Sub-millimeter nuclear medical imaging with reduced dose application in positron emission tomography using $\beta\gamma$ coincidences

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ABSTRACT: Positron emission tomography (PET) permits a functional understanding of the underlying causes of many diseases. Modern whole-body PET systems reach a spatial resolution of 2-6 mm (FWHM). A limitation of this technique occurs from the thermalization and diffusion of the positron before its annihilation, typically within the mm range. This diffusion motion and Compton scattering of the 511 keV photons within the patient, together with the acollinearity of the positron annihilation introduced by the momentum of the bound electron, limit the performance of PET imaging. We present a nuclear medical imaging technique, able to reach sub-millimeter spatial resolution in 3 dimensions with a reduced effective dose application compared to conventional PET. This $\gamma$-PET technique draws on specific medical isotopes, simultaneously emitting an additional photon accompanying the $\beta^+$ decay. Exploiting the triple coincidence between the positron annihilation and the third photon, it is possible to separate the reconstructed 'true' events from background. In order to characterize the potential of this technique, Monte-Carlo simulations and image reconstructions have been performed. The achievable spatial resolution has been found to reach ca. 0.4 mm (FWHM) in each direction for the visualization of a $^{22}$Na point source. Starting with a source activity of only 1.48 MBq for $^{89}$Zr, corresponding to ca. 130 - 270 times less compared to a conventional PET examination using $^{18}$F-FDG (fluorodesoxyglucose), about 40 intersections (sufficient for a reliable image reconstruction of a point source) can be identified after a typical examination time of 900 seconds. This results in a strongly reduced effective dose of, e.g., 0.785 mSv for $^{89}$Zr-cmAb-U36 (chimeric monoclonal antibody), compared to the applied effective dose in a typical human PET examination with $^{18}$F-FDG of about 7.5 mSv. Increasing the applied effective dose to 7.5 mSv, the examination time will be reduced to 94 s for only 14.2 MBq of $^{89}$Zr-cmAb-U36. The reduced effective dose, or, on the other hand, the reduced examination time, surpass the performance of a conventional PET device by more than one order of magnitude.

KEYWORDS: Image reconstruction in medical imaging, PET, PET/CT, Compton imaging.

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1. Introduction

Positron emission tomography (PET) is a nuclear medical imaging technique for measuring the position- and time-dependent concentration of radioactively labelled tracer molecules in an organism. It permits a functional understanding of the underlying causes of many diseases and had its breakthrough as an imaging instrument for clinical application studies (e.g., bone metabolism, myocardial perfusion and viability, lung embolism, tumours, thyroid function or even neurological disorders) in the last decade due to the large variety of different tracers and due to the significant improvement of the imaging performance [1]. These tracers are chemical compounds, carrying a positron emitting isotope to, e.g., a tumour site. Annihilation of the positron into two back-to-back 511 keV photons allows to restrict the source origin in 2 dimensions onto a line of response (LOR). Superimposing the LORs of different decay events locates the source distribution of the emitter, i.e. the concentration of the tracer molecules in a patient in 3D.

Modern whole-body systems are combined PET/CT scanners, where CT provides the anatomical information for a reference frame and also data for the attenuation and scattering correction, while PET provides the molecular information. These scanners, like the Philips Gemini TF [3] or the GE Healthcare Discovery ST [4], are able to reach a spatial resolution of 4.7 mm or (on average) 5.7 mm, respectively, which is a substantially lower resolution than those attainable with computed tomography (CT, several hundred micrometer) or magnetic resonance imaging (MRI, 5-10 µm). This disadvantage of PET results in a limited localization of, e.g., lesions and lesion borders [3]. The performance of new generation PET/CT, the Siemens Biograph mCT [2], with point-spread-function (PSF) correction can go down to 2.0 mm for the PET modality.

An improvement of conventional PET imaging is the Time-of-Flight (TOF) PET technique, where the flight time difference of the two annihilation photons registered in the responding pair of detectors is taken into account for achieving an improved spatial information. Annihilation events can be restricted to a certain area of the LOR, thus achieving an improved image quality by an improved signal-to-noise ratio. Moreover, the patient dose and the examination time can be reduced. So far the GEMINI TF and the Siemens Biograph mCT are the only PET/CT scanner on the market, where the TOF technology has been implemented with a timing resolution of ≈ 500 ps, resulting in a positioning uncertainty of ± 7.5 cm along a typically 70-80 cm long LOR.

However, especially biomedical research, using animal models of metabolism and disease mechanisms, would profit from a high-resolution small-animal PET device [3].

Presently, the microPET II device is the state-of-the-art small-animal PET system, its performance has been characterized by Tai et al. [8] and Yang et al. [9]. It consists of 17640 LSO crystals arranged in a contiguous ring of 16 cm diameter. The resolution of this system is 1.1 mm (FWHM) in the center of the field-of-view (FOV) and degrades to 2.2 mm (FWHM) at a position with 2 cm radial offset [3, 9].

It has also been shown that it is possible to reach submillimeter spatial resolution of 0.59 mm FWHM by placing an additional detector (14 x 28 array of 0.5 x 0.5 x 10 mm³ lutetium oxy-orthosilicate (LSO) elements) in the axial field of view of the microPET II [10].

Also solid-state detectors from cadmium zinc telluride (CZT) [11], germanium [11] or silicon [12] have been investigated for small-animal PET applications, and it has been shown that it is possible to reach a high spatial resolution (1.45 mm FWHM) with silicon pad detectors (32 x 16 array of
Even sub-millimeter spatial resolution may be reachable, as, e.g., first tests with continuous LYSO crystals (12 mm x 12 mm) coupled to a silicon photomultiplier matrix (8 x 8 pixel elements) have shown [7].

