Task-based design of a synthetic-collimator SPECT system used for small animal imaging

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Purpose: In traditional multipinhole SPECT systems, image multiplexing — the overlapping of pinhole projection images — may occur on the detector, which can inhibit quality image reconstructions due to photon-origin uncertainty. One proposed system to mitigate the effects of multiplexing is the synthetic-collimator SPECT system. In this system, two detectors, a silicon detector and a germanium detector, are placed at different distances behind the multipinhole aperture, allowing for image detection to occur at different magnifications and photon energies, resulting in higher overall sensitivity while maintaining high resolution. The unwanted effects of multiplexing are reduced by utilizing the additional data collected from the front silicon detector. However, determining optimal system configurations for a given imaging task requires efficient parsing of the complex parameter space, to understand how pinhole spacings and the two detector distances influence system performance.

Methods: In our simulation studies, we use the ensemble mean-squared error of the Wiener estimator (EMSE_W) as the figure of merit to determine optimum system parameters for the task of estimating the uptake of an ^{123}I -labeled radiotracer in three different regions of a computer-generated mouse brain phantom. The segmented phantom map is constructed by using data from the MRM NeAt database and allows for the reduction in dimensionality of the system matrix which improves the computational efficiency of scanning the system's parameter space. To contextualize our results, the Wiener estimator is also compared against a region of interest estimator using maximum-likelihood reconstructed data.

Results: Our results show that the synthetic-collimator SPECT system outperforms traditional multipinhole SPECT systems in this estimation task. We also find that image multiplexing plays an important role in the system design of the synthetic-collimator SPECT system, with optimal germanium detector distances occurring at maxima in the derivative of the percent multiplexing function. Furthermore, we report that improved task performance can be achieved by using an adaptive system design in which the germanium detector distance may vary with projection angle. Finally, in our comparative study, we find that the Wiener estimator outperforms the conventional region of interest estimator.

Conclusions: Our work demonstrates how this optimization method has the potential to quickly and efficiently explore vast parameter spaces, providing insight into the behavior of competing factors, which are otherwise very difficult to calculate and study using other existing means. © 2018 American Association of Physicists in Medicine [<https://doi.org/10.1002/mp.12952>]

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1. INTRODUCTION

The usage of pinhole SPECT systems has risen as the need for high-resolution preclinical imaging of small animals has grown.^{1,2} In pinhole SPECT, the system resolution is a function of the object distance, detector distance, detector resolution, and pinhole radius. While reducing the pinhole radius results in a linear improvement in the spatial resolution, the sensitivity of the system decreases quadratically. This effect is known as the sensitivity-resolution tradeoff and is a

limiting factor in the performance of SPECT systems.³ A common method to combat the sensitivity-resolution tradeoff is the multipinhole SPECT system.^{4,5} In this design, multiple pinholes are made in the aperture plane, with each pinhole forming an image on the detector. By increasing the number of pinholes, a system should be able to achieve a greater overall system sensitivity with minimal degradation of resolution. However, an increase in the density of pinholes can also result in multiplexing, which is the overlapping of two or more projection images. This complicates the inverse

problem, as determining which pinhole a photon striking the detector came from is ambiguous (Fig. 1). A consequence of this is seen in the presence of image artifacts in reconstructed images, which can lead to errors in both estimation and analysis.^{6,7} Thus, while adding more pinholes leads to an increase in system sensitivity, multiplexing limits the performance gains obtainable.

Synthetic-collimator SPECT is one design method that improves the sensitivity found in multipinhole SPECT systems,^{8,9,10,11} while simultaneously maintaining the system's spatial resolution. In synthetic-collimator SPECT, two planar detectors are used in tandem, with multiplexing possibly occurring on both, but is often found on the more distant detector due to greater magnification (Fig. 2). Since each detector experiences a different degree of multiplexing, a statistically based reconstruction algorithm can be used to reduce photon-origin uncertainty and a higher fidelity image can be reconstructed. These types of algorithms are able to accommodate the ambiguity occurring in one part of a projection by utilizing the information collected from other portions of the dataset, which provide information on the relative probabilities of photons having passed through one pinhole or another. Another advantage of the synthetic-collimator SPECT system is that the two detectors can be chosen such that they are sensitive to different photon energy ranges, which can increase the total photon collection efficiency if multiple photon energies are present in the radiotracer. Greater tolerance of image multiplexing, collecting data at multiple magnifications simultaneously, and having energy specific detectors, allow a synthetic-collimator SPECT system to offset the degradation caused by the sensitivity-resolution tradeoff, making it a viable imaging system for preclinical studies. However, to maximize the potential of the synthetic-collimator SPECT system, a method of optimization over the system's large parameter space must first be devised.

