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A Fillable Micro-Hollow Sphere Lesion Detection Phantom Using Superposition

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Abstract

The lesion detection performance of SPECT and PET scanners is most commonly evaluated with a phantom containing hollow spheres in a background chamber at a specified radionuclide contrast ratio. However there are limitations associated with a miniature version of a hollow sphere phantom for small animal SPECT and PET scanners. One issue is that the “wall effect” associated with zero activity in the sphere wall and fill port causes significant errors for small diameter spheres. Another issue is that there are practical difficulties in fabricating and in filling very small spheres (< 3 mm diameter). The need for lesion detection performance assessment of small-animal scanners has motivated our development of a micro-hollow sphere phantom that utilizes the principle of superposition. The phantom is fabricated by stereolithography and has interchangeable sectors containing hollow spheres with volumes ranging from 1 to 14 μL (diameters ranging from 1.25 to 3.0 mm). A simple 60° internal rotation switches the positions of three such sectors with their corresponding background regions. Raw data from scans of each rotated configuration are combined and reconstructed to yield superposition images. Since the sphere counts and background counts are acquired separately, the wall effect is eliminated. The raw data are subsampled randomly prior to summation and reconstruction to specify the desired spheres-to-background contrast ratio of the superposition image. A set of images with multiple contrast ratios is generated for visual assessment of lesion detection thresholds. To demonstrate the utility of the phantom, data were acquired with a multi-pinhole SPECT/CT scanner. Micro-liter syringes were successful in filling the small hollow spheres, and the accuracy of the dispensed volume was validated through repeated filling and weighing of the spheres. The phantom’s internal rotation and the data analysis process were successful in producing the expected superposition images. Visual inspection of the multi-contrast images provided simple determination of lesion detection thresholds for this scanner (4:1 ratio for 1.5 mm spheres and 3:1 ratio for 2.0 mm spheres) at a specified cumulated background concentration (30 $\text{kBq}\cdot\text{min}\cdot\mu\text{L}^{-1}$). In summary, the micro-hollow sphere phantom demonstrated its practical utility for lesion detection evaluation and is well suited for comparing task-based performance of small-animal SPECT and PET scanners.

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1. Introduction

1.1 Hollow spheres phantoms and the “wall effect”

Performance of single photon emission computed tomography (SPECT) or positron emission computed tomography (PET) systems is often evaluated using volumetric phantoms filled with radionuclide solutions. Standard phantoms are specified for acceptance testing of imaging systems and for laboratory accreditation of imaging departments. Such phantoms may be designed to produce a certain geometric test configuration or to mimic a certain imaging situation for task-based assessment of image quality. A common example of the latter is a phantom simulating radionuclide-avid tumors along with background activity, for the purpose of evaluating lesion detection performance of a SPECT or PET system. A conventional lesion detection phantom consists of a set of hollow spheres of various diameters located within a uniform background chamber. The spheres are filled with a radionuclide solution having the desired contrast ratio with respect to the background radionuclide solution. Typically the sphere diameters and activity concentrations are chosen to simulate the clinical or preclinical scan conditions for scanners designed for human or small-animal imaging, respectively. For example, the National Electrical Manufacturers Association (NEMA) NU-2 standard for clinical PET scanners specifies the thorax-shaped International Electrotechnical Commission (IEC) phantom with multiple hollow spheres of 10–22 mm diameters at 4:1 and 8:1 sphere-to-background ratios along with two cold spheres of 28 and 37 mm diameters (NEMA, 2007).

However, conventional fillable hollow sphere phantoms have significant limitations. One issue is that the sphere wall has nonzero thickness and therefore produces a shell of zero activity that separates the sphere solution and the background solution. Sphere walls are fabricated to be thin in order to minimize their effect on quantitative measurements and evaluation of lesion detection. For example, the IEC/NEMA PET phantom specifies the sphere wall thickness to be 1.0 mm or less. Although this wall thickness appears small in comparison to the 10 mm diameter of the smallest hollow sphere, the wall volume is surprisingly large (73% of the internal volume in this case). It is recognized that this “wall effect” can significantly affect quantitative accuracy of lesion contrast measurements (Daube-Witherspoon *et al.*, 2002). Because of the partial volume effect, the lack of activity in the wall space changes the amount of spillover from the background to sphere and vice-versa, thereby influencing the measured contrast and peak sphere activity along with lesion visibility. In addition, the wall effect may introduce errors in automated lesion segmentation (Hillel and Hastings, 1995; Hofheinz *et al.*, 2010), which impacts measurements of lesion volume, total activity, and boundaries for radiation treatment planning experiments. Since volume depends on the cube of the linear dimensions, the wall effect becomes very large for smaller spheres that are of interest for small animal imaging systems. For example in the case of a 3 mm sphere with 0.5 mm wall thickness, the wall volume would be 137% that of the internal volume. The fill port of this 3 mm sphere also would contribute significantly to the wall effect. Although the recently developed NEMA NU-4 standard (NEMA, 2008) for small animal PET systems resembles the NU-2 standard in many ways, a notable difference is that its image quality phantom does not contain hollow spheres for lesion contrast measurements, a likely reason being that the wall volume would dominate the sphere volume.

