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Design and performance of a multi-pinhole collimation device for small animal imaging with clinical SPECT and SPECT-CT scanners

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Abstract

A multi-pinhole collimation device is developed that uses the gamma camera detectors of a clinical SPECT or SPECT-CT scanner to produce high resolution SPECT images. The device consists of a rotating cylindrical collimator having 22 tungsten pinholes with 0.9 mm diameter apertures and an animal bed inside the collimator that moves linearly to provide helical or ordered-subsets axial sampling. CT images also may be acquired on a SPECT-CT scanner for purposes of image co-registration and SPECT attenuation correction. The device is placed on the patient table of the scanner without attaching to the detectors or scanner gantry. The system geometry is calibrated in-place from point source data and is then used during image reconstruction. The SPECT imaging performance of the device is evaluated with test phantom scans. Spatial resolution from reconstructed point source images is measured to be 0.6 mm full width at half maximum or better. Micro-Derenzo phantom images demonstrate the ability to resolve 0.7 mm diameter rod patterns. The axial slabs of a Micro-Defrise phantom are visualized well. Collimator efficiency exceeds 0.05% at the center of the field of view, and images of a uniform phantom show acceptable uniformity and minimal artifact. The overall simplicity and relatively good imaging performance of the device make it an interesting low-cost alternative to dedicated small animal scanners.

Keywords

SPECT; SPECT-CT; pinhole; collimation; high resolution; small animal

1. Introduction

1.1. Background

The value of non-invasive single photon emission computed tomography (SPECT) imaging of small animals in pre-clinical research is widely recognized (Meikle *et al.*, 2005). Because of the need for high spatial resolution, several advanced designs have been developed for small animal SPECT scanners (Rowland and Cherry, 2008). Most research and commercial small animal SPECT scanners utilize pinhole collimation with magnification in order to achieve sub-millimeter spatial resolution. Many designs have multiple detectors and multiple pinholes per detector to improve system sensitivity and overall image quality. Some commercial hybrid scanners integrate SPECT detectors with high resolution x-ray computed tomography (CT) detectors to generate multi-modality images with co-registered molecular (SPECT) and anatomic (CT) information (Schramm *et al.*, 2007; Gleason *et al.*, 2006; Hugg *et al.*, 2006;

Parnham *et al.*, 2006), while an alternate approach is to have separate scanners with interchangeable animal beds (Beekman and Hutton, 2007).

Although compact advanced gamma ray detectors with high intrinsic resolution are often selected, conventional gamma camera detectors are commonly used in small animal SPECT scanners. With a suitable magnification factor, the relatively poor intrinsic resolution of a gamma camera may have negligible impact on reconstructed spatial resolution. The large surface area of a gamma camera translates into a large space-bandwidth product (Barrett and Hunter, 2005), which is recognized as a figure of merit for imaging performance. Other favorable properties of a gamma camera include good energy resolution, high gamma ray absorption efficiency, and relatively low manufacturing cost. The widespread availability of gamma cameras in clinical imaging departments poses an opportunity for use in small animal SPECT research. Several research groups have developed custom-built pinhole collimator attachments for clinical gamma cameras to produce high-quality small animal SPECT images, including (Jaszczak *et al.*, 1994; Weber *et al.*, 1994; Schramm *et al.*, 2003; Moore *et al.*, 2004; Metzler *et al.*, 2005).

1.2. Detached collimation

An alternative to pinhole collimators mounted to gamma cameras is an independent collimation device that is not physically coupled to the gamma cameras and that requires no custom mounting hardware. An early version of this concept (DiFilippo *et al.*, 2006) consists of a shielded box with up to 14 pinholes. The object to be imaged is mounted vertically on a rotary stage within the shielded box. The entire device is placed on the patient table of a dual-detector clinical SPECT scanner with collimators removed. To acquire SPECT data, the object to be imaged is rotated in a step-and-shoot fashion while the pinholes and detectors are stationary. Geometric calibration is achieved by imaging point source markers along with the object to be imaged.

Although this device performs well and is very simple in design, it has some disadvantages. The vertical orientation is not ideal for animal imaging and may potentially interfere with the animal's physiology and the distribution of the SPECT radiopharmaceutical (Stevenson, 2005). The vertical orientation also causes difficulties when attempting to co-register the SPECT images with CT images acquired with the animal in a horizontal orientation. The lack of a linear drive mechanism prevents non-circular orbits of the pinholes relative to the animal, thereby limiting the SPECT data sampling.

1.3. Collimation device for SPECT-CT

To address these limitations, an improved collimation device for small animal imaging is developed that is compatible with both clinical SPECT scanners and new hybrid clinical SPECT-CT scanners. In this new design, the animal to be imaged is in a horizontal orientation, and the pinholes and gamma camera detectors both rotate independently around the animal. A linear drive mechanism moves the animal in the axial direction relative to the pinholes, improving the axial sampling over a larger field of view. The linear drive also allows the animal to be moved outside the collimator for CT imaging on SPECT-CT scanners.

