A line-source method for aligning on-board and other pinhole SPECT systems

Susu Yan^{a)}

Medical Physics Graduate Program, Duke University, Durham, North Carolina 27710

James Bowsher and Fang-Fang Yin

Medical Physics Graduate Program, Duke University, Durham, North Carolina 27710 and Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina 27710

(Received 17 May 2013; revised 9 September 2013; accepted for publication 10 October 2013; published 12 November 2013)

Purpose: In order to achieve functional and molecular imaging as patients are in position for radiation therapy, a robotic multipinhole SPECT system is being developed. Alignment of the SPECT system—to the linear accelerator (LINAC) coordinate frame and to the coordinate frames of other on-board imaging systems such as cone-beam CT (CBCT)—is essential for target localization and image reconstruction. An alignment method that utilizes line sources and one pinhole projection is proposed and investigated to achieve this goal. Potentially, this method could also be applied to the calibration of the other pinhole SPECT systems.

Methods: An alignment model consisting of multiple alignment parameters was developed which maps line sources in three-dimensional (3D) space to their two-dimensional (2D) projections on the SPECT detector. In a computer-simulation study, 3D coordinates of line-sources were defined in a reference room coordinate frame, such as the LINAC coordinate frame. Corresponding 2D line-source projections were generated by computer simulation that included SPECT blurring and noise effects. The Radon transform was utilized to detect angles (α) and offsets (ρ) of the line-source projections. Alignment parameters were then estimated by a nonlinear least squares method, based on the α and ρ values and the alignment model. Alignment performance was evaluated as a function of number of line sources, Radon transform accuracy, finite line-source width, intrinsic camera resolution, Poisson noise, and acquisition geometry. Experimental evaluations were performed using a physical line-source phantom and a pinhole-collimated gamma camera attached to a robot.

Results: In computer-simulation studies, when there was no error in determining angles (α) and offsets (ρ) of the measured projections, six alignment parameters (three translational and three rotational) were estimated perfectly using three line sources. When angles (α) and offsets (ρ) were provided by the Radon transform, estimation accuracy was reduced. The estimation error was associated with rounding errors of Radon transform, finite line-source width, Poisson noise, number of line sources, intrinsic camera resolution, and detector acquisition geometry. Statistically, the estimation accuracy was significantly improved by using four line sources rather than three and by thinner line-source projections (obtained by better intrinsic detector resolution). With five line sources, median errors were 0.2 mm for the detector translations, 0.7 mm for the detector radius of rotation, and less than 0.5° for detector rotation, tilt, and twist. In experimental evaluations, average errors relative to a different, independent registration technique were about 1.8 mm for detector translations, 1.1 mm for the detector radius of rotation (ROR), 0.5° and 0.4° for detector rotation and tilt, respectively, and 1.2° for detector twist.

Conclusions: Alignment parameters can be estimated using one pinhole projection of line sources. Alignment errors are largely associated with limited accuracy of the Radon transform in determining angles (α) and offsets (ρ) of the line-source projections. This alignment method may be important for multipinhole SPECT, where relative pinhole alignment may vary during rotation. For pinhole and multipinhole SPECT imaging on-board radiation therapy machines, the method could provide alignment of SPECT coordinates with those of CBCT and the LINAC. © 2013 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4828776>]

Key words: function and molecular imaging, line-source, on-board, pinhole, SPECT

1. INTRODUCTION

On-board image guidance such as cone-beam CT (CBCT) and KV/MV imaging is essential in many radiation therapy procedures, such as intensity modulated radiotherapy and stereo-

tactic body radiation therapy. These imaging tools enable high dose to be delivered precisely to the target with less injury of surrounding normal tissues, which is a goal of radiotherapy, in order to maximize local control of tumor and to minimize normal tissue complication. These imaging techniques

FIG. 1. Computer-aided design illustration of a robotic multipinhole SPECT system imaging a patient in position for radiation therapy. Also shown are a patient table and LINAC. The system involves a robotic arm (KUKA Robotics Corporation, Shelby Township, MI) which maneuvers a 49-pinhole-SPECT system about the patient. This multipinhole SPECT system would concentrate detector area on a limited region of interest, e.g., the radiation-therapy target, thereby improving SPECT sensitivity for that region of interest and potentially allowing relatively short scan times.

provide predominantly anatomic information for treatment planning and target localization.¹

Recently, studies have shown that treatment planning based on functional and molecular information about the tumor and surrounding tissue has potential to enhance the benefit of radiation therapy.^{2,3} For example, target regions can be improved by knowing the hypoxic cells in the tumor region.⁴ Nuclear medicine imaging methods, such as PET and SPECT, are established and still expanding methods for functional and molecular imaging. For instance, Tc-99m Technegas/macro aggregated albumin (MAA) has been used for lung cancer imaging,⁵ and Tc-99m MIBI has been used for detecting breast tumor.⁶

Current on-board imaging systems are limited in their functional and molecular imaging capability. SPECT is a candidate to achieve on-board functional and molecular imaging. However, traditional SPECT systems take 20 min or more for a scan, which is too long for on-board imaging. Robotic multipinhole SPECT methods could provide shorter imaging times, via multiple pinholes, with a robot maneuvering the multipinhole system around the patient in position for radiation therapy.⁷ Figure 1 illustrates one such system design.

For accurate target localization, the coordinate frame of the multipinhole SPECT system should be registered to that of the LINAC. Therefore, alignment methods are crucial.

Many alignment methods have been proposed for pinhole imaging and the closely related geometry of cone-beam imaging. A detailed and thorough review is beyond the scope of this paper. Here some previous work is described in order to convey that typically these methods have involved point sources and multiple projection views. Often a known shape has been assumed for the detector trajectory or the alignment method has been constructed to estimate deviations about a known shape. In some cases, knowledge of the azimuthal detector angles has been assumed. Alignment calibration methods for cone-beam geometry were developed in Refs. 8–11. One method⁸ used an alignment point source to estimate three alignment parameters (distance from focus to center of rota-

tion, focal length, and location of projection of center of rotation) plus the three-dimensional coordinate of the alignment point source. This method utilized multiple known projection angles over a 360° imaging trajectory. Later, a method⁹ suggested that seven parameters are sufficient to calibrate the cone-beam geometry for a circular motion in which the azimuthal angles are known. Those seven parameters were divided to intrinsic and extrinsic parameters. The intrinsic parameters describe the detector geometry, and can be measured using a grid of point sources and separately from the extrinsic parameters. The extrinsic parameters change with detector position, and were estimated using a point source. Another method¹⁰ also estimated three extrinsic parameters separately from intrinsic parameters using a grid of 9, 16, and 25 spheres. Although this method estimated the azimuthal angle of the camera, many spheres were used. Another method¹¹ was proposed that used a different optimization method to estimate six alignment parameters from two point sources and six detector views. Subsequently methods were developed for SPECT pinhole alignment,^{12–17} often incorporating methods similar to those for cone-beam. Many of these methods utilize multiple pinhole projection views. A second issue is that some previous methods have assumed a specific pinhole trajectory shape, such as a circle.¹² Third, studies^{13,15,16,18} have shown that there may be small deviations from the intended pinhole trajectory, and some methods have emphasized estimation of angle-dependent deviations from the assumed trajectory shape.¹⁶ Herein, a method is proposed which makes no assumptions about trajectory shape and which estimates alignment parameters from a single pinhole projection view. This allows determination of the relative orientations of individual pinholes within a multipinhole system, which may be important since these relative orientations can change with orientation of the overall multipinhole system, due to the changing effects of gravity.

