

Commissioning of a 2048 Element 3γ PET Demonstrator

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Abstract

In this thesis a new 2048 element Lutetium-Yttrium Oxyorthosilicate (LYSO) based gamma detection array and associated data acquisition, simulation, and data analysis methodologies are commissioned. The array is employed for the first time in measurements, detecting radiation from the annihilation of ^{18}F positrons in a range of media with different mean pore volumes. The annihilation site is reconstructed using a novel methodology that directly localises the 3γ decay of ortho-Positronium on an event-by-event basis. This methodology was developed by our group in collaboration with the University of Tokyo [1]. Standard 2γ reconstruction is also implemented, including the use of a Maximum Likelihood Expectation Maximisation (MLEM) approach. A first extraction of spatially resolved $3\gamma/2\gamma$ decay annihilation maps and ratios is obtained for the system using data employing a range of mesoporous annihilating media.

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Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for a degree or other qualification at this University or elsewhere. All sources are acknowledged as references.

Chapter 1

Introduction

The three-photon decay of the triplet (Spin=1) ortho-positronium (o-Ps) system offers exciting prospects for future fundamental tests of tri-partite quantum entanglement as well as for next generation medical imaging, where it has been shown to be sensitive to the environmental conditions in which the decay takes place [2, 3]. This environmental sensitivity arises from the influence of the size of free volumes in the bulk medium where the annihilation occurs on the effective lifetime of (o-Ps) [4]. The three-photon decay mode is not currently utilised in clinical Positron Emission Tomography (PET) due to the front end hardware of commercial systems filtering on 2-gamma events (within pre-defined energy windows) and a low relative event rate to the standard two-photon annihilation from (Spin=0) para-positronium (p-Ps). Thus, no 3γ imaging technique has yet been developed for clinical scanners.

Detecting 3-photon decays offers experimental challenges and requires detector arrays with large acceptance to obtain adequate yields and kinematic coverage as well as flexible (and user controllable) data acquisition systems to record the data. In this thesis a new LYSO-based gamma-detection array, associated data acquisition software, and data analysis methodologies are commissioned for this purpose. The array comprises 2048 detector crystals and is employed for the first time in measurements, detecting radiation from the annihilation of ^{18}F positrons. There exists a positive effect on the 3γ annihilation rate of the presence of free volumes, as such the measurements are carried out in a range of mesoporous annihilation media with different average pore sizes, with the aim of boosting the relatively small 3γ signal compared to the 2γ background. The annihilation site is reconstructed on an event-by-event basis using a new methodology developed with the University of Tokyo [1]. A first attempt at extracting the spatially resolved $3\gamma/2\gamma$ decay ratio as a function of pore sizes is carried out with the commissioning data.

1.1 Positron Emission Tomography background

Positron Emission Tomography (PET) is a non-invasive functional medical imaging modality, used primarily for oncology, neurology and cardiology. In PET, radiotracers – a biologically active molecule, tagged with a β^+ decaying radionuclide – accumulate preferentially in target tissues to detect trends in abnormal cell function via imaging of the resultant annihilation radiation [5]. In clinical application, the most common radiotracer is ^{18}F -FDG, an ^{18}F tagged glucose molecule, which is highly effective at accumulating in tumours due to their increased metabolism [6]. The ^{18}F decays via $^{18}\text{F} \rightarrow ^{18}\text{O} + e^+ + \nu_e$, with the emitted e^+ quickly annihilating close to the emission site with a nearby electron (e^-), typically within $\sim 1 - 2$ mm for ^{18}F in human tissue [7].

This annihilation overwhelmingly ($>99\%$ of events [8]) produces 2 back-to-back gamma photons of energy 511 keV (Figure 1.1a), which can then be detected in the scanner (Figure 1.1b). A line of response (LOR) is drawn between pixels that detect two incident gammas within a short timing window (typically ~ 10 ns [9]). By accumulating high statistics of these LORs, an image of radiotracer distribution is reconstructed.

According to a recent study of PET use cases in Germany (see Figure 1.2), it is utilised $\sim 89\%$ of the time for oncology, $\sim 4\%$ for neurology and $\sim 2\%$ for cardiology — with tumour detection being the vast majority of use cases [6]. Thus, ^{18}F radiotracers are used in this study as the best representative of standard clinical PET.

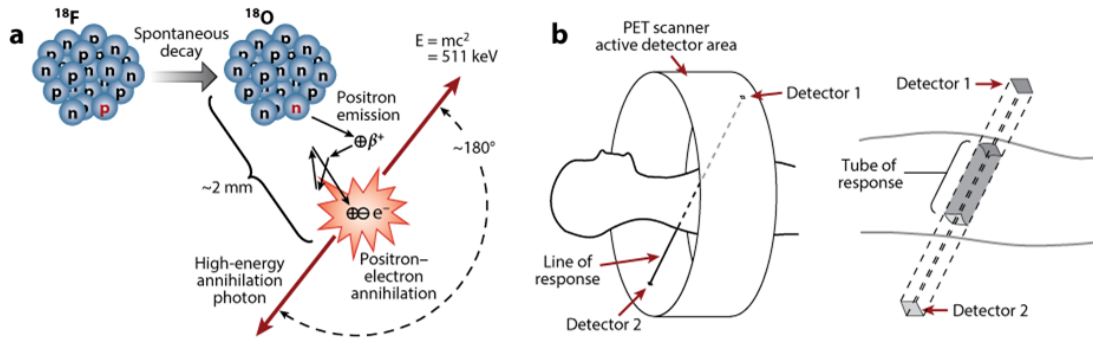


Figure 1.1: Schematics showing the basic mechanics of Positron Emission Tomography (PET). (a) Positron decay of ^{18}F , followed by $e^+e^- \rightarrow 2\gamma$ annihilation producing two back-to-back gammas (as exploited in current PET). (b) These gammas are detected by the scanner ring, where the hit positions are used to form a Line of Response (LOR) between them. Note the pixel size more correctly gives a "Tube of response" [5].

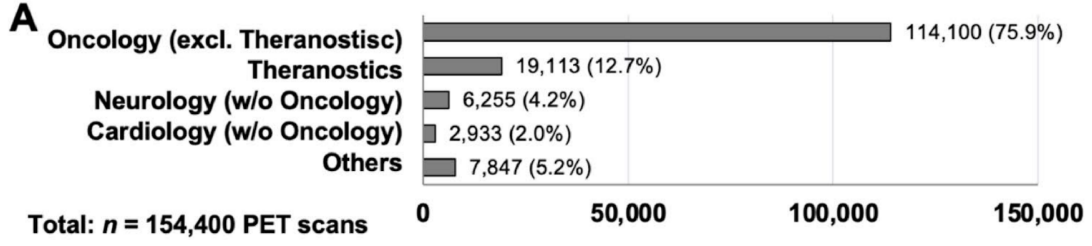


Figure 1.2: PET use cases in Germany for 2021, with the vast majority being for oncology and theranostics ($\sim 89\%$). This justifies the use of ^{18}F radiotracers as the best standard for this study. Reproduced from [6].

1.1.1 Current limitations of PET scans

PET scans stack back-to-back 2γ LORs to generate an image. The true LORs — where the two gammas are correctly identified from a single annihilation event — comprise only $\sim 25\%$ of the detected yield in a PET scan [10]. The significant sources of the non-true events are shown schematically in Figure 1.3 [5]. These comprise: lost (attenuated) events, where one of the gammas is absorbed or scattered out of the detector acceptance; scattered events, where one of the gammas has scattered in the patient, forming an incorrect correlation between LOR and annihilation site; and random events, where the two detected gammas are not from the same annihilation event. The latter two lead to "noise" in the image while the former gives reduction in yield that has to be corrected in the image for clinical applications. The scatter-to-true ratios, with application of energy windows where the detected photons are close to 511 keV and in a coincident timing intervals, range from ~ 0.2 to ~ 2 , while random-to-true ratios range from ~ 0.1 to greater than 1, dependent on detector properties [11].

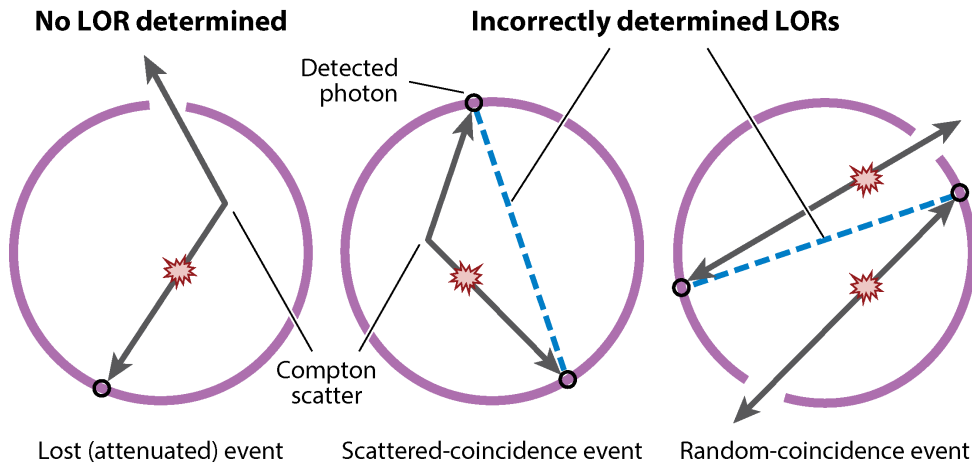


Figure 1.3: Schematic illustrating the major causes of noise in a 2γ PET scan. **(Left)** Lost (attenuated) event where one of the gammas has scattered out of the detector and not been detected. **(Middle)** Scattered event where the scattered gamma is still detected, creating a false LOR. **(Right)** Random coincidence events where the incorrect gammas are paired together. Reproduced from [5].

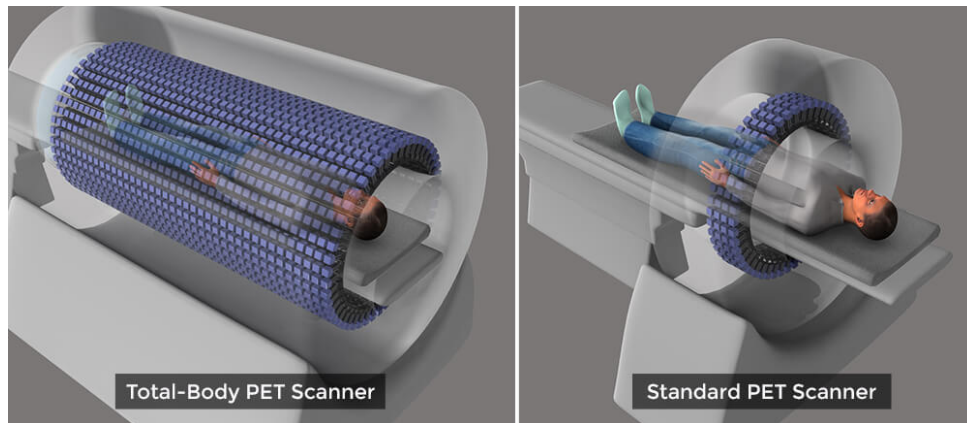


Figure 1.4: 3D render showing the difference in field of view between a Total-Body PET Scanner (left) and a Standard PET Scanner (right). Adapted from Figures 4a and 4b in [12].

Most current PET systems comprise a ring of scintillators with the patient located in the field of view using a motorised bed, as pictured in Figure 1.4. Next generation state-of-the-art systems are anticipated to be full body 3D PET scan, where the patient is enclosed by a cylindrical shell of detectors giving full field of view.

Although enhancing the detector efficiency and field-of-view, full-body systems allow gammas to pass more obliquely through the patient and structures, increasing scatter. Furthermore, the higher multiplicity of detector crystals can enhance the role of random events in the overall yield, which can be as high as 80% [13]. Scattering of either one of the photons along any part of its path can occur readily as there is a lot of e^- dense material off which to scatter (the body, detector structure, etc). Any scattering will create a false LOR if both photons are still detected. It is also likely for a scattering event to scatter the photon out of the plane of the detector, leaving only one to be detected. This is one of the causes for the other major contributor of noise, coincident events, with scattering events comprising $\sim 30 - 50\%$ of detected PET scan events [5]. Coincident events are events where more than 2 photons are detected within the timing resolution window of the system. This can occur if a random or scattered gamma is detected alongside a true pair, or if two real events are detected within coincidence of each other. At this point there is likely to be one or more false events recorded, as there is no methodology to differentiate each event. In a typical whole body PET scan, the rate of random coincidence hits constitutes a significant percentage of total events ($\sim 25\%$) [10]. Figure 1.5 shows an example of the balance of true, random and scatter events as a function of source activity, as well as the noise equivalent count rate (NECR) used to optimise activity levels.

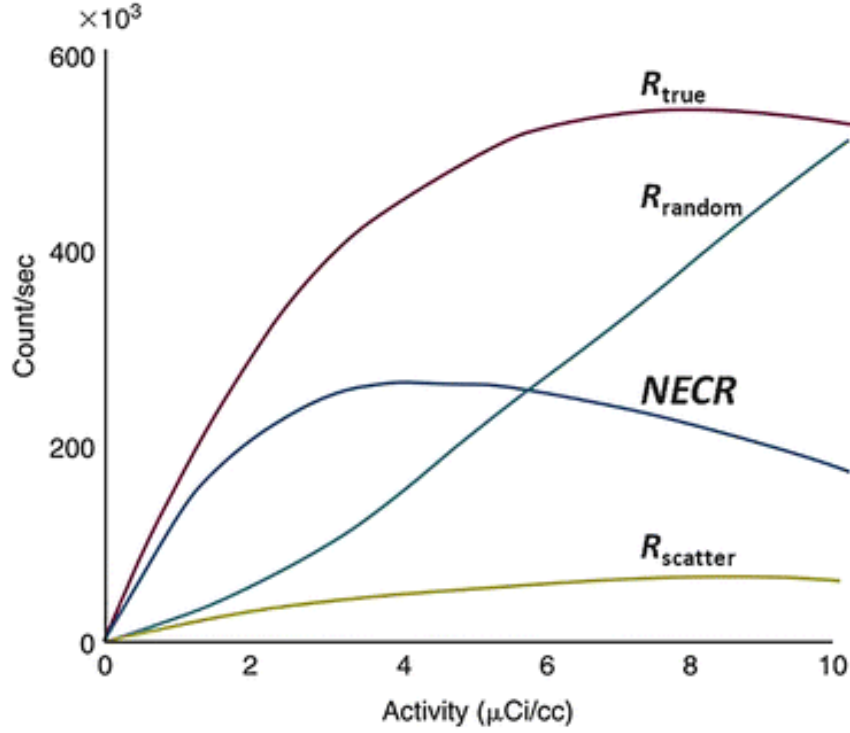


Figure 1.5: True (T), random (R) and scatter (S) event rates alongside the noise equivalent count rate ($NECR = \frac{T^2}{T+S+R}$) as a function of source activity. Note the random rate scales quadratically with activity. Reproduced from [14].

1.2 Positron annihilation physics

In order to annihilate with an electron, the positron emitted from the radiotracer first thermalises — losing almost all of its kinetic energy in a range of a 1-2 mm — equilibrating when it reaches thermal energies of order $k_B T \approx 0.025$ eV at room temperatures [15]. The annihilation probability (e.g. from free annihilation or the formation of positronium) markedly increases when the positron is thermalised (note the binding energy of positronium is 6.8 eV). The annihilation predominantly produces two near back-to-back gammas of energy 511 keV (half the combined rest masses of the $e^\pm$).

There are multiple annihilation modes that occur when the positron is produced in the annihilating medium (e.g. the body), shown in Figure 1.6. These stem from two primary modes: free annihilation and annihilation via positronium (Ps) formation. This section lays out the basic physics of these processes and discusses the relative annihilation rates.

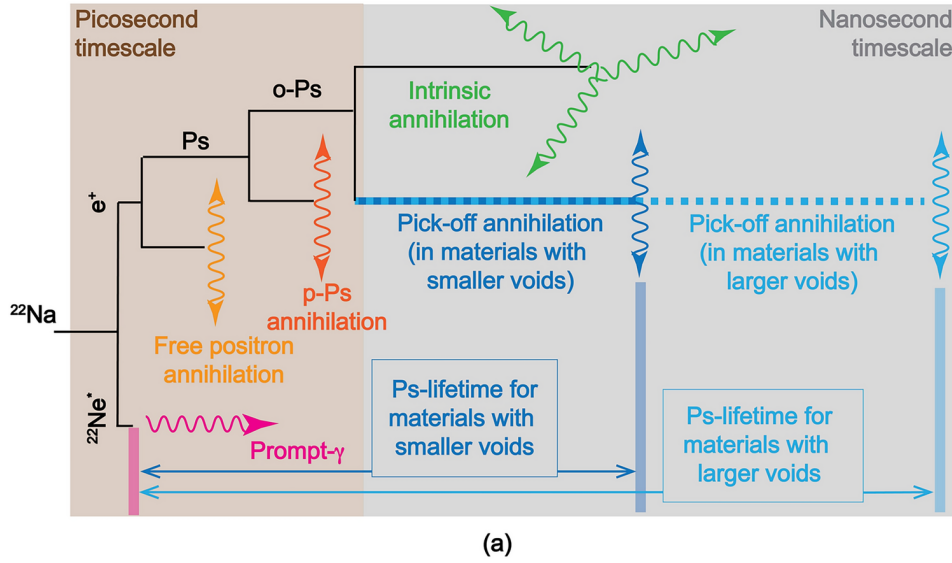


Figure 1.6: Flow chart illustration of the possible processes of positron–electron annihilation, showing the differing timescales between free, p-Ps, pick-off o-Ps and intrinsic o-Ps annihilation modes. In this instance the positron originates from ^{22}Na , which also highlights the prompt- γ emission used later in the analysis. Figure 1a adapted from [7]

1.2.1 Free annihilation

Free annihilation occurs when the thermalised positron annihilates directly with an electron in the surrounding medium. The cross-section of annihilation for a positron electron system, shown by West [16], taking the low-energy approximation of Dirac’s overall cross-section [17] is

$$\sigma_{(2\gamma)} = \frac{\pi r_0^2 c}{v}, \quad (1.1)$$

where r_0 is the electron radius and v is the velocity and c the speed of light in vacuum. The annihilation rate for a low velocity (thermalised) positron and bound electron is then

$$\lambda_{(2\gamma)} = \sigma_{(2\gamma)} v n_e = \pi r_0^2 c n_e, \quad (1.2)$$

where n_e is the electron density. Substituting in the electron density in water (with an analogous electron density to blood) this gives a free positron lifetime, τ of

$$\tau = \frac{1}{\pi r_0^2 c n_e} \simeq 400 \text{ ps}. \quad (1.3)$$

Although West notes the inaccuracy of not considering the Coulomb attraction of the annihilating pair, in water the opposing repulsion from the Oxygen nucleus effectively cancels this effect. The free lifetime in water is experimentally measured as 0.395 ± 0.0005 ns [3].

1.2.2 Positronium formation

Ps formation occurs when thermalised positrons instead capture an electron from the surrounding medium, forming a metastable bound state of a positron and an electron. As Ps consists of two spin-1/2 fermions, it can be formed in four different spin projection eigenstates, producing two distinct total spin states, $S = 0$ and $S = 1$, where S is the total spin. These comprise an anti-symmetric singlet state $S = 0$, known as para-Positronium (p-Ps) and a symmetric triplet state $S = 1$, known as ortho-Positronium (o-Ps):

$$\text{p-Ps} = |S = 0, S_z = 0\rangle = \frac{1}{\sqrt{2}}(|\uparrow\downarrow\rangle - |\downarrow\uparrow\rangle), \quad (1.4)$$

$$\text{o-Ps} = \begin{cases} |S = 1, S_z = 1\rangle & = |\uparrow\uparrow\rangle \\ |S = 1, S_z = 0\rangle & = \frac{1}{\sqrt{2}}(|\uparrow\downarrow\rangle + |\downarrow\uparrow\rangle) \\ |S = 1, S_z = -1\rangle & = |\downarrow\downarrow\rangle \end{cases} \quad (1.5)$$

All four eigenstates are equally likely to be formed, and thus there is a 3:1 production rate of o-Ps to p-Ps.

The probability of free annihilation versus Ps formation is dependent on the medium. In biological tissue, free annihilation accounts for roughly 60–65% of all annihilations. The remaining positrons form positronium, where the 3:1 ratio dictates that $\sim 25\text{--}30\%$ of the total form o-Ps, and $\sim 10\%$ form p-Ps [18].

1.2.3 2γ vs 3γ annihilation

Positronium intrinsically decays via 2 or 3 photons, due to charge conjugation parity (C-parity), with p-Ps intrinsically decaying to 2 photons and o-Ps to 3. Because Ps is a fermion-antifermion system, its C-parity is given by

$$C = (-1)^{L+S}, \quad (1.6)$$

where L is the orbital angular momentum quantum number of the system and S is the total spin quantum number. $L = 0$ for all ground state Ps systems, thus the equation simplifies to

$$C = (-1)^S = \begin{cases} 1 & \text{if } S = 0 \\ -1 & \text{if } S = 1 \end{cases}. \quad (1.7)$$

The charge parity of a system of n photons is given by

$$C_{n\gamma} = (-1)^n = \begin{cases} 1 & \text{if } n = \text{even} \\ -1 & \text{if } n = \text{odd} \end{cases}. \quad (1.8)$$

Thus, for the $S = 0$ state, p-Ps, $C = 1$ and the resulting annihilation photons must be of even multiples, with the lowest-order process being the decay to 2γ . Conversely, for the $S = 1$ state, o-Ps, $C = -1$ and the resulting annihilation photons must be of odd multiples. As a single photon annihilation cannot conserve momentum, the lowest-order o-Ps annihilation is into 3γ . Higher order annihilations do exist for both Ps states, with the next being the 4γ and 5γ decays for p-Ps and o-Ps, respectively. However, these decays are suppressed by a factor of α^2 (where $\alpha \approx 1/137$ is the fine-structure constant) due to their two additional interaction vertices, alongside far greater kinematic phase space restrictions over the 2 and 3γ decays, making them statistically negligible.

1.2.4 Positronium lifetimes and three gamma quenching

The dominant decay modes of Ps are p-Ps $\rightarrow 2\gamma$ and o-Ps $\rightarrow 3\gamma$. In a vacuum, this has a 3:1 split of o-Ps to p-Ps and thus a 3/4 3γ to 1/4 2γ yield. However, in electron-dense media — such as biological tissue or water — it is shown below that the production of 3γ is heavily quenched by the phenomena of pick-off events. These are events in which the bound e^+ annihilates instead with an external e^- , this happens far more readily than the intrinsic 3γ decay, due to the far longer lifetime exhibited by o-Ps than the mean lifetime of the o-Ps bound e^+ and external e^- annihilating. There are three lifetimes to note in Ps annihilations, p-Ps, o-Ps and pick-off, their respective interactions are shown in Figures 1.7 - 1.9.

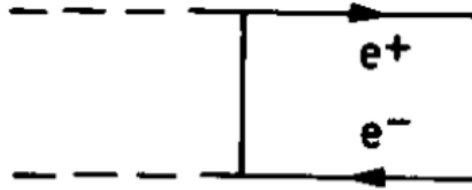


Figure 1.7: Feynman diagram for the 2-photon annihilation of an e^+e^- pair. This is the lowest-order process for free annihilation and p-Ps decay, producing two co-linear 511 keV gammas. Reproduced from [19].

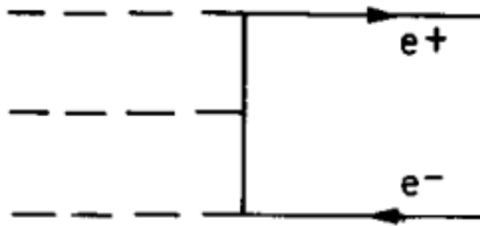


Figure 1.8: Feynman diagram for the 3-photon decay of an e^+e^- pair. This is the lowest-order process for o-Ps intrinsic decay, producing three co-planar gammas with energies ranging from 0 to 511 keV. Reproduced from [19].

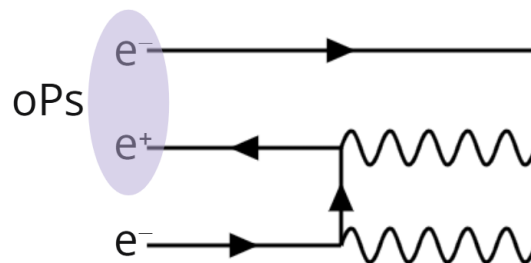


Figure 1.9: Feynman diagram for 2-photon pick-off event of an o-Ps e^+e^- pair with an external electron, producing two co-linear 511 keV gammas and leaving the original bound electron free.

Introduction

Unlike free positron annihilation, as Ps is in a bound state, the decay rate is a product of the low-velocity approximation of the Dirac cross-section velocity and the spatial wave function of the bound state [16, 17], with the lifetime then being

$$\tau_{\text{Ps}} = \frac{1}{\lambda_{\text{Ps}}} = \frac{1}{\sigma v \times |\psi(0)|^2}. \quad (1.9)$$

The spatial wavefunction component for both p-Ps and o-Ps is analogous to the 1s orbital of a hydrogen atom:

$$\psi(r) = \frac{1}{\sqrt{\pi a_{\text{Ps}}^3}} e^{\frac{-r}{a_{\text{Ps}}}}, \quad (1.10)$$

where a_{Ps} is the Bohr radius of Ps, given by $a_{\text{Ps}} = 1/\alpha\mu$, where α is the fine-structure constant and μ is the reduced mass, given as

$$\mu = \frac{m_e m_e}{m_e + m_e} = \frac{m_e}{2}, \quad (1.11)$$

where m_e is the mass of both the electron and positron, such that

$$a_{\text{Ps}} = \frac{1}{\alpha(m_e/2)} = \frac{2}{\alpha m_e}. \quad (1.12)$$

As the system is annihilating, this must occur at $r = 0$, as such the spatial probability density function is reduced to

$$|\psi(0)|^2 = \frac{1}{\pi a_{\text{Ps}}^3}. \quad (1.13)$$

For Ps this gives

$$|\psi(0)|^2 = \frac{1}{\pi(2/\alpha m_e)^3} = \frac{\alpha^3 m_e^3}{8\pi}. \quad (1.14)$$

The annihilation cross-section velocity is what differentiates the lifetimes of the two Ps states. The p-Ps cross-section velocity, using the low-velocity approximation defined by Wheeler [20] is derived from the

Dirac cross-section velocity. The Dirac cross-section velocity was defined for randomly distributed holes (analogous to the positron) and electrons, thus the calculated cross-section is an average over all spin states:

$$\sigma_{\text{Ps}} = \frac{1}{4}\sigma_{\text{singlet}} + \frac{3}{4}\sigma_{\text{triplet}}. \quad (1.15)$$

As p-Ps is the singlet state

$$\sigma_{\text{Ps}} = \frac{1}{4}\sigma_{\text{singlet}} + \frac{3}{4}0 \Rightarrow \sigma_{\text{p-Ps}} = 4\sigma_{\text{Ps}}, \quad (1.16)$$

where σ_{Ps} , as in (1.1), is given in natural units as

$$\sigma_{\text{Ps}} = \frac{\pi r_0^2}{v}. \quad (1.17)$$

Substituting for r_0 as

$$r_0 = \frac{e^2}{m_e c^2} = \frac{\alpha \hbar}{m_e c}, \quad (1.18)$$

the low-energy limit of the cross-section velocity of Ps, in natural units, becomes

$$(\sigma v)_{\text{Ps}} = \pi r_0^2 = \frac{\pi \alpha^2}{m_e^2}. \quad (1.19)$$

Thus, for p-Ps,

$$(\sigma v)_{\text{p-Ps}} = \frac{4\pi \alpha^2}{m_e^2}. \quad (1.20)$$

The decay rate of p-Ps is then

$$\lambda_{\text{p-Ps}} = \frac{4\pi \alpha^2}{m_e^2} \times \frac{\alpha^3 m_e^3}{8\pi} = \frac{m_e \alpha^5}{2}, \quad (1.21)$$

and the lifetime, converted back to SI units, is

$$\tau_{\text{p-Ps}} = \frac{2}{m_e \alpha^5} \times \frac{\hbar}{c^2} \simeq 125 \text{ ps}. \quad (1.22)$$

For o-Ps, the cross-section velocity is restricted by the allowed kinematics of the 3γ decay, and carries an extra α due to the extra photon vertex. Ore and Powell provide an analytical integration over the now continuous phase space of allowed final states [21], resulting in a cross-section velocity of

$$(\sigma v)_{\text{o-Ps}} = \frac{16(\pi^2 - 9)\alpha^3}{9m_e^2}, \quad (1.23)$$

giving a decay rate of

$$\lambda_{\text{o-Ps}} = \frac{16(\pi^2 - 9)\alpha^3}{9m_e^2} \times \frac{\alpha^3 m_e^3}{8\pi} = \frac{2(\pi^2 - 9)m_e \alpha^6}{9\pi}, \quad (1.24)$$

and thus a lifetime of

$$\tau_{\text{o-Ps}} = \frac{9\pi}{2(\pi^2 - 9)m_e \alpha^6} \times \frac{\hbar}{c^2} \simeq 142 \text{ ns}. \quad (1.25)$$

1.2.5 Pick-off

Pick-off refers to the case when a formed positronium atom does not decay by annihilation of its electron and positron constituents - but involves the bound positron annihilating with another electron from a nearby atom. The Pick-off event rate is therefore governed by the Dirac cross-section for the bound e^+ annihilating with an external e^- . The annihilation is approximated as a free e^+ annihilation because of comparatively weak positronium binding energy of 6.8 eV having a negligible effect of the bound e^+ wavefunction. As derived in equation 3 the lifetime of a free e^+ is ~ 400 ps.