To improve quantitative accuracy of lesion contrast measurements, several groups have implemented clever designs and technologies to eliminate or minimize the wall effect. One method was to use an ink-jet printer loaded with radionuclide solution to print patterns on paper, producing a virtually unlimited range of two-dimensional (2D) radionuclide distributions. (Larsson *et al.*, 2000) Three-dimensional (3D) distributions are possible by stacking multiple prints separated by thin slabs of other material. More recently, a 3D printer

has been used to produce true volumetric distributions, for which spheres may be embedded directly in the background. (Miller and Hutchins, 2007) Another approach is to embed solid radioactive spheres having no walls in a background chamber. For example, a long-lived positron-emitter (^{68}Ge) was mixed in an epoxy resin and cast into spheres, after which the hardened spheres were embedded in a background epoxy mixture. (Hamill *et al.*, 2005) A similar approach was to cast wax spheres containing ^{18}F and afterwards to embed the spheres in a conventional fillable thorax phantom containing ^{18}F solution. (Turkington *et al.*, 2001) More recently, spheres containing ^{68}Ge were cast having no walls and were introduced in background chambers containing ^{18}F solution (Kadrmas *et al.*, 2009). In these phantoms the wall effect was eliminated, though the preparation of the phantoms was complex. A porous lesion detection phantom having narrow channels and internal voids avoided sphere walls while being simple to prepare (DiFilippo *et al.*, 2004). However a micro-scale porous phantom with sub-millimeter channels would pose significant challenges (trapped bubbles and surface absorption of radionuclides) for small animal scanner evaluation. A promising approach for a small-animal phantom is stereolithography (Park *et al.*, 2008), which is capable of producing intricate shapes such as a rat brain phantom (Beekman *et al.*, 2009). A prototype lesion phantom having 3 mm hollow spheres with wall thickness as small as 0.15 mm has been fabricated by stereolithography (Park *et al.*, 2007). Although this phantom minimized the wall thickness, the sphere's support structure (stem and fill port) constitutes a large volume relative to the sphere internal volume and still remains an issue for quantitative accuracy.

1.2 Phantom preparation

The task of lesion detection in SPECT or PET depends on many factors, including scanner design and performance (spatial resolution, sensitivity, *etc.*), scan parameters (time, camera orbit, *etc.*), reconstruction algorithm, observer characteristics, and of course the radionuclide distribution of the phantom, patient, or animal to be imaged. Therefore a performance standard must specify completely the phantom dimensions, sphere diameters, and activity concentrations along with the scan parameters. Although studies with lesion detection phantoms are quite valuable in assessing scanner performance, there are practical constraints on the number of spheres that may be included in the phantom. Thus only a limited number of sphere diameters and sphere-to-background contrast ratios may be studied in a single experiment.

In order to study lesion detection over a wider range of sphere diameters or contrast ratios, flexibility in phantom preparation is desirable. The various phantom designs discussed above have different degrees of flexibility in their preparation. The conventional hollow spheres design has the advantage that it may be reconfigured with spheres of different diameters and refilled with radionuclide solutions of different activity concentrations. However this procedure is tedious, time-consuming (since typically the radionuclide solution is allowed to decay before refilling), and adds to radiation exposure. There also is the potential that errors are introduced in preparing the radionuclide solutions of the specified concentrations. The opposite extreme is the porous phantom (DiFilippo *et al.*, 2004), which requires minimal effort to prepare but can produce only fixed contrast ratios. The phantom designs with long-lived radionuclides have the advantage that the long-lived chambers need only to be prepared once. However, once prepared the contrast ratio either is permanent (Hamill *et al.*, 2005) or must be specified by filling the background chambers with a known absolute activity concentration (Kadrmas and Christian, 2002).

The task of lesion detection depends on a large number of parameters, and usually only a small number of data points can be obtained from a single prepared phantom. An exception to this observation is the case of long-lived lesions in a short-lived background (Kadrmas *et al.*, 2009). A powerful advantage of this technique is that multiple scans can be acquired

over a range of contrast ratios while the short-lived source decays. As a result, the contrast ratio can be treated nearly as a continuous variable in receiver-operator curve (ROC) studies of lesion detection without needing to refill the phantom. A phantom capable of variable spheres-to-background ratio without involving long-lived sources would be very attractive. Other lesion detection studies have utilized simulated lesions, which were computer-generated or derived from sphere data acquired in air and added to sinogram data (El Fakhri *et al.*, 2007). Although simulated lesions provide flexibility in spheres-to-background contrast and acquisition time, the simulated lesions do not account for errors encountered under actual scan conditions, such as detector pulse pile-up, count losses, and event mispositioning at clinical count rates, unlike an actual phantom experiment.

1.3 Superposition micro-hollow spheres phantom

Here, we present a micro-hollow sphere phantom for lesion detection studies of small-animal SPECT or PET scanners that uses the principle of superposition to overcome the wall effect and to provide variable contrast ratios. Instead of acquiring a single scan of a hollow spheres phantom with a specified contrast ratio, two scans are acquired of longer durations, and the raw projection or sinogram data are summed to create the composite data. One advantage of superposition is that it eliminates the wall effect, which is a major concern for small spheres in a miniature phantom. By adding separate scans of the sphere with no background and of the background only, the superposition image yields the desired radionuclide distribution with no wall effect (Figure 1). A second advantage of superposition is that images with various sphere-to-background ratios may be generated from data from a single acquisition session. By subsampling the raw data from the two scans and combining them in various proportions, a set of images with multiple contrast ratios is produced. An analogous approach has been described for generating a simulated dynamic imaging study from static phantom data, in which a multi-compartment phantom is scanned multiple times with radionuclide solution occupying one of each compartment (Sitek *et al.*, 2006). In our case, the goal instead is to generate multiple contrast ratios for the purpose of lesion detection assessment. A flow chart illustrating the data acquisition and processing is shown in Figure 2.

In order for superposition to be valid, the physics underlying the two scans must be constant or approximately constant. Gamma rays emitted during separate scans can be treated equally only if they experience the same system geometry, detection efficiency, attenuation, scatter, and dead time loss. The phantom therefore must be designed to switch the sphere and background regions without significantly altering the physics. The micro-hollow sphere phantom accomplishes this goal through symmetry and internal rotation in order not to disturb the system geometry. The phantom material is selected to have a linear attenuation coefficient similar to that of water over the gamma ray energies of interest. With a symmetric phantom design, the attenuation and scatter are nearly constant for the two rotated configurations. Although the radionuclide distribution differs between the two configurations, with careful design the differences in dead-time loss are minimized and acceptable.

