Production yields of β^+ emitters for range verification in proton therapy

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Abstract. *In-vivo* Positron Emission Tomography (PET) range verification relies on the comparison of the measured and estimated activity distributions from β^+ emitters induced by the proton beam on the most abundant elements in the human body, right after (looking at the long-lived β^+ emitters ^{11}C, ^{13}N and ^{15}O) or during (looking at the short-lived β^+ emitters ^{29}P, ^{12}N, ^{38m}K and ^{10}C) the irradiation. The accuracy of the estimated activity distributions is basically that of the underlying cross section data. In this context, the aim of this work is to improve the knowledge of the production yields of β^+ emitters of interest in proton therapy. In order to measure the long-lived β^+ isotopes, a new method has been developed combining the multi-foil technique with the measurement of the induced activity with a clinical PET scanner. This technique has been tested successfully below 18 MeV at CNA (Spain) and will be used at a clinical beam to obtain data up to 230 MeV. However, such method does not allow measuring the production short-lived isotopes (lower half-life). For this, the proposed method combines a series of targets sandwiched between aluminum foils (acting as both degraders and converters) placed between two $LaBr_3$ detectors that will measure the pairs of 511 keV γ-rays. The first tests will take place at the AGOR facility at KVI-CART, in Groningen.

1 Introduction

In comparison to conventional radiation therapy, proton therapy is able to reduce the radiation dose deposition in the healthy tissues adjacent to the tumor. The spatial dose distribution of the protons is characterized by its maximum dose deposition near the end of the trajectory, the Bragg peak, and its finite penetration in the patient, making proton therapy especially well-suited for tumor close to organs at risk and in pediatric cancers. However, current treatment plannings have to consider safety margins associated to the uncertainty in the actual beam range in the patient, hence limiting the potential benefits of proton therapy. For this reason, it is highly desirable to verify the particle beam range directly in-vivo. [1].

A possibility to verify the range of the proton beam is to use Positron Emission Tomography (PET) to look at the β^+ emitters produced in the body of the patient during the irradiation. Detecting in coincidence the simultaneous 511 keV photons allows the monitoring of the range during the irradiation (on-line range verification) or just after the irradiation (off-line range verification) [2, 3]. The relation between the induced activity distribution and the dose delivered is not straightforward due to different underlying physical processes. For instance, the threshold energies to produce β^+ emitters cause the activity to drop about 7-10 mm before the dose distribution does [2], and the activity distribution changes due to the wash-out effects [4]. Therefore, PET range verification relies in the comparison of the measured activity distribution with a Monte Carlo simulation, which accuracy is dominated by that of the underlying cross sections for producing the β^+ emitters of interest. A review of the experimental data available indicates that these are in many cases not available in the full energy range of interest (up to ~200 MeV) and, when they are, there are sizeable discrepancies between the different data sets [5]. Indeed, several studies [6, 7] confirm the need for more accurate measurements, especially in the case of the short-lived β^+ emitters, for which all the data available are just a measurement up to 48 MeV of the excitation function as function of the proton energy for the ^{12}C(p,n)^{12}N reaction [8] and the integral production yields of ^{12}N, ^{38m}K and ^{29}P β^+ emitters below 55 MeV [9]. This work aims to improve the knowledge of the production cross section of the mentioned long- and short-lived β^+ emitters in the full energy range of interest.

2 Production yields of ^{11}C and ^{13}N

Focusing in the production cross section of the long-lived β^+ emitters ^{11}C ($t_{1/2}$= 20,36 min) and ^{13}N ($t_{1/2}$= 9,97 min) in carbon, oxygen and nitrogen, the reaction channels of interest are ^{14}N(p,α)^{11}C, ^{12}C(p,pn)^{11}C, ^{12}C(p,γ)^{13}N,

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^{16}O(p,*)^{11}C and ^{16}O(p,α)^{13}N. Two of these, ^{14}N(p,α)^{11}C and ^{16}O(p,α)^{13}N, are also of interest for medical imaging and hence there are IAEA evaluations [10] in the low energy region, below 30 MeV. However, new measurements up to 200 MeV are needed to monitor the range. With this objective, a new method has been developed at the Centro Nacional de Aceleradores (CNA) in Seville, Spain. The method combines multi-foil activation with a PET scanner. The energy of the beam decreases as it traverses the different foils and hence the activation occurs at a different proton energy in each of them. The novelty of the method consists in the subsequent simultaneous measurement of the activity induced in each of the films by using a PET scanner. The method has been applied succesfully below 18 MeV at CNA (Spain). The higher energy region, up to 230 MeV, will be covered in a forthcoming measurement at a clinical proton therapy facility.