However, unlike the free e^+ case, the e^+ in the o-Ps is in a bound state with an e^- and as such is effectively neutral and does not attract the bulk e^- . Furthermore, the e^- in the o-Ps exerts a repulsive force on the bulk electrons, specifically the closed outer shell e^- , obeying the Pauli exclusion principle, creating a cavity wherein the o-Ps exists. This cavity can be semi-empirically approximated in liquids by the bubble model [22]:

$$a = (\pi \hbar^2 / 16m_e \sigma)^{\frac{1}{4}}, \quad (1.26)$$

where a is the bubble radius, and σ the coefficient of surface tension of the bulk medium. In order for the bubble to form, the Ps must at least produce enough outwards pressure from its zero-point energy to create an equilibrium such that $\frac{\delta E}{\delta r} = 0$. At room temperature, the inwards pressure is very high and the equilibrium radius is pushed to be very small, resulting in experimentally established radius in water of $a \approx 0.3$ nm (corresponding to a surface pressure of ≈ 340 MPa) [23]. This causes a significantly larger

fraction of the Ps spatial wavefunction overlapping the e^- bulk layer, increasing the probability of pick-off annihilation.

The pick-off rate of this system is best approximated by the Tao-Eldrup (TE) model [2, 3], in which the system is modelled as a bubble surrounded by an electron bulk layer, itself surrounded by an infinite spherical potential well. The pick-off rate is approximated as the product of the pick-off rate inside the bulk electron layer, λ_0 , and the probability of the o-Ps being inside the bulk electron layer, P_{overlap} defined by Eldrup et al. [24] as

$$P_{\text{overlap}} = 1 - \frac{R_1}{R_0} + \frac{1}{2\pi} \sin(2\pi R_1/R_0), \quad (1.27)$$

such that

$$\lambda_{\text{pickoff}} = \lambda_0 \left[1 - \frac{R_1}{R_0} + \frac{1}{2\pi} \sin(2\pi R_1/R_0) \right], \quad (1.28)$$

where R_1 is the radius of the bubble and R_0 is the radius greater than R_1 (such that $R_0 = R_1 + \Delta R$) in which there is an electron density and there exists an infinite potential energy for $r \geq R_0$.

Taking the experimental values of $\Delta R \simeq 1.66 \text{ \AA}$, $R_1 \simeq 2.9 \text{ \AA}$ and the spin-averaged $\lambda_0 = 2 \text{ ns}^{-1}$, gives a $\lambda_{\text{pickoff}} \simeq 0.54 \text{ ns}^{-1}$. Adding the intrinsic annihilation rate of $\lambda_{\text{o-Ps}} = 0.007 \text{ ns}^{-1}$ this gives an overall $\lambda_{\text{o-Ps}} \simeq 0.547 \text{ ns}^{-1}$ in water and a lifetime of just $\tau_{\text{o-Ps}} \simeq 1.8 \text{ ns}$.

It is now clear that the pick-off (2γ) annihilation rate of o-Ps in water, and for all e^- dense annihilating media, far exceeds that of the intrinsic 3γ annihilation of o-Ps. Furthermore, as the pick-off rate is dependent on the bulk medium's electron density, the overall 3γ yield is dependent on the local annihilation environment. This provides possibilities for the 3γ yield to be used as a novel environment sensitive imaging technique.

1.3 3γ PET pore size study for novel imaging

While current 2γ PET exclusively measures the metabolic distribution of the radiotracers, the ability to measure the localised rates of 3γ production allows for the potential to diagnose any environmental changes to the pick-off rate and thus the 3γ yield. As described above, the pick-off rate is proportional to the bulk medium electron density. One factor that decreases the o-Ps overlap with the bulk electrons is an increase in bubble radius, which is a product of the inward pressures exerted by the medium, and is thus medium sensitive. Moreover, microporous media are present in many tissues, wherein the pre-existing pores act as an environmental analogy of the bubble model, changing the lifetime.

1.3.1 Pore size change in cancerous extracellular matrices

As previously stated, the bulk of PET scan use cases are for the diagnosis or monitoring of cancers. One effect cancers can have is the remodelling of the extra cellular matrix (ECM) of the affected tissue, causing the pores of many cancerous tissues to shrink in size.

Drops in o-Ps lifetime have been experimentally shown by Moskal et al. [25] of 2.6 ns in healthy adipose tissue to 1.9 ns in a cardiac myxoma tumour. As the 3γ yield, $Y_{3\gamma}$ is roughly linearly proportional to the lifetime of o-Ps, a percentage change can be approximated as

$$Y_{3\gamma}(\text{healthy}) = \frac{\tau_{\text{healthy}}}{\tau_{\text{vacuum}}} = \frac{2.6}{142} \approx 1.83\%, \quad (1.29)$$

$$Y_{3\gamma}(\text{cancerous}) = \frac{\tau_{\text{cancerous}}}{\tau_{\text{vacuum}}} = \frac{1.9}{142} \approx 1.34\%, \quad (1.30)$$

$$\frac{\Delta Y_{3\gamma}}{Y_{3\gamma}(\text{healthy})} = \frac{1.83 - 1.34}{1.83} \approx 26.8\% \text{ decrease}, \quad (1.31)$$

constituting a roughly 31% decrease in the average 3γ yield in some cancerous tissues compared to healthy tissue. Furthermore, a leading cause of chemotherapy failure is the mechanical barrier formed by the stiffened ECM preventing the penetration of macromolecular ($\sim 10\text{-}15$ nm) monoclonal antibodies (MCAs) [26]. Assessing the structure of these stiffened ECMs is currently only achievable via indirect approximation such as ultrasounds [27]. As the reduction of 3γ yield is due to the shrinking pore size and higher wall density per voxel, it serves as a biological marker for a stiffening ECM, which itself is a proxy for the permeability for chemotherapy MCAs and nanomedicines.

The changes to the ECM occur over the nanoporous range (< 2 nm), with the radial changes themselves being on the order of 0.01 nm. This work serves as a proof that 3γ -PET can model changes in 3γ yield over the mesoporous range. While future work would be required to demonstrate the capability at nanoporous ranges and model the specific yield changes against the penetrative abilities of medicines, this work serves as a demonstration that the imaging of pore size changes can show a change in 3γ yield in a current PET array.

1.3.2 3γ yield changes over the mesoporous regime

While the nanoporous effects serve as a clinical motivation for the porosity study, the initial aims of the overall experiments at the focus of this paper are to boost as greatly as possible the 3γ yield. Establishing the enhanced relative yields of 3γ will benefit future studies exploring 3γ PET methodologies in

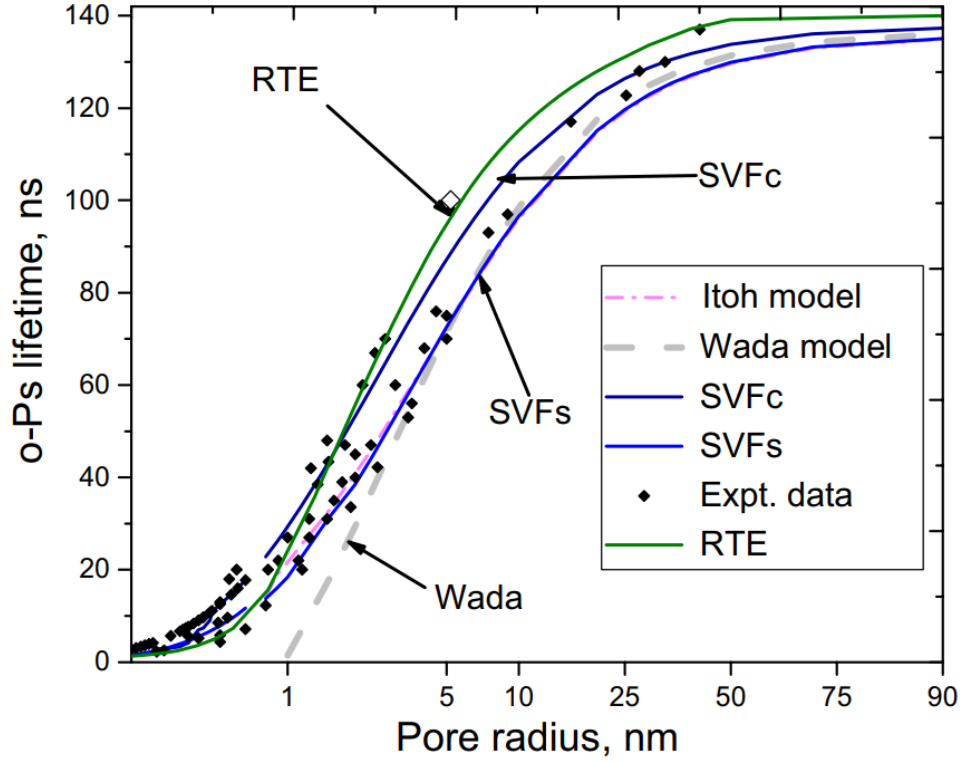


Figure 1.10: Ortho-positronium (o-Ps) lifetime as a function of pore radius for various experimentally measured materials (black data points). Prediction of this relationship for SVFc (cylindrical pores) and SVFs (spherical pores) shown by solid lines (see key in figure). Note also the rectangular Tao-Eldrup (RTE), and its slight overestimation of pore size in the mesoporous range. Reproduced from [4].

demonstrator apparatus as well as providing increased statistics for future fundamental tests of entanglement in the 3γ system.

The Surface-Volume Formula (SVF) presented by Trung et al. [4] extends the TE model to mesoporous (2-50 nm) ranges and accounts for various environmental factors affecting the average time to interact with a pore wall. This function is plotted in Figure 1.10, which shows that the o-Ps lifetime extends drastically towards its intrinsic lifetime of 142 ns as the pore size increases, with the largest change over the mesoporous range.

The pore size change effects in the mesoporous range are underpinned by a different physical process than the TE model presented for the nanoporous case. In TE, the primary effect is the overlap of the o-Ps wavefunction with the pore walls, analogous to the overlap with the electron layer in the bubble model. However, on the mesoporous scale, the size of the pore becomes so great relative to size of the o-Ps that the quantum energy levels become far closer together. This allows the ambient temperature to easily blur the energy states and thus the o-Ps acts like a classical gas particle. As such, the probability of the o-Ps annihilating in the electron layer becomes the ratio of the volume of the electron layer to the volume of

the pore, V . As the electron layer is extremely thin, its volume can be approximated as the product of the pore surface area, S , and the electron layer thickness, ΔR , giving

$$P_{\text{electron layer}} = \frac{S \cdot \Delta R}{V}. \quad (1.32)$$

Thus, where λ_0 is the electron layer annihilation rate, the pick off rate is given similarly to before as $\lambda_{\text{pickoff}} = \lambda_0 P_{\text{electron layer}}$, and thus the pick off rate is proportional to the surface-to-volume ratio of the pore. A benefit of the SVF model is its ability to account for any pore topology, due to the variable being in surface to volume, and not radius, thus adding confidence to its use case in selecting materials to boost the 3γ yield.

1.3.3 Material choices

This model demonstrates a rapid increase in o-Ps lifetime over the mesoporous range, as such the following materials were chosen (with their respective average pore diameter) XAD-4 (10 nm), A800 (~ 23 nm) and XAD-1180N (40 nm) to cover well the mesoporous range, with SVF derived lifetimes roughly 70, 110 and 130 ns respectively. Note that XAD-4 was chosen to be the baseline sample for these experiments as an initial experiment by Fujimoto et al. [1] saw a $\sim 250\%$ increase 3γ yield when compared to water and using ^{18}F . Note also that the SVF fits are plotted as a function of pore radius, yet are calculated as a function of the surface to volume ratio. This plotted radius, as described in detail in the paper, is a measure of a characteristic length dependent on the general shape of the material (see the SVFs vs SVFc plots above).

XAD is a series of divinyl benzene (DVB) polymerous resins produced by Amberlite [28, 29]. Crucially XAD is a hydrophobic resin, critical for the experiential setup to ensure the pores were not filled causing any lower electron concentration rendered moot. XAD molecules possess a spherical interconnected pore structure.

A800 is a hydrophobic activated carbon derived from alginic acid. This was provided by the Department of Chemistry at the University of York to meet the demands of a hydrophobic mesoporous material. The pore size distribution is wider than that in the XAD series, as seen in Figure 1.11, however the mean pore size is 22.9 nm as such it serves as a reasonable midpoint between the 2 XAD samples.

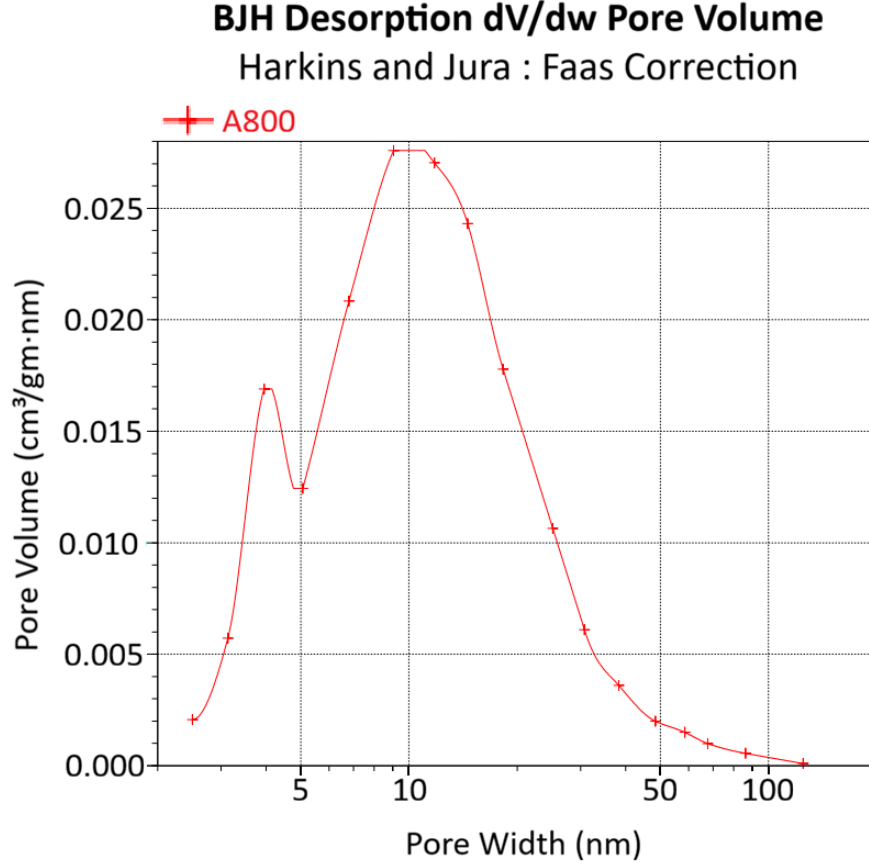


Figure 1.11: Pore volume measured at a range of pore widths throughout the A800 activated carbon sample, with a mean width of 22.9 nm.

1.4 Event-by-event spatial reconstruction from 3γ events

3γ PET offers the possibility of having directly localised, event by event reconstruction of the annihilation site. This utilises the kinematics of the 3γ annihilation: the gammas are strictly coplanar, their energies must sum to the 1022 keV of the positron-electron pair, and they must conserve the momentum. With these constraints, it is possible to calculate the annihilation vertex knowing just the energy and 3D position of the hits, both of which are available in conventional PET. This method was developed in collaboration with the University of Tokyo colleagues [1] and the work in this thesis informed enhanced event selection to achieve it.

The method is as follows. First, a plane is formed between the 3 hit positions shown in Figure 1.12 (left), with each position p_1, p_2, p_3 projected into 2D coordinates, relative to the origin, G, defined as the centroid of the positions, shown in Figure 1.12 (right). A local orthonormal basis is then constructed with basis vectors (e_1, e_2) .

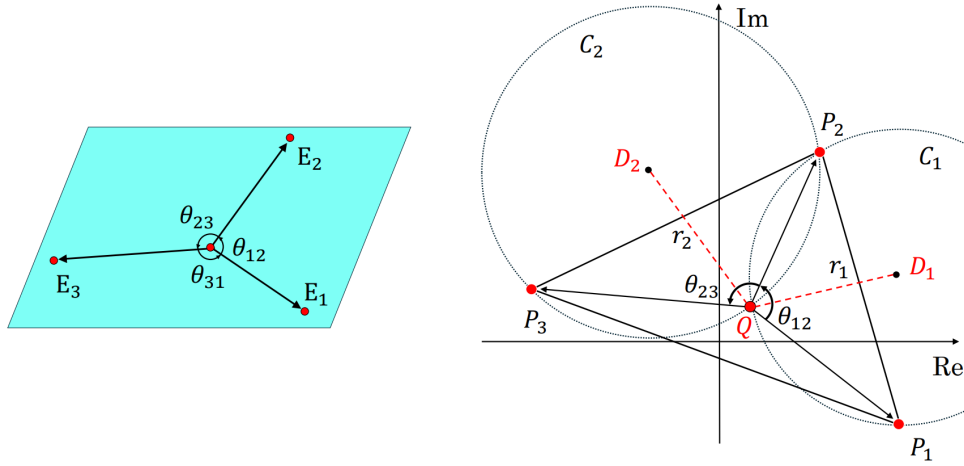


Figure 1.12: **(Left)** Schematic showing the plane of 3γ hits in real space. **(Right)** Hits mapped into the complex plane, allowing for the defining of inter-hit angles, detection points, calculated circles and annihilation vertex displayed. Figure reproduced from [1].

Using conservation of energy and momentum, the angles θ_{12} and θ_{23} , between the energy sorted gammas E_1, E_2, E_3 are given by

$$\cos \theta_{ij} = \frac{-E_i^2 - E_j^2 + E_k^2}{2E_i E_j}, \text{ for } (i, j, k) \in \{(1, 2, 3), (2, 3, 1), (3, 1, 2)\}, \quad (1.33)$$

where θ_{ij} is the angle between the gammas with E_i and E_j .

For each θ_{12} and θ_{23} , there exists a circle defined via the inscribed angle theorem such that

$$D_{1,2} = \frac{P_{1,2} - (P_{2,3} \cdot e^{-2i\theta_{12,23}})}{1 - e^{-2i\theta_{12,23}}}, \quad (1.34)$$

Where $D_{1,2}$ is the centre of the circles inscribed by $P_1 P_2 Q$ and $P_2 P_3 Q$ respectively. Thus, two circles are formed, C_1 which circumscribes $P_1 P_2 Q$ with inscribed angle θ_{12} and C_2 which circumscribes $P_2 P_3 Q$ with inscribed angle θ_{23} . These circles intersect at two points, with one always being P_2 and the other being the annihilation vertex, Q .

It is possible to express the entire system with the coupled equations:

$$r_{1,2} = |Q - D_{1,2}|, \quad (1.35)$$

where $r_{1,2}$ are the radii of circles $C_{1,2}$.

The annihilation vertex Q is then restored to a full 3D coordinate using the centroid G of the three hits and basis vectors e_1 and e_2 :

$$Q_{3D} = G + x \cdot e_1 + y \cdot e_2. \quad (1.36)$$

Finally, filters are applied to search within the specific ROI of the source dimensions. Outputs are given as 3D voxel intensity grid and an event file for further analysis.

1.5 Thesis motivation and outline

This thesis presents the first commissioning of a new 2048 element LYSO PET demonstrator system — with crystal sizes commensurate with the latest commercial PET systems. Calibration methodologies, first simulation frameworks and data analysis methods are established for the new system and will form the basis of a large future programme using the array. In the commissioning, first 3γ reconstruction and PET image formations (3γ -PET) are obtained using clinical radiotracer sources in annihilating media with a range of porosities, as well as industry standard PET clinical phantoms. The ability to enhance the 3γ yield in a realistic measurement environment through variation in annihilating media is investigated — with the aim of impacting future PET programmes investigating environmental sensitivities as well as programmes to measure the predicted (but unobserved) genuine multipartite entanglement in this 3-photon system — extending recent 2γ work by our group into new regimes [30].

Chapter 2

Experimental Methods

2.1 The LYSO array

The detector used for all analyses is a LYSO array of 2048 $3 \times 3 \times 20$ mm crystals arranged in two rectangular layers sandwiching the source plane, as shown in Figure 2.1. Each 8×8 block of LYSO crystals is wrapped in 0.2 mm of BaSO_4 and 0.03 mm Al to maximise optical photon efficiency reaching the silicon photomultiplier (SiPM) (see Figures 2.2 and 2.3). Each individual pixel has a further 0.2 - 0.36 mm layer of BaSO_4 between for the same effect.

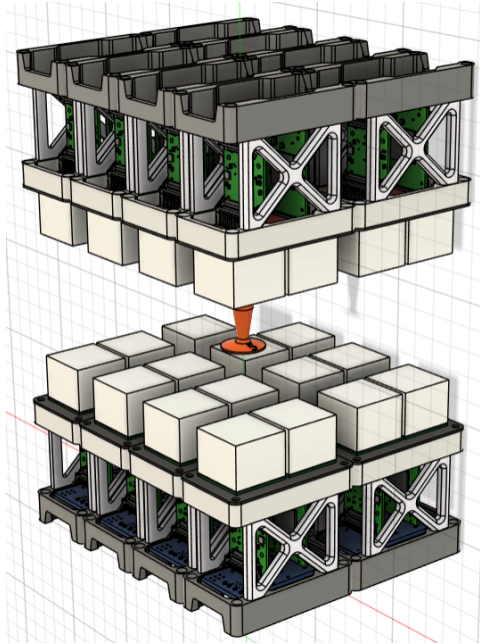


Figure 2.1: CAD orthographic view of the LYSO array, showing the location of the source holder. Each cuboid houses 64 LYSO crystals. Note the bottom grid top-right LYSO block is not present as the associated DAQ block was used for timing synchronisation pulses with the GAGG array. Also shown are the 3-D printed support frames for the crystals.

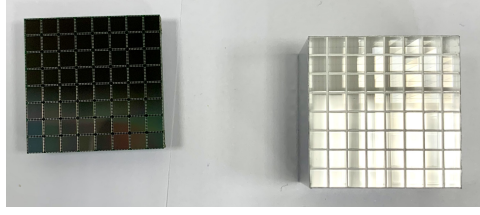


Figure 2.2: **(Left)** Hamamatsu 8×8 SiPM array. **(Right)** LYSO $3 \times 3 \times 20$ mm crystal block to which the SiPM array is attached.

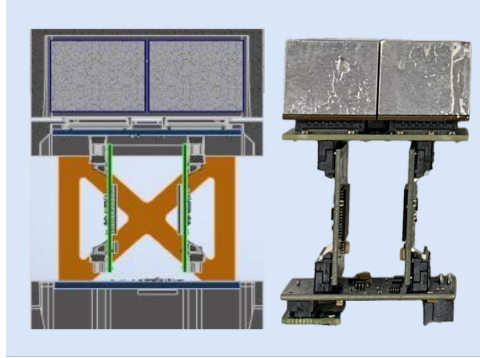


Figure 2.3: **(Left)** CAD cross-section of the PETsys front end module (FEM), housing 2 SiPM arrays both with 64 crystal blocks of LYSO. **(Right)** Reference photo, note the Aluminium wrapping described above.

This "slab" geometry was chosen to maximise the solid angle coverage when paired with a ring-shaped GAGG (Cerium-doped Gadolinium Aluminium Gallium Garnet) detector (shown in purple in Figure 2.4) which is the hardware contribution of our collaborators from the Institute of Science Tokyo and the University of Tokyo [31, 1]. The LYSO layers are separated by a distance such as to allow the fitting of the GAGG ring in-between the two layers. This both provides maximal solid angle coverage and an optimal geometry for detecting Compton scattering of photons from the GAGG scatterers into the LYSO array, with the aim of forming a polarimeter due to the polarisation dependence of Compton scattering. This capability underpins future measurements of the entanglement witness from the azimuthal correlations between the scatter directions of the 3-photons [30].

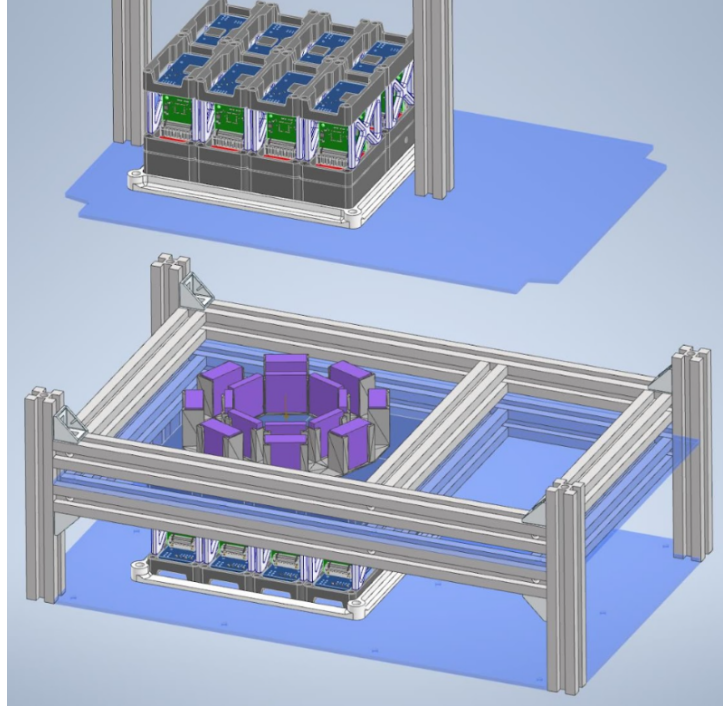


Figure 2.4: CAD model showing the integration of the LYSO array with the Tokyo GAGG array (purple). Note the upper layer of the LYSO array has been lifted to show the GAGG array.

