PET range verification in proton therapy (research at U. Sevilla and CNA)

PhD thesis, April 2024

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IGFAE workshop on technologies and applied research at the future Galician proton-therapy facility

First, what else do we do in Seville?

Proton therapy studies @ U. Sevilla & CNA (I)

Selected publications:

- M.A. Cortés-Giraldo, J. M. Quesada et al., *An implementation to read and write **IAEA phase-space files in GEANT4**-based simulations,* Int J Radiat Biol. 88, 2012
- M.A. Cortés-Giraldo et al., *A critical study of different Monte Carlo **scoring methods of dose average linear-energy-transfer maps** calculated in voxelized geometries irradiated with clinical proton beams,* PMB 60, 2015
- Allison et al. (including M.A. Cortés-Giraldo, J. M. Quesada), *Recent **developments in Geant4**,* NIM-A 835, 2016
- A. Bertolet, M.A. Cortés-Giraldo, A. Carabe-Fernández, *Segment-averaged **LET** concept and analytical calculation from **microdosimetric** quantities in proton radiation therapy*, Med. Phys. 46, 2019
- A. Baratto-Roldán, A. Bertolet, G. Baiocco, A. Carabe, M.A. Cortés-Giraldo, ***Microdosimetry and Dose-Averaged LET Calculations** of Protons in Liquid Water: A Novel Geant4-DNA Application*, Frontiers in Physics 9, 2021
- Daniel Suarez, this workshop!

Geant4 | Microdosimetry | LET

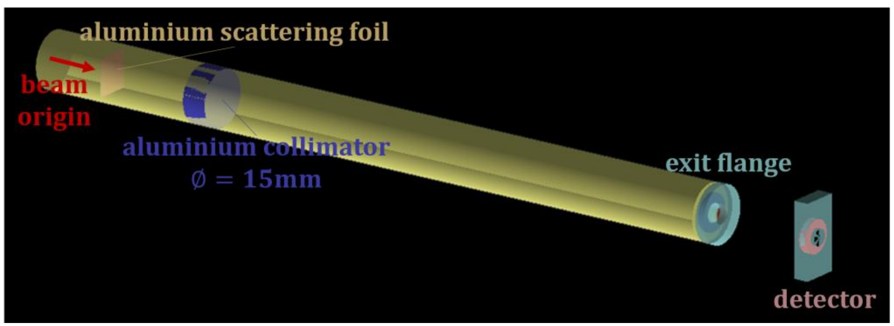
Proton therapy studies @ U. Sevilla & CNA (II)

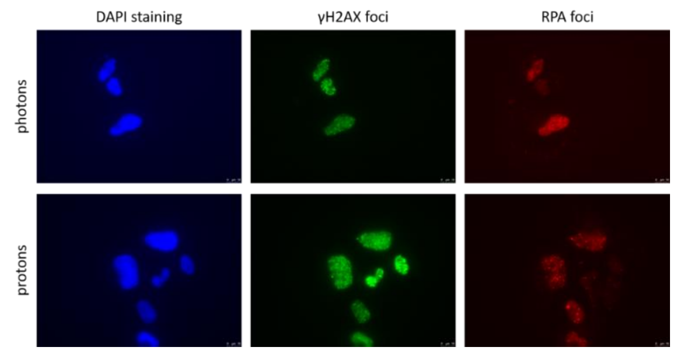
Radiobiology beamlines at the 3MV Tandem & 18 MeV Cyclotron (PhDs of Battaglia & Baratto)

- C. Battaglia et al., *EBT3 film calibration in the Bragg peak region for proton beams below 5 MeV*, NIM-B 444, 2019

- A. Baratto et al., *Feasibility study of a proton irradiation facility for radiobiological measurements at an 18 MeV cyclotron*, Instruments 2, 2018

- A. Baratto et al., *Preparation of a radiobiology beam-line at the 18 MeV proton cyclotron facility at CNA*, Physica Medica 74, 2020





Detector's characterization, beam tests, etc:

- Topics related to the acceleration of protons and ions by ultra-intense laser pulses, oriented to biomedical applications **[with I3M]**

- Characterization of new 3D-detectors for microdosimetry in hadrontherapy **[with IMB-CNM-CSIC, IJCLab-CNRS, USC]**

- Prompt gamma imaging with MACACO **[with IFIC-CSIC]**

Now, PET beam range verification

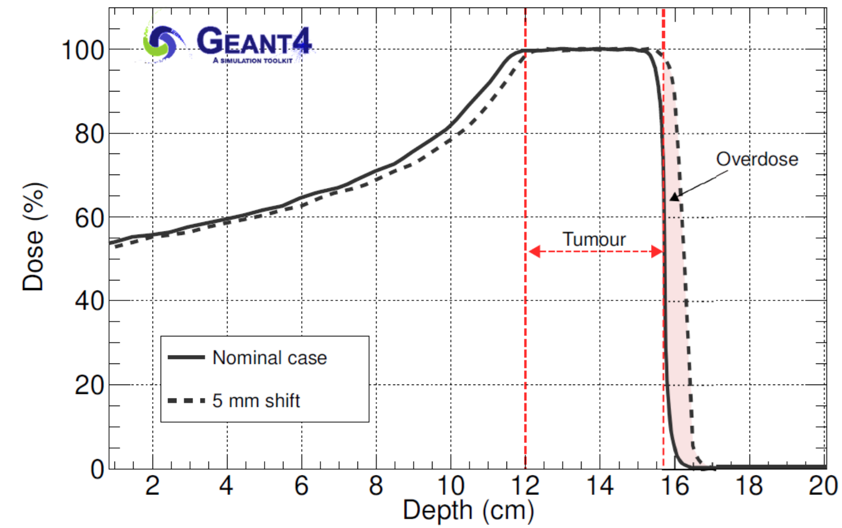
Uncertainties in the beam range

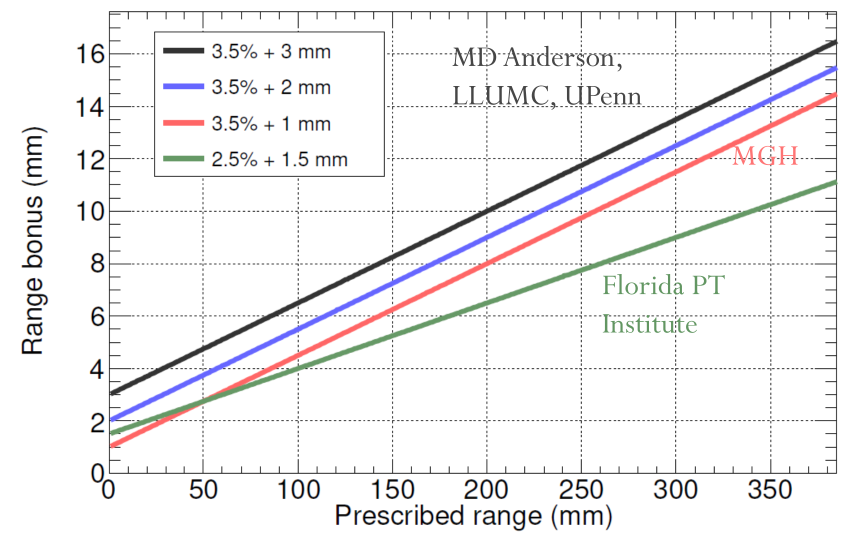
- Non-irradiation of part of the tumour and/or irradiation of healthy tissues

- Main sources of range uncertainty:
  - Stopping power
  - Algorithm used in treatment plannings
  - Changes in patient anatomy or position from the initial plans.
    - Changes in metabolism.
    - Changes during the beam delivery.

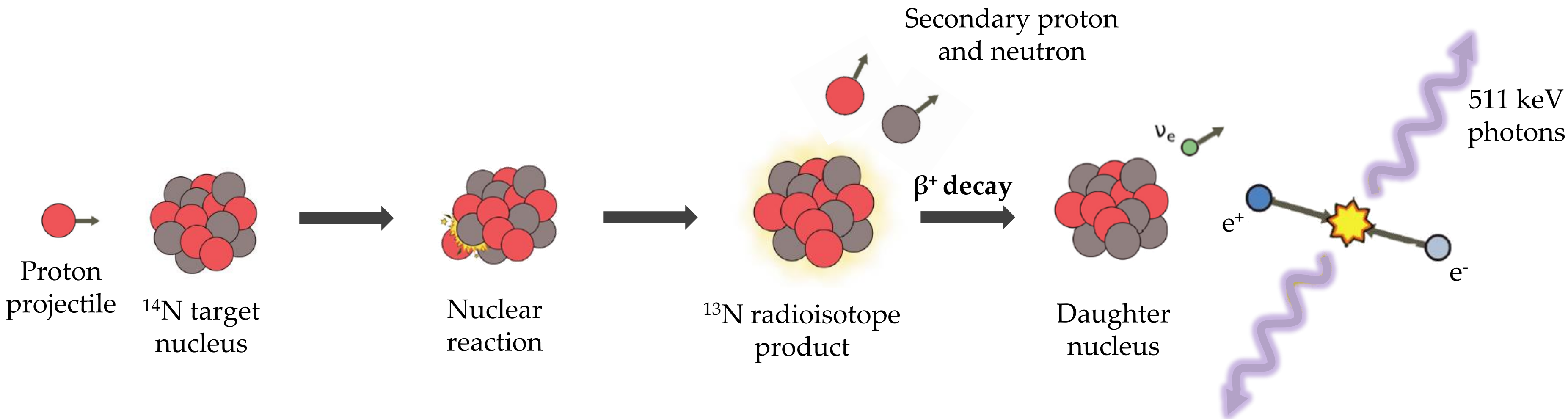
- Addition of a safety margin to the prescribed range to ensure the coverage of the tumour.

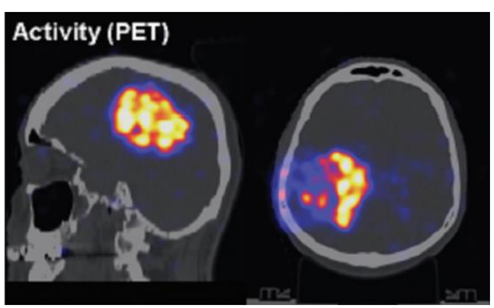
Need of range verification to reduce the high safety margins applied in the clinic to fully exploit the benefits of proton therapy



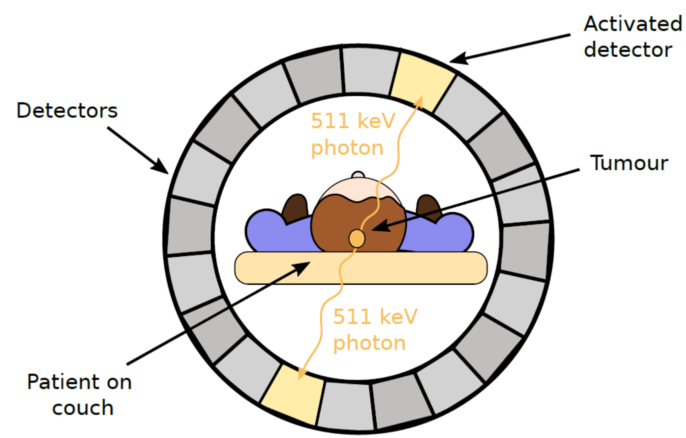


PET range verification





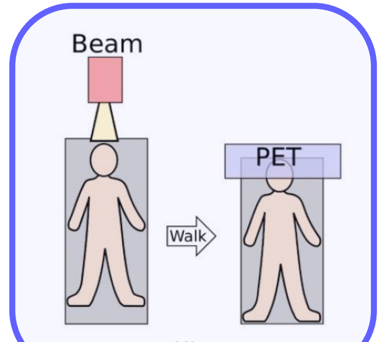
SE Combs, J Bauer, D Unholtz et al,
BMC Cancer **12** (2012)



Types of PET range verification

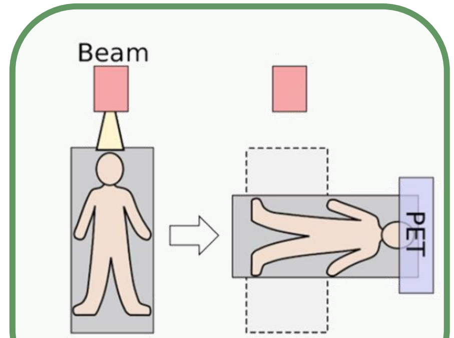
The PET imaging can be applied online or offline, depending on the half-lives of the β^+ emitters that one looks at, which can vary from milliseconds to minutes.

Isotope	Half-life	Q_{β^+} (MeV)	Reaction channel	Threshold (MeV)
^{11}C	20.36 min	0.960	$^{12}C(p,x)^{11}C$	17.9
			$^{14}N(p,x)^{11}C$	3.13
			$^{16}O(p,x)^{11}C$	23.6
^{13}N	9.97 min	1.198	$^{12}C(p,x)^{13}N$	-
			$^{14}N(p,x)^{13}N$	8.93
			$^{16}O(p,x)^{13}N$	5.55
^{15}O	122 s	1.735	$^{14}N(p,x)^{15}O$	-
			$^{16}O(p,x)^{15}O$	14.3
^{12}N	11 ms	16.316	$^{12}C(p,x)^{12}N$	19.6
^{38m}K	0.925	5.022	$^{40}Ca(p,x)^{38m}K$	14.0
^{29}P	4.14 s	3.921	$^{31}P(p,x)^{29}P$	15.6



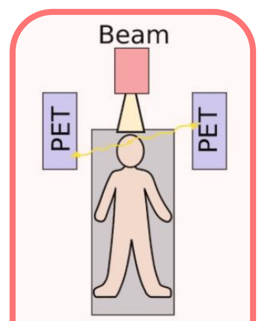
Offline

- Affected by wash-out effects
- No immediate feedback on the dose delivered
- Use of conventional PET scanners



