Università degli Studi di Pisa

DIPARTIMENTO DI FISICA

Dottorato in Fisica

Seminario di Pre-Tesi – XXX Ciclo

DIFFERENT ANALYSIS METHODS ON PET DATA FOR THE MONITORING OF PROTONTHERAPY TREATMENTS

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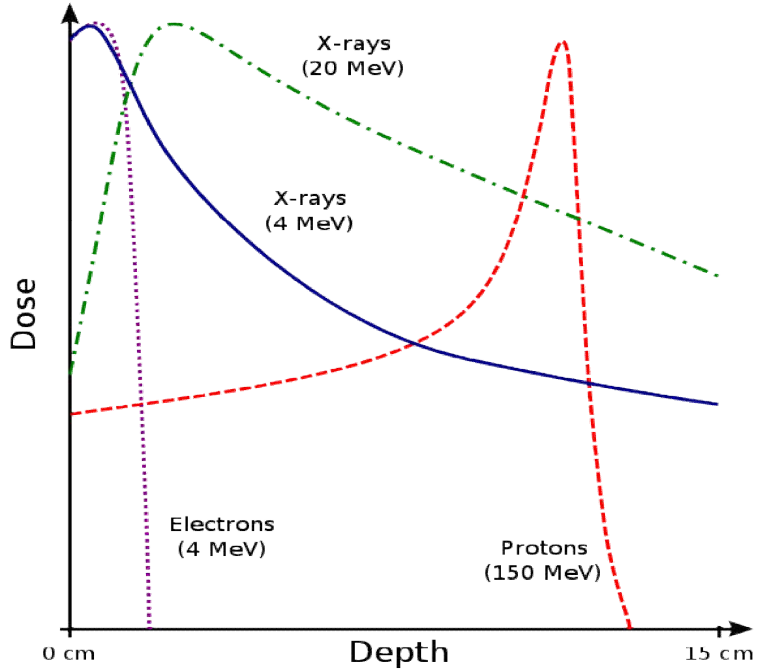
Overview

- The rationale for protontherapy;
- PET: a tool for protontherapy monitoring;
- DoPET system;
- Study with plastic phantoms;
  - Irradiation setup and phantoms' characteristics;
- Activity volume reconstruction and 1-D spatial analysis;
- DoPET temporal signal;
- DoPET random coincidence estimation;
- Elemental analysis (multi-exponential fit method);
- Monte Carlo simulations;
- Comparison Simulation vs. fit method;
- Isotopes percentages in different materials;
- Conclusion and future work.

The rationale for protontherapy

The favorable physical properties of ion beam interaction in matter with the characteristic dose maximum in depth known as "**Bragg peak**" offer the possibility of superior tumor-dose conformality with better sparing of surrounding critical organs and healthy tissue in comparison to conventional radiation in external beam radiotherapy.



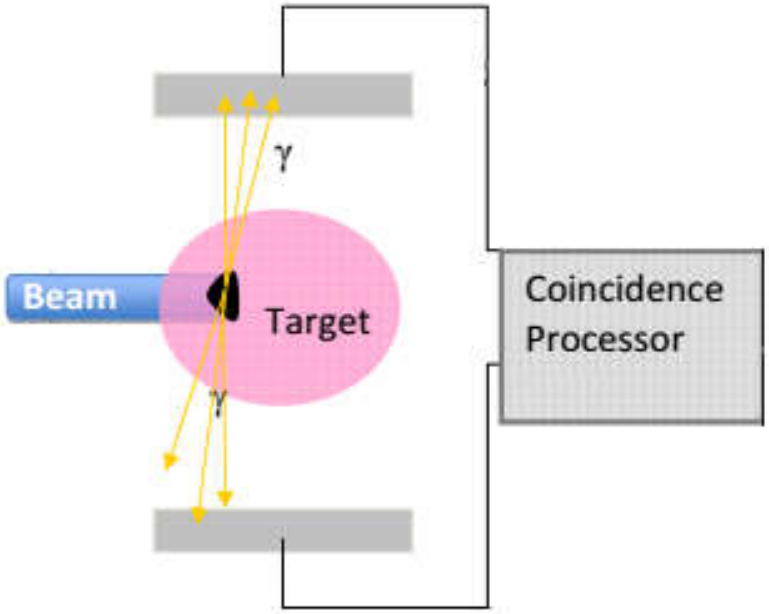
Advantages:

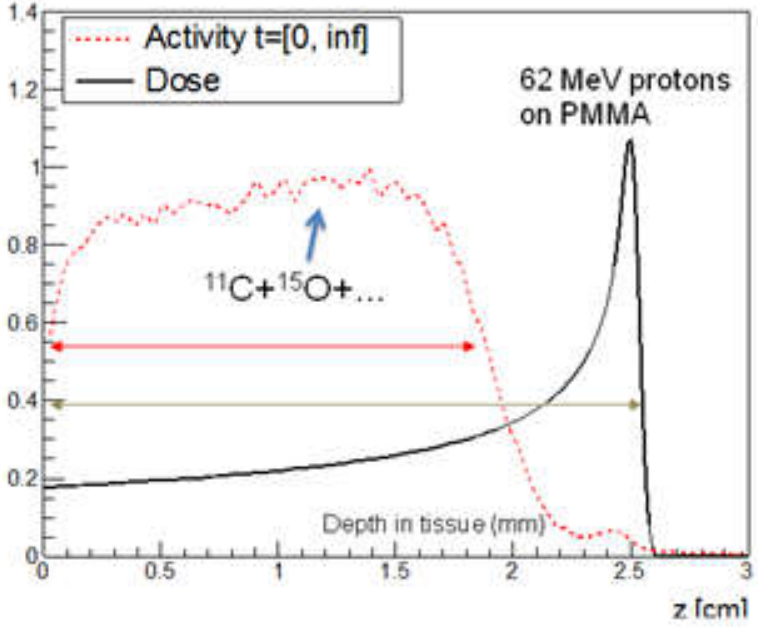
- More conformal dose delivery with respect to x-rays
- Higher relative biological effectiveness for heavy ions, e.g. carbon.

Open issues: Proton therapy is very sensitive to uncertainties introduced during treatment planning and dose delivery. It needs an accurate tool for monitoring dose/proton range. The tool discussed here for this purpose will be the **Positron Emission Tomography**.

PET: a tool for protontherapy monitoring

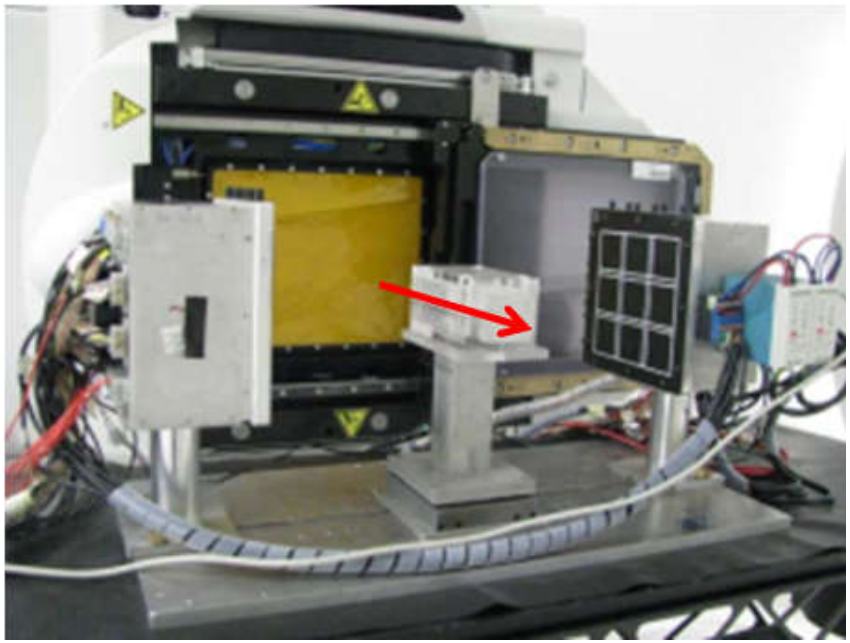
- Ions generate β^+ radioactive nuclei along beam path through nuclear reactions;
- This activity is (indirectly) correlated with dose deposited by the ions;
- The β^+ activity can be acquired with a PET scanner in the form of back to back photons from the e^+ annihilation with matter;
- At present, PET is the most common method for monitoring applied in clinics.

