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Positioning true coincidences that undergo inter- and intra-crystal scatter for a sub-mm resolution cadmium zinc telluride-based PET system

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Abstract

The kinematics of Compton scatter can be used to estimate the interaction sequence of inter-crystal scatter interactions in 3-D position-sensitive cadmium zinc telluride (CZT) detectors. However, in the case of intra-crystal scatter in a “cross-strip” CZT detector slab, multiple anode and cathode strips may be triggered, creating position ambiguity due to uncertainty in possible combinations of anode-cathode pairings. As a consequence, methods such as energy-weighted centroid are not applicable to position the interactions. In practice, since the event position is uncertain, these intra-crystal scatter events are discarded. In this work, we studied using Compton kinematics and a “direction difference angle” to provide a method to correctly identify the anode-cathode pair corresponding to the first interaction position in an intra-crystal scatter event. GATE simulation studies of a NEMA NU4 image quality phantom in a small animal positron emission tomography under development composed of 192, 40 mm×40 mm×5 mm CZT crystals shows that 47% of total numbers of multiple-interaction photon events (MIPEs) are intra-crystal scatter with a 100 keV lower energy threshold per interaction. The sensitivity of the system increases from 0.6 to 4.10 (using 10 keV as system lower energy threshold) by including rather than discarding inter- and intra-crystal scatter. The contrast-to-noise ratio (CNR) also increases from 5.81±0.3 to 12.53±0.37. It was shown that a higher energy threshold limits the capability of the system to detect MIPEs and reduces CNR. Results indicate a sensitivity increase (4.1 to 5.88) when raising the lower energy threshold (10 keV to 100 keV) for the case of only two-interaction events. In order to detect MIPEs accurately, a low noise system capable of a low energy threshold (10 keV) per interaction is desired.

Keywords

Compton; CZT; PET; cross-strip; small animal imaging

1. Introduction

Cadmium zinc telluride (CZT) is a wide band gap compound semiconductor that is attractive for room temperature, photon counting, energy resolving radiation detection in X-ray imaging, positron emission tomography (PET) and single photon computed tomography (SPECT). It has a relatively high effective atomic number ($Z_{CZT}=48.2$) with density of 5.78 g/cm^3 that provides high stopping power for X-rays and gamma-rays. It enables direct conversion of the absorbed high energy photons into electronic signals and better energy resolution than scintillator detectors. Different electrode geometries with very small pixel arrays ($<100 \text{ }\mu\text{m}$) can be reliably fabricated by depositing metal on CZT which eliminates the complexity of cutting tiny crystal segments in scintillator detector technology.

One electrode configuration frequently used in CZT detector is a cross-strip pattern [1, 2, 3]. This configuration provides an efficient way to achieve a fewer number of electronic readout channels (i.e. $2n$ vs. n^2) through the electrode pattern and it can achieve high spatial resolution in three dimensions (3-D). This presents an advantage in terms of channel density and physical form factor for the detector hardware design. The intersection of the anode and cathode strips that produce signals defines the x-y localization of photon interactions. In addition, cathode-to-anode signal ratio and/or charge drift time can be used to accurately estimate the position of photon interaction in the z direction [4].

In PET imaging, a coincidence event is assigned to a line of response (LOR) which is determined as the line through the detected positions in two opposing detector elements. At high energy (511 keV), CZT has a larger mass attenuation coefficient for Compton scatter than for photoelectric absorption and there are a large fraction of multiple interaction photon events (MIPEs). One challenge of using the cross-strip electrode configuration is finding the correct intersection between anode and cathode strips when multiple anodes and cathodes generate signals at the same time. This is an important problem in the case of large volume CZT detectors where a large percentage of MIPEs happen within the same CZT crystal slabs. These intra-crystal scatter event types are typically discarded since there is not an accurate method to position the anode-cathode pairs. However, in order to improve the sensitivity of PET, we should retain intracrystal MIPEs. If the position and sequence of both intra- and inter-crystal MIPEs can accurately be determined, the detection efficiency of the system can be significantly improved.

Several approaches have been investigated for identifying the first interaction in MIPEs [5, 6, 7, 8, 9, 10] such as energy-weighted spatial mean, Compton kinematics, and Bayesian reconstruction. However, resolving the degeneracy in the cross-strip anode-cathode pairing for intra-crystal scatter events has yet to be investigated.

