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Applications of the line-of-response probability density function resolution model in PET list mode reconstruction

Y Jian¹, R Yao², T Mulnix³, X Jin¹, and R E Carson^{1,3}

¹ Department of Biomedical Engineering, Yale University, New Haven, CT USA

² Department of Nuclear Medicine, University at Buffalo, SUNY, Buffalo, NY USA

³ Department of Diagnostic Radiology, Yale University, New Haven, CT USA

Abstract

Resolution degradation in PET image reconstruction can be caused by inaccurate modeling of the physical factors in the acquisition process. Resolution modeling (RM) is a common technique that takes into account the resolution degrading factors in the system matrix. Our previous work has introduced a probability density function (PDF) method of deriving the resolution kernels from Monte Carlo simulation and parameterizing the LORs to reduce the number of kernels needed for image reconstruction. In addition, LOR-PDF allows different PDFs to be applied to LORs from different crystal layer pairs of the HRRT. In this study, a thorough test was performed with this new model (LOR-PDF) applied to two PET scanners - the HRRT and Focus-220. A more uniform resolution distribution was observed in point source reconstructions by replacing the spatially-invariant kernels with the spatially-variant LOR-PDF. Specifically, from the center to the edge of radial field of view (FOV) of the HRRT, the measured in-plane FWHMs of point sources in a warm background varied slightly from 1.7 mm to 1.9 mm in LOR-PDF reconstructions. In Minihot and contrast phantom reconstructions, LOR-PDF resulted in up to 9% higher contrast at any given noise level than image-space resolution model. LOR-PDF also has the advantage in performing crystal-layer-dependent resolution modeling. The contrast improvement by using LOR-PDF was verified statistically by replicate reconstructions. In addition, [¹¹C]AFM rats imaged on the HRRT and [¹¹C]PHNO rats imaged on the Focus-220 were utilized to demonstrate the advantage of the new model. Higher contrast between high-uptake regions of only a few millimeter diameter and the background was observed in LOR-PDF reconstruction than in other methods.

Keywords

PET; Spatial resolution; Image reconstruction; resolution modeling

1. Introduction

Positron Emission tomography (PET) is a functional imaging modality that measures radioactivity distribution in vivo. Compared to the other medical imaging modalities, PET

has relatively low spatial resolution. For example, the spatial resolution is typically >1 mm for preclinical systems and 3-6 mm for clinical systems. The resolution of PET scanners is primarily determined by system specifications, such as detector type/size (Moses, 2011). In addition, spatial resolution degradation occurs as part of image reconstruction, particularly for filtered backprojection (FBP), which ignores a number of physical factors in coincidence detection. These resolution degrading factors include positron range, photon-pair non-collinearity, crystal penetration and inter-crystal scattering (Reader and Zaidi, 2007). Without sophisticated corrections for these effects, quantification accuracy is compromised in objects with size comparable to the intrinsic resolution of the system.

Resolution modeling (RM) is a common technique which takes into account the resolution degrading factors in the system matrix. The resolution-compensating component in the system matrix is known as the resolution kernel or point spread function (PSF). An accurate PSF model is spatially variant and of the same dimensions of the system matrix. Thus, obtaining the PSF for a modern PET scanner with a larger number of detection channels is a tedious task. Comprehensive efforts have been made to derive the PSF for image reconstruction during the past two decades. Some initial attempts focused on analytical derivation based on knowledge of positron emission and photon detection (Selivanov *et al.*, 2000; Rahmim *et al.*, 2008). For sinogram data with compressed projection space, it is also feasible to obtain the PSF experimentally by measuring the detection responses of a point source placed at different locations of the FOV (Panin *et al.*, 2006; Alessio *et al.*, 2010). Experimental measurement is usually more reliable than mathematical derivation, although it requires additional efforts to design and carry out the experiment. With the advance in computer hardware, Monte Carlo simulation provides the possibility to determine the PSF in a less laborious manner. Some researchers have incorporated simulated kernels into their image reconstruction algorithms and have shown promising results (Alessio *et al.*, 2006; Bataille *et al.*, 2004).

There are many different ways to define the resolution model. For example, the PSF can be explicitly modeled by decomposing the system matrix into the geometric projection and resolution kernel matrices. Depending the order of matrix decomposition, PSF can be described in either projection space (Panin *et al.*, 2006; Alessio *et al.*, 2006; Alessio *et al.*, 2010) or image space (Reader *et al.*, 2003; Sureau *et al.*, 2008; Kotasidis *et al.*, 2011; Angelis *et al.*, 2012). Alternatively, as the coincidence detection data are represented by lines of response (LOR) that connect a pair of detector, it is straightforward to expand the narrow LORs to tubes of response (TORs) that more accurately reflect the spatial uncertainty about the origin of the positron (Pratx *et al.*, 2009; Aguiar *et al.*, 2010). The resolution modeling techniques in the aforementioned literature typically were developed based on sophisticated models with multi-dimensional parameter spaces. Due to the large number of LORs, deriving the PSF in list-mode-based reconstruction is more difficult than that of sinogram reconstruction. The computational burden of the TOR model for event-by-event list mode reconstruction was previously discussed in (Pratx *et al.*, 2009). The image-space PSF, which is essentially a set of filters applied to the intermediate images in the iteration process, was proposed and tested in (Reader *et al.*, 2003; Sureau *et al.*, 2008). More recently, spatially-variant image-space models were derived by measuring the response function of reconstructed point sources arrays (Kotasidis *et al.*, 2011; Angelis *et al.*, 2012). However, the

two types of decomposition are not analytically equivalent, i.e., an exact image-space system matrix does not always exist, as discussed in (Cloquet *et al.*, 2010). In addition, an approximate image-space matrix amplifies image noise (Rahmim *et al.*, 2013).

In our previous work (Yao *et al.*, 2012), we have proposed a TOR-based resolution model derived from Monte Carlo simulation. This new model, denoted as the LOR-based probability density function (LOR-PDF), features the parameterization of the LOR spatial locations, grouping of LORs based on their spatial parameters, a spatially-variant response function along the LOR, and pre-stored kernels. To fully test the proposed model, we extended our methodology in system matrix simulation and implementation to list-mode reconstruction for two PET scanners: the HRRT and Focus-220 (Siemens Preclinical Solutions Knoxville, TN).

In this paper, a brief overview of our list mode reconstruction method is provided in Sec. 2, followed by a detailed description of the LOR-PDF model in Sec. 3, which includes the Monte Carlo simulation (Sec. 3.3) for LOR-PDF generation and point source measurements to validate the simulated results (Sec. 3.4). The design of experiments to test the new model is elaborated in Sec. 4, including phantom (Sec 4.1-4.3) and rat (Sec. 4.4) reconstructions. This is followed by the qualitative and quantitative comparisons of the reconstructed results between LOR-PDF and other resolution models (Sec 5). The discussion is given in Sec. 6.

2. Theory

PET measurements comprise a vector of Poisson random variables representing the number of coincidence events detected by pairs of detectors. The system model, from statistical point of view, is:

$$E[Y_i] = T \left(L_i A_i N_i \sum_{j=1}^J c_{i,j} \lambda_j + R_i + S_i \right), \quad i=1, \dots, I \quad (1)$$

where Y_i is the measured counts in a sinogram bin or line of response (LOR) i , λ_j is the radioactivity concentration (Bq/mL) at voxel j , and $c_{i,j}$ is a non-negative system constant representing the contribution of voxel j to LOR i . Note that the matrix representation $C \in \mathbb{R}^{I \times J}$ is usually used to characterize the system response of the entire tomograph. The definitions of the terms in (1) are given in Table 1. Statistics-based image reconstruction in principle aims at estimating the images of spatial activity distribution through maximizing the Poisson likelihood functions of up to I measurements with the aid of iterative numerical algorithms.