While the inclusion of the GAGG system dictates the detector geometry, the GAGG data itself is unavailable at the time of analysis but will be included in future work. Consequently, this thesis only analyses data collected from the York LYSO array.

2.2 Detector physics: Scintillation and LYSO

2.2.1 LYSO properties

The array consists of LYSO crystals coupled to Silicon Photomultipliers (SiPMs). LYSO is the industry standard for modern PET systems due to its good light yield (30 photons/keV), high density and fast rise and decay time [32, 33].

A high density ($\sim 7.1 \text{ g cm}^{-3}$) and effective atomic number ($Z_{\text{eff}} \approx 65$) maximises the absorption efficiency and, of the absorbed photons, the photofraction. The high density also minimises the mean free path (MFP) [35], and mitigates the contribution of inter-crystal scattering (ICS). Both these parameters are also energy dependent, shown for the absorption efficiency in Figure 2.5.

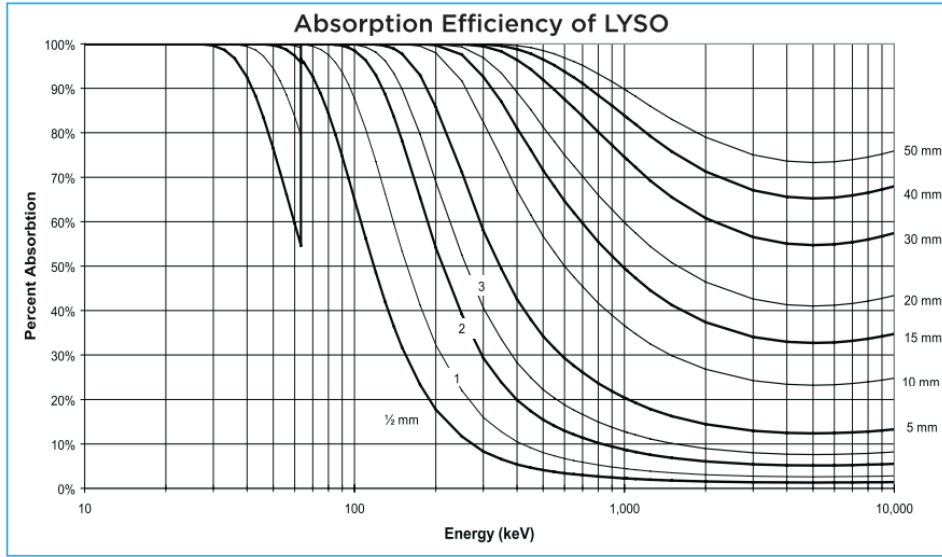


Figure 5 Gamma and X-ray absorption efficiency for various thicknesses of LYSO material.

Figure 2.5: Plot of the percentage absorption efficiency for LYSO of varying thicknesses (see labels on curves) versus the photon energy. For the 20 mm thickness, aligning with the crystal dimensions in this work, the percentage absorption is approximately 80% at 511 keV (larger for the lower typical photon energies in a 3γ event). Reproduced from [34].

3γ annihilation produces a continuous spectrum of photon energies from ~ 0 -511 keV. The photofraction (f_p) is simply the ratio of photoelectric cross-section (σ_{PE}) to the total cross section ($\sigma_{PE} + \sigma_{Compton}$):

$$f_p = \frac{\sigma_{PE}}{\sigma_{PE} + \sigma_{Compton}}. \quad (2.1)$$

σ_{PE} goes approximately with the inverse cube of energy, as such it approaches 100% for low energy photons and maintains a relatively high 32% at 511 keV. The MFP (λ), using mass attenuation coefficients (μ/ρ , where μ is the linear attenuation coefficient and ρ the density) from the NIST XCOM database for a 10 atomic % Yttrium LYSO is given by

$$\lambda = \frac{1}{\left(\frac{\mu}{\rho}\right)\rho}, \quad (2.2)$$

which ranges from <1 mm at 100 keV to ~ 12 mm at 511 keV [36]. A $3 \times 3 \times 20$ mm crystal maintains good spatial resolution whilst maintaining manageable ICS at the typical energies of a 3γ decay. It is worth remarking that at higher energies, such as the 511 keV from 2γ decays, there is a reasonable probability for the gamma(s) to scatter out of the crystal and potentially fire other detector crystals. As discussed in the analysis (Section 3.4.2) such events need to be suppressed so as not to give unwanted 3-hit backgrounds to the true 3-hit events from the 3γ yield. In dense media such as LYSO, which have short mean free

paths, such background events tend to have small separations between the first hit and the scatter-induced hit, offering enhanced prospects to suppress and study their contributions over less dense detector media.

2.2.2 Scintillation processes

One of the advantageous scintillator properties of LYSO is its light yield of $\sim 33,000$ photons/MeV [34]. For a full photoelectric (PE) absorption of a 511 keV gamma, this produces $\sim 17,000$ optical photons.

When a gamma incident on the detector medium interacts via PE absorption or Compton scattering, it imparts energy to the interacting e^- and liberates its binding in the crystal lattice. This excited and energetic e^- knocks out many further secondary e^- (and produces corresponding holes, h) as it thermalises throughout the lattice. These can in turn knock out further e^- , creating a cascade event or an electromagnetic "shower". In LYSO, the bandgap energy, $E_g \approx 6.5$ eV, meaning a 511 keV incident gamma (neglecting inefficiencies) can produce up to $\sim 31,500$ e-h pairs, given by

$$N_{e-h} = \frac{E_\gamma}{\beta E_g} = \frac{511000}{2.5 \cdot 6.5} \approx 31,500, \quad (2.3)$$

where N_{e-h} is the number of pairs produced and β is the inefficiency constant ($\beta \simeq 2.5$ in LYSO [37]). Note that from the creation of $\sim 31,500$ pairs, the quoted light yield is only $\sim 17,000$ photons, with the lost pairs being excited by lattice vibrations or other thermal processes.

Furthermore, in a typical detector configuration, not all of the scintillation light will be collected by the light sensor. The fraction detected, referred to as the light collection efficiency (LCE), is influenced by the quality of light propagation through the detector medium, the quality of the crystal surfaces in containing and reflecting light and the fraction that reach the light sensor face. Typical LCEs of $\sim 50 - 70\%$ are observed in LYSO crystals similar to the geometry here, so a typical final photon flux for a 511 keV incident on a LYSO is $\sim 8000-11000$ photons.

The LYSO crystal itself possesses a complex lattice structure, being composed of four elements. The band structure between the primarily Oxygen comprised valence band and primarily Lutetium comprised conduction band possesses a poor overlap of electron initial and final states. Recombination of excited electron - hole pairs ($e-h$) is thus highly unlikely and the decay time is very long, ~ 300 ns. A long decay time will blur timing and energy resolution of the next gamma hit. To counteract this for use in PET, LYSO is doped with Cerium (Ce^{3+}) ions (with concentrations on the order of $\sim 0.001-0.1$ atomic % [38]). Cerium doping also pushes the light yield close to the maximum attainable for scintillators with an inefficiency constant, β , of ~ 2.5 , which is the case for LYSO. This is shown in Figure 2.6, where the line

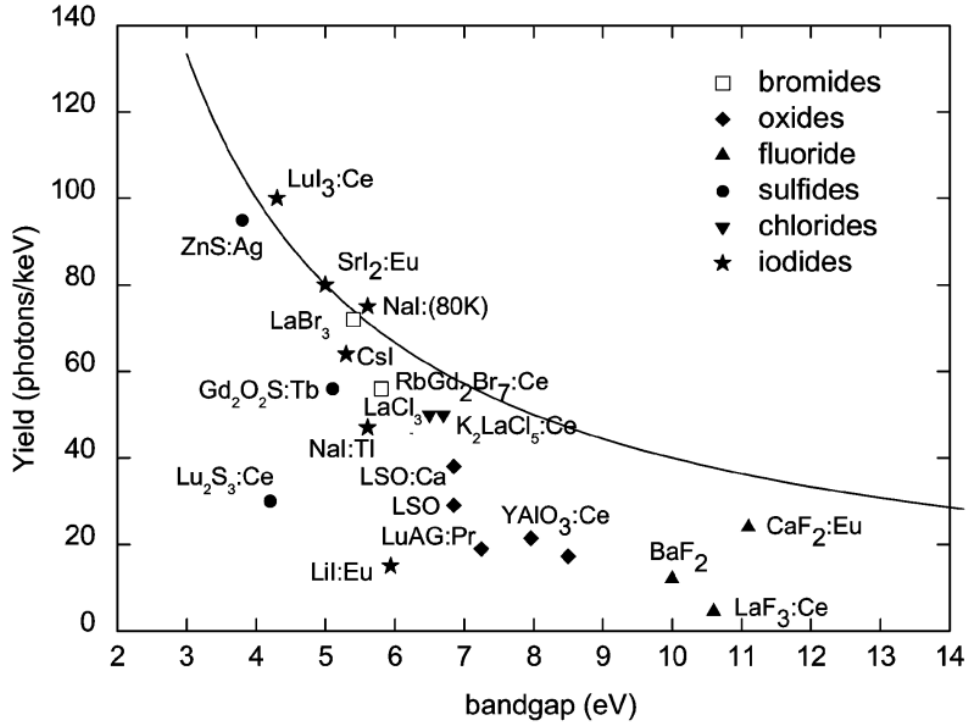


Figure 2.6: The scintillation yield as a function of bandgap (eV), for various inorganic scintillator crystals. The curve represents the maximum attainable yield assuming an inefficiency constant, β , of 2.5. Note the Ce doped compounds lie close to this line (see text). Reproduced from [37].

represents the maximum attainable yield assuming a β of 2.5, with many Ce doped scintillators close to this line.

The Ce ions are too sparsely populated to form band structures and possess an intrinsic transition, from its $5d \rightarrow 4f$ shell, that lies within the band gap of the LYSO. Thus, long living (~ 300 ns) e–h pairs in the conduction and valance bands of the LYSO will readily recombine through this intrinsic transition of the Ce ions. This produces a ~ 420 nm optical photon, aligning with the engineered peak photon detection efficiency (PDE) of the SiPM, shown in the dark and light blue lines in Figure 2.7. Furthermore, these intrinsic recombinations have a very short decay time of ~ 36 ps, improving both timing and energy resolution by reducing pulse pile-up (leftover decays from a previous hit still present in the crystal when the next hit arrives, falsely adding to that hit’s signal) [34].

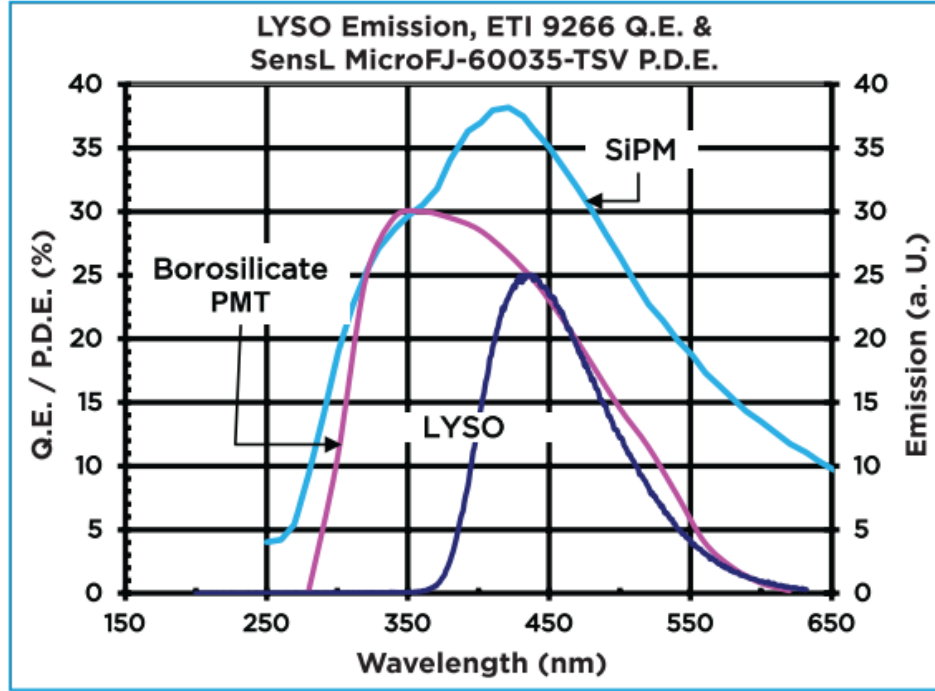


Figure 2.7: LYSO emission spectrum (dark blue line) with a peak at ~ 420 nm and a peak in SiPM photon detection efficiency (PDE) at a similar wavelength. Note that the PETsys system used in this experiment has a quoted PDE of 45% at 420 nm. Reproduced from [34].

2.3 Overview of the data acquisition

2.3.1 SiPM characteristics and detection signals

After the optical photons are produced in the LYSO crystal, they are directed towards the SiPM. The LYSO crystals are coated in optically reflective BaSO_4 , which aids the containment of the scintillation photons within the crystal volume such that they are most likely to leave the LYSO via the SiPM. Each SiPM contains 14,400 single photon avalanche diodes (SPADs) [39]. For a 511 keV photon, $\sim 8,000$ -11,000 optical photons reach the SiPM, thus, each photon generally fires its own SPAD. When an optical photon hits a Si atom in the SPAD it produces an e-h pair, this pair is then accelerated across the SPAD via a bias voltage ($V_{\text{bias}} = V_{\text{br}} + V_{\text{ov}}$). This is a sum of the breakdown voltage, V_{br} — which is the minimum voltage needed for a single e-h pair for impact ionisation to become sustaining and start a detectable avalanche — and an applied over-voltage, V_{ov} , used to increase the electric field further such that the initial e-h pair created gains enough energy to readily trigger the avalanche. The ensuing electron avalanche produces on the order of $\sim 10^5 - 10^6$ electrons as a current. This signal is then analysed in an ASIC.

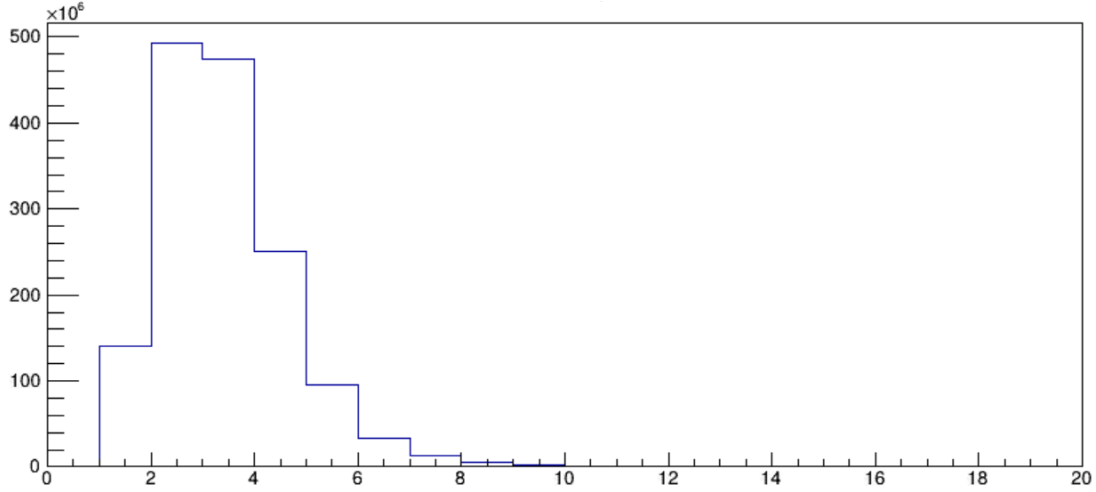


Figure 2.8: Number of hits per coincidence timing event window (20 ns) in the raw data files.

2.3.2 ASIC time and energy measurement

The PETsys application-specific integrated circuit (ASIC) takes the SiPM signal and measures the hit time and the integrated charge of the current in the signal. To measure the timing to high precision, the time when the leading edge of the current pulse crosses the low Leading Edge Discriminator (LED) voltage threshold is recorded. To measure energy, the current is fed into a capacitor over a set time window and the voltage gain of the capacitor is determined. The timing window is set to minimise the long trailing edge of the current to mitigate pile up from subsequent events. As the pulse shape is consistent (based on the SiPM properties) small effects from missing trailing edges will be remedied from calibration to known photon energy sources. The output is a charge-to-digital converted value (QDC), which is the integral of the measured current collected in the set timing window. These QDC values can be calibrated to energy (keV) by fitting the location of photopeaks from radioactive sources (of known energies) in QDC units.

For the data analysed in this thesis the data collection was run in "coincidence timing" mode. In this mode, an initial hit starts a timing coincidence window of 20 ns and events from all detectors in the array were recorded for all subsequent hits in this window. The distribution of hits within this timing window is displayed in Figure 2.8. Operation in coincidence mode drastically decreases the data rate by filtering out a large fraction of events arising from SiPM noise or intrinsic radioactivity in the LYSO crystals.

2.3.3 Timing resolution of the system

The Coincidence Timing Resolution (CTR) of the system is the precision to which the hit times of a given coincident event can be determined. The scintillation processes described above contribute to the timing resolution as a product of the optical photon rise time — how fast they are produced — and the light yield/optical photon efficiency in reaching the SiPM.

Once the optical photons have reached the SiPM, the timing resolution of the signals is governed by three main properties: the single photon timing resolution, SPTR, the intrinsic timing uncertainty of the individual SiPM cells; the photon detection efficiency, PDE, where the amount of photons detected change the pulse height and thus the time it takes to cross the threshold to be recorded as a hit; and the dark count rate, DCR, which introduces background thermal and electronic noise that falsely adds to the baseline on which the real pulse is measured.

Finally, the precision of the digital timestamp is constrained by the LED threshold level and the discrete bin size of the Time-to-Digital Converter (TDC). The LED threshold is the voltage required to record a hit and thus its timestamp. The timing uncertainty of the LED is dictated by the dV/dt of the produced current across it, where a faster rise in voltage allows for higher precision. Electronic noise adds to the time uncertainty at which the threshold is crossed. The timing precision of the TDC relates to its achievable timing bin width (30 ps for the PETsys TOFPET2 system used in this experiment [40]).

The PETsys TOFPET2 system quotes an SiPM single photon timing resolution SPTR sigma of 98 ps (Figure 2.9), photon detection efficiency (PDE) of 45% at 420 nm and a dark count rate (DCR) of $\sim 50^5$ cps at the lowest DAC threshold (Figure 2.10) [40]. The overall CTR is quoted as 183 ps (Figure 2.11).

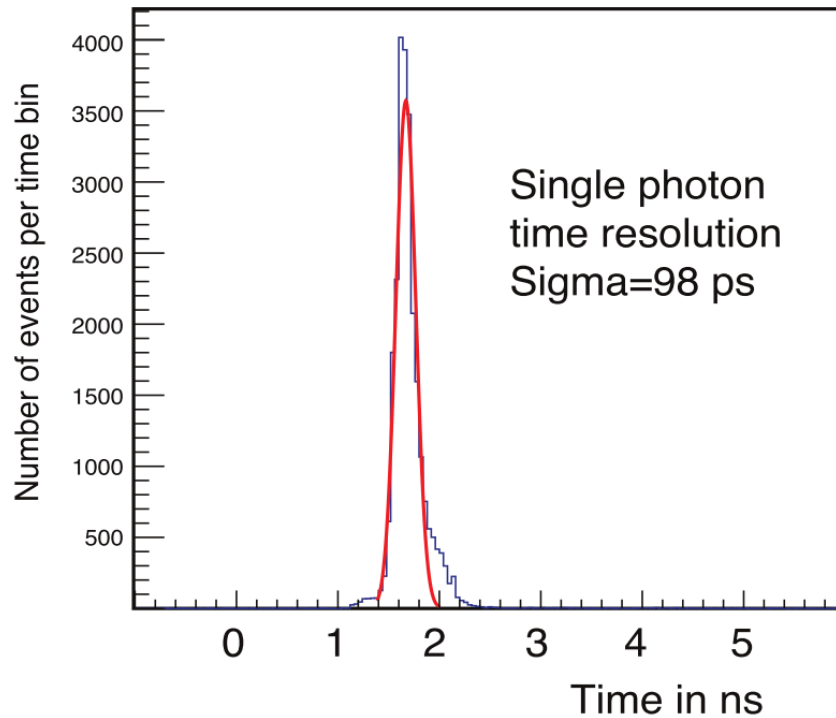


Figure 2.9: Time distribution histogram showing a PETsys ASIC single photon timing resolution (SPTR). The data exhibits a sharp peak, which has been fitted to give a quoted SPTR of 98 ps. Measurements were performed by PETsys using a PLP-10 picosecond light pulser and S13361-3050AE-04 MPPC SiPM, both from Hamamatsu, at 7.5 V over-voltage and 20°C. Reproduced from [40].

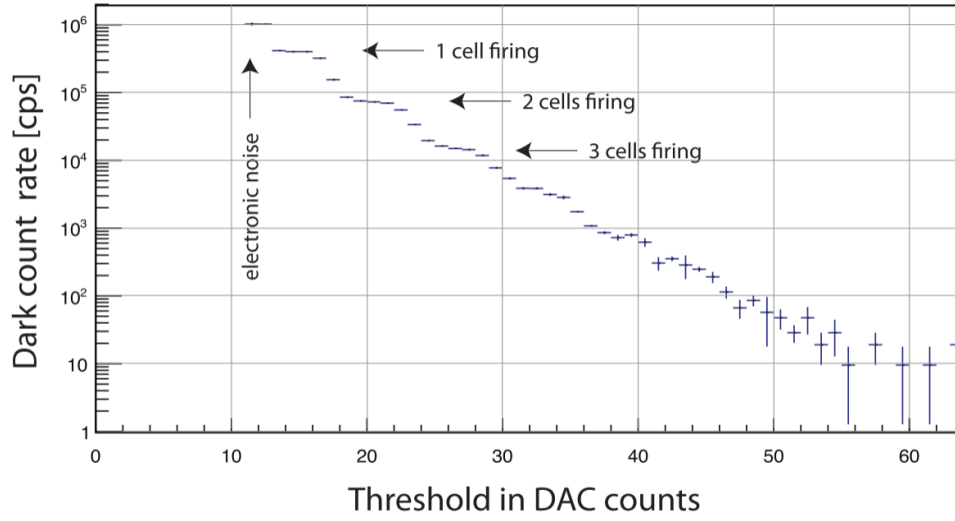


Figure 2.10: Dark count rate (DCR) as a function of threshold DAC setting. As the threshold rises, the DCR drops exponentially. Measurement quoted from PETsys with a KETEK-PM3325-WB SiPM at 4 V over-voltage and at 20° C. Reproduced from [40].

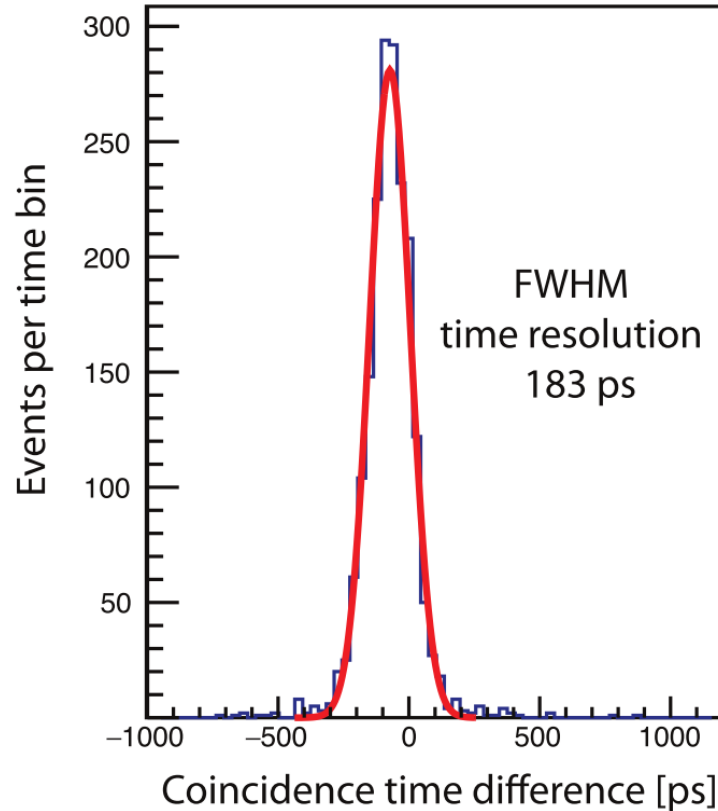


Figure 2.11: Coincidence Timing Resolution (CTR) measured with a ^{22}Na point source and two Hamamatsu S13361-3050AE-04 SiPM arrays. This SiPM array has pixels measuring 3×3 mm with $50 \mu\text{m}$ cells. CTR measured with two $3 \times 3 \times 20$ mm³ LYSO crystals at 15°C, 4V over-voltage. Reproduced from [40].

2.4 Overview of the commissioning experiment at King’s College London

To measure 3γ -PET and the quantum entanglement witness in QE-PET with industry standard PET radiotracers, a series of experiments were run at King’s College London’s Nuclear Imaging research laboratory at St. Thomas’ Hospital. This facilitated the use of ^{18}F -NaF, actively analogous to ^{18}F -FDG, of which this would be the first measurement of genuine tripartite quantum entanglement in a standard PET detector system with standard detection methodologies (LYSO) and standard radiotracers (^{18}F). Furthermore, due to the use of a liquid radiotracer (^{18}F -NaF is held in solution with water) this allowed for the measurement of the effects of a porous bulk material mixed with the radiotracer solution, mimicking potential biological mediums and providing initial measurements that could utilise 3γ effects for clinical diagnosis.

2.4.1 ^{18}F run specs

As discussed above, the mesoporous materials were chosen to provide a range of data points over which the o-Ps lifetime and thus $3/2\gamma$ ratio was believed to increase greatly over.

As part of the broader study, four runs were completed using these materials, one for each of XAD-4, XAD-1180N and A800 and an ^{18}F control. Note that due to time constraints, these runs differ in length. The specification of each run is shown in Table 2.1.

The experiment utilises residual ^{18}F produced for use at St Thomas’ Hospital, and as such supplies were limited, this combined with the ^{18}F half-life of ~ 110 mins meant the activity change was accounted for with more volume of source. All data has been normalised to mitigate this.

Run	Activity (MBq)	Activity measured to run start time (mins)	Material mass (mg)	Total Volume (μL)	Run time (mins)
^{18}F Control	9.18 1523	3	n/a	70	30
XAD-4	11.56	22	20.0	40	90
A800	10.40 1614	8	13.0	413	30
XAD-1180N	10.10 1331	12	20.3	40	90

Table 2.1: ^{18}F run specifications

2.4.2 Source preparation

As discussed above, all mesoporous materials used are required to be hydrophobic, the XAD-series are spherical beads of average diameter ~ 0.67 mm, the average diameter of A800 is not known. The Eppendorfs used to hold the source (see Figure 2.12) were thus first filled with a reasonable volume of material, such that the empty space could then be filled with the source solution. As shown in Table 2.1, these volumes vary to maintain source activity as the ^{18}F decays.

It was noticed once the sources were prepared that both the XAD-4/1180N fell out of solution, however due to the large negative volume between the beads in each of these materials, it was deemed that they were still adequately surrounded by source solution.

