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In-beam PET monitoring of mono-energetic $^{16}$O and $^{12}$C beams: experiments and FLUKA simulations for homogeneous targets

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Abstract

$^{16}$O and $^{12}$C ion beams will be used—besides lighter ions—for cancer treatment at the Heidelberg Ion Therapy Center (HIT), Germany. It is planned to monitor the treatment by means of in-beam positron emission tomography (PET) as it is done for therapy with $^{12}$C beams at the experimental facility at the Gesellschaft für Schwerionenforschung (GSI), Darmstadt, Germany. To enable PET also for $^{16}$O beams, experimental data of the $\beta^+$-activity created by these beams are needed. Therefore, in-beam PET measurements of the activity created by $^{16}$O beams of various energies on targets of PMMA, water and graphite were performed at GSI for the first time. Additionally reference measurements of $^{12}$C beams on the same target materials were done. The results of the measurements are presented. The deduction of clinically relevant results from in-beam PET data requires reliable simulations of the $\beta^+$-activity production, which is done presently by a dedicated code limited to $^{12}$C beams. Because this code is not extendable to other ions in an easy way, a new code, capable of simulating the production of the $\beta^+$-activity by all ions of interest, is needed. Our choice is the general purpose Monte Carlo code FLUKA which was used to simulate the ion transport, the $\beta^+$-active isotope production, the decay, the positron annihilation and the transport of the annihilation photons. The detector response was simulated with an established software that gives the output in the same list-mode data format as in the experiment. This allows us to use the same software to reconstruct measured and simulated data, which makes comparisons easier and more reliable. The calculated activity distribution shows general good agreement with the measurements.

(Some figures in this article are in colour only in the electronic version)
1. Introduction

At the experimental $^{12}$C ion beam facility at GSI the therapy is monitored by a PET camera fully integrated into the treatment place (Enghardt et al. 2004a). Since 1997 the correct application of the first field delivered in each treatment fraction of more than 400 patients was verified with this system. PET is currently the only technically feasible method for in situ and non-invasive control of the beam portal position and for detection of anatomical changes during fractionated treatment. Moreover, it can be a valuable tool for verification of the physical beam models implemented in the treatment planning system. In-beam PET monitoring is also capable of estimating the difference in dose in cases where the actual treatment situation differs from the planned one (Parodi and Enghardt 2002a, Parodi 2004, Enghardt et al. 2004b).

In-beam PET measures the $\beta^+$-activity arising from nuclear reactions between the ions of the beam and the nuclei of the tissue. The most important $\beta^+$-active isotopes created are $^{11}$C, $^{15}$O, $^{10}$C and $^{13}$N with half-lives of 1222.8 s, 121.8 s, 19.3 s and 597.6 s, respectively. The $\beta^+$-activity and the dose distribution are correlated but do not match, because of the different physical processes underlying. Dose arises from electromagnetic interactions between beam/secondary particles and atoms of the patient tissue while the origin for the activity is nuclear interaction. Compared to the primary particles the projectile fragments have a different range because of their different $A/Z^2$ ratio. Fragments of the target nuclei stay approximately where they are produced. The activity distribution induced by heavy ions like $^{12}$C or $^{16}$O shows a pronounced maximum because of the projectile fragments $^{11}$C and $^{15}$O, respectively which come to rest in close vicinity of the primary beam. Therefore, the maximum of the activity distribution is in vicinity of the dose maximum. For protons and light ions with $Z < 6$ no or only minor amounts of $\beta^+$-active projectile fragments are produced and no pronounced activity peak is created (Priegnitz et al. 2008).

The measured $\beta^+$-activity distribution is determined by a superposition of the distributions of the individual $\beta^+$-active nuclides. But the distributions of the individual $\beta^+$-active isotopes are different according to their origin (i.e. projectile or target fragment) and their residual range. Therefore, due to the different half-lives, the measured activity distribution shows a time dependence.

To enable in-beam PET monitoring despite the different shapes of $\beta^+$-activity and dose distribution, simulations of the expected activity based on the patient X-ray computed tomograms (CT), the treatment plan and the time course of the irradiation are needed. PETSIM (Pönisch et al. 2004), the code presently used for predicting the $\beta^+$-activity at GSI Darmstadt, is limited to the handling of primary $^{12}$C ions. It uses a database of measured $\beta^+$-activity distributions in PMMA which are properly weighted and stretched to simulate the activity in the patient anatomy given by the CT image. This approach demands that $\beta^+$-active target fragments play a minor role and therefore, the stoichiometry (i.e. the specific elemental composition) of the patient tissue is less important. This condition is fulfilled for $^{12}$C ions. For $^{16}$O beams target fragmentation plays an important role. The measuring effort of producing a database of $\beta^+$-activity distributions in different tissues for all relevant beam energies would be enormous. Additionally a better algorithm would be needed for describing the lateral beam broadening in depth, which is currently neglected in PETSIM.

