Minimization of parallax error in positron emission tomography using depth of interaction capable detectors: methods and apparatus

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Abstract

In this paper, the authors review the field of parallax error (PE) minimization in positron emission tomography (PET) imaging systems by using depth of interaction (DOI) capable concepts. The review includes apparatus as well as an overview of various methods described in the literature. It also discusses potential advantages gained via these approaches, as discussed with reference to various metrics and tasks, particularly in the improvement of spatial resolution (SR) performance. Furthermore, the authors emphasize limitations encountered in the context of DOI decoding, which can be a considerable pitfall depending on the task of interest.

1. Introduction

1.1. PET system and its applications

A brief description of PET imaging technology, its applications and terminology used in this review is provided in this section.

The field of medical imaging has the power of bringing together many different areas of scientific knowledge: mathematics, physics, biochemistry, engineering and medical sciences. Nuclear medical imaging, in particular, has always emphasized the objective evaluation and optimization of image quality and quantitative assessment of physiological parameters obtained from the information of radionuclide images. In PET, after administration, the radioactive molecule undergoes decay and emits positrons through beta decay. After traveling a short distance (range), the emitted positron meets an electron in the surrounding tissue, annihilation occurs and two gamma photons are emitted in approximately opposite directions and with a well defined energy (511 keV), both of which are needed for image reconstruction. To correlate the path travelled by the back-to-back gamma photons and the annihilation origin, the first step is to detect these two gamma photons. The gamma rays are detected in coincidence by detectors that surround the field of view (FOV), in the form of complete or partial rings [1–4].

When two gamma detector cells in a ring are triggered within an electronic coincidence time window, the line between the two cells is assumed to be the trajectory of the two gamma photons, and is called line of response (LOR). All coincident events are collectively called prompts, which include true, random, scattered, and multi-coincidence events. A true coincident event arises when two 511 keV photons from a single annihilation event are detected within the set energy and time window, without undergoing any form of interaction prior to detection [5–8].

Selecting the true coincidence is important to improve image quality because the scattered and random events deteriorate image resolution and contrast. A high energy resolution of the detectors helps to distinguish and reject scattered events. Good time resolution allows a narrower coincidence time window, which can reduce random events [9].

The annihilation process takes place at some point along the LOR, which cannot be known from a single detected event. The repetition of this process for all detected events allows drawing many different LORs, whose superposition on an image will enhance regions with higher density of LORs, which will represent the most likely distribution of the radioactive material, where it accumulates, thus allowing a spatial representation of its location (figure 1).

The physics of the emission, and the detection of the coincident photons, give PET imaging unique...
capabilities for both very high sensitivity and accurate estimation of the in vivo concentration of radiotracers. PET is a functional imaging modality with many clinical as well as research applications. PET imaging has been widely adopted as an important clinical modality for oncological, cardiovascular, and neurological applications. In these areas, clinical PET imaging is playing an important role in the understanding of biochemical and physiological disease mechanisms. PET imaging is able to provide relevant information on tissue perfusion, drug target binding and in vivo distribution of radiotracer drugs in cells. PET imaging has also become an important tool in preclinical studies, particularly for investigating murine models of disease and other small-animal models [7, 10].

1.2. Spatial resolution of PET system

SR is an important metric for performance characterization in PET systems. SR determines the smallest structure that can be clearly visualized, therefore a scanner with the highest possible SR is desirable, in order to resolve the finest details in an object. The SR measures the ability of a PET scanner to faithfully reproduce the distribution of radioactivity in the object. It is determined by the variability in estimating the interaction point of the 511 keV photon in the scintillator and empirically defined as the minimum distance at which two point sources can be distinguished in an image [5, 11, 12]. As recommended by the NEMA (National Electrical Manufacturers Association) standards for both clinical and small animal preclinical PET systems, the standard way to characterize the image resolution of a PET system is through point source measurements at different locations. SR is measured by reconstructing point source scans using the filtered back-projection algorithm and calculating the full width at half maximum (FWHM) from the profiles along the radial and tangential directions [13, 14].

SR of PET is influenced by factors such as the positron range, non-collinearity of annihilation photons and crystal/detector size.

Positrons are emitted with a continuous range of energies up to a maximum and they travel a certain distance in tissue, losing most of their energy by interactions with atomic electrons. An emitted positron follows a tortuous path until it annihilates with an electron when its energy becomes close to zero. Thus, the site of positron emission differs from the site of annihilation. Since coincidence detection is related to the location of annihilation and not to the location of positron emission, there is an uncertainty in the localization of the true position of positron emission, resulting in the degradation of SR. This contribution to the overall SR is determined from the FWHM of the positron count distribution, whose mean value is \( \approx 0.6 \) mm for \(^{18}\text{F}\) in water [15, 16]. Experimental data indicates that positron range in different tissue-equivalent materials has a strong effect on SR [17]. The positron range of some standard and non-standard PET radionuclides has been characterized through imaging of small-animal quality control phantoms on a benchmark preclinical PET scanner, showing that the degradation of small animal PET resolution and quantitative accuracy correlates with increasing positron energy [18].

Another factor of concern is the non-collinearity that arises from the deviation of the two annihilation photons from the exact 180° alignment [19]. Some residual momentum of the positron before annihilation leads to the emission of two annihilation photons in directions that are not exactly 180° from each other. However, the reconstruction algorithm will always assume the two photons to be collinear, which results in a slightly misplaced LOR (mean angle deviation of \( \approx 1/137 \) radians), causing a Gaussian blur in the image. The contribution from non-collinearity worsens with the increase of PET detector ring diameter (D), being given by 0.0022D (in mm) [15, 20]. Therefore, Gaussian blurring caused by non-collinearity
amounts to \( \approx 1.8 - 2 \text{ mm} \) for currently available 80–90 cm clinical PET scanners and is much less pronounced in smaller preclinical PET scanners (\( \approx 0.26 \text{ mm} \) for a 12 cm diameter system).