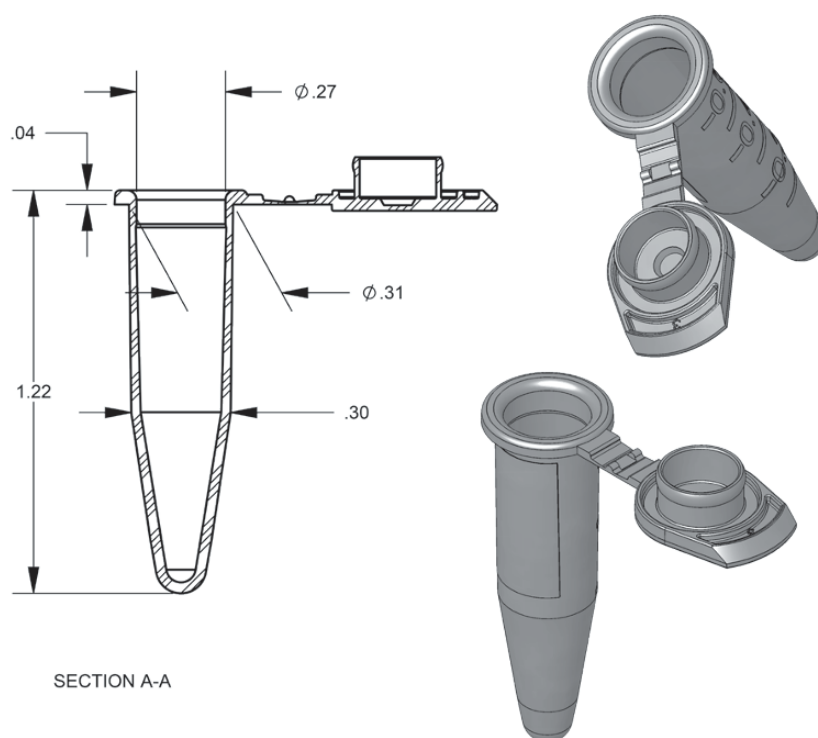


Figure 2.12: Technical Data Sheet of the source holder used in all runs. Note the volume filled is dependent on the volumes needed as tabled above to maintain activity levels.

Chapter 3

Calibration methodologies, data analysis and simulation

In this section the methods developed to calibrate the LYSO array in energy, time, and temperature, as well as the methodologies to analyse and reconstruct the 3γ yields, are outlined. Crucial to validating and checking these methodologies is a simulation of the detector response to 3γ and other events, obtained in Geant4.

3.1 Geant4

GEANT4 (Geometry and Tracking 4) is a powerful open-source software toolkit used for simulating the interaction of particles with matter, widely applied in fields such as high-energy physics, medical physics, and space science. Developed by an international collaboration, it enables researchers to model complex detector geometries, define materials, and track particles as they propagate and interact through different media using advanced Monte Carlo methods. The model includes the key physics processes relevant to the photon energies of our study viz. photoabsorption, Compton scattering and even the very small contributions of Rayleigh (atomic) scattering. For the (relatively) low energies of the gamma photons here the physics is encompassed in the `G4EMStandardPhysics_option4` constructor.

The LYSO crystal geometry of our PET demonstrator array was implemented into GEANT4. Figure 3.1 shows the tracks from simulation of a single 3γ event in GEANT4. Note that the current version of the simulation models the LYSO crystals only, and neglects the holding structures. Future work will enable a more detailed simulation - but this was beyond the scope of the current thesis. The current

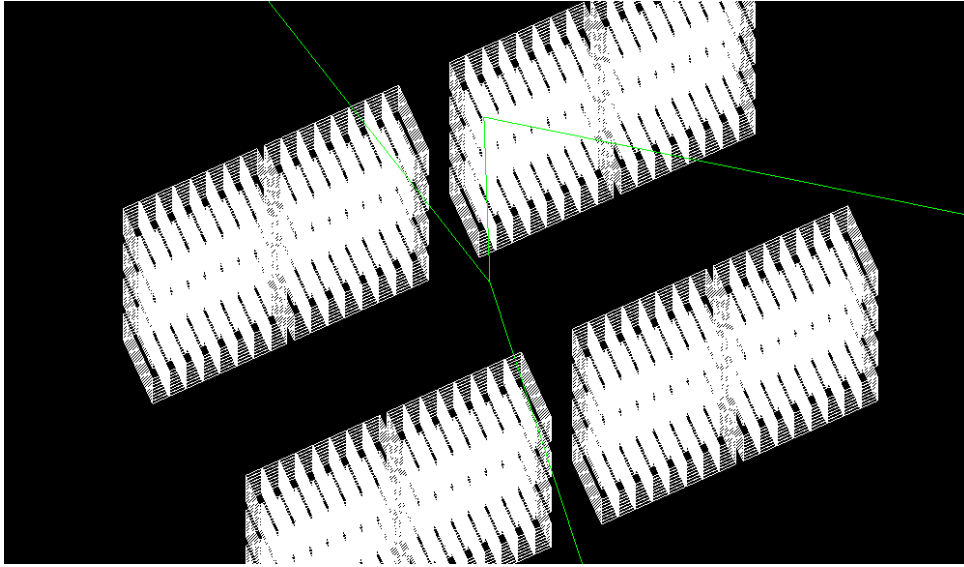


Figure 3.1: Visualisation of Geant4 LYSO geometry (white blocks) with one 3γ event generated from the point source (green lines).

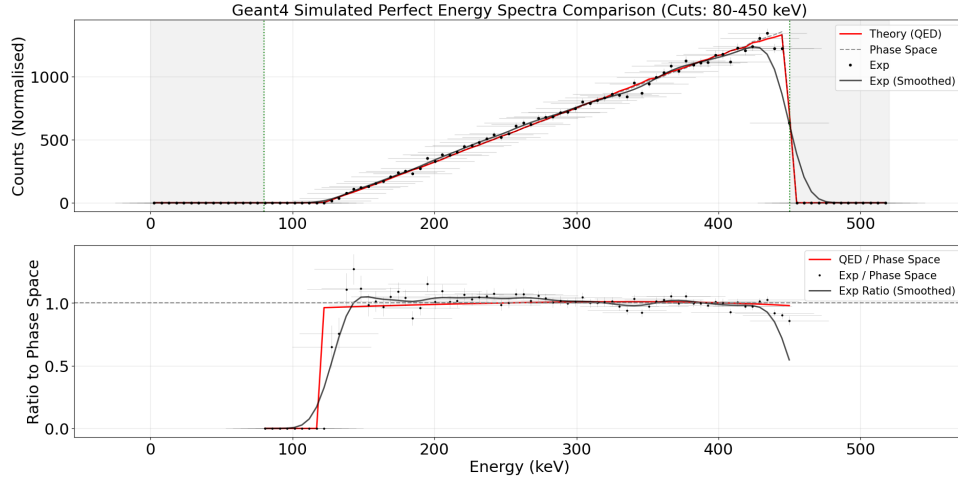
implementation utilises a point source, which was sufficient for this first commissioning study. Future work would implement detailed simulation of the target holding vessels and is in progress.

3.1.1 Simulated pseudo-data

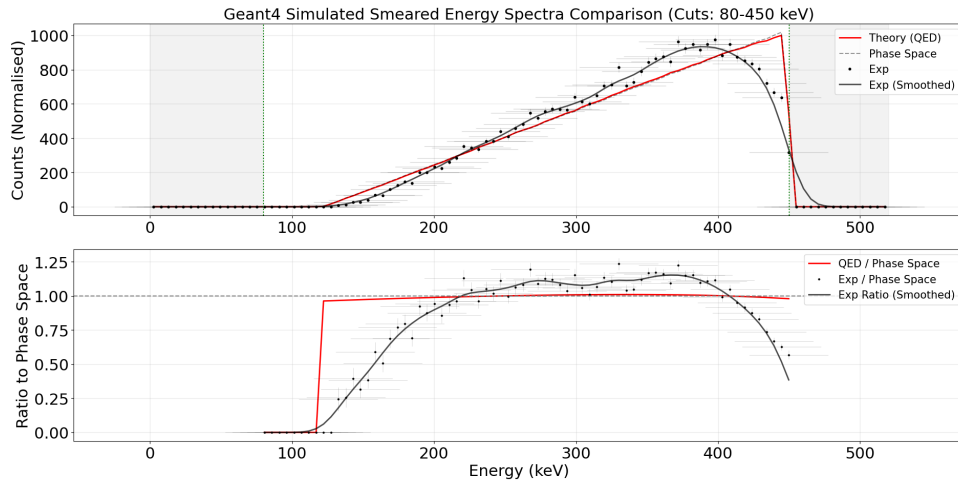
The Geant4 software predicts the energy and timing deposits from photon hits in the LYSO array. These are predicted with exact energies and timing - which is not the case for a realistic detector system. To allow direct comparison with experimental data the GEANT4 predicted energy deposits are smeared with a Gaussian of width matching that of the experimental detector. The timing of the individual hits are similarly smeared according to the experimentally observed resolution.

Figure 3.2 plots the cumulative single-photon energy distribution of both the smeared and non-smeared data produced by the simulation. The red line plotted with the data is the theoretical distribution, known as the Ore-Powell distribution [21], over this energy range. This distribution is used throughout the results to provide a comparison to the ideal case for each dataset. The smeared simulation data is also shown alongside the results (Figures 4.10 – 4.13) as a reference to the ideal expected results when accounting for the detector's solid angle, as well as energy and time resolutions.

The smeared simulation produces pseudo-data, giving energy and timing information for the hits based on crystal number, energy deposited and timing. This pseudo-data is produced in identical format to the experimental data - and can be analysed through the same data analysis pipeline discussed in the sections below to motivate selection cuts for maximising the signal-to-noise ratio (SNR).



(a) **(Top)** Perfect energy data. **(Bottom)** Ratio of the experimental distribution to the theoretical phase-space.



(b) **(Top)** Energy smeared data, using a single-hit energy FWHM of 66 keV at 511 keV and a timing FWHM of 0.7 ns. **(Bottom)** Ratio of the experimental distribution to the theoretical phase-space.

Figure 3.2: Geant4 simulated single-photon energy distributions for true 3γ events (black data points) plotted against the Ore-Powell theoretical distribution (red lines) [21]. **(a)** Shows the distribution for perfect energy resolution. **(b)** Shows the distribution with experimental energy resolutions added. For each, both the normalised counts and the ratio to the theoretical phase-space are plotted. The perfect energy data closely agrees with the theory. While the smearing of the energy has a noticeable effect on this, the agreement is still strong.

3.2 Data analysis pipeline

In this section the pipeline from the measured data (QDC and TDC channels) to calibrated energies (keV) and timing (ns) is outlined. The methodologies to select the 3γ (and 2γ) yields from the calibrated data are also outlined.

To generate reconstructed 2 and 3 photon events from raw QDC data, a set of calibrations and filters were applied to each dataset, the process of which is documented below. The statistical minority of the 3γ events compared to the 2γ and any 2γ scattering or coincident events that make up most of PET data, is such that selective filtering on energy, timing, event logic and spatial and angular reconstruction is necessary.

A pipeline is used that converts the digital detector signal in QDC value into keV valued hits, then applies a series of temperature and timing calibrations to produce calibrated energy and timing data. These event files are then passed into processing scripts that apply physically motivated filters, selection cuts and reconstruction algorithms.

3.3 Detector calibrations

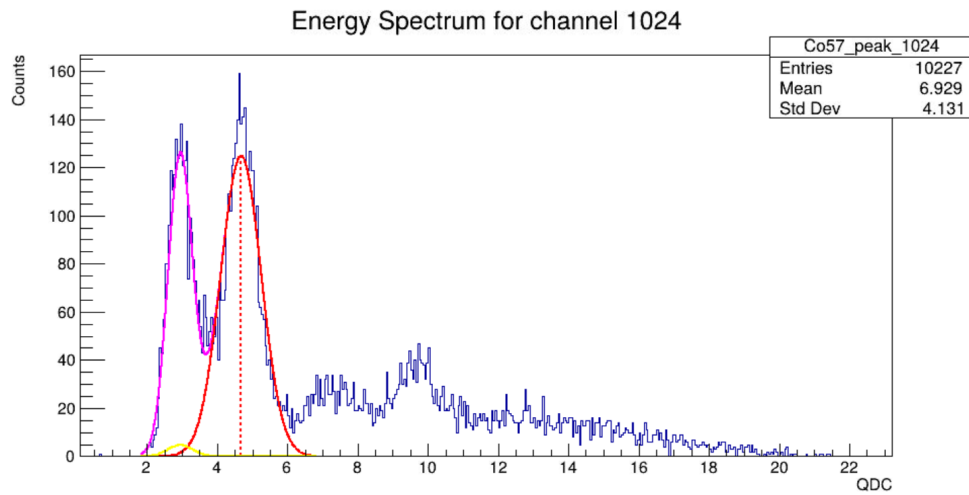
There are four calibrations applied sequentially to the data across a 7-script C++ workflow: QDC to keV conversion $\rightarrow$ run specific base timing 511 keV photopeak and temperature drift rescaling $\rightarrow$ LYSO/SiPM + ASIC leading-edge discriminator, energy-dependent timing correction $\Rightarrow$ (in iteration with) pixel-pixel base offset correction.

3.3.1 Energy calibrations

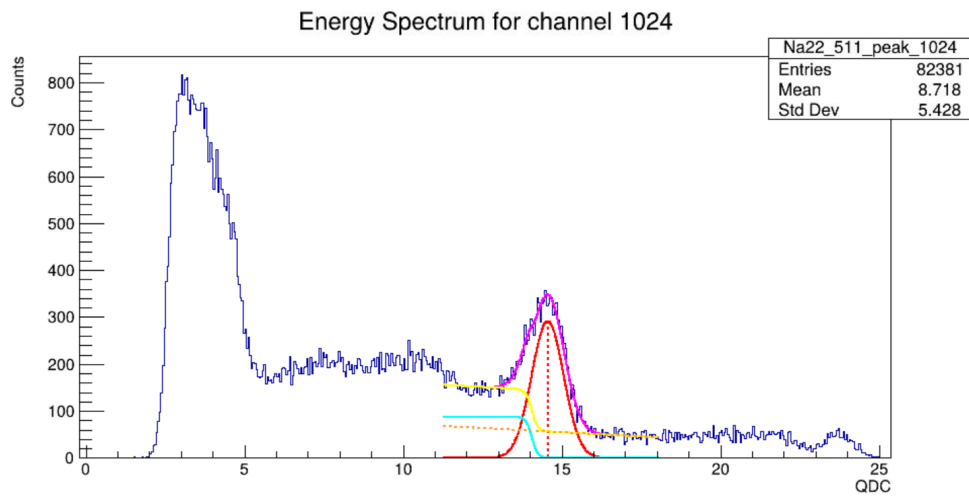
The data acquisition system outputs the area of the current pulses in QDC channels. This needs to be converted to energy (keV). The calibration is achieved by observing the photopeak locations (in QDC channels) of a range of laboratory sources with known energies - ^{57}Co , ^{22}Na and ^{137}Cs sources. The self-activity peaks of the ^{176}Lu in the LYSO crystals are also employed. In combination this gives calibration points at 122, 202, 307, 511, 662, 1275 keV. The relationship between QDC channel and energy is non-linear. To account for this, a four-parameter polynomial function provided by PETsys is used [41]:

$$E_{\text{keV}} = p0 \cdot p1 Q_{\text{QDC}}^{p2} + p3 \cdot Q_{\text{QDC}} - p0. \quad (3.1)$$

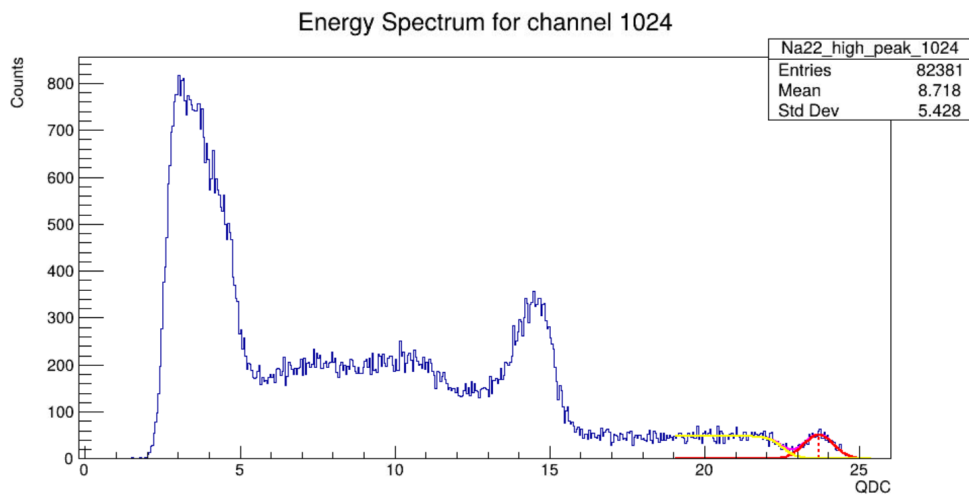
The script itself fits Gaussians to the 122, 202, 307, 511, 662 and 1275 photopeaks for each channel as shown in Figures 3.3a-e. These QDC values are plotted against the known energies and fitted using equation 3.1 in Figure 3.3f. The output is a .csv file containing the variables p0, p1, p2 and p3 for each channel. This .csv is then called by the second script, which applies them to any raw data file provided.



(a) ^{57}Co QDC spectrum (122 keV peak)

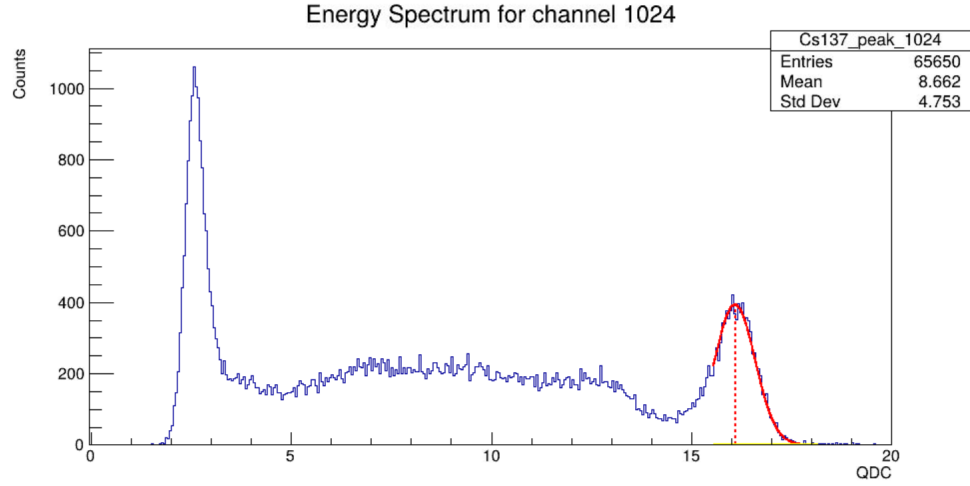


(b) ^{22}Na QDC spectrum (511 keV peak)

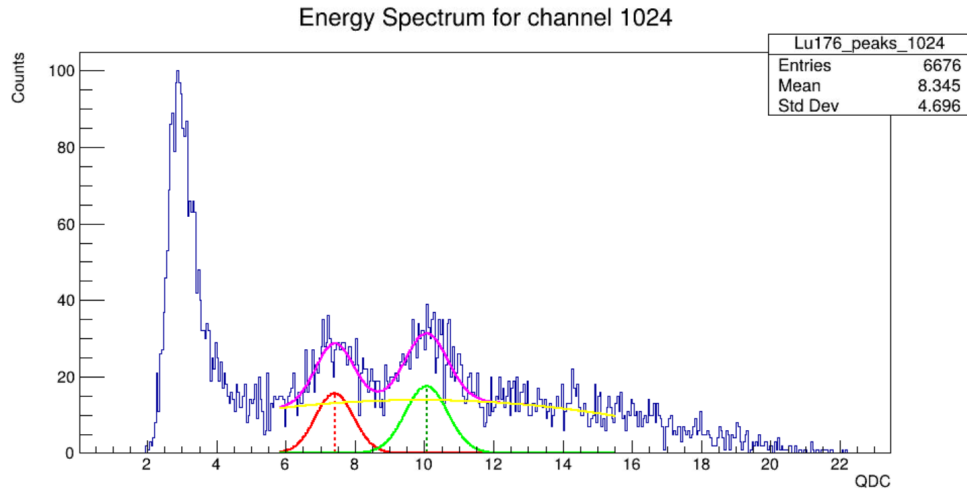


(c) ^{22}Na QDC spectrum (1275 keV peak)

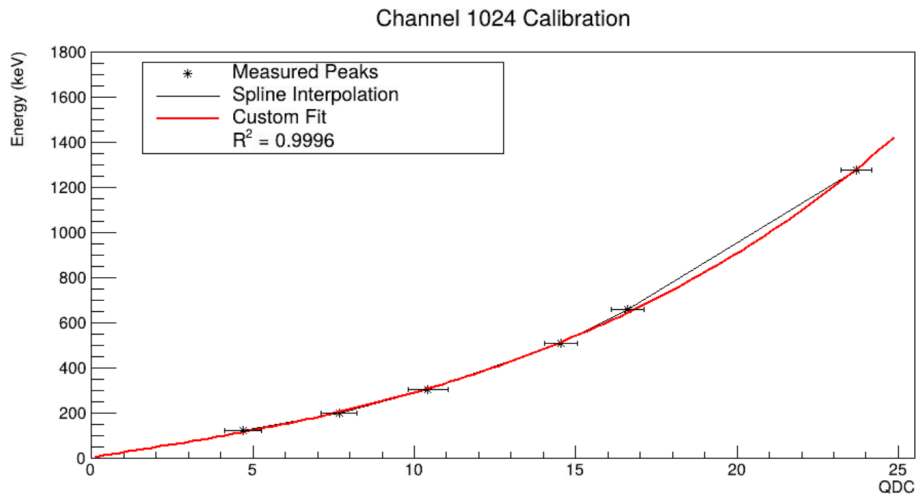
Figure 3.3: Energy calibration plots (part 1 of 2). (a)-(c) Integrated charge (QDC) values for the ^{57}Co (122), ^{22}Na (511) and ^{22}Na (1275) calibration peaks. Each peak is fitted and peak centroids determined for every channel (channel 1024 shown).



(d) ^{137}Cs QDC spectrum (662 keV peak)



(e) ^{176}Lu QDC spectrum (202 keV and 307 keV peaks)



(f) QDC to keV calibration fit for channel 1024.

Figure 3.3: Energy calibration plots (continued). (d)-(e) Integrated charge (QDC) values for the ^{137}Cs (662) and ^{176}Lu (202, 307) calibration peaks. (f) The above QDC centroids plotted against their known energies in keV. A four-parameter polynomial (equation 3.1) is fitted to extract calibration coefficients (red line).

3.3.2 Temperature dependence of the LYSO energy calibration

The parametrised QDC to keV calibration curves for the different laboratory sources provides a channel-by-channel determination of the shape of the dependence of energy with QDC channel. Although giving an absolute calibration at the temperature at which the source data was obtained, in general the temperature of the apparatus may vary and changes in the absolute calibration need to be taken into account. The apparatus included temperature sensors so these variations can be recorded. The run-by-run absolute energy calibration is done by fitting the 511 keV peak — which will have moved an unspecified amount — at the start of each data run (using the first 10 minutes of data recording), and generating a scalar to move the peak back to 511 keV, as shown in Figure 3.4. In addition a temperature drift script fits the position of the peak for every ± 5 mins block around each temperature recording throughout the run. This generates an additional scalar for each 10 minute block that further corrects for any drift in this time period, allowing for continuous temperature calibration across the run.

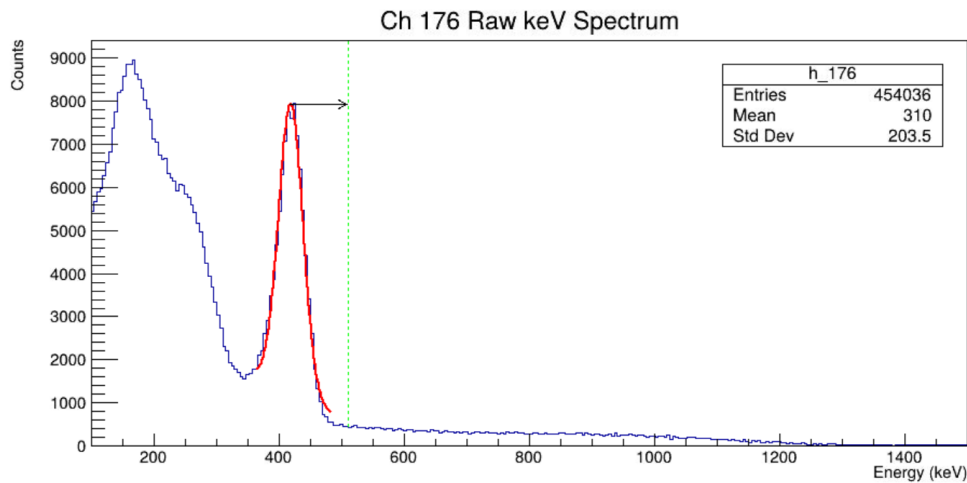
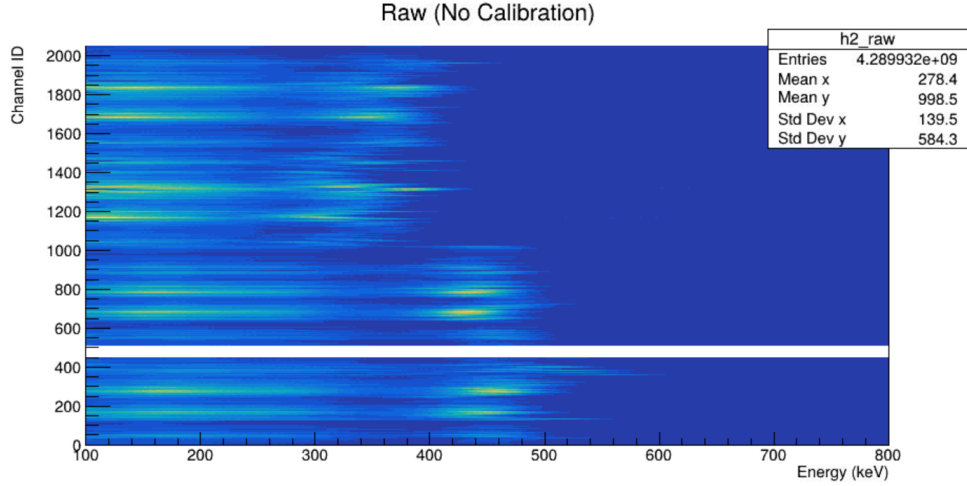
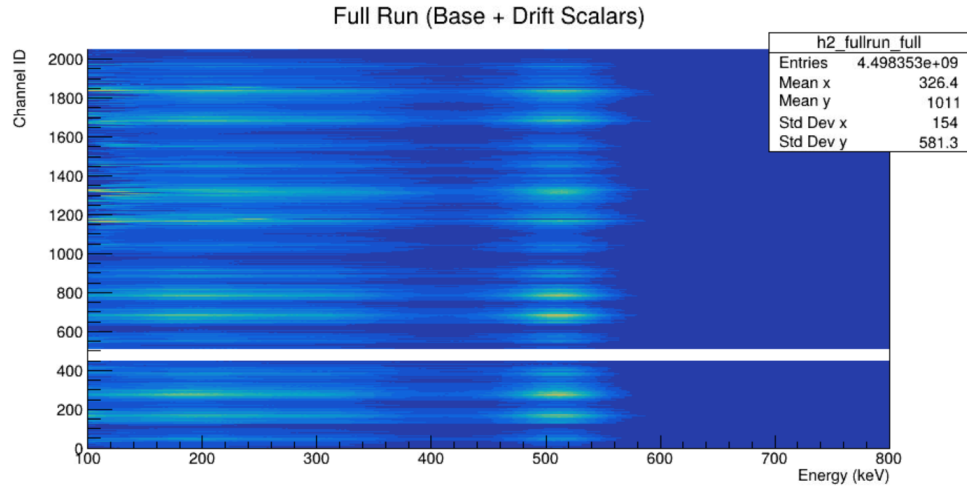


Figure 3.4: Raw energy spectrum of the first 10 mins of data in channel 176, note the 511 keV photopeak is around 400 keV, as such a scalar is used to scale it back to 511 keV (dashed green line).