A typical scintillator crystal material used for a long time in PET applications is BGO. It has a high density, a decay time of 300 ns and a resulting time resolution of about 3 ns. Since some years, improved performance can be obtained with LSO crystals, exhibiting a shorter decay time of 40 ns and a correspondingly improved time resolution of ca. 300 ps.

Also the concept of a Compton camera has been investigated for its applicability with the PET technique, however, so far only at the laboratory development level [13]. In this case, position and energy information of the Compton scattering kinematics are measured in a scatter and an absorber detector, together allowing for a reconstruction of the direction to the source position on the surface of the 'Compton cone'. Most approaches use segmented solid-state detectors as scatterer, because of the achievable high spatial resolution, in combination with scintillators for final absorption of the scattered photon due to their higher efficiency. The combination of a microPET device with a liquid xenon time-projection chamber (TPC), acting as Compton camera, has been studied in simulations, rendering a spatial resolution of 1.43 mm (FWHM) [13]. Even sub-millimeter image resolution (0.98 mm FWHM) has been shown, using a solid-state scatterer with high spatial resolution [14].

In general, the spatial resolution of a PET device is limited by several effects. Limiting factors are the spatial, temporal or energy resolution of the detectors, random coincidences or the resolving power of the source image reconstruction algorithm. Moreover, there are also inherent physical limits to the achievable image resolution, like Compton scattering of the 511 keV photons within the patient or biological sample or the diffusion range of the positron before its annihilation, presenting the dominant limitation in small-animal PET imaging. Another inherently limiting factor is the acollinearity of the positron annihilation, i.e. the angular deviation from $180^\circ$ between the two annihilation photons, originating from the momentum distribution of the annihilating electron-positron pair, after thermalization of the positron (within a few ps) and positronium formation. Because of the thermalization of the positron prior to its annihilation, the acollinearity is mainly caused by the significantly higher momentum of the bound orbital electrons. The acollinearity has been measured to result in a gaussian deviation from $180^\circ$ with a width (FWHM) of about 0.5$^\circ$ in water [15], while more recent studies [16] report a better description of the angular deviation by two components: a broad main component originating from orbital electrons with $\Delta \theta = 0.633(8)$ and a narrower component with $\Delta \theta = 0.27(10)$ resulting from positronium annihilation. In (healthy) human tissue slightly modified values of $\Delta \theta = 0.619(12)$ and 0.301(17), respectively, were found [16]. This corresponds to a spatial deviation of 2 mm in an average PET-ring radius of 40 cm and thus represents the dominant limiting factor for the spatial resolution of whole-body PET systems [17].

Another effect arising from the momentum distribution of the annihilating electron-positron pair is the Doppler broadening of the annihilation spectrum. The actual broadening depends on the annihilation medium and can be used as a measure for the longitudinal component of the momentum distribution [36, 37]. Besides the achievable spatial source reconstruction resolution, also the applied radioactive dose to the patient or sample, as well as the corresponding examination time, has to be taken into account when discussing medical imaging techniques. The applied radioactivity typically used in human PET studies is tracer specific and ranges from about 185 to 1850
MBq, while in small-animal PET even higher activities are applied. A typical human PET examination using the radioisotope $^{18}$F takes 10-45 minutes (depends on scanner, tumor and image reconstruction method), with injected activities of 200 - 400 MBq, the applied dose results to 7 - 10 mSv and thus to 3-4 times the annual natural dose.

While on the one hand such long examination times limit the number of patients’ access to PET devices, they are prohibitive for real-time metabolism studies, due to, e.g., organ movements. Therefore, this study was motivated not only by aiming at an improved spatial resolution for PET examinations, but, perhaps even more attractive, by targeting shorter examination times or lower radioactive doses applied to the patients. Moreover, the technique described in the following also bears the potential to be applicable for ion beam range monitoring in hadron therapy \[19, 20\], exploiting the online generation of $\beta^+$ emitting isotopes.

### 2. Decay properties of PET isotopes

Table 1 compares the decay properties of various presently used or potential future PET radioisotopes. The two isotopes $^{10}$C and $^{14}$O have been included here, despite of their short half-lives of 19.3 s and 70.6 s, respectively, since both can be produced during hadron therapeutic irradiations using a carbon or proton beam (\[21\], \[22\]). Thus they qualify as candidates for online ion-beam range monitoring during therapy treatment. Moreover, proposals have been presented to directly use positron emitter beams, such as $^{11}$C \[23\], \[24\], \[25\], $^{10}$C \[26\] or $^{15}$O \[27\] as therapeutic beams, allowing for fast online ion-beam range verification. In Tab. 1 in particular the positron diffusion range in water has been simulated with Geant4 (last column) and benchmarked against measured values (column 6), showing good agreement.

We used Geant4 (9.4) with the QGSP-BIC-HP physics list for hadronic interactions and the Livermore physics list for electromagnetic interactions \[30\]. In case of the positron range simulations, we placed the detector as close as possible to a water sphere of 6 cm diameter, thus ensuring to be in the regime where diffusion of the positron prior to its annihilation is the dominant factor for the position resolution, like in small-animal PET devices. $^{22}$Na is the only non-medical radioisotope listed in Tab. 1 due to its use in our laboratory as test source for the later-on discussed $\gamma$-PET technique.