In-room

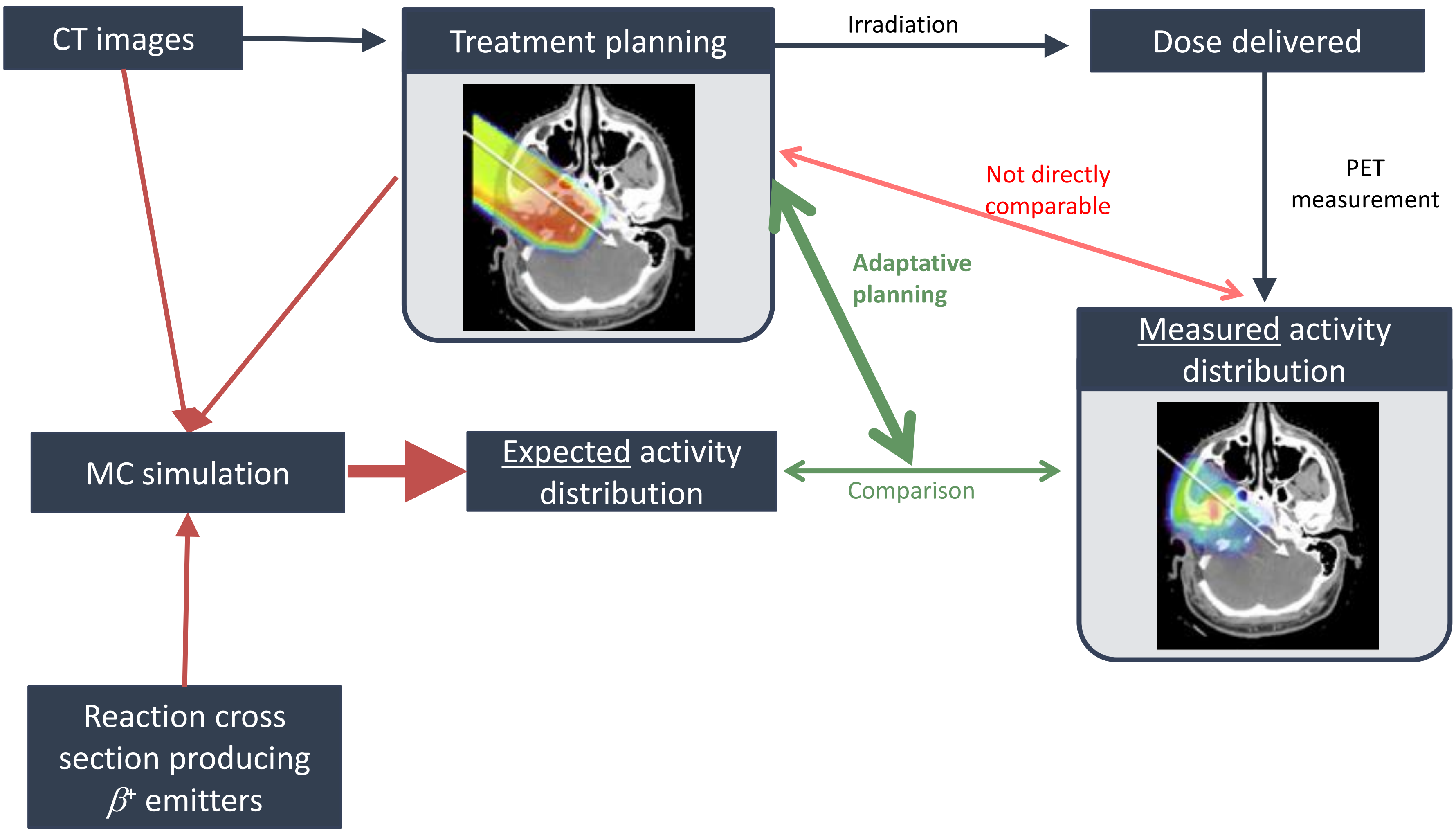
- Compromise solution
- Use of conventional PET scanners
- Less affected by biological wash-out effect



Online

- Not affected by wash-out effects
- Immediate feedback on the dose delivered
- Need a PET coupled to the gantry

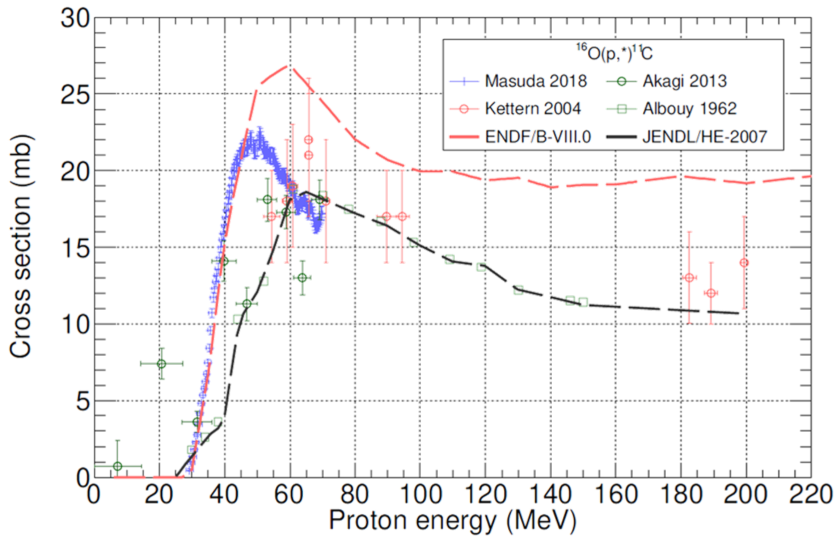
Full implemetation of PET range verification

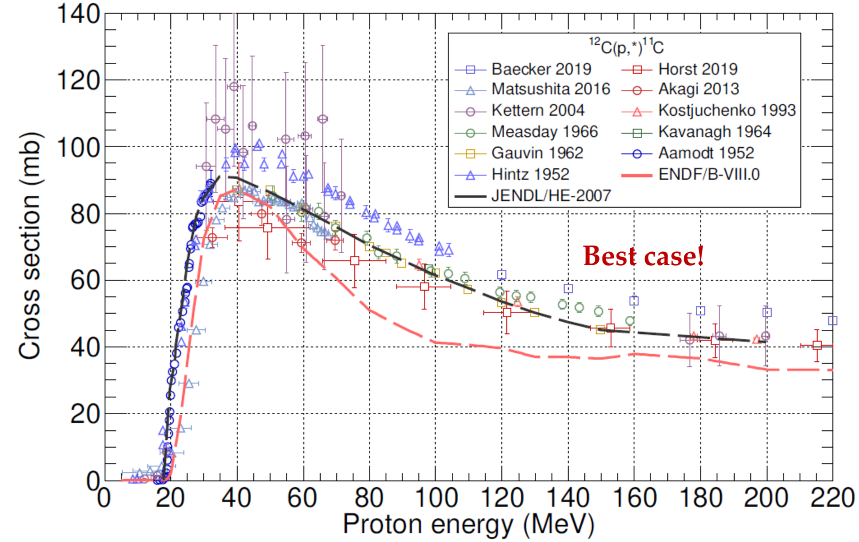


β^+ production cross section measurements

Nuclear cross sections: state-of-the-art

- **Long-lived β⁺ emitters:**



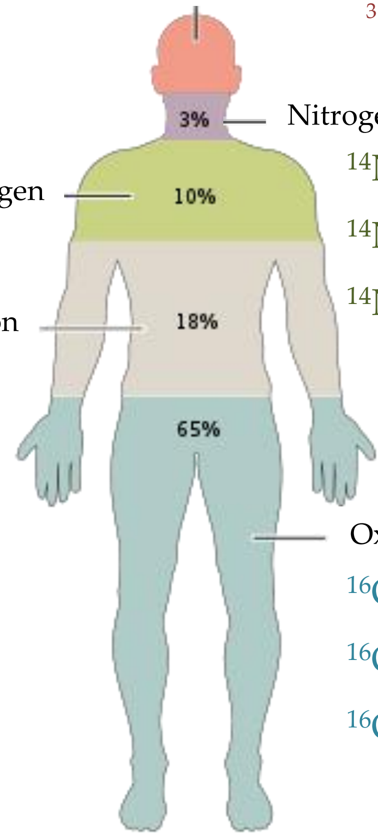


- **Short-lived β⁺ emitters:**
  - No differential data (integral production yield below 55 MeV).
  - Therefore, no reliable evaluated databases.

See España et al. (2011) for a detailed (but not up to date) study on "*Reliability of proton-nuclear interaction cross section data to predict proton-induced PET images in proton therapy*"

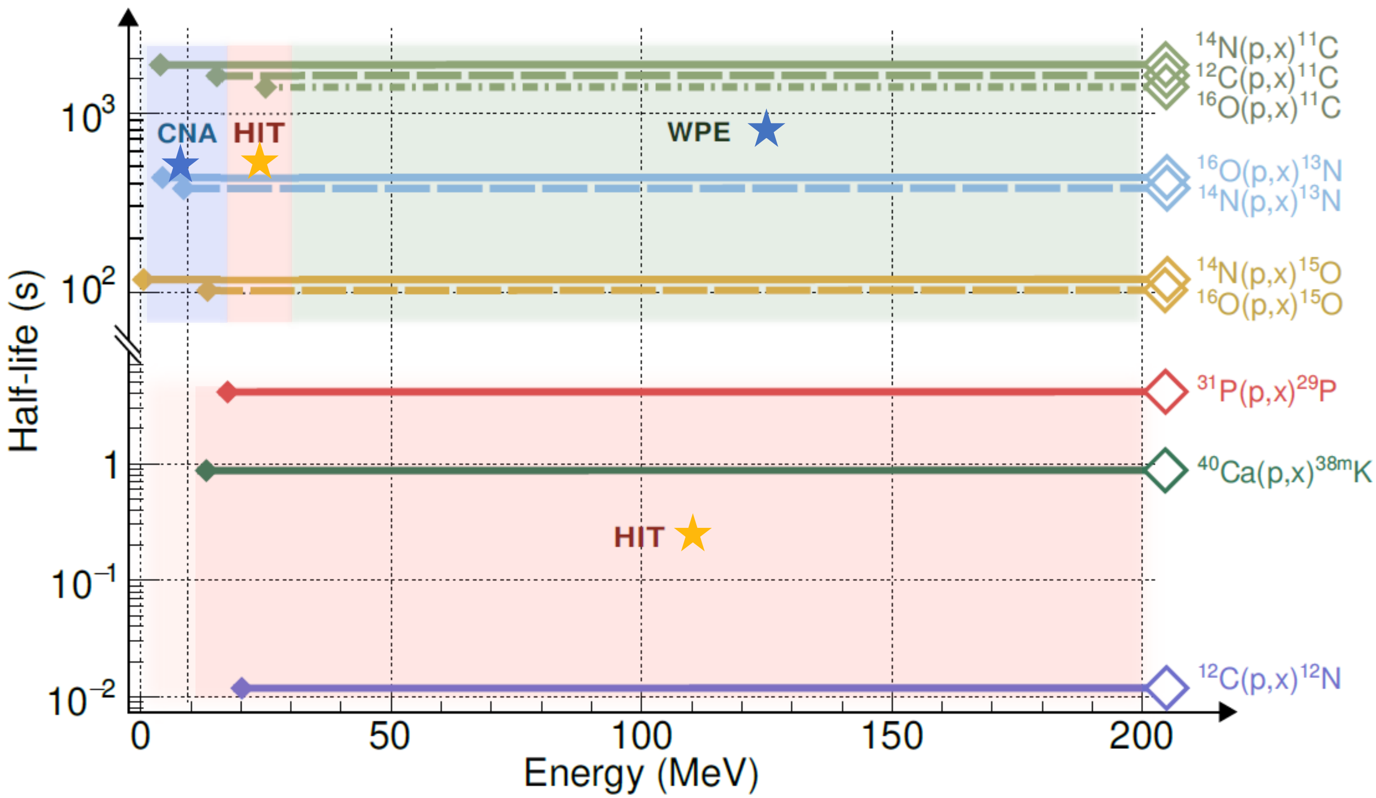
Goal: A New/**Accurate/Complete** XS data set

Measurement of the proton-induced reaction cross sections of the **long- and short-lived β^+ emitters** from threshold up to clinical energies (200 MeV) in the main elements of the human body.



But, can we do ~400 (11 reactions x 20to50 data points) experiments?

“Activation” experiments at CNA, WPE and HIT



Multi-foil activation and PET scanner ★

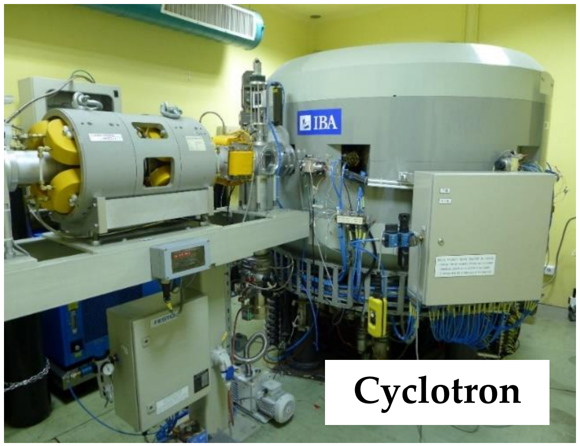
Single-foil activation and conventional detectors ★

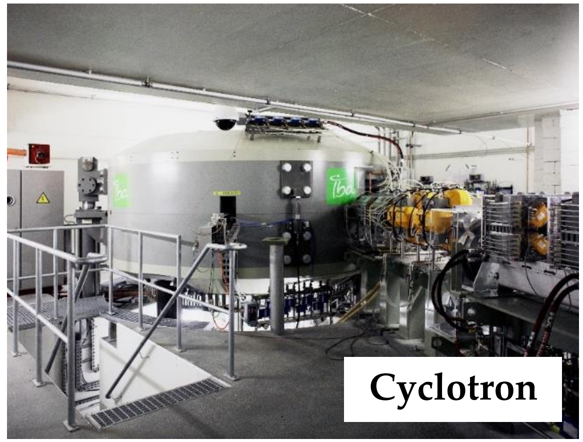
Irradiation facilities

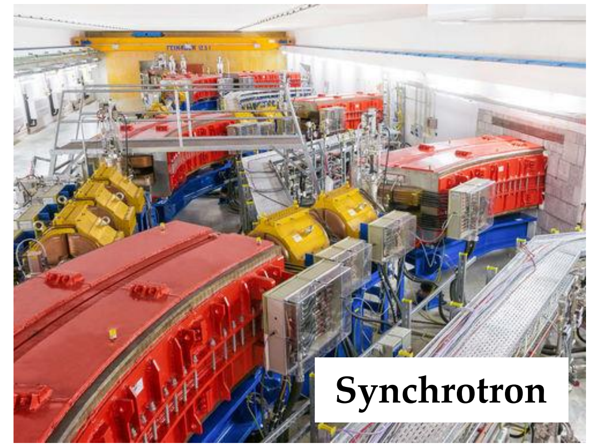
CNA Centro Nacional de Aceleradores — Infraestructuras Científicas y Técnicas Singulares

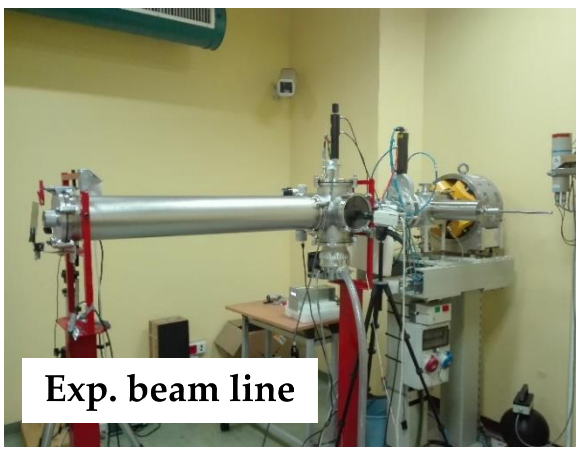
wpe Westdeutsches Protonentherapiezentrum Essen

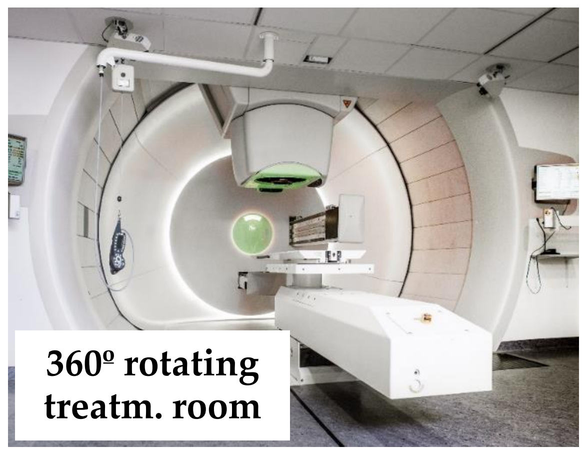
HIT Heidelberger Ionenstrahl-Therapiezentrum — HITRI Heavy Ion Therapy Research Integration