In this work, we studied a method that employs Compton kinematics in a data processing algorithm to pair the correct anode and cathode channels corresponding to first interaction position in intra-crystal scatter events. The same method is applied to positioning inter-crystal scatter events. The effect of the energy threshold of the system, i.e. the level of a signal that triggers the acquisition for individual interactions, on the capability of the system

to accurately detect the first interaction position of MIPes was quantified by measuring contrast-to-noise ratio (CNR).

2. Materials and methods

2.1. Identifying anode-cathode pair position in intra-crystal MIPes

In a cross-strip electrode pattern, the x-y localization of photon interaction is achieved by finding the intersection of the anode-cathode pair strips producing a signal. The interaction coordinate orthogonal to the cathode and anode (z localization) is achieved using the ratio of cathode signal to anode signal (C/A ratio). Intra-crystal Compton scatter causes the annihilation photon to deposit energy in multiple interaction locations within the relatively large volume of CZT crystal. Figure 1 shows an example of an incident photons that undergoes one Compton scatter (C) with a following photoelectric (P) absorption within one cross-strip CZT detector, depicting a potential positioning ambiguity, and a single interaction (without ambiguity) in the other detector.

In the data processing chain, there is a sorting stage to find the anode and cathode strips within one detector that get triggered within a time window. In the conventional approach, if there is more than one anode and one cathode channel triggered, they are discarded since there is ambiguity on pairing the correct anode-cathode strips corresponding to the first interaction location. However, in this work we are using the direction difference angle (DDA) [5] defined as $\theta_{DDA} = |\theta_E - \theta_P|$ to select the correct anode-cathode pair corresponding to the first interaction position. The Compton scattering angle θ_E is determined using equation 1:

$$\theta_E = \cos^{-1} \left(1 - mc^2 \left(\frac{1}{E_s} - \frac{1}{E_i} \right) \right) \quad (1)$$

where mc^2 is the photon rest energy, E_i is the incident photon energy and E_s is the scattered photon energy. The θ_P is determined as the angle between the incident and scattered photon using the equation 2:

$$\theta_P = \cos^{-1} \left(\frac{\mathbf{A} \cdot \mathbf{B}}{|\mathbf{A}| |\mathbf{B}|} \right) \quad (2)$$

where A and B are the vectors of the incident and scattered photons (using location information of the registered events). Table 1 shows all the possible anode-cathode pairing for identifying the first interaction location in figure 1. Since the Compton scattering angle is determined based on the anode energy, θ_E remains the same for both A_1C_1 or A_1C_2 positions. However, θ_P and as a consequence the DDA angle will change. Figure 1 indicates that the wrong set of anode-cathode pair led to a larger DDA. As a consequence a simple, fast algorithm is to consider all possible interaction sets and determine the anode-cathode pair with the lowest θ_{DDA} below an angular threshold (θ_P). GATE simulations were used to

determine θ_t to maximize the following figure of merit, NECm, inspired by noise equivalent counts:

$$\arg \max_{\theta_t} \text{NECm} = \arg \max_{\theta_t} \frac{T^2}{T+R+C+S}, \quad (3)$$

where T is the number of correctly positioned trues, R is the number of randoms, S is the number of detected events assigned to the system LORs that have undergone scatter in the phantom, and C is the number of mispositioned trues due to loss of first or second MIPes (these MIPes are lost since their energy is below the lower energy threshold of the system). The C term has been added to incorporate a penalty for reduction in CNR and resolution loss due to mispositioning.

In this paper, we considered the MIPes that are due to a Compton event followed by a photoelectric absorption. In the illustration in figure 1, two anodes and two cathodes are triggered. Since there are 2 anodes and 2 cathodes, we are able to calculate the depth of interaction for any possible anode-cathode pairing. There are other possible scenarios that the z coordinate using the C/A ratio cannot be determined: (i) same anode and same cathode are triggered for both interactions. These events correspond to single voxel MIPes since in the measurement we can not differentiate them as separate interactions. (ii) one anode and two cathodes are triggered. (iii) two anodes and one cathodes are triggered.

