DEVELOPMENT OF A SMALL ANIMAL MR COMPATIBLE PET INSERT

by

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Abstract

Positron Emission Tomography (PET) provides in vivo functional information about a living subject by imaging the distribution of biologically meaningful radiotracers such as 18F-fluoro-deoxy-glucose. PET data is complemented by anatomical information from an imaging modality that produces high tissue contrast such as MRI. The work presented in this thesis is a contribution to a collaboration aimed at creating an MRI compatible high-resolution small animal PET insert for simultaneous PET/MR imaging. The PET system was designed with an outer diameter of 114 mm in order to fit inside of a pre-existing 7T small animal MRI.

During the design of the PET system, Monte-Carlo simulations were created to estimate the resolution and count rate performance of various iterations of the design. These simulations showed that the proposed dual-layer detector design would be effective in mitigating off-centre spatial resolution degradation, and produced resolution of ~ 1 mm full-width at half-maximum in the centre of the field of view. The effective count rate of our system was estimated to be low in comparison to other small animal PET systems due to the small solid angle subtended by the detectors.

A prototype detector block was built incorporating an array of digital photon counters (DPCs) to test the suitability of DPCs as an alternative to silicon photomultipliers for our small animal PET application. Based on the characterization of energy resolution, timing resolution, and rates of count loss as a function of device settings, the most appropriate combination of device settings for our small animal PET application was identified.

Once constructed, the prototype PET system was characterized in terms of spatial resolution and count rate performance. Phantom and rodent images were reconstructed using filtered back projection – 3D reprojection (FBP-3DRP) and a novel point-spread-function modelling maximum likelihood expectation maximization (PSF-MLEM) algorithm. The PSF-MLEM reconstruction algorithm was updated to remove non-uniformity artefacts caused by lack of normalization and systematic inaccuracies present in its original implementation. PSF-MLEM
resulted in higher quality PET images than FBP-3DRP, resolving feature sizes of 0.7 mm in a resolution phantom and showing contrast between the cortex and ganglia in rodent brains.
Preface

The work presented in this thesis is part of a collaboration to design and build a small animal MR compatible PET insert. Unless otherwise stated, all work presented in Chapters 2 to 7 was performed by me. This includes creation and analysis on Monte-Carlo simulations to optimize the detector block design and estimate the system spatial resolution and count rate performance following from a given detector geometry (Chapter 2), characterization of digital photon counters (Chapter 3 and 4), creation of algorithms and software to sort coincidence data into normalized gap filled sinograms (Chapter 5), updating PSF-MLEM reconstruction code to remove non-uniformity artefacts (Chapter 6), and characterizing the completed PET system (Chapter 7). All PET images shown in this thesis were reconstructed by me.

§2.5.1 was previously published in:

A manuscript is currently is preparation to publish the work shown in §2.4.

The remainder of Chapter 2 was previously published in:

A version of the work presented in Chapter 3 (before the advent of incomplete neighbor-logic recovery) was previously published in:

The analysis of the digital photon counter efficiency was updated to reflect incorporation of *incomplete neighbor-logic recovery*. A description of *incomplete neighbor-logic recovery* was previously published in:


A manuscript is currently in preparation to publish the work shown in §5.6.

The reconstruction algorithm presented in §6.1 was developed by Dr. Xuezhu Zhang and was published in:


The measurement of spatial resolution and the results of PET/MR imaging of “Mouse 1” in Chapter 7 were previously published in:


A manuscript is currently in preparation to publish the work shown in Chapter 7.

The PET data and used to reconstruct the mice images in Chapter 5 was acquired by Siobhan McCormick from the University of British Columbia PET group.
The PET data used to measure NECR in §7.4 were acquired by Joel Toth from the Department of Radiology at the University of Manitoba.

The PET data used to reconstruct the NEMA image quality phantom in §7.5 was acquired by Joel Toth and Dr. Andrew L. Goertzen from the Department of Radiology at the University of Manitoba.

The mice presented in Chapter 7 were from a pilot study initiated by Dr. Benedict Albensi from the Department of Pharmacology and Therapeutics at the University of Manitoba. The rats presented in Chapter 7 were from a pilot study initiated by Dr. Ji Hyun Ko from the Department of Human Anatomy and Cell Science at the University of Manitoba.

Animal handing for all rodent imaging was performed by Dr. Michael Jackson at the University of Manitoba Small Animal and Materials Imaging Core Facility and Dr. Dali Zhang from the Department of Human Anatomy and Cell Science at the University of Manitoba.

All MRI imaging was performed by Dr. Richard Buist and Dr. Melanie Martin both from the Winnipeg Health Science Centre.

Ethics approval for mouse imaging presented in Chapter 5 was obtained from the University of British Columbia Animal Care Committee. The name of the study registered with the Animal Care Committee is “VECTor/CT Biodistribution and Imaging Studies” (reference number A12-0172). Ethics approval for simultaneous PET/MR imaging of mice and rats done to produce images Chapter 7 in this thesis was obtained from the Bannatyne Campus Animal Care Committee (University of Manitoba). The name of the study registered with the Bannatyne Campus Animal Care Committee is “Pilot studies of a new small animal PET system for simultaneous PET/MRI imaging” (reference number 15-014 (AC11033)).
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### List of Abbreviations

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>2D</td>
<td>Two Dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three Dimensional</td>
</tr>
<tr>
<td>3DRP</td>
<td>Three Dimensional Reprojection</td>
</tr>
<tr>
<td>APD</td>
<td>Avalanche Photodiode</td>
</tr>
<tr>
<td>CBN</td>
<td>Component Based Normalization</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>DOI</td>
<td>Depth of Interaction</td>
</tr>
<tr>
<td>DLO</td>
<td>Dual-layer Offset</td>
</tr>
<tr>
<td>DPC</td>
<td>Digital Photon Counter</td>
</tr>
<tr>
<td>dSiPM</td>
<td>Digital Silicon Photomultiplier</td>
</tr>
<tr>
<td>FBP</td>
<td>Filtered Back Projection</td>
</tr>
<tr>
<td>FDG</td>
<td>Fluoro-deoxy-glucose</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of View</td>
</tr>
<tr>
<td>FPGA</td>
<td>Field Programmable Gate Array</td>
</tr>
<tr>
<td>FWHM</td>
<td>Full Width at Half Maximum</td>
</tr>
<tr>
<td>FWTM</td>
<td>Full Width at Tenth Maximum</td>
</tr>
<tr>
<td>GATE</td>
<td>Geant4 Application for Tomographic Emission</td>
</tr>
<tr>
<td>GM-APD</td>
<td>Geiger-Mode Avalanche Photodiode</td>
</tr>
<tr>
<td>IF</td>
<td>Inhibit Fraction</td>
</tr>
<tr>
<td>LOR</td>
<td>Line of Response</td>
</tr>
<tr>
<td>LSO</td>
<td>Lutetium Oxyorthosilicate</td>
</tr>
<tr>
<td>LYSO</td>
<td>Lutetium Yttrium Oxyorthosilicate</td>
</tr>
<tr>
<td>MLEM</td>
<td>Maximum Likelihood Expectation Maximization</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NECR</td>
<td>Noise Equivalent Count Rate</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PMT</td>
<td>Photomultiplier Tube</td>
</tr>
<tr>
<td>PSF</td>
<td>Point Spread Function</td>
</tr>
<tr>
<td>RF</td>
<td>Radiofrequency</td>
</tr>
<tr>
<td>RTL</td>
<td>Row Trigger Line</td>
</tr>
<tr>
<td>SiPM</td>
<td>Silicon Photomultiplier</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal to Noise Ratio</td>
</tr>
<tr>
<td>STIR</td>
<td>Software for Tomographic Image Reconstruction</td>
</tr>
<tr>
<td>TS</td>
<td>Trigger Scheme</td>
</tr>
<tr>
<td>YSO</td>
<td>Yttrium Oxyorthosilicate</td>
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Chapter 1: Introduction and Background

The work presented in this thesis represents a contribution to a multi-institution collaboration aimed at designing and building a small animal MRI (magnetic resonance imaging) compatible PET (positron emission tomography) insert for simultaneous PET/MR imaging. The collaboration has consisted of faculty and students from The University of British Columbia in Vancouver, TRIUMF in Vancouver, The University of Manitoba in Winnipeg, Lawson Health Research Institute in London, Ontario, and McGill University in Montreal. Design of the PET system began in January 2011, and the first prototype was built in May of 2014.

An insert means that the PET system can be inserted into an existing MRI scanner. The PET insert was designed to fit inside of the 114 mm inner diameter Bruker BGA-12S gradient coil used in the 7T Bruker Avance III MRI installed at the Health Science Centre in Winnipeg. While operating simultaneously with MRI, the MRI radiofrequency (RF) coil needs to fit inside of the PET insert. The inner diameter of the PET insert was therefore constrained to be large enough to accommodate the 60 mm outer diameter Bruker 35 mm RF volume coil. The diameter of the imaging field of view (FOV) is appropriate for mouse or rat imaging.

Availability of simultaneous MR images to complement PET adds significant value to preclinical studies when compared to PET alone, or simultaneous PET / computed tomography (PET/CT), which has become a very mature technology. As described in more detail in §1.2.3, simultaneous MRI can provide an anatomic backdrop to complement a PET image, aid in image analysis, or be incorporated into PET image reconstruction. MRI provides far superior soft-tissue contrast when compared to CT and does not expose the subject to ionizing radiation. MRI can provide additional functional information such as perfusion, blood oxygen utilization, and molecular spectroscopy.

Although it is not the case today, when this project commenced no commercially available preclinical PET/MR system existed. An MR compatible PET insert rather than a fully integrated PET/MR system creates a cost-effective way of obtaining simultaneous PET/MR
data, and also provides the option for the PET and MR systems to be operated separately to increase workflow or to allow for more space in the field of view of each modality.

A design goal for the PET system was that its spatial resolution would be sufficiently good to resolve feature sizes of ~ 1 mm. PET spatial resolution is typically very non-uniform and degrades rapidly as one moves away from the radial centre of the FOV. This phenomenon is due to the parallax effect [1], and can be mitigated by use of advanced detector hardware that can measure the depth of interaction (DOI) of the incident annihilation photons [2]–[8] in the detector and use of sophisticated image reconstruction algorithms such as point spread function modelling maximum likelihood / expectation maximization (PSF-MLEM, also referred to as resolution recovery reconstruction) [9]–[12]. Both of these approaches to mitigate the parallax effect have been undertaken by our collaboration.

This chapter will introduce the relevant background material necessary to understand the context and motivation for the work performed in this thesis. It will finish by giving an outline of the work detailed in the later chapters.

1.1 Positron Emission Tomography

Positron Emission Tomography (PET) is an imaging modality that is capable of producing a 3D image showing the distribution of a positron-emitting isotope distributed within the FOV of the scanner. PET is useful in medicine because these positron-emitting isotopes can be tagged to biologically relevant molecules such as analogs of glucose or L-DOPA. Such a molecule tagged with a positron-emitting isotope is called a radiotracer. When injected into a subject (human or animal), the PET image will provide an in vivo map of the distribution of that molecule throughout the body with picomolar sensitivity [13], [14]. PET is a tool that is useful for both diagnostic medicine and also medical research.

A PET scanner does not detect the positrons themselves, for they very rarely exit the subject. Instead, a PET scanner detects the radiation following from the annihilation of positrons with electrons in the surrounding medium. A PET scanner is, at its core, a ring of radiation
detectors that surround the FOV. Through mathematical modelling, reconstruction converts the raw measurements into a PET image.

1.2 The Role of PET Imaging in Medicine

1.2.1 PET Tracers and Their Applications

The usefulness of PET is heavily dependent on the tracers that are available. The expansive catalogue of PET tracers that includes radioisotope labelled analogs of enzymes, neurotransmitters, drugs, and hormones make PET a very versatile medical tool in both clinical and research settings.

\(^{18}\text{F-FDG}\) \((^{18}\text{F labelled fluoro-deoxy-glucose})\) is an analog of glucose and is the most commonly used PET tracer. When introduced into the body, the body’s natural processes will treat it like glucose up to the point where it is taken up by cells and phosphorylated. Being only an analog of glucose with a slightly different chemistry, it will not participate in metabolism past the phosphorylation stage [15]. Nonetheless FDG PET provides insight into the rate and distribution of glucose metabolism in the subject. FDG is commonly used in oncology for detecting and staging tumours [15]–[17], which metabolize glucose much faster than the surrounding tissue.

PET tracers have seen wide use in neurology. FDG is used to investigate brain glucose metabolism and how it is affected by disease. \(^{18}\text{F-FDOPA}\) is an analog of L-DOPA, which is the precursor of dopamine. \(^{11}\text{C-DTBZ}\) \((^{11}\text{C labelled dihydrotetrabenazine})\) binds to VMAT2 (vesicular monoamine transporter 2), which is a transporter that facilitates the vesicular storage of neurotransmitters such as dopamine and serotonin. \(^{11}\text{C-Raclopride}\) is an antagonist to D\(_2\) dopamine receptors. These tracers have been used to study the dopaminergic system in the human brain and have led to insights into diseases such as Parkinson’s and Alzheimer’s disease [18]–[21].

\(^{82}\text{Rb, }^{13}\text{N-NH}_3\text{ and }^{15}\text{O-H}_2\text{O}\) have all been used as tracers to measure cardiac perfusion, which is relevant when detecting cardiac disease such as coronary artery disease [22]. PET
has the potential to be a useful tool to study gene expression in gene therapy. $^{18}$F-FGCV (fluoroganciclovir) has been used to image the expression of the herpes simplex virus type-1 thymidine kinase, which has been widely investigated as a potential transgene for use in gene therapy to treat cancer [23]. Although it is not directly applicable to medicine, it is interesting to know that PET has even been used to study photosynthesis in plants using $^{11}$C-CO$_2$ tracers [24], [25].

### 1.2.2 PET/CT

It is desirable to have an anatomical image of the subject to compliment the functional information provided by PET, otherwise it is difficult to determine the organ or region of an organ where a PET tracer is distributed. CT (computed tomography) provides a high-resolution anatomic image with contrast generated from the different x-ray attenuation power of different tissues. A PET/CT system combines a PET scanner and a CT scanner into the same gantry. The PET system cannot be housed directly inside of the CT, so the two systems sit side-by-side. A bed moves the subject through each scanner so that sequential imaging can be done.

Although imaging is not truly simultaneous, it is better than the alternative of imaging a subject with PET, and then transferring the subject to a separate CT scanner. In clinical settings this would create a burden of scheduling two separate examinations. Combined PET/CT also removes ambiguity when aligning the images, and eliminates the possibility of organ movement that can happen when a subject is transferred between beds [26]. Combined PET/CT has been shown to improve accuracy of malignant tumour detection and cancer staging as an alternative to separate PET and CT scans [27], [28].

The CT image also provides an excellent-quality map of photon attenuation power that can be used to perform corrections for scatter and attenuation (discussed in §1.4.3). The attenuation maps available from the transmission scans of stand-alone PET systems are very noisy, which has been shown to add noise to PET images [29] and can add bias due to various factors such as contamination from emission data [30].
1.2.3 PET/MR

The motivation for PET/MR is very similar to the motivation for PET/CT. When needed as an anatomic backdrop, MRI can provide much better soft-tissue contrast than CT [31]. This is especially true in regions such as the brain. Aside from tissue contrast, MRI is capable of imaging diffusion, blood flow, and spectroscopy. A major benefit of PET/MR over PET/CT is the reduction in radiation dose to the patient; MRI does not use any ionizing radiation. PET/MR systems have been made in the past that placed both systems side-by-side in the same gantry like PET/CT – but newer PET/MR systems place the PET scanner inside the MRI and so allow for true simultaneous imaging [32]. Simultaneous imaging opens the door for synergies that could not have been possible with separate examinations of PET and MRI. For example, simultaneous PET/MR could allow one to temporally correlate a process like blood oxygen utilization (measured with MRI, also known as fMRI) with the delivery of a pharmaceutical (measured with PET) [33]. MRI data acquired during a PET acquisition can be used to correct for patient motion in the PET reconstruction [34]. Simultaneous imaging also reduces the scanning time per patient (or per animal in the case of preclinical PET/MR). A notable drawback with PET/MR compared with PET/CT is that there is no unambiguous way to convert an MRI image to a map of photon attenuation power for use in scatter and attenuation correction [35].

1.3 Relevant Radiation Physics

1.3.1 Radioactive Decay

The isotopes used in PET tracers emit positrons because of the radioactive decay of their nuclei. As more nuclei decay, the abundance of these isotopes and therefore the activity of the tracer, decreases with time. If the activity of a sample of radiotracer at the time of production is $R_0$, its activity a time $t$ later is:

$$R(t) = R_0 \left( \frac{1}{2} \right)^{t/\tau_{1/2}} = R_0 e^{-t \ln(2) / \tau_{1/2}}$$  \hspace{1cm} (1.1)
Here $T_{1/2}$ is the *half-life* and is a property of the isotope that describes the amount of time necessary for the number of isotopes in the sample to decay by a factor of 2. The half-lives of isotopes used in PET are typically on the order of minutes to hours. It is therefore important to account for the decaying activity of the tracer to quantify its concentration during a PET scan.

### 1.3.2 Positron Emission

The emission of a positron from an isotope is the result of $\beta^+$ decay, where a proton within the nucleus of the unstable isotope converts into a neutron, resulting in a lower energy configuration of nucleons in the nucleus. In order to conserve charge and lepton number a positron ($e^+$) and a neutrino ($\nu$) are ejected from the nucleus. The decay can be represented by the following nuclear decay equation:

$$\frac{A}{Z}X \rightarrow \frac{A}{Z-1}Y + e^+ + \nu + \text{energy}$$

The mass deficit between the original unstable isotope and the products of its decay is converted to kinetic energy, which is shared between the positron and neutrino. This energy is on the order one MeV for isotopes used in PET.

### 1.3.3 Positron Annihilation

The positron, which is the anti-matter partner of an electron, is emitted from the nucleus of an unstable isotope at a relativistic speed. The positron will interact with the surrounding material and lose its energy through Coulombic interaction with charges in the material and rapidly come to a thermal energy. The time it takes for the positron to come to an energy on the order of 1 eV is on the order of 1 ps [36]. Once the positron has thermalized it will diffuse for a short while and then annihilate with an electron, producing two annihilation photons. The average distance that a positron travels between emission and annihilation is called the *positron range*. 
The energy and momentum of the annihilation photon pair must conserve the energy and momentum of the positron-electron pair. In the zero-momentum moving frame of reference, the annihilation photons will be exactly collinear and will each have energy equal to the rest-mass of an electron (511 keV). In the lab frame of reference, the electron-positron pair may have an appreciable amount of net momentum. The thermalized positron will have very little momentum; the majority of the momentum is due to the electron if it is bound to an atom [37]. This manifests in acollinearity between the annihilation photons on the order of 1°. There is also a shift in the energy of each annihilation photon away from 511 keV (Doppler broadening), but not by an amount great enough to be relevant to PET imaging.

1.3.4 Positron Emitting Isotopes Useful for PET

While hundreds of positron emitting isotopes exist, only a select few are useful for PET. Table 1.1 lists some of the most commonly used isotopes for PET. An isotope’s applicability depends on its half-life and range, as well as the chemical reactions that the element lends itself to. The average range shown in Table 1.1 is taken from [38].

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life (minutes)</th>
<th>Average Range (mm)</th>
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<tbody>
<tr>
<td>$^{15}$O</td>
<td>2.03</td>
<td>3.28</td>
</tr>
<tr>
<td>$^{14}$N</td>
<td>9.97</td>
<td>2.05</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20.3</td>
<td>1.52</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>109.8</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Table 1.1. Commonly used isotopes for PET

A very short half-life creates logistical problems when trying to administer a radiotracer to a subject. If a certain quantity of activity is needed for a PET scan, a significantly higher amount of activity needs to be produced to allow time for delivery to the PET facility and administration to the patient. A long half-life is problematic because of the reason of committed-dose. A long-lived tracer will stay in a subject’s body and continue to dose the subject for a period of time far exceeding the amount of time required for imaging.

Positron emitters with a short positron range are more appropriate for PET. As will become obvious in §1.4, a PET scanner actually images the spatial distribution of positron
annihilation, not positron emission. Because positrons will travel a short distance from the point of emission, the phenomenon of positron range blurs the image. Of the isotopes listed in Table 1.1, $^{18}$F has the lowest positron range.

Most PET tracers will have an isotope attached to a complex molecule (a notable exception is $^{15}$O-$\text{O}_2$, in which diatomic oxygen gas containing a small amount of $^{15}$O is inhaled). The chemistry of an isotope needs to be appropriate so that it can be incorporated into a radiotracer with useful biologic function at a high abundance, and in a short enough period of time so as to not decay before the tracer is manufactured.

### 1.3.5 Interaction of High Energy Photons with Matter

When an annihilation photon pair is emitted in the subject, these photons can interact in both the subject and in the detectors by photoelectric absorption and Compton scattering. The characteristics of how the photons interact in both the subject and the detectors are of crucial importance to understanding how a PET image is formed.

#### 1.3.5.1 Compton Scattering

A photon may have an interaction with an electron in which a fraction of the photon’s energy and momentum is transferred to the electron. This interaction follows the characteristics of a collision between two particles. The photon will be scattered, that is, its direction of travel will be altered by an angle $\theta$ and it will lose a fraction of its energy. If $h\nu$ is the energy of the original photon, the energy of the photon after scattering off an electron by angle $\theta$ is:

$$h\nu' = \frac{h\nu}{mc^2 (1 - \cos \theta) + 1} \quad (1.2)$$

The scattering angle following a Compton interaction is a random variable, whose probability distribution is described by the Klein-Nishina formula [39]. The scattering cross-section per unit solid angle is:
\[
\frac{d\sigma}{d\Omega} = \frac{r_0^2}{2} (1 + \cos^2 \theta) \left( \frac{1}{1 + \alpha (1 - \cos \theta)} \right)^2 \left( 1 + \frac{\alpha^2 (1 - \cos \theta)^2}{(1 + \alpha (1 - \cos \theta))(1 + \cos^2 \theta)} \right)
\]

(1.3)

Here \(r_0^2\) is the classical electron radius and \(\alpha\) is the energy of the photon as a fraction of the rest-mass of an electron. Once multiplied by the number of electrons per unit volume, the cross section gives the probability of undergoing a Compton scatter in the direction of \(d\Omega\) per unit solid angle per unit length that the photon travels through the material. Equations (1.2) and (1.3) are summarized in Table 1.2.

<table>
<thead>
<tr>
<th>Angle ([^\circ])</th>
<th>(h\nu) [keV]</th>
<th>(\frac{d\sigma}{d\Omega}) [relative to (\theta=0^\circ)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>511</td>
<td>1.00</td>
</tr>
<tr>
<td>15</td>
<td>494</td>
<td>0.90</td>
</tr>
<tr>
<td>30</td>
<td>451</td>
<td>0.69</td>
</tr>
<tr>
<td>45</td>
<td>395</td>
<td>0.48</td>
</tr>
<tr>
<td>60</td>
<td>341</td>
<td>0.32</td>
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<tr>
<td>75</td>
<td>293</td>
<td>0.23</td>
</tr>
<tr>
<td>90</td>
<td>256</td>
<td>0.19</td>
</tr>
<tr>
<td>105</td>
<td>226</td>
<td>0.18</td>
</tr>
<tr>
<td>120</td>
<td>204</td>
<td>0.18</td>
</tr>
<tr>
<td>135</td>
<td>189</td>
<td>0.19</td>
</tr>
<tr>
<td>150</td>
<td>178</td>
<td>0.19</td>
</tr>
<tr>
<td>165</td>
<td>172</td>
<td>0.20</td>
</tr>
<tr>
<td>180</td>
<td>170</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Table 1.2. Energy of a scattered photon and relative probability of scattering as a function of scattering angle for 511 keV photons.

Table 1.2 shows that Compton scattering is forward peaked at \(h\nu = 511\) keV; the photon is much more likely to scatter in a direction that deviates slightly from the initial direction than it is to scatter in a direction that deviates greatly from the initial direction. An annihilation photon can lose a significant fraction of its energy after scattering, but the amount of energy loss decreases for smaller scattering angles.

The total Compton cross-section can be found by integrating equation (1.3) over the unit sphere. Equation (1.3) has an energy dependence such that at very high and very low energy
the cross section goes to zero. At 511 keV, the cross section is relatively flat as a function of energy, dropping by \(-0.1\%\) per keV. Equation (1.3) is only valid for free electrons. Due to interaction with the nucleus, the Compton cross-section deviates slightly to lower values at lower energy for more tightly bound electrons [39].

1.3.5.2 Photoelectric Absorption

A second way that a photon can interact with matter is through *photoelectric absorption*. In this process, a photon will interact with an atom and will result in the ejection of one of its bound electrons. The entire energy of the photon is transferred to the atom, and so the photon ceases to exist after the interaction. The majority of the energy is transferred to the ejected electron in the form of kinetic energy.

Unlike Compton scattering which is an interaction between an electron and a photon, photoelectric absorption is an interaction between a photon and an entire atom. Photoelectric absorption between a photon and a free electron is in fact impossible because the interaction cannot conserve both energy and momentum. The interaction cross-section depends on the energy of the photon and the atomic number \(Z\) of the atom hosting the interaction. An analytic form of the cross-section is not possible to produce. Measurements show that the interaction cross section of an atom is roughly proportional to the inverse cube of \(h\nu\), and the dependence on \(Z\) is roughly proportional to \(Z^4\) [39]. The cross section per electron therefore has a \(Z^3\) dependence. Abrupt jumps in the cross-sections exist at values of \(h\nu\) corresponding to the binding energies of specific electrons bound to the atom.

1.3.5.3 Total Interaction Cross Section

Tabulated values of the photoelectric absorption cross section and total Compton cross section are available from the website of the National Institute of Standards and Technology (NIST; an agency in the U.S. Department of Commerce) [40] as mass attenuation coefficients. Values of the cross sections for two compounds – water and Lu₂SiO₅ – were downloaded from the website and converted to linear attenuation coefficients \(\mu_{\text{photoelectric}}\) and \(\mu_{\text{Compton}}\) (probability of an interaction per unit length travelled by a photon through the
material). Lu$_2$SiO$_5$ is a commonly used scintillator for PET detectors, usually called LSO. The total linear attenuation coefficient $\mu$ is the sum of the linear attenuation coefficient from all of the processes by which a photon can interact in matter. There exist other phenomena by which photons can interact with matter: for example Rayleigh scattering and pair production. At the photon energies encountered in PET, Rayleigh scattering occurs at a low enough probability as to be insignificant, and pair production does not occur at all. When the term linear attenuation coefficient is used in this thesis, it refers to the total effect of Compton scattering and photoelectric absorption. Fig. 1.1 shows the photoelectric, Compton, and total linear attenuation coefficients for water and LSO as a function of photon energy.

$$\mu = \mu_{\text{Compton}} + \mu_{\text{photoelectric}}$$

(1.4)

![Cross sections for Compton scattering and photoelectric absorption as a function of photon energy.](image)

Fig. 1.1 shows that for the photon energies relevant to PET the dominant process for photon interaction in water is Compton scattering. This is relevant to PET because the cross-sections that describe annihilation photon interaction with the subject (whether human or animal) are very similar to the cross-sections for water (with the exception of bone). At 511 keV, both Compton and photoelectric interaction are important factors in the interaction of annihilation
photons with LSO. The probability of photon interaction by either mechanism is higher for LSO than for water because it is significantly denser than water (7.44 g/cm\(^2\)), but is especially high for photoelectric absorption because LSO has a higher effective atomic number \((Z_{Lu} = 71, Z_{Si} = 14)\). When a 511 keV photon undergoes Compton scattering in a material like LSO, the scattered photon will have its energy lowered by an amount on the order of hundreds of keV (Table 1.2). It is very probable that the scattered photon will interact in the LSO a second time by photoelectric absorption. The properties of LSO (high density and high Z) are typical of most other scintillator materials used in PET.

1.3.5.4 Photon Attenuation

The linear attenuation coefficient defined in equation (1.4) is the probability that a photon will interact in a material per unit distance travelled in that material. It follows from this that if there is a flux of parallel photons \(\Phi\) moving through a material, the change in flux after moving a short distance \(dx\) is:

\[
d\Phi = -\mu dx
\] (1.5)

If the flux was \(\Phi_0\) at \(x=0\), the factor by which the flux has diminished a distance \(x\) into the material is:

\[
\frac{\Phi(x)}{\Phi_0} = e^{-\int_0^x \mu dx}
\] (1.6)

Here we have allowed \(\mu\) to be non-constant along the path of the photons. Note that here flux strictly means the flux of primary photons. When a photon interacts it may be due to a Compton scatter, in which case the photon may remain in the path of the beam as a secondary photon. When a single photon is travelling through a material, equation (1.6) may be interpreted as the probability that it can travel a distance \(x\) without interacting.
1.4 Basics of PET Imaging

The smallest unit of raw data that a PET scanner measures is a *single*. This refers to the detection of a single annihilation photon. A single is of no use to reconstruct the activity distribution unless it is detected in coincidence with its partner annihilation photon. When two annihilation photons are detected at the same time (or very nearly the same time), this is referred to as a *coincidence*. Although there do exist reconstruction methods that reconstruct an image directly from a list of detected coincidences [41], [42], the usual procedure for reconstructing PET data is to histogram the coincidences into a *sinogram* which forms the input to the reconstruction algorithm. This chapter will describe the processes of sorting the singles for coincidences, and histogramming the coincidences into sinograms. In this chapter, it is assumed that the PET scanner can accurately determine the position, energy, and time of each PET single. §1.5 will describe the physical processes by which a single is detected, and the limitations to the accuracy of the measurement.

1.4.1 Coincidence Sorting

A PET detector can measure the time at which an annihilation photon interacts in a detector to within a few nanoseconds (or even less than a nanosecond for more recent detector technology [43]–[45]). The difference between the actual time of interaction and the measured time of interaction has a probability distribution that is usually approximated by Gaussian curve. The timing resolution of a PET detector is described by the full width at half-maximum (FWHM) of this distribution.

Two singles are said to be in coincidence if their time-stamps are equal to within a pre-set *coincidence window*. The size of the coincidence window depends on the timing resolution of the PET detector. A coincidence window of twice the timing resolution FWHM is large enough to capture nearly all true coincidences while not being excessively large. A *true* coincidence refers to a coincidence where both detected photons are partners from the annihilation of the same positron.
The fundamental assumption in PET image reconstruction is that when a true coincidence is detected, the location of the positron emitting isotope which produced the two photons lies somewhere along the line of response (LOR) that connects the two points of detection. Each LOR is specified by four coordinates: \( r \), \( \phi \), \( z \), and \( \tan \theta \). As illustrated in Fig. 1.2, \( r \) is the radial distance between the LOR and the central axis of the PET scanner, \( \phi \) is the direction of the LOR when viewed from the front of the PET scanner, \( z \) is the axial position of the LOR (more precisely, the axial position of the point on the LOR closest to the central axis of the PET scanner), and \( \theta \) is the tilt angle of the LOR out of the transaxial plane.

![Fig. 1.2. Illustration of the meaning of the four LOR coordinates: \( r \), \( \phi \), \( z \), and \( \tan \theta \). (a) and (b) respectively show a simple PET scanner from the front and side.](image)

### 1.4.2 Sinogram Formation

A sinogram is a four dimensional histogram that counts the number of detected coincidences in uniformly spaced intervals of \( r \), \( \phi \), \( z \), and \( \tan \theta \). Each sinogram bin counts the number of coincidences in all of the LORs that map to that bin (more than one LOR with slightly different positions may map to the same bin). Assuming that the number of counts measured by each LOR is proportional to the concentration of radioisotopes along that LOR, the sinogram can be interpreted as a set of projections through the activity distribution. Fig. 1.3 illustrates this idea. Activity within the FOV is represented as red rectangles. Sets of parallel LORs are represented as dashed lines, and the projections represented by the counts in the corresponding sinogram bins are drawn above the scanner.
First consider a 2D PET scanner and a sinogram that histograms according to r and \( \phi \). It is easy to see from Fig. 1.3a that if one takes just the bins corresponding to a certain value of \( \phi \) and organizes those bins according to r, then this would create a 1D projection through the 2D activity distribution. The 2D sinogram contains projections from all angles around the unit circle. Now considering Fig. 1.3a and b together: if one takes just the bins corresponding to a particular combination of \( \phi \) and \( \tan(\theta) \), and then organizes those bins according to r and z, this would form a 2D projection through the 3D activity distribution. Unlike the 2D case, the 3D PET scanner does not measure 2D projections around the entire unit sphere because the PET scanner is a cylinder and is open at both ends.

1.4.3 PET Data Corrections

In the above explanation of why a sinogram can be viewed as a set of projections through the activity distribution, a number of complicating factors were ignored. In this section, we will describe certain phenomena that invalidate the assumptions made in the previous section, and discuss methods to correct for these effects.

1.4.3.1 Randoms Correction

Although it is true that the number of *true coincidences* measured along each LOR should be proportional to the amount of activity along that LOR, not all coincidences can be considered
as true coincidences. Fig. 1.4 illustrates examples of what are called random coincidences and scattered coincidences.

![Diagram of true, random, and scattered coincidences](image)

**Fig. 1.4.** Examples of a true coincidence (a), a random coincidence (b), and a scattered coincidence (c). The paths followed by annihilation photons are illustrated by solid blue lines, while the points of their emissions are illustrated in red. The LOR that these random and scattered coincidences would be assigned to is shown as a dashed line.

A random coincidence occurs when two annihilation photons from two separate annihilations are detected in coincidence. The annihilations that contribute to random coincidences do not necessarily have to originate in the FOV. If the subject is longer than the FOV, annihilation photons originating from outside of the FOV can be detected. If the rates of singles hitting detectors i and j are $S_i$ and $S_j$, the rate of random coincidence detection in LOR-ij will be:

$$R_{ij} = 2\tau S_i S_j$$  \hspace{1cm} (1.7)

Here $\tau$ represents the length of the coincidence window. If the electronics of the PET scanner are configured to report the rate of singles detection from each detector element, then one can use equation (1.7) to estimate how many randoms were recorded between each detector pair and subtract the estimate of randoms from the data.