### 3. The $\gamma$-PET imaging technique

We present a nuclear medical imaging technique, able to reach sub-millimeter spatial resolution in 3 dimensions with a reduced dose application compared to conventional PET. This technique ('$\gamma$-PET') draws on specific $e^+$ sources, simultaneously emitting an additional photon with the $\beta^+$ decay. Exploiting the triple coincidence between the positron annihilation and the additionally emitted photon, it is possible to efficiently separate the reconstructed 'true' events from background \[13\], \[31\]. Therefore the image reconstruction sensitivity can be significantly increased by an improved signal-to-noise ratio, achieved via exploiting the spatial and temporal coincidence with the additionally emitted photon. This works best in the direction normal to the annihilation.

Medical radioisotopes like $^{89}$Zr, $^{94(m)}$Tc, $^{67}$Br, $^{124}$I, $^{86}$Y, $^{152}$Tb, $^{52}$Mn, $^{82}$Rb and $^{44}$Sc are suitable candidates for the $\gamma$-PET technique (see Tab. 1 for details). Especially $^{44}$Sc is of interest,
Table 1. Decay properties of presently used or potential future PET isotopes. The positron diffusion range has been simulated with Geant4 (last column) and compared to experimentally measured values, where available.

| Isotope | decay mode | $E_{\text{e}^+}^{\text{max}}$ [MeV] | $I_\beta$ [%] | $E_\gamma$ [MeV] | mean range in water [mm] (experiment, this work) | mean range in water [mm] (simulation, this work) |
|---------|------------|-----------------|--------------|----------------|-----------------------------------------------|-----------------------------------------------|
| $^{22}$Na | $\beta^+ + \gamma$ | 0.54 | 100 | 1.27 | 1.5 ± 0.1 | |
| $^{18}$F | $\beta^+$ | 0.63 | 96.7 | 1.4 | 1.4 ± 0.1 | |
| $^{94}$Tc | $\beta^+ + \gamma$ | 0.81/1.83 | 10.5/70.8 | 0.87 | 1.4 ± 0.1 | |
| $^{89}$Zr | $\beta^+ + \gamma$ | 0.90 | 100 | 0.91 | 1.5 ± 0.1 | |
| $^{11}$C | $\beta^+$ | 0.96 | 99.8 | 1.7 | 1.8 ± 0.1 | |
| $^{13}$N | $\beta^+$ | 1.20 | 100 | 2.0 | 1.9 ± 0.1 | |
| $^{44}$Sc | $\beta^+ + \gamma$ | 1.47 | 94.3 | 1.16 | 2.1 ± 0.1 | |
| $^{15}$O | $\beta^+$ | 1.73 | 99.9 | 2.7 | 2.6 ± 0.1 | |
| $^{14}$O | $\beta^+ + \gamma$ | 1.81 | 99.2 | 2.31 | 2.6 ± 0.1 | |
| $^{68}$Ga | $\beta^+ + \gamma$ | 1.90 | 88.0 | 1.08 | 2.7 ± 0.1 | |
| $^{124}$I | $\beta^+ + \gamma$ | 1.53/2.14 | 11.7/10.8 | 0.60 | 2.9 ± 0.1 | |
| $^{10}$C | $\beta^+ + \gamma$ | 2.93 | 98.5 | 0.72 | 2.6 ± 0.1 | |
| $^{152}$Tb | $\beta^+ + \gamma$ | 2.62/2.97 | 5.5/6.2 | 0.34 | 3.6 ± 0.1 | |
| $^{86}$Y | $\beta^+ + \gamma$ | 1.22/1.55/ | 11.9/5.6 | 1.08 | 2.3 ± 0.1 | |
| $^{76}$Br | $\beta^+ + \gamma$ | 0.87/0.99 | 6.3/5.2 | 0.56 | 4.1 ± 0.1 | |
| $^{82}$Rb | $\beta^+ + \gamma$ | 4.39 | 100 | 0.78 | 4.9 ± 0.1 | |

which $\beta^+$-decays into the stable $^{44}$Ca, emitting an 1157 keV photon. It has already been tested clinically [33] and has a short half-life of 3.9 h. It has to be produced from a $^{44}$Ti generator ($t_{1/2} = 60.4$ a) [32], which presently cannot be performed in clinically relevant quantities, however, this may change with the soon expected availability of highly brilliant $\gamma$ beams [31].

We combined the Compton camera technique, i.e. the measurement of photon energies and positions of Compton scattering interactions, with a PET camera defining the LOR. Due to the kinematics of the Compton scattering process and subsequent photon absorption, a Compton camera allows for reconstructing the origin of a primary photon on the surface of the ‘Compton cone’. Superimposing different cones from different events reduces the reconstructed source distribution in 3 dimensions to the few-millimeter range [34]. The $\gamma$-PET technique is different, as it will intersect the Compton cone with the LOR from the same $\beta^+$-annihilation $\gamma$ coincidence event, thus allowing to reconstruct the source distribution in 3 dimensions from individual events.