2.2. CZT PET system

We are developing a small animal positron emission tomography (PET) system based on cross-strip CZT detectors configured to achieve high spatial resolution and high sensitivity (Figure 2) [11, 12, 13, 14, 3, 15, 16, 17]. This system comprises four panels providing an adjustable, box-shaped field of view with maximum field-of-view (FOV) of 100 mm $\times$ 100 mm $\times$ 80 mm. Each panel includes 48 tightly stacked 40 mm $\times$ 40 mm $\times$ 5 mm crystals arranged in an edge-on orientation. The novel CZT detector orientation (edge-on with only 50 μ m gaps) increases 511 keV photon detection efficiency. The CZT crystals are metallized with a cross-strip electrodes pattern (1 mm pitch anode strips with steering electrode strips in between on one face, and 5 mm pitch cathode strips on the other [3]). The cross-strip configuration reduces the number of electronic readout channels required for the same detector area compared to a fully pixelated anode while providing excellent spatial resolution ($<1 \times 5$ mm² in x-y plane, and <1 mm in z direction). The initial performance characterization of the prototype system with a 100 keV low energy threshold is summarised in Table 2 [16, 17].

When an interaction occurs, the drift of electron-hole pairs induces signals that triggers the anode and cathode channels. The readout electronics record the energy and time of the triggered channel. If we have MIPes that occurs in two adjacent crystals, there is no position ambiguity. The anode-cathode pair in each crystal determine the x-y position and the C/A ratio determine the axial z position. However if both interactions happened in the same crystals, we further enumerate all possible interaction sequence ordering.

2.3. Phantom

For this study, a NEMA-NU4 2008 Image Quality Mouse Phantom [18] was used for investigating contrast and noise. The base material was PMMA, a tissue-equivalent plastic. The main body and one of the fillable, cylindrical compartments were filled with a $^{264}\mu\text{Ci}$ aqueous solution of ^{18}F as background region, while the other fillable, cylindrical compartment was filled with an aqueous solution of ^{18}F with an activity concentration 3.8 times the background concentration. The total activity was $300\mu\text{Ci}$. The alignment of the phantom with respect to the system can be seen in figure 3.

To investigate the spatial resolution, a second phantom was used that consisted of an array of hot point sources embedded in a warm background. Somewhat influenced by [8], the point sources were 1, 1.5, and 2mm in diameter. A 3×3 array of similar size point sources with 3 mm centre-to-centre spacing were placed in a warm background in a 30 mm inner-diameter PMMA cylinder (figure 4) with a 10:1 hot-to-background activity concentration ratio.

2.4. Simulation setup

We used GATE [19] to simulate the CZT PET system. A simulation time of 30 s was used for the phantom, with the duration chosen to achieve a statistical uncertainty of $<3\%$ in events assigned to LORs through all voxels [20]. The hit mode output file of the GATE simulation was processed to calculate the distribution of the interactions recorded in the CZT crystals. The deposited energy was blurred according to a Gaussian distribution based on the system overall FWHM energy resolution which depends on the FWHM of each individual source of energy variation in the prototype system [16]. The position in the x-y plane was binned according to the anode and cathode strips that recorded signal above the low energy threshold and the interactions were assigned to the centre of the strips. The thickness of the crystal was divided into 1 mm slices based on the conservative estimate of spatial resolution in the z direction [3]. The z position was assigned to the centre of the slice. Based on initial characterization of the prototype [16], the system energy resolution at 511 keV was 8% FWHM. An energy window of $\pm 16\%$ around the photopeak (429-593 keV) was used, unless otherwise stated, because it yielded the highest CNR. A time window of 20 ns was used, also based on initial characterization [16]. Custom code was developed to sort the coincidences and to implement the Compton kinematics algorithm for events with two interactions: Compton scatter followed by the photoelectric interaction. In addition to the Compton kinematics method, the energy-weighted spatial mean method [10, 8] and random selection of first interaction were used for performance comparison. For image reconstruction, the following events were included:

- Coincidences where photoelectric-only interactions (within the energy window) were identified in opposite detectors. These events are called PP.
- Coincidences where on one side of the system, one interaction falls in the energy window and on the other side, two interactions (triggered in one CZT detector or two CZT detectors) deposited a combined energy within the energy window. These events are called PC or CP.

- Coincidences where in both sides, two interactions (triggered in one CZT detector or two CZT detectors) deposited a combined energy within the energy window. These events are called CC.