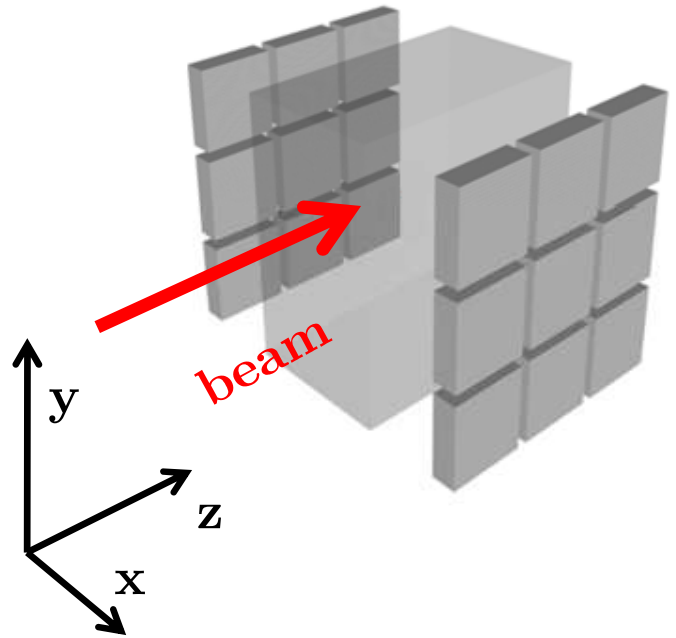




DoPET system

Planar dual-head PET scanner. Each head is composed by a set of 9 separated detector modules consisting of a LYSO matrix of 23x23 pixels, a position sensitive photomultiplier tube H8500 (Hamamatsu Photonics) and the front-end electronics.

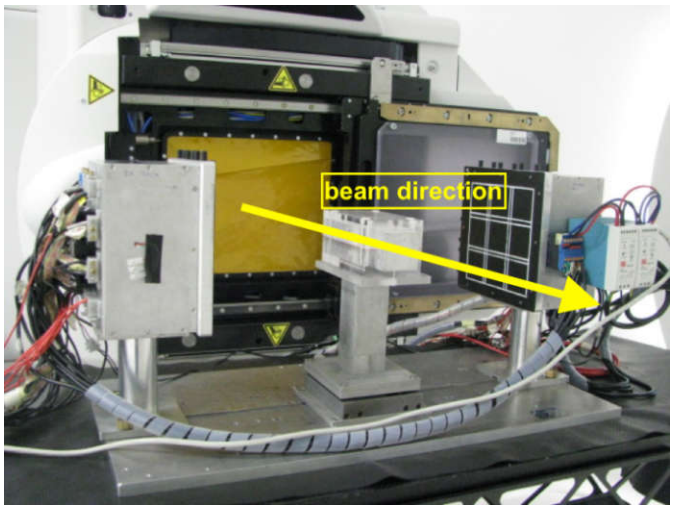




- Compact and portable detector → optimized for in-beam acquisition;
- Activity is reconstructed with a dedicated LOR based *Maximum Likelihood Estimation Maximization* (**MLEM**) with 5 iterations.

Study with plastic phantoms

Irradiations were performed at the cyclotron of Trento Proton Therapy Center using plastic phantoms. The aim is to investigate the DoPET capability of providing information on the irradiated phantom compositions both in space and in time domains.



Experimental setup

List of studied phantoms and beam parameters

Phantom type	Material	Proton energy	Proton statistics
Homogeneous	PMMA	130 MeV	10^{10}
	BRAIN	130 MeV	10^{10}
Zebra	BRAIN/PMMA	130 MeV	10^{9} and 10^{10}

Other features on the phantoms:

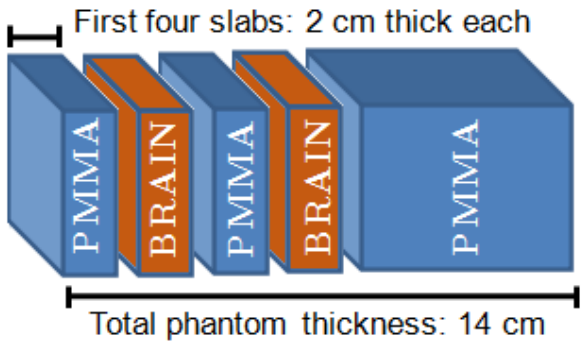
- 5x5 cm^2 transverse section and 14 cm length

Total dimension including holder:

- 8x8x14 cm^3

Elements composition for each studied phantom

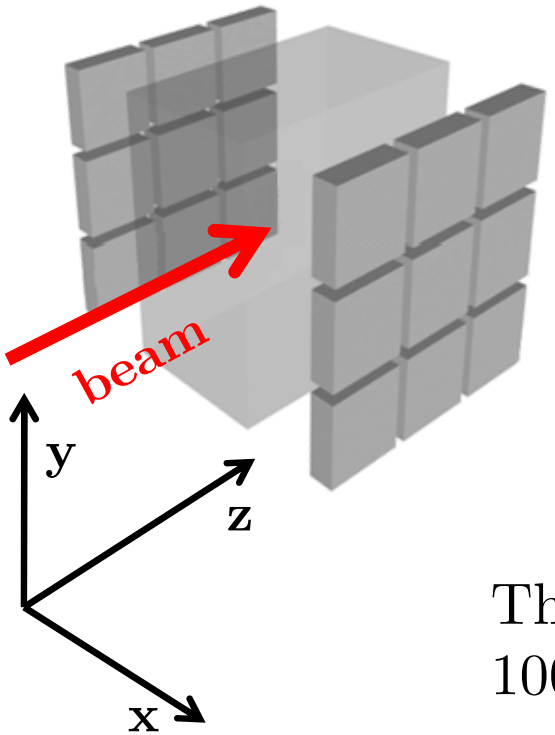
	Density (gcm^{-3})	H (%)	C (%)	O (%)	N (%)
PMMA	1.18	8.05	59.99	31.96	
Zebra	1.12	9.13	65.08	25.11	0.68
Brain	1.05	10.83	72.54	14.86	1.69