The physical size of the detector element usually plays an important role in determining resolution. One factor that greatly affects the SR is the intrinsic resolution given by the scintillation detectors used in PET scanners. For multi-pixel detector scanners, the intrinsic resolution can be given by \( d/2 \) at the centre of the FOV and by \( d \) at the detector face, where \( d \) is the detector front face width. Thus, it is highest at the centre of the FOV and deteriorates toward the edges. For monolithic detector scanners, the intrinsic resolution doesn’t depend on the detector size but on the number of photons detected, being given by the photopeak. The basic measurement in PET is the number of coincident events (LORs) recorded by a detector pair. Due to geometric effects, the sampling in the scanner FOV is not uniform. Some pixels have a large number of LORs going through them while others, particularly the ones outer from the centre of the FOV, are intersected by only a few possible lines of response. The fact that these LORs are spaced uniformly (separated by the crystal width \( d \)) creates a degradation factor that has been empirically observed to multiply all other contributions by a factor of 1.25 [21, 22].

Current trends in PET technology are to reduce the cost of the system and improve the SR. These objectives can be achieved by reducing the diameter of the ring and using detector crystals with small cross-sectional areas, long height and/or high atomic number to increase the sensitivity enhancing the detection efficiency of gamma rays produced after positron annihilation.

2. Depth of interaction and parallax error

The SR of PET systems is often degraded due to the lack of information about the DOI inside the crystal of the incoming gamma-photons, especially for smaller diameter rings. The DOI is the point in the detector crystal where the photon interacted. Depending on source position and geometry, when a photon reaches a detector element, it may deposit its energy at an unknown location in depth within that element or may exit to deposit energy in an adjacent element (figure 2). Conventional commercial PET scanners (which do not estimate the DOI) employ versions of Anger logic to position events [23]. In Anger logic, 2D positions of the interactions are obtained by calculating the energy-weighted centroid of the signals measured, while the DOI is assigned a constant value for all events based on the attenuation coefficient of the detector crystal, or simply defined as the centre position on the face of the interacted crystals. When drawing a LOR without DOI information, interactions occur only at the centre of FOV all emitted photons will enter the detectors perpendicularly to the detector face. However, when the source location has a radial offset from the centre, the detectors become angled with respect to the LOR and the annihilation photons may penetrate through the first detector they encounter and be detected in an adjacent detector as shown in figure 3(a). As a consequence, the resolution in the radial direction degrades toward the peripheral FOV. This effect, commonly referred to as PE (also known as radial astigmatism or radial elongation), arises from the lack of detailed information regarding the location of the annihilation photon interaction along the scintillator crystals and causes the radial elongation artifact that has long been recognized as an obstacle to high resolution PET.

In ring geometry PET systems, for a source at the centre of the FOV all emitted photons will enter the detectors perpendicularly to the detector face. However, when the source location has a radial offset from the centre, the detectors become angled with respect to the LOR and the annihilation photons may penetrate through the first detector they encounter and be detected in an adjacent detector as shown in figure 3(a). As a consequence, the resolution in the radial direction degrades toward the peripheral FOV. This effect, commonly referred to as PE (also known as radial astigmatism or radial elongation), arises from the lack of detailed information regarding the location of the annihilation photon interaction along the scintillator crystals and causes the radial elongation artifact that has long been recognized as an obstacle to high resolution PET.

Also, in ring geometry PET systems, in 2D cross-plane mode or fully 3D data acquisition mode (the most common detector configuration of a PET system), the PE limits the system volumetric SR even in the central region of FOV, for increasing acceptance.

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Figure 2. Sketch representing the PE resulting from an oblique LOR without DOI information. The dashed line represents the assumed LOR (which is the same for all coincidence events between those 2 detector pixels) while the solid line represents the true LOR (which can be drawn with DOI information from that specific event).
angles (long axial FOV) (figure 3(b)). PE effects occur because, for all source locations (even at the centre of the FOV), annihilation photons enter the detectors with a range of angles with respect to the detector face. These effects become increasingly problematic as the ring diameter is decreased or the axial length of the scanner is extended, although the sensitivity is increased in both cases.

Similarly to ring geometry PET systems in fully 3D data acquisition, polygonal geometry PET scanners (or flat head scanners) also suffer from detector PE effects, although the resolution degradation is spread fairly uniformly across the entire FOV rather than increasing towards the periphery (figure 3(c)).

There are two consequences of this effect. The coincidence response function becomes broader (because the detectors are at an angle and present a larger area for a LOR) and the event is also mispositioned towards the centre of the scanner with respect to the line joining the two detectors of interaction. The amount of broadening depends on the width and thickness of the scintillator elements, the absorption characteristics of the scintillator material and the separation of the detectors. It results in a deterioration in the radial component of the SR of PET images in the periphery of the FOV and also in a deterioration in the axial component of the SR in the centre of the FOV of 2D cross-plane, fully 3D and polygonal geometry PET systems. This effect could be reduced if the depth of the interaction in the detector could be measured, which would allow a correct placement of the event and consequently, to have PET reconstructed images with uniform SR in all directions without degradation due to PE.

A key component of a PET system is the detection of the coincident gamma rays associated with positron decay [25]. Depth-encoding detectors have the potential to allow a PET scanner to be built with a smaller ring diameter and/or using longer crystals while maintaining a good SR. Smaller ring diameter means higher sensitivity, lower cost and a smaller photon non-collinearity effect. Longer crystals mean higher sensitivity [26].

Time of flight (TOF) PET is a technique that reduces the positioning uncertainty of the emission point of gamma photons during PET data collection [27]. DOI may also assist in the quest for better timing resolution. In long narrow crystals, the ultimate timing resolution is limited by the light path lengths in the crystal (most light photons will undergo many reflections in the crystal before escaping to be detected by a photosensor). The number of such reflections is somewhat dependent on where in the crystal the gamma ray interacts. Thus, a correction can be made for timing skewing depending on the point of interaction in the crystal, allowing improved timing resolution. Therefore, the measured DOI can be used to correct the flight time of the gamma ray for each event, consequently improving image quality in TOF PET systems [25, 28].

Furthermore, there is a renewed interest in developing clinical PET scanners that have a large FOV in the axial direction, potentially to the extent that the entire body is covered. To fully exploit the sensitivity gains of extended axial length, and greater solid angle coverage, the axial acceptance angle will be large and cause a PE in the axial direction (a fully-3D 2 m long scanner with a diameter of 85 cm will have an axial acceptance angle of ±67°). This PE will be most pronounced in the centre of the axial and transverse imaging FOV, and in addition to an inherent radial PE associated with the ring geometry, it has been suggested that PET scanner designs with long-axial FOVs may have worse SR compared to more traditional scanner designs having a shorter axial FOV [29–31].