2.1 Measurements below 18 MeV at CNA

Three multi-foil targets rich in carbon (polyethylene), oxygen (polymethylmethacrylate) and nitrogen (Nylon-6) were irradiated. The foil thickness was chosen about 100-200 μm, as the energy steps must be small enough to be sensitive to the low energy resonances in the cross sections.

During the irradiation, the beam current was monitored using an electrically isolated graphite as beam dump (placed after the targets) connected to a Brookhaven 1000c Current Integrator. The targets were all mounted on a holder, coupled to a motorized table (figure 1, left) that allows placing different targets in the beam without entering the experimental room, hence minimizing the decay of the induced activity between consecutive irradiations. The first film in each stack is a PMMA monitor film, which serves to validate at the same time the measurement of the relative beam intensity and the calculations of the decay during the irradiation and during the transport from the experimental area to the PET scanner. After the irradiation of the three targets, the activity in each film was measured using a PET scanner for 5 hours in dynamic mode (acquisitions of 1 minute), obtaining the activity curve of all the irradiated films in a single measurement. Inside the PET scanner, the films were placed between thick layers of polyethylene acting as converters of the positrons into a couple of 511 keV photons (figure 1, right). A ^{22}Na calibrated source is used to convert the PET units to becquerels and to calibrate the PET scanner efficiency as function of the position.

In order to ensure the accuracy of the results, the IAEA monitor reactions ^{nat}Cu(p,x)^{62}Zn and ^{nat}Cu(p,x)^{63}Zn [11] were used for normalization and validation purposes. The integral production yield of ^{62}Zn and ^{63}Zn below 18 MeV, measured with $LaBr_3$ detectors looking at the 511 keV photons and other characteristics g-rays, was used to normalize and validate the value of the beam current.

2.2 Data analysis and results

The production cross sections are calculated from the induced activity at the end of bombardment (EOB). Taking into account the decay constant of ^{11}C and ^{13}N, and the background introduced by the ^{22}Na source and the ^{176}Lu present in the LSO scintillator crystals, the activity curves are fitted to

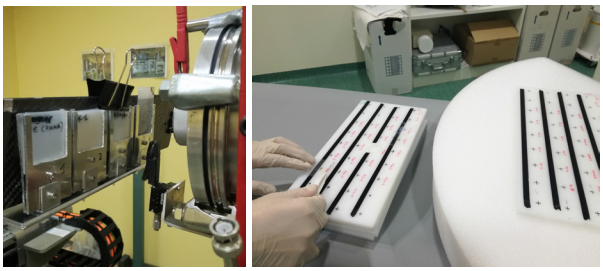

Figure 1. Left: Irradiation experimental set up. Right: films placed in the polyethylene matrix.

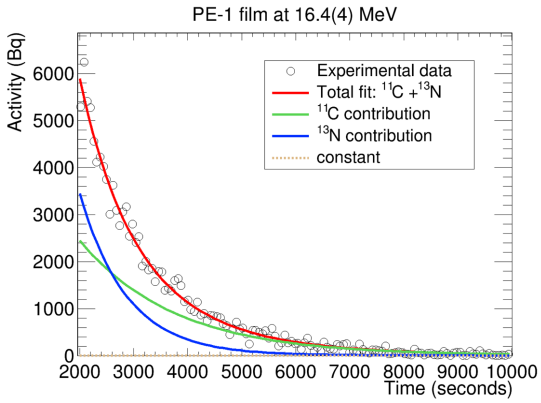

Figure 2. Activity curve obtained with a PET scanner.

