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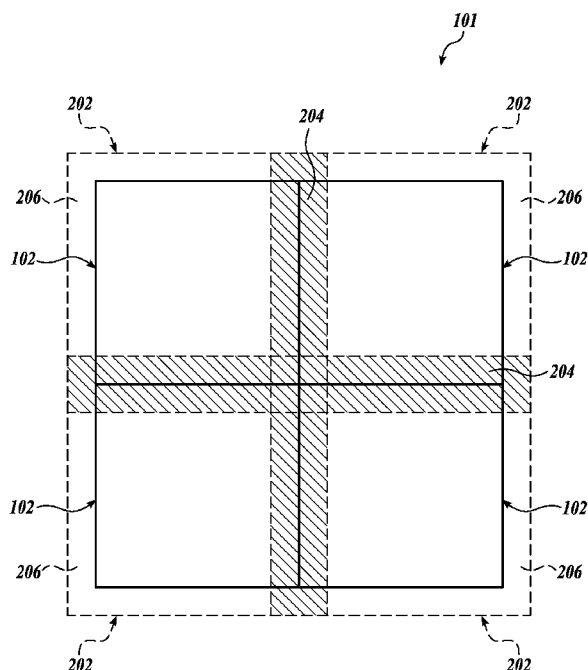


FIG. 6B

(57) Abstract: A method and system for a gamma camera in-
cludes a semi-monolithic crystal assembly having a plurality of
monolithic scintillation crystals that share light across adjacent
surfaces, and a photodetector array that detects scintillation
light from the crystals. During calibration, look-up tables for the
monolithic crystals are generated that correlate the response sig-
nals from the photodetectors with the location of scintillation
events within the crystal assembly obtained over a grid of
points, that is then interpolated and extrapolated. At least some
of the extrapolated points extend beyond the perimeter of the as-
sociated crystal, and overlaps with a look-up table for an adja-
cent crystal. The method provides greater sensitivity by includ-
ing more of the detected data, and reduces or eliminates artifacts
near the borders of the crystals.



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GAMMA CAMERA SCINTILLATION EVENT POSITIONING

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of Provisional Application No. 62/173277,
5 filed June 9, 2015, the disclosure of which is hereby incorporated by reference in its entirety.

STATEMENT OF GOVERNMENT LICENSE RIGHTS

This invention was made with Government support under R41 CA180191-01
awarded by the National Cancer Institute. The Government has certain rights in the
10 invention.

BACKGROUND

Two conventional technologies for gamma camera imaging (e.g., positron
emission tomography, etc.) are monolithic crystal systems that typically use a small
number of large scintillation crystals with a plurality of light detectors fixed to an outer
15 surface, and pixelated small crystal systems that use a large number of small scintillation
crystals that typically do not share light with adjacent crystals. Although pixelated crystal
systems are common, monolithic (or continuous) scintillator crystals have certain
attractive advantages. Using monolithic crystals coupled to photomultiplier tubes
(PMTs) or to silicon-photomultipliers (SiPMs), a spatial resolution close to 1 mm can be
20 reached and that the information about the depth-of-interaction of the 511 keV photon
can be obtained. Another advantage of monolithic crystal systems is the higher detection
efficiency at 511 keV, due to the higher fraction of volume covered by the scintillator.
However, some of the disadvantages of monolithic crystal systems are the high costs of
large area monolithic scintillator crystals and the degradation of the spatial performances
25 close to the edges of the detector.

An approach to obtain a more cost-effective PET system is disclosed in U.S. Pat.
No. 9,151,847 to Levin et al., which is hereby incorporated by reference in its entirety.
Levin et al. discloses a detector composed of two SiPM matrices coupled to two
monolithic crystals coupled by an optically transmissive resin.

30 The present inventors have developed a gamma camera module comprising an
array of a small number of large crystals, sometimes referred to herein as a semi-
monolithic crystal array, and further developed a novel method for determining
scintillation event positions in monolithic crystals and semi-monolithic crystal arrays.

Improvements in determining the precise location of scintillation events in the crystal, without generating (or reducing the generation of) artifacts at the boundaries or interfaces provides advantages over more conventional monolithic crystal systems. The semi-monolithic crystal system is also more cost effective because it is more economical to purchase four smaller scintillation crystals than one large scintillation crystal.

SUMMARY

This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description. This summary is not intended to identify key features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter.

A method is disclosed for generating look-up tables (LUT) for gamma cameras, for example, positron emission tomography (PET) scanners, single photon emission computed tomography (SPECT) scanners, and the like. A gamma camera may include a semi-monolithic crystal assembly having a plurality of monolithic crystals assembled in an array. Each monolithic crystal has an entrance face, a detector face opposite the entrance face, and a plurality of lateral faces, with a lateral face of each monolithic crystals adjacent to a lateral face of another of the monolithic crystals. A plurality of photodetectors configured to generate signals responsive to scintillation light detected in the plurality of monolithic crystals are attached to the detector faces of the monolithic crystals. The LUT generation method includes producing a plurality of scintillation events in the semi-monolithic crystal assembly by directing gamma rays into the crystal assembly at a plurality of grid points on the entrance faces of the monolithic crystals, and recording corresponding scintillation light response signals from the plurality of photodetectors. For each monolithic crystal, a look-up table (LUT) based on the recorded response signals is generated, the table including information for determining the position of the scintillation event within the crystal array. For example, the LUT may include a (i) mean values of the response signals for each of the plurality of photodetectors at each grid point of the plurality of grid points in the monolithic crystal; (ii) interpolated values of the mean value of the response signals providing interpolated values between grid points in the monolithic crystal; and (iii) extrapolated values of the mean value of the response signals for locations distal from the grid points in the monolithic crystal, wherein at least some of the locations of extrapolated values correspond to locations external of the monolithic crystal.

In some methods and systems in accordance with the present disclosure, at least some of the locations of the extrapolated values overlap locations of the extrapolated values in at least one adjacent monolithic crystal.

In some embodiments the photodetectors comprise one or more photomultiplier tubes, for example, a multi-anode photomultiplier tube.

In some embodiments the method further includes determining a depth-of-interaction (DOI) value for the plurality of scintillation events in the crystal assembly based on the scintillation light response signals, and separating the response signals into a number of DOI intervals, wherein the mean values, interpolated values, and extrapolated values are generated separately for each of the DOI intervals. In some embodiments the response signals are filtered prior to generating the LUT. In some embodiments there are at least four DOI intervals. In some embodiment the DOI values are determined using a multi-Lorentzian fit.

In some embodiments the monolithic crystals are joined with a light-transmissive adhesive. In some embodiments the outer faces of the monolithic crystals are coated with a light-absorbing material, for example, a black paint.

In some embodiments the generated LUTs include (i) standard deviation values of the response signals for each of the plurality of photodetectors at each grid point of the plurality of grid points in the monolithic crystal; (ii) interpolated values of the standard deviation values of the response signals providing interpolated values between grid points in the monolithic crystal; and (iii) extrapolated values of the standard deviation values of the response signals for locations distal from the grid points in the monolithic crystal, wherein at least some of the extrapolated values correspond to locations external of the monolithic crystal. At least some of the locations for the extrapolated values may overlap locations for the extrapolated values in at least one adjacent monolithic crystal.

In some embodiments the plurality of grid points on the entrance faces of the crystals extends beyond the plurality of photodetectors attached to the detector faces of the monolithic crystals.

In some embodiments the number of grid points in the plurality of grid points for producing scintillation events is at least sixteen times greater than the number of photodetectors in the plurality of photodetectors.

In some embodiments at least some of the locations for the extrapolated values are outside of the crystal assembly.

A gamma cameral system includes a semi-monolithic crystal assembly having a plurality of monolithic crystals, each monolithic crystal having an entrance face, a detector face that is opposite the entrance face, and a plurality of lateral faces, wherein the plurality of monolithic crystals are assembled in an array such that at least one lateral
5 face of each of the plurality of monolithic crystals is adjacent to at least one lateral face of another of the plurality of monolithic crystals. A plurality of photodetectors attached to the detector faces of the monolithic crystals, wherein the plurality of photodetectors are configured to generate signals responsive to scintillation light detected in the plurality of monolithic crystals. A plurality of look-up tables (LUTs) are associated with the
10 plurality of monolithic crystals, wherein the LUTs are generated from a calibration of the semi-monolithic crystal assembly. The LUTs characterize measured responses from the plurality of photodetectors for scintillation events produced in the semi-monolithic crystal assembly over a grid of points defined on an entrance face of the crystal assembly. Each LUT includes (i) mean values of response signals for each of the plurality of
15 photodetectors at each grid point of the plurality of grid points in the monolithic crystal; (ii) interpolated values of the mean value of the response signals providing interpolated values between grid points in the monolithic crystal; and (iii) extrapolated values of the mean value of the response signals for locations distal from the grid points in the monolithic crystal, wherein at least some of the extrapolated values correspond to
20 locations external of the monolithic crystal. At least some of the locations for the extrapolated values overlap locations for the extrapolated values in at least one adjacent monolithic crystal.