As a PET image reconstruction platform, MOLAR (the motion-compensation OSEM list-mode algorithm for resolution-recovery reconstruction) has been developed and applied to the HRRT (Carson *et al.*, 2003) and the Focus-220 (Jin *et al.*, 2014). The iterative reconstruction formula of MOLAR, an OP-OSEM algorithm, is written as:

$$\lambda_j^{(n+1)} = \frac{\lambda_j^n}{Q_j} \sum_{k=1}^K \frac{c_{k,j} L_k A_k N_k}{T \left(\sum_{j'} c_{k,j'} L_k A_k N_k \lambda_{j'}^{(n)} + R_k + S_k \right)} \quad (2)$$

where L , A , N , R and S are system correction factors defined in Table 1. Q in Eq (2) is the voxel-dependent sensitivity including effects of normalization, attenuation and motion. MOLAR performs list-mode reconstruction that intrinsically allows event-by-event motion correction. A computer cluster implementation is used to accelerate the reconstruction process. In this study, we focus on exploring the potential benefits of accurate system matrix with a LOR-based resolution model in MOLAR.

3. LOR-PDF framework

3.1 LOR PDF definition

The LOR-PDF proposed in our previous work (Yao *et al.*, 2012; Jian *et al.*, 2011) consists of multi-dimensional spatially-dependent resolution kernels that represent the detection probabilities of a local region of emission source by a given LOR. The rationale behind LOR-PDF is that due to resolution degradation factors, the detection probability depends on the LOR position in the scanner and the relative position of the emission points with respect to the corresponding LOR. Specifically, LOR position is characterized by four reference-frame parameters: detector layer pair (l), panel difference (p) between the starting- and ending-sides of a LOR, and in-plane (ϕ) and axial (θ) incident angles of the starting-side of the LOR. The reference frame is defined by rotating one end (starting-side) of the LOR to the bottom position of the scanner (Yao *et al.*, 2012). This facilitates the utilization of LOR in-plane symmetry to reduce the size of LOR-PDF. In addition, the resolution kernels, referred to as PDFs, are 2D point spread functions with in-plane (r) and axial (u) indices and located at a depth positions (d) along the LOR. All PDFs are aligned with image voxels (figure 1). This avoids the process of projecting the PDFs onto the voxel planes during image reconstruction and thus reduces the computational burden. Therefore, the LOR-PDF is written as a seven-dimensional model

$$c_{i,j} = P(r_{i,j}, u_{i,j}, d_{i,j}; l_i, p_i, \phi_i, \theta_i), \quad (r_{i,j}, u_{i,j}, d_{i,j}) \in V_i \quad (3)$$

where V_i is a local region containing voxels having non-zero contribution to LOR i . Each dimension in (3) contains a limited number of segments. To further reduce the size of LOR-PDF, the response functions of those LORs within a range of spatial parameters are grouped into the closest segment. The number of segments stored in each dimension is scanner-specific. Our hypothesis is that with appropriate spatial parameters and sampling, it is possible to manipulate a reasonable amount of PDFs in both LOR-PDF simulation and image reconstruction without reducing the accuracy of the resolution model. In this study, we first simulated the LOR-PDF for the HRRT and Focus-220 scanners, and empirically determined the number of values (segments) for each parameter to ensure that the difference in full width at half maximum (FWHM) of the PDFs between any two adjacent segments is less than 5%. The number of segments and the range of each segment for the LOR-PDF parameters for both HRRT and Focus-220 are provided in Table 2.

LOR-PDF is explicitly incorporated in MOLAR as a wide-band projection operator where the projection weight of voxels is determined by sampling the voxel-to-LOR distance of a PDF that matches the LOR. Note that the LOR-PDFs are pre-stored, but projection weights are computed on-the-fly in the reconstruction. The LOR-PDF approach is also important in this application because the relative positions of voxels and projection lines move with motion, so the system matrix must support a continuous representation of this relationship.

3.2 LOR PDF derivation from Monte Carlo simulation

Monte Carlo simulation with GATE (Jan *et al.*, 2004) was used to derive the LOR-PDF. Our previous study has shown that Monte Carlo simulation is an effective approach to generate the LOR-PDF for the Focus-120 (Yao *et al.*, 2012). GATE simulates the photon propagation process including the major resolution degrading factors, such as positron range, photon-pair non-collinearity, crystal penetration and inter-crystal scatter. The cumulative energy signal generated from the photon interaction in the scintillation crystal is read out, and the “crosstalk” between neighboring crystals and layer-dependent efficiency (HRRT only) are also included. One critical factor that could not be accurately modeled in our simulation is the quadrant-share photomultiplier design, which potentially leads to some position misidentification and resolution degradation (see Sec. 3.3).

LOR-PDFs were simulated for the HRRT and Focus-220. During the simulation, “coincident events” were collected from a cylindrical emission source placed in the entire FOV of the virtual scanner. Derivation of the LOR-PDF is feasible where the origins of the positron emission are known. However, the emission positions can also be estimated to some degree in real measurements with point sources (see Sec. 3.3). The LOR-PDF, in principle, can be obtained by binning events into the 7-dimensional PDF table (Eq (3)), so long as there are sufficient statistics.

There is flexibility in simulating multiple versions of LOR-PDF to accommodate the different positron ranges of isotopes in image reconstruction, as described in (Yao *et al.*, 2012). In our GATE simulations, ^{11}C , a common isotope for human brain studies, was used. For other isotopes, the mismatch of positron range can be approximately fixed by post-processing (see Sec. 5). The emission phantom is scanner-dependent in size so as to acquire the complete LOR-PDF. Although the imaging objects usually only cover a portion of the central FOV, one of the goals of this work is to improve the uniformity of resolution by incorporating LOR-PDF for the entire FOV, and thus PDFs corresponding to detector response throughout FOV are needed. Computation time increases dramatically with scatter and random coincidences included in the GATE simulation, so a computer cluster was used for the computations. The settings of the simulation are summarized in Table 3.

Simulated events were binned into the appropriate segments of the PDF based on the reference position of each LOR ($I_i, p_i, \varphi_i, \theta_i$) and relative displacement of the source voxel from the LOR ($r_{i,j}, u_{i,j}, d_{i,j}$), as in Eq (3). However, this binning method can only recover PDF shape, while the relative scales of different PDFs are inaccurate due to the fact the elements in the PDF are not uniformly sampled by the acquisition process. This issue was resolved by the following PDF normalization procedures: 1) each 2D PDF was normalized

by the total counts so it summed to 1, and 2) depth-dependent solid angle correction factors were applied to the PDFs to account for this sensitivity variation (Rodriguez *et al.*, 2007).

3.3 LOR PDF validation

GATE simulations for the HRRT have been shown to have better spatial resolution than the actual scanner (Bataille *et al.*, 2004). This is presumably due to the inaccurate modeling of the quadrant-sharing photomultiplier component in simulation. Therefore, experimental measurements of PDFs with point source scans were conducted to verify the simulation results.

For the HRRT, a point source set of three Lucite-embedded ^{22}Na sources (30 μCi , 0.25 mm in diameter, denoted PSS hereafter), were fixed to a rotatable arm attached to the patient bed. The PSS was used, rather than a single source, to accelerate the measurement. The goal of this experiment was to validate the simulated LOR-PDF, therefore, only coarse displacements of PSS were required within the FOV. As shown in figure 2, the PSS was first aligned with the center of the FOV horizontally (5 mm, 75 mm and 145 mm in radial offset for three points respectively), and then moved along with the bed vertically (0 to 145 mm) and axially (0 to 120 mm) from the center of FOV to the edge with a 5-mm interval between two adjacent positions. This led to 750 scans (5 min per scan) and 2250 positions (3 positions per scan with the PSS) covering one quadrant of the scanner's FOV.