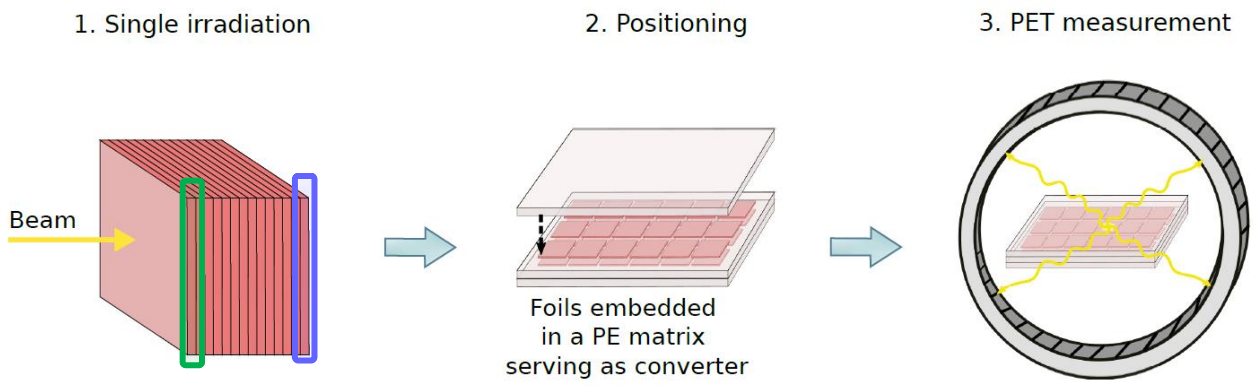


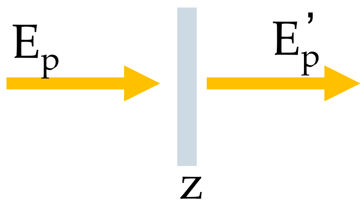


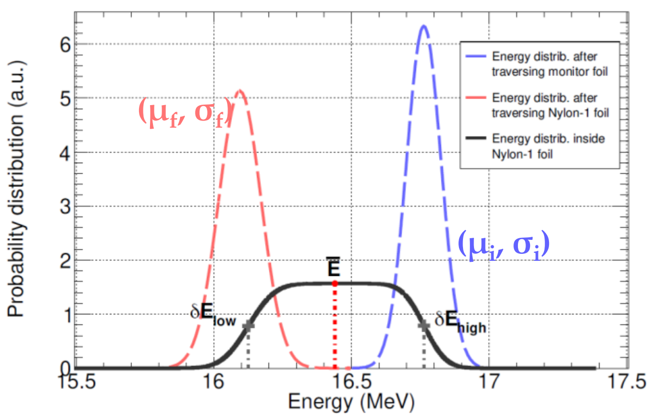


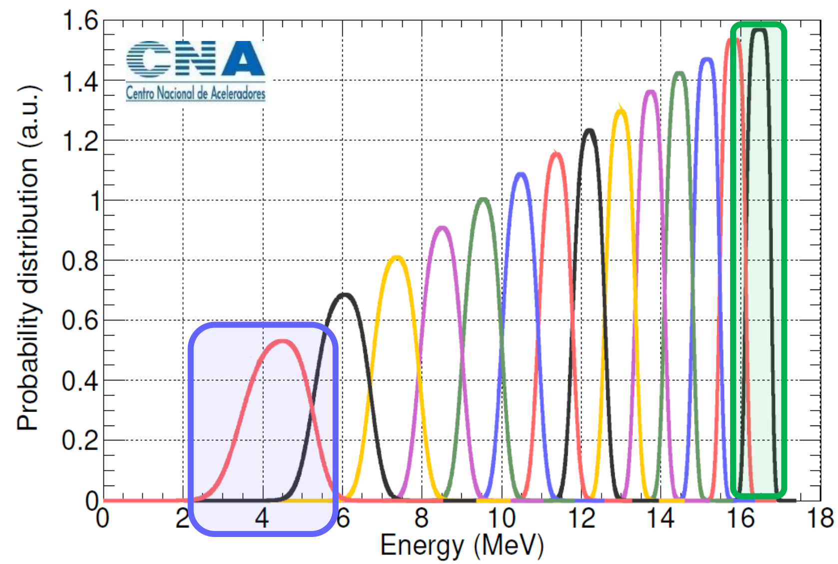


Multi-foil activation with PET scanner

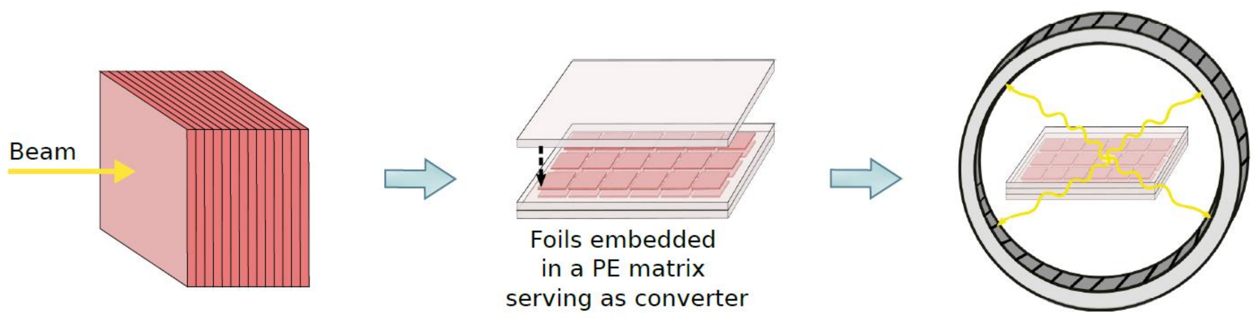


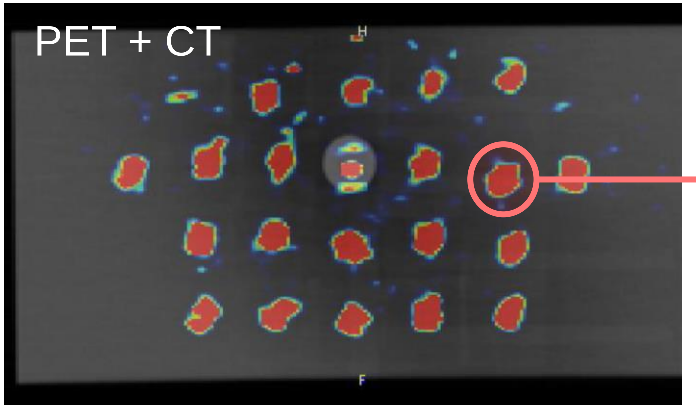


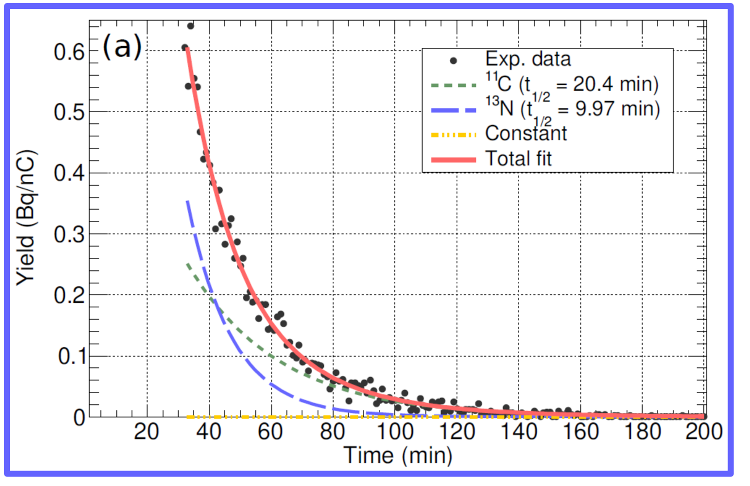




Multi-foil activation with PET scanner

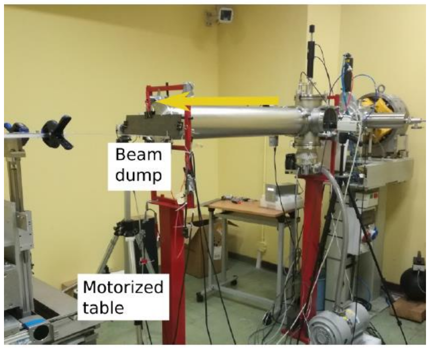


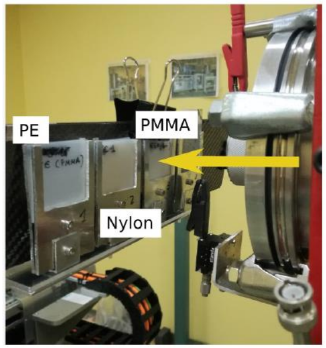


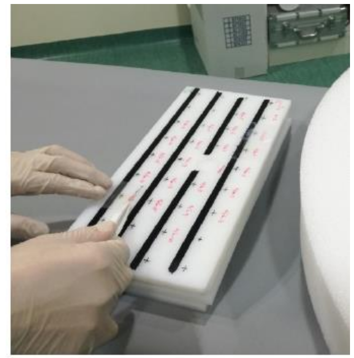


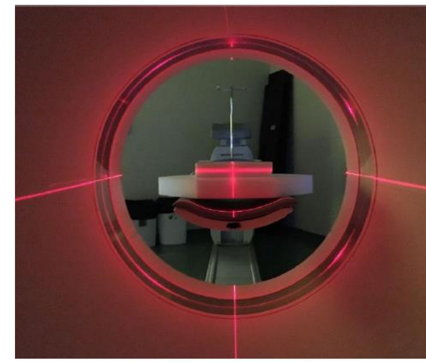
Mutifoil+PET @CNA & WPE

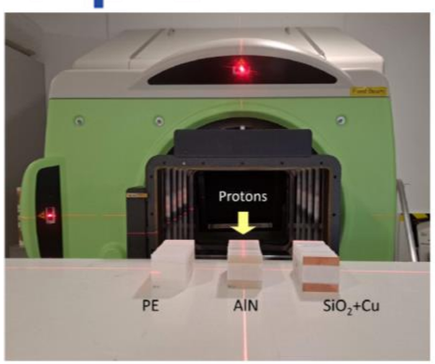
- **Long-lived isotopes: ^{11}C, ^{13}N and ^{15}O**

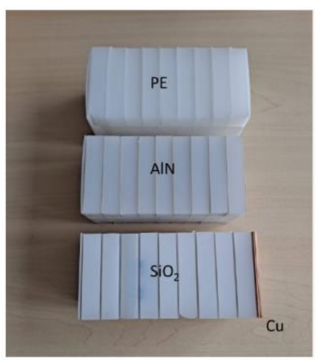


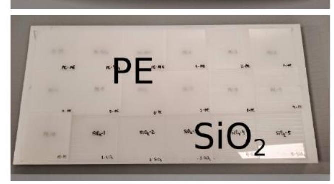






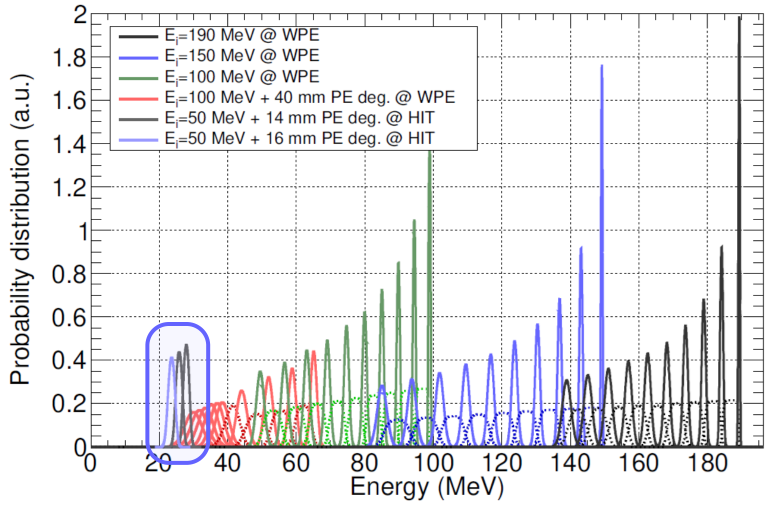


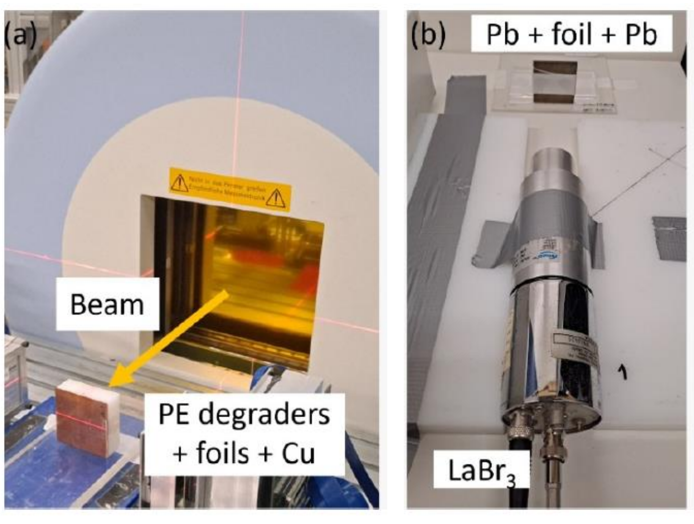




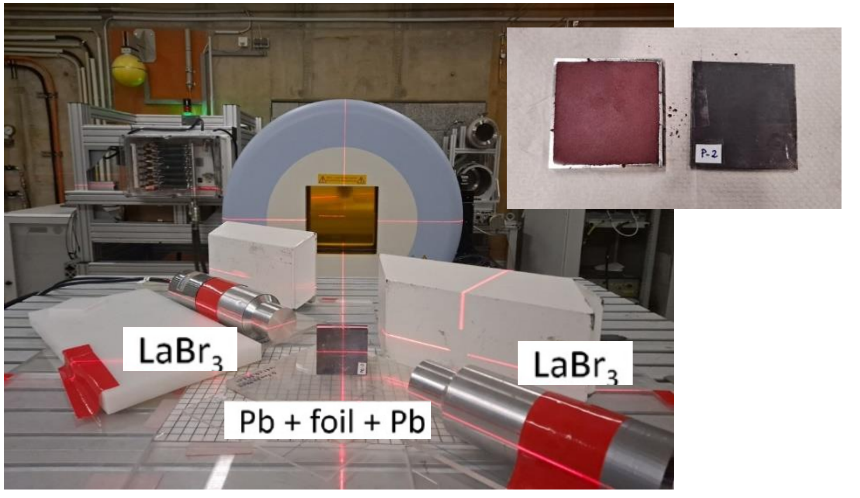
Single foil+$LaBr_3$ @HIT

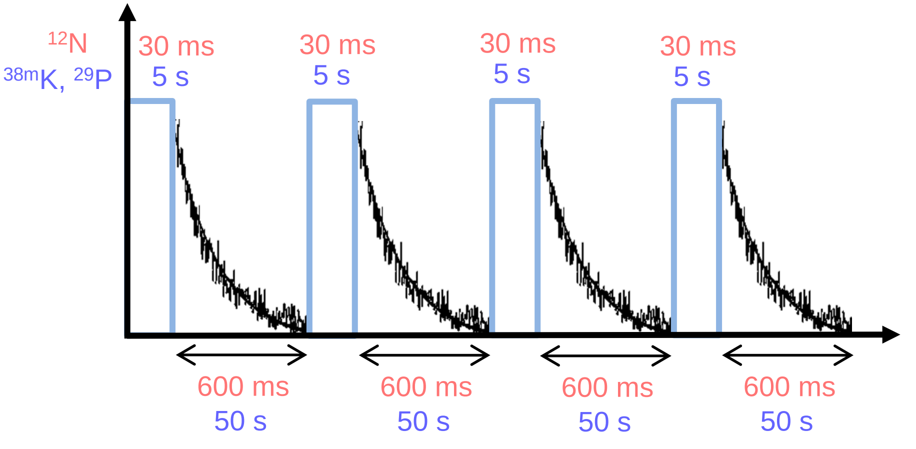
- **Long-lived isotopes: ^{11}C, ^{13}N and ^{15}O**