The design of this collimation device is described here in detail, and its imaging performance is evaluated with a series of phantom studies.

2. Materials and methods

2.1 Device design

Figure 1 shows the collimation device in a close-up view. The main component is a cylindrical multi-pinhole collimator which surrounds the animal and which projects multiple views onto the gamma camera detectors. The cylindrical collimator is mounted in a horizontal orientation to a rotary stage (Model RV80PP, Newport Corporation, Irvine, CA) having a double row of preloaded bearings to support a horizontal load. A cantilevered bed is attached to a linear stage (Model ILS250PP, Newport Corporation) and supports the animal in the center of the cylinder. The rotary and linear stages are mounted to a rigid aluminum base so that the entire device is easily transported and placed on the patient table of the clinical scanner. The entire device including the cylindrical collimator weighs 17 kg. A programmable motion controller (Model ESP300, Newport Corporation) enables the cylinder to be rotated and the bed to be moved in a timed sequence. The motion controller connects to both stages with 1.8 m flexible cables and is placed on a cart in close proximity to the device.

The collimator is a lead cylinder of 9 mm thickness, 53 mm inner diameter, and 280 mm length with removable tungsten pinhole inserts. The thickness of the cylinder provides adequate shielding of gamma rays with energy up to 250 keV. The diameter and length of the cylinder are suitable for imaging and shielding small rodents. A pair of circular lead baffles of 1 mm thickness is placed on each end of the animal bed to provide shielding in the axial direction, thus minimizing scattered gamma rays reaching the detectors. The linear stage has a 250 mm range of travel, allowing the animal to be moved outside of the cylinder for easy loading and unloading and for CT acquisition.

The collimator contains 22 pinhole inserts machined from a sintered tungsten material of mass density 17. The pinhole apertures have 0.9 mm diameter, 0.3 mm keel length, and 70° cone angle. The pinhole inserts are arranged such that there are 11 pinholes facing each detector of a dual-detector SPECT scanner. In the transaxial plane, each pinhole faces the central axis of the cylinder. In the axial direction, the pinholes are tilted up to 30° in a partially-focusing configuration. The pinhole apertures are located at a radius of 30 mm relative to the cylinder's central axis.

The pinholes are arranged to project overlapping views onto the gamma camera detectors. Unlike some mounted multi-pinhole collimators such as (Beekman *et al.*, 2005) that use internal shielding to avoid multiplexed projections, it is not practical to implement similar shielding external to this detached cylindrical collimator. Instead, multiplexing is accepted in the projection data and is modeled during image reconstruction. The degree of multiplexing depends on the arrangement of pinholes and on the distribution of the radionuclide activity being imaged. The topic of optimizing the pinhole arrangement and multiplexing is an active area of research (Cao *et al.*, 2005; Vunckx *et al.*, 2008) and is beyond the scope of this paper. Here, the performance of this collimation device is evaluated for this specific case of 22 pinholes for several test phantoms. Alternate pinhole arrangements are currently under investigation for various small animal imaging applications.

2.2. SPECT acquisition

Figure 2(a) shows the collimation device in use for SPECT acquisition. After removing the clinical collimators from the gamma camera detectors, the device is placed on the patient table of the scanner and positioned in the center of the SPECT field of view. Only visual alignment is used since there is no hardware attaching the device to the SPECT detectors or gantry. The SPECT detectors are configured for a circular orbit with radius large enough to clear the patient table during rotation. For the studies reported here, the detector's orbital radius is 240 mm

relative to the face of the scintillation crystal, and since the pinhole radius is 30 mm, the magnification factor is 7 at the detector's center. The precise geometric calibration is determined by imaging point sources, as described below. The typical accuracy of visual alignment is within ± 10 mm in the three linear dimensions and is sufficient for seeding the geometric calibration algorithm. The curvature of the patient table helps to center the device and to align the rotational axis with that of the SPECT detectors. Foam padding is removed from the patient table before placing the device on the table in order to prevent gradual drift in the device's position and orientation.

Since there is no custom hardware attaching the collimation device to the gamma cameras, the device in principle should work with any SPECT or SPECT-CT scanner model without any additional hardware. However, depending on the scanner's acquisition software and interlocks, there may be restrictions on performing step-and-shoot acquisitions or CT scans without a collimator in place. The SPECT-CT scanner used in these experiments (Symbia T6, Siemens Molecular Imaging, Hoffman Estates, IL) does have such restrictions. To enable step-and-shoot acquisition on this scanner, a pair of blank collimator frames (having no cores) is obtained and loaded onto the gamma cameras prior to the experiments.