In another embodiment, a method for generating look-up tables for a gamma camera is disclosed. The gamma camera may have at least one monolithic crystal having
25 an entrance face, a detector face that is opposite the entrance face, and a plurality of lateral faces, and a plurality of photodetectors attached to the detector faces of the monolithic crystal, wherein the plurality of photodetectors are configured to generate signals responsive to scintillation light detected in the monolithic crystal. The method includes producing a plurality of scintillation events in the monolithic crystal by directing
30 gamma rays into the crystal at a plurality of grid points on the entrance faces of the monolithic crystal, and recording corresponding scintillation light response signals from the plurality of photodetectors; and generating a look-up table (LUT) based on the recorded response signals. The LUT may include (i) mean values of the response signals

for each of the plurality of photodetectors at each grid point of the plurality of grid points in the monolithic crystal; (ii) interpolated values of the mean value of the response signals providing interpolated values between grid points in the monolithic crystal; and (iii) extrapolated values of the mean value of the response signals for locations distal from the grid points in the monolithic crystal. At least some of the locations of extrapolated values correspond to locations external of the monolithic crystal.

In an embodiment, a plurality of monolithic crystals re arranged in a array to define a semi-monolithic crystal array. The plurality of photodetectors may comprise a plurality of photomultiplier tubes, for example, a multi-anode PMT.

In an embodiment the method further includes determining a depth-of-interaction (DOI) value for the plurality of scintillation events in the crystal based on the scintillation light response signals, and separating the response signals into a number of DOI intervals, wherein the mean values, interpolated values, and extrapolated values are generated separately for each of the DOI intervals.

DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIGURE 1 shows a semi-monolithic crystal gamma camera in accordance with the present invention having four large crystals arranged in a 2 by 2 array;

FIGURE 2A illustrates a system for calibrating the gamma camera shown in FIGURE 1;

FIGURE 2B is a front face view of the gamma camera shown in FIGURE 1, and shows the scan point grid used to collect calibration data for lookup tables to be associated with the gamma camera;

FIGURES 3A-3C illustrate the modeling of light detected from events in the scintillation crystal subassembly of the gamma camera shown in FIGURE 1, wherein FIGURE 3A indicates several light paths for light detected at a particular location in the same crystal in which the scintillation event occurred, FIGURE 3B indicates several light paths for light detected at a particular location in a crystal adjacent to the crystal in which the scintillation event occurred, and FIGURE 3C indicates several light paths for light

detected at a particular location in a crystal disposed diagonally from the crystal in which the scintillation event occurred;

FIGURE 4 shows an example of a table with the mean value of width, internal reflectivity, and external reflectivity for each depth-of-interaction range and for three regions of the crystal detector for the gamma camera shown in FIGURE 1;

FIGURE 5A shows plots of a small one-dimensional portion of a look-up table having four depth-of-interaction regions, and spanning an interface between two crystals; illustrating the central extrapolation method;

FIGURE 5B shows plots of a small one-dimensional portion of a look-up table having four depths-of-interaction regions, and spanning an interface between two crystals; illustrating the perimeter extrapolation method in accordance with the present invention;

FIGURE 6A illustrates an exploded view of the crystal assembly shown in FIGURE 1, and illustrating look-up tables associated with each of the monolithic crystals wherein the look-up tables extend beyond the boundary of the associated crystal; and

FIGURE 6B illustrates the crystal assembly assembled, showing overlapping regions of the look-up tables.

DETAILED DESCRIPTION

A gamma camera, also called a scintillation camera or an Anger camera, is an imaging instrument based on detecting scintillation events in a crystal generated by high-energy photons (e.g., gamma rays). In a gamma camera (e.g., a positron emission tomography (PET) scanner, a single photon emission computed tomography (SPECT) scanner, etc.), two goals to optimize the image production are to accurately determine the position of scintillation events in the crystal, and to maximize the number of scintillation events that are detected and analyzed.

A semi-monolithic gamma camera module 100 in accordance with the present invention is shown schematically in FIGURE 1. The module 100 has four monolithic crystals 102 optically coupled in a 2 by 2 array to effectively operate as a single larger monolithic crystal. A gridded or position sensitive light sensor array, for example, a photomultiplier tube (PMT) assembly 104 is attached to the crystals 102 to detect scintillation light within the crystal array.

The gamma camera module 100 includes a semi-monolithic multi-crystal assembly 101 formed from the plurality of monolithic scintillator crystals 102. In this

embodiment the crystal assembly 101 comprises four monolithic crystals 102. The monolithic crystals 102 may comprise any suitable scintillation material as are known in the art. For example, the crystals 102 may comprise Lutetium-yttrium oxyorthosilicate (LYSO). For convenience X-Y-Z coordinate directions are indicated. Each of the
5 monolithic crystals 102 include an entrance face 106 aligned in an X-Y direction, a detector face 107 aligned in an X-Y direction, and lateral faces 103, 105 extending between the entrance face 106 and the detector face 107.

The detector faces 107 of the multi-crystal assembly 101 are coupled to the PMT assembly 104. An exemplary PMT assembly is the Hamamatsu™ H8500C multi-anode
10 photomultiplier tube (MAPMT) having sixty-four channels or anodes 104' (FIGURE 2B) arranged in a square 8 by 8 array. In a current system, the crystals 102 are 26 mm x 26 mm x 10 mm crystals, and form a 52 mm x 52 mm x 10 mm semi-monolithic crystal assembly 101. It will be appreciated that a different number of crystals and different sizes of crystals may be used. It is within the ability of persons of skill in the art to
15 determine suitable sizes and numbers of crystals for a multi-crystal assembly 101 to accommodate a particular application.

The crystals 102 in this embodiment are optically coupled across adjacent faces, such that light may be transmitted or shared between crystals 102. For example, semi-transmissive interfaces 103 between adjacent faces of the crystals 102 may be
20 joined with a conventional mounting media, for example, Cargille Meltmount™ Quick Stick™, which has a refractive index $n=1.704$.

The crystals 102 are coupled to the PMT assembly 104 surface using an optical grease, for example, BC-630 Saint-Gobain® optical grease (refractive index $n=1.465$). All lateral faces of the crystals 102 were roughened with 1000-grit sand paper and the
25 outward-facing lateral surfaces 105 are painted black to avoid internal reflections of the scintillation light. Edge reflection can cause the detector response to flatten near the edges, decreasing the spatial resolution. The crystal 102 surface coupled to the PMT assembly 104 is diffusive to maximize the light output, while the opposite side is polished and covered with four layers of polytetrafluoroethylene tape (e.g., Teflon®) and then with
30 a specular mirror film layer on top.

The gamma camera 100 is first calibrated, to correlate the location of scintillation events within the crystal assembly 101 with, in this example, sixty-four measured signals from the PMT assembly 104. The calibration data is used to reconstruct interaction

positions of scintillation events within the gamma camera 100 during image construction. Least Squares (LS) and Maximum Likelihood (ML) methods for image reconstruction were used, as are known in the art.

For the gamma camera 100 shown in FIGURE 1 a calibration was performed using a 34 by 34 point scan over the entrance face 106 of the crystal assembly 101. The calibration data generation is illustrated schematically in FIGURE 2A. A point flux is produced using, for example, a ^{22}Na radioactive source 90. A coincidence crystal 91, for example, a 4 mm x 4 mm x 20 mm LYSO crystal 91 coupled to a PMT 92, is oriented with an axis perpendicular to the surface of the crystal assembly 101.

For calibration, the radioactive source 90 is aligned with the axis of the coincidence crystal 91 at a location between the coincidence crystal 91 and the entrance faces 106 of the crystal assembly 101. The probe (the PMT 92 coupled to the coincidence crystal 91) was mounted on a 5-micron-precision 2-dimensional mechanical translator, indicated by arrows 96, and moved with the radiation source 90 to scan the surface of the crystal assembly 101.

Data were collected on a 34-by-34 grid of calibration scan points SP for gamma rays from the source 90 entering the entrance face 106 and generating a scintillation event, as shown in FIGURE 2B. The positions of the scan points SP with respect to the PMT 104 array of anodes 104', and to the crystals 102, are indicated by small circles. The scan points' row and column numbers are indicated along the vertical and horizontal edges. The scan points in rows and columns 17 and 18 are the scan points closest to the optical interface 103. In this example, a central portion measuring 50.16 mm x 50.16 mm of the crystal assembly 101 face is therefore spanned by the scan points in the calibration. Calibration data are filtered and used to construct look-up tables (LUTs) of the mean and standard deviation of the PMT 104 sixty-four detector responses. The detector response data in the LUTs is used to determine scintillation positions.

A detectable high energy photon, for example, a gamma ray from the source 90, enters one of the monolithic crystals 102 at a selected SP and interacts with the crystal in a scintillation event, generating a relatively large number of lower-energy photons that can be detected by the PMT assembly 104. It will be intuitively obvious that scintillation events occurring near the distal face (detector face 107 in FIGURE 1) of the crystal 102 will generate relatively larger signals from relatively fewer anodes 104', and scintillation events occurring nearer the entrance face 106 of the crystal 102 (i.e., farther from the

PMT assembly 104) will generate relatively smaller signals from relatively more anodes 104' in the PMT assembly 104.

In order to provide a more complete description of a particular embodiment of a system and method in accordance with the present invention, it will be appreciated that the particular filtering steps discussed below are for a current embodiment, and are not required, and the invention disclosed herein is not intended to be limited to the exemplary embodiment discussed. The following filtering steps were performed on the collected data to obtain the mean and standard deviation LUTs of non-scattered 511-keV photopeak events for the least-squares (LS) and maximum-likelihood (ML) estimates.

Energy windowing: Energy filtering of the photo-peak events in each acquisition was done using the integrated signal (200-ns gate) collected from the Fast channel. The energy window used was $[5/6, 3/2]$ of the photo-peak energy; this window equates to 425 keV lower and 765 keV upper thresholds. The lower energy threshold was chosen to be half way between the photo-peak and the Compton back-scatter peak. The upper threshold was used to reject down-scatter of the simultaneous 1274 keV gamma ray produced by ^{22}Na source 90. A high value was chosen to avoid cutting off the distribution, broadened by the increasing light collection efficiency with depth-of-interaction.

