

Development of high resolution, high sensitivity PET capability for awake and freely moving small animals

Francisco Eduardo Enríquez-Mier-y-Terán

A thesis submitted in fulfilment of the
requirements for the degree of
Doctor of Philosophy

School of Biomedical Engineering
Faculty of Engineering
The University of Sydney

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Statement of Originality

This is to certify that, to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Francisco E. Enríquez-Mier-y-Terán

Sydney, July 2024

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To the best of my knowledge this thesis contains no material previously published or written by another person except where due reference and acknowledgement is made.

Chapter 3 and Appendix A of this thesis were submitted to *IEEE Transactions on Radiation and Plasma Medical Sciences* on July 11th, 2024, as:

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I co-designed the study with A.Z. Kyme and S.R. Meikle; I conducted the experiments with the help of W. Pineda-Valencia and M.S. Judenhofer; I analysed the data with input from A.Z. Kyme and S.R. Meikle; I wrote the manuscript with support from A.Z. Kyme and S.R. Meikle.

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I co-designed the study with A.Z. Kyme, S.R. Meikle and L. Zhou; I conducted the experiments; I analysed the data with input from A.Z. Kyme, S.R. Meikle and L. Zhou; I wrote the manuscript with support from A.Z. Kyme and S.R. Meikle.

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I co-designed the study with S.R. Meikle, A.Z. Kyme and G. Angelis; I conducted the experiments with the help of G. Angelis; I analysed the data with input from S.R. Meikle, A.Z. Kyme and G. Angelis. I wrote the manuscript with support from S.R. Meikle, A.Z. Kyme and G. Angelis.

Francisco E. Enríquez-Mier-y-Terán

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Sydney, July 2024

As primary and auxiliary supervisors for the candidature upon which this thesis is based, we can confirm that the generative AI statement above is correct.

Andre Z. Kyme

Primary Supervisor

Sydney, July 2024

Steven R. Meikle

Auxiliary Supervisor

Sydney, July 2024

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Abstract

“Development of high resolution, high sensitivity PET capability for awake and freely moving small animals”

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Francisco E. Enríquez-Mier-y-Terán
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Primary Supervisor: Dr. Andre Kyme
Auxiliary Supervisor: Prof. Steven Meikle

Positron emission tomography (PET) imaging in small animals, such as mice and rats, holds great potential for advancing our understanding of neurological disorders and evaluating new treatments. However, translating findings from animal models to clinical applications faces two main challenges: quantitative inaccuracies due to limited PET system performance and the small anatomical structures of these animals, and the need for anaesthesia. Accurate tracer quantification in brain regions requires PET scanners that provide both sub-millimetre resolution and high sensitivity. Furthermore, to avoid the confounding effects of anaesthesia, scanners capable of imaging awake, freely moving rodents are essential—yet no such system currently exists. The Open-Field Mouse Brain PET (mousePET) scanner aims to overcome these limitations. This thesis addresses three main challenges: (i) developing cost-effective solutions for scalable detector data acquisition, (ii) improving event positioning in the PET detectors, and (iii) creating efficient methods for depth-of-interaction (DOI) image reconstruction. The use of a low-cost application-specific integrated circuit (ASIC) for multiplexed detector data acquisition was investigated. The optimised mousePET detector achieved mean energy, DOI, and coincidence time resolutions of 10.5%, 2.3 mm, and 1.3 ns, respectively, demonstrating strong performance. Deep learning techniques were applied to further enhance event positioning accuracy. A deep neural network (DNN), trained via Monte Carlo simulations, improved positioning accuracy by 28% compared to traditional Anger logic. Finally, virtual cylindrical detector geometries were tested for efficient DOI image reconstruction, showing that optimising virtual geometry balances computational efficiency and spatial resolution. In conclusion, this thesis develops and rigorously evaluates critical components of the mousePET scanner, laying a strong foundation for its final development.

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Outputs Arising from this Thesis

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Chapter 1

Introduction

1.1 Background and Motivation

The prevalence of neurological disorders, which encompass diseases of the central and peripheral nervous systems, is rising globally due to longer life expectancy and an ageing population [193]. However, our understanding of the onset and progression of these disorders remains limited. Fundamental questions, such as the underlying causes and potential preventability of these diseases, remain unanswered. In this context, positron emission tomography (PET) imaging of animal models offers significant potential. As a molecular imaging technique that enables *in-vivo*, non-invasive imaging of physiological processes, PET facilitates the study of disease progression from early stages and the effects and efficacy of potential drug treatments [36, 227].

Among different animal models, mice and rats are the most widely used in pre-clinical research, primarily due to the availability of well-established tools for gene manipulation and their high genetic homology with humans [64]. However, maximising our ability to translate findings from animal models into clinical settings is a major technical challenge on account of the tiny anatomical structures and the need for anaesthesia.

The scale issue becomes evident when comparing the brain volumes of these animals to that of humans. The rat brain is 600 times smaller than the human brain, and the mouse brain is 2400 times smaller. For mouse brain imaging specifically, the volume of several key regions is less than a few cubic millimetres [13, 158]. While the field of small-animal PET has progressed significantly since its inception [60, 171, 278], current systems often do not achieve the spatial resolution required for these animals. High spatial resolution is necessary to accurately image the brain regions of these rodents, but sensitivity is equally important. Accurate tracer quantification requires a high signal-to-noise ratio (SNR) at the voxel level, which can only be achieved by detecting a large number of coincidence photons. Therefore, small-animal PET systems that achieve both high resolution and high sensitivity are required. Whole-body small-animal PET systems achieve high sensitivity but have lower spatial resolution compared to brain-only small-animal PET systems. Conversely, brain-only PET systems

achieve high spatial resolution but often lack sensitivity. Clearly, this represents a significant gap that this thesis aims to address.

The use of anaesthesia is widespread in order to prevent motion-induced PET artefacts, such as blurred images and incorrect tracer quantification. However, evidence shows that anaesthetics can significantly disrupt brain function [3], which is a key reason why PET findings do not always translate to the clinical setting [170]. From a scientific perspective, anaesthesia also limits the ability to simultaneously correlate brain function with behaviour [229]. Truly understanding neurological disorders requires studying the brain without disturbing neurobiological function and investigating the correlations between brain changes and behaviour in response to external stimuli.

Several approaches have been reported to mitigate the impact of anaesthetics. The use of restraining devices, such as head holders [176], has proven to be cost-effective and easy to implement. However, these devices are often invasive, cause restraint-induced stress on the animal [249], and limit the full range of potential experiments for simultaneous brain function and behaviour assessment. Developing methods that allow animals to be imaged while awake and freely moving can overcome these limitations, but such approaches are technically much more ambitious. Among these, a surgically mounted PET scanner on the head of a conscious rat, known as the RatCap [258, 259], was the first major technological development. However, the RatCap is still invasive and its spatial resolution is insufficient for imaging the mouse brain. Instead, motion-compensated PET imaging presents a promising alternative.

Motion-compensated PET methods rely on tracking the animal motion to correct for it both before and during image reconstruction [207]. Methods to achieve this include the use of external optical cameras for marker-based [132, 131] and markerless [128] motion tracking, as well as the use of radioactive point sources for image-based motion tracking [169]. These methods have proven effective in reducing motion artefacts, producing images closely resembling those obtained with anaesthetised animals, and allowing the simultaneous correlation of behaviour and brain function. However, they have limitations. These methods cannot compensate when the animal exits the scanner field of view (FOV). Additionally, all of these techniques have been implemented on commercial scanners with insufficient resolution and sensitivity to accurately image the mouse brain.

The challenges posed by intrinsic scanner performance and anaesthetic drugs underscores the necessity of developing small-animal PET systems designed specifically for awake and freely moving rodents, capable of accurately compensating for motion throughout the study, including scenarios when the animal exits the FOV. The Open-Field Mouse Brain PET scanner [129] is a next-generation PET system aimed at overcoming these key technical challenges. The system is designed for high-resolution and high-sensitivity brain PET imaging of awake and freely moving mice. Using a movable gantry, the system will translate in response to the animal's movement, preventing the animal from escaping the FOV. An optical motion tracking system will continuously sample the animal's head pose with six degrees of freedom of motion, enabling motion-compensated

PET reconstruction. A runway with an integrated touchscreen will permit to simultaneously study brain function and cognition [26].

1.2 Aims of Thesis

The overarching objective of this thesis is to overcome three key technological challenges to bring the Open-Field Mouse Brain PET scanner from concept to reality. The three specific aims to achieve this goal are:

- i. To investigate the feasibility of all-in-one chip signal readout solutions based on low-cost application-specific integrated circuits (ASICs) for cost-effective multiplexed detector data acquisition and system scalability.
- ii. To explore the feasibility of deep learning methods for improved event positioning in the PET detectors compared to traditional positioning methods.
- iii. To develop and validate an accurate and computationally efficient algorithm for high resolution depth-of-interaction (DOI) PET reconstruction for the PET scanner.

1.3 Organisation of Thesis

The remainder of this thesis is organised as follows:

Chapter 2 presents the essentials of PET imaging, including its physics, detector instrumentation, image reconstruction, and overall system performance. The first section of this chapter concludes with the applications of PET in both clinical and preclinical contexts. The second section delves deeper into small-animal PET, focusing on DOI PET detectors, the current state-of-the-art small-animal PET systems, the confounding effects of anaesthetics, and advancements in the field aimed at limiting or completely eradicating the degrading effects of anaesthetics in small-animal brain PET imaging. The chapter concludes with the introduction of Open-Field Mouse Brain PET.

Chapter 3 addresses Aim 1 by integrating and optimising the performance of the PET detectors with the TOFPET2 ASIC (PETSys Electronics S.A., Portugal). The ASIC logic is optimised in terms of detector flood map quality, and the detector performance is evaluated in terms of energy resolution, DOI resolution, and coincidence time resolution (CTR) at different bias voltages.

Chapter 4 addresses Aim 2 by investigating the properties of inter-crystal scatter events in the PET detectors and developing a deep neural network-based positioning algorithm. The performance of the algorithm is then compared to the conventional Anger logic positioning method.

Chapter 5 addresses Aim 3 by investigating the use of virtual cylindrical geometries for DOI PET reconstruction. Various comparisons between virtual geometries with different sampling schemes and the Open-Field Mouse Brain PET geometry are conducted to determine the optimal virtual detector size in terms of computational efficiency and reconstructed spatial resolution.

Chapter 6 summarises the key findings of this thesis and presents avenues for future work.

Chapter 2

Background

Preamble

In this chapter, we review fundamental aspects of PET to provide readers with a comprehensive understanding of the theory and advancements in the field. This foundational knowledge is crucial for developing PET systems. Given the focus of this thesis on small-animal PET, we also examine the current state of this sub-field and its existing limitations.

The chapter begins with an exploration of PET radiation physics, including Compton scattering, which is a key discussion in Chapter 4. This is followed by an overview of PET detector instrumentation, the primary focus of Chapter 3. Next, we delve into PET reconstruction techniques, which are further elaborated in Chapter 5. Subsequently, we discuss the current state of small-animal PET and introduce the detrimental effects of anaesthetics when imaging the brain of an animal.

The chapter concludes by discussing advancements made in mitigating the negative impacts of anaesthetics, identifying gaps in current research, and outlining where Open-Field Mouse Brain PET fits into these gaps.

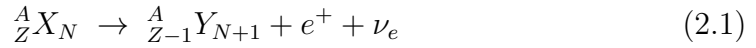
2.1 Positron Emission Tomography (PET)

2.1.1 PET Radiation Physics

Radioactivity, first discovered by Henri Becquerel in 1896, is the process by which atoms release energy in the form of waves or particles. Within an atom, the nucleus can exist in a ground state (of minimum energy) or in various excited states. Excited states are characterised by instability, and it is this nuclear instability that leads to spontaneous radioactive decay [120]. Common types of radioactive decay include alpha decay (He^{+2} emission), β^- decay (electron emission), and β^+ decay (positron emission). Since PET imaging exploits the physics of the positron, the following sections provide more details about β^+ decay and the interaction of positrons, and their products, with matter.

2.1.1.1 Positron Emission (β^+ decay)

β^+ decay occurs in unstable nuclei characterised by having a greater number of protons compared to neutrons. The decay involves the spontaneous conversion of a proton into a neutron. To conserve charge, a positron (e^+) is emitted. The positron, or positive electron, has the same mass and spin as an electron but carries an opposite charge. The kinetic energy distribution of the emitted positron is continuous (see Fig. 2.1), ranging from near 0 MeV to the energy released (Q value) during the decay (measured in MeV). To conserve energy, a second particle, the electron neutrino (ν_e), is also emitted. Equation 2.1 illustrates the β^+ decay from a parent nuclide A_ZX_N to its daughter nuclide ${}^A_{Z-1}Y_{N+1}$.



The Q value of the decay can be estimated using the following equation:

$$Q = (m({}^A_ZX_N) - m({}^A_{Z-1}Y_{N+1}) - 2m_e) c^2 \quad (2.2)$$

where $m({}^A_ZX_N)$ and $m({}^A_{Z-1}Y_{N+1})$ are the atomic masses of the parent and daughter nuclide, respectively, and m_e is the electron mass.

In Table 2.1, common radionuclides used in PET are shown together with their maximum and mean positron kinetic energy.

2.1.1.2 Positron-Electron Annihilation

In PET imaging, positron-emitting radionuclides are chemically bound to biomolecules of interest, such as fluorodeoxyglucose which is an analog of glucose. These radiomolecules, administered in tracer quantities (i.e., amounts that do not perturb the biological system), are typically delivered into a living subject via intravenous injection. Once inside the body, the emitted positrons lose energy through collisions with bound electrons in the tissue [92]. After a positron has lost most or all of its kinetic energy, it will either directly annihilate with an electron (60% of the time) or form positronium (40% of the time) [179].

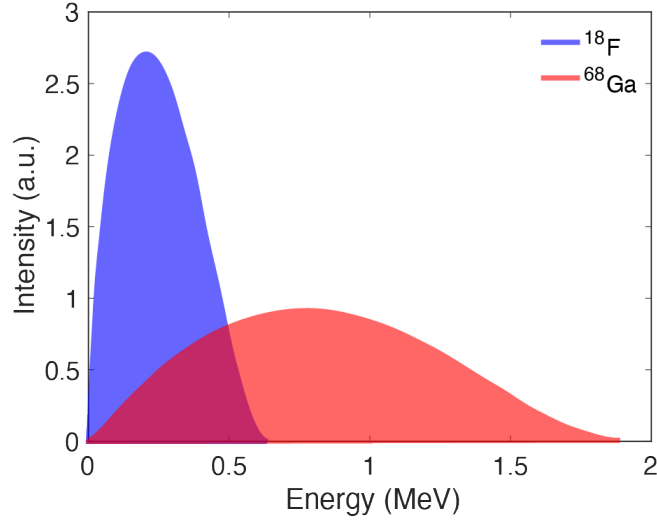


Figure 2.1: Positron energy spectra of two common radionuclides used in PET: ^{18}F and ^{68}Ga . Adapted from [220].

Table 2.1: Maximum and mean positron kinetic energy of common radionuclides used in PET. Data taken from [149, 220].

Radionuclide	Max (Mean) Kinetic energy [MeV]
^{11}C	0.97 (0.39)
^{13}N	1.19 (0.49)
^{15}O	1.72 (0.74)
^{18}F	0.64 (0.25)
^{68}Ga	1.90 (0.84)

Direct annihilation results in the production of two photons, each with an energy of 511 keV, emitted in opposite directions to conserve energy and momentum (see Fig. 2.2). This energy corresponds to the electron mass energy ($m_e c^2$). In contrast, positronium decay can produce either two photons (para-positronium) or three photons (ortho-positronium). Since three-photon emission is less likely to occur in living subjects [92], PET imaging generally assumes the emission of two photons. However, tissue microstructure, such as oxygen concentration, can influence the rate of three-photon emission [180]. Consequently, some research groups are exploring positronium imaging as a potential disease biomarker [178, 204].

2.1.1.3 Photon Interaction with Matter

PET imaging relies on the coincidence detection of the two 511-keV photons. Detecting these photons requires a medium in which they can deposit (lose) energy. Contrary to charged particles, photons are electrically neutral and do not continuously lose energy while penetrating matter [256]. Instead, photon interactions are said to be *catastrophic*, since they either interact or not with the medium. Photon interactions with matter include:

- Rayleigh scattering,

- Photoelectric absorption,
- Compton scattering,
- Pair production

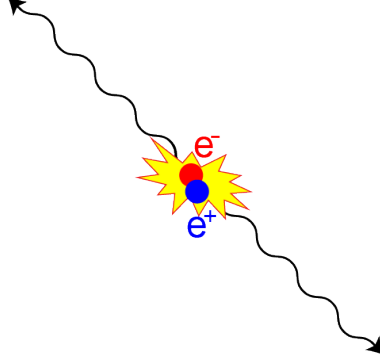


Figure 2.2: Annihilation of a positron (e^+) with an electron (e^-) results in the emission of two antiparallel 511-keV photons (curled lines).

Rayleigh scattering. Also known as coherent scattering, this interaction occurs between a photon and an atom as a whole [37]. During the interaction, almost no energy is transferred to the atom and the scattering angle is very small. Consequently, the photon energy loss is assumed to be negligible.

Photoelectric absorption. First explained by Albert Einstein in 1905 [63], this effect involves the interaction between a photon and an orbital electron of an atom, typically from the innermost shells. During this process, the photon is absorbed, transferring its energy (E_γ) to the electron. As a result, the electron (known as a *photoelectron*) is ejected from its orbital (see Fig. 2.3a). The kinetic energy of the ejected electron is:

$$T_{pe} = E_\gamma - \Phi \quad (2.3)$$

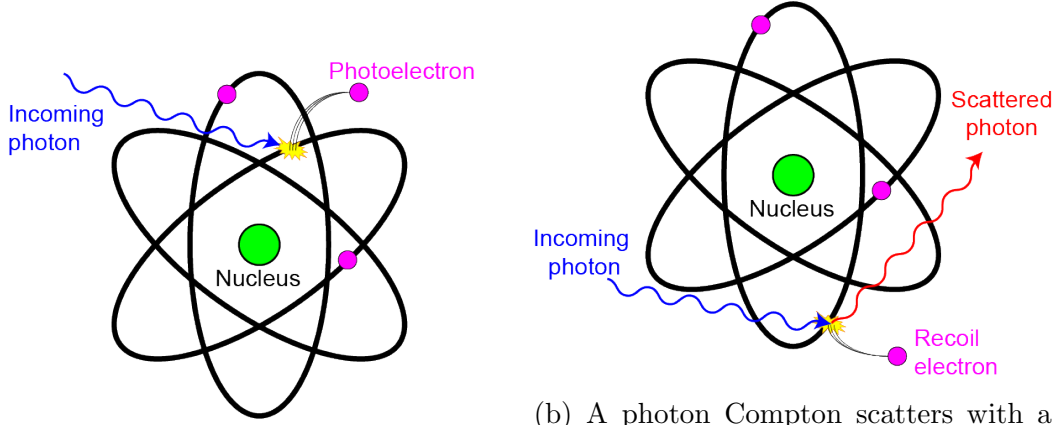
where T_{pe} is the photoelectron kinetic energy and Φ is the binding energy of the electron shell.

Compton scattering. Compton scattering occurs when a photon interacts with an outer-shell electron. Since the photon energy is greater than the electron binding energy, it is approximated that the photon collides with a 'free' electron [37]. Upon collision, the photon is scattered at an angle θ (see Fig. 2.3b). The energy of the scattered photon ($E_{\gamma'}$) can be determined from this angle if the initial photon energy (E_γ) is known [43]:

$$E_{\gamma'} = \frac{E_\gamma}{1 + \frac{E_\gamma}{m_e c^2} (1 - \cos \theta)} \quad (2.4)$$

where m_e is the electron mass and c is the speed of light.

After the collision, the electron recoils with kinetic energy equal to the energy difference between the incident photon and the scattered photon, given by $E_\gamma - E_{\gamma'}$.



(a) A photon is absorbed via a photoelectric effect, causing the ejection of a photoelectron.

(b) A photon Compton scatters with a loosely-bound electron. The electron recoils and the scattered photon deviates from its original trajectory.

Figure 2.3: Photon interactions with matter relevant to PET imaging.

The probability of Compton scattering at an angle θ for different photon energies, per unit of solid angle, is described by the Klein-Nishina formula [118]:

$$\frac{d\sigma}{d\Omega} = \frac{r_e^2}{2} \left(\frac{E_{\gamma'}}{E_{\gamma}} \right)^2 \left[\frac{E_{\gamma'}}{E_{\gamma}} + \frac{E_{\gamma}}{E_{\gamma'}} - \sin^2 \theta \right] \quad (2.5)$$

where r_e is the classical electron radius.

Equation 2.5 shows that for low energy photons (≤ 10 MeV), forward ($\theta \leq 90^\circ$) and backward ($\theta \geq 90^\circ$) scattering are almost equally probable. However, for higher photon energies (> 10 MeV), most scattering occurs in the forward direction. Figure 2.4 illustrates the differential Compton scattering cross-sections for photons with different energies.

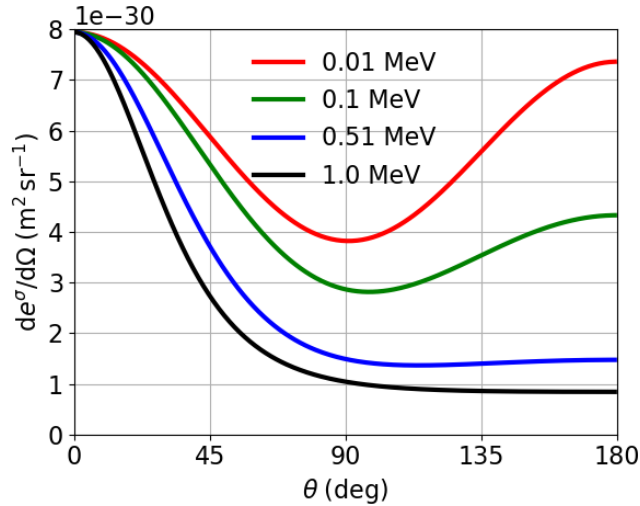


Figure 2.4: Differential scattering cross section for four different photon energies: 0.01 (red), 0.1 (green), 0.51 (blue) and 1.0 (black) MeV.

Pair production. Pair production occurs when photons have an energy (E_{γ})

of at least twice the electron mass (i.e., 2×0.511 MeV) and interact with the electric field of a charged particle [37]. This interaction typically involves a photon and an atomic nucleus, but it can also occur between a photon and an orbital electron [256]. During the interaction, the photon is absorbed, resulting in the creation of an electron and a positron. If the photon energy exceeds 1.022 MeV, the excess energy ($E_\gamma - 1.022$ MeV) is shared between the electron and the positron as kinetic energy.

Because photons traverse media composed of millions of atoms, the macroscopic probability, also known as attenuation coefficient, of photoelectric absorption (τ), Compton scattering (σ), and pair production (κ) depends on the photon energy, as well as the density (ρ) and atomic number (Z) of the medium through which the photons are traversing (see Fig. 2.5). Considering all these probabilities results in the total attenuation coefficient $\mu = \tau + \sigma + \kappa$. Since the attenuation coefficient increases linearly with the medium density, it is more common to express this as a mass attenuation coefficient (μ/ρ) [37].

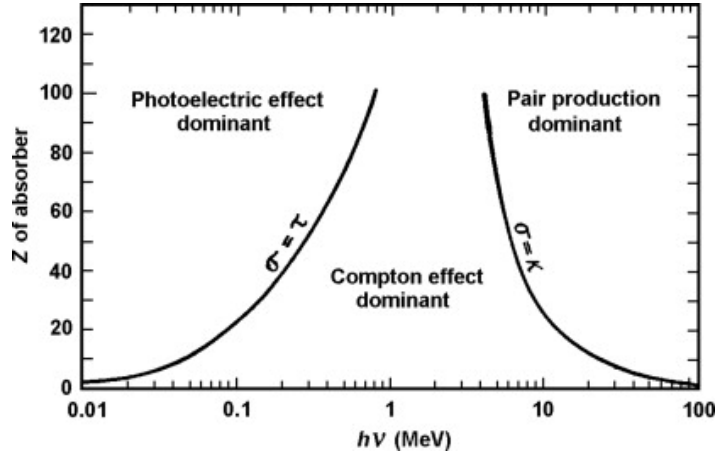


Figure 2.5: Dominant photon interaction as a function of the photon energy (MeV) and the atomic number (Z) of the absorber. Taken from [39].

2.1.2 PET Detectors

Photon detection in PET is commonly achieved using inorganic scintillation crystals coupled to photodetectors or semiconductor crystals [82]. In scintillation-based detectors, light is emitted after a photon interacts with the crystal. Some of this light reaches the photodetector(s), generating a current that is subsequently processed by the front-end electronics.

In semiconductor-based detectors, photon interactions with a semiconductor crystal produce charge carriers (electron-hole pairs). These charge carriers are drifted, by means of a high electric field, towards a pair of electrodes placed on opposite sides of the crystal [148]. The measured current is then processed by the front-end electronics.

Although semiconductor-based detectors are suitable candidates for high-resolution PET [1], there are currently no commercial scanners available based on this

technology [82]. Therefore, this section will focus on scintillation-based detectors.

2.1.2.1 Scintillation crystals

Scintillation crystals have the ability to emit visible (or ultraviolet) photons upon absorbing energy from ionising radiation [166] (see Fig. 2.6a). Within the crystal, photons can undergo Compton scattering and/or photoelectric absorption, causing electrons to be ejected or recoil from the crystal bulk (see Section 2.1.1.3). These electrons, through Coulombic interactions, may ionise the medium, giving secondary electrons enough energy to move from the valence band to the conduction band, resulting in electron-hole pair creation. Free electron-hole pairs may be trapped in the luminescent centres of the crystal (i.e., activator atoms) and, through subsequent de-excitation, a visible photon is emitted [82, 100] (see Fig. 2.6b).

The efficiency of this conversion process is quantified by the number of photons (N_{ph}) produced per unit energy of the incoming particle ($E_{incident}$) [18]:

$$N_{ph} = N_{e/h}SQ = \frac{E_{incident}}{E_{e/h}}SQ \quad (2.6)$$

where $N_{e/h}$ is the number of electron-hole pairs produced in the conduction and valence bands due to energy absorption, S is the efficiency with which the electron-hole pairs move into a luminescent centre, and Q is the quantum efficiency of the luminescent centre.

The desired properties of the ideal scintillation crystal for PET applications are shown in Table 2.2. Although no ideal scintillation crystal exists yet, lutetium oxyorthosilicate (LSO) and lutetium yttrium oxyorthosilicate (LYSO) are currently the most common crystals used in PET [12, 66, 203]. However, a promising candidate for next-generation total body time-of-flight (TOF) PET scanners is bismuth germanate (BGO). This due to its emission of Cherenkov photons and its cheaper growing process compared to LSO/LYSO [23, 121]. Table 2.3 shows the relevant properties of common scintillation crystals used in PET.

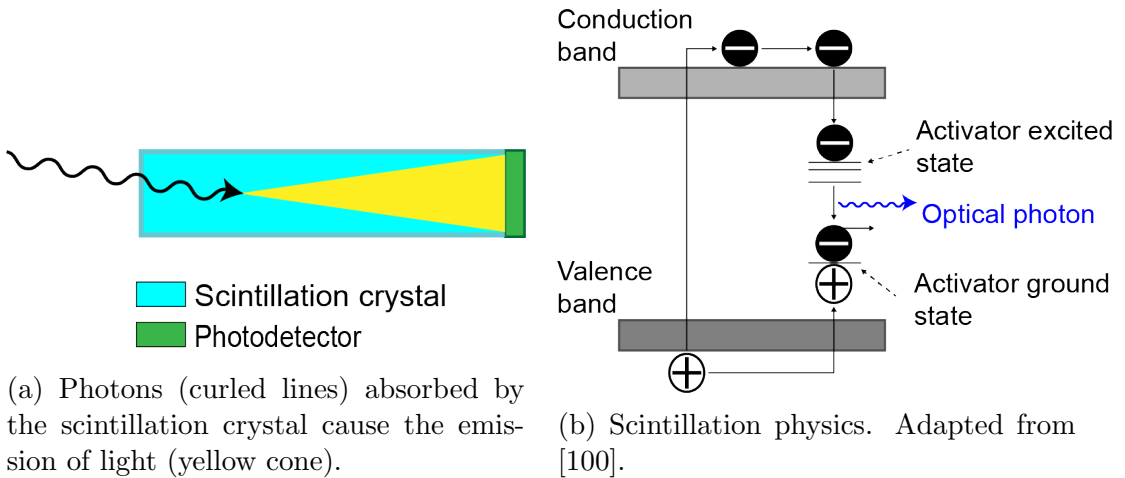


Figure 2.6: Basics of scintillation crystals.

Table 2.2: Ideal properties for a scintillation crystal in PET. Adapted from [166].

Crystal Property	Purpose
High density	High photon detection
High atomic number	High probability of photoelectric interaction
High light yield (photons/keV)	Good energy resolution
Short luminescence decay time	Good coincidence timing
Transparent at emission wavelength	Minimise optical photon absorption in the crystal
Index of refraction ≤ 1.5	Good light transmission between crystal and photodetector
Non-hygroscopic	Simple packaging/assembly
Economic growth process	Low manufacturing costs

Table 2.3: Properties of scintillation crystals used in PET. Taken from [281].

Material	Density (g/cm^3)	Z_{eff}	Light yield*	Decay time (ns)	Hygroscopic
NaI:Tl	3.67	51	41	230	yes
BGO	7.1	75	9	300	no
LSO/LYSO**	7.4	65-66	26-34	38-44	no
BaF ₂	4.9	54	1.3-1.4	0.8	no
CsF	4.6	52	1.9-2.0	3	yes
LaBr ₃ :Ce	51	45	64-76	16	yes

* Light yield units are photon/keV.

** LSO/LYSO are cerium doped (e.g., LYSO:Ce).

2.1.2.2 Photodetectors

Photomultiplier tube. The invention of the photomultiplier tube (PMT) in 1934 contributed to the development of the first PET scanners [142]. A PMT consists of a vacuum glass tube with a photocathode, a series of electrodes known as dynodes, and an anode (see Fig. 2.7a). Optical photons striking the photocathode may cause electrons to be ejected, with a typical quantum efficiency of 15-25% [142]. A high electric field applied between the photocathode and the first dynode accelerates the electrons, causing them to strike the dynode and eject additional electrons. Subsequent higher electric fields between the dynodes and the anode result in a final signal amplification gain of about 10^6 [142, 281].

For many years, PMTs were considered the photodetector of choice in PET [267, 271] due to their high gain, low dark counts (i.e., thermally generated electrons causing a spurious signal), and very short signal rise time [281]. However, the need for PET detectors with smaller crystals, necessary for better spatial resolution in PET, has made PMTs unsuitable for the new generation of PET scanners [12, 203].

Solid-state Photodetectors. The development of solid-state photodetectors [212] opened new possibilities in PET. These photodetectors are based on a p-

n junction (diode), which is a boundary between p-type (excess of holes) and n-type (excess of electrons) semiconductor materials (see Fig. 2.7b). When a reverse bias voltage is applied, free charge carriers leave the p-n junction, forming a region with a high electric field known as the depletion layer. Optical photons striking the depletion layer can create electron-hole pairs. Depending on the electric field strength, the electrons and/or holes are accelerated towards their respective electrodes, producing a measurable signal.

The avalanche photodiode (APD) was the first solid-state photodetector to be used in PET [140]. Unlike PIN photodiodes, which have no internal gain, APDs operate in the avalanche region. In this region, the electric field is strong enough for the free electrons to gain sufficient kinetic energy to produce secondary electron-hole pairs via ionisation. Although APDs have a higher quantum efficiency (80%) and can operate under strong magnetic fields, their internal gain ($\sim 10^2$) is significantly lower compared to PMTs [281]. Additionally, their moderate timing performance (in the nanosecond range) have limited the adoption of APDs in PET.

Unlike the invention of the APD, the development of the single-photon avalanche photodiode (SPAD) revolutionised the field. SPADs, also known as Geiger-mode APDs, are diodes designed to operate above the breakdown voltage. In APDs, only free electrons trigger the avalanche process. However, in SPADs, the electric field strength (10^5 V cm^{-1} [89]) causes both electrons and holes to trigger the avalanche process. During this process, the current rapidly increases and becomes self-sustaining [142]. To stop the avalanche, a quenching mechanism is required. A quenching circuit lowers the SPAD voltage to or below the breakdown voltage, after which the SPAD needs to recharge before it can detect subsequent photons.

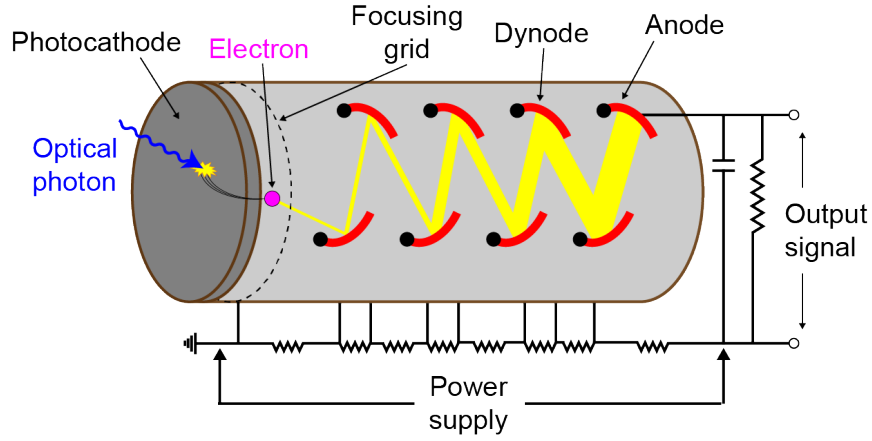
Due to the SPAD high intrinsic gain ($10^5 - 10^7$ [89]), it can detect single photons. However, this also prevents it from differentiating between one or more photons being detected. To overcome this limitation, arrays of thousands of SPADs are assembled together, each with its own quenching circuit. This device is known as the silicon photomultiplier (SiPM) (see Fig. 2.8) and is currently the state-of-the-art photodetector in PET.

During the scintillation process, thousands of optical photons are produced, causing multiple SPADs in an SiPM to fire almost simultaneously. To count the number of fired SPADs, two readout methods are used: digital SiPMs and analog SiPMs. In digital SiPMs, each SPAD is read out independently by its own electronics [225]. In analog SiPMs, all SPADs are connected in parallel (see Fig. 2.8a), and the signal amplitude is proportional to the number of fired SPADs. Although PET scanners using digital SiPMs have been implemented [230, 270], much of the detector work in PET has focused on analog SiPMs. For the purposes of this thesis, "SiPM" will refer to analog SiPMs. In analog SiPMs, quenching is achieved via a quenching resistor (R_q), and the SPAD recovery time is given by:

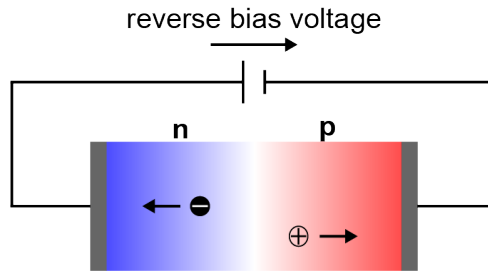
$$\tau_{recharge} = (C_d + C_q)R_q \quad (2.7)$$

with C_d the capacitance of the diode and C_q the parasitic capacitance of the quenching circuit, respectively.

The advantages and drawbacks of the SiPM are given in Table 2.4.

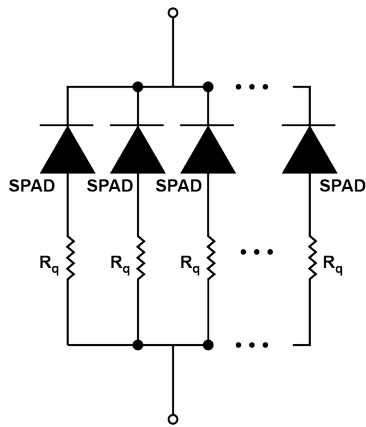


(a) Photomultiplier tube (PMT).

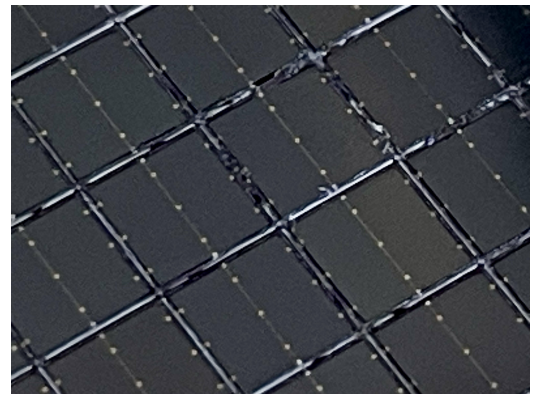


(b) Solid-state p-n junction.

Figure 2.7: Operational principles behind the photodetectors used in PET.



(a) Analog SiPMs consist of thousands of SiPMs connected in parallel, each with a quenching resistor.



(b) An array of MicroFJ-30035 SiPMs (ONSEMI, USA)

Figure 2.8: The silicon photomultiplier (SiPM)

Table 2.4: Advantages and drawbacks of the adoption of the SiPM as the photodetector in PET.

Advantages	Drawbacks
High photon detection efficiency (up to 60-70 % [90])	Limited dynamic range (insufficient number of SPADs)
Excellent electronic signal-to-noise ratio [142]	Higher dark count rate compared to PMTs [142]
High gain	Afterpulses (secondary pulses with lower amplitude)
Excellent single photon time resolution (70-135 ps [90])	Optical crosstalk (secondary photons triggering an avalanche in adjacent SPADs)
Insensitive to magnetic fields	
Highly granular (down to $1 \times 1 \text{ mm}^2$ active area)	

2.1.2.3 Front-end electronics

Front-end electronics are essential for extracting charge (proportional to the photon energy) and timing information from signals produced in a photodetector upon the detection of scintillation photons. Traditionally, this was achieved using a charge-sensitive amplifier (CSA) (see Fig. 2.9a) due to its low noise performance and high gain [71, 191, 201]. The CSA integrates the photodetector output current with a gain of $1/C_f$, where C_f is a feedback capacitor. After passing through a shaping circuit (e.g., RC filter), the CSA output provides both energy (signal peak) and timing information of the photon interactions.

With the increased adoption of SiPMs as the photodetector of choice in PET, however, CSAs are no longer the most suitable readout option [9, 27, 46]. The high gain of SiPMs requires large values of feedback capacitance (C_f) to keep the CSA output voltage within its operational range (i.e., supplied voltage). Additionally, since most of the charge released by the SiPM comes from its long signal tails, a CSA-based front-end readout cannot preserve the excellent timing properties of the photodetector [27].

Better timing properties can be achieved using a transimpedance amplifier (TIA) (see Fig. 2.9b). The TIA converts the SiPM output current into a voltage with a gain of $-R_f$, where R_f is a feedback resistor, and the negative sign indicates a change in signal polarity. With a sufficiently large bandwidth, the TIA can preserve the shape of the fast signal rise time. However, instabilities at the input of the amplifier necessitate the addition of a capacitance in parallel to R_f , which negatively impacts the SiPM timing properties [27, 215].

As PET scanners now consist of a large number of SiPMs [12, 203], compact and fully integrated front-end electronics are needed to preserve the excellent characteristics of the SiPM signal without introducing loading effects or bandwidth restrictions [46]. To achieve this, various application-specific integrated circuits (ASICs) designed in CMOS technology for SiPM readout have been proposed. These ASICs, working either in a voltage-mode [73, 2, 72] or current-mode [42,

55, 202, 241] readout approach, exploit the fast timing properties of the SiPM by using a low input impedance (R_{in}).

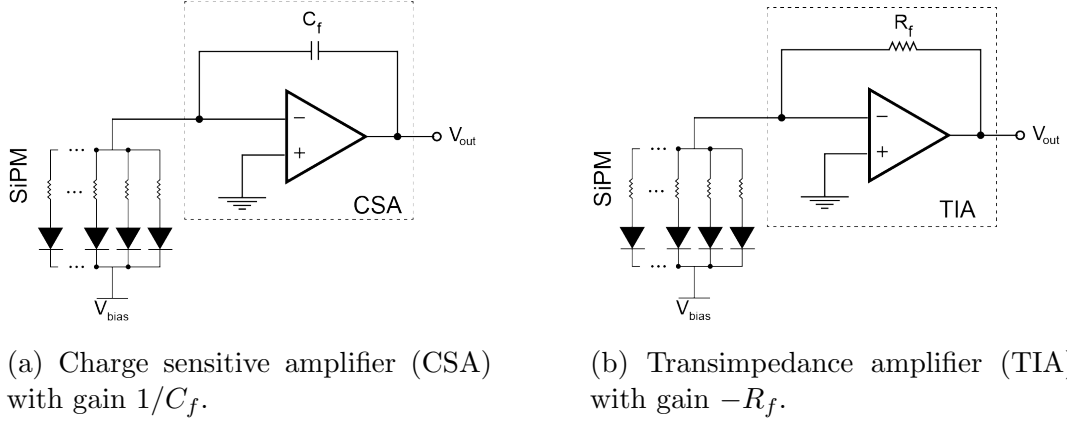


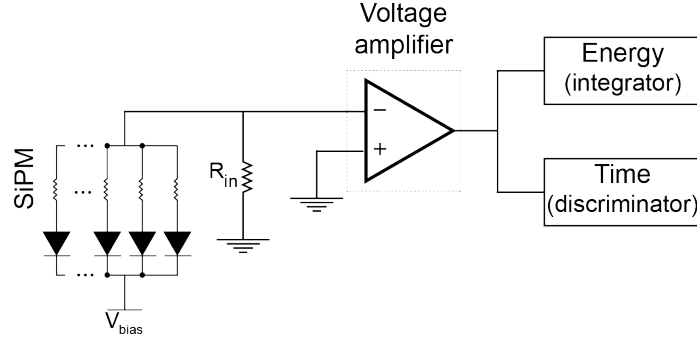
Figure 2.9: SiPM readout based on CSAs and TIAs.

In voltage-mode readout, a voltage-sensitive preamplifier is typically interfaced with an SiPM using an input impedance value $\geq 50 \, \Omega$ [2, 19] (Fig. 2.10a). The preamplifier output voltage is then split and sent via different paths to an integrator for energy measurement and a discriminator for timing measurement, respectively.

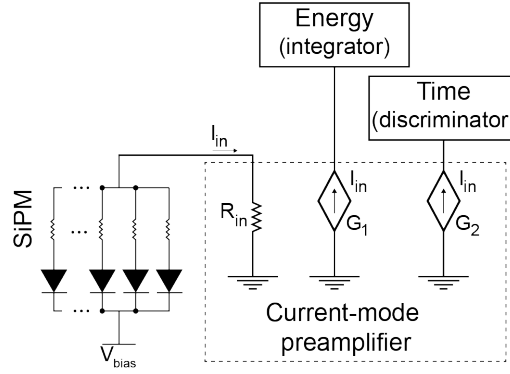
Current-mode readout, however, is more appealing due to the inherent characteristics of SiPMs [27]. By using a very low input impedance current buffer ($< 50 \, \Omega$) [46, 214], the SiPM output current is mirrored with different gains (G) along two signal paths for energy and timing measurement, respectively (Fig. 2.10b). The low input impedance allows for better timing performance compared to voltage-mode readouts.

Whether front-end electronics are based on a voltage-mode or current-mode approach, energy measurements are commonly based on signal integration. Various approaches have been implemented for this purpose, such as integrators based on CSAs with low feedback capacitances [9], and analog buffers based on capacitor arrays [19, 24]. After integration, the measured charge can be digitised by analogue-to-digital converters (ADCs) for further signal processing, e.g. energy-based event discrimination.