A second strategy to estimate the number of randoms detected by each detector pair is to use a delayed coincidence window approach. The mean number of random coincidences detected
between any two detectors i and j in the prompt window (where timestamp differences are in the range [-τ, τ]) should be equal to the mean number of random coincidences measured in the delayed window [delay - τ, delay + τ], where delay is an interval of time much greater than the timing resolution of the detectors. When the list of singles is sorted for coincidences, delayed coincidences can be subtracted from prompt coincidences.

1.4.3.2 Scatter Correction

As shown in Fig. 1.5c, a scattered coincidence occurs when one (or both) of the annihilation photons from the same annihilation scatters in the subject by Compton scattering before being detected. As was shown in Table 1.2, scattered photons lose energy and the larger the scatter angle, the more energy that is lost. The first line of defence against having scatter contaminate the data is to use an energy window, where any singles with detected energy outside of that window are discarded from the data set. A typical energy window is 300 to 700 keV. This way, photons that scatter at a large angle can be removed from the data set.

Some strategies to estimate the remaining scatter exploit the fact that Compton scattering of 511 keV photons in the subject is forward peaked. If a sinogram were created where the scatter was left in the data, the regions of the sinogram where the counts of true coincidences peaked would correspond very well with the regions where scattered coincidences peaked, with the distribution of scatters being broadened compared with the trues. A very simple way to correct for scatter is to fit a Gaussian function to the outer edges of each projection and then subtract these Gaussian functions from each projection [46]. More sophisticated strategies model the scatter sinogram as a convolution of a scattering kernel with the activity distribution [47].

The strategies mentioned above are quite simplistic and are not guaranteed to model the true form of the scatter sinogram. The best strategies to estimate the distribution of scatter in the data are ones that use Klein-Nishina cross-sections to estimate the distribution of scatter. For example, if one had a map of linear attenuation coefficient of the subject (a μ-map) one could start with an initial estimate of the activity distribution and model the amount of scatter that
would be detected by LOR using the Klein-Nishina cross-sections. This has been done with both analytic models [48], [49] and Monte-Carlo simulations [50], [51]. The initial estimate of scatter would then be subtracted from the data in order to get a more refined estimate of the activity distribution, and the process iterated a few times.

1.4.3.3 Attenuation Correction

As described in §1.3.5.4, photons travelling through a subject will be attenuated because of Compton scattering and photoelectric absorption. LORs that pass through more attenuating material will therefore underrepresent the projection of the activity distribution. This is illustrated in Fig. 1.5. Projections through the activity distribution (red square) are shown in two orthogonal directions. The activity is within an attenuating subject, represented in gray, with highly attenuating features (such as bones) represented in black.

Fig. 1.5. Illustration of how attenuation can alter the projections of an activity distribution.

The probability that a pair of annihilation photons can both exit the subject without interacting is the probability that the first photon will not interact, times the probability that the second photon will not interact. In one had a map of the attenuation coefficient for 511 keV photons (the μ-map, first mentioned in §1.4.3.2), one could use equation (1.6) to estimate these probabilities. With reference to Fig. 1.6, the probability that neither
annihilation photon originating at point o will interact before reaching points i and j is given by:

\[ \text{Prob}_{\text{NoScatter},ij} = e^{-\int_{i}^{j} \mu dx} - \int_{i}^{j} \mu dx = e^{-\int_{i}^{j} \mu dx} \]  

(1.8)

Fig. 1.6. Illustration of how the amount of attenuation along LOR-ij is calculated.

Conveniently, the probability of photon interaction along an LOR has no dependence on the position along that LOR where the annihilation occurred. The number of counts detected along each LOR can be rescaled by dividing by equation (1.8) to correct for the phenomenon of attenuation. This assumes that a \( \mu \)-map is available. The \( \mu \)-map can be produced from a CT image. It is very straightforward to convert a CT image from Hounsfield units into the linear attenuation coefficient for 511 keV photons [52]. Many PET scanners these days are paired with CT scanners for dual modality PET/CT imaging. When PET/MR is performed the MRI image can be converted to a \( \mu \)-map – although this conversion is not as straightforward as CT based attenuation [35]. Standalone PET systems are usually equipped with a radioactive point source that can rotate around the FOV. This acquisition is nearly identical to a CT acquisition with the exception that the source of photons is an isotope point source rather than an x-ray tube. The data are reconstructed using CT reconstruction algorithms to produce the \( \mu \)-map.
1.4.3.4 Normalization

Even once data are corrected for randoms, scatter, and attenuation, one cannot say that the sinogram represents a set of projections through the activity distribution unless each detector pair detects the radioactivity along the LOR joining them with the same sensitivity. In reality, the sensitivity of each detector pair is non-uniform, and correction for this variation in sensitivity is called *normalization*.

The most obvious way to correct for detector pair sensitivity is to expose each detector pair to a known amount of radioactivity for a known amount of time and record the number of detected coincidences (corrected for randoms, scatter, and attenuation). The sensitivity is then the ratio between the number of detected coincidences divided by the amount of activity along the LOR divided by the duration of the acquisition. This method is called *direct normalization*. It provides an unbiased estimate of the sensitivity of each LOR, but requires that a very large amount of data be collected to reduce noise in the estimates. Direct normalization can require many hours of acquisition [1], [53].

The sensitivity of each LOR tends to drift with time, so normalization needs to be repeated periodically (on the order of weeks to months). Direct normalization can be impractical due to the long amount of time required. A more sophisticated technique called *component based normalization* can produce low noise estimates of the sensitivity of each detector pair from a much smaller amount of data than direct normalization [54]–[58]. Component based normalization was implemented for our prototype PET system, and so the theory and details of its implementation will be given in Chapter 5.

1.4.3.5 Dead-time Correction

The rate at which a PET detector element can detect annihilation photons is limited. Once a photon is detected, a period of time must pass before another photon can be detected. This is due to the amount of time it takes for electronics to digitize and process the information about the detection, and the amount of time it takes for the detector to resettle to its resting state. This period of time is called the *deadtime* of the detector, $\tau_{dt}$. If two annihilation photon
interactions in the same detector are separated by a period of time less than $\tau_{dt}$, the second will not be detected. This causes a drop in sensitivity that needs to be corrected for.

Deadtime can be modelled as either non-paralyzable or paralyzable. In the non-paralyzable model, the detector will become re-armed a period $\tau_{dt}$ after it was first made dead, regardless of any second interaction that occurred in the detector when it was dead. In the paralyzable model, the detector will be dead for a period $\tau_{dt}$ that restarts every time the detector is hit, even when it is already dead. As the rate of photons hitting the detector becomes very high, the detection rate of a non-paralyzable detector will asymptotically approach $\tau_{dt}^{-1}$, while the detection rate of a paralyzable detector will asymptotically approach 0.

If the deadtime behaviour of the detectors in a PET scanner is understood, then the deadtime fraction (fraction of time it is non-responsive) of each detector block can determined from the instantaneous singles rate in that detector. The number of coincidences measured from each detector pair can then be rescaled by dividing by the deadtime fraction of each of the detectors involved.

1.5 PET Instrumentation

The detectors that surround the FOV detect annihilation photons and report the position of the interaction, deposited energy, and the time of the interaction. The majority of PET scanners are built from discrete detector blocks that detect annihilation photons using a scintillator coupled to one or more photomultipliers. Scintillators are a class of material that emits a small amount of visible light in response to a high-energy photon interacting in it (on the order of thousands to tens of thousands of visible photons per 511 keV of energy deposited [59]). When this visible light falls on a photomultiplier, the photons are converted to electrons. The photomultiplier then amplifies this current to the point where it can be detected. A small number of PET scanners use other technology such as CZT crystals [60], [61] that do not require readout from a photomultiplier. Those blocks work much differently than blocks incorporating scintillators, but their aim is still to detect the position, energy, and time of annihilation photon interactions.
Fig. 1.7 shows schematics of two very common designs for PET detector blocks. Fig. 1.7a shows a 2D representation of a detector block which uses one-to-one coupling between scintillator crystals and photomultipliers. In such a block design, crystals are optically isolated from their neighbours. When an annihilation photon interacts in the detector block, the position of the interaction can be localized to within one crystal. For such a block, higher spatial resolution can only be achieved by using smaller crystals. This necessitates the use of smaller photomultipliers. It becomes technologically cumbersome and expensive to readout many small photomultipliers. An alternative to one-to-one coupling is to have a large array of small detector crystals read out by a small number of larger photomultipliers. Fig. 1.7b and c respectively show side and front views of an example of such a detector block. In this case the crystals, which are still optically isolated from each other, are mated to the photomultipliers through a diffuser (shown in white), which allows scintillation light coming from the bottom of one crystal to spread out and fall on multiple photomultipliers.

![Fig. 1.7](image)

**Fig. 1.7.** (a) shows a side-view of a detector block made with one-to-one coupling between detector crystal and photomultiplier. (b) and (c) respectively show side and front views of a block made from coupling an array of small crystals to an array of larger photomultipliers through a diffusing layer.

The closer each photomultiplier is to the crystal that was struck by an annihilation photon, the greater the magnitude of its output (whether the magnitude is defined as the integrated current or the peak current). Anger-logic is a technique where the centroid of the light distribution is estimated based on the relative magnitude of the outputs from the photomultipliers [38], [62], [63]. Given the magnitudes from the photomultipliers: A, B, C, and D in Fig. 1.7c, the Anger-logic coordinate is:
\[ X = \frac{(B + C) - (A + D)}{A + B + C + D} \quad (1.9) \]
\[ Y = \frac{(A + B) - (C + D)}{A + B + C + D} \quad (1.10) \]

A flood histogram can be formed by exposing all of the crystals in the array to a flood of annihilation photons and making a 2D histogram of the Anger-logic coordinates recorded from each annihilation photon detection. Because the centroid of light distribution coming from each crystal should correspond with the position of that crystal relative to the photomultiplier array, a flood histogram that would be recorded from a block like the one in Fig. 1.7b would resemble Fig. 1.8.

![Fig. 1.8. Distribution of Anger-logic coordinates that would be produced from the detector block shown in Fig. 1.7a and b.](image)

Note that the flood histogram contains a peak corresponding to each crystal in the array. The Anger-logic coordinate is not greatly affected by the position of interaction within each crystal; scintillation light reflects on the walls of the crystal as it travels from the point of interaction to the bottom of the array, so the centroid of the distribution of light will have very little correspondence to the position within the crystal where the annihilation photon interacted. Calibration data, in the form of a crystal look-up table segments the flood histogram into domains corresponding to each crystal in the array.

Because the mean number of scintillation photons emitted from the scintillator is proportional to the deposited energy, and the output of each photomultiplier is proportional
to the number of scintillation photons that fall on them, the sum of the magnitude of the outputs from all photomultipliers in a block should be proportional to the deposited energy. Calibration data can be used to rescale the summed output of the photomultipliers to the energy deposited in the detector.

The assembled crystal array and photomultipliers are referred to as the front-end of the detector. Back-end electronics capture and digitize the analog signals produced by the detector front-end. An exception to this is made for PET detector blocks built using digital photon counters (also known as digital silicon photomultipliers, described in §1.5.1.4), which directly output digital information. The time associated with an annihilation photon can be determined from the time that the output from one or more photomultipliers in a detector block begins to rise. When the analog output passes a certain threshold (in the case of a leading edge discriminator) or when it reaches a certain fraction of its maximum (in the case of a constant fraction discriminator) a timestamp is generated.

1.5.1 Photomultipliers
A variety of technologies are available to detect scintillation photons. Here we describe four technologies. The first, photomultiplier tubes, are a very mature technology and have been the dominant choice of photomultiplier for most of the history of PET. The later three are more recent technological developments that have become important in the field of PET in the last decade. Each year sees rapid improvement in these technologies that enhance the capabilities of PET technology as a whole.

1.5.1.1 Photomultiplier Tubes
The principle by which a photomultiplier tube (PMT) works is illustrated in Fig. 1.9. A PMT is an evacuated tube in which is found a series of dynodes. The face of the PMT mated to the scintillator has a thin sheet of special material called a converter. Photons falling on the converter cause an electron to be injected into the PMT due to the photoelectric effect. The voltage of each dynode increases incrementally moving from the converter to the anode. The photoelectron is accelerated toward the first dynode to such a speed that when it hits the
dynode it results in the ejection of even more electrons. These electrons are then accelerated to the next dynode to produce even more electrons, and so on.

Fig. 1.9. Principal of operation of a photomultiplier tube.

PMTs can result in a multiplication factor (gain) of ~1 million [64]. Compared to newer photomultipliers, they are rather bulky and require a very high bias voltage (a few kilovolts). A major drawback relevant to this thesis is that they do not function inside of the strong magnetic field of an MRI. Because their operation relies on charged particles moving through free space, operation inside of a strong magnetic field would cause the path of the electrons to deflect into the walls of the PMT. The later three photomultiplier technologies use solid state technology that functions inside of a strong magnetic field.

1.5.1.2 Avalanche Photodiodes

An avalanche photodiode (APD) is a reverse biased P-N junction. When a photon reaches the depletion region of the APD, an electron-hole pair is created which allows current to pass through the diode. The diode is biased in proportional mode. In proportional mode, the electric field inside of the depletion region is strong enough that the electron will gain enough energy to liberate more charge carriers which themselves will accelerate and create even more charge carries (hence the avalanche in avalanche photodiode). The total current flowing through the APD is proportional to the flux of scintillation photons on the depletion region.

The gain on an APD is only on the order of 100 [65], so additional multiplication is necessary. In addition, the gain of an APD tends to have a higher temperature dependence.
than PMTs [66]. Benefits of APDs over PMTs are that they operate at a much lower bias voltage (hundreds of volts) [67], they are inexpensive, and can be produced in a very compact form [68].

1.5.1.3 Silicon Photomultipliers

Silicon photomultipliers (SiPMs) are made from a microscopic array of Geiger-mode APDs (GM-APDs). When biased in Geiger-mode, the electric field inside of the depletion region is so high that when a photon creates a charge carrier, the avalanche process will continue to amplify the number of charge carriers until a macroscopic self-sustaining current is reached. This steady state current will continue until the GM-APD is quenched. A GM-APD is quenched when its bias voltage is brought below the breakdown voltage, below which the run-away avalanche multiplication stops. GM-APDs in a SiPM are connected in series to a quenching capacitor. When the capacitor voltage reaches \( V_{\text{bias}} - V_{\text{breakdown}} \), the voltage across the GM-APD drops below the breakdown voltage and the GM-APD is quenched. This determines the gain of a GM-APD:

\[
\text{Gain}_{\text{GM-APD}} = \frac{C_{\text{quench}}(V_{\text{bias}} - V_{\text{breakdown}})}{e}
\]  

(1.11)

Here \( C_{\text{quench}} \) is the capacitance of the quenching capacitor and \( e \) is the charge of a positron. A GM-APD can only detect a single photon so it would not be of use as a photomultiplier, which is required to give an output proportional to the flux of scintillation photons impinging on it. This is why the SiPM has a microscopic array containing tens of thousands of GM-APDs in an area of \( \sim 10 \text{ mm}^2 \). The number of GM-APDs that break down when a flux of photons falls on the SiPM should be proportional to the flux of photons. The analog outputs of each GM-APD are added together, so that the magnitude of the output signal is proportional to the flux of photons impinging on the SiPM. This of course assumes that saturation is not being reached. Saturation occurs at high photon flux where a photon is likely to hit a GM-APD that has already broken down. Saturation correction corrects for the non-linear output of the SiPM at high photon flux.
The SiPM is a newer technology than the APD and has many advantages. Compared to APDs, SiPMs have high gain (~ 1 million), have relatively stable gain, and low excess noise factor [65]. The SiPM’s advantage over the PMT is its compact size and compatibility with high magnetic fields.

1.5.1.4 Digital Photon Counters

A digital photon counter (DPC), also known as a digital silicon photomultiplier (dSiPM) is very similar to a SiPM in that is it made from a microscopic array of GM-APDs. In a SiPM, the outputs of all GM-APD are added together in an analog fashion to give a signal proportional to the number of GM-APDs broken down at any moment. Whether a GM-APD breaks down is inherently a digital event – it either does or does not. In a DPC, the output of each GM-APD feeds into a digital circuit, and the number of GM-APD breakdowns is added in a digital fashion.

Much of the work that would otherwise be done by the PET scanner’s back-end electronics is done right on the DPC chip, including generation of a time-stamp. The exact method of how a time-stamp is generated is a matter of design and varies with different DPC models [69], [70]. Because the DPC has the capability of generating a timestamp at the moment of the first cell breakdown, the technology has the promise of very good timing resolution. One can no longer speak of the gain of a DPC because they do not output an analog current.

DPC technology will be described in much greater detail in Chapter 3, which evaluates the use of Philips DPC technology as a candidate photomultiplier for our prototype PET system.

1.5.2 Depth of Interaction Capable Detectors

In a detector block made from an array of scintillator crystals such as the one in Fig. 1.7, the position of interaction in a detector block is specified by the crystal of interaction and no further information is available about where in the crystal the interaction took place. The pitch of crystals in the array can be made fairly small – on the order of 1 mm – with no issues
in being able to properly identify the crystal using Anger-logic. One would not make the length of the crystals much shorter than one centimeter, otherwise the detectors would only stop a small fraction of the annihilation photons that reach the detector. The large uncertainty in the position of photon interaction along the length of a crystal results in increasing uncertainty in the measured radial position of a positron annihilation as one moves away from the centre of the FOV. This is illustrated in Fig. 1.10a. A pair of crystal that form an LOR that goes through the centre of the FOV is sensitive to positron annihilations in the region of the FOV highlighted in blue. A pair of crystal that is at a larger radial offset is sensitive to positron annihilations in a much wider region of the FOV highlighted in green. The decreased radial resolution of the projections that a PET scanner measures at higher radial offsets results in images with decreased radial resolution at higher radial offsets as well. This is known as the parallax effect [1].

![Fig. 1.10. Illustration showing why crystal pairs with a high radial offset sample the activity distribution with a poorer radial resolution than crystal pairs that pass through the centre of the FOV. The degradation of radial resolution is more severe in a PET system with single-layered detectors (a) than it is for a PET system with dual-layered detectors (b).](image)

The parallax effect can be mitigated by measuring information about the depth of interaction into the detector block of each annihilation photon. Fig. 1.10b shows an example of a PET scanner where each crystal is segmented into two layers. If the PET scanner can determine
which layer each annihilation photon interacted in, then the uncertainty in the radial coordinate sampled by each LOR is reduced significantly. In this chapter, we will review a number of block designs that are capable of measuring depth of interaction information: phoswich, dual-ended readout, and dual-layer offset design. The dual-layer offset design is of special importance to this thesis because this is the design that our collaboration used to build the prototype PET system.

1.5.2.1 Phoswich
The phoswich detector design splits each crystal into two layers each made from a different scintillator material [71]. Each scintillator material has a different decay time. The decay time describes how fast the scintillator releases the absorbed energy as scintillation light. The analog output of the photomultiplier will rise and fall at a different rate depending on what layer the annihilation photon deposited its energy. An example of a PET scanner incorporating the phoswich design is the Siemens HRRT [72]. The detector blocks in the HRRT are made from 2 mm long crystals composed of 1 mm of LSO (decay time = 40 ns) optically coupled to 1 mm of LYSO (decay time = 53 ns). The back-end electronics that readout the detector block need to be capable of detecting the decay time of the pulse.

1.5.2.2 Dual-Ended Readout
The depth of interaction of an annihilation photon in a crystal can be estimated if the array of crystals in a detector block is read out from photomultipliers on both ends of the crystals. The difference in the amount of scintillation light to reach each side of the block can be used to infer the depth of interaction [73]. Unlike the phoswich design where the location of interaction is placed within one of two layers, the dual-ended readout method estimates the depth of interaction as a continuous variable. This block design has been shown to be capable of measuring the depth of interaction with a resolution of less than 2 mm [74].

1.5.2.3 Dual-Layer Offset
Detector blocks employing the dual-layer offset (DLO) block design are made from two layers of scintillator crystals stacked on top of each other and offset by half of the crystal
pitch in both directions [6], [75], [76]. Fig. 1.11 shows a DLO detector block made from a 7×7 array of crystals in the top layer and an 8×8 array of crystals in the bottom layer. The crystals within each layer are optically isolated from each other, but the interface between the two layers allows scintillation photons to pass from the top layer to the bottom layer.

Just like the simple single-layered detector block shown in Fig. 1.7b and c, the crystal of interaction, be it in the top or bottom layer, is identified through Anger-logic. Because the Anger-logic coordinate corresponds with the centroid of scintillation light falling on the photomultiplier array, the distribution of Anger-logic coordinates corresponding to each crystal in the DLO array will resemble the pattern in Fig. 1.12.

Fig. 1.11. Schematic of a dual-layer offset detector block viewed from the side (a) and from the top (b).

Fig. 1.12. Distribution of Anger-logic coordinates that will be produced by the dual-layer offset array. Blue dots correspond to crystals in the bottom layer, and red dots correspond to crystals in the top layer.
Because a DLO detector block can incorporate two layers of short crystals rather than one layer of long crystals while still preserving the same sensitivity of detection, the error in identifying the radial coordinate of positron annihilations is reduced significantly.

1.6 Image Reconstruction

Techniques to reconstruct PET data into an image can be broken into two categories: analytic and iterative reconstructions. Analytic reconstructions assume that the PET scanner perfectly measures projections of the activity distribution and ignore the fact that the projections are sampled discretely and contain noise. Iterative reconstruction methods model the measured data in a more realistic way that sees the data as a number of discrete measurements of radioactivity that are subject to counting noise. In this section, we will describe the basic principals behind both categories of reconstruction methods.

1.6.1 Analytic Reconstruction

To explain how 3D analytic reconstruction is performed, it is better to begin with 2D reconstruction. A 2D PET scanner is not unrealistic – it is just a PET scanner made from a single ring of detector crystals. The sinogram would then represent a set of 1D projections around the 2D activity distribution. Mathematically, the transform that takes a 2D image to a set of its 1D projections is called the Radon transform. An analytical procedure will be shown here that inverts the Radon transform.

Fig. 1.13a shows the UBC logo along with integral projections through it in two orthogonal directions and Fig. 1.13b shows the Radon transform of the UBC logo. The Radon transform as a function of r with a constant value of φ represents the integral projection through the original image through angle φ.
If \( f(x,y) \) describes the original function, then its Radon transform is defined as:

\[
R_f(r, \phi) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} f(x, y) \delta(x \cos \phi + y \sin \phi - r) \, dx \, dy
\]  

(1.12)

\( \delta \) is the Dirac-delta function. An analytic procedure exists to invert the Radon transform called \textit{filtered back projection} (FBP). First consider the operation of \textit{back projection}, which transforms \( R_f \) to \( f'(x,y) \).

\[
f'(x, y) = \int_{0}^{\pi} R_f(x \cos \phi + y \sin \phi, \phi) \, d\phi
\]  

(1.13)

The procedure of back-projection can be intuitively thought of taking each 1D projection in the Radon transform and smearing it over the image space at an angle \( \phi \). The back-projection itself will not produce the original image \( f(x,y) \), but rather the original image convolved with a \( 1/r \) function. This is illustrated in Fig. 1.14 where the Radon transform of a single point is back-projected into image space.
One method of recovering the original image is to deconvolve the back-projected image with the $1/r$ function. It can be shown that deconvolving the image by the $1/r$ function is equivalent to filtering each projection in frequency space with the filter $|\omega|$, where $\omega$ is the spatial frequency in the $r$-direction of the Radon transform. The filter $|\omega|$ is called the ramp filter. The analytic inversion of the Radon transform is then equal to:

$$f(x, y) = \int_0^{\pi} R^*_f(x \cos \phi + y \sin \phi, \phi) d\phi$$  \hspace{1cm} (1.14)

Where $R^*_f$ is the Radon transform once filtered by the ramp filter

$$R^*_f = \mathfrak{F}_r \left[ |\omega| \mathfrak{F}^{-1}_r [R_f] \right]$$  \hspace{1cm} (1.15)

$\mathfrak{F}_r$ represents a 1D Fourier transform which takes the spatial variable $r$ to the frequency variable $\omega$. 

---

Fig. 1.14 Back projection of a Radon transform of a single point.
In practice, where data is discrete, the ramp filter is applied using the *fast Fourier transform* algorithm. When back-projection is done, the contribution that each bin in the projection makes to each pixel in the image is found using a *ray tracing* technique [77].

If one discarded all information from the sinogram corresponding to non-zero values of tanθ, one would have a set of 2D sinograms (parameterized by r and φ), with each representing projections through the activity distribution at each z coordinate. The entire 3D activity distribution could be reconstructed by reconstructing each plane separately with 2D FBP and stitching the images together. This is not desirable because the fewer the number of coincidences used to reconstruct a PET image, the poorer its signal to noise ratio. Two techniques that aim to reconstruct the PET image using all measured data, *Fourier Rebinning* and *Filtered Back Projection-3D Reprojection*, are described below.

### 1.6.1.1 Fourier Rebinning

Fourier Rebinning is a strategy to use all measured data in a PET reconstruction that works by adding information from the *oblique* sinogram planes (tanθ ≠ 0) into the direct (tanθ = 0) planes by exploiting a property of the 3D Radon transform. Here, a *sinogram plane* refers to a subset of the sinogram with constant z and tanθ. Defining the 3D Radon transform as $R_f(r, \phi, z, \tan \theta)$ and its Fourier transform in terms of r and φ as $P(\omega, k, z, \tan \theta)$, the following relationship can be shown [78]:

\[
P(\omega, k, z, 0) = P\left(\omega, k, z + \frac{k}{\omega} \tan \theta, \tan \theta\right) + \int_{0}^{\tan \theta} \frac{\delta}{\omega} \frac{\partial^3 P}{\partial \omega \delta z^2} d\delta 
\]

(1.16)

\[
P(\omega, k, z, 0) \approx P\left(\omega, k, z + \frac{k}{\omega} \tan \theta, \tan \theta\right) 
\]

(1.17)

The Fourier rebinning algorithm ignores the second term in (1.16). After Fourier transforms of each 2D sinogram plane are made, higher statistical quality versions of the direct sinogram planes can be found by adding data from oblique planes according to (1.17). Inverse Fourier
transforms are then performed on these planes, and then each is reconstructed with 2D FBP [79].

### 1.6.1.2 Filtered Back Projection - 3D Reprojection

3D FBP works in an analogous way to 2D FBP. In 2D FBP, a set of projections could be back-projected into image space, producing the original image convolved with a $1/r$ function. Consider what would happen if all of the projection data measured by the PET scanner were back-projected onto a 3D image space. If the image represented a point source in the centre of the FOV, the back-projection of the projections onto image space would create a $1/r^2$ distribution centred on the location of the original point source, as illustrated in Fig. 1.15. To be more precise, the back-projection has a $1/r^2$ distribution *truncated within the acceptance angle of the scanner*, and 0 outside.

![Fig. 1.15. LORs converge on a point in the centre of the FOV in a way where their density is described as $1/r^2$, where $r$ is the distance from the centre of the FOV. (a) shows the scanner from the front and (b) shows the scanner from the side.](image)

If the analogy to 2D FBP were to continue, any activity distribution could be reconstructed from the 3D PET data by back-projecting and then deconvolving the truncated $1/r^2$ function. A problem though is that the acceptance angle is different at different positions throughout the FOV, as illustrated in Fig. 1.16 (LORs sampled by the PET scanner are coloured black). Because the transfer function that describes how each point in the image is represented in the back-projection is spatially variant, deconvolution is not possible.
Fig. 1.16. Illustration of how the acceptance angle of the PET scanner varies throughout the FOV. LORs within the acceptance angle are black. Blue lines show LORs that would have to be made up in order for each point in the FOV to have the same acceptance angle. (a) shows a point offset axially from the centre of the FOV and (b) shows a point offset radially from the centre of the FOV.

The 3D Reprojection algorithm (FBP-3DRP) aims to estimate the data that is missing from the projection data (coloured blue in Fig. 1.16) so that the acceptance angle of the projections back-projected onto each point in the image space is the same for every point in the FOV [80]. To make up the missing data, the image is first reconstructed from the non-oblique sinogram planes using 2D FBP. Line integrals are then made through the reconstructed image to estimate the missing projections.

As in 2D FBP, the image can be reconstructed by first filtering the projections (which include the previously missing data) instead of filtering the back-projection. In this case, each projection is a 2D image in r and z for a constant combination of $\phi$ and $\tan \theta$. The filter that is applied is known as the Colsher filter [81].

1.6.2 Iterative Reconstruction
Iterative reconstruction begins with a model that describes how the activity distribution $\lambda$ should relate to the measured data $y$. The image space is discretized into voxels (volumetric pixels), and each element of $\lambda$ represents the activity concentration in each voxel. $y$ is a
vector that holds the number of counts in each measurement bin, whether that bin refers to a sinogram bin, or a single crystal pair (it is possible that more than one crystal pair is mapped to each sinogram bin). Iterative methods allow for noise in the measured data by making a distinction between the measured data \( y \) and the expectation value of the measured data \( \bar{y} \). The expectation value of the data is assumed to be a linear combination of the activity concentration in each voxel:

\[
\bar{y} = C\lambda
\] (1.18)

Here \( C \) is referred to as the system matrix. Many methods of calculating the system matrix with varying degrees of sophistication exist. If one could determine a volume of space that each measurement bin (indexed \( b \)) is sensitive to, one could define each \( c_{ab} \) as the overlap between voxel-a and that volume, as illustrated in Fig. 1.17. In this way, (1.18) still defines each measurement as a projection through the activity distribution.

![Fig. 1.17. Illustration of how system matrix elements may be calculated as an overlap between a voxel and the volume of space each measurement bin is sensitive to.](image)

The number of coincidences counted in measurement-\( b \) is a Poisson random variable. If the expected number of counts is equal to \( \bar{y}_b \), then the probability of measuring \( y_b \) is:

\[
Prob(y_b) = e^{-\bar{y}_b} \frac{\bar{y}_b^{y_b}}{y_b!}
\] (1.19)
If we assume that the expectation value of the measurement is known, then one can form a likelihood function that describes how likely it is that the measurement vector $\mathbf{y}$ would be measured given the expected value $\overline{\mathbf{y}}$.

$$L(\mathbf{y}|\lambda) = \prod_b e^{-\overline{y}_b} \frac{y_b}{y_b!}$$  \hspace{1cm} (1.20)

Here, we have defined the likelihood function as the likelihood of $\mathbf{y}$ given $\lambda$. Although the formulation of the likelihood function is not written in terms of $\lambda$, each $\overline{y}_b$ is related to $\lambda$ through equation (1.18). The image is reconstructed by finding the value of $\lambda$ that maximizes the likelihood of obtaining the measured data. One can equivalently maximize the logarithm of the likelihood function, which is easier to work with:

$$\lambda \xrightarrow{\text{arg max}} \ln L(\mathbf{y}|\lambda) = \sum_b \left[ y_b \ln \sum_a c_{ab} \lambda_a - \sum_a c_{ab} \lambda_a - y_b! \right]$$  \hspace{1cm} (1.21)

Equation (1.21) can be solved iteratively using the expectation maximization (EM) algorithm. This approach leads to the MLEM algorithm (maximum likelihood / expectation maximization) for PET image reconstruction, originally developed by Shepp and Vardi [82]. A more complete formulation of the solution to (1.21) was presented by Lange and Carson [83]. Starting with an initial estimate of $\lambda^0$ (usually initialized to 1), successive estimates of $\lambda$ can be computed according to:

$$\lambda_a^{k+1} = \frac{\frac{\lambda_a^k}{\sum_b c_{ab} \sum_b c_{ab}} y_b}{\sum_a c_{ab} \lambda_a^k}$$  \hspace{1cm} (1.22)
The MLEM algorithm can be thought of as an iteration through three steps, *forward projection*, *back projection*, and *image update*, the meaning of which are explained in Fig. 1.18.

<table>
<thead>
<tr>
<th>Forward Projection</th>
</tr>
</thead>
<tbody>
<tr>
<td>The expected value of the data based on the current image estimate is made.</td>
</tr>
<tr>
<td>$\overline{y}<em>b^k = \sum_a c</em>{ab} \lambda_a^k$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Back Projection</th>
</tr>
</thead>
<tbody>
<tr>
<td>The ratio between the measured data and the current forward projection is back-projected into image space, and then divided by the sensitivity of each voxel.</td>
</tr>
<tr>
<td>$correction_a^k = \frac{1}{\sum_b c_{ab}} \sum_b c_{ab} \frac{y_b}{\overline{y}_b^k}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Image Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each voxel in the image is multiplied by the correction factor.</td>
</tr>
<tr>
<td>$\lambda_a^{k+1} = \lambda_a^k \times correction_a^k$</td>
</tr>
</tbody>
</table>

Fig. 1.18. Explanation of the three steps on the MLEM algorithm.

Note that when forward projection of the current image estimate is equal to the measured data, the correction factors will equal unity and the algorithm will have converged.

1.6.2.1 LOR-Based versus Sinogram-Based MLEM

In the above derivation of the MLEM algorithm, each $y_b$ was allowed to represent either the number of counts in a particular sinogram bin, or the number of counts measured by a particular crystal pair (LOR). Recall that a sinogram histograms the detected coincidences into bins that are *uniformly spaced* in terms of $r$, $\phi$, $z$, and $\tan\theta$. However, PET scanners do not naturally sample projection space in uniform intervals of these variables. This is especially true for dual-layer detector blocks, which form a very complex pattern of positions within the space of $r$, $\phi$, $z$, and $\tan\theta$ that are sampled due to interleaving between different layers. To map a crystal pair to a sinogram bin, the counts from the crystal pair are added to
the sinogram bin that samples the most similar value of r, φ, z, and tanθ, or they may even be distributed to a number of nearby sinogram bins.