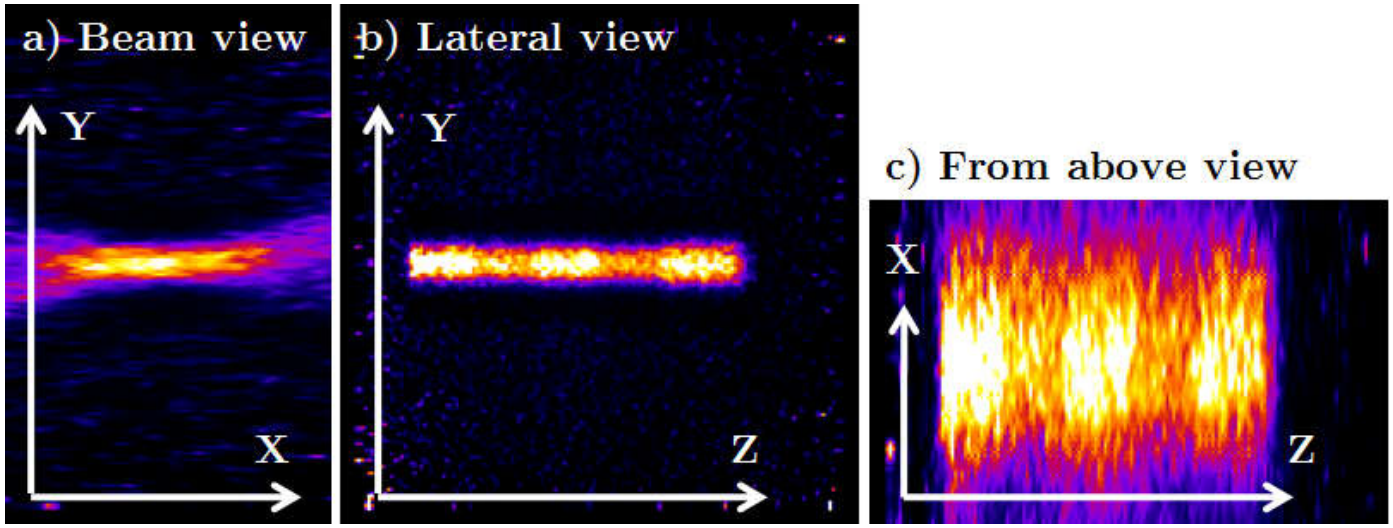


Zebra phantom schematics

Activity volume reconstruction

From acquired coincidences: 1) 3-D image reconstruction via **MLEM*** algorithm; **2)** visualization and choice of the **ROI**** with the software ***ImageJ***; **3)** projection of the 1D profile and finally spatial analysis.





The reconstructed Field of View (FOV) is composed by 100x160x160 voxels (each one representing 1 mm^3)

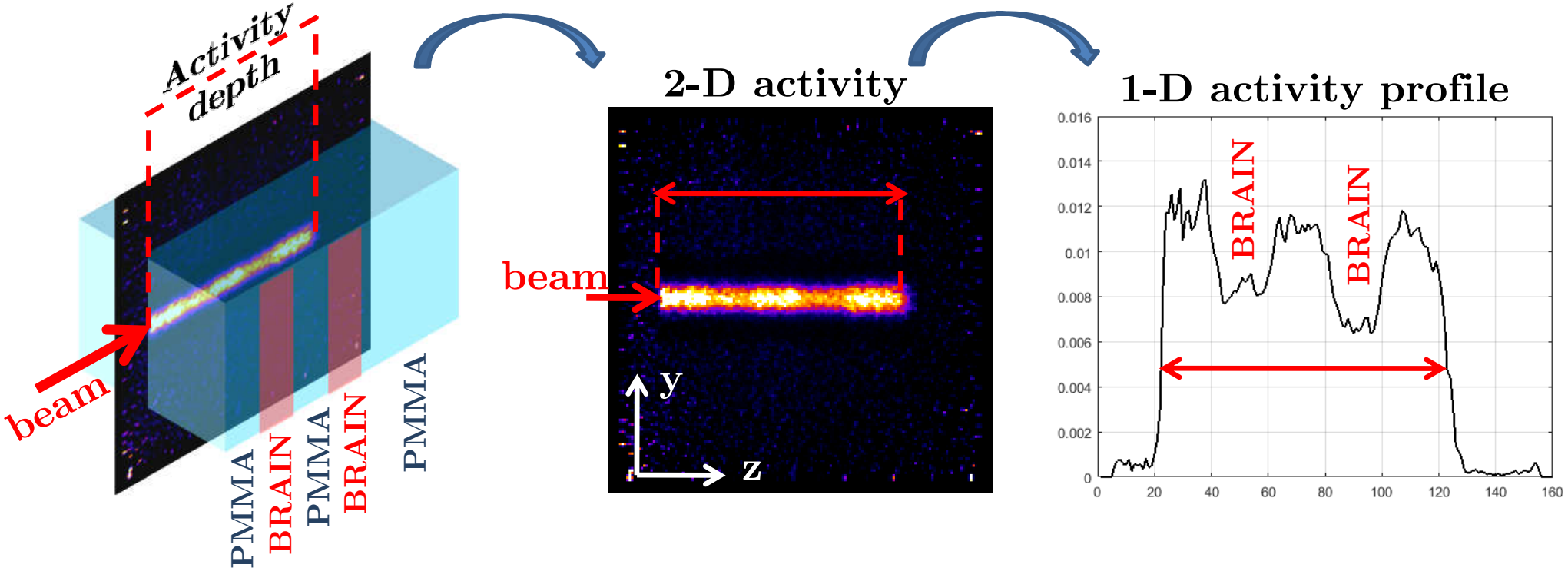
MLEM*: *Maximum Likelihood Expectation Maximization*

ROI**: *Region Of Interest*;

ImageJ*: *Image Processing and Analyzing in Java* (public domain software from National Institute of Health).

1-D Spatial analysis

The goal is to verify if DoPET is able to detect the different material used in the zebra phantom from spatial distribution of the activity produced in the target and how many it is possible to reduce the total acquisition time and still maintain this capability



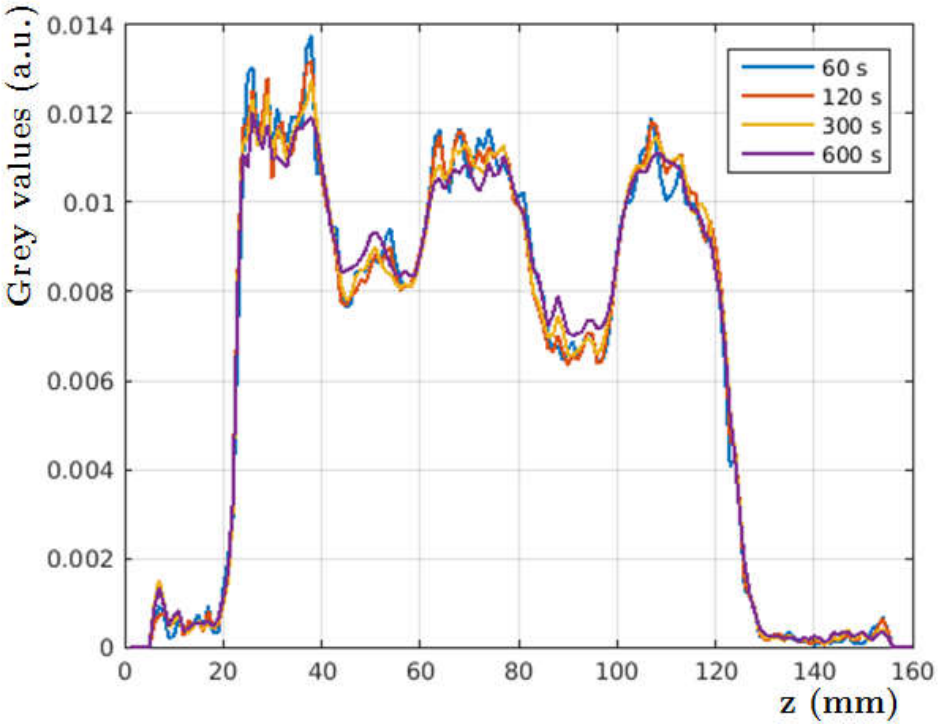
Studies: **1)** comparison of activity profiles for different acquisition time intervals (0-60 s, 0-120 s, 0-300 and 0-600 s);

2) Activity profiles for irradiation with 10^9 proton excluding the first seconds of acquisitions.