$$f(t) = A_0 + A_{11_C} e^{-\lambda_{11_C} t} + A_{13_N} e^{-\lambda_{13_N} t}, \quad (1)$$

where A_{11_C} and A_{13_N} and $\lambda_{11_C} = ln(2)/t_{1/2}^{11_C}$ and $\lambda_{13_N} = ln(2)/t_{1/2}^{13_N}$ are the activities at EOB and decay constants of ^{11}C and ^{13}N (see figure 2). The activity curves of all films have been fitted making use of the ROOT software whose algorithms are based on the minimum chi-squared method [12]. The induced activity at EOB of the isotope i in the target k, excluding the decay during the irradiation, is

$$A_i^k = \sum_j \lambda_i p_j n_j^k \sigma_{j\to i} I_k T_{irrad}, \quad (2)$$

where p_j is the abundance of the isotope j, n_j^k is the number of nuclei of the j element in k-target per unity of area, I_k is the flux of incident protons in k-target in particles per unity of time, and $\sigma_{j\to i}$ is the production cross section of element i. Considering the decay during the irradiation, the activity is corrected by a factor:

$$r = \frac{\lambda T_{irrad}}{1 - e^{-\lambda T_{irrad}}} \quad (3)$$

The production yield in oxygen and nitrogen were obtained by subtracting the carbon contribution in PMMA films and the carbon and oxygen contributions in nylon-6 films, respectively. The calculation of the beam energy degradation has been performed via SRIM [13] and

Geant4 [14] simulations, which produced compatible results. The cross section of ^{12}C(p,γ)^{13}N ^{14}N(p,α)^{11}C and ^{16}O(p,α)^{13}N resulting from the mentioned measurement and analysis are shown in figure 3, together with the available data in EXFOR data base and the IAEA evaluation [5].

For the reactions ^{14}N(p,α)^{11}C and ^{16}O(p,α)^{13}N, for which exist an IAEA evaluation, the production cross sections have a similar shape than that of the evaluation, although the production slightly higher. In the case of ^{14}N(p,α)^{11}C the production is 10% higher and in the case of ^{16}O(p,α)^{13}N the production is 43% higher. However, a study of the average deviation of the available data to the IAEA evaluation shows that the results presented herein are in good agreement with the deviation of the other measurements.

2.3 Measurements between 20 and 230 MeV

The measurement at high energy follows the same methodology discussed above but with some adaptations. First, the films will be separated by degraders in order to increase the energy step between consecutive films. Second, because the energy spread of the beam increases with the distance travelled, different beam energies will be used to study the full enery range of interest with enough energy resolution.

The optimal irradiation set-up has been designed by means of Monte Carlo simulations with Geant4. Considering both the beam energy loss and the straggling we have determined the number of films in each stack and the degrader thickness needed to cover the energy range of interest with the desired energy resolution. At the end of the stack, an additional energy degrader and a thick layer of ^{nat}Cu will be placed for measuring the integral production yield of ^{63}Zn and ^{65}Zn below 20 MeV, as these are considered reference cross sections [11]. As in the low energy experiment at CNA, the first film of each target will be a monitor film of PMMA.

The energy of the proton beam as it enters each film for each initial beam energy is shown in figure 4. This illustrates how the four initial beam energies allow covering the full energy range of interest for the cross section measurements.

3 Production yields of ^{12}N, ^{38m}K and ^{29}P

Using long-lived β^+ emitters to monitor the range has some limitations. Among others, the biological wash-out effect and the not immediate feedback on the dose delivery. As an alternative, beam-on PET imaging with short-lived isotopes provides real-time feedback and a largest number of counts, as well as it is least susceptible to biological wash-out [9, 15].

Focusing on the short-lived β^+ emitters (half-life shorter than that of ^{10}C, $t_{1/2}$ = 19 s), the isotopes of interest for range verification are ^{12}N (in carbon), ^{29}P (in phosphorus) and ^{38m}K (in calcium) [9]. In the three cases the corresponding production coss section are not available or poorly known, hence the need to measure them.

