The INSIDE project: on-line monitoring and simulation validation with the in-beam PET scanner

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Abstract. The quality assurance of particle therapy treatment is a fundamental issue that can be addressed by developing reliable monitoring techniques and indicators of the treatment plan accuracy. Monitoring using Position Emission Tomography (PET) systems is the only \textit{in-vivo} non-invasive technique employed clinically and has been carried out in particle therapy since 1997. However, the PET monitoring of $\beta^+$ emitter isotopes is typically done after the treatment, resulting in a large fraction of lost data because of the isotopes rapid physical decay. The INSIDE collaboration has recently installed an in-beam PET scanner at the Italian National Center of Oncologic Hadrontherapy in Pavia, Italy. Here, there is an ongoing project in order to start testing the method on patients. This work focuses on the online performances of the scanner with clinical beams.

1. Introduction

Particle range verification is one of the key issues for treatment quality assessment in hadrontherapy, and requires the development of reliable monitoring techniques and indicators of the treatment plan accuracy. Charged particles release all of their energy inside the body, with a sharp ionization peak at the end of their range called the Bragg Peak (BP), so the only non-invasive way to verify the treatment accuracy is to collect the secondary radiation generated by the beam-tissue interactions. Positron Emission Tomography (PET) has been employed clinically since 1997 \cite{1}, and offers the possibility to directly monitor the spatial distribution of positron ($\beta^+$) emitter isotopes created during irradiation. Specifically, the emitted positron annihilates with an electron in the tissue, producing two back-to-back 511 keV photons, which in turn can interact and release part (i.e., Compton scattering) or all (photoelectric effect) of their energy in the detection crystals. Two detectors triggering in time coincidence allow the definition of the line of response associated to a certain annihilation event. To correctly identify the lines of response the scattered events need to be discarded, so only the 511 keV events (correlated to the photoelectric effect) are selected. The reconstructed isotopes activity distribution inside the patient thus gives an insight about the delivered treatment.

Defining the particle range from the activity measurement is not straightforward, because it has a non-trivial dependency on the ion species, the energy, and the tissue composition. However, from the activity distribution it is possible to infer the BP position since its profile along the beam path has a characteristic fall-off a few millimeters before the BP itself \cite{2, 3, 4}.
PET monitoring is typically performed after the treatment session, which leads to a large fraction of lost treatment data. The $\beta^+$ emitter isotopes produced have a rapid physical decay (their half lives last from few us to a maximum of 20 min for the $^{11}$C isotope) and can undergo functional pathways such as perfusion and diffusion. Moreover, the radioactivity produced during the treatment is of a maximum of few kBq/ml/Gy, almost two orders of magnitude below the typical activity concentrations in nuclear medicine (about 50 kBq/ml in hot spots), and the loss of short half time nuclides combined with the physiological washout makes after-treatment PET not optimal for in-vivo monitoring. Dedicated PET systems integrated within the treatment room are being investigated, so as to detect both the long and short half time nuclides radioactivity signal, and to also minimize biological washout.

The INSIDE collaboration has recently completed the construction of an in-beam PET detector, now under commissioning at the Italian National Center of Oncologic Hadrontherapy (CNAO) synchrotron facility in Pavia. The system characterization using proton and carbon beams is ongoing, and first measurements showed the capability of the in-beam PET to operate during the irradiation delivery and to reconstruct the beam-induced activity map in real-time.

2. The INSIDE in-beam PET

The INSIDE in-beam PET mechanical structure has been optimized to fit the nozzle of the CNAO treatment room, and can be easily placed in working position by aligning the markers on the PET heads with the positioning lasers of the room.

The system features two planar heads of $10 \times 25$ cm$^2$ area, mounted on a mobile support and placed at a 25 cm distance from the isocenter. Each head is made of $2 \times 5$ detection modules based on $16 \times 16$ matrices of segmented Lutetium Fine Silicate (LFS) scintillating crystals coupled to Hamamatsu silicon photomultipliers [5]. A detection module is read out by 4 TOFPET ASICs [6], which give information about the energy and the detection time of each event.