The energy threshold (E_{thresh}) of the system, i.e. the level of a signal that triggers the acquisition, limits the capability of the system to detect MIPs with individual interactions below the threshold. For example, using Compton kinematics and the Klein-Nishina formula as a cumulative distribution function, all scattering interactions with scatter angle below 40° will deposit less than 100 keV in the first interaction. These low energy interactions will remain undetected in a system that employs an energy threshold of 100 keV, which can make a two-interaction event effectively appear to be a single interaction event. In this work, four energy thresholds (10, 50, 100, 150 keV) were considered. That is, the events with energy below the energy threshold were filtered from the simulation data. Previously, a z resolution of <1 mm was observed [3] for all photon interactions above the energy threshold of the prototype system (100 keV). In this work, we assume that the readout electronics have been upgraded so that the z resolution of 1 mm based on the C/A ratio is achievable down to photons with energy of 10 keV.

The flowchart in Figure 5 illustrates the basic structure of the interaction positioning identification algorithm incorporated in this work. Note that for inter-crystal scatter since there is no anode-cathode pairing ambiguity (i.e. no position ambiguity) there is no need to separate the anode and cathodes into all possible combinations.

2.5. Performance evaluation

The effect of the energy threshold on the performance of the system including MIPs was measured in terms of the CNR and system sensitivity. The system sensitivity was defined as the ratio (or percentage) of the number of events assigned to system LORs to the number of disintegrations.

A listmode OS-EM algorithm [21] was used to reconstruct images from the custom sorting code. The number of iterations for image reconstruction was chosen to maximize the CNR. The CNR and contrast were evaluated using the following equations:

$$CNR = \frac{I_{hot} - I_{background}}{\sigma_{background}}, \quad \text{Contrast} = \frac{I_{hot} - I_{background}}{I_{background}} \quad (4)$$

where I_{hot} and $I_{background}$ represent the mean intensity in the uniform hot and mean count in the background region of interest (ROI), respectively. Since the energy window also has an important role on performance, the CNR was calculated and compared for the following energy windows: 4%, 8%, and 16%. With the availability of the true interaction sequence from GATE simulation output, we also compute the percentage of events with correctly ordered interaction sequences, which provides an indication of how well the method is able to determine the correct sequence.

3. Results and discussion

3.1. Interaction event type distribution

Table 3 shows the distribution of events from GATE simulations with the image quality mouse phantom while applying different event trigger low energy thresholds. For the box-shaped system with edge-on CZT crystal configuration, 22.8% of the total number of single 511 keV detected events were photoelectric absorption (with an energy window of 429–592 keV) for a 10 keV threshold. As the energy threshold is increased, MIPes with energy below the threshold are not detected and appear as a single photoelectric event with energy within the accepted energy window, leading to a higher observed percentage of photoelectric events, 26.5% for 100 keV threshold vs 22.8% for 10 keV threshold. Detection of MIPes is strongly dependent on the energy threshold, e.g. the percentage of MIPes dropped from 77.2% for 10 keV threshold to 42.9% for 150 keV threshold. The number of 1 Compton + 1 photoelectric interactions increased going from an energy threshold of 10 keV to 100 keV. By increasing the energy threshold we are not able to detect interactions below the threshold of the system, therefore events with two Compton interactions and one photoelectric interaction are detected as one Compton and one photoelectric interaction. Depending on which interaction was rejected, this could lead to incorrect mispositioned LOR assignment. If the energy threshold is increased further, the sum of the energy detected is outside of the accepted energy window.

Table 4 shows all the possible MIPes scenarios (inter- and intra-crystal scatter) for one Compton followed by one photoelectric event (1C,1P) from the results of table 3 for an energy threshold of 100 keV, which is approximately the same lower energy threshold achieved with our prototype experimental system [16]. From the total numbers of MIPes, 53.37% are inter-crystal scatter and 46.73% are intra-crystal scatter. Based on a histogram of the distance between two interactions either within the same $4 \times 4 \times 0.5 \text{ cm}^3$ crystal or in two different crystals, the average distance between the MIPes is approximately $7.7 \pm 7.4 \text{ mm}$.