Two conditions are necessary to ensure the PDF measurements are accurate. First, the source size (0.25 mm) should be negligible compared to the PDF size (1-3 mm in FWHM). The maximum intrinsic error due to source size is about half of the diameter (0.12 mm). Second, the source positions must be known or estimated very accurately. In this experiment, the positions were estimated from a preliminary reconstruction. The center of mass (*CoM*) of each source was estimated from reconstructed images, as follow:

1. PSS images were reconstructed using fine voxels ($0.3 \times 0.3 \times 0.3$ mm) with a 2.5 mm isotropic Gaussian function as the resolution model. The Cartesian coordinates (x' , y' , z') of the point sources were obtained by calculating the *CoM* within the neighborhood ($10 \times 10 \times 10$ voxels) of the points.
2. For each event in each PSS scan, calculated the reference position (l , b , ϕ , θ) of the LOR; converted (x' , y' , z') into LOR-specific coordinates (r , u , d). This event was then binned into the corresponding LOR-PDF segment (r , u , d , l , p , ϕ , θ). Note that a small number of events (<1%) must be discarded if the LOR intersects more than one source.
3. As there was non-uniform sensitivity across segments in detection space, the obtained counts in each segment were scaled to eliminate the spatial sampling heterogeneity. The scaling factors, with the same dimensions as LOR-PDF, were calculated by back-projecting one event in each LOR to LOR-PDF space (r , u , d , l , p , ϕ , θ).
4. Repeat 1-3 by using the updated LOR-PDF in PSS reconstructions in step 1.

As this method relies on accuracy in estimating the *CoM* of the point sources, the iteration in step 4 was expected to improve the *CoM* estimation. When comparing the *CoM* values obtained from LOR- PDF reconstructions (step 4) with those from iso-Gaussian PDF reconstructions (step 3), we found that there was only minor variation (0.12 ± 0.07 mm) for 240 points close to the radial center, with slightly higher variation (0.27 ± 0.16 mm) for 140 points in the periphery, indicating that the estimation from the first iteration may be accurate enough.

For the Focus-220, a similar procedure was repeated for point source measurements. A single point source was first scanned in the center of the FOV and moved with the bed in three directions sequentially. The horizontal, vertical and axial ranges were 0-90 mm, 0-20 mm and 0-36 mm respectively. The interval between any two consecutive scan positions was 5 mm. Subsequently, the LOR-PDF for the Focus-220 was created by binning the measured events into the model.

3.4 LOR PDF characterization

Similar to full width at half maximum (*FWHM*) for characterizing one dimensional PSFs, we report two measures, $FWHM_{min}$ and $FWHM_{max}$, representing the maximum and minimum values of *FWHM* in two dimensional PDFs. These were calculated as follows:

1. Find the index of the bin (i_{max}) in each PDF (*r-u* table) with the maximum intensity (v_{max}), (usually the bin at the center of the table).
2. Sort all the bins of the 2D-PDF in ascending order of the distance (d_i) to i_{max} .
3. Pick the first bin m with a value smaller than half of the maximum value ($v_m < v_{max}/2$).
4. Pick the last bin n with a value greater than half of the maximum element ($v_n > v_{max}/2$).
5. $FWHM_{min}$ and $FWHM_{max}$ were the radial distances from bins m and n to i_{max} , respectively.

These *FWHM* measures were used to evaluate the dependency of PDF-shape on the spatial parameters, and to compare simulated and experimental LOR-PDFs. Accurate determination of $FWHM_{min}$ and $FWHM_{max}$ required spatial smoothness in the PDFs. This was guaranteed by using fine sampling (0.16 mm in the width of PDF elements) and high statistics (see Sec. 6) of PDFs in simulation.

3.5 Comparison with other resolution models

Image-space PSF (IM-PSF) (Reader *et al.*, 2003; Sureau *et al.*, 2008) is an alternative approach to perform resolution modeling for sinogram or list mode data. More recently, spatially-variant image kernels were measured from a printed point source array and applied to image reconstruction on two PET/CT scanners (Kotasidis *et al.*, 2011) and the HRRT (Angelis *et al.*, 2012). Following a similar procedure to that in (Kotasidis *et al.*, 2011), we generated spatially-variant image-space resolution kernels for the HRRT and the Focus-220 from the point source data measured in Sec. 3.4. First, the point source images were

reconstructed with a geometric projection operator that integrated over the tube connecting the pair of detector faces. This method was implemented in MOLAR and denoted as “no-PDF” hereafter. Second, a dual-Gaussian model (Kotasidis *et al.*, 2011) with 13 parameters (3 positioning and 3 FWHM parameters for each Gaussian, and one relative scaling parameter for two Gaussians) was utilized to fit the reconstructed points. The azimuthally-invariant property of resolution kernels was also verified as follows. For the HRRT as an example, 2250 point source positions in a quadrant of the transaxial FOV (see Sec. 3.3) were divided into 5 azimuthal-angle groups (i.e. 0° - 9° , 9° - 18° , 18° - 27° , 27° - 36° and 36° - 45°) and the average radial and tangential FWHMs were calculated within each group. The estimated radial / tangential FWHM values (mm) in these groups were $2.6 \pm 1.6 / 2.2 \pm 0.8$, $2.7 \pm 1.8 / 2.0 \pm 0.9$, $2.7 \pm 1.7 / 2.0 \pm 0.9$, $2.6 \pm 1.7 / 2.0 \pm 0.7$ and $2.6 \pm 1.6 / 2.1 \pm 0.8$, suggesting that the spatially-invariant property in azimuthal dimension. In addition, the axial invariant approximation validated in (Kotasidis *et al.*, 2011) was also applied to our model. Thus, the parameters in the dual-Gaussian function were modeled as the functions of only the radial position r of the point sources. The fitted parameters of the dual-Gaussian IM-PSF model are provided in Supplementary figure S1. IM-PSF was implemented in MOLAR by filtering the intermediate image with the spatially-variant kernels before forward projection and after backprojection (using the no-PDF projector) during each subset update.

In addition to the spatially-variant LOR-PDF and position-dependent IM-PSF, two other reconstructions were performed. In one case, we used an iso-Gaussian PDF model (IG-PDF), i.e., 2.5 mm (HRRT) and 1.5 mm (Focus-220) in *FWHM* for both r and u dimensions, with no dependence on depth along the LOR. Also, for the Focus-220, the manufacturer's MAP algorithm includes the modeling of detector response function for better resolution recovery. Iterations and subsets were matched to the MOLAR reconstruction and the hyperparameter β was set to 0.0001.

In summary, MOLAR reconstruction with various resolution models (no-PDF, IG-PDF, IM-PSF and LOR-PDF) were implemented for the HRRT and the Focus-220. With the availability of sinogram-based reconstruction in the manufacturer's software, we also included MAP reconstruction on the Focus-220 to compare with MOLAR. During image reconstruction, the same resolution model is used in both the Q calculation and the iterative forward/back projections.

4. Experiments

4.1 Point source

In-plane spatial resolution of the reconstruction was first evaluated with a ^{22}Na point source without background activity. The point source was scanned at difference radial positions in the scanners. On both scanners, a 10-min acquisition was performed at each static position of the point source and repeated by moving the source from the radial center towards the FOV edge (maximum radial offset: 19 cm for the HRRT and 9 cm for Focus-220) with an interval of 1 cm between points in two adjacent positions. About 2 million events were acquired at each position to guarantee high signal-to-noise ratio. Random events (less than 1%) were also taken into account during image reconstruction. We used 30 subsets and up to 10 iterations in OSEM for MOLAR reconstructions to maintain consistency with the

following experiments. To facilitate the estimation of *FWHM*, fine voxels of 0.3×0.3×0.3 mm were utilized in point source reconstructions. Resolution was characterized as radial, tangential and axial *FWHMs* obtained from fitting a 3D Gaussian function to the images.

Evaluating point sources in the presence of a warm-activity background is a more realistic approach to evaluate effective resolution, comparable to real studies. Therefore, we imaged three identical point sources suspended in a 20cm-diameter ¹⁸F-filled cylindrical phantom aligned axially in the HRRT. The true contrast between background and point source is ~ 1:500, based on a 30 μCi source with a size of 0.25 mm diameter. The phantom was scanned 11 times at different axial positions (from center to 10 cm off-center, a step of 1 cm). The radial offsets of the three point sources were always the same (10, 50, and 120 mm). Images were reconstructed from a total number of 50 million counts at each position, after which, *FWHMs* in three major directions of scanner coordinates were estimated from individual point source and then averaged over three different points within the same transaxial plane.