The principle of the $\gamma$-PET technique can be seen in the left panel of Fig. 1. The decay of certain radioisotopes generates a positron and a $\gamma$-ray quasi-simultaneously, i.e. within the typical lifetime of an excited nuclear state of fs - ps. The emitted $\gamma$ will first be Compton-scattered in a position-
sensitive double-sided silicon strip detector (DSSSD), where the position and energy deposition of the interaction is measured. Then the $\gamma$-ray will subsequently be absorbed in a thick scintillation crystal, in our case using a position-sensitive LaBr$_3$ scintillator, again measuring position and energy of this final interaction. Due to the Compton kinematics, its origin can then be restricted to a cone surface. The $e^+$ annihilation into two (almost) back-to-back 511 keV photons defines the line of response (LOR). Intersection of the Compton cone with the LOR restricts the source origin in 3 dimensions within one $\beta^+\gamma$ coincidence event, as shown in Fig. 1b). Figure 1b) shows the schematic geometry of a $\gamma$-PET setup as used in our simulations, consisting of four Compton cameras (each with a scatterer and an absorber), placed around a $\beta^+$ source isotope emitting a positron and a prompt $\gamma$ ray. The energy loss $\Delta E_{\gamma,1}$, the residual energy $E_{\gamma,2}$ and the interaction positions of the Compton scattering process of the prompt $\gamma$ are measured in a double-sided silicon strip detector (DSSSD) and an (LaBr$_3$) absorbing scintillator, respectively. The initial photon energy $E_{\gamma,1}$ can be calculated from summing $\Delta E_{\gamma,1}$ and $E_{\gamma,2}$. The opening angle $\theta$ of the Compton-scattering cone can be derived from the known initial photon energy $E_{\gamma,1}$ and the measured energy of the second interaction $E_{\gamma,2}$, considering energy conservation, according to

$$\cos \theta = 1 - \frac{m_e c^2}{E_{\gamma,1}(E_{\gamma,1} - E_{\gamma,2})}.$$  \hspace{1cm} (3.1)

This formula is not taking into account the effect of Doppler broadening, arising from the momentum of the bound electron. In contrast, it assumes the electron to be at rest before Compton scattering. The MC simulations, instead, take the non-zero momentum of a bound electron correctly into account. The Doppler broadening contributes to the physical limits of the achievable angular resolution of a Compton camera [35]. In case of an unknown initial photon energy $E_{\gamma,1}$, which could occur if the $\beta^+\gamma$-emitter were produced during hadrontherapy with e.g. a $^{12}\text{C}$ beam (potentially generating different $\beta^+\gamma$-emitters like $^{10}\text{C}$ or $^{14}\text{O}$), proper event and image reconstruction would require a full absorption of $E_{\gamma,1}$ in the scintillator. Detected by the Compton camera, the origin of the emitted prompt $\gamma$ ray can be restricted to a cone surface. The intersection (Fig. 1b) of the Compton cone and the LOR strongly suppresses background and restricts the reconstructed events to those belonging to the same $\beta^+\gamma$ coincidence event, originating from a volume defined by the displacement between the positions of the $\beta^+$ decay and the positron annihilation, depending on the time resolution of the detector system. In contrast to the restriction of the photon emission volume, the acollinearity effect cannot be removed by the $\gamma$-PET technique. Also Compton scattering of the 511 keV photons within the patient limits the performance. A further improvement of the $\gamma$-PET technique (so far not implemented in our simulation and analysis code package) would take attenuation and scatter corrections of the annihilation photons, defining the LOR, into account [38], [39].

4. Simulation and reconstruction setup

In order to characterize the spatial resolution of a PET scanner, a Derenzo phantom is commonly used [40]. We simulated a quasi-Derenzo phantom (see Fig. 2 for a sketch of the source geometry), consisting of twelve $^{22}\text{Na}$ point sources with 100 kBq activity each. Point sources were chosen for this exploratory study, while in a later stage it is foreseen to extend this to the realistic scenario
Figure 1. Principle of the $\gamma$-PET technique. a) The decay of certain radioisotopes produces a positron and a $\gamma$ ray quasi-simultaneously. The emitted $\gamma$ ray will first be scattered in a double-sided silicon strip detector (DSSSD), where the position and energy deposition of the interaction is recorded. Then the prompt $\gamma$ ray will subsequently be absorbed in a LaBr$_3$ scintillator, measuring again position and energy. Due to the Compton kinematics, its origin can then be restricted to a cone surface. The $e^+$ annihilation into two back-to-back 511 keV photons defines the line of response (LOR) via (partial) energy deposition in two opposite DSSSD’s. A full absorption of the 511 keV photons in the scintillator is not required, due to the unique characteristics of the annihilation. b) Intersection of the Compton cone with the LOR restricts the source origin in 3 dimensions within one $\beta^+\gamma$ coincidence event to a volume defined by the displacement between the positions of the $\beta^+$ decay and the positron annihilation, depending on the time resolution of the detector system. In order to optimize the detection efficiency, four Compton camera modules have been included in our simulations.

of an extended source. Four equilateral triangles are arranged in four sections, containing 3 point sources each, with a separation of 0.2 mm, 0.4 mm, 0.6 mm and 0.8 mm, respectively. This source arrangement was placed inside a water sphere of 6 cm diameter to imitate a medical or biological sample. Each of the four Compton camera modules consists of an absorbing LaBr$_3$ scintillator crystal (50 x 50 x 30 mm$^3$), read out by a 2D-segmented photomultiplier with 64 pixels (6 x 6 mm$^2$ each). An energy threshold of 5 keV (i.e. exceeding the electronic noise level) and an energy resolution varying from $\Delta E/E = 4.7\%$ at 500 keV to 3.5\% at 1 MeV were used. Furthermore, a double-sided silicon strip detector with 128 strips on each side, an active area of 50 x 50 mm$^2$ and
Figure 2. Sketch of the simulated source geometry, representing a quasi-Derenzo phantom [40], consisting of twelve $^{22}$Na point sources with 100 kBq activity each. Four equilateral triangles are arranged in four sections, containing 3 point sources each, with 0.2 mm, 0.4 mm, 0.6 mm and 0.8 mm separation, respectively.