LOR-based MLEM reconstructs directly from the counts measured by each crystal pair with no need to form the data into sinograms. Because of the interpolation between the projection directions that are naturally measured and the projection directions that are represented in the sinogram bins, sinogram based MLEM has shown to degrade spatial resolution compared to LOR-based MLEM [84]. Derivation of the MLEM algorithm assumes that the number of counts in each bin is an independent Poisson random variable. When counts from one crystal pair are distributed to a number of sinogram bins, the noise in these bins in no longer Poisson-like, and the noise between adjacent bins is correlated. MLEM has been shown to produce image with less desirable noise characteristics when non-Poisson-like data is used [84]–[86]. For these two reasons, LOR-based MLEM is more desirable than sinogram based MLEM. MLEM reconstruction can take a long time to complete (typically hours). The computation time scales with the number of bins in the vector y. Use of LOR-based MLEM over sinogram-based MLEM adds to the computation time because there are usually significantly more crystal pairs than sinogram bins.

### 1.6.2.2 Point Spread Function Modelling MLEM

Point spread function modelling MLEM (or PSF-MLEM) is a subset of MLEM algorithms that aim to improve reconstructed image quality by accurately modelling in the system matrix the physical processes that would otherwise degrade image resolution [9]–[12]. The most substantial of these effects in a PET system like ours with limited depth-of-interaction capability is the parallax effect discussed in §1.5.2 where the projection of an object blurs as one moves away from the centre of the FOV. Additional resolution degrading effects are intercrystal scatter, photon acollinearity, and positron range. Intercrystal scatter occurs when an annihilation photon interacts in multiple crystals of a detector block. When the crystal that is assigned as the crystal of interaction is not the same as the first crystal that the photon interacted in, the LOR that the coincidence is assigned to does not represent the path of the annihilation photons.
Consider the distribution of activity in Fig. 1.19a, which has two point sources represented as compact red dots. Because of resolution degrading effects, the measured projections of these point sources will be significantly wider than the true projections of the distribution. If the system matrix is simplistic and assumes that the data represents a prefect projection of the activity, the image estimate necessary for the forward projection to match the measured data will be blurred, as in Fig. 1.19b. However, MLEM will converge on a compact activity distribution in spite of blurred projection data if the system matrix accounts for the fact that the measured projections represent a blurred projection of the activity.

Fig. 1.19. (a) shows two small point sources (red dots) in the FOV of a PET scanner. The projections that the scanner measures (shown above) are much wider than the true projections due to image degrading effects. (b) shows the reconstructed activity distribution if those image degrading effects were not accounted for.

1.7 Metrics of PET System Performance
A good PET scanner should produce images that are of high spatial resolution and have high signal to noise ratio. The NEMA NU 4-2008 protocol, which was created by the National
Electrical Manufacturers Association in the United States, describes a set of experiments to characterize a small animal PET system [87]. This allows for fair and consistent reporting of the performance of small animal PET scanners. We will briefly describe here NEMA NU 4-2008 experiments to measure spatial resolution, sensitivity, and noise equivalent count rate.

1.7.1 Spatial Resolution

Spatial resolution is measured by acquiring data from a small $^{22}\text{Na}$ point source at radial offsets from the centre of 0, 5, 10, 15 mm, and then at 10 mm intervals if space in the FOV allows. Data are acquired at a number of radial offsets to investigate the resolution uniformity, which degrades due to the parallax effect. These are measured in the axial centre of the PET scanner, and again offset by a quarter of the PET scanner’s axial length from the centre. Data are reconstructed with either 2D or 3D FBP. The width of each reconstructed point source is characterized in terms of the FWHM and FWTM (full width at tenth maximum).

1.7.2 Sensitivity

Sensitivity is the fraction of positron annihilations from a point source that will be captured by the PET scanner as a coincidence. Sensitivity is variable throughout the FOV, and will peak in the centre. A sensitivity profile is the sensitivity as function of source location along the central axis of the PET scanner. The noise quality of a PET image increases as more coincidences are included to reconstruct the image. So in general, a higher sensitivity PET scanner is capable of producing images with better noise characteristics.

1.7.3 Noise Equivalent Count Rate

It is difficult to give a single number that characterizes the signal to noise ratio (SNR) that a PET scanner will produce, because SNR is affected by various factors such as the duration of the scan, the level of deadtime, and the relative rates of scattered and random coincidences. The noise equivalent count rate (NECR) is a widely used metric to communicate the capability of a PET scanner to produce images with high SNR. The derivation of NECR assumes that the variance of a PET image reconstructed by filtered back projection is
commensurate with the variance of the raw projection data [88]. Because the number of counts in each bin is a Poisson random number, the variance of the data is equal to its mean value. Therefore the variance is related to the rates of trues, randoms, and scatters (T, R, S) as:

\[
\text{variance } \propto T + S + kR \tag{1.23}
\]

Although estimates of the amount of scatters and randoms in the data can be subtracted, their impact on the variance remains. When the randoms are estimated using the delayed coincidence window method detailed in §1.4.3.1, the factor \( k \) is set to 2 because the randoms estimate has the same variance as the prompt randoms, adding even more noise to the data upon subtraction. A randoms estimate based on the single rates (equation (1.7)) has very little noise because the singles rate is much higher than the coincidence rate, in which case \( k \) is set to 1.

The rigorous derivation of NECR in [88] was clear to state that (1.23) refers to the variance at the centre of a reconstructed cylinder, and the T, S, and R, are the rates of trues, scatters, and randoms recorded within the boundaries of the cylinder. Without any post-reconstruction rescaling on the image, the mean value of a reconstructed cylinder should be proportional to T. The signal to noise ratio (mean to standard deviation ratio) is therefore related to T, R, and S as:

\[
\text{SNR } \propto \frac{T}{\sqrt{T + S + kR}} \tag{1.24}
\]

The noise equivalent count rate (NECR) is defined as:

\[
\text{NECR } = \frac{T^2}{T + S + kR} \tag{1.25}
\]
In a PET scanner free from the complicating phenomena of scatter and randoms, the rate of trues during an acquisition would give a direct indication of the noise quality of the resulting image \((\text{SNR} \propto \sqrt{T})\). The NECR relates to SNR the same way that the trues rate from an idealized scanner relates to SNR.

NECR should be reported as a function of activity over which the scanner will normally operate. At low count rates, where randoms are rare, the slope at which the NECR rises is mainly affected by the overall sensitivity of the scanner and the scatter fraction. Sensitivity is affected by the geometry of the scanner and also the thickness and type of scintillator used in the detectors. The scatter fraction is affected by the energy resolution of the detectors. A detector with high energy resolution can use a tighter energy window centred on 511 keV to reject as much scatter as possible. At higher count rates, the NECR curve will begin to drop. This is due to both the deadtime characteristics of the detectors as well as the timing resolution. Detectors with good timing resolution can use a very small coincidence window to suppress randoms. Because the randoms rate increases in quadratic proportion to the singles rate, the effect of randoms becomes significant at high activities. Using a smaller energy window not only reduces the scatter fraction (scatter as fraction of total counts), but also reduces the randoms fraction by reducing the singles rate. If the most significant source of deadtime is pulse processing in the back-end electronics, use of a smaller energy window will also reduce detector deadtime if the energy window is applied at the hardware level.

T, S, and R all depend on the distribution of activity and attenuating material placed in the scanner. The NEMA NU 4-2008 protocol requires the use of a standardized phantom with a distribution of activity and attenuation roughly approximating that of either a mouse or a rat (one can then report mouse-NECR or rat-NECR).

1.8 Outline

The work presented in this thesis can be divided into four streams: simulation of the PET system, hardware characterization, image reconstruction, and PET system characterization.
Chapter 2 presents a series of Monte-Carlo simulations created to aid in the design of the prototype PET system and predict the performance following from our chosen design.

Chapter 3 presents a characterization of a PET detector block incorporating the Philips DPC3200-44-22 DPC array [70], which is a digital photon counter technology. The characterization investigates properties of the detector block relevant to its suitability for our PET system design. Chapter 4 combines the measurements made in Chapter 3 with the Monte-Carlo simulations designed in Chapter 2 to optimize the DPC array device settings in terms of NECR.

Chapter 5 describes the processes created to reconstruct PET data from our prototype system into images using FBP reconstruction. Chapter 6 describes the implementation of a PSF modelling MLEM code that was made specifically for our PET scanner geometry. Although the reconstruction algorithm was created by another member of our collaboration, the original work presented in Chapter 6 describes how normalization was accounted for, and how certain non-uniformity artefacts in the reconstructed images were eliminated.

Chapter 7 presents a characterization of the prototype PET system that was built in 2014 in addition to phantom images and simultaneous PET/MR rodent images.
Chapter 2: Simulation of PET System

Before our collaboration constructed a prototype PET system with dual-layer offset (DLO) detector blocks, the system was simulated using a simulation tool called GATE (*Geant4 Application for Tomographic Emission*) V6.1 [89], [90]. These simulations served the following purposes:

1. Optimize design of the DLO detector block
2. Ensure that detector arrangement can produce an image free from major artefacts
3. Estimate system spatial resolution and resolution uniformity
4. Demonstrate that DLO detector blocks result in improved resolution uniformity
5. Estimate count-rate performance
6. Study the effect of hardware modifications on PET image quality

GATE is a widely used application in the field of nuclear medicine that allows for accurate Monte-Carlo simulation of the PET and SPECT data and has recently been extended to computed tomography (CT) and radiation therapy. GATE allows for a PET acquisition to be run *in silico* by specifying details of the acquisition in a macro. Macros interpreted by GATE define the distribution of material and activity in the environment. GATE is built upon software libraries that are part the Geant4 (GEometry ANd Tracking) simulation toolkit, which grew out of the CERN community. Geant4 describes itself as “a toolkit for the simulation of the passage of particles through matter” and models an assortment of electromagnetic and hadronic processes over a wide range of energies [91], [92]. Geant4 has seen wide adoption in many fields of physics, notably particle physics where it has been used to describe processes in the Large Hadron Collider [93], [94]. Of particular relevance to PET, GATE uses Geant4 to model photoelectric and Compton interactions using cross sections specific to photon energy and the materials used to build the environment. On top of the functionality borrowed from Geant4, GATE’s *digitizer* module adds the ability to process the interactions tracked by Geant4 code and use models of detector energy resolution, timing resolution, and deadtime to produce realistic output in the form of PET singles and coincidence data.
Early designs of the PET system included sizeable gaps between detector blocks, resulting in under-sampled sinograms. Pre-construction simulations were crucial to ensure that sinogram gaps were not so large as to result in undesirable image artefacts like the ones which are typical with limited angle PET systems [95].

It is desirable to estimate the reconstructed spatial resolution of a PET system before it is built to ensure that the spatial resolution design goals are met (or else the design would have to be modified). Although it is obvious that there would be some improvement in resolution uniformity resulting from use of a dual-layered block, simulation of a full system was desirable because it answers quantitatively by how much resolution uniformity would improve.

Like resolution, it is crucial to estimate count rate performance of a certain design before the system is built. To estimate count rate performance (sensitivity and noise equivalent count rate (NECR)) without the aid of Monte-Carlo simulations would require modelling of factors such as multiple interactions in the detector block (which determine the differential rates at which scattered and un-scattered photons are detected in different energy windows) and detector deadtime. These effects are implicitly accounted for by GATE.

Various iterations of our PET prototype system were simulated as the design was updated. The results of these simulations, which were published in a 2013 paper, showcased the spatial resolution, resolution uniformity, NECR, and peak sensitivity of an early version of our design [96]. Since that time, the design was significantly altered. The simulation tools developed to estimate the performance of the scanner design described in the 2013 publication were re-run to reflect the newer design. In some points in this chapter, reference will be made to the early design. However, most results presented here will be applicable to the design of the scanner that was ultimately built in 2014. This will allow for simulation results of PET system performance to be compared directly to measurements from the prototype system. The final design used 16 rectangular dual-layer offset (DLO) detector blocks arranged in a ring. Table 2.1 summarizes the design features of the scanner described
in our 2013 publication [96] and the scanner that was built in 2014. Fig. 2.1 shows the arrangement of detector crystals in the finalized design.

<table>
<thead>
<tr>
<th>Crystal material</th>
<th>2013 Publication</th>
<th>Final Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLO block dimensions</td>
<td>9×9/10×10 (front / bottom layer)</td>
<td>9×21/10×22 (front / bottom layer)</td>
</tr>
<tr>
<td>Crystal dimensions</td>
<td>1.345×1.345×(4 / 6) mm³ (front / bottom layer)</td>
<td>1.2×1.2×(4 / 6) mm³ (front / bottom layer)</td>
</tr>
<tr>
<td>Crystal Pitch</td>
<td>1.422 mm</td>
<td>1.27 mm</td>
</tr>
<tr>
<td>Blocks per ring</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Ring inner-radius</td>
<td>64.8 mm</td>
<td>65.8 mm</td>
</tr>
<tr>
<td>Number of detector rings</td>
<td>1 or 3 or 6</td>
<td>1</td>
</tr>
<tr>
<td>Ring pitch</td>
<td>16.0 mm</td>
<td>n/a</td>
</tr>
<tr>
<td>Axial length</td>
<td>14.4 or 30.4 or 46.4 mm</td>
<td>28 mm</td>
</tr>
<tr>
<td>Singles resolving time</td>
<td>2.25 to 3.25 ns FWHM</td>
<td>5.4 ns FWHM</td>
</tr>
<tr>
<td>Energy resolution</td>
<td>14 to 16 %</td>
<td>12.5 %</td>
</tr>
<tr>
<td>Block deadtime</td>
<td>500 to 600 ns</td>
<td>1.5 μs</td>
</tr>
<tr>
<td>Deadtime model</td>
<td>Non-Paralyzable</td>
<td>Paralyzable</td>
</tr>
</tbody>
</table>

Table 2.1. Design features and hardware traits of an early design and of the final design that was later built.

Fig. 2.1. Schematic showing the arrangement of detector crystals in the finalized design of the prototype DLO PET system. Views from the front and side are respectively shown in (a) and (b).
2.1 Building PET System in GATE

The following steps were followed to create the simulations used to estimate the spatial resolution and count rate performance of the prototype DLO PET system.

2.1.1 Customizing Materials Database

Because the probability of interacting by the Compton effect or photo-electric effect depends on the material composition, it is crucial to ensure that the materials used in the simulation match the physical system being simulated. GATE has a built-in library of common materials such as water and bone, in addition to commonly used scintillator materials such as NaI, LSO, and YSO. LYSO, which is used in our PET system, is a mixture of LSO and YSO. The exact composition of the mixture can vary, as it is not standardized. The chemical formula of LYSO is $\text{Lu}_2(1-x)\text{Y}_2x\text{SiO}_5$, where the mixing fraction $x = 0 / 1$ corresponds to pure LSO / YSO. The mixing fraction of the LYSO from our vendor was calculated by measuring the density of a sample of LYSO and using the density of mixtures approach [97]. Based on our measured LYSO density of 7.13 g/cm$^3$, and the known densities of LSO and YSO (7.44 g/cm$^3$ and 4.54 g/cm$^3$), the mixing fraction was determined to be 10.5% YSO. The customized LYSO composition was added to the materials database by specifying the density of the material, and the molar fractions of Lu, Y, Si, and O in the mixture.

2.1.2 Definition of System Geometry

The geometry of a PET scanner is defined hierarchically through a macro syntax. Each level of the PET system is defined using basic geometric shapes. Any daughters must be completely contained within their parent level. The world contains a scanner that contains multiple blocks, each of which contains multiple crystals. Different levels are conceptually important because they determine how GATE’s digitizer system converts the history of particle interactions into PET data. For example, when an annihilation photon undergoes multiple interactions, all interactions within the same block are grouped together to form a single, the energy of which is the sum of energy deposited by each interaction in the block. In our simulation, deadtime is added at the block level. It is possible to add additional deadtime at different levels of hierarchy.
2.1.3 Definition of Source Properties and Geometry

The source is defined in two stages that account for a) the geometry of the source object that positrons are emitted into (i.e. a water phantom) and b) the distribution of radioactivity throughout the source object and the properties of that radioactivity. It is important to define the source object in cases where scatter and attenuation must be simulated. The distribution of the source object and activity can be imported from a 3D image file (which is useful when representing a complex subject like an animal), or can be defined using basic geometric shapes.

The simulation engine will randomly generate particles according to the distribution of activity. The GATE macro specifies which type of particle is being emitted (i.e. gamma ray, proton, positron, etc.), the emission energy (or energy distribution) and the total activity within each source volume (which can optionally be made to decrease exponentially over time). The two types of particles used in this work are positrons and back-to-back gamma rays. When positrons are used as a source particle, GATE models positron diffusion within the source material. By specifying that the energy distribution of emitted positrons matches $^{18}$F, the positron range will accurately match the experimentally observed positron range of $^{18}$F in the given material. When a positron annihilates, two 511 keV photos are generated from that point and emitted with an acollinearity randomly drawn from a Gaussian distribution with 0.58° FWHM [89]. Because of the inclusion of positron range and annihilation photon acollinearity, positron sources are used when the spatial distribution of the detected annihilation photons are important (i.e. measuring spatial resolution). In studies of count rate performance, it is sufficient for the simulation to emit back-to-back 511 keV gamma ray pairs from the source instead of positrons, which lead to faster computation time but do not model positron range nor acollinearity.

2.1.4 Selecting Simulation Output

If desired, a list of every interaction from the simulation can be outputted. Alternatively, GATE’s digitizer module can process these interactions and output a much shorter list of
prompt and delayed coincidences. The behaviour of the digitizer is as follows: interactions within the same crystal are grouped together to form pulses. Pulses within the same block are grouped together to form singles. The time associated with each single is taken as the time of the first interaction, but can be blurred using a Gaussian distribution to simulate timing resolution. The single’s energy is the summed energy of all interactions, which can again be blurred to simulate energy resolution. The crystal of interaction is assigned to the crystal with the highest-energy pulse. If desired, a fraction of singles can be removed from the data set by applying an energy window. To model deadtime, singles will also be removed from the data set if they occur in a block that has been rendered ‘dead’ by a previous interaction. The digitizer identifies coincidences if any two singles are found to have time-stamps equal within a user-specified timing window.

In cases where the spatial resolution of the PET system is being studied, both the coincidences and the pulses will be outputted. GATE’s method of identifying the crystal of interaction (crystal with the highest energy pulse) following intercrystal scatter is too simplistic. A more accurate model to identify the crystal of interaction, which relies on knowledge of all pulses building a single, will be described in §2.2. The digitizer can produce prompt and delayed coincidence lists that are perfectly adequate to study the count rate performance of the PET system. In this work however, only the singles will be outputted for studies of sensitivity and NECR and coincidences will be identified in post-processing. As will be described in §2.3, this will allow the same data set to be reused many times to correspond to many different scenarios of the PET hardware performance.

### 2.2 Post-processing Data to Model Intercrystal Scatter

The key to crystal identification through Anger-logic is that the Anger-logic coordinate should approximately correspond to the centroid of the scintillation light distribution coming from a crystal array after the interaction of an annihilation photon. If an annihilation photon interacts in multiple crystals, it is logical to conclude that the centroid of the light distribution would be an average between the centroids of all crystals involved, weighted by the energy deposited in each crystal. The crystal of interaction would then be identified as the one
whose Anger-logic response is closest to this energy weighted coordinate. This scheme, proposed by Shao et al [98] as a method of modelling intercrystal scatter, is illustrated in Fig. 2.2. Blue and red dots respectively correspond to centroids of crystals in the bottom and top layer. Yellow bolts represent annihilation photon interactions in two crystals. The energy-weighted sum of these crystals’ centroids is marked with a black X. The identified crystal is circled in green.

![Diagram illustrating crystal misidentification](image)

**Fig. 2.2.** Illustration of how the list of pulses forming each single is used to compute the crystal of interaction in cases where there are multiple interactions in a block. The centroid of crystals in the bottom/top layer are shown with blue/red dots. Yellow lightening bolts show locations where the annihilation photon interacted. The energy weighted average of those interaction locations is marked by an X. The resulting estimated crystal of interaction is circled in green.

Crystal misidentification due to intercrystal scatter can cause resolution degradation. In the example illustrated in Fig. 2.2, the estimated crystal of interaction is assigned to the wrong layer. For the simulations to accurately predict the spatial resolution of a PET scanner, the pattern of crystal misidentification in the simulations should closely match the real PET detector block. For each coincidence in the simulation data, the pulses corresponding to the two singles making the coincidence were identified. These pulses were then used to find the energy-weighted centroid of all the interactions contributing to the single. The crystal whose centroid was closest to this energy-weighted centroid was reassigned as the crystal of interaction.
2.3 Post-processing Data to Model Energy and Timing Resolution

Simulations run to study the NECR and sensitivity model timing and energy resolution to be perfect, and no energy window is applied to the singles. As described in §1.7.3, NECR strongly depends on the energy and timing resolution of the PET scanner. In post-processing, the timestamp and energy of each single was adjusted by values pulled from Gaussian distributions to simulate imperfect timing and energy resolution. By post-processing data, the same data set can be reused many times to simulate the effect of different scenarios of energy and timing resolution, and different energy windows. Block-level deadtime was included in the GATE simulation to avoid the complexity of adding deadtime effects in post-processing. After the time-stamp and energy of each single was randomly perturbed according to whatever energy and timing resolution were being simulated, coincidences were identified when two (perturbed) time-stamps were identical to within a specified timing window.

2.4 Validation of PET System Response

To test that the detection process simulated in GATE is an accurate representation of reality, simulated coincidence profiles were compared to coincidence profiles measured between two prototype blocks. The coincidence profiles here correspond to the finalized PET system design shown in Table 2.1. A coincidence profile is created by stepping a source along a trajectory, and plotting the number of coincidences measured in a particular group of LORs as a function of source position. LORs connecting opposing detectors at the same radial offset in Fig. 2.3a are used to form 38 LOR groups.
Fig. 2.3 (a) shows a front-facing view of the scanner. Groups of LORs connecting top / bottom layer crystals on opposing detectors are illustrated in with red / blue lines. Although (a) gives the appearance that each group contains only one LOR, all LORs connecting crystals at the radial offset make up a group. (b), which is a side view, show all LORs in one such group.

The trajectory of the source is indicated as a black arrow in Fig. 2.3a. Coincidence profiles will peak as the source moves between the crystals in each group. The precise shape of a coincidence profile is affected by the physical processes of radiation interaction in the block. For example, a coincidence profile will begin to rise even before the source is between the crystals that the LORs connect. These counts are mostly caused by scatter within the block. Coincidence profiles derived from LORs that connect two crystals placed at an angle with respect to each other (such as the ones to the right side of Fig. 2.3a) will have a stretched out and skewed shape. The degree of skewing is affected by interaction with other crystals in the path of the annihilation photons. Simulated coincidence profiles that accurately match the shape of measured coincidence profiles would support the notion that the simulations accurately model the physical processes of radiation detection.
2.4.1 Method

To measure coincidence profiles, the assembled prototype PET scanner was positioned in front of a motorized stage capable of moving a source along the trajectory shown in Fig. 2.3a. A spherical 2.5 mm wide ~100 kBq $^{22}$Na source, embedded inside of a 10 mm wide acrylic cube was placed on the end of the motorized stage. Care was taken to make sure that the source was centred axially and radially within the FOV. The source was moved back 7.9375 mm, and then stepped forward in 0.15875 mm steps (one eighth of the crystal pitch). At each step, data were collected for one minute. Singles were filtered with a 300-800 keV energy window, and sorted for coincidences. If the coincidence corresponded to one of the groups of LORs indicated in Fig. 2.3a, the appropriate coincidence profile was incremented.

These experiments were then recreated in a GATE simulation. The source was made to emit positrons rather than back-to-back gamma rays. Simulations were post-processed by the method described in §2.2 to model intercrystal scatter. Another set of coincidence profiles was created from the same data set, but using GATE’s built-in method of crystal identification (crystal assigned to the one with most energy deposited). In this way, comparison with the measured data not only will confirm that the GATE simulations were set up correctly, but also that the customized method of crystal identification adds value to the simulations.

Each coincidence profile was fit with a sum of three Gaussian functions using least squares fitting. To quantify the differences between coincidence profiles, the FWHM, FWTM, and skewness were extracted from the fits. Skewness of a curve is quantified as the difference between the mean value and the median value, divided by the standard deviation (Pearson’s second skewness coefficient).
2.4.2 Results

Measured and simulated coincidence profiles are shown in Fig. 2.4.

Fig. 2.4. Coincidence profiles (in arbitrary units) connecting front layer crystals (red) and back layer crystals (blue). Triplet-Gaussian fits are shown with black lines.
The FWHM and FWTM of each coincidence profile are summarized in Fig. 2.5, while the skewness is summarized in Fig. 2.6.

Fig. 2.5. Plots of the coincidence profiles' widths as a function of coincidence profile ID. Coincidence profile ID increases as one moves left to right through the scanner in Fig. 2.3a. Data are organized into coincidence profiles connecting the offset blocks (at the right side of Fig. 2.3a) and the blocks that pass through the centre of the FOV.
Visual inspection of the coincidence profiles in Fig. 2.4 shows very good agreement between measured and simulated data in terms of their positions, widths, and relative heights, especially when the customized method of crystal identification is used. In the measured data, there is a clear pattern that the coincidence profiles from the top-layer crystals peak at a higher value than coincidence profiles from the bottom-layer crystals. This pattern is duplicated only when the customized method is used. This difference between the two
simulated sets of coincidence profiles is due to a difference in the amount of layer-
misidentification due to inter-crystal scatter.

In addition to what is observed visually, the quantitative measurements of the coincidence
profiles, summarized in Fig. 2.5 and Fig. 2.6, support the same conclusions. Table 2.2
summarizes the root-mean-square error between FWHM, FWTM, and skewness coefficients
between the simulated and measured coincidence profiles. In nearly every case, the
simulations using the customized crystal identification method outperform GATE’s built-in
method.

<table>
<thead>
<tr>
<th>Layer</th>
<th>FWHM [mm] Custom</th>
<th>FWHM [mm] GATE</th>
<th>FWTM [mm] Custom</th>
<th>FWTM [mm] GATE</th>
<th>Skewness Custom</th>
<th>Skewness GATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offset</td>
<td>Top 0.28</td>
<td>0.48</td>
<td>0.47</td>
<td>1.3</td>
<td>0.053</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Bottom 0.32</td>
<td>0.40</td>
<td>0.65</td>
<td>0.48</td>
<td>0.069</td>
<td>0.16</td>
</tr>
<tr>
<td>Central</td>
<td>Top 0.076</td>
<td>0.11</td>
<td>0.15</td>
<td>0.50</td>
<td>0.031</td>
<td>0.049</td>
</tr>
<tr>
<td>Blocks</td>
<td>Bottom 0.080</td>
<td>0.15</td>
<td>0.22</td>
<td>0.50</td>
<td>0.052</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Table 2.2. Root-mean-square error of coincidence profile characteristics between measured and
simulated coincidence profiles.

The width of each coincidence profile is highly influenced by the dynamics of inter-crystal
scatter. With no crystal misidentification from scattering, the width of the profiles that pass
through the centre of the FOV could not be very much larger than the width of a crystal (1.2
mm in this case). The finite width of the source, positron range, and photon acollinearity
could allow the coincidence profile to be only slightly wider than the crystals. Given the
good agreement between measurements and simulations, it was concluded that the GATE
simulations and data post-processing are providing a sufficiently accurate representation of
the processes of radiation detection by the detector blocks.

2.5 Experiments
This section will describe several studies that played a crucial role in the design of our
prototype DLO PET system. §2.5.1 describes a set of simulations made to optimize the
design of the dual layer offset detector block. §2.5.2 describes simulations used to estimate
reconstructed spatial resolution and resolution uniformity. §2.5.3 demonstrates the improvement in resolution uniformity following from the DLO block design. §2.5.4 describes simulations used to estimate peak sensitivity and mouse-NECR.

2.5.1 Optimizing Design of Dual Layer Offset Detector Block

Dual layered detectors reduce the parallax effect due to a reduction in the uncertainty of the radial coordinate of annihilations that they detect. The accuracy by which a DLO detector block can measure the radial coordinate of annihilation photons is affected by the thickness of each layer. A size constraint of our PET scanner design has been that space only allows for 10 mm of scintillator material in order to fit between the gradient and RF coils of the MRI system. However, the depth into the crystal at which we split the top layer from the bottom layer was still a parameter remaining to be chosen. If both were of equal thickness, the uncertainty in the radial coordinate would be equal for photons detected in either layer. A marginal shrinking of the top layer and growth of the bottom layer would benefit the accuracy by which photons are positioned in the top layer at the expense of the accuracy by which photons are positioned in the bottom layer. Because fewer photons are detected in the bottom layer (due to shielding from the top layer), it would seem intuitively that the optimal split between top and bottom layers would favour a slightly thinner top layer.

A simulation was set up with a pencil beam of 511 keV gamma rays incident on one crystal of a DLO detector block, as shown below in Fig. 2.7a. A pencil beam is defined as a beam of photons moving in parallel trajectories with a uniform flux. The block in this experiment was made of a 9×9+10×10 array of 1.345 mm wide LYSO crystals, arranged with a pitch of 1.422 mm. This does not correspond to the final design for the blocks in our prototype DLO PET system because these simulations were done in the early stages of design. For each photon that interacts in the array, the crystal of interaction is identified based on the method described in §2.2. The exact coordinate of interaction that would be assumed by a reconstruction is at the interaction centroid of the identified crystal. The depth into each crystal at which the centroid is placed is the expectation value of the probability density
function that describes the probability of photon interaction, as illustrated in Fig. 2.7b ($\mu = 0.82 \text{ cm}^{-1}$). The resulting formula used to compute the centroid of a crystal with length $L$ is:

$$< x > = \frac{1 + e^{-\mu L}(\mu L + 1)}{\mu e^{-\mu L}}$$

(2.1)

Fig. 2.7. (a) shown the arrangement of detector material relative to the pencil beam in the Monte-Carlo simulation. (b) illustrates the method used to compute the centroid of the crystal, which is not to be confused with the geometric centroid.

The radial mispositioning of each event is the radial distance (perpendicular to the direction of the pencil beam) between the centroid in the identified crystal of interaction, and the location in the block where the photon had its first interaction. It is this mispositioning that causes the parallax effect, so this quantity should ideally be as small as possible. For various block designs, simulations were run with the beam angle of incidence of either 0°, 22.5°, or 45°. These angles of incidence correspond to radial offsets from the centre of the FOV of 0, 10, and 20 mm in a 60 mm diameter PET scanner. The different simulated block designs had top / bottom layer splits ranging from 1 / 9 mm to 10 / 0 mm, in 1 mm increments. Energy resolution was modelled as 20%, which at the time of this work, was believed to be an energy resolution achievable in our PET insert. Singles were filtered with a 400 to 600 keV energy window. For each block design, and at each angle of incidence, a histogram of radial
displacement was created after hundreds of thousands of photon interactions were simulated. From this histogram, the average absolute radial displacement was calculated.

Fig. 2.8 shows histograms of the radial displacement at incidence angles of 0° and 45° for blocks with 5 different splits between top and bottom layer thickness. Positive displacement is toward the centre of the scanner. At a direct (0°) angle of incidence, the point of separation between the two layers is irrelevant to how well the block can measure the position of a photon. The width of the curve is exactly equal to the crystal pitch, 1.422 mm. Widening at the tails is due to intercrystal scatter. A different behaviour is observed at an angle of incidence of 45°. Here the distribution of radial displacement has a complicated pattern due to interactions detected by each layer with varying levels accuracy.

Fig. 2.8. Histograms of radial displacement of interaction location. (a) and (b) correspond on incidence angles of 0° and 45°, respectively.

The average absolute photon displacement at each angle of incidence is plotted as a function of top-layer thickness in Fig. 2.9. This figure shows that the greatest ability to measure the radial position of a photon interaction occurs when the split between the top the bottom layers is approximately equal. Another important fact learned from this analysis is that once the split is roughly even, there is not a major dependence on small changes in where the split is made. A final decision of splitting the block with 4 / 6 mm in the top / bottom layer was made. This split is within the optimal region in minimizing radial displacement, but also has
the benefit that blocks will form a trapezoid shape which is more optimal for being packed together in a ~60 mm wide ring with a smaller voids between the blocks (which ultimately is beneficial for the sensitivity of the PET scanner).

![Graph of average absolute radial displacement at three different incidence angles.](image)

**Fig. 2.9.** Average absolute radial displacement at three different incidence angles. The average radial displacement decreases when the top and bottom layer faces are roughly the same size. The left and right extremes of the graph correspond to a single-layer block.

### 2.5.2 Estimating Resolution and Resolution Uniformity

Of crucial importance to know before building a PET system is the anticipated resolution that the system will achieve. The spatial resolution was estimated with a series of GATE simulations that reproduced the procedure of measuring PET spatial resolution prescribed in the NEMA NU 4-2008 protocol [87]. Simulations were run using a 0.25 mm wide sphere emitting positrons with energy characteristic of $^{22}$Na embedded in a 10 mm wide acrylic cube. Data were collected with the source at radial offsets of 0, 5, 10, and 15 mm, both at the axial centre, and offset from the axial centre by a quarter of the axial length. Data were histogrammed into sinograms, normalized, and reconstructed according to the procedure later described in §5.4. Zoom-4 was used for the image reconstructions, so that the FWHM of the peak would span at least four voxels, as is required by the NEMA NU 4-2008 protocol. These simulations correspond to the finalized system design, detailed in the right-most column of Table 2.1.
For visualization, images of the four point sources at the axial centre were superimposed and are shown in Fig. 2.10. The FWHM and FWTM of each point were measured according to the NEMA NU 4-2008 protocol. The results, along with the volumetric resolution, are summarized in Table 2.3 (axial centre of the FOV) and Table 2.4 (¼ axial offset). Volumetric resolution is defined as the product of the FWHM in the three orthogonal directions. Resolution is plotted as a function of radial offset in Fig. 2.11 (value plotted is the average between the resolution measured at the axial centre and offset by a quarter of the axial length).

