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Chengeng Zeng
Paul E. Kinahan
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Chengeng Zeng,^{a,*} Paul E. Kinahan,^a Hua Qian,^b Robert L. Harrison,^a Kyle M. Champley,^c and Lawrence R. MacDonald^a

^aUniversity of Washington, Radiology Department, Seattle, Washington, United States

^bGE Global Research Center, Niskayuna, New York, United States

^cLawrence Livermore National Laboratory, Livermore, California, United States

Abstract. The goal for positron emission tomography (PET)/X is measuring changes in radiotracer uptake for early assessment of response to breast cancer therapy. Upper bounds for detecting such changes were investigated using simulation and two image reconstruction algorithms customized to the PET/X rectangular geometry. Analytical reconstruction was used to study spatial resolution, comparing results with the distance of the closest approach (DCA) resolution surrogate that is independent of the reconstruction method. An iterative reconstruction algorithm was used to characterize contrast recovery in small targets. Resolution averaged <2 mm full width at half maximum when using depth-of-interaction (DOI) information. Without DOI, resolution ranged from 2.1 ± 0.13 to 3.1 ± 0.42 mm for scanner crystal thickness between 5 and 15 mm. The DCA resolution surrogate was highly correlated to image-based FWHM. Receiver-operating characteristic analysis showed specificity and sensitivity over 95% for detecting contrast change from 5:1 to 4:1 (area under curve $>99\%$). For PET/X parameters modeled here, the ability to measure contrast changes benefited from higher photon absorption efficiency of thicker crystals while being largely unaffected by degraded resolution obtained with thicker crystals; DOI provided marginal improvements. These results assumed perfect data corrections and other idealizations, and thus represent an upper bound for detecting changes in small lesion radiotracer uptake of clinical interest using the PET/X system. © 2017 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: [10.1117/1.JMI.4.4.045502](https://doi.org/10.1117/1.JMI.4.4.045502)]

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1 Introduction

Breast cancer remains one of the most prevalent and lethal cancers in women in the U.S. and many other countries.¹ Great progress has been made in early detection and treatment options. Much of the progress can be attributed to the development of new and highly targeted therapeutics, with over 60 therapies approved by the US Food and Drug Administration to date. Greater understanding of the wide diversity of disease characteristics and signaling pathways has enabled the development of agents that target tumor-growth factors but also reveals biochemical complexities that make successful treatment challenging. This is reflected by the inconsistent response in cohorts of patients, which receive agents designed to target their specific disease phenotypes.²

Positron emission tomography (PET) imaging has gained attention in recent years as a potential early predictor of response to therapy through *in situ* measures of changes in tumor physiology using radiotracer techniques.³ Most commonly, using 18F-fluorodeoxyglucose (18F-FDG), it aims to measure changes in tumor metabolic activity following treatment. A number of other tracers exist for probing other physiologic pathways, such as 18F-FES, 18F-FLT, 89Zr-trastuzumab, and others.^{4–6} Research has shown that breast PET imaging can detect tumor responses to chemotherapy as soon as a few days after therapy,⁷ whereas the corresponding morphological change could take much longer to show up on anatomical

images, such as CT, US, mammography, and magnetic resonance imaging.^{8–10}

Using whole-body PET scanners to monitor breast cancer response to treatment is challenging due to the relatively small size (~ 2 cm and smaller) of many primary breast tumors. Such lesions suffer from partial volume effects that degrade quantitative accuracy for measuring tracer uptake. Dedicated breast PET scanners with improved spatial resolution have long been proposed.¹¹ Originally intended to improve breast cancer diagnosis and thus reduce rates of negative biopsies, improved resolution can also improve quantification for smaller tumors, which in turn could benefit therapy monitoring. Over the years, other dedicated breast PET scanners have been developed with varying attention to quantitative accuracy. One of the earliest was the commercial PEM flex solo 2 that consists of two detector heads moving synchronically in horizontal planes.¹² Focusing on diagnosis, the PEM flex does not incorporate full quantitative data acquisition or data corrections. In light of the growing interest to use PET for therapy monitoring, more recent dedicated breast PET systems have recognized the importance of quantitative accuracy. A number of dedicated breast PET projects are currently active, using either flat-panel detectors^{13–15} or a partial/full ring geometry.^{16–20} Integration with anatomical imaging has also been a theme.^{13,16,17,21}

We are currently building the PET/X scanner, which is a breast PET scanner combined with an x-ray mammography