A data processing system based on field programmable gate array (FPGA) selects the 511 keV events and transmits them to a custom data acquisition system implemented on a server (32 Hyper Thread cores and 128 GB RAM) with a real-time high performance software that applies on-line data sorting and writes time-tagged coincidence data.

The PET images are reconstructed through a maximum likelihood expectation maximization algorithm [7] with 5 iterations. The Field Of View (FOV) of the reconstructed images is $16 \times 10.4 \times 26.4$ cm$^3$, with a voxel size of $1.6 \times 1.6 \times 1.6$ mm$^3$.

3. Experimental set-up

The INSIDE in-beam PET was tested at the CNAO facility with different irradiation configurations. The first characterization tests were performed with single pencil beams on both homogeneous and inhomogeneous polymethyl methacrylate (PMMA) phantoms [8, 9, 10], showing the system capability to acquire and reconstruct data in real-time.

The INSIDE in-beam PET experimental set-up is shown in Fig. 1. The PET scanner is positioned in the treatment room so that the center of the FOV is at the isocenter. The working distance between the heads is set at 50 cm, symmetrical with respect to the isocenter.

The aim of the test was to perform a first evaluation of the system online performances for a real treatment plan (i.e. actually delivered in clinical treatments) delivery, in view of future applications with patients. A $15 \times 15 \times 20$ cm$^3$ homogeneous PMMA phantom was irradiated with proton beams. Two real Treatment Plans (TP A and TP B), were delivered twice each, respectively called TP A1 and TP A2, TP B1 and TP B2. The phantom was changed after each acquisition to avoid residual activity from the previous irradiation. Each phantom was positioned with the long side along the beam direction and it was centered at the isocentre.
Figure 1. Left: the INSIDE in-beam PET installed in one of the CNAO treatment rooms. Right: schematic picture of the experimental set-up. The beam direction is parallel to the positive z axis.

The total number of particles delivered per treatment was $38 \times 10^9$, resulting in about 1 Gy of dose. The energy ranges for each plan are reported in Tab. 1. The maximum single event rate in the photopeak window was 13 MHz, with a coincidence time window set at 2 ns. The irradiation lasted about 4 min, but data were also acquired in the after-treatment for about another 6 min.

Table 1. Range energies for two real Treatment Plans (TP), protons.

| TP | $E_{\text{min}}$ (MeV/u) | $E_{\text{max}}$ (MeV/u) |
|----|------------------|-----------------|
| A  | 83               | 150             |
| B  | 62               | 129             |

4. Simulations

Since the distributions of $\beta^+$ radioactivity and dose are not directly comparable, the quality assessment of charged particle therapy requires the prediction of the $\beta^+$ activity distribution from the treatment planning.

A dedicated simulation has been developed in FLUKA [11] and it comprises two steps. First, the primary beam is simulated with reduced statistics (about 1/100 of the primaries released in the whole treatment, thus reducing the simulation time of about 70x), and the 3D $\beta^+$ emitter distribution is scored. Then, a full statistic Monte Carlo simulation is performed by extracting the emission time of all positrons.

The simulation accounts for both the INSIDE in-beam PET characteristics and Figs. of merit and the delivery informations coming from the CNAO Dose Delivery System (DDS) [12]. The DDS is integrated in the CNAO synchrotron and monitors the space and time structure of the beam for each delivery. The average beam structure in time is 1 s beam on (in-spill) followed by 3-4 s beam off (inter-spill). The CNAO beam pipe and nozzle have a known geometry and have been simulated in previous works [13].

A C++ tool is developed for post-processing the FLUKA events and obtaining a time-based signal. The simulated and experimental data are analyzed with the same parameters (e.g. equal coincidence time window, energy window, and acquisition time).
The simulation plays a central role for in-beam PET clinical use, because the simulated image represents the prior to compare with the experimental image.

5. Activity comparison

The acquired data activity distribution was reconstructed by considering inter-spill and after-treatment only for a total of 700 s in all cases. The irradiation settings described previously for TP A and TP B were reproduced in the FLUKA simulations and the activity was reconstructed with the same parameters as the data.

Fig. 2 shows the activity profiles for the experimental data and the simulation for all the TPs under consideration. The experimental activity image is also encapsulated within the plots. The beam is directed along the positive z axis as shown in Fig. 1.