![Point source reconstructions](image)

**Fig. 2.10.** Point source reconstructions located at 0, 5, 10, and 15 mm from the radial centre of the PET scanner. Note that point sources were reconstructed and analyzed independently, and were only added together for visualization in this figure.

<table>
<thead>
<tr>
<th>Offset [mm]</th>
<th>FWHM [mm]</th>
<th>FWTM [mm]</th>
<th>Vol. Res. [µL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.09</td>
<td>1.08</td>
<td>1.44</td>
</tr>
<tr>
<td>5</td>
<td>1.40</td>
<td>1.32</td>
<td>1.59</td>
</tr>
<tr>
<td>10</td>
<td>1.59</td>
<td>1.31</td>
<td>1.62</td>
</tr>
<tr>
<td>15</td>
<td>1.80</td>
<td>1.45</td>
<td>1.62</td>
</tr>
</tbody>
</table>

**Table 2.3.** Summary of reconstructed point source widths at the axial centre of the scanner

<table>
<thead>
<tr>
<th>Offset [mm]</th>
<th>FWHM [mm]</th>
<th>FWTM [mm]</th>
<th>Vol. Res. [µL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.09</td>
<td>1.08</td>
<td>1.43</td>
</tr>
<tr>
<td>5</td>
<td>1.43</td>
<td>1.35</td>
<td>1.59</td>
</tr>
<tr>
<td>10</td>
<td>1.52</td>
<td>1.35</td>
<td>1.63</td>
</tr>
<tr>
<td>15</td>
<td>1.80</td>
<td>1.41</td>
<td>1.65</td>
</tr>
</tbody>
</table>

**Table 2.4.** Summary of the reconstructed point source widths at a ¼ axial offset
Simulated data from a microDerenzo phantom was also reconstructed. This microDerenzo phantom contains hot inserts running parallel to the axis of the scanner in six separate groups. The diameters of the rods in these six groups are 2.4, 2.0, 1.7, 1.35, 1.0, and 0.75 mm. The spacing between the rods in each group is equal their diameters. The six groups are contained inside of an annulus with inner / outer diameter of 27 / 28 mm. The purpose of the microDerenzo phantom is to give a more visually intuitive impression of the spatial resolution that the system achieves. One simulation was run with the phantom centred in the FOV, and another with the phantom shifted up by 5 mm to give an impression of the image quality near the edge of the FOV. Reconstructions, shown in Fig. 2.12, show that the system can adequately resolve a feature size of 1.0 mm (the second smallest rods). The smallest rods, which are 0.75 mm in diameter, cannot be resolved with FBP reconstruction.
The predicted radial resolution ranges from 1.09 to 1.8 mm moving from the centre of the FOV to a 15 mm offset. A comparison of the spatial resolution to other small animal PET system will be given in Chapter 7 where the constructed prototype DLO PET system is characterized. In spite of the fact that the dual layer offset design is meant to mitigate the parallax effect, resolution still drops off rapidly due to the small diameter. In the following section, it will be shown that the resolution uniformity would be substantially worse if a single-layer block design were used instead of a dual layer design.

2.5.3 Demonstration of the Effectiveness of the Dual Layer Offset Design

It was shown in §2.5.2 that the spatial resolution resulting from the DLO PET scanner is not uniform in spite of the fact that the DLO block design was employed to reduce the parallax effect. To quantify the effectiveness of the DLO block design to improve resolution uniformity, the analysis from §2.5.2 was repeated for a single layer system with an otherwise identical geometry. The top layer of each block was removed, and the bottom layer was extended to a thickness of 10 mm. All other details of the simulations and reconstruction were unchanged. The resulting reconstructions of the four point sources in the axial centre of the FOV are shown below in Fig. 2.13 (superimposed for visualization). It is visually apparent that the parallax effect discussed in §1.5.2 has become stronger, as would be expected from a system with no depth of interaction capability. The widths of these point
source reconstructions in the three orthogonal directions are summarized in Table 2.5 and Table 2.6 and visualized in Fig. 2.14. Fig. 2.15 shows slices through the reconstructed images of the simulated microDerenzo phantom at the centre of the FOV and at a 5 mm radial offset, alongside the reconstruction of the microDerenzo phantom images from the dual-layer simulation for comparison.

Fig. 2.13. Point source reconstructions from a single-layer PET scanner at 0, 5, 10, and 15 mm radial offsets. Note that point source reconstructions were reconstructed and analyzed independently, and were only added together for visualization in this figure.

Fig. 2.14. (a) shows the reconstructed point source width (FWHM and FWTM) as a function of radial offset for a single layered system. (b) shows the volumetric resolution as a function of radial offset.
### Table 2.5. Summary of point source widths from a single layer scanner at the axial centre of the scanner

<table>
<thead>
<tr>
<th>Offset [mm]</th>
<th>FWHM [mm]</th>
<th>FWTM [mm]</th>
<th>Vol. Res. [µL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.18</td>
<td>1.16</td>
<td>1.50</td>
</tr>
<tr>
<td>5</td>
<td>1.60</td>
<td>1.42</td>
<td>1.50</td>
</tr>
<tr>
<td>10</td>
<td>2.05</td>
<td>1.48</td>
<td>1.70</td>
</tr>
<tr>
<td>15</td>
<td>2.49</td>
<td>1.63</td>
<td>1.71</td>
</tr>
</tbody>
</table>

### Table 2.6. Summary of point source widths from a single layer scanner at a ¼ axial offset

<table>
<thead>
<tr>
<th>Offset [mm]</th>
<th>FWHM [mm]</th>
<th>FWTM [mm]</th>
<th>Vol. Res. [µL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.16</td>
<td>1.17</td>
<td>1.51</td>
</tr>
<tr>
<td>5</td>
<td>1.58</td>
<td>1.48</td>
<td>1.60</td>
</tr>
<tr>
<td>10</td>
<td>2.10</td>
<td>1.42</td>
<td>1.65</td>
</tr>
<tr>
<td>15</td>
<td>2.45</td>
<td>1.69</td>
<td>1.76</td>
</tr>
</tbody>
</table>

**Fig. 2.15.** Slices through the microDerenzo phantom reconstructed with data from the dual layered system (top) and from a single layered system (bottom).
By comparing the widths of the reconstructed point spread functions from the single-layer and dual-layer systems, it is clear that the DLO design makes a substantial improvement in resolution uniformity. At a radial offset of 15 mm, the radial FWHM and volumetric resolution worsen by 51% and 69%, respectively, when only a single layer of scintillator is used to build the system. The spatial resolution of the microDerenzo phantom (Fig. 2.15) in the radial direction is visually reduced when a single-layer block design is used. The shifted microDerenzo phantom shows that the impact that the DLO block design has on resolution is most substantial near the edge of the FOV.

2.5.4 Estimating Sensitivity and Noise Equivalent Count Rate

In order to estimate the count rate performance that our design would achieve, Monte-Carlo simulations were run mimicking actual experiments to measure the peak sensitivity and the mouse-NECR. These simulations correspond to the finalized system design, detailed in the right-most column of Table 2.1. For the sensitivity experiment, a 0.25 mm wide point source emitting 100 back-to-back 511 keV gamma ray pairs per second was positioned in the centre of the FOV and 1000 s of acquisition was simulated. As described in §2.3 of this chapter, data were post-processed to mimic the scanner properties listed in Table 2.1. Data were sorted for coincidences using a 10 ns coincidence window to count the number of true coincidences detected by the system during the acquisition. The coincidence window of the prototype DLO PET system can only be set in intervals of 2.5 ns, so 10 ns was considered most appropriate coincidence window (one that captures nearly all trues without capturing an excessively high number of randoms). A true coincidence is identified as a coincidence where the event ID of each single is the same. Coincidences where the difference in the z-coordinates of the detection points of each single is greater than 24.13 mm (19×1.27 mm) are removed from the data set. This is meant to mimic the maximum ring difference of 19 rings imposed for analytic reconstructions (described in §5.2). An energy window of 300 to 800 keV was also applied. Sensitivity is defined as the fraction of back-to-back gamma rays emitted from the source that are recorded by the scanner. The simulated sensitivity was measured as 2.5%.
The mouse equivalent phantom (as defined in the NEMA NU 4-2008 protocol) was positioned in the centre of the FOV. This phantom consists of a 70 mm long and 25 mm wide polyethylene cylinder. A 60 mm long and 3.2 mm wide active hot-rod runs parallel to the centre of the phantom with a radial offset of 10 mm. The source was set to emit back-to-back 511 keV gamma rays. Because NECR is quantified as a function of source activity, the simulations were run with the activity set to 13 values spaced logarithmically between 0.5 and 50 MBq. Data were once again post-processed and sorted for coincidences in the same way that the sensitivity data were. Each coincidence was identified as a true, random, or scattered coincidence. Random coincidences are defined as those with two different event IDs. Of the remaining coincidences, those where one or both singles had at least one interaction in the phantom were identified as scattered coincidences. All others were identified as true coincidences. As mandated in the NEMA NU 4-2008 protocol, all coincidences with a radial coordinate greater than 20.5 mm were removed from the data set. Based on the rates of trues (T), scatters (S), and randoms (R), the NECR was calculated according to equation (1.25). Because we use the delayed coincidence method of estimating the randoms, a value of 2 was used for \( k \) in equation (1.25). The simulated NECR as a function of activity is plotted in Fig. 2.16, along with the rates of trues, scatters, randoms, and \textit{prompts}. The rate of prompt coincidences is the sum of the rates of true, scattered and random coincidences.
Fig. 2.16. Simulated NECR, along with rates of true, scattered, random, and prompt coincidences as a function of source activity.

A 4th order polynomial was fit to the NECR curve to interpolate between the calculated values and find the maximum. The fit revealed the maximum NECR to be 22.0 kcps at an activity of 14.1 MBq. Another useful metric to describe the quality of an NECR curve is the NECR at 3.7 MBq (100 µCi), which is a much more usual activity for mice to be scanned at. The NECR at an activity of 3.7 MBq is 12.2 kcps. A discussion that will compare the NECR of this system with other commonly used small animal PET systems will be given in Chapter 7.

The accuracy of this simulation is limited by the deadtime model that we use. GATE provides the option of paralyzable and non-paralyzable deadtime models. More sophisticated deadtime models can be created by adding deadtime to different levels of the PET system (for example paralyzable singles-level detection deadtime plus additional non-paralyzable coincidence-level deadtime). Before our back-end electronics had been selected, we estimated that our system deadtime would be non-paralyzable and between 500 and 600 ns. The 2013 publication of these simulations modelled scenarios of the PET system with either 500 or 600 ns of deadtime to give a best- and worst-case scenario of how the PET system would perform [96]. When the prototype PET system was built using the OpenPET readout system for our back-end electronics [99], we observed very complicated deadtime behaviour.
This behaviour will be described in more detail later in Chapter 7, where the performance of the prototype is characterized. A 1500 ns paralyzable deadtime model was observed to roughly approximate the deadtime behaviour of the prototype DLO PET system, and so was chosen as the deadtime model used for the final simulation results presented in this thesis. The NECR simulations will continue to be a useful tool in finalizing the design of the next generation DLO PET system.

2.6 Conclusion

A set of macros was created to simulate the prototype DLO PET system using the Monte-Carlo simulation suite GATE. Following multiple interactions of an annihilation photon in a scintillator crystal array, GATE identifies the crystal of interaction as the one in which the most energy was deposited in. For simulations that aim to demonstrate the spatial resolution of the DLO PET system, data were post-processed so that instead the crystal of interaction would be identified using a centre-of-mass based approach. It was found that by comparing simulated coincidence profiles to measured coincidence profiles, that the post-processed data were a much better representation of the spatial response of the detector blocks.

GATE simulations of a single DLO detector block were created to optimize the thickness of the top and bottom layers with the total thickness constrained to 10 mm. It was found that a roughly even split between the top and bottom layers resulted in the minimum average absolute radial misplacement of detected photons. As a result of these simulations, a block configuration using 4 mm of LYSO in the top layer and 6 mm in the bottom layer was chosen.

A simulation of the prototype DLO PET system was created in GATE to estimate its spatial resolution and count rate performance. It was found that at the axial centre of the FOV that the radial resolution would range from 1.09 mm to 1.80 mm moving from the radial centre to a 15 mm offset, and the volumetric resolution would range from 1.68 µL to 4.18 µL over the same range of positions. When applying a 300 to 800 keV energy window, the peak
sensitivity was found to be 2.5%, and the peak NECR was found to be 22.0 kcps (peaking at 14.1 MBq).

These simulations have provided a useful tool to estimate the PET performance, in terms of spatial resolution and count rate, that would result from various design modifications, and will continue to serve that purpose as the next generation of the DLO PET insert is being designed.
Chapter 3: Characterization of Digital Photon Counter Detector Block

3.1 Purpose

The ability of a PET detector block to measure the energy, time, and position of an annihilation photon interaction is crucial to obtaining good PET image quality. With few exceptions [60], [61], some type of photomultiplier technology must be incorporated into the block design to convert visible light created in the scintillator into an electronic signal as discussed in §1.5.1. The choice of photomultiplier has an enormous impact on how accurately energy, time, and position can be measured, so special consideration should be used in selecting the photomultiplier. Although the necessity of our PET system to operate in a strong magnetic field rules out the use of widely used photomultiplier tube technology, many new technologies such as avalanche photodiodes and silicon photomultipliers are possible choices.

Digital photon counter (DPC) technology is a very recent evolution of the silicon photomultiplier. The nature of DPC technology offers the possibility of superior timing resolution and lower noise [70], [100]. In 2012, our group had the opportunity to test the Philips DPC3200-22-44 (rev. C) DPC array as a candidate photomultiplier for use in our PET system. In this chapter, a detailed description of the Philips DPC array will be given. Experiments to measure the timing resolution, energy resolution, and positioning accuracy in a DLO PET detector block incorporating a DPC array will be described here. The block will be made from an array of small scintillator crystals readout by an array of DPCs as photomultipliers (as in Fig. 1.7 in §1.5) via Anger-logic. Important performance metrics specific to the DPC array such as the rate of incomplete neighbor logic, which affects sensitivity, will also be characterized. These performance metrics will be shown to have strong dependencies on device settings and temperature.

3.2 Anatomy of the Digital Photon Counter Array

Like the silicon photomultiplier, at the heart of a DPC is a microscopic array of Geiger-mode avalanche photodiodes (referred to as a cell from here on). As described in §1.5.1, the output
of a silicon photomultiplier array is an analog sum of the output of each cell. The magnitude of the output signal (whether this be defined as the signal’s integral or the peak value) is proportional to the number of scintillation photons falling on the array of cells (neglecting saturation), which in turn is proportional to the amount of energy an annihilation photon deposits in the scintillator material. The novelty of the DPC over SiPMs is that the output of each cell is directly digitized as a 0 or 1.

In a silicon photomultiplier, electronic noise added to the analog sum of cells will manifest as noise in the measurement of annihilation photon energy and position. The arrival time of an annihilation photon is usually determined as the moment when the analog silicon photomultiplier output passes a certain threshold (in the case of a leading edge discriminator) or when it reaches a certain fraction of its maximum (in the case of a constant fraction discriminator). Analog noise will then add uncertainty to the estimation of arrival time too.

In the DPC, because the detection of each scintillation photon is digitized at the earliest possible moment, there is no opportunity for electronic noise to be added to the signal. The only sources of noise in the recorded energy are:
1. *Dark counts*, which occur when a cell breaks down in response to a thermally generated electron or hole entering the high field region of the cell.
2. Statistical variation in the number of photons detected by the DPC. Following the absorption of 511 keV of energy, the number of photons emitted by LYSO is on average $\sim 1.6 \times 10^4$ [59], but the actual number emitted is inherently random. There is additional uncertainty in the number of emitted photons that reach the DPC face, and the number of those photons that actually cause a cell breakdown.

Digitization of each breakdown is especially beneficial to timing resolution when considering how a time-stamp is generated. By “OR”-ing all outputs together and feeding this signal to a *time to digital converter*, it is possible to generate a time-stamp almost at the exact moment when the first cell breaks down. In the absence of high dark-count rates, this can lead to superb timing resolution [101]. To mitigate the presence of the higher dark-count
At rate typical of near-room-temperature operation, the trigger network can be configured as a more complicated network of OR and AND gates, which suppresses spurious dark-counts but still allows for the generation of a time-stamp once a very small number of cells have broken down. This will be described in more detail in §3.3.1.

The Philips DPC3200-22-44 array is a 4×4 array of dies (shown in Fig. 3.1a) each of which function autonomously from each other to count photons (with the exception of the neighbor logic signal which travels between dies, which will be discussed in §3.3.4). The DPC array sits on top of a printed circuit board hosting a field programmable gate array (FPGA), shown in Fig. 3.1a. The FPGA functions to:

1. Monitor temperature
2. Send configuration data to the DPC dies
3. Collect event data sent from the dies, which include a time-stamp, a photon count from the four pixels of each die, and current temperature
4. Filter undesired events, such as readout reports with a very low photon count
5. At the end of each 328 μs frame, send buffered readout reports back to the PC

Fig. 3.1. Photograph of an array of DPC dies sitting on top of an FPGA (a). The DPC array and FPGA are assembled in a black case interface to an acquisition PC through a control board (b). (Source: PDPC Users Manual [102], Used with permission).
Two DPC arrays interface to the acquisition PC via a base unit, all of which were included in a technology evaluation kit (Fig. 3.1b). The base unit also interfaces to a power supply, and allows for the optional connection of an external trigger. All coincidence detection is currently done in software on the acquisition PC although this could in theory be done by an FPGA.

The DPC array can be broken down into a hierarchy of ever-smaller functional units, which are summarized in Table 3.1 and the schematic of a die shown in Fig. 3.2. The DPC array contains a 4×4 array of dies, and each die is divided into four pixels. Upon readout, the DPC will report to the PC the number of cell breakdowns on the level of the pixel. Because Anger-logic identifies a crystal of interaction from the centroid of light distribution on the photomultipliers, the pixel pitch is ultimately what limits minimum crystal size that can be resolved. Each pixel is further divided into four sub-pixels, which are relevant to understanding how the trigger that begins an acquisition sequence is formed.

![Diagram of die, pixel, and sub-pixel]

Fig. 3.2. A single die is divided into four pixels. Each pixel is further divided into four sub-pixels.

<table>
<thead>
<tr>
<th>Name</th>
<th>Size [mm] X × Y</th>
<th>Pitch [mm] X × Y</th>
<th>Number of Cells X × Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPC Array</td>
<td>32.6 × 32.6</td>
<td>n/a</td>
<td>512 × 400</td>
</tr>
<tr>
<td>Die</td>
<td>7.15 × 7.875</td>
<td>7.95 × 7.975</td>
<td>128 × 100</td>
</tr>
<tr>
<td>Pixel</td>
<td>3.2 × 3.875</td>
<td>4.0 × 4.0</td>
<td>64 × 50</td>
</tr>
<tr>
<td>Sub-Pixel</td>
<td>1.6 × 1.9375</td>
<td>1.6 × 1.9375</td>
<td>32 × 25</td>
</tr>
</tbody>
</table>

Table 3.1. Names and dimensions of hierarchical levels of the DPC 3200-22-44 Array
3.3 Acquisition Sequence and Device Settings

When powered on, a DPC die will remain in a resting state until a sufficient number of cells break down causing the die to be triggered. Unlike analog SiPMs, where cell breakdowns are passively quenched, cell breakdowns are actively quenched, meaning they will discharge until the end of the acquisition cycle when they are actively reset. If a trigger is not formed by the end of each 328 µs frame, all cells are quenched and re-armed. When a trigger is formed, a pair of time to digital converters with a step-size of approximately 19.5 ps records a time-stamp, and the die will move into the validation stage of the acquisition cycle (Fig. 3.3).

![Fig. 3.3 A flowchart showing the behaviour of a die once triggered. (Source: PDPC Users Manual [102], Used with permission).](image)

The first stage of the acquisition cycle after triggering is called the validation stage and is meant to prevent a die from entering a readout cycle in response to triggers formed from the accumulation of dark counts (dark triggers). The rate of cell breakdowns needed to pass the validation stage is significantly higher than what is needed to form a trigger. The implementation of a two-staged test (trigger/validation) to enter an acquisition sequence allows for excellent timing resolution without excessive deadtime caused by dark readouts (when an acquisition sequence is entered in response to dark counts).

If a trigger is validated, the die enters an integration stage, which has a configurable length of time between 0 to 20.4 µs. Otherwise all cells are reset. The integration length should be adequately long to capture the light output from the scintillator, but not excessively long, which would only serve to add dark counts to the measurement. Of the options available, we
chose 165 ns as the most appropriate integration length to capture the full light output of LYSO, which has a decay constant of 50 ns.

Cell breakdowns are not actually summed until the readout stage begins. This is a key reason why cells cannot be passively quenched. Each row of 32 cells on each sub-pixel is called a row-trigger-line. During readout, the number of cell breakdowns in each pixel is accumulated one row-trigger-line at a time. The readout stage takes 680 ns and is a significant factor in the deadtime of the DPC. During readout, row trigger lines that have not been read out yet are still active, and breakdowns in those cells, along with breakdowns formed during the validation stage and the lead-up to the trigger will contribute to the total photon count. After being buffered in the FPGA and then sent back to the acquisition PC at the end of each 328 µs frame, each readout appears as a row of text in the acquisition .dpct file. An example of one such file is shown in Fig. 3.4.

<table>
<thead>
<tr>
<th># V1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td># Measurement started at: Mon Jul  8 15:11:09 2013</td>
</tr>
<tr>
<td># Tile 1: not configured</td>
</tr>
<tr>
<td># Tile 2: (Serial: 1475, Version: 201, Revision: DPC-3200-22-44_C), Settings: Trigger threshold: 1, Validation Pattern: 0x0, Validation Interval: 40 nsec, Integration Interval: 165 nsec</td>
</tr>
<tr>
<td># Tile 3: not configured</td>
</tr>
<tr>
<td># Tile 4: (Serial: 1351, Version: 201, Revision: DPC-3200-22-44_C), Settings: Trigger threshold: 1, Validation Pattern: 0x0, Validation Interval: 40 nsec, Integration Interval: 165 nsec</td>
</tr>
<tr>
<td># Capturing: 100000000 frames;</td>
</tr>
<tr>
<td># Coincidence: Window: 2048 FC bins (one FC bin ~19.5ps); Minimum tiles per coincidence: 2; Minimum dies coincidence: 2</td>
</tr>
<tr>
<td># measured in corrected mode</td>
</tr>
<tr>
<td># tile, die, frame_nr,delay,timestamp,p0, p1, p2, p3, temp, status,eventid, frame_counter</td>
</tr>
<tr>
<td>4, 0, 228, 0, 8727583, 18, 17, 64, 99, 14.8, 2, 0, 56</td>
</tr>
<tr>
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</tr>
<tr>
<td>2, 5, 228, 0, 8728274, 722, 112, 47, 241, 14.8, 2, 0, 56</td>
</tr>
<tr>
<td>2, 1, 228, 0, 8728368, 44, 24, 54, 143, 14.8, 2, 0, 56</td>
</tr>
<tr>
<td>4, 4, 241, 0, 15786971, 879 619, 95, 106, 14.8, 2, 1, 69</td>
</tr>
<tr>
<td>4, 0, 241, 0, 15786978, 63, 49, 239, 254, 14.8, 2, 1, 69</td>
</tr>
<tr>
<td>2, 1, 241, 0, 15786288, 20, 182, 52, 12, 14.8, 2, 1, 69</td>
</tr>
<tr>
<td>4, 0, 244, 0, 859101, 260, 321, 538, 503, 14.8, 2, 2, 72</td>
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</tr>
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<tr>
<td>2, 1, 155, 0, 14589270, 56, 25, 72, 402, 14.8, 2, 4, 239</td>
</tr>
<tr>
<td>2, 5, 155, 0, 14590127, 143, 47, 267, 220, 14.8, 2, 4, 239</td>
</tr>
</tbody>
</table>

Fig. 3.4. Example acquisition output file, showing a row for each die readout. Here “tile” refers to which DPC array in which each record originated. Up to four arrays can be connected to the base unit. The number of cell breakdowns in each pixel are labelled p0 to p3. Time-stamps are measured in units of TDC bins (each being ~19.5 ps), and temperature is measured in degrees Celsius.
Aside from the already mentioned integration length, other parameters that affect the acquisition sequence are:

### 3.3.1 Trigger Scheme

Each sub-pixel produces a logical state $T_i$ as indicated in Fig. 3.2 if one or more of its cells has broken down during the resting stage. The sub-pixel states of each pixel are combined through a configurable series of logic gates to form a trigger signal. Four available *trigger schemes* (TS) described in Table 3.2 define how these logic gates are configured. The DPC is triggered when any one of its four pixels generates a trigger.

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Logic</th>
<th>Average # of Cell Breakdowns to Form Trigger</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS1</td>
<td>$T_1$ or $T_2$ or $T_3$ or $T_4$</td>
<td>1</td>
</tr>
<tr>
<td>TS2</td>
<td>${(T_1 \text{ or } T_2) \text{ and } (T_3 \text{ or } T_4)}$ or ${(T_1 \text{ or } T_4) \text{ and } (T_2 \text{ or } T_3)}$</td>
<td>2.333</td>
</tr>
<tr>
<td>TS3</td>
<td>$(T_1 \text{ or } T_3) \text{ and } (T_2 \text{ or } T_4)$</td>
<td>3.0</td>
</tr>
<tr>
<td>TS4</td>
<td>$T_1$ and $T_2$ and $T_3$ and $T_4$</td>
<td>8.333</td>
</tr>
</tbody>
</table>

*Table 3.2. Definition of Trigger Schemes*

TS1 is passed when just one cell on the entire die breaks down. Higher trigger schemes require progressively more cell breakdowns to form a trigger and so are more immune to dark triggers. The number of cell breakdowns to form a trigger has a statistical variation for TS>1. The last column of Table 3.2 indicates the average number of cell breakdowns required to form a trigger, assuming a uniform distribution of breakdowns across the pixel [100]. With increasing number of necessary breakdowns compounded with variation in the number of detected photons that will cause a trigger, it is obvious that higher trigger schemes will lead to poorer timing resolution.

### 3.3.2 Validation Scheme and Validation Time

A validation signal is formed in a very similar way as the trigger signal. Each sub-pixel is divided into eight sub-regions made of either three or four row trigger lines. These sub-regions, which form a logical *true* signal when any of their cells break down during the validation stage, are connected with a series of logic gates as depicted in Fig. 3.5 to form a
validation signal. The validation scheme is specified by seven bits which set each of these gates to AND or OR. A die is validated as soon as any one of its pixels forms a validation signal. Certain revisions of the DPC 3200-44-22 (but not ours) can optionally require that all sub-pixels in a pixel must produce a validation signal. The validation time determines how long the validation window will remain open before a trigger is deemed invalid, and can be configured as 5, 10, 20, or 40 ns. Even if the validation criteria is met part-way through the validation stage, the die will not switch to the integration stage until the entire validation time has passed.

![Diagram](image)

**Fig. 3.5** Sub-regions of each sub-pixel are connected by a series of logic gates to form a validation signal. (Source: PDPC Users Manual [102], Used with permission).

### 3.3.3 Cell Inhibition

A novel feature of the Philips DPC is that each cell can be individually disabled. Any cell in a DPC can be a source of a dark count, but it has been empirically observed that the majority of dark counts are generated within a minority of ‘badly-behaved’ cells [70], [102]. Cells with defects in the semiconductor crystal structure are more likely to produce a dark count because the defect acts as a ‘stepping-stone’ which assists a valence electron to move into the conduction band [103] (the Shockley-Read-Hall process). Although the user of the DPC has absolute control over which cells are disabled, cell inhibition is mainly intended to disable the noisiest cells.
A routine run from the acquisition PC can measure the dark count rate from each cell by running many short acquisitions with only one cell enabled at a time. Following this, an inhibit map is created which flags the noisiest cells to be disabled. The fraction of cells which the user specifies to be inhibited is called the inhibit fraction (IF).

3.3.4 Neighbor Logic

A finely pixelated array of scintillator crystals such as the one in the DLO PET detector block relies on light being spread over and detected by multiple photomultiplier elements so that the centre of gravity (Anger-logic coordinate) can be calculated. If the Philips DPC array is employed to read out a crystal array, simultaneous readout from up to four dies might be necessary to properly calculate the Anger logic coordinate of a crystal. When operating the DPC array, dies that see only a modest amount of scintillation light may not actually pass the validation stage.

This problem is ameliorated by a setting called Neighbor-logic. When Neighbor-logic is turned on, the first die to pass the validation stage (the master die) will force its neighbour dies (slave dies) through the validation and integration stages. Slaves will generate a time-stamp at the moment they receive the neighbor-logic signal. Depending on how neighbor-logic is configured, the master may force all other dies on the tile to readout, or just a subset of the dies that sit close to the master. Neighbor-logic is especially useful for room temperature operation. At such a temperature, the strict validation scheme that is necessary to supress dark readouts likely will also prevent dies that see a modest amount of scintillation light from reading out independently.

3.3.5 RTL-Refresh

Because cell breakdowns are by default not quenched until the end of each 328 µs frame, dark triggers form very frequently from the accumulation of dark counts over a period of microseconds. Although these dark triggers will almost certainly not be validated, their presence can still be problematic; it will later be shown that a high dark-trigger rate interferes with the proper functioning of neighbor-logic. Row-trigger-line refresh (RTL-refresh) is a
setting designed to drastically reduce the rate of dark triggers. During resting state, the action of RTL-refresh loops through the 25 row-trigger-lines on each sub-pixel once every 10 ns. If on the first pass a breakdown is detected, the entire row-trigger-line is reset on the next pass unless a trigger is generated first. In the presence of an actual burst of scintillation light, 10 ns is adequate time for a trigger to be generated. However, the probability of a dark trigger being formed is drastically reduced for trigger scheme >1. There is no benefit to using RTL-refresh with trigger scheme 1 because the first cell breakdown immediately generates a trigger.

3.4 Detector Block Characterization

A prototype DLO PET detector block was constructed by mating an 8×8+7×7 DLO LYSO array to the DPC array through a 1.0 mm thick glass light guide. This block design is different than the design used in the full PET system that was built in 2014, for the characterization of the DPC array began before the design of the full PET system was finalized. The arrangement of the block relative to the DPC array as well as the crystal dimensions are shown in Fig. 3.6. Crystals were polished and individually wrapped with 3M enhanced specular reflector tape along their entire side edges, as well as any outer surfaces of the array not in contact with the light-guide. Optical grease was used on both sides of the light-guide. The footprint of the crystal array is much smaller than the 4×4 array of DPC dies. For this reason, only a 2×2 subsection of the DPC array was enabled; the other 12 dies were disabled by setting all bits to zero in their inhibit maps.

Fig. 3.6. A DLO detector block made from 7×7+8×8 LYSO crystals with a pitch of 1.27 mm from the side (a) and from the top (b). A 1.0 mm thick light guide couples the crystal array to a 2×2 array of dies. Dies are outlined in red, and purple lines show the division between pixels.
To test the suitability of this DLO detector block for a small animal PET application such as ours, several performance metrics of the block were quantified. The performance of the detector block was characterized in terms of spatial resolvability (i.e. the ability to resolve all crystals in a flood histogram), energy resolution, timing resolution, and count loss rates. These are important metrics to test because the ability of a detector block to accurately locate the position of an annihilation photon interaction directly impacts on the spatial resolution of reconstructed PET images. Likewise, energy resolution, timing resolution, and count loss rates impact the signal to noise ratio of reconstructed PET images.

All measurements reported in this chapter use validation scheme #8, which requires all eight sub-regions of any sub-pixel to have a cell breakdown to validate a trigger (all gates in Fig. 3.5 set as AND). We found that the dark readout rate was impractically high while operating near room temperature using more lenient validation schemes. Such a high validation scheme then requires use of neighbor-logic, without which dies that see only a modest amount of scintillation light are likely to not read out, possibly rendering the detected annihilation photon useless for PET imaging. The neighbor-logic signal takes up to 20 ns to propagate, so use of neighbor-logic requires that a 40 ns validation length (the longest period available) be used. A shorter validation length greatly increases the likelihood of incomplete neighbor-logic (which will be discussed in §3.4.4).

The detector block was characterized at 15 °C, which is an operating temperature that can be practically achieved in pre-clinical imaging (where body temperature must be maintained near 37 °C) without the need for complicated and expensive cooling equipment. Because the rate of count loss was found to have a strong dependence on temperature, these measurements were also made at 20 °C. Temperature was set and maintained to within 0.5 °C by operating the detector block inside of a temperature-controlled chamber. The DPC array is capable of running a routine that detects the breakdown bias of the cells. The bias voltage is then set based on an overbias specified by the user. For measurements at 15 °C, the overbias was set to the recommended 3.0 V. For measurements at 20 °C, the overbias was set to 2.9 V.
Considering that the breakdown voltage changes at a rate of -0.02 V/°C [102], this has the same effect of setting the overbias to 3.0 V at 15 °C and then allowing the temperature to drift to 20 °C without resetting the bias voltage. Doing this simulates a mid-scan 5 °C temperature fluctuation.

The aforementioned rates of count loss being characterized come from two sources. The first is dark readout deadtime: In cases where enough dark counts occur to validate a dark trigger, the device enters a readout cycle. This initiates a period of almost 1 µs during which the detector block is unable to successfully detect any annihilation photons.