*Address all correspondence to: Chengeng Zeng, E-mail: genguni@uw.edu

system. Our goal for the PET/X scanner is to precisely measure changes in radiotracer uptake after an initial dose of therapy and to determine correlations between the early changes in uptake and long-term response to the therapy. Based on discussions with radiologists and medical oncologists regarding potential clinical impact, the initial system performance target was that a measured 20% change in tracer uptake in 5-mm lesions with standardized uptake value (SUV) of five should correspond to at least 95% specificity (<5% false positive rate for detecting a true change in uptake). We would like to achieve this performance with 3 to 5 min scans and no more than 185 to 370 MBq (5 to 10 mCi) injections of 18F-FDG or other radiotracer. Guidelines for using PET to monitor response to therapy have been proposed, for example, the EORTC guidelines²² and PERCIST.²³ These guidelines are designed for whole-body 18F-FDG PET scanning. In general, the guidelines must carry conditions such as being applied to “evaluable” tumors, which impose restrictions on tumor size, baseline SUV, and other factors. Our goal with PET/X is to reduce the size of evaluable tumors to 5 mm. Thus, our scanner design focuses on this performance goal, as opposed to a specific spatial resolution or scanner efficiency. PET/X is designed to be fully tomographic to support quantitative accuracy and precision. Our design uses four flat panels (Fig. 1) similar to a breast PET scanner previously developed at the Lawrence Berkeley National Laboratory.^{24,25} This design faces similar constraints as other PET scanners, namely, trade-off between spatial resolution and scanner efficiency, and overall system complexity (e.g., measuring event DOI). This design also faces unique challenges associated with the rectangular geometry, e.g., tomographic data sampling patterns. The approach and preliminary descriptions of our image reconstruction algorithms have been reported;^{26,27} this paper represents a further assessment of these approaches.

This paper extends our previous analysis of trade-offs in crystal thickness selection^{28,29} by (i) including the use of two independent fully three-dimensional (3D) image reconstruction methods,^{26,27} (ii) adding a study of reproducibility through multiple simulation realizations, and (iii) performing a receiver-operating characteristic (ROC) analysis of the ability of the PET/X scanner to accurately measure changes in lesion contrast. In this first report of performance metrics from reconstructed PET/X images, we use idealized data models to investigate fundamental upper bound performance limits of the PET/X geometry and image reconstruction approaches. Several

Fig. 1 Schematic illustration of the PET/X scanner that consisted of four planar detectors. The rectangular FOV measured 200-mm wide by 80-mm high by 150-mm deep. Note that the axial view ($x - y$ plane) in PET/X corresponded to a coronal view of the patient.

physical phenomena important to PET imaging have been omitted for this work to focus on sources of fundamental constraints of the detector geometry and reconstruction algorithms.

2 Methods

We used the SimSET photon tracking simulation package³⁰ and two custom image reconstruction packages.^{26,27} The latter two were specifically written for the unique rectangular field of view (FOV) of the PET component.

2.1 Simulation and Reconstruction

2.1.1 Detector description

As shown in Fig. 1, the PET scanner consisted of four planar detectors, forming a rectangular system with a complete azimuthal angular sampling (around the z axis). In this study, the top and bottom panels measured 200-mm wide (x axis) and 150-mm deep (z axis). The panel-to-panel separation was set at 80 mm. The left and right panels measured 100-mm high (y axis) and 150-mm deep (z axis), with a panel-to-panel separation fixed at 200 mm. Each detector panel was modeled as one solid piece of 40-mm thick lutetium oxyorthosilicate (LSO). Data were later filtered to keep only events corresponding to certain crystal thicknesses under study, as described in Sec. 2.1.3.

2.1.2 Phantom description

We used a breast phantom that was analytically described as a truncated ellipsoid. About 10 spheres of either 5-, 10-, or 15-mm diameter were embedded in the breast volume as shown in Fig. 2. This version of the phantom was used to measure the contrast recovery coefficient (RC). Four spheres were in an axial plane 15 mm from the chest wall edge of the scanner, four were axially halfway, and two were near the nipple region. All 10 spheres were of the same size for any given simulated phantom object. The activity concentration target-to-background ratios (TBR) were set to 5:1 or 4:1.

Fig. 2 Orthogonal views of the breast phantom with 10 10-mm diameter hot spheres (red). Breast background data were taken from distributed spheres of the same size (shown in green). The phantom was voxelized on a 1-mm grid. The image slice shown in each view is indicated by the crosshairs in the other two views. Note that not all spheres lie in the cross-sections shown here. Also note that the axial view (top left) is along the PET/X scanner axis that will be along the patient in anterior–posterior direction, and thus corresponds to a coronal view in conventional tomographic orientations.