After initializing and homing the motion stages, the motion controller is set up with the desired pre-programmed motion sequence. A typical motion sequence consists of repeated commands to rotate the cylindrical collimator, to move the animal bed, and to wait for a specific time interval. The SPECT scanner is set up to perform a step-and-shoot acquisition with the same angular step as the cylindrical collimator and with the same time interval between steps. Since the collimation device and the SPECT scanner utilize independent motion controllers, the acquisition sequences of the collimation device and the SPECT scanner are executed by manually triggering both devices at the same time. The timing accuracy for manual triggering is better than 0.5 second, which is acceptable compared to acquisition time per step (typically 40 seconds).

With independent motion controllers, it is also important that the time interval between steps is matched with sufficient accuracy to maintain time synchronization throughout the entire study. A small discrepancy in the time interval may lead to a relatively large timing error because the time difference accumulates between steps. To address this potential error, an initial experiment is performed to measure the accumulated time difference over the entire study. The time interval on the collimation device's motion controller then is adjusted to compensate for the difference. Alternatively, the time discrepancy may be avoided by acquiring SPECT data in acquire-during-step mode, as is done in the studies presented here. Although there is blurring in the projection data when acquiring in this mode, the time during which the detectors are in motion (under 2 seconds per step) is small compared to the acquisition time per step and thus the resultant blurring may be neglected.

The axial position of the animal bed is stepped synchronously with the rotary motion of the cylindrical collimators and SPECT detectors. The axial motion sequence is chosen to optimize sampling over the desired field of view to improve overall image quality and minimize artifacts. One common approach is to use a constant axial step that produces a helical orbit of each pinhole relative to the animal. A different "ordered-subsets" approach is to acquire data in subsets of angular views at regularly spaced axial locations of the animal bed, as illustrated in Figure 3. This is analogous to ordered-subsets iterative reconstruction (Hudson and Larkin, 1994) for which the angular views are grouped into subsets and treated separately between iterative updates. Typical parameters for ordered-subsets axial sampling used in these phantom studies are 90 projections and 5 axial subsets covering a 30 mm axial range. Ordered-subsets axial sampling has advantages compared to helical sampling at the edges of the axial field of view. Although helical orbits are an effective way to address sampling completeness (Metzler

et al., 2003), there is incomplete sampling during the ramp-up and ramp-down periods of the scan. To compensate for poor sampling at the edges, the axial range for helical orbits is typically extended past the desired axial field of view. Extending the axial range appears less necessary for ordered-subsets sampling and potentially allows for more efficient use of SPECT imaging time. Further studies are ongoing to optimize data sampling for this multi-pinhole imaging device.

2.3. CT acquisition

Figure 2(b) shows the collimation device positioned for CT acquisition on a hybrid clinical SPECT-CT scanner. In order to acquire CT data, the animal must be moved outside the cylindrical collimator; otherwise the x-rays would be absorbed before reaching the animal. At the end of the SPECT acquisition, the motion controller for the device is programmed to move the animal bed to its maximum axial position. The Newport ILS250PP linear stage used here has a 250 mm range of travel that is sufficient to move the entire animal outside the cylinder, though it is possible to design a sliding multi-position animal bed that does not require such a long range of travel of the linear stage. After ejecting the animal bed, the SPECT-CT scanner is set up to move the patient table into the CT position. CT images then are acquired using one of the available clinical scan sequences on the console workstation.

Of course, the quality of these CT images is not comparable to those of dedicated small animal CT scanners typically having spatial resolution of 0.05 mm or better. The spatial resolution and contrast instead are limited by the design of the clinical CT scanner hardware and software, which varies substantially between SPECT-CT scanners. The SPECT-CT scanner used in these experiments (Symbia T6) consists of a six detector-row CT scanner that according to vendor specifications is capable of reconstructing slices up to 1 mm thickness with in-plane resolution up to 15 line-pairs per cm (at 2% modulation transfer function). Other commercially available SPECT-CT scanners currently have up to sixteen detector-rows and are capable of even better spatial resolution. For the phantom studies presented here, the typical CT acquisition protocol is 80 kVp, 400 mAs, 6×1 mm collimation, and 0.4 pitch, with reconstruction parameters of 1.25 mm slice thickness, 0.6 mm slice increment, B90s kernel, and 60 mm transaxial field of view.

2.4. Geometric calibration

The first step in data processing is to establish the geometric calibration of the system. Because the relative location and orientation of the collimation device change each time it is placed on the patient table of the SPECT-CT scanner, the geometric calibration must be determined in-place for each imaging session. A complete description of the system geometry and the calibration process has been reported previously (DiFilippo, 2008). For this multi-pinhole collimator design, a total of 95 independent parameters is needed to specify the geometry. A SPECT scan of four point sources over a 360° orbit is acquired, the locations of dot images within the projection data are determined, and the best estimates of the 95 parameters are obtained through a least squares fit.