Besides physics constancy, another challenge with a superposition phantom is specifying the contrast ratio, which depends on both the actual activity concentrations of the phantom's chambers along with the durations of the two scans. Due to radioactive decay it is difficult to precisely time the two scans to produce the desired contrast ratio and total number of counts acquired. Instead, we acquire two longer duration scans and randomly subsample the raw data while accounting for decay to yield the desired effective scan durations before summing and reconstructing the composite images. By repeating this subsampling procedure, we obtain a set of images over a range of contrast ratios for assessing the minimum detectable lesion contrast.

2. Materials and Methods

2.1 Micro-lesion detection phantom

A multi-chamber superposition phantom suitable for small animal SPECT and PET lesion detection studies was designed and fabricated as follows. This phantom contains three inserts in the shape of a 60-degree sector of a cylinder, each containing a hollow sphere within a background chamber. (Figure 3(a)) The sphere is filled with radionuclide solution through a narrow fill port on one side, and the background chamber is filled with non-radioactive water from a port on the other side. The sectors with internal spheres would be difficult to construct using conventional machining techniques since multiple components would need to be machined separately and glued into the complete assembly. Instead, the sectors and the other parts of the phantom were fabricated using stereolithography (SLA), a technique which is suitable for building fine structures in miniature nuclear medicine phantoms (Park *et al.*, 2008). The parts were built on a Viper si2 SLA system (3D Systems, Valencia, CA) having 0.075 mm beam diameter and 0.0025 mm vertical resolution. The SLA resin was RenShape SL 7870 (Huntsman Advanced Materials, The Woodlands, TX USA). Six sectors were fabricated, each containing spheres with inside diameters of 1.25, 1.5, 1.75, 2, 2.5, or 3 mm (corresponding to internal sphere volumes of 1.0, 1.8, 2.8, 4.2, 8.2, or 14.1 μL). The sectors are interchangeable, allowing the user to select the most appropriate sphere diameters for a specific study.

The assembled phantom contains three sectors within a cylindrical chamber having 28 mm inside diameter (Figure 3). The sectors are press-fit into a disk-shaped platform that freely rotates at the bottom of the cylinder. A cap having sector-shaped receptacles and o-ring seal presses into the top of the cylinder. When assembled, the inside height of the internal chamber of the phantom is 31 mm. The cap has a fill port for introducing background radionuclide solution into the main chamber. The cap is designed to rotate while maintaining its seal of the main cylinder. Lubricating the o-ring seal and the sliding surfaces with a thin layer of silicone grease minimized the torque needed to perform the rotation. Since the cap mates with the sectors, the sectors and disk platform also rotate along with the cap. The cap and the cylinder have tabs that restrict the rotation to a net angular range of 60°. When the cap is rotated from one rotation stop to the other over the entire 60°, the sectors and the sector-shaped background regions exactly switch locations. Note that the rotation of the cap, sectors, and platform occurs internally to the phantom, and that the main cylinder does not rotate. Thus the user can secure the cylinder to the animal bed of the small animal scanner and easily swap the locations of the sectors and background regions in-place without disturbing the global geometry of the phantom study.

2.2 Symmetry and superposition

Figure 4 shows a schematic of the phantom in the two rotation states. The boundaries between the background and sphere sectors are at 60 degree intervals, except for a small region in the center for fluid continuity. The sphere sectors contain activity only inside the spheres, while the background sectors consist of uniform activity. The superposition image is generated by summing the raw projections or sinogram data acquired while the phantom is in each rotation state and then reconstructing the composite raw data. There are a total of six spheres in the superposition image, since each sector contains a linear combination of a sphere from one of the two scans and the uniform background of the other scan. There are two contrast ratios that depend on the relative duration of the two scans. Since the background activity fills the entire 60° sector, there is no wall effect from the sphere shell or its support structure and fill port.

All chambers within the phantom are filled either with aqueous radionuclide solution or with non-radioactive water. Thus the radiographic density is 0 HU (Hounsfield Units), with the exception of the solid components of the phantom (sphere walls, chamber walls, and fill ports). The mass density of the cured SLA resin is 1.15, and its radiographic density is 126 HU (as measured with a 130 kVp CT scan) which is slightly higher than that of water. As a result, the linear attenuation coefficient (μ) is not constant over the entire volume of the phantom. However, the mean interaction distance ($1/\mu$) at the energies of interest (for example, $1/\mu \approx 6$ cm at 140 keV and 10 cm at 511 keV) is much larger than the size of the solid structures, and the linear attenuation coefficient is similar to that of water. Considering that a wall of 1 mm thickness increases the attenuation by only 0.3% over that of water (which is much less than the detector nonuniformity), the attenuation and scatter properties of the phantom are approximately constant between the two positions. Therefore when the sectors are rotated 60° between the two scans, the attenuation and scatter physics remain essentially unchanged.

2.3 Phantom preparation

The small sphere diameters introduce significant new challenges for phantom preparation. The conventional method of filling a lesion detection phantom is to prepare two radionuclide solutions of known relative concentrations (typically using the dilution method), to add solution to the spheres with a syringe until the spheres appear filled, and to add solution to the background chamber after positioning the spheres. The smallest commercially-available hollow sphere for small animal phantoms (Micro Hollow Spheres, Data Spectrum Corporation, Hillsborough, NC USA) has internal volume of 31 μL , which corresponds to an internal diameter of 3.9 mm. The visual technique for filling this sphere using a standard insulin syringe is a bit challenging but still feasible. However the excellent spatial resolution of small animal SPECT and PET scanners requires smaller spheres for lesion detection evaluation. Considering the small sphere diameters of the new lesion detection phantom (between 1 μL and 14 μL internal volumes), a standard syringe is not suited to reproducibly dispense such small volumes.