4.2 Minihot phantom

A further comparison was performed by imaging the Minihot phantom filled with 1 mCi ¹⁸F solution. Data acquisitions were performed with the phantom placed close to the edge of radial FOV, i.e., 16 cm and 6 cm off-center for the HRRT and Focus-220, respectively. High statistics are desirable to reduce the variation in resolution measurements. Therefore, at least 100 million prompt events were used for image reconstruction. LOR-PDF for the HRRT is designed to model crystal-layer-dependent resolution. We performed separate groups of reconstructions by selecting events belonging to specific layer pairs, i.e., only the front-front layer events or crossed-layer events. The crystal arrangement produces about threefold higher sensitivity in the front layer than in the back layer on the HRRT. To ensure a fair comparison between layer combinations, we kept the same number of events in three groups of reconstruction (all layer, front-front layer and crossed layer) by choosing the appropriate frame duration based on the sensitivity of layers. Note that back-back layers events only account for a small fraction of the total events (usually 1/16), so they were not analyzed.

To quantitatively evaluate the contrast properties of rods with various sizes in the phantom, we define the object contrast coefficient (*OCC*) between a group of hot rods and corresponding local background:

$$OCC^n = \frac{R_{hot}^n - R_{cold}^n}{R_{cold}^n} \times 100\% \quad (5)$$

where n is the OSEM iteration index, and R_{hot}^n and R_{cold}^n represent the average intensity in hot and cold ROIs, respectively, drawn on the targeted region. To place circular ROIs over the rods, the location of the center of the hot ROIs was estimated as the center of intensity (center of mass) from the voxels in the vicinity of the hot rods. The center of cold ROIs was located at the mid-points between two neighboring hot ROIs. All ROIs have the same physical dimensions as the actual rods. The average ROI value was calculated accounting for voxels at the boundary of each ROI, by weighting them based on the fraction of the voxel within the circles. *OCC* was calculated on groups of rods with different diameters. In addition, the coefficients of variation (COV) of the hot ROIs were calculated as

$$CoV^n = \frac{\sqrt{\sum_{i=1}^I (r_i^n - R_{hot}^n)^2 / n}}{R_{hot}^n} \times 100\% \quad (6)$$

where r_i^n is the mean intensity of i^{th} hot rod in the group.

To statistically compare *OCC* values from LOR-PDF to those from reconstructions with different resolution models, one-tailed paired t tests were performed. The original list mode data were sampled in an interleaved manner to generate 10 statistically equivalent and independent replicates for image reconstruction. Thus, 10 *OCC* values were obtained from 10 independently reconstructed images for each group of rods, after which p values were calculated based on two sets of *OCC* values (10 samples from LOR-PDF reconstruction and 10 samples from another resolution models) for different numbers of iterations (up to 10) and rods of different sizes. A p value < 0.05 designates a statistically higher *OCC* for LOR-PDF.

4.3 Contrast Phantom

To quantitatively compare contrast recovery at different noise levels, a cylindrical phantom of 20 cm diameter with two cylindrical inserts of 4 cm diameter was scanned in the HRRT. One insert and the background were filled with solutions of different activity concentrations (4:1) and the other insert was a cold reference region. Image reconstruction was performed from list mode data with ~300 million events. The contrast recovery coefficient (CRC) was calculated for hot and cold ROIs, as follows:

$$CRC_{hot} = \frac{R_{hot}/R_{bkg} - 1}{T_{hot}/T_{warm} - 1} \times 100\% \quad (7)$$

$$CRC_{cold} = \frac{R_{cold}}{R_{bkg}} \times 100\% \quad (8)$$

where R_{hot} , R_{cold} and R_{bkg} are the mean intensity values of voxels in hot, cold and background ROIs, and T_{hot}/T_{warm} is the true ratio of activity concentrations. Note that the hot and cold ROIs were drawn with the same diameter of two cylindrical inserts to include voxels that could potentially be affected by the partial volume effect. In addition, the coefficient of variation (*CoV*) was calculated as the fractional variability in mean values across 10 background ROIs.

4.4 [¹¹C]AFM and [¹¹C]PHNO studies

To validate the improvement in resolution uniformity in the FOV, we applied LOR-PDF in the reconstruction of multiple anesthetized rat studies. For the HRRT, three rats were positioned in tubes at about 10cm from radial center and were injected with 0.8 mCi [¹¹C]AFM a tracer that binds to serotonin transporters (SERT) (Naganawa *et al.*, 2013). For the Focus-220, two rats were positioned at 4.5 cm away from the radial center and were injected with 1.5 mCi [¹¹C]PHNO, a dopamine D₂/D₃ tracer. Thus, due to the separation of

the rats, none of the objects were placed in the center of the FOV. Reconstruction of both data sets with high statistics (10-60min post-injection) was performed with different resolution models. For the HRRT, LOR-PDF was compared primarily with IG-PDF and IM-PSF. For Focus-220, comparison was also conducted between MOLAR and the sinogram-based MAP from the manufacturer's software.

5. Results

5.1 LOR PDF simulation and validation

The characterization of LOR-PDF with inter-LOR (l, p, φ, θ) and intra-LOR (d, r, u) parameters is justified by the varying PDF shapes across segments of these parameters. For instance, comparison of HRRT PDFs belonging to three different segments of in-plane angle φ , axial angle θ and depth d are shown in figure 3(a), (b) and (c) respectively. In figure 3(a), the central PDF is circular, but the intensity is less concentrated in the PDF center and more widely distributed in the in-plane direction when φ progressively increases from left to right ($\varphi = 0^\circ, 15^\circ$ and 25°). A similar tendency is observed in the axial direction for three axial angles ($\theta = 0^\circ, 10^\circ, 17^\circ$) in figure 3(b). The variability of PDF shapes is consistent with the non-uniform system response caused by depth of interaction (DOI). Figure 3(c) demonstrates the variability of PDF shape from one end to the other for a LOR with asymmetric incident angles on two sides. A wider shape is observed for PDFs closer to the ends of the LOR compared to the ones in the middle segments.

We introduced two figures of merit, $FWHM_{max}$ and $FWHM_{min}$, to characterize the anisotropic shape of individual PDFs. The mean and standard deviation of $FWHMs$ calculated from specified groups of PDFs were calculated. Typical examples of the mean and standard deviation values calculated from PDFs in the same segment of a given parameter for both scanners are summarized in Table 4. It was found that the degree of resolution variation is highly dependent on two spatial parameters: incident angle and position along the LOR. For example, PDFs belonging to the central segments of a LOR typically have smaller $FWHMs$ (min/max = $1.66 \pm 0.13 / 1.69 \pm 0.17$ mm for HRRT and $0.78 \pm 0.10 / 0.85 \pm 0.14$ mm for Focus-220) than those at the edge segments (min/max = $2.29 \pm 0.57 / 2.41 \pm 0.63$ mm for HRRT and min/max = $1.12 \pm 0.22 / 1.33 \pm 0.46$ mm for Focus-220). Also, the variability in minimum and maximum $FWHM$ is larger for the edge segments. Even with different geometric configurations and intrinsic resolution, both scanners exhibit similar trends in spatial variation of response indicated by the corresponding shape-change of PDFs.

For the HRRT, experimental results had similarities and differences compared to their simulated counterparts, with consistency in the PDF shapes; examples are shown in figure 4. However, the experimental PDFs were in general wider than the simulated ones. Extra blurring unaccounted for by simulation was found to be mainly dependent on layer pairs. $FWHMs$ were compared between simulated and experimental PDFs belonging to the same layer pairs in the left column of figure 5. Many PDFs has an elliptical Gaussian distribution, as shown in figure 4. However, some PDFs (large incident angles and close to radial edge) had non-Gaussian shape (figure 3(c)). On the other hand, the two versions of LOR-PDFs had very similar distribution shapes of $FWHM$ values except that the distributions from the

measured PDFs were shifted to higher mean values (right column in figure 5). We attributed this phenomenon to the lack of PMT quadrant-sharing effects in the simulation (see Discussion). Therefore, to apply the simulated PDFs, we filtered the simulated PDFs for the HRRT with three layer-dependent 2D Gaussian filters to match the corresponding experimental results. In this study, filters with *FWHMs* of 0.8 mm, 1.0 mm and 1.2 mm were used for the three layer combinations. These values were chosen to match the means of both $FWHM_{min}$ and $FWHM_{max}$ distributions.