Fortunately, many of the 95 geometric parameters are associated with the collimation device itself and are constant from scan to scan. The remaining 22 parameters are associated with positioning the device relative to the SPECT scanners and must be estimated each time. The calibration of this subset of parameters uses a SPECT scan of two point sources over a 180° orbit. For these experiments with phantoms containing ^{99m}Tc , a pair of ^{153}Gd point sources (Model MMS04, Eckert & Ziegler Isotope Products, Valencia, CA) each of nominal activity 1.8 MBq (50 μCi) is taped to the edges of the animal bed and scanned along with the phantom. The approximate locations of the point sources for these phantom studies are ± 17 mm off-axis in the transaxial plane and ± 10 mm in the axial direction. The emission data and calibration

data are acquired simultaneously using separate energy windows for ^{99m}Tc (140 keV, 15%) and ^{153}Gd (100 keV, 20%).

For SPECT-CT scans, a second phase of geometric calibration is to determine the relative offset for SPECT and CT images to be used for image registration. Although the clinical SPECT-CT scanner already is calibrated for image registration, the accuracy of the hardware calibration is approximately 3 mm and would not be sufficient for small animal research. Software-based image registration available on the scanner's workstation based on the mutual information algorithm is found to work well in most cases for SPECT-CT image fusion. In cases where software-based registration is limited, the ^{153}Gd point source markers provide a more robust means of registering the SPECT and CT images.

2.5. SPECT image reconstruction

SPECT images are reconstructed using a voxel-driven implementation of the iterative ordered-subsets expectation maximization (OS-EM) algorithm (Hudson and Larkin, 1994). For SPECT data acquired with ordered subsets axial sampling, a different number of subsets is selected for the OS-EM reconstruction in order that the entire image volume is updated during each iterative step of the algorithm. Otherwise if the same number of subsets were used, it is possible that only part of the image volume contributes to the OS-EM calculation for that step, causing a division-by-zero situation that requires special attention. For the phantom experiments described below, the typical protocol is 90 projections acquired with 5 subsets for axial sampling and processed with 9 subsets for OS-EM reconstruction.

The system matrix elements are not pre-computed because they are unique to each imaging session. Instead, they are computed on-the-fly based on the geometric calibration parameters derived from the ^{153}Gd point source data. The forward projector model assumes a Gaussian point spread function whose width is estimated based on the pinhole diameter, the magnification factor, and the detector resolution. The pinhole efficiency is computed using a model whose parameters are estimated from a separate scan of point sources (DiFilippo, 2006).

For data acquired on a SPECT-CT scanner, the CT images offer the opportunity to perform SPECT attenuation correction. Preliminary SPECT images are reconstructed and transferred to the scanner workstation. Using the available clinical SPECT-CT software (Syngo MI Apps version 2007B, Siemens Medical Solutions), the CT images are registered to the preliminary SPECT images, converted from Hounsfield units to attenuation coefficient at 140 keV, and resampled to match the voxel dimensions of the SPECT images. The resultant attenuation map is then used in the final SPECT reconstruction with attenuation correction. The patient table is not included in the field of view of the CT images and must be handled separately. The patient table causes approximately 10% attenuation for 140 keV gamma rays and is modeled accordingly during SPECT image reconstruction.

3. Phantom studies

3.1. Spatial resolution

Reconstructed spatial resolution is evaluated through SPECT scans of a sealed ^{57}Co point source (Model MMS06 active element in a MMS04 package, Eckert & Ziegler Isotope Products) of nominal activity 3.7 MBq (100 μCi). The active element is a ceramic bead of diameter 0.25 mm. This point source is scanned at four locations, at approximately 0 and 10 mm radius and 0 and 12 mm axial position relative to the center of the field of view. SPECT data are acquired in 90 projection views and with ordered-subsets axial sampling with 5 planes over a 30 mm axial range. Images are reconstructed with 0.12 mm voxel size using OS-EM with 5 iterations, 9 subsets, and no post-filtering. Table 1 lists the full width at half maximum (FWHM) resolution

of the reconstructed point source images. The FWHM is measured from a least-squares fit of a Gaussian function to the line profile. The FWHM transaxial resolution is approximately 0.6 mm on-axis and 0.5 mm at 10 mm radius, and the FWHM axial resolution is approximately 0.4 mm.

The spatial resolution is also evaluated using a micro-Derenzo phantom (Ultra-Micro Hot Spot Phantom, Data Spectrum Corporation, Hillsborough, NC). This phantom has six sectors with rod diameters of 2.4, 2.0, 1.7, 1.35, 1.0, and 0.75 mm. To provide a different range of diameters, the solid spacer insert within the phantom is replaced with a custom-machined insert of equal size having six sectors with rod diameters of 1.1, 1.0, 0.9, 0.8, 0.7, and 0.6 mm. The phantom is filled with ^{99m}Tc solution of concentration 43 MBq/mL (1.2 mCi/mL) and scanned for 90 minutes (90 projections, ordered-subsets axial sampling with 5 subsets over 30 mm range). Figure 4 shows reconstructed SPECT images using 18 iterations, 9 subsets, 0.2 mm voxel size, and attenuation correction. All sectors of the Data Spectrum phantom are resolved. For the custom insert, the 0.7 mm sector is resolved, and the 0.6 mm sector is partially resolved.