The second source of count loss is from incomplete neighbor-logic: Sometimes neighbor-logic fails to invoke simultaneous readout from all four dies. This often occurs when a slave die is busy resetting an invalidated trigger and so cannot respond to the master die [104], [105]. In our early work characterizing the DPC detector block [106], any event in which incomplete neighbor-logic occurred was considered to be unusable because the Anger-logic coordinate used to identify that crystal would be so greatly altered that the crystal would be identified incorrectly. This fact is seen clearly when comparing the flood histograms shown in Fig. 3.7a to Fig. 3.7b. The latter includes all detected events, even those where one or more dies are missing on readout. Unlike in Fig. 3.7a where each crystal has a reproducible Anger-Logic coordinate, Fig. 3.7b is unresolved because each crystal’s response appears in many parts of the flood histogram depending on which dies were missing on readout. A method of properly identifying the energy and position of annihilation photon interactions in spite of missing dies called incomplete neighbor-logic recovery was later developed [107]. This method will be described in more detail in §3.4.4.
Fig. 3.7. Flood histogram constructed with detection events after events with incomplete neighbor-logic were removed (a) The flood histogram can be divided into unique domains corresponding to the response of each crystal. If events with incomplete neighbor-logic are included in the creation of the flood histogram, the Anger logic coordinate of each crystal appears in a number of places within the flood histogram (b).

When characterizing count loss from both dark readout deadtime and incomplete neighbor-logic, all four trigger schemes were characterized in depth. Because preliminary work showed that trigger scheme 1 provides unacceptable levels of count loss, it was characterized in less detail than the other trigger schemes. Unless otherwise stated, RTL-refresh was used for all measurements with trigger scheme >1. Because RTL-refresh has no affect when using trigger scheme 1, it was switched off for those tests.

3.4.1 Crystal Resolvability

A 150 kBq $^{22}$Na source was fixed 1.5 cm above the surface of the crystal array. Data were acquired with trigger scheme 4 and inhibit fractions of 5, 10, 15, and 20% at both 15 and 20 °C. The measurements made at 15 °C were repeated with RTL-refresh turned off. Measurements were also made with trigger schemes of 1, 2, and 3 for inhibit fractions of 5, 10, 15, and 20%. Data were collected long enough so that each data set recorded the interaction of at least 1.5 million annihilation photons (after events with incomplete neighbor-logic were discarded).
The output of each acquisition (Fig. 3.4) was analyzed with custom-made software. Groups of records with time-stamps equal to within 80 ns were interpreted as recording scintillation photons originating from the same annihilation photon (i.e. a single). Singles with less than four dies reading out were classified as cases of incomplete neighbor-logic and were discarded. The number of singles surviving this filter was not found to change at all as the coincidence window was raised past 80 ns, indicating that 80 ns is a sufficient amount of time to allow between when the master die is first triggered and when the neighbor-logic signal reaches all slaves.

The Anger logic coordinate of each single was found as a photon-count weighted average of the position of each of the 16 pixels. Flood histograms from each acquisition were formed by histogramming these Anger logic coordinates into a 256×256 matrix. Photon counts used for this weighting were corrected for saturation. Saturation occurs when photons land on the DPC at such a high rate that there is an appreciable probability that a photon striking a cell will not be counted because that cell has already broken down. Saturation is exacerbated on the DPC because cells are not quenched until the end of a readout cycle. Although dependent of the location of interaction, typically between 20 and 40% of cells on a pixel closest to the interaction location were observed to break down when 511 keV of energy is absorbed by the crystal. The saturation corrected cell count for each pixel, \( p \), is calculated according to the following formula:

\[
p = -N \ln \left(1 - \frac{k}{N}\right)
\]  

(3.1)

Here \( k \) is the number of cell breakdowns reported by the DPC and \( N \) is the number of active cells on the pixel, accounting for those disabled in the inhibit map. This correction assumes that photons are evenly distributed on a pixel. This is not the case for the DLO block studied here; one cannot assume that scintillation light from the 1.27 mm wide crystals will fall uniformly on ~3.5 mm wide pixels even after being spread by the light guide. Degenhardt et al [100] found that this correction resulted in a photon count that is proportional to the
deposited energy for energies up to 1.8 MeV with a residual error of 3%, although their crystal size was more comparable to the DPC pixel size.

Each flood histogram was analyzed first by identifying the centre of each crystal response by a local maximum corresponding to the centroid of its light distribution. Profiles were made by connecting each maximum in the $i^{th}$ row from the back layer to the $i^{th}$ row in the top layer (as later shown in Fig. 3.13a). For each maximum, we calculate the peak to valley ratio (the ratio of the peak value to the average of the two adjacent minima). Although the use of (3.1) to correct for saturation neglects that photon flux is non-uniform, flood histograms produced using (3.1) were more clearly resolved than if no saturation correction were applied (~25 % improvement in peak to valley ratio), providing evidence that it is better to use equation (3.1) than to apply no saturation correction at all.

3.4.2 Energy Resolution

From each acquisition described in §3.4.1, we also found the energy resolution obtained with those settings. Because energy resolution is estimated for each crystal in the array separately, a crystal look-up table was created from each flood histogram. This table is a matrix the same size as the flood histogram that holds integers ranging from 1 to 113, which correspond to the ID of the crystal whose response falls in that region of the flood histogram. The domain of each crystal in the look-up table is defined as all pixels within a distance of 15 pixels from the centre of the crystal response. Pixels that are within a 15 pixel distance of more than one crystal response maximum are assigned to the crystal whose response maximum is closest. Matrix elements outside of the domain of any crystal are set to zero. An example of one such crystal look-up table is later shown in Fig. 3.11a.

After all crystal look-up tables had been created, data sets were reprocessed. The Anger-logic coordinate of each event was passed through the crystal look-up table to identify the crystal. For each crystal, a histogram of saturation corrected photon counts was created. The energy resolution is defined as the FWHM of the photopeak divided by the photopeak position. The
photopeak corresponds to the peak in the histogram corresponding to 511 keV of absorbed energy. We report the energy resolution averaged over all crystals in the array.

3.4.3 Timing Resolution

To measure timing resolution, we operated our detector block in coincidence mode with a second identical block. Fig. 3.8 shows the arrangement of the $^{22}$Na source along with the two blocks, referred to as block #1 and block #2. The asymmetric positioning of the source between the blocks was done to ensure that all crystals from block #1 were involved in coincidence with block #2 allowing for the possibility of studying differences in timing resolution across the crystal array (which was not done). Timing resolution was measured at 15 °C with trigger scheme 2 to 4, both RTL-refresh on and off, at inhibit fractions of 5, 10, 15, and 20%. Measurements with trigger scheme 4 and RTL-refresh off were repeated at 20 °C to test the effect of raising the temperature. The timing resolution when using trigger scheme 1 was only measured at 15 °C with a 10% inhibit fraction and RTL-refresh off. Because of difficulties stabilizing both blocks to the same temperature, temperature was held to within 1.5 instead of 0.5 °C of the reported temperature.

![Fig. 3.8 Arrangement of DLO detector block in coincidence measurements. Block #1 is the detector block from which data were used to measure the probability of incomplete neighbor-logic.](image)

When using inter-block coincidence detection, the acquisition software will not save to file any record unless its time-stamp matches the time-stamp of another record originating from the opposite block to within the set coincidence window. All events falling within the same coincidence window are given the same “event ID” which is written into the acquisition file.
A wide coincidence timing window of 200 ns was used, allowing the DPCs to be operated before clocks between the arrays had been finely synchronized. Coincidences exhibiting incomplete neighbor-logic were discarded from the data set.

For each block, the time difference was calculated by subtracting the earliest time-stamp from block #1 from the earliest time-stamp from block #2. The earliest time-stamp from each block was used because it comes from the master die. Due to lack of synchronization of clocks (timing skew), time differences needed to be shifted by a constant so the mean time difference was zero regardless of which dies were involved. For the 16 combinations of dies between the two blocks, a histogram of time-stamp differences was made. These histograms were then shifted to have a mean value of zero, and then added together. This yields an average coincidence resolving time histogram, which is quantified by its FWHM.

### 3.4.4 Count Loss From Incomplete Neighbor Logic

The experimental setup in Fig. 3.8 was altered by replacing the scintillator array of block #2 by a 10 mm thick single layer LYSO array with a $18 \times 18$ mm$^2$ footprint. Block #2 was operated with trigger scheme 1, 5% inhibit fraction, and RTL-refresh off. With reference to Fig. 3.8, only data from block #1 were considered for these measurements; the purpose of using coincidence detection was to remove dark readouts from the data set. The count loss rate was characterized with the detectors set up with every combination of trigger scheme 2, 3, or 4, inhibit fraction of 5, 10, 15, or 20%, and temperature of 15 or 20 °C. All acquisitions were made with RTL-refresh on and acquisitions made at 15 °C were repeated with RTL-refresh off (except for trigger scheme 1).

For each acquisition, the fraction of annihilation photon detections that had to be discarded ($f$) was found. The probability of incomplete neighbor-logic may prove to have an energy dependence. This is because periphery dies that depend on the neighbor-logic signal to invoke readout for low energy photons may actually see enough scintillation light to independently readout for higher energy annihilation photons. Therefore, $f$ was quantified after applying a lower level energy cut off of 0, 250, or 350 keV. Equation (3.2) was used to
estimate the fraction of coincidence events that will be lost in a PET scanner due to incomplete neighbor-logic. Equation (3.2) is based on the fact that the fraction of coincidence events that can be kept is equal to the square of the fraction of annihilation photon detections that can be kept.

\[ \text{Coincidence Loss Fraction} = 1 - f^2 \]  

(3.2)

A method called incomplete neighbor-logic recovery was devised so that many events suffering from incomplete neighbor-logic could still be used in a PET application. In order to understand how incomplete neighbor-logic recovery works, it is useful to decompose the flood histogram shown in Fig. 3.7b into 15 different flood histograms corresponding to each permutation of either zero, one, two, or three dies missing on readout. The 15 flood histograms on the right hand side of the “equals sign” in Fig. 3.9 were created by first initializing 15 empty matrices. A data set from an acquisition using trigger scheme 1, inhibit fraction 10%, and RTL-refresh on was then processed without discarding events with incomplete neighbor-logic. Each flood histogram would only accumulate counts with the same combination of missing dies. For example, the flood histogram at the top-right of Fig. 3.9 corresponds to only the bottom-right die missing, and the flood histogram on the bottom-right corresponds to all dies except the top-left missing.
Fig. 3.9. Decomposition of an unresolved flood histogram including events with incomplete neighbor-logic into 15 separate flood histograms.

The key fact that enables recovery of incomplete neighbor-logic events is that many crystals are still resolved in certain regions of the decomposed flood histograms. Fig. 3.10 shows a close-up of the flood histogram created from only events where the top-left die was missing on readout. Red dots in the image show the positions of crystal responses when all dies were present. Although they are significantly perturbed relative to the original flood histogram, the Anger-logic coordinates of crystals far away enough from the missing die still carry enough information to be distinguished from other crystals. Other regions of these floods that appear cloudy are populated by the responses of crystals near the missing die. Clearly these crystals cannot be uniquely identified by their Anger logic coordinate, so they are still lost to incomplete neighbor-logic.
Crystal look-up tables are created for every combination of zero, one, or two missing dies. Very few crystals are resolvable when three dies are missing on readout, so no attempt is made to recover those events. Crystal look-up tables for cases where dies are missing will only identify a subset of crystals. Fig. 3.11 shows crystal look-up tables generated from segmenting flood histograms from cases where (a) all dies are present and (b) the top-left die is missing on readout. These look-up tables are visualized by drawing blue borders between crystal domains on top of the corresponding flood histograms. The unresolvable region of the flood histogram in Fig. 3.11b is overlain with a red grid. When an event is processed, its Anger logic coordinate will be compared to the crystal look-up table corresponding to the specific combination of dies that are present on readout. The event is only considered lost if it falls outside of the domain of a resolved crystal.
Fig. 3.11. The borders of crystal look-up tables for cases where all dies are present (a) and cases where just the top-left die is missing (b) are drawn on top of their corresponding flood histograms.

When one or more dies are missing on readout, fewer photons are counted than if all dies had been present. For this reason, the constant that scales the (saturation corrected) photon count to energy in keV for each crystal must be measured for each permutation of one or two dies missing for each crystal. Energy spectra were created for each properly identified crystal in each flood histogram created with one or two dies missing from which the peak position and width were found. Fig. 3.12 shows the peak position of the energy spectra for each resolved crystal in cases where (a) all dies are present and (b) the top-left die is missing on readout, by colouring in the corresponding region of the crystal look-up table.
Fig. 3.12. Photopeak position of all resolvable crystals in flood histograms corresponding to cases where all dies are present (a) and cases where just the top-left die is missing (b). The unresolvable region of (b) is also divided up into small regions for which the local photopeak position is found. The same colourmap is used for (a) and (b). Photopeak position refers to the number of photons counted when 511 keV is absorbed in the crystal.

The peak position was also found for each $8 \times 8$ pixel$^2$ region of the unresolved part of each flood histogram. This information would be completely irrelevant in a DPC PET scanner implementing this method of neighbor-logic recovery. However, it is useful when characterizing the fraction of counts lost from unrecovered incomplete neighbor-logic. If the number of usable events is filtered for energy, the number of unusable events should be filtered with the same energy window to make a fair estimate of the fraction of events that are lost. Measuring the photopeak position in the unresolved part of each flood histogram allows the photon count of unusable events to be converted into energy (albeit with poorer energy resolution).

3.4.5 Count Loss from Dark Readout Deadtime

A single DPC array was operated with no crystal array and no $^{22}$Na source present. Because RTL-refresh is known to sometimes cause emission of photon avalanches as row-trigger-lines are recharged (with hundreds of photons emitted in a short burst) [102], [105] the light-guide remained in place to facilitate cross-talk. The array was operated with settings identical to the settings used in section §3.4.4. Each acquisition was made for at least one minute. The
data set was analyzed to find the dark readout rate. A dark readout is defined as a group of DCP records (including those exhibiting incomplete neighbor-logic) with time-stamps that are simultaneous to within 80 ns.

Following a dark readout, a detector block is effectively dead for 905 ns beginning at the moment of triggering. With regards to Fig. 3.3, this includes 40 ns to validate, 165 ns of integration, 680 ns to readout, and 20 ns to recharge. Even if a true scintillation event began during the validation or integration stage of a dark readout, the position and possibly even the energy of the event may be properly recorded. However, the time-stamp will be misplaced so the event would be of no use for a PET application because it will not be found to be in coincidence with its partner annihilation photon. The dark readout rate is multiplied by 905 ns to yield the dark readout deadtime fraction. Similar to what was done in section §3.4.4, we find the fraction of coincidences that will be lost in a PET scanner because of dark readout deadtime using equation (3.2). Note that this is an intrinsic count loss fraction. At higher count rates, additional count loss will also occur from deadtime associated with reading true events.

### 3.5 Results

Fig. 3.13 shows a flood histogram made with trigger scheme 4 and an inhibit fraction of 5% at 15 °C. The profiles taken to compute peak to valley ratios are shown in red. Visually, the flood histogram resolves all crystals in the crystal array. The average peak to valley ratios from each flood histogram measured with trigger scheme 2 to 4 were all in the range of 10.5 ± 5.1 to 11.5 ± 6.5, although lower with trigger scheme 1 (5.7 ± 2.0 to 8.1 ± 3.4). It was found that the use of RTL-refresh had no impact on spatial resolvability (data not shown).
Fig. 3.13. A flood histogram showing excellent separation between different crystal responses. The centres of each response are connected with red lines, showing the path along which profiles were drawn.

Fig. 3.14. A representative energy spectrum (solid) with a Gaussian curve fit to the photopeak.

Fig. 3.14 shows a saturation-corrected energy histogram for the crystal in the centre of the top layer of the crystal array, created from the same data set used to create the flood histogram in Fig. 3.13. The photopeak and Compton edge are clearly visible. Fig. 3.15 shows the energy resolution measured with trigger scheme 4 as a function of inhibit fraction at both temperatures, averaged over all crystals in the block. Error bars represent standard deviation. The pattern of worsening energy resolution with a rising inhibit fraction makes sense in light of the fact that fewer photons are counted when fewer cells are enabled. Other trigger schemes showed no significant difference in energy resolution. It was found that use of RTL-refresh had insignificant impact on energy resolution (data not shown). Fig. 3.16 shows the energy resolution on a per-crystal basis in the top and bottom layer of the crystal array. The
three rows correspond to cases where either zero, one, or two dies are missing on readout, all from the same acquisition acquired with trigger scheme 4, inhibit fraction 5%, RTL-refresh on, and at a temperature of 15 °C. When all dies are present, energy resolution is 11.5 ± 0.7 %. When one / two dies are missing on readout, this figure degrades to 12.7 ± 1.4 % / 13.0 ± 0.8 %. Once again, the pattern of worsening energy resolution is due to fewer scintillation photons being counted when more dies are missing on readout.

![Energy resolution as a function of inhibit fraction using trigger scheme 4.](image)

Fig. 3.15. Energy resolution as a function of inhibit fraction using trigger scheme 4. (b) Energy resolution for all crystals in the bottom layer and (c) top layer, measured using trigger scheme 4 with 5% inhibit fraction at 15 °C.
Fig. 3.16. Visualization of the energy resolution seen across the crystal block. The left/right columns show the energy resolution in the bottom/top layers of the block. All images were generated from an acquisition collected with trigger scheme 4, inhibit fraction 5%, RTL-refresh off, and measured at 15 °C. The top/middle/bottom rows corresponds to events with all dies present / all but the bottom-left die present / only the two right dies present.
Fig. 3.17 shows histograms of the skew corrected time-stamp differences for the four different trigger schemes, operating with an inhibit fraction of 10%. All tests except one with trigger scheme 1 used RTL-refresh. Coincidence resolving time FWHM is shown in the legend. A clear trend of worsening timing resolution with higher trigger scheme can be seen. Another histogram corresponding to trigger scheme 4 with RTL-refresh turned off is included too. Fig. 3.18 shows the measured coincidence resolving time at 15 °C as a function of inhibit fraction for all trigger schemes > 1 and both RTL-refresh settings. The plot also shows the coincidence resolving time with trigger scheme 4 and RTL-refresh on repeated at 20 °C. Measurements of timing resolution in Fig. 3.18 were carried out on data sets where events with incomplete neighbor-logic were discarded. A subset of the data collected was reprocessed to measure the timing resolution when incomplete neighbor-logic events were recovered. Fig. 3.18 shows that including events with recovered incomplete neighbor-logic in the data set results in practically no degradation to timing resolution.

Fig. 3.17. Plots of time-stamp difference showing the effect of trigger scheme and use of RTL-refresh
Fig. 3.18. Timing resolution, quantified as the FWHM of the coincidence resolving time histogram was measured with trigger schemes 2, 3, and 4 with both settings of RTL-refresh. All measurements were made at 15˚C with the exception of one curve, which repeats the measurements with trigger scheme 4 and RTL-refresh on at 20˚C.

Fig. 3.19. Coincidence resolving time (FWHM) at each trigger scheme at 15˚C with a 10% inhibit fraction.

Fig. 3.20 shows the coincidence loss fraction due to incomplete neighbor-logic as a function of inhibit fraction for all four trigger schemes and at both 15 and 20˚C. Events in the data set (whether recoverable or not) were filtered with a 250-800 keV energy window. Three obvious patterns emerge from Fig. 3.20, which all support the notion that incomplete neighbor-logic occurs because dark triggers block the slave dies’ ability to receive the neighbor-logic signal. The dark triggering rate should decrease when the inhibit fraction is
raised, when the trigger scheme is increased, and when the temperature is lowered. All of these actions show themselves to decrease the rate of incomplete neighbor-logic.

Fig. 3.20. Coincidence loss fraction from incomplete neighbor-logic characterized for all four trigger schemes at both temperatures.

The coincidence loss fraction was calculated with three different energy windows for all four trigger schemes. All data sets were acquired at 15 °C with a 5% inhibit fraction and RTL-refresh turned on (except for trigger scheme 1). Fig. 3.21 shows that there is virtually no difference in the coincidence loss fraction whether the lower energy limit was 250 keV or 350 keV. The coincidence loss fraction was between 1 and 2% higher when no lower limit was applied. All further data presented regarding count loss from incomplete neighbor-logic will be processed using an energy window of 250-800 keV. The fact that there is no energy dependence on the probability of incomplete neighbor-logic when changing from a lower level discriminator of 250 to 350 keV simplifies DPC optimization in Chapter 4.
Fig. 3.21. The coincidence loss fraction calculated with a lower level energy threshold of either 0, 250, or 350 keV and an upper level threshold of 800 keV. All acquisitions were measured at 15 °C with a 5% inhibit fraction and RTL-refresh turned on (except when using trigger scheme 1).

Fig. 3.22 illustrates the beneficial effect of using the RTL-refresh setting. The coincidence loss fraction achieved with either RTL-refresh on or off using trigger scheme 2 to 4 is plotted as a function of inhibit fraction. Because RTL-refresh is a setting which reduces the rate of dark triggering, the large improvement in coincidence loss fraction that it produces again supports the idea that incomplete neighbor-logic is driven by dark triggers.

Fig. 3.22. Coincidence loss fraction from incomplete neighbor-logic as a function of inhibit fraction characterized for trigger schemes 2 to 4 with and without the use of RTL-refresh.
To demonstrate the benefit of incomplete neighbor-logic recovery, the same data sets used to compute coincidence loss fraction at 15 °C in Fig. 3.20 were reprocessed so that all events exhibiting incomplete neighbor-logic were discarded. The resulting coincidence loss fractions are plotted in Fig. 3.23 along with the original data that includes recovered events for comparison. Although the technique used to recover some events suffering from incomplete neighbor-logic adds substantial complexity to data processing, the benefits to detector efficiency are significant (with the exception of trigger scheme 4). Trigger scheme 4 has an incredibly low rate of coincidence loss regardless of the use of incomplete neighbor-logic recovery. Recovering otherwise lost events brings the coincidence loss rate from 0.98-0.55% to 0.60-0.33% for trigger scheme 4.

It was found that the coincidence loss fraction from dark readout deadtime was very small. The maximum dark readout rate at 15 °C was 860 counts per second. With trigger scheme 4, coincidence count loss ranged from 0.15 to 0.05% with inhibit fraction ranging from 5% to 20% at 15 °C, and 0.23 % to 0.8% at 20 °C. The dark readout deadtime decreased by about an order of magnitude by either moving to lower trigger schemes or by turning RTL-refresh.

![Figure 3.23](image)

**Fig. 3.23.** Coincidence loss fraction as a function of inhibit fraction calculated for all four trigger schemes with and without recovery of incomplete neighbor-logic. ‘R’ in the legend means the data set was processed with incorporation of incomplete neighbor-logic recovery.
off. Because dark readout deadtime is such a small effect even in the worst case, detailed results of this effect are not presented here.

3.6 Discussion and Conclusion

We have characterized the Philips DPC3200-22-44 digital photon counter array with specific interest in optimizing performance for small animal PET detector block using Anger-logic for crystal identification. Good spatial resolvability was found regardless of device settings or temperature. Energy resolution was found to have no significant dependence on trigger scheme, inhibist fraction, or temperature. Regardless of device setting or temperature, energy resolution fell in the range of 11.4 to 12.5%. Because these aspects of block performance have little to no dependence on temperature and device settings, optimization for other aspects of device performance is simplified.

Energy resolution is an improvement over the 16.2% energy resolution that was measured by our collaboration using the same crystal array with a SensL SPMArray4 SiPM array [76]. More recently we evaluated the SensL SB4-300-35-CER SiPM array and measured 11.1% average energy resolution [108] (this array had the same size LYSO crystals, but a $10 \times 10 + 9 \times 9$ array instead of the smaller array used with the DPC). The SiPMs in [76] were of the $M$-series which has a peak photon detection efficiency near 500 nm wavelength [109], while the DPC has peak efficiency better suited to LYSO (420 nm) [70]. The $B$-series of SensL SiPM reported in [110] were a major improvement over the $M$-series and performed as well as the DPC in terms of energy resolution. The $B$-series has a very high gain and a peak photon detection efficiency near 420 nm like the DPC. As well, the peak detection efficiency is $\sim 40\%$ compared to $\sim 20\%$ for the $M$-series [109] and $\sim 30\%$ for the Philips DPC [70]. The measured energy resolution is comparable to what has been measured by Kim et al [111], who measured an average energy resolution of 12% with an LYSO array coupled to an array of Hamamatsu SiPMs.

It was found that timing resolution and count loss has very strong dependence on device settings. Device settings that optimize timing resolution tend to have a detrimental effect on
count loss. Fig. 3.17 shows that the superb timing resolution that the DPC is capable of achieving (~300 ps) is only achieved at lower trigger schemes. Using trigger scheme 4, the timing resolution moves to the range of 1.25 to 1.44 ns, worsening with higher inhibit fraction. Although this is significantly worse than what can be achieved with lower trigger schemes, 1.44 ns is still adequate for small animal PET applications. The timing resolution worsens as expected from trigger scheme 1 to 4 because the effective leading edge threshold moves from 1 to (on average) 8.3 photons, and there is more variability in the number of cell breakdowns needed to generate the trigger due to the statistical nature of the trigger formation.

We found that use of RTL-refresh led to a noticeable worsening of the coincidence resolving time (from 1.01 to 1.26 ns for trigger scheme 4 and 5% inhibit fraction). RTL-refresh is an experimental setting that is known to sometimes create additional dark counts before the trigger is reached (this seems counter to the purpose of RTL-refresh, but we found RTL-refresh still reduced the dark-triggering rate). This would add variability to the number of actual photon detections needed to reach a trigger, degrading the coincidence resolving time.

Fig. 3.15 and Fig. 3.18 respectively show no significant degradation to energy resolution or timing resolution after the 5 °C temperature fluctuation. Fig. 3.20 however shows that the 5 °C temperature fluctuation can have a moderate impact on count loss for all trigger schemes except trigger scheme 4. A PET scanner for which the sensitivity is temperature dependent can lead to confusing results especially when considering dynamic PET. In dynamic PET, the changing activity concentration in the subject is analyzed to make conclusions about physiology. If PET sensitivity were to change throughout a study as the temperature drifted, the artefactual change in activity concentration could invalidate the techniques employed in dynamic PET. The insensitivity of trigger scheme 4 to temperature fluctuations is an additional benefit to using trigger scheme 4 in our case, in addition to the low overall count losses at either temperature.
Similar to what was reported by Degenhardt et al [100], we observed the photopeak position move to a lower value with increasing temperature, with roughly the same shift magnitude (-0.6%/°C). Degenhardt et al note that this is much smaller than the photopeak shift usually seen with analog SiPMs. Because of the shifting photopeak, it would be desirable to make use of the measured temperature during operation to properly convert the number of cell breakdowns to energy.

The findings presented in this chapter are applicable beyond the scope of our prototype, and advance the understanding of the behaviour any DPC-based PET detector block made from a finely pixelated array of detector crystals. The exact correspondence between performance metrics (such as timing resolution) and device settings (such as trigger scheme) depend on the dimensions and material of the scintillator crystal array. However the trends identified should still be valid. The method developed to reduce the sensitivity loss due to incomplete neighbor-logic is applicable to any group experiencing sensitivity loss using the DPC array due to the same phenomenon.

With timing resolution in mind, it would seem that the best performance could be achieved by lowering the inhibit fraction and using trigger scheme 1. However, this leads to undesirable performance in terms of count loss. Of the two source of count loss, incomplete neighbor-logic is significantly higher than dark-readout deadtime. The maximum level of coincidence count loss from dark-readout deadtime is just 0.15% at 15 °C, which is insignificant compared to the count losses from incomplete neighbor logic shown in Fig. 3.20. Use of trigger scheme 1 can be ruled out completely, as count losses are at best 30% of coincidences, and approach 55% at lower inhibit fractions. Trigger schemes 2 to 4 result in much more acceptable levels of count loss, diminishing to 0.6% for trigger scheme 4 at 15 °C.

Before the technique to recover incomplete neighbor-logic was developed, it was very clear that the best device configuration (in terms of optimizing NECR performance) was trigger scheme 4 with RTL-refresh on. This conclusion was made in the work we published in [106].
Although this configuration leads to the worst timing resolution, it was the only one that resulted in acceptable levels of count loss, as is shown in Fig. 3.23. In a full body PET system where meaningful time of flight measurement is possible, better timing resolution could significantly improve reconstructed signal to noise ratio by reducing uncertainty in the measured time of flight [112], [113]. However, the small radius of our PET scanner precludes time of flight utilization in the reconstruction. Improved timing resolution will then only affect reconstructed signal to noise ratio by reducing the randoms rate. The timing resolution with trigger scheme 4 is still excellent, so the randoms rate would never become significant until quite high activities are reached. Further improvements to the timing resolution result in ever diminishing gains in terms of NECR quality. Therefore it would be hard to imagine that this moderate improvement in timing resolution would be worth the large drop in the trues rate when using lower trigger schemes.

The advent of incomplete neighbor-logic recovery complicates the task of identifying the optimal device configuration for our PET application. The coincidence loss rate using trigger scheme 2 or 3 is now as low as 3% in certain cases. The gains in timing resolution when switching from trigger scheme 4 / RTL-refresh on to lower trigger schemes possibly with RTL-refresh off might actually be worth it in terms of the improved NECR by a reduction in the randoms rate.

The randoms rate not only depends on the hardware used to make the blocks, but also on the size of PET scanner and activity distribution. For example, an activity distribution where most activity is outside of the FOV results in a higher randoms fraction than if the activity were concentrated in the centre of the FOV. The best way to determine which configuration produces the optimal trade-off between efficiency and timing resolution is a simulation of a hypothetical PET scanner. In this way the rates of trues, randoms, and scatters can objectively be estimated in a way that properly accounts for the complex interaction between detector hardware and the geometry of the scanner and subject. This will be the focus of Chapter 4.
Chapter 4: Best Operating Point for Digital Photon Counter Array

Chapter 3 showed that the way in which a DPC array is configured has an enormous impact on the performance of a PET detector block incorporating such an array. Poor hardware performance ultimately results in poor PET image quality. Spatial resolution is affected by the ability of the block to identify the crystal that an annihilation photon interacts in. Except for trigger scheme 1 which resulted in slightly less resolved flood histograms, all device configurations would impact spatial resolution more or less equivalently.

Optimizing the device settings for reconstructed signal to noise ratio is not straightforward. If the question is “What combination of device settings results in the highest peak NECR?” the best answer is “It depends”. The optimal device configuration depends on both the distribution of activity in the field of view and the geometry of the PET scanner. For example, as the source becomes longer relative to the length of the PET scanner, the ratio of singles to coincidences will rise, which in turn causes the randoms fraction to rise. This would place more importance on controlling the randoms rate through lowering the timing resolution compared to a longer PET scanner. In this chapter, we will imagine two scenarios for a small animal PET scanner (with either a short or long axial field of view), both with a source distribution mimicking the NEMA NU 4-2008 mouse equivalent phantom, and demonstrate how one can use Monte-Carlo simulations of these scanners to optimize DPC device settings.

4.1 Experiments

The detector block characterized in Chapter 3 was modelled in GATE. A single ring of detector blocks was formed by repeating the block 16 times around a ring with a 66 mm inner diameter. The ring was repeated either two or six times in the z-direction, using a ring repeat pitch of 16 mm. The NEMA NU 4-2008 mouse equivalent phantom was placed in the centre of the tomograph. This phantom consists of a 70 mm long and 25 mm wide polyethylene cylinder. A 60 mm long and 3.2 mm wide active hot-rod runs parallel to the centre of the phantom, offset 10 mm radially. The source was configured to emit back-to-
back 511 keV gamma rays at one of twelve activities spaced logarithmically from 200 kBq to 400 MBq.

Detector block deadtime was set to be 905 ns for reasons described in Chapter 3. The main contributor to deadtime is the time spent in the integration / readout process. These processes run for a set period of time, regardless if a second photon hits the block as during integration or readout. Therefore deadtime model was nonparalyzable. The simulations assumed perfect energy and timing resolution. For each combination of device settings tested in Chapter 3 data were then post-processed to simulate the effect of imperfect energy and timing resolution. As described in §2.3, this allowed for the same data set to be reused multiple times corresponding to different hardware configurations. Note that the timing resolution measured in §3.4.3 is coincidence resolving time – which compounds the timing uncertainty from two blocks. The single resolving time needed for the GATE simulations was found by dividing the coincidence resolving time by the square root of two.

The effects of count loss from incomplete neighbor-logic were also simulated in post-processing. Data measured in Chapter 3 were analyzed to determine (for each combination of DPC device settings) the probability that the DPC will successfully readout with four, three, or two dies. Recall that when only three or two dies readout, the readout is only successful if the Anger-logic coordinate falls in the resolvable region of the flood histogram (see Fig. 3.11b). For each single, a random number was pulled from a flat distribution from 0 to 1. As illustrated in Fig. 4.1, the random value was used to determine if that single successfully reads out with four, three, or two dies. Upon successful readout, the time and energy of the event was randomly adjusted (with an energy resolution that corresponds to the number of dies reading out). Else, it was discarded from the data set.
After each single was adjusted (or discarded) to model the setting-specific DPC energy and timing resolution, another pass was made through the data set to sort for coincidences using a coincidence window of twice the singles timing resolution and an energy window of 250-800 keV. Like in §2.5.4, information from the simulation was used to classify each coincidence as a true, random, or scatter.

For both the long and short PET scanner, NECR curves were calculated for each combination of inhibit fraction = 5, 10, 15, or 20%, trigger scheme = 2, 3, or 4, and RTL-refresh either on or off. NECR curves were calculated for trigger scheme 1 only for the case of inhibit fraction = 10% and RTL-refresh off. Due to enormous levels of incomplete neighbor-logic, trigger scheme 1 would clearly not have the best NECR, so was not explored in greater detail. Continuous NECR curves were created by interpolating the twelve points where NECR was calculated using cubic splines. Each NECR curve was summarized with two metrics: the peak NECR and the NECR at 3.7 MBq. Although it is desirable to have a
higher peak NECR, it is arguably more important to have high NECR at the activity where most scans are done.