In separate simulations, the spheres were replaced with idealized point sources at the same locations. This phantom was used to study image spatial resolution. The analytical phantoms were pixelated into 1 cubic mm voxels, resulting in (roughly) 50, 550, and 1740 total voxels in each of the 5-, 10-, and 15-mm-diameter spheres, respectively. The attenuation coefficient of the entire phantom was modeled to be uniform adipose tissue.

To study activity recovery in an object that would not suffer from partial volume errors or resolution loss, we also simulated a 40-mm diameter hot sphere in a warm uniform background with the TBR set to 5:1. The background filled out the rectangular FOV. The volumes of interest (VOIs) were a 10 mm × 10 mm × 10 mm cube taken from inside the large sphere and another equal-sized background cube away from the sphere.

2.1.3 SimSET data generation and filtering

We simulated 500 M decays per realization, corresponding to roughly a 3-min scan with 3 kBq/mL activity concentration for the 900-mL breast phantom. The concentration is representative of a standard clinical FDG dose of 370 MBq uniformly distributed in an 80-kg person after a 60-min uptake time. Coherent scattering was modeled with perfect energy resolution while positron range and a collinearity were not. Only coincidence events were simulated.

To create an object that can occupy the entire rectangular FOV, we had to bypass the constraint in SimSET that required the object and detector to be separated by a cylindrical shell. First, photon pairs were tracked through the phantom object and recorded on an artificially oversized target cylinder. Second, a custom-user function was implemented to project the photons back onto the inner surface of the rectangular detector geometry. Finally, the SimSET detector module was used to simulate the interaction location of the annihilation photons within the LSO scintillators.

List-mode data, including all individual interactions in the 40-mm thick crystals, were saved, and postprocessing was done to filter interactions that would have been recorded by detector crystals of 5-, 10-, and 15-mm thick LSO. This data filtering process was validated in a prior study.²⁸ The total energy threshold was set at 510 keV to reject scattered events. The remaining interactions were then used to compute the line of response (LOR) as detailed below.

Simulations were separately run for the warm background alone and for the hot spheres embedded in activity-free attenuating background. The list-mode data of background and spheres were combined during the postprocessing before reconstruction to yield a TBR of either 5:1 or 4:1.

In total, 20 independent realizations were repeated for each sphere size to allow estimation of the variance.

2.1.4 Event position estimation

We modeled event positioning within the detectors in the following three ways:²⁸

1. The first vertex interaction location of the 511-keV photon.
2. The 3D center of mass (3D-COM) of the energy deposited from all interactions.
3. The two-dimensional COM (2D-COM).

The first vertex represented the true positioning of the event. In 3D-COM, the energy-weighted COM of all filtered interactions of the same incident photon was calculated to represent the event position. Note that first vertex and 3D-COM were equivalent for photoelectric absorption events (single interaction). The 2D-COM position estimation reassigned the DOI coordinate of the 3D-COM estimation to a fixed depth for all events. The fixed depth was calculated as the expected value of the mean penetration depth of 511-keV photons in the incident angle orthogonal to the front crystal face and is thus dependent on the total depth of the crystal thickness. No further detector blurring was added. The data files of first vertex, 3D-COM, and 2D-COM corresponded to the perfect LOR, LOR with DOI, and LOR without DOI, respectively.

2.1.5 Reconstruction algorithms and image processing

Two separate reconstruction codes were used. For spatial-resolution analysis with the idealized point sources, we used a fast analytical filtered back projection called planogram frequency-distance rebinning exact (PFDRX) algorithm.²⁶ The image voxel size was 0.25 mm.

For contrast RC analysis with the sphere sources, we used an iterative reconstruction algorithm that featured a distance-driven projector and maximum-likelihood estimation (ML-EM).²⁷ We applied 3D-Gaussian postreconstruction smoothing to control noise and used 15 iterations for all reconstructed images in this study. The image voxel size was 1 mm.

Both algorithms included attenuation correction (AC). In this work, we used the phantom itself as the attenuation map to correct the attenuated coincidence data.

2.2 Metrics

2.2.1 Spatial resolution and distance of closest approach

Images of the ideal point sources were reconstructed using PFDRX with no postreconstruction smoothing. For each point source, the image-based full width at half maximum (FWHM) in all three dimensions was calculated and then averaged to provide a single value per point source.