To measure the signal time of arrival, the leading edge discriminator (LED) method is commonly used [27, 61]. The 'timing' signal is compared with the discriminator threshold and, once the signal crosses this threshold, the signal timestamp is extracted. Since the LED method is energy dependant, time-walk corrections are sometimes employed (mainly in TOF-PET) [61, 279]. As with the energy, a time-to-digital converter (TDC) is used for further signal processing, e.g. coincidence detection.



(a) SiPM readout based on a voltage-sensitive preamplifier.

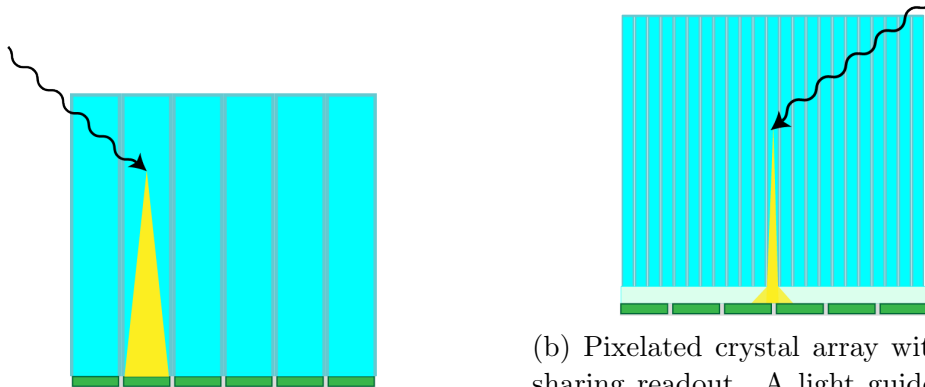


(b) SiPM readout based on a low input impedance current-based preamplifier.

Figure 2.10: Basic SiPM readout schematics for exploiting the high gain and good timing performance of the photodetector.

2.1.2.4 Detector configurations

To conclude this section, the most common scintillation-based detector configurations used in PET scanners are presented: pixelated and monolithic detectors, both read out by SiPM arrays.



(a) Pixelated crystal array (cyan) with 1-to-1 SiPM array (green) readout.

(b) Pixelated crystal array with light sharing readout. A light guide (teal) spreads the light among neighbouring SiPMs.

Figure 2.11: Scintillation-based PET detector with pixelated crystals.

In pixelated detectors, individual crystals are assembled together to form an array. Commonly, each crystal is optically isolated from the exterior using a reflective material (e.g., Toray, ESR and BaSO₄ reflectors) on the lateral and front faces [109, 211]. The coupling between the crystal array and the SiPM array can be either one-to-one (individual coupling) (Fig. 2.11a) or in a light-sharing configuration (Fig. 2.11b). In the latter, groups of crystals are coupled to the same SiPM, and light is spread among neighboring SiPMs using a light guide, usually made of glass or PMMA.

In monolithic detectors, a block of scintillation crystal, such as LYSO, is coupled to the SiPM array (see Fig. 2.12). Similar to pixelated detectors, the crystal block, with the exception of the side in contact with the SiPM array, is covered in a reflective or absorber material to enhance light collection and/or prevent edge effects [85, 112]. Currently, no whole-body PET scanners use monolithic configurations, but preclinical [69, 81, 122] and organ-dedicated [174] PET systems based on this configuration have been developed.

For TOF-PET, one-to-one pixelated configurations provide the best coincidence time resolution (CTR) [182, 186]. In contrast, light-sharing pixelated configurations are often preferred for small-animal PET, where TOF is less critical, due to their high detection efficiency and spatial resolution [111, 190]. Additionally, emerging detectors based on semi-monolithic crystals show significant promise for both small-animal and organ-dedicated PET systems. These detectors enhance sensitivity and resolution simultaneously, offering improvements over early fully monolithic designs [83].

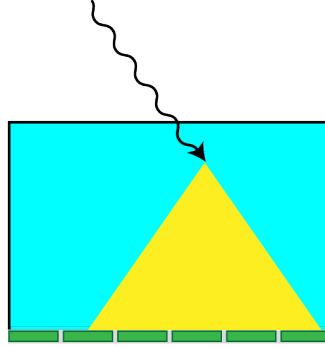


Figure 2.12: Scintillation-based PET detector with monolithic crystal.

2.1.3 PET Reconstruction

Upon digitising the energy and time of arrival of photons impinging on PET detectors, a coincidence time window, typically in the nanosecond range, is used to identify the two photons originating from the same electron-positron annihilation (see Fig. 2.13). A line extending from detector *A*, where the first photon was absorbed, to detector *B*, where the second photon was absorbed, is known as the line of response (LOR).

In a PET scanner, multiple detectors are arranged contiguously, typically in a cylindrical geometry (see Fig. 2.14), allowing for the collection of numerous

LORs. These multiple LORs serve as the starting point for image reconstruction.

Before discussing the most common reconstruction algorithms, the different event types in PET and the data pre-corrections need to be introduced.

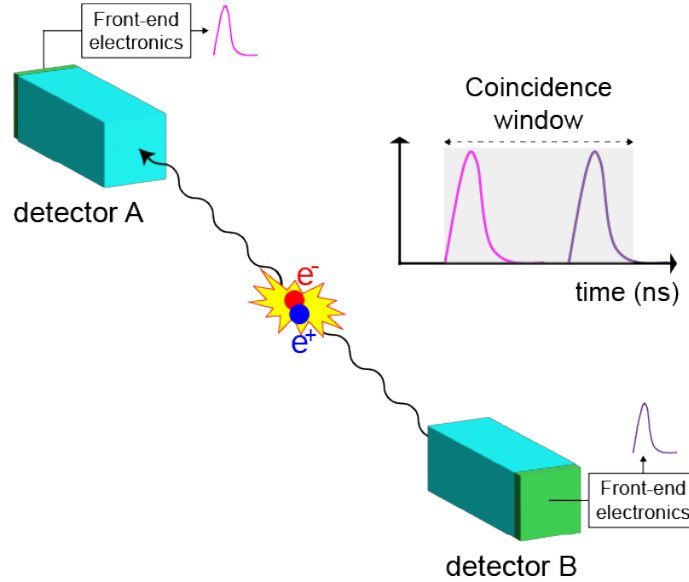


Figure 2.13: Detection of the two photons in coincidence serves for defining a line of response (LOR) (not shown) between the two impinged detectors.

2.1.3.1 Event types

True coincidences. These are detected photon pairs that originate from the same electron-positron annihilation. They escape the region of interest, such as the human body, without undergoing any interactions within it (Fig. 2.15a). In an ideal scenario, these are the only event types the system shall be detecting.

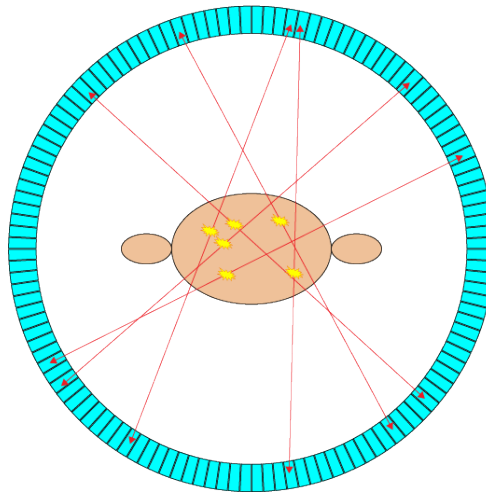


Figure 2.14: In a PET scan, multiple LORs (red lines) are collected prior to image reconstruction.

Random coincidences. These occur when two photons from different electron-positron annihilations are detected within the coincidence time window (Fig. 2.15b). Because the arrival times fall within this window, the event is accepted, even though the LOR does not correspond to the true annihilation locations. The rate of random coincidence events (R_{random}) depends on the coincidence time window (τ) and the singles event rates of each detector, $R_{singles}^A$ and $R_{singles}^B$ (see Eq. 2.8).

$$R_{random} = 2\tau R_{singles}^A R_{singles}^B \quad (2.8)$$

Scatter coincidences. As previously detailed, photons are likely to undergo Compton scattering while traversing a medium, changing their direction. After the electron-positron annihilation, one or both emitted photons may undergo Compton scatter within the scanned subject or object. This change in direction causes the LOR to be assigned to a crystal pair that does not correspond to the original photon paths if scattering had not occurred (Fig. 2.15c).

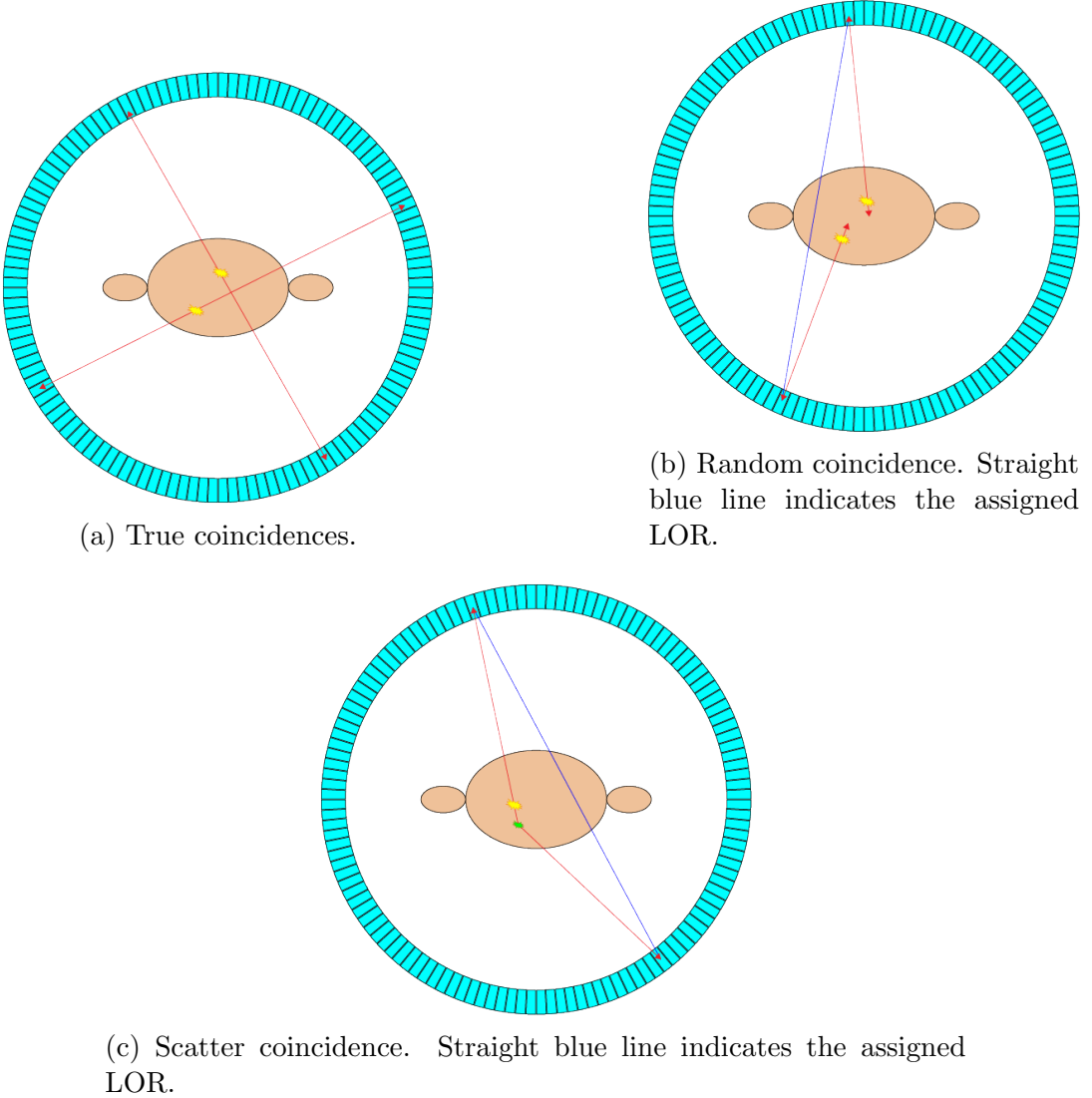


Figure 2.15: Coincidence event types in PET.

2.1.3.2 Data pre-corrections

Image reconstruction without data pre-corrections results in images plagued by artefacts and a poor signal-to-noise ratio (SNR) [11, 20, 280], rendering them unreliable for quantifying biophysically relevant parameters. With the advent of PET scanners that offer superior spatial resolution and sensitivity, dynamic PET imaging combined with robust kinetic modelling aims to provide deeper insights into various physiological processes within the body [264]. This underscores the necessity of correcting PET data before or during reconstruction to ensure accurate and reliable imaging results.

Below is a brief description of common data correction methods. However, it is important to note that, with the rapid growth of artificial intelligence (AI), deep-learning methods for data pre-corrections are gaining increasing attention [49, 56, 235].

Randoms Correction. Methods for correcting random coincidences include using a delayed time window or a 'singles-based' estimation [20, 97, 192]. In the delayed time window method, a secondary coincidence time window, operating in parallel with the main window, is shifted by a few tens of nanoseconds. The number of photon pairs detected within this delayed window (delayed coincidences) is assumed to closely approximate the randoms contribution during the scan. In the 'singles-based' estimation method, the individual count rate of each detector is continuously measured and the randoms rate along each LOR is estimated using Equation 2.8. The 'singles-based' estimation is less prone to amplifying noise compared to the delayed time window method, but it can be biased if any parameter is not accurately estimated [20].

Normalisation correction. Within a PET scanner, different detector pairs exhibit varying photon detection sensitivities due to factors such as variable detector gains (e.g., differences in SiPM gain and/or scintillation crystal light output) or the spatial positioning of the detectors within the scanner, which affects their ability to collect counts (events) [11, 52]. Therefore, each LOR within a PET scanner needs to be corrected for these variations. A simple model for the normalisation coefficients [52, 96] is given by:

$$N_{AB} = \epsilon_A \epsilon_B g_{AB} \quad (2.9)$$

where N_{AB} is the normalisation coefficient for the LOR between detector A and detector B , ϵ_A and ϵ_B are the intrinsic detection efficiencies of detectors A and B , respectively, and g_{AB} is the geometric factor accounting for sensitivity variations in the LOR due to the location of the two detectors within the scanner and/or detector block. In Figure 2.16, the effect of not accounting for g_{AB} in an irregular PET geometry is illustrated.

There are two common normalisation correction methods: direct normalisation and component-based normalisation. In direct normalisation, all of the LORs are uniformly irradiated, and the normalisation coefficient N_{AB} is calculated as the ratio of the measured counts along that LOR to the average measured counts along all LORs [37]. In component-based normalisation, each component in Equation 2.9 is measured independently and later combined [11, 52].

Although the estimation of components requires different measurement setups, component-based normalisation is less prone to noise compared to the direct method [52].

Attenuation correction. As detailed in section 2.1.1, photons are likely to interact with a medium while traversing it, either via photoelectric absorption or Compton scattering. 511-keV photons emitted from inside the patient might be absorbed or scattered before reaching their intended detector pair. Consequently, measured counts along the LOR connecting detectors A and B can be modelled according to:

$$p_{AB} = \int_{LOR} e^{-\int_{LOR} \mu(\mathbf{r}, E_{PET}) dl} f(\mathbf{r}) dl \quad (2.10)$$

where both integrations are along the LOR connecting detectors A and B , $\mu(\mathbf{r}, E_{PET})$ is the attenuation coefficient of the 511-keV photons in the 3D space $\mathbf{r} = (x, y, z)$, and $f(\mathbf{r})$ is the radiotracer distribution.

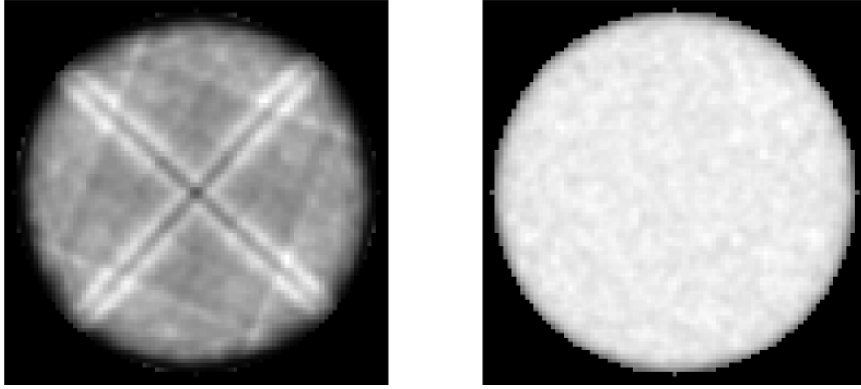


Figure 2.16: Reconstruction of a uniform cylinder without (left) and with (right) normalisation correction in an irregular (box) PET geometry.

The aim is then to estimate attenuation correction factors (ACFs):

$$ACF_{AB} = e^{\int_{LOR} \mu(\mathbf{r}, E_{PET}) dl} \quad (2.11)$$

so that the measured data can be corrected:

$$p_{AB}^{corrected} = (ACF_{AB})p_{AB} \quad (2.12)$$

In modern clinical practice, PET/CT scanners are commonly used and attenuation maps are derived from CT image values $\mu(\mathbf{r}, E_{CT})$ [116]. Since the attenuation coefficient depends on the photon energy, the CT attenuation maps need to be scaled to the energy of the photons used in PET:

$$\mu(\mathbf{r}, E_{PET}) \propto \beta \mu(\mathbf{r}, E_{CT}) \quad (2.13)$$

where β is a tissue-dependent scaling factor applied after the segmentation of the CT image.

Scatter correction. This process aims to model the scatter component (magnitude and spatial distribution) during a PET scan by utilising emission and transmission data, such as CT-based attenuation maps [280]. Clinically, this is commonly implemented using the Single-Scatter Simulation (SSS) framework [269], although methods based on Monte Carlo simulations are also employed [285].

In SSS, a non-scatter corrected PET image is first obtained. The single-scatter contributions along each LOR are then modelled using the Klein-Nishina equation, along with the non-scatter corrected PET image and transmission scans. If the reconstruction algorithm is linear, such as filtered backprojection, the correction can be performed post-reconstruction [269].

Dead-time correction. Dead time refers to the period during which a detector is insensitive (or at least to a certain degree) to incoming events because it is processing a preceding event [76]. This insensitivity can arise from various factors, including scintillation emission in the crystal, SPAD avalanche and/or discharge in the SiPM, or the front-end electronics processing the current pulse. Dead-time effects are particularly significant in scenarios with high count rates, i.e., high activity concentrations within the field of view (FOV) of the scanner [261, 274].

A common method for dead-time correction is based on a decaying source experiment. A model relating the true count rate to the measured count rate is proposed [76]. Since the true count rate must adhere to the physics of radioactive decay, which is proportional to $e^{-\lambda t}$ (where λ is the decay constant of the radionuclide), it can be estimated from the measured counts. For instance, adaptations of the decaying source method based on random coincidence rates [274] or singles to coincidence rates [261] have been proposed.

2.1.3.3 Data organisation

Prior to image reconstruction, the PET data are either organised into histogram bins (sinogram) or sequentially sorted in a list-mode fashion.

List-mode. In list-mode data, the endpoints of the recorded LORs are stored sequentially. List-mode data are generally preferred in applications where the number of possible LORs within the system is significantly greater than the number of recorded LORs during a PET scan. Additionally, list-mode is more convenient for applications that require LOR manipulation, such as motion correction [239, 287].

Sinogram. When counts are recorded along almost every LOR, data histogramming is often advantageous. In a 2D scenario, such as a single detector ring ($z = z_0$), the LOR defined between detectors A and B can be parameterised by its signed radial distance s from the center of the coordinate system (commonly the center of the detector ring) and its angular orientation ϕ ($0 \leq \phi < \pi$) (see Fig. 2.17a) [51]. This parameterisation is known as the sinogram $p(s, \phi)$. The sinogram uniquely defines all the LORs within a 2D plane of a PET detector ring. In the sinogram, the intensity of each bin (pixel) indicates the number of recorded events along that LOR (see Fig. 2.17b). For example

$$p(s_{AB}, \phi_{AB}) = p_{AB}(z = z_0).$$

Since PET scanners are composed of multiple detector rings, sinograms are divided into two types: direct sinograms and cross-plane sinograms. In direct sinograms, only LORs connecting detectors within the same ring are stored. In contrast, cross-plane sinograms store the LORs between detectors in different rings, thereby increasing the axial sampling. A 2D representation of the valid detector rings in coincidence is known as the Michelogram [70].

2.1.3.4 Reconstruction algorithms

Once the PET data have been organised and pre-corrected for various degrading effects (as previously described), tomographic reconstruction is the final step before obtaining an image of the radiotracer distribution. Since list-mode data reconstruction is only employed using iterative algorithms, this section assumes that the data have been histogrammed into their corresponding sinogram bins.

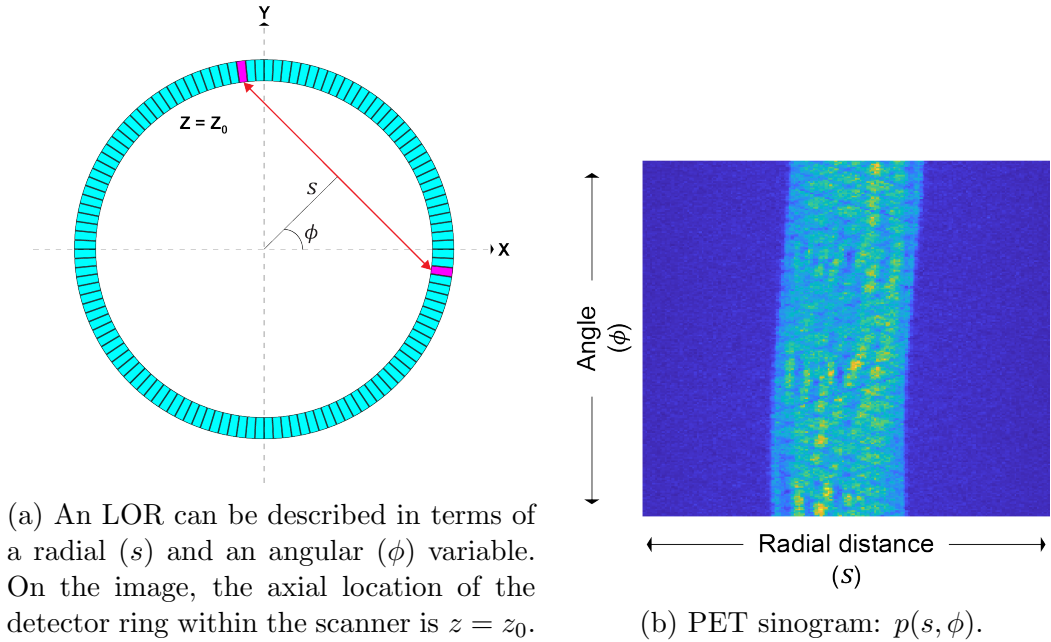


Figure 2.17: Organisation of the PET data in 2D.

Reconstruction algorithms can be divided into two categories: analytic and iterative algorithms. Analytic algorithms include direct Fourier reconstruction and filtered backprojection (FBP). However, direct Fourier reconstruction is rarely implemented in practice and will be omitted here.

Among iterative algorithms, the most common are the maximum-likelihood expectation maximisation (MLEM) and its accelerated version, ordered-subsets expectation maximisation (OSEM). Other iterative algorithms also exist, such as algebraic reconstruction technique (ART) and maximum a posteriori (MAP) [206], but describing all is beyond the scope of this thesis.

Filtered backprojection. At the heart of the filtered backprojection (FBP) method is the X-ray transform (X) and its inverse [51]. For 2D PET data,

the X-ray transform maps the radiotracer distribution $f(x, y)$ to its sinogram $p(s, \phi)$:

$$p(s, \phi) = Xf(x, y) \quad (2.14)$$

FBP retrieves the radiotracer distribution using the filtered projections $p^F(s, \phi)$ and the backprojection operator (X^{-1}):

$$f(x, y) = X^{-1}p^F(s, \phi) = \int_0^\pi d\phi p^F(s, \phi) \quad (2.15)$$

where the filtered projections $p^F(s, \phi)$ are defined as [115]:

$$p^F(s, \phi) = \mathcal{F}^{-1} \{ |\nu| \mathcal{F} \{ p(s, \phi) \} \} \quad (2.16)$$

where $\mathcal{F}$ denotes the 1D Fourier transform and $|\nu|$ the ramp filter.

In essence, the 1D projections are first filtered in the Fourier domain and then backprojected in the 2D image space to reconstruct the radiotracer distribution. Since the ramp filter tends to amplify high frequencies (i.e., noise), a low-pass filter is also applied to mitigate this effect [254].

Implementation of the FBP algorithm for 3D PET data is complex because not all the 2D projections are complete [209]. The 3D reprojection algorithm [117] (3D RP) addresses this by reconstructing an initial image estimate using only the 2D direct sinograms. The missing projections are then calculated by projecting this initial estimate. The final, fully 3D reconstruction is achieved using the complete 2D projections and the Colsher filter [41].

Due to the computational intensity of this algorithm, a more efficient approach is often used. Projections from cross-plane sinograms are often rebinned into neighbouring direct sinograms, allowing the use of 2D FBP to reconstruct the image. A common implementation of this technique is the Fourier rebinning (FORE) algorithm [53], which performs rebinning in the Fourier space.

Iterative algorithms (MLEM and OSEM). Analytical methods have limitations as they cannot incorporate more accurate models for data acquisition. These models should consider factors such as the statistical nature of photon detection (Poisson distributed), scanner geometry, photon transport (e.g., scattering) and positron physics [209]. In contrast, iterative algorithms can account for all these factors, albeit at the expense of increased complexity [254].

Iterative algorithms utilise a discrete representation of both the measured data and the reconstructed image [51]. The mean measured data along LOR i (q_i), where $i = 1, \dots, I$ and I is the total number of LORs, described as:

$$q_i = E \{ p_i \} = \int_{FOV} f(\mathbf{r}) \Psi_i(\mathbf{r}) d\mathbf{r} \quad (2.17)$$

Here, p_i represents the measured data along LOR i , E denotes the expectation (mean) of p_i , $f(\mathbf{r})$ is the radiotracer distribution, and $\Psi_i(\mathbf{r})$ is a sensitivity function that can model various physical effects (e.g., attenuation, scanner geometry, positron physics). For simplicity, the notation p_{AB} has been replaced by p_i .

The image model can be described in terms of linear combinations of basis functions:

$$f(\mathbf{r}) = \sum_j^J x_j \alpha_j(\mathbf{r}) \quad (2.18)$$

where x_j is the coefficient of the basis function $\alpha_j(\mathbf{r})$. In practice, $\alpha_j(\mathbf{r})$ is typically a voxel and x_j its value. The total number of voxels is J . The data model can then be written as follows:

$$q_i = \sum_{j=1}^J a_{ij} x_j \quad (2.19)$$

where a_{ij} is an element of the system matrix:

$$a_{ij} = \int_{FOV} \Psi_i(\mathbf{r}) \alpha_j(\mathbf{r}) d\mathbf{r} \quad (2.20)$$

The system matrix can be interpreted as the probability of detecting an emission from voxel j along LOR i . If this probability depends solely on the scanner geometry, a_{ij} can be calculated using ray-tracing algorithms [108, 236].

The key component of iterative algorithms is the cost function. The cost function aims to minimise the difference between the expected data q_i^k and the measured data p_i , by adjusting the values $\mathbf{x}^k$ (i.e., $q_i^k(\mathbf{x}^k)$), where k denotes the iteration number during the estimation process. Both MLEM and OSEM algorithms use the Poisson log-likelihood as the cost function:

$$\ln \{Pr(\mathbf{p}|\mathbf{q}^k)\} = \sum_{i=1}^I p_i \ln(q_i^k) - \sum_{i=1}^I q_i^k - \sum_{i=1}^I \ln(p_i!) \quad (2.21)$$

The MLEM algorithm [233] can then be formulated based on finding the gradient of the cost function (i.e., an optimisation problem) and selecting the appropriate step size for subsequent updates [209]:

$$x_j^{k+1} = \frac{x_j^k}{\sum_{i=1}^I a_{ij}} \sum_{i=1}^I a_{ij} \frac{p_i}{\sum_{j=1}^J a_{ij} x_j^k} \quad (2.22)$$

MLEM has the property of being monotonically convergent towards the maximum log-likelihood; however, this convergence is rather slow [254]. Additionally, MLEM often results in noisy images due to the ill-conditioning of the problem [51]. Consequently, the algorithm is often terminated before convergence, and/or the images are smoothed at each iteration.

The accelerated version of MLEM is known as OSEM. In OSEM, the measured data are divided into L subsets ($S_1, \dots, S_L$), and the image estimate is updated after a pass through each subset of data [99]:

$$x_j^{k,l+1} = \frac{x_j^{k,l}}{\sum_{i \in S_l} a_{ij}} \sum_{i \in S_l} a_{ij} \frac{p_i}{\sum_{j=1}^J a_{ij} x_j^{k,l}} \quad (2.23)$$

Because OSEM updates the image L times in a single pass through the entire dataset, it converges faster than MLEM. However, in addition to the issue of ill-conditioning, a drawback of OSEM is that it is not guaranteed to converge to the maximum likelihood solution. Instead, OSEM often cycles between L slightly different solutions [51].

The list-mode MLEM algorithm can be found in [196], while the list-mode OSEM algorithm is introduced in Chapter 5.

To conclude, it is important to note that data pre-corrections affect the Poisson nature of the measured counts [44, 208]. To preserve this, data corrections should be included within the reconstruction algorithm [94, 208, 260].

2.1.4 PET Scanner Performance

Having described key physical and computational aspects of PET imaging, the following section aims to briefly discuss the various factors that contribute to the performance of a PET scanner. These factors are crucial considerations in the design and development of new systems.

2.1.4.1 Spatial resolution

The seminal paper by W. Moses [177] outlines the various components that contribute to the spatial resolution of a PET scanner. These components include: (i) detector size; (ii) positron range; (iii) photon acollinearity; (iv) event decoding; and (v) photon penetration.

Detector size. We shall define the spatial resolution of an imaging system as its ability to distinguish between two adjacent objects. From a sampling perspective, this ability depends on how finely the objects are sampled. In a PET scanner, the sampling frequency is determined by the crystal size for pixelated detectors or by the intrinsic resolution of the detector for those based on monolithic crystals.

Positron range. As outlined in Section 2.1.1.1, positrons are emitted with kinetic energy during a β^+ decay. Consequently, positrons travel a certain distance within the body before annihilating, a phenomenon known as positron range (see Fig. 2.18). Positron range is a significant physics-related limitation on the spatial resolution in PET, as the point of positron emission does not coincide with the point of annihilation. Table 2.5 shows the positron range in water for common radionuclides used in PET. Clearly, the greater the kinetic energy of the positron, the longer the positron range.

Photon acollinearity. Another physics-related limitation is photon acollinearity. When a positron annihilates before losing all its momentum, the conservation of momentum causes the photons to be emitted at angles slightly different from 180° (see Fig. 2.18). This results in a distribution of $180^\circ \pm 0.25^\circ$ [100]. Photon acollinearity becomes more problematic as the scanner radius increases.

Event decoding. Event decoding refers to the methods used for detector readout and event positioning. As discussed in Section 2.1.2.4, PET detectors

can either have individual readout, where each crystal is paired with its own photodetector, or light-sharing configurations, where a pixelated crystal array or a monolithic block shares light among multiple photodetectors. In the case of individual readout, the electronics uniquely identify the event position of interaction. However, in light-sharing configurations, several factors can impact the positioning accuracy, including edge effects [84, 156, 238] and inter-crystal scatter events [232, 283].

Chapter 4 presents a deep learning algorithm designed to improve event positioning in light-sharing pixelated detectors.

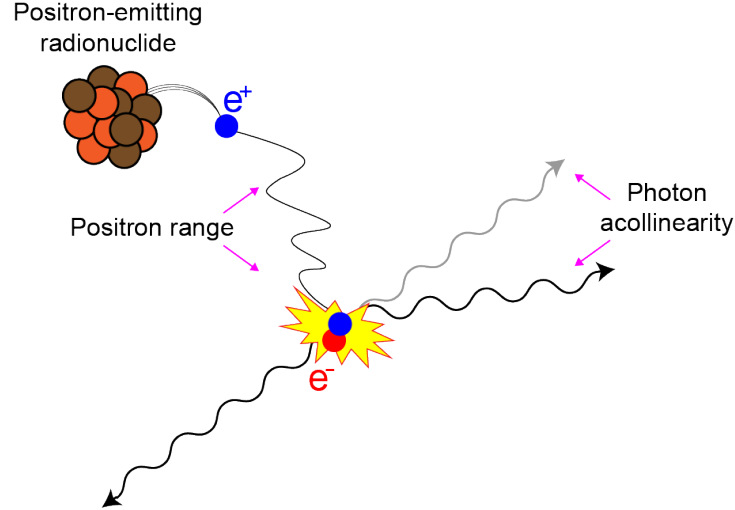


Figure 2.18: Positron range and photon acollinearity degrade the spatial resolution in PET. In the case of photon acollinearity, the angle deviation from the ideal 180° between the emitted photon pair is exaggerated.

Table 2.5: Maximum and mean positron range (in mm) in water of common radionuclides used in PET. Taken from [45].

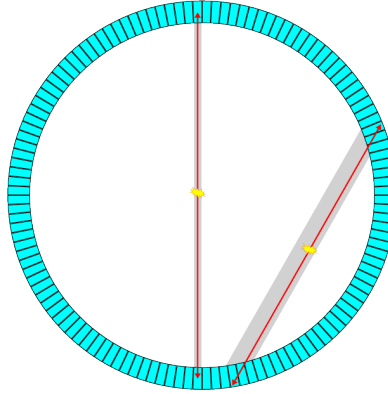
Radionuclide	Max (Mean) Positron range [mm]
^{11}C	4.2 (1.2)
^{13}N	5.5 (1.8)
^{15}O	8.4 (3.0)
^{18}F	2.4 (0.6)
^{68}Ga	9.2 (3.5)

Photon penetration. Photon penetration refers to the distance photons travel within the crystal before being absorbed. LORs from coincidence photons impinging perpendicularly to the crystal front face are correctly positioned. However, when photons impinge at different angles, photon penetration causes mispositioning of the LOR. This mispositioning results in an apparent 'elongation' of the LOR, known as parallax error (Fig. 2.19a). To correct such errors, PET detectors need to account for the depth of interaction (DOI) at which the photons are detected [103] (Fig. 2.19b).

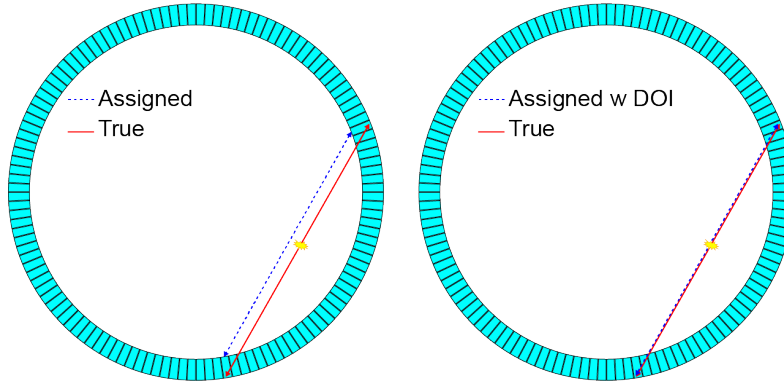
In conventional cylindrical PET geometries, the parallax effect only appears when imaging an object off-centre from the FOV. Therefore, DOI-capable PET detectors have commonly been used only in high-resolution, narrow-bore PET applications [122, 124, 162, 275]. However, in non-cylindrical PET geometries, the effect appears throughout the entire FOV [67, 205].

The scanner being developed as part of this thesis features an overlapping box geometry, making parallax errors a significant consideration. This is particularly important in Chapter 3, where a DOI-capable detector is developed, and in Chapter 5, where a DOI PET reconstruction framework is developed for the scanner.

Section 2.2.1 expands on various DOI-capable detector geometries for narrow-bore PET applications.



(a) Photons that do not impinge perpendicularly to the crystal front face experience parallax errors. This mispositioning of the LOR results in an apparent 'elongation' of the LOR, illustrated in grey.



(b) PET detectors that measure DOI can correct for parallax error. However, the correction is not perfect due to the limited DOI resolution of the detector.

Figure 2.19: Parallax error in PET and the impact of DOI-capable PET detectors.

Each of the aforementioned elements contributes to the overall spatial resolution of a PET system (R_{sys}). The total spatial resolution is given by the

equation:

$$R_{sys} = (R_{det}^2 + R_{range}^2 + R_{acol}^2 + R_{decod}^2 + R_{pen}^2)^{1/2} \quad (2.24)$$

where R_{det}^2 represents the spatial resolution contribution from the detector, R_{range}^2 is the contribution from positron range (dependent on the positron energy), R_{acol}^2 accounts for the contribution from photon acollinearity (dependent on the scanner radius), R_{decod}^2 denotes the contribution from event positioning decoding error (which is zero if individual crystal readout is used), and R_{pen}^2 reflects the contribution from photon penetration/parallax error.

2.1.4.2 Energy resolution

Energy resolution refers to the ability to discriminate between photons of different energies. It depends on several factors [82]: the amount of light emitted by the scintillation crystal (i.e., light yield), the proportion of this light reaching the photodetector, the photon detection efficiency (PDE) of the photodetector, and the linearity and noise contribution of the readout electronics. Good energy resolution is always desirable as it allows for better discrimination between true and scattered events.

2.1.4.3 Sensitivity

Sensitivity refers to the ability of the PET scanner to detect emitted 511-keV photons. It depends on the intrinsic efficiency and packing fraction of the detectors, and the solid angle covered by the PET scanner [68]. The intrinsic efficiency of the detector is determined by its thickness and the material used. For example, for LYSO and BGO crystals, the attenuation length ($\lambda = 1/\mu$) of 511-keV photons is 11.4 mm and 10.4 mm, respectively [100]. This means that with crystals of these thicknesses, approximately $\sim 63\%$ of photons will undergo either photoelectric absorption or Compton interaction within the crystal. In practice, to increase the probability of detection, thicker crystals (~ 20 mm) are used [12, 83, 124].

To improve solid angle coverage, the most straightforward approach is to increase the axial length of the PET scanner [12, 60, 203]. Additionally, various scanner geometries have been proposed to minimise detector gaps or dead spaces [91, 129]. Conventional ring geometries offer limited sensitivity due to inter-block gaps in the arrangement of detector blocks (see Fig. 2.20). In contrast, the overlapping box geometry, combined with the use of thick crystals (e.g., 20 mm), enhances system sensitivity. This configuration is employed in the PET scanner being developed as part of this thesis.

2.1.4.4 Coincidence time resolution

Coincidence time resolution (CTR) refers to the system ability to precisely measure the time difference between the arrival of the two coincidence photons at different detectors. CTR is influenced by the emission and transport of scintillation photons within the crystal [109], the type of photodetector used [89], and the readout electronics employed [182]. Conventional PET scanners achieve

CTR values in the nanosecond range; however, PET scanners with TOF capabilities can achieve values around 200 picoseconds [203]. Good CTR is desirable as it allows for the use of narrow coincidence time windows, which in turn reduces the contribution of random coincidences. For TOF-PET, the primary advantage of improved CTR is a better image signal-to-noise ratio (SNR) [142, 157]:

$$SNR_{TOF\ gain} = \sqrt{\frac{2D}{c\ CTR}} \quad (2.25)$$

where D is the diameter of the scanner FOV and c is the speed of light.

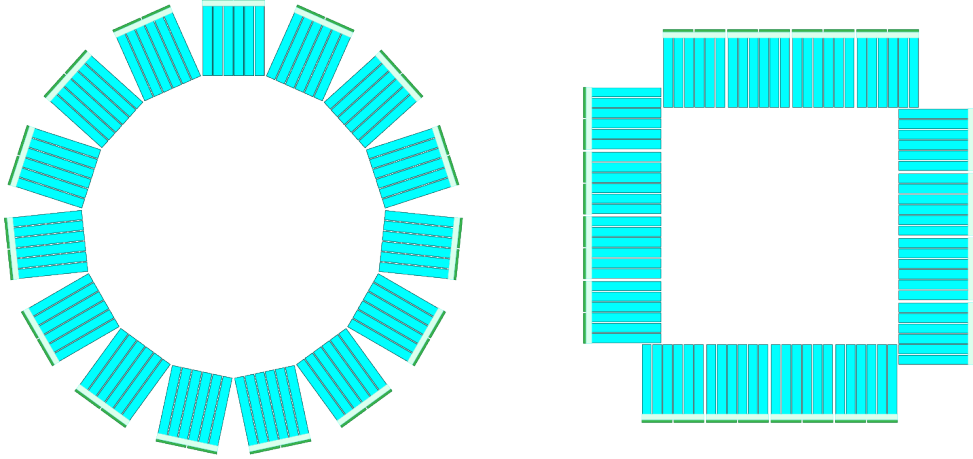


Figure 2.20: Two different PET scanner geometries: The conventional ring (left) and an overlapping box geometry (right). The latter configuration is employed in the PET scanner being developed as part of this thesis.

2.1.5 PET Applications

Pre-clinical PET imaging facilitates fundamental research on disease understanding and drug development. PET has applications in many clinical fields, including oncology, neurology, and cardiology. With the recent development of total-body PET (TB-PET) scanners, the clinical applicability of PET is expanding (e.g., in paediatrics [187]). This section briefly discusses the various applications of PET in both clinical and pre-clinical settings.

In oncology, ^{18}F -Fluorodeoxyglucose (FDG) is used as a marker for tumour glycolysis [77]. It enables the staging of cancer both before and after treatment (e.g., chemotherapy and radiotherapy), allowing the evaluation of treatment response. FDG-PET is particularly sensitive for staging various types of cancer, including lung, colorectal, and lymphomas [77, 213].

In cardiology, PET is employed to study myocardial blood flow, mechanical function, and metabolism [226]. The integration of complementary and synchronised electrocardiogram data with ^{82}Rb PET facilitates the detailed study of ventricular function [33]. Myocardial tissue viability is imaged using FDG, while ^{13}N -ammonia and ^{82}Rb are utilised to diagnose coronary artery disease [15].

In neurology, FDG-PET is used to assess brain glucose metabolism. This assessment can be utilised for brain tumour staging, early dementia diagnosis, and identification of epileptogenic foci in patients with uncontrolled seizures [248]. Other radiotracers are also commonly employed; for example, ^{18}F -6-Fluorodopa is used for studying the dopaminergic system in movement disorders, such as Parkinson’s disease [102], while H_2^{15}O provides insights into cerebral blood flow, identifying regions with severe tissue damage after stroke [161].

To understand human diseases and evaluate potential therapies, animal models are essential [36]. Pre-clinical PET serves as a crucial link between animal and human research, enabling the translation of animal experiments into clinical applications [22, 218]. Among different animal models, non-human primates (e.g., rhesus monkeys) [98] and small murine rodents (i.e., mice and rats) [278] have been used extensively in PET research. The latter is commonly referred to as small-animal PET.

Similarities in physiology, complex cognitive capabilities, reproductive biology, and brain organisation between non-human primates and humans make them a more robust model in fields such as neuroscience, immunology, and drug development [28, 98, 221, 251]. However, ethical regulations around the use of non-human primates, especially in certain countries (e.g., Australia [93]) leads to greater reliance on rodents for scientific research. Furthermore, small-animal PET has the advantage of leveraging extensive and well-understood tools for genetic manipulation, as well as the high genetic homology these animals share with humans [64].

