Quantification of radiotracer uptake with a dedicated breast PET imaging system

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Tomographic breast imaging techniques can be used to quantify radiotracer uptake in breast and tumor tissue. However, physical processes common to PET imaging can confound accurate quantification. In this investigation, we assessed the effects of these phenomena and tested correction schemes for our new positron emission mammography–tomography system (PEM–PET). The PEM–PET scanner utilizes two sets of rotating planar detector heads. Each unit consists of a 4×3 array of Hamamatsu H8500 flat panel position sensitive photomultipliers coupled to a 96×72 array of $2 \times 2 \times 15$ mm³ LYSO detector elements (pitch=2.1 mm). Image reconstruction is performed with a 3D-OSEM algorithm parallelized to run on a multiprocessor computer system. The reconstructed field-of-view is $15 \times 15 \times 15$ cm³. Much of the testing procedures were based on NEMA-NU2/2001 protocols. Count rate losses due to pulse pile-up, image contamination due to acceptance of random coincidences and Compton scatter, and image artifacts produced by photon attenuation were measured. It was found that the system was susceptible to count rate losses when moderate levels of radiation were present in the scanner due to the current design of the event trigger electronics. Application of corrections for Compton scattering, photon attenuation and dead time resulted in improved estimations of ¹⁸F concentration in simplified phantom studies. Results from these preliminary studies indicate that the PEM–PET scanner will be useful for the quantification of radiotracer uptake in breast tumors, possibly facilitating early assessment of cancer treatments. © 2008 American Association of Physicists in Medicine. [DOI: [10.1118/1.2990781](https://doi.org/10.1118/1.2990781)]

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I. INTRODUCTION

The nonoptimal imaging performance of x-ray mammography in the subset of women with radio-dense and/or fibroglandular breasts has led to the development of a number of specialized imaging systems designed for use with these patients. One of the most active areas of this work has been in the development of dedicated positron breast scanners. The first of these systems, known as a positron emission mammography (PEM) scanner, was proposed in 1994 by Thompson *et al.*¹ After several generations of improved small field-of-view (FOV) systems, a full breast size scanner that utilizes two sets of linearly scanning planar detectors has become the first commercially available PEM scanner (Nevision PET Systems, San Diego, CA).² As with the Thompson *et al.* system,¹ this scanner does not rotate, so it utilizes limited-angle tomography to produce images. Consequently, there is significant image blurring along the axis perpendicular to the planes of the detectors.

Additional efforts include work led by Doshi *et al.*³ to create a breast imaging system consisting of two 15×15 cm² arrays of $3 \times 3 \times 20$ mm³ cerium-doped, lutetium oxyorthosilicate detector elements coupled to arrays of position-sensitive photomultiplier tubes (PSPMT). This system rotates, permitting multiangle tomographic images to be produced. In addition to these and other efforts,⁴ our team has developed the positron emission mammography–tomography imager and biopsy system (called PEM–PET). PEM–PET utilizes large area (15×20 cm²) rotating detectors to produce tomographic images of radiotracer concentration in the breast. The reconstructed transaxial and axial spatial resolutions of the scanner are less than 2 mm.⁵ The system energy resolution is approximately 25%.⁶ The scanner also supports image-guided biopsy of suspicious lesions observed in the PET images. As this system employs multiangle tomography methods, it can also accurately measure radionuclide concentrations in tissue. In this work, we as-

sessed the effects of a number of physical processes that affect the accuracy and precision of estimation of radiotracer concentration *in vivo*, and discuss the results of correction schemes to mitigate the effects of sources of quantitative errors. The layout of the paper is as follows: We first conduct count rate and scatter-fraction measured based on the NEMA NU2/2001 PET scanner standard. This is followed by two experiments evaluating the effects of scatter and attenuation on PET images. We then implement and evaluate corrections for random and scattered coincidences, pulse pile up and attenuation. Finally, we evaluate the combined system quantitative accuracy for different test objects.

II. METHODS

II.A. Description of the PEM-PET system

The imaging component of the PEM-PET system consists of four radiation detectors designed by our team.⁵ Each detector head consists of a 96×72 array of $2 \times 2 \times 15$ mm³ LYSO detector elements (pitch=2.1 mm) coupled to a 4×3 array of a Hamamatsu H8500 PSPMT. The four detectors were mounted on a computer-controlled rotator. Detector separation is adjustable, for PET imaging operation the distance is set at 25.6 cm. The coincidence-timing window of the system is 3.5 ns. The system has no collimators, so it is possible to acquire data in three dimensions. The patient bed is partially constructed from 2-mm-thick tungsten alloy to shield the detectors below from radioactivity outside the scanners FOV. Additional 3-mm-thick tungsten alloy plates can be positioned to enhance shielding of areas with increased radiotracer uptake, such as the patient's liver or bladder. A photograph of the PEM-PET system is shown in Fig. 1.