We also calculated a spatial-resolution surrogate, d_{FWHM} , using the distance of closest approach (DCA) method, first introduced by MacDonald et al.²⁸ The appeal of the DCA method is that it is independent of the image reconstruction method; here, we used list-mode data, but it can also be estimated from sinogram data. The DCA is an event-by-event metric defined as the shortest distance from each positron annihilation position to the corresponding LOR determined by the detectors. The DCA thus represents the best possible estimate of the annihilation position that the LOR can provide. Of the three event-positioning estimations we described above, events using the ideal first vertex estimate had DCA equal to zero (apart from machine precision with which the list-mode data were stored and possible data discretization effect due to object voxelization). The 3D- and 2D-COM LORs were less accurate estimates of the true LOR position and consequently had DCA greater than zero.²⁸

Detected events from each point source simulation produced a distribution of DCA values: P_{DCA} . The spatial-resolution surrogate, d_{FWHM} , is then defined as the threshold value encompassing some percentage of the events; we used the 29th percentile of the P_{DCA} as follows to define d_{FWHM} :

$$\int_{r=0}^{r=d_{\text{FWHM}}} P_{\text{DCA}} dr = 0.29, \quad (1)$$

where the integration (dr) is over DCA values in the distribution P_{DCA} . Our use of the 29th percentile stemmed from the fact that integrating an isotropic 3D Gaussian distribution within a sphere with radius equal to one FWHM of the Gaussian yields 29% of the normalized distribution, as follows:

$$\int_{r=0}^{r=\text{FWHM}/2} P_{\text{Gauss}} dV = 0.29, \quad (2)$$

where integration is over the volume of a sphere of diameter FWHM, and

$$P_{\text{Gauss}} = (2\pi\sigma^2)^{-\frac{3}{2}} \exp\left(-\frac{r^2}{2\sigma^2}\right) \quad (3)$$

is the isotropic 3D Gaussian (FWHM = 2.35σ). A more detailed explanation of d_{FWHM} calculation and a comparison with measured data can be found in Ref. 28.

We hypothesized that the d_{FWHM} should scale proportionally with the spatial resolution obtained in a reconstructed image (with proportionality depending on the image reconstruction and filtering processes, among other factors). We investigated the relationship using the correlation between the image-based spatial resolution and d_{FWHM} : two LOR estimates (3D- and 2D-COM) and three different detector crystal thicknesses (5/10/15 mm) were included.

2.2.2 Scanner efficiency

Scanner efficiency was defined as the ratio of the number of accepted events into reconstruction over the number of decays in the phantom. As a first approach to test out our reconstruction algorithms, we used an energy threshold of 510 keV to filter out the scattered events, effectively simulating perfect scatter correction. This gave us a lower bound on the scanner efficiency for different crystal thicknesses.

2.2.3 Relative contrast recovery coefficient

We studied the quantitative precision and accuracy of reconstructed images using the iterative ML-EM algorithm. The relative contrast RC was calculated as

$$(\text{RC}_{\text{mean}})_{k,r} = \frac{\text{TBR}_{\text{image}}}{\text{TBR}_{\text{phantom}}} = \frac{(\text{VOI}_{\text{mean}})_{k,r}/(\text{VOI}_{\text{bkgd}})_r}{\text{TBR}_{\text{phantom}}}, \quad (4)$$

where k indicates the sphere index, $r = 1, \dots, 20$ is the independent realizations of simulation, VOI_{mean} is the mean voxel value within the target (i.e., sphere) VOI, VOI_{bkgd} is the background mean, and $\text{TBR}_{\text{phantom}}$ is the true target-to-background contrast in the phantom object (fixed at either 5:1 or 4:1). The sphere VOI used the same voxels as the sphere voxels in the phantom. The background mean (VOI_{bkgd}) was obtained by averaging nine background spherical samples of the same VOI size as the target spheres (Fig. 2).

RC_{max} was calculated similarly as RC_{mean} , only with VOI_{mean} replaced by VOI_{max} . VOI_{max} is the maximum voxel value within the VOI.

For each configuration of phantom and crystal thickness, we average the $\text{RC}_{k,r}$ across sphere indices k and realization indices r to get the mean. We calculated the associated uncertainty in RC using the ensemble root mean square error (ERMSE) with the following definition:

$$\text{ERMSE} = \frac{1}{K} \sum_{k=1}^K \text{RMSE}_k, \quad (5)$$

$$\text{RMSE}_k = \sqrt{\frac{\sum_{r=1}^R (\text{RC}_{k,r} - \overline{\text{RC}}_k)^2}{R-1}}, \quad (6)$$

$$\overline{\text{RC}}_k = \frac{1}{R} \sum_{r=1}^R \text{RC}_{k,r}, \quad (7)$$

where again k and r are the sphere and realization indices, respectively. $\overline{\text{RC}}_k$ is the average RC of lesion k among 20 realizations. RC can be either RC_{mean} or RC_{max} .