The development of the microPET scanner in 1997 [38], the first small-animal PET system with sufficient image resolution to visualise small rodents, marked a significant advancement. It facilitated investigations into models for brain injury and plasticity in rats, as well as antibody fragments in mouse tumour models, among other applications [35]. Since then, the scope of small-animal PET has expanded considerably [278]. For instance, in cancer research, small-animal PET imaging has been utilised to study cell proliferation, tumour angiogenesis (the formation of blood vessels for tumour growth), and cell apoptosis [54].

The next section focuses on small-animal PET technology, its applications and limitations.

2.2 Small-Animal PET

The advent of small-animal PET has enabled imaging of physiological processes in small laboratory rodents during both healthy and disease stages with acceptable resolution and sensitivity [36]. This advancement has significantly enhanced our understanding of disease progression and has driven improvements in drug development and efficacy. Although the field has made substantial progress since the development of microPET [34, 38], and numerous commercial and research-based PET scanners are now available, several challenges remain [60, 171, 278].

Currently, state-of-the-art clinical PET scanners achieve spatial resolution values of approximately 3 mm [12, 203]. To attain comparable performance in much smaller mammals, such as mice and rats, dedicated PET scanners for these animals should achieve a spatial resolution better than 0.2 mm and 0.4 mm, respectively [60]. However, current whole-body small-animal PET scanners typically achieve a spatial resolution of around 1 mm [87, 88, 122, 124].

Given our limited understanding of the onset and mechanisms of many neurological disorders, small-animal brain PET imaging holds significant potential [79]. State-of-the-art clinical brain PET scanners now achieve spatial resolution values of approximately 1.2-1.6 mm [30, 125, 141]. To achieve proportional performance in small-animal brain PET imaging, systems would need to achieve resolution values better than 0.1 mm [60]. However, this level of resolution is currently unattainable due to the physical limitations imposed by positron range and photon acollinearity. Mouse brain-dedicated PET scanners have achieved spatial resolution values around 0.5-0.6 mm [111, 275, 277], often with limited system sensitivity [275, 277], which precludes high-resolution dynamic brain imaging.

According to equation 2.24, much of the spatial resolution of a system depends on detector technology (i.e., ignoring positron range). Although reducing the diameter of the scanner can enhance resolution, it must still be large enough to accommodate mice and/or rats. To achieve high detector spatial resolution, highly pixelated crystals [190] or semi-monolithic crystal [127] blocks with (near) sub-millimetre crystal pitch are required. Additionally, due to the narrow bore requirements, detectors need to measure the photon depth of interaction (DOI), ideally, with sub-millimetre accuracy [171].

To enhance system sensitivity in small-animal PET scanners, various geometries have been proposed to minimise [91, 129] or completely eliminate detector gaps [74, 273]. Additionally, TB-PET scanners have now been developed [175, 224].

Although not frequently acknowledged, anaesthetics present a significant limitation in small-animal PET, particularly in brain imaging studies [170]. Animals must remain still to avoid motion-induced artefacts, frequently necessitating the use of anaesthesia prior and during imaging. However, several studies have demonstrated the disruptive effects of anaesthetics on neurophysiological processes of interest, such as reduced brain glucose metabolism [173], and changes in

cerebral blood flow [159] and neurotransmission [104, 253]. Additionally, anaesthesia precludes the use of PET imaging for behavioural studies [130, 167]. To address this issue, various methods for imaging awake animals have been proposed. These methods can be categorised into restrained and unrestrained approaches. Section 2.2.5 elaborates further on these methods.

The following sections present various detector geometries for retrieving depth-of-interaction (DOI) information (Section 2.2.1). This is followed by an overview of state-of-the-art PET systems for whole-body and brain-only small-animal PET imaging (Section 2.2.2). Next, the effects of anaesthesia are discussed (Section 2.2.3), along with methods for imaging small animals without anaesthesia (Section 2.2.4). The section concludes by introducing Open-Field Mouse Brain PET (Section 2.2.5), a high-resolution and high-sensitivity PET scanner for imaging awake and freely moving mice.

2.2.1 Depth-Encoding PET Detectors

As outlined in Section 2.1.4, parallax errors, resulting from the mispositioning of LORs, degrade spatial resolution. These errors are more pronounced in narrow-bore systems, making them a significant performance issue for small-animal PET. To achieve uniform high resolution, ideally in the sub-millimetre range, it is essential to correct for parallax errors.

To address these errors, various detector geometries capable of measuring the depth of interaction (DOI) at which the 511-keV photons were absorbed have been proposed [103]. These geometries can be categorised based on the readout configuration: single-ended and dual-ended.

2.2.1.1 Single-Ended Readout

In single-ended readout detectors, light is collected from only one end of the crystal array. In monolithic or semi-monolithic crystal blocks, continuous DOI information is retrieved from the inherent light distributions as a function of depth [84, 85] (Fig. 2.21a). An average DOI resolution of 1.6 mm has been reported in small-animal PET scanners using single-ended readout monolithic crystals [122, 87].

For pixelated detectors based on single-ended readout, one approach involves using multilayer scintillation arrays either (i) based on the same material but with each layer shifted by an offset [111] (Fig. 2.21b), or (ii) using different scintillation crystals and relying on the different timing properties of the crystals [88]. The latter approach is also known as *phoswich*. In both cases, the DOI resolution is determined by the crystal thickness.

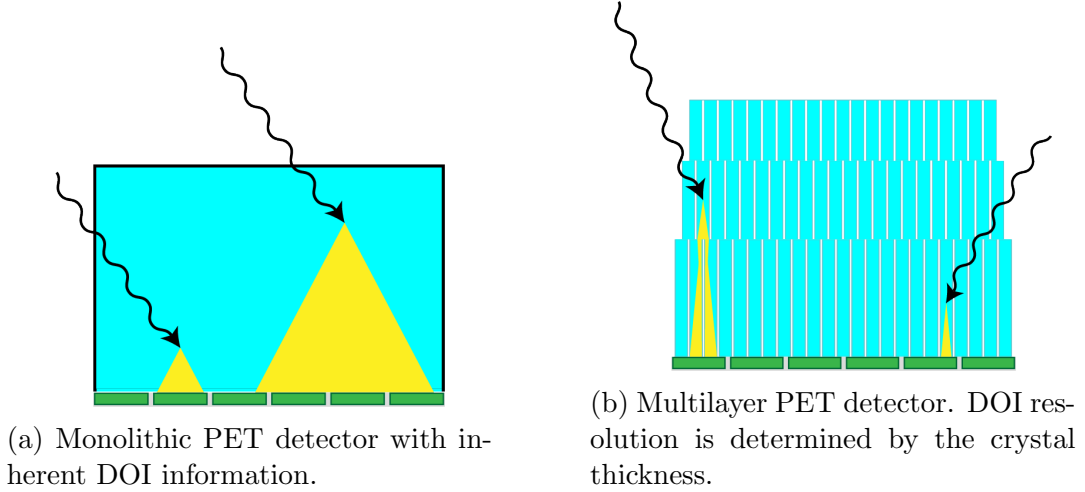


Figure 2.21: DOI-capable PET detectors based on (a) monolithic and (b) multilayer configurations

Another method for measuring DOI in pixelated detectors involves re-orienting the crystal and photodetector so that the DOI can be measured directly from the crystal where the 511-keV photons were absorbed. Multilayers of these detector configurations allow for the measurement of the 3D position of the photon interaction [257]. Due to the detector geometry, the DOI resolution equals one of the lengths of the crystal.

Additional DOI-capable geometries based on pixelated detectors include: (i) using reflector layers to partially limit optical crosstalk between neighbouring crystals [150, 172, 186], with DOI measured based on light ratios detected in both crystals; (ii) applying phosphor coatings to the first half of the crystal [16, 58], where the phosphor substrate absorbs the scintillation light and later emits wavelength-shifted light with a longer decay time, making the output pulse DOI-dependent (Fig. 2.22a); and (iii) using optical light guides at the front face of the scintillation array [136, 200], causing DOI-dependent light patterns in the photodetector arrays.

2.2.1.2 Dual-Ended Readout

Dual-ended readout involves reading out the scintillation crystal (monolithic or pixelated) from both front and back faces (Fig. 2.22b). In this case, DOI information is extracted by measuring the ratio of light collected at both crystal ends [59, 129, 276]. Using this approach, the SIAT aPET, a small-animal PET scanner based on 20-mm thick dual-ended readout detectors, has an average DOI resolution of 1.9 mm [124]. Additionally, a DOI resolution of approximately 2 mm is expected for the small-animal TB-PET currently under development at UC Davis [60].

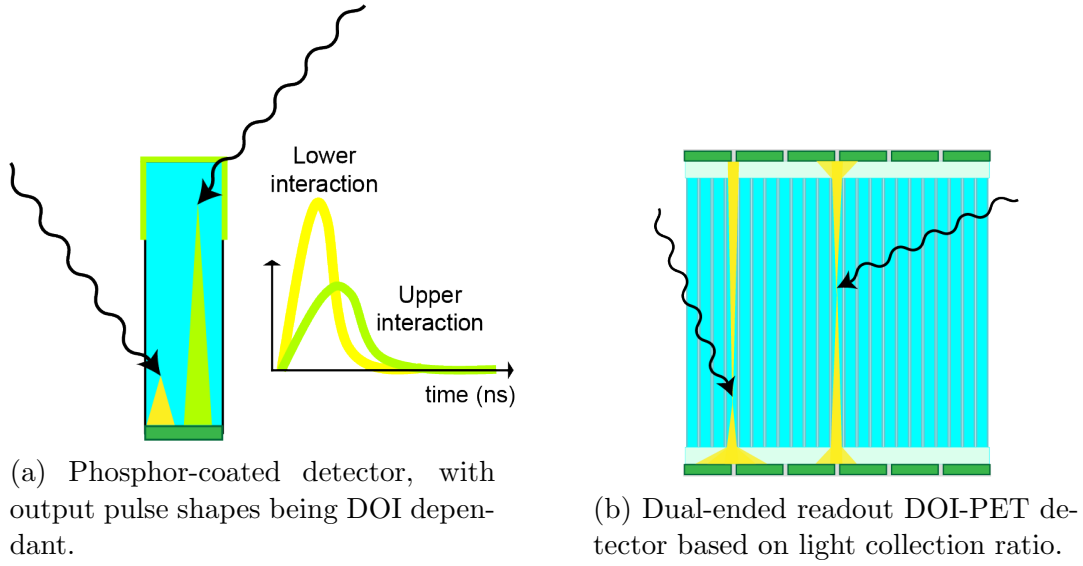


Figure 2.22: DOI-capable PET detectors based on (a) phosphor-coated configurations and (b) dual-ended readout.

2.2.2 Small-Animal PET Scanner Design

Many small-animal PET scanners have been developed for both research and commercial purposes. This section focuses on PET systems capable of achieving spatial resolution around or below 1 mm, reflecting the current trend in the field. System sensitivity was not used as a filtering criterion because all current systems achieve absolute sensitivity values of $\leq 16\%$. However, it should be noted that strict comparisons of reported spatial resolution values are difficult because resolution values are often presented using different reconstruction algorithms, such as FBP or MLEM/OSEM. The non-negativity constraint of iterative algorithms can lead to artificially enhanced resolution values [80].

The systems will be categorised into two groups: whole-body and brain-only PET imaging. For whole-body small-animal PET scanners, the same discrimination metric as in [60] was adopted, considering only systems with published system performance and with an axial FOV of 90 mm or greater, sufficiently to cover small rodents. A more comprehensive list of all commercially available PET scanners can be found in [6, 171].

2.2.2.1 Whole-body PET scanners

Five whole-body PET scanners are included in this list: Albira Si PET (Bruker BioSpin, Germany), β -CUBE (MOLECUBES, Belgium), HiPET, SimPET-X and SIAT aPET.

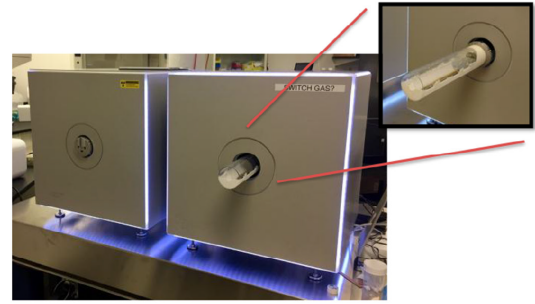
The SiPM-based Albira Si PET scanner (Fig. 2.23a) comprises three detector rings, each consisting of 8 monolithic PET detectors [81]. Each PET detector is constructed from a 10-mm thick tapered LYSO monolithic crystal and is read out by a 12×12 SiPM array. The front end of the crystal has dimensions of 48 mm $\times$ 48 mm, while the back end, in contact with the SiPM array, measures 50 mm $\times$ 50 mm. The axial and transaxial FOV of the scanner are 148 mm and

80 mm, respectively. Using the MLEM, the volumetric spatial resolution of the system ranges between 0.9-1.0 mm³. With an energy window (EW) of 256-767 keV, the system sensitivity is 9% at the center of the FOV.

The β -CUBE PET scanner (Fig. 2.23b) consists of five detector rings, each composed of nine PET detectors [122]. Each detector is made of monolithic LYSO blocks measuring 25.4 mm $\times$ 25.4 mm $\times$ 8 mm and is read out by an array of SiPMs. The scanner's transaxial and axial FOV are 72 mm and 130 mm, respectively. The DOI and volumetric spatial resolution of the system are 1.6 mm and 1.0 mm³ (OSEM), respectively. Using an EW of 255-765 keV, the system sensitivity is 12.4% at the centre of the FOV.



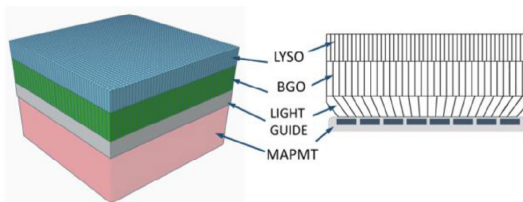
(a) Albira Si PET scanner. Taken from [81].



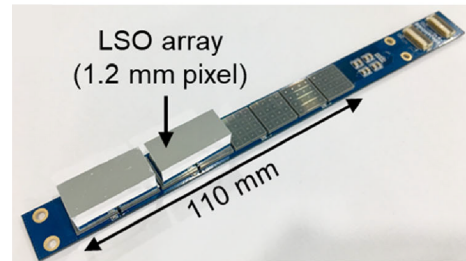
(b) β -CUBE with animal bed. Taken from [122].

Figure 2.23: Albira Si PET and β -CUBE scanners.

HiPET is based on two-layer pixelated crystals (Fig. 2.24a) [88]. The upper layer consists of 48 $\times$ 48 LYSO crystals measuring 1.01 mm $\times$ 1.01 mm $\times$ 6.1 mm, while the bottom layer is made of 32 $\times$ 32 BGO crystals measuring 1.55 mm $\times$ 1.55 mm $\times$ 8.9 mm. Scintillation light is detected using multi-anode PMTs. The transaxial and axial FOVs are 131 mm and 104 mm, respectively. A volumetric spatial resolution of 0.66-0.96 mm³ (OSEM) is reported. Due to the multilayer configuration, inter-layer Compton scatter (ILCS) events can be detected. The sensitivity of the scanner, using a low energy threshold of 250 keV, is 11.8% with ILCS events rejection and 13.5% without ILCS events rejection.



(a) HiPET multilayer PET detector. A light guide is used for coupling the BGO array with the multi-anode (MA) PMT. Taken from [88].



(b) A SimPET-X 'super' module showing 2 LSO crystal arrays and 8 SiPM arrays. Taken from [114].

Figure 2.24: HiPET and SimPET-X scanners.

SimPET-X is a PET insert designed for simultaneous PET-MR imaging [114]. The system comprises 16 'super' modules, each of which is made up of 4 detector blocks, with each block read out by SiPM arrays (Fig. 2.24b). Each detector block consists of an array of 20×9 LSO crystals, measuring $1.2 \text{ mm} \times 1.2 \text{ mm} \times 10 \text{ mm}^3$. The system has an axial FOV of 110 mm and a transaxial FOV of 50 mm. The SimPET-X detectors cannot measure DOI, and the spatial resolution along the radial component exceeds 1.0 mm when imaging a point source off-centre. To compensate for the lack of DOI, OSEM reconstructions with PSF modelling (including a 10% warm background) have demonstrated that the system can achieve a resolution of $\leq 1 \text{ mm}$ across almost the entire FOV. Using an EW of 250-750 keV, the system sensitivity at the centre of the FOV is 8%.

The SIAT aPET scanner is based on dual-ended readout detectors [124]. The scanner comprises four detector rings, each containing 12 detectors (Fig. 2.25). Each detector module consists of an array of 23×23 LYSO crystals, measuring $1.0 \text{ mm} \times 1.0 \text{ mm} \times 20 \text{ mm}$, and is read out using SiPM arrays. The axial and transaxial FOV of the scanner are 111 mm and 105.7 mm, respectively. The system has an average DOI resolution of 1.96 mm. With a 1% background (OSEM reconstruction), the volumetric spatial resolution remains $< 1 \text{ mm}^3$ throughout the FOV (exact numbers are not provided). Using an EW of 250-750 keV, the system sensitivity at the centre of the FOV is 16%.

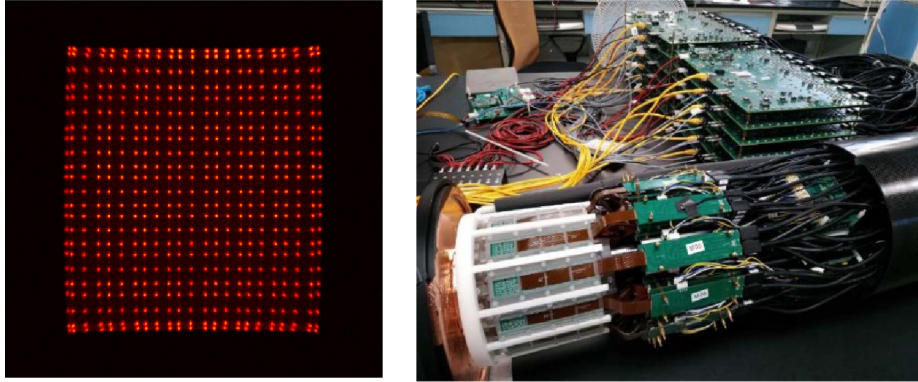


Figure 2.25: SIAT aPET scanner. (left) Detector flood map resolving the 23×23 LYSO crystals. (right) PET scanner fully assembled. Adapted from [124].

2.2.2.2 Brain-only PET scanners

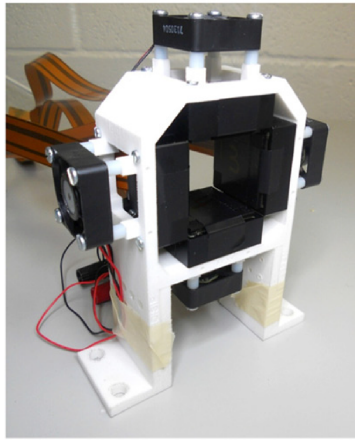
Four small-animal brain-dedicated PET scanners are highlighted below. These are: DigiPET, Yamamoto's PET, Yang's PET and SR-PET.

DigiPET consists of four monolithic LYSO crystal blocks, each measuring $32 \text{ mm} \times 32 \text{ mm} \times 2 \text{ mm}$, coupled to digital SiPM arrays (Fig. 2.26a) [69]. To limit the contribution of dark counts, the system operates at a temperature of 5-6 °C, necessitating its placement inside a temperature-controlled chamber. The axial and transaxial FOV are 32 mm and 34.5 mm, respectively. Due to the use of thin scintillators, DOI information is not required. Using MLEM, the volumetric spatial resolution throughout the FOV is approximately $(0.7)^3$

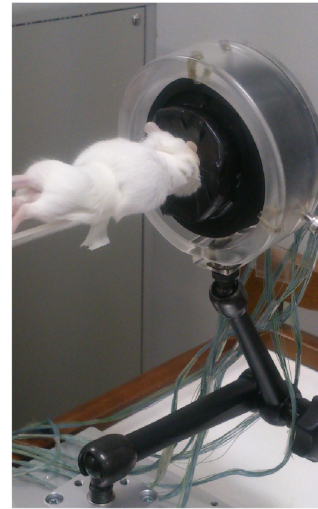
mm^3 . With an EW of 250-650 keV, the sensitivity at the centre of the FOV is 0.6%.

Yamamoto's PET scanner uses pixelated LYSO crystals measuring $0.32 \text{ mm} \times 0.5 \text{ mm} \times 5.0 \text{ mm}$, arranged in arrays of 22×15 crystals [275]. These pixelated crystals are interfaced with a single array of SiPMs through a 1-mm thick light guide, without DOI capability. The PET scanner consists of a single detector ring with 8 detector units (Fig. 2.26b). The scanner ring diameter is 22.3 mm and the FOV is approximately 9 mm. Using FBP, the radial and tangential spatial resolution values range from 0.6 mm to 0.8 mm. The system sensitivity at the centre of the FOV is 0.5%.

Yang's PET scanner consists of a single detector ring with 16 dual-ended readout detectors (Fig. 2.27) [277]. Each detector comprises 14×14 tapered LSO crystal elements. At the front end, each crystal measures $0.43 \text{ mm} \times 0.43 \text{ mm}$, while at the other end the size is $0.80 \text{ mm} \times 0.43 \text{ mm}$. Light is collected at both ends of the crystal using arrays of position-sensitive APDs. The system has a transaxial FOV of 30 mm and an axial FOV of 7 mm. The average DOI resolution is 1.7 mm, while the average spatial resolution (axial, radial, and tangential) is 0.55 mm throughout the FOV. Using a low energy threshold of 250 keV, the sensitivity of the scanner at the centre of the FOV is 0.7%.



(a) DigiPET scanner. Taken from [69].



(b) Mouse undergoing brain imaging in Yamamoto's PET. Taken from [275].

Figure 2.26: DigiPET and Yamamoto's PET scanner.

SR-PET scanner is the latest mouse brain-only PET scanner reported [111]. The system comprises four detector rings, each containing 16 DOI-capable detectors. These detectors are based on a three-layer configuration of pixelated LYSO crystals, with SiPM arrays used for light detection (Fig. 2.28). The first, second, and third LYSO layers consist of 10×9 , 10×10 , and 11×11 crystal elements, respectively. The crystal thicknesses for the first, second, and third layers are 4 mm, 4 mm, and 7 mm, respectively, with a cross-sectional crystal area of $0.9 \text{ mm} \times 0.9 \text{ mm}$ in all cases. Using OSEM, the system achieves a volumetric spatial resolution of approximately $(0.55)^3 \text{ mm}^3$ throughout the FOV.

The system sensitivity is 8.7% using an EW of 250-750 keV.

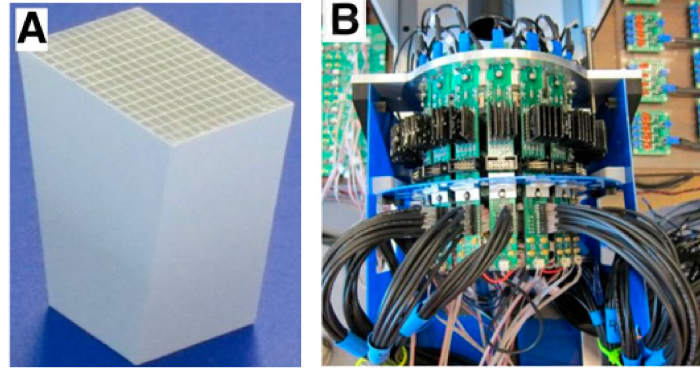


Figure 2.27: Yang's PET scanner. (a) Tapered LSO crystal array. (b) The fully-assembled scanner. Adapted from [277].

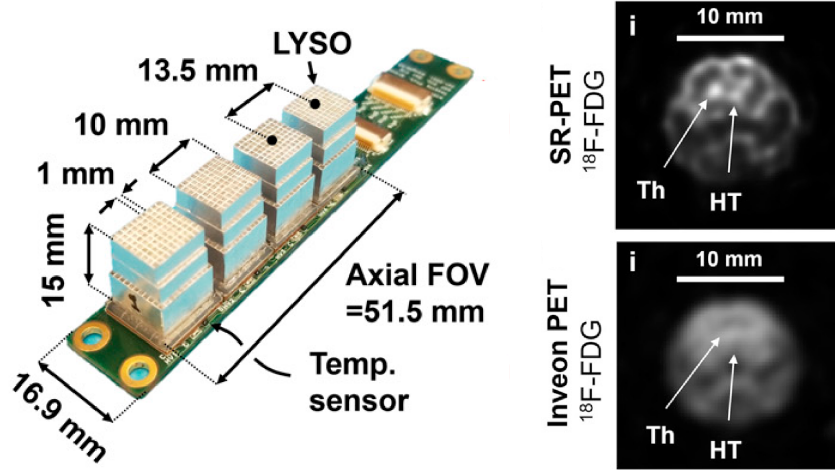


Figure 2.28: ((left) SR-PET detector module. (right) Performance comparison between SR-PET and a Siemens Inveon PET scanner. Th = Thalamus; HT = Hypothalamus. Adapted from [111].

2.2.2.3 Summary

Tables 2.6 and 2.7 summarise key performance characteristics of whole-body and brain-only small-animal PET scanners, respectively, previously detailed. It is evident that while whole-body PET scanners achieve (near) sub-millimetre spatial resolution, this resolution is not optimal for imaging the small structures in the mouse brain [111]. In contrast, brain-only PET scanners achieve superior resolution values, often at the expense of lower sensitivity. An exception is the SR-PET scanner, which achieves sensitivity values comparable to those of whole-body PET scanners.

However, in all these scanners, animals need to be anaesthetised before imaging. The following section discusses the negative effects of anaesthetics on neurophysiological parameters of interest. This highlights a significant limitation of all the

small-animal PET scanners presented here: their inability to image the brain of these rodents without the use of anaesthesia.

Table 2.6: Performance metrics of whole body small-animal PET systems.

System Name	Spatial resolution [mm]	DOI resolution [mm]	Sensitivity (in %)
Albira Si PET	0.9*	not reported	9.0
β -CUBE	1.0* / 1.0 [†]	1.6	12.4
HiPET	$\sim 1.1^*/\sim 1.3^\dagger$	>6.0	13.5
Sim PET-X	1.0**	no DOI	8.3
SIAT aPET	0.7**	2.0	16.0

Spatial resolution values are for the radial component.

Spatial resolution and sensitivity values are for measurements at the centre of the FOV.

[†] FBP

* OSEM/MLEM

** OSEM/MLEM with background

Table 2.7: Performance metrics of brain-only small-animal PET systems.

System Name	Spatial resolution [mm]	DOI resolution [mm]	Sensitivity (in %)
DigiPET	0.7*	no DOI	0.6
Yamamoto's PET	0.6 [†]	no DOI	0.5
Yang's PET	0.5**	1.7	0.7
SR-PET	0.6*/1.0 [†]	≥ 4	8.7

Spatial resolution values are for the radial component.

Spatial resolution and sensitivity values are for measurements at the centre of the FOV.

[†] FBP

* OSEM/MLEM

** OSEM/MLEM with background

2.2.3 Anaesthetics

Brain PET imaging of small animals aims to model aspects of the human brain to translate knowledge into clinical settings. However, the use of anaesthesia, which is necessary to keep the animal still during the scan, can limit this translation [164, 170]. Anaesthetics have been shown to affect physiological parameters such as body temperature (e.g., inducing hypothermia [40]), cerebral blood flow (CBF) [57, 159], cardiac output [3], and glucose metabolism [159, 163, 173, 255]. Additionally, anaesthetics interact with various neurotransmitter systems [104, 253], which are often the focus of PET neurological studies.

The kinetics of different PET radiotracers can be impacted by changes in CBF [3, 159]. Three commonly used anaesthetic agents — ketamine, propofol, and isoflurane/halothane [3] — have distinct effects on CBF. Ketamine and isoflurane are known to increase CBF [159], while propofol decreases it [4]. Studies using autoradiography have demonstrated that anaesthetic agents often reduce brain metabolism in rats [159]. Using FDG PET imaging, the same conclusion

was drawn, where a reduced FDG uptake in anaesthetised mice was observed compared to those in an awake state [163, 173, 255].

The study of monoaminergic neurotransmitters, such as dopamine, noradrenaline, and serotonin, is crucial for understanding human behaviour, as well as neurodegenerative and psychiatric disorders [3]. Abnormal dopamine levels are associated with Parkinson's disease [139] and psychosis, while the neurotransmission of noradrenaline and serotonin is linked to depressive and other mood disorders, such as bipolar disorder [155]. Various studies have shown changes in measured binding potentials (BP) of different radioligands targeting dopamine transporters and/or D1, D2/3 receptors when animals are anaesthetised compared to unanaesthetised or awake animals [164, 176]. In [176], the influence of various anaesthetic agents on the BP of ^{11}C -SCH23390, a selective dopamine D1 radioligand, was investigated. Compared to awake animals, ketamine anaesthesia significantly increased the BP in the rat striatum, while pentobarbital anaesthesia markedly decreased the BP. In [253], ^{18}F -FPWAY, a PET ligand for the serotonin 5-HT_{1A} receptor, was evaluated in terms of the distribution ratio between brain and plasma, using awake and isoflurane-anaesthetised rats. Both postmortem PET data and autoradiographic data showed higher tracer uptake (33%) in the hippocampus of the anaesthetised rats.

It is evident that anaesthetic agents have confounding effects when measuring physiological parameters of interest using PET imaging. To mitigate these effects, different methods have been proposed to minimise or eliminate its impact. One straightforward approach involves injecting the tracer while the animal is in an awake state, followed by euthanasia [163]. Brain images are then obtained either through ex-vivo PET imaging [255] or, more commonly, autoradiography [163]. However, this method has a significant limitation: tracer kinetics cannot be obtained from a single animal [170]. To study tracer kinetics, different animals must be euthanised at various time points, resulting in either limited kinetic data or the need for a large number of animals. Another approach involves sedating the animal after tracer uptake [32, 111]. This method assumes that after a certain period, tracer uptake in regions of interest reaches equilibrium, and the effects of anaesthetics on tracer kinetics are minimal or negligible [170]. In [163], FDG uptake in rats anaesthetised 40 minutes post-tracer injection showed no significant differences compared to the awake group when imaged using autoradiography. However, a comparison between fully awake (tracer uptake + PET scan) and 'partially' awake mice (only during tracer uptake) showed significant changes in the measured slopes of regional time activity curves [167], suggesting that anaesthetics may still influence PET quantification. Furthermore, a limitation of this approach is that it does not allow for the acquisition of early tracer kinetics [194], thus limiting the full potential of dynamic PET imaging.

While the aforementioned methods reduce or mitigate the impact of anaesthetic agents, none of them enable the full potential of small animal brain imaging since the animal is always imaged under anaesthesia - thus its behavioural response is never considered. However, behavioural response is a key aspect of fundamental brain understanding in health and disease. For example, human brain changes, also referred to as neuroplasticity, in response to external stimuli (e.g.,

drug addiction and trauma), are not yet well understood [21, 119]. When the animal is euthanised or sedated for PET imaging, in-vivo correlation of tracer kinetics with behavioural changes becomes impossible to perform. To address these challenges, methods for in-vivo PET imaging of awake rodents have been developed. These methods are discussed in the following section.

2.2.4 In-Vivo Awake Imaging Using PET

Methods for awake small-animal PET imaging shall be divided into restrained and unrestrained methods.

2.2.4.1 Restrained methods

The first reported fixation device for awake and fully conscious small animal PET imaging was detailed in [176]. The device consisted of a wooden frame with two attached plastic tubes to which a rat head would be glued post-surgery. After a nearly one-week training period, the rats remained calm for three hours when in the apparatus. After two weeks of training, the influence of various anaesthetic agents on the BP of ^{11}C -SCH23390, a D_1 receptor ligand, was investigated and compared to that of the conscious rats. An SHR-2000 animal PET scanner [266], with a radial spatial resolution of 3 mm at the centre of the FOV, was used for imaging. Animal motion was monitored throughout the scan using a video camera, and it was reported that the trained rats moved minimally during scans (< 1 mm). However, the authors acknowledged that stress-induced upregulation of the D_1 receptor could not be completely excluded. In [104], a similar head holder was used to image the kinetics of ^{11}C -(R)-rolipram, an inhibitor of the phosphodiesterase subtype 4, in awake and isoflurane-anaesthetised rats. In this case, animals were scanned using the ATLAS phoswich PET scanner, with a radial spatial resolution of 1.7 mm near the centre of the FOV [231]. As in [176], head movements were visible during scans but were not accounted for or corrected before data analysis.

With the development of PET scanners with higher spatial resolution, not only rats but also mice were imaged in awake states using restrained head devices. Using a Siemens microPET Focus 220 (spatial resolution of 1.3 mm at the centre of the FOV [247]), regional cerebral glucose metabolism was imaged in both conscious and isoflurane-anaesthetised mice [173]. The authors suggested that ambient stress might affect FDG uptake in the brain.

To reduce stress-induced changes in glucose metabolism or tracer kinetics, the concept of conscious mouse PET imaging using restraining devices was extended. While the animal head remained fixed during the scan, its limbs were free [249]. Mounted on a treadmill apparatus, a mouse could "freely walk" or exercise while being imaged in a microPET Focus 220. The authors demonstrated that the BP of ^{11}C -raclopride was significantly lower in isoflurane-anaesthetised mice and in whole-body restrained mice compared to "freely-walking" mice. Furthermore, emphasising the importance of minimising stress in the animal, the authors also reported that heart rate values in whole-body restrained mice were significantly higher than those measured in the freely-walk mice. This method was later extended to allow simultaneous optical and PET imaging [250].

Recently, a less invasive restraining method for imaging conscious rats has been proposed [246]. This method involves wrapping the animal in a soft piece of fabric. Prior to imaging, the animal must acclimate to the restrainer by being wrapped in the fabric daily, at least nine times, for periods of 75 minutes. Using this technique, 45-minute dynamic FDG PET imaging of fully conscious rats was conducted with a HITS-655 K PET scanner [268], a brain-dedicated PET scanner with a spatial resolution of less than 1.5 mm. Compared to other head restraining methods, the proposed method showed reduced levels of plasma corticosterone, a stress marker for rodents, in the animals during the FDG PET acquisitions.

While restraining devices are relatively simple to implement and cost-effective for imaging awake rodents, they have notable limitations. Studies comparing tracer uptake in brain regions of restrained animals with those not undergoing physical restraint suggest that restraint-induced stress affects multiple neurotransmitter systems and alters brain glucose metabolism [170]. Additionally, these techniques require extensive animal training and acclimatisation [176, 246], and they limit the possibility of more comprehensive behavioural studies where the animal can move and interact with its surroundings in response to external stimuli [130, 167]. Finally, as the spatial resolution of brain-only small animal PET scanners continues to improve, addressing animal motion will become increasingly important for accurate quantification. Currently, none of these methods effectively account for this issue.

2.2.4.2 Unrestrained methods

More exciting is the use of techniques for imaging awake and freely moving rodents. The RatCAP PET scanner [258, 272] was the first technology available for imaging the awake rat brain without the need for full restraining devices (i.e., the animal fixed in a single place). The system consists of 12 detector blocks arranged in a ring configuration, surgically mounted on the head of the animal. The system’s axial and transaxial FOV are 18 mm and 38 mm, respectively. To partially compensate for the system’s weight (~ 150 g), it is mounted on a structural support, allowing the animal to move within a bowl enclosure. In the first version of the scanner, each detector block consisted of 4×8 LSO crystals, each measuring $2 \text{ mm} \times 2 \text{ mm} \times 5 \text{ mm}$, with single-ended readout using an APD array in a one-to-one configuration [258]. This initial system achieved a spatial resolution of approximately 2 mm near the centre of the FOV. Several improvements to the system were later reported [229, 259], including the use of thicker LSO scintillators (8 mm) and a redesign of the structural support to enhance animal mobility and reduce stress caused by the system’s inertia. Using this improved system, the authors reported a direct correlation between changes in the behavioural activity of the animals and changes in the measured BP of ^{11}C -raclopride in the animals’ striata [229].

While the RatCAP represented a major breakthrough in imaging awake and freely moving animals, the method still requires the animal to undergo surgery for system mounting. Additionally, the authors reported that the movement of animals with the scanner attached caused temporary increases in stress hormone levels [229], potentially affecting tracer kinetics and the outcomes of be-

havioural studies. For these reasons, non-invasive methods for imaging freely moving awake rodents have been investigated [130]. These methods rely on motion tracking systems [132, 128, 169] to estimate the 3D position of the animal's head within the scanner. Because these methods are external to the PET scanner, they offer the flexibility to be integrated with almost any PET scanner. Event-by-event motion compensation algorithms [8, 207, 287] are then used to correct the measured LORs to their correct crystal pairs, as if there were no motion.

Motion tracking methods are divided into two types: optical cameras and radioactive point sources. In [132], the MicronTracker S60 (a system composed of two stereo-optical cameras) was integrated with a microPET Focus 220 scanner and validated for imaging the brain of awake rats. In a subsequent study [131], a rat injected with FDG was scanned while awake inside a PVC tube, with its head pose sampled at 30 Hz using the MicronTracker and a marker glued to its forehead. After LOR motion correction, the images demonstrated the feasibility of the approach. Although no ground-truth comparison was available, the images resembled those of a rat imaged under anaesthesia (i.e., no motion). The same optical motion tracking device was later used to study the effects of isoflurane on FDG uptake in awake rats [240]. In [168], the method was implemented in a Siemens Inveon PET scanner [168] (1.5 mm radial spatial resolution at the centre of the FOV [263]) together with spatially variant kernels for reducing errors associated with intra-sampling motion (i.e., motion between two samples).

Using the same camera-based motion tracking system (MicronTracker + markers) and a 6-degrees-of-freedom robotic arm, Open-Field PET imaging was developed [130]. Synchronicity between the tracking system and the robotic arm maintained the animal within the FOV of the scanner (microPET Focus 220). Using this technique, in-vivo displacement of ^{11}C -raclopride in a rat's brain after the administration of amphetamine was correlated with changes in behaviour. However, a limitation of the method is that to avoid inducing stress in the animal, a relatively low speed was necessary when moving the robotic arm. In studies characterised by high locomotion of the animal, this may cause the animal to spend a considerable percentage of the scan time outside the FOV. Additionally, the authors suggest that PET quantification could have been affected due to insufficient motion sampling and/or the presence of blind spots for animal tracking.

A limitation of marker-based methods is that markers can shift from their original positions (without detaching) or simply detach from the animal's head during the scan, decoupling motion tracking from actual head motion. To address these limitations, a multi-camera markerless approach was implemented [128]. This technique determines the animal's pose by identifying its features and spatially correlating them with a pre-established library of all possible features. Results from an awake rat FDG PET scan using a microPET Focus 220 showed that this technique produced comparable results to a marker-based approach using the MicronTracker system.

Narrow bore PET scanners present challenges for camera-based head motion

tracking because of the limited FOV [133]. To avoid the need for optical tracking systems, the use of radioactive point sources (with activity 150-250 kBq) glued to the rodent’s head has been proposed for pose estimation (using an Inveon PET scanner) [169]. This method involves identifying three or more [10, 123] point sources in image space using very short time frames (~ 32 ms). Although the process of locating these point sources in image space (i.e., reconstruction) is time-consuming (taking over 2 hours for a 20-minute scan using parallel computing), it has proven to be more accurate for tracking the rodent’s head compared to methods based on optical cameras. However, a limitation of this method is that it can affect the system counting rate performance [10] and cannot compensate for animals moving outside the FOV. On the other hand, the use of fiducials for estimating pose obviates the need for a cross-calibration between cameras and scanner since all measurements are in the native coordinate system.

In summary, significant progress has been made in imaging awake animals. Although several restraining methods have been developed, the stress induced in the animals remains a major concern. Freely moving imaging methods are preferable because they are commonly non-invasive and allow for more comprehensive studies that aim to correlate behaviour with tracer kinetics. However, several challenges remain. Accurate tracer quantification requires scanners with sub-millimetre spatial resolution to reduce partial volume effects and high sensitivity to improve image SNR. All the methods described here have been implemented in scanners with resolution capabilities significantly poorer than current state-of-the-art brain-only PET scanners [111]. Both the microPET Focus 220 and Inveon PET scanners are based on 10-mm thick crystals, resulting in suboptimal sensitivity. Additionally, current methods either cannot or can only partially correct for scenarios where the animal exits the FOV. The technological advancement, which is the focus of this thesis, is to develop a motion-adaptive PET system that translates in response to animal motion along a fixed runway. The following section introduces this concept — Open-Field Mouse Brain PET scanner — our effort to achieve all the aforementioned objectives.

2.2.5 Open-Field Mouse Brain PET

The Open-Field Mouse Brain PET scanner aims to establish a new paradigm in neuroscience and behavioural PET imaging [66, 129] (see Fig. 2.29). This PET scanner, currently under development in our group, is designed for high-resolution and high-sensitivity brain PET imaging in freely-moving mice. To achieve high resolution (< 1 mm), DOI-capable PET detectors based on $0.785 \text{ mm} \times 0.785 \text{ mm} \times 20 \text{ mm}$ crystals are used. To maximise sensitivity, four detector rings, each composed of 16 detectors, are arranged in an overlapping box configuration, enhancing sensitivity compared to the conventional cylindrical geometry.

An optical motion tracking system will record the animal position and orientation for two purposes: (i) to provide feedback to a movable gantry, which will translate the scanner according to the animal’s movements (i.e., maximising the time the animal is within the FOV); and (ii) to estimate head pose with six de-

degrees of freedom, enabling motion-compensated PET image reconstruction. The animal, enclosed within a sufficiently large runway, will be able to move back and forth in response to physical and/or chemical stimuli. Additionally, behavioural instruments (e.g., buttons, levers and/or touchscreens) will be included.

A preliminary characterisation of the dual-ended readout SiPM-based PET detector demonstrated excellent crystal resolvability (Anger readout) and achieved energy resolution values of 12-24%, DOI resolution of 2.8-3.5 mm, and time resolution of 1.4 ns [129].

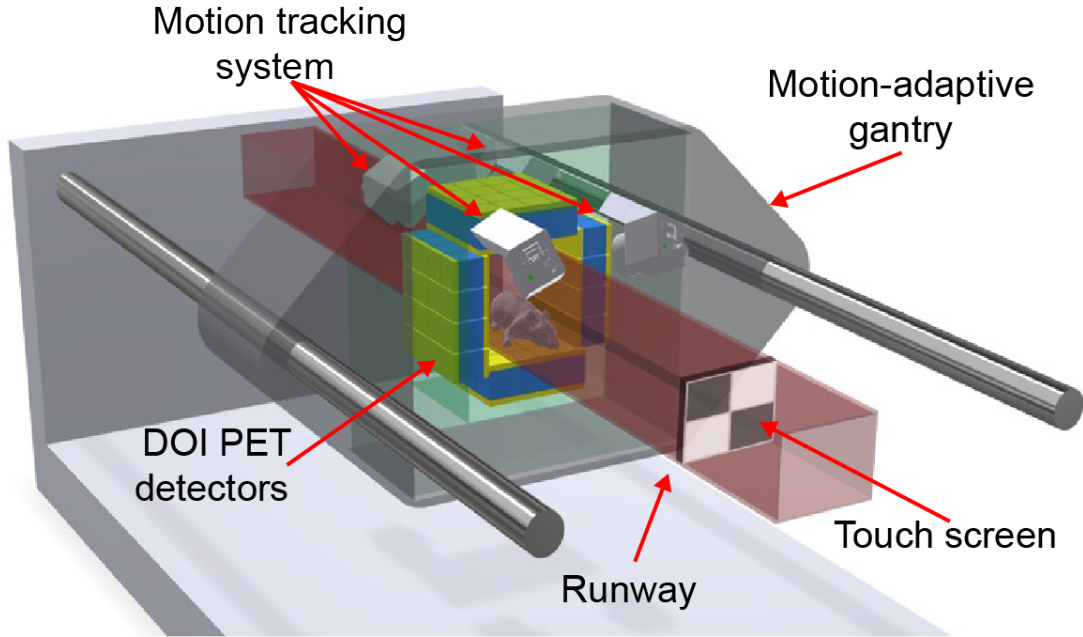


Figure 2.29: CAD design of Open-Field Mouse Brain PET scanner concept.