Simulations of both the long and short PET scanners were rerun with the device characteristics set to those corresponding to the analog SiPMs used to build our PET system (from Table 2.1). These settings are an energy resolution of 12.5%, a singles timing resolution of 5.4 ns, and a paralyzable block deadtime of 1.5 μs. These simulations allow for a direct comparison between blocks built with Philips DPCs and the SPMAArray4B series of SensL SiPMs in terms of NECR.

### 4.2 Results

Fig. 4.2 and Fig. 4.3 respectively show NECR curves for all DPC configurations under consideration for the two and six ring PET scanners. Due to the large number of curves, no attempt is made to distinguish them with a colour-code and legend. The message that these figures are meant to convey is that within each figure, there is quite a variation in the quality of the NECR curves – indicating that device settings would have an important impact on PET image quality if DPCs were incorporated into a scanner. A good NECR curve would have both a high peak NECR and a high NECR at 3.7 MBq.

![NECR curves](image_url)

**Fig. 4.2.** NECR curves corresponding to the 2-ring PET scanner configured with each combination of DPC device settings explored in this chapter.
Table 4.1 and Table 4.2 summarize the NECR for each combination of DPC device settings explored in this chapter. Cells are colour-coded, with deep red to deep green spanning the range of each variable (the colour-bar is shown at the bottom of Table 4.2).
<table>
<thead>
<tr>
<th></th>
<th>RTL=OFF</th>
<th></th>
<th>RTL=ON</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.7 MBq Act.</td>
<td>Peak</td>
<td>3.7 MBq Act.</td>
</tr>
<tr>
<td>TS1</td>
<td>IF=10%</td>
<td>24.9</td>
<td>350</td>
</tr>
<tr>
<td>TS2</td>
<td>IF=5%</td>
<td>30.6</td>
<td>380</td>
</tr>
<tr>
<td></td>
<td>IF=10%</td>
<td>33.9</td>
<td>423</td>
</tr>
<tr>
<td></td>
<td>IF=15%</td>
<td>35.5</td>
<td>441</td>
</tr>
<tr>
<td></td>
<td>IF=20%</td>
<td>36.7</td>
<td>452</td>
</tr>
<tr>
<td>TS3</td>
<td>IF=5%</td>
<td>31.1</td>
<td>373</td>
</tr>
<tr>
<td></td>
<td>IF=10%</td>
<td>35.3</td>
<td>416</td>
</tr>
<tr>
<td></td>
<td>IF=15%</td>
<td>36.8</td>
<td>424</td>
</tr>
<tr>
<td></td>
<td>IF=20%</td>
<td>40.0</td>
<td>466</td>
</tr>
<tr>
<td>TS4</td>
<td>IF=5%</td>
<td>38.6</td>
<td>406</td>
</tr>
<tr>
<td></td>
<td>IF=10%</td>
<td>39.5</td>
<td>408</td>
</tr>
<tr>
<td></td>
<td>IF=15%</td>
<td>39.7</td>
<td>399</td>
</tr>
<tr>
<td></td>
<td>IF=20%</td>
<td>39.9</td>
<td>402</td>
</tr>
</tbody>
</table>

Table 4.2. Summary of NECR low activity slope and peak NECR for the 6-ring PET scanner.

Fig. 4.4 shows NECR curves corresponding to the device settings of the analog SiPMs, along with the NECR curves corresponding to ‘the best’ combination of DPC device settings. The discussion section will explain how ‘the best’ combination of DPC device settings was determined. The curves in Fig. 4.4 are summarized in Table 4.3.

Fig. 4.4. NECR curves from simulations that assume detector block characteristics the same as the detector blocks built using analog SiPMs.
Table 4.3. NECR at 3.7 MBq and peak NECR for PET 2- and 6-ring PET scanners with simulated device settings corresponding to analog SiPMs and ‘the best’ configuration of DPC settings.

<table>
<thead>
<tr>
<th></th>
<th>SiPM</th>
<th>DPC</th>
<th>SiPM</th>
<th>DPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Ring</td>
<td>4.95</td>
<td>6.00</td>
<td>12.8</td>
<td>57.7</td>
</tr>
<tr>
<td>6-Ring</td>
<td>33.7</td>
<td>40.0</td>
<td>85.0</td>
<td>466</td>
</tr>
</tbody>
</table>

4.3 Discussion and Conclusion

The results in Fig. 4.3, Table 4.1 and Table 4.2 confirm the notion that DCP device settings will have a large impact on the performance of a small animal PET scanner made using DPC arrays. The trends in NECR are roughly the same between the 2-ring and 6-ring PET scanners. Clearly trigger scheme 1 is inappropriate to use, for it yields PET scanners with both low NECR at 3.7 MBq and low peak NECR. Still no configuration stands out as the absolute best. The highest NECR at 3.7 MBq is achieved by using trigger scheme 4 with RTL-refresh on (for both 2 and 6 rings systems), without a strong dependence on inhibit fraction. Trigger scheme 4 with RTL-refresh on, however, does not lead to the highest peak NECR due to the poor timing resolution that drives up the randoms rate.

From Table 4.1 we can pick out a number of configurations that score near the top in terms of both figures of merit. Trigger scheme 3 with a 20% inhibit fraction with RTL-refresh turned on stands out as ranking near the top for both figures of merit – therefore it would represent a logical combination of device settings for a 2-ring system. Likewise, Table 4.2 shows that trigger scheme 3 with a 20% inhibit fraction with RTL-refresh turned off ranks near the top in terms of both figures of merit, so it would be a logical combination of device settings for a 6-ring system. The NECR curves deemed to be the ‘best’ for each scanner are the ones shown as dark blue in Fig. 4.2 and Fig. 4.3.

The patterns in Table 4.1 and Table 4.2 are quite interesting and reflect the measurements made in Chapter 3. For example, Fig. 3.22 shows that use of RTL-refresh greatly improves over-all detector efficiency, and reduces the dependence of efficiency on inhibit fraction. These patterns are reflected in the 3.7 MBq NECR, which is driven mainly by detector efficiency. Trigger scheme 4 with RTL-refresh on performed better than all other
combinations in terms of NECR at 3.7 MBq because there is virtually no count loss from incomplete neighbor-logic. Peak NECR is affected by the sensitivity, but also the randoms rate that becomes significant at higher activities. Fig. 3.22 shows that when RTL-refresh is on, there is not such a large dependence of detection efficiency on trigger scheme. As a result, lower trigger schemes yield better peak NECR, because the randoms rate is reduced due to having better timing resolution (Fig. 3.18). With RTL-refresh turned off, detection efficiency does depend strongly on trigger scheme. The dependence between peak NECR and trigger scheme is now not so straightforward because timing resolution and detection efficiency pull the peak NECR in opposite directions. This type of complex behaviour is the reason why a quantitative approach like the one presented in this chapter is necessary when optimizing DPC device settings, rather than just using one’s intuition about what ought to be best.

When configured to their best combination of device settings, the imagined PET scanners incorporating DPCs outperform the PET scanners incorporating analog SiPMs by both the NECR at 3.7 MBq and the peak NECR. This is driven by the fact that the DPCs have much better timing resolution and lower deadtime than the analog SiPM blocks. One merit of the analog SiPMs over the DPCs is that there is no such factor as ‘incomplete neighbor-logic’ that causes events to be lost. However, use of trigger schemes 3 or 4 brought the loss rate from incomplete neighbor-logic to practically zero. Although this resulted in the worst timing resolution for the DPCs, the timing resolution was still excellent compared to our implementation of the detector block built from SiPMs. Note that the timing and deadtime of the SiPM blocks is not solely due to the SiPMs, but also on the surrounding electronics that shape and slow down the analog outputs.
Chapter 5: Analytic Reconstruction

Filtered back projection (FBP) reconstruction is seen as a gold-standard of PET image reconstruction in many applications due to its linearity and lack of bias [114]–[117]. Its use is mandatory when characterizing a PET system using the NEMA NU 4-2008 protocol [87]. This chapter describes how list-mode data were histogrammed into sinograms for reconstruction with FBP. Reconstruction was performed using the FBP 3D reprojection (FBP-3DRP) algorithm (described in §1.6.1.2) as implemented in the open source reconstruction suite STIR (software for tomographic image reconstruction) 3.0 [118].

Raw PET measurements need to be *normalized* to correct for the non-uniform sensitivity of different crystal pairs. A version of the *component based normalization* algorithm, described in §5.1, was implemented to achieve this task. The positioning of LORs in the prototype DLO PET system present unique challenges to histogramming PET data into sinograms that are consistent with the distribution of activity in the FOV. The methods used to create a consistent sinogram from the measured PET data are described in §5.2. These sinograms have large gaps in certain regions, which are the result of spatial gaps between detectors. §5.3 describes how these gaps are filled. §5.4 describes how the processes described in the first three subsections of this chapter are brought together to reconstructed a PET image with STIR 3.0.

§5.5 describes a novel approach to sinogram formation in which Monte-Carlo simulations are used to estimate the position of each LOR more accurately than the method used in §5.2. While this method did not result in any improvement in image quality for the prototype DLO PET system, it led to measurable improvement in image quality (in terms of increased contrast and reduction of streak artefacts) for data acquired from the Siemens microPET Focus 120 PET system [119], one of the scanners available in our PET centre. The implementation of the algorithm for the microPET Focus 120 is described in §5.6.
5.1 Normalization

As described in §1.4.3.4, each LOR has a different sensitivity for detecting radiation. The sensitivity of each LOR, referred to as the normalization factors, were calculated using a *component based normalization* procedure (CBN) [54]–[58], the details of which will be described in this chapter.

An annular normalization phantom was used to collect normalization data. The phantom was made with 3D printed material with an annular cavity fillable with an aqueous solution containing activity (such as $^{18}$F). The outer and inner diameters were respectively 44 and 36 mm and the width of the cavity was 32 mm. As shown in Fig. 5.1, two large rims were added to each side of the phantom with outer diameter matched to the inner diameter of our PET system – allowing it to be accurately positioned in the centre of the FOV. The only constraint on the geometry of the phantom used for a CBN procedure is that all LORs in the useful FOV are exposed to activity. The amount of activity along each LOR must be known and simple geometric shapes allow for this calculation to be made easily. Other groups have used a cylindrical phantom or a flat sheet of activity rotated through a number of different positions [120], [121]. Some publications have recommended that scatter be corrected for during normalization and detail how it should be incorporated into the CBN algorithm [120]. We have not yet implemented a method of correcting acquisitions for scatter and attenuation. The choice of an annular phantom was thus made because there is much less scatter and attenuation from this source configuration compared to others, such as a cylinder.
The expected number of coincidences $N_{ij}$ measured along an LOR connecting crystal-i to crystal-j during a normalization scan is proportional to the integrated activity along that LOR, $A_{ij}$. The constant of proportionality (in the absence of attenuation and scatter) is the normalization coefficient $n_{ij}$. Component based normalization models this coefficient as the product of three factors: $\varepsilon_i$, $\varepsilon_j$, and $g_{ij}$. This relation can be written as:

$$n_{ij} = \frac{N_{ij}}{A_{ij}} = \varepsilon_i \varepsilon_j g_{ij}$$  \hspace{1cm} (5.1)

The geometric factor ($g_{ij}$) depends on the geometric arrangement of the two crystals that form the LOR-ij relative to each other and to other crystals, and is therefore not separable into factors related only to crystal-i and crystal-j. Fig. 5.2 compares two LORs in the FOV to explain some of the reasons why different LORs have different geometric sensitivities. Each LOR subtends a volume of space from which it can accept true coincidences. The fact that the LOR highlighted in blue subtends a much smaller volume of space than the LOR highlighted in red lowers its effective sensitivity. However, the crystals highlighted in blue are not shielded by other crystals like the ones that form the LOR highlighted in red – a factor that works in the opposite direction. The amount of shielding seen by a crystal along the path of an LOR depends not only on what layer it is in, but also the angle at which the
LOR meets the crystal face. Yet another factor is the amount of scintillator material each annihilation photon sees as it passes through one of the crystals that form the LOR. Photon pairs detected by the LOR highlighted in blue see 4 mm of LYSO each. The LOR highlighted in red has 6 mm long crystals at either end – however the average amount of scintillator in the path of each photon is much less than 6 mm because the photons travel through the crystals at an oblique angle.

![Fig. 5.2. 2D schematic of the DLO PET system highlighting two LORs that have different geometric normalization factors.](image)

The remaining factors are the crystal-specific *intrinsic factors*: $\varepsilon_i$ and $\varepsilon_j$. These factors describe random variation in crystal efficiency. Such variations are due to several reasons. For example, inhomogeneity in material properties between crystals that affect light output and therefore energy resolution can lead to variations in crystal efficiency. Temporal drift (over the course of months) in the performance of photomultipliers and other electronics associated with the front end of the PET system can cause small amounts of crystal-misidentification (which raises the sensitivity of one crystal at the expense of another), and misreporting of photon energy (which effects the probability of an annihilation photon falling in the energy window).

To calculate the geometric factor for an LOR with indices $ij$, one must identify a group of LORs in the PET scanner that have the same geometric factor. Fig. 5.3 illustrates how such a group of degenerate LORs can be identified. Any LOR can be rotated $1/16^{th}$ of the way
around the FOV 16 times to form a group of 16 degenerate LORs (shown in black). If the original LOR is then mirrored vertically and then rotated around the FOV another 16 times, another 16 LORs can be added to the group (shown in blue). Although it is not possible to show in Fig. 5.3, each LOR can be mirrored in the z-direction to add another 32 LORs to the group. In general each LOR is part of a 64-member group of LORs with degenerate geometric factors. Special groups of LORs exist that have only 32, 16, or 8-fold degeneracy.

![2D schematic of the DLO PET system showing how groups of LORs with degenerate geometric factors can be identified.](image)

To calculate a geometric factor $g_S$ for all LORs in the degeneracy group $S$, one begins by averaging the number of counts measured by each LOR in group $S$. Following from equation (5.1):

$$
\frac{1}{\text{size}(S)} \sum_{i,j \in S} N_{ij} = g_S A_S \frac{1}{\text{size}(S)} \sum_{i,j \in S} \varepsilon_i \varepsilon_j
$$

(5.2)

Because each $\varepsilon$ is assumed to be a random number distributed about 1, the mean value of $\varepsilon_i \varepsilon_j$ over set $S$ is approximately 1 also. Because the amount of activity along each LOR in the set is known, equation (5.2) can be rearranged to find the geometric factor for each LOR in group $S$: 

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In practice, the geometric factors can be calculated just once at the beginning of a PET scanner’s lifetime. Because the calculation only needs to be done once, a very long acquisition can be made to ensure high statistics. Knowing each $g_{ij}$, calculation of the remaining intrinsic geometric factors can proceed. Because the intrinsic activity of each crystal changes over time, intrinsic normalization factors need to be recalculated periodically.

In this thesis, we will use the extended version of CBN due to Defrise [55], [56] adapted to 3D data. This method requires the PET ring to be broken down into $G$ groups each with $M$ crystals. Each block contains 409 crystals. Because 409 is a prime number, the only possible group sizes are integer numbers of full blocks. Groups will be formed from one block each. The CBN algorithm due to Defrise requires that each group have coincidences measured between all of its crystals and all crystals in the three groups opposite from it. In order to expose all of those LORs to activity, the normalization phantom needs to be at least 34 mm wide. Therefore the 44 mm wide phantom used to calculate the geometric factors can be reused to calculate the intrinsic factors too. The calculation begins by dividing the number of counts in each LOR by the known amount of activity along that LOR and by the geometric factor.

$$\eta_{ij} = \frac{N_{ij}}{g_{ij} A_{ij}}$$  \hspace{1cm} (5.4)

According to equation (5.1), each $\eta_{ij}$ is an independent measurement of $\varepsilon_i \varepsilon_j$. There are 6544 values of $\varepsilon$ that need to be calculated. The number of LORs that connect each block to its three opposite neighbours is 4,014,744. The power of CBN is that instead of calculating 4,014,744 independent normalization coefficients from 4,014,744 measurements, we are now calculating only 6544 independent values from 4,014,744 measurements. A few definitions
are necessary before the calculation of intrinsic normalization coefficients can proceed. The average efficiency of all crystals in group $A$ is:

$$\langle \varepsilon \rangle_A = \frac{1}{M} \sum_{i \in A} \varepsilon_i$$

(5.5)

The average LOR efficiency between crystal-$i$ and all crystals in some other group $B$ is:

$$\langle \eta \rangle_{i,B} = \frac{1}{M} \sum_{j \in B} \eta_{ij}$$

(5.6)

The average LOR efficiency of all LORs between group $A$ and $B$ is:

$$\langle \eta \rangle_{A,B} = \frac{1}{M^2} \sum_{i \in A} \sum_{j \in B} \eta_{ij}$$

(5.7)

Based on these definitions, the following properties are easy to prove:

$$\langle \eta \rangle_{A,B} = \langle \varepsilon \rangle_A \langle \varepsilon \rangle_B$$

(5.8)

$$\langle \eta \rangle_{iB} = \varepsilon_i \langle \varepsilon \rangle_B$$

(5.9)

The first task is to calculate the average efficiency of group $A$, $\langle \varepsilon \rangle_A$, based on the measured values of $\eta_{ij}$. Because each group $A$ is in coincidence with groups $A+7$ and $A+8$, the following quantity can be calculated from the measured data and it can be shown by using equations (5.8) and (5.9) that it produces an estimate of $\langle \varepsilon \rangle_A$:
Each group A is also in coincidence with each group A+9. This data can be used to create yet another estimate of $\langle \varepsilon \rangle_A$:

$$
\langle \eta \rangle_{A,A+9} \prod_{k=0}^{7} \frac{\langle \eta \rangle_{A+k,A+k+8}}{\langle \eta \rangle_{A+k+1,A+k+8}} = \langle \varepsilon \rangle_A \langle \varepsilon \rangle_{A+8} \prod_{k=0}^{7} \frac{\langle \varepsilon \rangle_{A+k}{\langle \varepsilon \rangle_{A+k+8}}}{\langle \varepsilon \rangle_{A+k+1}{\langle \varepsilon \rangle_{A+k+8}}}
$$

$$
= \langle \varepsilon \rangle_A \langle \varepsilon \rangle_{A+8} \prod_{k=0}^{7} \frac{\langle \varepsilon \rangle_{A+k}}{\langle \varepsilon \rangle_{A+k+1}}
$$

$$
= \langle \varepsilon \rangle_A \langle \varepsilon \rangle_{A+8} \left( \frac{\langle \varepsilon \rangle_A}{\langle \varepsilon \rangle_{A+1}} \times \frac{\langle \varepsilon \rangle_{A+1}}{\langle \varepsilon \rangle_{A+2}} \times \ldots \times \frac{\langle \varepsilon \rangle_{A+7}}{\langle \varepsilon \rangle_{A+8}} \right)
$$

$$
= \langle \varepsilon \rangle_A \langle \varepsilon \rangle_{A+8} \left( \frac{\langle \varepsilon \rangle_A}{\langle \varepsilon \rangle_{A+8}} \right) = \langle \varepsilon \rangle_A^2
$$

The two estimates of $\langle \varepsilon \rangle_A$ from equations (5.10) and (5.11) can be averaged together to give an estimate of each $\langle \varepsilon \rangle_A$ with higher statistical precision:

$$
\langle \varepsilon \rangle_A = \frac{1}{2} \sum_{p=0}^{1} \sqrt{\prod_{k=0}^{7} \frac{\langle \eta \rangle_{A+k,A+k+8+p}}{\langle \eta \rangle_{A+k+1,A+k+8+p}}}
$$

For each crystal, (5.6) can be used to calculate the efficiency of any crystal relative to another group. With the average efficiency of each group now calculated using (5.12), the efficiency of individual crystals can be calculated using (5.9). Because crystal-i in group A is in coincidence with groups A+7, A+8, and A+9, three estimates of the crystal efficiency can be made and averaged together.
As stated before, intrinsic normalization coefficients should be remeasured periodically to correct for the slow drift in their values as the PET scanner ages. No study has yet been done to determine how often it is necessary to remeasure the coefficients for our prototype PET system. For all PET images shown in this thesis, normalization data was measured within two weeks of the PET acquisition. Data were acquired for 2 hours with approximately 10 MBq of activity in the normalization phantom at the beginning of the scan.

Many of the PET images shown in this thesis come from simulated data. Although the simulation does not model random variation in the intrinsic efficiency of different crystals, geometric normalization factors still need to be applied. To find these normalization coefficients, the distribution of activity in the annular normalization phantom was simulated in GATE and the data were processed in the exact same manner as real normalization data is processed.

### 5.2 Sinogram Formation

List-mode data from the prototype PET system contains a list of singles detected during an acquisition. The record of each single contains a time-stamp with a step-size of 2.5 ns, the measured energy that the annihilation photon deposited in the detector, the ID of which block the single was detected in, and the ID of the crystal within that block that was identified as the crystal of interaction using Anger-logic. Custom made software sorts through the list of singles to identify coincidences. A prompt coincidence is found whenever two singles have timestamps identical to within a predefined coincidence window. The coincidence window should be approximately twice the singles timing resolution FWHM in order to capture all coincidences, while at the same time detecting as few random coincidences as possible. Random coincidences are identified using a delayed coincidence window technique. Data are sorted with a coincidence window of 10 ns and a delay of 100 ns for detecting random
coincidences. 10 ns is the most appropriate coincidence window based on the timing resolution of our detectors measured in §7.1.

Identified coincidences are counted in four-dimensional histograms called sinograms. For each pair of crystals involved in a coincidence, the LOR that connects the two crystals is characterized by four real-valued coordinates: $r$, $\phi$, $z$, and $\tan \theta$ as defined in §1.4.1. The coordinate of the LOR is defined by the line that connects the interaction centroids of the two crystals involved, as defined by equation (2.1). Each bin in the sinogram counts the number of coincidences with the same or similar LOR coordinates. Four IDs identify each sinogram bin: rID specifies the radial offset (along coordinate $r$), phiID specifies the view (along coordinate $\phi$), zID specifies the axial position (along coordinate $z$), and segID specifies the segment (along coordinate $\tan \theta$). The unique dual-layer design of the detector blocks used to build the PET system described in this thesis presents unique challenges as to how each LOR coordinate maps to a sinogram bin. In order to understand why the DLO design presents these challenges, it is first useful to study how a sinogram is formed for an idealized single-layer cylindrical PET scanner.

A 2D schematic of a cylindrical PET scanner is shown in Fig. 5.4 and illustrates how the rID and phiID are determined by the position of each LOR. Fig. 5.4a shows a group of LORs all with the same rID and different phiIDs, while Fig. 5.4b shows a group of LORs all with the same phiID and different rIDs. The counts in LORs shown as dotted lines in Fig. 5.4b are averaged together to approximate LORs that are parallel to LORs represented by solid lines. As a result of the cylindrical geometry, there exists sets of LORs which all share the exact same value of $\phi$, and so naturally they are given the same phiID. Unless a highly specialized reconstruction technique is used [122], it is required that sinograms histogram LORs with bins spaced uniformly in $\phi$, which conveniently follows when a cylindrical geometry is used. The radial bins illustrated in Fig. 5.4b do not sample the radial coordinate $r$ uniformly due to the curvature of the PET ring. The arc correction resamples the sinogram before reconstruction so that the radial spacing between bins is uniform.
The geometry created by our DLO PET detector design does not create an obvious way to group together sets of LORs with the same value of $\phi$ (as will later be show in Fig. 5.5). The best approximation to this ideal situation is to assign LORs with approximately equal values of $\phi$ and $r$ to the same bin. Each bin will contain counts from many LORs. Based on the real value of $\phi$, the phiID of any LOR can be found according to:

$$phiID = round \left( \frac{\phi}{\pi} N_\phi \right) \mod N_\phi$$  \hspace{1cm} (5.14)

Here $N_\phi$ represents the number of angular samples in the sinogram, $\text{round}$ is a function that rounds to the nearest integer, and $\text{mod}$ is the modulo operator. Fig. 5.5 shows all LORs with a phiID of 32 in a situation where $N_\phi$ is 104 drawn on a schematic of the DLO PET system. It is clear that for a given view, the spacing of LORs in the radial direction is very irregular compared to a single-layer cylindrical PET system. The method of calculating rID, given by equation (5.14), is very similar to how phiID is calculated.

Fig. 5.4. Illustration of how each crystal pair that terminates an LOR is mapped to a view ID (a) and a radial bin ID (b).
Here, $N_r$ is the number of radial bins in the sinogram, $\Delta r$ is the spacing between radial bins (which is half of the crystal pitch), and $\text{int}$ is a function that rounds down to the nearest integer. In using equation (5.15), radial samples will already be evenly spaced, so the arc correction is no longer needed.

The DLO design in comparison to a single layer cylindrical PET system creates ambiguities as to how the zID and segID should be calculated. In a single layer cylindrical PET system, the zID is simply the sum of the ringIDs at either end of each LOR. The ringID identifies the position of each crystal in the axial direction. A 2D schematic of a cylindrical PET system seen from the side is shown in Fig. 5.6. Fig. 5.6a shows a subset of LORs which all have a zID of 20. A segment groups together LORs that have the same or similar ring difference (difference in ringID). The span defines how many different values of the ring difference are grouped together in the same segment. When using span 3, segments are formed from LORs with ring differences in [-1, 1], [2, 4], [-2, -4], et cetera. Fig. 5.6b shows a number of LORs in the segment that corresponds to a ring difference in the interval [8, 10].
Difficulty arises when trying to assign a $z$ID and segID to LORs from the prototype DLO PET system based on ring sum and ring difference when those LORs connect bottom-layer crystals to top-layer crystals. To demonstrate this problem, Fig. 5.7 shows a schematic of the DLO PET system viewed from the side. The schematic corresponds to the finalized geometry of the PET scanner prototype that was built in 2014 (described in the right column of Table 2.1). Consider the ring numbering scheme shown in (a) where rings formed by crystals in the bottom layer are numbered $0, 2, 4, \ldots, 42$ and rings formed by crystals in the top layer are numbered $1, 3, 5, \ldots, 41$. In each of 17 situations shown in (b) to (r) the LORs indicated by the blue and red lines always have $z$IDs equal to 37. In these figures, the real-valued $z$-coordinate is equal to where the LOR crosses the dotted horizontal line. In (b), the $z$ coordinate of the blue LOR is less than that of the red LOR. As the ring difference progresses from negative to positive in moving from (b) to (r), the LORs swap position in terms in $z$. The reconstruction engine assumes that the $z$ID of a sinogram bin is proportional to the real-valued $z$ coordinates of the LORs that map to that bin – and this assumption is clearly broken in this situation. Because the sinogram that would be given to the reconstruction engine would not be consistent with the activity distribution being imaged, artefacts would appear in the reconstruction.
Fig. 5.7. Side views of the DLO PET system. Part (a) defines a numbering scheme for rings in a DLO PET system. Each other part shows two LORs both which have a zID of 37 (where zID is the sum of the two ringIDs which terminate the LOR).
We address this problem by developing a different method to determine the values of zID and segID. Instead of defining the zID and segID of an LOR based on the ringIDs of the crystals that terminate the LOR, these IDs will be determined from the two z-coordinates where that LOR penetrates the wall of an imaginary cylinder with a radius that places the walls inside of the detector block as shown in Fig. 5.8. By doing this the zID will always be proportional to the z-coordinate of the LOR. Equations (5.16) and (5.17) could be used to calculate the zID and the segID of an LOR based on the two locations where an LOR penetrates an imaginary cylinder.

![Diagram](image)

**Fig. 5.8.** Illustration of the imaginary ring (green) used to compute values of zID and segID that are proportional to the LOR coordinates z and tanθ. In this case, the z₁ and z₂ coordinates are calculated for the LOR that joins the two crystals highlighted in red.

\[
\text{zID} = \text{round} \left( \frac{(z_1 + z_2)/2 - z_0}{\Delta z} \right) \quad (5.16)
\]

\[
\text{segID} = \text{round} \left( \frac{z_2 - z_1}{2\Delta z \times \text{span}} \right) \quad (5.17)
\]

Here, z₁ and z₂ are the z-locations where the LOR penetrates the imaginary cylinder and Δz is the spacing between samples in the z-direction (which is half the crystal pitch). Although use of equations (5.16) and (5.17) remove the issue of nonlinear correspondence between zID and z, their use results in systematic bias due to rounding. The LORs that connect top-
layer to bottom-layer are still problematic. Consider the two sets of LORs shown in Fig. 5.9. LORs that join bottom-layer crystals to top-layer crystals are shown in green. All other LORs are shown in black. Blue circles mark values of z corresponding to the coordinates of z discretely represented by the sinogram. No matter what the ring difference, the LORs represented by black lines always have z-coordinates perfectly matching values sampled by the sinograms. In other words, equation (5.16) could be used without the rounding operation and the result would be an exact integer regardless. LORs represented in green often fall nearly half-way between values of z sampled by the sinogram. Rounding will move all LORs with the same ring difference in the same direction, which causes bias and sinogram inconsistency.

Fig. 5.9. Sets of LORs seen from the side of the DLO PET system. In (a), LORs map to segment 0 using equation (5.17) while (b) shows LORs that map to segment 4.

If the LORs that fall roughly midway between two zIDs have their counts averaged between two sinogram bins rather than added to the one that is slightly closer, such biases would be
removed. A weight can be calculated using a triangular function with a width of 2.0 and a height of 1.0, as shown in Fig. 5.10. In this example, if the non-rounded value of zID is 13.6, weights of 0.4 and 0.6 are given to the sinogram bins with zIDs of 13 and 14. Using a triangular function like this means that if a non-rounded zID falls directly on an integer, all weight is given to a single zID. If the non-rounded zID falls some distance between two integer values, the weights given to each zID will add to 1.0.

![Fig. 5.10. Illustration of how a triangle function can be used to find weights to interpolate the counts in an LOR between two adjacent zIDs. Here the non-rounded value of zID is 13.6 (represented by a dashed black line). The triangle function calculates weights to add the LOR to zID 13 and 14.](image)

A similar bias was observed when using the rounding function to calculate the segID of each LOR. The reason why this bias exists cannot be explained as clearly as the bias in zID. Instead, it is instructive to look at the distribution of the unrounded values of both zID and segID. For each combination of crystals in Fig. 5.8, the non-rounded values of zID and segID were calculated and are shown in Fig. 5.11. Coordinates representing LORs that connect top-layer crystals to bottom-layer crystals are shown in green, while coordinates representing all other LORs are shown in black.
Fig. 5.11. Distribution of the unrounded values of zID and segID for all LORs that pass through the radial centre of the FOV. LORs that connect top-layer crystals to bottom-layer crystal are represented in green, while all other LORs are represented in black.

The distribution of values of zID and segID that the tomograph naturally samples has a complex and systematic pattern. If nearest-neighbour rounding is used to move each LOR to one of the equally spaced values of segID, biases from rounding will also have a systematic pattern. Instead, interpolation of each LOR between the two closest zIDs and the two segIDs will be done. An LOR will now have two sets of weights; \( w_{Z1} \) and \( w_{Z2} \) correspond to the two axial positions, while \( w_{S1} \) and \( w_{S2} \) correspond to the two segments. The counts from each LOR will be added to four sinogram bins with weights of \( w_{Z1}w_{S1} \), \( w_{Z1}w_{S2} \), \( w_{Z2}w_{S1} \), and \( w_{Z2}w_{S2} \).
Unless otherwise stated, all sinograms created to histogram PET data in this thesis have the following dimensions:

- 67 radial bins (indexed by rID)
- 104 views (indexed by phiID)
- up to 43 axial positions (indexed by zID)
- 13 segments (indexed by segID), calculated using span = 3

Because the width of each radial bin is half of the crystal pitch (1.27 mm), 67 radial bins cover a FOV with a 42.5 mm diameter. The choice of 104 views is related to the choice of 67 radial bins. In order to represent a sinogram discretely without causing image artefacts upon reconstruction, the number of views should be approximately equal to the number of radial bins times $\pi/2$ [123].

The length of the PET system is long enough that some LORs have a difference in $z_1$ and $z_2$ large enough that they would fall in segment -7 or segment 7. However, each segment would only be filled with LORs on the lower end of the range of $|z_2 - z_1|$ that map to those segments. This would cause inconsistency between the average value of $\tan \theta$ that the sinogram samples, and what the reconstruction engine believes the sinogram samples. Therefore these segments are not included in the reconstruction. In a PET scanner with segments defined by ring difference, exclusion of segments ±7 would be equivalent to having a maximum ring difference of 19. That LORs with a very large ring difference are not used to reconstruct PET data results in a small drop in sensitivity at the axial centre of the FOV.

An energy window of 300 to 800 keV is applied to reject scatter. Coincidences are identified with a timing window of 10 ns, and a delay of 100 ns for delayed coincidences.

5.3 Gap Filling

Data from Monte Carlo simulations of a 30 mm wide cylinder centred in the FOV and a point source offset 5 mm from the centre of the FOV were histogrammed into sinograms and normalized. A slice through each sinogram is shown in Fig. 5.12. Here slice means a
histogram as a function of rID and phiID for constant values of zID and segID (zID=21, segID=0 in this case). The image reveals that there are gaps in the sinogram appearing as diagonal lines. These regions of the sinogram are not sampled because of physical gaps between the detectors. The absence of data in these regions is not a problem for iterative reconstruction methods. However, they need to be filled in for the image to be reconstructed analytically.

![Image](image_url)

**Fig. 5.12. Illustration of gaps in the sinograms.** Each sinogram slice contains 67 rows representing radial bins, and 104 columns representing views. Part (a) and (b) respectively show slices of a sinogram corresponding to simulated data from a uniform cylinder and a point source 5 mm off centre.