Signals from each PSPMT are processed using a fast resistive readout system based on a design previously developed at Jefferson Lab.⁷ A high-speed, field-programmable-gate-array (FPGA)-based data acquisition system accepts the signals from the PSPMT readout, integrates them within the software-defined gate width and digitizes them. The data are stored on dual-core computers with software that calculates the position of the photon interaction in the scintillator arrays using previously measured look up tables. The energy of each event is normalized using a table of calibration factors. Energy normalization is the initial step in correction of the data for physical effects present in the PEM-PET system.

Capture of the data by the FPGA electronics is initiated by the coincidence of trigger pulses generated by the sum of the PSPMT anode signals. The lower level energy threshold for the trigger pulses is 100 keV. This relatively low setting is dictated by the desire to detect interactions in the scintillator array corresponding to gaps between PSPMTs. In these areas, light collection efficiency is lower than at other areas of the array, resulting in lower-intensity signals that appear as low energy events. The energy normalization performed by the calibration software corrects for this effect, so the energy for each event recorded in the data reflects the actual energy of the detected photon. The normalization process, however, does not affect the amplitudes of the anode signals processed

(a)

(b)

FIG. 1. PEM-PET imager and biopsy system: (a) The complete system, including the shielded patient bed and (b) top view of the gantry showing the detector orientation.

by the coincidence circuit. Therefore, the ability to detect events near gaps in the PSPMT array is achieved at the expense of exacerbating pulse pile-up effects.

The output coincidence data are written to disk in list mode format. These data are reconstructed using a 3D-OSEM algorithm specially modified to run on an eight-CPU reconstruction engine.⁸ The size of the reconstructed volume is adjustable, but it is typically $15 \times 15 \times 15$ cm³ with $1 \times 1 \times 1$ mm³ voxels. The energy window applied to the list mode data during reconstruction is 350–650 keV. As the list mode data are energy-normalized (as described earlier), coincidence events from the gaps in the PSPMT array are not filtered out by application of this energy window.

(a)

(b)

FIG. 2. (a) Modified NEMA-NU2/2001 phantom and (b) phantom positioned in the scanner.

II.B. Assessment of scanner performance

The count rate performance characteristics of the PEM-PET scanner were assessed using methods based on the NEMA NU-2/2001 protocols.⁹ The NU2/2001 protocol utilizes a solid right cylinder of polyethylene, which, for whole body scanners, has a diameter of 20 cm and a length of 70 cm. This standard phantom was modified for use with our dedicated breast imager (cylinder diameter=11.7 cm and length=25 cm). The phantom has a 35 cm long polyethylene tube with an inside diameter of 3.2 cm offset from the central axis by 2.5 cm [Fig. 2(a)]. Thus, the NU2/2001 protocol includes the effect caused by radioactivity outside the scanner's FOV. The tube was filled with $\sim 300 \mu\text{Ci}$ of ^{18}F and placed in the scanner [Fig. 2(b)]. This amount of radioactivity is several times the maximum levels expected to be in the scanner's FOV in regular clinical use. Prompt and delayed coincidence data sets were collected periodically as the ra-

FIG. 3. Summed profile data used to calculate Compton scatter fraction.

dioactivity in the phantom decayed to less than 1% of the original amount. The true, random, and scatter coincidence event rates were calculated from these data (the 350–650 keV energy window was applied to the data), as were the noise equivalent count rates (NECR), Compton scattering fraction, and percentage detector dead time.

The scanner's Compton scatter fraction was measured using the data acquired for the final time point utilized in the count rate performance measurements described previously. These data were utilized so that there are minimal random coincidence events present. The NU2/2001 protocol requires analysis of a summed profile of the radioactivity in the phantom's tube from multiple projection angles; this profile is shown in Fig. 3. To evaluate the effect of Compton-scattered photons on the PET images, an 8-cm-diameter cylindrical phantom was filled with a water solution containing $10 \mu\text{Ci}$ of ^{18}F . A 2-cm-diameter cylinder filled with nonradioactive water was placed in the 8-cm diameter to create a "cold" region. PEM-PET images were then acquired using a step-and-shoot protocol (six steps, $30^\circ/\text{step}$ and an acquisition time of 60 s/step). Line profiles were drawn through images of the cold cylinder and in the "hot" regions surrounding this cylinder to assess the fraction of positron annihilations misplaced in the cold area due to Compton scattering of the photons. Finally, the effects of corrections for photon attenuation on quantitative accuracy were assessed by imaging an 8-cm-diameter, water-filled cylinder containing a uniform activity distribution of ^{18}F .

