Development of a dual modality imaging system: a combined gamma camera and optical imager

This article has been downloaded from IOPscience. Please scroll down to see the full text article.
(http://iopscience.iop.org/0031-9155/54/14/011)

View the table of contents for this issue, or go to the journal homepage for more

Download details:
IP Address: 171.67.172.41
The article was downloaded on 05/02/2011 at 04:31

Please note that terms and conditions apply.
Development of a dual modality imaging system: a combined gamma camera and optical imager

Jin Ho Jung, Yong Choi, Key Jo Hong, Byung Jun Min, Joon Young Choi, Yearn Seong Choe, Kyung-Han Lee and Byung-Tae Kim

Department of Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-Dong, Gangnam-Gu, Seoul 135-710, Korea

Received 7 May 2009
Published 26 June 2009
Online at stacks.iop.org/PMB/54/4547

Abstract
Several groups have reported the development of dual modality Gamma camera/optical imagers, which are useful tools for investigating biological processes in experimental animals. While previously reported dual modality imaging instrumentation usually employed a separated gamma camera and optical imager, we designed a detector using a position sensitive photomultiplier tube (PSPMT) that is capable of imaging both gamma rays and optical photons for combined gamma camera and optical imager. The proposed system consists of a parallel-hole collimator, an array-type crystal and a PSPMT. The top surface of the collimator and array crystals is left open to allow optical photons to reach the PSPMT. Pulse height spectra and planar images were obtained using a Tc-99m source and a green LED to estimate gamma and optical imaging performances. When both gamma rays and optical photon signals were detected, the signal interferences caused by each other signal were evaluated. A mouse phantom and an ICR mouse containing a gamma ray and optical photon source were imaged to assess the imaging capabilities of the system. The sensitivity, energy resolution and spatial resolution of the gamma image acquired using Tc-99m were 1.1 cps/kBq, 26% and 2.1 mm, respectively. The spatial resolution of the optical image acquired with an LED was 3.5 mm. Signal-to-signal interference due to the optical photon signal in the gamma pulse height spectrum was negligible. However, the pulse height spectrum of the optical photon signal was found to be affected by the gamma signal, and was obtained between signals generated by gamma rays with a correction using a veto gate. Gamma ray and optical photon images of the mouse phantom and ICR mouse were successfully obtained using the single detector. The experimental results indicated that both optical photon and gamma ray imaging are feasible using a detector based on the proposed PSPMT.
1. Introduction

Optical imaging has been widely used for the \textit{in vivo} imaging of small animals, and has become an essential tool for studying biological processes at molecular and cellular levels, e.g., gene expression, cell trafficking and drug efficacy (Andersson-Engels \textit{et al.} 1997, Wagnieres \textit{et al.} 1998, Bugaj \textit{et al.} 2001, Beuthan \textit{et al.} 2002, Lewis \textit{et al.} 2002). The advantage of this technique is that optical probes permit the sensitive detection of many biological molecules. Furthermore, the majority of optical probes are easy to handle because they involve non-ionizing low-energy radiation. Additionally, this technique allows continuous data acquisition, and thus, is suitable for the real-time monitoring of target molecules.

Optical imaging techniques, on the other hand, are not currently quantitative because the intensities of optical signals are reduced by the absorption and scattering of optical photons, which are dependent on source depth in tissue (Contag \textit{et al.} 1995). Furthermore, findings obtained using this technique cannot be easily transferred from preclinical models to clinical applications, with the exception of some specific applications at or near the skin surface. Hence, a dual modality technique that combines nuclear medicine imaging, CT or MRI to optical imaging is required to overcome these drawbacks of optical imaging.

Among the various imaging modalities available, the gamma camera has several advantages over other modalities in terms of providing functional information about a specific organ or body system. Furthermore, gamma cameras are usually cheaper and simpler than PET, CT or MRI instrumentations (Kim \textit{et al.} 2000, Verger \textit{et al.} 2004, Despres \textit{et al.} 2006). In addition, gamma cameras, unlike PET, are capable of providing images of multiple radio-labeled probes using energy discrimination methods if each molecular probe is labeled with radioisotopes that emit gamma rays of different energies. Moreover, gamma camera imaging can be used to complement optical imaging in the molecular imaging field. For example, quantitative measurements of biological processes deep inside tissues can be achieved using a gamma camera, whereas optical imager is limited in this context.