3. Flood histogram and segmentation

When an incident annihilation photon is absorbed by a scintillator a proportional number of optical photons is routed towards the readers. In Anger logic, the position of the interaction is obtained by using a centre of mass approach [23]. When a detector is uniformly irradiated, calculated positions can then be binned into a 2D histogram known as a flood histogram (FH). The FH represents the distribution of the counts in the crystals. A crystal position map (CPM), should be pre-generated from the detector’s FH. Each of the zones in the segmented FH represents a crystal number and any event falling within a zone in the segmented FH is assigned to its specific location. The DOI information
can then be obtained by segmenting the CPM accordingly. The distortions in the FH are the result of large variations between crystal efficiencies, complex product of readout electronics, capacitance of the photodetector, how the optical light is transmitted within the crystal array, and the centre of mass positioning detector, how the optical light is transmitted within the crystal array, and the centre of mass positioning equations.

The accuracy of FH is crucial to the detector’s intrinsic SR. Several approaches have been proposed to perform an appropriate segmentation of the FH.

A statistical model based on likelihood boundaries of Gaussian mixture models is applied for segmentation of FH produced from a multilayer DOI capable detector. The distribution of events in the FH originating from one crystal is represented by a Gaussian allowing the complete FH of k crystal responses to be represented by a Gaussian mixture model with k mixture components. This algorithm is based on maximum likelihood iterations to converge to an optimum fitting of the Gaussian parameters. These parameters are usually the vector means as well as the covariance matrices for each distribution [32, 33]. To reduce the large amount of prior knowledge required from the user that is typical of Gaussian mixture model, this algorithm is paired with thin plate splines that allows an iterative updating of the estimates of the individual crystal centre starting conditions [34].

Neural network based approaches are a kind of machine learning algorithm that learns the distribution characteristics from all the samples of the training data. These approaches involve collections of nodes (crystals) and the corresponding connections between them allowing passage of information from node to node. In the Siemens Inveon PET scanner (with an array of 64 20 × 20 segmented LSO detectors in a tomographic arrangement to allow small animal PET imaging), an unsupervised self-organizing feature map has been trained by the incoming events to construct a CPM [35]. Another work uses a learning system based on k-nearest neighbour statistical method to estimate the entry points of gamma photons in a monolithic scintillator crystal from the measured distribution of the scintillation light over an avalanche photodiode (APD) array [36]. By dividing the whole volume of a monolithic crystal block into a number of small cuboids, DOI neural networks have been developed and trained with training data obtained from one of the side surfaces, and by combining DOI network estimating and plane positioning, the precise estimation of 3D position of interaction in the crystal was obtained [37, 38]. A combination of two machine-learning methods, a finite mixture model and a non-linear dimensionality reduction (depth embedding), have been used to estimate DOI in gamma cameras from simple pencil-beam measurements [39].

A crystal identification method using non-rigid registration to a Fourier-based template is proposed. In this method, intensities across the FH are corrected for uniformity, then a discrete Fourier transform is used to filter the FH and create a template which corresponds to the crystal arrangements of the physical array and is also a lower order spatial approximation of the FH. This template is created such that it lends itself easily to proper segmentation/crystal identification. Lastly the template is deformed to match the FH using an intensity based warping scheme with polynomial bases such that an error function is minimized [40, 41].

Moreover, a principal component analysis based algorithm [42] and a probabilistic graphical model based algorithm [43] were also proposed to build CPMs.

In the neighbourhood standard deviation (NSD) based algorithm, the NSD of each pixel is first calculated from neighbourhood pixels weighted by the event counts. NSD maps have strips whose peaks highly correspond to the valley of the FH. The peaks were identified by fitting the NSD profiles to Gaussian mixture functions using nonlinear least-square method. Using the peaks, the CPM was generated by a scan line algorithm [44].

Figure 4. Various DOI detector schemes: (a) Standard detector (non-DOI) (b) Phoswich detector (c) Offset structure (d) Mixed shapes (e) Multiple crystal-photodetector layers (f) Monolithic crystal block (g) Laser engraving (h) Dual ended readout and (i) AX-PET. Different incident annihilation photons (whose scintillation light is shown in blue and green) interact in the two different parts of the detector producing a proportional number of optical photons that are routed towards the readers. The DOI information can then be obtained by appropriate PSD or FH segmentation method.
Table 1. General summary of main types of DOI encoding technologies, with information on detectors used, their spatial and DOI resolution performance and scanners employing them.

