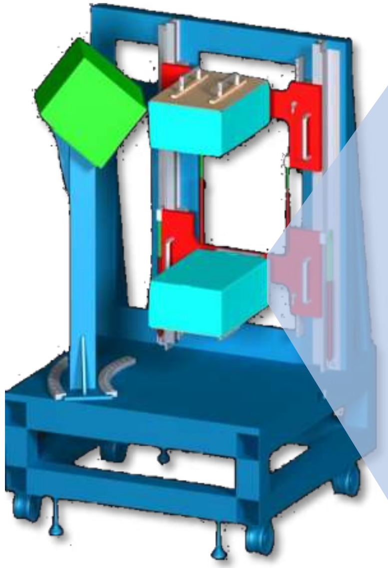


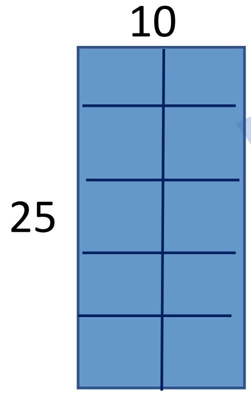
INSIDE: in-beam PET

Main features

- coincidence window = 2 ns
- CTR (Ge68) = 1.2 ns FWHM
- Avg energy resolution = 13 MeV
- image reconstruction method: MLEM

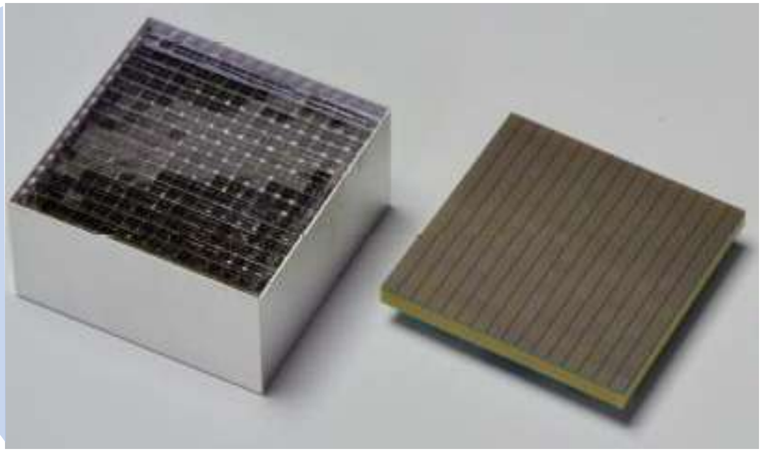
G.M. Bisogni et al.:Journal of Medical Imaging4 (Dec. 2016), p. 011005.





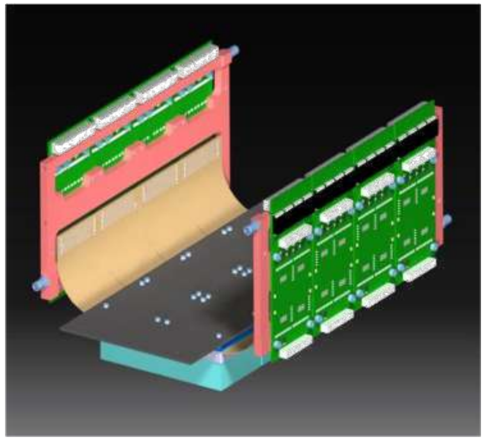
10x 20 x 5 cm^3
Distance from the isocenter=25 cm

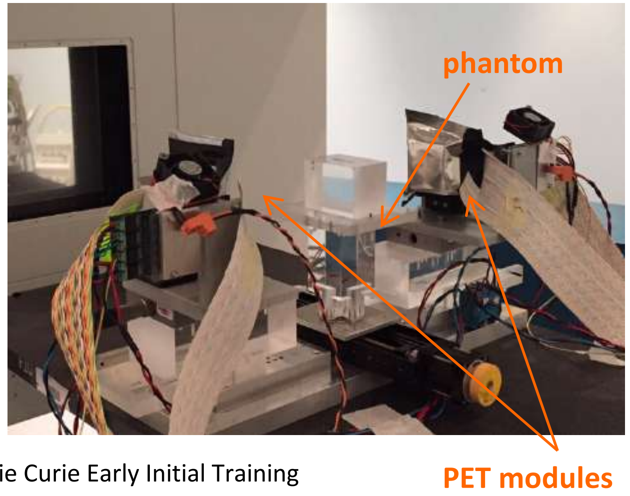
Courtesy of A. Del Guerra. Krakow 2015



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

Solid model Of the PET head

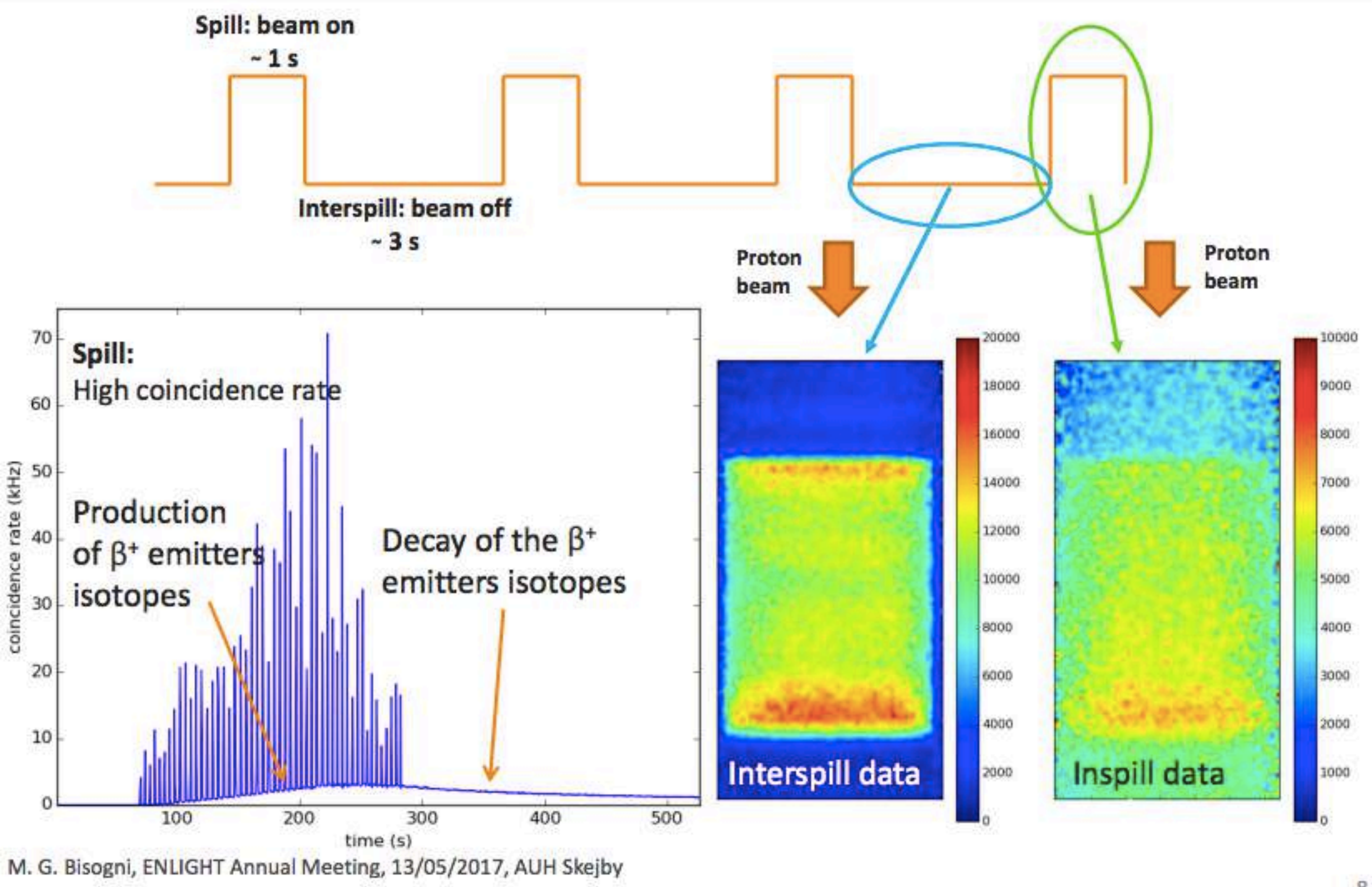




Demonstrator 1 vs 1 module

Work partly supported by European Union: EndoTOFPET-US project and Marie Curie Early Initial Training Network Fellowship (PITN-GA-2011-289355-PicoSEC-MCNet).