The primary objective of our study was to develop and use objective measures of image quality to quantitatively assess the performance of different parameter configurations of the synthetic-collimator SPECT system. The task was to estimate

FIG. 1. A simplified illustration of image multiplexing. Photons emitted from the upper and lower regions of the object are detected by the same pixels which lead to photon-origin ambiguity. Artifacts in object reconstructions are a consequence of this uncertainty. [Color figure can be viewed at wileyonlinelibrary.com]

the uptake percentage of ^{123}I activity in regions of interest (ROIs) within a mouse brain phantom. ^{123}I was chosen due to its common presence in radiotracers which target dopamine receptors (IZBM, etc.) as well as for its high-specific activity ($> 1850 \text{ GBq}/\mu\text{mol}$) to avoid mass effects and limit radiation dose.^{12,13} One major advantage of using ^{123}I is that it emits photons at various energies which allowed us to utilize the multienergy approach described before, with the silicon detector (Si), placed in front, being sensitive to the $\sim 30 \text{ keV}$ photons and the germanium detector (Ge), in the back, being sensitive to the 159 keV photons.¹⁰ The relative abundances of photons at these two energy ranges are relatively similar; however, the exact values were not modeled in our simulations. The germanium detector used in the system has an exquisite energy resolution, while maintaining similar spatial resolutions to conventional detectors. The energy resolution allows for accurate detection of 159 keV photons as well as filtering out photons of different energies and scattering events (not modeled in our simulations). The observer used in this analysis was the Wiener estimator which is the linear estimator that minimizes the ensemble mean-squared error (EMSE).¹⁴ We used the Wiener estimator to search for the system configuration that had the lowest EMSE.

2. MATERIALS AND METHODS

2.A. Forward model

A geometrical optics model was used in simulating the propagation of photons traveling from the object phantom and striking the detector. Scattering and absorption were not modeled in the propagation through the object. A Gaussian blur ($\sigma = 1.4 \text{ mm}$) was added to simulate the effects of a finite pinhole size as well as the position estimation used in the detectors. Due to the finiteness of the gaussian, a cutoff was enforced which was dependent on the magnification and object location. Pinholes were assumed to be circular and parallel to the detector plane. When studying the synthetic-collimator SPECT system, a dual detector system, scattering and attenuation of photons that could occur within the front detector was not modeled. The decision to ignore these factors follows from the work conducted by Peterson et al., which found that in a similar dual detector system, only 1.6% of photons incident on the rear detector would be from scattering events occurring in the front detector.¹⁵ Additionally, the stopping potential of higher energy photons in the front detector is negligible to have significant consequences in the final image present on the rear detector.

To find optimal system configurations, we focused on varying pinhole spacing as well as silicon and germanium detector distances. Object distance was held constant for all simulations. The range of these values are reported in Table I. The variation of these parameters allowed us to study the effects of magnification and multiplexing on system optimization.

In our studies, we represent imaging as a linear transformation between two vector spaces,

FIG. 2. A diagram of a synthetic-collimator SPECT system. The two tandem detectors experience the different levels of image multiplexing and magnification. The two detectors are sensitive to two different energy ranges which increase photon collection.

TABLE I. Parameters used in varying system configurations to be used in simulation studies.

Parameter	Value
Number of pinholes	7
Pinhole distribution	Hexagonal
Pinhole spacing (center-to-center distance)	2–9 mm
Pinhole diameter	0.5 mm
Object-to-aperture distance	40 mm
Aperture-to-silicon detector distance	10–40 mm
Aperture-to-germanium detector distance	25–110 mm

$$\vec{g} = \mathcal{H}\vec{f}. \quad (1)$$

Here, both the object ($\vec{f}$) and mean image ($\vec{g}$) are discrete vectors, making the operator $\mathcal{H}$ a $M \times N$ matrix (system matrix), where M is the total number of measurements and N is the total number of object voxels. This formalism of discrete-to-discrete imaging is powerful; not only it affords us all of the mathematical benefits of linear algebra and eigen analysis, but it also allows us to quickly and frequently perform the imaging task over a statistically significant object ensemble. To best approximate continuous objects, we used a fine voxel grid (i.e., large N). The noise was modeled as a Poisson distributed random vector with mean given by $\vec{g}$ in Eq. (1).

2.B. Object representation

We utilized a segmented object representation to describe the imaged object phantoms,

$$\vec{f}_{N \times 1} = \mathbf{A}_{N \times Q} \vec{\theta}_{Q \times 1}. \quad (2)$$

Here, $\vec{\theta}_{Q \times 1}$ is a low-dimensional vector that contains the uptake for each of the Q object segments and $\mathbf{A}$ is the segmentation mask matrix, whose columns corresponds to a portion of the object (i.e., a segment) to be imaged. The Q rows of the $\mathbf{A}$ matrix correspond to the number of unique segments in the object.

To represent the object in such a fashion, prior knowledge of the object's spatial distribution was needed — a benefit of computer generated phantoms. In our studies, varying levels of activity were simulated in spatially fixed segments in our object phantom. This representation greatly reduced the computational load of generating simulated datasets.

2.C. Reduced system matrix

To generate the image data $\vec{g}_{M \times 1}$, construction of the reduced $\mathbf{H}$ matrix was needed where $\mathbf{H}$ is defined as

$$\mathbf{H} = \mathcal{H}\mathbf{A}. \quad (3)$$

Here, $\mathcal{H}$ is the full system matrix and has dimensions $M \times N$ and $\mathbf{A}$ is the segmentation mask matrix with dimensions $N \times Q$. From here, the noise-free image data ($\vec{g}$) is simply:

$$\vec{g}_{M \times 1} = \mathbf{H}_{M \times Q} \vec{\theta}_{Q \times 1}. \quad (4)$$

Again, Poisson random noise was sampled using the mean vector shown in Eq. (4).