2.3 Sensitivity and Specificity of Detecting Changes in Sphere Uptake

We investigated the sensitivity (i.e., true positive rate) and specificity (1-false positive rate) of detecting a change in TBR and performed an ROC analysis for detecting such change. We simulated cases of a pretherapy TBR of 5:1 and a posttherapy TBR of 4:1 and calculated associated RC means and variances (ERMSE). Based on the two end point TBR values, we interpolated the RC mean and variance for any intermediate posttherapy TBR value. Using RC_{mean} and ERMSE in an ROC analysis, we estimated the sensitivity and specificity of measuring TBR changes, which is the ultimate clinical task intended for PET/X. We then plotted the sensitivity as a function of TBR drop, given several specificity cutoffs. We also computed the ROC curve for several posttherapy TBR values. The associated areas under the curve (AUCs) were computed.

3 Results

3.1 Spatial Resolution and d_{FWHM}

Figure 3 shows the correlation between image spatial resolution and the DCA resolution surrogate d_{FWHM} for various detector crystal thicknesses. The correlation was very high with a Pearson correlation coefficient of 0.9167.

The 2D-COM resolution showed a larger variation with respect to the crystal thickness. The first vertex LOR estimate (representing perfect LORs) was not included, because d_{FWHM} was effectively 0, as positron range, noncollinearity effects, and detector point spread function were not modeled.

3.2 Scanner Efficiency

The scanner efficiency (Fig. 4) for true (unscattered) coincidences ranged from 2% to 18.2% as the crystal thickness increased from 5 to 40 mm. With thinner crystals, the dependency was approximately linear.

Fig. 3 Scatterplot showing the correlation between the image spatial resolution using PFDRX reconstruction (vertical axis) and d_{FWHM} derived from DCA method (horizontal axis). Each data point represents one of the 10 point sources in the phantom for a given detector crystal thickness and LOR estimate method. The phantom consisted of analytical point sources in a uniform background.

Fig. 4 Scanner efficiency as a function of crystal thickness for the rectangular geometry of Fig. 1. LSO was used as the scintillator material. Events that were scattered in the object and events that were scattered in the crystals and eventually escaped were both rejected by an energy threshold of 510 keV.

3.3 Contrast Recovery Coefficient

3.3.1 Sample reconstructed image

Figure 5 shows three sample images of the 5-mm diameter spheres using first vertex, 3D-COM, and 2D-COM LOR estimations [Figs. 5(a)–5(c)]. All three images were adjusted to the same gray scale. It was visually clear that the RC was the best with first vertex and worst with 2D-COM. Minor artifact could be observed in the near-chest wall region in the 2D-COM images, possibly due to the lack of DOI and unoptimized normalization. In the analyses that follow, RC values were averaged across the six interior spheres, away from the chest wall.

3.3.2 Postreconstruction smoothing

Postreconstruction processing and image regularization have yet to be optimized for this system. We applied varying degrees of 3D-Gaussian smoothing to the image containing the 40-mm diameter hot sphere. The smoothing curbed the divergence of VOI_{max} as a function of iteration number and had little effect on VOI_{mean} . Based on this exploration, we applied smoothing with standard deviation (σ) = 0.8 mm for subsequent analyses of RC.

3.3.3 Contrast recovery coefficient as a function of lesion size or crystal thickness

Figure 6 plots RC as a function of sphere size (a) or detector crystal thickness (b), with the error bars representing the ERMSE [Eq. (5)].

On the left: The RC difference between 3D- and 2D-COM (DOI versus no DOI) was more significant with smaller spheres. Also, note that the error bars were smaller for larger spheres for all three LOR estimation methods.

On the right: With first vertex LORs, RC was essentially independent of detector thickness as expected. However, with 3D- and 2D-COM, thicker detectors led to lower RCs. In particular, the RC difference between 3D- and 2D-COM was larger for thicker crystals. It was also important to point out that the error bars were smaller with thicker crystals, albeit with lower RC values.

Fig. 5 Orthogonal views of sample reconstructed images using the iterative algorithm (top row is PET/X axial cross-section at the anterior-posterior center, cf. Fig. 2). (a)–(c) The LOR estimation methods were first vertex, 3D-, and 2D-COM. All images shared the same gray scale. Sphere diameter was 5 mm and crystal thickness was 10 mm. Image voxel size was 1 mm. Iteration number was 15. No Gaussian smoothing was applied in this image.