II.C. Correction methods

To accomplish accurate radiopharmaceutical quantification, corrections for the physical processes common to PET imaging must be performed. For example, the effects of random coincidences on PEM-PET images can be corrected by estimating the amount of these events that are contaminating

the data. One method for performing this estimation is the delayed coincidence technique.¹⁰ In the PEM-PET system, correction for random coincidences is accomplished by the subtraction of the coincidences delayed by 15 ns from the prompt-coincidences data. The random coincidence rates were also estimated from the single photon count rate using the equation $R = 2\tau S_1 S_2$ (where τ = coincidence window (3.5 ns), S_1 = average single event rate from detector 1, and S_2 = average single photon rate from detector 2). These values were compared to the measured values using the delayed window technique. To correct for the effects of pulse pile up, the relationship between detector dead time and single photon count rate determined in our measurement of percentage detector dead time was used to modify the length of the data acquisition. Specifically, the percentage detector dead time–single photon rate relationship was used to calculate the amount of additional data acquisition time required to account for detector dead time-induced loss of coincidence events.

There are two methods for performing PET attenuation correction. The first method requires the measurement of photon attenuation via the acquisition of a separate transmission scan¹¹ using either a 511 keV source (such as ^{68}Ge), or more recently, an x-ray computed tomography (CT) scanner. These data are then used to produce attenuation correction factors for each line of response. An alternate method is the application of calculated correction factors.¹² A mathematical model of the object is used to calculate the attenuation of photons along each line of response, using the assumption that the density distribution is known. As PEM-PET does not currently possess the ability to perform transmission imaging, the calculated attenuation correction method is used.

There are a number of methods for correction of the effect of Compton scattering on PET images.^{13,14} We have chosen to apply a modified, two-dimensional Bergström correction method¹⁵ that we adapted for PEM imaging.¹⁶ Briefly, this method utilizes the deconvolution of the uncorrected PET image with two-dimensional Compton scattering kernels. These kernels were estimated using data acquired from a series of capillary tube sources placed in water. The effectiveness of the scatter correction was assessed by applying it to data acquired from the 8-cm-diameter cylindrical phantom containing a 2-cm-diameter cold region described earlier.

Finally, to test the quantitative characteristics of the PEM-PET system, a 1.5-cm-diameter hollow sphere was filled with liquid containing $\sim 8.5 \mu\text{Ci/ml}$ of ^{18}F . The sphere was then placed in an 8-cm-diameter cylinder filled with water containing no radioactivity. Several scans of the test object were acquired by the PEM-PET system as the ^{18}F decayed. These initial data acquisition used a protocol of six steps (nominal 30 s/step in increments of 30°). Subsequent scans used longer data acquisition times to account for radioactive decay of the source to achieve equivalent counting statistics throughout the experiment. Note that, as described previously, to account for count rate losses due to event pile up, the actual length of data acquisition per step is increased by an amount based on the percentage detector dead time

FIG. 4. Count rate performance test results.

corresponding to the current single photon event rate. Data were obtained until the concentration reached $\sim 0.5 \mu\text{Ci/ml}$, which is similar to the concentration of ^{18}F -fluorodeoxyglucose (FDG) often reported for breast cancer. After each data acquisition, a second scan was performed in the delayed coincidence mode to estimate random coincidence contamination of the data. All images were reconstructed using a 3D-OSEM algorithm (12 iterations and 3 subsets). Corrections for photon attenuation, Compton scattering, and random coincidences were applied to the data. Regions of interest (ROIs) were drawn on the images of the sphere to produce a mean count rate. Finally, a previously measured calibration factor converting reconstructed PET counts to tracer concentration was applied to the data from the ROI. The measured ROI values were then compared to the known activity concentration to assess the overall accuracy of the system. The data acquisition and measurement procedures described earlier were repeated with the sphere (containing the same original amount of ^{18}F , $\sim 8.5 \mu\text{Ci/ml}$) mounted in the cylinder after the water had been drained.