In future ion therapy facilities like the Heidelberg Ion Therapy Center (HIT), Heidelberg, Germany (Haberer et al. 2004), $p$, $^3$He, $^{12}$C and $^{16}$O will be available and it is planned to monitor the therapy by means of in-beam PET. To enable the monitoring of all beams of therapeutic interest, also possible future ones, a general and flexible solution is needed. Because of the problems of extending the PETSIM code an established code is preferred. This code must
be capable of handling all ions of current therapeutical interest, including also possible future ones.

We have chosen to investigate the FLUKA Monte Carlo transport and interaction code (Fassò et al. 2003, 2005) for this purpose. FLUKA is capable of reading CT and can handle the transport and nuclear interaction of protons and ions. With FLUKA good results for predicting dose and fragmentation of various ion beams and protons could be achieved (Sommerer et al. 2006, Parodi et al. 2007a).

The feasibility of using FLUKA for the simulations necessary for PET monitoring of proton therapy was already shown with high accuracy on the basis of experimental cross section data for homogeneous and inhomogeneous targets (Parodi et al. 2002b, Parodi 2004) as well as in clinical application (Parodi et al. 2007b).

A first step in the investigation of the capability of FLUKA for in-beam PET monitoring of ion beams is to simulate the activity created by $^{12}$C and $^{16}$O beams in homogeneous targets. Therefore, for the first time, at GSI in-beam PET measurements of $^{16}$O beams of various energies were performed. Additionally, reference measurements with $^{12}$C beams were performed for the same target materials.

The experiments were simulated by FLUKA taking into account the exact time structure of the irradiation, the time structure of the measurement and modelling accurately the setup and the detector response. Since the execution time of such simulations is very long, FLUKA built-in variance reduction techniques were extensively used and new dedicated methods were implemented.

The paper is organized as follows: section 2.1 describes the experiments. Section 2.2 explains the physics underlying the simulations and the simulation methods. The results of the experiments are given in section 3.1 and the results of the simulations are given in section 3.2. Conclusions are outlined in section 4.

2. Material and methods

2.1. Experiments

2.1.1. Setup. The experiments were performed with the double head in-beam PET camera that is integrated in the $^{12}$C ion treatment place at GSI. Each of the two detector heads (dimensions: $21 \text{ cm} \times 42 \text{ cm}$) is assembled of $4 \times 8$ ECAT EXACT block detectors consisting of a BGO crystal $54 \text{ mm} \times 54 \text{ mm}$ front face and $20 \text{ mm}$ depth and four photomultiplier tubes. The crystal is further subdivided into $8 \times 8$ subcrystals on a pitch of $6.75 \text{ mm}$ (Casey and Nutt 1986). According to the shape of the block detectors, their front faces are arranged on the surface of a sphere of $415 \text{ mm}$ radius.

The coincidence detection efficiency at the time of the experiments was measured by means of a $^{22}$Na source and was found to be $2.14\%$ in the centre of the tomograph. In order to allow time-dependent reconstruction of the measured activity, the data acquisition can be performed in list mode where a time stamp is inserted every $10 \text{ ms}$. The reconstruction of the activity can be done by a backprojection or an iterative maximum likelihood expectation maximization algorithm (Lauckner 1999).

A description of experiments similar to those presented here using $p$, $^3$He, $^7$Li and $^{12}$C beams can be found in Fiedler et al. (2006), Parodi et al. (2002b) and Priegnitz et al. (2008). Although the treatment place at GSI is dedicated to $^{12}$C beams also $^{16}$O beams can be delivered. The raster scanner, a device used to deflect the beam laterally during patient irradiation, was not used. Targets made of polymethyl methacrylate (PMMA, density: $1.18 \text{ g cm}^{-3}$), graphite (density: $1.69$–$1.78 \text{ g cm}^{-3}$) and water were used. The target sizes were about $9 \text{ cm} \times 9 \text{ cm}$...
The first column shows the identifier of the experiment: first three characters indicate the beam, the fourth character the target and the last three digits give the energy.

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<th>Target material</th>
<th>Energy (A MeV)</th>
<th>Range (cm)</th>
<th>Number of spills</th>
<th>Particles per spill</th>
<th>Spill duration (s)</th>
<th>Pause duration (s)</th>
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in the transverse plane and between 15 and 30 cm along the beam direction, depending on the energy of the beam. Since the measuring time is long unavoidable convection in the water targets would make it impossible to acquire spatial activity distributions. Therefore, gelatine (agar–agar) was added to suppress the convection. This changes the chemical composition of water to H_{66.2} O_{33.1} C_{0.7}. Since the amount of the added gelatine is small, the additional carbon content has minor effect on the observed activity.

At the treatment place at GSI the beam is not horizontal but declined by 2.203° with respect to the horizontal plane. The targets were positioned horizontally and therefore the activity appears compressed. However, the compressed activity does not constrain the study presented here because in the simulation the declination of the beam was taken into account.

For each target material, irradiations with 16O beams of four energies (200, 250, 300 and 350 A MeV) were carried out. Because the 12C beam was used only as reference, only one measurement at 260 A MeV was performed per target material.