Instead, a precision micro-liter syringe was used to dispense the small volumes. Micro-liter syringes having full-scale volumes of 5 μL and 10 μL (Model 75 and Model 701, Hamilton Company, Reno, NV USA) were selected for these experiments. The syringes were fitted with a removable 26s-gauge blunt-tipped needle of 51 mm length (Model 7768-01, Hamilton Company), which allowed for easy insertion through the fill port into the sphere. Food coloring was added to the radionuclide solution to improve visibility and detect air bubbles while priming and filling the syringe to the specified volume. Surfactant (polysorbate 20) was added to the radionuclide solution to reduce surface tension. Even with surfactant added, there were instances when an air bubble remained in the sphere after the solution was dispensed. The chance of an air bubble remaining was minimized by slow dispensing of the liquid and by placing the needle at the side of the fill port to allow air to escape. In practice, a user has one initial opportunity to fill the dry sphere with radioactive liquid. If refilling is necessary, the radioactive liquid must be removed, and the sphere must be dried completely before attempting another refill, in order not to affect the radionuclide concentration. Injecting isopropyl alcohol (using a second micro-liter syringe) was effective in flushing out the aqueous solution and accelerating the drying process. As an alternative to refilling the sphere, placing the sphere sector inside a centrifuge was an effective method for removing an air bubble if present.

2.4 Imaging

To demonstrate the use of the lesion detection phantom under actual imaging conditions, data were acquired with the small animal SPECT/CT collimation device developed at the

Cleveland Clinic (DiFilippo, 2008). This low-cost device consists of a multi-pinhole cylindrical collimator and an animal bed and uses the gamma ray and x-ray detectors of a clinical SPECT/CT scanner. The collimation device is placed on the patient bed of the clinical SPECT/CT scanner, and the system geometry is determined by scanning a pair of ^{153}Gd point sources simultaneously with the animal or phantom. Tomographic data were acquired with independent step-and-shoot rotation of the detectors and collimator (90 projections, 4° angular step) and with “ordered-subsets” stepping of the animal bed at five positions over a 30 mm axial range.

For this imaging study, the lesion detection phantom was configured with three sphere sectors having internal diameters of 1.5, 2.0, and 3.0 mm. The phantom was prepared with $^{99\text{m}}\text{Tc}$ solution such that the sphere and background activity concentrations at the scan start time were 11.2 MBq/mL and 2.8 MBq/mL, respectively. The dilution technique was used in preparing the solutions to ensure that the concentration ratio was 4.00. The sphere sectors were weighed to 0.01 mg precision with a calibrated analytical balance (Model AE 163, Mettler-Toledo, Columbus, OH USA) before and after filling the spheres. The weight differences of the 1.5, 2.0, and 3.0 mm spheres were measured to be 1.70, 4.18, and 14.18 mg, respectively. The actual liquid volumes (assuming density of 1 mg/ μL) differed by less than 5% from the expected volumes of 1.77, 4.19, and 14.14 μL . The background chambers of the sphere sectors were then filled with non-radioactive water. After positioning the sphere sectors within the cylinder and attaching the cap, the main background chamber was filled with the second radionuclide solution. Afterwards, the phantom’s outer cylinder was securely taped to the animal bed for imaging.

Two raw SPECT projection data sets were acquired of the phantom, with the first scan of 30 minutes duration and the second scan of 45 minutes duration. In between the two scans, the cap of the phantom was rotated by 60° in order to switch the locations of the sphere and background sectors. The animal bed was programmed to eject the phantom outside the collimator prior to the manual rotation step and then to return the phantom to its original location in the field of view. The rotation was performed carefully so as not to disturb the position of the external cylinder. Superposition raw projection data sets were generated of various sphere-to-background contrast ratios according to the process described below. The resultant data were then reconstructed with an iterative OS-EM algorithm (10 iterations, 9 subsets, Butterworth 4th order postfilter with 1 mm cutoff) and CT-based attenuation correction.

2.5 Simulations

In addition to the above imaging experiments, the phantom was studied by computer simulation to evaluate the constancy of detector event rates for small animal pinhole SPECT and small animal PET geometries. Since the radionuclide distribution of the phantom is not cylindrically symmetric, the event rate and associated dead time loss varies between detectors or as the phantom rotates. The phantom and detectors were modeled using the Geant4 Monte Carlo simulation software (Allison *et al.*, 2006) for SPECT (140 keV gamma rays) and PET (511 keV gamma rays). The SPECT simulations assumed a single 1 mm-diameter pinhole at 30 mm radius with a planar NaI(Tl) gamma camera detector (390 mm $\times$ 510 mm) at a 220 mm radius. The PET simulations assumed a cylinder of LSO crystal mimicking the Siemens Inveon scanner: 161 mm ring diameter, 10 mm thickness, 127 mm axial field of view (Kemp *et al.*, 2009). Gamma ray events (1 billion per step) were simulated for the phantom rotated in 3° steps over a 120° range (since the phantom has three-fold rotational symmetry). The detected singles rate over the gamma camera detector or a single PET block detector (32 mm $\times$ 32 mm) was measured versus angular step.

3. Data Processing

The raw data from the two acquisitions were processed prior to reconstructing the superposition images. For each scan, a fraction of counts (f_1 or f_2) was randomly extracted and summed to create new sinograms or projections with the desired contrast ratios. Radionuclide decay complicates the determination of f_1 and f_2 . The timing of the dual-scan data acquisition is illustrated in Figure 5. The actual background activity concentration C_0 is assayed at reference time $t = 0$ and decays as a function of time as $C_0 e^{-t/\tau}$, where τ is the radionuclide mean lifetime. The two scans are acquired with durations T_1 and T_2 , starting at t_1 and t_2 , respectively.