| Sub-type | Crystal material | Element size (mm) | Total crystal number | Photo-detectors (PD) | FOV Ø × axial length (cm) | DOI info discrete/continuous | DOI res. (mm FWHM) | Transaxial SR | Axial SR | Used by scanner(s) | Year | References |
|----------|------------------|-------------------|----------------------|----------------------|---------------------------|-----------------------------|---------------------|--------------|----------|---------------------|------|------------|
| Phoswich | LYSO + GSO       | 1.45 × 1.45 × 7+8 | 12168                | PMT                  | 6.7 × 4.8                 | discrete                    | 7-8                 | 1.4 in centre | 1.8 at 2.5 cm | GE eXplore VISTA, Sedecal Argus (preclinical) | 2006 | [46]       |
|          | LYSO + LGSO      | 2 × 2 × 12/14     | 3072                 | APD                  | 10 × 7.5                  | discrete                    | —                   | 1.8 in centre | 2.3 at 2.5 cm | GE Triumph (LabPET-8) (preclinical) | 2008 | [47]       |
|          | LSO/LSO/GSO      | 2.1 × 2.1 × 7.5+7.5 | 119808              | PMT                  | 20 × 25.2                 | discrete                    | 7.5                 | 2.4 in centre | 2.8 at 10 cm | Siemens ECAT HRRT (brain) | 2001 | [48]       |
|          | LYSO + LuYAP     | 2 × 2 × 10+10     | 5120                 | PMT                  | 12–23.5 × 11              | discrete                    | 10                  | 1.25 in centre | 1.75 at 2.5 cm | Raytest ClearPET (preclinical) | 2006 | [49]       |
|          | LYSO + GSO       | 2 × 2 × 7+8       | 1458                 | PMT                  | 6 × 2                     | discrete                    | 7-8                 | 1.8 in centre | 2.5 at 3 cm  | ATLAS (preclinical) | 2002 | [50]       |
| Offset structure | LYSO (2 layer)       | 1.28 × 2.68 × 7   | 41088                | PMT                  | 10.2 × 15.1               | discrete                    | 7                   | 2.3 in centre | 3.2 at 2.5 cm | ClaarivoPET (preclinical) | 2016 | [51]       |
|          | LSO (4 layer)     | 2.9 × 2.9 × 7.5   | 122880               | PMT                  | 26 × 26                   | discrete                    | —                   | 3.2 in centre | 3.25 at 2.5 cm | JPET-D4 (brain) | 2009 | [52]       |
|          | Zr-doped GSO     | 2.8 × 2.8 × 7.5   | 163840               | PS-PMT               | 66 × 21.5                 | discrete                    | —                   | —            | —       | Whole-body DOI-PET (prototype) | 2019 | [53]       |
| Mixed shapes | LYSO             | 3 × 3 × 10        | —                    | PMT                  | —                         | discrete                    | 10                  | —            | —       | (not implemented) | 2008 | [54]       |
|          | LYSO             | 3 × 3 × 10+10     | 16                   | SiPM                 | —                         | discrete                    | 10                  | —            | —       | TOF/DOI-PET module (not implemented) | 2016 | [27]       |
|          | LYSO (single layer) | 1.47 × 1.47 × 15 | 3888                 | dSiPM                | 10 × 2.83                 | contin.                     | 4.25                | 1 in centre  | 1.2 at 2.5 cm | (not implemented) | 2017 | [55]       |
| Multiple crystal-PD layers | LYSO (4 layer)       | 9.5 × 9.5 × 2+/2.5+3.1+4.3 | 4                  | APD                  | —                         | discrete                    | —                   | <2          | —       | (not implemented) | 2005 | [56]       |
|          | LSO              | 4 × 4 × 5(×3)     | 12                   | SiPM                 | 4 × 4                     | discrete                    | 5                   | 0.4 (intrinsic) | centre     | (not implemented) | 2006 | [57]       |
|          | LYSO             | 0.91 × 0.91 × 1   | 4608                 | APD                  | 9 × 16                    | discrete                    | 1                   | 1            | 1       | (not implemented) | 2010 | [58]       |
| Monolithic | LYSO             | 25.4 × 25.4 × 8   | 45                   | SiPM                 | 7.2 × 13                  | discrete                    | 1.6                 | 1.1 in centre | 0.97 at 3.25 cm | Molecules beta-cube (preclinical) | 2018 | [59]       |
|          | LYSO             | 50 × 50 × 10      | 24                   | PMT                  | 8 × 14.8                  | contin.                     | 4                   | 1.5 in centre | 2.5 at 2.5 cm | Albira Trimodal scanner (preclinical) | 2014 | [60]       |
| Laser-engraving | LYSO (2 layer)       | 2 × 2 (and 3 × 3) | 2                    | PMT (SiPM)            | —                         | contin.                     | 3–5                 | —            | —       | (not implemented) | 2016 | [61]       |
|          | LYSO             | 0.99 × 0.99 × 0.99 | 4096                | SiPM                 | —                         | contin.                     | 1                   | 1            | 1       | (not implemented) | 2011 | [62]       |
| Dual readout | LSO              | 0.922 × 0.922 × 20 | 392                  | APD                  | 4 × 0.7                   | contin.                     | 2                   | —            | —       | (not implemented) | 2008 | [63]       |
|          | LYSO             | 1 × 1 × 10        | 144                  | SiPM                 | —                         | contin.                     | 1.5                 | —            | —       | (not implemented) | 2010 | [64]       |
Stratified peak tracking method was developed to generate the CPMs in dual-layer-offset DOI-PET detectors. First, the square image of the FH is generated. This squared image is decomposed using a singular value decomposition algorithm, and then a principal component image of the top layer is generated using the largest eigenvalue. Then, by subtracting the image related to top layer from the original image, a new image is obtained, which mainly includes the responses of the bottom layer. Due to the half crystal offset design, the crystal responses in the top and bottom layers are in a staggered arrangement. To generate the CPM, distances from each pixel in the FH to the peaks are calculated. Each pixel is assigned to a unique crystal with the minimum distance value [45].

The performance of these methods depends on their accuracy, level of automaticity (automatic, semi-automatic or manual), the time required for implementation and their practicability for large dimension position histograms.

4. Apparatus and methods for DOI encoding

Various DOI encoding apparatus and methods have been studied including multi-layer crystals (phoswich, offset structure, mixed shapes), multiple crystal-photodetector layers, monolithic crystal blocks, laser engraving, dual ended readout and AX-PET (figure 4). A previous review of PET detectors with DOI capability has been published in 2011 [9]. In this work, we provide an updated and complete review focused on the apparatus and methods for DOI encoding, highlighting the details and advantages of different approaches. Table 1 summarizes the main types of DOI encoding technologies, including specifications of different systems employing them.

4.1. Multi-layer crystals

Gamma detectors in this category consist of multiple layers of scintillation crystal arrays read out by the same photodetector. Several configurations of multi-layer crystals have been implemented for acquiring DOI information.

4.1.1. Phoswich

One of the widely used configurations is ‘phoswich’, a combination of ‘phosphor’ and ‘sandwich’. In this design the scintillation element is composed of two or more different materials with measurable differences in their scintillation decay times (figures 4(b) and 5). Table 2 shows the properties of scintillator materials that have been used in phoswich configurations.

The emission of optical light from a scintillation crystal has a fast exponential rise followed by a slower exponential decay. The time constants of these two parameters depend on the materials and doping concentrations of activator within the crystal. The layer of interaction is then determined from pulse shape discrimination (PSD) in the readout electronics, determining the decay time of the scintillation light [69, 70].

Various methods were proposed to quantify the differences in pulse shape, as follows: constant fraction discrimination, rise time discrimination, constant time discrimination, charge comparison and delayed charge integration methods.

In constant fraction discrimination (figure 6(a)), DOI is related to the cross-over time between the time zero and the time at a fixed fraction of the maximum pulse amplitude [71].