2.2.6 Summary

The high genetic homology between humans and small-animal rodents (i.e., mice and rats) makes these animals invaluable for investigating human diseases. Small-animal PET imaging allows in-vivo visualisation of physiological changes in these animals, serving as a crucial tool for studying disease progression and drug development. Since the development of the microPET scanner [38], numerous commercial and research-only PET scanners have been developed. Current whole-body and brain-only small-animal PET systems achieve spatial resolutions around 1 mm and 0.6 mm, respectively. While the advancements in instrumentation are remarkable, small-animal brain PET imaging still has limitations. Brain-only small-animal PET systems with both high spatial resolution and high sensitivity are rare. Even rarer are systems that enable non-invasive awake-animal imaging, which opens up the possibility of studying brain function and behaviour simultaneously. These technological gaps are the motivation for Open-Field Mouse Brain PET (mousePET), a novel scanner designed to deliver high spatial resolution and high sensitivity in fully awake and freely moving mice. This thesis aims to bring the mousePET from concept to reality by addressing three key technological challenges:

- i. Finding low-cost, all-in-one chip solutions for cost-effective detector data acquisition and system scalability.
- ii. Developing methods for improved event positioning in the PET detectors.
- iii. Developing accurate and computationally efficient methods for DOI image reconstruction for this unique system.

Chapter 3

Development and Performance Optimisation of a Multiplexed DOI-Encoding PET Detector Using the TOFPET2 ASIC

Submitted to *IEEE Transactions on Radiation and Plasma Medical Sciences*: F. E. Enríquez-Mier-y-Terán et al. “Development and Performance Optimisation of a Multiplexed DOI-Encoding PET Detector Using the TOFPET2 ASIC”

Preamble

The mousePET scanner was introduced in Chapter 2. An initial characterisation of a mousePET detector, using NIM electronics for signal processing and a DAQ board for signal digitisation, was reported in [129]. While suitable for lab-based evaluation of prototype detectors, these data acquisition configurations are expected to be intricate and costly when implemented at the scanner level. Therefore, finding cost-effective solutions for the data acquisition of the mousePET detectors is essential for the successful development of the scanner.

The objective of this chapter is to integrate and optimise the performance of the mousePET detectors using the TOFPET2 ASIC, a low-cost, all-in-one chip solution for SiPM signal processing and digitisation.

3.1 Abstract

Depth-of-interaction (DOI) PET detectors are essential in high-resolution small animal PET. The dual-ended readout detector configuration provides high DOI resolution; however, signal multiplexing schemes are often needed to reduce manufacturing costs. TOFPET2 is a low-cost, multi-channel application-specific integrated circuit (ASIC) designed for individual silicon photomultiplier (SiPM) readout, with performance in multiplexed configurations not well known. This study evaluates a highly multiplexed, high-resolution, dual-ended readout PET detector using TOFPET2. The PET detector was constructed with a 23×23 array of LYSO crystals ($0.785 \times 0.785 \times 20 \text{ mm}^3$) coupled to 6×6 SiPM arrays via 1.2 mm PMMA sheets. Custom boards reduced 72 SiPM signals to 8 (4 per end) before feeding into TOFPET2 channels. The detector was biased at 27, 27.5, and 28 V, with ASIC discriminator thresholds optimised based on flood map quality. Optimal flood maps were obtained at 27.5 V. The mean energy and DOI resolution were $10.5 \pm 1.6\%$ and $2.3 \pm 0.3 \text{ mm}$, respectively, with a coincidence time resolution (CTR) of 1.3 ns between two detectors. This work demonstrates the feasibility of employing TOFPET2 to achieve high spatial, energy, and DOI resolution in a 9:1 multiplexed system.

Keywords: DOI PET detector, multiplexed readout, TOFPET2 ASIC

3.2 Introduction

In-vivo imaging and quantification of molecular changes occurring in the brain structures of mice and rats requires narrow-bore PET scanners targeting sub-millimetre spatial resolution [95, 111, 129]. Parallax error resulting from the narrow-bore geometry easily degrades the off-centre spatial resolution, necessitating PET detectors with depth of interaction (DOI) capability.

Although monolithic PET detectors are cost-effective for measuring DOI, they have only achieved sub-millimetre resolution for thin ($\leq 10 \text{ mm}$) scintillators [69, 87, 122], which limits sensitivity. More commonly, highly pixelated detectors with sub-millimetre crystal pitch and thickness $> 10 \text{ mm}$ are used [124, 277] to provide simultaneously high spatial resolution and detection efficiency. Among different approaches for measuring DOI in pixelated detectors (e.g. [103, 136, 200]), the dual-ended readout configuration supports high DOI resolution and light collection efficiency [62, 190, 211]. However, these advantages come at increased manufacturing costs due to the two-fold increase in the required number of photodetectors and associated electronics. To mitigate costs, signal multiplexing schemes can be used to reduce the number of signal processing and digitisation channels [59, 129, 156, 276].

The adoption of the silicon photomultiplier (SiPM) as the photodetector in PET [142, 216] has driven the development of fast-timing detectors and readout electronics [143]. This has led to several application-specific integrated circuits (ASICs) for fast SiPM signal digitisation [14, 55, 72, 73, 199, 202, 222, 241], capable of precisely measuring both the energy and arrival time of gamma ray interactions within a single chip. One of these ASICs is the 64-channel TOFPET2

[24, 55] (PETSys Electronics S.A., Portugal), which has low power consumption [185], three-threshold trigger logic (for dark count rejection) and good timing properties [184, 183]. However, the TOFPET2 ASIC was primarily designed for time-of-flight (TOF) PET applications, which typically involve individual (i.e., 1:1) photodetector readout [17, 75, 138, 152, 153, 160, 186, 264]. Its potential for interfacing with multiplexed detectors remains largely unexplored. One semi-monolithic detector and one pixelated detector, both with a signal multiplexing ratio of 4:1, have been interfaced with the ASIC [83, 154]. However, the pixelated detector required deep learning techniques to generate usable crystal flood maps. Higher multiplexing ratios present additional challenges, particularly due to the increased current at the ASIC channel input (resulting from the analog summation of multiple SiPM signals), which can cause saturation. Signal attenuation can be used to mitigate this, but improper attenuation may reduce the ability to resolve crystals in the flood map and/or introduce unwanted artefacts.

This study investigates the feasibility of using the TOFPET2 ASIC for signal readout in a dual-ended PET detector with a 9:1 multiplexing ratio. We demonstrate that with appropriate optimization, high spatial, energy, and DOI resolution can be achieved in such highly multiplexed configurations. For PET scanners like the one described in [66], this level of multiplexing reduces the number of TOFPET2 ASICs required from 72 to 8, significantly lowering ASIC-related costs and simplifying system complexity.

3.3 Materials and Methods

3.3.1 Dual-Ended Readout PET Detector

The PET detector consists of an array of 23×23 LYSO crystals (Boya Advanced Materials Co. Ltd., China) of dimension $0.785 \text{ mm} \times 0.785 \text{ mm} \times 20 \text{ mm}$ (pitch = 0.85 mm), optically isolated using Lumirror Toray reflector (Fig. 3.1a). Both ends of the crystal array are optically coupled to a 6×6 array of SiPMs (MicroFJ-30035, ONSEMI, USA), each SiPM measuring $3.16 \text{ mm} \times 3.16 \text{ mm}$ and having a pitch of 3.3 mm that results in overall array dimensions of $19.6 \text{ mm} \times 19.6 \text{ mm}$ (Fig. 3.1b). A 1.2-mm thick optical grade PMMA sheet (Eljen Technology, USA), with a refractive index of 1.5 (@436 nm) coupled the SiPM and crystal arrays using EJ-550 optical grease (Eljen Technology, USA).

The readout electronics for the multiplexing scheme were previously reported in [129]. Briefly, the 36 standard output SiPM signals in each array were reduced to 6 row and 6 column signals using a resistor network. Row and column signals were weighted with different resistor gains, dependent on position in the array, and combined to produce four signals for Anger logic positioning (X^+ , X^- , Y^+ and Y^-). The final amplification gain reported in [129] was reduced by $1/3$ to avoid saturating the TOFPET2 ASIC. In total, 8 signals from the front and back SiPM arrays were fed into one ASIC using custom electronic boards (Fig. 3.1c).

3.3.2 Detector Integration with the TOFPET2 ASIC

A FEB/D_v2 board was used for ASIC powering and data transmission between the ASIC and data acquisition computer. It can also provide bias voltage for up to 1,024 SiPMs using a high-voltage digital-to-analog converter (HV-DAC) mezzanine, however we performed biasing using a custom electronic board (Fig. 3.1c) since our system consists of 64 dual-ended PET detectors with a total of 4608 SiPMs. Therefore, the ASIC calibration subroutines provided by PET-Sys were modified to allow manually setting the SiPMs to their pre-breakdown voltage and desired operating voltage when calibrated. In all cases, ASIC calibrations were performed at an operating voltage of 27.5 V. Calibrations and the experiments detailed later were conducted inside a light-tight enclosure with the temperature regulated at 22.0 ± 0.2 °C.

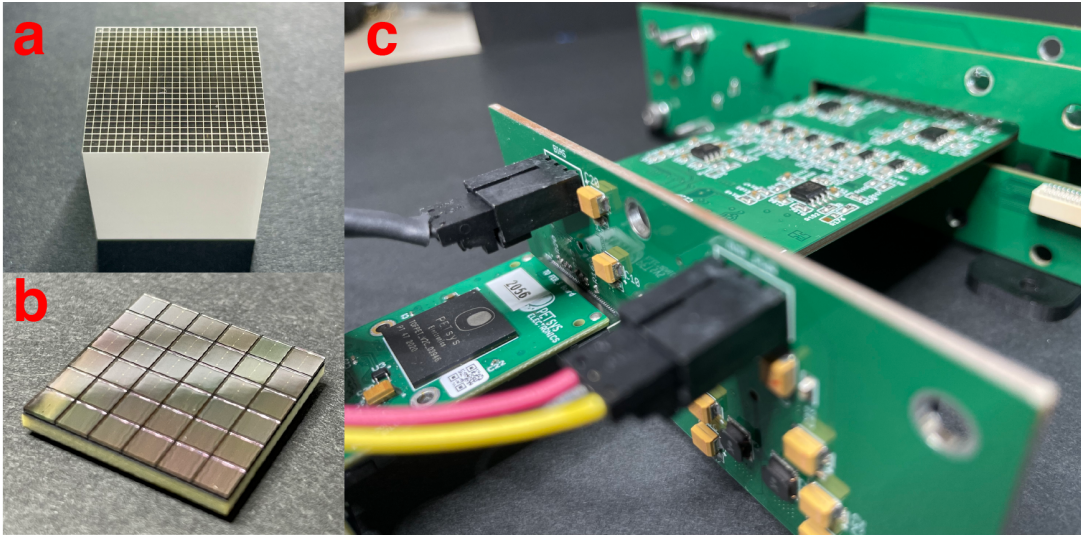


Figure 3.1: (a) LYSO array comprising 23×23 crystals with 0.85 mm pitch. (b) 36 SiPMs in a 6×6 array with 3.3 mm pitch. (c) Custom PCB used for SiPM biasing, powering of the amplification board, and interfacing the detector with the TOFPET2 ASIC.

Although the ASIC can measure the event energy using a time-over-threshold method, non-linearity makes it unsuitable for a multiplexed detector. Instead, the time and charge method (QDC) was used to measure the contribution from each signal to the event energy. The ‘convert_raw_to_singles’ subroutine provided by PETSys was used in combination with look up tables (LUTs) to map the energy and timing information from a given ASIC channel ID to its corresponding signal. Unless otherwise stated, a time window of 100 ns was used to group signals originating from a single gamma ray interaction. For a valid gamma ray interaction, clusters of 8 different channel signals were required. If more or fewer than 8 signals were recorded within the same time window, the event was discarded. After extraction and mapping of the singles data, the gamma ray position of interaction (x , y) and energy (E) were calculated as follows:

$$x = \frac{1}{2} \left(\frac{X_1^+ - X_1^-}{X_1^+ + X_1^-} + \frac{X_2^+ - X_2^-}{X_2^+ + X_2^-} \right), \quad (3.1)$$

$$y = \frac{1}{2} \left(\frac{Y_1^+ - Y_1^-}{Y_1^+ + Y_1^-} + \frac{Y_2^+ - Y_2^-}{Y_2^+ + Y_2^-} \right), \quad (3.2)$$

$$E = E_1 + E_2 \quad (3.3)$$

where the subscripts 1 and 2 indicate the front and back SiPM arrays, respectively, and E_1 and E_2 are given by:

$$E_1 = X_1^+ + X_1^- + Y_1^+ + Y_1^- \quad (3.4.1)$$

$$E_2 = X_2^+ + X_2^- + Y_2^+ + Y_2^- \quad (3.4.2)$$

3.3.3 Optimisation of the TOFPET2 ASIC Discriminators

Incoming signals into a TOFPET2 ASIC channel are replicated and amplified with different gains in three independent circuits for signal timing (branch T), signal integration (branch Q) and energy discrimination (branch E), respectively. Valid events require the output of three discriminators to be true: D_T1 and D_T2 in branch T, and D_E in branch E. The ASIC measures the arrival time of an event at the rising edge of the ‘trigger_T’ signal, which is generated once the output of D_T1 (plus a delay) and D_T2 are true. Threshold voltages for these discriminators, respectively V_{th_T1} and V_{th_T2} , are set by two 6-bit DACs named vth_t1 and vth_t2 . For the ASIC logic to work properly, V_{th_T2} must be greater than V_{th_T1} . In QDC, the event energy (integrated current) is measured starting from the rising edge of the ‘trigger_Q’ signal until the end of a configurable integration window. The ‘trigger_Q’ signal is generated once the output of discriminator D_T2 is true. Additionally, a ‘trigger_E’ signal originating from discriminator D_E is used for rejecting low energy events. The threshold voltage for this discriminator (V_{th_E}) is set by another 6-bit DAC named vth_e . The logic of the TOFPET2 ASIC is summarised in Figure 3.2.

A correct signal (current) integration is needed for optimal crystal flood maps. We examined the effect on flood map quality caused by changing the discriminator threshold vth_t2 and adjusting the SiPM bias voltage to 27.0 V, 27.5 V and 28.0 V. In all experiments, the default integration time window of 300 ns was used. The LSB of the discriminator D_T1 was set to 57, corresponding to about 5 mV per DAC unit; D_T2 and D_E were kept at their nominal values of 48 and 40, respectively, corresponding to about 15 and 20 mV per DAC unit [228]. 10-min irradiations using a 0.28-MBq ^{22}Na source (active diameter 0.25 mm) positioned 5 cm from the front face of the detector were performed. For each irradiation, vth_t2 was varied from 16 to 24 DAC units in steps of 2, with vth_t1 and vth_e fixed at 50 and 15 DAC units, respectively. The effect of changing threshold vth_t1 was also examined: our hypothesis was that this threshold should not impact flood map quality but only impact the upstream signal time differences due to varying signal amplitudes (time walk effect) when grouping coincidence events. For this test, vth_t1 was varied from 10 to 60 DAC units in steps of 10, with vth_t2 and vth_e held fixed at 20 and 15 DAC units, respectively. In each experiment, flood map quality was evaluated based on peak-to-valley ratios for line profiles were drawn through the central row and column crystals.

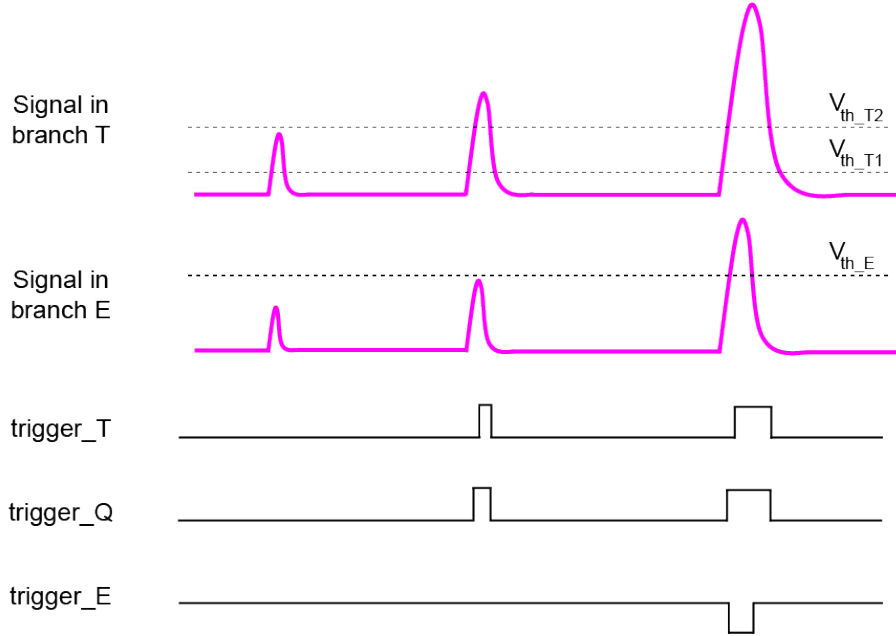
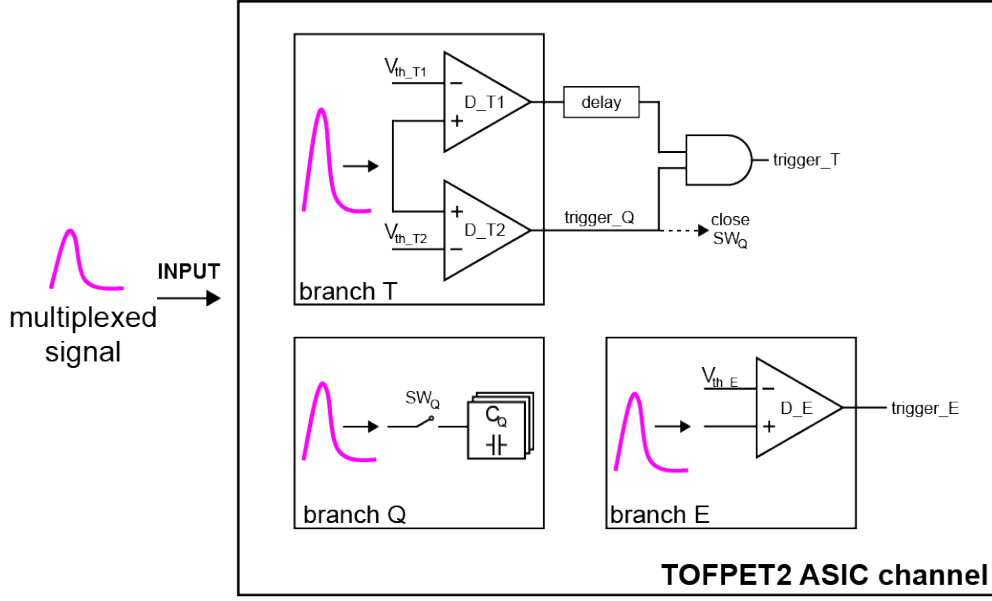


Figure 3.2: (top) Simplified schematic of one TOFPET2 ASIC channel. ‘trigger_Q’ causes switch SW_Q in branch Q to close. (bottom) ASIC trigger logic. Signals in branch Q are omitted since no thresholds are present in this branch. ‘trigger_T’ signals appear later in time due to the delay in discriminator D_{T1} . Only the first (right) signal causes all discriminators to be triggered.

3.3.4 Energy and DOI Resolution

Energy and DOI resolution were measured for the three bias voltages tested. For each bias voltage, measurements were obtained at five different detector depths: 2, 6, 10, 14 and 18 mm. Electronic collimation was achieved by coupling a Teflon-wrapped LYSO slab ($0.5 \text{ mm} \times 20 \times 20 \text{ mm}$) to a 6×6 array of SiPMs, and acquiring coincidences between this reference detector and the dual-ended test detector under irradiation from the ^{22}Na source (Fig. 3.3a). In all cases a

20 ns coincidence time window was used. For each detector, event timestamps were calculated from the average time of arrival of all signals contributing to an event (i.e., 8 for the test detector and 4 for the LYSO slab). With the LYSO slab and source fixed, a Zaber X-LSM100A stage (Zaber Technologies, Canada) was used to translate the test detector perpendicularly to the slab. Approximately, 400k coincidence events were recorded at each depth. In all cases the SiPM array reading the LYSO reference detector slab was kept at a bias voltage of 27.5 V. For both detectors, the ASIC thresholds vth_t1 , vth_t2 and vth_e were fixed at 50, 20 and 15 DAC units, respectively.

Following a Voronoi-based flood map segmentation [5], energy resolution was measured for each individual crystal element of the test detector by fitting a Gaussian function to the photopeak. For DOI resolution, DOI ratios were calculated for each crystal according to:

$$DOI_{ratio} = \frac{E_1}{E_1 + E_2} \quad (3.5)$$

Linear fitting was applied to calibrate DOI ratios to depth and the full-width at half maximum (FWHM) values computed. Global performance measurements excluded the two outer row and column crystals since edge effects precluded these outermost crystals from being resolved.

3.3.5 Coincidence Time Resolution

A second dual-ended readout detector was calibrated using the procedure described in Section 3.3.4, for a bias voltage of 27.5 V (see Appendix A). After calibration, the two identical detectors were placed face-to-face with a separation of 10 cm and the ^{22}Na source located centrally between them (Fig. 3.3b). The histogram of timestamp differences of coincidence events within the photopeak was fitted using a Gaussian and the FWHM was computed as the CTR. Since for each event, eight arrival times are obtained, two methods for event timestamping were compared:

- i. Earliest recorded time of arrival as the event timestamp.
- ii. Averaging of the 8 recorded arrival times as the event timestamp (as in Section 3.3.4)

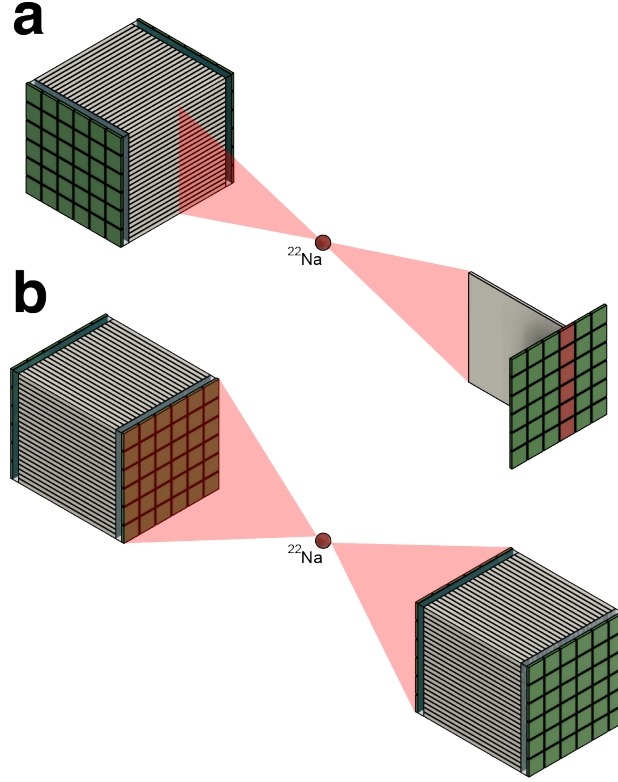


Figure 3.3: Experimental setup for measuring (a) energy and DOI resolution, and (b) coincidence time resolution. The SiPMs in direct contact with the LYSO slab reference detector are indicated in red.

3.4 Results

3.4.1 Optimisation of the TOFPET2 ASIC Discriminators

Figure 3.4 shows crystal flood maps obtained using all events (i.e. no energy windowing) at three bias voltages and for varying threshold vth_t2 . Maps corresponding to the same bias voltage (i.e. the same row in Fig. 3.4) are scaled to the same maximum. Below each map is the line profile passing through the central row of crystals. It is clear that regardless of bias voltage, the nominal value of the discriminator (20 DAC units) yields the best maps in terms of crystal resolvability. Although resolvability of the central crystals is not affected when decreasing vth_t2 , resolving crystals in the corner of the array is impacted by the presence of a cross artefact. Increasing vth_t2 also had a major impact on the flood map quality near the periphery due to a comet-like artefact. This artefact is likely caused by poor signal (current) integration since for edge and/or corner crystals at least one of the eight signals has very low amplitude. Accordingly, high vth_t2 values may not sufficiently capture (integrate) the signal shape. Visual comparison at nominal vth_t2 as a function of bias voltages shows best crystal resolvability for 27 and 27.5 V. For bias voltage ≥ 28 V (data not shown), a strong comet-like artefact was observed. This may be due to higher

dark count pulses and/or system non-linearities (see Section 3.5).

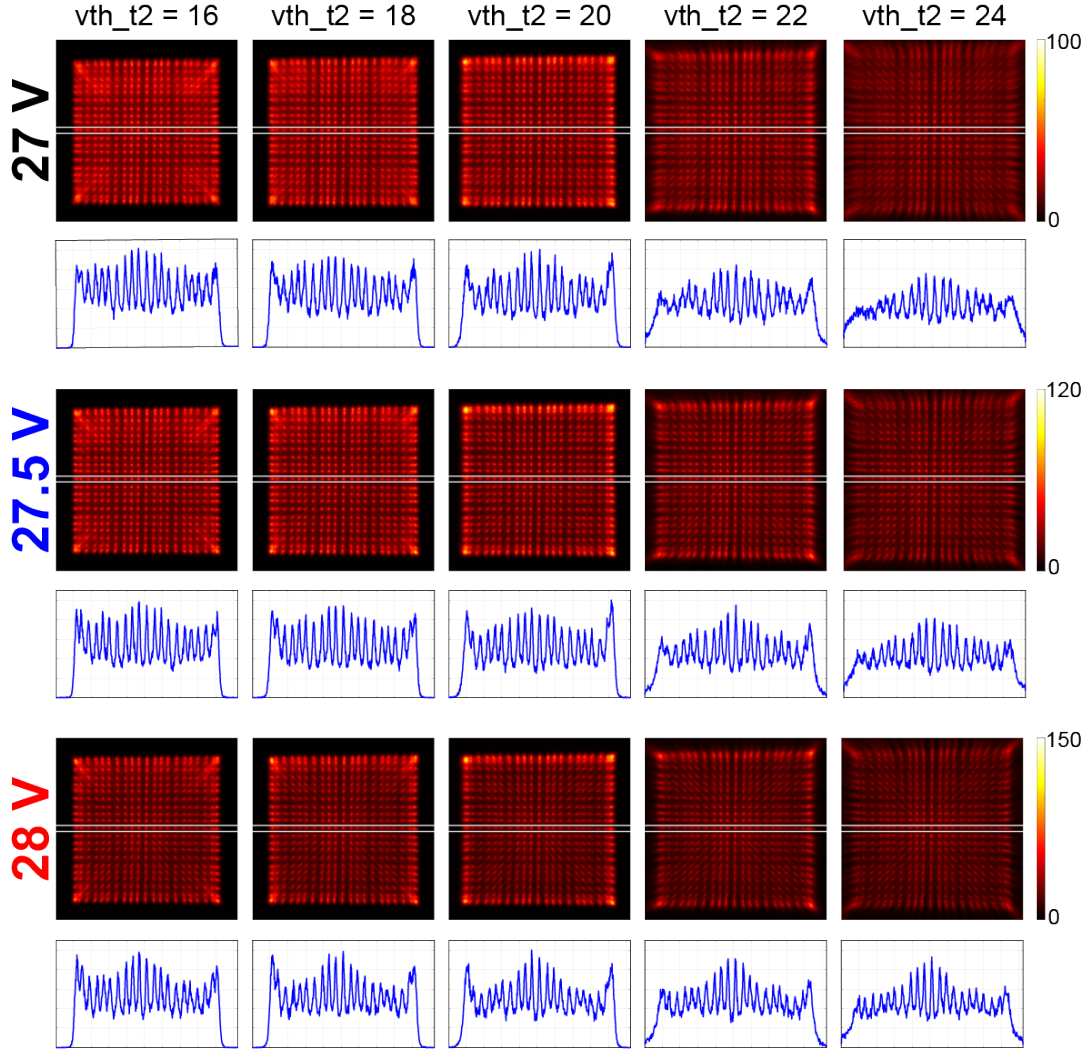


Figure 3.4: Crystal flood maps as a function of vth_t2 (columns) and the three different bias voltages (rows). Maps within the same row are scaled to the same maximum. Below each map, line profiles corresponding to the central row of crystals (between the white lines) are shown. Lines profiles within the same row were normalised with respect to the profile obtained using $vth_t2 = 20$ DAC units.

Figure 3.5 shows flood maps for different vth_t1 thresholds at 27.5 V bias voltage (top), along with the corresponding line profile traversing the central row of crystals (middle). Contrary to our expectation, lower vth_t1 values had a negative impact on flood map quality. Figure 3.5 (bottom) shows normalised histograms of the arrival time differences between the first and last recorded signal per event, as a function of vth_t1 . Increasing vth_t1 led to larger time differences, an expected trend due to a larger time walk effect. Despite this trend, the peak of the distributions only shifted from 3.9 to 4.9 ns as vth_t1 was varied from 20 to 60 DAC units.

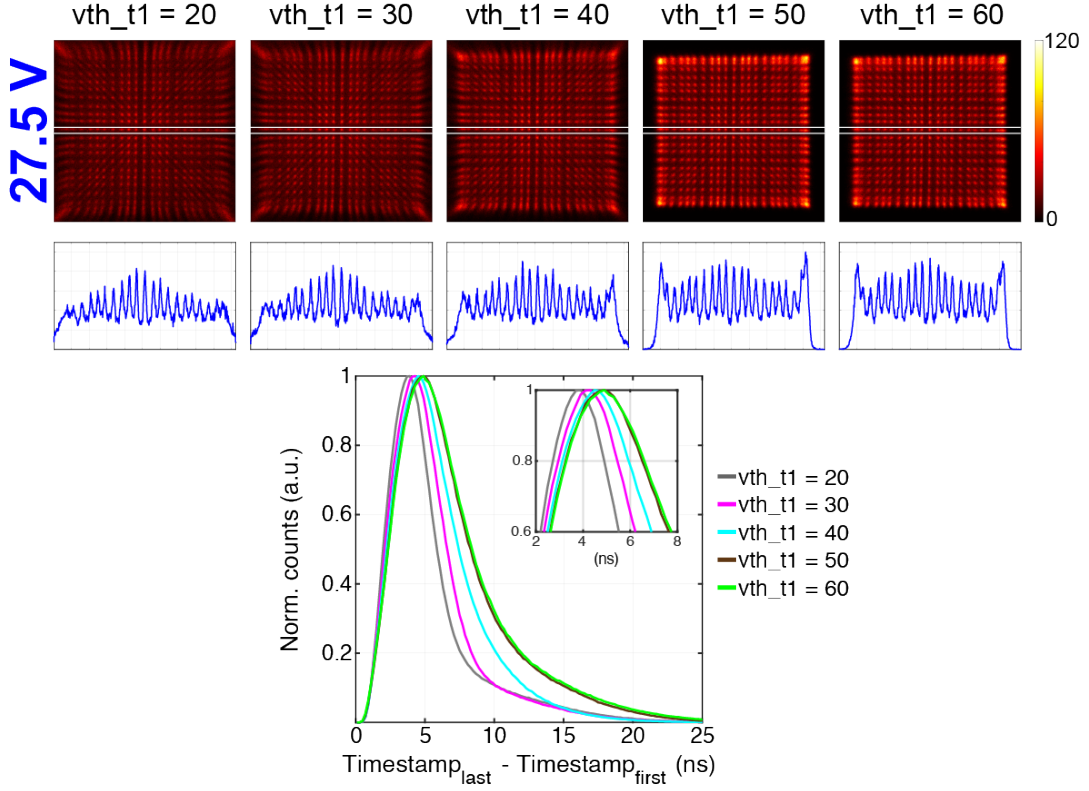


Figure 3.5: (top) Crystal flood maps as a function of vth_t1 . (middle) Line profiles normalised with respect to the profile obtained using $vth_t1 = 50$ DAC units. (bottom) Histograms of the time stamp difference between the first and last signals corresponding to the same event, shown as a function of vth_t1 threshold. Bias voltage was 27.5 V in all cases.

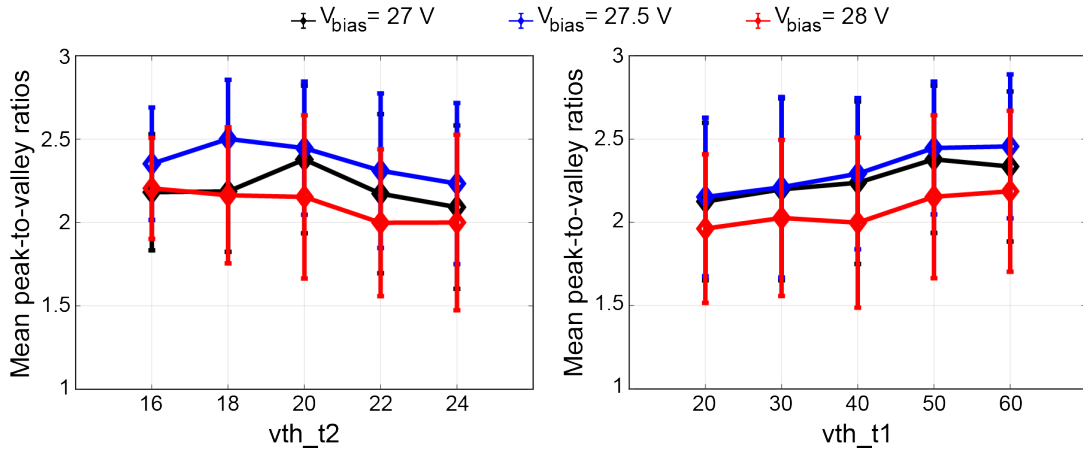


Figure 3.6: Mean peak-to-valley ratios of line profiles for different vth_t2 (left) and vth_t1 (right) threshold values and 3 different bias voltages: 27 V (black), 27.5 V (blue) and 28 V (red). Error bars indicate ± 1 standard deviation.

Figure 3.6 shows a quantitative analysis of the flood map quality in terms of mean peak-to-valley ratio of line profiles drawn along the central row and column crystals for different vth_t2 (left) and vth_t1 (right) thresholds. Flood map

quality improved for lower vth_t2 and higher vth_t1 , with optimal values of 20 DAC units and 50-60 DAC units, respectively, and a bias of 27.5 V. The strong map quality dependence on vth_t1 was observed at all bias voltages.

3.4.2 Energy and DOI resolution

Figure 3.7 (top) shows photopeak position for each crystal in the array irradiated at 10-mm (left) and 18-mm (right) depth using 27.5 V bias voltage. Both maps exhibit a uniform detector response across the central region of the array. At each irradiation depth, mean photopeak positions were estimated to be 116 ± 9 (10-mm) and 135 ± 9 (18-mm) a.u., respectively. Figure 3.7 (bottom) shows photopeak position as a function of depth for the three different bias voltages. Irrespective of bias, there was a strong depth dependence of photopeak position; the smallest value occurred at the centre depth and the largest at the ends. The depth dependence is attributed to differences in the number of optical photons detected, the lowest value expected when the event is half-way between the two SiPM arrays.

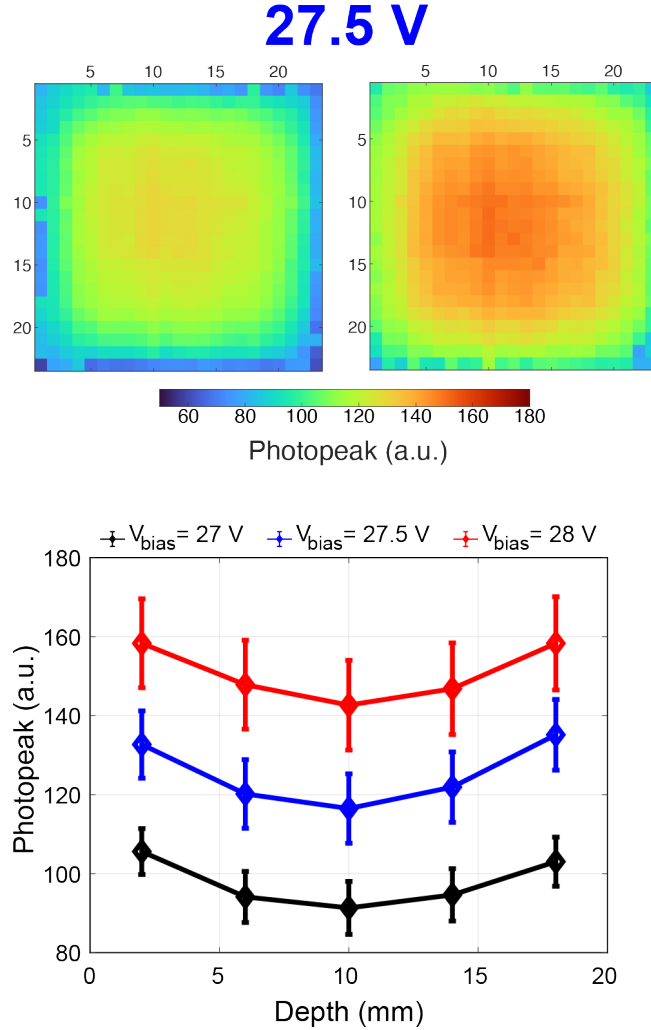


Figure 3.7: (top) Photopeak position at 10-mm (left) and 18-mm (right) irradiation depth. (bottom) Photopeak position as a function of depth for different bias voltage. Error bars indicate ± 1 standard deviation.

Figure 3.8 (top) shows energy resolution as a function of depth for 3 different bias voltages. The best energy resolution was measured at the central depth, degrading towards the ends. Poorer energy resolution at the periphery of the array is likely due to the relatively low photon collection far from the source. Conversely, energy resolution improved at higher bias voltage due to higher light collection. The energy resolution at a 10-mm irradiation depth was estimated to be 10.1% (27 V), 9.3% (27.5 V) and 9.1% (28 V), respectively. Figure 3.8 (bottom) shows the mean energy resolution across the crystal array for all depths. This mean energy resolution was $12.2 \pm 2.6\%$ (27 V), $10.5 \pm 1.6\%$ (27.5 V) and $9.8 \pm 2.0\%$ (28 V) for the 3 bias voltages.

Failure to account for the strong depth dependence of the photopeak results in photopeak broadening (see Appendix A, Fig. A.1) and artificially high energy resolution measurements: $24.9 \pm 3.0\%$ (27 V), $23.2 \pm 2.7\%$ (27.5 V) and $19.9 \pm 3.0\%$ (28 V).

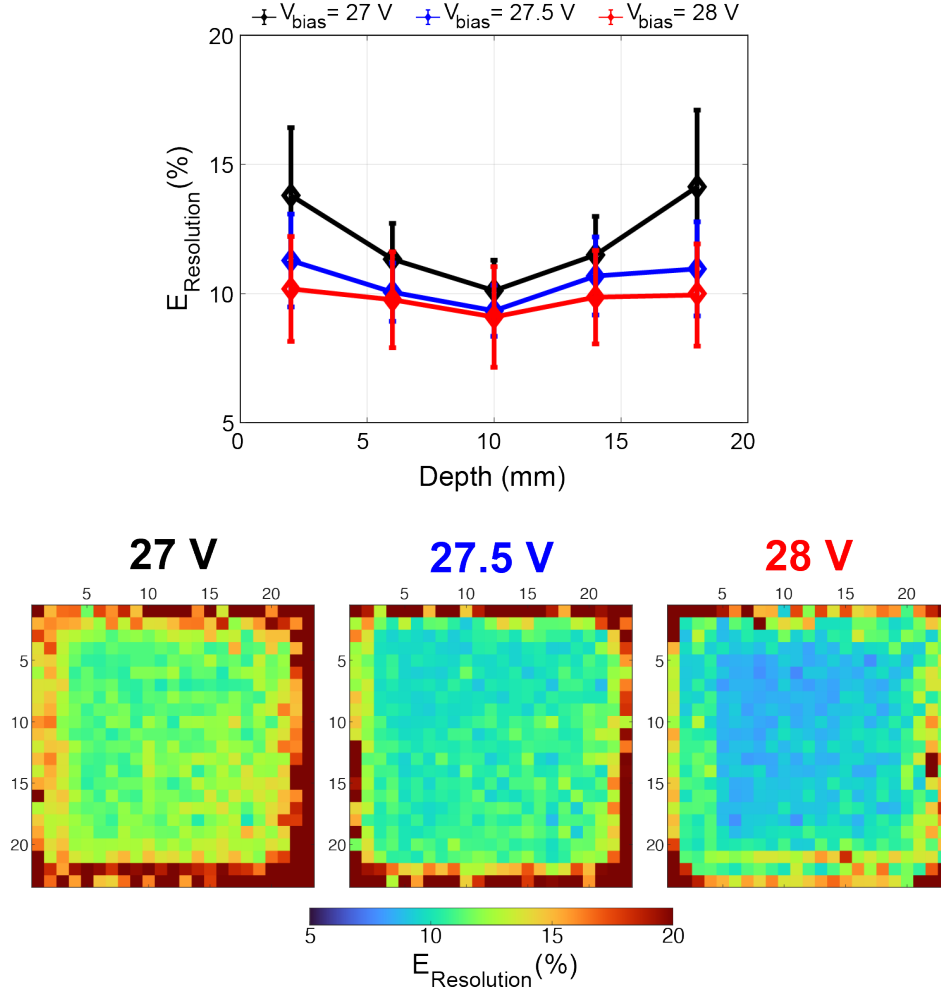


Figure 3.8: (top) Energy resolution as a function of source depth at different bias voltages. (bottom) Individual crystal energy resolution averaged across all depths.

Figure 3.9 (top) shows the mean DOI resolution as a function of irradiation depth; Figure 3.9 (bottom) shows DOI resolution across the array, averaged

across all depths. DOI resolution <3 mm FWHM was observed at all bias voltages. Asymmetry in the Figure 3.9 data is a consequence of irradiating the crystal from the left: lower counts from crystals on the right due to longer attenuation path lengths and higher contribution of Compton scatter events. Detector mean DOI resolution was measured to be 2.4 ± 0.3 mm (27 V), 2.3 ± 0.3 mm (27.5 V) and 2.5 ± 0.3 mm (28 V), respectively. The DOI ratios and calibration for a central crystal of the array are included in Appendix A (Fig. A.1).

3.4.3 Coincidence Time Resolution

Figure 3.10 (top) shows the events used for measuring the coincidence time resolution between the two identical detectors, biased at 27.5 V. (Energy and DOI calibrations for detector 2 are provided in Appendix A, Fig. A.2) Figure 3.10 (bottom) shows histogrammed timestamp differences between coincidence events, based on the earliest (brown) and average (pink) timestamp methods, respectively. The CTR was 2.10 ns using the earliest timestamp method and 1.34 ns using the average method.