(a) Uncalibrated 2D energy histogram for every channel.



(b) Calibrated 2D energy histogram for every channel. Note the now aligned photopeaks.

Figure 3.5: 2D energy spectra (for ^{22}Na data) across all channels showing the effect of temperature on calibration. **(a)** Uncalibrated spectra showing significant drift across channels. Note the 511 keV photopeak is the right most intensity spike in colour. **(b)** Spectra with temperature calibration scalars applied, showing the 511 keV photopeak perfectly distributed around 511 keV for every channel.

Figure 3.5a shows a 2D plot of channel ID versus energy (keV) for uncalibrated data and fig. 3.5b for data calibrated for these temperature induced drifts. Note, different parts of the array can have significant variations in temperature due to system electronics locations.

3.3.3 Timing calibrations

The timing of the signals (in TDC channels) needs to be converted to absolute time (ns). This section outlines the procedures used to achieve this. Note that it is required to have fully energy calibrated data for these calibrations as both the timing offset and time walk calibration have energy dependent effects.

There are two major contributors to timing error in the system, channel-to-channel offsets, and per channel time walk. Channel-to-channel offsets are the direct time offset caused by hardware effects such as different cable lengths and resistances and DAQ data processing time. The channel-to-channel variations were ~ 0.5 to 2 ns.

Time walk reflects how the timing of the crystal hit is determined when the signal exceeds a discriminator threshold. Large amplitude signals reach this threshold more quickly (and with steeper dV/dt) than lower amplitude signals, even if the true timing is identical. This effect is on the order of ~ 2 ns at its greatest, occurring between hits at the extremes of the energy window (80 keV and 511 keV).

The overall timing correction applied to the raw hit time (T_{raw}) to determine the true hit time ($T_{\text{corrected}}$) is given by:

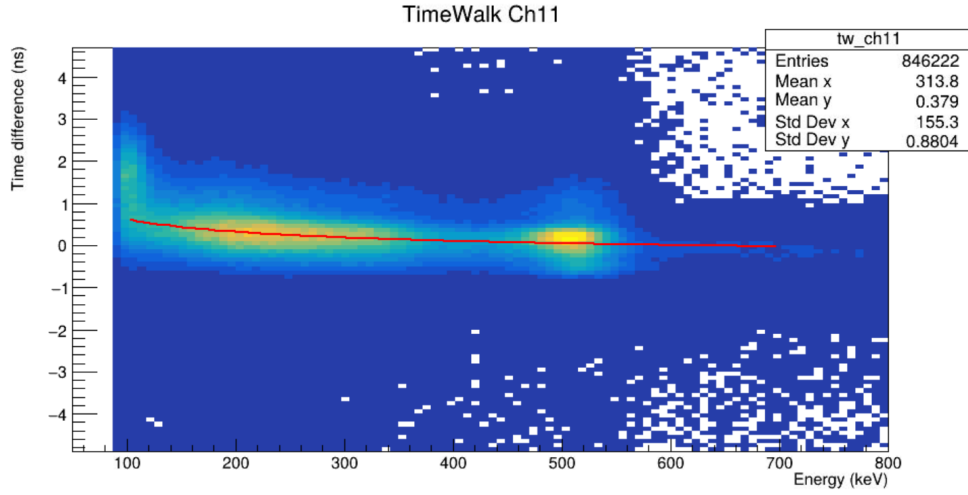
$$T_{\text{corrected}} = T_{\text{raw}} - \text{offset} - r \left(\sqrt{\frac{a_0}{E}} - \sqrt{\frac{a_0}{511}} \right), \quad (3.2)$$

where E is energy, a_0 is the hardware threshold energy, offset is the channel-specific timing offset, and r is the channel-specific rise time scaling constant used to correct for time walk.

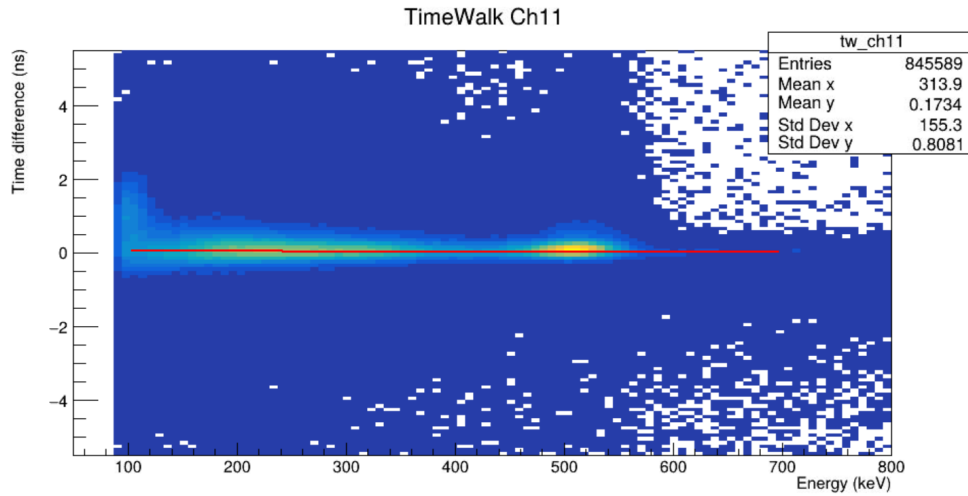
Time walk correction

The time walk calibration isolates the r parameter by using coincident events between a 511 keV (or prompt gamma) and a partner hit within a broad timing window of 6 ns. These partner hits are allowed to be any energy within 80-650 keV (covering the entire 511 scattering range down to the noise threshold and allowing for a broad 511 peak). For any event satisfying this logic the partner hit is saved for its detector channel. For each partner channel a 2D histogram of energy vs hit time is obtained. An example is shown in Figure 3.6a, where the drift in timing with the energy is clearly observed.

To correct this effect, a Gaussian fitting function to the timing in each energy bin of this histogram is obtained. The centroid of this peak position for each energy is fitted such that the curvature of the time walk is modelled, updating the r value to flatten the curvature.



(a) Uncalibrated hit times as a function of energy.



(b) Calibrated hits times as a function of energy after 15 iterations.

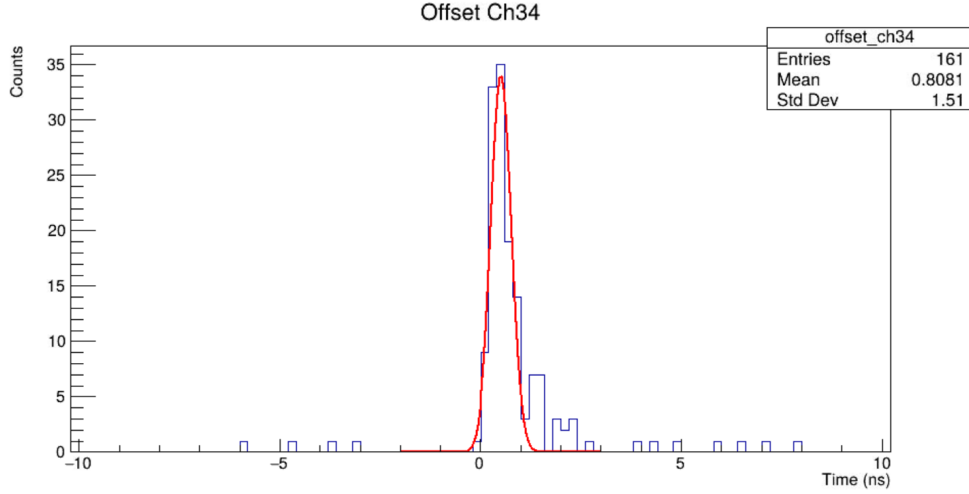
Figure 3.6: 2D histograms of hit energy versus time difference to the initial hit in the event (for ^{22}Na data), showing the effect of time walk before and after correction. **(a)** Uncalibrated data showing a ~ 1 ns delay between the 511 keV peak and 100 keV hits. **(b)** The same channel after 15 iterations, showing a flattened curve across the entire energy range.

Timing offset correction

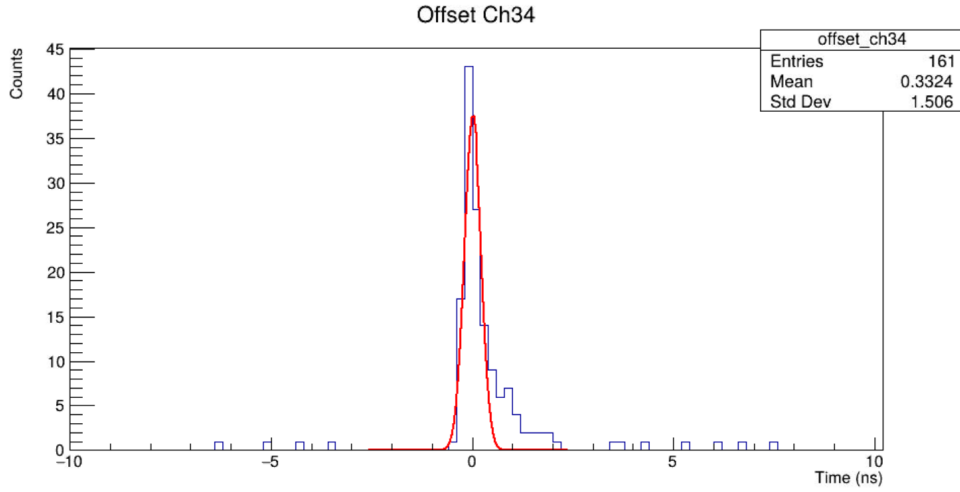
Simultaneously, the base channel-to-channel offsets are determined by fitting 1D timing histograms for each channel against a global reference channel. A standard channel was taken against which all other channels are synchronised. Channel 176 was chosen as it is one of the closest pixels to the source, and thus will have the highest statistics and lowest time difference between the event and detection.

To detect gammas across the detector geometry and calibrate every channel, it was decided to select only prompt gammas in this reference crystal - which are emitted isotropically with respect to the 511 keV yields, such that partner 511 hits can be measured throughout the detector.

If any 511 keV (>450 keV) hit is detected in any channel within ± 50 ns of a reference hit >650 keV (thus only allowing prompt gammas) in channel 176, the hit and its timing difference to the reference hit is recorded. Example 1D histograms fitting this observable are shown in Figure 3.7. The resulting peak in each channel is fitted with a Gaussian and an offset to align all the channels is produced.



(a) Uncalibrated timing offset hits relative to the reference channel.



(b) Calibrated timing offset after 10 iterations.

Figure 3.7: 1D histograms showing the distribution of time offsets between prompt gamma hits in an example channel (34) and 511 keV partner hits in the reference channel (176). **(a)** Uncalibrated distribution, showing a peak ~ 0.8 ns late. **(b)** The same distribution having converged after 10 iterations, showing a significantly reduced offset of ~ 0.3 ns.

3.3.4 Iterations

As the timing is influenced by a number of factors (offsets and time-walk) and as the reference crystal itself is affected by the calibration - the calibration is required to optimise both correction parameters iteratively such that the overall correction converges to a minimal value. The initial offset and time walk values from the first iteration are applied with a damping of 0.5 to the raw data. This moves any offset halfway towards the initial iteration's calculated true value. A damping is used in order to avoid over correction and thus a fit that oscillates too far each way per iteration. The subsequent iteration takes data aligned to the previous iterations calculated offsets and time walk coefficients and repeats the process. Thus, each iteration will take a half step towards a converged solution, without concern of overfitting. The iterator stops when the mean change across all channels is <50 ps, a value less than the overall timing resolution of the crystals. The final iterations time walk and offset distributions can be seen in Figures 3.6b and 3.7b respectively, noting the narrow and flat distribution in time walk and the centring around zero for both plots, showing timing delays between detected hits have been minimised successfully.

3.4 Event reconstruction

In this section the analysis cuts and criteria to identify 2γ and 3γ events are outlined.

3.4.1 2γ reconstruction

As one of the aims of the project is to establish capabilities of the array to characterise the $3\gamma/2\gamma$ ratio reconstructing 2γ events is crucial.

The 2γ script initially filters the data by applying a cut on the energy of the event to be $511 \text{ keV} \pm 2\sigma$, or $459 \leq E \leq 563 \text{ keV}$. 2γ events are accepted as an event if two such hits occur in the array within a coincidence timing window of $\pm 0.5 \text{ ns}$.

For each valid coincidence event, a line of response (LOR) between the centre of the two pixels is constructed. To build an image of the source, the LORs are mapped to a 3D voxel grid of the detector space, with voxels of $0.5 \times 0.5 \times 0.5 \text{ mm}$ using a maximum likelihood expectation maximisation algorithm (MLEM).

A geometric probability matrix is first calculated, weighting the probability of an annihilation occurring in every voxel to be detected along every possible LOR. A measurement vector is generated from the filtered detected list of events, mapping every event to an LOR. The algorithm then initialises a 3D image of the detector space which is multiplied with the probability matrix to generate an error ratio of how far off this image was from the measurement vector's LORs. These errors are then accounted for in the next

image, reducing the error each iteration. 15 iterations are run to allow a converged image accounting for the detector system resolution.

3.4.2 3γ reconstruction and backgrounds

The reconstruction of the annihilation site uses the reconstruction methods outlined in section 1.4. An initial selection of events within 2σ of the expected total energy of the three photons is applied, all within a timing coincidence of 1 ns.

It was found that as well as the desired true 3γ yield, the 3-hit yield contains significant background from events where one of the back-to-back gamma from a 511 keV decay interacts in the LYSO crystals through Compton scattering and then fires a separate crystal (giving 2 hits from a single photon).

To reduce this contribution, in addition to standard energy and timing windows, two kinematically motivated filters are applied prior to reconstruction to suppress these false Compton scattered 2γ events. The first is a spatial separation cut, requiring a minimum distance of 10 mm between all hit pairs in the event. This reduces the role of such inter-crystal scattering (ICS). Without this spatial filter, the close proximity of the scatter pair can be within the tolerance of the momentum conservation selection of the reconstruction algorithm, causing it to be falsely reconstructed as a 3γ event. A second filter rejects any event where the energy of a single hit pair sums to 511 keV (± 70 keV). This further suppresses ICS events on an energy basis, irrespective of their spatial distribution.

Chapter 4

Results

The key results are described in the following sections. Firstly, the extraction of the key performance parameters of the array viz. energy, timing and spatial resolutions are presented. Secondly, experimental distributions without any selection cuts are compared with the 3γ annihilation theoretical distributions, demonstrating the necessity for motivated kinematic selection cuts.

Following this, the experimental results with motivated selection cuts applied are compared to Geant4 simulated 3γ data — accounting for energy and timing resolutions — and the same theoretical distributions as before. These are compared through three distinct distributions: Ore-Powell plots of single-photon energy distribution; angular distributions of each gamma pairs opening angles; and Dalitz plots of the kinematic distributions of the annihilation gammas. Details of the comparison plots are provided at their respective first instances in section 4.2. These plots serve to benchmark the experimental data selection cuts and reconstruction algorithms — as well as the accuracy of the simulation — against theoretical expectations. The difference in distribution between the unfiltered dataset and those with the motivated selection cuts applied allows for assessment of the purity of the 3γ yield with the event selections.

The reconstructed annihilation positions for 2γ (MLEM) and 3γ (event by event reconstruction) for each of the experimental datasets are presented in section 4.3, along with their $3\gamma/2\gamma$ ratios, comparing the effects of the different mesoporous media on the 3γ yield.

4.1 Key results from the detector commissioning

In this section the key quantities of the new array are presented viz the energy, timing and spatial resolutions in reconstruction.

4.1.1 Energy Resolution

The single-photon energy resolution, totalled across all channels, at 511 keV is measured at a FWHM of 65.32 keV (12.78% at 511 keV) as shown in Figure 4.1. The summed 3γ (E1+E2+E3) energy resolution, total across all channels, at ~ 1022 keV is measured at a FWHM of 68.04 keV (6.64% at 1024.94 keV) as shown in Figure 4.2. The single-photon energy resolution aligns closely with state-of-the-art clinical LYSO PET scanners [42] and our Tokyo collaborators' 3γ GAGG detector [1].

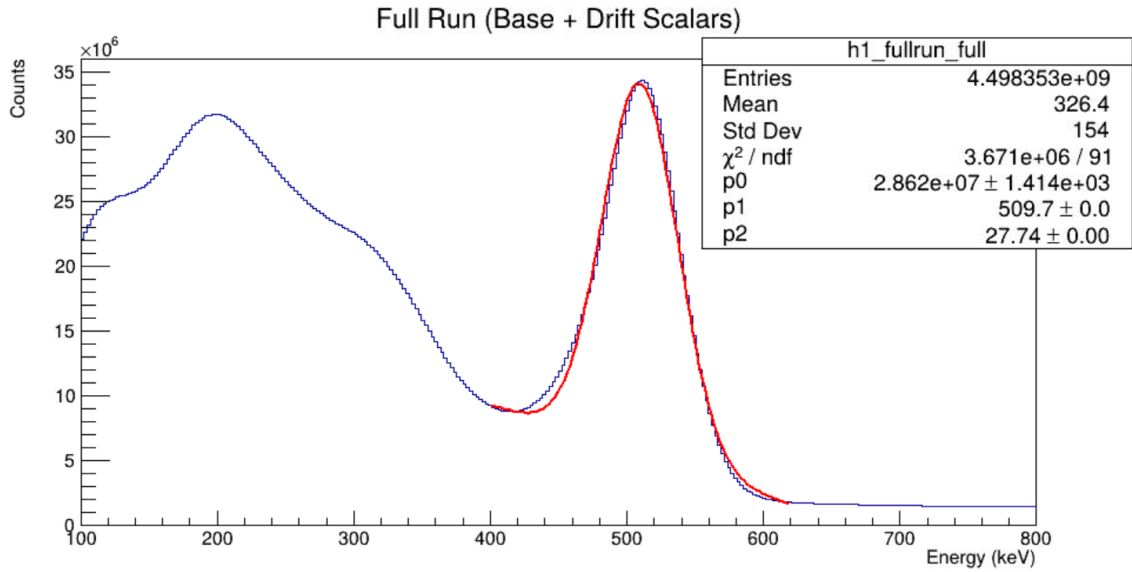


Figure 4.1: 1D histogram of the summed energy spectra of all channels (for ^{22}Na data), with all energy calibrations applied. A fitted Gaussian shows a 511 keV resolution of $\sigma \approx 28$ keV (FWHM = 65.32 keV).

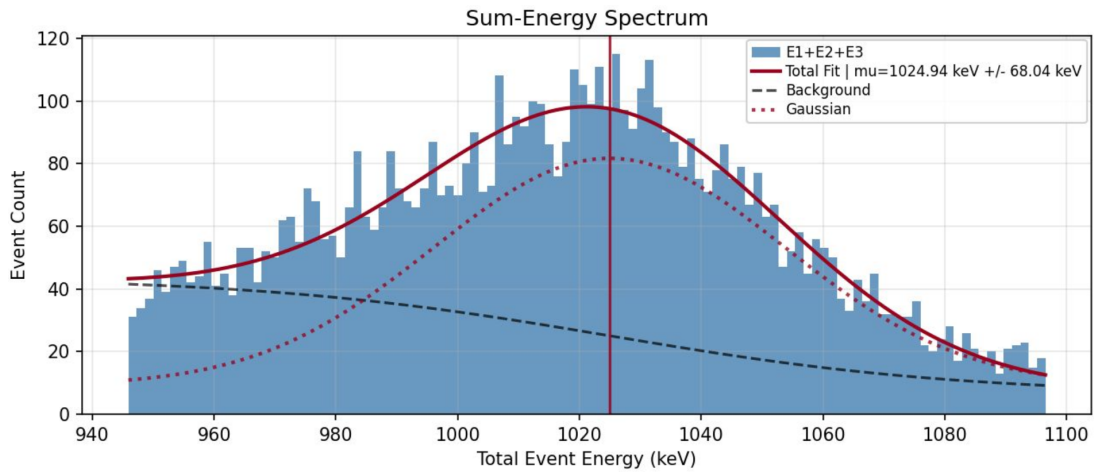


Figure 4.2: 1D histogram of the sum energy spectrum of all channels for reconstructed 3γ events (^{18}F data). Fitted with a Gaussian (red dotted line) on top of a Fermi-Dirac background (black dashed line), showing a resolution of FWHM = 68.04 keV at 1024.94 keV.

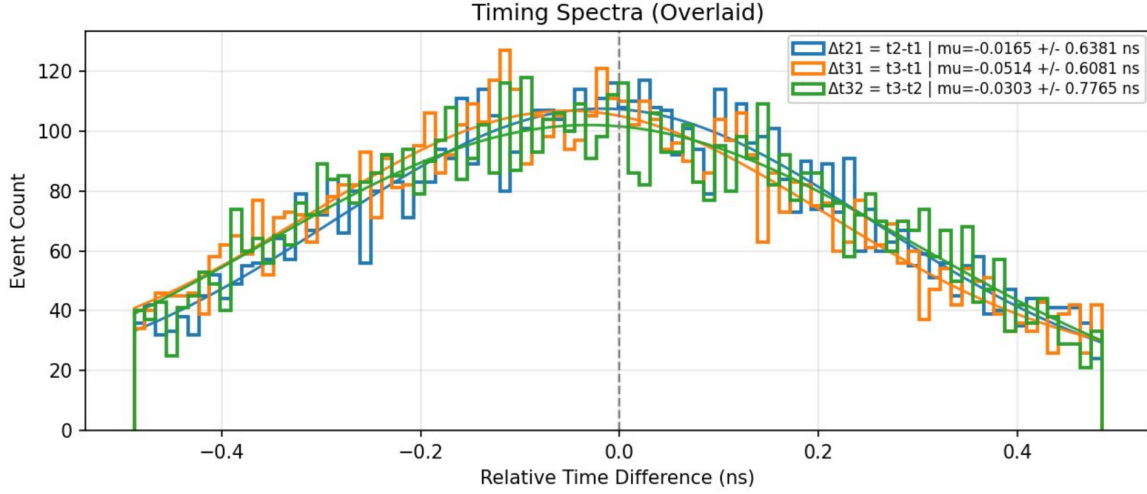


Figure 4.3: Coincidence timing resolution (CTR) between each gamma pair ($t_2 - t_1, t_3 - t_1, t_3 - t_2$) in 3γ events. Each timing interval is fitted with a Gaussian, showing a maximum resolution between the $t_3 - t_1$ pair of FWHM = 0.61 ns and a minimum resolution between the $t_3 - t_2$ pair of FWHM = 0.78 ns.

4.1.2 Coincidence Timing Resolution

The CTR of each reconstructed pair in the 3γ viz. ($t_2 - t_1, t_3 - t_1, t_3 - t_2$) was extracted. These are shown in Figure 4.3. The largest FWHM, from the $t_3 - t_2$ pair (the two lowest energy γ), was measured at ~ 0.78 ns. Comparison to other novel 3γ systems is somewhat redundant as notable publications use different scintillators and vary drastically: 80 ps for plastic scintillators used by the J-PET group at the Jagiellonian University [43] using an alternate methodology; 10 ns for GAGG scintillators used by our Tokyo collaborators [1] using the same methodology as this work. A LYSO based detector has been used previously for triple-photon detection (albeit from unspecific triple coincidence events as supposed to specifically 3γ annihilations) quoting a timing resolution of 1.3 ns [44].

4.1.3 Spatial Resolution

Due to the lack of a 3γ emitting point source, a convolved fit using the known source volume of the ^{18}F control run was used to estimate the spatial resolution of the detector system in each axis (Figures 4.4 - 4.6). The resolution in the Z-axis (axial) of a PET scan is often the worst due to the solid angles, the measured worst (Z-axis) resolution is FWHM = 10.11 mm. This aligns closely with the reported sub-1.1 cm spatial resolution of the GAGG system using the same reconstruction methodology [1].

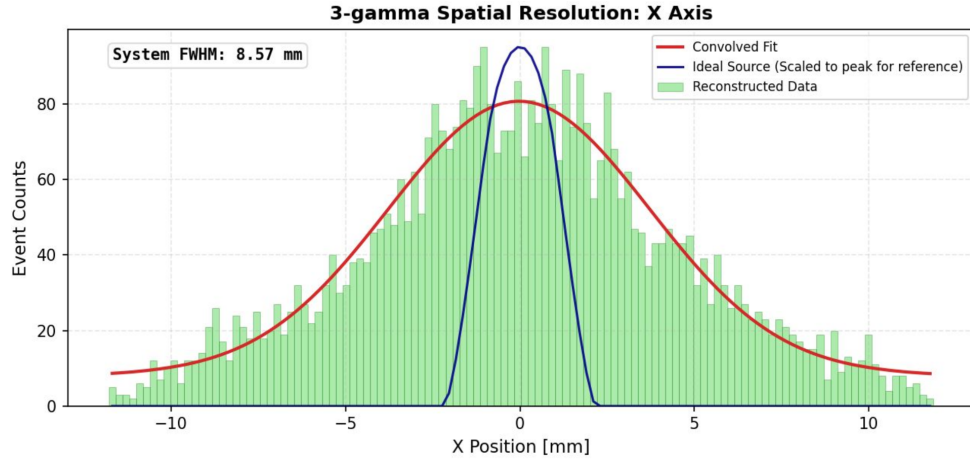


Figure 4.4: Spatially convolved 3γ spatial resolution in the X-axis, imaging a $70\ \mu\text{L}$ filled source holder (see Figure 2.12). The source's perfect spatial resolution is shown (blue line) alongside the convolved fit (red line). The spatial resolution is found to be $\text{FWHM} = 8.57\ \text{mm}$.

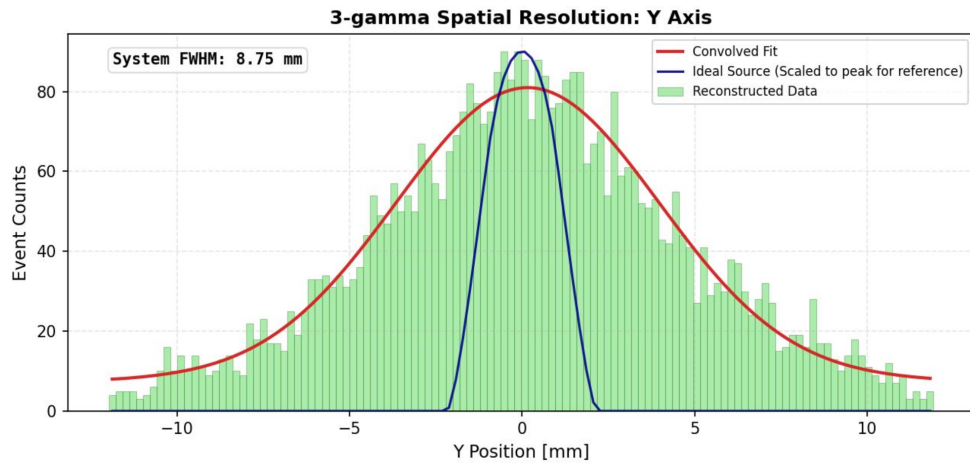


Figure 4.5: Spatially convolved 3γ spatial resolution in the Y-axis, imaging a $70\ \mu\text{L}$ filled source holder (see Figure 2.12). The source's perfect spatial resolution is shown (blue line) alongside the convolved fit (red line). The spatial resolution is found to be $\text{FWHM} = 8.75\ \text{mm}$.