Finally, point sources can be challenging to produce. For example, if the point source consists of a droplet of radiotracer together with x-ray or MRI contrast agent, it can be challenging to enclose this droplet in a container that is uniformly attenuating in all directions of three-dimensional space. Consequently, with attenuation greater in some directions, scatter will also be greater, and this can shift the apparent location of the point source. If the point source is generated by more sophisticated processes that can achieve uniform attenuation in all directions, then it may be necessary to use long-lived radionuclides in order to justify the cost of more sophisticated procedures. Long-lived radionuclides present increased costs for secure storage and management of regulatory issues. Another approach to generating point sources is to construct a line source that has very short length in the linear direction. Here again though it can be cumbersome to achieve a short length in the linear direction. In contrast, a line source can simply be a straight tube which is capped after a solution of radiotracer and contrast agent is simply injected into the tube with a syringe. The process is fast and simple, so short-lived radionuclides can be used. Therefore, this paper proposes an alignment method that is derived assuming—and therefore accurately models—line sources. In a line-source model, the

FIG. 3. (a) The gray broad line segment is a single pinhole projection of a line source. The superimposed narrow dark gray line is the estimated ridge of the line-source projection and is computed using (15), where (α_0, ρ_0) corresponds to the maximum pixel value determined from the Radon transform of the line-source projection. The offset (ρ) is the perpendicular distance from the center of the projection image to the ridge of the line-source projection. The angle (α) is between the horizontal-axis and the offset-axis. (b) Radon transform of line-source projection in (a), where (α_0, ρ_0) is the angle and offset corresponding to the maximum pixel value of the Radon transform and is used to draw the red line in (a).

The pinhole translations u_f , v_f , and w_f are assumed to be known. Consider an isolated radioactive point source k , where (X_k, Y_k, Z_k) could be known by, for example, CBCT imaging. The (x_k, y_k, z_k) of Eqs. (12) and (13) could then be determined by Eqs. (3)–(6) given the alignment parameters θ , Φ , and Ψ . The projection (u_{p_k}, w_{p_k}) of k could be observed on the detector. The unknowns in Eqs. (12) and (13) would therefore be the six alignment parameters (x_{det} , y_{det} , and z_{det}) (explicitly) and (θ, Φ, Ψ) (implicitly). Explicitly means that the three translation parameters are directly expressed in Eqs. (12) and (13). Implicitly means that the three rotation parameters are not directly expressed in Eqs. (12) and (13). They are instead implied by rotation matrix in Eqs. (3)–(6) and expressed as x_k , y_k , and z_k in Eqs. (12) and (13).

2.B. Estimation of alignment parameters

To estimate alignment parameters from line sources, two points (p_{jk} : $k = 1, 2$) are selected on each line-source projection (j : $j = 1 \dots \text{NumLines}$), where the earlier single-indexing over points k is replaced with double-indexing over line sources j and points k on each line source. The two points are selected to be far apart yet still within the pinhole field of view. Projection coordinates of these points are now denoted $(u_{p_{jk}}, w_{p_{jk}})$.

Compared to point sources, line sources introduce implicit unknown point coordinates (X_{jk}) in Eqs. (12) and (13). These unknowns need to be estimated in addition to the six alignment parameters (x_{det} , y_{det} , z_{det} , θ , Φ , and Ψ). The XYZ coordinates of a point source can be obtained from CBCT, whereas the coordinates of a point on a line source cannot be observed by CBCT. However, CBCT can observe the line source which contains the point. This information is reflected in the coefficients $\{a_j, b_j, c_j, d_j$: $j = 1 \dots \text{NumLines}\}$ which specify that if the X coordinate of a point is known, then so also are the Y and Z coordinates.

The two point sources on each line source provide four independent equations—two instances each of Eqs. (12) and (13). Thus three line sources provide 12 inde-

pendent equations and also 12 unknowns, which are the six alignment parameters and the six point coordinates (X_{jk}) .

An objective function F is formed as the sum of the squares of the differences between iteratively estimated point-source projections $(u_{p_{jk}}^{(n)}, w_{p_{jk}}^{(n)})$ and measured projections $(u_{p_{jk}}^M, w_{p_{jk}}^M)$:

$$F = \sum_{j=1}^{\text{NumLines}} \sum_{k=1}^2 (u_{p_{jk}}^{(n)} - u_{p_{jk}}^M)^2 + (w_{p_{jk}}^{(n)} - w_{p_{jk}}^M)^2. \quad (14)$$

The alignment parameters and point coordinates (X_{jk}) were then iteratively estimated by a Levenberg-Marquardt algorithm, which was implemented on a commercial software package (MATLAB R2011b Optimization Toolbox™, The MathWorks Inc., Natick, MA, 2000).²⁰ The input equations to this optimization algorithm were Eqs. (1)–(9) and Eqs. (12)–(14). Equations (12) and (13) enable the algorithm to calculate the estimated projections $(u_{p_{jk}}^{(n)}, w_{p_{jk}}^{(n)})$ at iteration n . In turn, the relations of the parameters in Eqs. (12) and (13) are provided by Eqs. (1)–(9). The input also included initial values for the estimated alignment parameters (x_{det} , y_{det} , z_{det} , θ , Φ , and Ψ) and point coordinates (X_{jk}) . The measured projections $(u_{p_{jk}}^M, w_{p_{jk}}^M)$ were also given to the algorithm. The $(u_{p_{jk}}^M, w_{p_{jk}}^M)$ are any two points selected from a line-source projection, where the angle and offset of the line-source projection are determined using the Radon transform, as described in Sec. C.