In rise time discrimination (figure 6(b)), DOI is related to the rise time, defined as the time difference between when the pulse crosses a lower fraction and an upper fraction of the maximum pulse amplitude [72].

For the constant time discrimination method (figure 6(c)), DOI relates to the amplitude of the normalized pulse at a fixed delay time after time zero [73].

In charge comparison method (figure 6(d)), DOI is related to the sum of the amplitudes in a time window from time zero normalized by the maximum pulse amplitude [69].

Finally, in delayed charge integration method (figure 6(e)), DOI relates to the ratio of the integrated signal in a fixed time window with and without a time delay [74].

The performance of different PSD methods depends on the radiation detector and signal-to-noise ratio [73, 75].

In the phoswich PET detector configuration, measured peak-to-valley ratios in the FH have also been used to discriminate the interaction position [76].

PET scanners utilizing phoswich type of DOI detector have been commercialized. For example, a dedicated human brain PET system created by Siemens/CTI High Resolution Tomograph (HRRT) that used a dual layer design with either an LSO/LSO or LSO/GSO phoswich [48], the GE eXplore VISTA dual-ring small-animal PET scanner [46] assembled from phoswich detectors made of a top and bottom layer of cerium doped LYSO and GSO with dimensions $1.45 \times 1.45 \times 7$ and $1.45 \times 1.45 \times 8$ mm$^3$ respectively. NIH ATLAS small animal PET scanner had 18 phoswich detector modules, comprised of a $9 \times 9$ array of $2 \times 2 \times 7$ mm$^3$ LYSO crystal optically glued end-on to $2 \times 2 \times 8$ mm$^3$ GSO crystal, arranged around a ring 11.8 cm in diameter [50]. Also, Raytest ClearPET scanner had 80 two-layer phoswich detectors consisting of $8 \times 8$ LYSO and $8 \times 8$ LuYAP arrays with crystal element sizes of $2 \times 2 \times 10$ mm$^3$ [49]. The GE trividmodality PET/SPECT/CT small animal scanner (10 cm ring diameter and 7.5 cm axial FOV) employs $2.0 \times 2.0 \times 14$ mm$^3$ phoswich pair of LYSO and LGSO to permit DOI measurement [47].

Recently a simulation study based on phoswich arrangement of three scintillator layers (LYSO/GSO/BGO) with a fixed length of 15 mm showed that two
designs of these phoswich detectors (4 mm LYSO—4 mm GSO—7 mm BGO and 5 mm LYSO—5 mm GSO) provide the best DOI results and can potentially be used in a small animal PET scanner to simultaneously achieve high sensitivity and superior uniform radial and tangential SR [77].

Problems with phoswich designs arise from the differences between scintillation materials which can affect timing or energy resolution, if one of the materials has a much slower decay time or light output than the other. However, with new doping techniques it is possible to get two materials with very similar properties and fast decay times that vary by only 20–30 ns. Moreover, the DOI resolution of a Phoswich detector is limited by the number of layers and the thickness of the scintillator in each layer, and thus it only provides discrete and relatively coarse DOI information. To date, commercial implementations have used only 2 layers [46, 48–50], thus DOI information is confined to a binary assignment of events to one of the two layers.

Table 2. Properties of scintillator materials that have been used in phoswich configurations.

| Scintillator | BGO | LSO | GSO | LYSO | LGSO | LuYAP |
|--------------|-----|-----|-----|------|------|-------|
| Effective atomic number (Z) | 74 | 66 | 59 | 65 | 59 | 60 |
| Density (g/cm³) | 7.13 | 7.40 | 6.71 | 7.2 | 6.5 | 7.2 |
| Scintillation decay time (ns) | 300 | 40 | 50 | 65 | 31 | 29 |
| Peak of fluorescence spectra (nm) | 480 | 420 | 430 | 380 | 415 | 385 |
| Photon yield (photons/keV) | 7 | 29 | 10 | 25 | 23 | 10 |
| Attenuation coefficient (cm⁻¹) | 0.96 | 0.87 | 0.67 | 0.87 | 0.70 | 0.77 |
| Energy Resolution (% at 511 keV) | 10 | 10.1 | 9.5 | 20 | 12.4 | 12 |

from [63–68].
4.1.2. Offset structure
A dual-layer structure wherein the top crystal layer is offset by half a crystal pitch with respect to the bottom layer has been proposed [78]. In this design, two layers of the same crystal are involved and are read out in only one end by photodetectors. As the interactions of annihilation photons in the top and bottom layers result in different light output profiles, their positions can be extracted [45].

The feasibility of combining the relative offset and the PSD methods for three or four-layer DOI detectors has been demonstrated [79]. An eight-layer DOI detector was also devised by combining PSD with a 4-layer encoding method based on a smart reflector arrangement, the jPET method [80].

A stair-shaped reflector arrangement with a relative offset of one crystal pitch in both x and y directions between the upper and lower segments was presented [81]. Furthermore, a four-layer DOI detector array of $8 \times 8$ scintillation crystals with reflectors between elements is shown in figure 7(a), with reflector arrangement visible in figure 7(b). The reflector arrangement for each layer is intended to project the 3D interaction position of a gamma ray within each crystal onto a FH. The reflector arrangement in the fourth layer with a shift of one crystal element pitch in both x and y directions. The arrangements in the second, third, and fourth layers are the ones with a shift of one crystal element pitch in an x direction, in a y direction, and in both, respectively. The FH when each array is coupled to position-sensitive photomultipliers (PS-MPTs) independently and uniformly irradiated by gamma rays is shown in figure 7(c) [82–84].

Because assembling crystals of a tiny size tends to be very costly, and fine tuning of the front-end circuit is required to have fine crystal identification, a more practical four-layered DOI detector has been proposed recently. Here, the key concept is that the detection efficiency of each crystal element largely depends on the DOI layer and the top layer has the highest detection efficiency. The first layer used scintillator crystals of quarter size compared to crystals of the other layers. Positioning performance on the FH depends on the crystal dimensions, the crystal surface finish, and gap materials between the crystals [85]. At the edge of the crystal, the crystal identification performance degraded and reflected scintillation photons cause mispositioning of interaction points at the edge of the small crystals of the first layer.