It should also be noted that the image dimension M contains all of the pixels on both detectors for all projection angles:

$$M = \left(\text{Total number of detector pixels} \right) \times \left(\text{Number of projections} \right).$$

Using a reduced system matrix allowed for rapid generation and storage of many system matrices. In our simulations $N = 300^3$ with 0.1 mm isotropic voxels and $M = 16$ ($256^2 + 160^2$), where 16 was the number of projections, 256^2 was the number of pixels on the first detector (silicon), and 160^2 was the number of pixels on the second detector (germanium). This resulted in a full system matrix of 3.9×10^{13} elements, which required several gigabytes of memory for storage, whereas the reduced system matrix had 7×10^6 elements and only required several megabytes to store a significant reduction in memory and hardware strain.

2.D. Mouse brain phantom

A mouse brain phantom was used to simulate the realistic task of imaging dopamine receptors (Fig. 3). This phantom was placed in a $300 \times 300 \times 300$ voxel space, with voxel length sizes measuring 0.1 mm. The resulting field of view (FOV) was a $30 \times 30 \times 30$ mm³ volume.

To generate this phantom, object data from the MRM NeAt database were used.¹⁶ This mouse brain atlas contained high-resolution MRI-segmented images of C57BL/6J mice. The estimation was done under a signal known exactly case with no variation in object size, and so only one of these mouse brain scans was used. The chosen mouse brain was that of minimum deformation, a mouse brain where the size and location of the different regions were determined from the statistical average of an ensemble of real mouse brains. Uptake uniformity in the different mouse brain regions was assumed. The uptake percentages can be found in Table II and were calculated based on previously published studies.^{17,18}

The three mouse brain regions of interest in this study were (a) the striatum, (b) the cerebellum, and (c) the cerebral cortex. These three regions all play important roles in studying the dynamics of dopamine uptake, with the striatum having the most dopamine-specific receptor sites and thus the highest uptake.¹³ In contrast, the uptake found in the cerebellum is much lower and consists mostly of nonspecific binding and free radiotracer. Regional uptakes were assumed to be independent of one another, though correlations between regions were allowed in the methodology. A constant weak

FIG. 3. A cut away three-dimensional model of the mouse brain phantom to show the size and relative locations of the brain regions of interest: striatum, cerebellum, and cerebral cortex. The background region extends and encompasses over the exposed brain regions in the real simulations. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE II. Simulate uptake activity in different regions of phantom mouse brain.

Region	Percentage of uptake (%ID/g)
Striatum	5.0 ± 0.75
Cerebellum	1.5 ± 0.1
Cerebral cortex	2.5 ± 0.5
Background	0.5 ± 0.1

but nonzero background was also applied over all other unspecified brain regions.

2.E. Activity calculation

Activity concentrations in Table II are reported as uptake percentages in percent injected dose per gram (%ID/g). However, the true voxel counts of the mouse brain phantom were measured in becquerels, and the conversion from uptake percentage to becquerels was needed. We correct Eq. (2) by introducing the conversion factor α :

$$\vec{f}_{N \times 1} = \alpha \mathbf{A}_{N \times Q} \vec{\theta}_{Q \times 1} \quad (5)$$

where

$$\alpha = \left(\text{Injected Dose} \right) \times \left(\text{Specific Activity} \right) \times \left(\text{Density} \right) \times \left(\text{Voxel Volume} \right). \quad (6)$$

Factoring in the image acquisition time, t_{acq} , the imaging equation becomes:

$$\begin{aligned} \vec{g}_{M \times 1} &= \alpha t_{\text{acq}} \mathbf{H} \mathbf{A} \vec{\theta} \\ &= \alpha t_{\text{acq}} \mathbf{H}_{M \times Q} \vec{\theta}_{Q \times 1}. \end{aligned} \quad (7)$$

Here, $\vec{g}_{M \times 1}$ is the mean image data over all projection angles and has units of photon counts.

The simulated values used in Eq. (6) for the calculation of α are summarized in Table III. The densities of all brain regions were assumed to be equal to that of the density of water. The injected dose amount was chosen to reflect the 80 MBq dose used in work of Andringa et al.¹⁸

TABLE III. Parameters used for determining activity concentrations and simulation settings.

Parameter	Value
Injected dose	0.075 nmol
Specific activity	750 MBq/nmol
Density	0.001 g/mm ³
Voxel volume	0.001 mm ³
Total acquisition time	480 s
Projection angles	16
Total photon counts	$\sim 700,000$ (Si: 360,000; Ge: 330,000)