2.C. Angles and offsets of line-source projections

The coordinates of the measured projection $(u_{p_{jk}}^M, w_{p_{jk}}^M)$ can be obtained by using the Radon transform to detect the ridge of the line-source projection. The Radon transform converts the line-source projections into angles (α) and offsets (ρ) that parameterize line-source projections. Figure 3 demonstrates a case with a single line source. The gray broad line segment in Fig. 3(a) shows a single pinhole projection of a line source. The offset (ρ) is the perpendicular distance from the center of the projection image to the line-source

FIG. 4. (a) Computer simulated line-source phantom with five line sources. (b) Projection image of the line-source phantom with pseudo random sampling from corresponding Poisson distributions.

projection. The angle (α) is between the horizontal-axis and the offset-axis. Figure 3(b) shows the Radon transform of this line-source projection. The (α_0, ρ_0) corresponding to the maximum pixel value of the Radon transform represents the ridge of the line-source projection, as shown by the superimposed narrow dark gray line in Fig. 3(a). Coordinates $(u_{p_{jk}}^M, w_{p_{jk}}^M)$ of points on this superimposed narrow dark gray line can be calculated via:

$$\rho_0 - u_{p_{jk}}^M \cos \alpha_0 - w_{p_{jk}}^M \sin \alpha_0 = 0. \quad (15)$$

2.D. Evaluation of alignment model

To evaluate the proposed alignment approach, a series of computer simulations were performed. Figure 4(a) shows the computer simulated 3D phantom with dimensions of $256 \times 256 \times 256$ and voxel width of 0.05 cm. The phantom includes five line sources. Table I shows the geometries of the five line sources used in this paper. Each line was simulated to have 7.4 MBq of Tc-99m and with a diameter of 1.4 mm. A noise-free 2D projection of these line sources was computer simulated on a 256×256 grid with 0.1 cm-wide pixels. The simulation modeled sensitivity²¹ using effective pinhole diameter for a tungsten pinhole with 2 mm pinhole diameter, a 100° full pinhole opening angle, 18 cm pinhole-to-image distance (focal length), detector intrinsic resolutions of 1.5 mm, 2.5 mm and 3.5 mm, a Tc-99m branching ratio of 0.879, a gamma camera efficiency of 0.86, and a 10 sec acquisition time. This 10 sec acquisition time was only used for the simulation. In the actual measurement, 13 min and 1 min were used for acquiring projection image. Pinhole resolution was modeled by tracing ray distribution through the pinhole. Pin-

TABLE I. Simulated line source geometry used in this paper as shown in Fig. 4(a), specified using the coefficients (a,b,c,d) of Eqs. (1) and (2).

Line	a	b	c	d	X	Y	Z
1	2.00	3.075	1.00	2.00			
2	-2.85	-5.14	3.15	6.31			
3	-0.96	1.14	0.96	-0.89	X_j	$Y_j = a_j X_j + b_j$	$Z_j = c_j X_j + d_j$
4	3.50	-7.31	-3.00	5.70		$j = 1, 2, \dots 5$	
5	1.00	-1.50	-6.38	2.53			

TABLE II. Four experiments designed to evaluate the proposed alignment procedure.

Study	Parameters estimated		Number of line sources	Method for line projection positions
	Detector translation	Detector rotation		
A	$x_{\text{det}}, z_{\text{det}}, y_{\text{det}}$	θ, Φ, Ψ	3	True angle and offset
B	$x_{\text{det}}, z_{\text{det}}, y_{\text{det}}$	θ, Φ, Ψ	3	Radon transform
C	$x_{\text{det}}, z_{\text{det}}, y_{\text{det}}$	θ, Φ, Ψ	4	Radon transform
D	$x_{\text{det}}, z_{\text{det}}, y_{\text{det}}$	θ, Φ, Ψ	5	Radon transform

hole septal penetration was simulated. Photon scatter was not simulated. Noisy projections, shown in Fig. 4(b), were generated by pseudo random sampling from corresponding Poisson distributions. The random Poisson noise was used to generate different noisy projections (noisy realizations) which were used to perform statistical analysis.

Study A as specified in Table II was conducted to evaluate the estimation of six alignment parameters from three line sources when true values of angles (α) and offsets (ρ) were given. In the other studies, these true values were replaced with angles and offsets estimated by Radon transform, which are subject to error, and the accuracy with which the Radon transform determined angles (α) and offsets (ρ) was evaluated as $|\alpha_{\text{Radon}} - \alpha_{\text{True}}|$ and $|\rho_{\text{Radon}} - \rho_{\text{True}}|$.

Studies B, C, and D were conducted with three, four and five line sources as detailed in Table II. These studies evaluated the error in estimation of six alignment parameters when line-source-projection angles (α) and offsets (ρ) are determined from Radon transform. The estimation error was calculated as the absolute error between estimated and true values of alignment parameters, $|\text{Parameters}_{\text{Estimated}} - \text{Parameters}_{\text{True}}|$. For each study, 400 noisy realizations were generated. Two-tailed Wilcoxon rank sum tests with 5% significance level were performed to calculate the p -values for study B, C, and D. These tests have the null hypothesis that distribution of errors from four line sources are equal to that of three line sources; distribution of errors from five line sources are equal to that of three line sources and distribution of errors from five line sources equal to that of four line sources.

The simulations involving three different detector intrinsic resolutions, 1.5 mm, 2.5 mm, and 3.5 mm, were used to investigate the effects of blur on estimation of alignment parameters. For each detector intrinsic resolution, 400 noisy realizations were generated. Two-tailed Wilcoxon rank sum tests with 5% significance level were performed to calculate the p -values for study B, C, and D. These tests have the null hypothesis that distribution of errors from 1.5 mm are equal to that of 3.5 mm, distribution of errors from 2.5 mm are equal to that of 3.5 mm and distribution of errors from 1.5 mm are equal to that of 2.5 mm.

The influence of activity concentration was investigated with three difference concentrations of 1.85 MBq, 7.40 MBq, and 14.80 MBq per line. For each activity concentration, 400 noisy realizations were generated. Two-tailed Wilcoxon rank sum tests with 5% significance level were performed to

TABLE III. Four different acquisition geometries. The top first row of each acquisition geometry is the true values of alignment parameters. The true values are those used to compute the 2D line-source projections. The start points are the initial values in the iterative parameter estimation.

Acquisition geometry		Unknown alignment parameters						Pinhole position		
		x_{det} (mm)	z_{det} (mm)	y_{det} (mm)	θ (deg)	Φ (deg)	Ψ (deg)	u_f (mm)	w_f (mm)	$-v_f$ (mm)
1	True value	30	20	300	30	10	5	-20	-30	180
	Start point	10	0	280	28	8	2			
2	True value	20	40	300	10	5	60	-10	-30	180
	Start point	0	10	280	0	0	53			
3	True value	30	40	300	72	47	12	-10	-10	180
	Start point	10	10	280	70	44	9			
4	True value	10	20	320	10	160	5	-20	-10	180
	Start point	0	0	290	6	155	0			

calculate the p -values for study B, C, and D. These tests have the null hypothesis that distributions of errors from 1.85 MBq per line are equal to 7.40 MBq per line, distributions of errors from 1.85 MBq per line are equal to 14.80 MBq per line, and distributions of errors from 7.40 MBq per line are equal to 14.80 MBq per line.