Recently, several groups have devised dual modality imaging systems, combined a gamma camera and an optical imager, and have demonstrated the potential usefulnesses of these combined systems (Celentano \textit{et al.} 2003, Autiero \textit{et al.} 2005, Peter and Semmler 2007). The advantage of the dual modality approach is that biological information can be acquired simultaneously without moving the animal concerned, which allows results to be cross-validated. Another advantage is that it allows multiple molecular target images simultaneously by using probes labelled with different radionuclides and/or fluorescence probes with different emission spectra.

However, previous studies on the combined systems have usually used a separate gamma camera and optical imager, whereas we have designed a detector based on a position sensitive photomultiplier tube (PSPMT) that is capable of imaging gamma rays and optical photons. The devised dual modality imaging instrumentation consisted of a parallel-hole collimator, an array-type scintillator and a PSPMT. A small size detector and amplifier circuits dedicated to gamma ray and optical photon signal processing were fabricated. The intrinsic and system performances of the proposed detector for both signal types were measured. Mouse phantom and institute for cancer research (ICR) mouse images were acquired to assess the gamma and optical imaging capabilities of the devised system.
Development of a dual modality imaging system

2. Materials and methods

2.1. Detector design of the dual modality imaging system

The dual modality imaging instrumentation proposed in this study consists of a parallel-hole collimator, an array-type scintillator and a position sensitive PMT (PSPMT). The black cover usually applied at the entrance surface of the collimator was removed to allow optical photons that passed through the collimator holes to be detected, as shown in figure 1. The white reflector that is normally covered on the top surface of the crystal was also not applied for optical imaging. The detector was designed for operation in a light tight box.

In order to test the detector concept, we constructed a small-size detector that consisted of a general-purpose parallel-hole collimator, a CsI(Tl) array crystal and a H8500 flat panel PSPMT (Hamamatsu Photonics K. K., Hamamatsu City, Japan). Collimator hole size, length and septa thickness were 1.5 mm, 24 mm and 0.2 mm, respectively. The crystal consisted of a $24 \times 24$ array of $1.6 \times 1.6 \times 4$ mm CsI(Tl). Individual crystal elements were mechanically polished on all sides, and were optically isolated using a white epoxy resin of 0.2 mm thickness. The crystal was optically coupled to the PSPMT.

2.2. Readout circuit

Sixty-four anode signals and the dynode signal of the PSPMT were fed into a preamplifier circuit, which incorporates a resistive charge divider and a current-to-voltage amplifier. The charge divider circuit reduced readout channel numbers from 64 to $8X+8Y$ (Popov et al 2006).
Figure 2. Output pulses from the shaping amplifiers obtained using Tc-99m (a) and a green LED (b).

Figure 3. Schematic diagram of the readout circuit used to process gamma rays and optical signals.

After initial amplification, the 8X+8Y anode signals were fed into custom-made shaping amplifiers and then digitized using an analog-to-digital converter (ADC). Shaping times and gains of the shaping amplifiers designed for the gamma ray and optical signal processing were 1.5 μs/10 and 0.03 μs/25, respectively. Figures 2(a) and (b) show pulses from one output of the 8X and 8Y shaping amplifiers obtained using Tc-99m and a green LED. Amplitudes of the shaped signals generated by a 140 keV gamma ray and a 3 eV single photon were 2 V and 0.4 V, respectively.

The dynode signal was sent to the constant fraction discriminators (CFD) to generate timing pulse on the input signals. The CFD low-level discriminator (LLD) threshold for the gamma signal was set just above the amplitude of the optical signal. The LLD threshold for optical signal was chosen to be as low as possible, but sufficiently high to avoid triggering electrical noise. CFD pulses were fed into GATE and Delay Generators (G&D) to provide a trigger to the ADC when an event was detected. The widths of trigger pulses were adjusted according to the widths of shaping amplifier outputs for gamma ray and optical signals. Trigger pulses generated by gamma rays were also used to generate veto pulses of width 4 μs, which suppress the digitization of false optical photon signals caused by low energy scattered events or scintillator afterglow. Standard nuclear instrumentation modules were used for the CFD and G&D. A schematic diagram of the readout circuit is illustrated in figure 3.

2.3. Measurement of the gamma-imaging performance

2.3.1. Intrinsic performance. A Tc-99m point source with an activity of 2.2 MBq was located 120 mm above the CsI(Tl) array crystal. A flood image was then acquired for 30 min. Average peak-to-valley ratio of the row profile in the flood image was calculated to assess pixel identification ability. In addition, a position look-up table for crystal pixels was
produced using a flood image to classify the boundaries of pixel elements. The look-up table was applied to both gamma and optical planar images.