2.F. Wiener estimator

The uniform activity simulated in each segment of the mouse brain was sampled from a Gaussian distribution, and thus, to determine the system configuration with the lowest EMSE, we decided to use the Wiener estimator as our observer. The Wiener estimator not only has the lowest EMSE for all linear estimators when the data are Gaussian distributed but it also only requires knowledge of the first- and second-order statistics of the raw image data.¹⁴ Working with direct image data allowed us to bypass the traditional step of image reconstruction, which can introduce additional variables such as iteration number that further complicate the process of determining optimal system designs.¹⁹ The Wiener estimate is given by

$$\vec{\theta}_w = K_{g,\theta}^\dagger K_g^{-1} (\vec{g} - \vec{\bar{g}}) + \vec{\bar{\theta}}, \quad (8)$$

where $K_{g,\theta}$ is the cross-covariance of the signal parameters and the data, K_g is the data covariance, and $\vec{\bar{g}}$ is the mean noise-free image data averaged over Poisson noise and all object distributions. The EMSE of the q th object segment using the Wiener estimator is given as

$$\text{EMSE}_q = \left(\text{diag} [K_\theta - K_{g,\theta}^\dagger K_g^{-1} K_{g,\theta}] \right)_q. \quad (9)$$

In both Eqs. (8) and (9), we see that the calculation of K_g^{-1} is required, a difficult task to do computationally due to the large dimensions of K_g . However, we can decompose K_g as

$$K_g = \mathbf{H} K_\theta \mathbf{H}^\dagger + K_n \quad (10)$$

and use the Woodbury matrix identity¹⁴ to represent the inverse as

$$K_g^{-1} = K_n^{-1} - K_n^{-1} \mathbf{H} (K_\theta^{-1} + \mathbf{H}^\dagger K_n^{-1} \mathbf{H})^{-1} \mathbf{H}^\dagger K_n^{-1}. \quad (11)$$

Assuming uncorrelated noise, this simplifies the problem of finding the inverse of a $M \times M$ matrix to solving the inverse of two $Q \times Q$ matrices, greatly reducing the computation load and time when Q is small relative to M . This condition was satisfied in our studies as $M = 1458176$ and $Q = 4$ (Table II).

To get an aggregate of the EMSE of the Wiener estimator that was independent of the different uptake activities in each mouse brain region, we normalized each region's EMSE _{q} by the square of its mean uptake activity ($\vec{\bar{\theta}}_q$). This value was then summed over all regions of interest in the mouse brain,

$$\text{EMSE}_w = \sum_{q=1}^Q \frac{\text{EMSE}_q}{\vec{\bar{\theta}}_q^2}. \quad (12)$$

The final result in Eq. (12) is the full EMSE of the Wiener estimator and was used to compare different system configurations.

2.G. ROI estimation using MLEM reconstructions

We compared the performance of the Wiener estimator against a region of interest estimator using MLEM-

reconstructed image data (MLEM + ROI estimator) as a benchmark test. MLEM (maximum-likelihood expectation maximization) is an iterative algorithm that converges to an object which maximizes the likelihood function: $\text{pr}(\vec{g}|\vec{f})$.²⁰ While the MLEM reconstruction algorithm is ideal when the image data are Poisson, it is computationally strenuous and was somewhat impractical in our studies given the large number of system designs considered. The primary reason for this inefficiency was that the MLEM algorithm required the full system matrix, $\mathcal{H}$, which in our case could not be stored and was instead recalculated at each iteration. We improved computation speed and efficiency by enforcing a nonlinear operation after each iteration: voxel values in the reconstructed object below a certain threshold were set to zero. Projection data were simulated using a highly sampled $300 \times 300 \times 300$ object ($\vec{f}$) and the reconstructed object ($\vec{\hat{f}}$) was a $50 \times 50 \times 50$ object. Although both modeled objects were discrete, the finer sampling and higher dimensionality of $\vec{f}$ relative to $\vec{\hat{f}}$ better represent the continuous nature of true objects. However, the reduction in the number of voxels of the MLEM reconstruction introduced errors in the ROI estimation due to pixelation, a problem which could be avoided by using the Wiener estimation approach outlined in this paper. MLEM reconstructions of 90 iterations were performed on our computer-generated data ensemble, which consisted of 15 different object activity realizations sampled from the distributions specified by Table II, each with ten noisy images. In the performance evaluation between the MLEM + ROI estimator and the Wiener estimator, this same object ensemble is used.

Segmentation of the regions of interest was then performed on the MLEM reconstructions (Fig. 4). Extensive computation of object segmentation was unnecessary in our signal known exactly simulations. To generate the template masks used in the ROI analysis, dimensional compression of the highly sampled mouse brain was needed. This was completed by first individually segmenting the $300 \times 300 \times 300$ voxel phantom and then compressing each segmented ROI into the properly reduced dimensions of $50 \times 50 \times 50$ voxels. The template mask was applied to the MLEM reconstructions, and then, the total object activity in the ROI was summed. Dividing by the conversion parameter α [Eq. (6)] and t_{acq} and then normalizing by the total number of voxels in the ROI, we obtained an estimate of the uptake percentage for a specific mouse brain region. The dimensionality reduction and the stopping condition in the MLEM algorithm both introduced errors and biases in this estimation technique, limiting the accuracy of the MLEM + ROI estimator.²¹ However, this estimator could still be used for task performance and system optimization, albeit being a much slower and more computationally expensive choice when compared to the Wiener estimator.