The Shimadzu Clairvivo small animal PET employs the crystal offset method in the axial direction [51, 86, 87]. This design was applied to three and four-layer structures in combination with the PSD approach [79] and by relative shifting of all four layers by half a crystal pitch [87, 88]. A similar light spreading method, in which the centroid of light spreading is shifted in the same way without offsetting a crystal layer has also been applied to the development of a brain-dedicated PET (jPET-D4 [85] and jPET-RD [89]).

Very recently a whole-body prototype PET scanner (66 cm ring diameter and 21.5 cm axial FOV) with 163840 Zr-doped GSO scintillators ($2.8 \times 2.8 \times 7.5$ mm$^3$) in 160 ($16 \times 16$ in 4 layers offset structure) detector blocks has been developed. For the NEMA NU 4 image quality phantom, acquired list-mode data were reconstructed using ordered subsets expectation maximization algorithm employing ten iterations and eight subsets and results showed that the image with four-layer DOI could visualize the 2 mm-diameter hot cylinder while it could not be recognized in the image without DOI information [53].

4.1.3. Mixed shapes
Another design consists of multiple crystal layers built from crystals of different shapes. Here the amount of light shared is related to the DOI.

A detector unit consisting of two optically coupled crystals was proposed in which the interface between crystals was designed so that a significant amount of
light is shared when a photon interacts near the front face of a crystal and very little light is shared when an interaction occurs near the back of a crystal \[^{90}\]. In this case, there was an increase of position uncertainty in the centre section of the detector units.

Other different reflector arrangements were proposed. In one design with two crystal layers, represented in figure 8, the bottom layer of the crystal array is made of rectangular prisms and designed to couple one-to-one to a silicon photomultiplier (commonly known as SiPM) array. This design was described for a TOF/DI PET module using multiplexing and a binary position sensitive network \[^{27}\], allowing the acquisition of PET data from many photodetectors using fewer readout channels.

The top layer of the crystal array consists of triangular prisms that are optically coupled to the lower layer of crystals. Due to the geometric differences between the two layers, each crystal in the two layers will have a unique distribution of light projected onto the SiPM array. Light from bottom layer scintillation events will primarily be sensed by the SiPM directly beneath the crystal, while light from top layer scintillation events will primarily be shared between the two SiPMs beneath it \[^{27, 54, 91}\].

These and offset structure designs return discrete DOI information. Since the two layers are made of the same material, no significant light loss occurs at the interface. However, these structures increase the path length of scintillation photons, causing light attenuation and deterioration of energy and time performance, resulting in different peak values in the energy distribution of individual layers that requires a very low threshold and application of different energy windows to select photoelectric events in individual layers. In this approach the limitation is mainly related to the complexity and relatively high cost in manufacturing triangular shape crystals, and some light loss at interfaces between the two layers \[^{9}\].

A proof of concept prototype PET system using an unpolished LYSO crystal array and a triangular-shaped reflector with digital SiPM (dSiPM) readout was developed. In the layer identification method, DOI accuracy is estimated by a peak-to-valley ratio in the FH. To encode DOI information in a continuous single-layer crystal array with single-ended readout, the method proposed uses reflectors with the shape of triangular teeth that are perpendicularly crossed over each other \[^{55}\].

Because a teeth-shaped reflector partially covers each crystal, optical photons can disperse through the crystal array. Moreover, because reflectors are configured in opposite directions along the x- and y-directions, the amount and direction of light dispersion shows different patterns depending on the 3D interaction position of gamma rays. Consequently, DOI information is encoded through different light dispersion patterns along the x- and
y-directions that are recorded as detector responses with their own statistical characteristics [55, 92, 93].

This method shows good intrinsic DOI detection performance except for crystal blurring at the edges of the FH. Also, since DOI measurement relies upon using rough (unpolished) surface crystals to tailor DOI dependency using scintillation light, the rough surface increases the light path length and causes light absorption within the crystals. Thus, light collection efficiency decreases rapidly with increasing distance between the DOI position and photosensors. The light collection loss along the DOI position results in degradation of detector time performance [55].

A method that uses a light-guide, a reflector at the top of the crystal-array and SiPM readout at the bottom has been proposed to obtain continuous DOI information. For each incident gamma ray, the crystal of interaction is identified based on the application of Anger-logic to the combination of detected charges. The ratio of the maximum charge collected to the sum of the light collected by all the detectors provides information about the depth of interaction. The mean DOI resolution achieved was 4.1 mm FWHM on a 15 mm long LYSO crystal [94].

Very recently a detector design consisting of two $3 \times 3 \times 20$ mm$^3$ LYSO crystals coupled together from top to bottom with 5 mm optical glue, 9 mm triangle and 6 mm rectangle enhanced specular reflector has been proposed. The detector unit consisting of two crystals is coupled to two SiPMs. The ratio of the amplitude of one SiPM signal to the sum of the amplitudes of the two SiPM signals was used to measure DOI. The assessment of depth encoding was carried out with a detector module consisting of an $8 \times 8$ LYSO-SiPM array (32 detector units) with one-to-one coupling. An average DOI resolution of 4.62 mm is obtained [95].

4.2. Multiple crystal-photodetector layers
This approach breaks traditional scintillation elements into two or more separate layers coupled individually to their own photodetector. Each crystal/photodetector pair acts as a traditional pair would, with reduced sensitivity if the overall crystal length is reduced.

A design in which the detection crystal is divided into four layers along its length with an APD inserted between each layer was presented. In this design the thickness of the crystal layers increases from the front to the back of the detector to ensure equal probability of interaction in each layer [56]. According to the conventional Anger logic [23] and a method termed statistics-based positioning [96], the interaction position in each crystal layer is calculated based on the relative intensity values recorded in the APD pixels.

Such APD arrays are very attractive in this context as they are compact, rugged and have a well-suited pixel size for PET imaging. However, APDs still suffer from instabilities at high gains. The SiPM detector, on the other hand, has similar benefits to the APD, but in addition is operated at very high gain, resulting in a very good signal-to-noise ratio and a minimal requirement of additional amplification. A multi-headed PET prototype has been proposed with a PET detector head composed of three equal stacks of detectors units, with each unit consisting of a SiPM array coupled to an LSO slab of 5 mm thickness, through a quartz light pipe (figure 10). The DOI information is given by the thickness of the LSO slab (5 mm) [57].