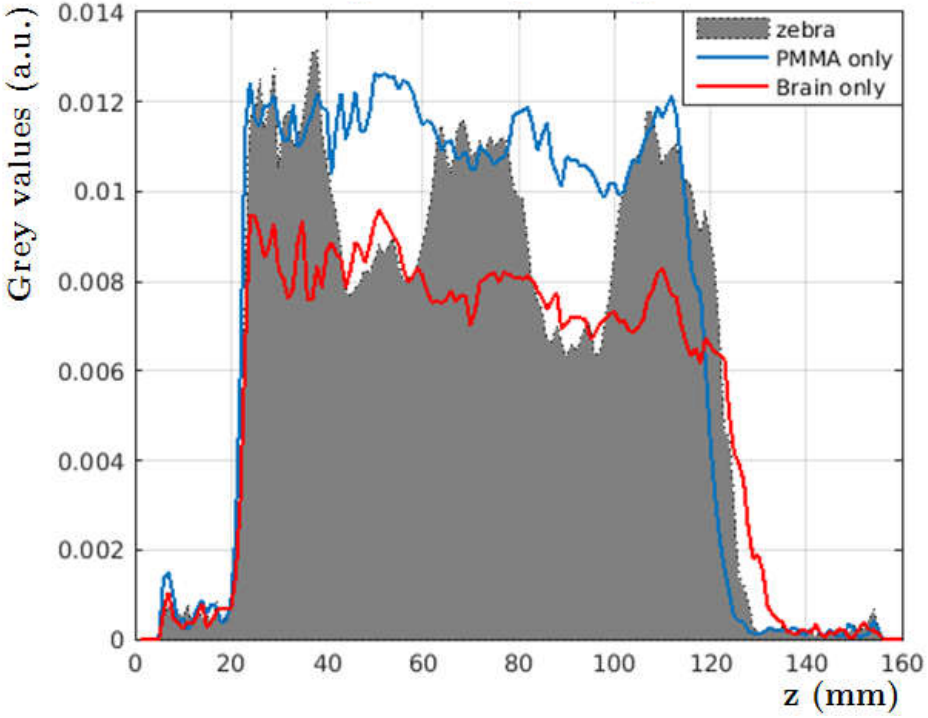
1-D Spatial analysis

The results presented here are for irradiations performed with 10^{10} proton (130 MeV) and delivery time of 8.5 seconds.

➢ Spatial profiles calculated for several acquisition time interval after proton delivery.



➢ Spatial profiles for homogeneous phantoms (PMMA and BRAIN) and zebra phantom.

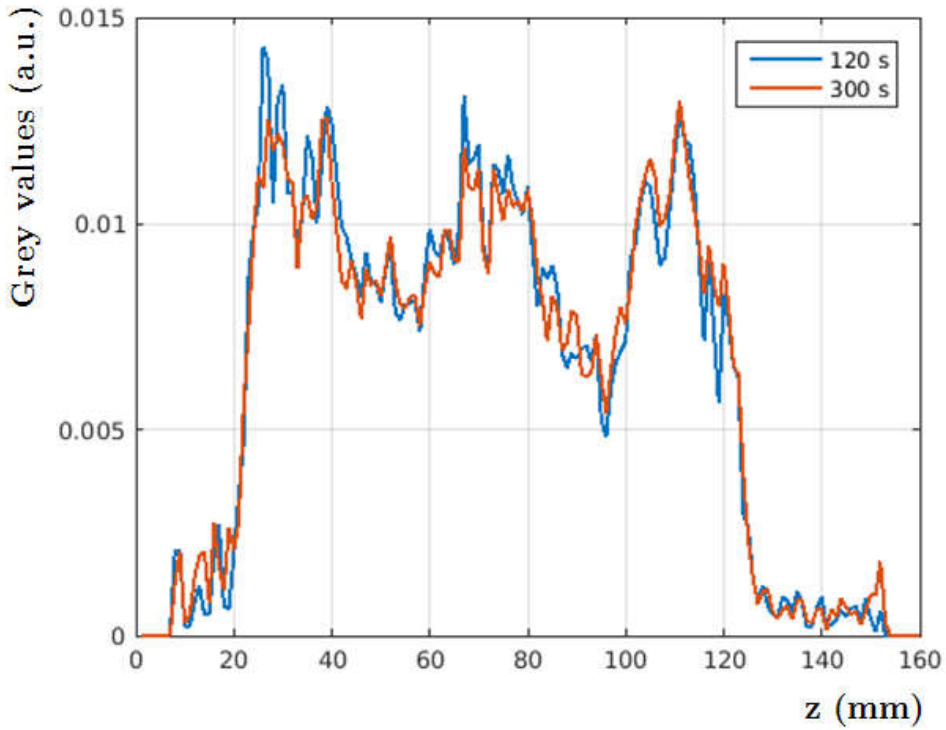


In the left figure, the information on the slabs are well defined independently of the acquisition time interval. In the right figure, the comparison shows compatible values for the reconstructed activity in the homogeneous phantoms comparing with their respective slabs on the zebra phantom.

1-D Spatial analysis

The result presented here is for a irradiation performed with 10^9 proton (130 MeV) and delivery time of 8.5 seconds.

➢ Spatial profiles calculated for two acquisition time intervals: 120 and 300s

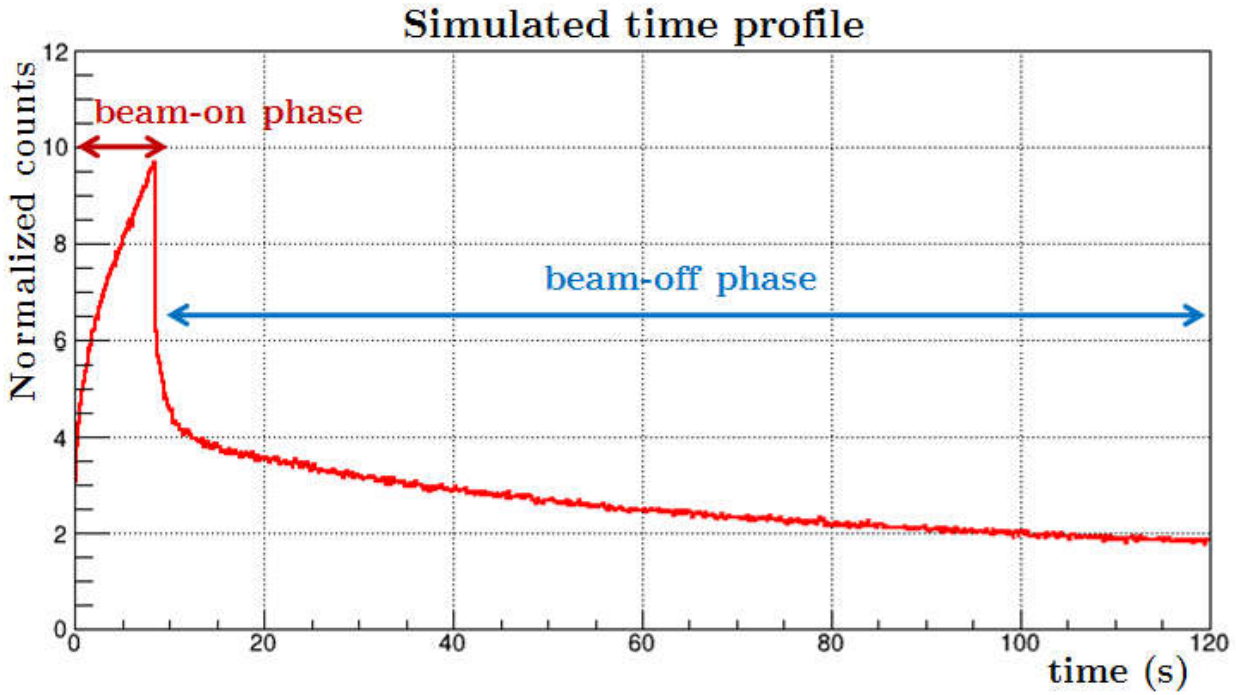


As observed, the profiles show a **noisier aspect**.