2.H. Determining percent multiplexing

In our simulations, we defined percent of image multiplexing as the fraction of photon counts incident on pixels with

FIG. 4. A diagram describing how ROIs – in this example the cerebellum – are segmented from reconstructed objects in order to generate estimates of uptake activity. [Color figure can be viewed at wileyonlinelibrary.com]

multiplexing relative to the total number of photon counts accumulated over all active pixels:

$$\% \text{Multiplex} = \frac{\sum_{i,j \in X_m} \beta_{i,j} g_{i,j}}{\sum_{i,j \in X} g_{i,j}} \quad (13)$$

where X_m is the set of all pixels with multiplexing present and X is the set of all pixels with counts. $\beta_{i,j}$, the fraction of multiplexed subpixels within pixel (i,j) is obtained by simulating the projection data on a three-time finer grid. When this subpixel calculation of $\beta_{i,j}$ was ignored and all values set to 1, sharp jumps in the percent multiplexing function as a function of germanium detector distance were observed. This was a consequence of the quantization of image data, which resulted in discontinuities in the total number of active pixels as image magnification is increased.

We also considered other definitions for image multiplexing such as only considering the fraction of multiplexed pixels to the total number of active pixels.⁷ However, this definition ignored the distribution of activity within an object and did not fully correlate with the results we found in our studies.

3. RESULTS

In this section, we present the results from our simulation study of the synthetic-collimator SPECT system and how different parameter configurations (Table I) affect overall system performance. The figure of merit (FOM) in this study was the Wiener ensemble mean-squared error (EMSE_w), with lower values of the EMSE_w indicating better system performance. We examined the performance of the synthetic-collimator system:

1. Relative to a single detector multipinhole SPECT system.
2. Under different detector distances.
3. With varying image multiplexing due to different pinhole spacings.
4. When optimization is done for an adaptive system.

We also report the comparative performance of the Wiener estimator against a region of interest estimator based on

images reconstructed using MLEM to provide context of the utility of our method.

3.A. Synthetic-collimator SPECT vs single detector SPECT

We examined the differences between the synthetic-collimator SPECT system and a traditional multipinhole system, and how the inclusion of a second detector plane, placed in front of the germanium detector, influenced system performance. To model a single detector multipinhole SPECT system, we used our forward model to simulate projection data which ignored the contributions from the silicon detector. As stated previously, the low influence of the silicon detector on the higher energy photons (159 keV) which are collected by the germanium detector essentially makes the two detectors independent of one another. Thus, the removal of the silicon detector under these conditions would be expected to have a negligible effect on the final image produced by the germanium detector. Detector scatter is again ignored in the germanium detector. We used the Wiener estimator to compare this single detector system against a synthetic-collimator SPECT system (which included data from both detectors) under several different parameter settings.

The difference in performance between the single and dual detector systems is shown in Fig. 5(a). Here, the systems are compared over several different pinhole spacings, ranging from 4 to 6 mm. The silicon detector distance was fixed at 10 mm for all pinhole spacings of the synthetic-collimator system. We found that the dual detector system outperformed its corresponding single detector system for all pinhole spacings.

Although the behavior trends for the two system types were similar, differences between the two are seen when the range of EMSE_w values is normalized on a scale from 0 to 1 [Fig. 5(b)]. Again, a silicon detector distance of 10 mm was used for the dual detector system and a 6 mm pinhole spacing was chosen for both system types. The use of dual detectors resulted in greater optimal germanium detector distance, favoring the presence of greater magnification and multiplexing on the germanium detector in the synthetic-collimator SPECT system.

FIG. 5. (a): Performance differences between SPECT systems using single and dual detectors for varying germanium distances (25–110 mm) and a silicon detector distance set at 10 mm. Although both system designs demonstrate similar performance trends, dual detector systems have better performance and a narrower range. (b): When data from the silicon detector are utilized, we observe that the dual detector system favors greater magnification and multiplexing on the germanium detector, shifting the optimal germanium detector distance further back. Dual detectors also reduce the performance degradation caused by increased image magnification. A silicon detector distance of 10 mm is used in the dual detector system. [Color figure can be viewed at wileyonlinelibrary.com]

3.B. Relationships between dual detectors

The results shown in Fig. 5 demonstrated how the presence of the silicon detector could influence the optimal location of the germanium detector. We continued to explore this relationship by keeping the silicon detector in front of the germanium detector and varying the silicon detector distance from 10 to 40 mm in 2 mm increments. Pinhole spacing of 5 and 6 mm are shown. The optimal germanium detector distance for both pinhole spacings were recorded for each step (Fig. 6). We found that with increased silicon detector distance, the optimal germanium detector distance tended to that of a single detector system (dashed red line) which was determined by simulations on a finer increment to occur at 40 mm and 53 mm for the 5 and 6 mm pinhole spacings, respectively.

We also looked at how a fixed germanium detector distance would influence the optimal location of the silicon detector. The germanium detector distances of 30 mm and

55 mm were determined by using the minima locations of Fig. 8 for pinhole spacings of 4 and 6 mm. Silicon detector distances were then varied for the two pinhole spacing cases to determine optimal locations (Fig. 7). For the two parameter cases, we observed different optimal silicon detector distances, occurring at 22 and 28 mm for the 4 and 6 mm pinhole spacing cases, respectively.

