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A small animal PET based on GAPDs and charge signal transmission approach for hybrid PET-MR imaging

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ABSTRACT: Positron emission tomography (PET) employing Geiger-mode avalanche photodiodes (GAPDs) and charge signal transmission approach was developed for small animal imaging. Animal PET contained 16 LYSO and GAPD detector modules that were arranged in a 70 mm diameter ring with an axial field of view of 13 mm. The GAPDs charge output signals were transmitted to a preamplifier located remotely using 300 cm flexible flat cables. The position decoder circuits (PDCs) were used to multiplex the PET signals from 256 to 4 channels. The outputs of the PDCs were digitized and further-processed in the data acquisition unit. The cross-compatibilities of the PET detectors and MRI were assessed outside and inside the MRI. Experimental studies of the developed full ring PET were performed to examine the spatial resolution and sensitivity. Phantom and mouse images were acquired to examine the imaging performance. The mean energy and time resolution of the PET detector were 17.6% and 1.5 ns, respectively. No obvious degradation on PET and MRI was observed during simultaneous PET-MRI data acquisition. The measured spatial resolution and sensitivity at the COFOV were 2.8 mm and 0.7%, respectively. In addition, a 3 mm diameter line source was clearly resolved in the hot-sphere phantom images. The reconstructed transaxial PET images of the mouse brain and tumor displaying the glucose metabolism patterns were imaged well. These results demonstrate GAPD and the charge signal transmission approach can allow the development of high performance small animal PET with improved MR compatibility.

KEYWORDS: Gamma camera, SPECT, PET PET/CT, coronary CT angiography (CTA); Multimodality systems

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1 Introduction

Positron emission tomography (PET) has attracted considerable interest for the non-invasive visualization of small animals for various preclinical studies. Currently, combined positron emission tomography and computed tomography (PET-CT) dedicated to small animal imaging is commercially available [1–5] and has proven to be a valuable imaging tool providing a fused image of high resolution anatomical and quantitative functional information. Moreover, combined PET and magnetic resonance imaging (PET-MRI) has been proposed for simultaneous functional and morphological images [6–8]. Extensive studies have been carried out by several research groups to develop MR-compatible PET based on photomultiplier tube (PMT) using optical fiber technology [9–12], and avalanche photodiodes (APDs) using RF shielding technology [13, 14].

Recently, the next generation photosensor Geiger-mode avalanche photodiodes (GAPDs) [15], also called a solid state photomultiplier (SSPM) [16], silicon photomultiplier (SiPM) [17], multi pixel photon counters (MPPC) [18] and micro-pixel avalanche photodiode (MAPD) [19], was developed. GAPDs consist of a densely packed matrix with many microcells (~1000–10000) ranging from 5×5 to 100×100 μm² size, and each microcell operates independently in a Geiger mode.
as on/off switch for the photons. The amplitude of output pulse is proportional to the total number of fired microcells, reflecting the number of absorbed photons. GAPDs have been studied actively as a PET photosensor owing to their several key properties [20]. Compared to PMT, GAPDs have compactness and insensitivity to high magnetic fields. This allows GAPD to be located inside the MR bore without the need for optical fibers to integrate hybrid PET-MRI. In contrast to APDs, GAPDs have high gain \((\sim 10^6)\) and low excess noise factor \((\sim 1.1)\), allowing operation with a simple preamplifier. Their fast response time \((< 1 \text{ ns})\) allows a high true-to-random ratio as well as the development of a hybrid PET-MRI with time-of-flight (TOF) capability in human whole-body application. Further advantages over PMT and APDs are the low operating voltage \((< 100 \text{ V})\) and high uniformity \((< 20\%)\) among the pixels. In addition, the fabrication costs can be reduced substantially because it can be manufactured using a standard Metal Oxide Semiconductor (MOS) production process [21].

The utility of the charge signal transmission approach, which relays the charge signal from the photosensor to the remotely located preamplifiers for PET signal transmission, was recently reported [22]. This detector concept has several potential merits because it allows the placement of amplifier units at a safe distance for integrated PET-MR scanner, can decrease the space requirements to insert a PET scanner into the restricted MR bore, minimize the mutual interference between PET and MRI, and eliminate the need for placing RF shielding materials close to field of view of the MR scanner. Moreover, it can reduce the deterioration by temperature-related performance changes, which result from the local heat production generated in the amplifier unit, in the PET system based on semiconductor photosensor. A previous study verified that there was no considerable degradation in PET detector performance, such as photopeak position of the 511 keV energy resolution and time resolution, even though the PET charge signal was transferred via long cables (300 cm). On the other hand, the scope of our previous study was limited to the performance characterization of the PET detector that did not use the channel reduction circuits to acquire tomographic image from a PET scanner.