2.3.2. System performance. A Tc-99m point source with an activity of 0.7 MBq and green LED were located 120 mm above the collimator. Data for gamma ray imaging were acquired for 10 min, and then system sensitivity was measured. Pulse height spectra were also acquired with the LED turned on and off. Energy resolutions and photopoint positions of the spectra were measured to access the effect of signal interference due to optical photon signals from the LED.

Two capillary tubes (0.5 mm inner diameter, 50 mm length and 20 mm pitch) filled with 2.2 MBq Tc-99m were placed in direct contact with the collimator. A planar image was then acquired for 30 min. The row profile of the planar image was then plotted and fitted with a Gaussian function. The full width at half-maximum (FWHM) of the fitted curve was calculated to estimate the spatial resolution of the system.

In addition, a Micro Deluxe phantom with rod diameters ranging between 1.2 and 4.8 mm was placed in direct contact with the collimator. The phantom was filled with 27.7 MBq Tc-99m. The planar image of the phantom was acquired for 30 min.

All experimental data were acquired using the 20% energy window applied globally based on the location of the photopoint of the pulse height spectrum of the entire CsI(Tl) array.

2.4. Measurement of the optical imaging performance
2.4.1. Intrinsic performance. In order to test the optical imaging performance of the proposed detector, a green LED was used as an optical source, because it emits lights at wavelengths that correspond to those emitted from fluorescence sources. Black paper (52 mm × 52 mm) containing four 1.6 mm holes separated by 6 mm was placed on top of the crystal, and then planar images of the four holes were obtained for 1 min by moving a green LED along the holes. Row profiles of the planar images were plotted and then fitted with a Gaussian function. The FWHM of the fitted curve was calculated to estimate intrinsic spatial resolution.

2.4.2. System performance. Two black masks, shown in figure 4, were placed on the collimator entrance surface, and a green LED was located 50 mm above the collimator. LED and background pulse height spectra were measured to evaluate the signal-to-noise ratio and to set an energy threshold to improve optical image contrast. The threshold value was chosen by selecting an energy region corresponding to the dark count from the total pulse height spectrum.

A Tc-99m point source with an activity of 1.8 MBq was then located at same position with the green LED. In order to access the possibility of signal interference due to the gamma ray signal, pulse height spectra were obtained for 1 min with the LED turned on and off while the gamma ray from Tc-99m was emitted.

Planar images were also acquired for 1 min using only the LED to examine the optical source localization performance.

2.5. Measurement of the dual modality imaging performance
2.5.1. Phantom study. A mouse phantom containing an optical source (Xenogen, Hopkinton, MA) was used. A Co-57 phantom source of diameter 1 mm with activity 0.3 MBq was also used and attached to the surface of the left leg of the mouse phantom where the optical source was located. The phantom was positioned at 85 mm from the collimator. A xenon-arc
lamp (Sutter Instrument Corp., Novato, CA) equipped with a 530–560 nm excitation filter (Chroma Technology Corp., Brattleboro, VT) was used to excite the fluorophore within the mouse phantom. An emission filter (590–650 nm) was mounted on the collimator to collect light emitted within the mouse phantom. Planar images of gamma ray and optical signals were sequentially obtained for 1 min each to assess the imaging ability of the proposed system.

2.5.2. Animal study. An ICR male mouse was used for planar animal imaging. The mouse was injected with 259 MBq of Tc-99m methylene diphosphonate (MDP) via a tail vein for gamma imaging, and SNU-C5 cells ($1 \times 10^8$), which express the green fluorescent protein (GFP) gene, were injected subcutaneously into the right shoulder for optical imaging. The mouse was anesthetized subcutaneously with a mixture of ketamine and xylazine in the abdominal region and then positioned at 50 mm from the collimator. GFP imaging was performed using 460–500 nm excitation and 510–560 nm emission filters.

An optical image was obtained for 1 min at 2 h after Tc-99m MDP injection, and then a gamma image was sequentially acquired for 5 min. These two images were then superimposed to assess the imaging ability of the proposed system. All animal experiments were conducted according to the guidelines issued by the Samsung Medical Center Laboratory Animal Care, which comply with the National Institutes of Health guidelines.

3. Results

3.1. Measurement of the gamma imaging performance

3.1.1. Intrinsic performance. Figure 5 shows a flood image, the position look-up table and the row profile of the CsI(Tl) array crystal acquired using a Tc-99m source. All crystal elements were clearly identified. The average peak-to-valley ratio was 6.7:1.