➢ The more the number of **delivery protons is reduced**, the more will be difficult to extract information about the phantom composition. The alternative is to use a **complementary analysis** to confirm what is observed in the spatial information.

DoPET temporal signal

The frequency of detected coincidence as a function of time carries information on the elemental composition of the irradiated phantoms. So, one can try to individuate the contribution of each isotope from the total signal measured by DoPET.



However, before analyzing the time behavior of the acquired signal, the coincidences generated by random events, i.e., un-correlated events detected within the coincidence window and erroneously stored as a true coincidence, must be subtracted from data. The other source of randoms events is the LYSO scintillator itself, due to the natural radioactivity of Lutetium-176.

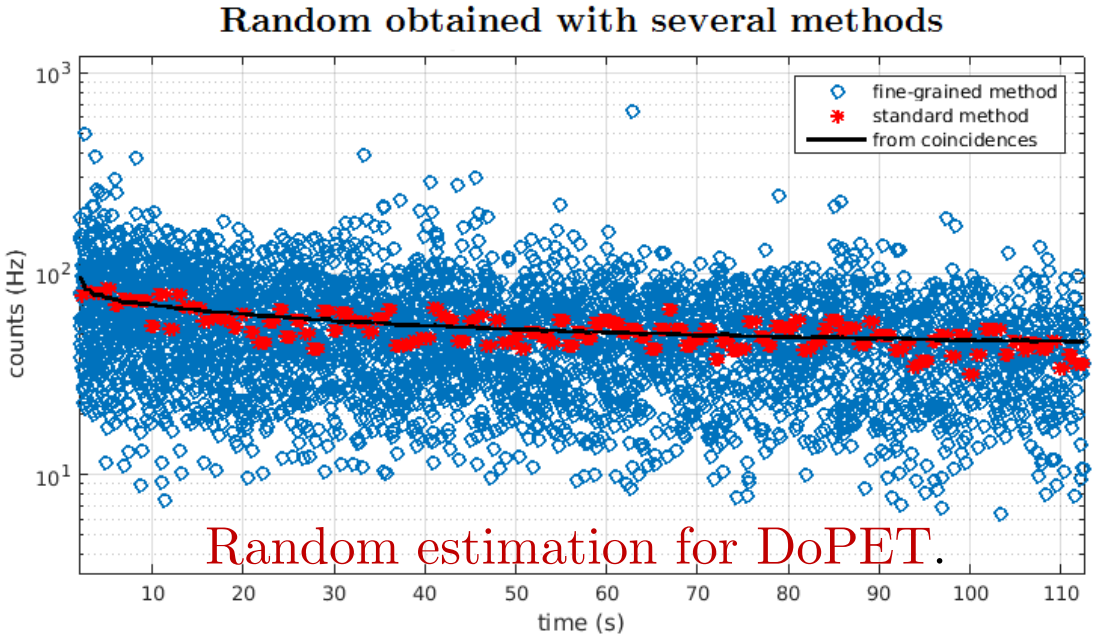
DoPET Random coincidence estimation

PET coincidence counts include random or accidental coincidences that raise the background on the count rate. Random events occur when two 511-keV photons from two separate positron annihilation locations are detected by a detector pair within the set energy and timing window. Random coincidences (N_R) can be measured in two ways. In one method, the rate of random coincident events is given by **single count rates** as:

$$N_R = N_1 \cdot N_2 \cdot 2\tau$$

where τ is the time width of the pulses in nanoseconds for the system and N_1 and N_2 are the single count rates in counts/s on each of the two detectors along the LOR. The quantity 2τ is the coincidence timing window.

The other method is the **delayed window technique**. Once a signal or a coincidence is detected the same signal is repeated after a time longer than the coincidence window. The delayed signal opens a new coincidence window (so called ***delayed window***): all the coincidences detected in the delayed window are random.



Random estimation for DoPET.

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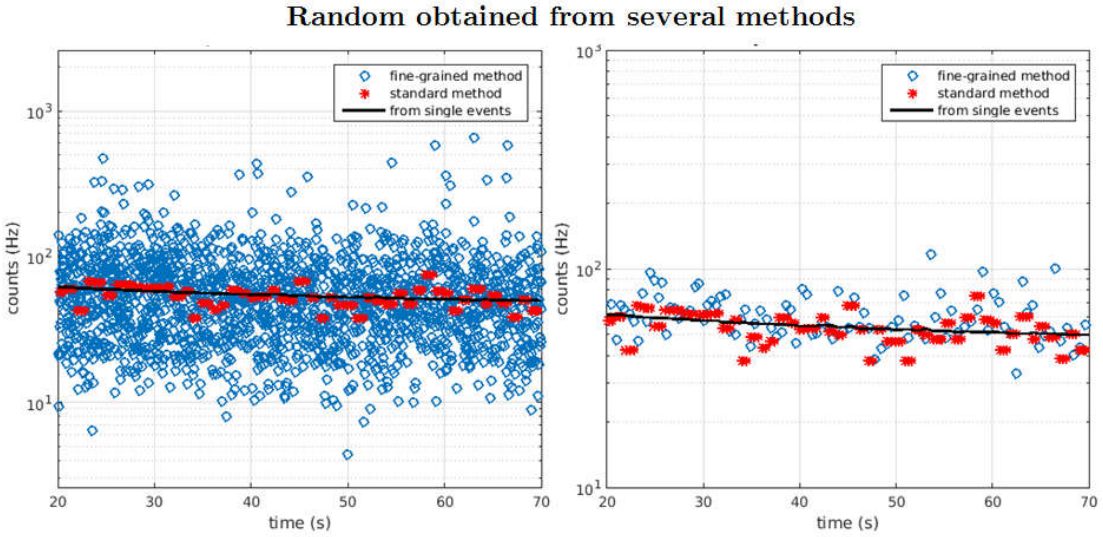
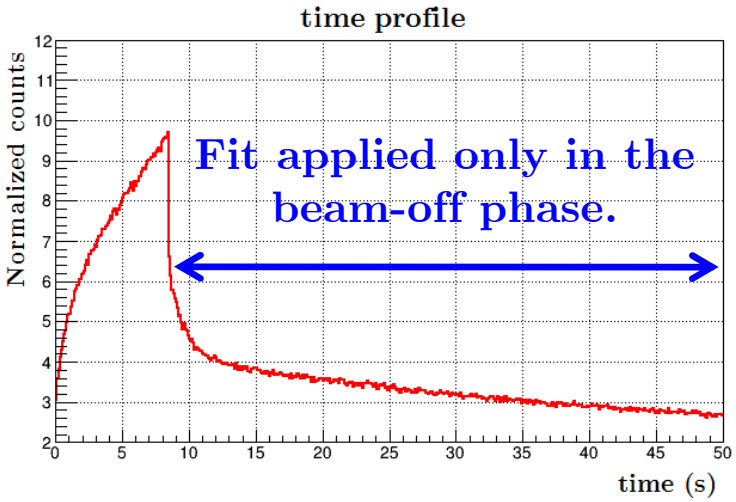


Random estimation for DoPET.

Elemental analysis (multi-exponential fit)

Elemental analysis is performed modeling the DoPET coincidence rate signal with a multi-exponential fit as:

$$f(t) = \sum_{i=1}^{n} a_i e \exp\left(-\frac{t \ln 2}{T_i}\right)$$



a_i is the amplitude and T_i the half-life of each isotope.

The percent contribution of a given isotope to the overall signal (C_i) in a given time window $[t_1;\ t_2]$ is computed as:

$$C_i(\%) = \frac{\int_{t_1}^{t_2} a_i \exp\left(-\frac{t \ln 2}{T_i}\right) dt}{\int_{t_1}^{t_2} f(t)\, dt} \times 100$$

where t_1 refers to the beginning of the beam-off period and $t_2 = t_1 + 300$ s.