The task of lesion detection depends on both the total number of counts acquired as well as the contrast ratio, since increasing each of these parameters will suppress the background noise or increase the signal, respectively. Thus f_1 and f_2 must be specified according to two conditions: cumulated background activity concentration (integrated time-activity concentration) and the desired spheres-to-background concentration ratio. A pair of data sets may be subsampled multiple times with various choices of f_1 and f_2 to obtain reconstructed images with different count levels and/or contrast ratios. The determination of f_1 and f_2 is as follows:

3.1 Cumulated background activity concentration (Condition #1)

In order to normalize the background noise level between superposition images, we define an effective background activity concentration C^* and an effective scan time T^* . The product $\tilde{C} = C^* T^*$ is the cumulative counts per unit volume in the reference region and reflects the Poisson noise in the superposition data. However the superposition images contain two background activity concentrations, depending on which of the two scans (of different durations) contributed background counts for a specific sector (see Figure 4). Thus the background region must be specified in a consistent manner between studies.

Let $\tilde{C}_1$ and $\tilde{C}_2$ represent the cumulated background activity concentrations for each scan (accounting for decay) contributing to the superposition images.

$$\tilde{C}_1 = f_1 \int_{t_1}^{t_1+T_1} C_0 e^{-t/\tau} dt, \quad \tilde{C}_2 = f_2 \int_{t_2}^{t_2+T_2} C_0 e^{-t/\tau} dt \quad (1)$$

These equations are valid for full-ring tomography (non-rotating systems) where the entire sinogram is acquired at once. For non-stationary systems it is assumed here that the step time is negligible in comparison to the radionuclide decay time, although more complex equations with step-dependent fractions ($f_1(\theta)$ and $f_2(\theta)$) may be derived to fully account for decay as a function of projection time.

Three ways to define the cumulated background activity concentration in the superposition images are:

Case 1—Background local to the spheres of scan #1 (for example, the lighter-shaded sectors of the superposition image in Figure 4(c)):

$$C^* T^* = \tilde{C}_2 = f_2 \int_{t_2}^{t_2+T_2} C_0 e^{-t/\tau} dt \quad (2)$$

Case 2—Background local to the spheres of scan #2 (for example, the darker-shaded sectors of the superposition image in Figure 4(c)):

$$C^*T^* = \tilde{C}_1 = f_1 \int_{t_1}^{t_1+T_1} C_0 e^{-t/\tau} dt \quad (3)$$

Case 3—Average background over all sectors

$$C^*T^* = \frac{1}{2}(\tilde{C}_1 + \tilde{C}_2) = \frac{f_1}{2} \int_{t_1}^{t_1+T_1} C_0 e^{-t/\tau} dt + \frac{f_2}{2} \int_{t_2}^{t_2+T_2} C_0 e^{-t/\tau} dt \quad (4)$$

If selecting *Case 1* or *Case 2*, the local cumulated background will only be relevant for three of the six spheres in the superposition image. An additional note is that the initial activity and scan durations must be large enough to acquire sufficient counts to support the desired range of superposition images (*i.e.*, f_1 and f_2 are between 0 and 1).

3.2 Contrast ratio (Condition #2)

The second condition for choosing the subsampled fractions f_1 and f_2 is to yield the desired contrast ratio. Let R_0 be the actual spheres-to-background ratio of the prepared phantom. The superposition images contain two sets of virtual spheres, the contrast ratios of which are denoted as R_1 and R_2 corresponding to the locations of the actual spheres of scan #1 and scan #2. The contrast ratios are:

$$R_1 = \frac{R_0 \tilde{C}_1 + \tilde{C}_2}{\tilde{C}_2}, \quad R_2 = \frac{\tilde{C}_1 + R_0 \tilde{C}_2}{\tilde{C}_1} \quad (5)$$

For a specific R_1 and *Case 1*, solving (1) and (4) yields:

$$f_1 = \frac{(R_1 - 1)}{R_0} \frac{C^*T^*}{C_0 \tau e^{-t_1/\tau} (1 - e^{-T_1/\tau})} \quad (6)$$

$$f_2 = \frac{C^*T^*}{C_0 \tau e^{-t_2/\tau} (1 - e^{-T_2/\tau})} \quad (7)$$

$$R_2 = \frac{R_0^2}{R_1 - 1} + 1 \quad (8)$$

For a specific R_2 and *Case 2*, a similar set of equations is obtained by solving for R_1 , f_1 , and f_2 , where the solution is given simply by switching the subscripts “1” and “2” in the above equations.

For *Case 3*, the cumulated background activity concentration is averaged over the entire phantom. For a specific R_1 , the solution is:

$$f_1 = \left(\frac{2(R_1 - 1)}{R_0 + R_1 - 1} \right) \frac{C^* T^*}{C_0 \tau e^{-t_1/\tau} (1 - e^{-T_1/\tau})} \quad (9)$$

$$f_2 = \left(\frac{2R_0}{R_0 + R_1 - 1} \right) \frac{C^* T^*}{C_0 \tau e^{-t_2/\tau} (1 - e^{-T_2/\tau})} \quad (10)$$

As above, for a specific R_2 the solution for R_1 , f_1 , and f_2 is obtained by switching the subscripts “1” and “2” in these equations.

3.3 Subsampling by data rejection

After specifying f_1 and f_2 for the desired contrast ratio and cumulated background counts, the next task is to subsample the scan data to generate valid subsets that are consistent with the Poisson nature of the data. The method of subsampling depends on whether the data are collected in binned mode (projections or sinograms) or in list mode. In both cases, it is assumed that the total mean counts in the subsampled data sets are $f_1 N_1$ and $f_2 N_2$, where N_1 and N_2 are the total counts in the original data sets. Though this is an approximation, the relative uncertainties in the mean total counts ($1/\sqrt{N_1}$ and $1/\sqrt{N_2}$) are quite small due to the large numbers of counts acquired.

For binned projection or sinogram data, Poisson deviates of mean counts $f_1 N_1$ and $f_2 N_2$ are generated to determine the number of counts to subsample. Counts are then individually withdrawn from the projection or sinogram data using the rejection method (Press *et al.*, 2007), until the desired remaining number of counts is reached. SPECT projection data may be subsampled over the entire angular range or on a projection-by-projection basis if angular-dependent fractions $f_1(\theta)$ and $f_2(\theta)$ are used. PET sinogram data should be collected as separate prompts and randoms to avoid non-Poisson data associated with on-line randoms subtraction.