3.2 Axial sampling

A cylindrical micro-Defrise phantom is imaged to compare acquisition protocols with differing axial sampling. The phantom (Ultra-Micro Defrise Phantom, Data Spectrum Corporation) contains discs of 1.62 mm thickness and spacing and of 27 mm diameter. When filled with radionuclide solution, the phantom produces alternating “hot” and “cold” slabs stacked in the axial direction. With the cone-beam geometry associated with pinhole collimation, it is often challenging to reconstruct artifact-free images unless there is sufficient data sampling. To investigate the dependence on axial bed motion, this phantom is filled with ^{99m}Tc solution of concentration 4.4 MBq/mL (0.12 mCi/mL) and scanned over 90 projection views (45 steps over 180°). Three SPECT acquisitions are performed with different axial motion sequences: (1) no axial motion, (2) helical sampling (45 equal steps over a 30 mm axial range), and (3) ordered-subsets sampling (5 subsets over a 20 mm axial range).

Reconstructed coronal images for the three acquisition sequences are shown in Figure 5. The case of circular sampling with no axial motion leads to significant artifacts in the reconstructed images. The artifacts vanish when either helical sampling or ordered-subsets sampling is utilized. The individual slabs of the micro-Defrise phantom are well resolved for both helical and ordered-subsets sampling, thereby illustrating that the data sampling is acceptable in either case.

3.3 Efficiency

A key performance characteristic is the counting efficiency of the SPECT imaging system, which is determined mainly by the geometry of the multi-pinhole collimator and detectors relative to the object being imaged. Many geometric factors affect the system sensitivity, including the pinhole orbit radius, detector orbit radius, multi-pinhole pattern, pinhole aperture design, and detector field of view. The sensitivity depends strongly on the location within the field of view due to the inverse-square dependence of the pinhole efficiency on the distance from the pinhole and due to the cosine dependence on the angle of incidence. In addition, the axial bed motion extends the field of view and thereby affects the sensitivity profile.

For the particular geometry of this scanner, the detection efficiency for 140 keV gamma rays is computed for both helical sampling and ordered-subsets axial sampling over 30 mm ranges. The system model used in image reconstruction is used to compute the efficiency over the entire imaging volume. Contour plots of the detection efficiency are shown in Figure 6 for transaxial planes at the center of the axial field of view and at 10 mm axial offset. In both cases, the peak efficiency is at the center of the field of view, where over 0.05% of emitted gamma

rays is detected. Ordered-subsets sampling produces a circularly symmetric efficiency profile, whereas helical sampling does not.

3.4 Uniformity

A phantom with uniform activity distribution is imaged to evaluate system uniformity. The inserts of the Data Spectrum Ultra-Micro phantom are removed so that the phantom is a hollow cylinder of 30 mm internal diameter and 30 mm internal height. The phantom is filled with ^{99m}Tc solution of concentration 4.59 MBq/mL (0.12 mCi/mL). SPECT data are acquired with 45 angular steps (90 projection views), 60 seconds per step, and ordered-subsets axial sampling (five subsets over 30 mm axial range). Images are reconstructed while applying attenuation correction (based on fused CT images) and scatter correction (with the scatter component estimated from a lower energy window). Since this multi-pinhole configuration is designed mainly for mice, the larger diameter of the phantom leads to a relatively high degree of multiplexing in the SPECT projection data. Consequently, a larger number of iterations are needed during reconstruction to reach an acceptable level of convergence. Here, 30 iterations and 9 subsets are used with a Butterworth filter (fourth order, 3 mm cutoff) applied after each group of 10 iterations so that the uniformity measurement is not dominated by statistical noise.

Reconstructed images are shown in Figure 7. The reconstructed images show reasonably good uniformity, although a small degree of artifact related to multiplexing is visible. The root mean square (RMS) deviation for these images is measured to be 5.1%, calculated as the standard deviation divided by the mean for a 20 mm diameter region of interest over the central 24 mm of the phantom. The integral uniformity is measured to be $\pm 23\%$, calculated as the difference between the overall maximum and minimum value divided by the mean.

3.5 Quantitation

A goal of many small animal studies is to obtain quantitative measurements of the radionuclide distribution. To evaluate quantitative accuracy, the average radionuclide concentration measured in the reconstructed images of the uniform cylinder phantom is compared to the expected concentration. The ^{99m}Tc activity added to the phantom is first assayed in a standard 5 mL glass ampoule in a dose calibrator (Model CRC-15R, Capintec Inc., Ramsey, NJ). The total volume of liquid added to the phantom is measured by subtracting the weights of the full and empty phantom as measured with an analytical balance. The expected radionuclide concentration of 4.59 MBq/mL for this scan is calculated while accounting for decay time between assay and imaging. The accuracy of the concentration is estimated to be within 4% based on the specifications of the dose calibrator.