Table 1 shows the irradiation parameters. To facilitate the identification of the experiments an alphanumerical identifier (cf column ID in table 1) has been chosen for each experiment. The identifier is composed by the particle type (16O or 12C), the target (W for water, P for PMMA and G for graphite) and the beam energy. Typically 120 spills of about 1.9 s duration and roughly 1.9 s pause were delivered (cf table 1). Sometimes the irradiation was interrupted for several seconds due to accelerator failures. These interruptions are not given in table 1 but were taken into account in the simulations.

The activity was measured during the irradiation and until 30 min after irradiation end and the data were stored in list-mode format to allow for time-dependent reconstruction. An additional file provides information on the parameters of the beam delivery (energy, focus, intensity) correlated in time with the list-mode data acquisition.

2.1.2. Data evaluation. The activity measured during the irradiation was evaluated only in the pauses between the spills because the signal during beam extraction is compromised by
prompt $\gamma$-rays from nuclear reactions (Parodi et al. 2005, Crespo et al. 2005). The evaluation of the activity was done by the same mathematical method developed for in-beam PET experiments with proton beams. Below only a brief description of the method is given, a more detailed one can be found in Parodi et al. (2002b). This method consists of two parts. The first part is fitting the decay after irradiation end by a superposition of decay curves for a set of expected nuclides with the relative amount as free parameter. This method has the shortcoming that nuclides with a short half-life, which contribute only for a short time after irradiation end, or nuclides with a small abundance and a low activity are difficult to fit. Because of this limitation in practice only a set with up to three nuclides gives reliable results. The activity from the neglected nuclides is addressed to those chosen for fitting which leads to a slight overestimation of their amount.

In a second step from the set of nuclides, their relative amount and the time course of the irradiation, the average production rate per spill is calculated. This is done by a mathematical formulation taking into account the activation level after each spill. Because this formalism uses only the nuclides found in the first step a further overestimation of the activity can be introduced.

The result of these calculations has to be multiplied by a correction factor $C$ to account for the response of the detector. This factor includes the measured detection efficiency for annihilation photons with a $^{22}$Na source and spatial and attenuation correction factors. A detailed description on how $C$ is calculated can be found in Parodi et al. (2002b).

The spatial distribution of the activity was obtained by using a backprojection algorithm. For each experiment two reconstructions at different time windows were done. The first time window is during the irradiation taking into account only the pauses between the spills and the second is from 10 to 20 min after irradiation end. Ten minutes after irradiation end nuclides with short half-life e.g. $^{15}$O do not contribute significantly to the activity distribution any more, therefore the two backprojections of the same experiment differ. This allows us to separate the spatial contributions from isotopes with short and long half-lives.

2.2. Simulations

2.2.1. FLUKA. FLUKA (Fassò et al. 2005, 2003) is a general purpose particle and ion transport and interaction Monte Carlo code. Originally developed for high energy physics it can be used nowadays for a vast variety of problems like proton and electron accelerator shielding applications, target design, calorimetry, activation, dosimetry, detector design, accelerator driven systems for transmutation of radioactive waste, space radiation and cosmic ray showers, neutrino physics and radiotherapy. It can handle arbitrarily complex combinatorial geometries but is also capable of reading computed tomograms. A user interface is available which facilitates the creation of the input and the execution of the simulation. FLUKA is written in FORTRAN and can be used for standard tasks without any programming. For more specific problems the user can extend the code by modifying so-called user routines written in FORTRAN. FLUKA can run in full analogue mode but offers also various built-in biasing methods to increase the execution speed. In the following, the main FLUKA features used in the simulations presented here are briefly described.

The transport of ions is done by an original treatment of multiple Coulomb scattering. Energy loss is handled by an implementation of the Bethe–Bloch theory and optional $\delta$-ray production and transport accounting for spin effects and ionisation fluctuations. Also electrons and positrons are transported with an original multiple Coulomb scattering algorithm. The lowest transport limit is 1 keV. For photon transport incoherent scattering, pair production
and photoelectric effect are taken into account. For neutrons with energy lower than 20 MeV FLUKA uses a multigroup treatment.

2.2.2. Nuclear reaction models. A general description of hadronic interactions in FLUKA and their most recent developments can be found in Ferrari et al (1998) and Battistoni et al (2006). The standard event generator in FLUKA to handle nucleus–nucleus interactions of ions in the energy range of therapeutic interest is an interface to a modified version of the relativistic quantum molecular dynamics (RQMD) code (Sorge et al 1989a, 1989b), which can be considered reliable down to about 100 AMeV. This has the consequence that below this energy no nuclear reactions are performed and the ions are only transported. This threshold corresponds to about 2.5 cm range for 12C and about 2 cm for 16O in water. Therefore, activity production is missing at the end of the particle range, i.e. at the peak region and close to. This does not imply that no activity is created at the peak region since projectile fragments which are created at higher energies reach this depth. Therefore, still an activity peak is formed. However, due to the 100 AMeV threshold a fraction of the activity is missing.