3.C. Influence of percent multiplexing on system performance

We also examined how image multiplexing impacted system performance by varying both the spacing between pinholes and the germanium detector distance (Fig. 8). Pinhole spacing was varied from 2 to 9 mm at 1 mm steps. Germanium detector distance was varied between 25 and 115 mm in steps of 5 mm. Silicon detector distance was fixed at 20 mm in all cases. System performance response to varying pinhole spacings is shown in Fig. 8(a), with a subset of those pinhole

FIG. 6. Optimal germanium detector distance of a dual detector system (circle) tends toward a single detector system (dashed) when the amount of multiplexing on the silicon detector is increased. Pinhole spacings of (a) 5 and (b) 6 mm are shown. [Color figure can be viewed at wileyonlinelibrary.com]

spacings shown in Fig. 8(b) to allow for a more detailed view of the trends.

We found that, in general, systems with increased pinhole spacings had overall lower EMSE_W . A nonlinear increase in the EMSE_W minima locations was also observed with increased pinhole spacing.

The percent multiplexing of system configurations with pinhole spacings between 4 and 9 mm is shown in Fig. 9(a) and the derivative of this function is shown in Fig. 9(b). We found that the percent multiplexing as a function of germanium detector distance followed a logistic growth model, with the location of maxima in the rate of change of multiplexing increasing nonlinearly with pinhole spacing.

FIG. 7. The optimal silicon detector distance for 4 (circle) and 6 (x) mm pinhole spacing configurations when using a fixed germanium detector. The optimal location of the silicon detector is dependent on the multiplexing present on the germanium detector. [Color figure can be viewed at wileyonlinelibrary.com]

3.D. Adaptive system performance

Motivated by the previous results, we also examined the performance of an adaptive synthetic-collimator system, which allowed the germanium detector distance to differ at each projection angle. To determine the optimal detector distance for a single angle, EMSE_W values at varying germanium detector distances were calculated for a dual detector system whose image data consisted only of single angular projection (Fig. 10). This process was repeated for the 16 unique angles in the synthetic-collimator system to generate a set of optimal germanium detector distances. Finally, this set of detector distances was then used as parameters to simulate the adaptive synthetic-collimator system. Table IV summarizes the performance of this adaptive strategy for several systems with varying pinhole spacings ranging from 4 to 6 mm.

3.E. Wiener estimation vs ROI estimation

A comparative study between the Wiener estimator and a region of interest estimator using MLEM-reconstructed image data (MLEM + ROI estimator) was performed. From our results in Section 3.C, we chose to study two systems with the following parameter configurations:

1. Pinhole spacing: 6 mm; Germanium distance: 30 mm
2. Pinhole spacing: 6 mm; Germanium distance: 55 mm

For both systems, the silicon detector distance was fixed at 20 mm. The first system configuration had a low level of image multiplexing (3%), whereas the second configuration experienced a higher level of multiplexing (28%).

For both system parameter configurations, estimates were determined for the three mouse brain regions: striatum, cerebellum, and cerebral cortex. The mouse brain region estimates generated by the Wiener estimator (dot) and the MLEM + ROI estimator (open circle) are compared against their true values (Fig. 11). A perfect estimator,

FIG. 8. The effect of pinhole spacing on system performance. The silicon detector distance is fixed at 20 mm for all pinhole spacing configurations. The data in (b) are a subset of (a). Lower EMSE_W values indicate better system performance. The optimal germanium detector distance increases nonlinearly with increasing pinhole spacing. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 9. (a): Logistic growth behavior of percent multiplexing as a function of germanium detector distance for pinhole spacings between 4 and 9 mm. The silicon detector distance is fixed at 20 mm for all pinhole spacing configurations. (b): The derivative of multiplexing for different pinhole spacings. Germanium detector distances which result in optimal system performances occur around derivative maxima. [Color figure can be viewed at wileyonlinelibrary.com] [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 10. Variations in the $EMSE_w$ for different projection angles are caused by rotational asymmetries in the object. Changing the germanium detector distance for each projection leads to improved performance over a fixed detector distance system. The silicon detector distance is fixed at 20 mm and a pinhole spacing of 6 mm was used. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE IV. Performance differences between a fixed detector distance system and a system with varying detector distance at each projection angle.

Pinhole spacing (mm)	Fixed $EMSE_w$	Adaptive $EMSE_w$	Relative change
4	6.16×10^{-4}	6.15×10^{-4}	1.24%
5	5.73×10^{-4}	5.71×10^{-4}	6.51%
6	5.47×10^{-4}	5.44×10^{-4}	4.32%

lying on the line at 45° and passing through the origin, is also shown. We found that, under both configurations, the estimates calculated by the Wiener estimator were closer to

the truth when compared to those formed by the MLEM + ROI estimator.