Similarly for the Focus-220, the *FWHM* distributions of simulated PDFs had smaller mean values (min/max = 0.85 ± 0.09 / 1.02 ± 0.09 mm), compared to those from measurements (min/max = 1.16 ± 0.12 / 1.29 ± 0.13 mm). Since there is only one crystal layer in this scanner, a Gaussian post-smoothing filter with 0.8 mm *FWHM* was applied to simulated PDFs to match with the experimental results.

5.2 Point source reconstructions

The in-plane variability of resolution was evaluated in point source experiments on both scanners. In the left column of figure 6, radial *FWHMs* of point sources reconstructed with different resolution models were plotted as a function of radial distance from the center of the FOV. As expected, no-PDF, which only models the detector size in the projector, produced higher *FWHM* values than any other methods. Considering the intrinsic detector resolution is 2.5 mm for the HRRT and 1.5 mm for Focus-220, the resulting point source *FWHMs*, 1.5mm in-plane in the center of FOV for the HRRT and 0.7 mm for Focus-220, were fairly small for no-PDF reconstruction. However, the non-PDF results showed higher radial non-uniformity than other reconstructions, and higher variability in *FWHM* estimation between points due to higher image noise. IG-PDF produced the lowest *FWHMs* near the center of the FOV, but the values increased substantially towards the edge, suggesting a spatially-variant kernel is necessary. In contrast, the two spatially-variant models, LOR-PDF and IM-PSF, improved in-plane resolution uniformity of the point source. The ranges of radial *FWHM* values were small for IM-PSF and LOR-PDF, i.e., 1.1-1.4 mm and 0.6-0.7 mm for the HRRT and Focus-220, respectively, after 10 iterations / 30 subsets. The spatial resolution distribution is similar between LOR-PDF and IM-PSF reconstructions, mainly because the same point sources were utilized in generating these kernels. However, LOR-PDF performed slightly better than IM-PSF in reducing the resolution degradation close to the radial edge (radial offset larger 120 mm in figure 6(a)) of the HRRT.

As a measure of the isotropy of in-plane resolution, ratios between radial and tangential *FWHMs* of the same point sources were calculated and plotted in the right column of figure 6. Due to DOI-induced radial uncertainty of LOR positioning, radial resolution degraded more dramatically than tangential resolution in the periphery, producing anisotropic in-plane resolution. This discrepancy was reduced by using the appropriate anisotropic resolution kernels consistent with the local detector response. In this experiment, both LOR-PDF and IM-PSF produced relatively consistent ratios between two *FWHM* measures than those obtained from no-PDF and IG-PDF reconstructions. This is especially evident beyond 110 mm for the HRRT. This position is the physical edge of the detector panels. Therefore, using appropriate PDFs for LORs belonging to various panel combinations presumably

compensated for the anisotropic detector responses and resulted in more isotropic resolution. In this comparison using only point sources, anisotropic and position-dependent image kernels achieved similar improvement as LOR-PDF reconstruction.

Point source resolution was generally worsened by background activity. For example, radial *FWHMs* from point sources in air at the axial center of the HRRT were 1.1-1.4 mm for various resolution models (figure 6), but the corresponding values were 1.7-2.0 mm when the source was surrounded by a warm background (figure 7(a)). The changes in radial, tangential and axial *FWHMs* as a function of axial position are shown in figure 7. That is, radial and tangential *FWHMs* increased, and axial *FWHM* decreased as a function of axial position of the point source. There was relatively large in-plane resolution non-uniformity over the axial FOV for IG-PDF reconstruction, with a progressive increase of in-plane *FWHMs* from 1.7 mm at axial center to 2.4 mm at 10 cm axial offset. This was caused by the mismatch between spatially-invariant kernels and radial-position-dependent system responses. The two spatially-dependent models reduced the *FWHM* difference between center (1.9 mm) and edge (2.2 mm). The pattern was different for axial resolution with slightly improved resolution at the edge of the axial FOV attributed to the reduced number of contributing LORs with large axial acceptance angles. However, no significant impact in the decreasing position-dependent axial *FWHM* was observed with the spatially-dependent models, as shown in figure 7(c).

In figures 6 and 7, the data were based on images reconstructed with fixed numbers of iterations (2 iterations / 30 subsets and 10 iterations / 30 subsets). At matched higher iterations, in-plane resolution was consistently more uniform with the two spatially-variant models than that with no-PDF (data not shown). Iteration effects are shown in more detail in the next section.

5.3 Minihot phantom

Qualitative and quantitative comparisons of resolution were conducted with the Minihot phantom imaged off-center on both scanners.

For the HRRT, transverse images reconstructed with the four aforementioned resolution models are shown in figure 8(a). Although the three groups of largest rods ($d = 3.2, 4.0$ and 4.8 mm) are visible in all images, no-PDF had higher noise (1st image), and IG-PDF produced relatively low contrast (2nd image). The group of 2.4-mm rods (bottom-left sector) was best delineated in IM-PSF and LOR-PDF reconstructions. A line profile was drawn on six hot rods as indicated in figure 8(a) and plotted in figure 8(b). Substantial improvement in contrast was observed in IM-PSF and LOR-PDF reconstructions, compared to that in IG-PDF reconstruction.

For the 2.4-mm rods, object contrast coefficients, defined in Eq. (5), were plotted against the coefficient of variation (*CoV*), defined in Eq. (6). To evaluate layer-dependent resolution, images were also reconstructed with events associated with specified crystal layer combinations. The *OCC* and *CoV* values obtained from four methods are shown in figures 8(c)-(e), corresponding to the reconstructions with all-layer events, front-front-layer events and cross-layer events, respectively. The relationships between these curves are similar in

the three layer combinations. Specifically, reconstruction with a resolution model resulted in a noticeably better tradeoff between contrast and noise than the no-PDF method. Among the three resolution models, LOR-PDF and IM-PSF outperformed IG-PDF for all layer combinations. Note that LOR-PDF with the layer-dependent kernels led to an OCC value of 52% at 300 effective iterations, a 9% improvement compared to 43% of IM-PSF in the crossed-layer reconstruction (figure 8(e)). In addition, regardless of the resolution model, images reconstructed from front-front-layer data (figure 8(d)) appear to have higher OCC and lower CoV than those from crossed-layer data (figure 8(e)). This is presumably due to the fact that the positioning of front-layer events is more accurate than that of back-layer events, as a consequence of pulse pileup (Jian *et al.*, 2010) and higher inter-crystal scattering in the back layer. LOR-PDF reduced the difference between layers. However, crossed-layer LOR-PDF reconstruction still resulted in 12% lower contrast than the front-front counterpart, presumably due to different convergence speeds in the layer-dependent reconstructions. LOR-PDF OCC values were compared to those in no-PDF, IG-PDF and IM-PSF statistically with the paired t tests. At 2 and 10 iterations, the p values calculated from two sets of OCC values are summarized in Table 5. LOR-PDF resulted in a statistically significant increase in OCC compared with no-PDF and IG-PDF for rods of 2.4 mm, 3.2 mm and 4.0 mm in diameter, indicated by the p values less than 0.05 in the table. The difference between LOR-PDF and IM-PSF was at or near significance at 2 iterations and not significant at 10 iterations.