The aim of this study was to develop a small animal PET scanner based on GAPDs and the charge signal transmission approach. The performance of the PET detector modules was evaluated and the cross-compatibility between the PET detector module and MRI was assessed. Quantitative analysis of the full ring prototype PET was performed and tumor mouse images were acquired.

2 Materials and methods

2.1 System description

The full-ring PET contained 16 detector modules arranged in a ring, 70 mm in diameter with an axial field of view (FOV) of 13 mm (figure 1). Each PET detector was comprised of a \(4 \times 4\) lutetium yttrium oxyorthosilicate array (LYSO array, Sinocera, Shanghai, China) with an individual crystal size of \(3 \times 3 \times 10\)-mm, arranged with a \(3.3 \text{ mm}\) pitch. All crystal elements were polished and separated with white epoxy except for the photosensor face. The crystal block was coupled directly to a 3-side buttable GAPD array (SPMArray2, SensL, Cork, Ireland). Each pixel of the GAPD arrays had a \(2.85 \times 2.85\)-mm active area and 3,640 microcells of the \(35 \times 35-\mu\text{m}\). The feasibility of these GAPDs for the development of PET has been reported elsewhere [23–26].
Figure 1. Schematic diagram (a) and electronic components (b) of small animal PET. (a): The animal PET contained 16 LYSO and GAPD detector modules arranged in a 70 mm diameter ring with an axial field of view (FOV) of 13 mm. (b): The GAPD outputs were transmitted to the amplifier units and further processed in a PDC multiplexing 64 GAPD pixel output to one analog pulse signal and 6 bit position information.

The 3-meter flexible flat cables (FFCs, New Grand TECH, Shenzhen, China) were used to transmit the charge signal from the PET detector to remotely located amplifier units, which consisted of a 16 channel trans-impedance preamplifier (TIA) and a bias regulation circuit.

The TIA converted the GAPD outputs to differential voltage signals providing high gain ($\times 10^3$) without introducing additional noise and temperature-related gain instability. The bias regulation circuit could adjust the bias voltage (28.5–32.5 V) finely at \( \sim 8 \text{ mV} \) intervals using a programmable digital potentiometer (AD5231, Analog Devices, MA, USA) and it was possible to provide optimal operating conditions for the GAPDs.

The position decoder circuits (PDC) [27] that were capable of multiplexing the 64 GAPD pixel output (4 PET detectors $\times$ 16 channels/detector) to one analog pulse signal and 6 bit position information were used. In addition, the PDC contained the gain adjustable circuits to achieve gain homogeneity for all channels of the PET detectors. The 4 PDCs were used to multiplex all the 256 electrical PET signals (16 PET detectors $\times$ 16 channels/detector), which simplified the PET system design by reducing the required ADC number and analog output lines from 256 to 4 channels. Four PDC output signals were fed into the data acquisition (DAQ) unit using 10-meter twist-paired cables and co-axial cables to process the interaction position and analog signal, respectively.

The DAQ unit (Lyrtech, Quebec, Canada) consisted of free-running analog to digital converters (ADC) and a field programmable gate array (FPGA). The analog signals of the PDCs were digitized at a 105 MHz sampling rate and a 14-bit vertical resolution in the -1.25–+1.25 V range. The digitized signals were processed further by FPGA to calculate the accurate energy and time information [28]. After signal processing, the output data containing the pulse energy, arrival time and position information were recorded in the 128 MB RAM in list mode format.

2.2 Performance measurement of the PET detector modules outside MRI

A 200-kBq $^{22}$Na point source placed centrally between the paired PET detectors was used to irradiate the LYSO-GAPD arrays. The energy and time spectra were acquired at room temperature without additional cooling of the PET detectors. The energy and time resolution were calculated as the full width at half maximum (FWHM) of the Gaussian distribution plot. The lower energy
threshold was set to $\sim 350$ keV and the coincidence time window was 4 ns. The variation of the count uniformity and photopeak position of the 16 channels flood histogram were calculated as the ratio of the standard deviation to the average value.