4. DISCUSSION

Our results demonstrate that the synthetic-collimator SPECT system outperforms a single detector multipinhole system. The improved performance is mainly due to the increased information collected when using two detector planes, which is made possible due to the multiphoton approach described in earlier sections. While this point may seem trivial, as a higher collection efficiency of using two detectors should result in higher performance, it is an important demonstration of the benefits achieved when using dual detectors and the need to study optimization strategies for such systems, despite the increased difficulty. However, it is important to note that the inclusion of the silicon detector does not only increase the total number of collected photons but can also affect the optimal germanium detector distance. The difference in optimal germanium detector distance between a dual detector and single detector system is dependent on the amount of multiplexing present on the silicon detector. For small levels of multiplexing on the silicon detector, we find that the synthetic-collimator SPECT system performs better with larger germanium detector distances, even if it results in a greater level of multiplexing. When the multiplexing on the silicon detector is low, there is more statistical information about a photon's pinhole origin, and thus, it is easier to use this information to decode the multiplexing occurring on the germanium detector. However, as the silicon detector is moved farther away from the aperture, multiplexing increases and the usefulness of the silicon image data is diminished. Thus, under these cases, systems with less multiplexing on the germanium detector (i.e. smaller germanium detector distances) are preferred. Eventually, the multiplexing on the silicon detector is too great and provides no useful information to the estimator and the optimal germanium detector distance of the dual detector system converges toward the optimal detector distance of a single detector

FIG. 11. The estimated activity of the three mouse brain regions calculated by the Wiener estimator (dot) and MLEM + ROI estimator (open circle) is plotted against the true activity values. The Wiener estimator performs very closely to a perfect estimator (solid line) and outperforms the MLEM + ROI estimator for both parameter configurations: (a) Pinhole spacing of 6 mm and germanium distance of 30 mm, (b) Pinhole spacing of 6 mm and germanium distance of 55 mm. [Color figure can be viewed at wileyonlinelibrary.com]

multipinhole system. A similar conclusion to the aforementioned phenomenon, only now in reverse, can be drawn from Fig. 7, with the difference being that in this simulation we have chosen to fix the germanium detector instead. Thus, we see that, for a dual detector system, multiplexing on either detector is not a detriment to the overall system performance and in some cases, desirable. Additionally, the influence two detectors have on one another demonstrates the need for an efficient optimization strategy, such as the Wiener estimator, to understand and explore the dynamics of the synthetic-collimator's parameter space.

The impact multiplexing has on system performance is further explored — demonstrating that lower levels of multiplexing result in better overall task performance for the synthetic-collimator SPECT system. This is best seen in Fig. 8, where the average EMSE_W for a system decreases with increased pinhole spacing. However, the average improvement response is nonlinear, with higher multiplexed systems experiencing more improvement when the pinhole spacing is increased. In contrast, the performance separation between lower multiplexed systems (large pinhole spacings) is smaller, allowing other factors to influence overall system performance, resulting in the transitions between different EMSE_W curves. The 8 and 9 mm pinhole spacing cases also provide some insight into the performance of the synthetic collimator SPECT system in the absence of multiplexing. Despite having no multiplexing present on the germanium detector, the EMSE_W of both pinhole spacings remain relatively similar to those with low multiplexing. However, a drawback of greater pinhole spacings is observed in the sharp rises in the EMSE_W for these pinhole spacings, which are caused mainly by detector walk-off, in which photons passing through the pinhole aperture miss the detector due to its finite size and contribute no information to the image data. We also notice that, for the smallest pinhole spacings, the performance improves with increased germanium detector distance, which seemingly conflicts with our remarks on multiplexing. However, we find that under these conditions and at sufficiently large detector

distances, both detectors experience such high levels of multiplexing that the projection images from adjacent pinholes converge and begin to appear as one projection image. Thus, the multipinhole system begins to behave like a single pinhole system with a larger effective aperture radius and poorer resolution. Thus, when the germanium detector distance is increased, image magnification grows, whereas the percent multiplexing remains relatively unchanged, resulting in improving system performance. Despite all these, such a system is still unable to outperform multipinhole systems with lower levels of percent multiplexing.

However, simply reducing the percent multiplexing by moving the germanium detector closer does not always lead to better system performance due to the trade-off between image magnification and multiplexing. Instead, we find that it is the rate of change of the percent multiplexing that influences the optimal location of the germanium detector. Comparing Figs. 8(b) and 9(b), we find that the germanium detector distance with the lowest EMSE_W for a given pinhole spacing occurs at the maximum of the percent multiplexing derivative, when taken with respect to germanium detector distance. However, it should be noted that in the cases of 8 and 9 mm pinhole spacings, this derivative maxima is never reached before detector walk-off occurs. The reason the system performance is maximized at these locations is that the derivative maxima occur when the contribution to the image data from multiplexing-free pixels is the greatest. While the fraction of multiplexing-free pixels would be greatest when the percent multiplexing is at a minimum, the total number of multiplexed-free pixels is dependent on the magnification of the system. Therefore, while there may be higher levels of percent multiplexing at these germanium detector distances, the total number of pixels without multiplexing is also at a maximum. Returning to our definition of multiplexing [Eq. (13)], we see the importance of β_{ij} , as it allows us to more accurately determine the distribution of photons incident on multiplexing-free pixels and subpixels. When β_{ij} is set to one, not only we observe jumps in the percent multiplexing

function but also jumps in the EMSE_W in Fig. 8. It is important to note that the calculation of $\beta_{i,j}$ can only be determined in a simulation study. However, the optimal germanium detector distance is shifted slightly away from these locations due to the additional information provided by the silicon detector, which helps reduce the negative influences of multiplexing. We also observe that the curvature of the minimum of the EMSE_W function is positively correlated with the magnitude of this derivative maximum. Thus, for a system with a large derivative maximum value, minor perturbations from the optimal germanium detector distance result in a faster decay of the system performance.