Fig. 6 (a) RCs for various sphere sizes with crystal thickness of 10 mm. Both RC_{max} and RC_{mean} were plotted. (b) RCs with various crystal thicknesses for both lesion sizes of 10 and 5 mm. Only RC_{mean} values were shown. (a) and (b) All three LOR estimate methods were included. The error bars represented ERMSE. Each image was treated with a postreconstruction Gaussian smoothing with $\sigma = 0.8$ mm as mentioned previously.

3.3.4 Recovery coefficient variance

Table 1 shows the ratio of ERMSE to mean of the RCs for cases of 5/10-mm crystals and 5/10-mm spheres. The values outside parenthesis were calculated using RC_{mean} and inside using RC_{max} . In each configuration, we simulated both TBRs (5:1 and 4:1) independently. The ERMSE ratio ranged from less than 1% to 6% depending on the configuration of crystal thickness and sphere size. In all configurations, the results were similar between 2D- and 3D-COM.

3.4 Sensitivity and Specificity of Detecting Changes in Sphere Uptake

Results from the ROC analysis are shown in Fig. 7. We found essentially equivalent results when using either RC [Eq. (4)] or just the sphere VOI data ($VOI_{mean/max}$) as the radiotracer uptake metric. The radiotracer uptake metric used clinically, SUV, is based on data from an image region of interest without regard to the local background or true contrast. Our results were similar for sphere VOI and RC because in our case, the background

Table 1 Ratio of ERMSE/global mean of the recovery coefficients (all units are %).^a

Crystal thickness	5-mm sphere		10-mm sphere	
	2D-COM	3D-COM	2D-COM	3D-COM
TBR = 5				
5 mm	5.33 (8.03)	5.49 (8.72)	1.55 (4.10)	1.51 (4.18)
10 mm	2.85 (4.57)	2.81 (4.41)	0.74 (2.68)	0.72 (2.29)
TBR = 4				
5 mm	5.42 (8.18)	5.90 (9.03)	1.72 (4.64)	1.66 (4.60)
10 mm	2.98 (4.58)	3.03 (4.68)	0.92 (3.12)	0.88 (2.35)

^aThe percentages outside of the parentheses were calculated using RC_{mean} , and those inside using RC_{max} .

VOI data were very stable (i.e., low and consistent variance in all cases).

Figure 7(a) shows the sensitivity for detecting a change in TBR as a function of the reduction in true TBR. The results show that 95% sensitivity (horizontal dashed line) can be achieved for a true TBR reduction of ~13% to 18%, with a corresponding specificity of 80% to 95%, respectively. Figure 7(b) shows the calculated ROC curves. The AUC of a TBR change of -20% was over 99%. For the other scanner designs and sphere sizes in this study, the AUCs of a -10% TBR change are given in Table 2. Again, the values outside parenthesis were calculated with RC_{mean} and inside were with RC_{max} .

4 Discussion

In this paper, we present a preliminary analysis of how scanner crystal thickness and DOI information affects the ability of the proposed rectangular PET/X to accurately measure changes in radiotracer uptake. We used image reconstruction algorithms recently customized to the rectangular scanner geometry and multiple independent statistical realizations to investigate metrics aimed at characterizing the ability to reliably measure changes in tracer uptake in target lesions. The results indicated that, for fixed scan time, thicker crystals were beneficial to the system's ability to detect changes in lesion uptake (Table 2), despite the associated loss of spatial resolution and contrast recovery due to the thicker crystals [Figs. 3 and 6(b)]. The benefits stem from reduced image noise (lower variances, Table 1) achieved through the greater detector efficiency of thicker crystals. Improvements to spatial resolution using DOI information did not have a substantial impact on the ability to detect changes in radiotracer uptake.

Spatial resolution followed the expected trend of increasing (i.e., worsening) for thicker crystals and improving with the use of DOI information. Notably, thicker crystals also led to more spatial resolution variation throughout the scanner FOV.

It is important to note the idealized conditions of the simulations when assessing these results. Our goal was to establish the feasibility of quantitative precision for the rectangular scanner and customized image reconstruction algorithms. This paper represents a further, albeit still intermediate, assessment of these reconstruction approaches. We also examined fundamental improvements provided by near-ideal DOI information.

Fig. 7 (a) Sensitivity as a function of reduction in TBR from a pretherapy value of 5:1. Each curve corresponds to one of four specificity values. (b) ROC curve for four TBR reductions: -20%, -15%, -10%, and -5%. Both plots were computed with the data set of sphere diameter of 5 mm and crystal thickness of 10 mm. The LOR estimation method was 2D-COM (without DOI).

Table 2 AUCs of various configurations of crystal thickness, sphere size, and LOR estimate method^a (in each AUC analysis, $\Delta\text{TBR} = -10\%$).