For each list mode PET data set, a uniform deviate x is generated for each event, and the event is kept if $0 < x < f_1$ (or $0 < x < f_2$ if data set #2) and rejected if not in that range. After subsampling, the two list files are combined into a composite list and then histogrammed and reconstructed. Alternatively, the subsampled list files may be histogrammed individually and the resulting sinograms summed prior to reconstruction.

3.4 Subsampling by list truncation

An alternate approach to subsampling list mode data is to truncate the list such that only the first portion of the events is histogrammed. If the list data streams are truncated with durations T_1' and T_2' instead of their actual durations T_1 and T_2 , then Eq. (1) is rewritten as:

$$\tilde{C}_1' = \int_{t_1}^{t_1 + T_1'} C_0 e^{-t/\tau} dt, \quad \tilde{C}_2' = \int_{t_2}^{t_2 + T_2'} C_0 e^{-t/\tau} dt \quad (11)$$

Expressions similar to those above then follow, which must be solved for T_1' and T_2' (instead of for f_1 and f_2). Eq. (8) is unaffected. For *Case 1* and specified contrast ratio R_1 , the solution is:

$$T'_1 = -\tau \ln \left(1 - \frac{(R_1 - 1)}{R_0} \frac{C^* T^*}{C_0 \tau e^{-t_1/\tau}} \right) \quad (12)$$

$$T'_2 = -\tau \ln \left(1 - \frac{C^* T^*}{C_0 \tau e^{-t_2/\tau}} \right) \quad (13)$$

The solution for *Case 2* and specified contrast ratio R_2 is obtained by switching the subscripts “1” and “2”.

For *Case 3* and specified contrast ratio R_1 :

$$T'_1 = -\tau \ln \left(1 - \left(\frac{2(R_1 - 1)}{R_0 + R_1 - 1} \right) \frac{C^* T^*}{C_0 \tau e^{-t_1/\tau}} \right) \quad (14)$$

$$T'_2 = -\tau \ln \left(1 - \left(\frac{2R_0}{R_0 + R_1 - 1} \right) \frac{C^* T^*}{C_0 \tau e^{-t_2/\tau}} \right) \quad (15)$$

As above, if R_2 is specified then the solution involves switching subscripts “1” and “2”.

4. Results

4.1 Phantom preparation

Our experience was that proper and reliable filling of the multiple chambers of the phantom required some degree of skill and practice in comparison to that needed for conventional larger phantoms. The small sphere volumes meant that the volume dispensed must be accurate to a fraction of a micro-liter, and the increased surface-to-volume ratio meant a higher likelihood of bubble formation. Although micro-liter syringes have the necessary precision for filling the spheres, a trapped bubble within the syringe could jeopardize its accuracy. It was necessary to prime the micro-liter syringe by drawing and expelling the solution several times until verifying that bubbles were no longer present. Adding a dye or food coloring improved bubble visibility and simplified this step. In all cases a centrifuge was successful in removing a bubble if one remained within a sphere. The remaining chambers of the phantom (sector interiors filled with non-radioactive water and main background chamber filled with lower-concentration radionuclide solution) have larger volumes and were filled using conventional syringes without needing to dispense precise volumes.

To validate the accuracy and reproducibility of dispensing the liquid inside the spheres, the sphere sectors were weighed before and after filling to determine the amount of solution added, assuming a density of 1.00. In 21 independent measurements, the actual volume dispensed differed from the expected volume by an average of 0.01 μL with a standard deviation of 0.12 μL . The micro-liter syringes were further evaluated by dispensing the liquid on the surface of an aluminum weighing tray instead of within the spheres. In 26 measurements (half with a 5 μL syringe and half with a 10 μL syringe), the difference between actual and expected dispensed volumes averaged 0.02 μL with a standard deviation of 0.11 μL .

4.2 Count rate simulations

The single-pinhole SPECT count rate versus rotation angle from the Monte Carlo simulations is plotted in Figure 6. As expected, a small variation in count rate was observed ($\pm 7\%$), with the maximum and minimum count rates occurring when one sector was at its closest and farthest distances from the pinhole, respectively. The simulated PET data demonstrated negligible variation in the singles rate versus rotation angle ($\pm 0.1\%$).

4.3 SPECT images

Superposition images were reconstructed from subsampled projection data for a range of spheres-to-background ratios (Figure 7). The data were subsampled to produce a cumulated background activity concentration of 1000 Bq/ μ L (27 μ Ci/mL) for a 30 min scan period. Based on the actual background activity concentration of 3000 Bq/ μ L, the actual spheres-to-background concentration ratio of 4:1, and the actual scan times of 30 and 45 minutes, the subsampled data produced spheres-to-background concentration ratios ranging from 2.5:1 and 11.7:1 (Equations 5–8). Two sets of images were reconstructed with each set subsampled to reach the target cumulated background concentration at the locations of the spheres for each rotation stop (Case 1 and Case 2, as described above). Visual inspection of the images revealed that the 3 mm spheres were visualized well in all cases, that the 2 mm spheres were visualized at 3:1 or greater ratios, and that the 1.5 mm spheres were visualized at 4:1 or greater ratios.

Region of interest (ROI) measurements were performed of the maximum sphere concentration (Figure 8) and of the mean background concentration (Figure 9) averaged over a 5 mm slab located 5 mm away from the spheres. The maximum sphere concentrations of the large 3 mm spheres agreed well with the values expected by superposition. The measured ratios for the 2 mm and 1.5 mm spheres were smaller because of partial volume effects. The measured background concentration (approximately 800 Bq/ μ L) differed from the actual value expected by superposition (1000 Bq/ μ L), attributed most likely to limited quantitative accuracy of the pinhole efficiency model used in SPECT reconstruction and to a lesser extent to dose calibrator accuracy. The background concentration displayed a slight increase versus sphere-to-background ratio because of increased scatter from the opposite sectors having higher concentration. No scatter correction was included in the image reconstruction model.