To examine the effects of acquisition geometry on alignment parameter estimation, four tests were conducted as detailed in Table III. For statistical analysis, an ensemble of 100 noisy projection images was generated for each acquisition geometry. The nonparametric Kruskal-Wallis test was used to compare the medians of the estimation errors from four different acquisition geometries. This test has the null hypothesis that all samples are drawn from the same distribution with p -value of 5% significance level. For p -value less than 5%, this test rejects the null hypothesis and suggests that at least one sample median is significantly different from the others.²²

To further evaluate the effects of blur and noise on estimation accuracy, noise-free line-source projections were simulated with 0 mm detector intrinsic resolution and perfect pinhole spatial resolution. These noise-free, unblurred line-source projections were used to estimate alignment parameters for each acquisition geometry. The errors in estimating each alignment parameter were compared to those for noisy projections and 3.5 mm detector intrinsic resolution.

Seven parameters (x_{det} , z_{det} , y_{det} , Φ , Ψ , u_f , and v_f) are also estimated using five lines with activity concentration of 14.80 MBq per line and 3.5 mm intrinsic detector resolution. An ensemble of 400 noise realizations was used to generate the box-and-whisker plot.

2.E. Experimental evaluation of alignment method

The alignment method was also evaluated using a physical line-source phantom and a robotic SPECT system with a single 2-mm-diameter pinhole collimator attached (Fig. 5). The robotic SPECT system consists of a Digirad 2020tc detector (Digirad Corporation Poway, CA) attached to a KUKA KR150-L110 robot (KUKA Robotics Corporation, Shelby Township, MI).

The Digirad 2020tc consists of 64×64 3.25-mm-wide pixels with CsI(Tl) scintillator. The imaging area is 20.8

$\times 20.8$ cm². In order to measure pinhole focal length, two parallel line sources were positioned 10 cm apart and scanned at 5 pinhole-to-line-source distances. The measured focal length was 174.6 mm. By scanning one of these line sources, pinhole shifts relative to the detector were measured to be $u_f = 1.6$ mm and $v_f = 7.3$ mm.

The line-source phantom consists of 4 acrylic sides and 11 acrylic tubes with 3/16" inner diameter. For this experiment, Tygontubes with 1/16" inner diameter were inserted in 5 of the 11 acrylic tubes. A CT image of the line-source phantom was acquired. For each of the five lines, the coefficients (a,b,c,d) as shown in Eqs. (1) and (2) were determined in the CT (XYZ) coordinate frame from the CT image. These coefficients are shown in Table IV. The robot system includes tool and base coordinate frames along with techniques for registering these frames.²³ The ($u_T v_T w_T$) axes of the tool coordinate frame were calibrated to be parallel to the detector (uvw) coordinates, with their origin along the pinhole symmetry axis and in the plane of the phantom-side surface of the pinhole insert. The (XYZ) axes of the robot base coordinate frame were registered to the CT (XYZ) axes, using the orientation of the line-source phantom as an indication of the CT (XYZ) axes. Since there is no CT scanner in the room with the robotic SPECT system, the above procedure was performed so that the robot base coordinate frame would serve the role of the

FIG. 5. (a) Line-source phantom with Tc-99m injected in five lines. (b) Single pinhole collimated SPECT detector with line-source phantom. (c) SPECT detector attached to robotic arm imaging line-source phantom.

TABLE IV. Physical line source geometry determined in the CT (XYZ) coordinate frame from the CT image, specified using the coefficients (a,b,c,d) of Eqs. (1) and (2).

Line	a	b	c	d	X	Y	Z
1	2.60	-2.05	-2.43	1.68			
2	-2.19	3.13	7.03	0.74			
3	-0.60	-2.06	1.77	6.47	X_j	$Y_j = a_j X_j + b_j$	$Z_j = c_j X_j + d_j$
4	-0.26	-3.09	0.34	0.23		$j = 1, 2 \dots 5$	
5	-0.17	1.02	-0.30	0.87			

CT coordinate frame. If this experiment had been performed on a commercial SPECT-CT system, true alignment parameters for the pinhole-collimated SPECT system would presumably have been obtained from detector position and angle read-outs on the SPECT-CT system. Here, by calibrating the robot tool coordinate frame with the pinhole-collimated SPECT detector, true alignment parameters can similarly be given by the robot system. These true alignment parameters were then compared with those estimated using the alignment method and line-source phantom developed herein.

SPECT projections were acquired at three different detector locations, as indicated in Table V. The start point of each parameter was varied to investigate the convergence of Eq. (14). At each detector location, acquisitions were obtained with 13 min and 1 min scan times. The five tubes of the line-source phantom were filled a Tc-99m activity concentration that was 0.725 MBq/cm at the time of acquisition for geometry 2, which averages to about 10.73 MBq per line. Geometries 1 and 3 were acquired 47 min before and 147 min after geometry 2, respectively.

3. RESULTS

Study A shows perfect results in estimating six alignment parameters with three line-source projections using theoretical angles (α) and offsets (ρ). The average error in estimating line angle (α) and offset (ρ) from Radon transform of three line sources are 0.34° and 0.27 mm, respectively.

Figure 6 shows box-and-whisker plots of alignment parameter error across an ensemble of 400 noisy realizations for studies B, C, and D with three, four, and five line sources, respectively. The box-and-whisker plot is implemented as fol-

FIG. 6. Errors in estimating six alignment parameters for Study B using three line sources, Study C using four line sources, and Study D using five line sources (from left to right). Each distribution is obtained from 400 noisy realizations. The number above each whisker is the number of outliers. The mean of each distribution is represented by an “x”. Errors in parameter estimation from noise-free projections are represented by a “+”.

lows: the length of the box represents the interquartile range (IQR), the bottom end of the box is the 25% quartile (Q1), the horizontal line inside the box is the median quartile (Q2), the top end of the box is the 75% quartile (Q3), the whiskers are on the last data point within 1.5 IQR from the end of the box. If there are no data points between the end of the box and 1.5 IQR, the whisker is placed at the end of the box. The square boxes outside the whiskers are outliers which are the data points outside the 1.5 IQR from either end of the box. Table VI shows the Q1, Q2, and Q3 values, the highest outlier value and the percent of outliers for each study, along with p -values from two-tailed Wilcoxon rank sum tests with 5% significance level. Parameters estimation errors for Study C (four line sources) and Study D (five line sources) both differ from those of Study B (three line sources) at statistically significant levels, with less error when using four or five line sources as compared to three. In comparing Study C and Study D, there were statistically significant less errors in estimating z_{det} and

TABLE V. Three acquisition geometries for scanner-acquired projections of the physical line-source phantom. The top first row for each acquisition geometry is the true value as given by the robot tool coordinate frame. The second row gives initial values in the iterative parameter estimation.