Relevant reaction channels for the materials studied in this work. Energies labeled with * are calculated in experimentally.

Isotopes	Half-life (s)	Reaction channel	Threshold energy (MeV)
^{11}C	1220	$^{12}C(p,pn)^{11}C$	20.61
		$^{16}O(p,3p3n)^{11}C$	59.64
^{10}C	19.3	$^{12}C(p,2pn)^{10}C$	35*
		$^{16}O(p,3p4n)^{10}C$	72*
^{13}N	597.9	$^{16}O(p,2p2n)^{13}N$	5.66
^{15}O	122.2	$^{16}O(p,pn)^{15}O$	16.79
^{8}B	0.770	$^{12}C(p,2p3n)^{8}B$	61*

Elemental analysis – experimental data

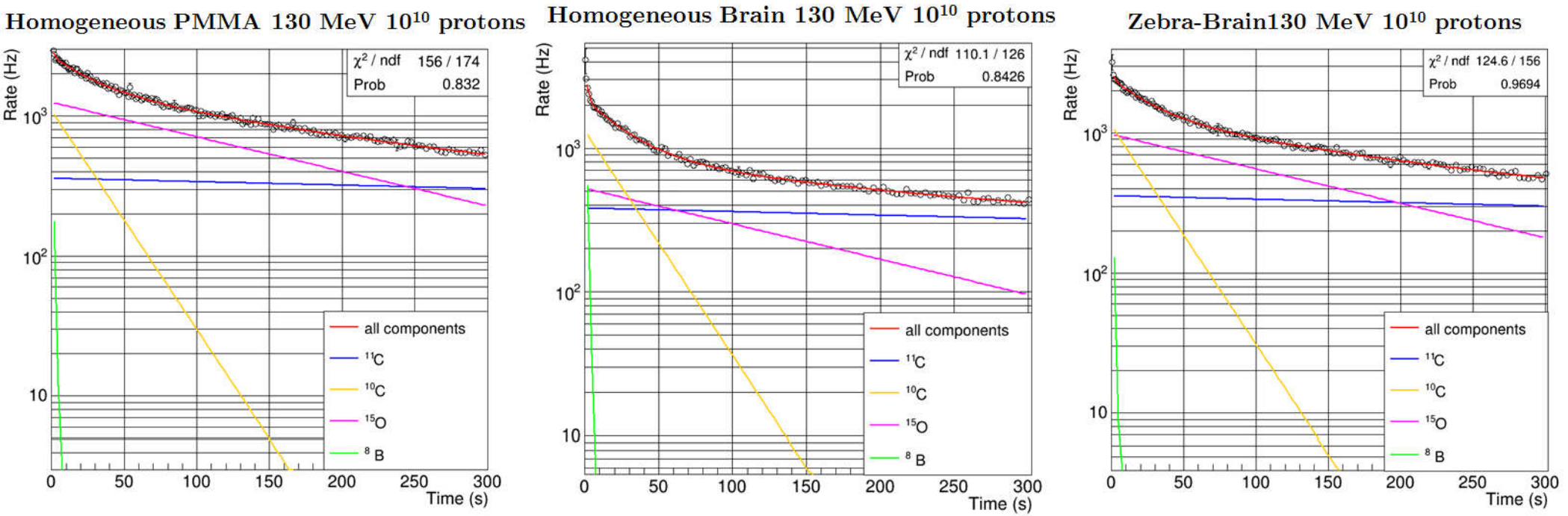


Table. Contribution in the DoPET signal of the main isotopes produced during the phantoms irradiation. The integration was performed for the signal interval between 0 (end of irradiation) and 300 s.

Phantom and proton statistics	Energy (MeV)	^{11}C (%)	^{15}O (%)	^{10}C (%)	^{8}B (%)
PMMA 10^{10}	130	31.91 ± 0.57	58.21 ± 0.76	9.75 ± 0.46	0.13 ± 0.20
BRAIN 10^{10}	130	47.93 ± 1.44	34.25 ± 1.74	16.55 ± 0.58	1.27 ± 0.31
Zebra BRAIN 10^{9}	130	36.83 ± 0.67	50.18 ± 2.27	12.45 ± 2.63	0.54 ±0.51
Zebra BRAIN 10^{10}	130	36.14 ± 0.68	52.23 ± 0.86	11.48 ± 0.37	0.16 ± 0.13

Monte Carlo simulations

The FLUKA code (Version "Development" INFN-Milan) was used to simulate proton interactions with targets. The goal is to compare the simulations with experimental results obtained for the irradiation on phantoms described previously. Only homogeneous phantoms were simulated.

Parameters of the performed FLUKA simulations.

Label	Energy (MeV)	Proton statistics	Delivery time (s)
PMMA130	130	10^9	8.5
BRAIN130	130	10^8	8.5

FLAIR (FLUKA Advanced Interface) was used to create input geometry.

The most important scores quantities:

- ❑ Total number (count) for each produced isotope;
- ❑ Space and time coordinates for each β+ decay.

➢ **1) From counts**, it is calculated the percentages that will be used as reference for DoPET experimental results;

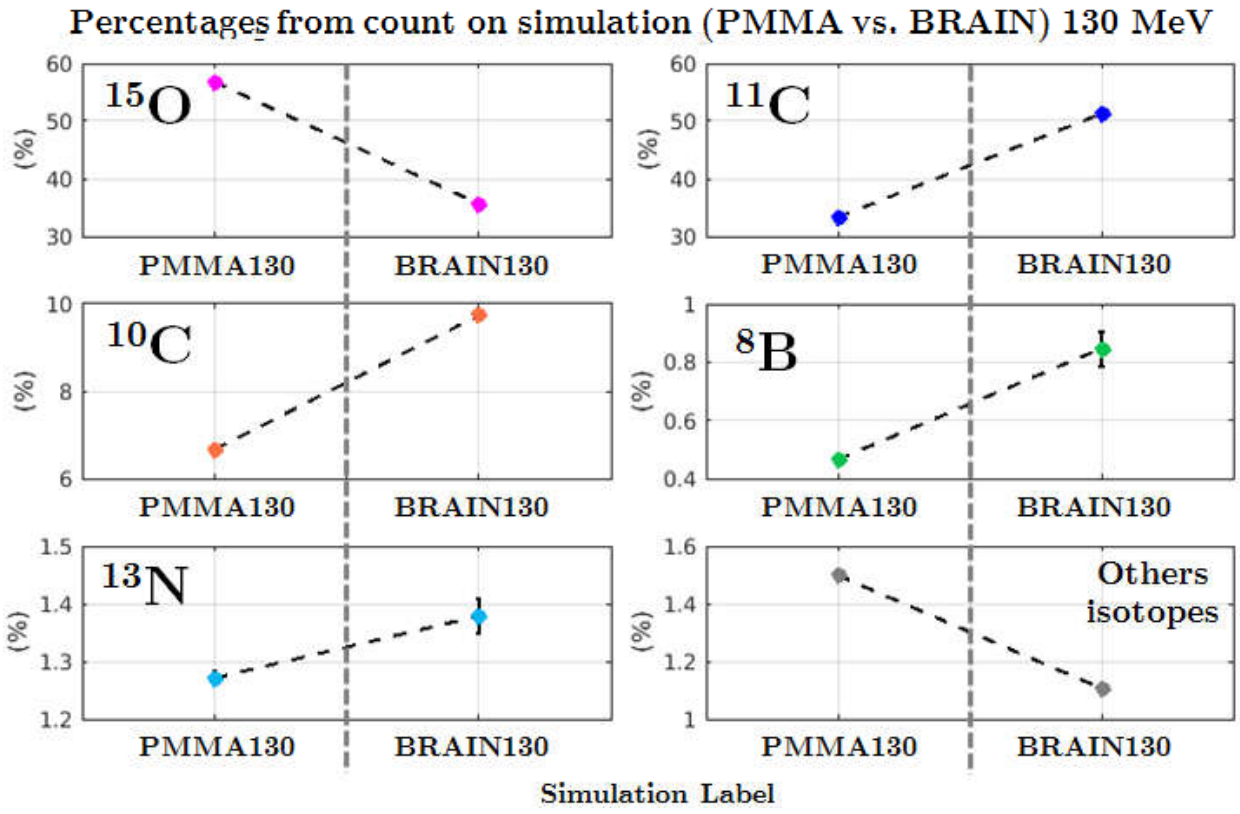
➢ **2) Activity time profiles obtained from simulation** are used to test the fit method.