3.2. Figure of merit and DDA threshold

Figure 6(a) shows the figure of merit (NECm) obtained for different θ_r . As the DDA threshold is increased, the number of accepted trues, randoms, and mispositioned trues changes and leads to an increase or drop in the figure of merit. Note that the spatial resolution of the detector as well as energy blurring impact the sharpness of the peak near the optimal figure of merit. As the position estimate of the first interaction in a MIPe gets more accurate, the error for trues decreases, the optimal θ_r decreases, and the figure of merit increases (figure 6(b)). Energy blurring has a similar effect but is not able to improve the figure of merit as much as improving the spatial resolution alone. With an energy blurring of 8% and the spatial resolution of the current prototype system [16], there is limited benefit of choosing an angular difference threshold since the peak is only slightly larger than for the case of accepting all DDA (setting the threshold to 90°). The effect of energy threshold on the figure of merit is shown in figure 7. As the energy threshold increases the figure of merit decreases because MIPes with energy below the energy threshold are not detected, which leads to potential mispositioning of trues.

3.3. CNR

Figure 8 shows an example of the reconstructed phantom and the ROIs used for the hot regions and background. The CNR was calculated using the defined regions of hot (1 region) and background (9 regions). The CNR for the 9 background regions was calculated and the mean and standard deviation from these 9 CNR calculations is reported. Figure 9 shows the CNR as a function of the iteration number for an energy threshold of 100 keV and coincidences that include just PP events and PP+MIPEs. The maximum CNR for PP was achieved after 4 iterations. However, when including the MIPEs, the maximum CNR was achieved after 6 iterations. Hereafter, for reconstruction the number of iterations that led to the optimal CNR was used. The line profile through the phantom is shown in figure 10 considering different types of coincidences. Including the MIPEs with ambiguity increases the total number of accepted events significantly.

Table 5 shows the CNR and sensitivity for different energy threshold and event types: photoelectric coincidences only (PP), including coincidences with MIPEs. The sensitivity and CNR improves drastically when MIPEs are included for all energy thresholds investigated. There is a slight increase in sensitivity observed with increasing energy threshold, which is a consequence of our analysis, which considers only two-interaction events. As it was shown in table 3, by increasing the energy threshold from 10 to 100 keV, a fraction of events with two Compton and one photoelectric interactions are detected as one Compton and one photoelectric interactions. This increases the observed sensitivity, however depending on which interaction was rejected, the CNR can be degraded, as seen in table 5. Thus, to achieve the best performance and assure that MIPEs are positioned correctly a lower energy threshold (down to 10 keV) is desired.

The results of CNR for different energy windows are shown in figure 11. Using a small window leads to a significantly reduced amount of accepted events, and the CNR is reduced. Using 8%, which is closest to the energy resolution of the system leads to comparable CNR as 16%, but better contrast, making it the preferred choice.

3.4 Comparison of event position accuracy versus energy weighting and random first interaction

The percentage of coincidence events with correctly identified first interactions is shown in Table 6 for several cases. Note that for the random first interaction method, the results represent the best case, since it is assumed there is no position ambiguity in intra-crystal scatter. For the Compton kinematics method, a lower, low energy threshold per interaction yields a more accurate interaction sequence and the reduction in coincidence timing window (from 20 ns to 10 ns) has a minor (less than 1%) effect on performance.

Figure 12 shows the CNR and contrast for the Compton kinematics, energy-weighted spatial mean positioning, and random selection methods. The Compton kinematics method yields better CNR and contrast. The sensitivity is essentially the same between the methods since they differ in how they position the event LOR. Reconstructed images using either of the methods are shown in figure 13.

3.5. Spatial resolution using the point source phantom

The point source phantom was simulated for the three interaction event sequencing methods and the case of no MIPes. A line profile passing through 3 similar size point sources was measured (and averaged across 3 similar line profiles) for comparison of the spatial resolution (figure 14). Although the 1 mm sphere is not clearly discernible, the change in intensity for 1.5 and 2 mm spheres is visible for all reconstruction methods. The inclusion of MIPes using the Compton kinematics method does not appear to significantly degrade the resolution in these cases and the intensity change observed is highest for the Compton kinematics method.

4. Conclusions

GATE simulation studies of singles in a NEMA NU4 image quality phantom show that 47% of the total numbers of MIPes are intra-crystal scatter and 53% are inter-crystal scatter in our small animal PET system based on $4 \times 4 \times 0.5$ cm³ CZT crystals. We demonstrate the effect of energy threshold of the system in detecting and positioning multiple interaction events. It was shown that raising the lower energy threshold limits the capability of the system to accurately identify the first interaction position in MIPes and reduces the CNR. The increase in the sensitivity associated with raising the lower energy threshold per interaction is a consequence of our analysis, which considers only two-indication events. In order to detect MIPes, a low noise system with low energy threshold (10 keV) per interaction is desired.