Images reconstructed from sinogram-based MAP and MOLAR with various resolution models for the Focus-220 are shown in figure 9(a). MAP (1st image) and IM-PSF (4th image) resulted in the best recovery of the circular shapes for rods larger than 2.4 mm, while images reconstructed with IG-PDF (2nd image) and LOR-PDF (5th image) suffered from distortion on some of the large rods, especially for the 4.8-mm rods, with LOR-PDF showing less distortion than IG-PDF. We attribute this behavior to the highly anisotropic property of LOR-PDF, producing inconsistent object convergence in different directions. The resolution of the 1.6-mm rods (see line in figure 9(a)) was evaluated with line profiles (figure 9(b)). LOR-PDF outperformed MAP and IM-PSF in delineating this group of objects. In quantitative evaluation of contrast in 1.6-mm rods (figure 9(c)), LOR-PDF showed the best contrast at given noise levels, e.g., LOR-PDF resulted in up to 34% OCC while the corresponding value was 29% for IM-PSF. However, LOR-PDF led to slightly higher CoV than IM-PSF (34% vs. 31% at 300 effective iterations). Similar to the HRRT, the improvement in OCC by using LOR-PDF was statistically validated by t test. The p values, summarized in Table 5, indicated that LOR-PDF generally produce statistically better contrast than no-PDF and IG-PDF. However, similar to the HRRT, differences between LOR-PDF and IM-PSF were only at trend level.

OCC measurements from different reconstructions methods were not found to be substantially affected by the choice of the ROI size, i.e., using shrunken ROIs (80% of the rod diameter in Supplementary figure S2) produced very similar results to those shown in figures 8(c) and 9(c).

5.4 Contrast phantom

The tradeoff between resolution and noise was evaluated with a contrast phantom imaged on the HRRT. As shown in figure 10, reconstruction with resolution models demonstrated significantly improved results over the one with no PDF modeling. Hot ROI contrast increased from a peak of 60% (no-PDF) to above 80% with a resolution model, and residual intensity in the cold region was reduced from 30% (no-PDF) to <20% of the background activity. Thus, as expected, resolution modeling provides improved contrast recovery. On the other hand, a more accurate resolution model tends to further improve image contrast. In figure 10, 2-5% contrast improvement in the hot ROI was observed in LOR-PDF reconstruction compared with other models (IG-PDF and IM-PSF) at matched noise levels. The improvement was apparently smaller for the cold region (figure 10(b)). It is noteworthy that background CoV increased faster in LOR-PDF reconstruction than other models, in terms of iterations. However, the overall CRC/CoV performance of LOR-PDF was the best of the methods tested.

5.5 Rat studies

To test the resolution improvement with LOR-PDF, we investigated two studies where multiple rats were simultaneously imaged at radial positions off the center of FOV.

For the [^{11}C]AFM study on the HRRT, images reconstructed with IG-PDF, IM-PSF (kernel obtained from point source 10 cm away from radial center), and LOR-PDF at 5 iterations are shown in figure 11(a). These images are visually similar at the same iteration number. Note that the spinal cord, a thin high-uptake region with the thickness of 4-5 mm, is clearly identifiable in the sagittal view. The line profiles across the spinal cord after 150 and 300 effective iterations are given in figure 11(b) and 11(c). Note that LOR-PDF produced the best contrast between the spinal cord and the background among the three models. This improvement by using LOR-PDF was also found at both iteration numbers.

For the [^{11}C]PHNO study on the Focus-220, images reconstructed with four methods (MAP, IG-PDF, IM-PSF and LOR-PDF) are shown in figure 12. These images were truncated to focus on the heads of two rats. Notice that MAP and IG-PDF produced the noisiest images among all the methods. LOR-PDF resulted in slightly better delineation of structures such as the caudate nuclei, but also had higher noise than MAP and IM-PSF, as shown in figure 12(a). The line profiles on the caudate are shown for comparison purpose in figures 12(b) and 12(c) after 150 and 300 effective iterations. Worse resolution (lower peaks) was found with IG-PDF, while LOR-PDF produced the highest contrast among all the methods.

6. Discussion

We extended our previous work (Yao *et al.*, 2012) in developing a novel resolution model for PET image reconstruction. The concept of LOR-PDF was motivated by list mode data format where the coincident events are processed sequentially. Ideally, the resolution kernel would be modeled individually for every LOR. However, a size-reducing strategy was adopted in this study by grouping LORs based on the similarity of their spatial positions, and modeling the “average” response for LORs in the group. The 3D line spread function

associated with a LOR is discretized as a series of 2D functions, denoted as PDFs. Note that PDFs are associated with LORs and can be used with any voxel organization. For any given coincident event, PDFs reflect the uncertainty in determining the origin of positron emission. Although we implemented LOR-PDF on an event-by-event manner in MOLAR, it is suitable for both list-mode and sinogram reconstructions.

The proposed LOR-PDF was derived from Monte Carlo simulation (GATE) for two PET systems, the HRRT and Focus-220. With the aid of GATE, LOR-PDFs were generated including multiple resolution-degrading factors at both the positron-emission and photon-detection levels. The simulated PDFs showed responses that were dependent on depth and crystal layer. The PDFs typically had non-Gaussian shape (figure 3) depending on the spatial location of each LOR. For instance, 2D PDFs are elongated due to large incident angles of the LOR in certain directions, and the PDFs on both ends of a LOR are asymmetric with respect to the central segment if the incident angles on the ends of the LOR differ. However, we also believe that there is some resolution underestimation by the GATE simulation, due to the lack of simulating quadrant-sharing PMT effects. This was verified by the point source experiment where the measured PDFs were generally wider than their simulated counterparts. We thus corrected the FWHM underestimation in the simulated PDFs by using Gaussian filters that matched the FWHMs to the experimental results.

The simulation generated on average 50 counts / bin in the vicinity (22×22 bins in a 3.4×3.4 cm² region) of the peak of the original PDFs, producing 14% statistical error based on Poisson statistics. Further, the post Gaussian filters (0.8 - 1.2 mm FWHM) reduced the statistical error to < 3%. This error was lower for the Focus-220 with ~ 3 times more counts per bin as the HRRT. Thus, the final PDFs had very small statistical fluctuations.

An alternative to storing the PDFs for image reconstruction is to parameterize the spatially-variant kernels (as in IM-PSF). However, the latter approach would be less effective for two main reasons. First, finding a suitable parameterization is very challenging. For example, although some PDFs with small incident angles have Gaussian shapes (Figure 4), many at larger incident angles towards the ends of the LOR are far from Gaussian (Figure 3 (c)). Second, parameterization requires on-the-fly computation of PDFs, which increases computation time.

Positron range can be incorporated either in the PDF kernels or in image space as a post-filter. In this work, the simulated PDFs were post-filtered to match the width of the measured kernels, derived from ²²Na sources. Thus, the positron range of ²²Na was naturally included in the LOR-PDF. Similarly, the image kernels used in IM-PSF in our study were also derived from the ²²Na point sources (Section 3.5). Therefore, we believe the comparison between LOR-PDF and IM-PSF was fair, given that the same positron range was included in both models. Except for regions near air, we expect that the mismatch of positron range will have a global effect on the FWHMs of PDFs, either over- or underestimation in resolution depending on the isotope, rather than impacting the shapes of PDFs. Thus, positron-dependent LOR-PDFs can be simulated for specific applications, or positron-range correction can be implemented separately in the reconstruction (Fu and Qi, 2010).

Note that the PDFs generated from our measurements are not a complete resolution model for image reconstruction. In this experiment, about 80% of the PDFs were binned with sufficient events, while 20% of the PDFs had very low statistics due to low spatial sensitivity. This non-uniform sensitivity effect causes resolution kernel measurement to be a challenging task. However, it might be possible to design the experiment in a more sophisticated way, with longer scan times for point sources at lower-sensitivity positions.