A new event generator which models nucleus–nucleus interactions below the RQMD threshold has been recently added to the development version of FLUKA and is used for the calculation presented here. This event generator (Cerutti et al 2006a, 2006b) is called BME and handles fusion and collisions more peripheral. It is based on the Boltzmann master equation theory (BME; Cavinato et al 1998) and handles nuclear interactions from the Coulomb barrier up to 100 AMeV. Because the BME theory is too complex to be implemented for runtime calculations in a Monte Carlo code like FLUKA, the BME event generator depends on pre-calculated parametrization of the predictions obtained by the original BME code (Cavinato et al 1998). The BME event generator has been used for the first time for this work. It will become part of the public FLUKA distribution with the next releases of FLUKA.

2.2.3. Simulation setup. In FLUKA, default settings for different problem scenarios exist, among which there is a setting for hadron therapy which was used in this work. However, the hadron therapy defaults are optimized for the accurate calculation of dose and include therefore, the CPU-consuming $\delta$-ray production. Since this latter process is purely related to electromagnetic energy deposition but does not influence $\beta^+$-activity production, it was switched off.

Apart from size, composition and density specified in the input, the physical properties of the targets were taken into account by means of giving the accurate material parameters described in Sternheimer et al (1982). All material in the beam was modelled including the air and beam diagnostics material. The 0.7% carbon content in the water targets, due to the addition of gelatine, was modelled. Because of the declination of the beam mentioned before, the beam was modelled also declined to match the experimental setup. For each individual experiment the exact time macro structure of the beam, i.e. beam on or off, was taken into account considering all interruptions of the irradiation. The intensity of the beam was modelled as uniform during each spill and assumed to be constant over all spills which is a reasonable approximation because the intensity fluctuations in the experiment were at a few percent.

2.2.4. Biasing. Variance reduction methods (biasing) are needed to speed up the simulations. Because of the small solid angle of the detector only a marginal fraction of the annihilation photons reaches the detector. This slows down the simulation because CPU time is wasted to create and transport annihilation photons which do not contribute to the final signal. Another
fraction of annihilation photons is reaching the detector but does not contribute either because they are detected at a time when no backprojection is performed, i.e. during a spill or after measuring end.

To speed up the simulations the decay of each $\beta^+$-active residual nucleus, i.e. a nucleus that comes to rest, is replicated 250 times. This means that the time when it is created and the position where it comes to rest stay the same but the time of the decay, the energy and the direction of the emitted positron is different for each repetition. To compensate for the unphysical replication each particle gets a weight assigned. The weight of each incident particle is unity therefore, the sum of the weights of the 250 replicated $\beta^+$-active nuclides has to be also unity. This leads to a weight of $1/250$ for each replicated nucleus. Consequently all decay products, i.e. the positron and the annihilation photons, inherit also this weight.

This biasing alone was not enough to give reasonable execution times due to the fundamental geometrical problem i.e. that only a fraction of the annihilation photons is reaching the detector.

None of the various biasing methods already implemented in FLUKA was able to overcome this problem. Therefore, direction biasing for annihilation photons was introduced into FLUKA. This biasing method allows us to preferentially emit one of the annihilation photons into a wanted direction, which corresponds to a direction pointing to one of the detector heads. The direction of each photon is sampled individually to give a uniform distribution at the detector head. To compensate for the change of direction the weight of the photon has to be adjusted, taking the weight of the positron and multiplying it by a further weighting factor, calculated from the angle between the original emission direction and the biased direction. The second photon is emitted in the opposite direction and gets the same weight attached as the first one. The further transport of the photons is done the same way as for all other photons.

The biasing methods are necessary to improve the calculation speed but they have the disadvantage of introducing weighted events which have to be handled in the software simulating the detector response and in the reconstruction algorithm.

2.2.5. Scoring. In a first try a simple and fast simulation approach was chosen. The positions where the annihilations take place were scored. The distribution found this way was additionally smeared with a Gaussian to compensate for the finite spatial resolution of the detector and to account for the reconstruction. However, the result of this approach gave no satisfactory results due to the space-dependent spatial resolution because of the limited angle detector geometry. Therefore, the approach of smearing the residual nuclei distribution with a Gaussian was abandoned and a more precise approach was chosen.

For each pair of annihilation photons leaving the target time, positions, energies, direction cosines and weight were stored on an event-by-event basis in a file. For additional investigations also the $\beta^+$-active residual nucleus position was scored. To save disk space and to assure that no precision is lost, the information was stored in binary format.

With PETSIM a well-benchmarked code is available that can handle the detector response and the conversion to list-mode data format. Using parts of the PETSIM code allows us to use the same backprojection routines as in the experiment which avoids ambiguities in the comparisons.