INSIDE: in-beam PET



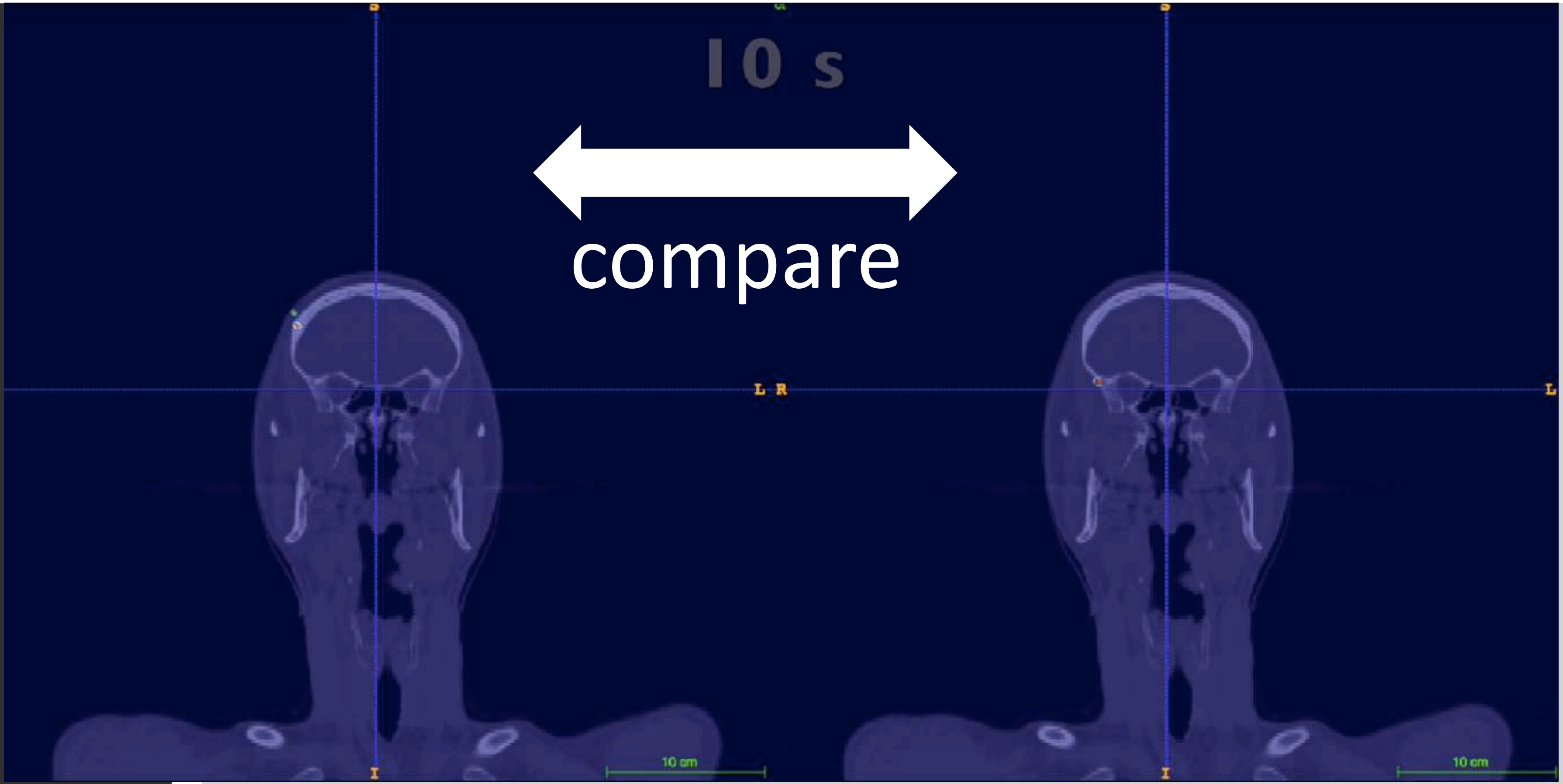
Courtesy of M.G. Bisogni, SIF, Italy, 2019

INSIDE: in-beam PET

V. Ferrero et al., "Online proton therapy monitoring: clinical test of a Silicon-photodetector-based in-beam PET"
Scientific Reports, *(2018) 8:4100*

E. Fiorina et al, Front. Phys. 2021

F. Pennazio et al. :Phys.Med. Biol.63 2018



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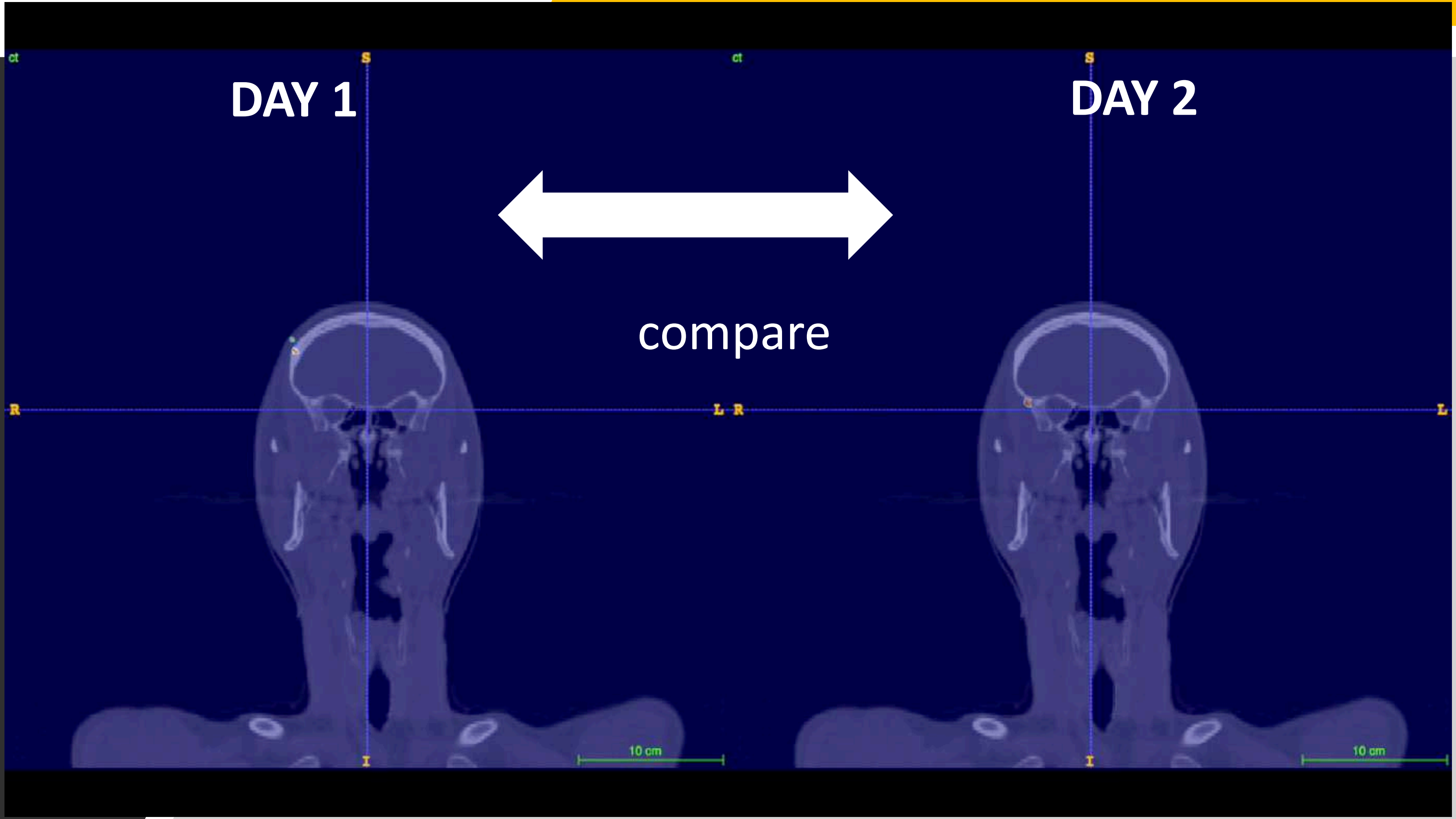
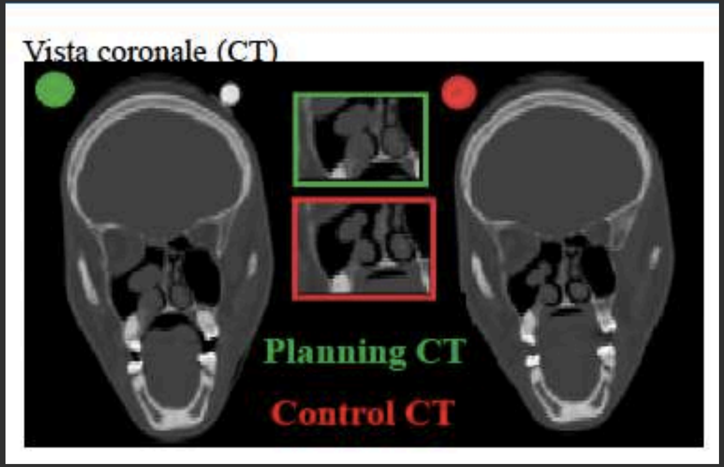


INSIDE: in-beam PET

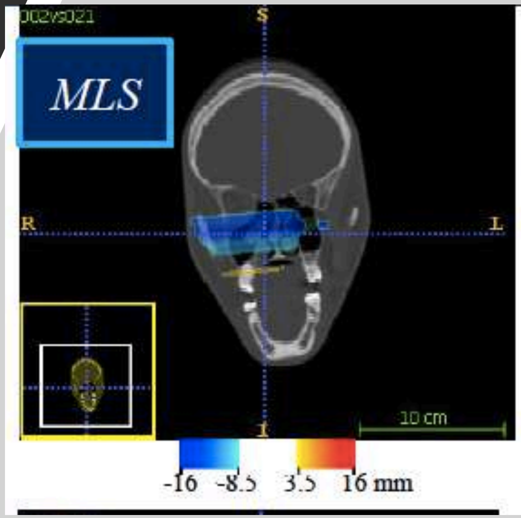
Work in progres…

- ACC (adrenocortical carcinoma) patient part of clinical trial
- Thesis work (M. Mogliorni)
- In-beam PET data for various fractions

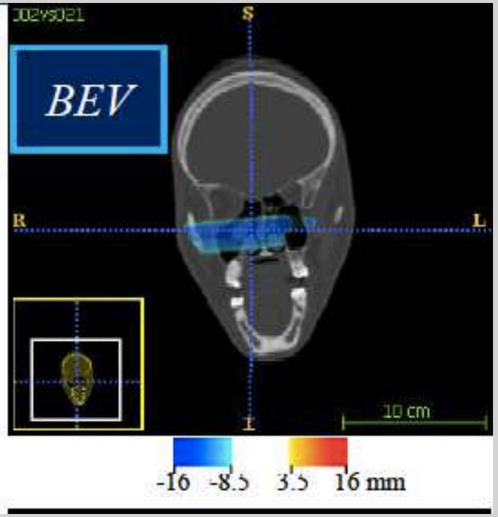


Different range identification methods compared for patient subject to small anatomical changes