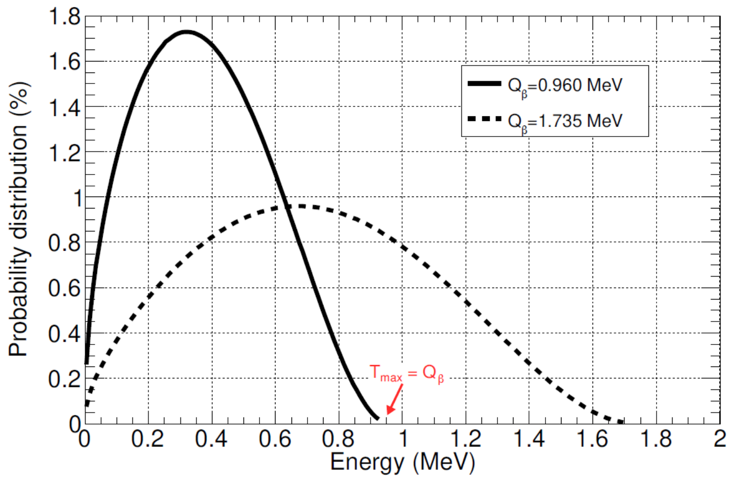


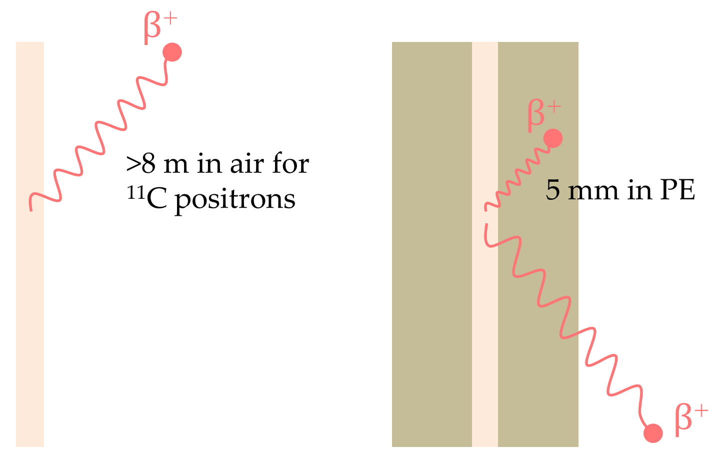
- **Short-lived isotopes: ^{12}N, ^{38m}K and ^{29}P**



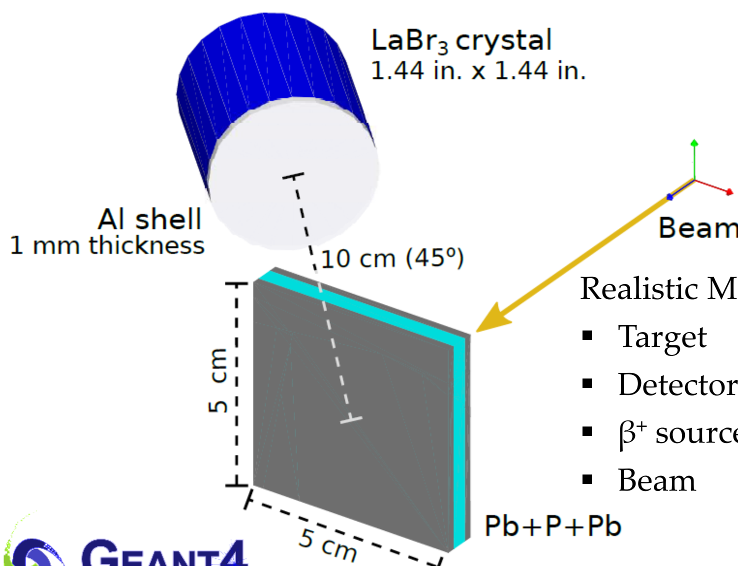


Escaping positrons and photon attenuation



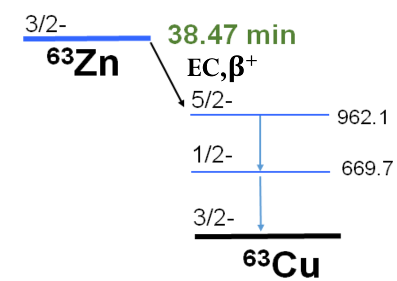


$\varepsilon_{conv} \neq 100\%$



Realistic MC:

- Target
- Detector
- β^+ source
- Beam



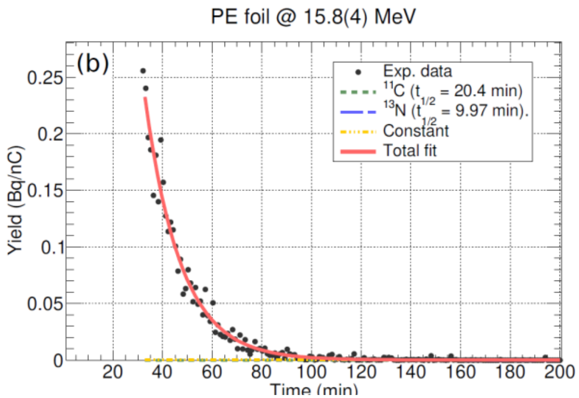
Activation:
$^{63}Cu(p,n)^{63}Zn$

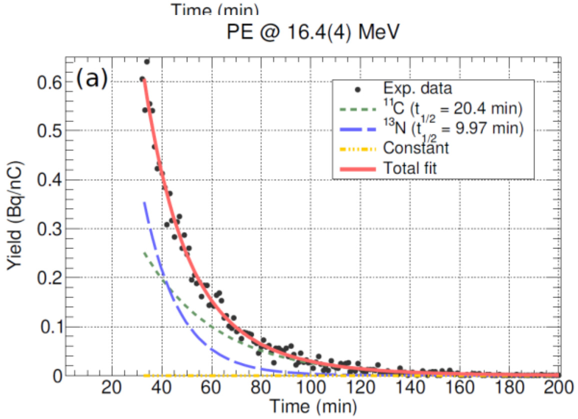
	Source	I (%)	ε (%)	Yield (kBq/nC)
✓	**670 keV**	8.19(32)	0.1284(18)	2.24(11)
✓	**962 keV**	6.50(16)	0.1773(14)	2.31(11)
✓	**e⁺**	92.8(5)	0.459(6)	2.24(11)
✗	**(2x) 511 keV**	92.8(5)	0.572(8)	1.80(9)

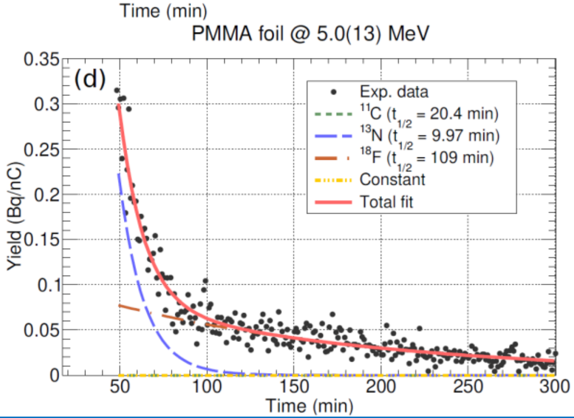
~1.7%

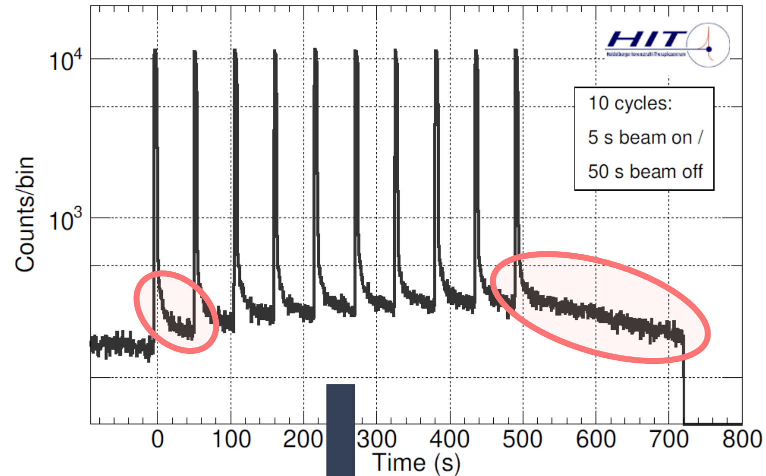
25%

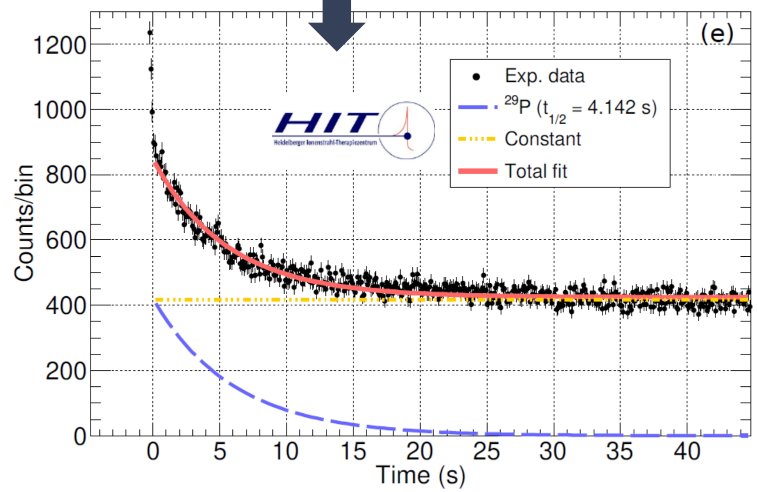
Analysis of the decay curves





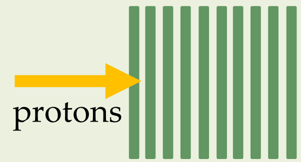


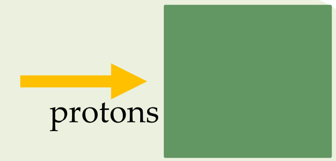


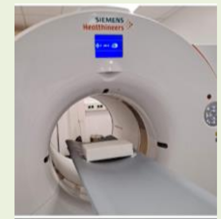


Validation techniques: accuracy & reliability

1) **Integral vs. differential yields of ^{11}C and ^{13}N**

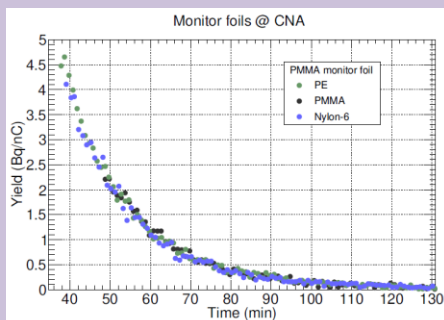


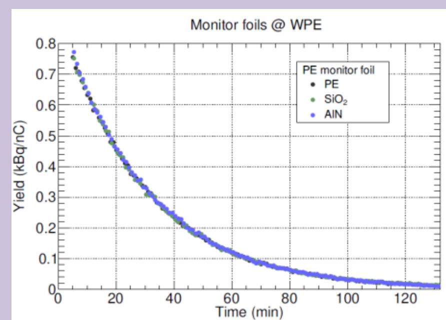




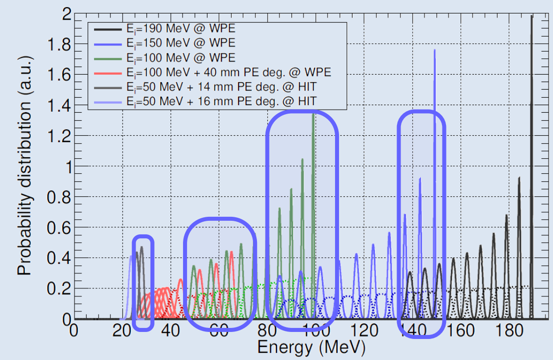
VS.

2) **Monitor foils (multi-foil activation experiments)**

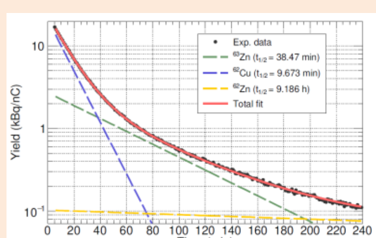




3) **Overlapping between consecutive irradiations**



4) **IAEA $^{nat}Cu(p,x)^{63}Zn$ monitor reaction**

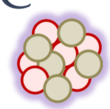


Systematic uncertainties:

	ε	n_s	N_p	Reproducibility	Total
CNA	5%	1%	4%	4.5%	8%
WPE	4%	1%	1%	1.8%	5%
HIT	2%	1-3%	5%	-	6%

Long-lived β⁺ emitters

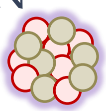
^{11}C



$t_{1/2}$=20.36 min

- $^{12}C(p,x)^{11}C$
- $^{14}N(p,x)^{11}C$
- $^{16}O(p,x)^{11}C$

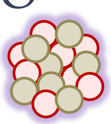
^{13}N



$t_{1/2}$=9.97 min

- $^{12}C(p,x)^{13}N$
- $^{14}N(p,x)^{13}N$
- $^{16}O(p,x)^{13}N$

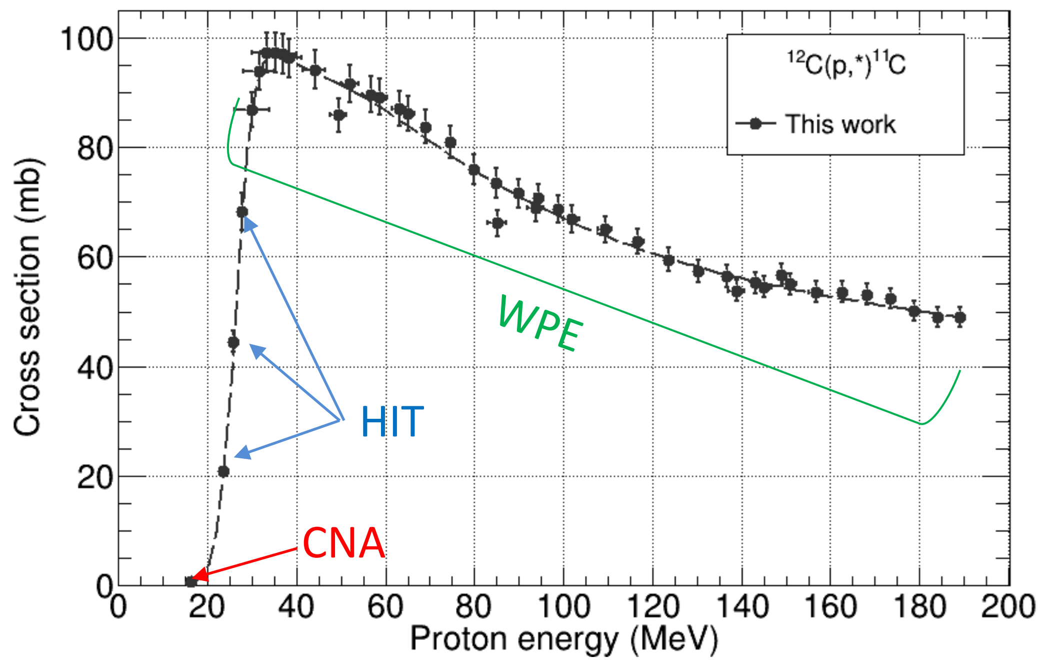
^{15}O



$t_{1/2}$=122 s

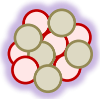
- $^{14}N(p,x)^{15}O$
- $^{16}O(p,x)^{15}O$

$$f(x) = \frac{\sum_{i=0}^{4} a_i \cdot x^i}{x^5 + \sum_{j=0}^{4} b_j \cdot x^j}$$