Therefore, the following approach was chosen: the transport of the ions, the creation of the $\beta^+$-active nuclei, the decay, the electron–positron annihilation and the transport of the annihilation photons in the target were simulated with FLUKA. The output of this simulation was used as input for the modified PETSIM, which handles the response of the detector. The output of PETSIM is list-mode data and can therefore be handled with the same reconstruction
Figure 1. Measured activity profiles generated by 260 AMeV $^{12}$C beams in different targets. The left side shows PMMA, in the middle is water and on the right graphite. The blue solid lines are the backprojection during the spill breaks, the black dashed lines show a backprojection from 10 to 20 min after irradiation end. All curves are normalized to the maximum.

programmes as the experimental data. This approach has two advantages: the modelling of the detector is already done and artefacts of the backprojection are the same for experiment and simulation and are not constraining the comparison.

PETSIM is written in C. To read the binary FORTRAN output of FLUKA a special format conversion routine was linked to the modified PETSIM. The original PETSIM cannot handle annihilation photons with different weights, therefore a further modification was introduced. The weights distribution is monotonically decreasing starting from a minimum weight $w_0$. To ensure that each event is used in the backprojection routine, the events with the lowest weight are backprojected one time. Events with a higher weight are put into the backprojection routine more times according to their weight renormalized to $w_0$. Because the renormalized weights are not integer values the number of backprojections per pair of annihilation photons is calculated the following way: the closest lower integer value is the number of times the pair of annihilation photons is put into the backprojection routine. Then the reminder gives the probability that the same photons are used an additional time. The resulting backprojection has to be multiplied eventually by $w_0$ to get the correct intensity.

3. Results and discussion

3.1. Experiments

3.1.1. Activity profiles. The reconstructed activity profiles of the irradiation with $^{12}$C beams of 260 AMeV on targets of PMMA, water and graphite are shown in figure 1. The blue solid lines show the activity during the spill breaks; the black dashed lines show the activity from 10 to 20 min after irradiation end. The distributions are obtained by a summation over the $10 \times 10$ inner voxels in the plane perpendicular to the axis of the target which is parallel to the beam axis. The edge of the cubical voxels is 1.6875 mm. All curves are normalized to their maximum. The upstream edge of the targets is at position 0 cm. The PMMA target was 20 cm long. The activity in front and behind of the targets reflects the intrinsic spatial resolution of the positron camera (6.75 mm).

Figure 1 shows that compared to the height of the peak, the height of the plateau at the entrance region decreases with time. The reason for that is the contribution of different nuclides to the activity at the plateau and the activity of the peak. For the PMMA and water target the activity of the plateau region is dominated by $^{15}$O and $^{11}$C while the main contribution to the peak is by $^{11}$C. The start time chosen for the backprojection after irradiation corresponds to about 5 half-lives of $^{15}$O and to about half a half-life of $^{11}$C. Therefore, the later backprojection is dominated by $^{11}$C and the contribution of $^{15}$O to the plateau region is negligible.
Figure 2. Measured activity profiles induced by $^{16}$O beams of various energies on different targets. The left column shows PMMA targets, the middle column water and the right one graphite. Each row shows another energy, from top to bottom: 350, 300, 250 and 200 $\text{A MeV}$. The activity during the spill breaks, normalized to the maximum, is shown as a blue solid line. The black dashed lines show the activity from 10 to 20 min after irradiation end, also normalized to the maximum.

Graphite target no $^{15}$O is produced. The small difference between the two backprojections in the plateau is due to $^{10}$C target fragments and the difference of the shape of the peak is due to $^{10}$C projectile fragments which have a shorter range than the $^{11}$C fragments. For all three targets the downstream side of the peak remains at the same position for both time windows. There is also activity found behind the peak (i.e. the tail) which is produced by secondary particles which interact with the target nuclei. The time-dependent behaviour of the tail is similar as the entrance region. For the graphite target no significant time dependence of the shape of the tail can be seen which indicates that the $\beta^+$-activity in this region is dominated by $^{11}$C.

Figure 2 shows the reconstruction of the $\beta^+$-activity created by $^{16}$O beams of energies of 200, 250, 300 and 350 $\text{A MeV}$ on the same target materials as for the $^{12}$C irradiation. The backprojections were done for the same time windows as for the $^{12}$C irradiations and are indicated by the same colours as in figure 1. The activity distributions show two fundamental differences compared to the $^{12}$C irradiation. The first is the inverse behaviour of the peak-to-plateau ratio over time, i.e. a higher plateau with respect to the peak is found after irradiation...
end. The reason for that finding is that to the peak position mainly $^{15}$O and $^{11}$C contribute with $^{15}$O at highest abundance. For the backprojection during the irradiation, the activity is dominated by the decay of the short lived $^{15}$O; for the backprojection done after irradiation end $^{11}$C dominates. This lowers the height of the peak or if displayed normalized to the maximum, the plateau rises. The evaluation over time of this phenomenon is illustrated in figure 3. The left side shows the evaluation of the peak-to-plateau ratio of the $\beta^+$-activity induced by $^{12}$C beams with $260$ A MeV on PMMA, water and graphite. The right side gives the ratio for $^{16}$O beams with $300$ A MeV. The irradiation stops after about $500$ s. Only the contributions during the pauses between the spills were taken into account.