Spatial filtering: Event position estimates far from the center of the ensemble distribution in each acquisition were ignored. Events outside of a contour (e.g., 5% of the peak ensemble distribution) obtained with Anger logic positioning were rejected as these events have Compton scattered in the crystal 102 before being photoelectrically absorbed and therefore are not useful for calibrating the detector light response function. About 25% to 30% of the events were discarded with this selection method. For points closer to the central interface the fraction of the rejected events increased up to 40%.

Filtering of the events: An event was discarded if the channel or anode with the maximum signal collected less than 15% of the total amount of light (to reject Compton scatter in the detector) or if the channel with the maximum value differed from that in front of the collimated beam. This second selection is particularly useful close to the optical interfaces 103 because the lateral tail of the collimated beam can interact in a neighboring crystal 102 and generate events with a very different light distribution. Between 5% and 8% of the events were discarded during this step. As in the previous case, the fraction increased close to the central interface 103 to about 14%.

Filtering based on the light-distribution fit: To determine depth-of-interaction, light distribution was fit with a multi-Lorentzian function (accounting for reflections). Fit results that did not correspond to real possible solutions (e.g. positions reconstructed out of the crystal boundaries) or which had a low Coefficient of Determination (e.g., CoD below 0.90) were discarded. Here, the CoD is defined as 1 minus the sum of the squares fit residuals divided by the measured light-distribution standard deviation. The fraction of events discarded was always lower than 15%.

Outlier filtering: Signals collected far from the median of the distribution in the acquisition were discarded. The tail of the signal distribution was truncated and not included in the construction of the LUTs because these signals tend to be quite noisy. For each position, for each depth and for each channel, the median of the distribution of the signals was calculated, and data farther than N times the median distance from the median of the distribution were rejected. A value of N equal to 12 was chosen, since a low value of N reduces the estimation of the standard deviation of the signal, while too high a value reduces the precision in the estimation of the mean.

Depth-of-interaction

The depth separation was performed by fitting the light distribution collected for each event and by sorting the events using the width of the obtained distribution. The light spread is assumed to increase monotonically with distance of interaction from the anodes 104'. In particular, a Lorentz function was considered to model the spatial distribution of light on the PMT assembly 104, and additional Lorentzians were used to model the reflected light, using two different parameters for the reflection probabilities from internal and external surfaces. A uniform background was used to model light diffused from the top surface. This contribution is weighted considering the number of inner interfaces between the scintillation point and the detection point. The number of image sources needed to take into account the inner and lateral reflections depends on the position of the detection point with respect to the position of the scintillation point. For the analysis it is assumed that only light coming from no more than one reflection and no more than two transmissions contributes significantly to the signal. This choice was done to avoid too high a number of image sources and because we expected a high transmission coefficient for the inner surfaces and a low reflection probability at the edge of the crystal. The contribution of image sources for three different sets of scintillation and detection points are shown in FIGURES 3A-3C.

FIGURE 3A schematically illustrates the multi-crystal assembly 101 with a scintillation event SE occurring in the upper right crystal 102. The light detected at point P1 in the same crystal 102 may come from photons that travel directly from the scintillation event SE to point P1, as indicated by path 80. Other potential scintillation photons paths to P1 include reflections from the outer lateral face 105 (path 81), reflections from semi-transmissive interface 103 (path 82), transmission through the semi-transmissive interface 103 followed by reflection from the outer face 105 and transmission back into the crystal 102 through the semi-transmissive interface 103 (path 83).

FIGURE 3B schematically illustrates the multi-crystal assembly 101 with a scintillation event SE occurring in the upper right crystal 102. The light detected at point P2 in an adjacent crystal 102 may come from photons that travel directly from the scintillation event SE to point P2 passing through the semi-transmissive interface 103, as indicated by path 80'. Other potential scintillation photons paths to P2 include reflections from the outer lateral face 105 and through the semi-transmissive interface 103, in either order (path 81').

FIGURE 3C schematically illustrates the multi-crystal assembly 101 with a scintillation event SE occurring in the upper right crystal 102. The light detected at point P3 in the diagonally aligned crystal 102 may come from photons that travel directly from the scintillation event SE to point P3 after passing twice through the semi-transmissive interface 103, as indicated by path 80". Other potential scintillation photons paths to P3 include reflections from the outer lateral face 105 and twice through the semi-transmissive interface 103, in any order (path 81").

A total of 8 parameters were used to estimate the curve shaping:

- Offset: contribution of diffused light;
- Amplitude: amplitude of the Lorentzian representing the direct light;
- X_0 , Y_0 : coordinates of the center of the scintillation;
- W_X , W_Y : width of the Lorentzian in the two directions;
- R_{int} : internal surfaces reflection probability;
- R_{ext} : external surfaces reflection probability.

The mean value and the standard deviation of the internal and external reflectivity and of the curve width obtained in the fit are shown in FIGURE 4 for each range of depth-of-interaction and for three different regions of the detector: the scan positions at

the center of each crystal, the two positions at the edges of the detector and the region corresponding to the two columns and rows closer to the inner interface were considered.

An acceptance window was applied both to the scintillation position (X_0 , Y_0) and to the external reflectivity (R_{ext}) to discard the events that did not have realistic fit results for the calibration. In particular, only events with the scintillation center reconstructed closer than 5 millimeter in both directions to the real beam position were used, and fits that gave a R_{ext} higher than 0.9 were discarded. Even if a high transparency is expected, no limitations were applied to the internal reflectivity (R_{int}) because the behavior of the light at this internal interface was part of the study and the introduction of constraints could bias the evaluation. Even if the width of the Lorentzian (W_X and W_Y) was expected to be the same in both directions, the two parameters were left independent and they were summed in quadrature to estimate the width of the curve.

Accepted events were divided into four groups according to the 2D geometric-average width of the Lorentzian bell. The number of events in each group was imposed to be the same. In this way, by using the attenuation coefficient of the LYSO and the exponential attenuation law, the boundaries of the 4 depth-of-interaction intervals (whose width increases with depth in the crystal) were obtained. Considering an attenuation length of the scintillator of 12 mm, the four DOIs corresponded to the intervals [0 mm, 1.83 mm], [1.83 mm, 3.99 mm], [3.99 mm, 6.62 mm] and [6.62 mm, 10 mm] (where DOI = 0 mm at the entrance of the scintillator).

Look-up table (LUT) Generation

Beginning with the 34 by 34 acquisition points SP shown in FIGURE 2B, mean and standard deviation LUTs for each PMT channel are built. The size of each LUT depends on the number of possible depth-of-interaction ranges are selected, and on the size of the interpolation region obtained from the calibration grid. For example, as discussed above, four DOI ranges may be used. It will be obvious to persons of skill in the art that more or fewer DOI ranges may alternatively be used.

Three different methods were tested to generate the LUTs:

1. Standard interpolation. The values of mean and standard deviation of the distribution of the selected events were obtained for each anode 104' and for each depth-of-interaction. Inside each crystal volume, four interaction points were interpolated between measured calibration points of the grid using a bi-cubic fit. Other interpolation methods may alternatively be used. Each monolithic crystal 102 was interpolated

separately to avoid the introduction of artifacts and oscillations in the interpolated trend due to the discontinuity of the mean value at interfaces.

At the inner interfaces 103, the four interpolation points that connect each pair of crystals (between the 17th and 18th point in each direction as shown in FIGURE 2B) were obtained by means of a linear extrapolation of two points from each side. At the outer lateral faces 105, four points were linearly extrapolated: the first three corresponded to real positions inside the crystal between the first or the last scan position and the crystal edge, while the last point was used to collect and discard the events that did not converge to any possible value of the LUT.

The size of the LUT in both X or Y direction for each depth and each channel using this approach was $\text{Size1} = N_{\text{pt}} + (N_{\text{pt}} - 1) * N_{\text{inter}} + N_{\text{extrap}} = 174$, where $N_{\text{pt}} = 34$ is the number of calibration points, $N_{\text{inter}} = 4$ is the number of interpolated points between each step of the initial grid and $N_{\text{extrap}} = 8$ is the number of extrapolated points at the boundaries in the x and y directions. The attractiveness of this technique is that it is simple. Its shortcoming is that it can lead to hot spots in a uniform flood crystal map which in turn can lead to artifacts in a reconstructed images, for example, in PET images.

2. Central Extrapolation. In central extrapolation the LUTs were built as in the previous one, except that one row and one column of extrapolated points were added at each interface 103. This new region that separates each pair of crystals does not correspond to any real physical position in the detector and was used merely to collect and discard events that in the previous case were arbitrarily positioned closer to the optical interfaces 103. The artifact introduced in the previous method by the accumulation of events at the boundary, due to the discontinuity in the mean LUTs, was partially solved with this approach, at the expense of a lower sensitivity close to the crystal interfaces 103.

The size of the LUT in each direction is now $\text{Size2} = 176$, because two extrapolated points were added in the x and y directions. An example of LUT behavior near the optical interfaces 103 (shown as vertical dotted line) with this method is shown in FIGURE 5A, where the black dots at the center of the LUT (on either side of the optical interface) represent the positions in which the events were discarded. In FIGURE 5A, the curves on the left side of the vertical dotted line represent the look-up values in one dimension (for example, the x-direction) in the LUT for one crystal 102 near the optical interface at each of the four DOI, and the curves on the right side of the

vertical dotted line represent the corresponding look-up values in the LUT for an adjacent crystal 102 near the optical interface.