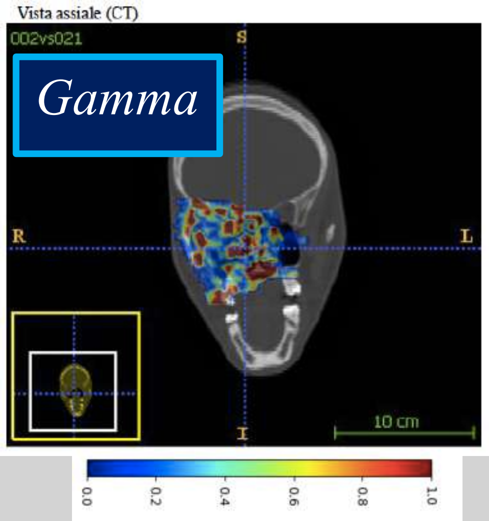
Fraction 2 versus 21



Fraction 2 versus 21



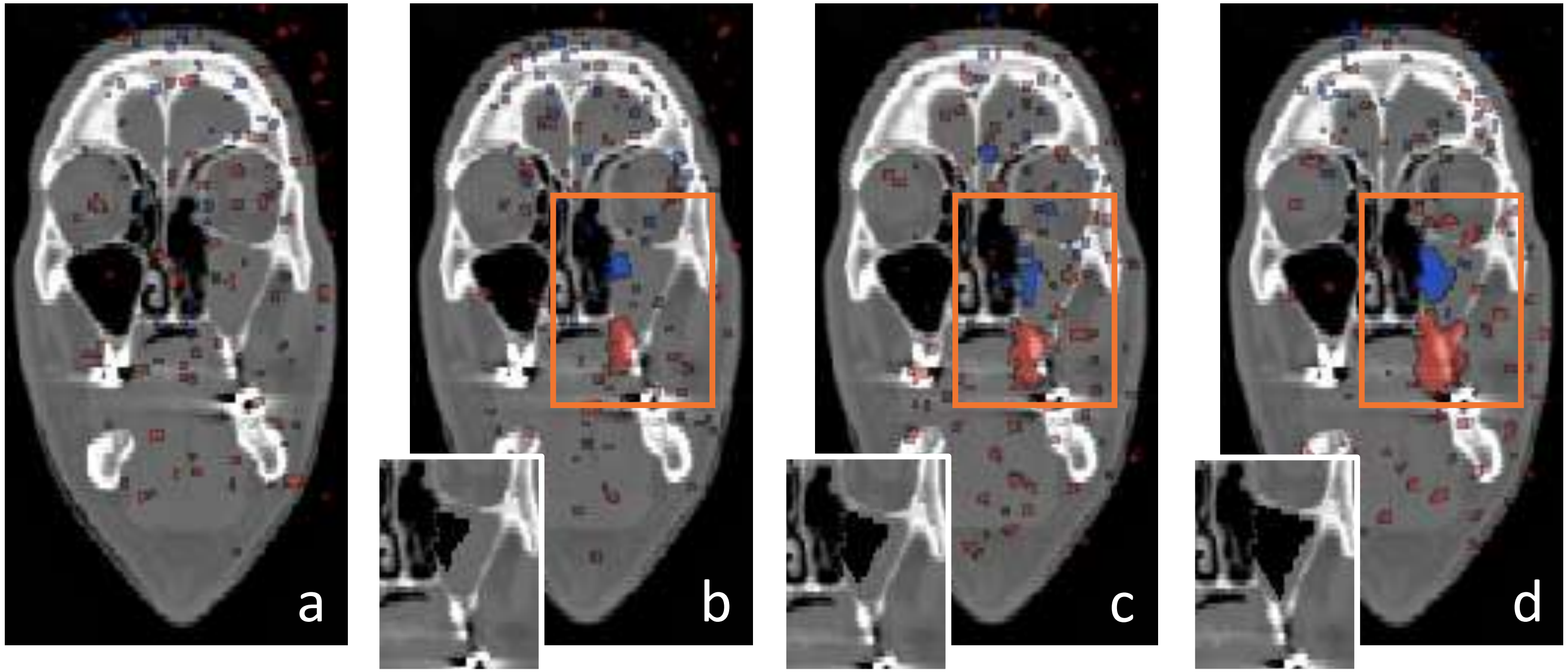
Fraction 2 versus 21



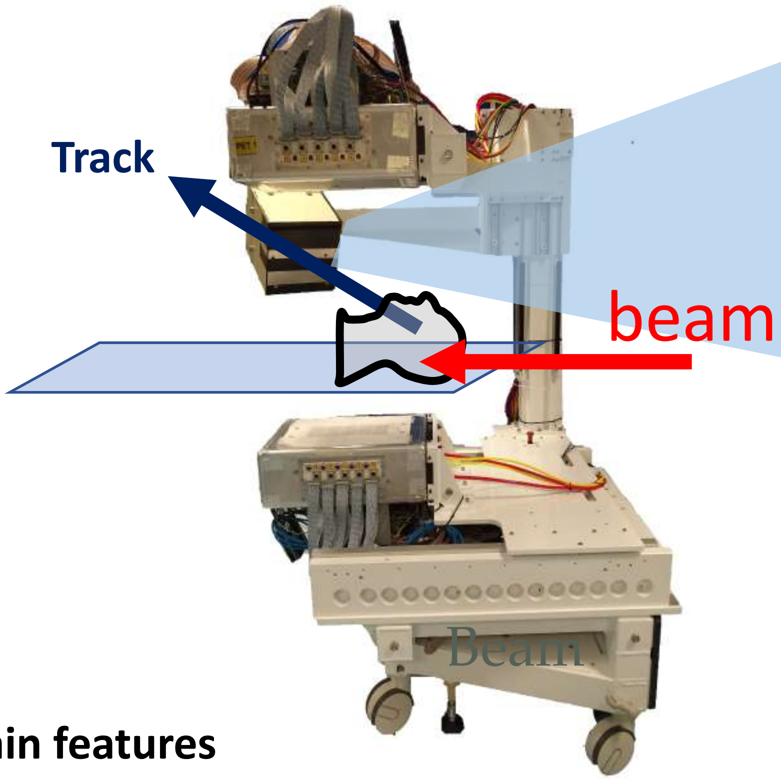
INSIDE: in-beam PET

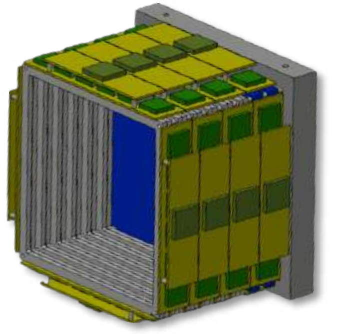
- New analysis methods are being developed…
- Voxel-Based Morphometry approach
- Monte Carlo study: voxel-wise two-tailed statistical tests of the simulated PET images
- Can locate changes with respect to expectations