III. RESULTS

Analysis of the profile shown in Fig. 3 revealed that the global scatter fraction for PEM-PET measured using the NEMA-NU2/2001 PET protocol was 35%. Figure 4 shows plots of true, scatter, NECR and random coincidence event rates versus the amount of radioactivity in the phantom. Also shown on this plot is the extrapolated true coincidence event rate. A comparison between the measured and calculated random coincidence rates are shown in Fig. 5. Figure 6 shows a plot of the percentage detector dead time versus single photon rate. As expected, percentage detector dead time is strongly dependent upon the detector single event rate. This relationship permits us to estimate count rate losses due to pulse pile up and correct the data accordingly.

FIG. 5. Measured and calculated random coincidence rates versus single event rate.

The images in Fig. 7 demonstrate how the misplacement of photon event caused by Compton scatter affects PET images, and how the scatter correction method reduces this effect. Specifically, the scattered event rate was reduced from $\sim 30\%$ in the cold region to $\sim 2\%$. The profiles in Fig. 8 illustrate this effect. The images in Fig. 9 and profiles in Fig. 10 show the effect of corrections for random coincidences and photon attenuation on PEM-PET images of a uniform phantom. Most notably, the correction of the cupping effect at the center of the image produced by attenuation is evident in the image. Finally, the graphs in Fig. 11 of measured radiotracer concentration in the 1.5-cm-diameter sphere plotted versus the known concentration show that the slope was es-

FIG. 6. Percentage detector dead time plotted versus single event rate. The data were fit to a logarithmic function.

(a)

(b)

FIG. 7. PEM-PET images of the Compton scatter demonstration phantom. (a) Without scatter correction applied and (b) with Compton scatter correction applied. Random coincidence correction was applied to both images.

entially equal to 1 for both objects, and that the R value was also equal to one in both cases. These results demonstrate the PEM-PET system's ability to accurately and precisely quantify radiotracer concentration in two very different photon-attenuation environments.

IV. DISCUSSION

The application of dedicated breast imaging systems to the assessment of cancer therapies is a relatively new and

FIG. 8. Normalized intensity profiles drawn on the images shown in Fig. 7.

emerging potential use of these devices. To accomplish this task, it is necessary to quantify the concentration of radiotracer in tissue. In this investigation, we have explored some of the performance characteristics of our new PEM-PET breast imager and evaluated data correction schemes necessary for accurate tracer quantification. PEM-PET is especially suited to quantitative imaging because it is a multi-angle tomographic system, compared to other breast scanners that utilize a single pair of stationary detectors and limited-angle tomography reconstruction techniques, which significantly reduces their quantitative capabilities.

The data shown in Fig. 4 exhibit the expected behavior of an efficient small bore system. The plateaus in the curves for true and scatter coincidence rates at radioactivity levels above $\sim 100 \mu\text{Ci}$ are due to loss of detection efficiency caused by pulse pile-up effects. The random coincidence rate grows almost linearly with increasing radioactivity, where as it should grow in a parabolic fashion. This effect is also due to count rate losses caused by event pile up. The NECR curve shows that the peak rate is achieved at radioactivity levels close to the amounts expected in a normal-sized breast with FDG uptake reported in the literature.¹⁷ The count rate performance of the current PEM-PET system is slightly hampered by the necessity to set the lower energy threshold at 100 keV so that photon interactions above gaps in the PSPMT array can be detected (as described previously). Although this threshold is necessary to detect these events, it forces the coincidence circuitry to process lower energy photon interactions from other areas of the PSPMT array where light collection is good, thus increasing the amount of pulse pile up. These low energy interactions (mostly Compton-scattered photons) are later rejected during reconstruction of the normalized list mode data. There are at least two methods to address this problem. One is to implement a spatially variant triggering system that will allow different energy thresholds (up to four) to be applied to the detected events. Thus, an appropriate threshold is applied to events based on their

position in the PSPMT array. Another potential scheme is to divide each detector head into zones that each have separate circuitry, but use the same energy threshold. The latter method is somewhat simpler to implement as the goal is to spread the event processing over more electronics, thus reducing pulse pile up in the individual channels.