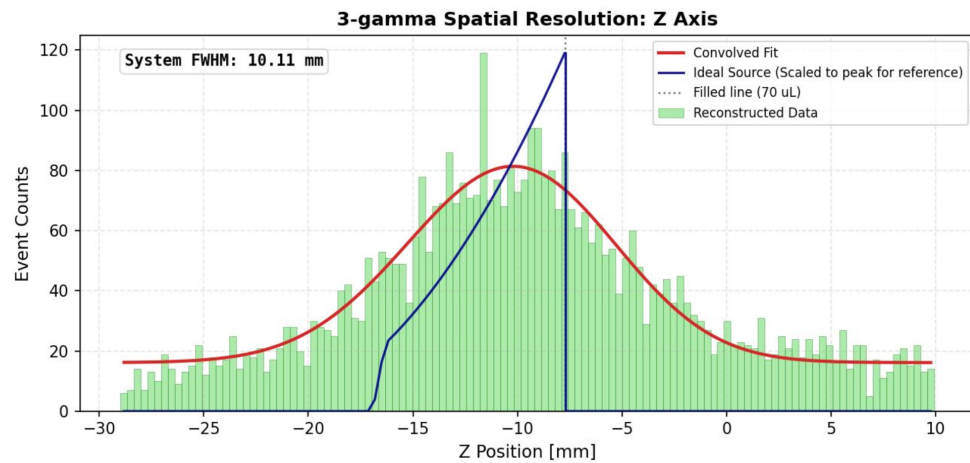


Figure 4.6: Spatially convolved 3γ spatial resolution in the Z-axis, imaging a $70\ \mu\text{L}$ filled source holder (see Figure 2.12). The source's perfect spatial resolution is shown (blue line) alongside the convolved fit (red line). The spatial resolution is found to be $\text{FWHM} = 10.11\ \text{mm}$. Note the non-trivial Eppendorf volume over which the resolution was convolved.

4.2 Experimental 3γ distributions

This section will present a number of kinematical observables which possess defined characteristics for true 3γ events vs false reconstructions. The first is the Ore-Powell distribution [21] of measured single-photon energies from a 3γ annihilation. The second consists of opening angle distributions for each $\gamma_{12, 23, 31}$ pair. Finally, Dalitz plots are presented alongside single photon energy distributions. Dalitz plots, plotting the invariant squared masses of the γ_{12} and γ_{23} pairs, map the kinematical phase space of three-body decays. As such, any differences in the pair energies between the expected and measured distributions will be highlighted. Each of these experimental distributions is compared to theoretical and Geant4 simulated distributions to derive cuts to isolate the 3γ yield.

4.2.1 Experimental distributions without selection cuts

First, the experimentally measured energy distribution with no selection cuts is compared to the Ore-Powell theory in Figure 4.7. Note the data still has the lower and upper energy bounds (80 - 450 keV) and sum energies of the 3 photons being in the expected energy window (945 - 1099 keV). It is clear the measured distributions show strong discrepancies with the theory, which can be attributed to significant contributions from 2γ annihilation gammas and their Compton scatters to the yield with these simple cuts.

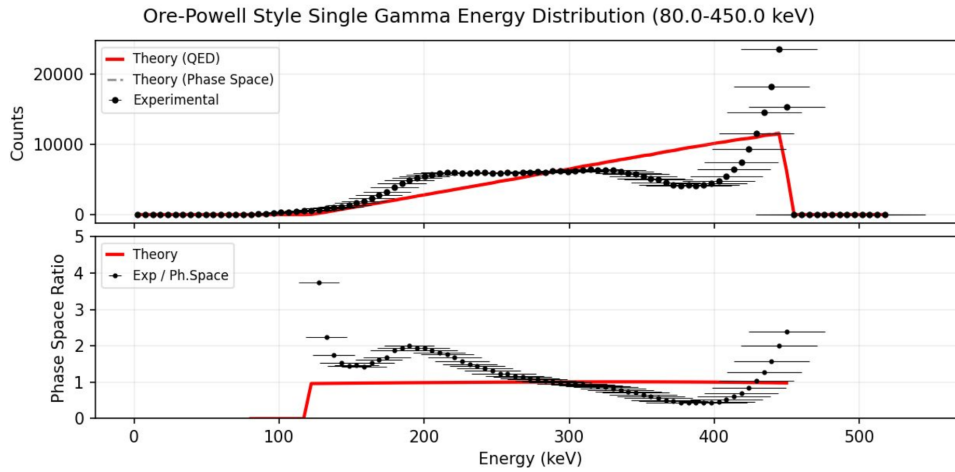


Figure 4.7: Single-photon energy distribution for measured 3γ events (black dots) with no selection cuts applied. Data only limited by 3γ event sum energy (945 - 1099 keV) and individual photon energy (80-450 keV). Note the discrepancy in comparison to the theoretical 3γ distribution (red line), due to large 2γ background contributions.

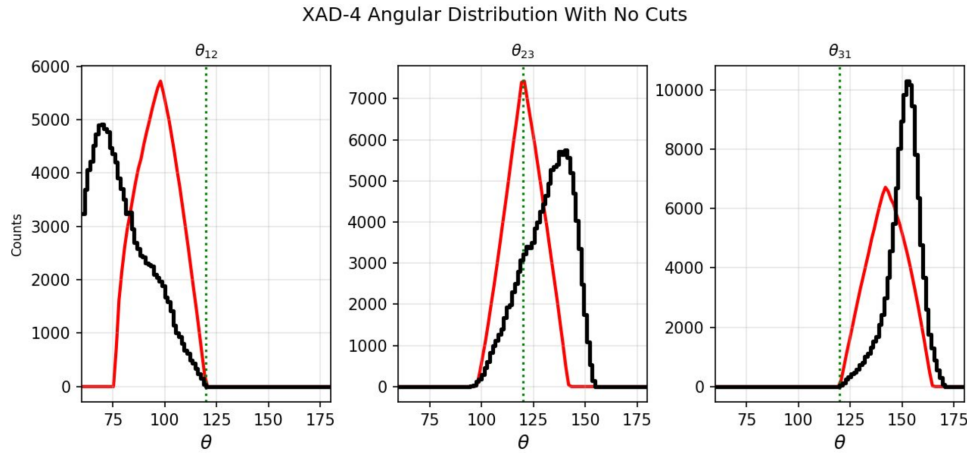


Figure 4.8: Angular distributions of experimental data (black) with no selection cuts applied. Data only limited by 3γ event sum energy (945 - 1099 keV) and individual photon energy (80-450 keV). Note the discrepancy in comparison to the theoretical 3γ distribution (red line), due to large 2γ background contributions.

As well as discrepancies in the energy distributions, the angular distributions shown in Figure 4.8 again highlight the strong discrepancies with these simple selection cuts. The data shows significant strength where one pair has close to 180° opening angles, as expected where two high energy back-to-back photons have a split off event. Note also the tendency for the smallest angle, θ_{12} , to be much smaller than predicted by the Ore-Powell theory.

The Dalitz plot of invariant mass squared (m^2) of $\gamma_{1,2}$ versus $\gamma_{2,3}$ — where $E_{\gamma_1} < E_{\gamma_2} < E_{\gamma_3}$ — for the same conditions as described above are shown in Figure 4.9. Such plots show the distribution of the measured events over the kinematic phase space. The individual energy spectra for the three photons are also shown. Once again, it is seen that these simple cuts result in a strong peaking of the high energy gamma close to 511 keV - as expected for backgrounds deriving from the 2γ process.

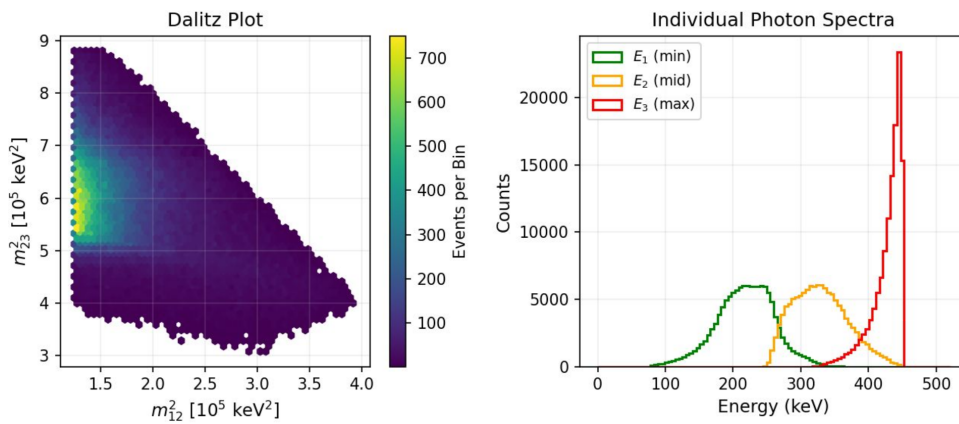


Figure 4.9: Dalitz plot (left) and energy spectra of individual photons (right). Data only limited by 3γ event sum energy (945 - 1099 keV) and individual photon energy (80-450 keV). Note the high intensity of low m^2_{12} energies for relatively high m^2_{23} energies, alongside the intense E_3 spectrum, showing strong 511 keV 2γ contamination.

4.2.2 Comparison of experimental and simulation data with selection cuts applied

It is clear from the above that the simple restriction of sum energies and individual photon energies is not sufficient to obtain a clean 3γ yield. The following comparisons have, as described in section 3.4.2, a restriction on the distance between any of the two hit clusters to be above 10 mm and a restriction that none of the cluster pairs have energy within 70 keV of 511 keV.

Figures 4.10-4.13 show the comparison of the experimentally measured single-photon energy distributions with these motivated selection cuts applied (black data points) to the resolution smeared Geant4 distribution (green data points) and the Ore-Powell theory (red lines). The Geant4 distribution used for comparison is the same as is shown in Figure 3.2b, and serves as the most accurate benchmark for the Ore-Powell distribution when incorporating this detector's solid angle and (energy and timing) resolutions.

These plots are the most crucial comparison for the data analysis and it is clear that a good agreement is observed between the 3γ yield and the predicted yield in the detector apparatus for 3γ annihilation. This agreement gives confidence the 3γ yield has been extracted relatively cleanly.

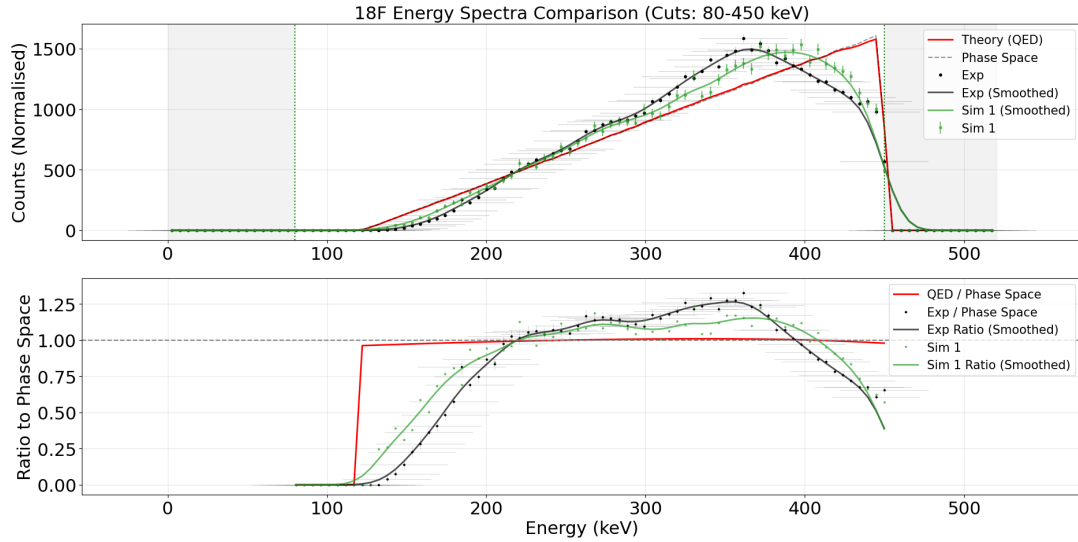


Figure 4.10: ((**Top**) Single-photon energy distribution of 3γ events in ^{18}F experimental data with the final selection cuts applied (black). This is compared with the Geant4 energy and time smeared data (green) and the theoretical Ore-Powell distribution (red). (**Bottom**) Ratio of the events to the phase space of the theory.

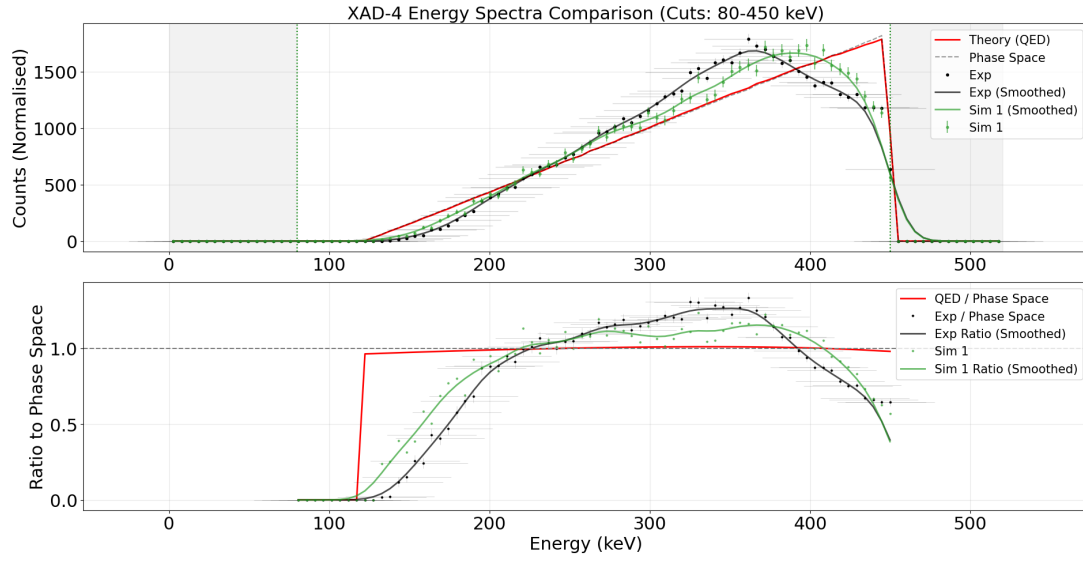


Figure 4.11: **(Top)** Single-photon energy distribution of 3γ events in XAD-4 experimental data with the final selection cuts applied (black). This is compared with the Geant4 energy and time smeared data (green) and the theoretical Ore-Powell distribution (red). **(Bottom)** Ratio of the events to the phase space of the theory.

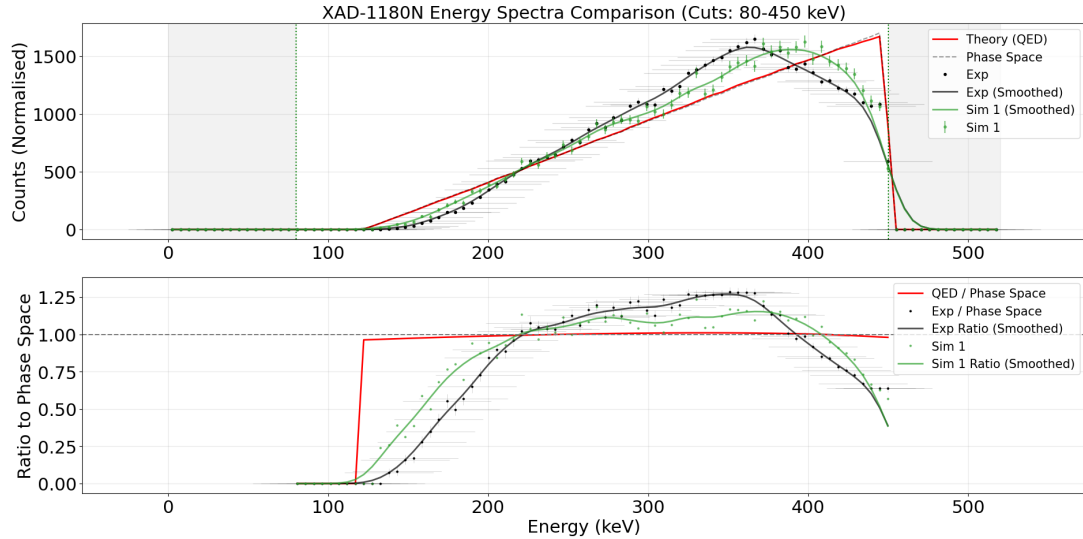


Figure 4.12: **(Top)** Single-photon energy distribution of 3γ events in XAD-1180N experimental data with the final selection cuts applied (black). This is compared with the Geant4 energy and time smeared data (green) and the theoretical Ore-Powell distribution (red). **(Bottom)** Ratio of the events to the phase space of the theory.

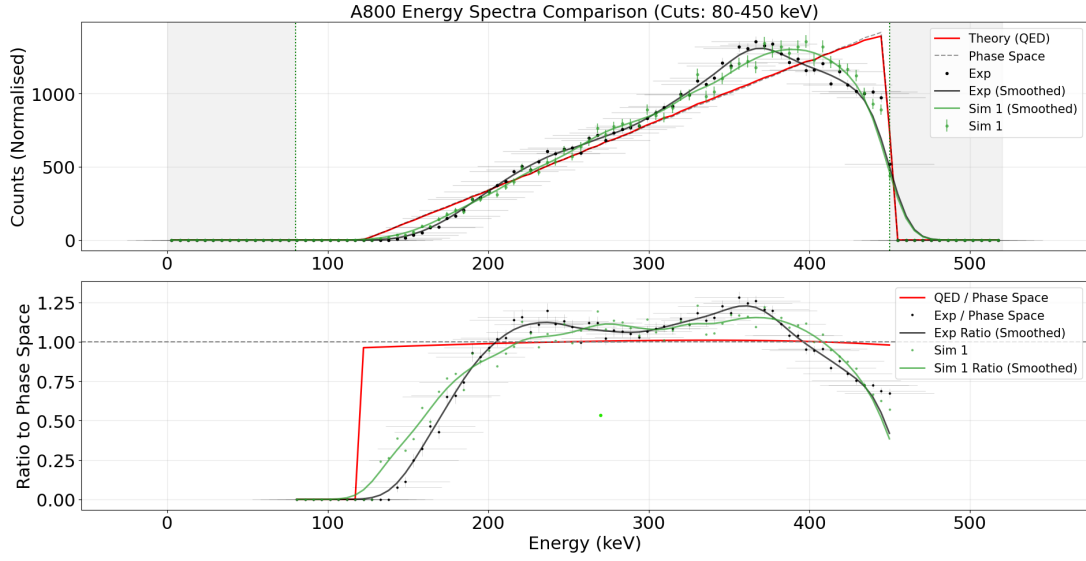


Figure 4.13: **(Top)** Single-photon energy distribution of 3γ events in A800 experimental data with the final selection cuts applied (black). This is compared with the Geant4 energy and time smeared data (green) and the theoretical Ore-Powell distribution (red). **(Bottom)** Ratio of the events to the phase space of the theory.

With these additional cuts, each datasets angular distributions are also compared against the theory. Firstly, Geant4 simulated angular distributions with perfect resolution in Figure 4.14 and smeared resolution Figure 4.15, followed by the experimental runs angular distributions in Figures 4.16 to 4.19. It is clear the developed 3γ model with the additional selection cuts gives reasonable general agreement between the experimental data and Geant4 simulation (based on the fundamental theory of Ore-Powell).

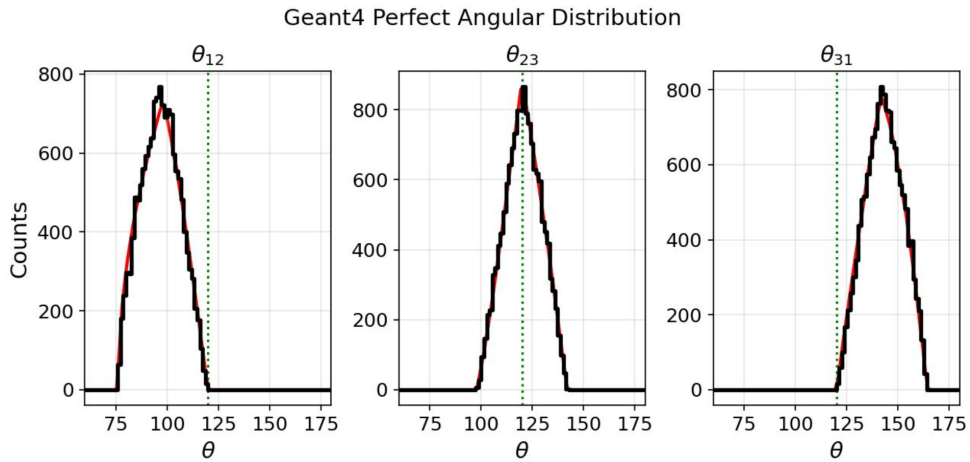


Figure 4.14: Distributions of the ordered opening angles $\theta_{12} < \theta_{23} < \theta_{31}$ for each 3γ annihilation event with the final selection cuts applied. Each distribution shows the number of events for a given angle (left = θ_{12} , middle = θ_{23} , right = θ_{31}). Geant4 perfect resolution data is shown in black alongside the theoretical Ore-Powell distributions in red.

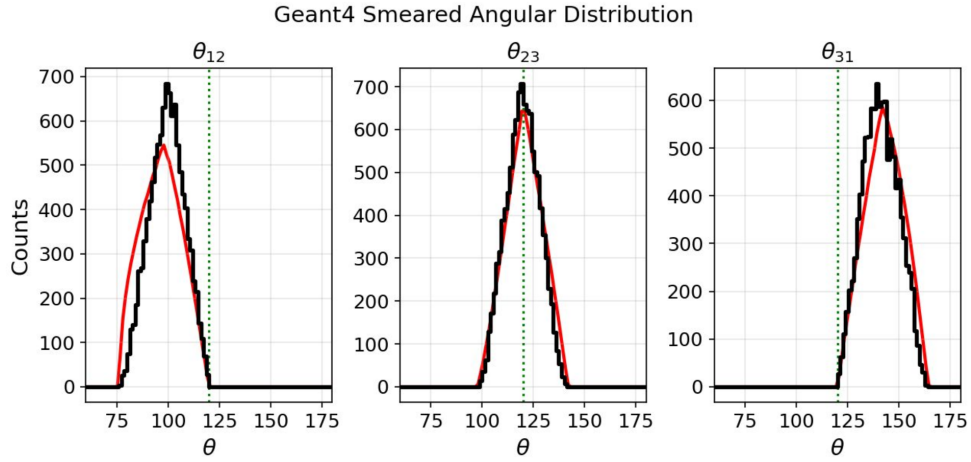


Figure 4.15: Distributions of the ordered opening angles $\theta_{12} < \theta_{23} < \theta_{31}$ for each 3γ annihilation event with the final selection cuts applied. Each distribution shows the number of events for a given angle (left = θ_{12} , middle = θ_{23} , right = θ_{31}). Geant4 smeared resolution data is shown in black alongside the theoretical Ore-Powell distributions in red..

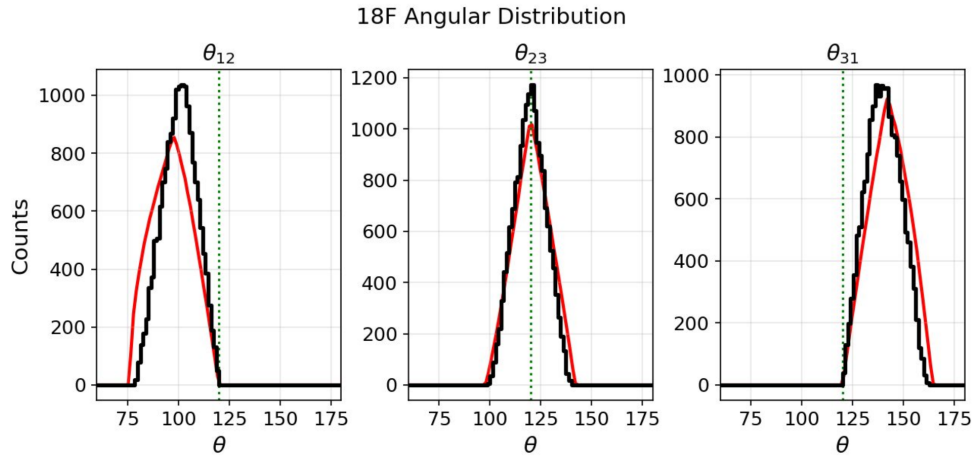


Figure 4.16: Distributions of the ordered opening angles $\theta_{12} < \theta_{23} < \theta_{31}$ for each 3γ annihilation event with the final selection cuts applied. Each distribution shows the number of events for a given angle (left = θ_{12} , middle = θ_{23} , right = θ_{31}). ^{18}F control run experimental data is shown in black alongside the theoretical Ore-Powell distributions in red.

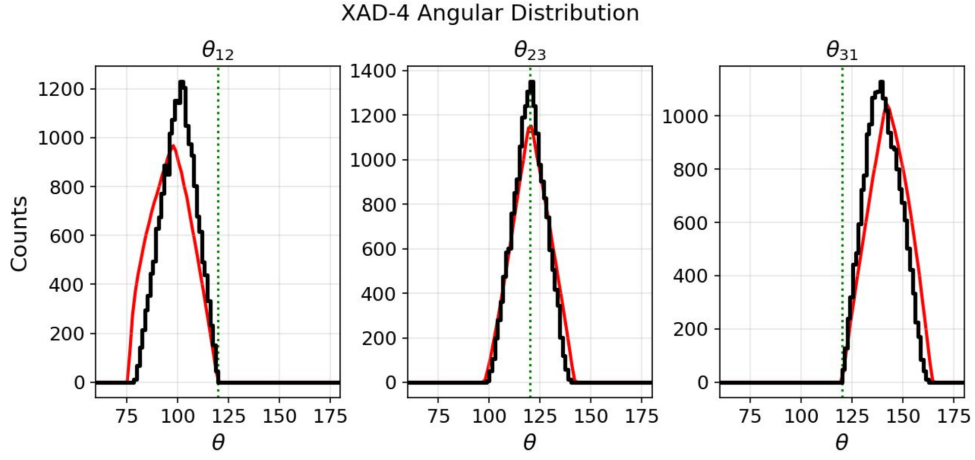


Figure 4.17: Distributions of the ordered opening angles $\theta_{12} < \theta_{23} < \theta_{31}$ for each 3γ annihilation event with the final selection cuts applied. Each distribution shows the number of events for a given angle (left = θ_{12} , middle = θ_{23} , right = θ_{31}). XAD-4 experimental data is shown in black alongside the theoretical Ore-Powell distributions in red.

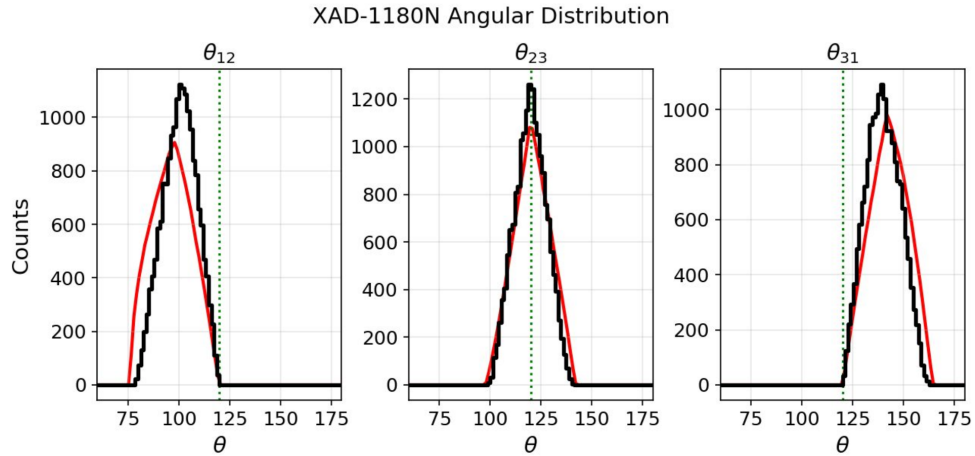


Figure 4.18: Distributions of the ordered opening angles $\theta_{12} < \theta_{23} < \theta_{31}$ for each 3γ annihilation event with the final selection cuts applied. Each distribution shows the number of events for a given angle (left = θ_{12} , middle = θ_{23} , right = θ_{31}). XAD-1180N experimental data is shown in black alongside the theoretical Ore-Powell distributions in red.