The second difference compared to the $^{12}$C irradiation is the change of shape and position of the peak. The explanation for this behaviour is the different ranges of the projectile fragments. $^{11}$C projectile fragments have an about $30\%$ longer range and $^{13}$N fragments have an about $15\%$ longer range than $^{15}$O fragments with respect to the residual range of the primary ions. Therefore, the peak of the backprojection done after irradiation, which is dominated by $^{11}$C and $^{13}$N, is shifted downstream and becomes less sharp. An example of the time-dependent behaviour is shown in figure 4. Backprojections of the activity created by a $300$ A MeV $^{16}$O beam on PMMA are shown in steps of $5$ min starting after irradiation end. The backprojections are normalized to the peak. The pad in the top left corner of the figure shows a zoom to the peak. It can be seen that the position of the maximum moves about $4$ mm in $20$ min and the peak width becomes larger.

3.1.2. Quantitative analysis of activity. The totally created activity in each experiment was calculated by fitting the count rates (cf section 2.1.2). The created activity is shown in table 2. The production is given by $10^6$ incident particles (IP). As already explained in section 2.1.2, it was not possible to fit the decay curves with more than three nuclides. For the case of the $^{12}$C beam on graphite only two nuclides ($^{11}$C and $^{10}$C) could be found. The last column gives the activity rate (per second) produced in each spill.

An estimate of the ratio $r$ between the activity created by $^{16}$O and $^{12}$C beams of similar primary range can be given. For a reliable comparison it is necessary to normalize to the same dose level which can be done by the following formula (cf Parodi et al 2002b):

$$r = 0.56 \frac{A_{^{16}O}}{A_{^{12}C}}.$$
In-beam PET monitoring of mono-energetic $^{16}$O and $^{12}$C beams

**Figure 4.** Measured activity profile of a 300 AmMeV $^{16}$O beam on PMMA. The backprojections are done each over 5 min starting from 0, 5, 10, 15 and 20 min after irradiation end. All curves are normalized to the maximum. It can be seen how the peak-to-plateau ratio changes over time (see also figure 3). From the zoom of the peak region on the top left corner it can be seen that the peak is shifted downstream by about 4 mm in 20 min.

**Table 2.** Number of $\beta^+$-active nuclei created per $10^6$ incident particles. The first column shows the identifier of the experiment: first three characters indicate the beam, the fourth character the target and the last three digits give the energy. The second and third columns give the number of $^{11}$C nuclei produced and the error. The next columns show $^{15}$O, $^{10}$C and $^{13}$N. The last column gives the activity production rate.

<table>
<thead>
<tr>
<th>ID</th>
<th>$N_{^{11}C}$ ($10^6$ IP) (%)</th>
<th>$N_{^{15}O}$ ($10^6$ IP) (%)</th>
<th>$N_{^{10}C}$ ($10^6$ IP) (%)</th>
<th>$N_{^{13}N}$ ($10^6$ IP) (%)</th>
<th>$\frac{dA}{dt}$ (Bq s$^{-1}$)</th>
</tr>
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<tr>
<td>C12W260</td>
<td>117 907</td>
<td>20</td>
<td>92 659</td>
<td>20</td>
<td>5465</td>
</tr>
<tr>
<td>C12P260</td>
<td>193 337</td>
<td>20</td>
<td>39 695</td>
<td>20</td>
<td>13 449</td>
</tr>
<tr>
<td>C12G260</td>
<td>324 265</td>
<td>20</td>
<td>–</td>
<td>21 843</td>
<td>35</td>
</tr>
<tr>
<td>O16W350</td>
<td>93 479</td>
<td>20</td>
<td>198 204</td>
<td>20</td>
<td>–</td>
</tr>
<tr>
<td>O16W300</td>
<td>65 889</td>
<td>15</td>
<td>143 116</td>
<td>20</td>
<td>–</td>
</tr>
<tr>
<td>O16W250</td>
<td>53 688</td>
<td>15</td>
<td>120 079</td>
<td>20</td>
<td>–</td>
</tr>
<tr>
<td>O16W200</td>
<td>37 254</td>
<td>15</td>
<td>84 576</td>
<td>20</td>
<td>–</td>
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<tr>
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<td>20</td>
<td>112 443</td>
<td>20</td>
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<td>15</td>
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<tr>
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<td>39 730</td>
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<td>26 335</td>
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</table>

where the factor 0.56 accounts for the different stopping power of $^{12}$C and $^{16}$O ions. The ratio between the activity created by $^{16}$O and $^{12}$C beams of similar primary range, i.e. 300 AmMeV and 260 AmMeV, respectively, is 0.6 ± 0.2 for water and 0.5 ± 0.1 for PMMA. Assuming that the activity created in a real patient situation is similar to the activity created in water and PMMA, one can expect that an $^{16}$O beam leads to an activity production rate being about a factor 2 lower than for comparable $^{12}$C irradiations. However, because of the higher abundance of $^{15}$O and its short half-life, more annihilation events can be registered during irradiation.
3.2. Simulations

3.2.1. Execution time. The simulations were done on the EET cluster at CERN. This cluster consists of one master and 48 computers (nodes), each equipped with Intel Pentium bi-processors leading to a total number of 96 available CPU. 16 nodes have a clock rate of 2.66 GHz, further 16 nodes have 3.0 GHz and the last 16 have 3.2 GHz.