3. Perimeter extrapolation. In this approach, a novel additional region is extrapolated across the interface 103 between each of the adjacent crystals 102, resulting in overlapping LUTs. Each additional extrapolated point had a corresponding physical position in the detector in the adjacent crystal 102 so that each position close to the optical interface 103 corresponded to more than one position in the LUTs. A total of $N_{\text{overlap}} = 7$ overlapping positions on each side were added in this exemplary embodiment, corresponding to an overlap region of 4.3 mm. The reconstructed position in the overlap region might not correspond to the real interaction position, and a reduction in the spatial resolution close to the interface region was introduced because the extrapolation was done across a discontinuity. The reconstructed positions in this extrapolated region correspond to points that had a completely different distribution of light in the real calibration grid. In this embodiment, a linear extrapolation was used, although other extrapolation methods may alternatively be used.

An advantage of this method is that the loss in sensitivity is reduced compared to the previous approach, and the distribution of events close to the interface 103 has a more symmetric shape and less discontinuity. If the overlap region is too large, part of this region can be excluded and events that converge there can be discarded. The size of the LUT in the x and y direction is now $\text{Size3} = \text{Size2} + 2 * N_{\text{overlap}} = 190$.

An example of LUT behavior in the overlapping region is shown in FIGURE 5B, where the interface 103 is indicated by a vertical line. The dotted lines represent the overlapping extrapolated region. It will be appreciated that even if the extrapolated region of the left crystal is used, the events in that region are reconstructed in the adjacent crystal. The terminal black dots represent the points in which the event was discarded.

It will be appreciated that the perimeter extrapolation method differs fundamentally from the other methods in that the LUTs are not co-extensive with a single one of the monolithic crystals 102. The values in the LUTs for the crystal 102 on the left side of the semi-transmissive interface 103 (represented by the vertical dotted line in FIGURE 5B) are extrapolated into a region in an adjacent crystal 102 on the other side of the semi-transmissive interface 103.

No filters were applied to the LUTs obtained for the mean, while the LUTs related to the standard deviation were usually noisier and some correction of outlier points was

used to minimize the artifacts in the position reconstruction. In particular, outliers of the standard deviation LUTs (before the interpolation) were replaced by an average of their eight nearest neighbors: the variation between a point and each point in its neighborhood was calculated, and if one of these variations was greater than twice the average of the group of points, the value was replaced with that obtained with a 5 x 5 Gaussian filter. No changes were applied to those points where the distribution was continuous.

The same technique may be used near the lateral surfaces 105, wherein the LUT values near the lateral faces 105 are extrapolated to extend into physical space that is outside of the multi-crystal assembly 101. The perimeter extrapolation method extends the region that the position of scintillation events may be placed to include space outside of the crystal.

Refer now also so FIGURES 6A and 6B, which illustrate the monolithic crystals 102 in the semi-monolithic crystal assembly 101 in plan view, with the spatial extent of the corresponding LUTs 202 for each crystal 102, using the perimeter extrapolation method shown in dashed line. In this embodiment, the perimeter extrapolation method described above is modified (as suggested above) to also extrapolate the LUTs beyond the lateral (non-adjacent) faces 105 of the monolithic crystals 102. FIGURE 6A shows the crystal assembly 101 in exploded view, and FIGURE 6B shows the assembled view.

In the perimeter extrapolation method the LUTs 202 are extrapolated to incorporate a physical space beyond the boundaries of the associated crystal 102. As shown in FIGURE 6B, the LUT 202 for each crystal 102 overlaps LUTs 202 for adjacent crystals 102 indicated by overlap regions 204. The LUTs 202 also include extended portions 206 that extend into space exterior to the crystal assembly 101.

In an alternative embodiment the gamma camera may comprises one or more isolated monolithic crystals (e.g., one crystal 102 shown in FIGURE 6AA) and a single LUT (e.g., corresponding to LUT 202) that extends into space surrounding and external to the monolithic crystal.

Position Estimation

For example, in the least squares (LS) analysis, the position of the events are estimated by searching the LUTs for the position that minimized the least-squares difference between observation and mean response. In this case the position was found

by minimizing the distance between the value of the position in the LUT and in the collected events:

$$Pos = \min_{X,Y,Z} \left(\sum_{i=1}^{64} (a_i - \mu_i(X,Y,Z))^2 \right)$$

where μ_i is the value recorded in the mean LUT and a_i are the measured values.

5 The sum runs over the sixty-four channels of the PMT assembly 104 in this example. To speed up the process, a hierarchical search was used. The first search used 5 points in the x and y direction and all 4 possible depth-of-interaction positions. The search was then refined in the neighborhood of the selected position. No evidence of loss in resolution using the hierarchical search was found with respect to using an exhaustive search. Only
10 events corresponding to the photo-peak were used in the position estimation. No difference in the least squares search was implemented for the three different sets of LUTs.

The perimeter extrapolation LUT method was also tested using a Maximum Likelihood (ML) search assuming an independently distributed normal signal probability
15 model. In this case, the standard deviation LUT was also used in the estimation of the gamma interaction position, maximizing the logarithm of the likelihood:

$$-\log(L(\mu(X,Y,Z), \sigma(X,Y,Z))) + \sum_{i=1}^{64} \left(\frac{(a_i - \mu_i(X,Y,Z))^2}{2\sigma_i(X,Y,Z)^2} \right)$$

where σ_i is the value of the standard deviation in the LUT.

The energy resolution for each beam position was evaluated by dividing the
20 FWHM of the peak distribution by the value of the peak position. The resolution obtained close to the inner interfaces was compared with the one at the center of each crystal.

The resolution and bias of the position estimate were analyzed separately in three regions: at the center of a crystal, in the region close to the internal boundaries and at the
25 external edges. For each crystal 102 of the semi-monolithic crystal assembly 101, a subset of beam positions corresponding to the central part of each was selected (positions from 6 to 12 and from 23 to 29 in both directions) and the mean values of the results were evaluated.

In the interface region the subset in which the beam is close to the optical interface (position 17 and 18 in both directions) was chosen. The 5 rows and columns closest to the external boundary were discarded to avoid artifacts due to the black external surface. To estimate the performances at the edges of the detector the first two and the last two scan positions were used: the acquisition close to the optical interfaces was not used to avoid the effect of the optical coupling. For each beam position a contour was found, corresponding to the half maximum and to the tenth maximum of the distribution, and a circular fit was applied to the polygon. The full width at half max (FWHM) and full width at the tenth max (FWTM) of the distribution were then expressed as the diameter of such circles. Due to partial reflection at the interface, the distribution can be asymmetric, therefore the mean and median distances of the single reconstructed point with respect to the ensemble average center of each beam position were considered to better quantify the spread of the distribution. Furthermore, the sum in quadrature of bias and median distance from the center of the reconstructed distribution were also evaluated for each region.

Finally, an additional metric "r" was considered, combining the bias and the spread of the estimate distribution, defined as the value at which the distance of the reconstructed positions for the beam positions $x=x_0-r$ and $x=x_0+r$ is equal to the mean spread of the distribution on these two points.

Positioning performance (resolution and bias) and energy resolution are comparable for all the three methods in the four continuous regions of the scintillator. The small discrepancies in the results for the four crystals can be due to slight differences in the optical coupling between crystals and PMT assembly, between crystal and reflective surface, and to differences in sensitivity in the sixty-four channels of the PMT assembly.

Due to the difference in gain of each anode of the PMT assembly and to the absorption of the optical photons at the lateral surfaces, the 511 keV photo-peak position varies with interaction position in the crystal. About 2% degradation in energy resolution can be seen near the crystal interfaces as compared to the center of each crystals; this degradation is lower than that due to the black lateral surfaces of the crystals.

The first LUT-generation method (standard interpolation) is consistent with the methodology applied with a single monolithic crystal. This naive approach seems the

most promising in terms of median distance and FWHM of position estimates near the quadrant interfaces. However, the artifacts in the distribution of the estimated event positions can induce errors in the reconstructed PET image. This estimate-distribution artifact is a result of the discontinuity of the values in the LUT along the optical surface.

5 Fluctuations in the measured signals would cause some events to be positioned across the boundary region, if there were no boundary in the LUT. These events are now confined by the LUT discontinuity and are instead reconstructed as close as possible to the discontinuity, on the side in which the photon interacts. The discontinuity in the LUT appears to improve the spatial positioning in that region; however, the "improved" spatial

10 resolution is an artifact caused by events being piled up at the region of the crystal interface.

Using the second method (central extrapolation), events that pile up at the interface in the previous case are placed in the rejection region and are discarded, thus reducing the sensitivity at the interface region by about 30%. As mentioned above, part

15 of these discarded events are true events and the rejection is due to the statistical distribution of the signals. Thus, the central extrapolation method results in an asymmetric and biased estimate distribution and is undesirable for using PET imaging as a quantitative metrics.

The new method (perimeter extrapolation) mitigates the reduction in sensitivity.

20 Many of the events that were previously discarded are now positioned in the other quadrants. This method broadens the FWHM of the reconstructed distribution, but the shape obtained is now symmetric, as we would like it to be if we do not account for a spatially variant point spread function in the image reconstruction. Using this method the point spread function representing the detector response is more uniform in the whole

25 area of the detector.

We have also shown for this detector (and the third method), that assuming an independent normal probability model for the signal distribution, the performance of a maximum likelihood position estimator is comparable to the positioning performance by least squares estimator.

30 The perimeter extrapolation method described here matches together the capability to have a high sensitivity close to the optical interface, corresponding to a higher signal-to-noise ratio SNR in the PET image, with a high uniformity in the shape of

the point response function of the detector, which simplifies the modeling of the detector in the image reconstruction algorithm.