Acquisition geometry		Unknown alignment parameters					
		x_{det} (mm)	z_{det} (mm)	y_{det} (mm)	θ (deg)	Φ (deg)	Ψ (deg)
1	True value	-1.7	-7.3	378.9	180	0	0
	Start point	20	10	350	174	3	4
2	True value	-1.6	-7.4	385.7	225.0	-0	0
	Start point	20	10	420	220	4	3
3	True value	-1.85	-7.3	400.4	180	-60	-0.1
	Start point	30	20	450	175	-55	3

TABLE VI. The 25% quartile (Q1), the median quartile (Q2), and the 75% quartile (Q3) values of the estimated alignment parameters of Study B, C, and D. The highest outlier values and the percent of outliers of each estimated alignment parameters of Study B, C, and D. P -values are from two-tailed Wilcoxon rank sum test with 5% significance level. Numbers in bold are $p < 0.05$.

		x_{det} (mm)	z_{det} (mm)	y_{det} (mm)	θ (deg)	Φ (deg)	Ψ (deg)
Study B (3 line sources)	Q1	0.10	0.14	0.64	0.59	0.29	0.30
	Q2	0.20	0.36	1.30	1.07	0.60	0.59
	Q3	0.37	0.85	3.84	2.43	1.56	1.39
	Highest outlier	1.55	6.06	17.55	16.40	12.91	13.38
	Percent of outliers (%)	4.00	8.50	4.25	8.75	9.25	11.25
Study C (4 line sources)	Q1	0.07	0.12	0.40	0.17	0.16	0.14
	Q2	0.12	0.22	0.71	0.42	0.32	0.30
	Q3	0.20	0.32	1.13	0.74	0.57	0.61
	Highest outlier	0.57	1.05	2.87	3.37	1.75	2.71
	Percent of outliers (%)	0.50	4.00	4.00	6.25	2.50	4.75
Study D (5 line sources)	Q1	0.06	0.08	0.36	0.18	0.23	0.11
	Q2	0.13	0.18	0.70	0.45	0.43	0.24
	Q3	0.22	0.31	1.13	0.74	0.76	0.48
	Highest outlier	0	0.88	3.01	2.24	1.777	1.86
	Percent of outliers (%)	0	1.75	1.00	5.25	1.25	7.75
P -values	Study C vs. Study B	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Study D vs. Study B	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Study D vs. Study C	0.207	0.006	0.667	0.907	<0.001	0.008

Ψ from five line sources. There were no statistically significant less errors in estimating x_{det} , y_{det} , θ , and Φ using five line sources than four line sources.

Table VII shows the Q1, Q2, and Q3 values, the highest outlier value and the percent of outliers of alignment parameter errors across an ensemble of 400 noisy realizations using five line sources with three different detector intrinsic resolutions of 1.5 mm, 2.5 mm, and 3.5 mm. P -values from two-tailed Wilcoxon rank sum tests with 5% significance level

were also shown in Table VII for differences in estimating alignment parameters given detector intrinsic resolutions of 1.5 mm, 2.5 mm, and 3.5 mm. For 1.5 mm vs. 3.5 mm detector intrinsic resolution, statistical significant differences were found: detector intrinsic resolution of 1.5 mm has less error for all six alignment parameters x_{det} , y_{det} , z_{det} , θ , Φ , and Ψ . For 2.5 mm vs. 3.5 mm detector intrinsic resolution, statistically significant differences were found: detector intrinsic resolution of 2.5 mm had less error for z_{det} , y_{det} , and Φ . For

TABLE VII. The 25% quartile (Q1), the median quartile (Q2), and the 75% quartile (Q3) values of the estimated alignment parameters of intrinsic detector resolution of 1.5 mm, 2.5 mm, and 3.5 mm. The highest outlier values and the percent of outliers of each estimated alignment parameters. The p -values are from a two-tailed Wilcoxon rank sum test with 5% significance level. Numbers in bold are $p < 0.05$.

		x_{det} (mm)	z_{det} (mm)	y_{det} (mm)	θ (deg)	Φ (deg)	Ψ (deg)
1.5 mm	Q1	0.04	0.06	0.29	0.18	0.16	0.09
	Q2	0.11	0.14	0.57	0.41	0.36	0.23
	Q3	0.21	0.25	0.90	0.63	0.60	0.43
	Highest outlier	0.47	0.72	2.40	2.20	1.61	1.69
	Percent of outliers (%)	0	2.5	1.5	5.25	1	5.25
2.5 mm	Q1	0.05	0.06	0.33	0.15	0.19	0.10
	Q2	0.13	0.15	0.62	0.45	0.38	0.21
	Q3	0.24	0.25	1.00	0.67	0.64	0.43
	Highest outlier	0.24	0.84	3.12	2.61	1.87	2.13
	Percent of outliers (%)	0	2.75	2	4.25	2	6
3.5 mm	Q1	0.06	0.08	0.36	0.18	0.23	0.11
	Q2	0.13	0.18	0.70	0.45	0.43	0.24
	Q3	0.22	0.31	1.13	0.74	0.76	0.48
	Highest outlier	0.22	0.88	3.01	2.24	1.77	1.86
	Percent of outliers (%)	0	1.75	1	5.25	1.25	7.75
P -values	1.5 mm vs. 3.5 mm	0.033	<0.001	<0.001	0.073	<0.001	0.088
	2.5 mm vs. 3.5 mm	0.845	0.001	0.061	0.315	0.015	0.111
	1.5 mm vs. 2.5 mm	0.019	0.855	0.111	0.378	0.068	0.883

FIG. 7. Box-and-whisker plots of alignment parameter error with different activity concentration of 1.85 MBq, 7.4 MBq, and 14.8 MBq per line (from left to right). Each distribution is obtained from 400 noisy realizations. The mean of each distribution is represented by an “x”. Errors in parameter estimation from noise-free projections are represented by a “+”.

1.5 mm vs. 2.5 mm detector intrinsic resolution, statistically significant difference was found: detector intrinsic resolution of 1.5 mm had less error for x_{det} and Φ .

Figure 7 shows the box-and-whisker plots of alignment parameter errors across an ensemble of 400 noisy realizations using five line sources with 3.5 mm detector intrinsic resolution for line-source with activity concentration of 1.85 MBq, 7.40 MBq, and 14.80 MBq per line. Table VIII shows the Q1, Q2, and Q3 values, the highest outlier value and the percent of outliers, along with p -values from two-tailed Wilcoxon rank

sum tests with 5% significance level for differences in estimating alignment parameters given activity concentration of 1.85 MBq, 7.40 MBq, and 14.80 MBq per line. For 7.40 MBq vs. 14.80 MBq activity concentration, statistical significant differences were found: activity concentration of 14.8 MBq per line has less error for all six alignment parameters x_{det} , y_{det} , z_{det} , θ , Φ , and Ψ . For 1.85 MBq vs. 14.80 MBq activity concentration, statistically significant differences were found: activity concentration of 14.80 MBq per line had less error for y_{det} , z_{det} , θ , Φ , and Ψ . For 1.85 MBq vs. 7.40 MBq activity concentration, no statistically significant difference was found.