5. Discussion

5.1 Utility

In order to be effective for scanner performance evaluation, a phantom must be designed so that its preparation is straightforward, reproducible, and accurate. Besides using the principle of superposition, the lesion detection phantom developed here is unique in that it contains fillable hollow spheres smaller than have been previously reported in the literature. The smallest commercial hollow sphere at this time (Data Spectrum Micro Hollow Spheres) has internal diameter 3.9 mm (31 μ L volume), which can be filled with a conventional syringe. A smaller hollow sphere of internal diameter 3.0 mm (14 μ L volume) has been fabricated (Park *et al.*, 2007), however there is no report of its use as of yet to our knowledge. The challenges associated with filling hollow spheres of internal diameter 3 mm and smaller are quite significant.

Micro-liter syringes proved to be essential for preparing the micro-hollow spheres for this new lesion detection phantom. Practice and experience were necessary to achieve consistent results. Key details such as proper priming of the micro-liter syringes and slow filling of the spheres improved reproducibility. However the limited accuracy of the micro-liter syringes

imposes a practical limit on the minimum sphere diameter of a lesion detection phantom. Although a standard deviation of 0.12 μL is acceptable in most cases, it may be an issue in experiments with very small spheres. For a 1.25 mm diameter sphere (1.02 μL volume), the 95% confidence level corresponds to 24% of the sphere volume. The possibility of outliers due to air bubbles from incomplete syringe priming must not be overlooked. Although the micro-liter syringes demonstrated reasonable accuracy and reproducibility, for precise work it is recommended that one verifies the dispensed volume by pre- and post-weighing with an analytical balance scale and to flush, dry, and refill the sphere if necessary.

The imaging studies demonstrated the ability of the phantom to acquire superposition data. The 60° rotation of the internal components was simple to perform in-place without disturbing the overall system geometry between scans. The rotation tabs built into the cap and outer cylinder enabled a precise 60° rotation. Securely taping the outer phantom cylinder to the animal bed maintained the phantom's location in the field of view during the rotation step. The reconstructed superposition images (Figure 7) did not exhibit any artifacts associated with a shift in the phantom's location during rotation. In fact, the superposition images with equal 5:1 and 5:1 spheres-to-background ratio showed nearly uniform background intensity across the field of view.

5.2 Image analysis

The SPECT imaging experiment was intended mainly to demonstrate the capabilities of the small animal lesion detection phantom and not primarily to evaluate the performance characteristics of this particular small animal SPECT/CT scanner. Even so, the multi-contrast reconstructed images (Figure 7) were found to be quite valuable in understanding the capabilities and limitations of the scanner in ways that other phantoms could not. A common phantom for evaluating small animal SPECT and PET scanners is the Derenzo phantom with hot rod patterns in a cold background. The hot rods Derenzo phantom has infinite contrast ratio and is normally filled with high activity concentration for optimal assessment of spatial resolution. Prior work with this scanner showed the ability to resolve a 0.75 mm rod pattern. On the other hand, the multi-contrast superposition images from the lesion detection phantom showed that spheres much larger than the 0.75 mm rods of the Derenzo phantom could not be resolved with this phantom in some cases. For example, a spheres-to-background ratio of 4:1 or greater was necessary to resolve the 1.5 mm sphere at a cumulated background activity concentration of 30 kBq-min/ μL . Future studies will investigate the lesion detection capabilities of this particular scanner at other cumulated concentrations and ratios and for other configurations and scan protocols. For example, the pinhole inserts of this collimator are removable and may be replaced with pinhole inserts having larger or smaller aperture diameter. A similar study with this lesion detection phantom could determine which aperture diameter is optimal for an imaging experiment having a certain sphere diameter, contrast ratio, and cumulated background activity concentration.

The multi-contrast images generated by superposition provided a convenient visual means of evaluating scanner performance. There are similarities in this regard to the Rollo phantom traditionally used for contrast-detail experiments in planar scintigraphy (Rollo and Harris, 1977). A potential application of this lesion detection phantom would be for comparing the relative performance of scanners or modalities, since there is currently no standard lesion detection phantom for small animal imaging. An impressive variety of commercial and research scanners have been developed for small animal SPECT and PET which often differ significantly in design and performance. PET of course has significantly higher efficiency than SPECT because of coincidence detection versus collimation. However SPECT is able to achieve significantly better spatial resolution than PET because of pinhole collimation.

The superposition phantom would provide more insight as to the better performer for the task of lesion detection under various imaging conditions.

5.3 Summary and limitations

This lesion detection phantom has several key features that make it well suited for performance characterization of small animal SPECT or PET scanners. Its spheres of 1.25 to 3.0 mm diameter (1 to 14 μ L volume) are the smallest hollow spheres imaged thus far to our knowledge. With spheres of this size, the zero-activity regions of the sphere wall and fill port would normally cause significant quantitative errors and influence lesion contrast measurements. Superposition of two separate scans with activity only in the sphere or in the background completely eliminates this “wall effect” problem. The phantom is designed with separate sphere and background sectors that are interchanged between scans with a simple twist of the cap without disturbing the phantom’s position in the field of view. The phantom’s symmetry versus 60° rotation produces non-overlapping background regions and six virtual spheres in the reconstructed superposition images. Superposition is valid though only if the physics of the two scans are consistent between scans so that the detected events may be treated independently. The phantom’s approximate cylindrical symmetry ensures nearly-constant attenuation and scatter profiles between scans with minimal variations in detector dead time loss. The benefits of the new phantom design are of course tempered by certain other characteristics. A main issue with the small spheres is the difficulties associated their accurate preparation using micro-liter syringes. A centrifuge and an analytical balance scale are useful to eliminate air bubbles and to verify the dispensed volumes. However these instruments are not available in all laboratories, in which case there would need to be greater reliance on the micro-liter syringes for accuracy.