2.3 Characterization of the cross-compatibility of PET detector module and MRI

The performance measurements of the PET detectors were also repeated in 7-T MRI (Bruker BioSpec, Ettlingen, Germany) to characterize the effect of MRI on the PET detector module. A pair of LYSO-GAPD PET detectors was inserted inside the MRI bore between the RF coil and gradient coils. The GAPD outputs were transmitted to the amplifier units using 3-meter FFCs. The PET electronics were positioned outside of the 5-Gauss line ($\sim$1.5-meters away from the magnet isocenter) in the MR to minimize the mutual interference between PET and MRI. In this study, no electromagnetic shielding was introduced to protect the PET components from the MR gradient and RF field.

A uniform cylindrical phantom (30 mm diameter, 100 mm length) filled with a copper sulfate solution was imaged to examine the effect of the PET detector modules on MR images. The CuSO$_4$-filled phantom was placed isocentrically inside the RF-coil, and the transaxial images were acquired with and without a pair of LYSO-GAPD PET detectors inside the MR bore. The standard MR imaging sequences, including the Gradient echo (TR = 205 ms, TE = 6 ms, FA = 15 degree), Spin echo T1 (TR = 419 ms, TE = 8 ms) and Spin echo T2 (TR = 3,000 ms, TE = 75 ms) were used in this study. The ParaVision software (Bruker BioSpec, Ettlingen, Germany) was used to acquire and process the MR data, such as data acquisition, analysis, reconstruction and visualization. Representative three transaxial MR image slices with a 5 mm interval in the axial direction were analyzed quantitatively. A region of interest (ROI) was drawn at the center of the phantom image enclosing approximately 80% of the phantom and the uniformity and signal to noise ratio (SNR) were calculated from the ROI. The experimental tests were repeated five times to minimize the measurement errors. In each measurement, the MR phantom was re-positioned and the RF-coil was re-inserted and re-tuned.

2.4 Phantom and small animal imaging of the full ring PET

The list-mode data of the full ring PET were rebinned using a single slice rebinning (SSRB) method and the valid events were sorted into the 2D sinogram, which had 43 samples in the transverse direction and 79 angular samples. The transverse sampling distance was 1.5 mm near the CFOV. The sinogram was normalized for the detector efficiency, and these normalization factors were estimated from a direct inversion of the sinogram acquired with a uniform cylindrical phantom filled with a $^{18}$F-FDG solution. The missing data caused by the effect of the gaps was compensated for by a nearest neighbor 1-D interpolation in the radial direction [29]. The PET images were reconstructed by a 2D filtered backprojection (2D FBP) using a Hanning filter with a cutoff at the Nyquist frequency.

2.4.1 Spatial resolution and sensitivity

The spatial resolution of the prototype PET was measured using a glass capillary tube with an inner diameter of 0.5 mm. The line source was placed at five radial offset locations of 0, 10, 15,
20 and 25 mm in the FOV. Each line source was filled with approximately 370-kBq of a $^{18}$F-FDG solution. The radial profiles of each location were fitted with Gaussian profiles and its width was measured by the FWHM. The coincidence sensitivity of the prototype PET was measured using a point source with an inner diameter of 0.5 mm. A 200-kBq $^{22}$Na point source was located precisely at the center of the ring and the PET data was acquired for 1 min. The data recorded in list mode format was sorted using four different energy windows ranging from $\pm 10\%$ (460–560 keV) to $\pm 40\%$ (300–710 keV). A coincidence time window of 4 ns was applied.

The system sensitivity was calculated as the number of detected events divided by the number of decays by positron emissions that were predicted to have occurred during the acquisition period.

### 2.4.2 Phantom images

Two cable lengths (10 cm and 300 cm FFCs), connecting the GAPD arrays to the amplifier units, were used to evaluate the effect of the cable length on the PET image. Custom-made hot-sphere phantoms, 60 mm in diameter, were used to examine the imaging performance. The sphere diameters were 3, 4, 5, 6 and 7 mm and the center-to-center distance between the spheres was twice their diameter. The phantoms were filled with a 20 MBq $^{18}$F-FDG solution. The PET imaging data was acquired for 10 minutes.

### 2.4.3 Mouse images

An in vivo rodent imaging study was performed in accordance with the protocols approved by the Samsung Biomedical Research Institute (SBRI) in Korea. A male mouse with a tumor in the right thigh was injected with 100-MBq of $^{18}$F-FDG through the tail vein and imaged after 1 hour of radiotracer uptake. The mouse was placed on a carbon animal bed with a heating pad that maintained a temperature of 37 °C. During the PET scan, the mouse was anesthetized by isoflurane inhalation and respiration was monitored. The PET imaging data was acquired for 10 minutes/bed at 2 different bed positions. Figure 2 shows the experimental setup.