The p -values from nonparametric Kruskal-Wallis test for each alignment parameters x_{det} , z_{det} , y_{det} , θ , Φ , and Ψ from the four different acquisition geometries (Table III) using five line sources with 3.5 mm detector intrinsic resolution are less than 0.001. For every alignment parameter, the median errors for at least one of the acquisition geometries were statistically significant different from the others. In addition, the errors in alignment parameters estimated from noise-free and unblurred five line-source projections were smaller than the median error of the noisy projections with 3.5 mm detector intrinsic resolution.

Figure 8 shows the box-and-whisker plots of error of seven alignment parameters using five line sources with 3.5 mm detector intrinsic resolution across an ensemble of 400 noisy realizations. Errors of alignment parameters y_{det} and v_f were relative larger than other five parameters.

Table IX shows the error in the six alignment parameters estimated from five line sources using the robotic pinhole SPECT system and physical line-source phantom. Errors estimated from the image with 13 min scan time are similar to those for 1 min scan time.

TABLE VIII. The 25% quartile (Q1), the median quartile (Q2), and the 75% quartile (Q3) values of the estimated alignment parameters of five line sources with 1.85 MBq, 7.40 MBq, and 14.80 MBq per line with 3.5 mm intrinsic resolution. The highest outlier values and the percent of outliers of each estimated alignment parameters. P -values are from two-tailed Wilcoxon rank sum test with 5% significance level. Numbers in bold are $p < 0.05$.

		x_{det} (mm)	z_{det} (mm)	y_{det} (mm)	θ (deg)	Φ (deg)	Ψ (deg)
1.85 MBq	Q1	0.06	0.07	0.35	0.19	0.21	0.08
	Q2	0.13	0.15	0.68	0.45	0.40	0.21
	Q3	0.21	0.28	1.07	0.71	0.66	0.46
	Highest outlier	0.47	0.87	3.16	2.64	2.28	2.05
	Percent of outliers (%)	0.5	4	1.75	8.75	2	9
7.40 MBq	Q1	0.06	0.08	0.36	0.18	0.23	0.11
	Q2	0.13	0.18	0.70	0.45	0.43	0.24
	Q3	0.22	0.31	1.13	0.74	0.76	0.48
	Highest outlier	0.22	0.88	3.01	2.24	1.77	1.86
	Percent of outliers (%)	0	1.75	1	5.25	1.25	7.75
14.80 MBq	Q1	0.05	0.04	0.27	0.23	0.15	0.06
	Q2	0.11	0.11	0.43	0.35	0.27	0.22
	Q3	0.22	0.19	0.56	0.50	0.43	0.39
	Highest outlier	0.22	0.58	1.46	1.97	1.14	1.43
	Percent of outliers (%)	0	0.25	3.5	1.75	0.5	1.75
P -values	7.40 MBq vs. 14.80 MBq	0.027	<0.001	<0.001	<0.001	<0.001	<0.001
	1.85 MBq vs. 14.80 MBq	0.128	<0.001	<0.001	<0.001	<0.001	0.009
	1.85 MBq vs. 7.40 MBq	0.566	0.112	0.424	0.763	0.065	0.133

FIG. 8. Box-and-whisker plots of alignment parameter error for seven parameters with activity concentration of 14.80 MBq per line and 3.5 mm intrinsic resolution. The number above each whisker is the number of outliers. Each distribution is obtained from 400 noisy realizations. The mean of each distribution is represented by an “x”. Errors in parameter estimation from noise-free projections are represented by a “+”.

The estimated parameters converge to the same results with the variation of translation over a range of 300 mm and the rotations over a range of 20° .

4. DISCUSSION

Herein a method is proposed for estimating SPECT pinhole alignment parameters using line sources and a single pinhole projection.

In the proposed method, each line-source introduces not only four generally independent equations but also two unknowns. Thus, for example, 3 line-sources and 6 unknown alignment parameters results in 12 equations and 12 unknowns. To investigate convergence and uniqueness of the optimization [Eq. (14)], different initial values of the alignment parameters were considered. Initial values varied by ± 300 mm for translation parameters and $\pm 20^\circ$ for angle parameters. The optimization results were the same for different initial values.

TABLE IX. The error in alignment parameters estimated from five line-source projections with physical line-source phantom using robotic pinhole SPECT system.

Acquisition geometry	Scan time (min)	x_{det} (mm)	z_{det} (mm)	y_{det} (mm)	θ (deg)	Φ (deg)	Ψ (deg)
1	13	-2.28	2.81	-0.53	0.19	-0.68	0.82
	1	-2.35	2.81	-0.20	0.49	-0.57	0.97
2	13	0.57	1.94	-0.18	0.74	0.29	1.89
	1	0.63	2.01	-1.89	0.91	0.49	1.93
3	13	-0.35	2.74	-1.66	-0.46	-0.34	0.77
	1	-0.37	2.75	-1.91	-0.45	-0.17	0.68

The alignment method can be thought of as involving two components. First, the Radon transform is used to determine the central line of each line-source projection, characterized by angle (α) and offset (ρ). Second, alignment parameters are estimated based on the angles (α) and offsets (ρ). Studies A and B considered three line sources and six unknown alignment parameters. It was found that if true values were used for angles (α) and offsets (ρ), then alignment parameters were estimated without error. This suggests that errors in estimated alignment parameters are associated with errors in determining angles (α) and offsets (ρ). Studies C and D showed that alignment errors can be reduced statistically significantly by using more line sources as compared to Study B. Compared to four line sources, five line sources resulted in only a minor reduction of estimation errors. Therefore, four line sources may be preferred because fewer line sources results in less complicated configurations and less radiation dose to personnel.

Sources of error in Radon transform determinations of α and ρ include rounding errors, finite line-source width, SPECT detector blur, and Poisson noise. The Radon transform routine used in this paper reports line integrals in steps of 1 mm and 0.25° (Fig. 3). Selection of the maximum pixel in Fig. 3 amounts to a rounding to the nearest step. For noise-free and unblurred line-source projections, average errors in α and ρ were 0.20° and 0.24 mm. Since noise and blur are absent, these errors may largely reflect round-off.

In addition, the line-source in 3D space has a diameter of 1.4 mm. This finite volume of the line-source also could affect Radon transform accuracy. The errors in alignment parameters estimated from noise-free and unblurred projection data show the combined effects of round-off and finite line-source width on the alignment parameters (x_{det} , y_{det} , z_{det} , θ , Φ , and Ψ), since other sources of error (Poisson noise and detector blur) are absent.

Estimation accuracy was studied with different intrinsic detector resolutions of 1.5 mm, 2.5 mm, and 3.5 mm. The 1.5 mm detector intrinsic resolution projections yielded statistically significant lower error in estimated alignment parameters than that of 2.5 mm and 3.5 mm intrinsic resolution. A typical intrinsic spatial resolution for sodium iodide detectors is 3.5 mm. For detectors with better intrinsic resolution, such as cadmium zinc telluride (CZT) detectors which can achieve intrinsic resolutions of 1.4 mm,²⁴ estimation accuracy may be improved.