Long-lived β^+ emitters

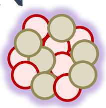
^{11}C



$t_{1/2}$=20.36 min

- $^{12}C(p,x)^{11}C$
- $^{14}N(p,x)^{11}C$
- $^{16}O(p,x)^{11}C$

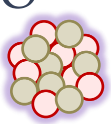
^{13}N



$t_{1/2}$=9.97 min

- $^{12}C(p,x)^{13}N$
- $^{14}N(p,x)^{13}N$
- $^{16}O(p,x)^{13}N$

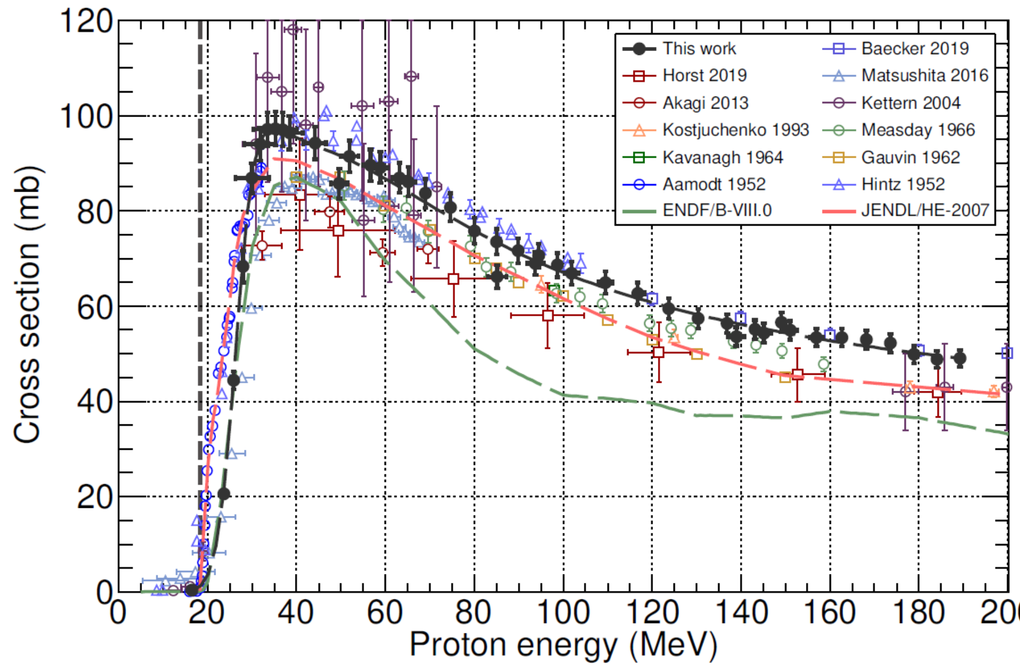
^{15}O



$t_{1/2}$=122 s

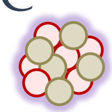
- $^{14}N(p,x)^{15}O$
- $^{16}O(p,x)^{15}O$

$$f(x) = \sum_{i=0}^{4} a_i \cdot x^i$$



Long-lived β⁺ emitters

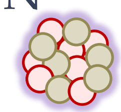
^{11}C



$t_{1/2}$=20.36 min

- $^{12}C(p,x)^{11}C$
- **$^{14}N(p,x)^{11}C$**
- $^{16}O(p,x)^{11}C$

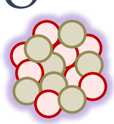
^{13}N



$t_{1/2}$=9.97 min

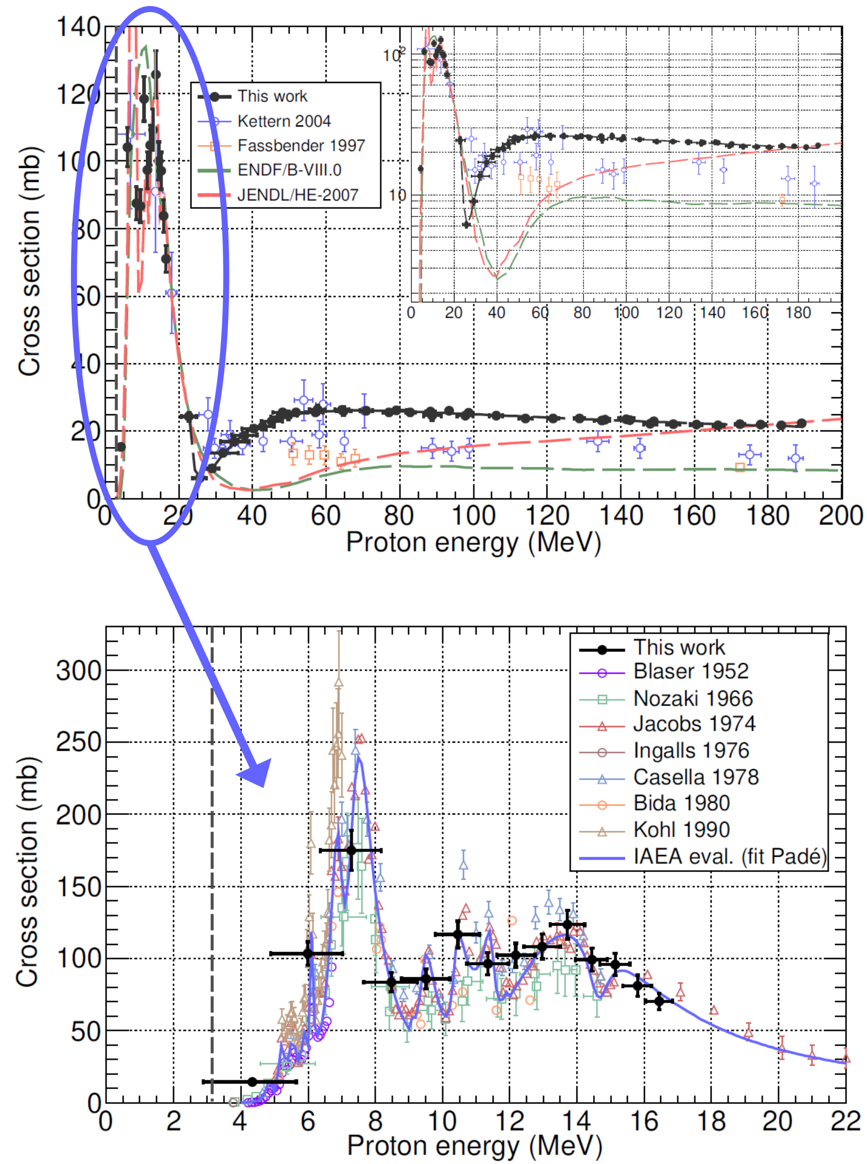
- $^{12}C(p,x)^{13}N$
- $^{14}N(p,x)^{13}N$
- $^{16}O(p,x)^{13}N$

^{15}O



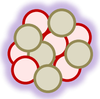
$t_{1/2}$=122 s

- $^{14}N(p,x)^{15}O$
- $^{16}O(p,x)^{15}O$



Long-lived β^+ emitters

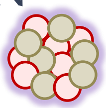
^{11}C



$t_{1/2}$=20.36 min

- $^{12}C(p,x)^{11}C$
- $^{14}N(p,x)^{11}C$
- $^{16}O(p,x)^{11}C$

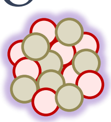
^{13}N



$t_{1/2}$=9.97 min

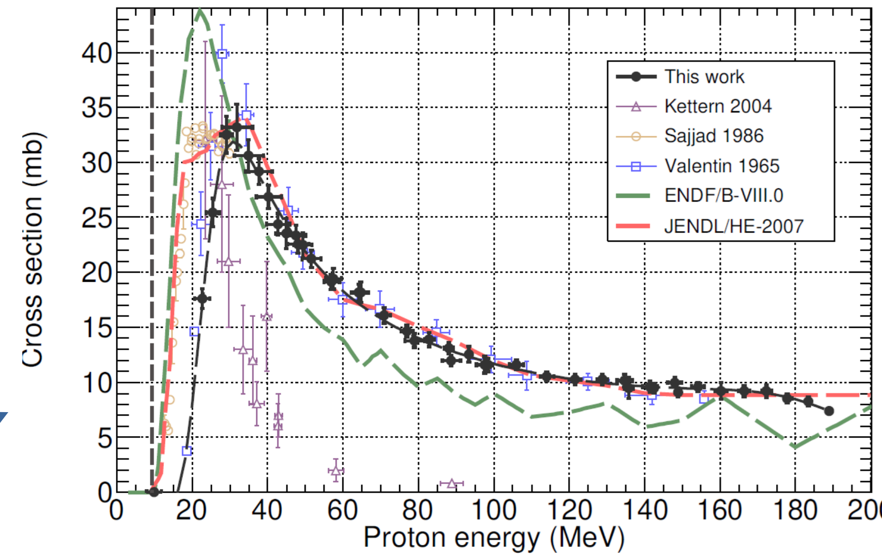
- $^{12}C(p,x)^{13}N$
- **$^{14}N(p,x)^{13}N$**
- $^{16}O(p,x)^{13}N$

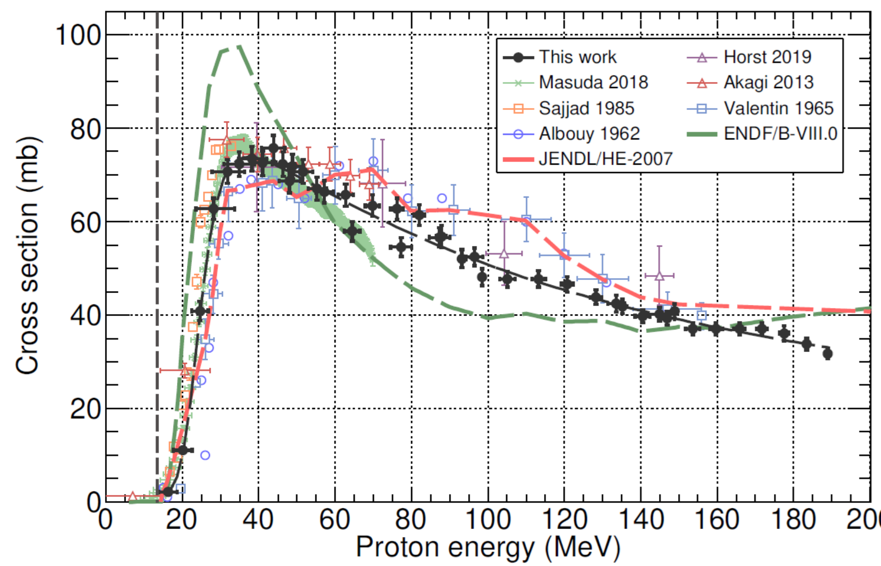
^{15}O



$t_{1/2}$=122 s

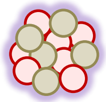
- $^{14}N(p,x)^{15}O$
- **$^{16}O(p,x)^{15}O$**





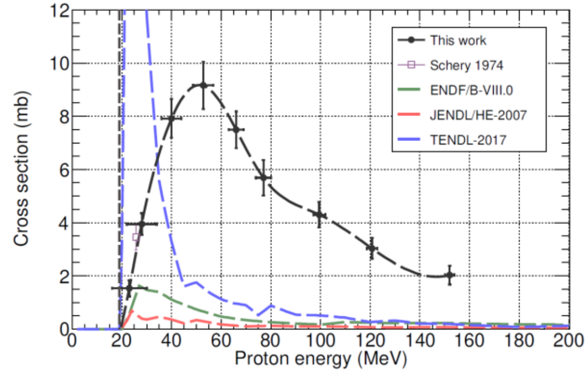
Short-lived β^{+} emitters

^{12}N



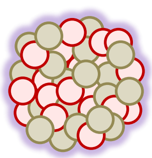
$t_{1/2}$=11 ms

$^{12}C(p,x)^{12}N$



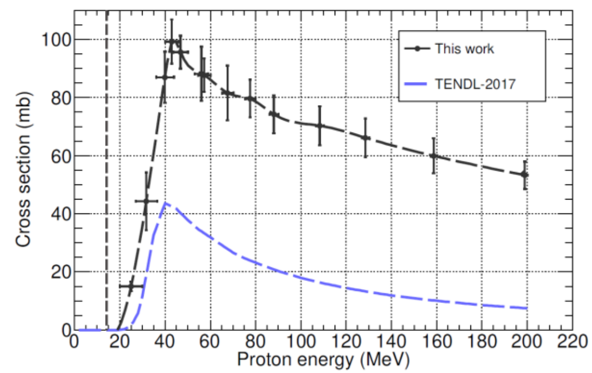
Integral below 55 MeV:
=> 60% higher than Ref. [1]

^{38m}K



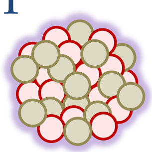
$t_{1/2}$ = 925 ms

$^{40}Ca(p,x)^{38m}K$



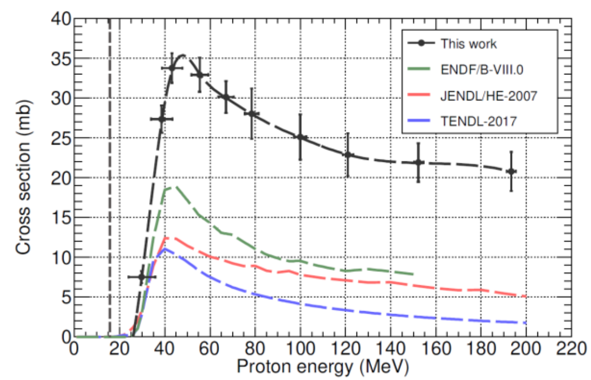
Integral below 55 MeV:
=> 40% lower than Ref. [1]

^{29}P



$t_{1/2}$=4.14 ms

$^{31}P(p,x)^{29}P$



Integral below 55 MeV:
=> 20% lower than Ref. [1]

[1] Dendooven et al. PMB **64** (2019)

MC simulations for PET range verification:
- Impact of improved cross section database
- Identification of the dominant contributors