A.C.Kraan, A.Berti, A. Retico, et al, accepted in Medical Physics

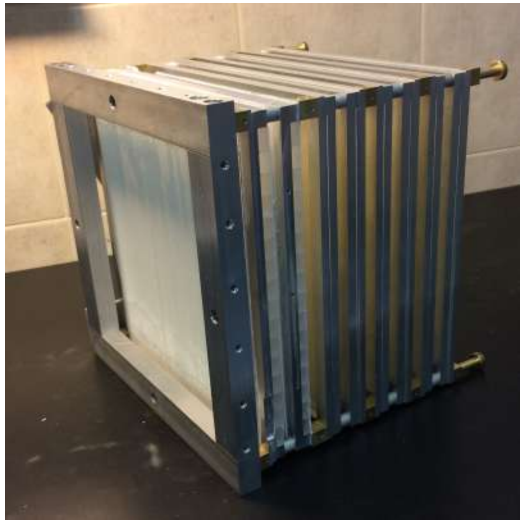


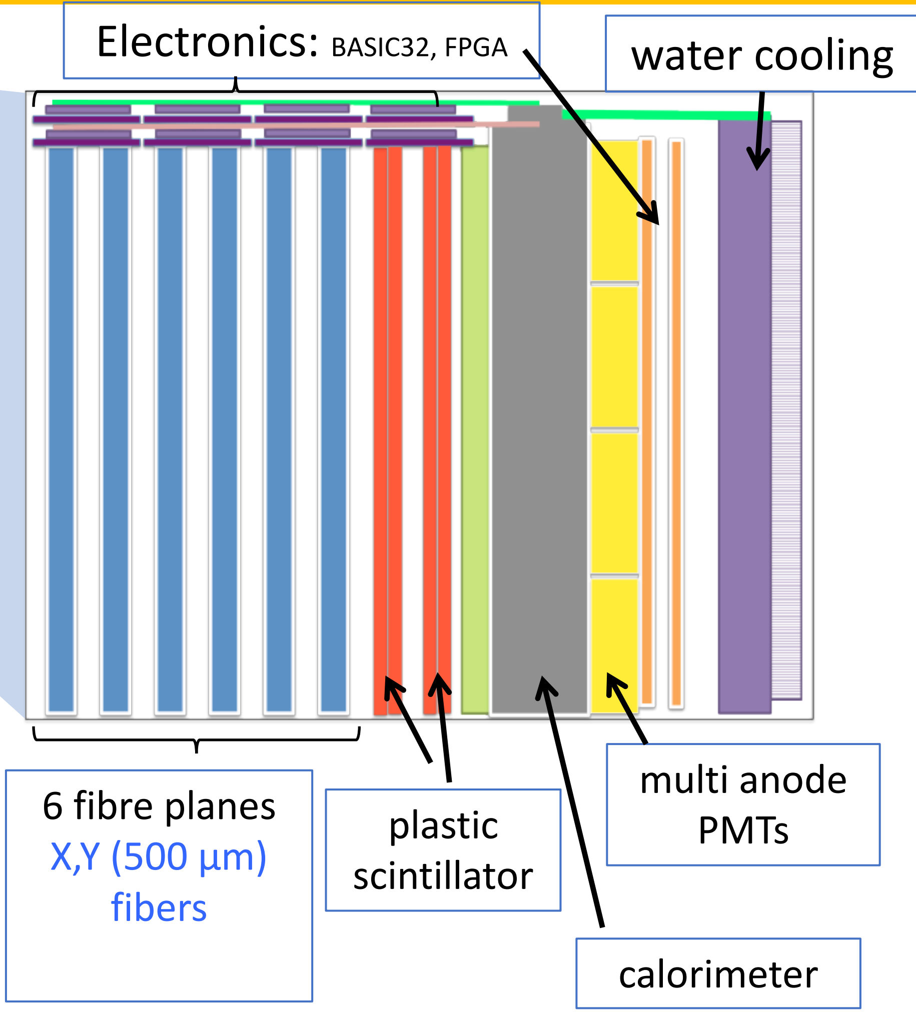
INSIDE: particle tracker





28 x 28 x 35 cm^3

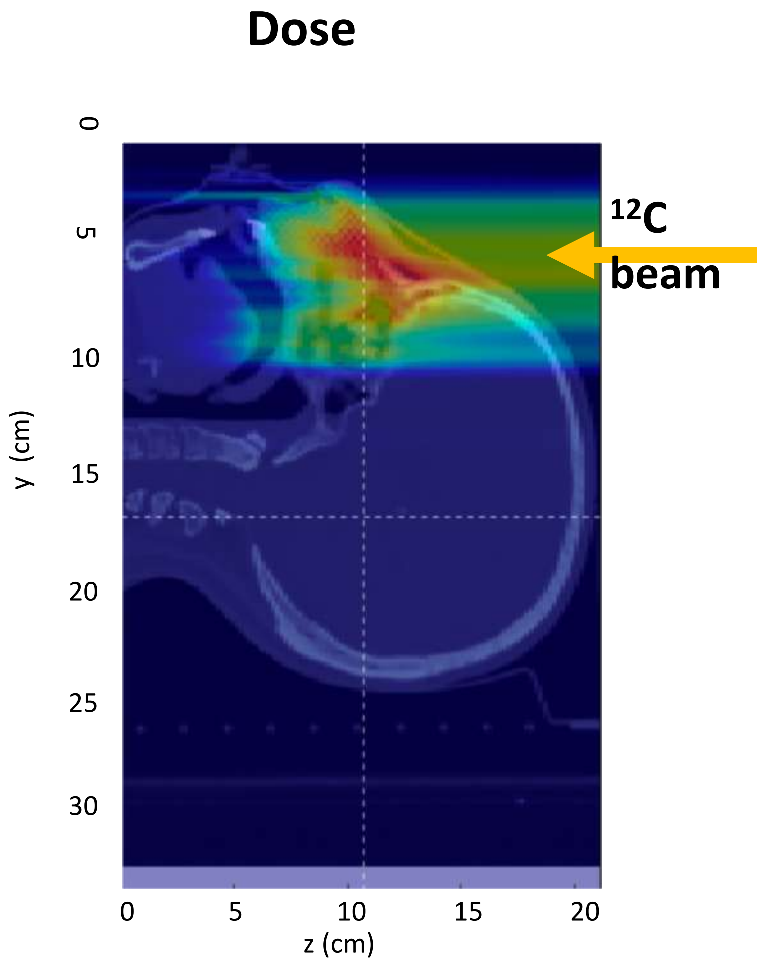


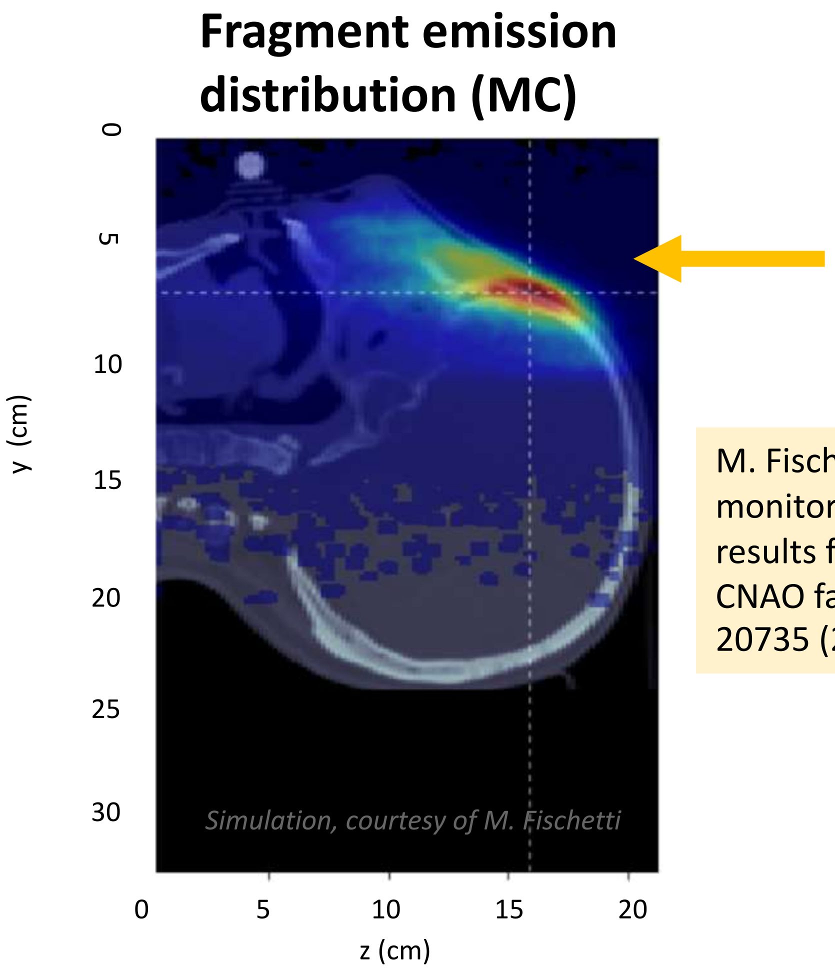


Main features

- Synchronization with Dose Delivery System signal (carbon only!)
- Image reconstruction method: backtracking with Point Of Closest Approach

INSIDE: particle tracker

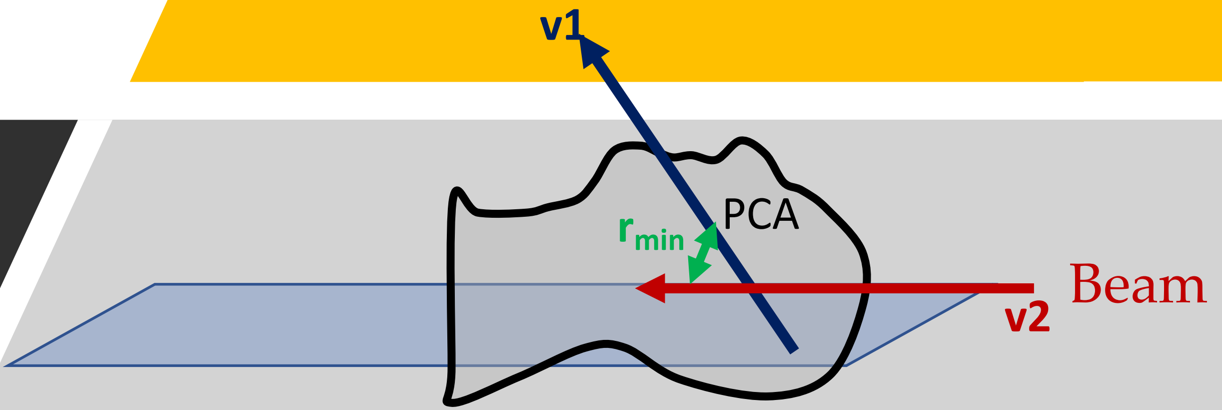


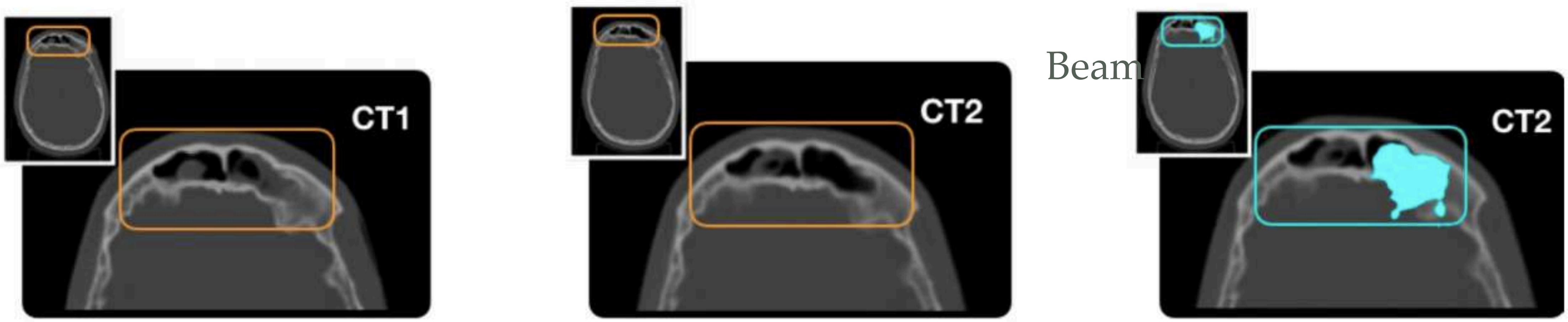


M. Fischietti et. a., Inter-fractional monitoring of ^{12}C ions treatments: results from a clinical trial at the CNAO facility, Scientific Reports 10, 20735 (2020)

INSIDE: particle tracker

Production points of the fragments obtained as Points of Closest Approach (PCA) of the reconstructed track with the nominal incoming beam direction





(a) (b) (c)

M. Fischietti et. a., Inter-fractional monitoring of ^{12}C ions treatments: results from a clinical trial at the CNAO facility, Scientific Reports 10, 20735 (2020)