Crystal thickness	5-mm sphere		10-mm sphere	
	2D-COM	3D-COM	2D-COM	3D-COM
5 mm	0.7927 (0.7473)	0.7953 (0.7404)	0.9995 (0.9049)	0.9997 (0.8988)
10 mm	0.8987 (0.8364)	0.9342 (0.8847)	1.0000 (0.9772)	1.0000 (0.9913)

^aThe AUCs outside of the parentheses were calculated using RC_{mean} , and those inside using RC_{max} .

The unconventional scanner geometry contributed to our motivation to study performance at a basic level.

Following our earlier work,²⁸ we studied a potential spatial-resolution surrogate [d_{FWHM} , Eq. (1)] that is calculated from list-mode (or sinogram) data, independent of an image reconstruction method. Such a metric would have utility in scanner design optimization by allowing assessment of intrinsic spatial resolution trends without the need for image reconstruction, whose properties may influence the resolution taken from images. We found a strong correlation between d_{FWHM} and 2D-COM (no DOI) image FWHM (Fig. 3). However, while the d_{FWHM} metric using 3D-COM data (with DOI) was also sensitive to changes in crystal thickness, spatial resolution from images reconstructed using 3D-COM LOR estimates was not (Fig. 3). Thicker crystals allow a wider distribution of event interaction positions, which will affect d_{FWHM} in the manner observed. The DOI information used for this study was idealized in which we did not model finite DOI resolution. As such, the DOI estimates in 3D-COM data could act as ideal DOI data from which one would not expect to see variations in image FWHM as a function of crystal thickness.

Testing the AC process was part of this initial test of the new image reconstruction algorithm for the PET/X geometry. We used the known, true AC maps with a goal of validating the

AC process (with the test phantom of a 40-mm sphere, full contrast recovery of $\text{RC} = 1$ was obtained, indicating effective AC.) The ultimate goal is to couple PET/X to an x-ray mammography/tomosynthesis system, which will provide data from which a spatially variant AC map could be estimated. At this stage, we are not in a position to speculate on the quality of measured AC data, and further details of AC approaches are beyond the scope of what was studied here.

Sphere size has an apparent influence on the RC value. For smaller spheres, RC values among the three LOR estimation methods were ordered as expected: first vertex was the highest, followed by 3D-COM, and finally 2D-COM. The impact of the partial volume effect is seen in Fig. 6(a).

Crystal thickness was one of the design questions we investigated in this simulation study. Thicker crystals yielded lower mean activity RC [Fig. 6(b)]. The degradation was greater when no DOI information was available (2D-COM versus 3D-COM), likely due to a relatively high percentage of oblique LORs in the rectangular FOV geometry. It should be pointed out that, in evaluating the scanner's ability to detect change between two scans, both the mean and variance of RC matter. As shown in Fig. 6(b), thicker crystals led to a lower RC but also lower variance, presenting a potential trade-off between accuracy and precision. We suspected that the lower variance from thicker crystals was due to higher scanner efficiency (Fig. 4), which resulted in higher counts per scan for the fixed scan time that we simulated.

This analysis omitted several important physical phenomena (scattered photons, positron range, and detector point-spread-function). Detailed effects of optical photon transport were not included in the event-positioning modeling. Our lab has investigated spatial response functions for monolithic crystals,^{31,32} which can have advantages over pixelated crystal detectors. Modeling the performance of monolithic crystal detectors requires more consideration of optical photon transport than does modeling pixelated detector response. The first prototype PET/X scanner has been constructed using pixelated scintillator detector blocks, with a 20×20 matrix of 2-mm crystals resolved by a 12×12 array of 3-mm SiPM's. Although idealized in several ways, the event-positioning model used here should

be a good first-order model of the positioning in these first prototype PET/X blocks.

Detector energy resolution was not modeled so that we could study scatter-free coincidence events by setting the energy cutoff at 510 keV. From parallel work on detector hardware development, however, we estimate that the energy resolution will be approximately 18% at 511 keV. If this is the case, then using a lower energy threshold around 400 keV would result in the detection of the great majority of true coincidences for which both annihilation photons deposit 511 keV in the detectors, as well as many where one or both photons escape after scattering one or more times, as shown by Lewellen et al.³³ This energy threshold would also result in the detection of undesirable scattered coincidences, thus reducing the effective count rate. Thus, the overall impact on the effective count-rate is not clear, and there is very little published literature on this specific question. Levin et al.³⁴ showed that for energy resolutions of 3% for cadmium zinc telluride and 12% for LSO, the peak effective count-rate did not change appreciably when the energy threshold was optimized for each material. We note that there were multiple changes for the very different detector systems, such as photo-fraction and timing resolution, etc., so the results of Levin et al. and Lewellen et al. may not apply in our situation. Nonetheless, we believe that while there may be some loss in effective sensitivity with a typical energy resolution, it will be a small enough decrease to not impact our conclusions. We anticipate acquiring measured data to study this effect empirically.