The technique of subsampling the original raw data to create superposition images with a range of sphere-to-background contrast ratios allows one to determine lesion detection thresholds from a single scan session. This approach not only saves time in data acquisition, it also saves time and radiation dose from the tedious process of phantom preparation. It must be emphasized however that the various superposition images are not true independent noise realizations. Depending on the subsampling method used and on the count fractions sampled, there will be some correlation between images which may affect lesion detection evaluation. Such correlation may be minimized by acquiring more counts (increased activity or scan time) or by repeating scans. A disadvantage of superposition is that it introduces complexity in data processing. Since the contrast ratio depends on the exact durations of the two scans, the fraction of events retained must be computed according to the above equations and the desired contrast ratios. Software must be written to randomly subsample the individual raw projections, sinograms, or list mode files and to create a summed data file with the proper header attributes and file formats compatible with the specific model of small animal scanner. This step is straightforward for scanners storing data in standard DICOM format. However many scanners use proprietary formats for raw data (especially list mode), which means that these formats must be obtained from the vendor and software custom-written for them. Once the raw data processing is complete, the reconstruction of the superposition images proceeds as usual.

Another potential issue is variation in dead time with respect to rotation angle and with respect to decay between scans. Dead time losses complicate the superposition analysis in several ways. The equations for the subsampled count fractions must be modified to account for the dead time loss as a function of projection angle or as the source decays. Although the subsampled data produce the desired background activity concentration and scan time, the actual concentration during the scan is higher, meaning that detector issues such as pile-up and mispositioned events are present in the data when they would not be for a lower activity scan. The subsampled count fractions must account for this. Also, if the scanner performs

dead time corrections during image reconstruction, the headers or tags in the superposition raw data file must properly reflect the actual scan conditions. The Monte Carlo simulations showed that the single pinhole SPECT configuration had a $\pm 7\%$ variation in singles rate versus rotation angle, whereas the small animal PET configuration showed a negligible variation. Fortunately, the count rate in small animal SPECT is typically very low, and dead time loss is not a significant issue. For PET however, there is more concern over variation in count-rate-related parameters with respect to radionuclide decay since half-lives are typically short. Depending on the source activity and scanner characteristics, dead time loss could be quite high (exceeding 20%) and could limit the accuracy of the superposition images. For high count rate situations, a series of short scans may be acquired instead of a pair of longer scans, in order to better equalize the dead time loss and randoms fraction between the two rotated positions.

6. Conclusion

A lesion detection phantom with micro-hollow spheres was developed for performance evaluation of small animal SPECT and PET scanners. The phantom uses in-place rotation, symmetric design, and the principle of superposition to eliminate the wall effect and to produce images with multiple spheres-to-background ratios. With sphere volumes as small as 1 μL (1.25 mm diameter), micro-liter syringes are necessary to accurately and consistently fill the spheres with radionuclide solution. Imaging experiments with a small animal SPECT/CT scanner demonstrated the utility of the phantom in characterizing lesion detection performance. Although there are some limitations in regards to complexity and detector dead time constancy, the phantom is valuable for task-based comparison of small animal SPECT and PET scanner performance.

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Figure 1.

Illustration of the principle of superposition for the lesion detection phantom. Left: The conventional hollow sphere phantom contains activity inside the sphere and the background chamber, leaving regions (sphere wall and fill port) containing zero activity. Right: In a superposition phantom, separate scans are acquired with activity only in the sphere or only in the background. Summing the raw data prior to reconstruction results in the desired activity distribution with no regions of zero activity.

Figure 2.

Flow chart describing the data acquisition and processing for the superposition lesion detection phantom. Two scans are acquired, subsampled by fractions f_1 and f_2 , and summed, after which the data are reconstructed to produce a specified contrast ratio and cumulated background activity. The data processing is repeated to create a series of images with a range of contrast ratios for evaluating lesion detection.

Figure 3.

Photographs of the micro-lesion detection phantom components. From left to right: (a) Fillable sphere sector, showing the internal hollow sphere, sphere fill port, and background fill port. (b) Exploded view of the phantom, showing the main outer cylinder, three sectors, rotatable sector platform, and cap. (c) Assembled phantom with cap removed, showing the sector configuration and the rotation stops on the cap and cylinder.

Figure 4.

Superposition of two scans acquired with the lesion detection phantom at the rotation stop positions (#1 and #2). The shaded regions in (a) and (b) indicate the chambers containing radionuclide solutions. The superposition image is generated by random sampling of the raw data from (a) and (b) and reconstructing the summed data. Note that in this example (c), the cumulated activity from scan #1 has been chosen to be larger than that of scan #2. Since the unshaded chambers in (a) and (b) are filled with non-radioactive water, the attenuation map (d) is approximately constant with respect to the two rotated positions, thereby maintaining constancy of the attenuation and scatter physics.

Figure 5.

Activity versus scan timing for superposition studies, where two scans (#1 and #2) are acquired separately. The cumulated activity (integrated activity over time as the radionuclide decays) is then sub-sampled in order to produce the desired contrast ratios and background concentration in the superposition images.

Figure 6. Simulated single-pinhole SPECT count rate versus detector rotation angle, showing a small variation ($\pm 7\%$) in count rate due to the asymmetric radionuclide distribution.

Figure 7.

Reconstructed superposition images of the central spheres slice, at various spheres-to-background ratios. The actual spheres from the first acquisition (Group 1) are located at the 9 o'clock (3 mm), 5 o'clock (2 mm), and 1 o'clock (1.5 mm) positions. The actual spheres from the second acquisition (Group 2) are located at the 11 o'clock (3 mm), 7 o'clock (2 mm), and 3 o'clock (1.5 mm) positions. For the upper and lower rows, the sub-sampling was performed for constant background concentration for the Group 1 spheres and the Group 2 spheres, respectively.

Figure 8.
Measured sphere-to-background ratios for the superposition images of Figure 6.

Figure 9. Measured background activity concentrations versus sphere-to-background ratio for the superposition images of Figure 6.