A thickness of 2 mm was used as scatterer. The pitch size of 390 $\mu$m correspondingly leads to a width of the LOR of 390 $\mu$m (FWHM). An energy resolution of 10 keV (FWHM) and a detection threshold of 10 keV in the Monte Carlo simulation (due to the assumed electronic noise level of the DSSSD) was chosen.

For the detector system a time resolution of 1 ns was (conservatively) assumed. The rise time of signals from the LaBr$_3$ scintillator is about 8 ns, resulting in a time resolution of 560 ps for our 50x50x30 mm$^3$ crystal. With a typical signal rise time of around 2 ns for the silicon strip detector, the time resolution of the combined detector system can be expected to be even faster than 1 ns.

In order to test the feasibility of the $\gamma$-PET technique, Monte-Carlo simulations and image reconstruction have been performed using the 'Medium Energy Gamma-Ray Astronomy' library MEGAlib [35]. MEGAlib is a software framework designed to simulate and analyze data from Compton cameras. The library consists of a Monte-Carlo simulation package, which utilizes the
ROOT and Geant4 (9.4) software library, an event reconstruction and an image reconstruction section based on a list-mode maximum likelihood expectation maximization algorithm (LM-ML-EM). This algorithm is an iterative method to reconstruct the most probable source distribution. For the requirements of the $\gamma$-PET technique, we modified MEGAlib to realize an event reconstruction from the intersection between the Compton cone and the LOR. Subsequently, after successful event reconstruction, this information serves as starting point for an iterative image reconstruction of the $\gamma$-source positions.

5. Results

Before showing results for the efficiency achievable with $\gamma$-PET and the corresponding radiation dose requirements, we briefly discuss the spatial resolution estimate for the Compton camera setup studied here.

5.1 Spatial source reconstruction resolution

The $\gamma$-ray energy spectrum, as emitted from the twelve $^{22}$Na point sources, and detected by one Compton camera module (including the detector resolution), placed outside a water sphere of 6 cm diameter, is shown in Fig. 5.1. The spectrum was obtained from a Monte-Carlo simulation using Geant4 (9.4).

The decrease of the $\gamma$-ray yield with energy is due to incompletely absorbed $\gamma$ rays. Clearly visible are the 511 keV positron annihilation line, as well as the 1275 keV line from the $\gamma$ ray of the $\beta^+$ decay of $^{22}$Na. The strong contribution at 340 keV comes from electrons due to Compton backscattering of 511 keV while the peak at 1062 keV originates from Compton-backscattered 1275 keV photons. The trigger condition in these simulations required three hits in three of the DSSSD modules and one hit in one of the the LaBr$_3$ absorbers. The line at 1786 keV is due to pileup between the 1275 keV transition and one of the 511 keV annihilation photons.

Based on the geometrical arrangement of $^{22}$Na sources (Fig. 2) and detector modules (Fig. 1a), the underlying data of the detected $\gamma$-ray energy spectrum (Fig. 5.1) are first used for a kinematical event reconstruction. The event reconstruction identifies Compton events in an energy window of $1275 \pm 50$ keV, corresponding to the $\gamma$-ray energy from the $^{22}$Na decay, also identifying simultaneous hits above the detection threshold in the DSSSD for reconstruction of the LOR. In Fig. 5.1, the resulting image of the reconstructed $\gamma$-source geometry is shown, as obtained from exploiting the $\gamma$-PET technique. It was possible to clearly resolve the two largest triangles with spacings of 0.8 mm and 0.6 mm, respectively. The triangle with 0.4 mm spacing still could be resolved sufficiently well, while the 0.2 mm spaced triangle could not be resolved at all. The black crosses indicate the original source positions in the simulation.

Due to the $\gamma$-PET technique, the imaging sensitivity for positron annihilation significantly displaced from the initial decay spot via thermalization and diffusion is strongly suppressed, and only positron annihilation photons emitted in spatial and temporal coincidence with the third (prompt) $\gamma$ are included for image reconstruction.

While the acollinearity of annihilation photons in our close detector geometry (distance 50 mm to the source) contributes only about 0.3 mm to the position uncertainty, Fig. 5.1 shows the correlation between the spatial resolution (as estimated via the above described quasi-Derenzo
Figure 3. γ-ray energy spectrum emitted from the twelve $^{22}$Na point sources, as detected in one of the 4 Compton camera modules placed outside a water sphere of 6 cm diameter. The point sources were arranged in the geometry of the Geant4 Monte-Carlo simulation as indicated in Fig. 2. The trigger condition in these simulations required three hits in three of the DSSSD modules and one hit in one of the the LaBr$_3$ absorbers. The decreasing yield with increasing energy is due to incompletely absorbed γ rays. Visible are the 511 keV positron annihilation line, as well as the 1275 keV line from the γ ray of the $\beta^+$ decay of $^{22}$Na. Strong contributions at around 340 keV and around 1062 keV arise from electrons of the Compton backscattering of the 511 keV and the 1275 keV γ rays, respectively. Also visible at 1786 keV is the pileup of 511 keV and 1275 keV γ rays.

phantom) and the $\beta$ end-point energy $E_{e^+}^{max}$ for the three isotopes $^{22}$Na, $^{89}$Zr and $^{10}$C. Isotopes with $E_{e^+}^{max} < 4$MeV are promising candidates for sub-millimeter imaging in our geometrical detector arrangement.

5.2 Efficiency considerations

After having shown that the γ-PET technique allows for sub-millimeter spatial resolution in the position reconstruction of the underlying radio-tracer independent of its $\beta^+$ energy, we address a further major advantage of this method, which is the dose reduction achievable with the highly sensitive triple-γ coincidence measurement.