The average radionuclide concentration is measured from reconstructed images over the phantom's central volume (20 mm diameter $\times$ 24 mm length) to be 4.19 MBq/mL, which differs by 9% from the expected value. The quantitative accuracy of the reconstructed images depends on attenuation correction and scatter correction applied during image reconstruction and on the computation of the system matrix elements in the OS-EM algorithm. In addition to the pinhole efficiency model (DiFilippo, 2006), there are several estimated inputs that affect calculation of the system matrix elements. These include conversion of the measured pinhole aperture diameter from ^{57}Co (122 keV) to ^{99m}Tc (140 keV), in-window detection efficiency of the NaI(Tl) scintillation crystal, dead-time loss of the detectors, and attenuation of the patient table and detector covers. Uncertainties from all of these factors combined with uncertainty in assaying the radionuclide concentration contribute to the 9% difference between expected and measured concentrations.

4. Discussion

4.1 SPECT performance

The transaxial reconstructed spatial resolution at the center of the field of view is measured to be 0.6 mm FWHM using a ^{57}Co point source with 0.25 mm diameter active element. The transaxial resolution of 0.5 mm FWHM at 10 mm radius is slightly better since the magnification factor is greater at this location for many of the projection views. The micro-Derenzo phantom images agree reasonably well with these resolution measurements. In Figure 4(c) the 0.7 mm sector is resolved, and the 0.6 mm sector is partially resolved. In Figure 4(a) the 0.75 mm sector is resolved but not so clearly, since the larger number of nearby rods leads to increased noise from scattered counts.

The axial resolution of the reconstructed point source is even better, measured to be 0.4 mm FWHM. The difference is attributed mainly to reduced error from depth-of-interaction effects (Hwang *et al.*, 2001). The gamma camera detectors have smaller axial field of view (388 mm) than transaxial field of view (532 mm), and thereby the detectors' mean axial angle of incidence is less than the mean transaxial angle of incidence. The OS-EM reconstruction algorithm is able to recover some spatial resolution through a two-dimensional Gaussian model of the pinhole blur and detector blur. However this implementation does not model the exponential depth dependence within the crystal, which is significant for gamma rays having large angle of incidence. Future work is planned to model depth-of-interaction within the reconstruction algorithm to further improve the spatial resolution. In addition to depth of interaction errors, the pinhole diameter and detector intrinsic resolution also are main contributors to the measured spatial resolution. The geometric calibration is not considered to be a significant contributor based on prior characterization of its accuracy (DiFilippo, 2008) that estimated the resolution loss in reconstructed images to be 0.12 mm.

The SPECT efficiency of the scanner exceeds 0.05% at the center of the field of view for this particular arrangement of 22 pinholes at a 30 mm radius with helical or ordered-subsets sampling over 30 mm axial range. For comparison, a single pinhole of similar effective diameter of 1.04 mm has an efficiency of 0.0075% at a distance of 30 mm with normal angle of incidence. Although the 22-pinhole collimator increases the peak efficiency only by about a factor of seven compared to that of a single pinhole, the multi-pinhole configuration and axial sampling scheme used here are selected to spread the efficiency over a larger volume of interest that is more appropriate for imaging a mouse. The optimal pinhole arrangement depends on the radionuclide distribution being imaged. In cases where the distribution is small, a more focused pinhole arrangement with less axial motion would be more optimal. Larger number of pinholes then may be used while avoiding multiplexing and would result in scanner efficiency significantly larger than the 0.05% for this particular 22-pinhole collimator.

The reconstructed images of the uniform phantom show uniformity (5.1% RMS deviation) that is acceptable for typical small animal studies. One concern is the integral uniformity ($\pm 23\%$) that is accompanied by small but noticeable artifact in the reconstructed images (Figure 7). The likely explanation for image artifact is that it arises from multiplexing in the data projections combined with imperfect characterization of the system matrix elements in image reconstruction. Since the transaxial extent of the uniform phantom is large (30 mm diameter), there is substantial overlap between pinhole projections. The multi-pinhole configuration is designed to have minimal overlap when imaging a smaller transaxial field of view (approximately 20 mm for typical mice), and so this larger uniform phantom represents a worst case scenario for artifact and non-uniformity related to multiplexing. Work is ongoing to further improve the uniformity of reconstructed images through better characterization of the pinhole efficiency, improved data sampling, and optimization of image reconstruction parameters (iterations, subsets, and regularization).