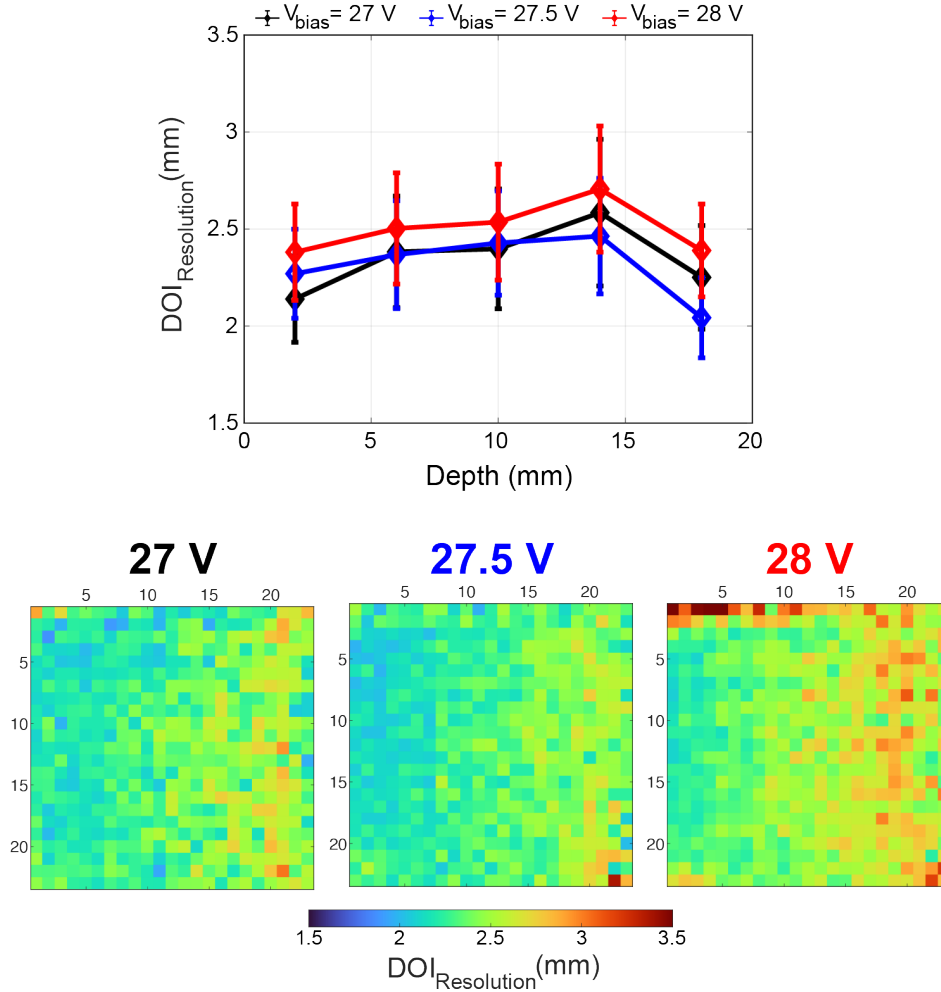


Figure 3.9: (top) DOI resolution as a function of source depth and bias voltage. (bottom) Individual crystal DOI averaged across all depths.

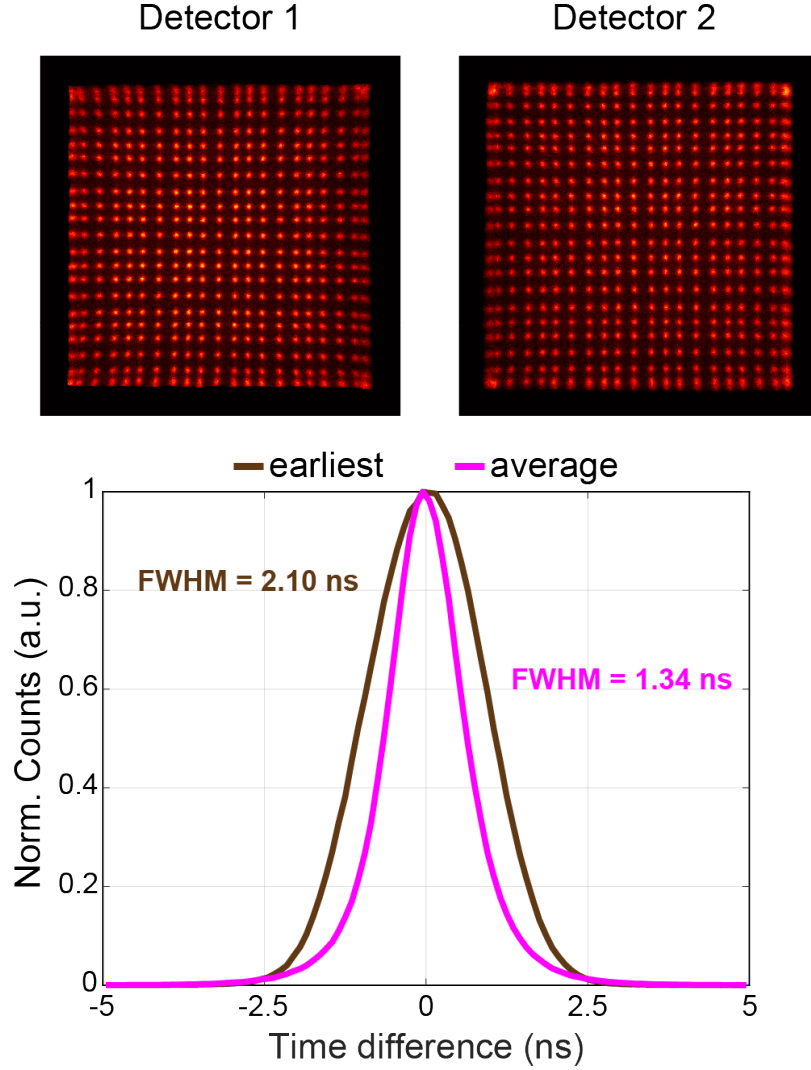


Figure 3.10: (top) Flood maps of the coincidence events used for measuring the CTR between the two detectors. (bottom) Timestamp difference histogram for coincidence events using the earliest (brown) and average (pink) event timestamp methods, respectively.

3.5 Discussion

Dual-ended readout PET detectors with DOI-encoding often use multiplexing schemes to reduce the number of readout channels and associated costs. Typically, ASICs developed for fast SiPM signal readout have typically focused on individual photodetector readout to exploit the excellent timing resolution of these configurations for TOF-PET applications. The TOFPET2 ASIC was initially proposed for the individual SiPM signal digitisation of a dual-ended readout detector [152]. In this study, we demonstrated that precise event positioning and excellent detector performance are attainable when interfacing a highly multiplexed dual-ended readout PET detector (9:1 multiplexing ratio) with the TOFPET2 ASIC.

Our results indicate a strong dependence on discriminators D_T1 and D_T2 for

constructing the crystal flood maps. The dependence on D_T2 is expected since it initiates signal integration. Optimal flood map generation requires accurate sampling of all contributing signals. For high-amplitude signals, a low D_T2 threshold, combined with a fixed integration time window, may fail to sample the entire signal. Conversely, a high D_T2 threshold can lead to incorrect sampling of low-amplitude pulses. In both cases, such pulses (whether high or low amplitude) appear at the edges and corners of the array, explaining the presence of artefacts in off-centre locations of the flood map. The influence of D_T1 ; however, which serves only for event timestamping, is unexpected. Adjusting D_T1 threshold (vth_t1) should primarily impact the channel grouping time window and the detector CTR in coincidence measurements. This aspect is currently under investigation.

The flood map quality, quantified using mean peak-to-valley ratios, indicated that the best maps were obtained by setting the ASIC thresholds vth_t1 , vth_t2 within the range 50-60 and 18-20 DAC units, respectively, while keeping vth_e fixed at 15 DAC units. However, a limitation of the metric used here is that it only accounts for the central row and column crystals, excluding artefacts that may be visible in other regions of the array, such as the corners. In future work we will use a more robust metric like the one reported in [59]. Both the measured ratios and visual inspection confirm that good crystal maps were obtained by setting the ASIC thresholds to 50 (vth_t1), 20 (vth_t2) and 15 (vth_e) DAC units. Given that different channels may have slightly different gains, methods for optimising the flood map while allowing variable thresholds among channels need to be explored.

The flood map quality was also examined as a function of three bias voltage values. The best maps were achieved at bias voltages of 27 and 27.5 V. Increasing the bias voltage ≥ 28 V introduced a comet-like artefact in off-centre crystals, possibly due to (i) higher dark count rates and/or (ii) system non-linearities. For (i), higher dark count rates may contribute to the signal baseline, introducing an offset that is not fully cancelled during the x and y calculations. Regarding (ii), accurate flood map construction requires a relatively linear system response. Non-linearities can arise due to SiPM saturation and/or the intrinsic non-linearities of the ASIC. Photopeak ratios between the 511 keV and 1275 keV signals (data not shown) suggest that the system's response may not be linear for high-energy pulses (1275 keV gammas). Linearity correction will therefore be essential when implementing such detectors in a scanner system. Setting the SiPM bias voltage to 27.5 V allowed clear resolution of a 21×21 array of sub-millimetre crystals. Although the outermost row and column crystals were lost due to insufficient light spreading among SiPMs, the results are acceptable considering the multiplexing ratio. To recover the entire crystal array, future work will evaluate the use of a single continuous light guide for light sharing between neighbouring detector modules.

The mean energy resolution of the detector at different irradiation depths was $10.5 \pm 1.6\%$ for a bias voltage of 27.5 V. Energy resolution worsens to $23.2 \pm 2.7\%$ when the photopeak position depth dependence is not accounted for. Therefore, depth-dependent photopeak shifting should be applied as a correction when implementing such detectors at a scanner level. At the same bias voltage,

the mean DOI resolution was 2.3 ± 0.3 mm. Unlike the energy resolution, which worsened in edge and corner crystals, DOI resolution remained relatively constant across the entire array. The degraded energy resolution in these regions is likely due to variations in light collection, while DOI resolution is primarily affected by factors such as surface treatment (e.g., polished or unpolished crystals) and inter-crystal reflector. Our findings suggest that despite reduced light collection in edge and corner crystals, depth-dependent light collection is still maintained.

Compared to our previous report on the performance of a similar detector [129], both energy and DOI resolution were improved. In the previous work, a different crystal manufacturer was used and the eight signals were further shaped and amplified before being digitised using a data acquisition board (Powerdaq, United Electronic Industries). In that study, the mean energy resolution was $17.6 \pm 5.3\%$, and the mean DOI resolution ranged from 2.8 ± 0.4 mm at the centre to 3.5 ± 1.0 mm at the edges. It is important to note that the crystal manufacturing in the previous work was not optimal, which may explain the observed differences. A direct comparison using the new crystal array would provide a more stringent evaluation. Despite these advancements, the detector CTR remained at 1.3-1.4 ns in both studies, suggesting that the excellent timing capabilities of the TOFPET2 ASIC [25] are compromised by the signal multiplexing used in our setup. In Table 3.1, a direct comparison between this work and other dual-ended PET detectors for high-resolution small-animal PET imaging is presented. Aside from [124], which uses dedicated singles processing units (SPUs), most other systems rely on traditional NIM electronics. This confirms that reliable performance can be achieved when using the TOFPET2 ASIC with highly multiplexed detector readout configurations.

Table 3.1: Comparison of dual-ended PET detectors for high-resolution small-animal PET imaging.

Reference	LYSO array	SiPM array	Multiplexing ratio	Energy (%)	DOI (mm)
This work	23×23 ($0.785 \times 0.785 \times 20$ mm ³)	6×6 (3.16 $\times$ 3.16 mm ²)	9:1	23.2 ± 2.7 $10.5 \pm 1.6^*$	2.3 ± 0.3
[126]	17×17 ($0.513 \times 0.513 \times 20$ mm ³)	4×4 (3.0×3.0 mm ²)	4:1	24.4 ± 1.3	2.3 ± 0.2
[124]	23×23 ($1.0 \times 1.0 \times 20$ mm ³)	8×8 (3.0×3.0 mm ²)	16:1	19.1 ± 2.9	2.0 ± 0.3
[190]**	38×38 ($0.4 \times 0.4 \times 20$ mm ³)	8×8 (2.0×2.0 mm ²)	16:1	18.2	1.8

* After photopeak depth-dependence correction.

** No standard deviation is reported.

For multi-channel experiments, various event timestamp methods have been proposed, including using the earliest signal as the event timestamp and averaging (weighted or unweighted) signal timestamps. The earliest signal method is assumed to capture the very first photoelectrons triggering the SiPM, providing accurate event time measurements [152]. However, timestamp averaging methods have been reported to yield better coincidence time resolution (CTR) values [48, 138]. Our CTR experiments confirmed that averaging timestamps results in better coincidence timing performance compared to using the earliest timestamp method. A limitation of this work is that both time skew (time differences due to different electronic signal paths) and time walk effects were not corrected. However, since the detector is designed for small animal PET imaging, where TOF capabilities are not required, the measured CTR is deemed acceptable for its intended application. To improve the detector’s CTR, machine learning methods could be explored, as they have demonstrated superior performance compared to traditional analytical calibrations [137, 189, 188]. Additionally, implementing deep learning techniques for retrieving DOI information and/or improving event positioning in light-sharing detector configurations is expected to significantly boost overall detector performance [197, 65].

Based on this work, future development will involve assembling 64 dual-ended readout detectors to form a prototype small animal PET scanner capable of sub-millimetre spatial resolution [66, 67]. The entire system will be read out using only eight TOFPET2 ASICs. Due to the compact footprint and characteristics of the ASIC and the custom-designed electronics boards, the system is expected to be both compact and low in power consumption. This system configuration (multiplexed detector + ASIC) is thus suitable for other high-resolution small animal PET scanners. It achieves excellent detector performance while reducing the costs and complexity associated with individual photodetector readout and the need for different electronic modules for signal timing, digitisation, and coincidence sorting.

3.6 Conclusion

We have optimised and evaluated the performance of a highly multiplexed DOI-encoding PET detector based on a dual-ended readout configuration using the TOFPET2 ASIC. The detector is designed for small animal PET applications, with the goal of achieving sub-millimetre reconstructed spatial resolution. Operating at a bias voltage of 27.5 V, we measured mean energy, and DOI resolution values of $10.5 \pm 1.6\%$, 2.3 ± 0.3 mm, respectively. A CTR of 1.3 ns was obtained between two detectors in coincidence. In future work, the detector will be scaled, and a high-resolution small animal PET scanner will be assembled using only eight ASICs.

Chapter 4

A Deep Neural Network for Positioning and Inter-crystal Scatter Identification in Multiplexed PET Detectors: A Simulation Study

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Preamble

In Chapter 3, the performance of the light-sharing and multiplexed mousePET detectors was optimised. Event positioning in these PET detectors utilises an Anger logic decoding approach. While this method is efficient for localising events within their respective crystals, it has certain limitations. Specifically, events interacting at the edges of the crystal array and/or inter-crystal scatter events are likely to be incorrectly positioned.

The objective of this chapter is to study the properties of inter-crystal scatter events and develop a proof-of-concept deep learning algorithm capable of improving positioning accuracy in these PET detectors.

4.1 Abstract

Objective: High-resolution PET relies on the accurate positioning of annihilation photons impinging the crystal array. However, conventional positioning algorithms in light-sharing PET detectors are often limited due to edge effects and/or the absence of additional information for identifying and correcting scattering within the crystal array (known as inter-crystal scattering). Using GATE simulations, this study explores the feasibility of deep neural network techniques for more precise event positioning in finely segmented and highly multiplexed PET detectors with light-sharing.

Approach: Initially, the spatial and statistical properties of inter-crystal scatter (ICS) events in finely segmented LYSO PET detectors were investigated. Next, a deep neural network (DNN) for crystal localisation was designed, trained and tested with light distributions of photoelectric (P) and Compton + photoelectric (CP) events simulated using optical GATE and an analytical method to speed up data generation. Using the statistical properties of ICS events, an energy-guided positioning algorithm was then built into the DNN. The positioning algorithm enables selection of the unique or first crystal of interaction in P and CP events, respectively. Performance of the DNN was compared with Anger logic using light distributions from simulated 511-keV point sources placed at different locations around a single PET detector module.

Main results: The fraction of events forward and backward scattered in the LYSO detector was 0.54 and 0.46, respectively, whereas naïve application of the Klein-Nishina formulation predicts 70% forward scatter. Despite coarse photodetector data due to signal multiplexing, the DNN demonstrated a crystal classification accuracy of 90% for P events and 82% for CP events. For crystal positioning, the DNN outperformed Anger logic by at least 34% and 14% for P and CP events, respectively. Further improvement is somewhat constrained by the physics – specifically, the ratio of backward to forward scattering of gamma rays within the crystal array being close to 1. This prevents selecting the first crystal of interaction in CP events with a high degree of certainty.

Significance: Light sharing and multiplexed PET detectors are common in high-resolution PET, yet their traditional positioning algorithms often underperform due to edge effects and/or the difficulty in correcting ICS events. Our study indicates that energy-guided DNN-based event positioning has the potential to enhance 2D coincidence event positioning accuracy by nearly a factor of 3 compared to Anger logic. However, further improvements are difficult to foresee without additional information such as event timing.

Keywords: multiplexed PET detector, inter-crystal scatter, neural networks, optical simulations.

4.2 Introduction

High-resolution positron emission tomography (PET) requires accurate positioning of annihilation photons in the transverse plane and in the depth direction

(referred to as depth of interaction, DOI). In practice, event positioning accuracy is highly dependent on the detector design, including the crystal geometry, photodetector configuration, and readout electronics.

In PET, typically two crystal configurations are used: monolithic blocks or pixelated arrays. Positioning in monolithic blocks is based on light spreading across photodetectors and extensive calibrations of light fields [84]. Achieving high resolution in early monolithic detectors required thin scintillators (≤ 10 mm) [69, 122], albeit at the expense of sensitivity. However, recent advancements in detectors based on thick semi-monolithic designs have shown promise in achieving both high spatial resolution and sensitivity [74, 181].

For pixelated arrays the spatial resolution depends primarily on the transverse crystal size, while sensitivity – as for monolithic blocks – depends on the crystal thickness. Positioning in pixelated detectors further depends on the crystal to photodetector ratio. For 1:1 coupling (i.e., where each individual crystal is coupled to its own unique photodetector), positioning is performed by assigning the event to the crystal that caused the photodetector to fire. However, for high resolution applications, such as small animal PET, where finely pixelated and tightly packed crystal arrays are needed [275, 277, 242], 1:1 coupling is impractical due to space and cost constraints. Instead, such systems usually rely on light-sharing schemes in which groups of crystals are coupled to the same photodetector (typically via a light guide) (Fig. 4.1a), and event positioning is based on centre-of-mass calculations.

Although light-sharing schemes can achieve similar performance to 1:1 coupling [31, 106], there are two common drawbacks: poor performance at the edges of the crystal array due to insufficient light sharing among neighbouring photodetectors; and the inability to identify and correctly position events within the same detector array due to inter-crystal scattering (ICS). As shown in Fig. 4.1b-c, the multiple interactions of annihilation photons within the crystal array in ICS events can introduce event positioning error that propagates to the reconstruction and, ultimately, compromises the spatial resolution of the system [232, 285].

To address edge effects, different hardware-based solutions have been proposed, including the addition of slits into the light guides [198, 238] and using more complex detector designs [156]. The degradation caused by ICS can be handled by rejecting these events [110], however this is at the expense of system sensitivity. Instead, approaches based on ICS identification and correction are preferable. Improved positioning of ICS events based on maximum likelihood [234] and convex constrained optimisation [144] are feasible but offer only minor improvements (compared to Anger logic), even at low light sharing ratios.

More recently, positioning algorithms based on deep neural networks (DNNs) have been reported for both monolithic PET detectors [29, 50, 101, 105, 219] and light-sharing pixelated PET detectors [135, 145, 146, 197]. Contrary to other machine learning techniques (e.g., nearest neighbours and gradient tree boosting), deep learning methods have demonstrated superior ability to account for ICS events, thereby improving positioning in PET detectors [245]. In the case of light-sharing pixelated detectors, convolutional neural networks (CNNs)

can improve event positioning through edge crystal identification [135], DOI estimation [197] and ICS correction [145, 146, 197]. For example, Lee and Lee [145] reported $\sim 40\%$ accuracy in selecting the first crystal of interaction in ICS events and a resulting volumetric resolution improvement of 47-64% in a detector with high light sharing ratio. However, all of the prior work assumes that each individual photodetector signal is accessible for analysis, which is not always the case. Signal multiplexing of the electronic readout is sometimes used to further simplify the electronic configuration and overall cost [114, 154, 195, 276]. Yet little is known about the feasibility of DNNs (or CNNs) for event positioning in multiplexed detectors and how these compare to conventional algorithms (e.g., Anger logic). A CNN-based demultiplexing method was proposed in [154] for a 64-to-16 signal multiplexed PET detector, but this approach does not account for positioning errors caused by ICS events.

The aim of this Monte Carlo simulation study was to investigate whether DNN-based algorithms can outperform Anger logic for event positioning in light sharing and multiplexed PET detectors, accounting for ICS events in the absence of timing information. We start by characterising ICS events in finely segmented LYSO detectors. We then introduce a DNN-based pipeline designed for 2D event positioning and multiplexed photodetector data. Proof-of-concept of the DNN-based positioning algorithm is demonstrated using optical Monte Carlo data from spatially distinct sources and compared to that of Anger logic. While this work does not encompass DOI estimation, we describe how the method can be adapted to include DOI within the pipeline.

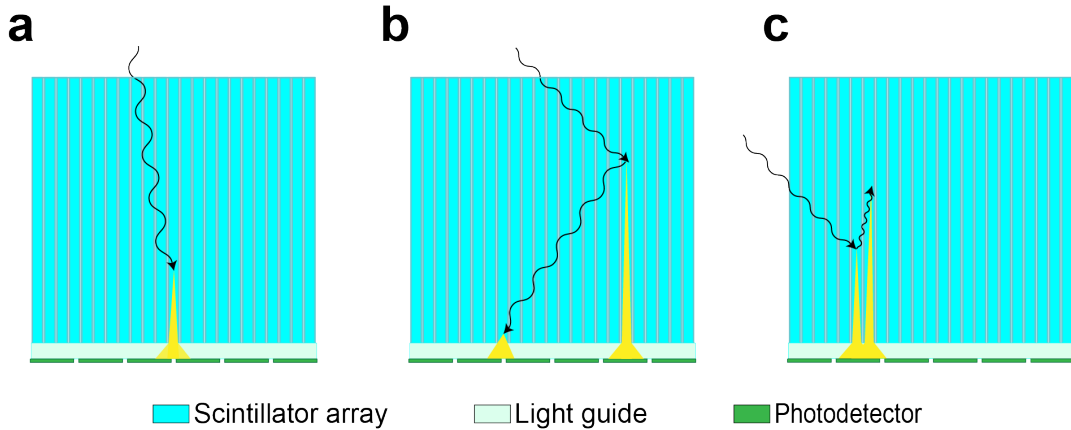


Figure 4.1: Light spreading in light-sharing PET detectors. (a) Optical photons emitted from a photoelectric interaction in the scintillation crystal array are detected by two of six photodetectors at one end of the array. Inter-crystal scatter (ICS) events in the forward (b) and backward (c) directions produce optical photons at multiple locations in the crystal array and the event position is typically estimated based on the centre-of-mass of the total light distribution.

4.3 Methods

4.3.1 ICS in Finely Segmented LYSO crystals

To characterise the spatial and statistical distribution of ICS events in finely segmented LYSO PET detectors, we used Geant4 Application for Tomographic Emission (GATE) v8.2 [223] to simulate the high resolution open-field mouse brain PET scanner [66]. The scanner is composed of four detector panels with each panel supporting 4×4 detector blocks and each block comprising 23×23 LYSO crystals. Individual crystals are $0.785 \times 0.785 \times 20 \text{ mm}^3$ (pitch = 0.85 mm), forming a total block size of $19.6 \times 19.6 \times 20 \text{ mm}^3$. Two photodetector arrays, each consisting of a 6×6 array of silicon photomultipliers (SiPMs) ($3.16 \times 3.16 \text{ mm}^2$ TSV J-Series, ONSEMI, USA) (pitch = 3.3 mm), read out the scintillation light from both ends of each detector block for DOI estimation.

Events were generated using a point source positioned at the centre of the FOV and emitting back-to-back 511 keV gamma rays. We focused on events characterised by a photoelectric interaction as the sole interaction (a ‘P’ event), or as the last interaction after a series of Compton scatter interactions (‘CP’, ‘CCP’, ‘3CP’, etc events). In a light-sharing PET detector, all of these events would fall within the photopeak window since they finish with a P interaction (i.e. the total energy of the original annihilation photon is eventually deposited in the crystal). We simulated ~ 60 million events, for each one recording the number of scatter interactions (prior to the photoelectric interaction) within the same detector block, and the ID of the crystals in which the events interacted. Interactions happening within the same crystal were ignored since they only impact DOI positioning accuracy without impacting the 2D positioning of the annihilation photons. Thus, a CP event occurring within the same crystal was treated as a P event for the purposes of this study. CP events were later categorised into *neighbouring CP* events (nCP) and *distant CP* events (dCP) based on the crystal index difference – what we refer to as the crystal window – between the scatter and photoelectric interaction (Fig. 4.2a). Four crystal windows were considered with index differences ranging from 0 to 3 crystals. For each crystal window we analysed the backward and forward scattering ratios, which in turn guided the DNN-based positioning algorithm in selecting the crystal of first interaction (Section 2.3).

4.3.2 DNN Implementation

In this work we used optical GATE simulations and an efficient analytical method to generate the training dataset. We focused exclusively on P and CP events, with the rationale for this choice becoming evident in Section 4.4.1.

4.3.2.1 Optical Simulations

Optical simulations were performed using the single PET detector described in Section 4.3.1. Teflon wrapping of each LYSO crystal was modelled using the ‘PolishedTeflon_LUT’ surface [217, 244]. Crystal to photodetector coupling was

via 1.2 mm thick PMMA light guides (refractive index 1.5) with polished surfaces (UNIFIED model, [147]). Photon detection within the active areas of the photodetector array was implemented using the 'Detector_LUT' surface with an efficiency of 1. The 35% SiPM photon detection efficiency (PDE) was modelled by randomly deleting 65% of photons from each SiPM in a post-processing step. Further information on the optical properties of LYSO crystals can be found in [243, 134].

We simulated a 511-keV pencil beam gamma source pointing towards the crystal front face and moving in a direction parallel to it, along the X and Y axes (Fig. 4.2b). 66 crystals, corresponding to $1/8$ of the array, were irradiated and, at each position, 40,000 photoelectric events were collected. Optical photons produced from these photoelectric events were collected to simulate the two (i.e. front and back) 6×6 SiPM array light distributions, based on the number of photons reaching each SiPM. To include the light contribution from the remainder of the array we relied on symmetry, mirroring the light distributions along the X and Y axes. Since we ignored DOI for this study, the front and back 6×6 light distributions were combined to enhance the dataset statistics. To account for the electronic signal multiplexing of the photodetector data in our small animal system [129], the 6×6 light distributions were compressed into a 1×6 row and a 1×6 column distribution by summing the values along rows and columns, respectively. Finally, we calculated the mean and variance of the row and column light distributions for each crystal in the array. Given that each crystal has a unique combination of row and column light distributions, we refer to them as 'basis distributions'.

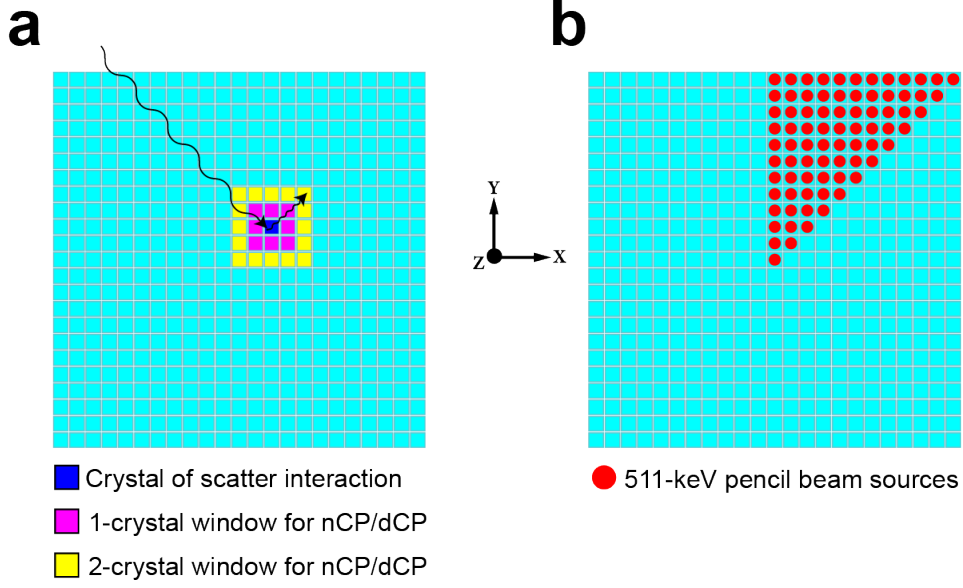


Figure 4.2: (a) A “CP event”, in which an incoming 511-keV photon scatters inside a crystal (dark blue) before undergoing a photoelectric interaction. CP events were divided into two groups: neighbouring (nCP) and distant (dCP). Photoelectric interactions of the scattered photon within a defined window of either 1 crystal (magenta region) or 2 crystals (yellow region) from the crystal of first interaction are considered nCP events; if outside this window they are treated as dCP events. For example, using a 1-crystal window the scattered photon interacting in the yellow zone corresponds to a dCP event whereas using a 2-crystal window this still would be considered a nCP event. (b) To determine basis distributions, 1/8 of the crystal array was irradiated with monoenergetic (511 keV) pencil beam sources (red circles) impinging perpendicular to the crystal front face. Only the light distributions from photoelectric events were recorded.

4.3.2.2 CP Events as Weighted Combinations of Basis Distributions

With the basis distributions established, we simulated the row/column distributions from CP events using an energy-weighted combination of the basis distributions corresponding to the crystals involved in the CP event:

$$CP^{row} = e_a \times row_a + e_b \times row_b \quad (4.1)$$

$$CP^{col} = e_a \times col_a + e_b \times col_b \quad (4.2)$$

where $CP^{row/col}$ is the row/column light distribution of a CP event involving crystals a and b ; row_a/col_a and row_b/col_b are the row/column basis distributions of crystals a and b , respectively; and e_a and e_b are the energies deposited in each crystal, with $e_b = (511 - e_a)$ keV.

Using the basis distributions and their variance, together with the crystal IDs obtained from CP events in Section 4.3.1, we generated a dataset comprising approximately 127 million distinct CP row-column light distributions for training the NN. The CP light distributions were randomly combined with approximately

19 million light distributions from photoelectric events. Finally, the light distributions were made independent of energy by normalising to the area under the curve. This enabled handling of ICS events of diverse energies (e.g., CC events at or below the energy window) and with different SiPM overvoltages. Post-normalisation, the sum of the energy weights is constrained to unity (i.e., $e_a + e_b = 1$).

4.3.2.3 Neural Network Architecture and Training Method

The DNN was implemented using Keras and TensorFlow-GPU v2.6.2 and an NVIDIA GeForce RTX 2060 GPU. The architecture consisted of 12 input neurons (6 for the row light distributions and 6 for the column light distributions), 3 fully-connected hidden layers each with 512 neurons, and 1 partially-connected hidden layer with 936 neurons and 93 output neurons (Fig. 4.3c). All hidden layers were activated with rectified linear unit (ReLU) functions. Four groups of 23 output neurons each were activated using softmax functions. These neurons represent the row and column crystal indices ($c_a^{row}, c_a^{col}, c_b^{row}, c_b^{col}$), $a, b \in 0 - 22$, and predict the likelihood (0-1) of a crystal being involved in a P and/or CP event. For each group, the crystal index with the highest likelihood was chosen as the crystal of interaction (Fig. 4.3c). The 2D crystal locations were then:

$$\mathbf{c}_a = (\text{argmax}(\mathbf{c}_a^{row}), \text{argmax}(\mathbf{c}_a^{col})) \quad (4.3)$$

$$\mathbf{c}_b = (\text{argmax}(\mathbf{c}_b^{row}), \text{argmax}(\mathbf{c}_b^{col})) \quad (4.4)$$

The last output neuron was activated with a sigmoid function to predict the energy deposition in crystal a ($0 \leq e_a \leq 1$). For P events e_a is set equal to 1.

The loss function comprised five terms:

$$\alpha_1 ||e_a^{pred} - e_a^{true}||^2 + \alpha_2 (CE(\mathbf{c}_a^{row}) + CE(\mathbf{c}_b^{row}) + CE(\mathbf{c}_a^{col}) + CE(\mathbf{c}_b^{col})) \quad (4.5)$$

where α_1 and α_2 are weights. The term regressing the error between the true (e_a^{true}) and predicted energy (e_a^{pred}) is weighted by α_1 . The remaining four terms, weighted by α_2 , represent the categorical cross-entropy (CE) for each row and column crystal index. Combined, the loss minimises the discrepancy in energy and crystal index between true and predicted values.

Training commenced with a ‘warm-up’ session (20 epochs), during which α_1 and α_2 were set to 0 and 1, respectively. Subsequently, an alternating-loss approach was adopted. We alternated between the energy regression term ($\alpha_1 = 1, \alpha_2 = 0$) and the four crystal index classification terms ($\alpha_1 = 0, \alpha_2 = 1$) in 5-epoch steps for a total of 600 epochs. The learning rate was set to 0.001 and mini batches were used to avoid saturating the GPU. To avoid overfitting the network a dropout of 0.5 was used in all hidden layers during network training.

4.3.3 DNN-Based Positioning Algorithm

4.3.3.1 Algorithm Implementation

We assume that event energy is measured using the sum of the row and column signals and that events of interest are P and CP events only (i.e., photopeak events). For CP events, however, since no timing information was considered during network training, we did not assume that the neural network could discover the order of the interactions – that is, whether $\mathbf{c}_a$ or $\mathbf{c}_b$ was the first crystal of interaction ($\mathbf{c}_1$). To select $\mathbf{c}_1$, a guided discrimination was implemented. While it may be tempting to assume that most CP events involve forward scattering according to the Klein-Nishina formulation [118], results in Section 4.4.1 demonstrate that this assumption does not hold for small crystals - and indeed penalises the network positioning performance if it is imposed. Instead, we classified the network outputs into three categories - P, nCP, and dCP events - prior to selecting the first crystal of interaction. To categorise the events, we relied on the difference between the two predicted crystals (i.e., $\mathbf{c}_a - \mathbf{c}_b$). P events exhibited a crystal difference of 0, while nCP and dCP events were distinguished using a 1-crystal window, as outlined in Section 4.3.1. To position P events, either of the two crystal indices could be chosen since they were the same. To position CP events, we based the selection on findings from Section 4.4.1 and Compton kinematics. As shown later, using the 1-crystal window, nCP and dCP events are more likely to be backward and forward scattered, respectively. We then assumed that all nCP events involved backward scattering, selecting $\mathbf{c}_1$ as the one with the highest energy deposition (i.e., $\max(e_a, e_b = 1 - e_a)$). Conversely, we assumed that all dCP events involved forward scattering and chose $\mathbf{c}_1$ as the one with the lowest energy deposition (i.e., $\min(e_a, e_b)$). This selection criteria becomes evident from the Compton formula for 511 keV gamma rays [43]:

$$E_{\gamma'} = \frac{511 \text{keV}}{2 - \cos\theta} \quad (4.6)$$

where $E_{\gamma'}$ is the energy of the scattered photon and θ the scatter angle. In forward scattering ($0^\circ < \theta \leq 90^\circ$), the scattered photon exits the first crystal with an energy of at least half the energy of the original photon, meaning that most of the original photon energy (511 keV) is deposited in the second crystal (assuming photoelectric absorption, as in a CP event). Conversely, in backward scattering ($90^\circ < \theta \leq 180^\circ$), the energy of the scattered photon exiting the first crystal is less than half of 511 keV, meaning that most of the energy was deposited during the scatter interaction in the first crystal.

Using the example in Figure 3, where $\mathbf{c}_a = (9, 10)$ and $\mathbf{c}_b = (8, 6)$, the crystal difference is beyond the 1-crystal window and, therefore, the event is classified as a dCP event. Using the assumption that all dCP events are forward scattered, if $e_a > e_b$, then $\mathbf{c}_b$ is correctly chosen as the first crystal of interaction ($\mathbf{c}_1$). In the opposite case (i.e., $e_a < e_b$), despite the correct DNN prediction of the two crystals of interaction, the event is incorrectly positioned within the crystal array.

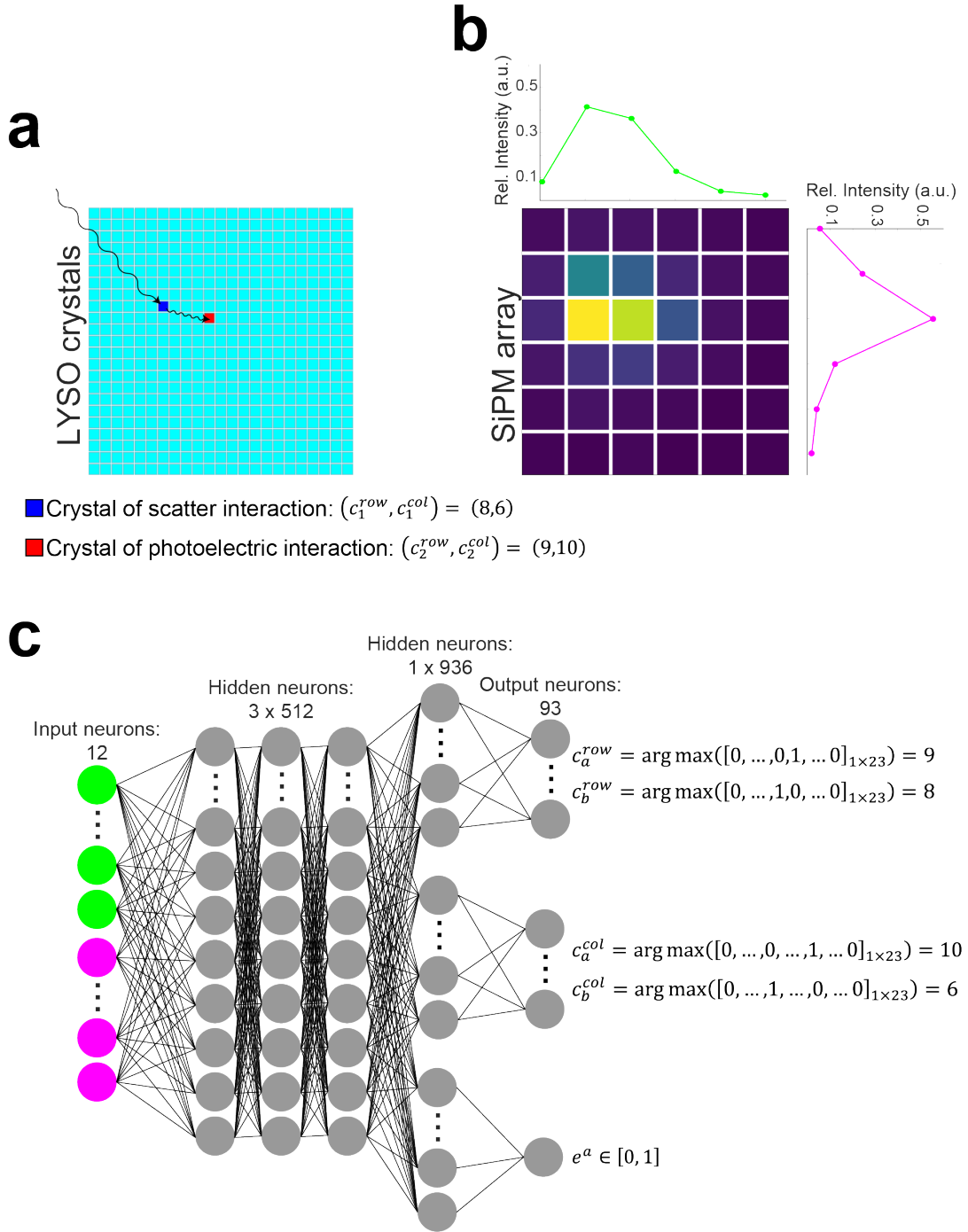


Figure 4.3: DNN-based crystal prediction. (a) A 511-keV gamma ray scatters inside crystal $\mathbf{c}_1$ (dark blue), with row-column indices (8,6), and then undergoes a P interaction inside crystal $\mathbf{c}_2$ (red), at indices (9,10). (b) Light produced at both interactions is recorded on the SiPM array and the row-column signal reduction algorithm is applied giving rise to the light distributions shown in magenta and green, respectively. (c) Normalised row (magenta) and column (green) light distributions are fed into the neural network. The row and column crystal indices with highest likelihood are selected as the crystals of interaction.

4.3.3.2 Performance Evaluation

To assess the DNN-based positioning performance, we simulated a single PET detector in GATE (see Section 4.3.1) and three point sources emitting isotropic 511-keV gamma rays. The point sources were positioned 3 cm from the detector front face along the Z -axis and at different locations in the XY -plane (Fig. 4.4a). Point source 3 was offset by 2 cm to the side of the detector so that gamma rays impinged on the detector obliquely. From the simulation, we extracted light distributions for algorithm testing, along with ground-truth data comprising the first crystal of interaction and deposited energy.

Initially, we assessed the performance of the DNN architecture solely in terms of correctly predicting (i) the 2 crystals of interaction and (ii) the energy deposited. Since the network does not predict crystal indices in order (i.e., $\mathbf{c}_a$ is not necessarily $\mathbf{c}_1$), two scenarios arise: $\mathbf{c}_1 = \mathbf{c}_a$ or $\mathbf{c}_1 = \mathbf{c}_b$. However, we note that if $\mathbf{c}_1 = \mathbf{c}_a$, then $\|\mathbf{c}_1 - \mathbf{c}_a\|_1 + \|\mathbf{c}_2 - \mathbf{c}_b\|_1 < \|\mathbf{c}_1 - \mathbf{c}_b\|_1 + \|\mathbf{c}_2 - \mathbf{c}_a\|_1$, where $\|\cdot\|_1$ denotes the $L1$ distance. Conversely, if $\mathbf{c}_1 = \mathbf{c}_b$, the opposite holds true. Under these assumptions we measured (i) using the minimum $L1$ distance between these two possible cases:

$$\min(\|\mathbf{c}_1 - \mathbf{c}_a\|_1 + \|\mathbf{c}_2 - \mathbf{c}_b\|_1, \|\mathbf{c}_1 - \mathbf{c}_b\|_1 + \|\mathbf{c}_2 - \mathbf{c}_a\|_1) \quad (4.7)$$

The crystal sequence corresponding to the minimum $L1$ distance was used to measure (ii). The network energy performance was evaluated by calculating the difference between the true first energy (e_1) and the energy deposited in the crystal within the term containing $\mathbf{c}_1$. For instance, in scenarios where $\|\mathbf{c}_1 - \mathbf{c}_a\|_1 + \|\mathbf{c}_2 - \mathbf{c}_b\|_1 < \|\mathbf{c}_1 - \mathbf{c}_b\|_1 + \|\mathbf{c}_2 - \mathbf{c}_a\|_1$, the network energy performance is $e_1 - e_a$.

To evaluate the performance of the positioning algorithm – comprising the DNN architecture plus scatter assumptions – we followed the methodology outlined in Section 4.3.3.1. The predicted first crystal of interaction was compared with ground-truth data. To evaluate the effect of the scatter assumptions on the final energy prediction, the predicted energy after scatter assumptions was compared with the ground-truth. We also compared the positioning performance with the conventional approach using Anger logic. For Anger logic, the detector readout circuitry, based on a resistor ladder approach [129], was simulated, excluding the amplification stages. The row-column light distributions were reduced to four signals (X^+ , X^- , Y^+ , and Y^-), which were then combined to calculate the x and y position values. A segmented crystal map was generated using the basis distributions from Section 4.3.2.1 and the watershed method [262] (Fig. 4.4b). The map was used to translate the x and y positions into row and column crystal indices $\in 0 - 22$.