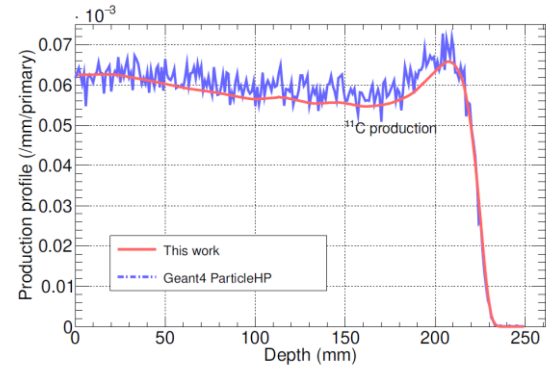
MC simulations with Geant4

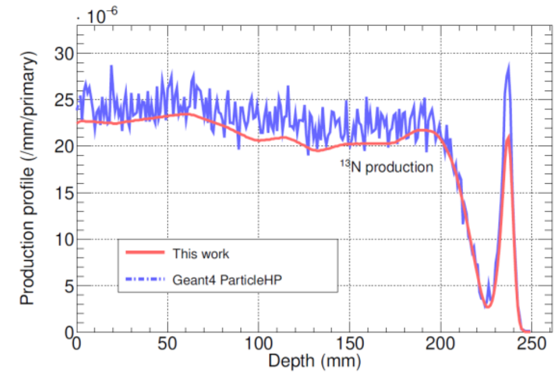
- **Microscopic calculation:** Using *G4ParticleHP* package:
  - ENDF/B-VII.1 (E_p<150 MeV) + TENDL (E_p>150 MeV)
  - Computationally inefficient

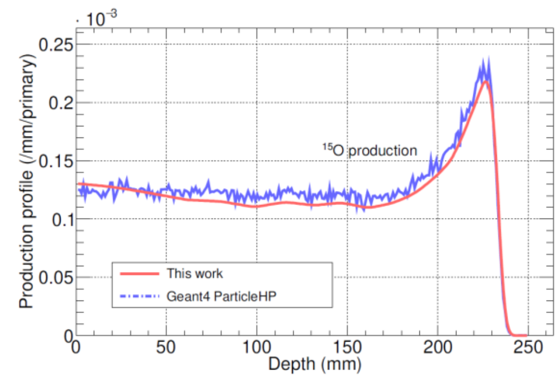
- **Macroscopic calculation:** Two steps method:
  - Transport of the proton beam in a phantom of choice using Geant4.
  - Calculation of the corresponding production of β^+ emitters using an external cross section data of choice:

$$P_z = n_s \int_z^{z+\Delta z} \left(\frac{dN}{dE}\right) \sigma(E) dE$$

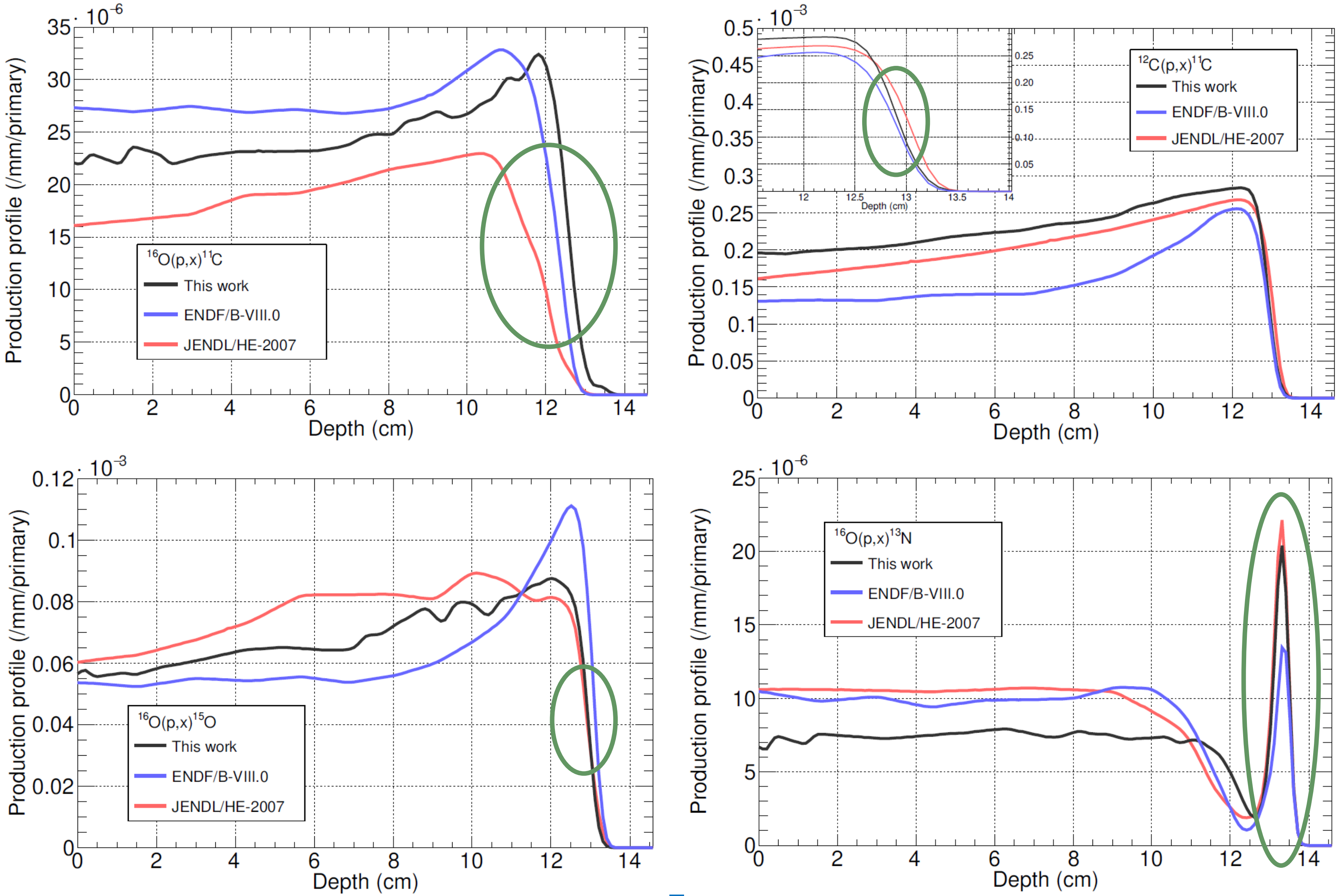
  - Computationally more efficient → Realistic adaptative treatment planning system.





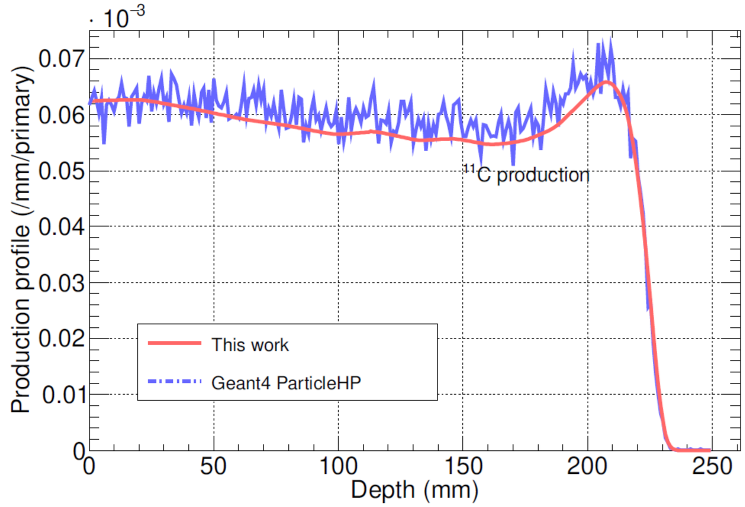


β+ emitter profiles: data vs. evaluations

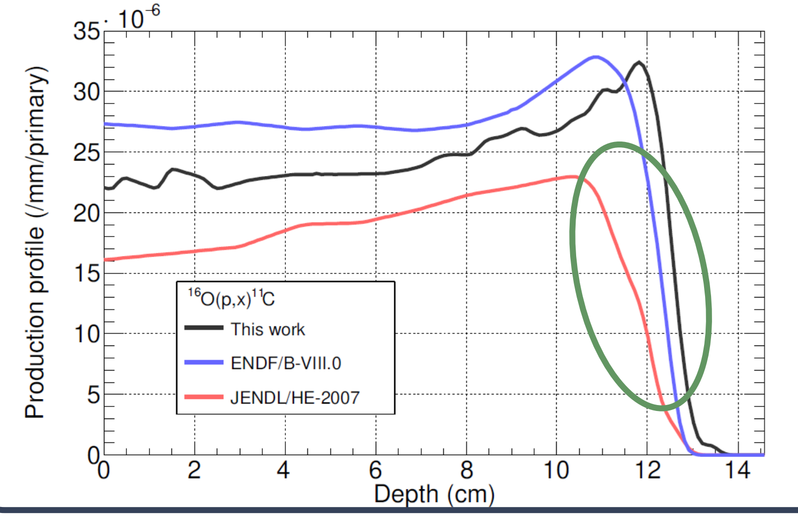


MC => production => activity

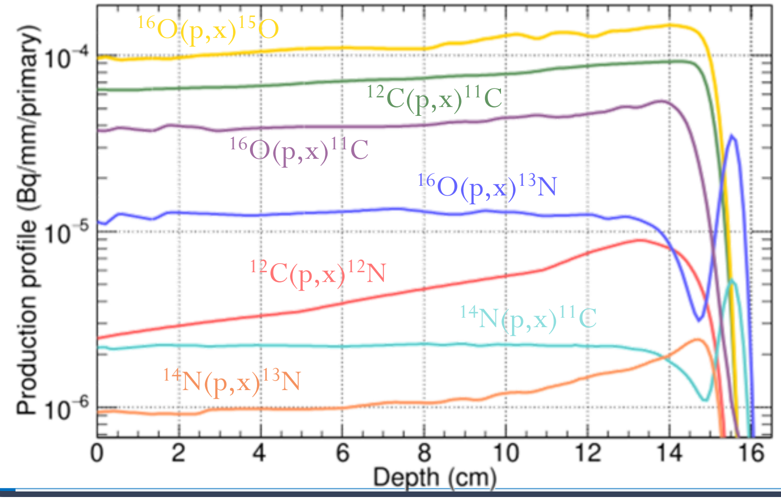
1. Computational optimization of the G4 simulation



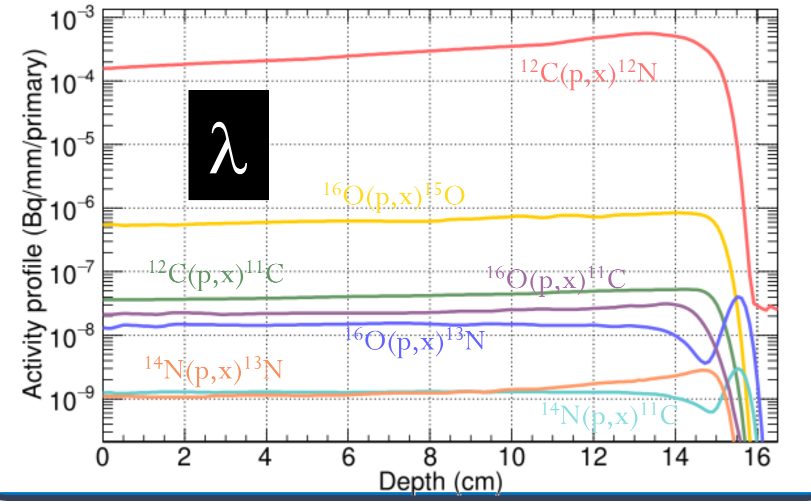
2. β+ emitter profiles: data vs. evaluations



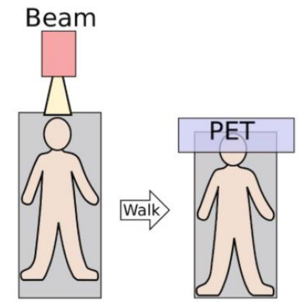
3. β+ profiles in tissue-equivalent phantoms

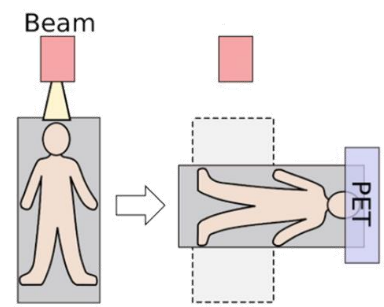


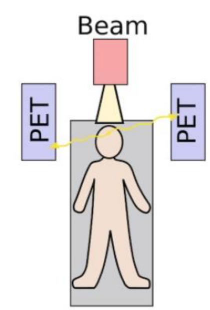
4. Activity profiles in tissue-equivalent phantoms



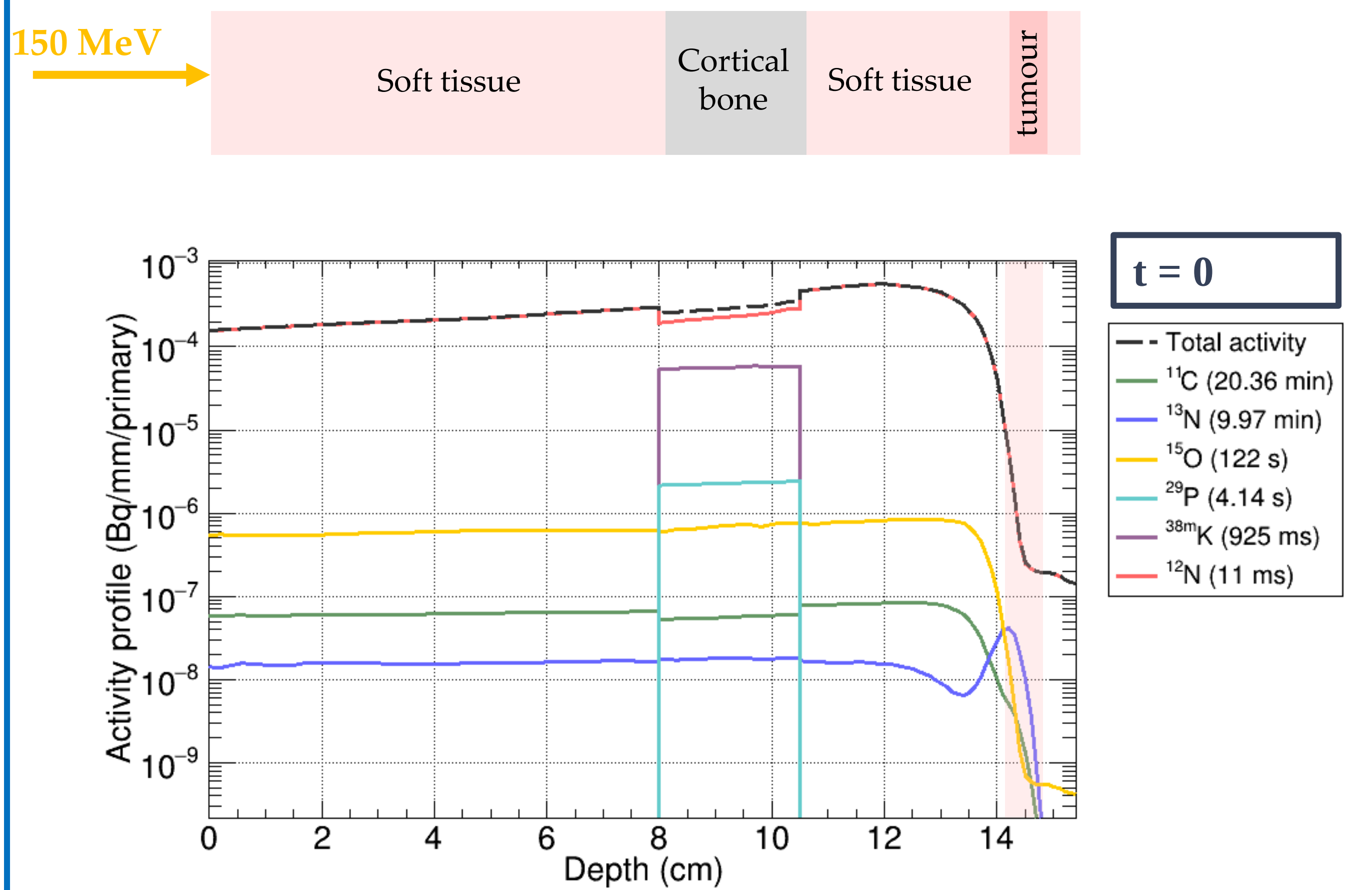
Activity depth profiles as function of time