During the analysis of the 511 keV annihilation photons, no energy conditions have been ap-
Figure 4. Image of the reconstructed \( \gamma \)-source geometry of the quasi-Derenzo phantom introduced in Fig. 2, using the \( \gamma \)-PET technique after 100 iterations (depending on start parameters) using a maximum-likelihood algorithm. The two largest triangles with spacings of 0.8 mm and also the 0.6 mm, respectively, are clearly resolved. In case of the 0.4 mm spaced triangle, the resolution is sufficient, however not as conclusive as for the previous two cases, while the smallest triangle with distances of 0.2 mm could not be resolved. The black crosses indicate the original source positions.

The simulations showed that there is no necessity for a stricter event definition than requiring an energy deposit (within a coincidence time window of 1 ns) above a threshold of 10 keV in three DSSSD detectors (two of them diametral) and a (completely absorbed) 1275 keV (prompt gamma from \(^{22}\)Na decay) signal from the summed signal of the third scatterer and its scintillator to generate the LOR and still reach sub-millimeter spatial resolution. This can mainly be attributed to the capability of the event reconstruction algorithm to provide a reliable reconstruction even on the basis of an incomplete photon energy absorption. Additional energy conditions would discard this latter class of events (containing \(5.8 \cdot 10^{-2} (3.4 \cdot 10^{-3})\) of all events for one (two) incompletely absorbed 511 keV photon(s)) and unnecessarily lead to a drastic reduction of the reconstruction.
Correlation between the spatial resolution (as estimated from an image reconstruction using the quasi-Derenzo phantom described before) and the β end-point energy $E_{e^+}^{\text{max}}$ for the isotopes $^{22}\text{Na}$, $^{89}\text{Zr}$ and $^{10}\text{C}$.

Moreover, the narrow timing coincidence of 1 ns significantly helps to remove random background. One individual Compton camera module simulated here provides an event reconstruction efficiency of $3.3 \times 10^{-5}$. Thus the geometry studied with 4 camera modules exhibits an overall reconstruction efficiency for the Compton cone of $1.3 \times 10^{-4}$.

Moreover, a 5 (8) times thicker scatterer (or a stack of 5 (8) scatter detectors with a summed thickness of 10 (16) mm) per Compton camera module would increase the reconstruction efficiency of the Compton cones by an additional factor of 4.4 (5.8) to a value of 5.7 (7.5) $\times 10^{-4}$. In the case of thicker scatterer, where no depth information of the scattering point is measured, the spatial resolution increases from 0.4 mm (for 2 mm scatterer) to 0.6 mm (for 16 mm scatterer).

This efficiency could easily be further increased by replacing our prototype geometry with a pyramidal arrangement of a scatter detector and a larger absorber covering the opening angle of the cone seen from the photon source at the top of the pyramid. For our detector geometry, this would require an absorber with an area of $114 \times 114 \text{ mm}^2$, about 5 times larger than the one used in our study.

Finally, when extending the Compton camera to a γ-PET device, the temporal and spatial coincidence with the annihilation LOR has to be considered. The simulated triple-coincidence detection
efficiency for the $\gamma$-PET technique amounts to $7.0 \cdot 10^{-8}$ reconstructed intersections per $^{22}$Na decay between the LOR of the annihilation photons and the Compton cone of the third photon. This reduction of the above given Compton camera efficiency is on the one hand due to the solid angle acceptance of the scatter detectors entering the LOR reconstruction, in our scenario resulting in a geometrical coincidence probability of 0.026. Moreover, a loss of those events has to be considered, where due to the diffusion of the positron before its annihilation no intersection between its reconstructed LOR and the Compton cone of the third photon, i.e. a spatial and temporal coincidence, could be found. This fraction amounts to ca. 91.8%, in total resulting in the above given overall $\gamma$-PET reconstruction efficiency of $7.0 \cdot 10^{-8}$ for $^{22}$Na.

This value would be further reduced to a prohibitively low value of $1.1 \cdot 10^{-10}$, if in addition to the condition set to the energy deposition of 1275 keV in the scatterer and absorber from the third photon also conditions on the energy of the two diametral 511 keV annihilation quanta (besides their temporal coincidence within 1 ns) would have been required. In a pyramidal arrangement of a scatter detector and a larger absorber covering the full opening angle of the scatterer as seen from the emission point, such an additional energy condition would not reduce the efficiency, but would reduce random coincidences.

The efficiencies of other isotopes are different, due to the individual $\gamma$ energies $E_\gamma$, the different positron endpoint energies $E_{\text{max}}^e$ and the branching ratio of $\gamma/\beta^+$. The simulated reconstruction efficiencies for various $\beta^+ - \gamma$ emitter are listed in Tab. 2.

| Isotope | $^{22}$Na | $^{89}$Zr | $^{14}$O | $^{68}$Ga | $^{124}$I | $^{76}$Br | $^{82}$Rb |
|---------|-----------|-----------|----------|----------|---------|---------|---------|
| $\epsilon_{\text{reco}}$ | $7.0 \cdot 10^{-8}$ | $3.0 \cdot 10^{-8}$ | $1.6 \cdot 10^{-8}$ | $9.3 \cdot 10^{-10}$ | $2.0 \cdot 10^{-7}$ | $4.7 \cdot 10^{-7}$ | $2.6 \cdot 10^{-8}$ |

**Table 2.** Simulated reconstruction efficiencies for various $\beta^+ - \gamma$ emitter. In case of $^{124}$I and $^{76}$Br, which emit several prompt $\gamma$ rays with considerable branching ratio, the individual efficiencies have been summed up ($^{124}$I: 0.60 MeV, 0.72 MeV, 1.5 MeV and 1.7 MeV, $^{76}$Br: 0.56 MeV, 0.66 MeV, 1.13 MeV, 1.22 MeV and 1.85 MeV).