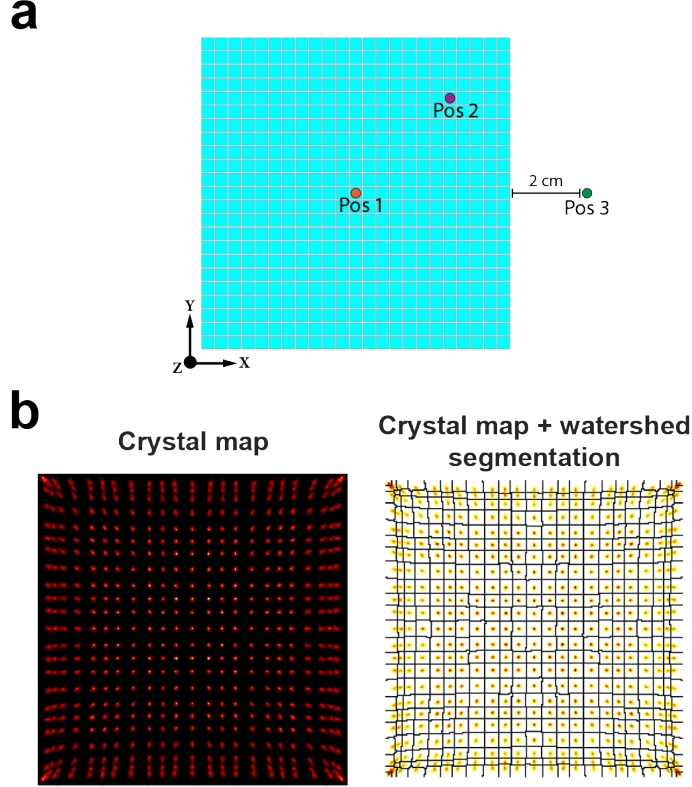


Figure 4.4: (a) Three point sources were simulated to test the performance of the DNN positioning approach. In all cases, the distance along the Z axis between the crystal array front face and the point sources was 3 cm. (b) Crystal flood map (left) obtained using the basis distributions (Section 4.3.2.1) and later segmented using a watershed segmentation algorithm (right). Black lines indicate the boundaries between neighbouring crystals.

4.4 Results

4.4.1 ICS Statistical Distribution

Figure 4.5a displays the statistical distribution of P and ICS events terminating in a photoelectric interaction. Out of 60 million recorded events, 55% involved photoelectric interaction without scattering in the crystal array. Events characterized by a single scatter preceding photoelectric absorption accounted for 34%. Multi-scatter ICS events, denoted as 'other' in the plot, constituted only 11% of the total events. The distribution of multi-scatter ICS events is depicted in figure 4.5b, which indicates that the vast majority ($\sim 83\%$) were CCP. Figures 6a-d illustrate the forward and backward scatter ratios of CP events, categorised as neighbouring (nCP) and distant (dCP) events. In figure 4.6a, no crystal window was considered, and all events were treated as dCP events, resulting in forward and backward scatter ratios of 0.54 and 0.46, respectively. With a 1-crystal window (Fig. 4.6b), the forward and backward ratios for dCP events were 0.60 and 0.40, while for nCP events these ratios were 0.41 and 0.59, respectively. As the window size increased to 2 and 3 crystals (Figs. 4.6c-d), there was a shift in favour of forward scattering for dCP events and a shift in the opposite direction,

resulting in a flattening of the ratio, for nCP events.

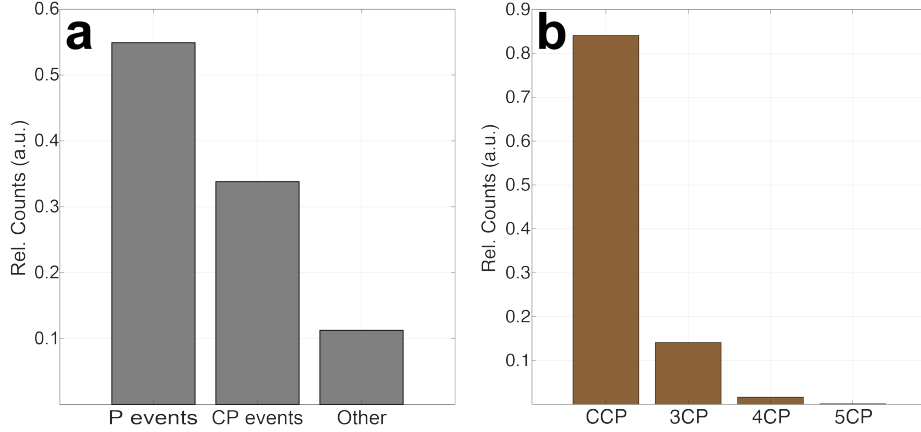


Figure 4.5: (a) Distribution of photoelectric (P), Compton followed by photoelectric (CP) and multi-scatter ('other') events based on the simulation of 511-keV gamma rays impinging all crystal arrays in the scanner. (b) Distribution of multi-scatter events within the scanner.

4.4.2 Network Performance

4.4.2.1 Crystal Identification

Figure 4.7 shows the $L1$ distance between the true and DNN-predicted crystal indices involved in P events (top) and CP events (bottom). In table 1, the mean $L1$ distance between true and DNN-predicted crystal indices is given for the different point source locations and event types. The mean distance for all event types (P + CP events) is given as a metric for the overall network performance.

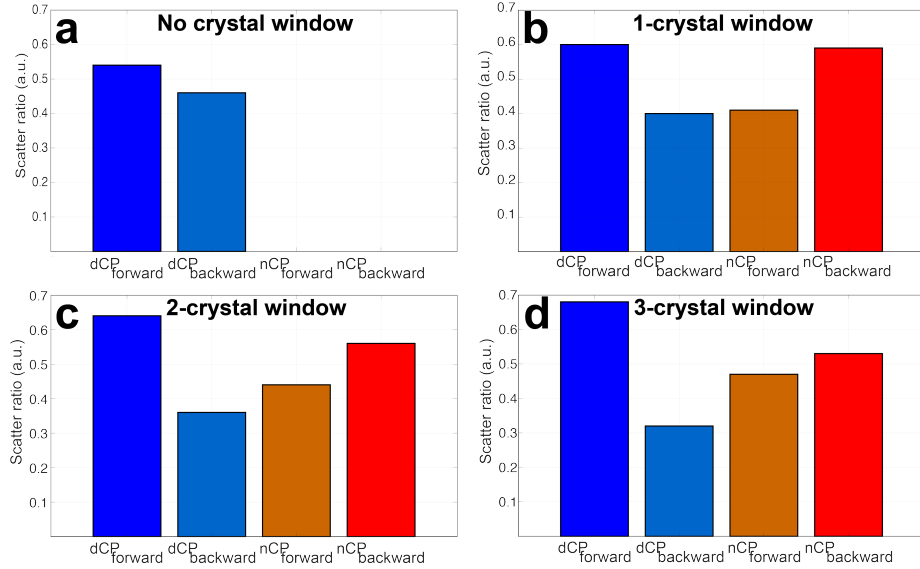


Figure 4.6: (a) Forward and backward scatter ratios for dCP events without a crystal window. (b-d) Forward and backward scatter ratios for nCP and dCP events while varying the crystal window from 1 to 3 crystals, respectively.

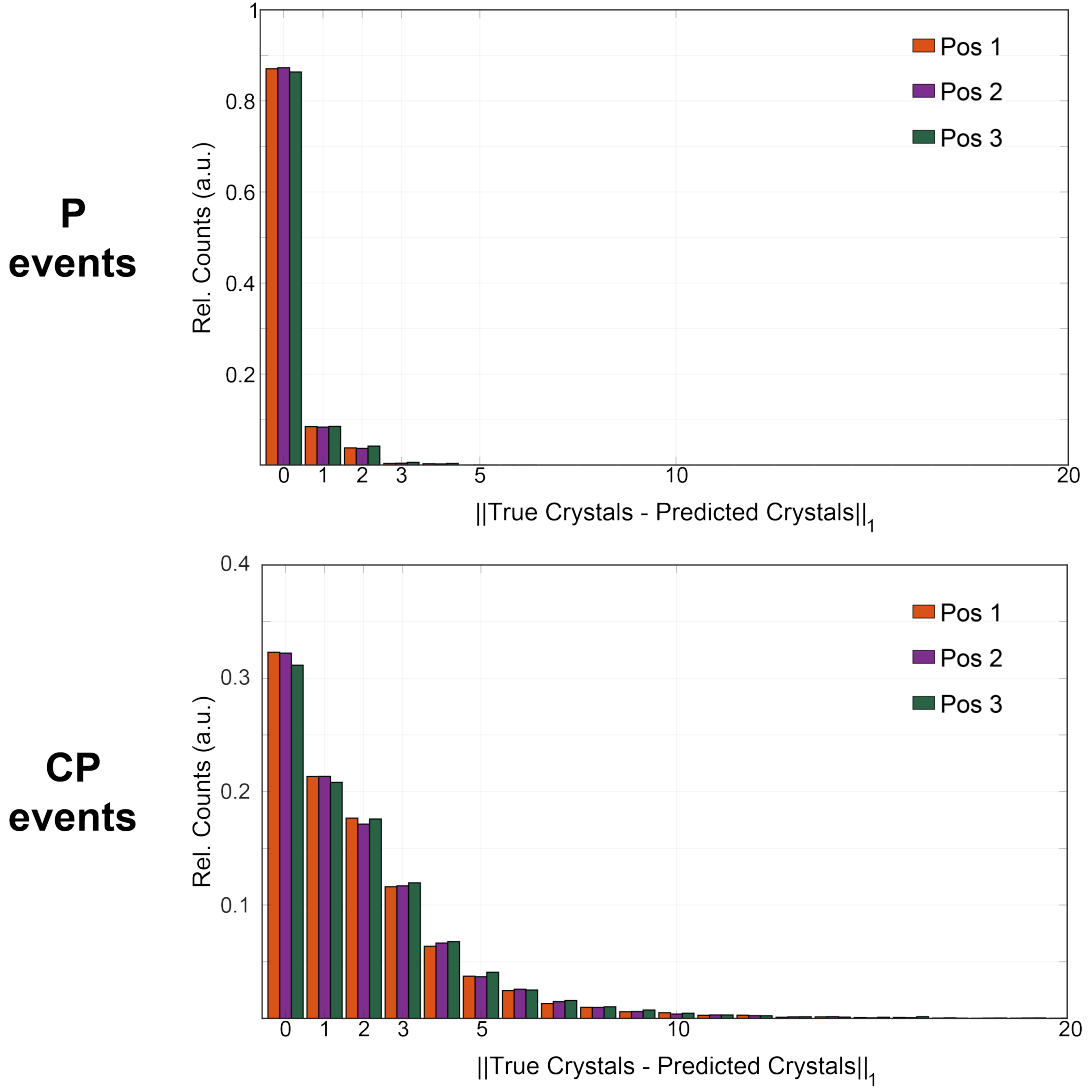


Figure 4.7: $L1$ distance between the true (simulation) and predicted (DNN) crystal indices involved in P (top) and CP (bottom) events from the three different points source locations: Pos 1, orange; Pos 2, purple; Pos 3, green.

Table 4.1: Mean $L1$ distance values between true and DNN-predicted crystals for P, CP, and all events (P + CP) across the different point source locations

Source position	P events	CP events	All events
Pos 1	0.19	1.95	0.79
Pos 2	0.18	1.97	0.79
Pos 3	0.20	2.04	0.83

4.4.2.2 Energy Prediction

Figure 4.8 shows the performance of the DNN energy prediction for CP events, prior to any scatter assumptions. Histograms depict the disparity between DNN-predicted energy and the ground-truth. Across all point source positions, 55% of the predictions fall within an energy difference of ± 50 keV relative to their true energy values. This increased to 78% for a ± 100 keV energy difference.

4.4.3 Positioning Algorithm Performance

4.4.3.1 Event Classification

For the DNN-based positioning algorithm to work, a correct event classification is needed. Figure 4.9 shows the confusion matrices for DNN-based event classification accuracy for the three point sources. In all cases, the crystal window is one crystal. Across all point source positions, the DNN exhibited 90% accuracy in classifying P events. For nCP and dCP events, the accuracy was consistently $\geq 70\%$ and $\geq 62\%$, respectively. The most common classification error for nCP events was misclassifying them as P events; for dCP events, the most common classification error was misclassifying them as nCP events. 11-13% of dCP events were erroneously classified as photoelectric events. Inspection of such events showed that 53% of these corresponded to events in which either the energy deposition during the first interaction was ≤ 100 keV or an edge/corner crystal was involved. Overall, the classification accuracy for all event types across all point source locations was 82%. The classification accuracy of CP (ncP and dCP) events across all point source locations was 84%.

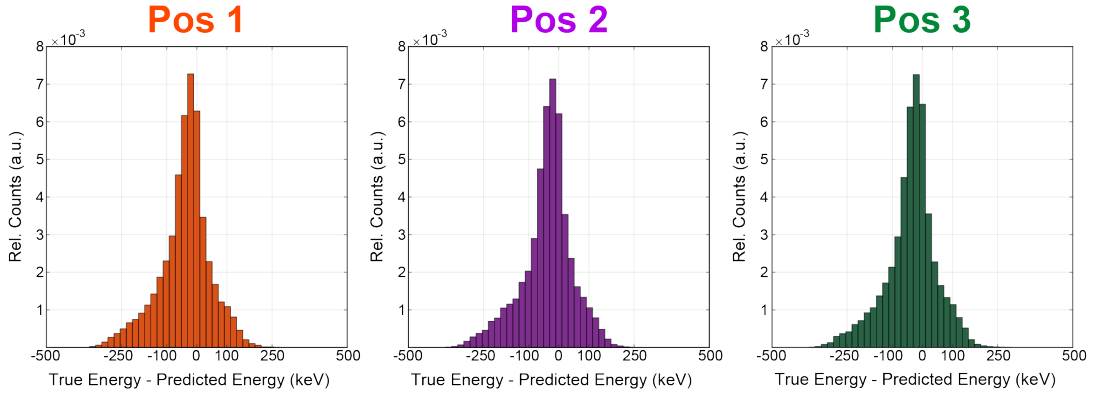


Figure 4.8: Energy differences between DNN predictions and ground-truth data. From left to right, the differences are for events from Pos 1 (orange), Pos 2 (purple) and Pos 3 (green) sources.

Pos 1					Pos 2					Pos 3				
DNN prediction					DNN prediction					DNN prediction				
Ground truth		P	nCP	dCP	Ground truth		P	nCP	dCP	Ground truth		P	nCP	dCP
	P	0.90	0.09	0.01		P	0.90	0.09	0.01		P	0.90	0.09	0.01
	nCP	0.26	0.70	0.04		nCP	0.25	0.70	0.05		nCP	0.25	0.72	0.03
	dCP	0.11	0.25	0.64		dCP	0.12	0.25	0.63		dCP	0.13	0.25	0.62

Figure 4.9: Confusion matrices of DNN classification accuracy for the three point sources and different event types (P, nCP and dCP).

4.4.3.2 Energy Prediction

Figure 4.10 shows the energy prediction performance when accounting for forward and backward scatter assumptions. Although the energy prediction is relatively poor, it still functions to guide the network in estimating the first crystal of interaction in CP events, as will be shown in Section 4.4.3.3. Across all three point source positions, 43% of events fell within a ± 50 keV range of the true energy. This increased to 66% for a ± 100 keV range.

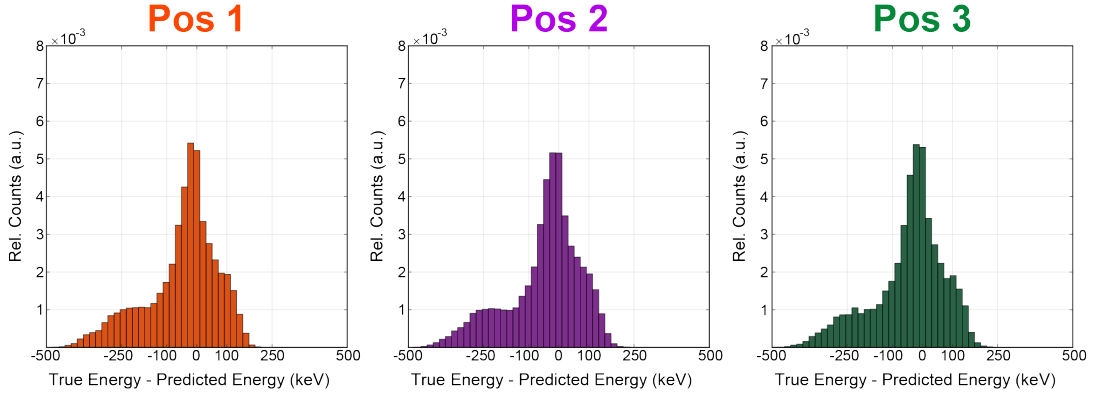


Figure 4.10: Energy difference, after scatter assumptions, between the true and predicted energy deposition during the scattering of CP events.

4.4.3.3 Positioning Performance

Figure 4.11 compares the DNN-based and Anger logic-based positioning performance for the three point source locations for both P events and CP events. Accuracy is reported for two scenarios: (i) accepting events only when the crystal difference was zero, and (ii) allowing a 1-crystal window error. For case 1 (exact), the DNN and Anger based approaches achieved an accuracy of 92-93% and 55-58%, respectively, for P events. For CP events, the accuracy was 26-27% (DNN) and 11-12% (Anger logic). Considering all events for case 1, the positioning accuracy was 70% (DNN) and 42% (Anger logic). For case 2 (1-crystal margin) and considering all events, the accuracy was 87% (DNN) and 82% (Anger logic).

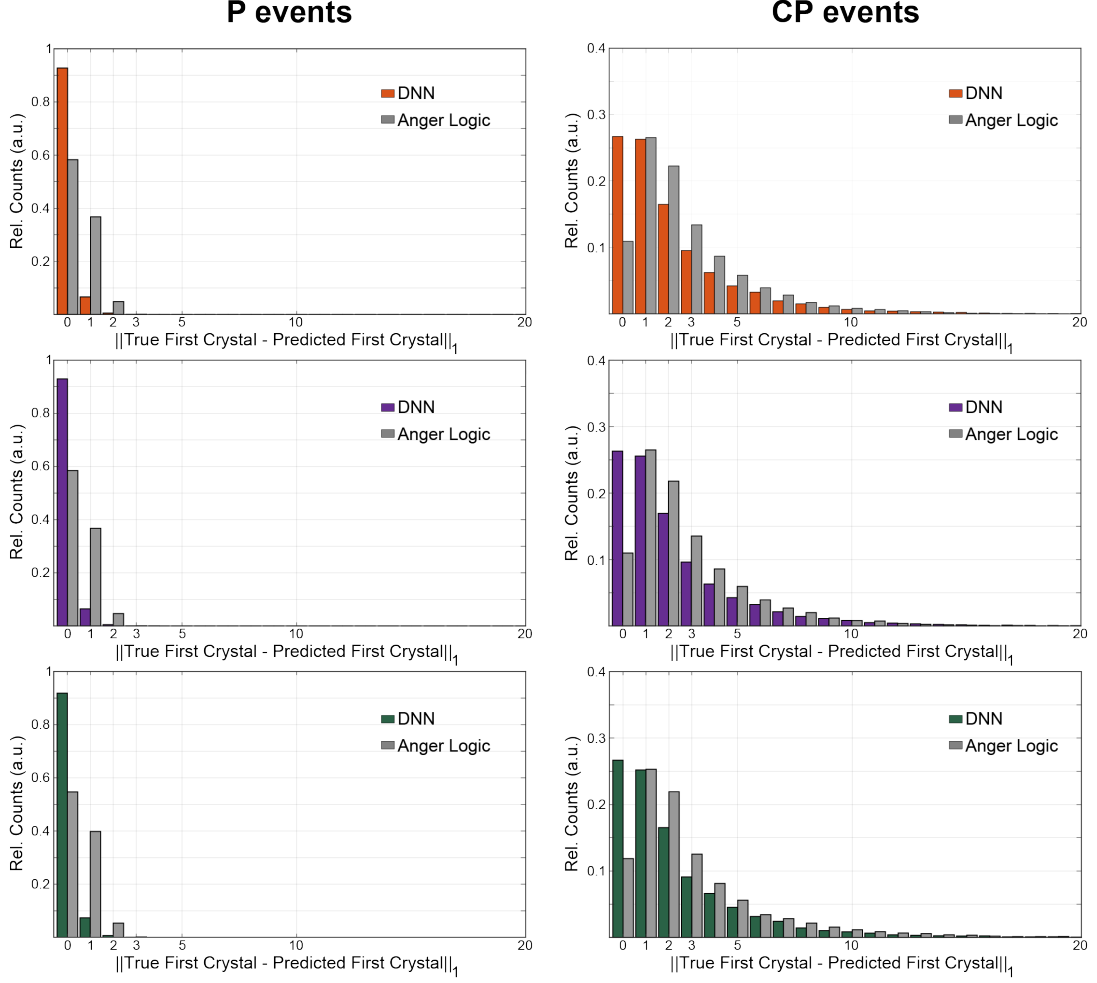


Figure 4.11: Positioning performance comparison between the DNN- and Anger logic-based approach for the three point sources: Pos 1 (top), Pos 2 (middle) and Pos 3 (bottom). Positioning comparison for P events (left) and CP events (right). In all cases, the coloured bars indicate the DNN performance and the light grey bars indicate Anger logic performance.

4.5 Discussion

4.5.1 ICS Forward and Backward Scatter Ratios

The limited time resolution in PET detectors due to scintillation processes and readout electronics complicates the use of pulse discrimination methods in light-sharing detectors for distinguishing multiple scatter interactions in ICS events. Instead, ICS event discrimination most commonly relies on identifying atypical light distribution patterns on the detector, which differ from those generated by single photoelectric interactions [145, 146, 197]. However, once these atypical patterns are recognised, the following questions arise: which two crystals (in the case of CP events) are responsible for these patterns, and in which crystal did the scatter interaction occur? These questions do not have straightforward answers. Assuming knowledge of the two interacting crystals and their respective energy depositions, one might naturally apply the Klein-Nishina formulation [118] to

select the crystal with the lowest energy deposition as the first crystal. The results in Section 4.4.1 demonstrate that, for 20-mm thick crystal needles (width < 1 mm), such an assumption is poor. The scatter ratios are nearly equal for forward and backward scattering, which results from the different photoelectric attenuation lengths (λ_p) of the scattered photons [197]. With such constraint, we implemented crystal windows to determine the most appropriate ratio for categorizing events as forward or backward scattered. We found that a 1-crystal window results in forward-backward ratios of 60-40 and 40-60 for dCP and nCP events, respectively. However, these ratios imply that, even in an ideal scenario where our network achieved 100% accuracy in crystal and energy predictions, the positioning method would be penalized 40% of the time due to the inherent physics of the problem. Expanding the crystal window to more than one crystal introduces the drawback of nearly equalising the ratios for nCP events in terms of forward and backward scattering, rendering wider windows impractical. In future work, a more thorough investigation of the scatter properties of LYSO crystal needles could provide better guidance when selecting the first crystal of interaction [197].

4.5.2 DNN Algorithm Performance

The network distinguished photoelectric events and single-scatter events with an accuracy exceeding 80%. This result is comparable with previously reported performance [146]; however, in our study this was obtained using multiplexed photodetector signals rather than the individual signals. Network performance identifying the 2 crystals involved in CP events was $\sim 32\%$. This relatively low value can be attributed to the non-uniqueness of decomposing CP light distributions in terms of two energy-weighted basis distributions. The non-uniqueness can lead to different combinations of crystal basis distributions and energy weights giving the same or very similar CP row-column light distributions (see Fig. 4.12). The latter is particularly true for basis distributions of crystals adjacent to the actual impinged crystals. The crystal-to-photodetector ratio of the detector studied here was 14.69 ($23^2/6^2$). For smaller ratios we anticipate a reduction in the non-uniqueness of the decomposition problem and, consequently, an improvement in algorithm performance.

The energy prediction capability of the algorithm exhibits certain limitations. While positioning P events does not necessitate energy guidance, CP events demand energy assumptions for selecting the first crystal, hence emphasising the need for improved energy predictions. Although alternative network architectures may offer superior energy prediction performance, the inherent ratios of backward and forward scattering will consistently challenge the proposed algorithm (Section 4.4.1). In the architecture under examination, the application of scatter assumptions results in a 12% reduction in the number of predicted energies within ± 50 keV of the true energy.

Crystal identification performance for P events by the network is notably higher compared to Anger logic (87% v 53%) primarily because of better performance on edge crystals. For CP events, the DNN algorithm improves the crystal positioning by 15% with respect to Anger logic. Positioning of CP events using

Anger logic shows that, across all point sources, a one crystal difference is most likely to be observed (Figure 4.11). This systematic error is likely to arise from the shifting of the centre of gravity of the detected scintillation light due to the double interaction of the gamma ray within the crystal.

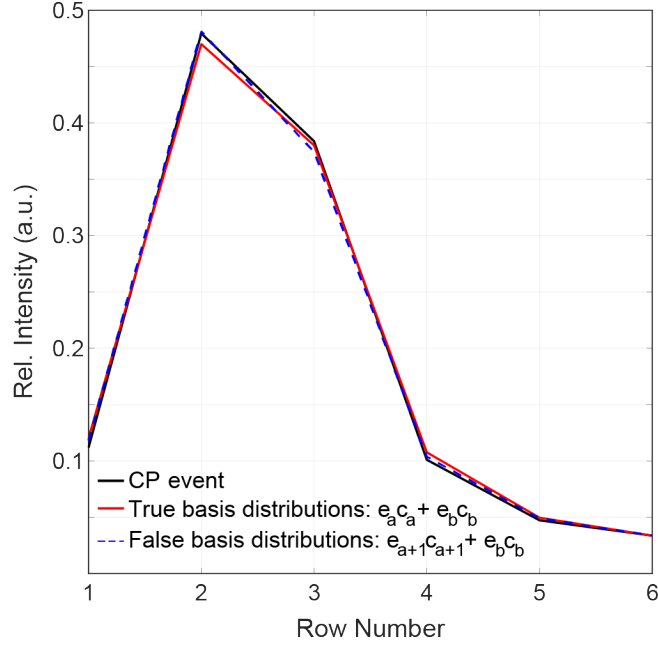


Figure 4.12: Solid black line: a CP-event row light distribution from GATE simulations (Section 4.3.2) involving crystals $\mathbf{c}_a$ and $\mathbf{c}_b$; solid red line: energy-weighted combination of the row light distributions of true two crystals involved in the CP event; dashed blue line: a row light distribution obtained using the wrong basis distributions ($\mathbf{c}_{a+1}$ instead of $\mathbf{c}_a$) and wrong energy weights ($e_{a+1} \neq e_a$).

4.5.3 3D Positioning (DOI)

Modern PET scanners now integrate DOI to mitigate parallax errors. Although it was beyond the scope of this study, incorporating DOI into the DNN-based event positioning method could be achieved via at least two adaptations:

- DOI could be calculated as a post-processing step from the DNN results. For example, after obtaining an initial DOI estimate based on the energy ratio between both photodetectors, an updated estimate could then be determined after classifying the event into nCP or dCP. The forward and backward scatter assumptions in both groups would then be applied to rebin the calculated DOI value into its ‘true’ bin.
- A more ambitious approach is to incorporate DOI directly into the network predictions (as in [197]). However, this would necessitate modifications to the current proof-of-concept method. Specifically, the network inputs should transition from a row and column light distribution to a 24-entry vector, representing the row and column light distributions from each photodetector. An alternative normalisation technique preserving relative differences between photodetectors would be required.

In this work, we restricted our focus to a 2D DNN-based positioning algorithm. Our findings, based on Monte Carlo simulated data, indicate that this algorithm, with an event positioning accuracy of 70%, outperforms the conventional Anger logic method (42% accuracy) by 28%. Given that PET relies on the coincidence detection of two annihilation photons, the 2D coincidence positioning accuracy of the DNN algorithm is estimated to be 49%, surpassing the 18% achieved by Anger logic. We note that a fairer comparison might involve comparing the algorithm with a row-column positioning algorithm, where the number of inputs (12) is matched. However, this work is based on simulated data, and no modelling of the noise properties of the readout electronics was accounted for. We have confirmed that such an algorithm performs equally to Anger logic (data not shown). This highlights a limitation of this work, the lack of experimental data. Both, DNNs and traditional positioning algorithms can be quite sensitive to final detector arrangements. Future work will extend this proof-of-concept algorithm to encompass DOI considerations, with implementation on a physical PET detector. True basis functions will be measured using coincidence acquisitions between the detector and a reference detector consisting of a single crystal needle, as in [145]. DNN training can be performed using a combination of simulated and real data.

4.6 Conclusion

We successfully developed a proof-of-concept 2D positioning algorithm utilising deep neural networks for light-sharing and multiplexed PET detectors. The algorithm can identify single scatter events from pure photoelectric events with an accuracy of 82%. For event positioning, the method demonstrates a 28% improvement over Anger logic for both photoelectric and single-scatter interactions. Since PET relies in the coincidence detection of two photons, the coincidence positioning accuracy of the DNN algorithm is expected to be ~ 2.7 times higher than that achieved with Anger logic.

Chapter 5

Virtual Cylindrical PET for Efficient DOI Image Reconstruction with Sub-Millimetre Resolution

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Preamble

In high-resolution, DOI-capable PET systems, image reconstruction poses a challenge due to the large number of LORs, which grow almost quadratically with the number of DOI bins. In Chapter 3, the mean DOI resolution of the mousePET detectors was estimated to be 2.3 ± 0.3 mm. Given the detector crystal thickness of 20 mm, it is anticipated that 8 DOI bins will be utilised during image reconstruction.

The objective of this chapter is to develop a highly computationally efficient method for DOI PET reconstruction without significantly compromising the spatial resolution of the system. It is important to note that this work was conducted prior to the integration of the detectors with the TOFPET2 ASIC. In [129], 6 DOI bins were estimated based on the measured DOI resolution (2.8-3.5 mm). Consequently, the methodology in this work was based on that estimation.

5.1 Abstract

Objective: Image reconstruction in high resolution, narrow bore PET scanners with depth of interaction (DOI) capability presents a substantial computational challenge due to the very high sampling in detector and image space. The aim of this study is to evaluate the use of a virtual cylinder in reducing the number of lines of response (LOR) for DOI-based reconstruction in high resolution PET systems while maintaining uniform sub-millimetre spatial resolution.

Approach: Virtual geometry was investigated using the awake animal mousePET as a high resolution test case. Using GATE, we simulated the physical scanner and three virtual cylinder implementations with detector size 0.74 mm, 0.47 mm and 0.36 mm (vPET1, vPET2 and vPET3, respectively). The virtual cylinder condenses physical LORs stemming from various crystal pairs and DOI combinations, and which intersect a single virtual detector pair, into a single virtual LOR. Quantitative comparisons of the point spread function (PSF) at various positions within the field of view (FOV) were compared for reconstructions based on the vPET implementations and the physical scanner. We also assessed the impact of the anisotropic PSFs by reconstructing images of a micro Derenzo phantom.

Main results: All virtual cylinder implementations achieved LOR data compression of at least 50% for DOI PET reconstruction. PSF anisotropy in radial and tangential profiles was chiefly influenced by DOI resolution and only marginally by virtual detector size. Spatial degradation introduced by virtual cylinders was most prominent in the axial profile. All virtual cylinders achieved sub-millimetre volumetric resolution across the FOV when 6-bin DOI reconstructions (3.3 mm DOI resolution) were performed. Using vPET2 with 6 DOI bins yielded nearly identical reconstructions to the non-virtual case in the transaxial plane, with an LOR compression factor of 86%. Resolution modelling significantly reduced the effects of the asymmetric PSF arising from the non-cylindrical geometry of mousePET.

Significance: Narrow bore and high resolution PET scanners require detectors with DOI capability, leading to computationally demanding reconstructions due to the large number of LORs. In this study, we show that DOI PET reconstruction with 50-86% LOR compression is possible using virtual cylinders while maintaining sub-millimetre spatial resolution throughout the FOV. The methodology and analysis can be extended to other scanners with DOI capability intended for high resolution PET imaging.

Keywords: DOI PET reconstruction, sub-millimetre resolution, virtual detectors.

5.2 Introduction

Narrow bore PET scanners, typical of small animal and organ-dedicated systems, aim to achieve uniformly high spatial resolution and sensitivity throughout the field of view (FOV). For high sensitivity, scanners typically consist of

detectors comprising long crystals with minimal gaps between them [30, 252, 265]. For high resolution, detectors often use finely segmented (thin) crystals [111, 125, 282]. However, the combination of narrow bore and long crystals means that annihilation photons impinging at oblique angles with respect to the crystal front face are commonly mispositioned (known as parallax error), resulting in degraded and non-uniform spatial resolution. To correct this, detectors must account for the depth of interaction (DOI) of the annihilation photons. In DOI-capable detectors, the lines of response (LORs) are not assigned to a single crystal location (e.g., the crystal front face) but to the centre of the DOI bin where the interaction took place. More precise DOI localisation of events leads to reduction of parallax errors and more uniform spatial resolution across the FOV [110, 129, 282].

An important cost of DOI-capable systems is that the number of LORs increases $\sim N^2$ (N the number of DOI bins). For iterative reconstruction algorithms, this can quickly create computational bottlenecks from the forward and back projection at each iteration, and calculation of the system matrix. Computation of the system matrix elements requires passing through all possible LORs within the system. Typically, these elements are pre-calculated once and stored on disk [286] or calculated on-the-fly [78]. Pre-calculation consumes considerable disk space for DOI-capable systems, while on-the-fly calculations, though less demanding in terms of disk storage, are time-consuming as they must be repeated at each reconstruction, making them less preferable. A one-off system matrix calculation, however, is not always possible. For example, LOR-based motion compensation with precise attenuation correction requires repeated computation that accounts for the time-weighted effect of each sampled movement of the subject [8, 207]. This is not always practical, especially for DOI-capable systems.

As the limits of PET spatial resolution continue to be pushed in novel application-specific scanners with DOI and motion compensation, there is a parallel need for computationally efficient reconstruction algorithms to support this trend. One approach for LOR reduction (compression) is the use of virtual geometries to rebin multiple physical LORs from different crystals and DOI bins into a single virtual LOR (Fig. 5.1) [86, 113, 151, 265, 284]. Previous work on virtual geometries for PET reconstruction is, however, rather inconclusive for several reasons: (i) performance comparisons between uncompressed (full) and compressed system matrices are not always reported [86, 265] or have been inconclusive [151]; (ii) conclusions regarding their effect on preserving spatial resolution are inconsistent, with some suggesting it is well preserved [284] and others that it is degraded unless sub-sampling methods are employed [113]; and (iii) there has been very little reported on the use of a virtual cylinder with smaller radius than the physical scanner [151, 265]. Compared to virtual geometries coinciding with the first DOI bin of the physical scanner [86, 113, 284], the use of a smaller virtual ring radius provides further LOR compression. This is at the expense of a reduced effective FOV and spatial resolution, but the precise cost and implications are not well understood.

In this work we implemented virtual cylindrical detectors for DOI PET image reconstruction in the context of the open-field Mouse Brain PET scanner

(mousePET) [66, 129], an overlapping box-shaped PET scanner for awake animal imaging. The implementation is based on a virtual cylinder configuration with smaller radius than the original FOV. The combination of (i) finely segmented crystals ($0.785 \text{ mm} \times 0.785 \text{ mm} \times 20 \text{ mm}$) with 3-mm DOI resolution [129] and (ii) the need for a time-varying system matrix for motion correction [8, 207], makes the scanner a highly LOR-intensive PET system and, therefore, a good case study for investigating potential benefits of a virtual detector. The primary objective of this study was to assess the impact of the virtual cylinder compression method (referred to as 'virtual PET') on the spatial resolution and DOI performance of mousePET, and hence to extrapolate some general principles of virtual detector performance for other high resolution systems.

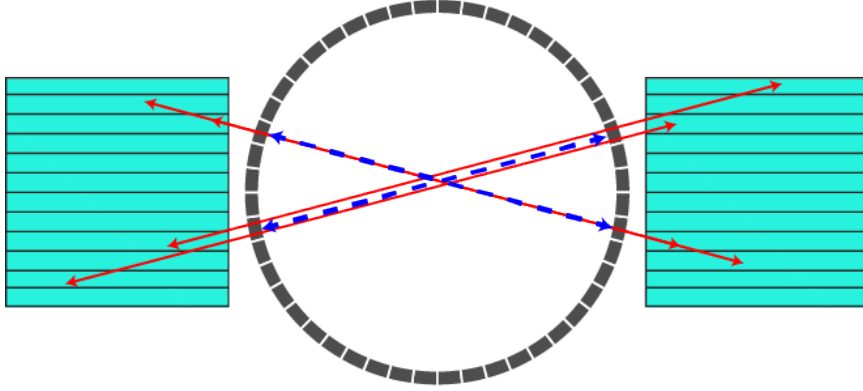


Figure 5.1: DOI-based PET reconstruction using a virtual cylindrical geometry. A virtual detector ring (black) consolidates multiple physical LORs (red lines) from various crystals and DOI bins in the physical detector (cyan) into single virtual LORs (dashed blue lines).

5.3 Methods

The experimental work is organized as follows: Section 5.3.1 outlines the process by which physical LORs are mapped onto virtual LORs; Section 5.3.2 details the simulation of the mousePET scanner; Section 5.3.3 introduces the reconstruction pipeline, including computation of normalisation factors and leveraging scanner symmetries for statistical robustness; and Section 5.3.5 describes the simulation experiments we conducted to characterise and compare physical mousePET and virtual PET implementations.

5.3.1 Virtual PET Implementation

The implementation of a virtual cylindrical PET scanner proceeds similarly to [151]. The end points of a physical LOR connecting crystals i and j , and any DOI bin combination (assuming the LOR endpoints are at the centre of each DOI bin), are defined using six spatial coordinates: $\mathbf{S}_i = (x_i, y_i, z_i)$ and $\mathbf{S}_j = (x_j, y_j, z_j)$ (Fig 5.2a). It is convenient to express the LOR as a line, given by:

$$\mathbf{l} = \mathbf{S}_i + t \left(\frac{\mathbf{S}_j - \mathbf{S}_i}{\|\mathbf{S}_j - \mathbf{S}_i\|} \right) \quad (5.1)$$

where $\mathbf{l}$ is any point on the LOR and its position along the LOR starting from $\mathbf{S}_i$ is parameterised by t . The point can be decomposed into its 3 spatial coordinates according to:

$$x = x_i + t\beta(x_j - x_i) \quad (5.2.1)$$

$$y = y_i + t\beta(y_j - y_i) \quad (5.2.2)$$

$$z = z_i + t\beta(z_j - z_i) \quad (5.2.3)$$

with $\beta = \frac{1}{\|\mathbf{S}_j - \mathbf{S}_i\|}$.

The intersection, (x', y', z') , of this LOR with an axially aligned virtual cylinder of radius R satisfies:

$$x'^2 + y'^2 = R^2 \quad (5.3)$$

Substituting equations 5.2.1 and 5.2.2 into 5.3:

$$(x_i^2 + y_i^2) + 2t\beta(x_i\Delta x + y_i\Delta y) + t^2\beta^2(\Delta x^2 + \Delta y^2) - R^2 = 0 \quad (5.4)$$

where $\Delta x = x_j - x_i$ and $\Delta y = y_j - y_i$. The solution for t in this quadratic equation is given by:

$$t_{\pm} = \frac{\beta^{-1}}{(\Delta x^2 + \Delta y^2)} \left(\pm \sqrt{R^2(\Delta x^2 + \Delta y^2) - (x_i\Delta y - y_i\Delta x)^2} - (x_i\Delta x + y_i\Delta y) \right) \quad (5.5)$$

which provides the intersection points of the LOR with the virtual cylinder:

$$\mathbf{S}'_i = \mathbf{S}_i + \frac{\min(t_{\pm})}{\beta} (\mathbf{S}_j - \mathbf{S}_i) \quad (5.6.1)$$

$$\mathbf{S}'_j = \mathbf{S}_i + \frac{\max(t_{\pm})}{\beta} (\mathbf{S}_j - \mathbf{S}_i) \quad (5.6.2)$$

Since the starting point on the LOR is $\mathbf{S}_i$, the minimum value of the scaling factor ($\min(t_{\pm})$) gives the solution to $\mathbf{S}'_i$ and the maximum value gives the solution to $\mathbf{S}'_j$.

Once all LOR intersections with the virtual cylinder have been calculated, a segmentation of the cylinder allows the definition of virtual detectors. We chose virtual detectors with equal length and width (i.e., even segmentation along the radial and z directions). Physical LORs intersecting the same virtual detector pair are consolidated into a single virtual LOR (Fig. 5.1). The number and size of the virtual detectors, along with the radius of the virtual ring, can all be adjusted for a given application. This is important because the granularity of the virtual detectors impacts the coarseness of sampling in image space, which in turn impacts the trade-off between computational efficiency and accuracy. The virtual PET radius was set to $R = 33$ mm to accommodate mice inside the FOV. We evaluated three virtual detector sizes (d) (Fig. 5.2a): 0.74 mm (vPET1), 0.47 mm (vPET2), and 0.36 mm (vPET3). To select the virtual detector size, a first estimate was obtained based on naïve application of equation 2 in [177]. Disregarding photon acollinearity and positron range, the equation predicts that, for the given virtual PET radius, a 0.81-mm virtual detector

will achieve the same resolution as mousePET. However, since it was unclear whether the equation holds for unconventional PET geometries, we chose a more conservative virtual detector size as our baseline (vPET1). vPET2 and vPET3 detector sizes were arbitrarily chosen to provide a range of LOR compression factors and evaluate their effect on reconstructed resolution.

To assess the impact of DOI resolution on mousePET performance, we considered three DOI resolution settings - no DOI, 5-mm DOI resolution (comprising 4 DOI bins), and 3-mm DOI resolution (comprising 6 DOI bins) – for the three virtual PET implementations. (Note that 3-mm DOI with 6 bins is the specification of the final mousePET system.) The LOR compression factors (equation 5.7) resulting from these implementations are shown in Table 5.1.

$$1 - \frac{\text{Number of virtual LORs}}{\text{Number of physical LORs}} \quad (5.7)$$

Table 5.1: LOR compression factors for the different virtual PET implementations and number of DOI bins used during reconstruction. The number of physical LORs in mousePET as a function of the number of DOI bins is included as a reference (top row).

	no DOI bins	4 DOI bins	6 DOI bins
	281,851,200	3,203,541,778	7,211,211,922
vPET1	0.38	0.95	0.97
vPET2	0.05	0.73	0.86
vPET3	0.02	0.50	0.69

5.3.2 System Simulation

The mousePET scanner (Fig. 5.2b) features a box-shaped geometry for high sensitivity [91, 129] and consists of 4 overlapping detector panels of 4×4 detector modules, each comprising a 23×23 LYSO crystal array ($0.785 \text{ mm} \times 0.785 \text{ mm} \times 20 \text{ mm}$, crystal pitch = 0.85 mm) read out at back and front faces for DOI encoding by a 6×6 array of 3-mm SiPMs. This system was simulated using GEANT4 Application for Tomographic Emission (GATE) v8.2 [107, 223]. Energy and timing resolution were set to 18% (at 511 keV) and 2 ns, respectively. Coincidences were allowed between any pair of detector panels, with random coincidences excluded in a post-processing step and multiple coincidences handled using the ‘takeWinnerOfGoods’ policy. A coincidence time window of 6 ns was used in all experiments. DOI was implemented by reassigning LORs to the centre of their corresponding DOI bins.