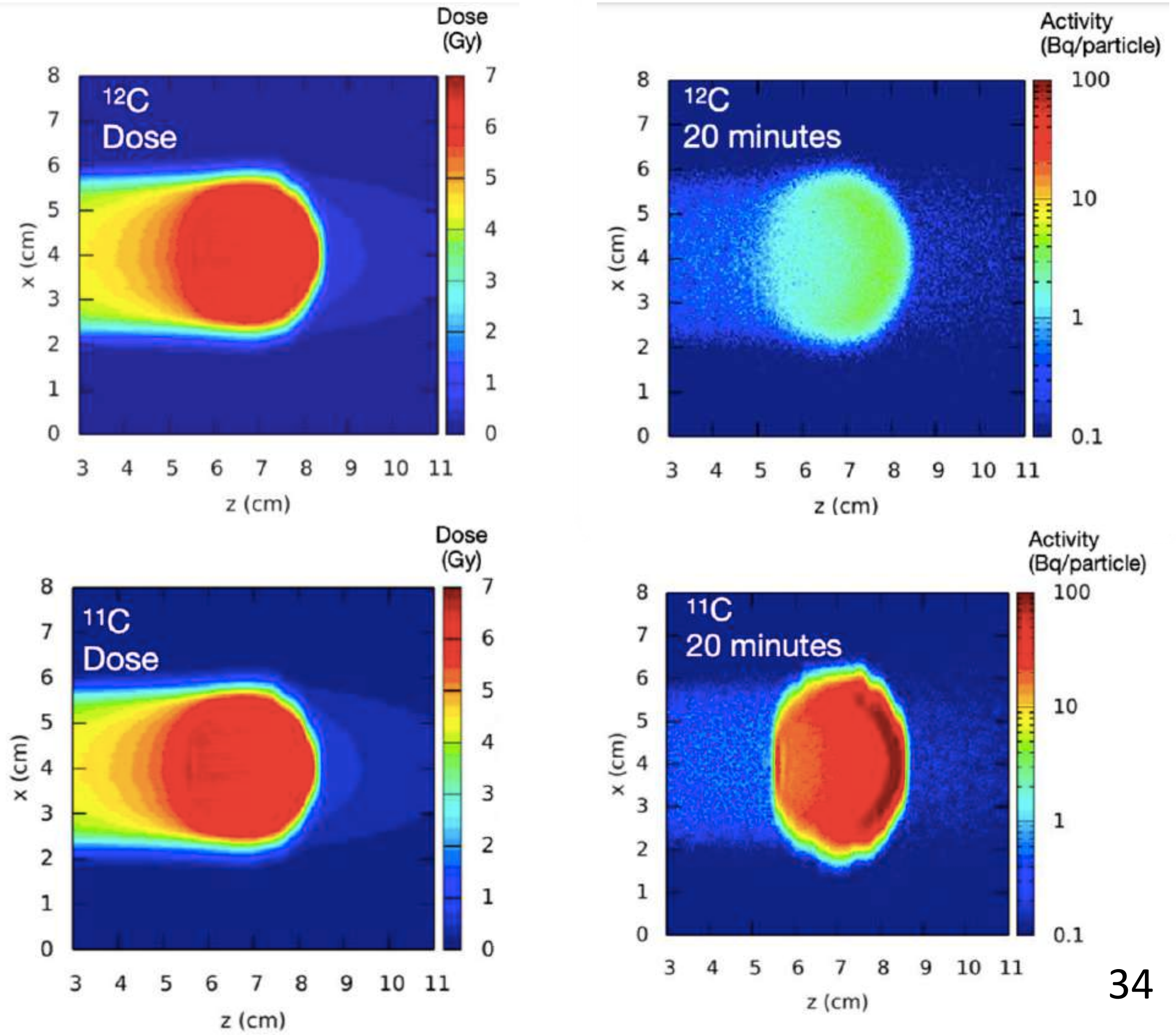
(a) of CT1 , (b) CT2 (c) CT2 with superimposed the distribution of the PCAs belonging to the SPBs that have a **p-value below 0.02 when testing the consistency between the first monitored fraction and the last one.**

Daria Boscolo et al., Front Oncol 2021. eCollection Radioactive Beams for Image-Guided Particle Therapy: The BARB Experiment at GSI

BARB project

(Biomedical Applications of Radioactive ion Beams)

- FAIR project Darmstadt
- Carbon beams: not much beta+ activity generated…
- But higher intensity for the PET signal can be obtained using beta+ -radioactive beams directly for treatment
- Difficult (low intensity)
- Intensity upgrade of the SIS-18 synchrotron and improved isotopic separation at FAIR (Facility for Antiproton and Ion Research at GSI) → now possible to reach radioactive ion beams with sufficient intensity to treat a tumor in small animals
- ^{11}C and ^{15}O beams



BARB project

(Biomedical Applications of Radioactive ion Beams)

- Small-animal PET scanner in development

Daria Boscolo et al., Front Oncol 2021. eCollection Radioactive Beams for Image-Guided Particle Therapy: The BARB Experiment at GSI

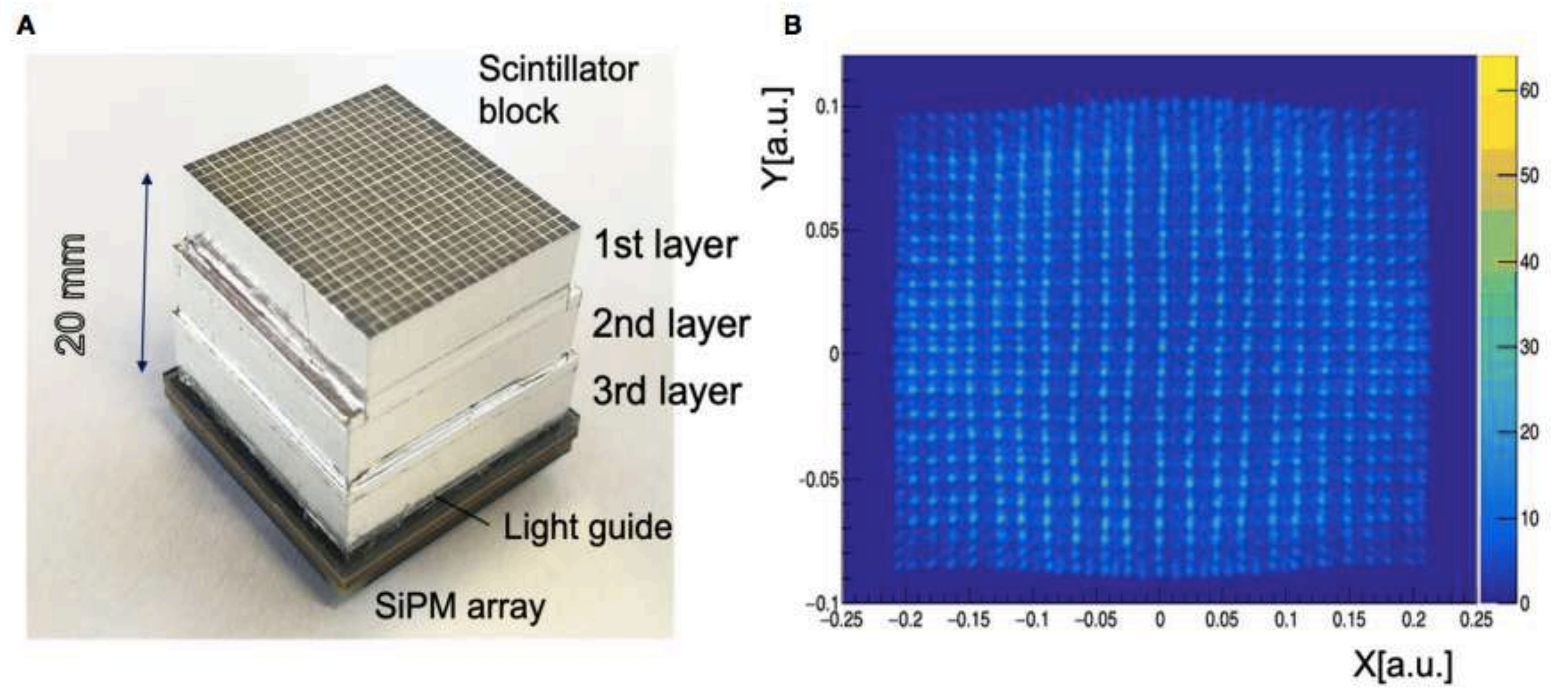
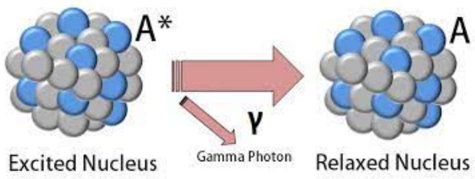


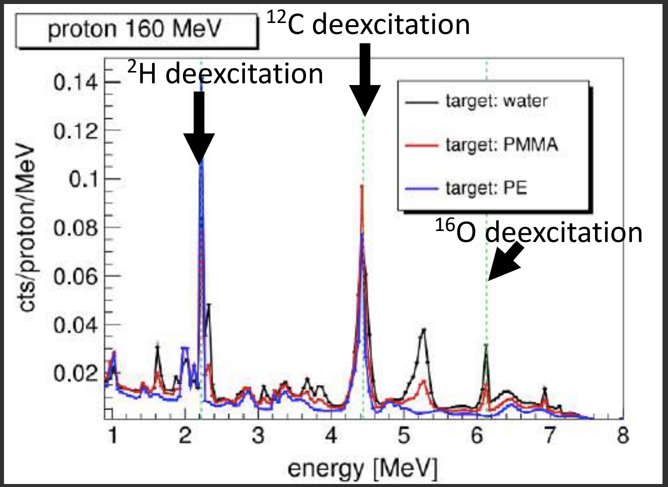
FIGURE 6 | LMU hybrid γ-PET detector **(A)** A 3-layer PET detector developed at LMU Munich in collaboration with NIRS-QST. The PET detector consists of a 3-layer scintillator block, a light guide and an 8 × 8 SiPM array. **(B)** A flood map of the 3-layer PET detector exposed to a ^{22}Na radioactive point source.