Although in a current embodiment the location of the depth-of-interaction for the scintillation events is calculated, for example, as discussed above, it will be appreciated
5 by persons of skill in the art that the perimeter extrapolation method may readily be performed without taking into account different depths of interaction information for the scintillation events, for example, by approximating the depth-of-interaction is at a predetermined location in the crystals 102, albeit with some loss in accuracy. In an
10 embodiment, the depth-of-interaction is assumed to be along a common center-plane of the crystals 102. The look-up tables in this embodiment extrapolate into adjacent crystals (or into space outside of lateral faces 105) of the crystals 102, but for a single DOI.

While illustrative embodiments have been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

15

CLAIMS

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method for generating look-up tables for a gamma camera, the gamma camera comprising:

a semi-monolithic crystal assembly comprising a plurality of monolithic crystals, each monolithic crystal having an entrance face, a detector face that is opposite the entrance face, and a plurality of lateral faces, wherein the plurality of monolithic crystals are assembled in an array such that at least one lateral face of each of the plurality of monolithic crystals is adjacent to at least one lateral face of another of the plurality of monolithic crystals;

a plurality of photodetectors attached to the detector faces of the monolithic crystals, wherein the plurality of photodetectors are configured to generate signals responsive to scintillation light detected in the plurality of monolithic crystals;

the method comprising:

producing a plurality of scintillation events in the semi-monolithic crystal assembly by directing gamma rays into the crystal assembly at a plurality of grid points on the entrance faces of the monolithic crystals, and recording corresponding scintillation light response signals from the plurality of photodetectors;

for each monolithic crystal, generating a look-up table (LUT) based on the recorded response signals, wherein the generated LUT includes:

(i) mean values of the response signals for each of the plurality of photodetectors at each grid point of the plurality of grid points in the monolithic crystal;

(ii) interpolated values of the mean value of the response signals providing interpolated values between grid points in the monolithic crystal; and

(iii) extrapolated values of the mean value of the response signals for locations distal from the grid points in the monolithic crystal, wherein at least some of the locations of extrapolated values correspond to locations external of the monolithic crystal;

wherein at least some of the locations of the extrapolated values overlap locations of the extrapolated values in at least one adjacent monolithic crystal.

2. The method of Claim 1, wherein the plurality of photodetectors comprise a plurality of photomultiplier tubes.

3. The method of Claim 2, wherein the plurality of photomultiplier tubes comprise a multi-anode photomultiplier tube.

4. The method of Claim 1, further comprising determining a depth-of-interaction (DOI) value for the plurality of scintillation events in the crystal assembly based on the scintillation light response signals, and separating the response signals into a number of DOI intervals, wherein the mean values, interpolated values, and extrapolated values are generated separately for each of the DOI intervals.

5. The method of Claim 1, further comprising the step of filtering the response signals for detected events prior to generating the LUTs.

6. The method of Claim 5, wherein the number of DOI intervals is at least four.

7. The method of Claim 5, wherein the DOI values are determined using a multi-Lorentzian fit to the detector signals.

8. The method of Claim 1, wherein the adjacent faces of the monolithic crystals in the semi-monolithic crystal assembly are joined with a light-transmissive adhesive.

9. The method of Claim 8, wherein the plurality of lateral faces of the monolithic crystals that are not adjacent to a lateral face of another monolithic crystal are coated to be light-absorbing.

10. The method of Claim 1, wherein the generated LUTs further comprise:
(i) standard deviation values of the response signals for each of the plurality of photodetectors at each grid point of the plurality of grid points in the monolithic crystal;
(ii) interpolated values of the standard deviation values of the response signals providing interpolated values between grid points in the monolithic crystal; and

(iii) extrapolated values of the standard deviation values of the response signals for locations distal from the grid points in the monolithic crystal, wherein at least some of the extrapolated values correspond to locations external of the monolithic crystal; wherein at least some of the locations for the extrapolated values overlap locations for the extrapolated values in at least one adjacent monolithic crystal.

11. The method of Claim 1, wherein the gamma camera comprises one of a positron emission tomography scanner and a single photon emission computed tomography scanner.

12. The method of Claim 1, wherein the plurality of grid points on the entrance faces of the crystals extend beyond the plurality of photodetectors attached to the detector faces of the monolithic crystals.

13. The method of Claim 1, wherein the number of grid points in the plurality of grid points for producing scintillation events is at least sixteen times greater than the number of photodetectors in the plurality of photodetectors.

14. The method of Claim 1, wherein at least some of the locations for the extrapolated values are outside of the crystal assembly.

15. A gamma camera system comprising:

a semi-monolithic crystal assembly comprising a plurality of monolithic crystals, each monolithic crystal having an entrance face, a detector face that is opposite the entrance face, and a plurality of lateral faces, wherein the plurality of monolithic crystals are assembled in an array such that at least one lateral face of each of the plurality of monolithic crystals is adjacent to at least one lateral face of another of the plurality of monolithic crystals;

a plurality of photodetectors attached to the detector faces of the monolithic crystals, wherein the plurality of photodetectors are configured to generate signals responsive to scintillation light detected in the plurality of monolithic crystals;

a plurality of look-up tables (LUTs), each LUT associated with one of the plurality of monolithic crystals, wherein the LUTs generated from a calibration of the semi-monolithic crystal assembly wherein the LUTs characterize measured responses from the plurality of photodetectors for scintillation events produced in the semi-

monolithic crystal assembly over a grid of points defined on an entrance face of the crystal assembly, each LUT having:

- (i) mean values of response signals for each of the plurality of photodetectors at each grid point of the plurality of grid points in the monolithic crystal;
- (ii) interpolated values of the mean value of the response signals providing interpolated values between grid points in the monolithic crystal; and
- (iii) extrapolated values of the mean value of the response signals for locations distal from the grid points in the monolithic crystal, wherein at least some of the extrapolated values correspond to locations external of the monolithic crystal;

wherein at least some of the locations for the extrapolated values overlap locations for the extrapolated values in at least one adjacent monolithic crystal.

16. A method for generating look-up tables for a gamma camera, the gamma camera comprising:

at least one monolithic crystal having an entrance face, a detector face that is opposite the entrance face, and a plurality of lateral faces;

a plurality of photodetectors attached to the detector faces of the monolithic crystal, wherein the plurality of photodetectors are configured to generate signals responsive to scintillation light detected in the monolithic crystal;

the method comprising:

producing a plurality of scintillation events in the monolithic crystal by directing gamma rays into the crystal at a plurality of grid points on the entrance faces of the monolithic crystal, and recording corresponding scintillation light response signals from the plurality of photodetectors;

generating a look-up table (LUT) based on the recorded response signals, wherein the generated LUT includes:

- (i) mean values of the response signals for each of the plurality of photodetectors at each grid point of the plurality of grid points in the monolithic crystal;
- (ii) interpolated values of the mean value of the response signals providing interpolated values between grid points in the monolithic crystal; and
- (iii) extrapolated values of the mean value of the response signals for locations distal from the grid points in the monolithic crystal, wherein at least some of the locations of extrapolated values correspond to locations external of the monolithic crystal.

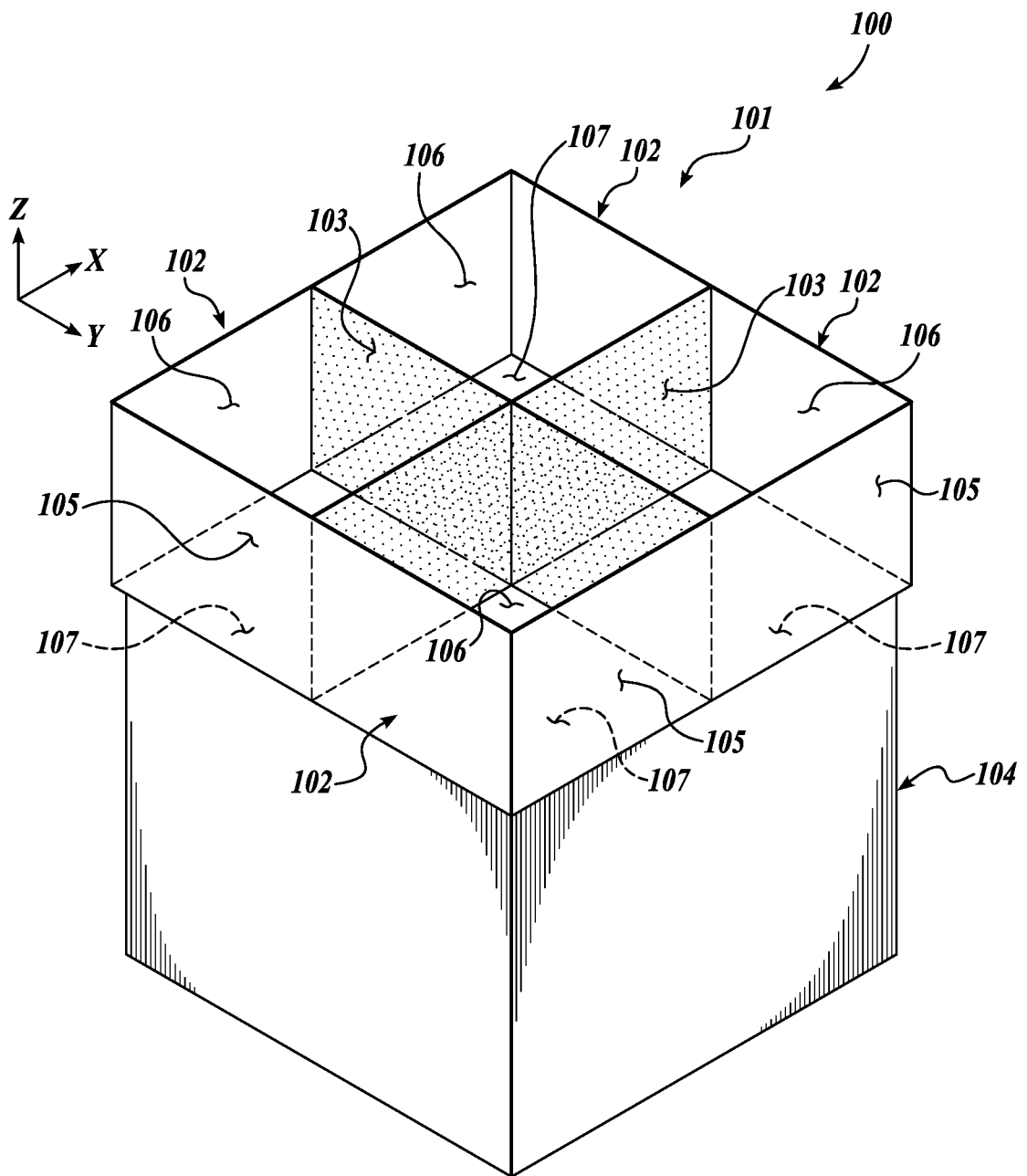
17. The method of Claim 16, wherein the at least one monolithic crystal comprises a plurality of monolithic crystals arranged in an array to define a semi-monolithic crystal assembly.