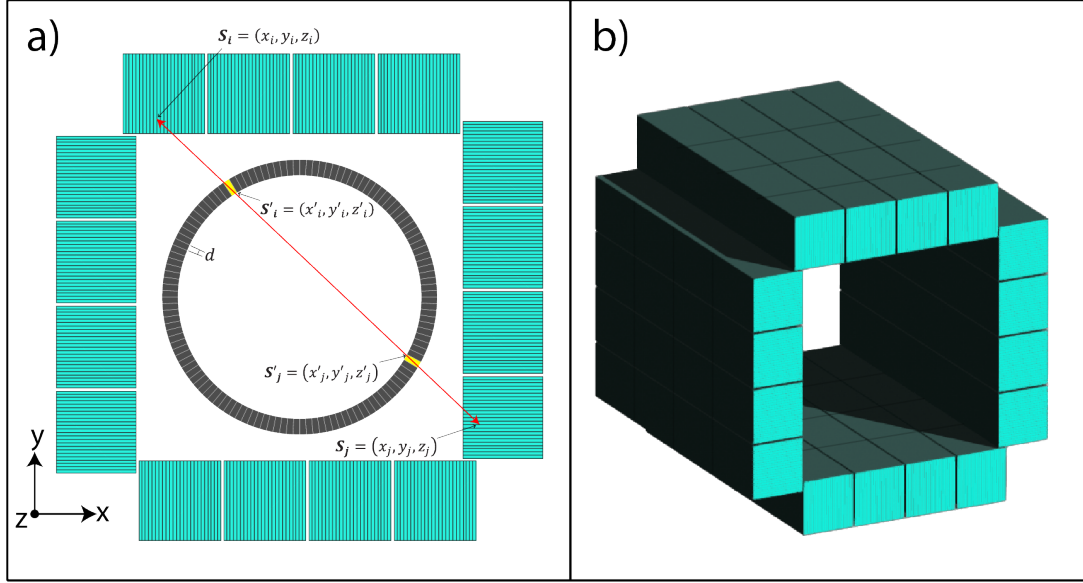


Figure 5.2: (a) The LOR (red line) between crystal i and crystal j is defined by its end points: $\mathbf{S}_i = (x_i, y_i, z_i)$ and $\mathbf{S}_j = (x_j, y_j, z_j)$. The LOR intersects the virtual ring at points $\mathbf{S}'_i = (x'_i, y'_i, z'_i)$ and $\mathbf{S}'_j = (x'_j, y'_j, z'_j)$. A single virtual LOR (not shown) connecting the centre of two virtual detectors with size d (in yellow) replaces the red LOR and any other LOR intersecting the same virtual detector pair. (b) 3D rendering of the unconventional box-shaped mousePET scanner showing its 4 detector panels. Each panel comprises 4×4 detector blocks, each consisting of 23×23 LYSO crystals read out from back and front faces for DOI capability.

5.3.3 Image Reconstruction

Image reconstruction was performed using a list-mode ordered subsets expectation maximisation (OSEM) algorithm [210] with the sensitivity image pre-corrected for the different detector efficiencies:

$$x_q^{kS+s+1} = \frac{x_q^{kS+s}}{\sum_{p=1}^P n_p a_{pq}} \sum_{p \in T_s} a_{pq} \left(\frac{1}{\sum_{q=1}^Q a_{pq} x_q^{kS+s}} \right) \quad (5.8)$$

where P and Q are the total number of LORs and voxels, respectively, S is the number of subsets, $s \in 1, \dots, S$, kS is the number of effective (full) iterations after k passes through the data, x_q^{kS+s} is the mean activity in voxel q after the k th iteration due to T_s number of LORs in subset s , n_p is the normalisation factor of LOR p and a_{pq} is the probability of detecting an emission from voxel q on LOR p , calculated using Siddon ray-tracing algorithm [236].

In all phantom experiments the image matrix size was set to $179 \times 179 \times 189$ voxels and the voxel size to $0.3925 \times 0.3925 \times 0.4250$ mm³.

5.3.4 Normalisation

Normalisation factors n_p were proportional to the detection efficiencies of the pair of detectors connecting the LOR. For LOR p , the normalisation coefficient

is calculated as the ratio of the ideal measured counts (A_p) of a known object to the true measured counts (M_p), obtained experimentally or through Monte Carlo simulation:

$$n_p = \frac{M_p}{A_p} \quad (5.9)$$

To calculate M_p values of both the mousePET scanner and virtual PET implementations, we conducted simulations using a uniform cylindrical source with an activity of 16 MBq. This source effectively covered the entire FOV with a radius of 32.8 mm. For the non-DOI and 4-bin DOI case we simulated acquisitions of 6 h duration to accurately estimate the correction factors. The simulation duration was extended to 10 h for the 6-bin DOI case. To expedite the simulation process we used back-to-back gamma events instead of a positron-emitting source (i.e., no positron range and photon acollinearity were modelled). The A_p values were calculated by forward projecting the cylindrical source through all possible LORs.

To better estimate the normalisation factors, we harnessed symmetries inherent in the scanner geometry, effectively augmenting the number of counts per LOR (M_p). In the transaxial plane, there are three rotational symmetries for the majority of the LORs (Fig. 5.3a). Four more symmetries are obtained by mirroring the LOR across the axial plane and considering its corresponding three rotational symmetries (Fig. 5.3b). The exception to these symmetries is the small group of LORs shown in figure 5.3c, which exhibit only three symmetries. The 4- and 8-fold increment in the number of counts per LOR was applied prior to calculating the normalisation coefficients of each system.

To normalise the virtual PET implementations, the correction term for a virtual LOR p' ($n_{p'}$) was derived according to:

$$n_{p'} = \frac{\sum_{p \in p'} M_p}{A_{p'}} \quad (5.10)$$

where the numerator represents the sum of M_p terms associated with all physical LORs assigned to the virtual LOR, and the denominator $A_{p'}$ represents the forward projection along the virtual LORs for the same cylindrical source.

5.3.5 Simulation Experiments

5.3.5.1 Spatial Resolution Measurements

To compare the reconstruction performance of the physical scanner and the virtual PET implementations, we performed simulations using a fluorine-18 point source of radius 0.0625 mm, modelling photon acollinearity and positron range effects. The source was located within the central axial plane of a cylindrical water phantom covering the entire FOV, and offset transaxially to 4 positions: 0, 10, 20, and 25 mm from the centre (Fig. 5.4a). A fifth point source position, offset by 1/4 of the axial FOV on the central axis was also analysed. We applied a point source to background ratio of 1.1:1 (i.e., the point source was 10% hotter than the background) to avoid artificial improvement of the system resolution when using iterative reconstruction [80]. After subtracting the background from

the reconstructed source, the resulting point spread function (PSF) was fitted using a double Gaussian. Full-width-at-half-maximum (FWHM) and full-width-at-tenth-maximum (FWTM) values were estimated along four directions: radial, tangential, axial and diagonal (Fig. 4a). In all cases, 200 iterations of MLEM (i.e., 1 subset) were performed before fitting the data.

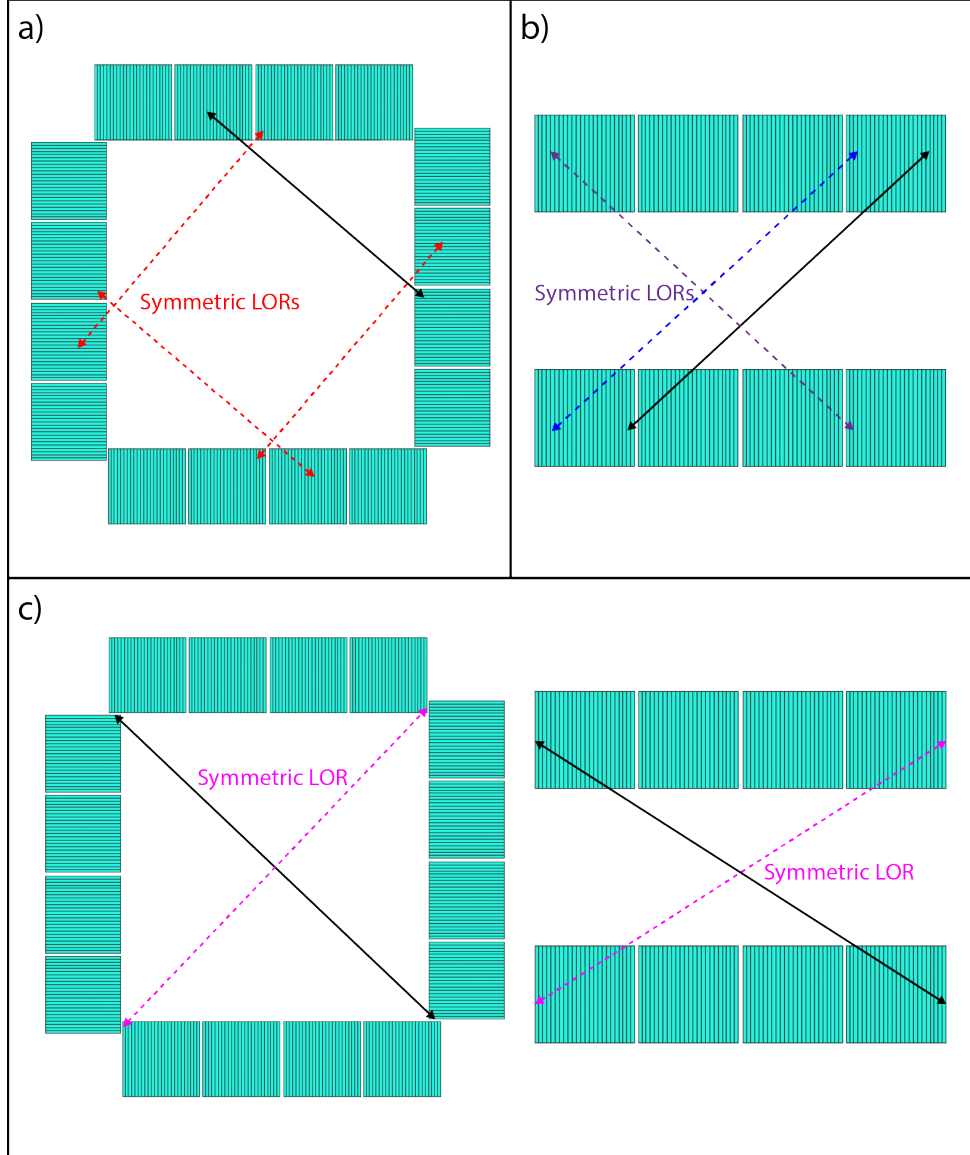


Figure 5.3: Scanner symmetries leveraged to augment count statistics per LOR before implementing normalisation: (a) three symmetries in the transaxial plane (dashed red lines) by rotating each LOR in 90-degree increments; (b) four more symmetries by mirroring the LOR across the axial plane (1 symmetry, purple dashed line) and rotating the mirrored LOR on the transaxial plane (3 symmetries, blue dashed line as one example); (c) the subset of LORs exhibiting no more than three symmetries (dashed magenta lines). The third symmetry (not shown) is derived by a 90-degree rotation of the mirrored LOR (bottom right, dashed magenta line) along the axial plane.

Volumetric PSF values were measured from the reconstructed PSFs. Before

calculations, PSFs were normalised by its maximum voxel value. The volumes were calculated as the number of voxels exceeding a specific threshold (0.5 for FWHM and 0.1 for FWTM) times the volume of a single voxel. To ensure comparability with measurements from conventional PET scanners, we incorporated a correction factor of $6/\pi$ before presenting the results. The correction factor accounts for the volume disparity between an ellipsoid (representing a 3D PSF) and the circumscribed box resulting from the product of the radial, tangential and axial PSF values.

5.3.5.2 Micro Derenzo Phantom

A micro Derenzo phantom filled with fluorine-18 was simulated in GATE to evaluate the influence of the system PSF on the resolution of high-frequency objects, while also facilitating a comparative analysis of the reconstructed images from the mousePET scanner and virtual PET implementations. To expedite the simulation and reconstruction processes, we focused on the 0.7 mm, 0.9 mm and 1.2 mm hot-rod diameters only (Fig. 5.4b). The number of coincidence events during reconstruction was set to approximately 70 million events in all cases, and 10 subsets and 10 iterations were performed for all geometries. For the 6-bin DOI PET geometries, a 2D image-based resolution modelling method [7] was applied to assess the effect of PSF modelling on image quality. This was done by performing 5 full OSEM iterations (10 subsets) in which each sub-iteration was interleaved with 2 iterations of a Lucy-Richardson deconvolution algorithm. For each geometry, the reconstructed PSF at the centre of the FOV (Section 5.3.5.1) was used as the deconvolution kernel.

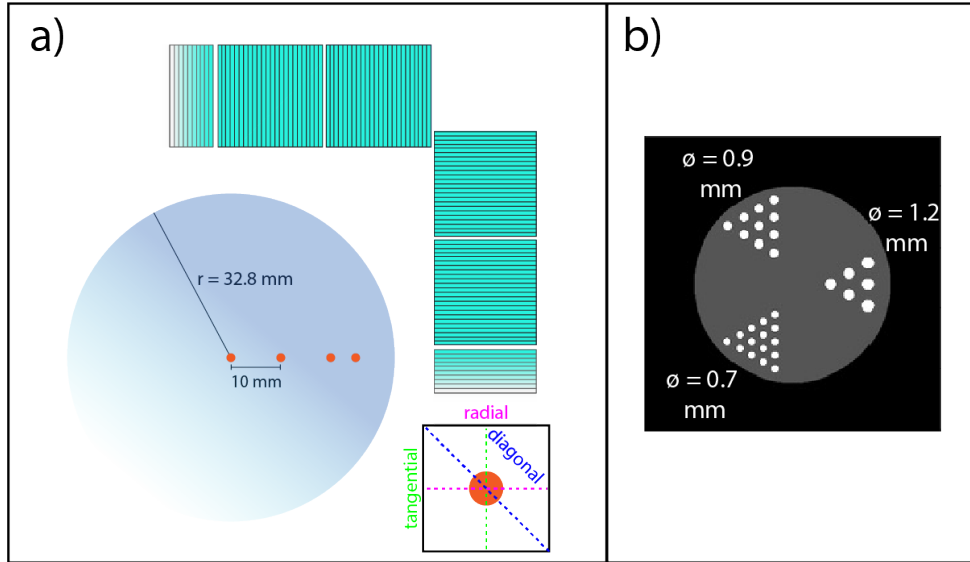


Figure 5.4: (a) Fluorine-18 point sources (red circles) placed at the centre of the axial FOV and at different transaxial offsets. Dashed lines indicate the direction of the PSF measurements, while axial profiles (not shown) were along the z axis. (b) Transaxial view of the 3 hot-rod segments of a simulated micro Derenzo phantom ($\varnothing = 0.7, 0.9$ and 1.2 mm).

5.4 Results

5.4.1 PSF Measurements

Figures 5.5 and 5.6 show the zoomed reconstructed PSFs for the physical scanner (mousePET) and virtual PET implementations with the point source offset radially by 0 mm (Fig. 5.5) and 20 mm (Fig. 5.6) in the central transaxial plane. Dashed and solid colour boxes were added to each geometry to easily associate images with measurements. Below each PSF, its radial line profile is given. In all cases, the line profiles were normalised by their area. Improved DOI resolution (top to bottom row) results in a clear reduction in the characteristic tails of the PSF caused by the rectangular scanner geometry [205, 129]. Figure 5.7 shows FWHM along the radial, tangential, axial and diagonal directions. Several features are notable: (i) there was a modest (approximately 8%) improvement in FWHM in transitioning from 4 to 6 DOI bins for the radial component across all geometries; (ii) additional DOI bins reduced the deterioration of the tangential profile of the offset point source; (iii) for a given number of DOI bins, the largest difference in FWHM between the physical scanner and virtual implementations was in the axial and diagonal profiles. Overall, the physical scanner exhibited the highest resolution, followed in order by vPET3, vPET2 and vPET1. For example, for the 6-bin DOI geometries and the source located at a radial offset of 10 mm, the measured diagonal FWHM values were 0.740, 0.763, 0.804 and 0.851 mm for mousePET, vPET3, vPET2 and vPET1, respectively.

PSF measurements for the fifth point source position are included in Appendix B (Fig. B.1).

The FWTM data (Figure 5.8) show a reduction in the tails by a factor of 3 and 4 when 4-bin and 6-bin DOI, respectively, was incorporated during reconstruction. Similarly to FWHM, the main difference in FWTM between the physical scanner and virtual implementations (for the same number of DOI bins) was in the axial and diagonal profiles.

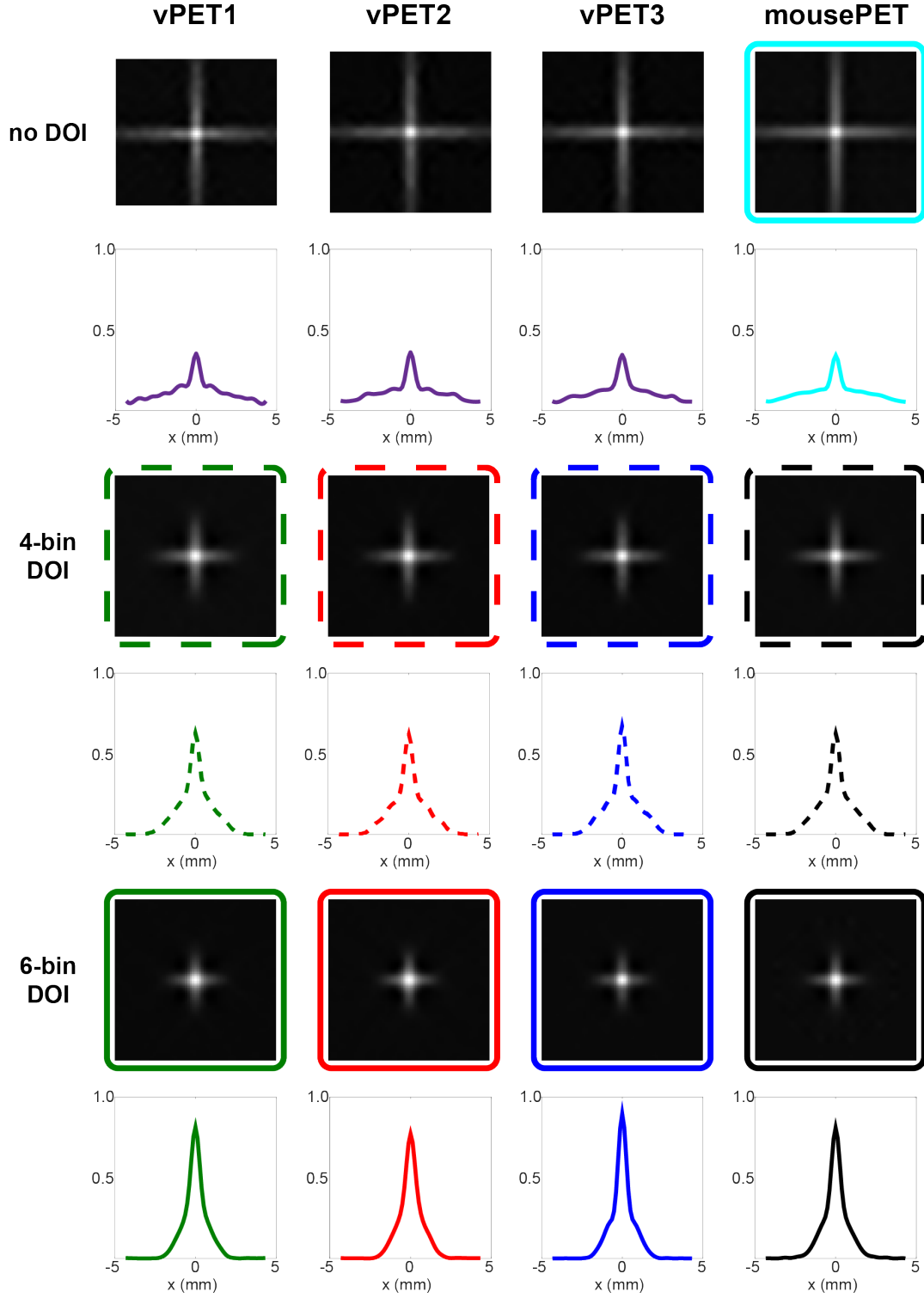


Figure 5.5: Zoomed PSF (after background subtraction) for a point source at the centre of the FOV, shown for the physical scanner and virtual PET implementations (columns) with 3 DOI resolutions (rows). Normalised radial line profiles are shown below each PSF).

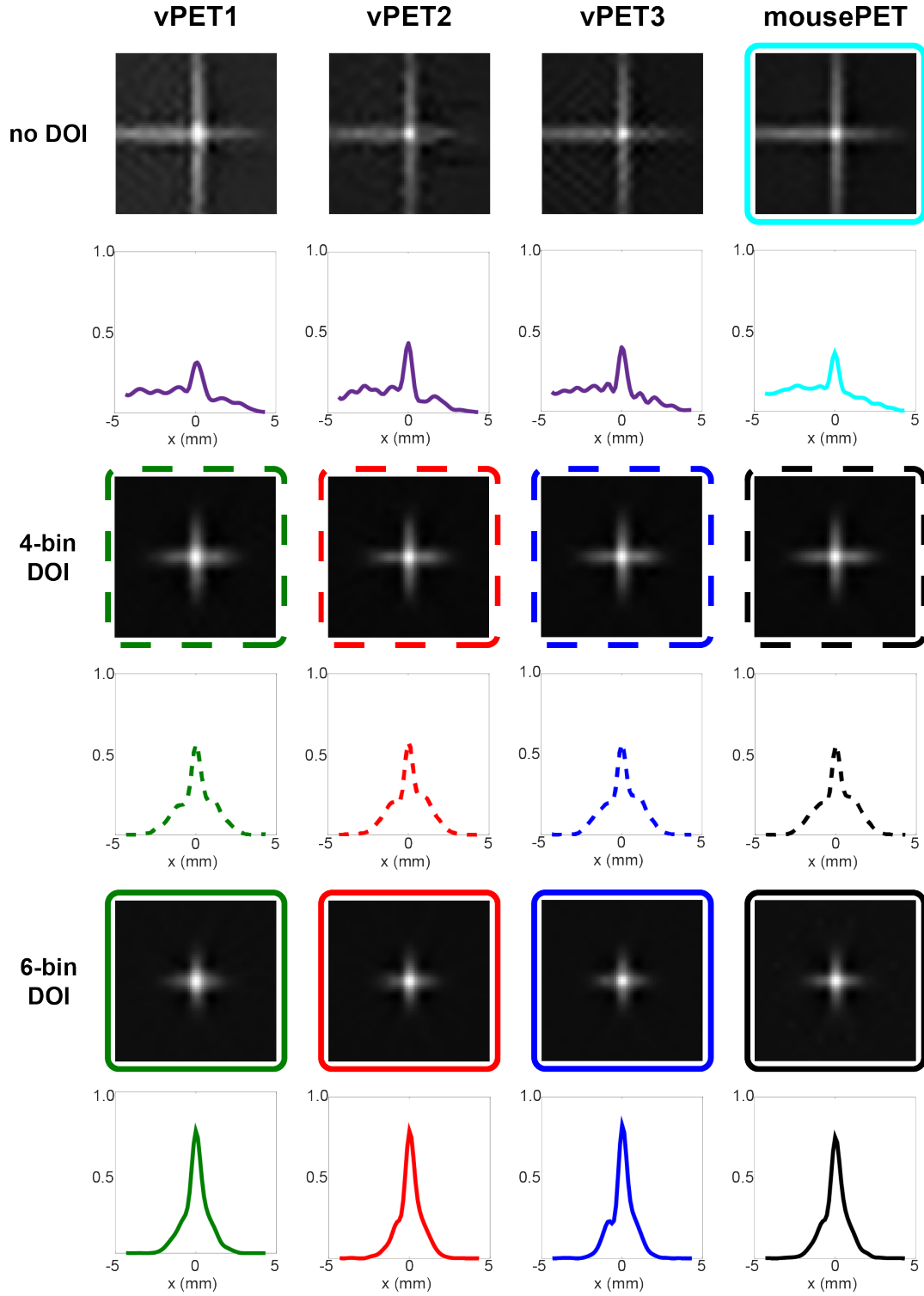


Figure 5.6: Zoomed PSFs (after background subtraction) for a source 20-mm radially offset in the central transaxial plane. Normalised radial line profiles are shown below each PSF.

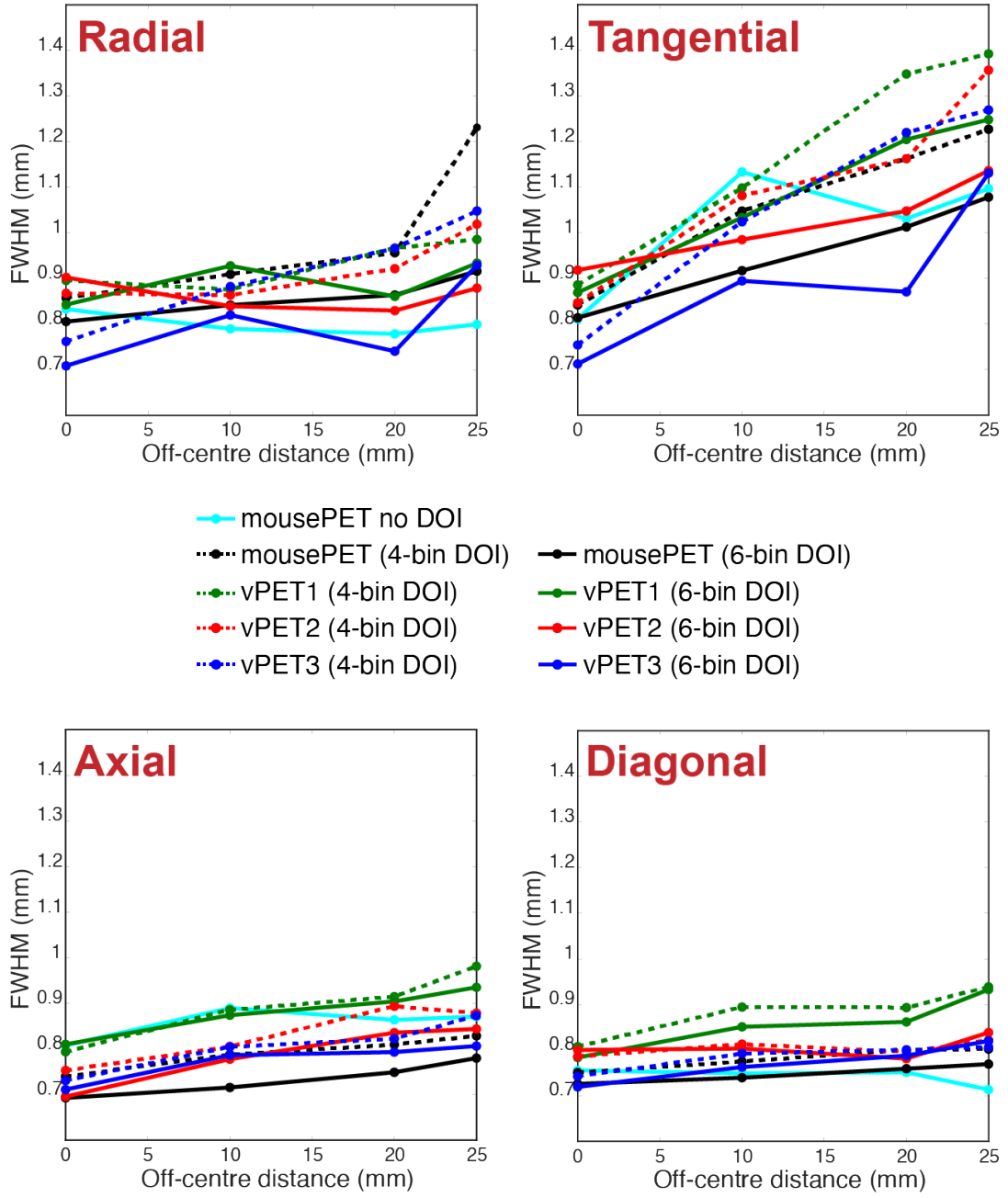


Figure 5.7: Radial, tangential, axial and diagonal FWHM measurements for the physical scanner and virtual PET implementations with 3 DOI resolutions. Dashed and solid lines correspond to measurements performed using 4 and 6 DOI bins during reconstruction, respectively. In each case the cyan solid line represents the performance for the non-DOI physical scanner.

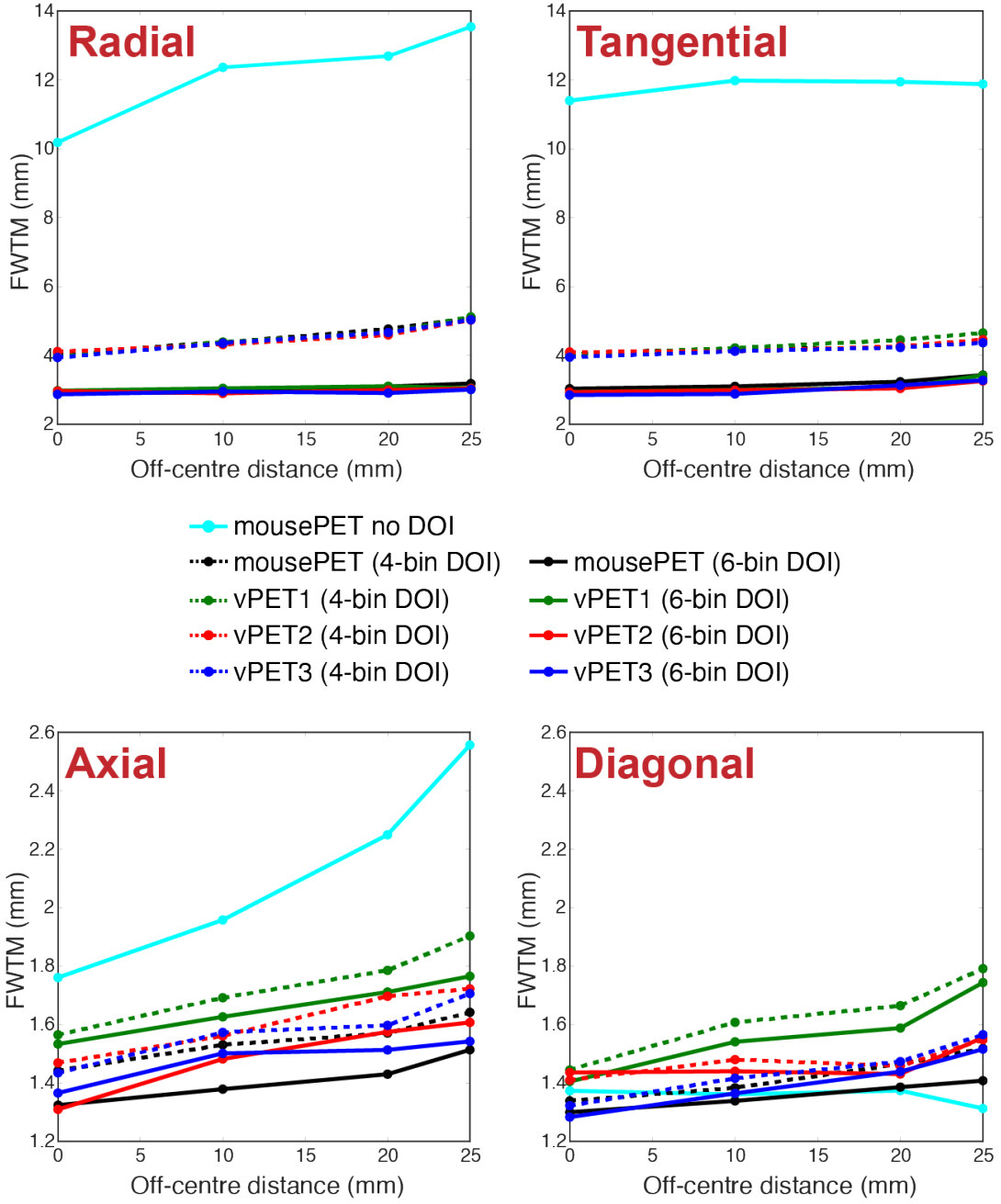


Figure 5.8: Radial, tangential, axial and diagonal FWTM measurements for the physical scanner and virtual PET implementations with 3 DOI resolutions. Line colours and styles are the same as in figure 5.7.

Figure 5.9 illustrates the volumetric FWHM (left) and FWTM (right) values for the physical scanner and virtual PET implementations with 4-bin (dashed lines) and 6-bin (solid lines) DOI, respectively. The solid cyan line corresponds to measurements for the non-DOI physical scanner. Overall, at the FWHM level, the improvements for the virtual implementations when transitioning from 4 to 6 DOI bins were 8.9%, 7.1% and 12.2% for vPET 1, 2 and 3, respectively. For the physical scanner the improvement was 14.7%.

5.4.2 Micro Derenzo Reconstructions

Figure 5.10 shows the reconstructed central slice of the micro Derenzo phantom for the different geometries as a function of the number of DOI bins used during reconstruction. Despite sub-millimetre FWHM values for the non-DOI physical scanner (Figure 5.7), the long PSF tails led to a very poor reconstruction with no rods being clearly distinguishable. In contrast, using 4-bin or 6-bin DOI resulted in the 0.9- and 1.2-mm rods being resolvable for all geometries. Figure 5.11 compares line profiles through the 0.9- and 1.2-mm rods (top) and through the 0.9- and 0.7-mm rods (bottom). The 4- to 6-bin DOI transition resulted in improved contrast recovery coefficients for almost all rods (expected activity: 55 a.u.). Tables 5.2 and 5.3 show the peak-to-valley ratios for the different rods and for the 4- and 6-bin DOI geometries, respectively. A mean improvement of 25% was obtained when transitioning from 4 to 6 DOI bins.

CPU time for the different geometries and number DOI bins are included in Appendix B (Table B.3).

Figure 5.12 compares the micro Derenzo reconstructions with and without PSF modelling. PSF modelling resulted in suppression of the PSF tails, which was more pronounced for the larger rods. It provided no discernible improvement in the resolvability of the 0.7-mm rods. For all geometries, the mean improvement in the peak-to-valley ratio due to PSF modelling was: 12%, 62% and 145% for the 0.7-mm, 0.9-mm, and 1.2-mm rods, respectively. A direct comparison between the non-PSF and PSF-modelled OSEM reconstructions is provided in Appendix B (Fig. B.2).

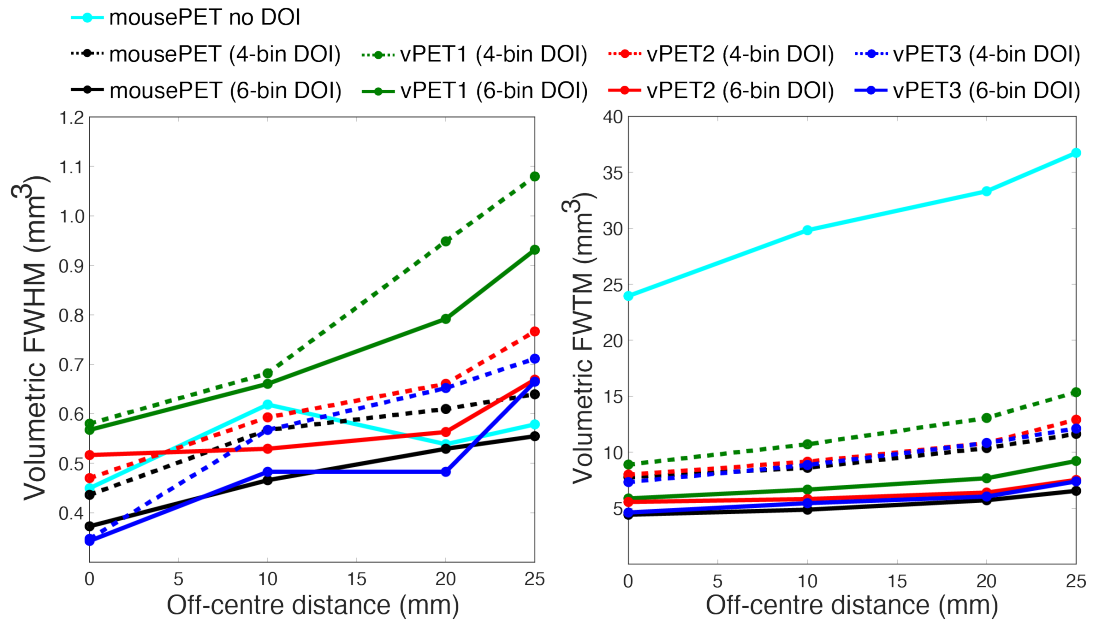


Figure 5.9: Volumetric FWHM (left) and FWTM (right) for the physical scanner and virtual PET implementations with 3 DOI resolutions. Line colours and styles are the same as in figure 5.7.

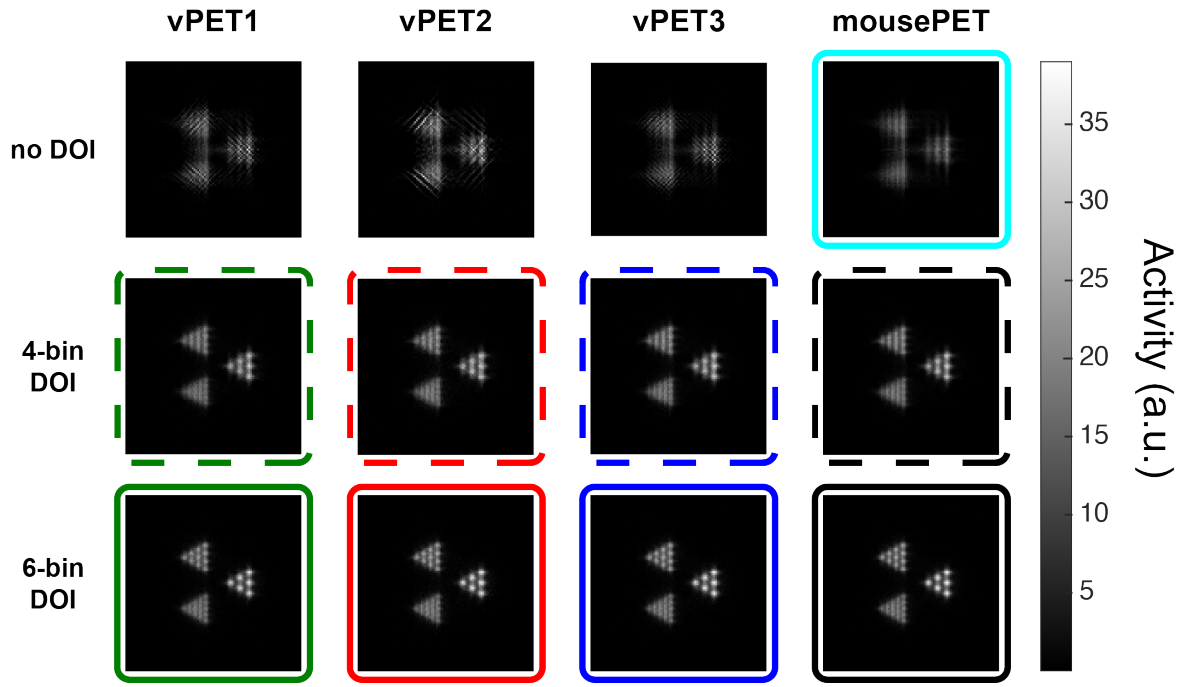


Figure 5.10: Micro Derenzo reconstructions (central slice) for the physical scanner and virtual PET implementations (columns) with different DOI resolution (rows).

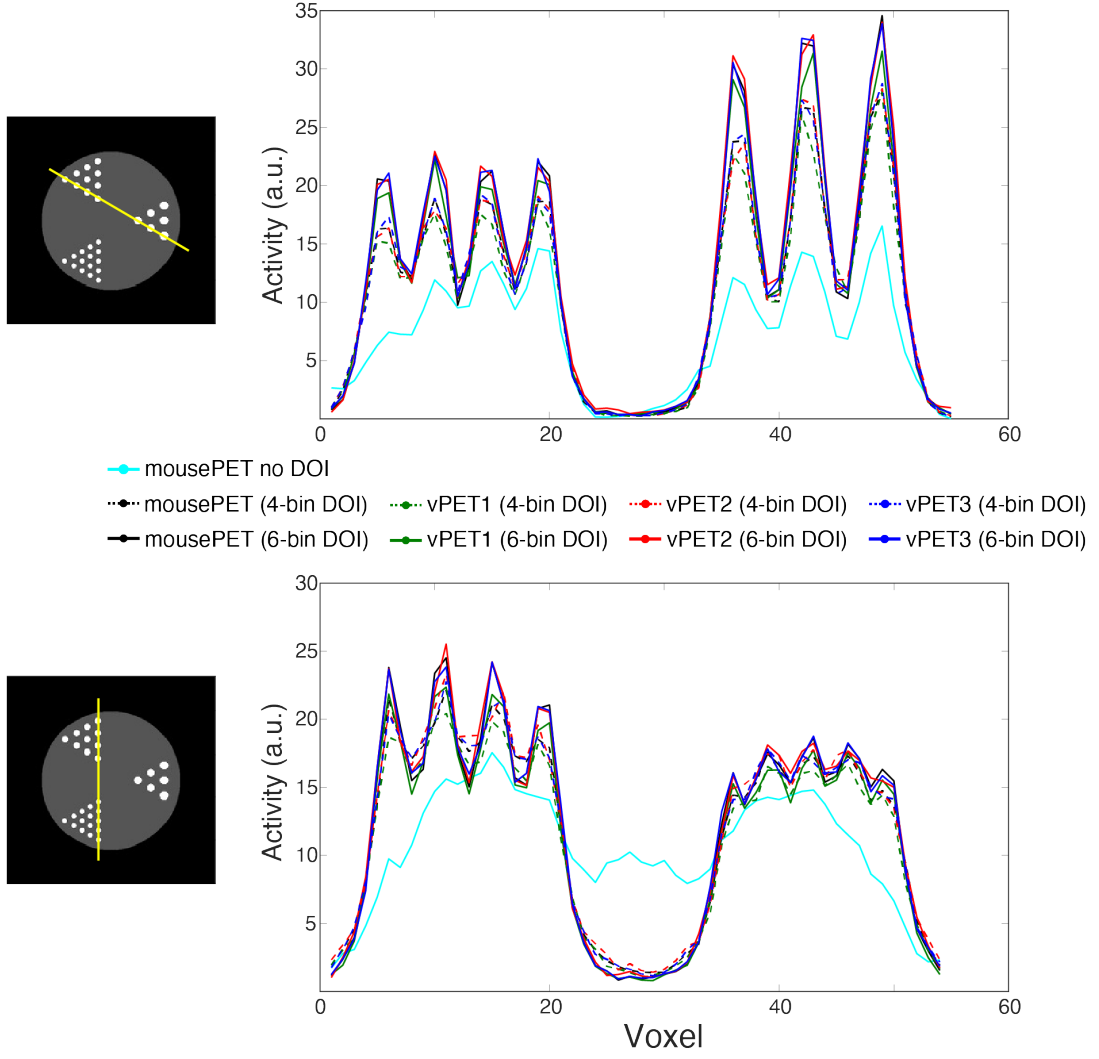


Figure 5.11: Line profiles through the 0.9 and 1.2 mm rods (top), and the 0.9 and 0.7 mm rods (bottom) in the reconstructions of the micro Derenzo phantom, shown for different DOI resolutions.

Table 5.2: Peak-to-valley ratios across the 0.7-mm, 0.9-mm and 1.2-mm rods for the 4-bin DOI geometries.