The simplest way of filling the gaps is to interpolate the values from nearby sinogram bins. A method of filling gaps was developed where each zero sensitivity bin was filled with a weighted average of the non-zero-sensitivity sinogram bins in a local neighbourhood around the bin being filled (±2 bins the φ direction, ± 4 bins in the r direction). The weighting factors were pulled from a pyramid function. If Δφ and Δr are the absolute distances to the bin being sampled in the φ and r directions, the weighting factor for that bin is \((3 – Δφ)×(5 – Δr)\). The sinogram slices shown in Fig. 5.12 were filled using this method and are shown in Fig. 5.13.
The gap filling method appears to work quite well for the cylinder data because the sinogram has no abrupt changes near the gaps. However, problems from this gap filling method appear when applied to sinograms corresponding to more heterogeneous activity distributions. A 2D slice through a sinogram of a point source should look like a segment of a sine function when properly filled; in our case regions along this sinusoidal trajectory that correspond to the gaps are highly under-estimated in Fig. 5.13b. In addition, regions just above and below the sinusoidal trajectory that pass through gaps have non-zero values when they should be zero.

More sophisticated methods of gap filling have been developed for other PET scanners with detector gaps [124], [125]. In order to fill gaps more successfully than what is shown in Fig. 5.12, a method similar to [126] is employed. This begins by filling gaps using the interpolation method previously detailed. The data is then reconstructed with 15 iterations of MLEM, implemented by STIR 3.0. The reconstruction is then forward projected by a utility available in the STIR 3.0 software suite. Forward projection transforms the image back into a sinogram by computing line integrals through the image along lines parameterized by the values of \( r, \phi, z, \) and \( \tan \theta \) represented by each sinogram bin. Gaps in the original sinogram are then filled with the values from this forward projection. Fig. 5.14a shows a slice through the forward projection of the point source image. The original sinogram slice with the gaps filled with values from this forward projection is shown in Fig. 5.14b. The problems that were present when the gaps were filled with interpolation are no longer present.
5.4 Image Reconstruction

To reconstruct a PET image, *trues* corrected coincidences and normalization coefficients \( n_{ij} \) are histogrammed into separate sinograms using the method described in §5.2. The trues sinogram is divided by the normalization sinogram, and gaps are filled with the technique described in §5.3. Normalization is applied after histogramming into a sinogram instead of the alternative of normalizing the number of counts in each LOR before histogramming. It has been shown that the later results in added noise to the reconstructed PET images [127]. These sinograms are then reconstructed with FBP-3DRP (described in §1.6.1.2) as implemented in STIR 3.0 [118]. By default, the size of the voxels in the reconstructed image matches the spacing between radial samples in the sinogram. A parameter called *zoom* allows for smaller voxels to be used. The size of the voxels in the transaxial plane (x and y) is equal to the default spacing divided by the zoom-factor.

5.5 Monte-Carlo Simulation to Estimate LOR Positions for DLO PET

In §5.2 of this chapter, the real-valued \((r, \phi, z, \tan\theta)\) coordinate of each LOR was calculated assuming that the coordinates in projection space that best represents how the crystal pair samples the activity correspond to line that connects the *interaction centroids* of the two crystals. In reality, each crystal pair samples the projection of the activity not at a point in projection space, but over a small volume of projection space. This is illustrated in Fig. 5.15. A selection of lines shown in blue, each with a slightly different \((r, \phi)\) coordinate, are all...
sampled by the crystal pair highlighted in red. The LOR that connects the centroids of the two crystals is represented by a thick black line. In 3D, the \((z, \tan\theta)\) values of the lines that connect the crystal pair would also be distributed over a small space. The \((r, \phi, z, \tan\theta)\) coordinate used to calculate the sinogram IDs for that LOR can be thought of as the average \((r, \phi, z, \tan\theta)\) coordinate that best represents how the crystal pair samples projection space.

Fig. 5.15. 2D schematic of the DLO PET system. The assumed LOR coordinate of the crystal pair highlighted in red is shown as a black line that connects the centroids of those two crystals. In reality, many projection lines (illustrated in blue) with a distribution of projection coordinates are sampled by that crystal pair.

The assumption that the line connecting the interaction centroids of each crystal pair best represents the point in projection space that that crystal pair samples may to too simplistic for the following reasons:

1) The depth of interaction (the distance between the top face of a crystal and its interaction centroid) cannot be assumed to be constant. The average interaction depth of annihilation photons that enter the detector block at an angle will be slightly smaller than the average depth of interaction of annihilation photons that enter perpendicular to the crystal face. As the crystal thickness becomes larger than the mean free path of a 511 keV photon in LYSO (\(\mu^{-1}\), \(\mu\) being the linear attenuation coefficient), the average interaction depth of an annihilation photon that enters the block at an angle \(\xi\) approaches \(\cos(\xi)/\mu\).

2) The differential amount of shielding by neighbouring crystals can bias the average sinogram coordinate sampled by a crystal pair. For example, lines which connect the back of one crystal to the back of the other crystal in Fig. 5.15 see substantially more shielding by neighbouring crystals than lines which connect the fronts of the crystals.
This would bias the average radial coordinate of annihilation photon pairs detected by this crystal pair toward the centre of the scanner.

3) Compton scattering is forward peaked so an annihilation photon that enters a detector block at an angle, scatters, and interacts in a second crystal is more likely to be misidentified in a crystal closer to the centre of the FOV. This biases the average radial coordinate of annihilation photon pairs detected by each crystal pair to the outside of the FOV. The centroid-to-centroid model assumes that each annihilation photon is detected in the first crystal that it interacts in.

Here we propose a method where instead of assuming that the \((r, \phi, z, \tan \theta)\) coordinate that best represents each LOR is a line that connects the interaction centroids of the crystals that terminate each LOR, we estimate the average \((r, \phi, z, \tan \theta)\) coordinate that each crystal pair samples using data from a Monte-Carlo simulation of the PET scanner. Using the Monte-Carlo simulation macros developed to estimate the spatial resolution of the PET system in §2.5.2, a simulation was run with a 60 mm wide and 30 mm long cylinder centred in the FOV emitting back-to-back 511 keV gamma rays. The simulation was run long enough to record approximately one billion coincidences filtered by an energy window of 300 to 800 keV. The simulation data were post-processed by the technique described in §2.2 to model intercrystal scatter.

The exact \((r, \phi, z, \tan \theta)\) coordinate of every back-to-back gamma ray pair is known from simulation data, although this would be impossible to know in a real experiment. For every crystal pair in the FOV we calculate the average values of \(r, \phi, z_1, \) and \(z_2\) of all annihilation photon pairs detected by that crystal pair. \(z_1\) and \(z_2\) are the locations where each photon penetrated the imaginary cylinder introduced in §5.2 of this chapter. The geometric symmetries described in §5.1 of this chapter were used to increase the number of coincidences recorded by each crystal pair by up to a factor of 64. The average values of \(r, \phi, z_1, \) and \(z_2\) were then used to calculate the IDs of the sinogram bins according to equations (5.14), (5.15), (5.16), and (5.17). The procedure for reconstructing PET data described in §5.4 is still applicable.
Simulation data of the microDerenzo phantom described in §2.5.2 were histogrammed using LOR positions derived from Monte-Carlo simulations and reconstructed. The reconstruction used an image zoom of 2, so the resulting image size was $133 \times 133 \times 43$ with voxel dimensions of $0.3175 \times 0.3175 \times 0.635 \text{ mm}^3$. The same data set was histogrammed again using LOR positions calculated by assuming each crystal pair samples a line that connects the centroids of each crystal (the default method). Fig. 5.16a and b respectively show slice 20 of the reconstructed images created using the Monte-Carlo method and the default method to estimate LOR positions. Fig. 5.17 shows profiles taken through the vertical line that goes through the right-most columns of 1.7 mm rods and 1.0 mm rods.

Fig. 5.16. Slices through the reconstructed microDerenzo images. Rod diameters are 2.4, 2.0, 1.7, 1.35, 1.0, and 0.75 mm. Data used to reconstruct (a) and (b) were respectively histogrammed using the Monte-Carlo and the default method of estimating LOR positions.
Visual inspection of the images and the profiles show that there is no significant improvement in image resolution or overall image quality between the two methods of positioning LORs. Reconstruction of simulated point sources and real PET data of point sources, phantoms, and rodents also indicate that there is no benefit to estimating LOR spacing from Monte-Carlo simulations. One major reason why the Monte-Carlo method of estimating LOR positions had no impact on image quality is that there was not a very large difference in the values of $r$, $\phi$, $z_1$, and $z_2$ when estimating them from a Monte-Carlo simulation or from assuming that each LOR connects the centroids of the two crystals that terminate the LOR. Fig. 5.18, Fig. 5.19, and Fig. 5.20 respectively show the average absolute difference in $r$, $\phi$, and $z_1$ between the two methods of estimating the LOR coordinates as a function of rID and phiID (where rID and phiID were calculated using default LOR spacing). The plot of the difference in $z_2$ resembles Fig. 5.20 very closely, so is not shown.

The difference in $r$ between the two methods is as high as 0.39 mm, but only for a small fraction of sinogram bins. The average difference is 0.12 mm, which is much smaller than the spacing between sinogram bins in the radial direction (0.635 mm). The average difference in the value of $\phi$ is 0.0035 radians, which is very small compared to the spacing between views in the sinogram (0.030 radians when using 104 views). Finally, the average difference in both $z_1$ and $z_2$ between the two methods of estimating the LOR position was 0.089 mm. The spacing between rings is 1.27 mm, so the slight difference in $z_1$ and $z_2$ will...
not have a very large impact in the weighting of each LOR between adjacent axial positions and segments.

Fig. 5.18. Average absolute difference in the $r$ value from the two methods of estimating LOR positions. Each image contains 67 rows representing radial bins, and 104 columns representing views. Units are in mm.

Fig. 5.19. Average absolute difference in the $\phi$ value from the two methods of estimating LOR positions. Each image contains 67 rows representing radial bins, and 104 columns representing views. Units are in radians.
Fig. 5.20. Average absolute difference in the $z_1$ value from the two methods of estimating LOR positions. Each image contains 67 rows representing radial bins, and 104 columns representing views. Units are in mm.

Each LOR is distributed between two planes and two segments due to the histogramming method described in part A of this chapter. However, each LOR is only assigned to one radial bin and one view, due to equations (5.14) and (5.15) in §5.2 of this chapter. Because of the rounding functions in these equations, any small difference in the value of $r$ or $\phi$ will likely not affect the sinogram at all unless the value of $r$ or phi is close to mid-way between two radial bins or views.

5.6 Monte-Carlo Simulation to Estimate LOR Positions for microPET Focus 120

The idea of using a Monte-Carlo simulation to estimate the position of LORs was originally developed for the Siemens microPET Focus 120 PET scanner [119] with the hope of adapting it to our DLO PET prototype. While this turned out not be relevant for our system, this work is still being presented here because it produced positive results for the microPET Focus 120 and so represents a valuable contribution to the field of PET in general. This chapter will conclude with a discussion of why this technique produced positive results for the microPET Focus 120 but was ineffective for our prototype PET system. By necessity, the implementation of the technique was slightly different. In this section, we describe how the technique of using a Monte-Carlo simulation to estimate the LOR positions was implemented for the microPET Focus 120, and show the resulting improvement in image quality.
The microPET Focus 120 uses single-layered detectors that are arranged in a very close approximation to a cylindrical PET system. The technique to form a sinogram from data from a cylindrical PET system was described in §5.2 of this chapter (with reference to Fig. 5.4 and Fig. 5.6). The result of the cylindrical geometry of the scanner is that the LORs naturally sample sinogram space in uniformly spaced intervals of $\phi$, $z$, and $\tan \theta$. Before the arc correction is applied, the sinogram samples sinogram space irregularly in the radial direction. The result of using the default method of positioning LORs is that the spacing of the radial bins is described as a sine function, which is obvious from Fig. 5.4b. The radial position sampled by a sinogram bin indexed rID is:

$$r = R \times \sin \left( \frac{\pi}{N_{\text{crystals}}} \left( rID - \frac{N_r}{2} \right) \right)$$  \hspace{1cm} (5.18)

Here $N_r$ is the number of samples in the radial direction, $N_{\text{crystals}}$ is the number of crystals that form a ring and $R$ is the effective radius of the PET scanner, which is the radius defined by the front faces of the crystals plus the interaction depth (the distance between the front face of a crystal and the interaction centroid). When the arc correction is done, each column of each sinogram slice (subset of the sinogram data with constant value of phiID, zID, and segID) is resampled into uniformly spaced values of $r$ using linear interpolation assuming that equation (5.18) describes the spacing of the original samples. In this work, a Monte-Carlo simulation of the microPET Focus 120 will be used to estimate the average radial coordinate sampled by each sinogram bin. The arc correction will use these values rather than the values predicted by equation (5.18) to interpolate the original sinogram data into uniformly spaced radial bins.

The geometry of the Siemens microPET data was modelled in a GATE simulation. The energy resolution of the detectors was set to 18.3%, which is the measured energy resolution from the actual system. A 13 cm wide and 7.7 cm long cylindrical phantom, which filled the entire FOV, was set up to emit back-to-back 511 keV gamma rays. The simulation was run long enough to record over one billion coincidences after being filtered for energy. An
energy window of 350-750 keV was applied, which is the same energy window that we apply when doing rodent studies with the microPET Focus 120 scanner in our PET centre. Simulations were post-processed to reassign the identified crystal of interaction following Compton scattering in the detector block using the method described in §2.2. Geometric symmetries allowed for the number of coincidences recorded by each crystal to be increased by a factor of up to 96 (each ring of the microPET Focus 120 is made from 24 detector blocks).

For each coincidence detected in a given sinogram bin, the location in the FOV where the annihilation occurred is known. The radial offset of the location where the annihilation occurred is calculated as the perpendicular distance to the annihilation from the line which represents \( r = 0 \) for that particular view, as illustrated in Fig. 5.21. For each sinogram bin, the average radial offset of all annihilation events recorded in that bin is found. These radial offsets are then assumed to represent the average radial offset sampled by each sinogram bin when the arc correction is done.

![Fig. 5.21. 2D schematic of a cylindrical PET system. Blue lines show many annihilation photon pairs (each originating from a yellow circle) being detected by the two crystals highlighted in red.](image)

PET data from a microDerenzo phantom and two mice were processed using the default method of arc correction, and the method relying on Monte-Carlo simulations. Normalization was applied to the sinograms before arc correction. Arc corrected sinograms were reconstructed using filtered back projection with Fourier rebinning as implemented in the reconstruction software provided by Siemens for the microPET Focus 120. The image zoom
was 4, resulting in images with $512 \times 512 \times 95$ voxels each $0.216 \times 0.216 \times 1.592 \ mm^3$ in volume. No correction for scatter or attenuation was done. The microDerenzo phantom contained hot inserts with diameters of 1.70, 1.50, 1.30, 1.10, 0.95, and 0.85 mm. The phantom was filled with 60 MBq of $^{18}\text{F}$ and was scanned for 18.3 hours. Slices through the phantom reconstructed using Monte-Carlo spacing and default LOR spacing are respectively shown in Fig. 5.22a and b.

![Fig. 5.22. Slices through the reconstructed images of the microDerenzo phantom. Rod diameters are 1.70, 1.50, 1.30, 1.10, 0.95, and 0.85. (a) shows data processed using the Monte-Carlo method of estimating LOR positions, while (b) shows data processed using the default method.](image)

Care was taken to ensure that both images are displayed with the same colour scale. Both images were divided by the maximum value of either image and the colour scale was set to range from -0.1 to 1.0. Although there is no significant improvement in the resolvability of the rods, there is a noticeable reduction in the magnitude of the streaking artefacts. Streak artefacts appear most prominently in the region of the image outside of the phantom. The streak artefacts appear as an oscillation in the image value around zero, and have a structure of lines radiating away from the phantom. White contour lines were added to one side of each image to demonstrate more quantitatively that the image processed assuming the default LOR spacing has streaks of greater magnitude. Contour lines separate image values between -0.1 and 0.1 in intervals of 0.02.
The first mouse was given an intraperitoneal injection of 68 MBq of $^{18}$F-FDG, while the second was given a tail vein injection of 37 MBq of $^{18}$F-FDG. Data were acquired for 1 hour after a 30 min uptake period. Slices through the reconstructed images of the first mouse reconstructed using both methods of estimating LOR positions are shown in Fig. 5.23 (brain) and Fig. 5.24 (heart). In both figures, image (a) shows the reconstruction using LOR spacing estimated from the Monte-Carlo simulation, and (b) uses the default method. The colour scales in these images were set in the same way they were set for the phantom images. The mouse heart images are cropped to a $6 \times 8$ mm$^2$ region around the heart.

![Fig. 5.23](image)

Fig. 5.23. (a) and (b) respectively show slices through the reconstructed images of the brain of the first mouse processed using the Monte-Carlos method of estimating LOR positions, and the default method. (c) shows profiles through the images connecting the striata. The path of these profiles are indicated in (a) and (b) as black lines

![Fig. 5.24](image)

Fig. 5.24. Slices through the reconstructed images of the heart of the first mouse. (a) shows data processed using the Monte-Carlo method of estimating LOR positions, while (b) shows data processed using the default method. Each image is cropped to show an $8 \times 6$ mm$^2$ region. ROIs used to measure heart contrast are outlined in white.
The mouse brain image demonstrates the same pattern of a reduction in streaking artefacts. The colour scale of a region of the images in Fig. 5.23 is set to -0.1 – 0.1 in order to highlight the streaks. In addition to the reduction in streaking artefacts, the mouse images also show a small improvement in contrast. The striata appear in the mouse brain image as two prominent peaks. Profiles were measured along a line connecting the striata for the two reconstructions. These profiles are shown in Fig. 5.23c. The valley between the two striata is slightly deeper when using the Monte-Carlo method of estimating LOR spacing. The heart images in Fig. 5.24 also show a slight improvement in contrast as well. Two regions of interest were placed on the heart images: one inside the blood pool and one covering the cardiac muscle. The blood pool region of interest was a 1.5 mm wide circle, and the cardiac muscle region of interest was a 1 mm thick ring. The activity inside each region of interest was averaged and heart contrast was calculated as:

\[
C_{\text{Heart}} = \frac{\langle \text{cardiac muscle} \rangle - \langle \text{blood pool} \rangle}{\langle \text{heart muscle} \rangle}
\]  

(5.19)

Table 5.1 summarizes the heart contrast for both of the mice that were scanned, and for both methods calculating the spacing of LORs. The last row of the table calculates the percentage improvement in heart contrast when using the Monte-Carlo simulation to estimate the LOR positions.

<table>
<thead>
<tr>
<th>Method</th>
<th>Mouse 1</th>
<th>Mouse 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monte-Carlo</td>
<td>0.173</td>
<td>0.266</td>
</tr>
<tr>
<td>Default</td>
<td>0.145</td>
<td>0.197</td>
</tr>
<tr>
<td>% Improvement</td>
<td>19%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Table 5.1. Summary of heart contrast measured from two mice, where data were processed by both methods of estimating the position of LORs.

One reason that the Monte-Carlo technique improves image quality for the microPET Focus 120 but not the prototype DLO PET system may be that the microPET Focus 120 has larger crystals than the prototype DLO PET. The crystal size from the microPET Focus 120 is
1.5×1.5×10 mm³ versus 1.20×1.20×(4/6) mm³ for the prototype DLO PET. As crystals become shorter, the average interaction depth becomes very close to half the length of the crystal and has less dependence on the angle of incidence. Therefore, there is less variation in the interaction depth for shorter crystals. Fig. 5.25 shows the average absolute difference in the radial coordinate as a function of rID and phiID for the microPET Focus 120. The average difference in r for all bins 0.25 mm, although the difference is sometimes as high as 0.65 mm. The spacing between radial bins in a sinogram for the microPET Focus 120 is 0.815 mm, so refinements in the position of LORs by up to 0.65 mm can have an appreciable impact on the sinogram. Recall from §5.5 of this chapter that the average difference in the radial coordinate between the two methods applied to the prototype DLO PET system was only 0.12 mm. As a result of how the arc correction is done for the microPET Focus 120, the precise radial coordinate of each LOR will always have an impact on the two nearest LOR bins. This is in contrast to the histogramming method for the prototype DLO PET system, where the rounding function usually rendered small shifts in the r and φ coordinates of each LOR inconsequential.

![Image](image.png)

**Fig. 5.25.** Average absolute difference in the r value from the two methods of estimating LOR positions. Each image contains 128 rows representing radial bins, and 144 columns representing views. Units are in mm.

### 5.7 Conclusion

This chapter described how PET data were sorted for coincidences, and how those coincidences were sorted into sinograms to be reconstructed using FBP-3DRP as
implemented in the open source reconstruction suite STIR 3.0. PET data were normalized using a component based normalization procedure. A method was devised to histogram coincidences into a sinogram that would consistently represent the projection of an activity distribution in the FOV. Gaps in the sinogram are initially filled with a simple interpolation method. This sinogram is reconstructed and then forward projected back into sinogram space. The values in the forward projection corresponding to the zero-sensitivity bins in the sinogram are then used to fill these gaps.

A method was developed to more accurately estimate the coordinates of LORs using Monte-Carlo simulations rather than assuming that the coordinates of each LOR correspond to a line joining the centroids of the crystal forming the LOR. Although it was not effective for the prototype DLO PET insert, it was effective for the Siemens microPET Focus 120, where the improved estimates of LOR positions were incorporated into reconstruction during the arc correction step. The technique led to a reduction in the magnitude of streak artefacts in reconstructions of a microDerenzo phantom and two mice. A small improvement in image contrast was observed in the mice. Although the improvement in image quality is slight, the improvement comes at no extra burden in terms of computation (except for the original task of estimating the LOR positions). Likely reasons why the method had no effect for the prototype DLO PET system are that smaller crystals in the prototype DLO PET system meant that any discrepancies between the two methods of computing the LOR positions would be proportionately smaller. Also, the method of histogramming data for the prototype DLO PET system used a rounding function, which mean that small shifts in the radial position and view of each LOR were unlikely to have any impact on the sinogram.
Chapter 6: Point Spread Function Modelling Reconstruction

Software implementing an LOR-based point spread function modelling maximum likelihood / expectation maximization (PSF-MLEM) reconstruction technique was created by Dr. Xuezhu Zhang at the University of Manitoba. This software, which was tailored specifically to our PET system design, used an analytic model to calculate each system matrix coefficient. A 2013 publication resulting from this method used reconstructions of simulated microDerenzo phantoms to demonstrate that the technique was able to produce very high-resolution images [128], far superior to analytic reconstructions like those shown in Chapter 2. Detector normalization correction was not incorporated into the reconstruction, and as a result, the reconstruction did not result in uniform images.

This chapter describes the work done in order to ensure that the reconstruction software produces images that are free from non-uniformity artefacts. §6.1 provides an overview of the reconstruction algorithm developed in [128]. Because the calculation of the system matrix coefficients accounts for some geometrical effects that are traditionally accounted for by normalization, a novel approach to normalization (described in §6.2) was necessary to ensure that these factors were not accounted for twice. After normalization was incorporated into the reconstruction, reconstructions of data from a simulated uniformity phantom showed that the software still did not produce uniform images. Two factors that were identified as causing these remaining non-uniformity artefacts are described in §6.3, along with the steps taken to address them. The modifications made to the algorithm to eliminate the non-uniformity artefacts significantly increased the amount of time needed to perform a reconstruction. §6.4 describes steps taken to reduce the reconstruction time to a more manageable level.

6.1 Description of Previously Developed Technique

The technique developed by Dr. Xuezhu Zhang is classified as an LOR-based PSF modelling ML-EM reconstruction. The advantages of LOR-based MLEM over sinogram based MLEM were discussed in §1.6.2.1, and the advantages of PSF-MLEM over regular MLEM were discussed in §1.6.2.2. An analytic model was developed to calculate each system matrix
coefficient $c_{ab}$. The first step to calculate $c_{ab}$ is to model the probability of detection in LOR-b of a pair of annihilation photons emitted from the centre of voxel-a in the direction $n$. This probability is:

$$P_{ab}(n) = [(1 - e^{-\mu L_1})e^{-\mu S_1}][(1 - e^{-\mu L_2})e^{-\mu S_2}] \quad (6.1)$$

With reference to Fig. 6.1, $L_i$ is the intersection length between the crystal that defines the end of the LOR in block-$i$ (shaded in blue) and the ray originating from voxel-a. Likewise, $S_i$ is the intersection length with all of the crystals that that ray penetrates before reaching the crystal of interest (shaded in green). $\mu$ is the linear attenuation coefficient of the detector material for 511 keV photons, which in our case is 0.82 cm$^{-1}$.

Fig. 6.1. Illustration showing the meaning of quantities used in equation (6.1).

To complete the calculation of $c_{ab}$, equation (6.1) must be integrated over the unit sphere. An analytic formulation of this integral would be extraordinarily complicated if it even exists at all. Instead, the integral is done by discretely sampling $n$ around the unit sphere. The reconstructions in [128] used 360 samples in the $\phi$ direction and 360 samples in the $\theta$ direction, distributed using Archimedes’ theorem to ensure sampling density is uniform over the unit sphere [129].

$$c_{ab} = \sum_n P_{ab}(n) \Delta \Omega \approx \int_{\Omega} P_{ab}(n) \, d\Omega \quad (6.2)$$
Symmetries in the system matrix were exploited to boost reconstruction time. When one system matrix element is calculated, three degenerate ones can be identified by rotating the crystals and voxel by 90°, 180°, and 270°. If these crystals and voxels are then mirrored in the axial direction of the scanner, four more degenerate system matrix elements can be identified. These symmetries are illustrated in Fig. 6.2.

Fig. 6.2. DLO PET system shown from the front (a) and side (b). Only system matrix elements for voxels in the volume shaded in light blue need to be computed. Seven additional degenerate voxel-LOR pairs can be found by rotating the system 90° (shown in a) and by flipping the system in the axial direction (shown in b).

6.2 Incorporation of Randoms and Normalization

During development the reconstruction code was tested with randoms-free simulated data; proper handling of scatter and randoms was not a concern at the time. Since real data from the prototype PET system became available in 2015, the software had to be modified in order to properly handle randoms. No method has yet been implemented for our prototype PET system to estimate the scatter distribution, so it is left in the data and ignored. The MLEM algorithm does not function properly when the data it operates on has had randoms subtracted. We saw in the derivation of the MLEM algorithm in §1.6.2 that the data is assumed to be a Poisson random variable. Once randoms have been subtracted, the data is no longer Poisson-like and in fact contains negative values that are not possible to reach in a Poisson distribution. Negative values in the data will cause the MLEM algorithm to rapidly
diverge [130], [131]. Simply setting the values to zero fixes the issue of rapid divergence but introduces a positive bias to the data [131].

The ordinary Poisson (OP) method of dealing with randoms in MLEM was incorporated into the reconstruction software. Measured data are left un-corrected to preserve their Poisson distribution. So that images are not biased to higher activities, randoms are added to the forward projection on each iteration [83]. Equation (1.22) in §1.6.2 becomes:

\[ \lambda_{a}^{k+1} = \frac{\lambda_{a}^{k}}{\sum_{b} c_{ab}} \sum_{b} \frac{y_{b}}{\sum_{a} c_{ab} \lambda_{a}^{k}} + r_{b} c_{ab} \]  

(6.3)

Here, \( r_{b} \) represents the number of randoms measured in LOR-b.

In §1.6.2 we saw that the MLEM algorithm is built upon the assumption that the measured data \( y \) can be modelled as a multiplication of the system matrix with the image vector \( \lambda \). Although the method of calculating the system matrix coefficients captures many of the geometric factors affecting the sensitivity of each LOR, other factors such as intrinsic detector efficiency still need to be explained. By multiplying the system matrix by a diagonal matrix \( N \) containing normalization factors, the foundational assumption that MLEM is based on holds true, and we can expect convergence to the correct activity distribution. Equation (1.18) from the introduction then becomes:

\[ \bar{y} = NC\lambda \]  

(6.4)

The effect of including \( N \) in equation (6.4) is that every \( c_{ab} \) in equation (6.3) is now replaced by \( n_{b} c_{ab} \), where \( n_{b} \) is the normalization coefficient for LOR-b.

A method of deriving normalization coefficients was detailed in §5.1. The normalization coefficients derived in §5.1 accounted for both the intrinsic efficiency of each crystal, as well as non-separable geometric factors. These normalization coefficients cannot be used to
normalize data for this PSF reconstruction technique because the system matrix already accounts for many of the geometric factors of LOR efficiency; use of the same normalization coefficients will result some factors of geometric efficiency being accounted for twice. For example, §5.1 described systematic variations in the length of detector material photons travel through as they pass through a crystal, which affects the probability of interacting in that crystal. There are also systematic variations in the amount of shielding of each crystal by surrounding crystals. These factors are inherently accounted for in the calculation described in equations (6.1) and (6.2).

There are certain systematic geometric factors that are not accounted for in equations (6.1) and (6.2). For example, there is no consideration of inter-crystal scatter at all. Because Compton scattering is forward-peaked, the degree of crystal misidentification depends on the angle of incidence. Crystal misidentification has the effect of lowering the effective sensitivity of some crystals while raising the sensitivity of others. Photons that have a second or third interaction in the detector will deposit more energy and are therefore less likely to be rejected once an energy window is applied. The probability of multiple interactions has a strong dependence on the angle of incidence and position at which a photon enters the block. These mechanisms for geometric variations in LOR efficiency still need to be accounted for by normalization.

Equation (5.1) can be modified so that the geometric factors are now separated into factors accounted for by the system matrix ($h$), and factors which need to be accounted for in the normalization coefficients ($g$).

$$N_{ij} = \varepsilon_i \varepsilon_j g_{ij} h_{ij} A_{ij}$$  \hspace{1cm} (6.5)

The subscript $ij$ from Chapter 5 is equivalent to the subscript $b$ in this chapter. In equation (5.1) in Chapter 5, the number of counts measured by each LOR ($N_{ij}$) was divided by the known activity along that LOR ($A_{ij}$), after which point a method was described to calculate the geometric factors $g_{ij}$ and the intrinsic factors $\varepsilon_i$ and $\varepsilon_j$. Here, if $h_{ij} A_{ij}$ was known, it could
be divided out of equation (6.5), after which point the same procedure could be followed to find the remaining normalization factors.

When the system matrix is used to forward project an image without incorporation of normalization, the value contained in each LOR in the forward projection is proportional to the amount of activity along that LOR multiplied by the factors of efficiency that are accounted for in the system matrix. Therefore, one can calculate each \( h_{ij}A_{ij} \) by initializing a voxel matrix to match the distribution of activity in the normalization phantom (\( \lambda^{\text{annulus}} \), an annulus with inner / outer radii of 18 / 22 mm) and forward projecting it using the system matrix.

\[
h_{b}A_{p} = \sum_{a} c_{ab} \lambda^{\text{annulus}}_a
\]  

This is similar to the approach taken by Bai et al [132] who developed a maximum a posteriori reconstruction algorithm that accounted for a subset of the geometric normalization factors. After forward projecting the known distribution of the cylindrical normalization source to determine the factors of normalization incorporated in the system matrix, the remaining factors of normalization were found using a joint maximum likelihood optimization algorithm.

### 6.3 Modification of Technique to Eliminate Uniformity Artefacts

Lack of normalization results in non-uniformity artefacts. To ensure that incorporation of normalization resulted in the removal of these artefacts, simulated PET data corresponding to a uniform 15 mm wide cylinder were reconstructed. It is best to test for uniformity with simulated data rather than measured data because certain physical effects related to temperature and count rate that might complicate normalization are eliminated. Shown in Fig. 6.3 are reconstructions of the same cylinder data before and after inclusion of normalization factors. These reconstructions were done with a 67×67×43 grid with using a zoom factor of 1, resulting in voxel size of 0.635×0.635×0.635 mm\(^3\). 20 iterations of the MLEM algorithm were used to compute these images.
The un-normalized cylinder clearly has non-uniformity artefacts. Unfortunately, inclusion of normalization replaces these artefacts with a new flavour of artefact, suggesting residual inaccuracies in the system matrix. An obvious place to look for as the source of system matrix inaccuracies is the number of samples taken around the unit sphere to approximate the integral in equation (6.2). Under-sampling could cause systemic biases in system matrix coefficients. In order to visualize the system matrix, three lines of response are chosen for inspection. These three lines of response are illustrated in Fig. 6.4. All lines of response end on crystals ten steps into the FOV relative to the back of the scanner. A very finely sampled image space is initialized, with a size of $319 \times 319 \times 175$ and an isotropic voxel pitch of $0.15875$ mm ($1/8^{th}$ the crystal pitch). For each voxel, the value of $c_{ab}$ according to equation

Fig. 6.3. Images at the top result from reconstruction with no normalization. Images at the bottom had normalization incorporated into the reconstruction, but still showed major non-uniformities. Images on the left/right are transverse/sagittal cross-sections through the uniformity phantom.
(6.2) is calculated using either $360^2$ samples or $2500^2$ samples. If there are systematic biases in the coefficients, visualization of their spatial variability on a finely sampled grid should be informative. The visualization of the system matrix elements for these three LORs is shown in Fig. 6.5.

![Diagram showing three lines of response](image)

**Fig. 6.4.** Three lines of response chosen to inspect the quality of the system matrix coefficients. The lines are drawn from the front faces of the crystals they are meant to connect.
Fig. 6.5. Visualizations of the system matrix elements for three chosen LORs. Calculations on the left/right used $360^2/2500^2$ samples to approximate the integral in equation (6.2).
As seen in Fig. 6.5, the system matrix calculated with only $360^2$ samples contains patterns that are clearly artefactual when compared to the calculation made with $2500^2$ samples. Patterns of higher/lower probability in the centre of the LORs alternate as one moves forward through the slices. There is a dark band directly through the centre of the central LOR. Intuitively, the probability of detection by an LOR should change smoothly as one moves about in the volume of image space sampled by that LOR. It seems that these odd patterns result from systematic sampling bias when a small number of samples are used. This idea is supported by the fact that these odd patterns vanish when a substantially larger number of samples are used. Because a smoothly varying pattern of detection probability was produced when $2500^2$ samples were taken from each point, it was assumed that this number of samples sufficed to accurately calculate the detection probability.