In this study, we did not perform a systematic evaluation of how performance metrics (spatial resolution, RC) varied within the PET/X rectangular FOV. We note however that some variation was observed at the FOV axial edge (e.g., image slices parallel to and near to the patient chest wall) where coincidence event sampling is reduced and reconstruction normalization has yet to be optimized. Variations within the interior FOV were encompassed by the calculation of ERMSE.

Under the idealized conditions mentioned above, the PET/X system easily met our initial target performance of < 5% type-1 error when measuring 20% TBR changes in 5-mm spheres. This is a promising indication that the PET/X scanner has the potential for measuring TBR changes that may prove clinically useful, even after including the omitted physical effects that will likely degrade the results found here.

As a starting point, this analysis used idealized data to demonstrate the feasibility of reaching the goals for the PET/X scanner. It also established a viable framework to quantitatively evaluate the scanner performance for phantom scans. The analyses will be carried forward in the future by introducing more accurate data modeling and ultimately using measured PET/X scanner data. Based on these results, we expect the PET/X scanner to meet clinical requirements even when more realistic features are incorporated. Sensitivity and specificity data (Fig. 7) measured on the scanner from phantom imaging will be useful for designing clinical trials that use PET to monitor therapy response.

5 Conclusion

For the PET/X design parameters and clinical goals studied here, thicker crystals (≥ 10 mm) provided an advantage in image noise that outweighed associated disadvantages in spatial resolution and RCs. This advantage assumed a fixed scan duration for which thicker crystals provided higher image data

counts through the higher efficiency for annihilation photon absorption relative to the thinner comparators. Including idealized DOI information did not substantially improve AUC in the ROC analysis.

The results of this work represent best-case scenarios for identifying changes in radiotracer uptake using the proposed rectangular PET/X scanner and the current version of image reconstruction algorithm; perfect correction for attenuation, scatter, and normalizations are assumed, and positron range was not included. It is encouraging that the sensitivity was >95% (for 95% specificity) and AUC was over 0.995 for the task of measuring a 20% change in tracer uptake in a 5-mm lesion, which was the initial, prospective goal of the PET/X scanner. While image quality degradations due to the neglected physical effects will reduce the statistical power, this work establishes a performance bound on which to base future studies that introduce additional physical effects.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

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Chengeng Zeng received his BS degree in physics and minor in mathematics from Denison University in Granville, Ohio, USA. He is a PhD student from the Physics Department, University of Washington. His PhD work involves simulation and system development of the PET/X scanner. He is interested in pursuing machine learning and data science related topics after the PhD program.

Paul E. Kinahan received his BASc and MASc degrees in engineering physics from the University of British Columbia and his PhD in bioengineering in 1994 from the University of Pennsylvania. He is a professor and vice chair for research in the Department of Radiology, University of Washington, with joint appointments in physics, radiation oncology, and bioengineering. He is a director of UWMC PET/CT imaging physics and head of the Imaging Research Laboratory.

Hua Qian received his PhD in physics from the University of Melbourne, Australia, in 1996. He was a postdoc at Brandeis University from 1996 to 1998 and a research associate at Robarts Research Institute, Canada, from 1998 to 2002. He joined GE in 2003 and he is now a senior scientist at GE Global Research Center, USA. His research interests include PET system simulation, design, data correction, and image reconstruction.

Robert L. Harrison has been working on the development and use of the simulation system for emission tomography (SimSET) photon-tracking simulation package for over 30 years. His current research has two main foci: development of improved importance sampling (statistical techniques that significantly improve computational efficiency) for SimSET and application of virtual clinical trials (a series of linked simulations covering all steps of image generation and assessment) to improve nuclear medicine research and practice.

Kyle M. Champley received his MS degree in mathematics from Oregon State University and his MS and PhD degree in electrical engineering from the University of Washington in 2010. He is a research scientist in the Nondestructive Characterization Institute at the Lawrence Livermore National Laboratory.

Lawrence R. MacDonald received his PhD in physics from the University of California, Los Angeles. He is a research associate professor in the Department of Radiology, University of Washington. His areas of research involve high-resolution nuclear medicine technologies and applications. He has experience in academia and industry developing preclinical and application-specific single-photon emission computed tomography, PET, and imaging probe systems. His current research focuses on the use of PET imaging as a quantitative biomarker of disease.