Based on the uniform phantom study, the measured concentration from reconstructed images is within 9% of the expected value. This measurement is over a large volume of interest spanning most of the cylinder volume and is minimally sensitive to small artifacts related to multiplexing. Considering the many sources of uncertainty in deriving absolute concentration from reconstructed images, this level of accuracy is surprisingly good. Absolute quantitation may be improved by introducing a 9% calibration factor based on this uniformity phantom study in order to account for the cumulative error in estimating the system matrix elements during image reconstruction. This 9% factor is unique to this particular 22-pinhole collimator and SPECT scanner and would need to be measured for other hardware configurations. Implementing a global calibration factor based on a uniform phantom is similar to the approach used in clinical positron emission tomography (PET) and small animal PET scanners and may improve quantitative accuracy to better than 5% for this small animal SPECT device.

4.2 SPECT multiplexing

The use of 22 pinholes significantly increases the collimator efficiency and also the transaxial and axial data sampling. However, there are no shields between the collimator and the detector to prevent cross-talk between the pinhole projections, and as a result the pinhole projections may overlap when the extent of the radionuclide distribution is sufficiently large. Because of data multiplexing, the corresponding improvement in image quality does not scale linearly with the collimator efficiency because the detected counts in the multiplexed regions carry less information than do counts in non-multiplexed regions (Defrise and Gullberg, 2006). The optimal number and distribution of pinholes depends on the typical radionuclide distribution of a specific imaging application and should be investigated accordingly (Cao *et al.*, 2005; Vunckx *et al.*, 2008). The 22-pinhole configuration of this device and axial sampling protocols are intended to be used for general purpose whole-body imaging of mice. Future work is planned to design focused multi-pinhole configurations for other applications.

Optimizing image quality via multiplexing is currently an active area of research in multi-pinhole SPECT. Since the time of initial research in coded apertures (Fenimore and Cannon, 1978) and multiplexed multi-pinhole SPECT (Rowe *et al.*, 1993), many researchers have investigated ways to optimize the degree of pinhole overlap and to optimize image reconstruction for their actual collimators. In the uniform phantom study described above having greater multiplexing compared to the other phantom studies, a larger number of iterative updates is found to be needed. Some artifact remains, though it is unlikely that similar artifact will be noticeable in animal studies that experience little or no multiplexing.

4.3 CT

A main benefit of this device design is the ability to acquire CT images without disturbing the animal's location and orientation. In clinical SPECT-CT and PET-CT, it is widely accepted that interpretation of fused multi-modality images often improves diagnostic accuracy. The same is most likely true for small animal studies. One issue is that the spatial resolution of the clinical CT scanner (15 line-pairs per cm, for the scanner used in this study) is not sufficient for visualization of detailed anatomy in small animals. This task would require a separate "micro-CT" scanner with high resolution detectors. Even so, the contrast resolution of the clinical CT scanner is sufficient for imaging the gross anatomy of the small animal: bones, lungs, fatty tissue, etc. The CT image of the micro-Derenzo phantom shows the ability of the clinical CT scanner to resolve the 0.75 mm structures under low contrast conditions where the background material (acrylic) differs from the rod material (water) by 85 Hounsfield units. This level of CT performance is expected to be sufficient for localization of the radio-tracer uptake in small animal studies and for use in image analysis.

One concern in small animal research studies is radiation dose from both radio-labeled tracers (Funk *et al.*, 2004) and x-ray CT scans (Boone *et al.*, 2004), especially when the same animal is subjected to multiple imaging procedures. For high resolution CT scans, a high x-ray flux is needed to maintain acceptable image noise for small voxels but at the expense of a rather high radiation burden (Ford *et al.*, 2003). When radiation dose is a concern in the experimental design, lower CT resolution may be necessary, and the clinical CT scanner would be adequate in such cases.

A second main benefit of the clinical CT images is attenuation correction. Attenuation may not seem at first to be a significant issue for ^{99m}Tc imaging of mice, since gamma ray attenuation is quite small in comparison to clinical imaging. Assuming that the animal tissue has a linear attenuation coefficient equal to that of water (0.15 cm^{-1}), tissue thicknesses of 1 cm and 2 cm would cause attenuation of 14% and 26%, respectively. However, with a partially-focused multi-pinhole configuration, many detected gamma rays travel through the animal at oblique angles for which the attenuation may exceed 50%. Thus it is important to properly account for non-uniform attenuation in order to reach an acceptable level of quantitative accuracy. Accurate attenuation correction is needed especially in situations with multiplexing where proper system modeling is essential for minimizing artifacts. The clinical CT images serve this purpose well.

4.4 Device usage

The small animal imaging device described here is not intended as a dedicated micro-SPECT/CT scanner for a busy research laboratory. Instead, it is intended more as a “starter” scanner for laboratories which have off-hours access to a clinical SPECT/CT scanner and which have occasional need for imaging small animals. Fortunately the collimation device is rather simple to set up for data acquisition, requiring about twenty minutes for removal of the scanner collimators, placement of the device, and initialization of the motion control stages. The simple design requires relatively inexpensive hardware and avoids the need for a dedicated room and additional service contract, thereby lowering the up-front costs needed for a laboratory to begin small animal SPECT imaging.