18. The method of Claim 16, wherein the plurality of photodetectors comprise a plurality of photomultiplier tubes.

19. The method of Claim 18, wherein the plurality of photomultiplier tubes comprise a multi-anode photomultiplier tube.

20. The method of Claim 16, further comprising determining a depth-of-interaction (DOI) value for the plurality of scintillation events in the crystal based on the scintillation light response signals, and separating the response signals into a number of DOI intervals, wherein the mean values, interpolated values, and extrapolated values are generated separately for each of the DOI intervals.

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**FIG. 1**

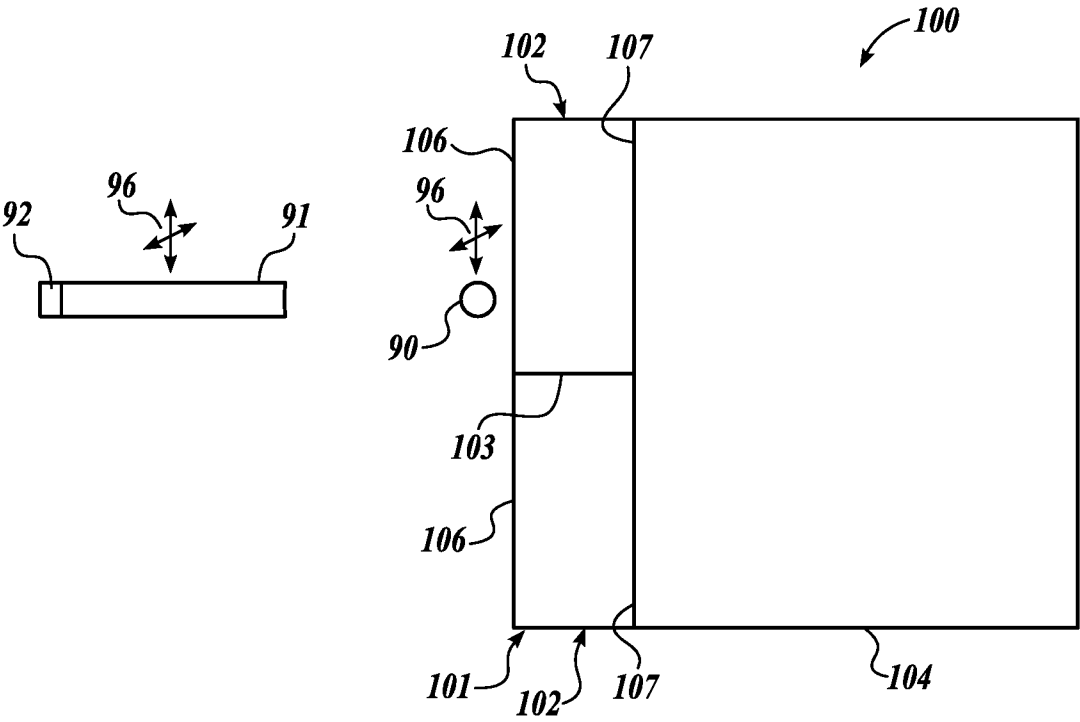


FIG. 2A