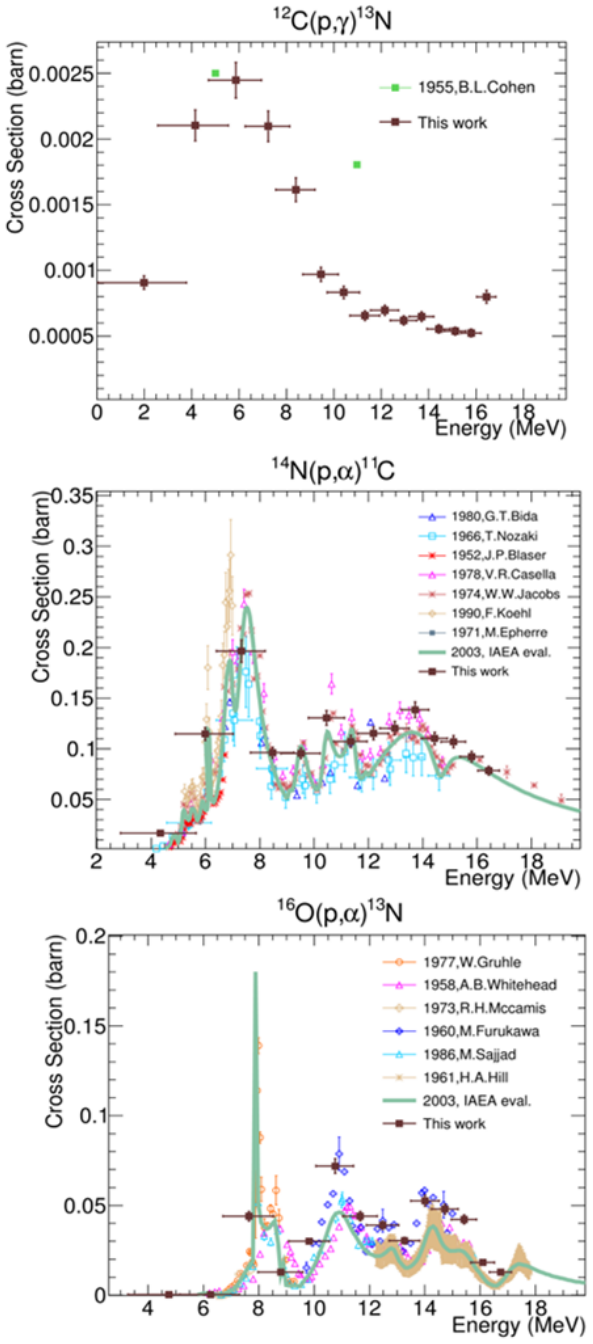

Figure 3. Production cross section for the reaction channel ^{12}C(p,γ)^{13}N (top), ^{14}N(p,α)^{11}C (middle) and ^{16}O(p,α)^{13}N (bottom) below 18 MeV.

3.1 Experimental setup at the 190 MeV KVI-CART AGOR cyclotron

An experiment aiming at measuring the reaction cross section of ^{12}C(p,n)^{12}N, ^{40}Ca(p,2pn)^{38m}K and ^{31}P(p,p2n)^{29}P up to the maximum energy available at the AGOR cyclotron (Groningen), covering most of the energy range of interest (up to ~200 MeV), has been designed. At high energies, the production cross sections do not vary abruptly with energy, and, additionally, for range verification are not really significant at the very entrance of the patient

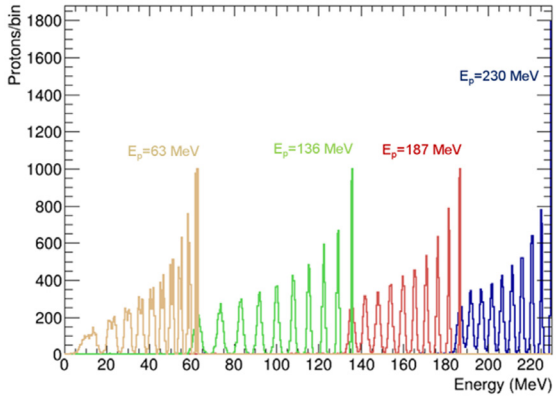

Figure 4. Geant4 calculations of the proton energy degradation considering 1 mm target thickness and a polyethylene degrader thickness of 1 cm with protons of 230, 187, 136 MeV and 0.25 cm with protons of 62 MeV.