3.1.2. System performance. System sensitivity measured using a Tc-99m source was 0.1 cps/kBq. Pulse height spectra for Tc-99m acquired with the LED turned on and off are shown in figure 6(a). Energy resolution in both cases was 26%, and the difference in photopeak positions was 2%. Average system spatial resolution of the two capillary tubes image was 2.1 mm.

A planar image of the Micro Deluxe phantom was obtained using the proposed detector. As shown in figures 6(b) and (c), rod sizes from 4.8 to 2.4 mm were clearly resolved.
3.2. Measurement of the optical imaging performance

3.2.1. Intrinsic performance. Figure 7 shows the planar image and the row profiles of the four hole mask acquired using the green LED. The average intrinsic spatial resolution of the planar image was 3.5 mm.

3.2.2. System performance. Green LED and background pulse height spectra were acquired, as illustrated in figure 8(a), the signal-to-noise ratio was 2.8:1. The empirically determined energy threshold channel was 35, which was the position where the ratio of signal to background counts was higher than 3. Figure 8(b) shows pulse height spectra obtained using the green LED turned on and off in the presence of 1.8 MBq Tc-99m. The pulse height spectrum of the optical photon signal was affected by the gamma signal from Tc-99m. The ratios of the background, gamma ray and total counts were 0.3:0.2:1. Pattern images of three and four hole black masks acquired with the green LED are shown in figures 9(a) and (b). Each hole was well localized, and differences in the hole size were evident in the image.

3.3. Measurement of the dual modality performance

3.3.1. Phantom study. Optical photon and gamma ray images from the mouse phantom containing an optical source and a Co-57 source were successfully obtained using the proposed
Figure 6. Pulse height spectra (a) measured using Tc-99m when the green LED was turned on (gray dashed line) or turned off (black solid line). Photograph (b) and gamma ray image (c) of the hot-rod insert of the micro deluxe phantom.

Figure 7. Planar image (a) and row profiles (b) of the 4 holes mask obtained using the green LED.
Development of a dual modality imaging system

Figure 8. Pulse height spectra (a) of background (dotted line) and green LED without Tc-99m (solid line). Pulse height spectra (b) of the background (dotted line) and green LED turned off (dashed line) or turned on (solid line) with Tc-99m.

Figure 9. Three (a) and four hole (b) black mask images obtained using the green LED.

detector. These images were then fused with a photograph of the mouse phantom, as shown in figure 10.

3.3.2. Animal study. Figure 11 illustrates the photograph, optical photon, gamma ray and fused images of an anesthetized ICR mouse injected with SNU-C5 cells and Tc-99m MDP. The gamma ray image showed activity distributions in bone structures, such as, the skull, forelimbs and cervical spine, whereas the optical image demonstrated the biodistribution of the SNU-C5 cells.

4. Discussion

The dual modality imaging technique can provide more information on biological processes in living organisms than single imaging modality (Beyer et al 2000, Hong et al 2006, Judenhofer et al 2008). In this study, dual modality imaging instrumentation combining gamma camera and optical imager was constructed because sequentially or simultaneously acquired gamma and optical images can provide complementary information as previously described (Zhang et al 2005, Li et al 2006, Culver et al 2008). For example, the localization and quantitative
Figure 10. Planar images of the mouse phantom containing an optical source (a) and a Co-57 (b) obtained using the proposed detector (top row). Both images were fused with a photograph of the mouse phantom (bottom row).

evaluation of the target biological process can be achieved using the gamma images, and subsequent long-term changes can be monitored longitudinally using the optical images.

The amplitudes of analog pulses generated by gamma signals were at least 10 times larger than those generated by optical signals. Thus, gamma signals were easily distinguished from the optical signals by setting a trigger level above the voltage level corresponding to the optical signal. Signal interferences caused by optical signals in the gamma pulse height spectra were also negligibly small, as shown in figure 6(a). On the other hand, optical photon signals must be acquired between signals generated by gamma rays, because it is difficult to distinguish real optical signals from overlapped gamma and optical signals during the scintillation decay time of CsI(Tl). This introduces a dead time corresponding to the decay time of CsI(Tl) in the optical signal processing system. In order to reject bad optical photon signals due to low energy scattered events or scintillator afterglow, a veto gate was utilized. The width of the veto pulse was set at 4 μs because the slowest decay time of CsI(Tl) was 3.3 μs at the room temperature (Valentine et al 1993). As shown in figure 8(b), optical pulse height spectra of a green LED were successfully acquired using the above-mentioned readout scheme in the presence of Tc-99m, and these data were similar to the findings of a previous optical/PET study (Prout et al 2005). However, residual distorted optical signals, which corresponded to about 20% of total counts, were still detected, as demonstrated by pulse height spectra obtained with the LED turned off (figure 8(b)). These unexpected events could be reduced by setting a wider veto gate in the readout circuit.