Prompt gamma

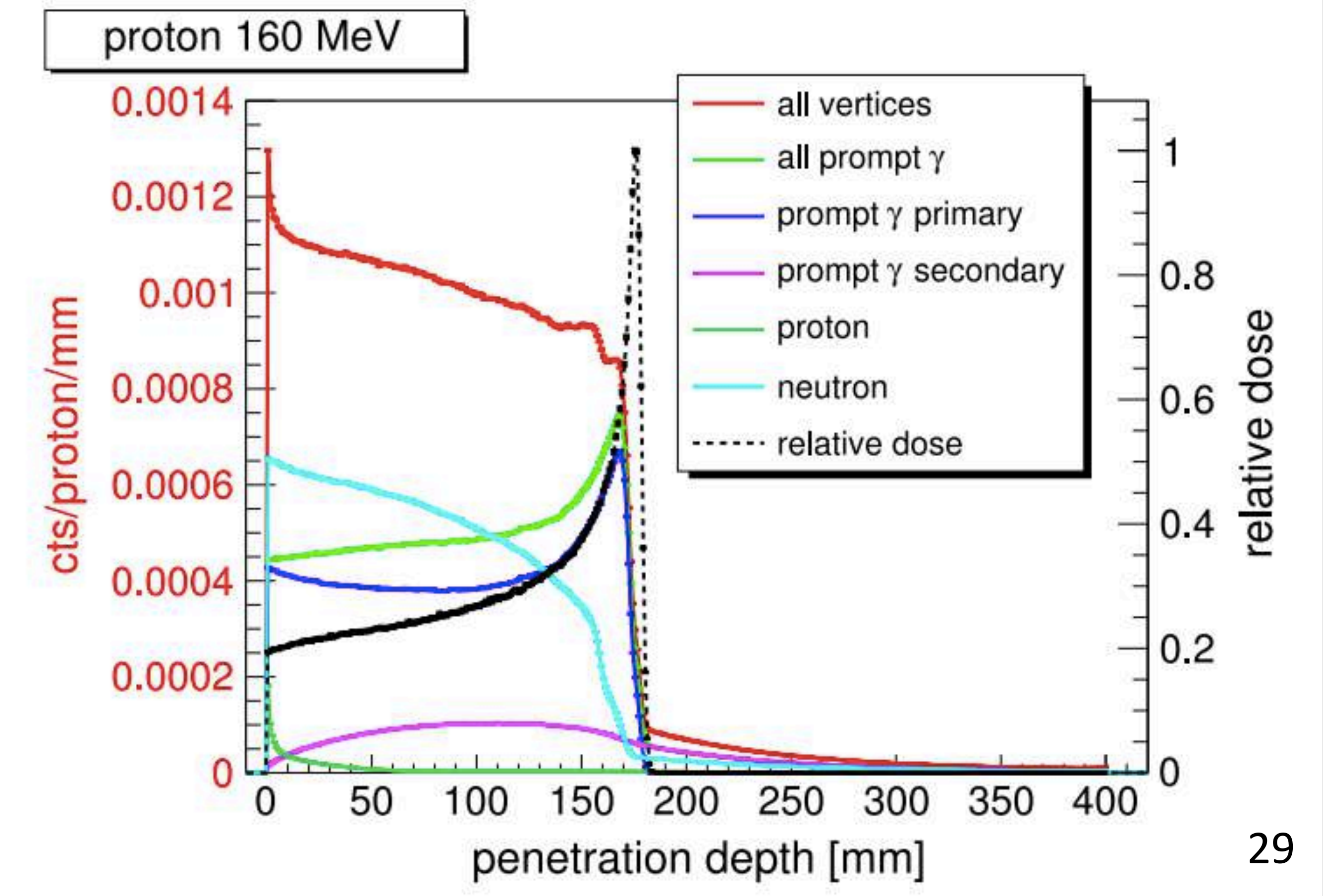


First proposed in 2003 by Stichelbaut and Jongen, first prototype by Min in 2006

Difficulties with detecting prompt gamma's:
- Broad energy spectrum (up to 10 MeV!!)
- Large background (neutrons)
- High instantaneous count rates
- Compatibility constraints with patient irradiation.



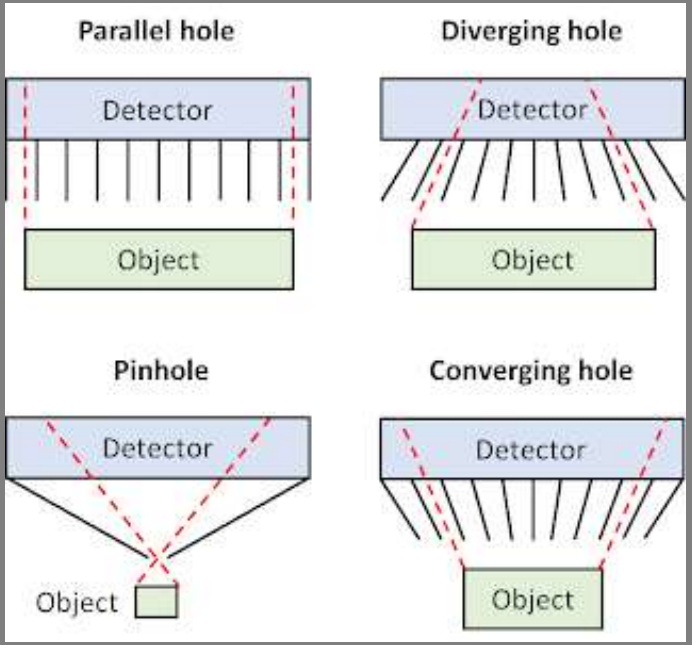
J.Krimmer, D.Dauvergne, J.M.Létang, É.Testa, Prompt-gamma monitoring in hadrontherapy: A review, NIM A 878, 2018, pp 58-73



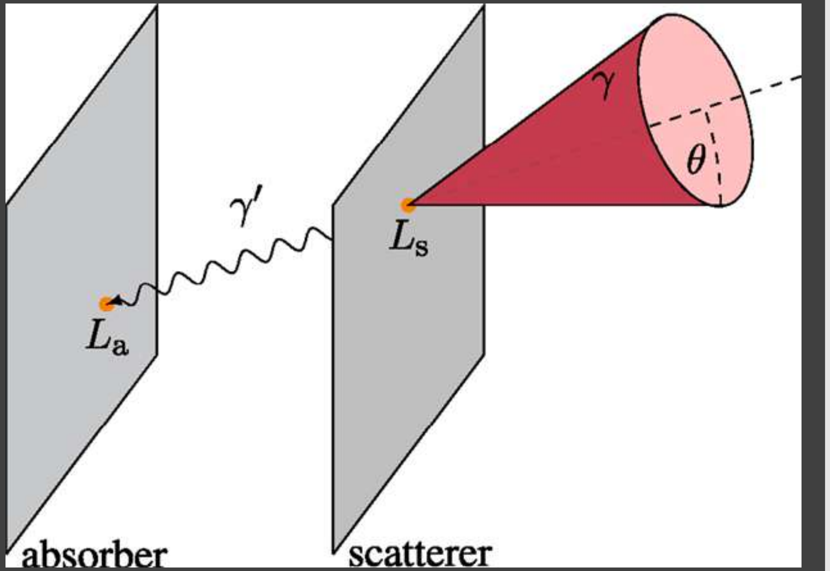
Prompt gamma

See for information and references: J.Krimmer, D.Dauvergne, J.M.Létang, É.Testa, Prompt-gamma monitoring in hadrontherapy: A review, NIM A 878, 2018, pp 58-73