Compton kinematics and the concept of a “direction difference angle” was used to find the anode-cathode pair corresponding to first interaction position in intra-crystal scatter as well as inter-crystal scatters. The sensitivity of the system was improved nearly an order of magnitude (7.4x for 100 keV lower energy threshold) including inter- and intra-crystal scatter compared to the case of only considering photoelectric-photoelectric events. With the spatial resolution and energy resolution of the current system, choosing a DDA threshold was not imperative, since the peak value of the figure of merit, NECm, (at the optimal threshold) was only marginally above the value when no threshold was chosen. A comparison of event positioning accuracy versus the energy-weighted spatial means and random selection methods showed that using Compton kinematics yields better performance in terms of CNR, contrast, percentage of correctly ordered interaction sequences, and spatial resolution.

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References

1. Kalemci E, Matteson JL. Investigation of charge sharing among electrode strips for a CdZnTe detector. *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*. 2002; 478(3):527–537.
2. Lee, Kuen, Martin, JW., Garson, AB., III, Beilicke, M., Guo, Q., Li, Q., De Geronimo, G., Groza, M., Burger, A., Krawczynski, H. SPIE Defense, Security, and Sensing. International Society for

Optics and Photonics; 2010. Development of x-ray and gamma-ray CZT detectors for homeland security applications; p. 766423

3. Gu Y, Levin CS. Study of electrode pattern design for a CZT-based PET detector. *Physics in Medicine and Biology*. 2014; 59(11):2599. [PubMed: 24786208]
4. Kalemci, Emrah, Matteson, James L., Skelton, Robert T., Hink, Paul L., Slavis, Kimberly R. SPIE's International Symposium on Optical Science, Engineering, and Instrumentation. International Society for Optics and Photonics; 1999. Model calculations of the response of CZT strip detectors; p. 360-373.
5. Chinn, Garry, Levin, Craig S. A maximum NEC criterion for compton collimation to accurately identify true coincidences in PET. *IEEE Transactions on Medical Imaging*. 2011; 30(7):1341–1352. [PubMed: 21317079]
6. Kim, Jae Cheon, Kaye, William R., Yang, Hao, Brown, Cassarah R., He, Zhong. Improvement of sub-pixel position sensing in nonuniform large-volume pixelated CdZnTe crystals. *IEEE Transactions on Nuclear Science*. 2013; 60(2):1201–1207.
7. Yoon, Changyeon, Lee, Wonho, Lee, Taewoong. Simulation for CZT compton PET (Maximization of the efficiency for PET using Compton event). *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*. 2011; 652(1):713–716.
8. Prax, Guillem, Levin, Craig S. Bayesian reconstruction of photon interaction sequences for high-resolution PET detectors. *Physics in Medicine and Biology*. 2009; 54(17):5073. [PubMed: 19652293]
9. Champley, Kyle M., Lewellen, Thomas K., MacDonald, Lawrence R., Miyaoka, Robert S., Kinahan, Paul E. Statistical lor estimation for a high-resolution dmice pet detector. *Physics in Medicine Biology*. 2009; 54(20):6369. [PubMed: 19809102]
10. Comanor KA, Virador PRG, Moses WW. Algorithms to identify detector compton scatter in PET modules. *IEEE Transactions on Nuclear Science*. Aug; 1996 43(4):2213–2218.
11. Matteson, James L., Gu, Yi, Skelton, Robert T., Deal, Aaron C., Stephan, Edwin A., Duttweiler, Fredric, Huszar, George L., Gasaway, Thomas M., Levin, Craig S. Nuclear Science Symposium Conference Record, 2008 NSS'08 IEEE. IEEE; 2008. Charge collection studies of a high resolution CZT-based detector for PET; p. 503-510.
12. Gu Y, Levin CS. Studies of electrode design for a sub-mm resolution 3-d position sensitive CZT PET detector. 2011 IEEE Nuclear Science Symposium Conference Record. Oct.2011 :2303–2305.
13. Gu Y, Matteson JL, Skelton RT, Deal AC, Stephan EA, Duttweiler F, Gasaway TM, Levin CS. Study of a high-resolution, 3D positioning cadmium zinc telluride detector for PET. *Physics in Medicine and Biology*. 2011; 56(6):1563. [PubMed: 21335649]
14. Gu, Yi, Levin, Craig S. Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC), 2012 IEEE. IEEE; 2012. Characterization of inter-detector effects in a 3-d position-sensitive dual-CZT detector modules for PET; p. 4088-4090.
15. Abbaszadeh S, Gu Y, Sikora U, Levin CS. First acquisition of data from a prototype 3-D position sensitive CZT PET system. 2014 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC). Nov.2014 :1–2.
16. Abbaszadeh, Shiva, Gu, Yi, Reynolds, Paul D., Levin, Craig S. Characterization of a sub-assembly of 3D position sensitive cadmium zinc telluride detectors and electronics from a sub-millimeter resolution PET system. *Physics in Medicine and Biology*. 2016; 61(18):6733. [PubMed: 27551981]
17. Abbaszadeh, Shiva, Levin, Craig S. New-generation small animal positron emission tomography system for molecular imaging. *Journal of Medical Imaging*. 2017; 4(1):011008. [PubMed: 28097211]
18. Bindseil, GA. PhD thesis. 2013. Approaches toward combining positron emission tomography with magnetic resonance imaging.
19. Jan S, Santin G, Strul D, Staelens S, Assi K, Autret D, Avner S, Barbier R, Bardis M, Bloomfield PM, Brasse D, Breton V, Bruyndonckx P, Buvat I, Chatzioannou AF, Choi Y, Chung YH, Comtat C, Donnarieix D, Ferrer L, Glick SJ, Groiselle CJ, Guez D, Honore P-F, Kerhoas-Cavata S, Kirov AS, Kohli V, Koole M, Krieger M, van der Laan DJ, Lamare F, Largeron G, Lartizien C, Lazaro