Another type of layered crystal DOI design is one of pixelized 1 mm crystals mounted in layers on position-sensitive APDs (PSAPDs) (figure 11). This design was used for a 1 mm$^3$ resolution breast-dedicated PET system [58]. The interacted crystal in the crystal array is identified by the FH calculated with four output signals per PSAPD [97]. Because of the crystal size, this detector has ~1 mm position resolution for gamma ray interaction in all directions. Using two detector units, the coincidence point spread function (PSF) was obtained, with an average of 0.84 mm FWHM, uniform across the arrays [98].

However, this technique requires very thin circuit boards and PSAPD elements to maintain a good packing fraction [9, 99]. The manufacturing cost is also a problem because the cost rapidly increases with the great number of crystals, photosensors and output channels.

A side-readout detector configuration with different length of $3 \times 3$ mm$^2$ cross-sectional area LYSO
crystals coupled to a single dSiPM tile was proposed. Using 20 mm crystal length, a DOI resolution of 0.8 mm FWHM was computed. However, complexity and the expense of increased number of photosensors and electronics are challenges for scaling up side-readout detectors to a full PET system [100].

4.3. Monolithic crystal block
A disadvantage of PET scanners based on a pixelated design is the need to manage many small scintillating crystals, increasing cost and complexity. Moreover, there is an unavoidable loss of sensitive area in these scanners due to the extra material needed to individualize the scintillating elements (pixels, blocks and rings) which reduces the sensitivity of the system [101]. The alternative is to use monolithic crystals.

Monolithic crystal designs rely on multiple photodetectors or a position sensitive photodetector with multiple independent readouts, attached to a single monolithic crystal. The photodetectors employed are then able to measure the extent to which the scintillation light has spread at the detector surface by comparing the values of the independent readouts across the crystal. Events absorbed further from the photodetector will have a larger optical light spread than events closer to it and in this way, these detectors are able to measure DOI [102–105].

While this detector provides both good energy and timing resolution at low cost, it is difficult to measure the light response function accurately over the entire crystal. Determining the position of side and corner events can be complicated in this design as the optical light, within the crystal, will dominantly spread inwards [106].

Furthermore, quasi-monolithic crystal arrays where crystal elements are separated from each other in the axial direction but are monolithic in the transaxial direction where used [107]. Because only transaxial and DOI positions should be estimated from monolithic crystals, positional accuracy and DOI estimations may be better than those determined using the pure monolithic crystal approach [107–109].

In monolithic crystals, surface treatments may be better than those determined using the pure monolithic crystal approach [107–109]. The AnnPET scanner was designed with 12 flat facets around the outer surface of the scintillator to accommodate the placement of SiPM arrays. Its performance characteristics were explored using Monte Carlo simulations and sections of the NEMA NU4-2008 protocol. Results from this study revealed that reconstructed SR is predicted to be ~1 mm FWHM in the radial, tangential and axial directions [111].

A planar positioning algorithm based on the supervised machine learning technique gradient tree boosting (GTB) has been applied to DOI calibration by side irradiation of a monolithic LYSO scintillator of dimensions 32 × 32 × 12 mm³ matching the active sensor area of the tile. GTB utilizes training data with known irradiation positions to establish predictive regression models. A set of decision trees have been built which were evaluated as simple comparisons with two possible outcomes. The algorithm handles different sets of input features and their combinations as well as partially missing data. The root-mean-square error employed as training loss of the objective function. Using this method an average SR of 2.12 mm FWHM has been achieved [113].

The imaging performance of an emulated 70 cm diameter PET system (figure 12), comprising two coaxial rotating arms, each carrying detector modules (containing 2 × 2 detectors, each using 32 × 32 × 22 mm³ monolithic LYSO scintillator), and a central, rotating phantom table has been demonstrated. Image reconstruction with a TOF maximum likelihood expectation maximization algorithm of a ²²Na filled Derenzo-like phantom at different locations within

Figure 11. Discrete crystals mounted in layers on PSAPDs for directly measuring 3D position of gamma ray interactions [98].
compact detector structure to measure DOI [120]. The X’tal cube, a SiPM-based isotropic-3D PET detector based on the light sharing concept, is shown in figure 13 [62, 121]. Interaction positions within the crystal array were estimated using a 3D extended Anger-type calculation.

However, the subsurface laser engraving technique still faces some challenges when applied to thicker monolithic scintillation crystals. It is hard to focus the laser beam tightly at a point far from the material’s surface due to the large refractive index of the scintillation crystal.

4.5. Dual ended photodetectors
Dual ended readout systems utilize photodetectors on both sides of a scintillation element. The DOI is then measured by comparing the proportional signal strength from both ends, for each scintillation event.

This approach was first proposed using a detector composed of a 4 × 8 BGO crystal array and position-sensitive PMTs coupled to both ends of the array [122]. A prototype PET scanner using dual-ended readout of finely pixelated LSO arrays with two PSAPDs was developed. The LSO arrays have 7 × 7 elements, with a crystal size of 0.92 × 0.92 × 20 mm³ and pitch of 1.0 mm. The arrays are read out by two 8 × 8 mm² area PSAPDs placed at opposite ends and DOI is measured by the ratio of the signals amplitudes. In this system, crystals with a size down to 1 mm were resolved and a uniform DOI resolution of 2 mm achieved [63, 123]. SiPMs such as the MPPCs are typically used with ‘dual-ended’ readout methods to measure DOI [64, 124]. A design for a detector module measuring the pulse-height ratio of large-area MPPC arrays coupled to both ends of a scintillation crystal block wherein walls of BaSO₄ reflectors divide side-by-side crystals in the 2D direction and a thin layer of air divides crystals in the DOI direction was introduced [125].

In this design optical light is spread isotropically, therefore more light and a more intense signal will result from the closest photodetector. Also, since this design is sharing the light from one event between two detectors it suffers from reduced energy resolution and increased noise. Precise calibration of the photodetector pairs is also required for accurate DOI measurements as the gain directly affects positioning.

A Dual-ended Readout Innovative Method for PET (DRIM-PET) was developed using individual SiPM readout in the outer detector ring and wavelength-shifting fibers (WSF) in the inner ring, sharing the light output from several LYSO crystals (1.5 × 1.5 × 20 mm³) and then read using only one or two SiPMs at one or both ends of each fiber (figure 14) [126].