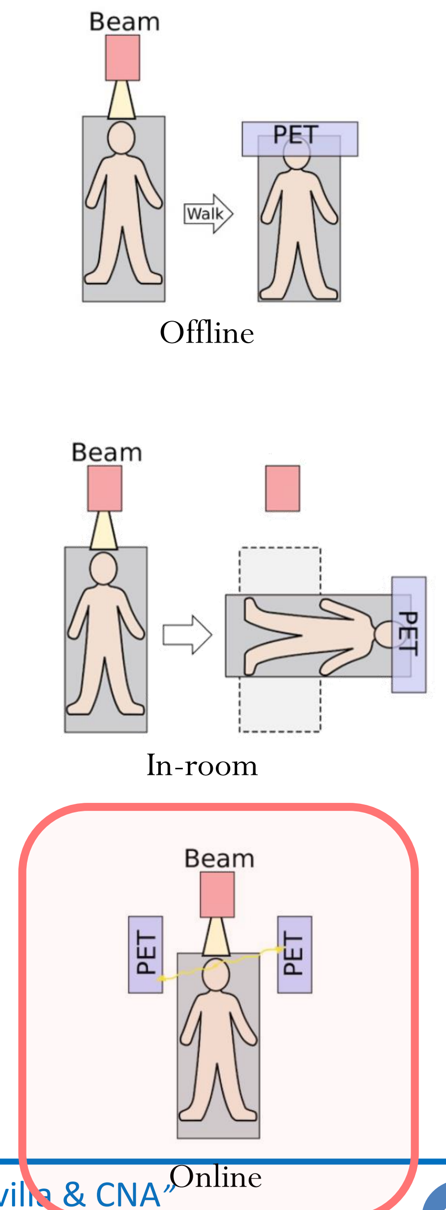




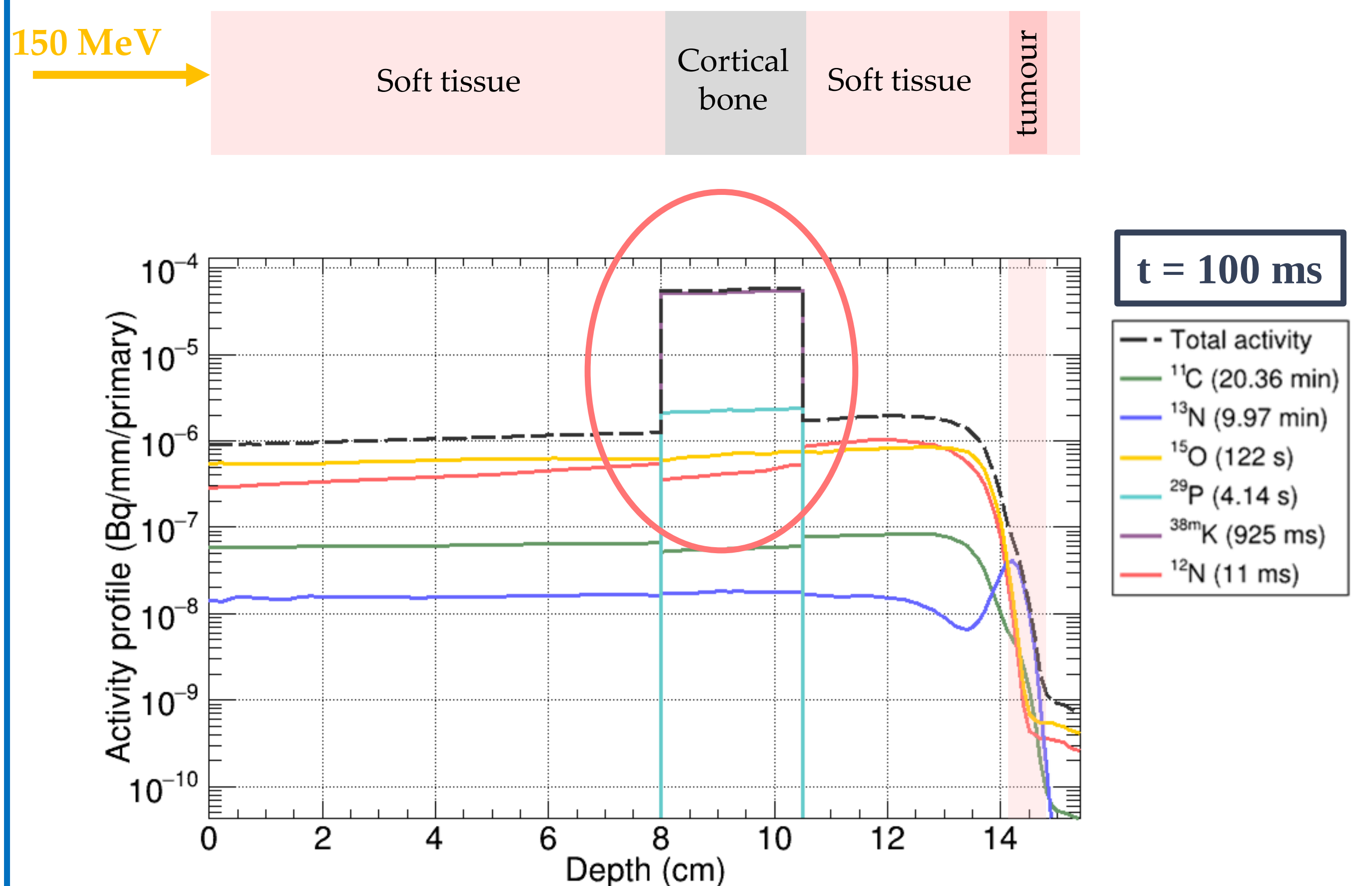


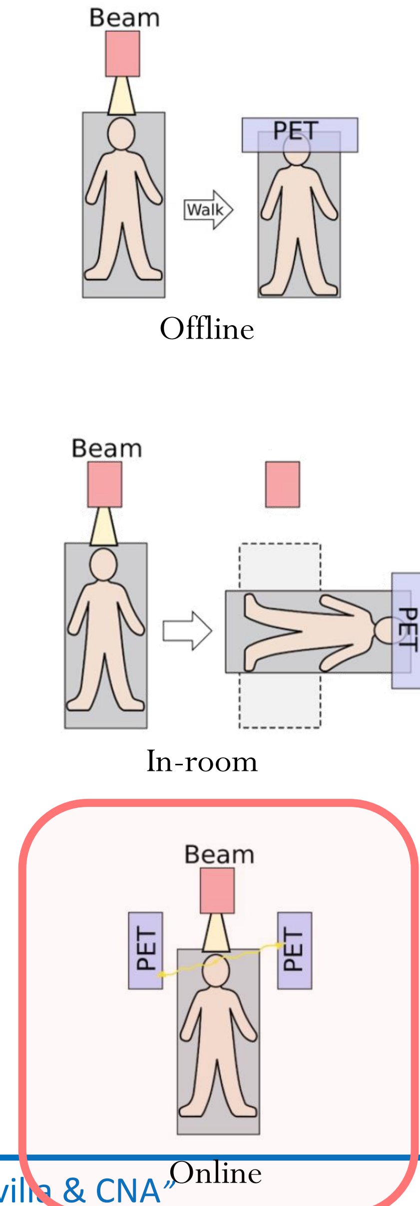
Activity depth profiles as function of time



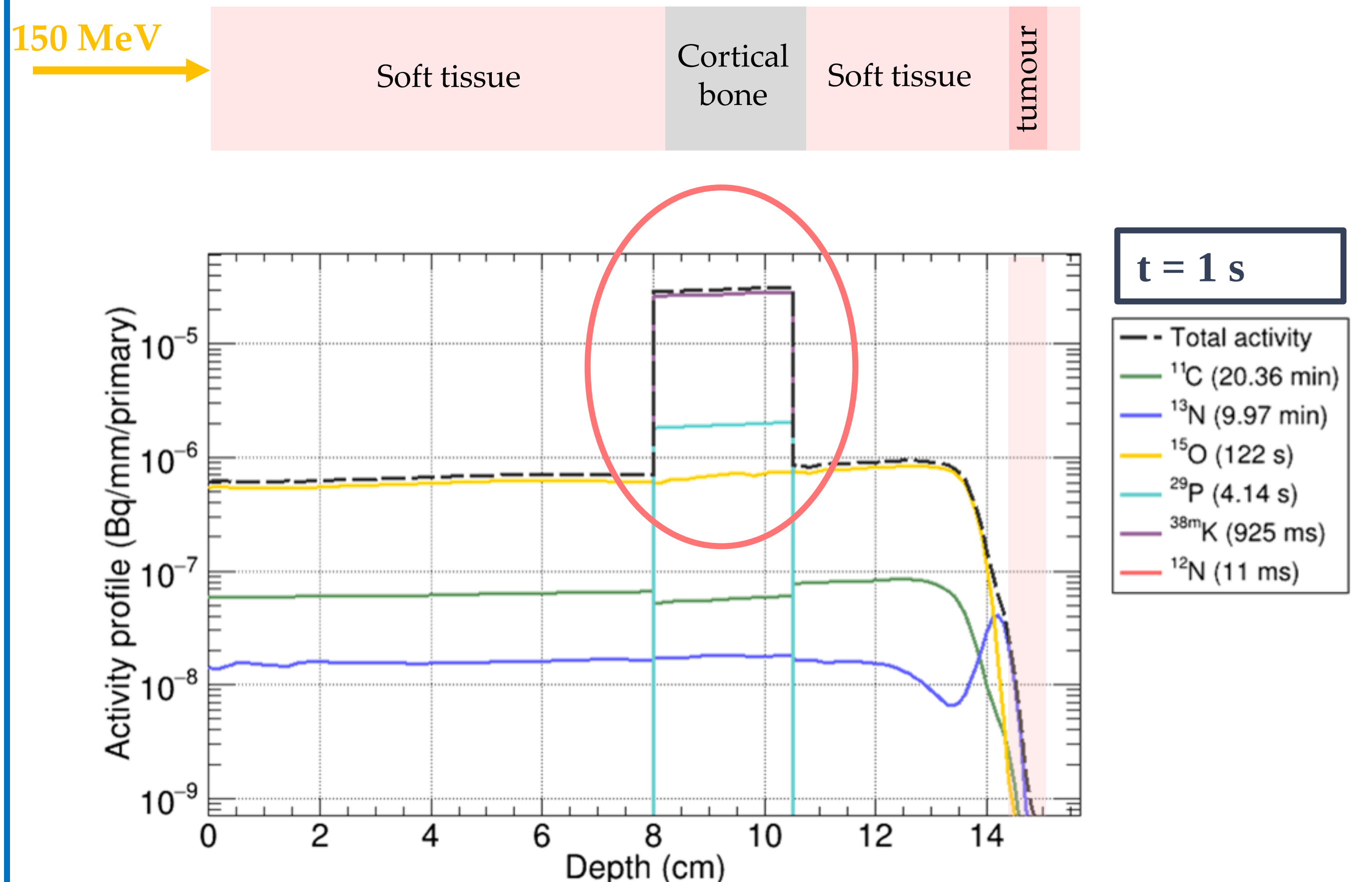


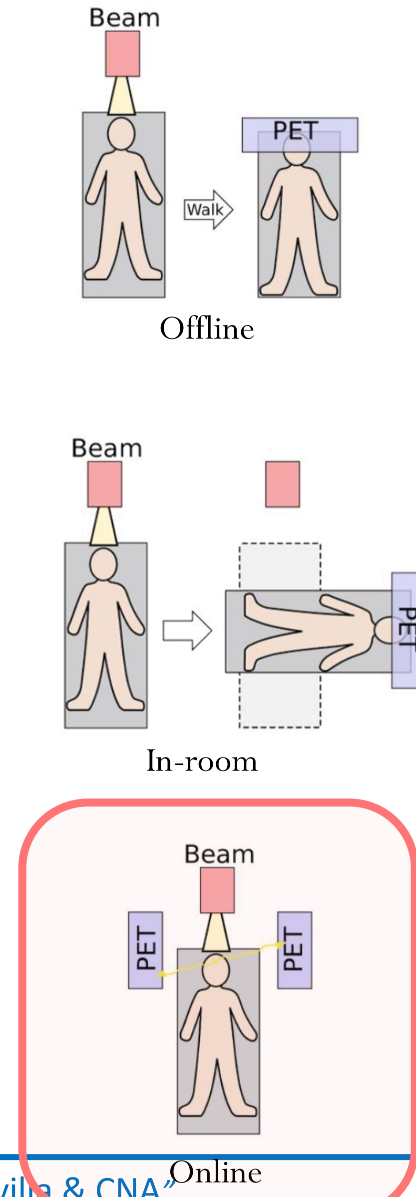
Activity depth profiles as function of time