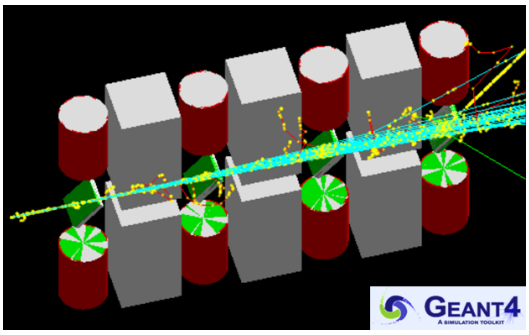

Figure 5. Geant4 simulation of the experimental set up to measure the short-lived β^+ emitters.

body. Thus, the coverage up to 190 MeV is enough for range verification.

The methodology followed in this case varies with respect to that for the long-lived isotopes. A set of 1, 2 and 3 mm targets of C, CaF_2 and P, respectively, sandwiched between aluminum layers of 3 mm, are placed along the beam line in such a way that the energy of the beam traversing each target decreases from one target to the next. The aluminum layers act as energy degraders and positron converters. The activity induced in each target is determined from the coincidences of the annihilation photons registered in a pair of $LaBr_3$(Ce) scintillation detectors that look at each target. A scheme of the irradiation set up is displayed in figure 5. The Monte Carlo simulations indicate that the optimum aluminum thickness regarding the positron annihilation ranges between 5 and 17 mm, depending on the β^+ emitter of interest, but such thickness would degrade the energy of the beam far more than is desirable. Therefore, a thickness of 3 mm is proposed. As a fraction of the positrons can not be stopped in just 3 mm of aluminum, the associated correction will be estimated during the data analysis by means of Geant4 Monte Carlo simulations, which have been already validated in experiments at CNA, Seville. The beam energy distributions in each target are obtained from Geant4 simulations, so that the overlapping between the energies of two consecutive irradiations validates the measurement.

4 Conclusions

There is a need for more accurate production yields of β^+ emitters for PET range verification in proton therapy [7, 10], both for the long-lived (minutes) for offline monitoring and for the short-lived (miliseconds) for online monitoring. Thus two projects are ongoing to measure the production of both types of isotopes in the full range of interest, using the 18 MeV proton beam of CNA to design, test and validate reliable, versatile and accurate measuring techniques.

The production cross sections of the long-lived β^+ emitters ^{11}C and ^{13}N in carbon, nitrogen and oxygen have been successfully measured in the Bragg peak region below 18 MeV. These are obtained by means of a multi-foil activation technique, taking advantage of the high spatial resolution of a clinical PET scanner to measure the activation of all the foils in a single acquisition. The measurement of the ^{nat}Cu(p,*)^{63}Zn integral cross section [11] validates our results, which are a 43% and 10% higher than the recommended IAEA evaluations for ^{16}O(p,α)^{13}N and ^{14}N(p,α)^{11}C, respectively. The measurement from 20 to 250 MeV will be carried out at the beginning of 2020 at a clinical facility.

However, the problems associated to the use of long-lived isotopes to monitor the range make necessary to use beam-on PET imaging with short-lived isotopes. The production cross section of these will be measured at the beginning of July at the KVI-CART 190 MeV cyclotron.

References

[1] Knopf and Lomax, Phys. Med. Biol. **58**, R99-107 (2012)
[2] Oelfke et al., Phys. Med. Biol. **41**, 177 (1996)
[3] Parodi et al., Phys. Med. Biol. **52** 3369–87 (2007)
[4] Parodi et al., Int. J. Radiat. Oncol. Biol. Phys. **68** 920–34 (2007)
[5] EXFOR data base, https://www-nds.iaea.org/exfor/
[6] España et al., Phys. Med. Biol. **56** 2687–98 (2011)
[7] Seravalli et al., Phys. Med. Biol. **57**(6) (2012)
[8] Rimmer and Fisher, Nucl. Phys. **A108** 561-566 (1968)
[9] Dendooven et al., Phys. Med. Biol. **60** 8923 (2015)
[10] Gul et al., IAEA report IAEA-TECDOC-1211, May 2001, IAEA, Vienna, Austria.
[11] Hermanne et al, Nucl. Data Sheets **148** 338-382 (2018)
[12] CERN, "ROOT. Data Analysis Framework." https://www.root.cern.ch.
[13] Ziegler et al, Pergamon Press, New York (1985)
[14] Allison et al, Nucl. Instrum. Meth. A **835** 186-225 (2016)
[15] Buitenhuis et al., Phys. Med. Biol. **62** 4654 (2017)