### 5.3 Radioactive dose considerations

A minimum of 40 reconstructed intersections between the LOR and the reconstructed emission direction towards the detected position of the third photon is sufficient for a reliable image reconstruction of a point source with a ratio of true-to-false reconstructed events allowing for a correct reconstruction of the (point) source position without fragmentation of the source image. Choosing an examination time of 900 seconds and taking into account our intersection reconstruction efficiency, results in the requirement of only a rather low source activity 1.48 MBq for $^{89}$Zr, corresponding to ca. 130 - 270 times less compared to conventional PET examinations using $^{18}$F-FDG.

The most commonly used effective dose estimates for PET examination stem from Monte Carlo simulations, like the Medical Internal Radiation Dose (MIRD) [41] approach, providing tables of organ specific absorption values for different isotopes. These values are deduced from Monte Carlo simulations according to the decay properties of the radioisotopes, the different uptake times of the tracers and the individually absorbed doses in specific organs. The absolute activity $A_s$,
in the source organ and the physical half-life $t_{1/2}$ of the isotope, as well as the residence time of the radioactively labeled tracer in the body, have to be measured experimentally.

| Isotope | $t_{1/2}$ [min] | $\gamma/\beta^+$ [%] | Tracer | $h_T$ [μSv/MBq] | Ref. | $E_{typ}$ [mSv] | $A_{typ}$ [MBq] |
|---------|----------------|----------------------|--------|-----------------|------|----------------|----------------|
| $^{18}$F | 109.8          | 0                    | FDG    | 30              | [49] | 7.5            | 250            |
|         |                |                      | NaF    | 27              | [49] | 6.8            | 250            |
| $^{11}$C | 20.4           | 0                    | Methiodine | 5.2  | [48] | 2.1            | 400            |
| $^{13}$N | 10.0           | 0                    | Ammonia | 1.9  | [48] | 1.1            | 550            |
| $^{15}$O | 2.0            | 0                    | Water  | 0.93           | [48] | 0.93           | 100            |

| Isotope | $t_{1/2}$ [min] | $\gamma/\beta^+$ [%] | Tracer | $h_T$ [μSv/MBq] | Ref. | $E_{min}$ [mSv] | $\tau_{min}$ [s] | $A_{max}$ [MBq] |
|---------|----------------|----------------------|--------|-----------------|------|----------------|------------------|----------------|
| $^{89}$Zr | 4704          | 100                   | cmAb U36 | 530            | [44] | 0.785          | 705              | 1.89            |
| $^{14}$O | 1.2           | 99                   | Water  | 0.88           | [42] | 0.0024         | 2.20             | 1136            |
| $^{68}$Ga | 67.6          | 3                    | citrate | 23             | [45] | 1.10           | 989              | 43.5            |
|         |                |                      | DTPA   | 41             | [45] | 1.96           | 1763             | 24.4            |
|         |                |                      | EDTA   | 53             | [48] | 2.53           | 2276             | 18.9            |
| $^{124}$I | 6013         | 90                   | MIBG   | 250            | [46] | 0.056          | 50               | 4.00            |
|         |                |                      | NaI    | 6500           | [47] | 1.44           | 1299             | 0.154           |
| $^{76}$Br | 16.2          | 100                  | MAb-38S1 | 410           | [52] | 0.039          | 35               | 2.44            |
| $^{82}$Rb | 1.3           | 13                   | Chloride | 1.28         | [51] | 0.0022         | 1.97             | 781             |

Table 3. Radiation dose estimates of commonly used PET isotopes. In the upper part, besides the half-life $t_{1/2}$, standard tracer and associated equivalent dose coefficients $h_T$ are shown. Listed is the individually applied effective dose given to an adult male due to different tracers and medical isotopes. The last two columns contain values for the typical effective dose $E_{typ}$, resulting from typical activities $A_{typ}$ given to the patient during a PET examination. The lower part contains isotopes with an additional photon emitted simultaneously with the $\beta^+$ decay. In column 7, values are given for the minimum effective dose $E_{min}$ for 900 s examination time, which results from the minimum requirement of 40 reconstructed intersections, that corresponds to minimum required activity values of 1.48 MBq, 2.78 MBq, 47.8 MBq, 0.222 MBq, 0.095 MBq and 1.7 MBq for the isotopes $^{89}$Zr, $^{14}$O, $^{68}$Ga, $^{124}$I, $^{76}$Br, $^{82}$Rb, respectively, taking into account the isotope-specific reconstruction efficiencies. Alternatively, under the limiting condition of an applied dose of 1 mSv, the corresponding minimum examination time $\tau_{min}$ and the maximum applied activity $A_{max}$ is given in the last two columns.