Monte Carlo simulations

1) Percentages obtained by count of isotopes' production on simulation..

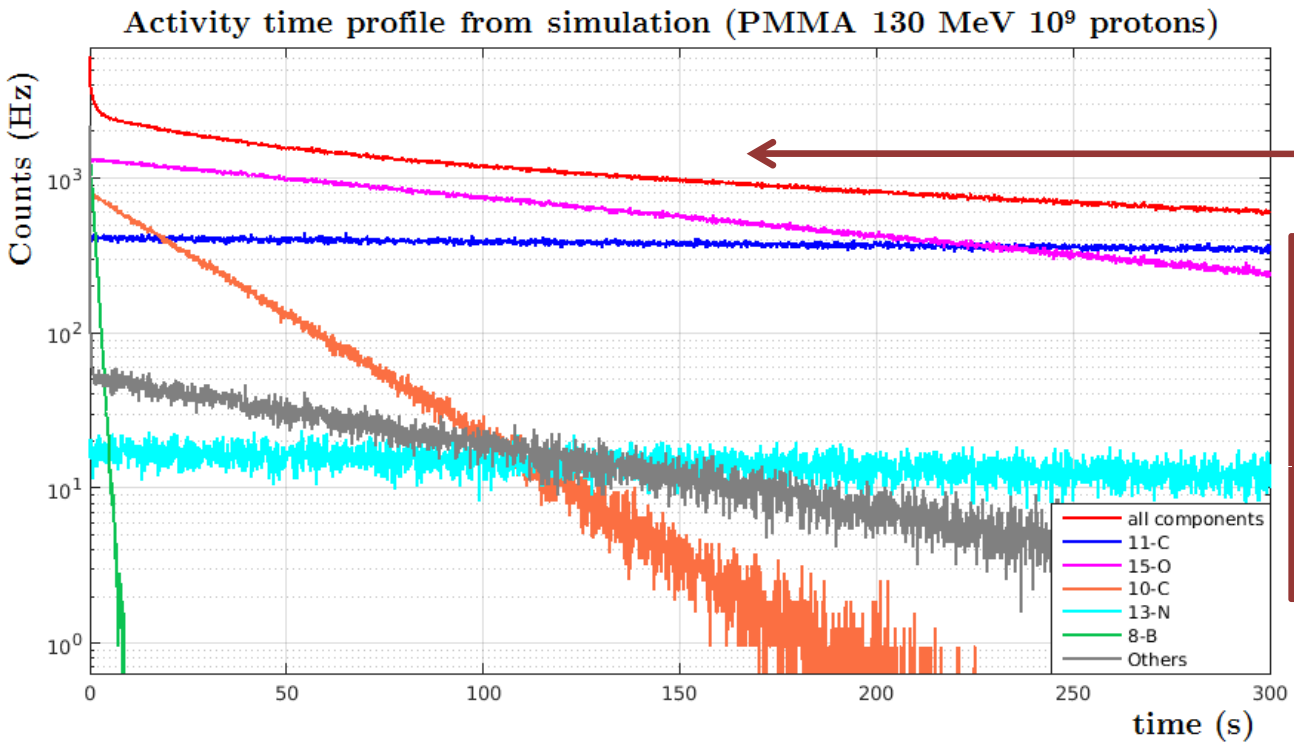
Table. Percentages of isotopes calculated (count) from the results of the simulations performed in this work. The percentages were calculated for an interval between 0 (beam-off beginning) and 300 seconds.

Label	^{11}C (%)	^{15}O (%)	^{10}C (%)	^{8}B (%)	^{13}N (%)	*Others* (%)
PMMA130	33.31 ± 0.03	56.79 ± 0.03	6.65 ± 0.04	0.46 ± 0.01	1.27 ± 0.01	1.50 ± 0.01
BRAIN130	51.26 ± 0.05	35.66 ± 0.07	9.74 ± 0.07	0.85 ± 0.06	1.38 ± 0.03	1.11 ± 0.01



Monte Carlo simulations

2) Percentages obtained by fit method applied on simulated time profile.



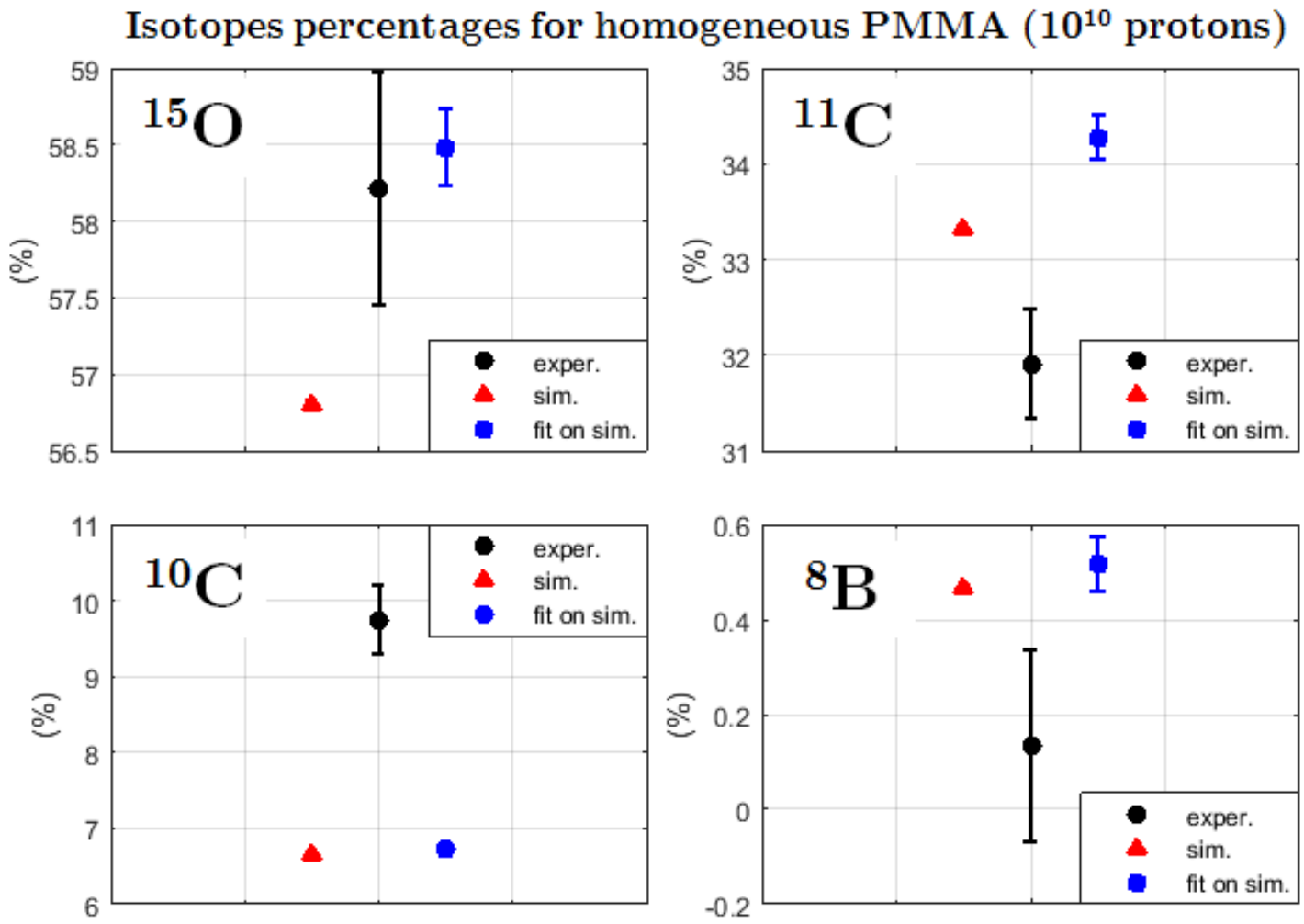
Fit applied in the simulated time profile