Estimation accuracy was studied with different activity concentration of 1.85 MBq, 7.40 MBq, and 14.80 MBq per line. The 14.80 MBq per line activity concentration projections yielded statistically significant lower error in estimated alignment parameters than that of 1.85 MBq and 7.40 MBq.

The Poisson noise effects were studied with noise-free projections. The alignment errors from noise free projections were generally less than that of noisy projections. The plus signs in Figs. 6–8 show the combined effects of round-off, finite line-source width, and detector blur with the absent of noise. These errors are generally lower than the mean noisy-data errors which are shown as the “x” sign.

Estimation accuracy is also affected by acquisition geometry. The length and the relative orientation of line-source

projections vary with acquisition geometries, and therefore can affect estimation accuracy. Certain acquisition geometries can cause two line projections that are superimposed or a line projection appeared as a point. These projections would reduce estimation accuracy. For example, if a line projects approximately to a point, the condition number is poor. If a line projects to a point, then alignment parameters may not be possible to be estimated.

There could be other factors that affect estimation accuracy, such as the length of line-source and the size of detector and its field of view. Longer line-source projections might improve the Radon transform in determining line angles, and therefore the estimation accuracy.

For the computer-simulation studies involving five line sources, median errors were less than 0.5° for angles, 0.7 mm for the detector-to-center-of-rotation distance y_{det} , and less than 0.2 mm for the detector shifts x_{det} and z_{det} . A rotation of 0.5° corresponds to a 0.35 mm shift over the radius of an 80-mm-diameter region of interest that might be scanned by the robotic multipinhole system described in the Introduction. This shift and the less-than 0.2 mm detector shifts are much less than the typical translation tolerances of 1 mm or 2 mm for radiation therapy. The distance y_{det} is perpendicular to the planes in which a given pinhole provides localization, and the effect of error in y_{det} may be on the distance scale in reconstructed images. For a 15° pinhole half-opening angle and $y_{\text{det}} = 300$ mm, a 0.7 mm change in y_{det} would change the pinhole field-of-view radius by about 0.2 mm out 80 mm, which is 0.25% effect. The errors reported here are for one pose of a single pinhole, whereas imaging with the robotic SPECT system described in the Introduction would typically involve 10 or more stops with 49 differently posed pinholes at each stop. Alignment calibration errors may vary with pinhole pose such that when averaged over 500 or more different poses, the errors have little effect on localization and scale. In addition to localization and scale, alignment errors may also affect the quality of reconstructed images, as investigated in previous paper.^{11,13,14,25}

In alignment tests with the physical phantom and robotic SPECT system, angles θ and Φ were in all cases estimated to within 1° of the values given by the CT scan and its registration to the robot base and tool coordinate frames. For angle Ψ , radius of rotation y_{det} , and detector translations x_{det} and z_{det} , errors were within 2° , 2 mm, and 3 mm, respectively. These maximum errors are moderately worse than those obtained in the comparable simulation studies. In simulation studies, true parameter values are known exactly, whereas in physical studies the gold standard values (here taken from the registered CT scan) can also include error, and this may partly account for the moderately greater alignment errors observed in the physical alignment tests.

The estimation of seven alignment parameters shown in Fig. 8 could be used to compare the present line-source method with the method¹³ which uses three point sources. The seven parameters (x_{det} , z_{det} , y_{det} , Φ , Ψ , u_f , and v_f) estimated for Fig. 8 here span a comparable parameter space to that considered by method.¹³ However, multiple projection

views are used in Ref. 13, whereas only one projection view is used here.

For onboard SPECT imaging in radiation therapy, alignment calibration would be done with the line-source phantom on the table—without the patient on the table—either before or after treatment. Once a trajectory is established, many robots can reproduce that trajectory with excellent precision. For example, the robot utilized in the alignment study here provides reproducibility to within a few tenths of a mm. Hence, the calibration—obtained during one execution of a trajectory—will be valid for the patient-imaging execution of the trajectory. For a multipinhole system, the relative alignment of individual pinholes may vary slightly with the angle of the overall system because the relative effects of gravity may vary. The proposed alignment method, as developed and evaluated here, utilizes a single pinhole projection and line sources. Consequently, it could be utilized to determine the relative alignment of individual pinholes at each different angle of the overall system, and therefore it may be beneficial to perform the alignment procedure at each stop of the imaging trajectory is to be used for the patient.

The calibration procedure would begin with the SPECT system retracted away from the radiation therapy gantry and table. The line-source phantom—on the table—would be scanned by CBCT to determine its alignment in the CBCT and LINAC coordinate frames. The CBCT detector and x-ray tube would then be retracted, and the robot would maneuver the multipinhole SPECT system about the phantom for calibration. Finally, the robot would retract the SPECT system away from the LINAC and patient table, the line-source phantom would be removed, and the table would be available for patient positioning followed by CBCT and SPECT imaging of the patient and radiation therapy.

Currently cone-beam CT imaging is widely employed on-board radiation therapy machines, in order to image patients as they are in position for radiation therapy. Studies have shown that radiation therapy treatment planning based on functional and molecular information about the tumor and surrounding tissue has potential to enhance the benefit of radiation therapy.² SPECT is a candidate for providing functional and molecular information, including onboard radiation therapy machines. For this, high quality and fast SPECT imaging is essential. A multipinhole SPECT system could provide the sensitivity and resolution needed for high quality and fast imaging of regions of interest. The alignment method developed in this paper could enable registration of the SPECT coordinate frame with that of the cone-beam CT and LINAC, and it has potential to improve SPECT image reconstruction by measuring angle-dependent changes in relative pose among the multiple pinholes.

5. CONCLUSIONS

Estimation of alignment parameters can be achieved by using one pinhole projection of line sources. Alignment errors are largely associated with limited accuracy of the Radon transform in determining angles (α) and offsets (ρ) of line-source projections. This alignment method may be important

for multipinhole SPECT, where relative pinhole alignment can vary during rotation. For pinhole and multipinhole SPECT imaging on-board radiation therapy machines, the method could provide alignment of SPECT coordinates with those of CBCT and the LINAC.

ACKNOWLEDGMENTS

This work is supported by PHS/NIH/NCI Grant No. R21-CA156390-01A1. The authors would like to thank Bernie Je-linek and Richard Nappi from the Duke University physics instrument shop for constructing the line-source phantom and the connection joint between detector and the robotic arm; KUKA Robotics Corporation (Shelby Township, MI), and Digirad Corporation (Poway, CA) for their assistance with the robot and detector, respectively; and the Duke University Medical Center Radiopharmacy for providing Tc-99m radio-tracer for the experiment.