Positioning distortions caused by the non-uniform spatial response of the PSPMT were improved by implementing a position look-up table for planar images (Wojcik et al 1998).
In this study, the look-up table was made using a flood image acquired with the gamma ray source, because individual crystal pixels were not resolved by using low energy (3 eV) optical signals. The look-up table was applied to gamma and optical images, and the positioning distortion was not found in corrected images, as shown in figures 6(c) and 9.

The system sensitivity of the proposed detector on gamma ray signal was 0.1 cps/kBq, which compares with those of dedicated gamma cameras with CsI(Tl) array crystal (Pani et al 2002, Jeong et al 2004). Energy resolutions of the dedicated gamma cameras have been reported to range from 19% to 24% (Herbert et al 2002, Pani et al 2003, Trotta et al 2007) and that of our system in this study was slightly worse at 26%. This degradation can largely be attributed to the fact that the numbers of scintillation lights collected by the sensor were reduced by removing the white reflector covering the top surface of the crystal. Energy resolution could be improved by acquiring the pulse height spectra of individual crystals (Wojcik et al 1998) and by employing a dichromic mirror on the upper crystal surface.

The dependence of light transmission through the CsI(Tl) crystal on wavelength needs to be considered when using the proposed detector as an optical signal detection sensor. Previously reported transmission fractions for wavelengths (from 510 to 700 nm) of interest for optical imaging range from 70% to 80% (Woody et al 1992), which is sufficient for our dual modality imaging system.

In a previous study, the length of the veto gate chosen to block optical signals generated by gamma ray was 12 μs, which was 20 times longer than the slow decay time (0.6 μs) of GSO. Sensitivity of the detector used in this previous study was comparable to a conventional optical imager based on a charge-couple device (CCD) (Prout et al 2004, 2005). Therefore, the sensitivity of the detector proposed in this study, which employs CsI(Tl), might be four times less than that of a conventional optical imager, assuming that the veto gate is set at 60 μs. Additionally, the existence of a collimator in front of the detector significantly reduces the overall sensitivity of the optical imager and increases the acquisition time compared with a conventional optical imager. Nevertheless, the acquisition time for optical imaging would considerably be shorter than that for gamma imaging because the number of incident optical photons is higher.
Average intrinsic spatial resolution of the proposed detector for optical imaging was 3.5 mm, which would be sufficient for the in vivo imaging of a source embedded at a depth of a few millimeters within tissue (Rice et al 2001). Planar optical images of the black mask with different hole sizes were successfully acquired using the PSPMT-based detector. Hole locations were clearly delineated, and differences between hole sizes were evident.

A fused mouse phantom image demonstrated that each source was accurately localized without distortion of positioning by the other signal, even when gamma and optical sources were located at the same position. Small animal experiment results (figure 11) demonstrated that the proposed dual modality imaging instrumentation can provide functional information, such as, on the distribution of SNU-C5 cells, and anatomical information, such as, on bone structure simultaneously in one animal. In addition, the gamma images acquired with that instrumentation would allow quantitative analysis of the image because of less attenuation in tissue.

5. Conclusion

In this study, a detector concept of dual modality Gamma camera/optical imager capable of imaging both gamma ray and optical photon using a single detector was proposed and a proof-of-principle system was fabricated. The experimental results indicate that both gamma ray and optical imaging are feasible using the detector based on a PSPMT proposed in this study. This detector is both simple and cost effective and could allow simultaneous optical and gamma camera data acquisition, which would be useful for imaging and analyzing in vivo biological processes.

Acknowledgments

This study was supported by a grant of the Industrial Source Technology Development Programs, the Ministry of Knowledge Economy and by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MEST) (No. 2007-00321), Republic of Korea.

References

Culver J, Akers W and Achilefu S 2008 Multimodality molecular imaging with combined optical and SPECT/PET modalities J. Nucl. Med. 49 169–72
Herbert D J, Meng L J and Ramsden D 2002 Investigating the energy resolution of arrays of small scintillation crystals


Prout D L, Silverman R W and Chatziioannou A 2004 Detector concept for OPET-A combined PET and optical imaging system IEEE Trans. Nucl. Sci. 51 752–6