Rod Diameter (mm)	vPET1	vPET2	vPET3	mousePET
0.7	0.86	0.58	0.81	1.12
0.9	1.55	1.52	1.65	1.62
1.2	2.34	2.31	2.45	2.37

Table 5.3: Peak-to-valley ratios across the 0.7-mm, 0.9-mm and 1.2-mm rods for the 6-bin DOI geometries.

Rod Diameter (mm)	vPET1	vPET2	vPET3	mousePET
0.7	1.19	0.85	1.18	1.18
0.9	1.75	1.90	1.92	1.98
1.2	2.86	2.84	2.91	3.01

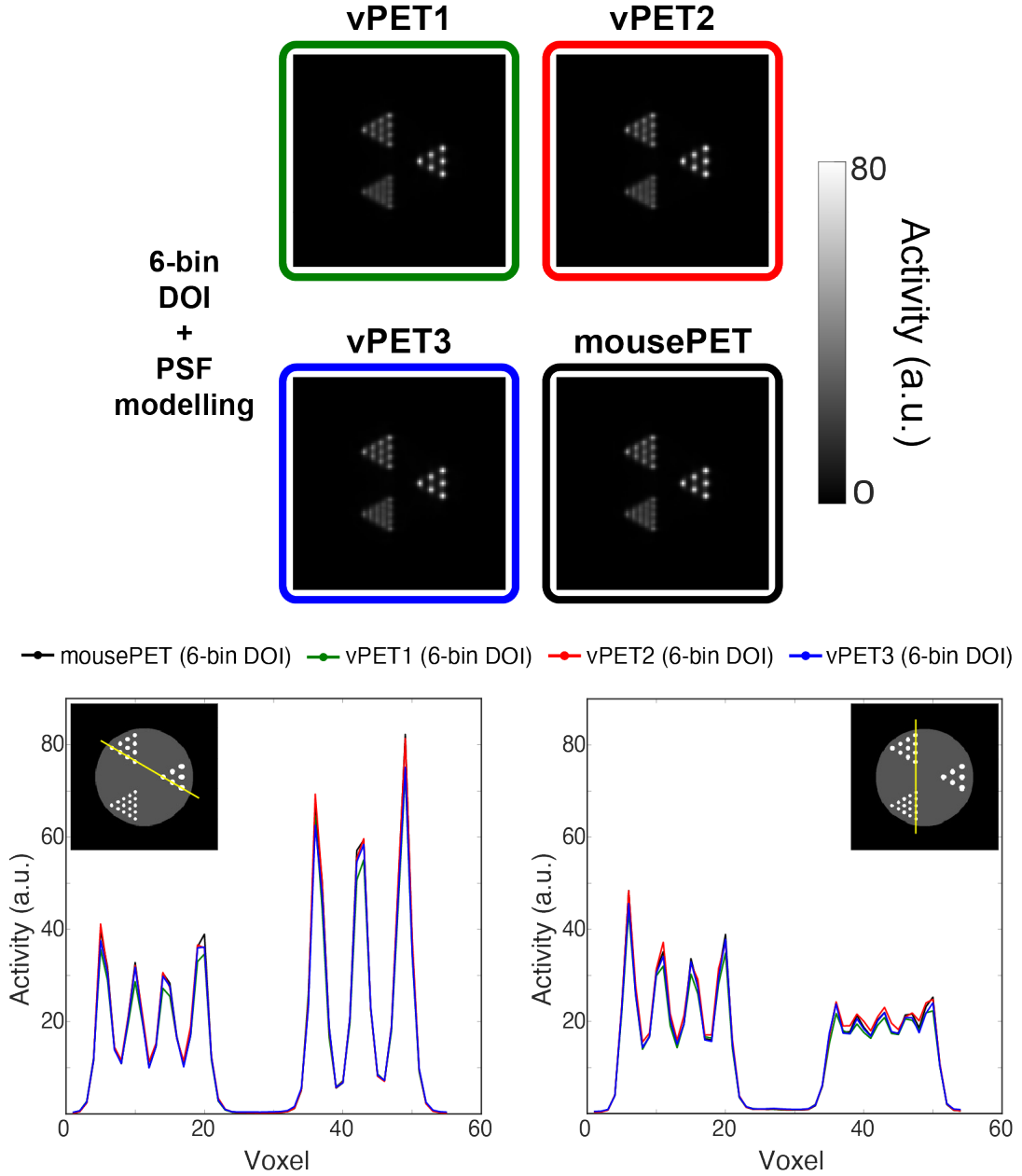


Figure 5.12: (top & middle) Micro Derenzo phantom reconstructions with 6-bin DOI resolution and PSF modelling. (bottom) Line profiles through the 0.9 and 1.2 mm rods (left) and the 0.9 and 0.7 mm rods (right).

5.5 Discussion

This study investigated the impact of virtual detector geometries on the spatial resolution and computational efficiency trade-off, focusing on the open-field mouse brain PET system (mousePET) as a case study of high resolution and DOI-capable application-specific PET scanners under development. The combination of highly segmented detectors and 3-mm DOI resolution results in almost 7.3 billion LORs for the mousePET system. On-disk storage of the system matrix is impractical considering the number of LORs and voxels (~ 8 TB assuming 4-byte precision), while on-the-fly calculations translate into very lengthy recon-

structions. The challenge is exacerbated by the fact that motion compensation with attenuation correction requires repeated calculation of a time-weighted sensitivity matrix [8]. Extending on previous work, we tested three different virtual cylindrical PET implementations (virtual detector sizes) to investigate the trade-off between LOR data reduction and spatial resolution degradation. For DOI-based reconstruction in mousePET, the virtual implementations provided an LOR reduction of at least 50%, with most achieving resolution values comparable to mousePET.

5.5.1 Spatial Resolution Measurements

The PSF anisotropy in mousePET, which arises due to the highly non-uniform parallax effect [129], makes the radial and tangential profiles more dependent on DOI resolution than on detector size of the virtual PET implementations. Instead, most of the resolution degradation introduced by these implementations occurs in the axial and diagonal profiles. The volumetric FWHM and FWTM values provide a practical means of choosing a virtual detector size for an application. The method of calculation we used acknowledges the unusual shape of our asymmetric PSF, which would be unduly penalised if we had used the conventional method of multiplying the 3 independent components (which assumes a symmetric PSF). Based on the volumetric FWHM measurements, it is clear that vPET1 is inferior to the other geometries, while vPET2 and vPET3 have comparable performance except for the central measurement. The difference in the central measurement may stem from variations in the sensitivity matrix of the two systems. Comparison of the central voxel of the sensitivity images showed that for vPET2 (6-bin DOI) this region is poorly sampled. For vPET3 the opposite is true (super-sampling), and which might explain its superior resolution compared mousePET at that point. This effect thus highlights a limitation: different voxel grids may better suit specific virtual geometries. Typically, the voxel size in cylindrical PET systems is chosen as $D/2$ (or $D/3$), where D is the detector size. We used a voxel size suitable for the physical scanner but not necessarily optimal for all virtual implementations. Nevertheless, both vPET2 and vPET3 provide almost identical reconstructions to the physical scanner in the transaxial plane. For mousePET we conclude that the optimal choice is a virtual detector size of 0.47 mm (vPET2 detector size), achieving 86% reduction in LOR data while maintaining sub-millimetre spatial resolution. In future work, performance comparisons will be done using real scanner data with a more accurate DOI resolution model – that accounts for DOI event mispositioning that might arise, particularly, when the gamma ray interacts at the boundary of two DOI bins – not considered here.

5.5.2 Micro Derenzo Reconstructions

The micro Derenzo phantom reconstructions reveal the impact of the PSF tails when imaging high-frequency objects. Although it is primarily noticeable at the FWTM range, it also affects the peak-to-valley ratio measurements (Table 5.2). For a given rod set, the ratios depend on the rod arrangement and line profile orientation. We observed that peak-to-valley ratios improved when line

profiles were drawn away from the tails (e.g., Fig. 5.10, top line profile). Ratios shown in Tables 5.2 and 5.3 correspond to those from lines not crossing the tails. As an example, for the 1.2-mm rods, deterioration of these ratios when passing through the tails was measured to be 68% and 34% when using 4-bin and 6-bin DOI, respectively. In agreement with the PSF measurements, the best ratios were achieved by the physical scanner followed by the virtual implementations. Although vPET1 achieved better ratios than vPET2, the line profiles indicate that the reconstructed activities in this virtual implementation did not converge to the same reconstructed activity as the other geometries. For the 6-bin DOI geometries, the difference in ratio between vPET2 and the physical scanner was 0.0706 and 0.1765 for the 0.9- and 1.2-mm rods, respectively.

As highlighted previously [7], 2D image-based PSF modelling can significantly enhance the reconstructions and increase the recovery coefficient of the hot rods (12-145% improvement in our experiments). Given the unconventional box-shaped geometry of mousePET, resolution modelling is very effective in minimising the effect of the relatively long and asymmetric PSF tails. However, all reconstructions were performed for noise-free data. Extrapolating to more realistic data, where the noise level is not zero, differences may appear. Different geometries have different convergence properties. Since image deconvolution tends to amplify noise, we expect different noise levels across different geometries for a matched resolution. Conversely, for a fixed noise level, differences in resolution are expected to appear.

In future work, a 3D image-based PSF modelling approach will be implemented and compared. Similarly, deep learning methods for PSF modelling, such as those discussed in [47, 237], will be also compared. The latter could be beneficial for further resolution improvement of mousePET in the context of virtual detectors.

5.5.3 Virtual geometries for DOI reconstruction

Although it has been suggested that the classic PET resolution equation [177] enables one to calculate the maximum virtual detector size before spatial degradation is observed [151], our results show that this equation does not hold for unconventional geometries and that it considerably over-estimates the virtual detector size required to achieve this outcome. Instead, we suggest that equation (2) from [177] should only be used as the starting point for optimising the virtual detector size on a particular PET geometry.

Contrary to [113], our results also indicate that sufficient (sub-millimetre) spatial resolution is preserved without the need for subsampling the image space. Instead, in agreement with [284] we note that a simple LOR rebinning (from physical to virtual LOR) is appropriate when the differences between physical and virtual geometries are sufficiently well modelled. In [284], differences were calculated using a maximum likelihood framework, while in this work these are accounted for through appropriate normalisation of the virtual geometries.

5.6 Conclusion

High resolution, narrow bore PET scanners such as mousePET result in a very large number of LORs due to the high number of detector pairs and DOI binning. In such systems, LOR data reduction is desirable due to the computational demands of image reconstruction. The introduction of virtual cylinders for DOI-based reconstruction in such systems can achieve sub-millimetre spatial resolution while reducing the number of LORs by 86%. Preserving high spatial resolution, together with the high level of data compression, makes virtual cylinders an attractive option for application-specific DOI-capable PET scanners. For mousePET and other non-cylindrical geometries, resolution recovery methods are further recommended to better suppress the effects of the asymmetric PSF on reconstructed image resolution.

Chapter 6

Summary, Conclusions & Future Work

6.1 Summary

Small-animal PET imaging is an essential tool for understanding human diseases through animal models and studying potential drug treatments. However, the full potential of small-animal PET, and thus the translation of pre-clinical findings to clinical settings, is limited by two major technical challenges: (i) quantitative inaccuracies resulting from the limited performance of current PET scanners and the small anatomical brain structures of these animals, and (ii) the necessity of anaesthesia before and during imaging.

Accurate tracer quantification in the small brain structures of mice and rats requires PET scanners capable of achieving both high resolution and high sensitivity. Although achieving a proportional level of detail to state-of-the-art human brain PET systems is currently unfeasible due to physical constraints, systems with high sensitivity and 0.6-mm resolution have demonstrated that detailed imaging of mouse brain structures is possible [111]. Nonetheless, current PET technology has the potential to achieve resolution values of ≤ 0.5 mm [277] while maintaining high sensitivity. To this date, such a scanner does not yet exist.

Despite extensive evidence showing the disruptive effects of anaesthetics on brain function (Chapter 2), almost all rodent brain PET imaging is conducted with the animals under anaesthesia. Although several methods have been proposed to address this issue (Chapter 2), they typically present at least one of the following limitations: they are surgically invasive, induce stress on the animal, restrict the potential for imaging freely moving animals, fail to fully compensate for the animal exiting the FOV, or do not meet the required PET scanner performance specifications.

The Open-Field Mouse Brain PET (mousePET) is a next-generation PET scanner designed to address these limitations [129]. The objective of this thesis was to overcome three key technological challenges to bring the mousePET scanner from concept to reality. The specific aims of this thesis were:

- i. To investigate the feasibility of all-in-one chip signal readout solutions based on low-cost ASICs for cost-effective multiplexed detector data acquisition and system scalability.
- ii. To explore the feasibility of deep learning methods for improved event positioning in the PET detectors compared to traditional positioning methods.
- iii. To develop and validate an accurate and computationally efficient method for high resolution DOI PET reconstruction for the PET scanner.

Chapter 3 addresses Aim 1 by integrating the multiplexed mousePET detectors (9:1 multiplexing ratio) with the TOFPET2 ASIC and optimising their performance. While this ASIC is widely used for individual SiPM readout, its performance with multiplexed detector configurations was largely unknown. Custom-designed electronic boards were developed to interface the detector with the ASIC. It was found that the original amplification gain of the multiplexing circuit [129] caused saturation in the ASIC. To address this, the amplification was reduced by nearly one-third. With the optimal signal amplification gain, the ASIC threshold logic was optimised for flood map quality (i.e., crystal resolvability) at different SiPM bias voltages. Unexpectedly, flood map quality was affected by changes in the threshold used for signal timestamping, requiring further investigation. Using the optimal ASIC threshold values and three SiPM bias voltages (27 V, 27.5 V, and 28 V), the energy and DOI resolution of the mousePET detector were measured. The best crystal flood maps and DOI resolution were obtained at 27.5 V, while the best energy resolution was at 28 V. Balancing these factors, the optimal SiPM bias voltage for the mousePET detectors was determined to be 27.5 V. A second mousePET detector was calibrated at this bias voltage, and the CTR of the two detectors was measured. The optimised mousePET detector achieved an energy resolution of $10.5 \pm 1.6\%$, a DOI resolution of 2.3 ± 0.3 mm, and a CTR of 1.3 ns.

Chapter 4 addresses Aim 2 by investigating the relevance and properties of inter-crystal scatter events in the mousePET detectors. Among the different scatter event types, single scatter events were the most common, leading to a focus on accurately positioning photoelectric (P) and single scatter (CP) events. CP events were further classified into neighbouring (nCP) and distant (dCP) events using ‘crystal windows,’ and their forward-to-backward scattering ratios were investigated. Contrary to the direct application of the Klein-Nishina equation [118], the forward-to-backward scattering ratios were found to be nearly 50:50. Using a 1-crystal window, the largest ratio was observed: 0.60:0.40 for dCP events and 0.41:0.59 for nCP events. Based on these findings, a DNN was implemented to predict the crystal(s) where the photon(s) deposited energy, along with the energy deposited in each. For selecting the first crystal of interaction in dCP and nCP events, energy-guided selection and Compton kinematics were used. The performance of the DNN alone and the DNN-based algorithm were evaluated, with the latter compared to Anger logic. The energy prediction performance of the algorithm was somewhat limited, with only 43% of events falling within the ± 50 keV range of the true energy. However, significant improvements in positioning accuracy were obtained. Specifically, a 34% improvement for P events and a 14% improvement for CP events were found when compared to

Anger logic.

Chapter 5 focuses on addressing Aim 3 by investigating the use of virtual cylinders for reducing LOR data in mousePET. Three virtual cylinders with the same radius but different detector sizes were investigated: 0.74 mm (vPET1), 0.47 mm (vPET2), and 0.36 mm (vPET3). The mousePET LORs stemming from different detector pairs and DOI bins intersecting the same virtual detector pair were replaced by a single virtual LOR. Three different numbers of DOI bins (DOI resolution) for mousePET were examined: no DOI bins, 4 DOI bins, and 6 DOI bins. Quantitative comparisons between the mousePET scanner geometry and the virtual implementations were conducted through PSF measurements at different locations in the FOV and peak-to-valley ratio measurements on a micro Derenzo phantom reconstruction. For the DOI mousePET geometries, all virtual implementations achieved compression factors of at least 50%. The PSF reconstructions revealed that the unconventional geometry of mousePET introduces a cross-shaped artefact on the system PSF, which is reduced as the DOI resolution of the system improves. Fully suppressing this artefact, however, requires PSF modelling. All the DOI PET geometries achieved sub-millimetre spatial resolution, with both 4-bin and 6-bin DOI geometries resolving the 0.9-mm micro Derenzo rods. In-plane reconstructions using 6-bin DOI vPET2 yielded nearly identical reconstructions to the fully sampled mousePET geometry while achieving an LOR compression factor of 86%.

6.2 Conclusions

Leveraging the full potential of small-animal brain PET imaging requires systems that simultaneously deliver high resolution and high sensitivity, and can image awake and freely moving rodents. The Open-Field Mouse Brain PET scanner (mousePET) aims to achieve this. The highly pixelated crystals with sub-millimetre pitch, combined with the detector DOI resolution, will enable the system to achieve sub-millimetre spatial resolution (≤ 0.9 mm). The 20-mm thick crystal arrays, along with the unconventional overlapping box geometry, will provide high sensitivity. An optical tracking system and a movable gantry will allow motion-compensated PET reconstruction of a free and fully conscious mouse, while maximising its time within the FOV.

This thesis developed key software and hardware components necessary for the realisation of the mousePET scanner.

Detector configurations based on highly multiplexed signal readouts, such as those used in the mousePET detectors, are appealing in small-animal PET due to the reduced costs compared to individual photodetector readout and relaxed timing requirements (i.e., no TOF). However, finding low-cost and all-in-one chip solutions for data acquisition in these detectors is also desirable. Ensuring such a solution was an important aspect of the ongoing cost-effective development of the mousePET scanner. This thesis demonstrated that the TOFPET2 ASIC is an excellent candidate for this purpose. Integrating the multiplexed mousePET detectors with this ASIC revealed that the detector achieves mean energy and DOI resolution values of $10.5 \pm 1.6\%$ and 2.3 ± 0.3 mm, respectively, and a CTR

of 1.3 ns. The improved DOI resolution over the initial reported values of 2.8-3.3 mm [129] suggests that more than the 6 DOI bins recommended in Chapter 5 (e.g. 8 bins) may be needed during image reconstruction when the scanner is assembled. Consequently, the PSF values (i.e., spatial resolution) measured in Chapter 5 are expected to be further enhanced. However, supporting this claim requires experimental evaluation. A deeper understanding of the effect of the ASIC discriminators on flood map quality is still needed, but current findings confirm that excellent system performance can be expected when reading out all the mousePET detectors using the TOFPET2 ASICs.

The light-sharing detector configuration of the mousePET detectors, necessitated by the crystal size of each LYSO needle, poses a challenge for accurately positioning events at the edges of the array and during inter-crystal scatter events. Consequently, achieving the highest possible spatial resolution in the mousePET scanner requires not only high-quality detector flood maps (Chapter 3), but also mitigating detector edge effects and resolving the inter-crystal scattering problem. Deep learning methods are promising candidates for addressing both issues. Focusing on single scatter events should effectively address the inter-crystal scattering problem. The deep learning-based positioning algorithm developed in this thesis improves event positioning accuracy by 28% compared to Anger logic and is expected to provide nearly three times higher accuracy when positioning coincidence events. While further improvements are challenging due to the physical properties of the inter-crystal scattering problem, the enhanced performance is anticipated to significantly improve the spatial resolution of the mousePET. However, the feasibility of this approach must still be validated with real detector data.

The unconventional geometry of the mousePET scanner results in a system with a cross-shaped PSF, necessitating DOI information to shorten its tails and improve resolution. The DOI-capable mousePET detectors will achieve sub-millimetre spatial resolution throughout the FOV. However, the enhanced spatial resolution provided by the DOI-capable detectors comes at the cost of either memory-intensive or time-consuming PET reconstructions. The implementation of virtual cylindrical geometries for DOI PET reconstruction in mousePET demonstrated the efficacy of this approach in substantially addressing both issues. While a trade-off between computational efficiency and spatial resolution exists, it was demonstrated that tuning the virtual detector size leads to the optimal compromise between these two. It is expected that once the mousePET scanner is fully assembled, highly computationally efficient sub-millimetre PET reconstructions will be achieved. However, since the detector DOI resolution was improved (Chapter 3), further optimisation of the virtual detector size is recommended.

In summary, various building blocks for the realisation of the mousePET scanner have been successfully developed, implemented, and characterised. The main contributions of this thesis are:

- i. Integration of the highly multiplexed mousePET detectors with the TOFPET2 ASIC.
- ii. Performance optimisation of the mousePET detectors using the TOFPET2

ASIC.

- iii. Characterisation of inter-crystal scattering in LYSO crystal needles (e.g., mousePET detectors).
- iv. Development and evaluation of a proof-of-concept deep learning algorithm with improved positioning accuracy in mousePET detectors.
- v. Development and evaluation of an accurate and highly computationally efficient DOI PET reconstruction framework for the mousePET scanner.

6.3 Future Work

There is considerable scope for future research. The contributions of this thesis mean that we are now poised to assemble and test the complete mousePET system. The primary and additional areas of research are detailed below.

6.3.1 Towards mousePET 1.0

Various detector elements, such as crystal arrays, SiPM arrays, and light guides, have already been purchased or manufactured. Given the requirement for precise alignment (with mispositioning errors ≤ 0.1 mm), the careful design of the electronic boards that hold 16 detector blocks (i.e., one detector panel) and the mechanical structure that secures the four detector panels together is currently underway. Additionally, since single, continuous light guides will be used to couple the 16 crystal arrays to their corresponding front and back SiPM arrays to improve mechanical stability, the effect of light spreading in neighbouring detectors will be evaluated to recover the outermost row and column crystals. The more frequent SPAD firing, however, is likely to impact the detector's dead time and, consequently, its count-rate performance. Although this drawback is not expected to significantly affect mouse imaging (count rates are typically low), future work should focus on evaluating the detector's dead time (via a decaying source experiment) and, if necessary, on developing hardware-based alternatives (e.g., individually glued light guides).

Once the scanner is assembled, its static performance will be evaluated, including full NEMA assessments of spatial resolution, sensitivity, and count rate performance.

We have previously evaluated the translation of the movable gantry (without the scanner) in response to the movement of a checkerboard pattern (via a robotic arm), simulating animal movement through the runway [66]. Future work will involve repeating and extending these experiments using taxidermal mouse head phantoms once the scanner is mounted on the gantry. Additionally, the optical tracking system for estimating the six degrees of freedom motion of the mouse head, essential for motion-compensated image reconstruction, needs to be implemented and calibrated before imaging an awake mouse.

6.3.2 Advanced PET quantification

Accurate PET quantification requires performing data pre-corrections and correcting for partial volume effects. For awake small-animal PET imaging, more accurate attenuation correction has been achieved using virtual cylinders that discard LORs traversing the animal torso, moving in conjunction with the changing pose of the animal’s head [8]. In Chapter 5, the virtual cylinder serves to reduce DOI data and remains static, but combining both methodologies could achieve highly efficient and accurate PET reconstruction and tracer quantification. The results in Chapter 5 suggest that resolution modelling is needed to effectively suppress the cross-shaped artefact of the PSF and, consequently, improve image quantification. This thesis used image-based resolution modelling to suppress this artefact, but no noise was accounted for during simulations. In a more realistic scenario, noise amplification is likely. Recently, deep learning-based resolution modelling methods have shown promising outcomes [47, 237]. Future work could explore similar algorithms for this PET geometry.

6.3.3 Awake animal PET studies using mousePET 1.0

A range of PET studies using awake and freely moving mice will be conducted. For example, we plan to replicate our previous studies using rats for in-vivo imaging of ^{11}C -raclopride displacement by endogenous dopamine, and corresponding behavioural changes, following amphetamine drug delivery [130]. Additionally, with the aid of behavioural instruments integrated within the runway, more advanced behavioural studies could be undertaken. For instance, cognitive impairment is a core feature of schizophrenia [165]. Tests for investigating cognition in animal models have been proposed using animal interaction with touchscreens that enable studies of reward-driven learning [26]. We plan to place a touchscreen on the runway to enable such studies of brain function during cognitive tasks.

6.3.4 DNN-based Positioning Algorithm

The next step is to conduct the experimental evaluation of the DNN-based algorithm, which requires the integration of various electronic boards for the detector and ASIC. Re-training the DNN architecture with both simulated and physical detector data is critical for translating the algorithm to a full mousePET prototype scanner. Additionally, exploring methods to generalise its performance across different detectors is essential. Performance evaluation can follow the approach described in [145], utilising mousePET detectors and other configurations, ideally with a lower crystal-to-photodetector ratio. Comparisons could be made against conventional techniques, such as Anger logic and statistical methods like k-means clustering. However, it is important to note that these methods cannot retrieve the same information as the DNN-based algorithm. Further investigation should focus on improving the selection of the first crystal of interaction in single-scatter events and incorporating DOI estimation. One possible approach for including DOI within the framework is to feed 24 signals, corresponding to the 6 row and 6 column signals from both SiPM arrays (i.e., 12 signals per SiPM). Alternatively, the trade-offs between reduced

counts (low SNR) and improved spatial resolution from excluding ICS events could be investigated. Improved spatial resolution at the expense of noisy reconstructions could potentially be mitigated using deep learning-based denoising methods [49].

Finally, assuming these improvements are successfully implemented, the algorithm could be integrated at the scanner level, operating on firmware (mousePET 1.1). The energy outputs from the ASIC would then be processed by the DNN for event positioning before coincidence sorting and image reconstruction.

6.3.5 Cost-effective state-of-the-art PET scanners

The use of signal multiplexing schemes combined with low-cost ASICs has the potential to incentivise the development of high-performance and cost-effective PET scanners, making this technology more accessible worldwide. However, as highlighted in this thesis, little is known about these ASICs when interfaced with such detector configurations. A comprehensive study of various ASICs with different multiplexed readout schemes could guide the selection of the most suitable ASIC for specific configurations.

6.3.6 Towards the Physical Limits of PET (mousePET 2.0)

While it has been demonstrated that 0.5–0.6 mm spatial resolution can be achieved in high-resolution small-animal PET systems [111, 277], initial numerical evaluations of mousePET [67] suggest that this level of resolution may not be possible with current implementations. However, several improvements can still be made (mousePET 2.0). On the detector side, the development of ultra-pixelated BGO-based PET detectors with a crystal pitch of ≤ 0.5 mm could be explored, as BGO is less expensive than LYSO, potentially alleviating the costs associated with high crystal pixellation. Although such thin crystal needles are likely to suffer from ICS events, the implementation of the DNN-based positioning algorithm [65] could mitigate this issue. Additionally, improved DOI estimation using a 3D implementation of the DNN algorithm may further enhance resolution. Finally, on the reconstruction side, the use of virtual geometries, combined with voxel sizes as small as 0.1×0.1 mm² and deep-learning-based PSF modelling, could push the system’s resolution to its limits.

6.4 Concluding Remarks

The work in this thesis has made substantial progress towards bringing the mousePET scanner from concept to reality. It has laid the foundations for success in the final stage of development of this imaging technology. It is our hope that mousePET will significantly contribute to a better understanding of neurological disorders and the more rapid development and evaluation of promising new treatments, thereby improving patient outcomes.

Appendix A

Development and Performance Evaluation of a Multiplexed DOI-Encoding PET Detector Using the TOFPET2 ASIC

Submitted as Supplementary Material in *IEEE Transactions on Radiation and Plasma Medical Sciences*: F. E. Enríquez-Mier-y-Terán et al. “Development and Performance Optimisation of a Multiplexed DOI-Encoding PET Detector Using the TOFPET2 ASIC”

Individual crystal energy spectra and DOI ratios

Figure A.1 shows (a) the location of the crystal (in red) within the array. The normalised energy spectra of the crystal irradiated at various depths, alongside the combined spectra (i.e., summing over all depths), are presented in (b). DOI ratios and calibration are shown in (c) and (d), respectively. In all cases, the detector bias voltage was 27.5 V.

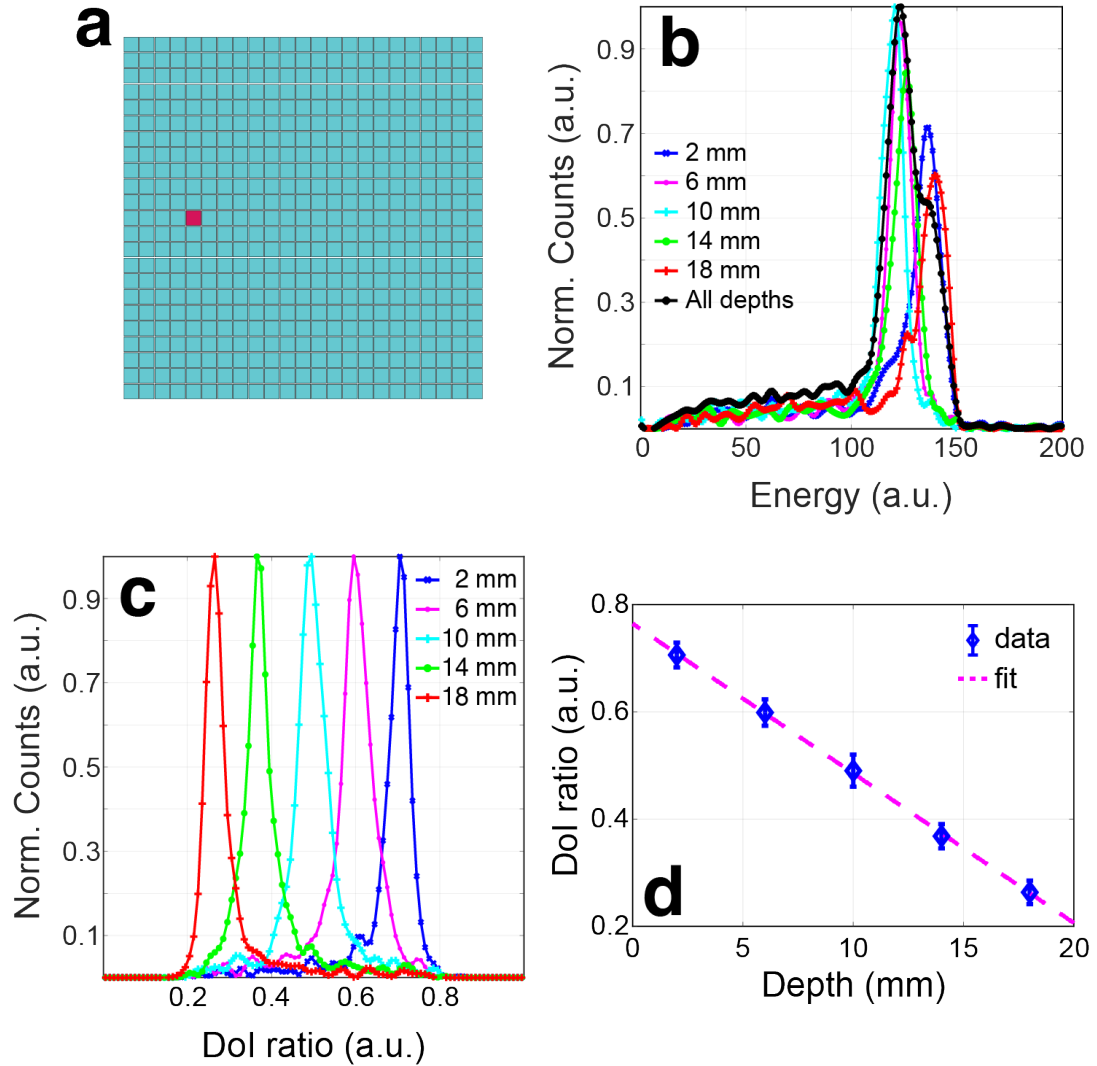


Figure A.1: (a) Location of the crystal (red) in the array. (b) Normalised energy spectra for the different irradiation depths and their combined spectra. (c) DOI ratios and (d) calibration curve (for the DOI ratio) as a function of irradiation depth.

Detector 2 – Energy and DOI resolution

Figure S2 shows the measured energy and DOI resolution for a second dual-ended readout PET detector, biased at 27.5 V. The top row illustrates the energy resolution: (a) as a function of the irradiation depth, averaged across all crystals, and (b) for each individual crystal, averaged across all depths. Similarly, the bottom row shows the DOI resolution: (c) as a function of the depth, and (d)

for each individual crystal.

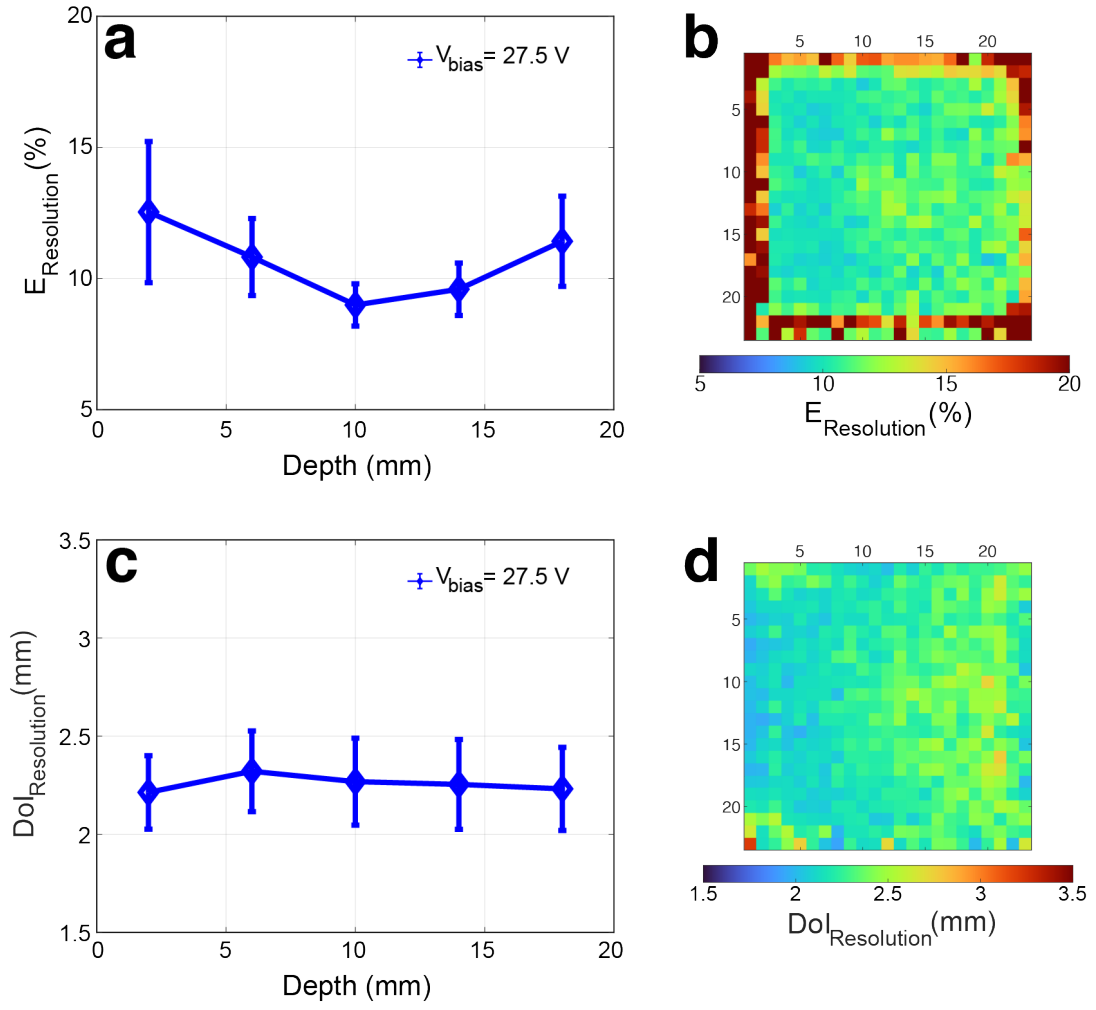


Figure A.2: Detector 2 energy and DOI resolution. (a) Energy resolution as a function of the irradiation depth. (b) Individual crystal energy resolution. (c) DOI resolution for the different irradiation depths. (d) Individual crystal DOI resolution.

Appendix B

Virtual Cylindrical PET for Efficient DOI Image Reconstruction with Sub-millimetre Resolution

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“Virtual Cylindrical PET for Efficient DOI Image Reconstruction with Sub-
millimetre Resolution”. In: *Physics in Medicine & Biology* 69.11 (2024), p.115043.

PSF Measurements at 1/4 of the Axial FOV

Figure B.1 shows the zoomed reconstructed PSF for the physical scanner (mousePET) and virtual PET implementations with the point source at 1/4 of the axial FOV and radially centred. Tables B.1 and B.2 display the FWHM and FWTM measurements, respectively, along radial, tangential, axial, and diagonal profiles. No reconstructions were conducted for the non-DOI geometries.

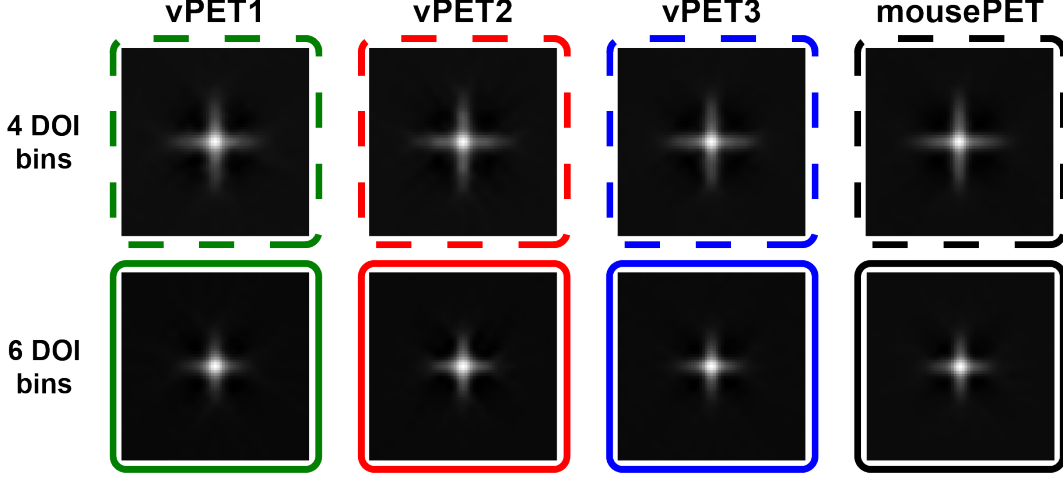


Figure B.1: Zoomed PSF (after background subtraction) for a point source at 1/4 of the axial FOV and radially centred, shown for the physical scanner and virtual PET implementations (columns) with 2 DOI resolutions (rows).

Table B.1: Full-width-at-half-maximum (FWHM) measurements for the fifth point source

	Radial (mm)		Tangential (mm)		Axial (mm)		Diagonal (mm)	
	4-bin DOI	6-bin DOI	4-bin DOI	6-bin DOI	4-bin DOI	6-bin DOI	4-bin DOI	6-bin DOI
vPET1	0.952	0.870	0.951	0.872	0.769	0.787	0.831	0.783
vPET2	0.864	0.950	0.873	0.944	0.775	0.768	0.794	0.783
vPET3	0.896	0.873	0.890	0.867	0.757	0.771	0.743	0.723
mousePET	0.900	0.833	0.890	0.827	0.772	0.700	0.750	0.719

Table B.2: Full-width-at-tenth-maximum (FWTM) measurements for the fifth point source

	Radial (mm)		Tangential (mm)		Axial (mm)		Diagonal (mm)	
	4-bin DOI	6-bin DOI	4-bin DOI	6-bin DOI	4-bin DOI	6-bin DOI	4-bin DOI	6-bin DOI
vPET1	3.821	2.766	3.852	2.754	1.646	1.607	1.493	1.402
vPET2	4.055	2.927	4.064	2.911	1.509	1.494	1.425	1.400
vPET3	3.937	2.857	3.918	2.813	1.512	1.541	1.329	1.290
mousePET	3.973	2.820	4.001	2.810	1.389	1.381	1.341	1.283

Micro Derenzo Reconstruction CPU Time

Table B.3 shows the CPU times for the micro Derenzo reconstruction, for the different geometries and number of DOI bins. Reconstructions were conducted in a high performance computer (HPC), in which different nodes (with different processors) are allocated at different runs. The HPC consists of various nodes with Intel Xeon processors: E5-2680 V3, E5-2697A V4 and Platinum 8160. To reduce the hardware dependence due to HPC, we reconstructed the micro Derenzo data three times, and the mean and standard deviations of CPU time are presented below. In all cases, 1 node with 10 cores was requested.

Table B.3: Micro Derenzo reconstruction CPU time (in minutes).

	no DOI	4-bin DOI	6-bin DOI
vPET1	120 $\pm$ 1	111 $\pm$ 2	113 $\pm$ 9
vPET2	124 $\pm$ 3	167 $\pm$ 1	176 $\pm$ 3
vPET3	130 $\pm$ 3	230 $\pm$ 6	274 $\pm$ 7
mousePET	158 $\pm$ 3	446 $\pm$ 4	853 $\pm$ 13

Comparison Between Non-PSF and PSF-Modelled OSEM Reconstruction

Figure B.2 shows a line profile comparison between the reconstructed 0.9 and 1.2 mm rods with and without 2D PSF modelling. Comparison is done for two of the 6-bin DOI PET geometries from main text, physical scanner and vPET2.

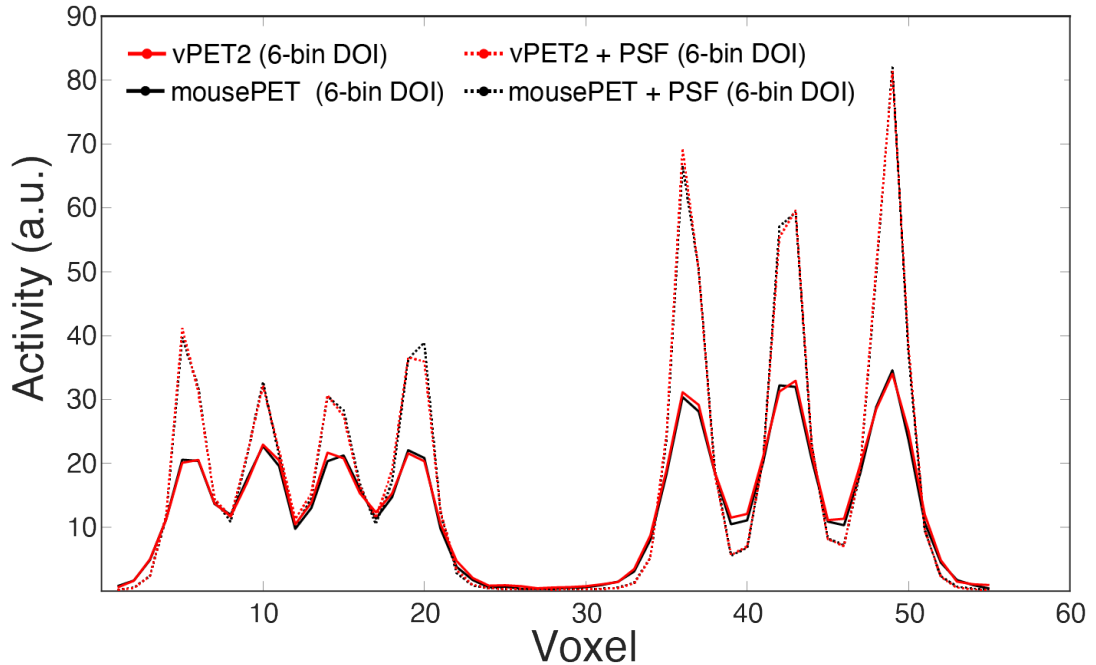


Figure B.2: Line profiles across the 0.9 and 1.2 mm rods of the micro Derenzo phantom.

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