There are some disadvantages associated with this device, however. Since the scanner collimators are removed, the SPECT detectors are not shielded from background gamma rays. Although the animal is well shielded within the cylindrical collimator, the user must be careful that there are no stray sources of radiation within the room that may contribute excessive background counts. Therefore the animal should be injected and prepared for imaging in a separate room so that radioactive residue is not present near the scanner. Of course, a main source of background radiation in a clinical environment is the injected patients, and so the collimation device should be used after the clinical schedule is complete.

Another possible disadvantage is that the animal is not visible and not easily accessible within the narrow cylindrical collimator. This configuration prevents the user from visually monitoring the animal and may limit the size and number of sensors and electrical leads for monitoring the physiologic state of the animal. The narrow cylinder may preclude the use of gaseous anesthesia if the tubes and breathing apparatus cannot fit within the cylinder. Injected anesthesia may be the only practical option in some animal studies.

For many laboratories, however, the benefits of the collimation device would outweigh these limitations. The growing number of clinical SPECT-CT scanners presents an opportunity for many laboratories to enter the field of small animal SPECT without excessive start-up costs. The device has SPECT imaging performance that is competitive with that of many dedicated commercial small animal scanners and is expected to produce useful images for research.

5. Conclusion

This multi-pinhole collimation device utilizes clinical SPECT detectors to produce images with sub-millimeter resolution suitable for small animal research. When used with a clinical SPECT-CT scanner, the high resolution SPECT images may be co-registered with CT images acquired after moving the animal bed outside the multi-pinhole collimator. Although the CT images do not have ultra-high resolution, they are acceptable for attenuation correction and for anatomic localization in many cases. Though there are some disadvantages compared to dedicated commercial small animal SPECT-CT scanners, the simplicity and performance of the device coupled with the growing availability of clinical SPECT-CT systems offers an attractive alternative in many situations.

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Figure 1. Photograph of the multi-pinhole collimation device with its main components identified. The patient table and gamma camera detectors of the SPECT scanner are visible.

Figure 2. Collimation device in use with a clinical SPECT-CT scanner. For SPECT acquisition (a), the device is placed on the patient table and visually centered in the field of view of the gamma camera detectors with clinical collimators removed. For CT acquisition (b), the animal bed is extended outside the cylindrical collimator, and the patient table is moved toward the rear of the gantry to position the animal for the CT scan.

Figure 3.

Illustration of helical sampling versus ordered-subsets axial sampling. This example assumes two detectors, 180° rotation, 12 angular steps (24 projection views), and 4 subsets. The axis of rotation is indicated with an arrow in the transaxial view (a) and axial views (b) and (c). In the transaxial view, the central pinhole coordinates are drawn with a repeating sequence of 4 different symbols. The axial views show the pinhole's vertical position versus its axial position. For the case of helical sampling (b), the animal bed is moved in constant intervals between angular steps. For the case of ordered-subsets sampling (c), the animal bed is moved in a repeating sequence to 4 different axial positions.

Figure 4.

Reconstructed transaxial images of a micro-Derenzo phantom. The SPECT image resolves all sectors of the Data Spectrum insert (a) with rod diameters of 2.4, 2.0, 1.7, 1.35, 1.0, and 0.75 mm. The co-registered CT image (b) is generated by the clinical CT scanner and illustrates image quality under low contrast conditions (water versus acrylic). The SPECT image of a custom-machined insert (c) having rod diameters of 1.1, 1.0, 0.9, 0.8, 0.7, and 0.6 mm is also shown.

Figure 5.

Reconstructed coronal slice images of a micro-Defrise phantom for various axial sampling schemes: (a) circular sampling (no axial bed motion), (b) helical sampling (30 mm axial range), and (c) ordered-subsets sampling (20 mm axial range)

Figure 6.

Contour maps of system efficiency for transaxial slices: (a) helical sampling, center slice, (b) helical sampling, 10 mm axial offset, (c) ordered-subsets sampling, center slice, (d) ordered-subsets sampling, 10 mm axial offset.

Figure 7.
Reconstructed images of a uniform cylindrical phantom: (a) transaxial slices, (b) coronal slices.

Table 1
Spatial resolution (full-width at half-maximum) measured from reconstructed SPECT images of a ⁵⁷Co point source at various locations within the field of view.

Source location [mm]			FWHM Resolution [mm]		
X (radial)	Y (tangential)	Z (axial)	ΔX	ΔY	ΔZ
0.2	0.7	-0.4	0.58	0.63	0.38
0.5	1.0	11.5	0.57	0.61	0.37
10.1	3.5	-1.3	0.45	0.53	0.36
10.3	4.0	12.4	0.47	0.53	0.32