The plots in Fig. 5 show a comparison of the measured random coincidence rates to those calculated from the single event rates. At high single photon rates, the disparity of the two curves is due to count rate losses incurred by the measured results. At low single photon rates the disparity in the curves (more random coincidences are calculated than measured) is due to the natural radioactivity in the scintillator material (the single event rate with no radioactivity present is 118 kHz) and the lower level energy threshold setting of 100 keV. The single photon rate is measured from data passing through the discriminators set at 100 keV, whereas the measured random coincidence results were measured from the raw coincidence data using the 350 keV lower energy threshold. Thus, the calculated results will slightly overestimate the actual random rate present in the reconstructed images, as the hardware-measured single photon rates were used in the calculation. Fortunately, this is a known effect so the appropriate corrections can be applied, permitting future use of the calculated random coincidence correction method. Figure 6 shows a plot of percent detector dead time versus single photon rate. It demonstrates how rapidly pulse pile-up effects increase with a modest increase in the single photon rate. It is expected that implementation of a new trigger scheme (described earlier) will increase the system's ability to rapidly process events, thus altering the relationship between percentage detector dead time and single photon rates. It should be noted that this relationship has a logarithmic behavior (as demonstrated by the fit to the curve), so it is possible to calculate count loss corrections for PEM-PET data based on the system single photon rates and extend the data acquisition time to account for these losses. Indeed, this capability has recently been added to the PEM-PET system.

The images in Fig. 7 illustrate the effect that acceptance of Compton scattered photons have on PEM-PET images. Specifically, these events cause the misplacement of radionuclide position, as demonstrated by the fact that there appears to be some radioactivity in the cold region of the phantom in Fig. 7(a). The correction of this effect using the 2D-deconvolution method appears to work well [Fig. 7(b)]. Indeed, following application of the correction, the Compton-scattered events were reduced to 2% from 30% in the uncorrected image. The normalized profiles shown in Fig. 8 illustrate this reduction. The 2D-deconvolution technique works best when the scattering kernels of the system are known for a particular medium. In practice, breasts can have some areas of heterogeneous density. Thus, it is possible that some errors can be induced by assuming a uniform density.

The images of Fig. 9 demonstrate that even for relatively small objects, photon attenuation can produce significant artifacts in breast-PET images. This effect and that of random coincidences are made more evident by the profiles drawn through the images shown in Fig. 10. The use of the calcu-

FIG. 9. PEM-PET images of a uniform cylinder containing ^{18}F . (a) No corrections applied, (b) random coincidence correction applied, and (c) random and attenuation corrections applied.

lated attenuation method restored the relative intensity between the edges and center in the PET images of the phantom. This procedure also increased the overall image intensity by approximately a factor of 2. It should be noted that the calculated attenuation correction method works best when the shape and size of an object, as well as its density distribution, are known. For arbitrary-shaped and -sized objects with an unknown density distribution, this method may not work well. Therefore, for use in the clinic where the shape and density distribution of an individual breast may not be well known, it will likely be necessary to add the

ability to perform x-ray CT imaging. Not only will the addition of this capability assist in quantification radiotracer concentration, the anatomical information provided by CT images may facilitate more effective detection and diagnoses of breast cancer.

Finally, the ability of the PEM-PET system to quantify radiotracer concentration in a phantom was assessed. The plots of measured versus known amounts of ^{18}F in a 1.5-cm-diameter sphere, shown in Fig. 11, demonstrate the ability of the PEM-PET system to accurately quantify radiotracer concentration. Specifically, these results show that

FIG. 10. Intensity profiles drawn through the images shown in Fig. 9.

the corrections described previously for physical phenomena affecting PET quantification are effective in their application to the PEM-PET system. The data also indicate that these corrections are somewhat robust given that similar results were obtained with significantly different photon attenuating media over a range of radioactivity levels. We note that this was a simple phantom with no background activity. More definitive conclusions regarding the ability of this system to provide quantification with more complicated activity distributions will require additional investigations.

In summary, we have explored the quantitative capabilities of a new breast-PET system. NEMA-NU2/2001-based count rate measurements revealed that the system's dead time performance needs some improvement. This deficiency is due to the utilization of PSPMT arrays that necessitate a

FIG. 11. Measured radiotracer concentrations as a function of the known concentrations for two different attenuating media. Noted that the data were corrected for detector dead time, Compton scattering, random coincidences, and photon attenuation.

lower energy threshold than is typically used on a PET scanner. Work is in progress to address this minor shortcoming. In addition, the effects and correction of photon attenuation, random coincidences, pulse pile up, and Compton scattering were assessed. These methods were successfully tested in application to the measurement of radiotracer concentration in a phantom. These promising results indicate the potential for utilizing PEM-PET in applications where quantitative aspects of PET imaging are required, such as in the early evaluation of cancer treatments.

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