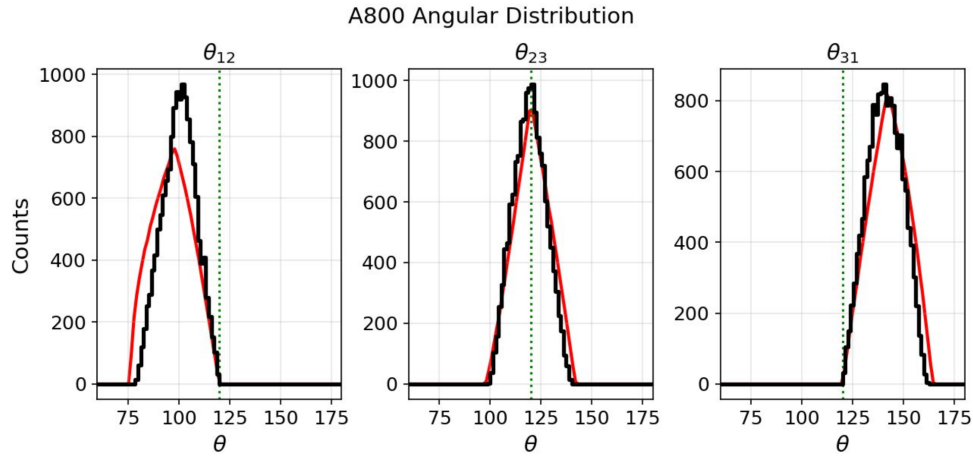


Figure 4.19: Distributions of the ordered opening angles $\theta_{12} < \theta_{23} < \theta_{31}$ for each 3γ annihilation event with the final selection cuts applied. Each distribution shows the number of events for a given angle (left = θ_{12} , middle = θ_{23} , right = θ_{31}). A800 experimental data is shown in black alongside the theoretical Ore-Powell distributions in red.

4.2.3 Dalitz plot and energy distributions

The Dalitz and individual photon energies of the reconstructed events are shown for the Geant4 perfect resolution in Figure 4.20 and the Geant4 smeared resolution in Figure 4.21, followed by the experimental distributions in Figures 4.22 - 4.25. It is clear that the event selection, including the cuts to reject 2γ background, result in measured distributions giving correspondence to those predicted from Geant4. There are some small discrepancies, mainly near to the high and low energy thresholds. Overall the results indicate the background has been suppressed to a good degree, as features associated with the 2γ background, which has very different dependencies, do not show up strongly in the data. Note that for these plots no theoretical distribution is presented but it is a safe assumption based on the prior plots that the Geant4 perfect resolution mirrors the theory closely, and can be used for comparison.

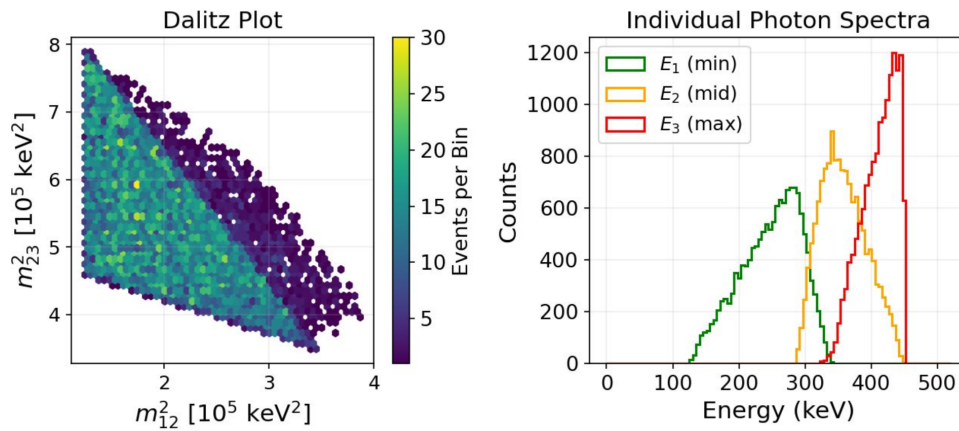


Figure 4.20: Dalitz plot (left) and energy spectra of individual photons (right). Both for the Geant4 simulated data with perfect energy and timing resolutions and the final selection cuts applied.

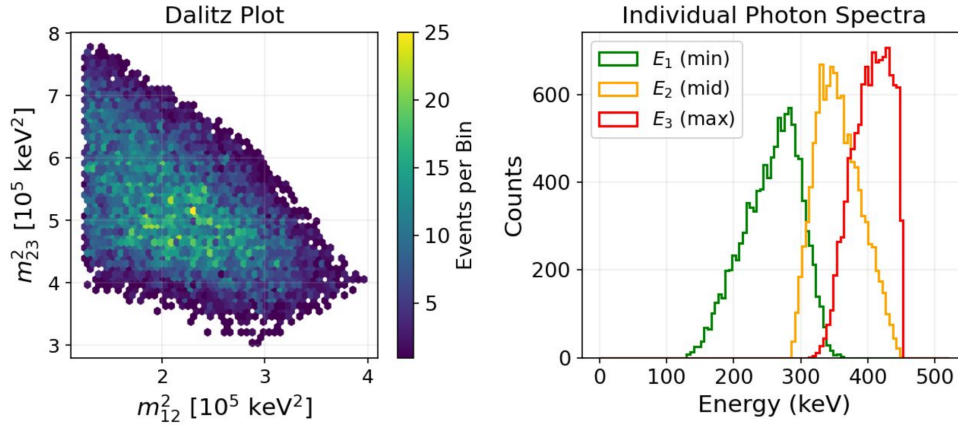


Figure 4.21: Dalitz plot (left) and energy spectra of individual photons (right). Both for the Geant4 simulated data with smeared energy and timing resolutions and the final selection cuts applied.

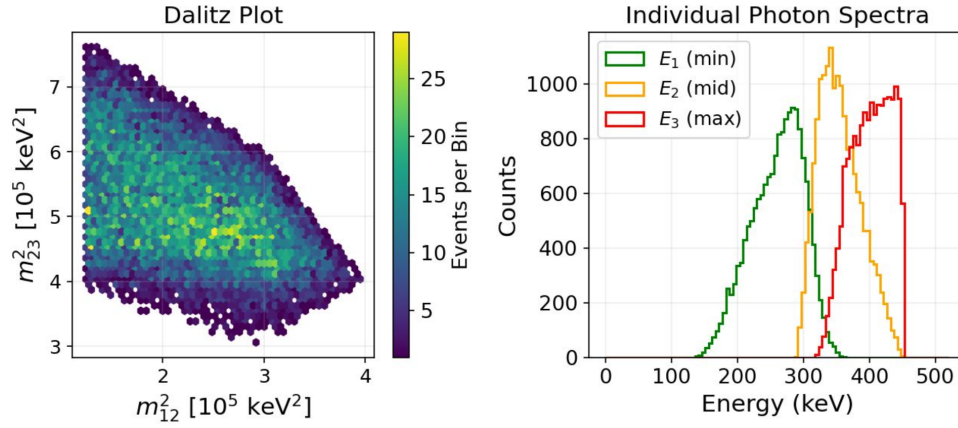


Figure 4.22: Dalitz plot (left) and energy spectra of individual photons (right). Both for the ^{18}F control experimental data with the final selection cuts applied.

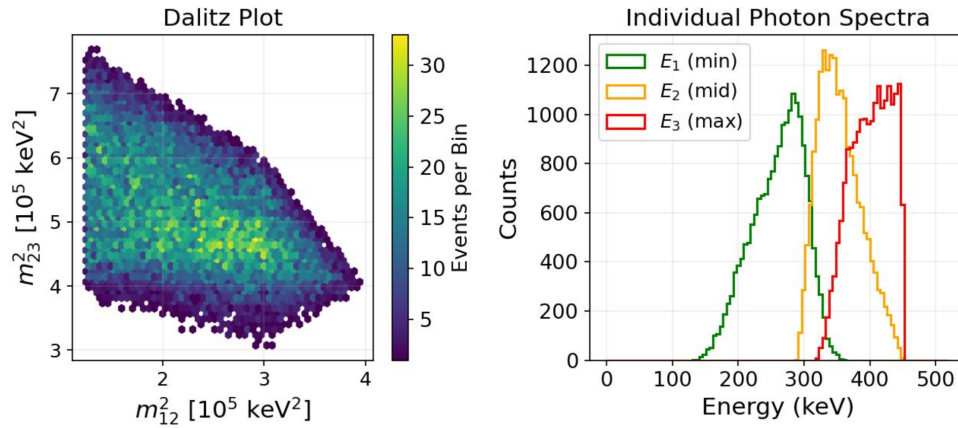


Figure 4.23: Dalitz plot (left) and energy spectra of individual photons (right). Both for the XAD-4 experimental data with the final selection cuts applied.

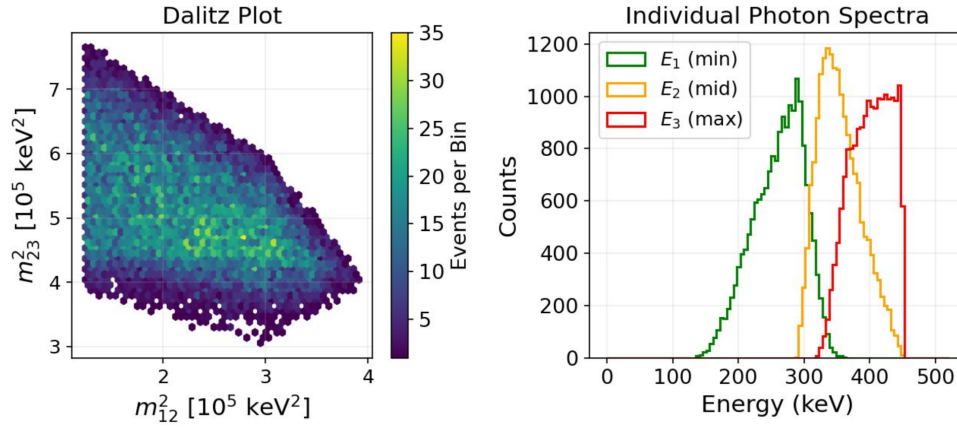


Figure 4.24: Dalitz plot (left) and energy spectra of individual photons (right). Both for the XAD-1180N experimental data with the final selection cuts applied.

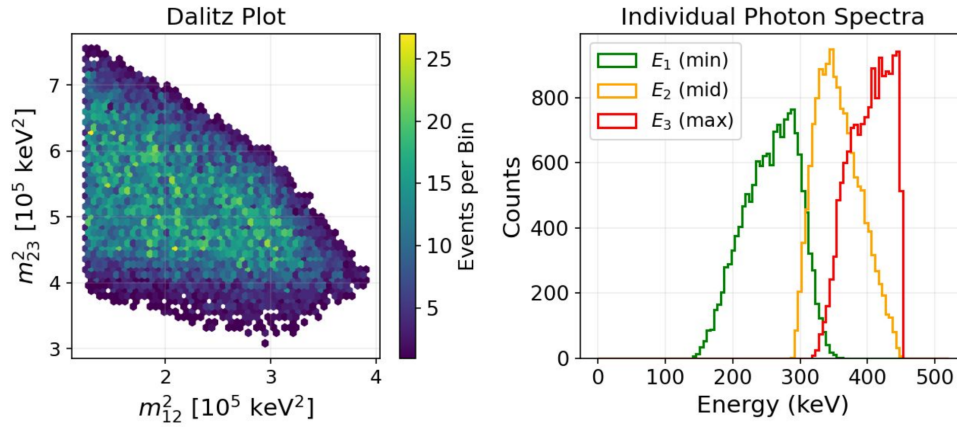


Figure 4.25: Dalitz plot (left) and energy spectra of individual photons (right). Both for the A800 experimental data with the final selection cuts applied.

4.3 Reconstructed 3γ and 2γ annihilation maps and their ratios

In this section, annihilation site reconstruction methods (Sections 1.4 and 3.4) are used to reconstruct the annihilation map in 3D from the 3γ and 2γ events. 2D integrations of these annihilation maps are presented in Figures 4.26 - 4.31. Following this, the $3\gamma/2\gamma$ ratios are determined from the ratio of these plots and presented in Figures 4.34 to 4.37. The overall $3\gamma/2\gamma$ ratio dependency on pore size is plotted in 4.38.

4.3.1 Annihilation maps

The annihilation maps provide axial (X-Y) and coronal (X-Z) integrated intensities of the 2γ and 3γ reconstructed images for each imaged mesoporous material. These are then directly compared to get the annihilation ratio in both the source ROI and the surrounding 2σ volume. For comparison between the

reconstructed images, the fill line (pink line), Eppendorf location (white outline) and 2σ volume (green box) are projected on the annihilation maps.

The 3γ reconstruction resolution is poorer than that of the 2γ , due to the dependence on energy in the reconstruction algorithm demonstrated in equations 1.33 - 1.36. As such, the 2γ distribution is artificially smeared to match the 3γ resolution for more accurate volume ratio comparison. This is done through the use of a 3D Gaussian filter, wherein the required smearing along each axis is calculated from the quadrature difference between the 2γ and 3γ resolutions.

4.3.2 ^{18}F control

The control run as detailed in Table 2.1 consists of a $70\ \mu\text{L}$ filled $0.6\ \text{mL}$ Eppendorf. The annihilation maps for 3γ and 2γ yields are shown in Figures 4.26 and 4.27 respectively. The ratios extracted in the Eppendorf region and 2σ region are presented in Table 4.1 below.

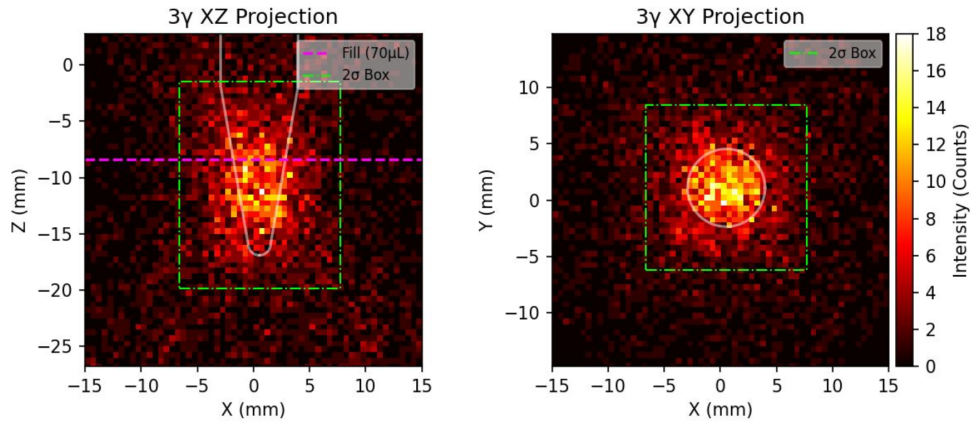


Figure 4.26: Integrated intensities in the coronal (left, X-Z) and axial (right, X-Y) planes for ^{18}F control 3γ reconstructed events. Overlaid on the maps are the liquid source fill line (pink line), the Eppendorf tube location (white outline), and the 2σ surrounding region (green box).

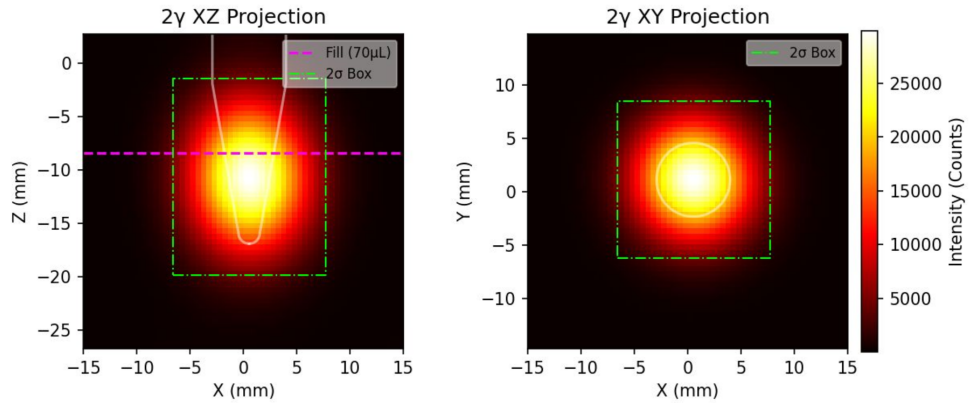


Figure 4.27: Integrated intensities in the coronal (left, X-Z) and axial (right, X-Y) planes for ^{18}F control 2γ reconstructed events. Overlaid on the maps are the liquid source fill line (pink line), the Eppendorf tube location (white outline), and the 2σ surrounding region (green box).

4.3.3 XAD-4

The XAD-4 resin run as detailed in Table 2.1 consists of a 40 μL filled 0.6 mL Eppendorf, with a filling height of ~ 6.4 mm. The mass of added XAD-4 is 20.0 mg. Note that the XAD resin (in the form of sub mm sized beads) fell out of solution, however the spatial resolution of the system detailed above is such that the ~ 6.4 mm source height is less than that of the Z-axis spatial resolution of 10.11 mm. The annihilation maps for 3γ and 2γ yields are shown in Figures 4.28 and 4.29. The ratios in the Eppendorf and 2σ ROI are presented in Table 4.2 below.

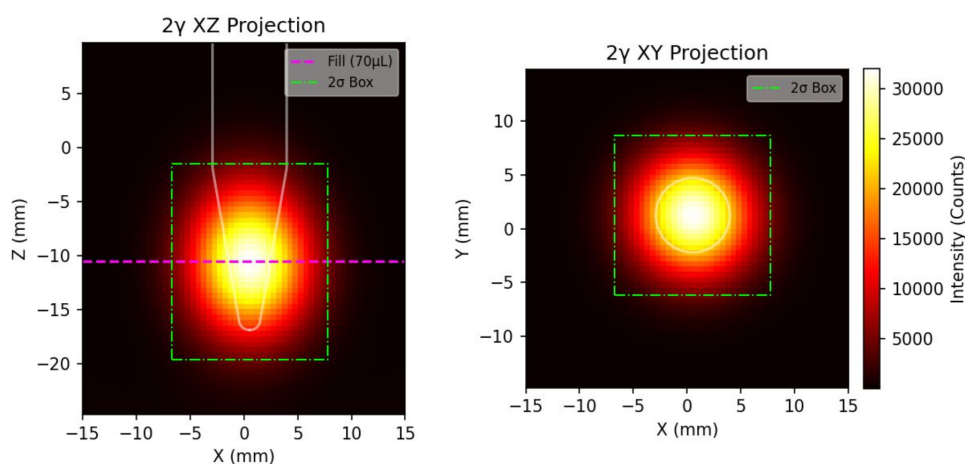


Figure 4.28: Integrated intensities in the coronal (left, X-Z) and axial (right, X-Y) planes for XAD-4 3γ reconstructed events. Overlaid on the maps are the liquid source fill line (pink line), the Eppendorf tube location (white outline), and the 2σ surrounding region (green box).

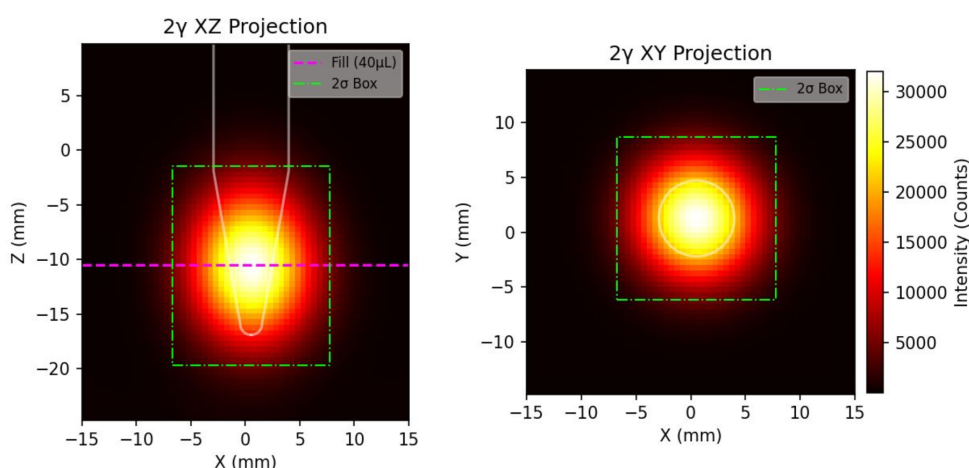


Figure 4.29: Integrated intensities in the coronal (left, X-Z) and axial (right, X-Y) planes for XAD-4 2γ reconstructed events. Overlaid on the maps are the liquid source fill line (pink line), the Eppendorf tube location (white outline), and the 2σ surrounding region (green box).

4.3.4 A800

The A800 activated carbon sample is significantly less dense than the XAD resins, requiring a total volume (A800 + ^{18}F -NaF) of 413 μL to maintain the ~ 10 MBq source activity used in the prior runs whilst also maintaining full submersion of the A800, the mass of which was prioritised to increase total porosity. This can be seen in the elevated fill height (~ 19.5 mm) and source distribution. The annihilation maps for 3γ and 2γ yields are shown in Figures 4.30 and 4.31. The ratios in the Eppendorf and 2σ ROI are displayed in Table 4.3 below.

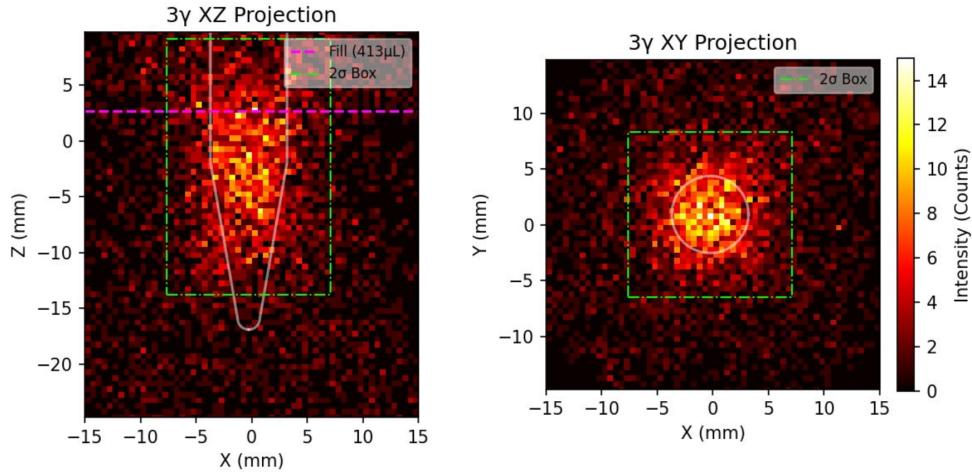


Figure 4.30: Integrated intensities in the coronal (left, X-Z) and axial (right, X-Y) planes for A800 3γ reconstructed events. Overlaid on the maps are the liquid source fill line (pink line), the Eppendorf tube location (white outline), and the 2σ surrounding region (green box).

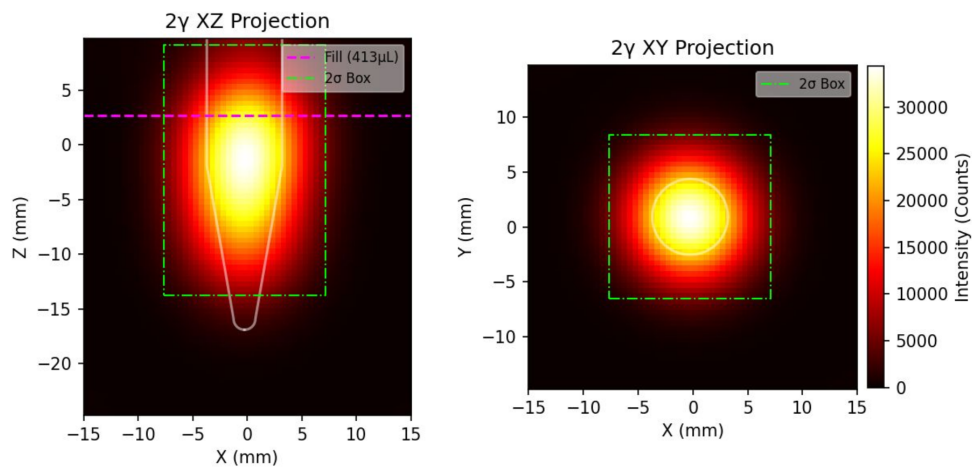


Figure 4.31: Integrated intensities in the coronal (left, X-Z) and axial (right, X-Y) planes for A800 2γ reconstructed events. Overlaid on the maps are the liquid source fill line (pink line), the Eppendorf tube location (white outline), and the 2σ surrounding region (green box).

4.3.5 XAD-1180N

The XAD-1180N resin run is near identical to the XAD-4, including also falling out of solution. The annihilation maps for 3γ and 2γ yields are shown in Figures 4.32 and 4.33. The ratios in the Eppendorf and 2γ ROI are displayed in Table 4.4 below.

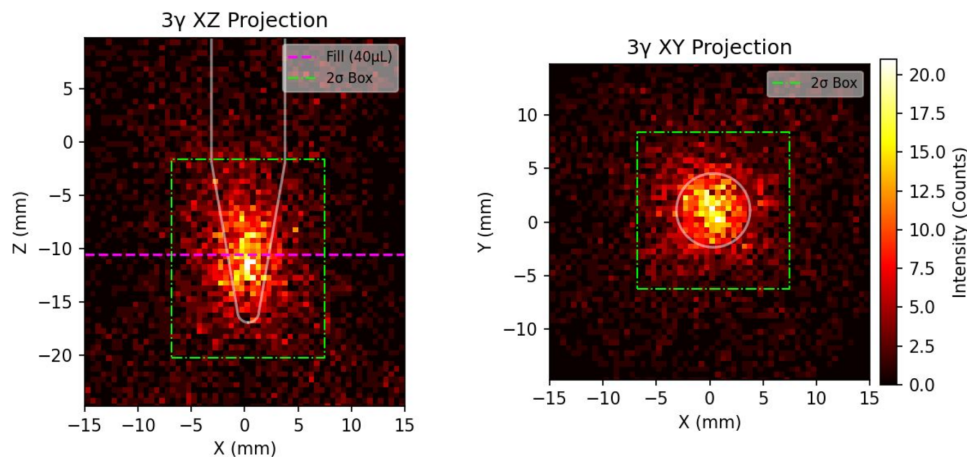


Figure 4.32: Integrated intensities in the coronal (left, X-Z) and axial (right, X-Y) planes for XAD-1180N 3γ reconstructed events. Overlaid on the maps are the liquid source fill line (pink line), the Eppendorf tube location (white outline), and the 2σ surrounding region (green box).