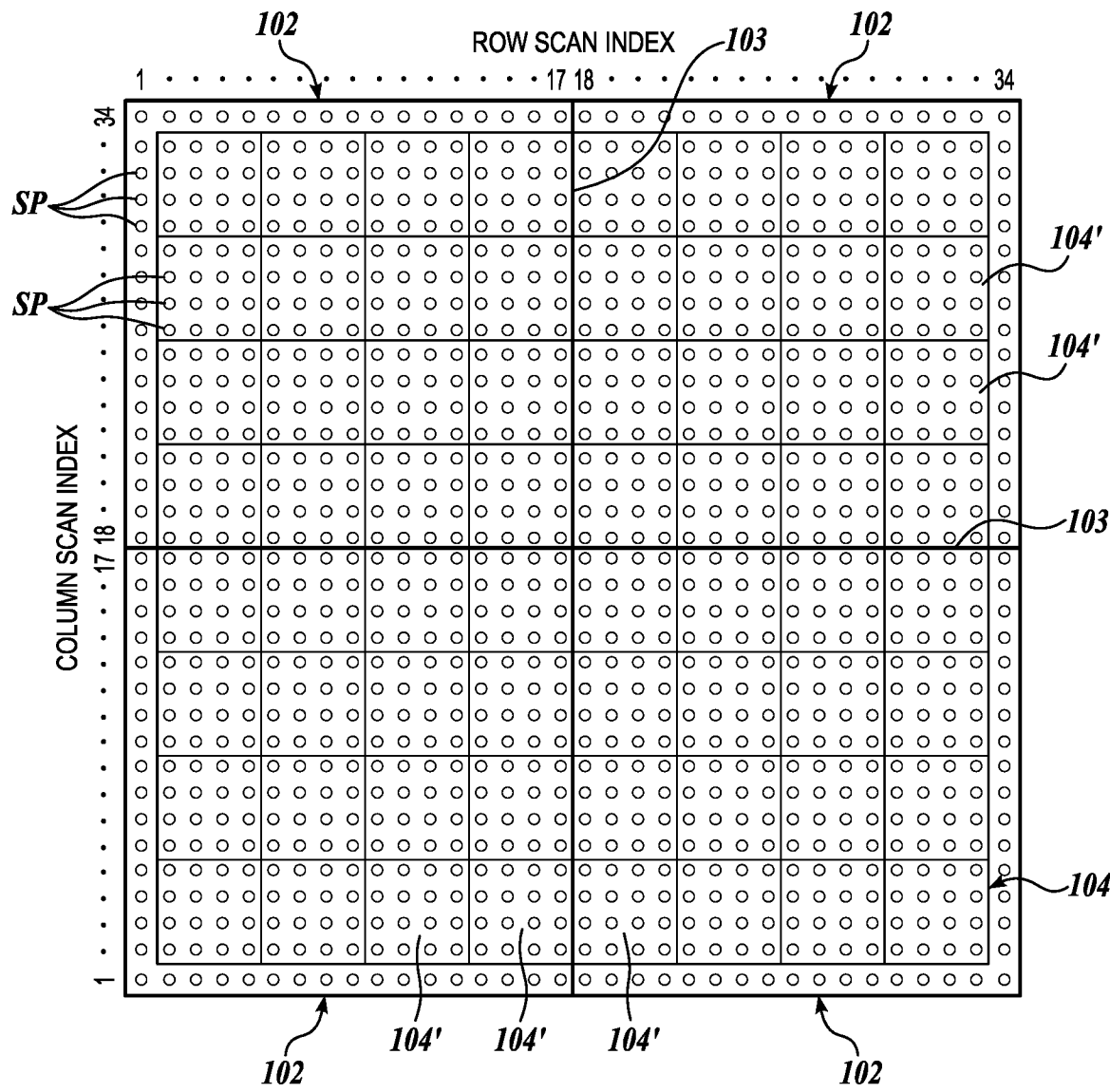


FIG. 2B

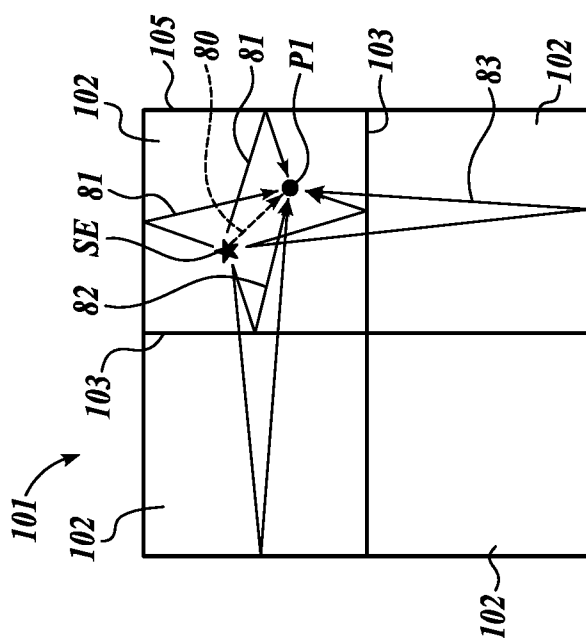


FIG. 3A

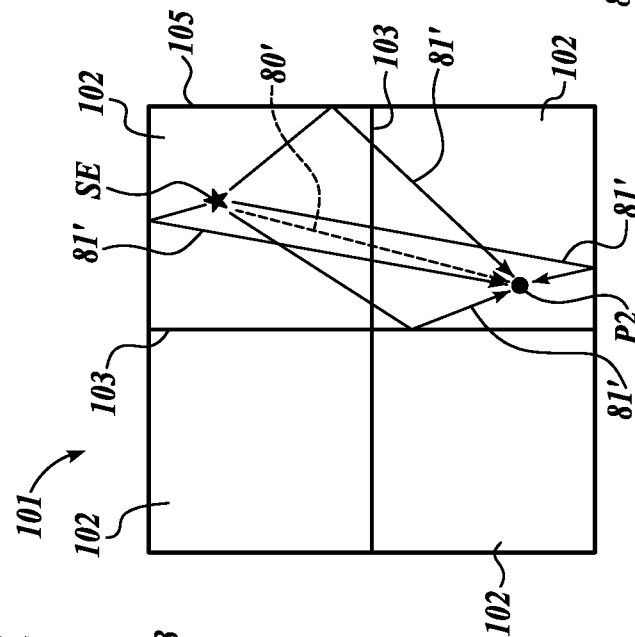


FIG. 3B

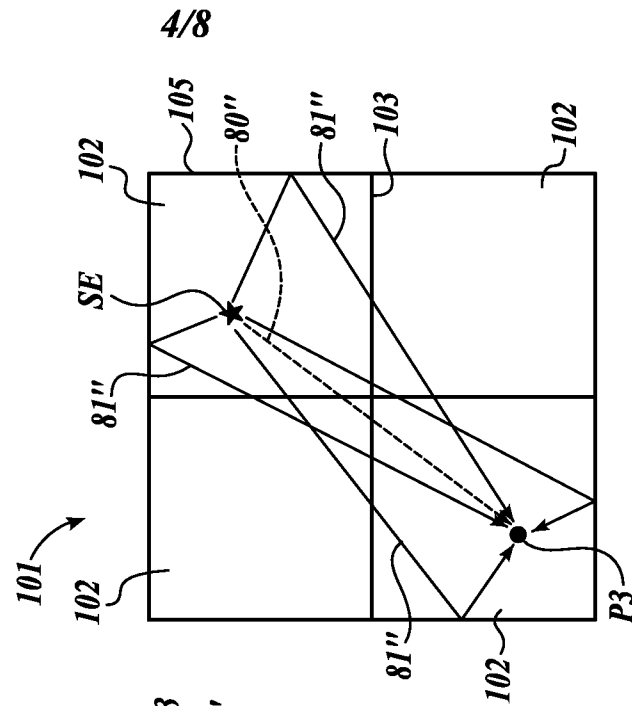


FIG. 3C

	Inner Interface		Centre		External part	
	μ	σ	μ	σ	μ	σ
Width (mm)	DOI 1	3.1	0.6	2.8	0.8	2.4
	DOI 2	6.5	0.5	6.6	0.6	6.1
	DOI 3	8.5	0.5	8.9	0.6	8.4
	DOI 4	11.0	0.7	11.2	0.7	10.7
Internal Reflectivity	DOI 1	0.25	0.04	0.15	0.04	0.30
	DOI 2	0.25	0.03	0.16	0.03	0.22
	DOI 3	0.27	0.03	0.16	0.03	0.19
	DOI 4	0.31	0.03	0.18	0.03	0.19
External Reflectivity	DOI 1	0.17	0.10	0.06	0.05	0.25
	DOI 2	0.14	0.11	0.06	0.04	0.27
	DOI 3	0.08	0.07	0.04	0.03	0.16
	DOI 4	0.04	0.03	0.02	0.01	0.07

FIG. 4

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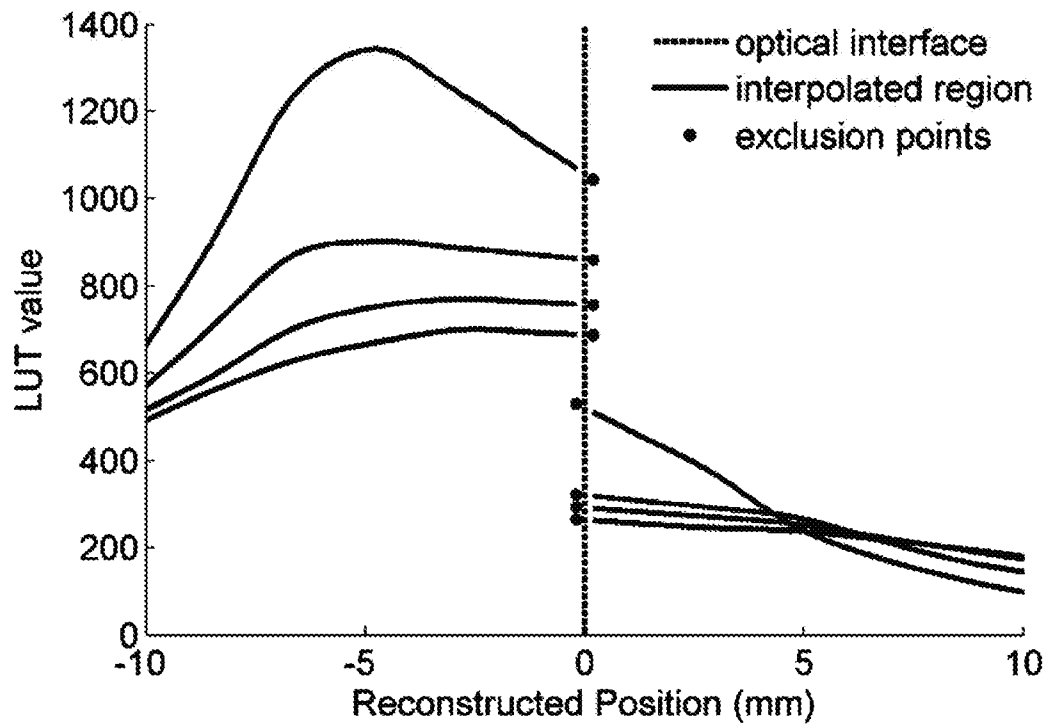