![Figure 2](image)

**Figure 2.** Experimental (black curves) and simulated (red curves) activity profiles of real treatment plans (TP). The energy ranges are reported in Tab. 1. Each TP configuration was delivered twice. The central section parallel to the PET heads of the reconstructed experimental activity image is also shown. The beam enters from the left, in the direction of the positive z coordinate.

The profiles are calculated along the beam axis, in a square area of $0.96 \times 0.96 \text{ cm}^2$ in the transverse plane from the center of the image. The images, and thus the activity profiles, are not normalized. The plots in Fig. 2 show a satisfactory agreement between data and simulations for all the cases under consideration. The shape of these activity profiles is influenced by the chosen treatment delivery modality, in which there is a Spread Out Bragg Peak (SOBP) that depends on the energy ranges used and the material traversed. In previous works [8 - 10] the activity measurement was validated by evaluating the distal fall off of the activity profile and comparing it to the expected Bragg peak position. In the case of a SOBP though, the distal fall off is not as clearly defined, and a more complex analysis is needed. For this reason, a 3D comparison was implemented with ITK [14] libraries, applying a median filter with a $5 \times 5 \times 5$ kernel to the whole FOV to reduce the noise, followed by a threshold filter to select only the voxels with values higher than 10% with respect to the maximum relative intensity. To further
eliminate any remaining background spots, smoothing, erosion and dilation filters are applied. The DDS information about the proton beam position in the transverse plane is also applied to select the most meaningful volume of the image where the TP was actually delivered and ignore eventual artifacts from the reconstruction algorithm. Through this process a selection of the activity is made for all the images. The image activity range is then calculated by considering the depth along the z axis contained in the selected volume. The resulting distribution of the activity range of one image is then subtracted to the distribution of the image to be compared. The activity depth difference histogram is shown in Fig. 3 for the two repeated acquisitions of the TP A (TP A1 and A2), and the simulation. The corresponding activity images are also reported with the contours of the selected volume (TP A1 in white, TP A2 in green, simulation in red).

Figure 3. Example of activity depth difference histogram for the two experimental acquisitions of the TP A (TP A1 and TP A2, upper panel) and the TP A1 with the simulation (lower panel). The activity images in the plane parallel to the PET heads are shown with the contour of the selected volume: TP A1, white; TP A2, green; simulation, red. The superimposed contours of the compared images are also shown.

The agreement between TP A1 and TP A2 3D activity distributions results to be of (0.82 ± 0.01) mm, while the agreement of the TP A1 with the simulation is of (1.34 ± 0.02) mm. The activity depth difference histogram between data and simulation is not symmetric, with a tail on the right side. That is because the activity distribution of the simulation is slightly shorter than that of the data. Further studies will be carried out to improve the simulation, and to better characterize the activity comparison. Nonetheless, an agreement within 1.5 mm between the expected and experimental activity distribution is way below the safety margins (3 mm). The same analysis carried out comparing the experimental TP B and the correspondent simulation showed similar consistency.
These results are a milestone for the INSIDE project, because they prove the capability of the INSIDE scanner to acquire real-time images with a precision within 1 mm. Moreover, they validate the simulations with which the experimental data must be compared. Knowing the expected activity distribution, the on-line validation of the treatment deliver becomes possible. These results pose very promising prospects for in-beam PET monitoring and quality assurance in particle therapy.

6. Conclusions
Particle range monitoring is a key issue to improve quality assurance in particle therapy. In this work the INSIDE in-beam PET scanner response was tested for repeated irradiations on PMMA phantoms with clinical proton beams. Comparing the detected 3D activity distributions of two different experiments, we found them to be in agreement within 1 mm, while, when comparing the experiments with the simulated analysis, we found them to be consistent within 1.5 mm.

A satisfactory qualitative agreement was also found for the activity profiles along the beam direction.

The detected 3D activity distribution was found to be in agreement within 1 mm for the experimental data comparison, and within 1.5 mm for the experimental and simulated analysis.

In the near future the INSIDE in-beam PET will be further characterized in order to start testing the method on patients at CNAO.

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