- D, Maas MC, Maigne L, Mayet F, Melot F, Merheb C, Pennacchio E, Perez J, Pietrzyk U, Rannou FR, Rey M, Schaart DR, Schmidtlein CR, Simon L, Song TY, Vieira J-M, Visvikis D, Van de Walle R, Wiers E, Morel C. GATE: a simulation toolkit for PET and SPECT. *Physics in Medicine and Biology*. 2004; 49(19):4543. [PubMed: 15552416]
20. Cherry, Simon R., Sorenson, James A., Phelps, Michael E. *Physics in Nuclear Medicine* Elsevier. Fourth. Positron Emission Tomography; 2012. ch.18
21. Cui, Jing-yu, Pratx, Guillem, Prevrhal, Sven, Levin, Craig S. Fully 3D list-mode time-of-flight PET image reconstruction on GPUs using CUDA. *Medical Physics*. 2011; 38(12):6775–6786. [PubMed: 22149859]

Figure 1.

Positioning ambiguity for MIPES that occur within the same crystal. Comparing θ_E and θ_p (see equation 1 and 2) enables us to choose the first interaction position. An example situation is illustrated where two anodes and two cathodes are triggered on one of the crystals. Two interaction sets in that crystal are shown, each using a different anode/cathode pair as the first interaction position. In one case, $\theta_E \neq \theta_p$, while in the other $\theta_E = \theta_p$. In the latter case, the LOR passes through the point source.

Figure 2.
Schematic of box-shaped CZT-based small animal PET system.

Figure 3.
(a) and (b) The CZT system (red) and contrast phantom (green, blue, white) as modeled in GATE. (c) The activity concentration in the phantom.

Figure 4.

(a) The point source phantom where the yellow, blue, and red circles represent 1, 1.5, and 2 mm diameter hot spheres, respectively. (b), (c) An example reconstructed image of the point source phantom from transaxial and coronal views, respectively.

Figure 5.
Flowchart of identification of first interaction position.

Figure 6.

(a) Figure of merit versus DDA threshold (θ_t) for 100 keV energy threshold. (b) Figure of merit versus DDA threshold for 100 keV lower energy threshold with exact x-y-z positioning and 8% energy blurring.

Figure 7.
Figure of merit versus DDA threshold (θ_t) for different energy thresholds.

Figure 8. Reconstructed image of contrast phantom where the hot and background regions are defined for calculating the CNR.