The nodes can be accessed by submitting a simulation (job) to the batch system. The batch system decides on which node the job is executed. Because of the different clock rates the execution time of a job depends on the node on which it is performed. It further depends on other jobs running on the same node. The simulations presented here were done in up to 20 parallel runs therefore, the execution times of the simulations can be given only on average.

The detector covers only about 9% of the solid angle. Therefore, for getting a given number of events at the detector, statistically meaningful, the gain in execution speed due to the decay direction biasing is about a factor of 10. Each decay of a $\beta^+$-active nucleus was replicated 250 times. The gain in execution speed due to this biasing method alone was measured to be about a factor of 25. It is not simply 250 because the transport of the decay particles has to be taken into account.

For each target material simulations with the 260 AMeV $^{12}$C beam were performed. For the $^{16}$O beams only the experiments at 350 AMeV and 200 AMeV were simulated. The number of simulated primaries varied from $3.65 \times 10^6$ up to $4.0 \times 10^6$ depending on time constraints and the different performances of the nodes where the jobs were running. The average execution time per $10^6$ primaries was for the $^{16}$O beam simulations around 26 h for 350 AMeV and 10 h for 200 AMeV. The execution times depend on the target material simulated but also on the performance of the actual nodes used. The number of simulated annihilation events increases about 3–4 times when the energy is raised from 200 AMeV to 350 AMeV. For the $^{12}$C beam simulations the execution time was about 18 h per $10^6$ primaries.

3.2.2. Residual nuclei distributions. Figure 5 shows the calculated distribution of $\beta^+$-active residual nuclei of the experiments with the 260 AMeV $^{12}$C beam. The figures show, from left to right, PMMA, water and graphite target. All figures are normalized to $10^6$ incident $^{12}$C ions and only the most abundant $\beta^+$-active nuclei are shown. $^{11}$C is shown with a red dashed line, $^{10}$C with a blue dotted line, $^{15}$O in a dashed dotted magenta line and $^{13}$N is shown by a dashed orange line. The black solid line gives the sum of all $\beta^+$-active residual nuclei including also
As figure 5 but with a $^{16}\text{O}$ beam of 350 MeV.

For all targets $^{10}\text{C}$ and $^{13}\text{N}$ play a minor role. It can be seen that for all target materials the peak is dominated by $^{11}\text{C}$. In the PMMA target simulation, in the entrance region and the tail more $^{14}\text{O}$ than $^{15}\text{O}$ is found. For the water target it is the opposite. In the graphite target, as expected, no $^{15}\text{O}$ was found. The activity distribution for this target is dominated by $^{11}\text{C}$. $^{10}\text{C}$ and $^{9}\text{C}$ play a minor role. It is interesting that for residual nuclei the entrance region shows a pronounced slope while in the reconstruction of the experimental $\beta^+$-activity distribution the entrance region looks flatter (see figure 7).

For all targets it can be seen that there is a small gap just before the peak. The reason for this was identified as the transition between the RQMD event generator and BME at 100 MeV. This transition is not smooth, this means that RQMD yields more $\beta^+$-active fragments than BME.

Figure 6 shows simulated $\beta^+$-active residual nuclei distributions of $^{16}\text{O}$ beams of 350 MeV. The colours are the same as for figure 5. For the PMMA and the water targets the peaks are dominated by $^{15}\text{O}$. The graphite target $^{15}\text{O}$ is found only at the peak but not at the entrance or tail region. This finding is obvious because the target contains no oxygen and therefore, the only source of $^{15}\text{O}$ is projectile fragments, apart from the possible minor contribution of low energy complete and incomplete fusion reactions. However, the overall abundance of $^{11}\text{C}$ is higher compared to the abundance of $^{15}\text{O}$. That makes the case of $^{16}\text{O}$ on graphite the only one where the peak is not dominated by a single nuclide.

Also for the simulations of $^{16}\text{O}$ beams the non-smooth transition between the event generators influences the distribution of residual nuclei, in particular that of $^{11}\text{C}$.

The calculated amount of residual nuclei is too low by 30–50% compared to the experimental findings. A preliminary evaluation of the residual nuclei can be found in Sommerer (2007). These results deserve further investigations, thus no detailed comparison is shown here. However, in-beam PET is not a quantitative method therefore, the absolute production is less critical than the shape of the reconstructed $\beta^+$-activity.

Because the total residual nuclei distribution is composed by nuclides of different half-lives it cannot be compared directly to the reconstructed activity.