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**Figure 2.** Experiment setup for the mouse imaging study. The prototype PET was installed with a heating pad, anesthesia and respiration monitoring systems for the in-vivo study.
3 Results

3.1 Performance of the PET detector modules outside the MRI

Figure 3 shows the representative energy and time spectrum of the PET detector. The mean energy resolution was 17.6%, ranging from 16% to 19%. The time resolution obtained was 1.5 ns for 511-keV photons. Figure 4.a shows the flood histogram of the data acquired from the PET detector. The variation of the count uniformity was 3.3%. The variation of the photopeak position of the LYSO-GAPD detector was 3.9% and was improved after gain adjustment of the PDC (figure 4.b).
Figure 5. Energy spectra (a) and Time spectra (b) acquired both outside and inside the MRI. No obvious performance degradation of the PET detectors was observed.

Figure 6. Quantitative analysis of the MR phantom images in terms of the SNR (left) and uniformity (right): gradient echo (first row), T1 weighted spin echo (second row) and T2 weighted spin echo (third row).

3.2 Characterization of the cross-compatibility of PET detector module and MRI

The energy and time spectra were acquired simultaneously for approximately 5 min, whereas MR imaging was performed using three different sequences, as shown in figure 5. No obvious performance degradation of the PET detectors was observed, as measured by the energy and time resolution. In addition, the photopeak position and coincidence count rate were similar regardless of whether the PET detectors had been operated outside or inside the MRI.
Figure 7. Spatial resolution of the developed PET. The measured radial resolution ranged from 2.8 mm to 4.1 mm.

Table 1. Sensitivity at the CFOV for the 4 different energy window settings.

<table>
<thead>
<tr>
<th>Energy window</th>
<th>Total counts</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>460–560 keV (10%)</td>
<td>11,396</td>
<td>0.29</td>
</tr>
<tr>
<td>410–615 keV (20%)</td>
<td>18,894</td>
<td>0.48</td>
</tr>
<tr>
<td>350–650 keV (30%)</td>
<td>25,843</td>
<td>0.65</td>
</tr>
<tr>
<td>300–710 keV (40%)</td>
<td>31,050</td>
<td>0.78</td>
</tr>
</tbody>
</table>

There were no significant artifacts or distortions observed in the MR phantom images. Figure 6 shows the calculated values of the uniformity and SNR for three MR sequences. There was no major loss caused by inserting the PET detector modules in the SNR and uniformity of MR images.

3.3 Phantom and small animal imaging of the full ring PET

3.3.1 Spatial resolution and sensitivity

Figure 7 shows the measured phantom images and radial profiles for 5 different radial offsets across the useful FOV. The radial resolution was 2.8 mm FWHM at the CFOV, which increased to 4.1 mm with a 20 mm offset.

Table 1 lists the sensitivity at the CFOV for different energy window settings. The sensitivity was corrected for a branching ratio of $^{22}\text{Na}$ (0.906). The system sensitivity increased approximately four times as the energy window was changed from 460–560 keV to 300–710 keV. The prototype PET had a peak sensitivity of 0.65% in the standard energy window of 350–650 keV.

3.3.2 Phantom images

Figure 8 shows transverse phantom images and line profiles acquired using the 10 cm (a) and 300 cm (b) FFCs connecting GAPDs and preamplifiers. The 3 mm diameter was clearly resolved in the hot-sphere phantom images. As expected from previous studies [22], there was no degradation of the PET image quality caused by employing a long cable (300 cm) from the GAPDs to the preamplifiers used for PET signal transmission.
Figure 8. Hot-sphere phantom images and line profiles were acquired using the 10 cm (a) and 300 cm (b) FFCs between GAPDs and preamplifiers. There was no degradation of the PET image quality caused by the long cable (300 cm) from the GAPDs to the preamplifiers in the PET signal transmission.

3.3.3 Mouse images

A PET mouse image was acquired to demonstrate the potential of this prototype system for an in vivo study. Figure 9 shows the reconstructed transaxial PET images of a mouse. The mouse brain and tumor displaying the glucose metabolism patterns were well imaged.

4 Discussion

A small animal PET based on the GAPDs and a charge signal transmission approach was developed. In this system, the charge signals of GAPDs were transmitted to the amplifier units positioned far away from the PET detectors or outside the MR bore using long transmission cables. The initial PET images of the phantom and tumor mouse were obtained in this study. In addition, simultaneous PET and MR data was acquired with no deterioration in the performance of both PET detector modules and MRI. The concept proposed in this study might provide several technical advantages.