Collimated gamma cameras

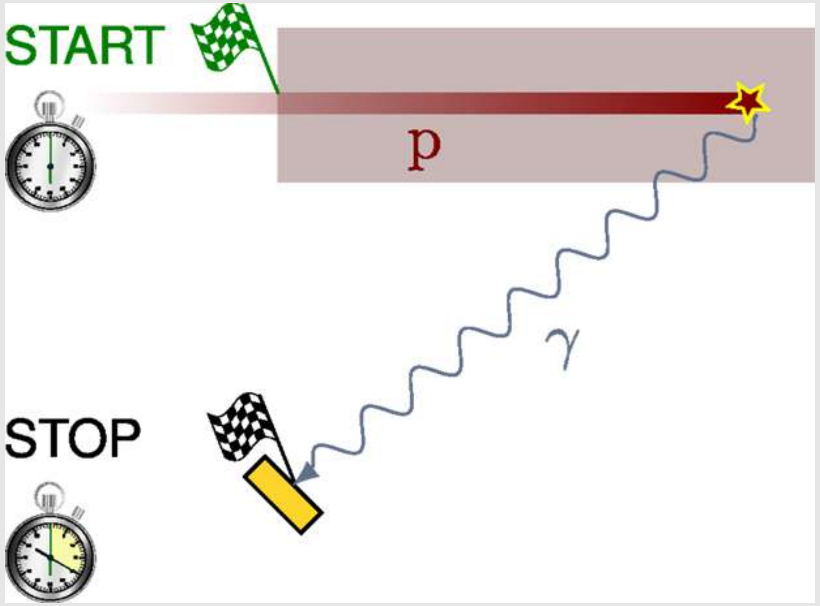


Compton cameras



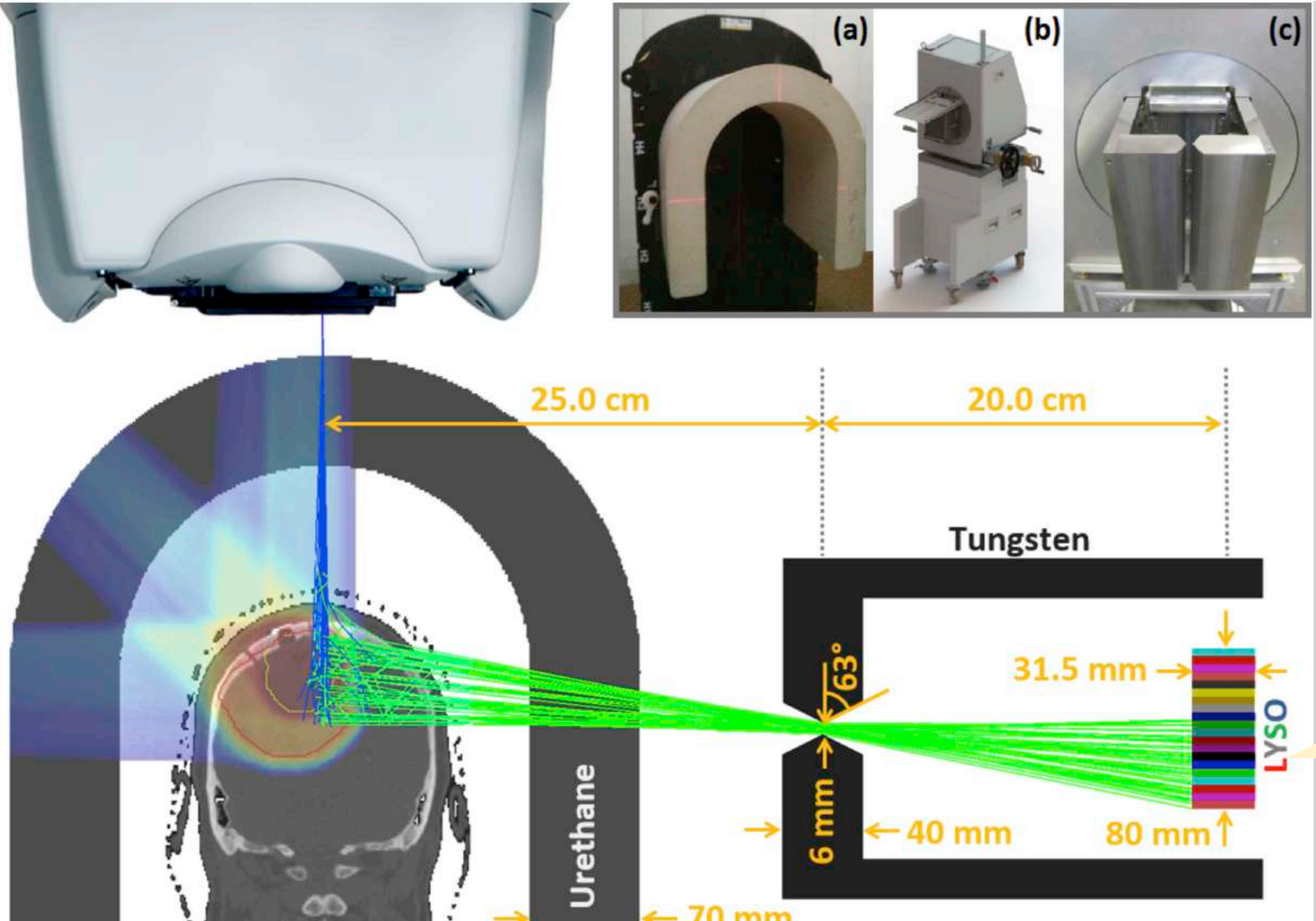
From F. Hueso-González, Front. Oncol., 2016

Others, for instance timing



From F. Hueso-González, Front. Oncol., 2016

Prompt gamma



Example of clinical applications of **collimated gamma** imaging systems:

IBA-USA collaboration: report 2 mm precision to detect shift

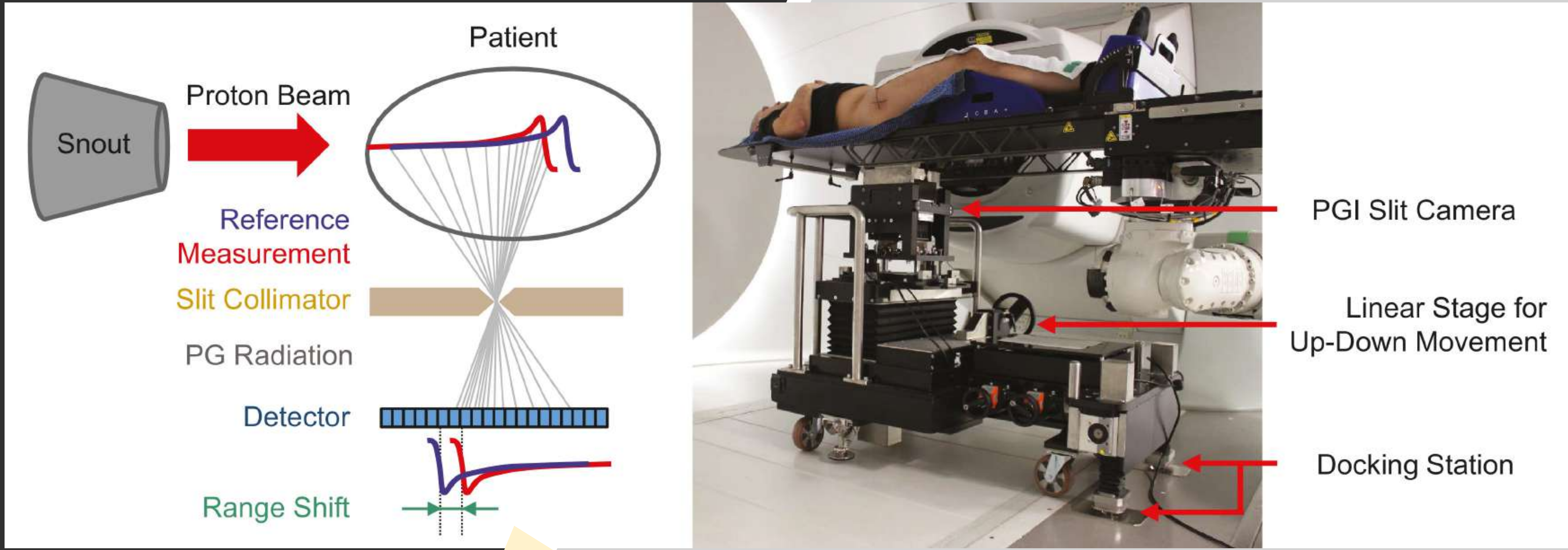
Yunhe Xie et al , Prompt Gamma Imaging for In Vivo Range Verification of Pencil Beam Scanning Proton Therapy Int. J. Rad. Onc. Bio. Phys. 99, 1, 2017, pp 210-218

Reversed projection of the prompt gamma depth emission profile is produced on the crystals

Prompt gamma

Other example of clinical applications of **collimated gamma** imaging systems:

J. Berthold et al, Int. J. Rad. Onc. Bio. Phys. 111, 4, **15 November 2021**, Pages 1033-1043



Reversed projection

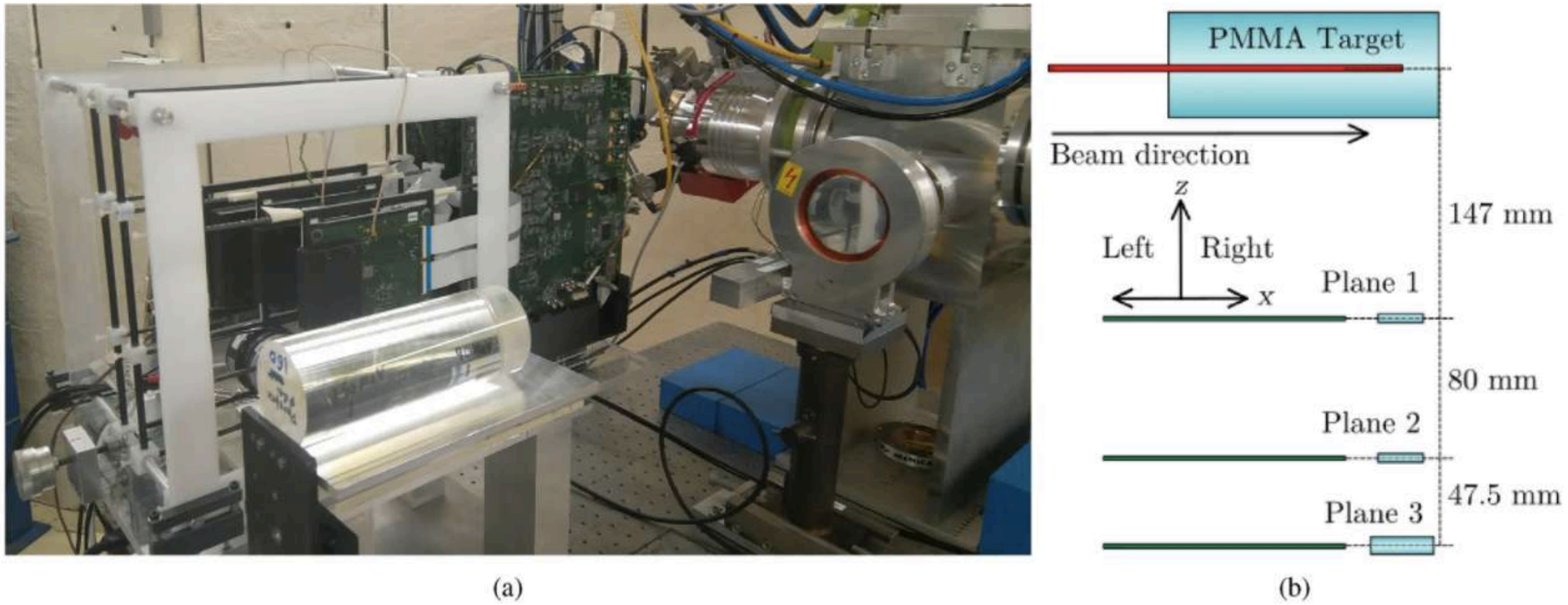
validation uncertainty of this second-generation PGI slit camera is about 1 mm (2σ)

Prompt gamma

MACACO II Compton camera multi-layer Compton camera based on LaBr3 scintillator crystals and SiPMs

E. Muñoz et al, Nature Scientific Reports 2021

- Allows calculation of the distal fall-of and identifcation of target displacements of 3 mm.



(**a**) Picture of the experimental set-up showing beam exit, PMMA target and Compton camera. (**b**) Diagram of relative distances in the experimental set-up.