Individually applied effective dose values given to an adult male due to medical radioisotopes using different tracers are presented in Tab. 3 (upper part for PET and lower for $\gamma$-PET isotopes). Besides the half-life $t_{1/2}$, the $\gamma/\beta^+$ ratio of the isotope, standard tracer and the associated equivalent dose coefficients $h_T$ are listed (references are given in Tab. 3). In the upper part we used the published $h_T$ values to calculate typical effective dose values $E_{typ}$, based on typically applied activities $A_{typ}$ [48]. In the lower part, we calculated the minimum effective dose $E_{min}$ for 900 s examination time, applying an activity of 1.48 MBq, 2.78 MBq, 47.8 MBq, 0.222 MBq, 0.095 MBq and 1.7 MBq for the isotopes $^{89}$Zr, $^{14}$O, $^{68}$Ga, $^{124}$I, $^{76}$Br, $^{82}$Rb, respectively, which provides the minimum of 40 reconstructed intersections between positron LOR and Compton cone of the third photon. This
results in a strongly reduced effective dose of, e.g., 0.785 mSv for $^{89}$Zr-cmAb-U36 compared to the applied effective dose in a typical PET examination with $^{18}$F-FDG of 7.5 mSv. As an alternative scenario, we can derive a minimum PET examination time achievable by increasing the dose to, e.g., 1 mSv, which is the limiting annual effective dose to the general public (as recommended by the International Commission on Radiological Protection (ICRP) [53]) and corresponds to about half of the typically absorbed annual environmental dose. Taking 1 mSv as a conservative effective dose limit for a $\gamma$-PET examination, the minimum examination time $\tau_{\text{exam}}^{\text{min}}$ results to only, e.g., 705 s for 1.89 MBq of $^{89}$Zr-cmAb-U36 (column 8).

In case of small-animal PET, where even higher effective doses are injected, real-time imaging of the metabolism, or a study of biological washout diffusion processes in animal experiments with implanted radioisotopes [26], appears feasible with the $\gamma$-PET technique.

6. Conclusion and Outlook

Most medical radioisotopes typically give rise to a lower spatial resolution for PET imaging, compared to the most widely used $^{18}$F, due to their higher $\beta^+$ decay energies, resulting in a larger positron diffusion range. We investigated the '$\gamma$-PET' imaging technique, taking advantage of detecting the additionally emitted $\gamma$ ray in coincidence with the $\beta^+$ annihilation photons. The triple-coincidence measurement allows to reduce the image-blurring effect of the diffusion range of the positron prior to its annihilation, which increasingly gains importance when comparing medical radioisotopes with higher $\beta^+$ endpoint-energies compared to the rather low value of 634 keV for $^{18}$F.

In addition, Compton scattering of the annihilation radiation within the patient limits the imaging performance, a further improvement of the $\gamma$-PET technique would have to take attenuation and scatter corrections of the annihilation photons, defining the LOR, into account [38], [39]. Simulations showed that it is possible to reach sub-millimeter spatial resolution in case of a small-animal imaging scenario, i.e. a small distance between the source and the detector, where the limiting influence of the acollinearity can be neglected. Even in case of high-energy positron emitting isotopes like $^{76}$Br ($E_{\text{max}}^{\beta^+} = 3.38$ MeV) or $^{10}$C ($E_{\text{max}}^{\beta^+} = 2.93$ MeV), the image reconstruction will again result in sub-millimeter spatial resolution. Moreover, being left only with the limiting effect of the acollinearity for whole-body PET scanning, most of the radioisotopes listed in Tab. 1 still allow to reach sub-millimeter spatial resolution also for a clinical scenario.

Particularly promising with the $\gamma$-PET technique is the strongly reduced applied effective dose of only several $\mu$Sv (when keeping the presently typical examination times). In this case, the applied effective dose results in 1-2 orders of magnitude less compared to typical PET examinations with $^{18}$F-FDG. Or, alternatively, short examination times of some tens of seconds could be realized when applying an effective dose limit of only 1 mSv. In addition, one Compton camera module, having a rather limited field-of-view, shows a Compton-cone reconstruction efficiency of $3.3 \cdot 10^{-5}$. However, the $\gamma$-PET technique requires at least 3 camera modules. We simulated a $\gamma$-PET prototype consisting of 4 Compton camera modules, resulting in a Compton-cone reconstruction efficiency of $1.3 \cdot 10^{-4}$, which in turn leads to an intersection reconstruction efficiency of $7.0 \cdot 10^{-8}$. Using a thicker scatter detector compared to the 2 mm thick scatterer included in our study, or a larger
absorber detector, matched to the solid angle covered by the scatterer, would allow for a significant increase of the reconstruction efficiencies both for the Compton cone as well as for the LOR. This would result in a drastically increased overall intersection reconstruction efficiency between the two, in turn allowing to further decrease the examination time or the applied dose by more than an order of magnitude.

These attractive properties result from the highly sensitive image reconstruction capability provided by the $\gamma$-PET technique, largely surpassing a conventional PET treatment. Thus in case of small-animal PET, real-time imaging of the metabolism is feasible using activities of some GBq, while in whole-body clinical applications much reduced dose levels, time and saving of isotope consumption will be achievable. Finally, the Compton camera described here could also turn out to be beneficial in a therapeutic hadron beam irradiation, where $\beta^+(\gamma)$ emitter ($^{10}\text{C}, \; ^{14}\text{O}$) are generated via, e.g., the carbon beam. Especially the projectile (fragment) $^{10}\text{C}$ with its short half-life of 19.3 s and the quasi-simultaneous emission of a third photon from an excited state qualifies as an online marker isotope during hadron therapy. Its spatial distribution within the patient could be tomographically reconstructed, either from a (quasi-realtime) PET analysis (i.e. direct reconstruction using TOF-PET) or using the hybrid $\gamma$-PET technique to achieve an improved spatial resolution together with an enhanced sensitivity, i.e. reduced requirements to the signal strength. The presented Compton camera (eventually upgraded by a thicker scatterer), could provide a versatile setup to assist with targeting one of the crucial issues of hadron therapy, which is ion beam range verification, either by detecting prompt $\gamma$ radiation during the irradiation \[5\] or (delayed) short-lived $\beta^+$-decaying reaction products (PET- or $\gamma$-PET operation) in between the irradiation cycles.

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