It is feasible to develop a PET system based on a semiconductor photosensor with no obvious loss of PET performance. Unfortunately, APDs have not achieved the traditional PMT performance. The low internal gain of the APD ($< 10^2$) requires the use of sophisticated low noise preamplifiers [30]. The overall time resolution of the imaging device is reduced by the significantly inferior timing properties of the APDs due to the slow rise time, high time jitter, high noise factor, and low signal-to-noise ratios [21]. This results in a wider coincidence time window and an
increased number of random coincidence counts, which will degrade the image quality of PET. On the other hand, GAPD can overcome these technical challenges. Simple electronics can be used in the development of PET based on GAPD. In addition, GAPD can provide good PET performance, such as energy resolution (figure 3. (a)), time resolution (figure 3. (b)), count uniformity (figure 4. (a)) and long-term stability [25]. The inherent characteristics of the GAPDs could improve the PET image performance by providing a high SNR and high true-to-random coincidence rates.

In addition, the energy resolution of the 511-keV photopeaks was $\sim 17\%$ on average for all crystals, which is better than the $\sim 25\%$ [31] and $\sim 27\%$ [32] energy resolutions obtained for previously reported animal PET scanners based on GAPD and LGSO. This may be the result of the detector configuration, where the individual LYSO crystal was coupled one to one to a separate pixel of the GAPD and the output signals from each PET detector module were processed independently using the PDC, which could eliminate the performance degradation caused by optical crosstalk through the light guide inserted between the crystal block and photosensor array in the conventional detector configuration based on the Anger type channel reduction circuit.

As shown in figure 8, the developed PET system using 300 cm long cables produced phantom images without noticeable quality degradation. Moreover, the charge signal transmission approach could minimize the deterioration by temperature changes. A potential technical hurdle is that the PET performance degrades gradually by the heat generated from the amplifiers unit in the PET system based on semiconductor photosensor [22]. Previous studies using a semiconductor photosensor
employed a costly cooling system or gain control system to minimize the temperature-related performance variations of the photosensor [33–36]. This detector concept, photosensors and amplifiers fabricated in the separated housing box, could minimize the temperature-related performance variations of the photosensor, such as the gain, PDE and changes in dark currents, which could affect the PET performance, such as altered photo-peak position, decreased count rate, degraded energy resolution and time resolution.

In terms of the MR compatibility, the developed PET system only requires the placement of non-magnetic PET components, scintillation crystals and GAPD arrays without preamplifiers and subsequent electrical circuits, inside the MR bore. The PET system requires only low DC power supplies with low current consumption (∼32 V, < 2 mA) inside the MR bore. Moreover, this system does not introduce conducting materials, such as RF shielding materials and electronic circuits inside the MR bore, which can produce eddy currents and heat from the high power switching gradient coil [37–39]. The free scalability of the PET geometry, such as transaxial and axial FOV, are an additional advantage by locating the amplifier units at low fringe field areas, which could decrease the space requirements to insert a PET scanner into the restricted MR bore.

This study had some limitations. First, the spatial resolution was relatively poor compared to other systems based on the Anger logic circuit, which was caused by the one to one coupling of an individual crystal with a separate pixel of large area GAPDs (∼3 × 3 mm²). Although the PET spatial resolution was poor, these results demonstrate that it was feasible to develop small animal PET using GAPDs and charge signal transmission approach technologies. Moreover, the coincidence detection efficiency was improved by a factor of ∼2 when the crystal length was increased from 5 mm to 10 mm at the expense of parallax error. A sensitivity of ∼0.7% was acquired using the developed PET, even though it had a shorter axial FOV and larger transaxial FOV than other prototype systems [12-14, 40]. Second, simultaneous PET-MR images were not acquired because it was difficult to use a radioisotope in a MR imaging site. On the other hand, the feasibility of hybrid PET-MRI with this system design was observed to some extent (figure 5 and 6). Nevertheless, further studies will be needed to improve the spatial resolution using smaller size GAPDs and acquire simultaneous PET-MR images using a range of MR imaging sequences.

5 Conclusion

A small animal PET was developed based on GAPDs and the charge signal transmission approach. The PET detector performance and cross-compatibility were examined. Quantitative analysis of the full ring prototype PET was performed and the tumor mouse images were acquired successfully. These results demonstrated that the GAPD and charge signal transmission approach allow the development of high performance small animal PET with improved MR compatibility.

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