### 3.2.3. Reconstruction of simulated activity

Figures 7 and 8 show comparisons between measured and simulated reconstructed activity distributions. The experimental distributions are shown with black dashed lines and are normalized to the maximum. The simulations are shown in blue lines and are normalized to the same area as the corresponding experimental distribution. This normalization was chosen because the height of the peak depends on the momentum spread which was not measured in the experiments. For the simulation it was...
Figure 7. Backprojected activity distributions for $^{12}$C beams with 260 AMeV on PMMA, water and graphite. The black dashed lines give the experimental activity distributions; the blue solid lines show FLUKA simulations. On the left side, backprojections of the annihilations during the pauses between the spills are shown, the right side shows backprojections from 10 to 20 min after irradiation end.

assumed to be the nominal one (i.e. 0.1%). No range adjustment of any kind was applied. From top to bottom the figures show PMMA, water and graphite targets. The left side shows the reconstructed activity from all events in the pauses between the spills (first time window), the right side shows reconstructions from 10 to 20 min after irradiation end (second time window). For all distributions the artefact of the activity in front of the target is well reproduced. This justifies the chosen approach of using the same reconstruction algorithm for experiment and simulation.

Figure 7 refers to the 260 AMeV $^{12}$C beam. For the first time window an overestimation of the entrance region was found for all targets. The gap before the peak (see section 3.2.2)
is clearly visible for the water target. The height and shape of the peaks are generally well reproduced, only for graphite a significant overestimation was found. For the second time window the entrance region for PMMA and water targets is reproduced excellently. The entrance region for the graphite target is overestimated. The gap in front of the peak is clearly visible for the graphite target, for the other targets it almost vanishes. The peaks are overestimated for all three cases. For PMMA and water targets the first 2 cm after the peak show a slight underestimation of the activity while the tail is well reproduced. For the graphite target the downstream edge of the calculated peak is shifted a little bit upstream.

Figure 8 concerns the 350 AMeV $^{16}$O beam. For the first time window an overestimation of the peak was found for all three targets while the entrance and the tail regions were found in excellent agreement with the experiment. It can be seen that the entrance region of the reconstructed activities looks almost flat while in the residual nuclei distribution a slope was
found. For the second time window it can be seen that for PMMA and graphite simulations give a too high activity in the entrance region. There the simulated activity is not smooth due to statistical errors. Running the simulation with more particles would remove this effect. However due to limitations in computing time this was not done. The peak region is well reproduced for all target materials, only for water some overestimation can be appreciated. The tail is a little bit underestimated. The gap before the peak becomes visible, most pronounced in the case of the graphite target.

3.3. Clinical application

Although FLUKA gives good agreement in terms of activity distributions it is not directly applicable to clinical practice because of too long execution times. In clinical practice in-beam PET simulations have to be performed within a few minutes. Even by using several CPUs in parallel this seems to be hard to achieve. A solution could be the subdivision of the simulation in such steps that can be calculated on the basis of the treatment planning and those steps which need the information of the time course of the irradiation to be correctly performed.

4. Summary and conclusions

In beam PET experiments of \(^{16}\text{O}\) beams were performed for the first time. Activity profiles at different time windows were reconstructed and production rates were calculated. It was found that different to irradiations with \(^{12}\text{C}\) beams, the \(^{16}\text{O}\) induced activity profiles show a significant time dependence of the position of the peak. This effect will need to be carefully modelled in clinical applications to enable millimetre-accurate monitoring of the beam range from in-beam PET measurements. The experiments were used for benchmarking the FLUKA code. It was found that scoring only the position where annihilations take place is not sufficient to perform reliable comparisons with the experimental reconstructed activity profiles for a limited angle detector configuration. Therefore, a more complicated and time consuming simulation approach was used.

The small solid angle of the double head detector and the limited measuring time constrain the performance of the simulation. The use of biasing methods is necessary to keep the simulation time within reasonable limits. A new biasing method, i.e. direction biasing of annihilation photons, was introduced in the development version of FLUKA and will be available in the next public releases of the code. It helps to overcome the speed limitations related to the small solid angle and brought a gain in computing time of about a factor of 10. This biasing method is also useful for simulations of PET with ring detectors because it assures that at least one photon of each pair of annihilation photons reaches the sensible volume. Biasing by means of replicating the decay of a \(\beta^+\)-active nucleus helps to overcome the limitations due to measuring time windows bringing a gain in execution time of about a factor of 25 for the measuring time windows considered in this work.

The BME event generator was used for the first time and it has been found that it is necessary to tune it against the RQMD event generator to get a smooth transition in the yield of \(\beta^+\)-active nuclei. Therefore, experimental data of thin target yields of \(\beta^+\)-emitters created by beams of energies below 100 AMeV are highly desirable. A reason for an underestimation of BME in the production rates of \(^{11}\text{C}\) and \(^{15}\text{O}\) was identified and the work on the improvement has already started.
While a good agreement in the shape of the activity distributions was found, the total production rates of $\beta^+$-active nuclei were much lower than in the experiment. This finding deserves further evaluation experimentally and in the calculation models.

The long execution times prevent a direct application of the here presented methods into clinical practice. Further investigations are needed to speed up the simulation process.

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