LOR-PDF and IM-PSF are the two main resolution models compared in this study. The final blurring in IM-PSF is a combination of the effects of the geometric projector in the reconstruction plus the post-reconstruction image space kernel. For the PDF approach, the reconstruction kernels are wide-band projectors which implicitly include the geometric projector. This explains why the PDF kernels were always larger than the IM kernels. The results of the point source reconstructions were consistent for the two scanners. For instance, the *FWHMs* of reconstructed point sources were very similar between LOR-PDF and IM-PSF reconstructions. Also, LOR-PDF provided much more uniform resolution than IG-PDF and no-PDF (figure 6). On the other hand, the impact of resolution modeling in the Minihot phantom reconstructions was slightly different between the HRRT and the Focus-220. LOR-PDF accounts for the resolution difference between crystal layers for the HRRT. The improvement in signal-to-noise in different layer groups was demonstrated in figures 8(c)-8(e). On the other hand, based on visual evaluation and the *t* test results, IM-PSF outperformed IG-PDF on the HRRT, while IG-PDF resulted in better resolution than IM-PSF in the small objects on the Focus-220. Thus, image-space kernels or iso-Gaussian kernels are probably not accurate enough in these reconstructions.

In Minihot images reconstructed with IG-PDF and LOR-PDF on the Focus-220, there was slight distortion of the circular shapes in the 4.8 mm rods located at the radial edge of the FOV. The simulated PDFs failed to eliminate this distortion, possibly because the anisotropic PDFs have different convergence speeds. In real-object reconstruction experiments, rats placed at a various distance from the radial center of the FOV were used to test the proposed resolution model. Higher contrast in small regions, such as the spinal cord and caudate nucleus, was found in LOR-PDF reconstruction than in the other methods. With the improvement in resolution uniformity, it is feasible to take advantage of most or all of the FOV of the scanners without sacrificing image quality, thus allowing multiple rodents to be scanned simultaneously. The ability to use resolution modeling to produce uniform spatial resolution may also influence the design of new PET scanners with small FOV and high sensitivity.

In list mode reconstruction, the PDF models are computationally more expensive than the image- space model. This is mainly due to the fact that PDFs are applied to the forward- and back-projection of every event, while image space kernels are only convolved with the emission images at each iteration. Since PDF kernels are applied to individual events, LOR-PDF is computationally more expensive than IM-PSF. For example, in MOLAR reconstruction from 10 M events, LOR-PDF requires 85 minutes for one iteration (30 subsets), while IM-PSF only requires 45 minutes. This computation time increase may be worthwhile in some reconstruction tasks where spatial resolution is of critical importance. In addition, LOR-PDF reconstruction requires 200 M memory to store the 7 dimensional PDF

table for the HRRT, while the memory consumption for the IM-PSF parameters and IG kernels is almost negligible. We believe improving memory caching in the implementation will reduce the difference in computation time between LOR-PDF and IG-PDF reconstructions.

LOR-PDF is a promising resolution model that can be adapted to any PET systems. In sinogram reconstruction, LOR-PDF is an alternative to experimental measurement of detector response functions. With the knowledge of the scanner specification, it is relatively easy to generate the LOR-PDF kernels with GATE software. In list-mode reconstruction, LOR-PDF seems to be a more accurate method than an image-space resolution model because the latter does not directly model some subtle effects occurring in the detection process. For instance, image-space PSFs do not directly account for the detector layer effects on the HRRT, and the depth-dependent response functions of LORs is not explicitly modeled in IM-PSF. However, LOR-PDF is computationally more complex than its image-space counterparts.

Although accurate resolution modeling is promising in improving spatial resolution, there are several remaining issues to determine the best use of resolution modeling. Image convergence speed depends on the detector response as well as the radioactivity distribution in the FOV. For example, it was shown in the point source experiment that LOR-PDF is still not sufficient to produce perfectly uniform resolution throughout the radial FOV of both scanners (figure 6), presumably due to different convergence speeds with different resolution kernels. In addition, all resolution models were tested here in high-count reconstruction experiments to achieve the best possible resolution. However, in cases where the number of events is relatively low, the noise increase produced by achieving the highest resolution may not be warranted, and thus the characterization of “best resolution” may be less meaningful in these applications. Finally, within the scope of this paper, we only applied LOR-PDF in reconstructing motion-free objects. List-mode reconstruction algorithms, such as MOLAR, typically have the ability to perform a more accurate motion correction than sinogram-based algorithm (Jin *et al.*, 2013). The structure of MOLAR easily allows the combination of event-by-event motion correction with LOR-PDF.

7. Conclusion

We have extended our previous work in generating an accurate resolution model through Monte Carlo simulation. The new model, denoted as LOR-PDF, is a set of the spatially-variant response functions of parameterized LORs. We have incorporated LOR-PDF into our list mode image reconstruction platform (MOLAR) on the HRRT and Focus-220, and performed image reconstruction experiments to explore the benefits of LOR-PDF in improving spatial resolution compared with other resolution models. In point source experiments, LOR-PDF has shown to produce consistent *FWHM* values from the center to the edge of the FOV of both scanners. The qualitative and quantitative analysis of small objects in contrast phantom and rat images has also indicated that better contrast recovery is achieved by using LOR-PDF than other models. Our future work is to improve LOR-PDF parameterization and optimize the implementation to reduce computation time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

An illustration of the LOR-PDF scheme. (a): the voxel location with respect to the LOR is uniquely determined by three parameters: r (in-plane offset from the LOR), u (axial offset from the LOR) and d (distance along the LOR from the starting-side). (b): A LOR is rotated to a reference frame where the starting side of the LOR is associated with the bottom panel 0. The LOR in the reference frame can be determined by four parameters: φ (in-plane incident angle of the LOR starting-side), θ (axial incident angle of the LOR starting-side), b (the panel index of the LOR ending-side after rotation) and l (the detector layer combination index, not shown here).

Figure 2.

The scheme of measuring LOR-PDF with point source set (PSS). The PSS (red dots) attached to the patient bed was moved vertically and axially to cover a quadrant of the FOV. The reason of bundling three point sources together is to acquire more samples at each position. The events are treated to be associated with the point source that is closest to their corresponding LORs. However, those events (less than 1% of the total) intercepting the neighborhood (sphere with a diameter of 5mm) of more than two points are not differentiable in terms of emission source, and thus discarded.

Figure 3.

Examples of HRRT PDF shapes in different segments of LOR-PDF. PDFs with one spatial parameter varied from the central segment to edge are shown from left to right in each row. (a) From left to right: in-plane incident angles $\varphi = 0^\circ$, 15° and 25° . These PDFs have common values for the central depth segment ($d = 0$) and axial angle ($\theta = 0$) (b) Axial incident angles $\theta = 0^\circ$, 10° and 17° . These PDFs have common values for the same the central depth segment ($d = 0$) and in-plane incident angle ($\varphi = 0^\circ$) (c) Depth position $d = -4$, -2 , 0 , $+2$ and $+4$ (Depth segments are indexed from -4 to $+4$, with 0 in the center). These PDFs have common values for $\varphi = 25^\circ$ and $\theta = 17^\circ$. The display scale is set to the maximum value of each PDF to provide better visualization of their shape.

Figure 4.

Comparison of simulated PDFs (top) and experimental PDFs (bottom) with the same spatial parameters ($l = 0$, $b = 1$, $\phi = 25^\circ$, $\theta = 7^\circ$) for the HRRT. There are 7 PDFs from the starting side (left) to the end side (right) of the LOR. The PDFs become wider when they are close to the ends of the LOR. While they have the very similar shapes, the experimental results are more blurred than the simulated result.

Figure 5. Comparison of $\text{FWHM}_{\min}$ and $\text{FWHM}_{\max}$ between simulated PDFs (diamonds) and measured PDFs (triangles) across three different layer combinations on the HRRT. (a), (b) and (c) are plotted with the PDFs belonging to front-front, crossed, and back-back layers, respectively. In the left column, each symbol represents one PDF with the minimum and maximum FWHMs shown in x and y axes. The distribution of the minimum FWHMs is plotted in the right column.

Figure 6.

Resolution of point sources at various radial positions. Image reconstruction was performed with no PDF (no-PDF), iso-Gaussian PDF, image-space PSF (IM-PSF) and LOR-PDF. FWHMs are shown for (a) HRRT, (b) Focus-220. Radial FWHMs from the center to the edge of the FOV are plotted in the left figures, and the ratios between radial and tangential FWHMs are plotted in the right figures.

Figure 7.