Figure 9. CNR as a function of number of iterations in the image reconstruction. The green and black lines include only the photoelectric events as coincidences (PP). The red line also includes the MIPEs without position ambiguity (w/oPA) while the blue line includes MIPEs with and without position ambiguity.

Figure 10. Line profile for 100 keV lower E_{thresh} for coincidences with photoelectric only (PP), photoelectric plus MIPEs without position ambiguity (PP+MIPEsw/oPA), and photoelectric plus all MIPEs (PP+MIPEs).

Figure 11.
(left) CNR and (right) contrast as a function of number of iterations for different energy acceptance windows centered on the photopeak.

Figure 12.
(left) CNR and (right) contrast for the Compton kinematics, energy weighted, and random selection event positioning methods.

Figure 13.

Transverse, coronal, and sagittal views (9 per method) of the reconstructed images for the (a) Compton kinematics, (b) energy weighted, and (c) random selection event positioning methods. The centre (x,y,z) coordinates and the views are listed as insets of each reconstructed image.

Figure 14. Line profiles for (a) 2, (b) 1.5, and (c) 1 mm hot spheres. Illustrations of the point source locations are shown (in purple) at their respective locations.

Table 1

All the possible anode-cathode pair for identifying the first interaction location in figure 1.

Anode-cathode pair	θ_E	θ_p	θ_{DDA}
A ₁ C ₁	θ_{E1}	θ_{p1}	θ_{DDA1}
A ₁ C ₂	θ_{E1}	θ_{p2}	θ_{DDA2}
A ₂ C ₁	θ_{E2}	θ_{p3}	θ_{DDA3}
A ₂ C ₂	θ_{E2}	θ_{p4}	θ_{DDA4}

Table 2

CZT-based small animal initial system characterization. Note that the spatial resolution includes the charge sharing effect.

Energy resolution at 511 keV (FWHM)	7.35±1.75 %
Intrinsic spatial resolution (tangential)	0.78±0.1 mm
Time resolution (FWHM)	18±0.1 ns

Table 3

Distribution (in percentage) of single 511 keV events in a CZT system with different event trigger low energy threshold, $E_{threshold}$ where P =photoelectric, and C =Compton. The same column values increase or decrease with changing threshold due to redistribution and accounting for dropped interactions that fell below the threshold. All percentages are with respect to totals from a 10 keV threshold. Only events whose energy sums to within the energy window (429–592 keV) are considered.

$E_{threshold}(keV)$	P	1C,1P	2C,1P	3C,1P	4C,1P	5C,1P	>6C,1P
10	22.8	38.6	25.6	9.8	2.6	0.5	0.1
50	24.8	46.0	23.4	4.5	0.4	0.0	0.0
100	26.5	49.0	11.4	0.2	0	0	0
150	26.5	41.6	1.3	0	0	0	0

Table 4

All the possible MIPES scenarios (inter- and intra-crystal scatter) for interactions that have 1C, 1P for a per-interaction lower energy threshold of 100 keV.

MIPES (1C,1P)	Percentage (%)
1anode-1cathode	12.46
2anode-1cathode	20.4
1anode-2cathode	2.07
2anode-2cathode	11.7
Different crystals	53.37

Table 5

Contrast-to-noise ratio (CNR) and sensitivity for different energy thresholds.

$E_{thresh}(\text{keV})$	Method	CNR	Sensitivity (%)
10	PP	5.81 ± 0.30	0.60
10	PP+MIPEs	12.53 ± 0.37	4.10
50	PP	5.92 ± 0.30	0.66
50	PP+MIPEs	12.05 ± 0.41	5.30
100	PP	6.24 ± 0.30	0.70
100	PP+MIPEs	11.09 ± 0.40	5.88

Table 6

Percentage of coincidence events with correctly ordered interaction sequences.

$E_{thresh}(\text{keV})$	Coincidence time window (ns)	Method	Phantom	% Correct
10	20	Compton kinematics	NEMA-NU4	64.9
50	20	Compton kinematics	NEMA-NU4	60.3
100	20	Compton kinematics	NEMA-NU4	55.9
100	10	Compton kinematics	NEMA-NU4	56.3
100	20	Random	NEMA-NU4	41.2
10	20	Compton kinematics	Point sources	65.3
50	20	Compton kinematics	Point sources	60.6
100	20	Compton kinematics	Point sources	56.3
100	20	Random	Point sources	41.0