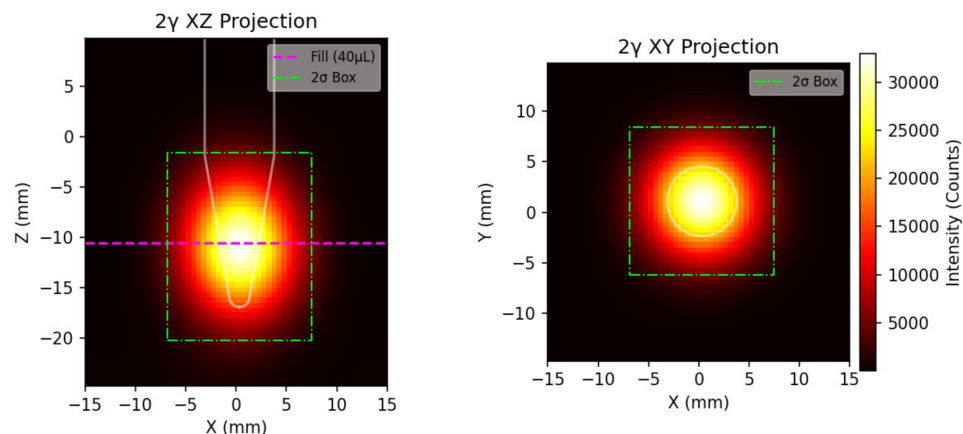


Figure 4.33: Integrated intensities in the coronal (left, X-Z) and axial (right, X-Y) planes for XAD-1180N 2γ reconstructed events. Overlaid on the maps are the liquid source fill line (pink line), the Eppendorf tube location (white outline), and the 2σ surrounding region (green box).

4.3.6 $3\gamma/2\gamma$ and enhancement ratios

Figures 4.34 to 4.37 show the ratios of the annihilation maps presented above (note a mask negating voxels where 2γ intensity drops below 15% of the maximum is applied to remove noise far away from the source). The results are presented numerically, integrated over the Eppendorf volume and a wider 2σ region in Tables 4.1 to 4.4. Figure 4.38 plots the ratio as a function of the pore size for the material added to the sample.

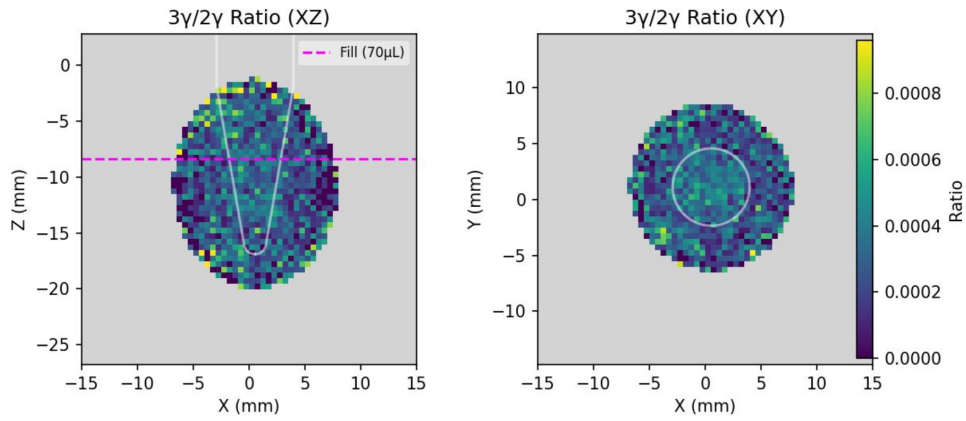


Figure 4.34: Coronal (left, X-Z) and axial (right, X-Y) $3\gamma/2\gamma$ annihilation ratio maps for the ^{18}F control data. The data is masked to exclude voxels where the 2γ intensity falls below 15% of the maximum. Overlaid is the liquid source fill line (pink line) and the Eppendorf location (white outline).

Integrated Intensity in	Eppendorf Stats	2σ Stats
3γ (counts)	2028	2718
2γ (integrated intensity)	6334549.57	9064719.17
Ratio	0.00032015	0.00029984

Table 4.1: ^{18}F Control Run Statistics

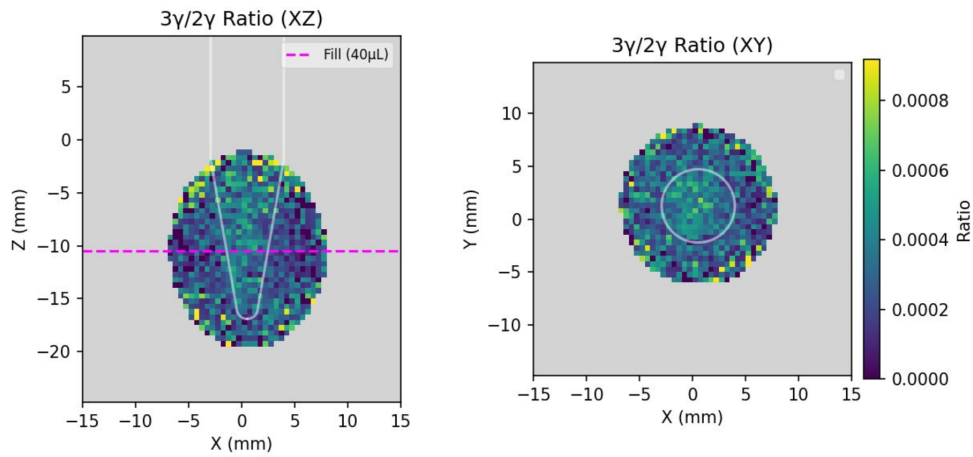


Figure 4.35: Coronal (left, X-Z) and axial (right, X-Y) $3\gamma/2\gamma$ annihilation ratio maps for the XAD-4 data (average pore radius of 5 nm). The data is masked to exclude voxels where the 2γ intensity falls below 15% of the maximum. Overlaid is the liquid source fill line (pink line) and the Eppendorf location (white outline).

Integrated Intensity in	Eppendorf Stats	2σ Stats
3γ	1505	2919
2γ	4915729.37	9807762.34
Ratio	0.00030616	0.00029762

Table 4.2: XAD-4 Run Statistics

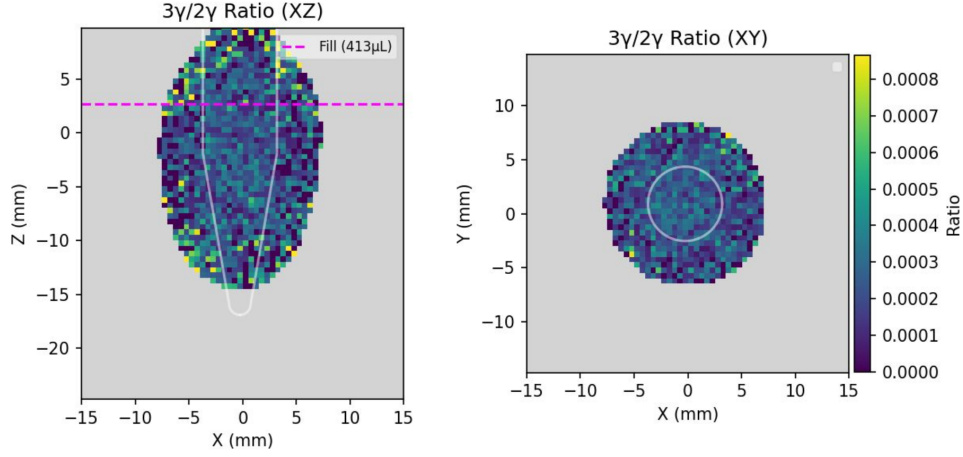


Figure 4.36: Coronal (left, X-Z) and axial (right, X-Y) $3\gamma/2\gamma$ annihilation ratio maps for the A800 data (average pore radius of 11.45 nm). The data is masked to exclude voxels where the 2γ intensity falls below 15% of the maximum. Overlaid is the liquid source fill line (pink line) and the Eppendorf location (white outline).

Integrated Intensity in	Eppendorf Stats	2σ Stats
3γ	2946	2532
2γ	10219418	11135150
Ratio	0.00028827	0.00022739

Table 4.3: A800 Run Statistics

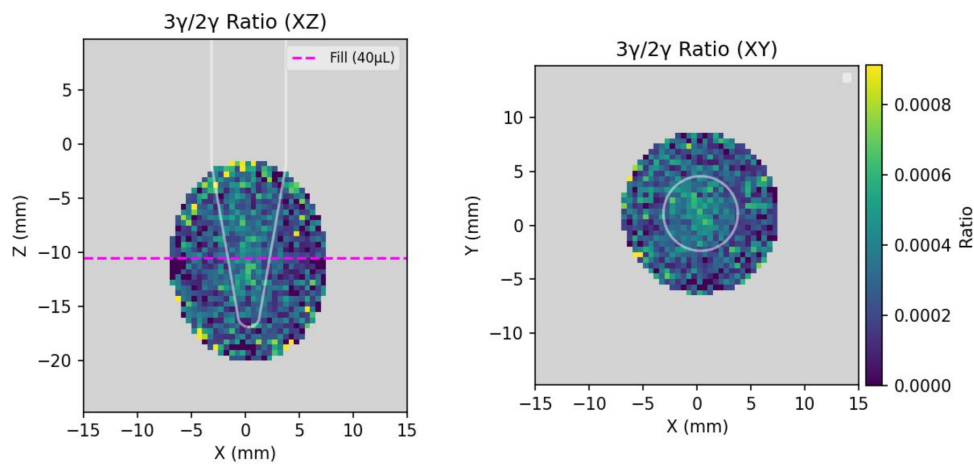


Figure 4.37: Coronal (left, X-Z) and axial (right, X-Y) $3\gamma/2\gamma$ annihilation ratio maps for the XAD-1180N data (average pore radius 20 nm). The data is masked to exclude voxels where the 2γ intensity falls below 15% of the maximum. Overlaid is the liquid source fill line (pink line) and the Eppendorf location (white outline).

Integrated Intensity in	Eppendorf Stats	2σ stats
3γ	1557	2818
2γ	5116509.50	10042877.76
Ratio	0.00030431	0.00028060

Table 4.4: XAD-1180N Run Statistics

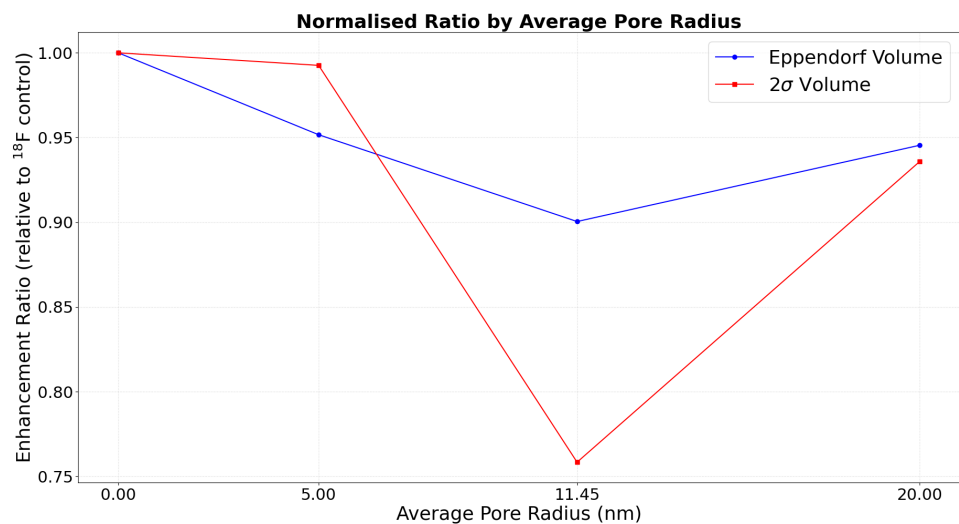


Figure 4.38: Enhancement ratio as a function of average pore radius. Unfortunately, no enhancement was detected in the experiment. XAD-4 exhibits the largest enhancement ratio of 0.9926, with all sources thus decreasing the $3\gamma/2\gamma$ ratio.

4.4 Outlook and discussion

The lack of clear 3γ enhancement seen in this commissioning experiment gives a direction for future studies. It is of note that enhancement was previously observed using XAD-4 and similar reconstruction techniques [1]. The source cell in this previous study used a smaller fraction of ^{18}F solution compared to the mesoporous components than employed here. Clearly, future work should explore the relative ratios of source solution and additive materials and their influence on the $3\gamma/2\gamma$ ratio. It is possible that for this (or other reasons) the pores in the mesoporous materials became filled with solution in the current work, spoiling the enhancement effects. Although the mesoporous materials are hydrophobic it may be that this does not fully eliminate ^{18}F liquid into the pore structure. Another difference is that the previous work used ^{18}F -FDG rather than ^{18}F -NaF in solution. Future work could investigate whether this difference in chemical composition somehow affected the hydrophobic nature of the mesoporous materials.

Another possible cause would be large contamination for 2γ annihilations into the assumed 3γ yield. The preliminary cuts and analysis presented here do not give strong suggestions that this is the case. Future work should include detailed comparison of the reconstructed annihilation maps in Geant4 with experimental data which was beyond the scope of the current work. Future work could also develop more refined cuts and analysis to reject possible backgrounds. It is worth noting that as the array employed here has geometry and properties similar to commercial PET, the methods found in all aspects would have direct application to any future implementation into clinical PET applications.

The combined dataset with the GAGG detector developed by the group's collaborators at the Institute of Science Tokyo and the University of Tokyo [31, 1] is also a clear next step. This was beyond the scope of this thesis and the GAGG system data was not available in a calibrated form for this study - and is currently under analysis to remedy issues with the DAQ system at the high data rates of the experiment. This would enhance the acceptance for 3γ events and enable future measurements of entanglement and polarisation correlations.

Chapter 5

Conclusions and Future Work

In this study a new 2048 element LYSO gamma detection array is commissioned with a medically relevant ^{18}F positron source annihilating in a range of mesoporous annihilating media. The work develops a data analysis and simulation pipeline to demonstrate the detection and characterisation of 3γ positron annihilation events. Detailed studies to establish the background from 2γ annihilation events where one of the gammas Compton scatter, producing a false 3γ event, are carried out using comparisons of simulated and experimental data.

The 3γ yield is analysed to obtain event-by-event reconstruction of the annihilation site. The 3γ yield from the experimental data gives good agreement with the energy and angular distributions expected in 3γ decay, agreeing with both theoretical predictions and simulated data (passed through the detector acceptance and modelled with realistic experimental resolutions). The reconstructed annihilation maps correlate with the known source location and dimensions. For this commissioning test the resolution was found to be ~ 1 cm standard deviation. Future work with more optimised configurations (cylindrical geometries and increased distance from the source) would give improvements, but the current thesis establishes the methodologies. The current setup comprised two "slabs" of detectors placed close to the source (at closest point ~ 27 mm).

The 2γ yield is analysed using MLEM methodologies. The reconstructed annihilation sites correlate with the target cell. The ratio of $3\gamma/2\gamma$ was extracted from the ratio of these maps of reconstructed annihilation sites (with 2γ map smeared to match the resolution of the 3γ events). For this commissioning experiment, no significant enhancement of the 3γ yield from employing mesoporous materials was evidenced. A possible explanation is that the ^{18}F saturated the pores in the materials negating the benefits. Another possible explanation would be that the 3γ yield was strongly contaminated by 2γ split-off backgrounds,

although strong contaminations were not suggested from the preliminary analysis here. Clearly, further analysis of the current data and potentially new measurements will be necessary in the future programme.

The work presented reports a commissioned 2048 crystal LYSO PET detector along with calibration, data analysis, simulation and event reconstruction methodologies for future use in both standard 2γ and novel 3γ imaging studies. The array has spatial, energy, and timing resolutions commensurate with current commercial PET machines. It will underpin future programmes at York having synergy with clinical systems. It will also underpin a future programme aiming to establish the predicted quantum entanglement of the 3γ systems as well as in 2γ systems with greatly increased acceptance compared to earlier apparatus [45, 30].

References

1. Fujimoto M, Sato R, Hamdan M, Uenomachi M, Caradonna P, Stephenson L, Montgomery A, Bordes J, Brown JR, Watts DP and Shimazoe K. Advancing PET through direct imaging of three-photon decay using pure positron emitters. *Communications Physics* 2026 Aug; 9:254. DOI: 10.1038/s42005-026-02782-6. Available from: <https://www.nature.com/articles/s42005-026-02782-6>
2. Tao SJ. Positronium annihilation in molecular substances. *The Journal of Chemical Physics* 1972; 56:5499–510. DOI: 10.1063/1.1677067
3. Eldrup M, Mogensen O and Trumpy G. Positron lifetimes in pure and doped ice and in water. *The Journal of Chemical Physics* 1972; 57:495–504. DOI: 10.1063/1.1677990
4. Trung NT, Duong NT, Hien NQ, Tap TD and Thanh ND. Investigation of ortho-positronium annihilation for porous materials with different geometries and topologies. *Scientific Reports* 2023 Dec; 13. DOI: 10.1038/s41598-023-40901-3
5. Vaquero JJ and Kinahan P. Vaquero PET. 2015 Dec. DOI: 10.1146/annurev-bioeng-071114-040723
6. Holzgreve A, Hellwig D, Barthel H, Beer AJ, Kobe C, Lapa C, Miederer M, Schwarzenböck S, Seifert R, Todica A, Herrmann K, Bengel FM, Schäfers M, Moka D, Luster M and Fendler WP. PET imaging utilization and trends in Germany: a comprehensive survey. *European Journal of Nuclear Medicine and Molecular Imaging* 2025 Oct; 52:4390–8. DOI: 10.1007/s00259-025-07323-x
7. Avachat AV, Mahmoud KH, Leja AG, Xu JJ, Anastasio MA, Sivaguru M and Di Fulvio A. Ortho-positronium lifetime for soft-tissue classification. *Scientific Reports* 2024 Dec; 14. DOI: 10.1038/s41598-024-71695-7
8. Mercurio K, Zerkel P, Laforest R, Sobotka LG and Charity RJ. The three-photon yield from e^+ annihilation in various fluids. *Physics in Medicine and Biology* 2006 Sep; 51. DOI: 10.1088/0031-9155/51/17/N05

References

9. Freedenberg MI, Badawi RD, Tarantal AF and Cherry SR. Performance and limitations of positron emission tomography (PET) scanners for imaging very low activity sources. *Physica Medica* 2014 Feb; 30:104–10. DOI: 10.1016/j.ejmp.2013.04.001
10. Newton R. Entangled polarisation correlations of annihilation gamma and their applications to PET Imaging. Tech. rep. 2022
11. Cherry SR, Sorenson JA and Phelps ME. *Physics in Nuclear Medicine*. Elsevier, 2012 Jan :1–523. DOI: 10.2967/jnumed.113.123125
12. D’Addabbo J, Wardak M and Nguyen PK. Recent Advances in Imaging Inflammation Post-Myocardial Infarction Using Positron Emission Tomography. 2019 Oct. DOI: 10.1007/s12410-019-9515-3
13. Daube-Witherspoon Life Fellow ME, Moore Member SC and Karp Life Fellow JS. Randoms Estimation for Long Axial Field-of-View PET. Tech. rep.
14. Zanzonico P. Instrumentation for Positron Emission Imaging. *Nuclear Oncology: From Pathophysiology to Clinical Applications*. Ed. by Strauss HW, Mariani G, Volterrani D and Larson SM. Cham: Springer International Publishing, 2016 :1–34. DOI: 10.1007/978-3-319-26067-9_{_}37-1. Available from: https://doi.org/10.1007/978-3-319-26067-9_37-1
15. Bass SD, Mariazzi S, Moskal P and Stępień E. Colloquium: Positronium physics and biomedical applications. *Reviews of Modern Physics* 2023 Apr; 95. DOI: 10.1103/RevModPhys.95.021002
16. West RN. Positron studies of condensed matter. *Advances in Physics* 1973 Jan; 22:263–383. DOI: 10.1080/00018737300101299
17. Dirac PA. On the Annihilation of Electrons and Protons. *Mathematical Proceedings of the Cambridge Philosophical Society* 1930; 26:361–75. DOI: 10.1017/S0305004100016091
18. Berens L, Hsu I, Chen CT, Halpern H and Kao CM. An analytic, moment-based method to estimate orthopositronium lifetimes in positron annihilation lifetime spectroscopy measurements. *Bio-Algorithms and Med-Systems* 2024; 20:40–8. DOI: 10.5604/01.3001.0054.9141
19. Harpen MD. Positronium: Review of symmetry, conserved quantities and decay for the radiological physicist. 2004. DOI: 10.1118/1.1630494
20. Wheeler JA. Polyelectrons. *Annals of the New York Academy of Sciences* 1946; 48:219–38. DOI: 10.1111/j.1749-6632.1946.tb31764.x
21. Ore A and Powell+ JL. Three-Photon Annihilation of an Electron-Positron Pair. Tech. rep. 11. 1949
22. Ferrell RA. Q4 journal of experimental and theoretical physics established by E L Nichols in 1S99 Long Lifetime of Positronium in Liquid Helium*. Tech. rep. 1957

23. Kotera K, Yamanaka T and Saito T. Measurement of positron lifetime to probe the mixed molecular states of liquid water. Tech. rep. 2004
24. Eldrup M, Lightbody D and Sherwood JN. THE TEMPERATURE DEPENDENCE OF POSITRON LPPFETIMES IN SOLID PXVALIC ACID. Tech. rep. 1981 :51–8
25. Moskal P, Dulski K, Chug N, Curceanu C, Czerwiński E, Dadgar M, Gajewski J, Gajos A, Grudzień G, Hiesmayr BC, Kacprzak K, Kapłan Ł, Karimi H, Klimaszewski K, Korcyl G, Kowalski P, Kozik T, Krawczyk N, Krzemień W, Kubicz E, Małczak P, Niedźwiecki S, Pawlik-Niedźwiecka M, Pędziwiatr M, Raczyński L, Raj J, Ruciński A, Sharma S, Shopa RY, Silarski M, Skurzok M, Ł Stępień E, Szczepanek M, Tayefi F and Wiślicki W. Positronium imaging with the novel multiphoton PET scanner. Tech. rep. 2021 :4394–407
26. Chauhan VP, Stylianopoulos T, Martin JD, PopoviÄ Z, Chen O, Kamoun WS, Bawendi MG, Fukumura D and Jain RK. Normalization of tumour blood vessels improves the delivery of nanomedicines in a size-dependent manner. *Nature Nanotechnology* 2012; 7:383–8. DOI: 10.1038/nnano.2012.45
27. Sigrist RM, Liao J, Kaffas AE, Chammas MC and Willmann JK. Ultrasound elastography: Review of techniques and clinical applications. 2017. DOI: 10.7150/thno.18650
28. Product Data Sheet DuPont™ Polymeric Adsorbent DuPont™ AmberLite™ XAD™4 Polymeric Adsorbent Macroporous, Adsorbent Resin. Tech. rep. 2023. Available from: www.dupont.com/water/contact-us
29. Product Data Sheet DuPont™ Polymeric Adsorbent DuPont™ AmberLite™ XAD™1180N Polymeric Adsorbent Macroporous, Adsorbent Resin. Tech. rep. 2023. Available from: www.dupont.com/water/contact-us
30. Watts DP, Bordes J, Brown JR, Cherlin A, Newton R, Allison J, Bashkanov M, Efthimiou N and Zachariou NA. Photon quantum entanglement in the MeV regime and its application in PET imaging. *Nature Communications* 2021 Dec; 12. DOI: 10.1038/s41467-021-22907-5
31. Shimazoe K, Yoshino M, Ohshima Y, Uenomachi M, Oogane K, Orita T, Takahashi H, Kamada K, Yoshikawa A and Takahashi M. Development of simultaneous PET and Compton imaging using GAGG-SiPM based pixel detectors. *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* 2020 Feb; 954:161499. DOI: 10.1016/j.nima.2018.10.177
32. Enríquez-Mier-y-Terán FE, Ortega-Galindo AS, Murrieta-Rodríguez T, Rodríguez-Villafuerte M, Martínez-Dávalos A and Alva-Sánchez H. Coincidence energy spectra due to the intrinsic radioactivity of LYSO scintillation crystals. *EJNMMI Physics* 2020 Dec; 7. DOI: 10.1186/s40658-020-00291-1

References

33. Thien TC and Nemallapudi MV. Determination of lutetium density in LYSO crystals: methodology and PET detector applications. *Physics in Medicine and Biology* 2024 Apr; 69. DOI: 10.1088/1361-6560/ad2e6e
34. Luxium Solutions. LYSO Scintillation Material. Tech. rep. Hiram: Luxium Solutions, LLC. Available from: <https://luxiumsolutions.com/radiation-detection-scintillators/crystal-scintillators/lyso-scintillation-crystals>
35. Park CH, Lee A, Kim R and Moon JH. Evaluation of the detection efficiency of Lyso scintillator in the fiber-optic radiation sensor. *Science and Technology of Nuclear Installations* 2014; 2014. DOI: 10.1155/2014/248403
36. 'Berger MJ, 'Hubbell JH, 'Seltzer SM, 'Chang J, 'Coursey JS, 'Sukumar R, 'Zucker DS and 'Olsen K. XCOM: Photon Cross Sections Database. 2010. Available from: <https://www.nist.gov/pml/xcom-photon-cross-sections-database>
37. Dorenbos P. Fundamental limitations in the performance of Ce³⁺-, Pr³⁺-, and Eu²⁺-activated scintillators. *IEEE Transactions on Nuclear Science*. Vol. 57. 3 PART 2. 2010 Jun :1162–7. DOI: 10.1109/TNS.2009.2031140
38. Wehr J, Blaaderen JJ van, Rasch CR and Schaart DR. Comparative analysis of three generations of LYSO:Ce crystals for medical imaging applications. *Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* 2026 Feb; 1082. DOI: 10.1016/j.nima.2025.170919
39. Broadcom. AFBR-S4K33P6425B 8 × 8 SiPM Array, WB-Type, 3 × 3 mm² Channel Size Data Sheet. Tech. rep. 2021. Available from: <https://www.broadcom.com/products/optical-sensors/silicon-photomultiplier-sipm>.
40. PETsys Electronics S.A. PETsys TOFPET2 ASIC. Tech. rep. Oeiras: PETsys Electronics S.A., 2020 Oct. Available from: <https://www.petsyselectronics.com/web/public/products/1>
41. PETsys Electronics S.A. [Proprietary equipment manual]. TOFPET2 ASIC Evaluation Kit: Software user guide v2019.09. Tech. rep. Oeiras: PETsys Electronics S.A., 2019
42. Chen S, Hu P, Gu Y, Yu H and Shi H. Performance characteristics of the digital uMI550 PET/CT system according to the NEMA NU2-2018 standard. *EJNMMI Physics* 2020 Dec; 7. DOI: 10.1186/s40658-020-00315-w
43. Gajos A, Kamińska D, Czerwiński E, Alfs D, Bednarski T, Białas P, Głowacz B, Gorgol M, Jasińska B, Kapłan, Korcyl G, Kowalski P, Kozik T, Krzemień W, Kubicz E, Mohammed M, Niedźwiecki SZ, Pałka M, Pawlik-Niedźwiecka M, Raczyński L, Rudy Z, Rundel O, Sharma NG, Silarski M, Słomski

- A, Strzelecki A, Wieczorek A, Wiślicki W, Zgardzińska B, Zieliński M and Moskal P. Trilateration-based reconstruction of ortho-positronium decays into three photons with the J-PET detector. *Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment* 2016 May; 819:54–9. DOI: 10.1016/j.nima.2016.02.069
44. Lage E, Parot V, Moore SC, Sitek A, Udías JM, Dave SR, Park MA, Vaquero JJ and Herraiz JL. Recovery and normalization of triple coincidences in PET. *Medical Physics* 2015 Mar; 42:1398–410. DOI: 10.1118/1.4908226
45. Bordes J, Brown JR, Watts DP, Bashkanov M, Gibson K, Newton R and Zachariou N. First Detailed Study of the Quantum Decoherence of Entangled Gamma Photons. *Physical Review Letters* 2024 Sep; 133. DOI: 10.1103/PhysRevLett.133.132502