In DRIM-PET, less components and electronic channels are required but light losses due to an extra LYSO-WSF interface and escape of converted photons
with angles above critical trapping angle in the WSF, result in a lower DOI resolution compared to direct dual-ended readout.

Although X'tal cube detector for isotropic SR was developed with six-sided readout using MPPCs, it is challenging to apply the detector in PET systems due to its geometry and the high cost of six-sided readout electronics [62, 121]. Recently, a more practical X'tal cube detector with dual ended readout by through silicon via MPPCs, made of crystal bars segmented in the height direction, was proposed. Figure 15 shows the 3D CPM, 2D CPMs (slices from the 3D CPM) for the top and the centre segments and count profiles in the x, y and z directions for the detector of the 8 × 8 array of 1.5 × 1.5 × 20 mm³ crystals with 13 DOI segments with partial reflectors between the crystal bars [127].

Another variation of a layered crystal DOI design is one that uses sheets of WSF to provide crystal identification and then any one of photodetectors at the ends of the crystal stacks for energy and timing (figure 16). In this design DOI is obtained by introducing orthogonal layers of thin WSFs between the layers of scintillation crystals [128].

In this approach, DOI can be determined at the cost of a significant increase in the number of detector and electronics channels [25]. In contrast to the above-mentioned design (discrete crystals mounted in layers on the PSAPDs), this approach using WSF is not suitable for TOF detection; time dispersion occurs due to measuring divided scintillation light by several photosensors, different transit distances between interaction position and individual photosensors, and the light absorption/reemission process in WSF [9, 99].

A different geometrical concept of a PET system using Hybrid Photon Detectors (HPDs) has been proposed [129], although the envisioned brain scanner was not eventually built. The detector modules consist of axially oriented matrices of 16 × 13 long polished LYSO scintillator bars optically coupled at both ends to two PET-HPDs. The auto-triggering front-end electronics is encapsulated in the detector body. A complete cylinder is formed around the patient using 12 camera modules (figure 15(c)). The scintillation light produced by a gamma photon interacting in a polished crystal bar propagates by total internal reflection to the ends with an absorption characterized by the bulk attenuation length of the crystal and the light path length. A prototype HPD for this PET concept was tested and the transverse coordinates x and y of the interaction point were given by the address of the hit crystal bar with a resolution of 0.9 mm. The third (axial) coordinate z

Figure 13. (a) Conceptual sketch of the X’tal cube detector, (b) MPPCs, light guides and crystal block of 1.0 mm³ cubic crystal segments (for ease of understanding, the light guides, the reflectors and the MPPCs are removed from four faces) and (c) Views of the 3D FH image obtained by the 3D Anger-type calculation from ¹³⁷Cs uniform irradiation [62].

Figure 14. DRIM-PET detector ring sketch, using 128 LYSO crystals and 4 WSFs for DOI determination.
was derived from the ratio of the photoelectron yields measured at the two ends of the crystal bar with an accuracy that depended on the light absorption length and the length of the bar [130].

The primary drawbacks of dual-ended readout detectors are higher cost due to the use of photosensors on both sides of the crystals and their associated electronics, attenuation and scatter of incident

\[130\]

\[131\]

\[132\]

\[133\]
gamma-rays caused by the front photo-sensors located at the inner detector ring, and complicated signal/power wiring for the front photo-sensors [120].

5. Conclusion

DOI determination capability is one of the most important improvements in new generations of high-resolution PET detectors. Accurate DOI information is used to properly calculate true LORs helping to reduce PE and provide more uniform SR across the entire FOV. This paper presents a general review of the many strategies and apparatus employed for DOI measurement and mitigation of PE, through practical examples of systems developed in the last years.

DOI encoding strategies can generally be divided in two types: discrete DOI measurement (phoswich, relative offset structure and multiple crystal-photodetector layers) and continuous DOI measurement, by single-ended readout using detector with triangular teeth shape reflectors, dual-ended readout detectors, and monolithic and quasi-monolithic crystal detectors.

The DOI uncertainty of PET detectors increases for smaller diameter scanners, due to more oblique penetration of 511 keV photons in the detectors, and for longer axial FOV scanners, due to the larger acceptance angle. Therefore, depth-encoding detectors are essential in PET scanners with small diameter and long axial FOV, to reduce DOI uncertainty and achieve uniform high SR.

The diameter of a PET detector ring can be made smaller when using DOI capable detectors, bringing additional advantages: a smaller detector ring increases the geometric coverage and improves the system detection sensitivity; it reduces the non-collinearity effect and improves the physical SR limit; and it cuts costs by reducing the number of required detector modules. The concept is also promising for positron emission mammography where both high SR and sensitivity are required to meet the needs for early and accurate diagnosis of breast tumours, hence avoiding unnecessary biopsy interventions.

For monolithic crystal detectors, DOI estimation is achieved by analysing the light response function, which requires careful calibration and statistical position estimation methods. A great deal of effort has been devoted to enabling DOI estimation for block detectors. The phoswich method utilizes the different decay times of different scintillators arranged in depth, which requires PSD methods. The crystal shifting method applies lateral shifts across different crystal layers, changing the light response function across different layers, and attempts to associate depth with lateral position; however, this method also increases decoding difficulty. Dual-sided readouts have also been explored for DOI estimation, but at a cost of increased number of readout channels.

Some efforts have been focused in developing detectors with combined TOF and DOI information which require an increase in PET detector complexity. For high performance TOF detectors, DOI can help to accurately place TOF kernels during image reconstruction by reducing the uncertainty in the LOR endpoints.

One of the challenges in image reconstruction for DOI-PET scanners is the increase in the number of DOI-based lines of response, proportional to the square of the number of DOI bins. Therefore, the size of the system matrix of a DOI-PET scanner is much larger than that of a non-DOI PET scanner and so the use of DOI compression methods based on data redundancy is necessary.

Continuous efforts to integrate the latest research findings for the design of PET scanners with DOI capable detectors have become the goal of both the academic community and nuclear medical imaging industry and are expected to bring additional benefits to the performance of next generation PET scanners, particularly for smaller diameter FOV applications such as small animal imaging preclinical research and organ-specific clinical imaging.

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