Particle therapy

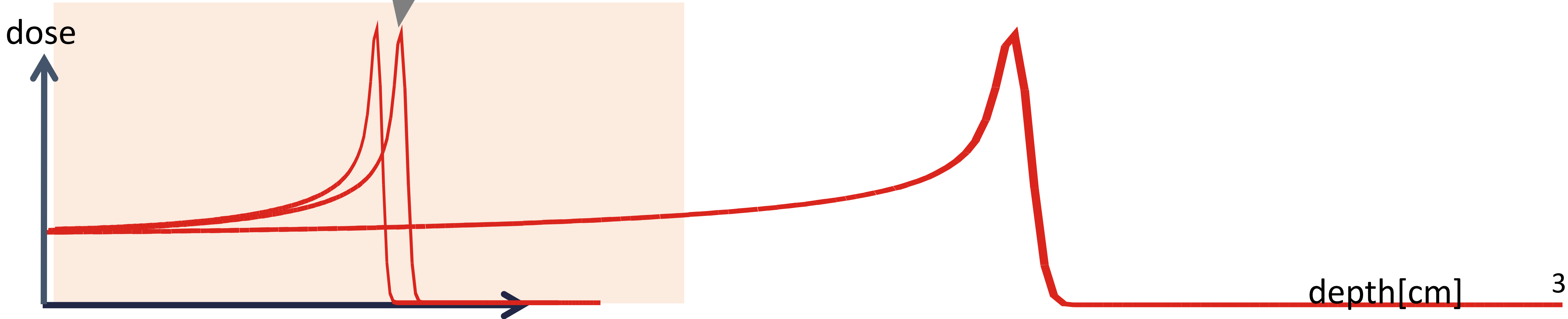
Based on Nuclear Reactions of Hadrons in Tissue

- Off-line & On-line PET
- Prompt gamma's and neutrons
- Prompt charged particles (only for Ions)

Beam stopping inside patient

Based on X-ray CT- analogous: pCT (only for Protons)

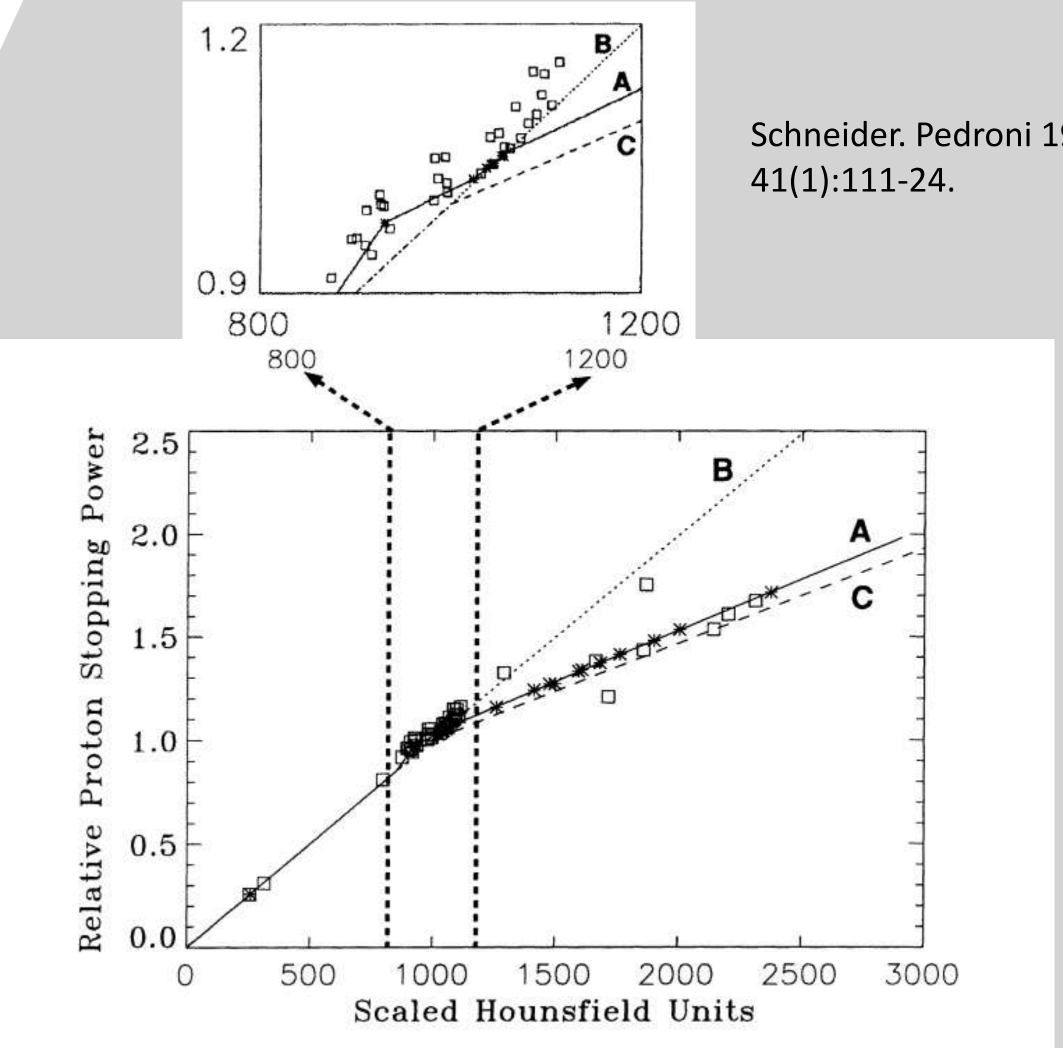
Beam going through



Proton CT: motivation

- Proton range depends on stopping power along the proton path.
- Currently stopping power determined by CT scan (x-Ray based)
- CT Hounsfield units have to be converted to particle stopping power… based on calibration curves → uncertainties!

- Can be improved…
  - Dual energy CT
  - Proton CT (see next)
  - …



Schneider. Pedroni 1996 41(1):111-24.

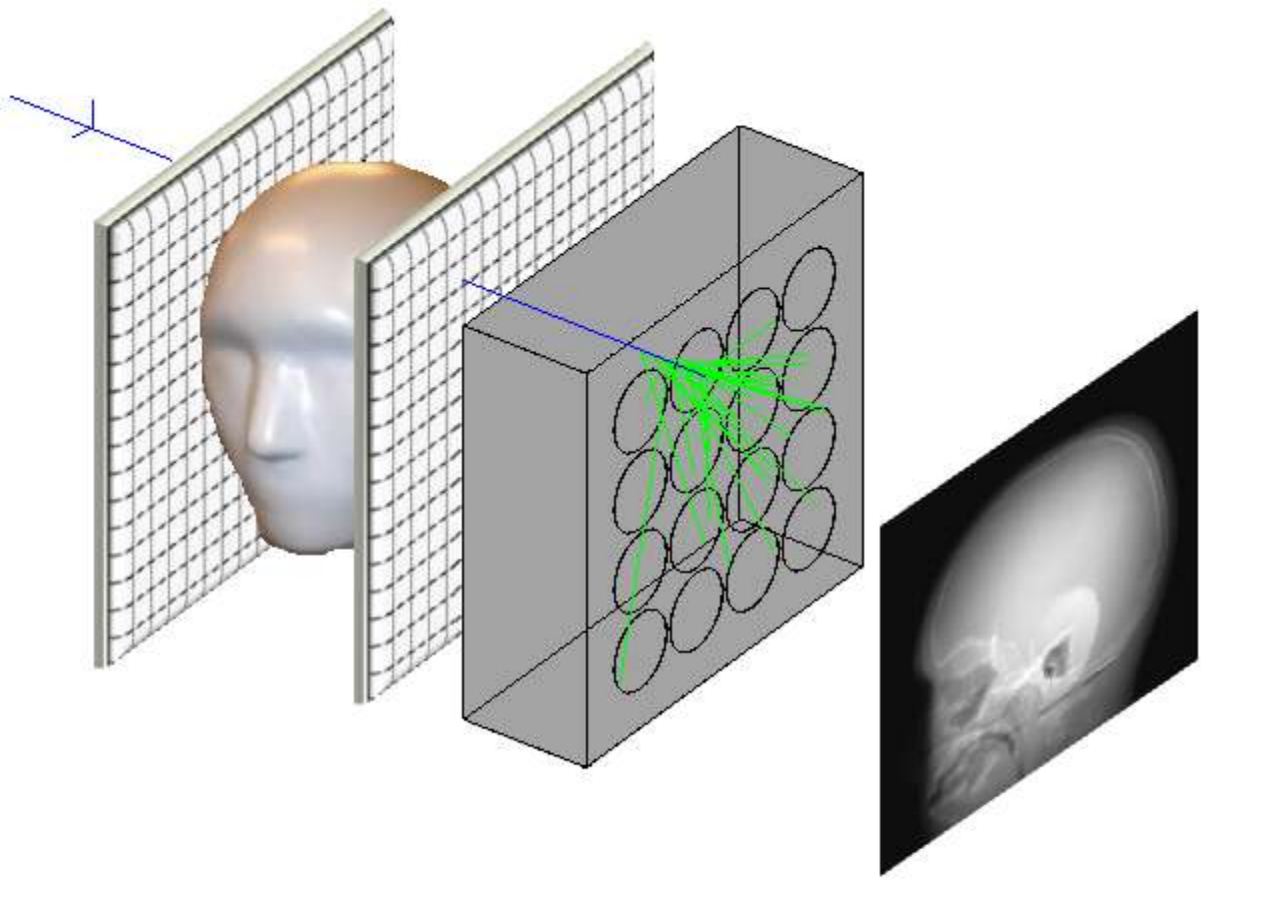
Proton CT

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

- Measure the position with a tracker before and after the target
- Measure the residual energy with an energy detector (calorimeter) downstream
- Make one planar view to obtain a proton-radiography (pR)
  - Source of image contrast is the energy loss of the transmitted protons (the integrated stopping powers of protons in the patient).
- Make many projections to obtain a proton-CT (pCT)
- Idea was originally proposed by Allan Cormack in 1963 (J.Appl. Phys.1963,34, p.2722)

Courtesy of A. Del Guerra. Krakow 2015

https://www.niu.edu/crcd/prospective-user/projects/proton-medical-imaging.shtml



Proton CT

Many initiatives…and much literature

Robert P Johnson,
Review of medical radiography and tomography with proton beams
Rep. Prog. Phys. 81 (2018) 016701 (21pp)

Conclusions

- Many applications of detectors and instrumentation in particle therapy
- Imaging is used during all stages of particle therapy
- Today discussed a few of the techniques, focusing on techniques used for treatment monitoring

Many thanks to the organizers of this workshop for the opportunity to give this lecture today!