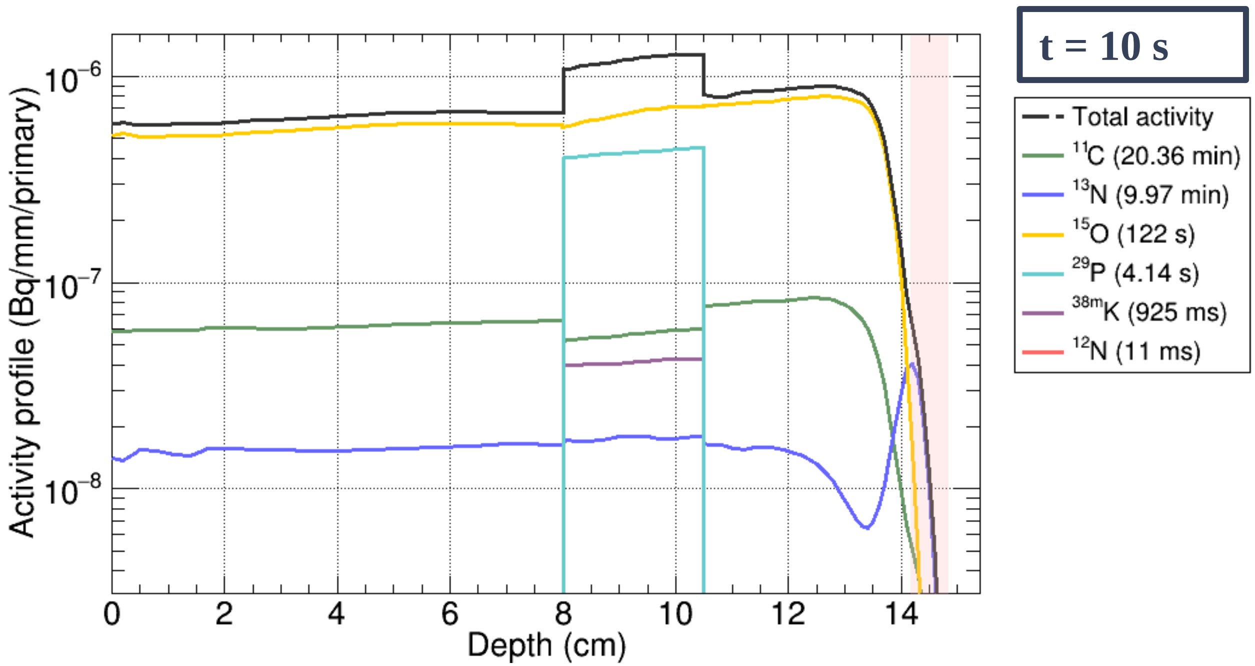


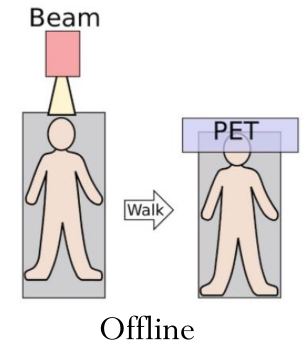
Activity depth profiles as function of time

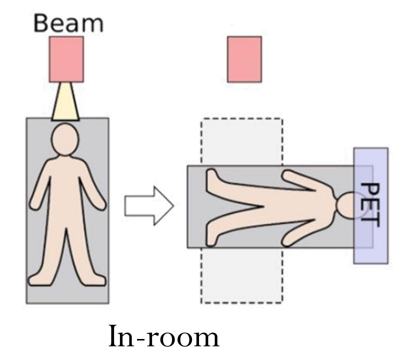


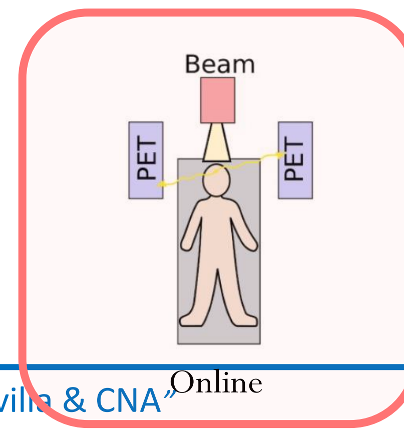


Activity depth profiles as function of time

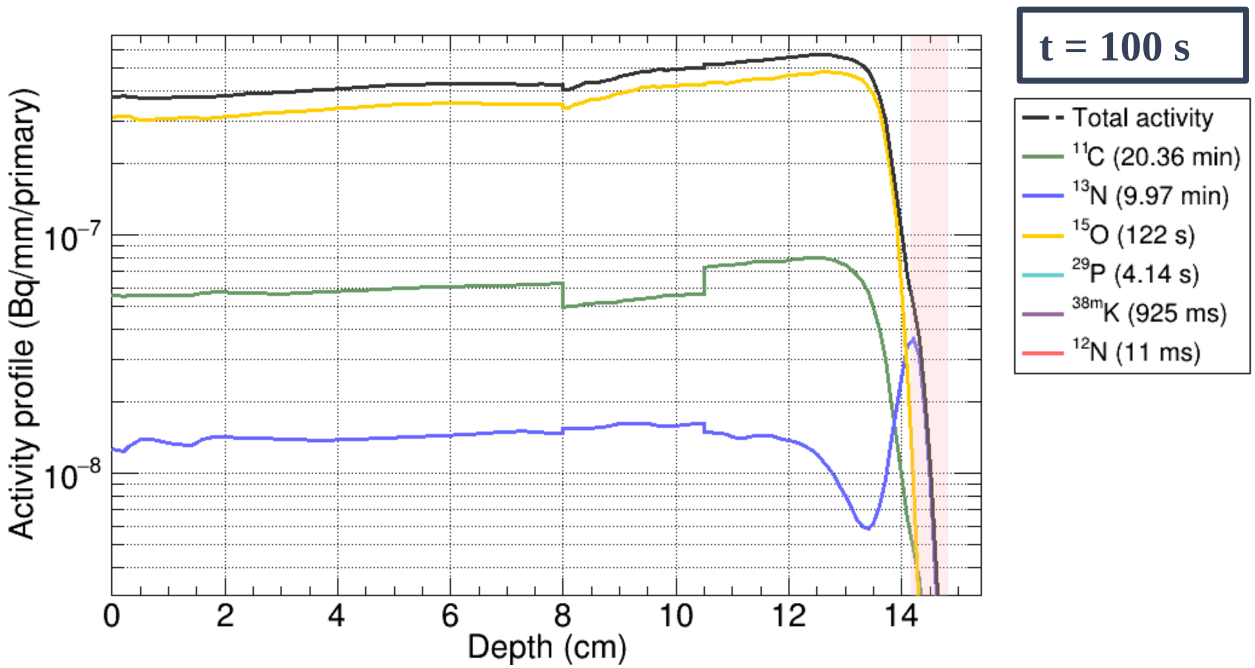


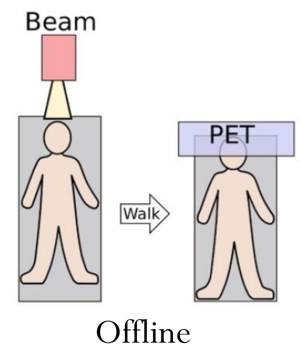


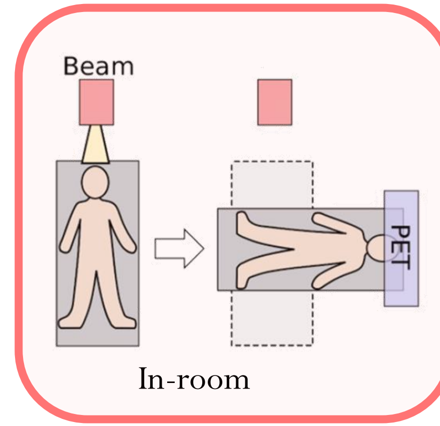


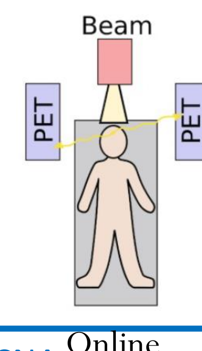


Activity depth profiles as function of time

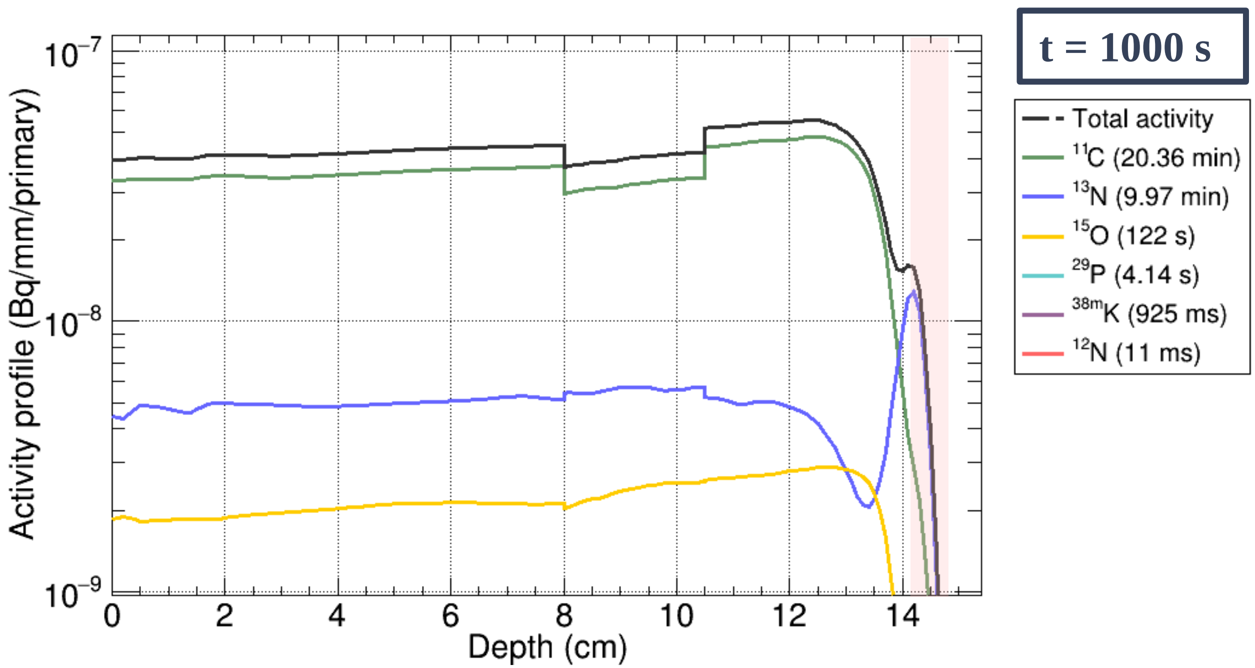


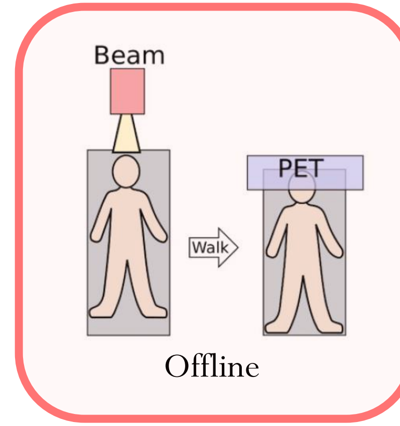


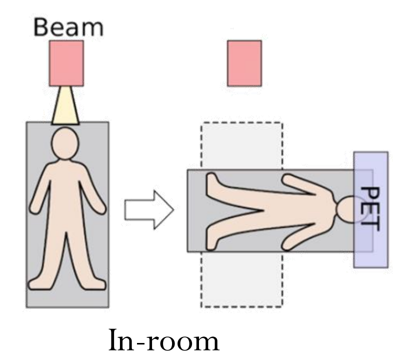


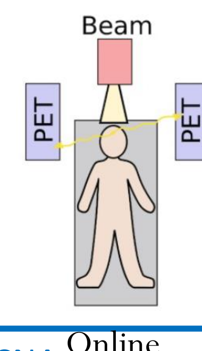


Activity depth profiles as function of time





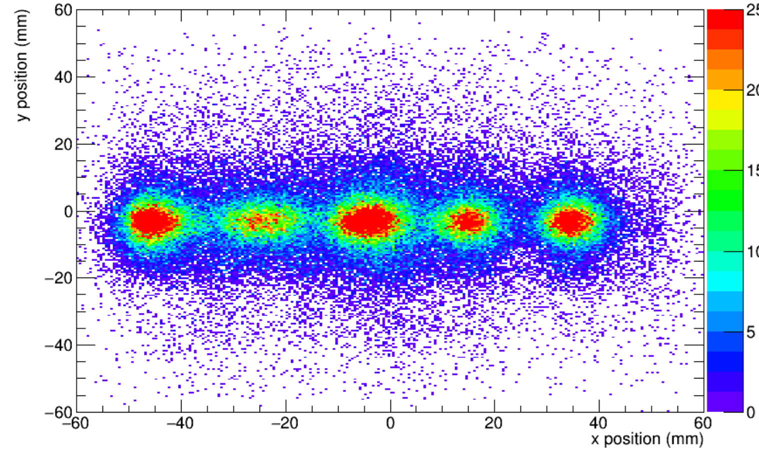




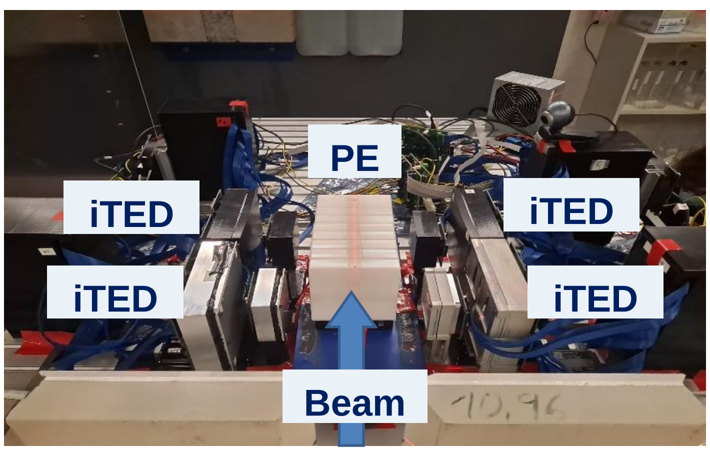
PET range verification experiments

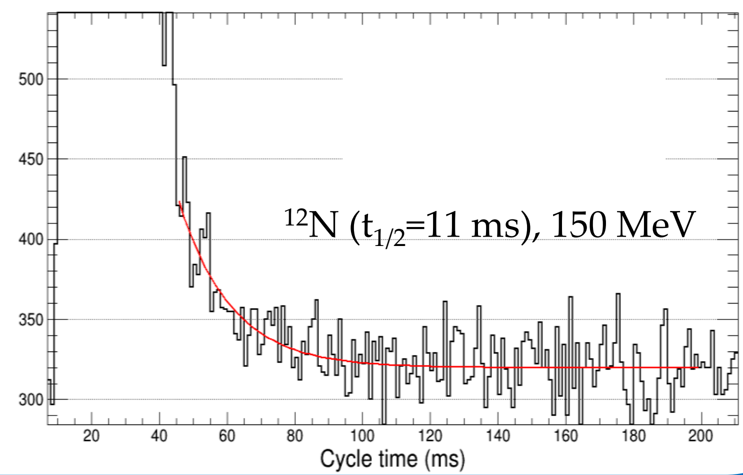
IFIC’s iTED for PET range verification (see Domingo’s)

Feasibility studies at CNA (18 MeV)



PET rage verfication at HIT





Outlook

1. Cross sections

- Production cross sections by C and He beams: Experiments performed at HIT (analysis ongoing)
- Publication into the EXFOR database (process ongoing)
- Participation in the forthcoming IAEA evaluations (invited to IAEA TM in August 2023)

2. Simulations

- β+ profiles not just for heterogeneous phantoms but for realistic patient's geometry, including CT geometries and clinical treatments plans (SOBP) (with TOPAS?)
- Inclusion of the finite β^{+} range, study the subsequent blurring of the PET images

3. Others

- Continue collaboration with CSIC-IFIC to fully analyze and further exploit the use of iTED for PET range verification
- Teresa Rodríguez's postdoc at Harvard Medical School: start collaboration with MGH on "acoustics" methods for range verification

More details in:

XS for long-lived below 18 MeV => *T. Rodriguez-Gonzalez et al. RPC* ***190*** *(2022)*
XS for long lived up to 200 MeV =>*T. Rodriguez-Gonzalez et al. NDS* ***187*** *(2023)*
XS for short-lived => *Coming soon*
Impact of XS and MC simulations => *Coming soon*