^{a)} Author to whom correspondence should be addressed. Electronic mail: susu.yan@duke.edu; Telephone: (516) 782-4701; Fax: (919) 681-7183.

¹ J.-P. Bissonnette, P. A. Balter, L. Dong, K. M. Langen, D. M. Lovelock, M. Miften, D. J. Moseley, J. Pouliot, J.-J. Sonke, and S. Yoo, "Quality assurance for image-guided radiation therapy utilizing CT-based technologies: A report of the AAPM TG-179," *Med. Phys.* **39**, 1946–1963 (2012).

² C. C. Ling, J. Humm, S. Larson, H. Amols, Z. Fuks, S. Leibel, and J. A. Koutcher, "Towards multidimensional radiotherapy (MD-CRT): Biological imaging and biological conformality," *Int. J. Radiat. Oncol., Biol., Phys.* **47**, 551–560 (2000).

³ H. P. Rodemann, "Molecular radiation biology: Perspectives for radiation oncology," *Radiother. Oncol.* **92**, 293–298 (2009).

⁴ M. Höckel and P. Vaupel, "Tumor hypoxia: Definitions and current clinical, biologic, and molecular aspects," *J. Natl. Cancer Inst.* **93**, 266–276 (2001).

⁵ K. Suga, Y. Kawakami, M. Zaki, T. Yamashita, K. Shimizu, and N. Matsunaga, "Clinical utility of co-registered respiratory-gated 99mTc-Technegas/MAA SPECT-CT images in the assessment of regional lung functional impairment in patients with lung cancer," *Eur. J. Nucl. Med. Mol. Imaging* **31**, 1280–1290 (2004).

⁶ H. Palmedo, A. Schomburg, F. Grünwald, P. Mallmann, D. Krebs, and H.-J. Biersack, "Technetium-99m-MIBI scintimammography for suspicious breast lesions," *J. Nucl. Med.* **37**, 626–630 (1996).

⁷ J. E. Bowsher, J. R. Roper, S. Yan, W. M. Giles, and F.-F. Yin, "Regional SPECT imaging using sampling principles and multiple pinholes," *IEEE Nuclear Science Symposium Conference Record*, Knoxville, TN, 30 October–6 November 2010 (IEEE, Piscataway, NJ, 2010), pp. 2071–2076.

⁸ G. T. Gullberg, B. M. W. Tsui, C. R. Crawford, J. G. Ballard, and J. T. Hagi-us, "Estimation of geometrical parameters and collimator evaluation for cone beam tomography," *Med. Phys.* **17**, 264–272 (1990).

⁹ P. Rizo, P. Grangeat, and R. Guillemaud, "Geometric calibration method for multiple-head cone-beam SPECT system," *IEEE Trans. Nucl. Sci.* **41**, 2748–2757 (1994).

¹⁰ K. J. Kyriakopoulos, P. Yiannakos, V. Kallipolites, and K. Domales, "A geometric calibration methodology for single-head cone-beam x-ray systems," *J. Intell. Robotic Syst.* **24**, 151–174 (1999).

¹¹ F. Noo, R. Clackdoyle, C. Mennessier, T. A. White, and T. J. Roney, "Analytic method based on identification of ellipse parameters for scanner calibration in cone-beam tomography," *Phys. Med. Biol.* **45**, 3489–3508 (2000).

¹² A. V. Bronnikov, "Virtual alignment of x-ray cone-beam tomography system using two calibration aperture measurements," *Opt. Eng.* **38**, 381–386 (1999).

¹³ D. Beque, J. Nuyts, G. Bormans, P. Suetens, and P. Dupont, "Characterization of pinhole SPECT acquisition geometry," *IEEE Trans. Med. Imaging* **22**, 599–612 (2003).

¹⁴ S. Metzler, K. Greer, and R. Jaszczak, "Determination of mechanical and electronic shifts for pinhole SPECT using a single point source," *IEEE Trans. Med. Imaging* **24**, 361–370 (2005).

¹⁵ Y. Wang and B. M. W. Tsui, "Pinhole SPECT with different data acquisition geometries: Usefulness of unified projection operators in homogeneous coordinates," *IEEE Trans. Med. Imaging* **26**, 298–308 (2007).

¹⁶ D. Bequé, C. Vanhove, A. Andreyev, J. Nuyts, and M. Defrise, "Correction for imperfect camera motion and resolution recovery in pinhole SPECT," *Nuclear Science Symposium Conference Record*, Rome, Italy, 16–22 Oct. 2004 (IEEE, Piscataway, NJ, 2004), Vol. 4, pp. 2507–2510.

¹⁷ S. Metzler, R. Jaszczak, K. Greer, and J. Bowsher, "Angular-dependent axial-shift correction for pinhole SPECT," *IEEE Trans. Nucl. Sci.* **54**, 124–129 (2007).

¹⁸ M. Defrise, C. Vanhove, and J. Nuyts, "Perturbative refinement of the geometric calibration in pinhole SPECT," *IEEE Trans. Med. Imaging* **27**, 204–214 (2008).

¹⁹ R. Zhou, T. Ma, Y. Liu, X. Sun, X. Kang, Z. Wu, S. Wang, Y. Jing, and J. Cheng, "Calibration of pinhole microSPECT system using line sources," *IEEE Nucl. Sci. Symp. Conf. Rec.* **5**, 3364–3367 (2007).

²⁰ MathWorks, *Optimization Toolbox User's Guide R2011b* (The MathWorks, Inc. Natick, MA, 2011).

²¹ S. Metzler, J. E. Bowsher, M. Smith, and R. J. Jaszczak, "Analytic determination of pinhole collimator sensitivity with penetration," *IEEE Trans. Med. Imaging* **20**, 730–741 (2001).

²² MathWorks, *Statistics Toolbox For Use with MATLAB User's Guide Version 4* (The MathWorks, Inc. Natick, MA, 2002).

²³ KUKA Robotics Corporation, *KUKA Basic Programming Manual* (KUKA Robotics Corporation, Shelby Township, MI, 2009).

²⁴ H. Kim, L. R. Furenlid, M. J. Crawford, D. W. Wilson, H. B. Barber, T. E. Peterson, W. C. Hunter, Z. Liu, J. M. Woolfenden, and H. H. Barrett, "SemiSPECT: A small-animal single-photon emission computed tomography (SPECT) imager based on eight cadmium zinc telluride (CZT) detector arrays," *Med. Phys.* **33**, 465 (2006).

²⁵ T. A. White, T. J. Roney, R. J. Pink, F. Noo, R. Clackdoyle, M. Smith, and W. F. Jones, "Comparison of fan-and cone-beam imaging capabilities on a portable x-ray imaging system," in *SPIE's International Symposium on Optical Science, Engineering, and Instrumentation*, Denver, CO, 18–23 July 1999 (International Society for Optics and Photonics, Bellingham, WA, 1999), pp. 138–146.