FIG. 5A

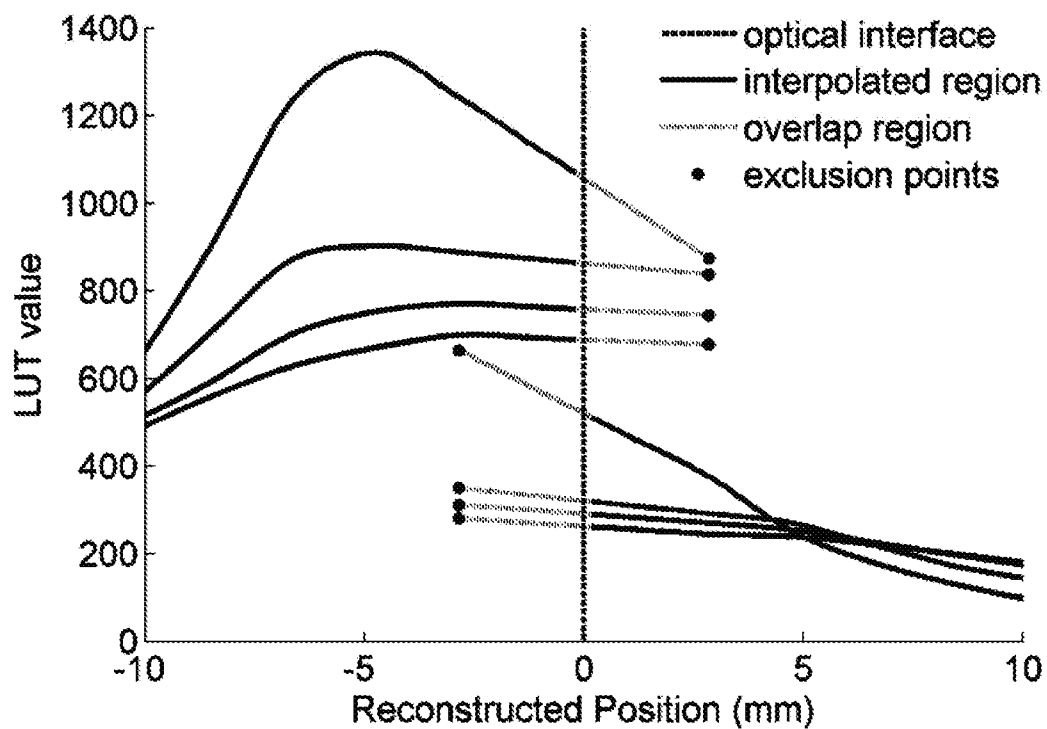


FIG. 5B

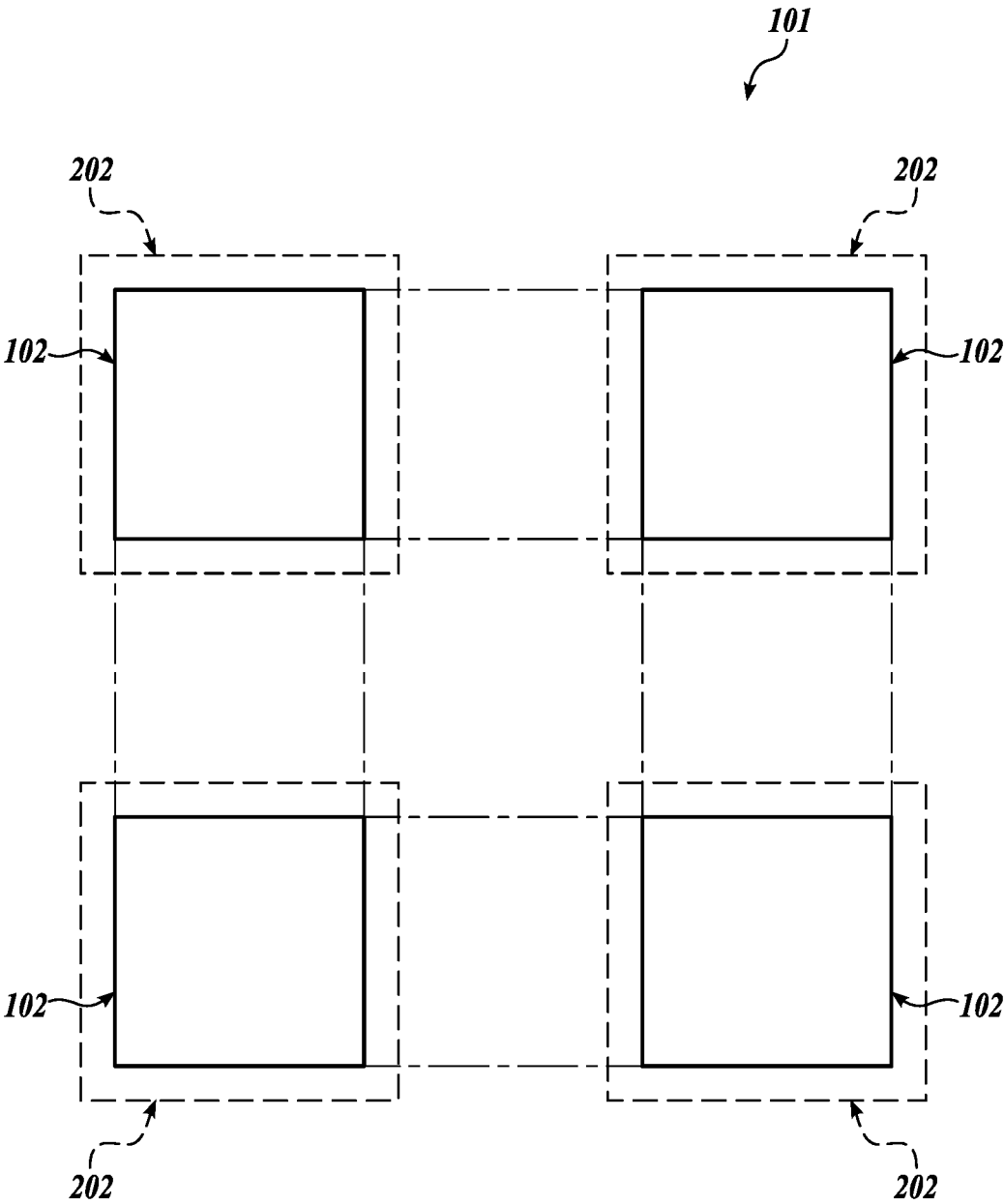


FIG. 6A

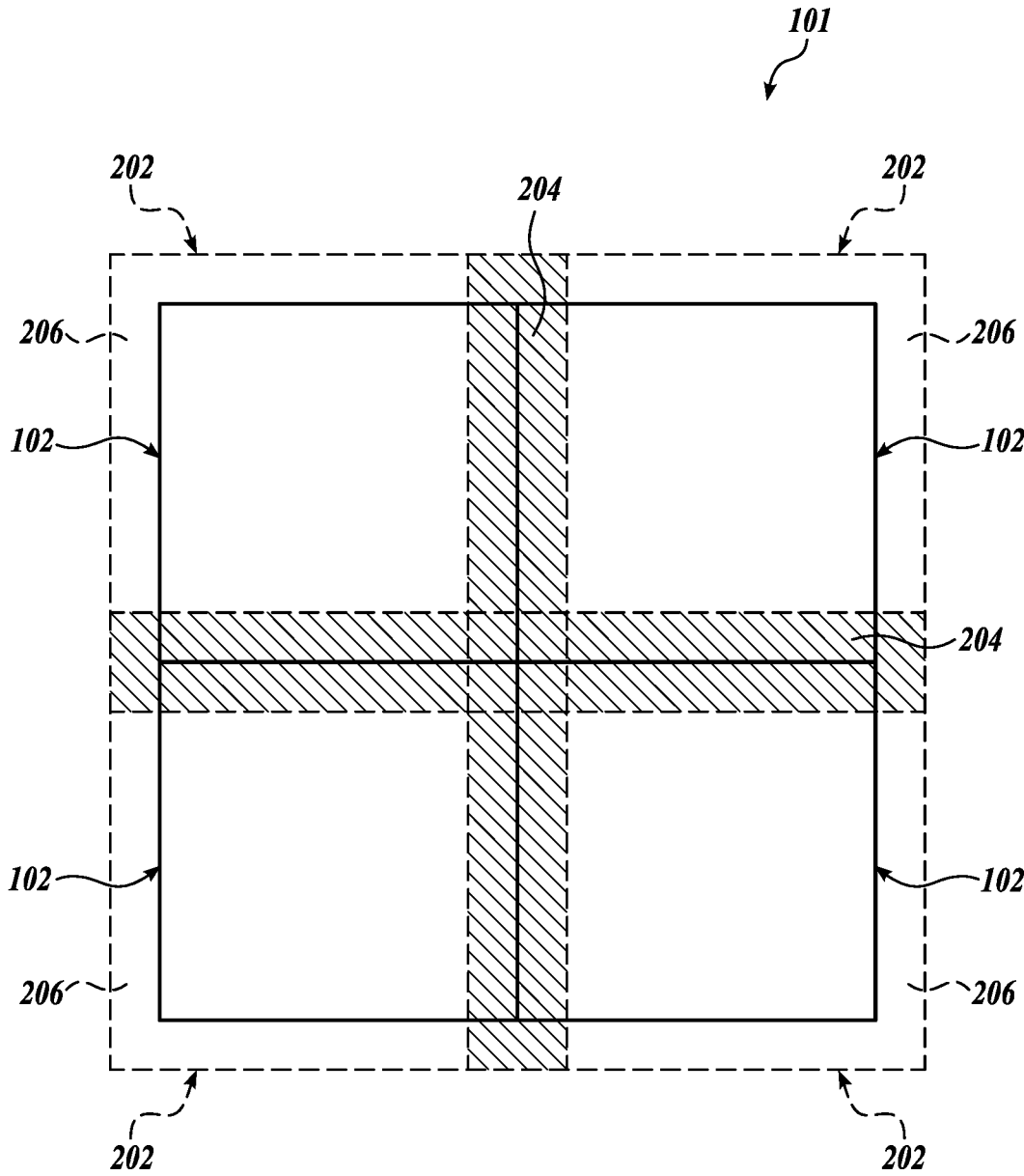


FIG. 6B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/036745

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - G01T 1/164; G01T 1/166; G01T 1/20; G01T 1/202; G01T 1/208; G01T 1/29; G01T 5/08 (2016.01)

CPC - G01T 1/1642; G01T 1/164; G01T 1/166; G01T 1/20; G01T 1/202; G01T 1/208 (2016.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC - G01T 1/164; G01T 1/166; G01T 1/20; G01T 1/202; G01T 1/208; G01T 1/29; G01T 5/00; G01T 5/08; G21K 7/00

CPC - A61B 6/037; A61B 6/4258; G01T 1/164; G01T 1/1642; G01T 1/166; G01T 1/20; G01T 1/202; G01T 1/208; G01T 1/249; G01T 1/29; G01T 5/00; G01T 5/08; G21K 7/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 250/362; 250/363.02; 250/363.03; 250/370.09; 250/370.11; 378/4 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Orbit, Google Patents, Google Scholar, ProQuest.

Search terms used: gamma, camera, imaging, lookup table, mean, crystal, monolithic, scintillation, interpolate, extrapolate, photodetector, face, array, position, location.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2014/0042326 A1 (UNIVERSITY OF WASHINGTON) 13 February 2014 (13.02.2014) entire document	1-20
Y	US 2005/0006589 A1 (JOUNG et al) 13 January 2005 (13.01.2005) entire document	1-20
Y	US 2004/0124360 A1 (LEVIN) 01 July 2004 (01.07.2004) entire document	7
Y	US 2013/0301806 A1 (LIANG et al) 14 November 2013 (14.11.2013) entire document	8, 9
A	US 2009/0050811 A1 (BARRETT et al) 26 February 2009 (26.02.2009) entire document	1-20
A	US 6,603,125 B1 (COOKE et al) 05 August 2003 (05.08.2003) entire document	1-20
A	WO 2014/180734 A2 (KONINKLIJKE PHILIPS N.V. et al) 13 November 2014 (13.11.2014) entire document	1-20
A	US 2013/0299707 A1 (THE BOARD OF TRUSTEES OF LELAND STANFORD JUNIOR UNIVERSITY) 14 November 2013 (14.11.2013) entire document	1-20
A	US 6,291,825 B1 (SCHARF et al) 18 September 2001 (18.09.2001) entire document	1-20

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

 Date of the actual completion of the international search
 15 August 2016

Date of mailing of the international search report

01 SEP 2016

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