$$f(t) = \sum_{i=1}^{n} a_i e \exp\left(-\frac{t \ln 2}{T_i}\right)$$

Table. Percentages of isotopes calculated applying the fit-method on the activity time profiles obtained in the simulations The percentages were calculated for an interval between 0 (beam-off beginning) and 300 seconds.

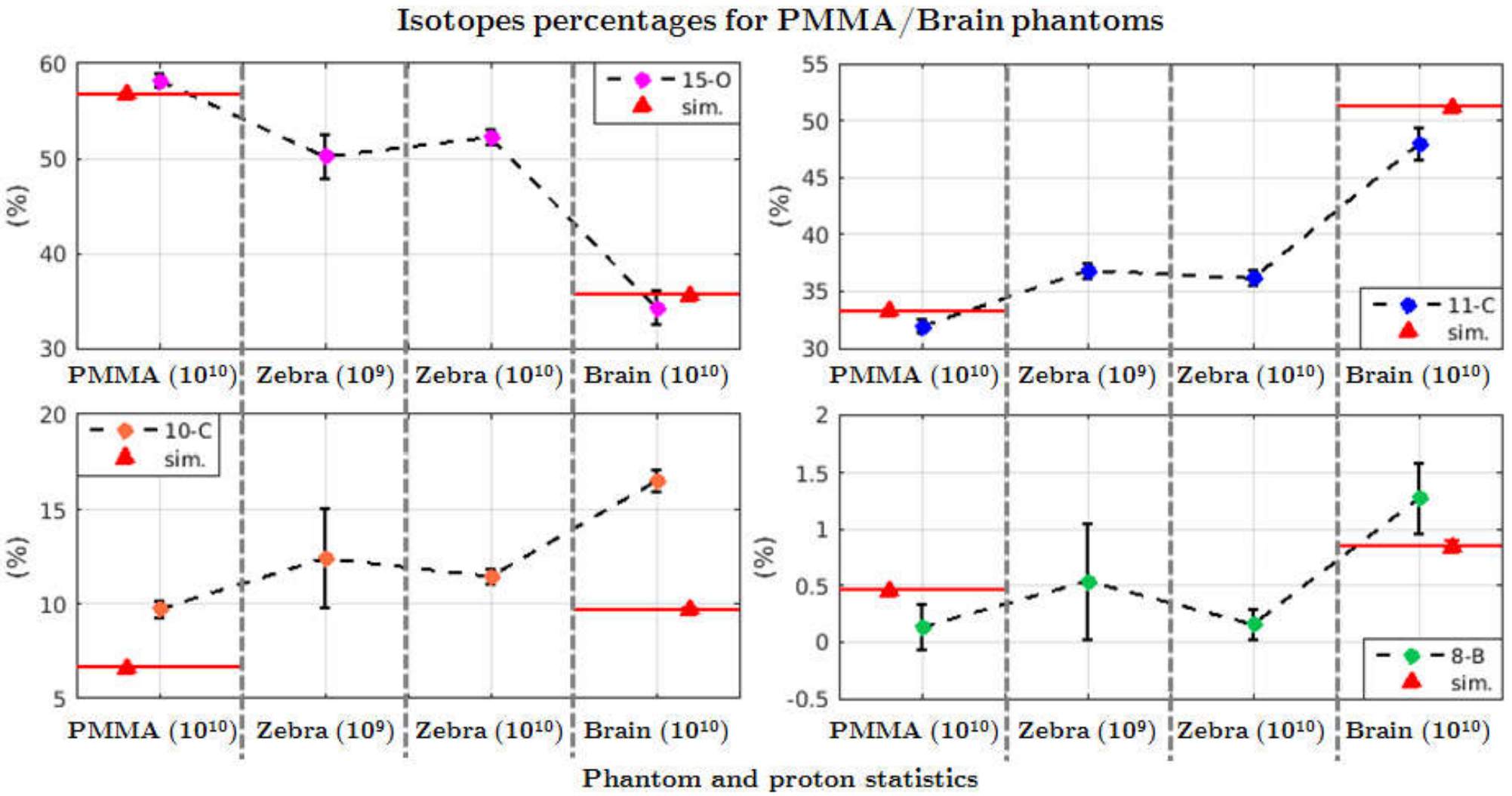
Label	^{11}C (%)	^{15}O (%)	^{10}C (%)	^{8}B (%)
PMMA130	34.28 ± 0.24	58.48 ± 0.25	6.72 ± 0.07	0.52 ± 0.06
BRAIN130	52.53 ± 0.09	36.72 ± 0.05	9.84 ± 0.18	1.02 ± 0.10

Comparison simulations vs. fit method



Comparison between values of experimental isotopes percentages observed in the irradiation of PMMA with the fit-method and values calculated from the simulation. Each subplot shows experimental (**black**) and simulation (**red**) results for an isotope. The result of the fit on simulated time profile is plotted in **blue**.

Isotopes percentages for different materials



Comparison between the percentages obtained from the fit-method applied in the DoPET experimental data. The subplots are divided in four parts, each one representing the isotope percentage for one phantom. Isotopes percentages calculated from the simulations for the homogeneous phantoms are plotted in **red**.

Conclusion and future work

The studies presented in this Pre-thesis aimed to evaluate the capability of a PET dose monitoring prototype, the DoPET, in evaluate **elemental constitution of different irradiated targets**.

The tool proposed and studied was **the multi-exponential fit method of the activity temporal profile detected with DoPET**. The production of β+ emitters by the therapeutic proton beam can provide important information about the irradiated material.

The elemental and spatial studies presented here, **at this point performed separately**, focused essentially in the most abundant isotopes as they are more easily identified in the DoPET temporal signal. Even if experimental results are not in perfect agreement with simulations, they have been verified to be related with variation in the target's materials.

For **less abundant isotopes this observation is more challenging** due to several factors regarding the uncertainties on the DoPET data acquisition, especially for the first seconds of temporal data. The studies on beam-on phase are essential for the improvement of DoPET signal analysis.

Conclusion and future work

For the third year of the PhD activities, the following studies are predicted based on the presented results:

1 – Study of short-lived isotopes contribution.
The studies of specific isotopes are planned, mainly for some specific materials (bone equivalent, for example). The short-lived emitters are especially important as they can provide rapid and accurate information on the presence of a material in the target composition. The procedure for the fit method will be reviewed, regrouping the isotopes steps by step in the multi-exponential fit according to their decay characteristic and not according to their production abundance.

2 – Implementation of spatial-dependent activity time profile measurements.
Use of 3-D activity reconstruction for the estimation of the $\beta+$ emitter annihilation position inside the target selecting only the LORs that are unequivocally originated from a specific region of the activated volume. Combining the annihilation position with the registration in time for each coincidence it is possible to perform elemental analyses for sub-volumes of an irradiated phantom.