From our understanding of how percent multiplexing influences the synthetic collimator SPECT system, we propose an adaptive approach to achieve better system performance. In contrast to a fixed detector system, where the system parameters are dictated by the rate of multiplexing averaged over all projection angles, this adaptive system allows for the germanium detector distance to be varied at each projection. Our motivation for this type of system lies in the lack of rotational symmetry found in our objects, and thus, we expect that the rate of multiplexing is a function of not only distance but also projection angle. Under this system design, the data shown in Fig. 10 are our scout data from which we generate the different germanium detector distances. It is important to note that while the scout data generated by the single projection angle system will result in poor image reconstruction due to a limited number of angular views, we can still extract useful information regarding the rate of multiplexing and task performance using the Wiener estimator and the methods covered in this manuscript. Our results demonstrate improvements in system performance under the three considered pinhole spacings (Table IV). While the change in EMSE_W is not drastic, the benefit of this adaptive approach becomes more apparent when we consider the percent change relative to the total range of values for the fixed system's EMSE_W from 25 to 115 mm (Fig. 8). Additionally, while not simulated in this study, we have confidence that further improvements in task performance can be achieved when allowing both the silicon and germanium detectors to move during data acquisition.

When compared to MLEM + ROI estimation, we find that the Wiener estimator under both system parameter configurations, on average, produces estimates which are closer to the truth and with less variance. The performance of the Wiener estimator benefits from the relative simplicity of the task, as the object in our simulations is only a 4×1 vector, whereas when using real data, the task is much more difficult, with $\vec{\theta}_Q \times 1$ having a much higher dimensionality. Under such circumstances, we expect to see a decrease in the Wiener estimator's performance, but still expect the Wiener estimator to outperform the MLEM + ROI estimator. Another advantage of the Wiener estimator is that it is more computationally efficient as its estimates are formed directly by using the first- and second-order statistics of the raw image data. In contrast, the ROI estimator requires a reconstruction step, which makes its EMSE sensitive to a number

of free parameters and constraints, such as iteration number, smoothness conditions, and object priors, all of which make it difficult to use when trying to identify optimal system configurations. Additionally, we find that the MLEM + ROI estimator underestimates the activity for all three mouse brain regions. One factor for this bias is that the MLEM algorithm produces noisy reconstructions with artifacts due to noisy image data. Another reason is that the MLEM algorithm does not preserve sharp boundaries between different regions due to a finite number of iterations, and thus, some of the activity lies outside of a ROI's template mask, which have sharp edges.

5. CONCLUSION

In this manuscript, we present the utility of the Wiener estimator for optimizing for a synthetic-collimator SPECT system. Due to its computation efficiency and need for only the first- and second-order statistics of the image data, the Wiener estimator can be used to quickly search through large parameter spaces to find optimal system configurations. Furthermore, by using the Wiener estimator, we can make optimization decisions without the need of a reconstruction algorithm, a major advantage as reconstruction algorithms are computationally expensive and have additional degrees of freedom that influence the outcome.

In our simulations, we considered the task of estimating the uptake of different regions in a mouse brain phantom. The locations of these regions were known and were placed on a constant background signal. The EMSE_W was used as FOM for task performance. The estimation tasks we performed in this paper were model based; a known object model was used to generate the data and to perform the estimation task. Thus, the EMSE_W values we observe are likely smaller than those that could be achieved when the object model is unknown. One shortcoming of our simulations was that we did not account for the relative abundances of photon emissions. However, the results and techniques presented in this manuscript are still relevant to understanding the synthetic-collimator SPECT system and system optimization. One implicit assumption in this work is that the performance using the model-based methods will trend with other, more complicated methods. This assumption is partly validated by the fact that the Wiener estimator for all methods utilizes the projection data and the first- and second-order statistics of that data. The object-model-based methods presented in this work simply offer an efficient method for estimating these statistics.

Our studies demonstrate that the synthetic-collimator SPECT can outperform traditional multipinhole SPECT systems in the task of estimating signal activity. Additionally, by studying the behavior of the EMSE_W of different system configurations, we show how the rate of image multiplexing can influence task performance, and by taking advantage of the asymmetry in our objects, we can achieve better estimates using an adaptive scheme. However, the improved results from the adaptive strategy must be carefully considered when extended to a real system, as they do not take into account

other factors — such as the time needed to determine the optimal configuration. Finally, we have provided a comparative study between the Wiener estimator and the MLEM + ROI estimator. We find that Wiener estimates experience less bias and are closer in value to true signal activities. While not presented here in this manuscript, due to the large parameter space already being explored, one area of interest in future studies is to consider pinhole radius and object-to-aperture distance variations and how they can influence system performance due to increases in overall sensitivity, magnification, and multiplexing. In addition to this, once a better understanding of the role between multiplexing and system performance is achieved, we will also like examine how each individual region contributes to the system optimization — a study which may hold relevance when specific brain regions may be more important for a particular study.

The strengths of the Wiener estimator and the methods presented here are not restricted to the synthetic-collimator SPECT system and can be extended to other cases where large parameter spaces are encountered and the optimization of other gamma-ray imaging systems.

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DISCLOSURE

The authors have no conflicts to disclose.

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