Average radial(a), tangential(b) and axial(c) FWHMs of point sources in warm background in the HRRT as a function of axial positions. Images were reconstructed with iso-Gaussian PDF(IG-PDF), image-space PSF(IM-PSF) and LOR-PDF after 10 iterations/30 subsets. FWHMs were estimated by fitting 3D Gaussian functions to individual points and then averaged over three points sources in the same transaxial plane.

Figure 8.

Reconstructions of Mini-hot phantom placed at 15cm away from radial center on HRRT with different resolution models incorporated in MOLAR. (a) Transverse images in the axial center after 2 iterations / 30 subsets. Images from left to right were reconstructed with no-PDF, IG-PDF, IM-PSF and LOR-PDF respectively (see text for definitions). Images are displayed on the common scale. (b) Line profiles on 2.4 mm rods (denoted in (a)) are compared among three reconstruction methods with 2 iterations / 30 subsets. (c)-(e) The object contrast coefficients are plotted against the coefficients of variation for the 2.4mm rods on the images reconstructed with (c) all-layer events, (d) front-front layer events, and (e) cross layer events. To provide a fair comparison, the total number of events was the same (100M) in three groups. Each curve reflects data over OSEM iterations (up to 10 iterations / 30 subsets).

Figure 9.

Reconstruction of Minihot phantom placed at 8cm from the radial center of the Focus-220.

(a) Transverse images at the axial center after 2 iterations / 30 subsets. Images from left to right were reconstructed with MAP (manufacturer's software), no-PDF, IG-PDF, IM-PSF and LOR-PDF respectively. Images are displayed on a common scale. (b) Line profiles on 1.6mm rods (denoted in (a)) across three reconstruction methods with 2 iterations / 30 subsets. (c) The object contrast coefficients are plotted against the coefficients of variation for the 1.6mm rods. Each curve reflects data over OSEM iterations (up to 10 iterations / 30 subsets)

Figure 10.

Resolution and noise properties of a contrast phantom imaged on the HRRT. Contrast recovery coefficients (*CRC*) of hot (a) and cold (b) ROIs are plotted against coefficients of variation (*CoV*) in background ROIs. Each point represents one iteration with thirty subsets (up to 10 iterations / 30 subsets).

Figure 11. $[^{11}\text{C}]$ AFM rat images on the HRRT. The animal was scanned at about 10 cm from the radial center of the FOV. Reconstructions were performed with IG-PDF, IM-PSF and LOR. (a) The sagittal images (5 iterations / 30 subsets) are displayed scaled to permit visualization of the spinal cord. Images are displayed on a common scale. Profiles are drawn across the spinal cord (lines shown in (a)) on the images reconstructed after (b) 5 iterations and (c) 10 iterations.

Figure 12. $[^{11}\text{C}]$ PHNO rat images on the Focus-220. The animals were scanned at about 5 cm from the radial center of the FOV. Reconstructions were performed with MAP (manufacturer's reconstruction) and MOLAR (IG-PDF, IM-PSF and LOR-PDF). (a) The images are displayed scaled to permit visualization of the caudate. Images are displayed on a common scale. Profiles are drawn across the caudate nucleus (lines shown in (a)) on the images reconstructed after (b) 5 iterations and (c) 10 iterations.

Table 1

Definitions of terms.

Terms	Definitions	Units
λ	Voxel intensity	Bq/mL
c	System matrix	mm
T	Frame duration	sec
L	Live time and Decay factor	-
N	Sensitivity (Normalization) factor	(counts/sec)/(Bq/mL·mm)
A	Attenuation factor	-
R	Random coincidence rate	counts/sec
S	Scatter coincidence rate	counts/sec
Q	Voxel sensitivity	(counts/sec)/(Bq/mL)
j, j'	Voxel index	-
k, i	LOR index	-
n	Iteration number	-

Table 2

LOR-PDF sampling parameters for the HRRT and Focus-220. The segment size for each parameter is scanner-dependent and selected to maintain a balance between sampling accuracy and memory requirements.

Dimensions	HRRT		Focus-220	
	Number/range of segments	Segment size	Number/range of segments	Segment size
Layer pairs l	3	-	-	-
Panel separation indices p	5	-	21	-
In-plane incident angles φ (degree)	$[\varphi_b - 11^0 \varphi_b + 11^0]^*$	3^0	$[\varphi_b - 2^0 \varphi_b + 2^0]^*$	1^0
Out-of-plane incident angles θ (degree)	$[-30 \ 30]^{**}$	7^0	$[-18 \ 18]^{**}$	3^0
Along-LOR depth position d	9	~35mm	21	~5mm
Transaxial offset r (mm)	10mm	~0.16mm	5mm	~0.08mm
Axial offset u (mm)	10mm	~0.16mm	5mm	~0.08mm

* φ_b is the angle of the LOR connecting the centers of panel 0 and panel b.

** LORs perpendicular to the surface of detector are assigned with 0 incident angle.

Table 3

GATE simulation parameters for the HRRT and Focus-220. The actual computation time was much less than listed due to the use of a computer cluster. The total time is calculated based on a computer node with 3.2GHz single-core CPU and 2GB RAM.

	HRRT	Focus-220
Cylindrical source (radius $\times$ length, cm)	21 $\times$ 35	12 $\times$ 20
Isotope	^{11}C	^{11}C
Total PDF counts ($\times 10^8$)	~9.1	~23.1
Total computation time ($\times 10^5$ hours)	~2.8	~6.6
Average counts per PDF	8,320	22,450

Table 4

Minimum and maximum FWHM (mm) estimated from simulated PDFs. Mean and standard deviation are calculated from all the PDFs belonging to the same segment of a given space parameter, i.e., layer-pair, panel separation or depth position along a LOR.

	HRRT			Focus-220	
	FWHM_{min}	FWHM_{max}		FWHM_{min}	FWHM_{max}
<i>Front-front layer</i>	1.85±0.22	2.15±0.31	-	-	-
<i>Cross layer</i>	2.02±0.38	2.44±0.42	-	-	-
<i>Back-back-layer</i>	2.19±0.47	2.44±0.55	-	-	-
<i>Panel Sep. =4</i>	1.78±0.21	1.84±0.26	<i>Panel Sep.=21</i>	0.85±0.16	0.92±0.19
<i>Panel Sep. =3</i>	1.88±0.26	2.22±0.43	<i>Panel Sep.=18</i>	1.02±0.22	1.49±0.32
<i>Panel Sep. =2</i>	1.95±0.45	2.62±0.59	<i>Panel Sep.=15</i>	1.28±0.26	1.91±0.46
<i>Pos. in LOR =5</i>	1.66±0.12	1.69±0.17	<i>Pos. in LOR =11</i>	0.78±0.10	0.85±0.14
<i>Pos. in LOR =3</i>	1.89±0.21	2.07±0.41	<i>Pos. in LOR =6</i>	0.89±0.18	1.07±0.22
<i>Pos. in LOR =1</i>	2.29±0.57	2.41±0.63	<i>Pos. in LOR =1</i>	1.12±0.22	1.33±0.46

Table 5

P values of the t test performed on the object contrast coefficient (OCC in Eq(5)) between reconstruction methods. List mode data were acquired from the Minihot phantom scan and downsampled to generate 10 independent data sets for image reconstruction. T tests were performed to statistically compare the OCC values between LOR-PDF and other resolution models (no-PDF, IG-PDF and IM-PSF). A p value < 0.05 designates a statistically higher OCC for LOR-PDF.

	Diameter (mm)	2 Iterations			10 iterations		
		vs. no-PDF	vs. IG-PDF	vs. IM-PSF	vs. no-PDF	vs. IG-PDF	vs. IM-PSF
HRRT	2.4	0.001	0.005	0.055	0.001	0.004	0.123
	3.2	0.002	0.003	0.049	0.002	0.004	0.099
	4.0	0.002	0.002	0.041	0.002	0.002	0.102
Focus-220	1.6	0.022	0.149	0.221	0.031	0.033	0.223
	2.4	0.020	0.176	0.098	0.041	0.031	0.109
	3.2	0.017	0.199	0.079	0.038	0.029	0.234