The simulated uniformity data were reconstructed once again using a system matrix calculated with $2500^2$ samples. The normalization coefficients were recalculated so that the forward projection of the annulus used in their computation was made with the same system matrix used for this reconstruction. The matrix size and number of iterations is the same as for the previous reconstructions.

![Transverse view and Sagittal View](image)

*Fig. 6.6. Reconstructed uniformity data after the system matrix calculation had been updated to incorporate $2500^2$ samples rather than $360^2$. Images on the left/right are transverse/sagittal cross-sections through the uniformity phantom.*
The resulting reconstructions, shown in Fig. 6.6, come a lot closer to being uniform than the reconstructions in Fig. 6.3, although issues still linger. There is still a doughnut shaped depression around the centre of the phantom, and streaks can be seen at angles (measured from standard position) of 0°, 45°, 90°, and 135°. The sagittal view shows that there is a pattern of alternating slice intensity, which was already present in the previous reconstructions. Inspection of the forward projections produced by the system matrix show systematic under- and over-biases for LORs parallel to the directions of the streaks in the image (i.e. 0°, 45°, 90°, and 135°). Here, we will inspect the forward projection of the digital annulus to demonstrate these patterns.

Because the method presented in the chapter is an LOR-based reconstruction, forward projections are not stored in sinograms. They are stored in data structures (jagged arrays) with one element for every crystal pair that samples the FOV. A visualization of the forward projection is shown in Fig. 6.7. It is necessary to clearly explain how these forward projection images are to be interpreted. Each square region outlined in black in Fig. 6.7 is a 409×409 region showing all of the crystal combinations between a certain combination of blocks (each block contains 409 crystals). With reference to the block numbering in Fig. 6.8, the top row of Fig. 6.7 shows the forward projection between block 0 and the seven blocks opposite from it (5 to 11). Similarly, the lower three images show the forward projections of blocks 1, 2, and 3 in coincidence with their seven opposite blocks. Other parts of the forward projection are not show because they are redundant (i.e. the forward projection of block 4 in coincidence with its seven opposite blocks is identical to the top row of Fig. 6.7).
Fig. 6.7. Visualization of the forward projection of a digital version of the annular normalization phantom.

Fig. 6.8. Schematic showing LORs that cross the FOV at angles parallel to spacing of voxels. (a) and (b) respectively show front and side views of the scanner.
The 409×409 region corresponding to the forward projection into all LORs between block 0 and block 8 is shown in a close-up in Fig. 6.9a. The indexing of crystals in the figure is such that the top-right quadrant connects bottom-layer crystals to bottom-layer crystals, and the bottom-left quadrant front-layer to front-layer. Focussing on the region of Fig. 6.9a that connects the bottom-layers of blocks 0 and 8, the region is divided by red lines into a 10×10 region corresponding to the 100 combinations of the yIDs of the crystals in each block (recall that the top-layer is a 10×22 array of crystals in the y- and z-directions). Fig. 6.9b shows a close-up of one of the regions highlighted in red in Fig. 6.9a. It shows a 22×22 region holding the forward projection value of every combination of zIDs in the two blocks for a particular combination of yIDs.

![Image](image.png)

**Fig. 6.9.** (a) shows a close-up of the forward projection in the 409×409 region connecting block 0 to block 8. (b) shows a close-up of the 21×21 values inside one of the squares outlined in red.

Clearly there is a checkerboard pattern in Fig. 6.9a and b. Sets of LORs that connect special top-top or bottom-bottom crystal combinations are highlighted with black arrows. These LORs are the same LORs drawn in Fig. 6.8. These LORs are unique because they run parallel to the spacing of voxels in the image space. The checkerboard patterns continue as one moves a small distance from the black arrows in Fig. 6.8. This reflects an alternating pattern of over- and under- bias in the forward projection as the directions of the LORs deviate slightly from the directions of the LORs in Fig. 6.8. A similar but more muted pattern
exists in the forward projection between blocks 2 and 10 for LORs that are 45° to the
direction of spacing of voxels in the image space.

The reason LORs at special directions relative to the voxel spacing are biased is because the
system matrix value represents the probability of detection \textit{from a point in the centre of the voxel}. Fig. 6.10 illustrates why this causes biases in the forward projections. Consider a case
where the FOV is full of uniformly distributed activity. Fig. 6.10a shows (in gray-scale) the
local probability of detection as a function of position, calculated using (6.2) for an LOR that
crosses the FOV at an arbitrary angle. Voxels are outlined in red. If the FOV is filled
uniformly with activity, then the forward projection into that LOR is the sum of the value of
the probability function evaluated at the centre of each voxel. \textit{There is an error in calculating
the contribution from each voxel because the probability function is only sampled at the
centre of each voxel, although its value changes appreciably in each voxel}. The error may
under- or over-estimate the contribution from the activity from each voxel depending on how
the voxel aligns with the probability function. In the case where the LOR crosses the FOV at
an arbitrary angle, these errors should average out over the length of the LOR. Conversely,
when an LOR crosses the FOV in a direction parallel to the spacing of the voxels, as in Fig.
6.10b, \textit{the voxels add their activity to the forward projection consistently with the same error}. This is the origin of the checkerboard patterns in Fig. 6.9.
This type of bias at special angles (like 0°, 45° and 90°) in forward projections has been observed by other researchers [133], [134]. The issue can be solved by no longer treating the system matrix element as the probability of detection from a point at the centre of a voxel. Rather, the system matrix elements should be treated as the probability of detection from anywhere in the voxel. With reference to Fig. 6.10, the contribution to the forward projection into an LOR from any voxel should be the activity represented in that voxel times the integrated value of the probability in that voxel.

One more step should now be added to the calculation of each system matrix element where equation (6.2) is integrated over the volume of the voxel. This will be done numerically instead of analytically. For a zoom-1 reconstruction, where the voxel size is one half of the crystal pitch, equation (6.2) was calculated at each point in a 5×5×5 grid inside each voxel and averaged together. A second version of the system matrix to be used with zoom-2 reconstructions (where the voxel size is one quarter of the crystal pitch) was also calculated using a 3×3×3 grid of points inside of the voxel. The average of the probability inside each voxel was a weighted average, with weights determined according to the following rules:
• Position inside the voxel  \(\rightarrow\) weight = 1
• Position on the face of the voxel  \(\rightarrow\) weight = \(\frac{1}{2}\)
• Position on an edge where two faces meet  \(\rightarrow\) weight = \(\frac{1}{4}\)
• Position on a corner where three faces meet  \(\rightarrow\) weight = \(\frac{1}{8}\)

Such a weighting scheme was needed to prevent biasing of special LORs by a very similar mechanism as what happened before when there was no averaging at all. If all weights are set to one, it was observed that LORs running along seams between voxels were biased up because activity at the same location was being added to that forward projection bin by two or more voxels. The forward projection of the digital annular phantom using the system matrix elements that are the average of \(5 \times 5 \times 5\) sample points per voxel, each of which uses \(2500^2\) angular samples in equation (6.2), is shown in Fig. 6.11, with a close-up in Fig. 6.12.

![Visualization of the forward projection of a digital version of the annular normalization phantom. The system matrix used to compute the forward projection sampled the detection probability in each voxel 125 times to approximate an integral.](image)
Fig. 6.12. (a) shows a close-up of the forward projection between blocks 0 and 8, and (b) shows a close-up of one of the regions outlined in red in (a).

It is very hard to see any artefactual patterns in the forward projection like those seen in Fig. 6.7 and Fig. 6.9. By adjusting the colour-map to match the range of values in the forward projection only between block 0 and block 8, we can still see some very minor artefactual patterns. Fig. 6.13 shows high contrast block 0 – block 8 forward projections for the system matrix with no averaging (a), the system matrix with averaging with equal weights to all points (b), and the system matrix with weighted averaging (c).

Fig. 6.13. High contrast visualizations of the block 0 – block 8 forward projection of the annular phantom for three different versions of the system matrix. (a) uses the system matrix representing the probability of detection at the centre of each voxel, (b) uses the system matrix where 125 sampling points inside each voxel are averaged together and (c) uses the system matrix where these 125 sampling points are averaged together with a carefully chosen weight.
There is a very slight downward bias to LORs parallel with the voxel grid in the improved system matrix. Perhaps by averaging more than 125 points, this pattern would disappear. What matters is that the resulting images using the improved matrix do not show any uniformity artefact. Images of the uniformity phantom reconstructed using the improved system matrix are shown in Fig. 6.14. The images appear to be uniform as they should. Profiles through the uniformity phantom images at the four stages of algorithm improvement are shown in Fig. 6.15. Although the final improvement shows noise that is very typical of PET, no structured deviation from the mean value can be seen like in the earlier three reconstructions.

**Fig. 6.14.** Reconstructed uniformity data after the system matrix had been updated to represent the probability of detection *anywhere in the voxel* rather than from the centre of each voxel.

**Fig. 6.15.** Profiles through the centre of the central slice of the uniformity phantom at different stages of improvement of the reconstruction algorithm.
6.4 Efforts to Boost Computation Speed

The artefacts in the lower half of Fig. 6.3 were eliminated by two steps that greatly increased the computational burden of calculating the system matrix. The original reconstruction software computed the system matrix elements \textit{on-the-fly}. Based on the amount of time it took to compute a small part of the system matrix (with parallel computations running on 12 threads), it is estimated that the time to reconstruct the full field of view with 20 iterations would take in excess of a year, which is an unacceptably long period of time. Additional symmetries in the system matrix were discovered which enormously decreased the number of voxels for which unique system matrix elements need to be computed.

Inclusion of a symmetry that mirrors each voxel-LOR pair in the x-axis, as shown in Fig. 6.16a, doubled the degeneracy of each system matrix element compared to the symmetries shown in Fig. 6.2. If it is enforced that the width of a voxel in the axial direction is an integer fraction of the crystal pitch, the opportunity to exploit massive symmetries opens up. If any voxel-LOR pair is moved forward or backward by a distance equal to the crystal pitch, that voxel-LOR pair should have the same system matrix element as the original one. This is illustrated in Fig. 6.16b. When using zoom-1 only two planes of voxels out of 43 need their system matrix elements calculated, and all others are found by degeneracy. With these new symmetries accounted for, only 0.58\% of the voxels in the FOV have a unique system matrix element. For the zoom-2 matrix, only 0.74\% of voxels have a unique system matrix element.
Now that only 0.58% or 0.74% of system matrix elements need to be known to fill in the rest using symmetries, it is possible to save the system matrix to the hard-drive without taking an excessive amount of storage. The column of the system matrix corresponding to any particular voxel is mostly zeros. Instead of storing the entire column of the system matrix, a list of 32-bit floats holding only the non-zero elements is stored. In addition to this list of floats, a list of 16-bit integers is stored, holding the IDs of the LORs that have non-zero system matrix elements. The resulting system matrix takes 1.5 GB of storage space for zoom-1 and 5.8 GB for zoom-2 matrices. The reconstruction software is parallelized and compiled with OpenMP [135]. When running on twenty threads, reconstruction takes approximately 25 minutes per iteration for zoom-1 and 105 minutes per iteration for zoom-2. The reconstruction speed could be boosted even further with GPU implementation. Even though the enormous task of calculating the system matrix during reconstruction time is eliminated, the distribution of each system matrix element to all of the degenerate LORs during the forward projection, and all degenerate voxels during the back projection is still an intensive task. A GPU implementation could see each thread simultaneously spreading different system matrix elements over all of their degeneracies.

Fig. 6.16. DLO PET system shown from the front (a) and side (b). Illustration of massive degeneracies in the system matrix due to geometric symmetries. The side-view shown in b) its axial dimension exaggerated to make the illustration easier to read. A dotted line shows the axial centre of the FOV.
6.5 Reconstructed Images

The simulated microDerenzo phantom data first introduced in §2.5.2 was reconstructed using the PSF-MLEM code in order to show the resulting improvement in spatial resolution. Fig. 6.17 shows slices through the microDerenzo phantom reconstructed with FBP-3DRP (top) and 100 iterations of PSF-MLEM (bottom). The left and right columns respectively use a reconstruction zoom of 1 and 2. Fig. 6.18 shows vertical profiles through the right-most columns of 1.0 mm and 1.7 mm wide rods from the zoom-2 reconstructions.

Fig. 6.17. Reconstructons of the simulated microDerenzo phantom using FBP-3DRP (top) and PSF-MLEM (bottom). Rod diameters are 2.4, 2.0, 1.7, 1.35, 1.0, and 0.75 mm.
Both the images and profiles through the 1.0 mm rods show that image resolution benefits greatly from the PSF-MLEM reconstruction compared to FBP-3DRP.

6.6 Conclusions

In this chapter, we described how a PSF-MLEM algorithm was updated to incorporate normalization factors. Care had to be taken to ensure that these normalization factors did not account for certain geometric effects that are already inherently accounted for in the calculation of the system matrix. Even once normalization factors were included in the reconstruction algorithm, non-uniformity artefacts remained in the images.

Two steps were taken in order to correct these artefacts. The first is that the number of angular samples used to calculate the integral in equation (6.2) was increased by a factor of ~50. The second was that the meaning of the system matrix elements were changed to represent the probability of an annihilation photon pair emitted from anywhere in the volume of voxel-a being detected by LOR-b. Previously, they were defined to represent the probability of an annihilation photon pair emitted from the centre of voxel-a being detected by LOR-b. This was achieved by numerically integrating equation (6.2) over the volume of each voxel.
Both of the changes made to the reconstruction code to eliminate non-uniformity artefacts drastically increased the computational burden of reconstruction. The reconstruction code was altered so that instead of calculating system matrix coefficients on-the-fly, the system matrix was calculated once and stored to disk. Massive symmetries in the system matrix allowed for the system matrix elements to be calculated for less than 1% of the voxels in the FOV, so that the system matrix could be stored to disk.

Reconstructed simulation data of a microDerenzo phantom shows that the PSF-MLEM reconstruction code results in significantly better contrast than FBP-3DRP. Elimination of non-uniformity artefacts and the innovation that allows for the system matrix to be saved to the disk rather than being calculated on-the-fly allow for this PSF-MLEM algorithm to reconstruct real PET data in a practical time frame. This advances one of the project goals, which is to achieve high spatial resolution. Reconstructions of real PET data rather than simulation data will be shown in Chapter 7.

In addition to being beneficial for our PET insert, this PSF-MLEM algorithm could be adapted to other PET systems. Although the current implementation is tailored toward the dual-layer-offset detector block, the calculation defined by Zhang et al [128] should be able to produce an analytic method of calculating system matrix coefficients which takes into account the arbitrary geometry of whatever scanner it is applied to. The advances made in this thesis to increase the accuracy of the system matrix coefficients should be equally important when this PSF-MLEM is applied to other geometries. The method of accelerating the reconstruction time can also be adapted to other scanners assuming similar symmetries can be identified.
Chapter 7: Characterization of Prototype PET System

The prototype DLO PET system was built using two 4×4 arrays of SensL SPMArray4B analog SiPMs [136] to read out the crystal arrays. 32 analog outputs from the SiPMs that read out each block were multiplexed to four outputs using a charge division multiplexor [137]. Signals from the scanner were transmitted through HDMI cables [138] and captured/digitized with the OpenPET data acquisition system [99]. Fig. 7.1 shows images of the 16 detector modules before assembly (a), and after being assembled into a ring (b). (c) shows the PET system inside of its housing, made from carbon fibre. HDMI cables can be seen coming out of the back.

![Prototype DLO PET system images](image)

Fig. 7.1. Photographs of the prototype DLO PET system at various stages of construction. (a) shows 16 detector modules. (b) shows the 16 detector modules assembled around a ring, next to a loonie for comparison. (c) shows the assembled scanner inside of its carbon fibre housing.

After construction of the prototype DLO PET system, a number of experiments were performed in order to characterize it. The energy and timing resolution of the detectors were measured. The spatial resolution, sensitivity profile, and NECR were measured according to the NEMA NU 4-2008 protocol. To further demonstrate the image quality that the system can attain, a number of phantom and rodent images were acquired and reconstructed.

7.1 Detector Energy and Timing Resolution

A $^{68}$Ge rod (approximate activity of 37 MBq) was placed along the axial centre of the FOV and data were collected in singles mode for 10 minutes. Histograms of the detected energy (detector pulse height) were made on a per-crystal basis. Each histogram was fit using the
sum of a Gaussian and a line. Energy resolution was quantified as the FWHM of the Gaussian function divided by its mean value. The average energy resolution of all crystals in the prototype was found to be $12.50 \pm 1.80\%$ [136].

The timing resolution was measured by placing a $\sim 10$ MBq $^{18}$F source in the centre of the FOV and acquiring data long enough to record $\sim 5$ million coincidences within a coincidence window of 25 ns. A histogram of the time stamp difference was created and is shown in Fig. 7.2. A function made from the sum of a Gaussian and a line was fit to the data. The FWHM of the Gaussian was found to be 7.6 ns. Note that 7.6 ns represents the coincidence resolving time, and compounds the uncertainties in both detectors that recorded each coincidence. The singles resolving time is therefore 5.4 ns (reduced by a factor of the square root of two).

![Histogram of time-stamp differences. Data are shown in blue, with a least-squares fit (Gaussian plus a line) shown in red.](image)

**Fig. 7.2.** Histogram of time-stamp differences. Data are shown in blue, with a least-squares fit (Gaussian plus a line) shown in red.

### 7.2 Spatial Resolution

A 125 kBq 0.25 mm diameter spherical $^{22}$Na source, embedded in a 1 cm wide acrylic cube, was placed on a motorized stage and imaged at radial offsets of 0, 5, 10, and 15 mm at both the axial centre of the FOV, and at one quarter of the distance between the axial centre and the edge of the scanner. Data were collected for 5 minutes per position. FBP-3DRP reconstructions were done according to the procedure outlined in §5.4. Zoom-4 was used for the image reconstructions so that the FWHM of each point spread function would span at least four voxels, as is required by the NEMA NU 4-2008 protocol.
For visualization, images of the four point sources at the axial centre were superimposed and are shown in Fig. 7.3. The FWHM and FWTM of each point source image were measured according to the NEMA NU 4-2008 protocol in the three orthogonal directions. FWHM and FWTM along with the volumetric resolution are summarized in Table 7.1 (axial centre of the FOV) and Table 7.2 (¼ axial offset). Volumetric resolution is defined as the product of the FWHM in the three orthogonal directions. Resolution is plotted as a function of radial offset in Fig. 7.4 (value plotted is the average between the resolution measured at the axial centre and at ¼ of the axial offset).

Fig. 7.3. Reconstructed images of the $^{22}$Na point source located at 0, 5, 10, and 15 mm from the radial centre of the PET scanner (shown from left to right in this image). Note that images were reconstructed and analyzed independently, and were only added together for visualization in this figure.

<table>
<thead>
<tr>
<th>Offset [mm]</th>
<th>FWHM [mm]</th>
<th>FWTM [mm]</th>
<th>Vol. Res. [µL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.17</td>
<td>1.36</td>
<td>1.35</td>
</tr>
<tr>
<td>5</td>
<td>1.27</td>
<td>1.30</td>
<td>1.45</td>
</tr>
<tr>
<td>10</td>
<td>1.53</td>
<td>1.38</td>
<td>1.49</td>
</tr>
<tr>
<td>15</td>
<td>1.86</td>
<td>1.49</td>
<td>1.46</td>
</tr>
</tbody>
</table>

Table 7.1. Summary of point source reconstruction widths at the axial centre of the scanner.

<table>
<thead>
<tr>
<th>Offset [mm]</th>
<th>FWHM [mm]</th>
<th>FWTM [mm]</th>
<th>Vol. Res. [µL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.23</td>
<td>1.41</td>
<td>1.23</td>
</tr>
<tr>
<td>5</td>
<td>1.27</td>
<td>1.37</td>
<td>1.30</td>
</tr>
<tr>
<td>10</td>
<td>1.56</td>
<td>1.46</td>
<td>1.45</td>
</tr>
<tr>
<td>15</td>
<td>1.87</td>
<td>1.53</td>
<td>1.50</td>
</tr>
</tbody>
</table>

Table 7.2. Summary of point source reconstruction widths at a ¼ axial offset.
Fig. 7.4. (a) shows the point source reconstruction width (FWHM and FWTM) as a function of radial offset. (b) shows the volumetric resolution as a function of radial offset.

### 7.3 Sensitivity

Sensitivity, defined as the fraction of annihilations detected by the PET scanner, was measured as a function of position along the axis of the scanner. The same $^{22}$Na source used to measure resolution was stepped along the axis of the PET scanner with a step size of 0.635 mm (half the crystal pitch) using a motorized stage, with 30 s of data acquired at each position. Each acquisition was processed to identify coincidences and create randoms-corrected sinograms according to the procedure specified in §5.2. In accordance with NEMA NU 4-2008, all bins in each sinogram within 10 mm from the centre of the FOV were summed to yield the number of true coincidences at each bed position. The number of trues was divided by the expected number of annihilations during the acquisition period (activity $\times$ scan duration $\times$ branching ratio for $e^+$ decay for $^{22}$Na) to yield the sensitivity. Sensitivity as a function of source position is plotted in Fig. 7.5.
7.4 Noise Equivalent Count Rate

The NEMA NU 4-2008 mouse equivalent phantom was filled with approximately 40 MBq of ¹⁸F and was positioned in the centre of the FOV of the PET scanner. Data were collected for periods of 10 minutes once per hour for 14 hours. Data from each acquisition were histogrammed into sinograms for both prompt and delayed coincidences using the procedure detailed in §5.2. Rates of trues, scatters, and randoms were calculated from the sinograms according to the procedure defined in the NEMA NU 4-2008 protocol. NECR was then calculated according to equation (1.25), using a value of $k = 2$. NECR as a function of the average activity for the duration of each scan is plotted in Fig. 7.6. Rates of true, scattered, random, and prompt coincidences are plotted in addition to NECR.

In order to report the maximum NECR, a ⁴th-degree polynomial was fit to the NECR data to interpolate NECR between the measured values. From this fit, it was determined that a peak
NECR of 20.8 kcps was reached at an activity of 14.5 MBq, and the NECR at 3.7 MBq was 11.1 kcps.

7.5 Phantom Images
Two phantoms were scanned in the prototype PET insert. The first one was the image quality phantom described in the NEMA NU 4-2008 protocol. The image quality phantom is a 58 mm long and 33.5 mm wide Lucite cylinder with three distinct sections that are filled with activity. The first section contains five 20 mm long cylinders with widths of 1, 2, 3, 4, and 5 mm. The second section is a large cylindrical cavity 18 mm long and 30 mm wide. The third section is a 15 mm long extension of the cylindrical cavity with two smaller cylindrical ‘cold inserts’. Each cold insert is 15 mm long with an outer diameter of 10 mm. One is filled with air and the other is filled with non-radioactive water. Not only does this phantom give a visually intuitive sense of the image quality that the PET system can produce, it also facilitates quantitative measurements of image uniformity, recovery coefficients, and spill-over ratios once the data are reconstructed.

Because the phantom is longer than the axial FOV, it was scanned in three bed positions. The motorized stage previously described allowed for the phantom to be moved between bed positions in precise intervals. Data acquisition began with 8.6 MBq of $^{18}$F in the phantom. The section of the phantom with the rod inserts was scanned for 20 minutes. The phantom was then moved 20 mm forward to scan the uniformity section for 20 minutes. Following this, the phantom was moved another 20 mm forward to scan the cold-insert section. The phantom was then moved back to its original position for each scan to be repeated three more times.

The four data sets from each bed position were appended together. Following this data were reconstructed with both FBP-3DRP (following the procedure outlined in §5.4) and the PSF-MLEM algorithm described in Chapter 6. The numbers of true and random coincidences acquired for each bed position are summarized in Table 7.3. Both FBP-3DRP and PSF-MLEM reconstructions used a zoom of 1, resulting in $67 \times 67 \times 43$ images with voxel size
equal to $0.635 \times 0.635 \times 0.635$ mm$^3$. Cross sections through the three sections of the phantom reconstructed with both FBP-3DRP and the PSF MLEM are shown in Fig. 7.7.

<table>
<thead>
<tr>
<th>Section</th>
<th>1 - Hot Rods</th>
<th>2 - Uniformity</th>
<th>3 – Cold Inserts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net Trues (millions)</td>
<td>19</td>
<td>110</td>
<td>80</td>
</tr>
<tr>
<td>Randoms (millions)</td>
<td>5.5</td>
<td>7.9</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Table 7.3. Number of net true (prompt minus random) and random coincidences acquired in each bed position during scanning of the NEMA IQ Phantom.

![Reconstructions of the NEMA IQ Phantom](image)

Fig. 7.7. Reconstructions of the NEMA IQ Phantom. The top row shows FBP reconstructions, while the bottom row shows PSF-MLEM reconstructions. The right, middle and left columns respectively show the hot-rod section, uniformity section, and cold-insert section of the phantom.

Uniformity is quantified by reporting the maximum, minimum, average, and standard deviation of the reconstructed activity inside of a 22.5 mm wide and 10 mm long cylindrical region of interest centred on the uniformity region. Results of the uniformity analysis are shown in Table 7.4. Lack of deadtime correction precludes the calculation of the recovery coefficients and spill-over ratios. The recovery coefficients are measured by dividing the
mean activity measured along the axis of each insert and dividing by the mean activity in the uniformity region. The spill-over ratios are measured by dividing the mean activity in each of the cold inserts by the mean activity in the uniformity region. Because different levels of deadtime effect the acquisition differently at each bed position, PET image values from each of the three sections cannot be compared quantitatively. The acquisition began with 8.6 MBq in the phantom. The NECR curve shows that the trues rate is not linear with activity at such a high activity, so deadtime has a significant effect over the range of activity during the acquisitions. Image quantification is currently being investigated by another collaborator.

<table>
<thead>
<tr>
<th></th>
<th>Maximum</th>
<th>Minimum</th>
<th>%STD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBP-3DRP</td>
<td>127%</td>
<td>58%</td>
<td>7.6%</td>
</tr>
<tr>
<td>PSF-MLEM</td>
<td>123%</td>
<td>76%</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

Table 7.4. Maximum, minimum, and standard deviation of values in uniformity region (all as a percentage of the mean value).

The second phantom that was imaged was a Derenzo phantom. This phantom will be referred to a nanoDerenzo phantom in this thesis. This name is meant to distinguish it from the microDerenzo phantom that was simulated and reconstructed in Chapter 2. The nanoDerenzo phantom contains six sets of rods each 12 mm long. The diameters of the rods in each section are 1.5, 1.2, 1.0, 0.9, 0.8, and 0.7 mm. The edge-to-edge distance between adjacent rods in each section is equal to the rod diameter. With an initial activity of 8.7 MBq of $^{18}$F, data were acquired for 60 minutes, resulting in 199.7 million net trues and 13.5 million randoms. Data were histogrammed and reconstructed in the same manner as for the NEMA image quality phantom. In addition to zoom 1 reconstructions, reconstructions were also performed with zoom 2. The resulting zoom-2 image dimensions were $133 \times 133 \times 43$ (0.3175×0.3175×0.635 mm$^3$ voxels) for the FBP-3DRP reconstruction, and $133 \times 133 \times 87$ (0.3175×0.3175×0.3175 mm$^3$ voxels) for the PSF-MLEM reconstruction. Slices through the nanoDerenzo phantom reconstructed with both FBP-3DRP and PSF-MLEM and both zoom 1 and zoom 2 are shown in Fig. 7.8. Profiles through the right-most column of 1.0 mm inserts were taken through the zoom-2 images, and are shown in Fig. 7.9.
Fig. 7.8. Reconstructions of the nanoDerenzo phantom. The top row shows FBP reconstructions, while the bottom row shows PSF-MLEM reconstructions. The right column and left columns respectively show zoom-1 / zoom-2 reconstructions. The diameter of the rods in the six sections are 1.5, 1.2, 1.0, 0.9, 0.8, and 0.7 mm.

Fig. 7.9. Profiles through the right-most column of the 1.0 mm rods of the nanoDerenzo phantom.
As expected, the zoom-2 reconstructions outperform the zoom-1 reconstructions in terms of resolving the smaller rods. The resolution is much better when using the PSF-MLEM algorithm compared with FBP-3DRP. This is evident in both the reconstructed images, and also the profiles shown in Fig. 7.9. All six sections are clearly resolved in the zoom-2 PSF-MLEM reconstruction. In the zoom-2 FBP-3DRP reconstruction, the smallest rods that can be fully resolved are the 1.0 mm rods. Here fully resolved means that each rod appears as a distinct peak in the image. The profiles in Fig. 7.9 show a much larger peak to value ratio between adjacent rods when the PSF-MLEM code is used.

### 7.6 Rodent Images

This section shows images of six mice and one rat scanned after intraperitoneal injection of $^{18}$F-FDG. These animals were scanned with the PET scanner installed inside of the 7T Bruker Avance III MRI in the Health Science Centre in Winnipeg. MR images were acquired simultaneously with the PET data. All PET data were processed and reconstructed in the same manner as the phantom studies earlier in this chapter. Details of each scan are shown in Table 7.5.

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial Activity (MBq)</th>
<th>Scan Duration (min)</th>
<th>Net Trues (millions)</th>
<th>Randoms (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse 1</td>
<td>3.1</td>
<td>30</td>
<td>8.9</td>
<td>0.96</td>
</tr>
<tr>
<td>Mouse 2 (brain)</td>
<td>3.6</td>
<td>20</td>
<td>7.6</td>
<td>0.39</td>
</tr>
<tr>
<td>Mouse 2 (heart)</td>
<td>3.2</td>
<td>10</td>
<td>4.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Mouse 3</td>
<td>5.2</td>
<td>20</td>
<td>10.9</td>
<td>0.47</td>
</tr>
<tr>
<td>Mouse 4</td>
<td>4.1</td>
<td>20</td>
<td>6.03</td>
<td>0.28</td>
</tr>
<tr>
<td>Mouse 5</td>
<td>5.8</td>
<td>20</td>
<td>11.3</td>
<td>0.70</td>
</tr>
<tr>
<td>Mouse 6</td>
<td>6.9</td>
<td>20</td>
<td>13.7</td>
<td>0.77</td>
</tr>
<tr>
<td>Rat</td>
<td>14.8</td>
<td>30</td>
<td>18.7</td>
<td>1.27</td>
</tr>
</tbody>
</table>

Table 7.5. Details of the seven rodent scans used to produce images for this chapter.

Shown in Fig. 7.10 are maximum intensity projection images (which project through the reconstructed image) through “Mouse 1” for both FBP-3DRP and PSF-MLEM (21 iterations). “Mouse 1” was reconstructed using zoom-2. The image extends from the mouse’s
heart at the left side to the nose at the right side. Blue lines indicate the location of slices that are shown individually in Fig. 7.11. These slices show the heart, thorax, and head. Fig. 7.12 shows the PSF-MLEM PET images fused with the MRI images that were acquired simultaneously. The MR image was acquired using a HASTE sequence, which resulted in a $128 \times 128 \times 53$ (0.3175\times0.3175\times0.635 mm$^3$ voxels) T2 weighted image. The PET/MR fusion images show alignment between the morphology of the PET and MR images. There was very little FDG uptake in the brain. The PET/MR fusion of the ‘head’ image show that the regions of high-uptake are outside of the brain altogether and are in-fact the Hardarian glands.

Fig. 7.10. Maximum intensity projection images through “Mouse 1” in both the sagittal and coronal directions. The two images on the left were reconstructed with FBP-3DRP, while the images on the right were reconstructed with PSF-MLEM. Blue lines indicate the position of the transaxial planes shown in Fig. 7.11.
Fig. 7.11. Slices through the PET image of “Mouse 1” showing the heart, thorax, and brain from left to right. The top/bottom rows show reconstructions with FBP-3DRP / PSF-MLEM.

Fig. 7.12. Stand-alone MRI images of “Mouse 1” are shown on the top row. The bottom row shows PET/MR fused images, with MRI images represented with a gray colour-map, and PET images represented with a red/orange colour-map.
Profiles were measured through the FBP-3DRP and PSF-MLEM reconstructions of the mouse heart in the vertical direction, and are shown in Fig. 7.13. Like the profiles through the nanoDerenzo phantom, they again show that the PSF-MLEM reconstruction produces higher contrast images than FBP-3DRP.

![Graph showing profiles through the mouse heart](image)

**Fig. 7.13. Profiles through the mouse heart.**

The remaining images in this chapter were reconstructed with zoom-1. “Mouse 2” was scanned in two different positions, one centred on the brain and the other on the heart. Fig. 7.14 shows reconstructions of the brain. Reconstructions using FBP-3DRP and 21 iterations of PSF-MLEM are respectively shown at the top and bottom of the figure. Slices through the centre of the brain are shown on the left. Maximum intensity projections in the sagittal and coronal directions are respectively shown in the centre and right-side of the figure. In contrast to “Mouse 1”, this mouse shows a clear pattern of FDG uptake in the brain. The PSF-MLEM reconstruction shows clear separation between the cortex of the brain (the outer surface) and the ganglia at the centre. This amount of detail did not show in the FBP-3DRP reconstruction. Fig. 7.15 shows the PSF-MLEM reconstruction fused with the HASTE MR image that was acquired simultaneously with the PET data. A surface coil was used instead of the volume coil that was used for “mouse 1”. Because of this, only the top of the head appears in the MR image. The PET/MR fusion confirms that the structure seen in the PET image is indeed the separation between the cortex and ganglia.
Fig. 7.14. PET reconstructions of brain of “Mouse 2” done with FBP-3DRP (top) and PSF-MLEM (bottom). Images from left to right show a slice through the brain, and maximum intensity projections in the sagittal and coronal directions.

Fig. 7.15. Fused PET and MRI images of the brain of “Mouse 2”.

Fig. 7.16 shows PET reconstructions centred on the heart of “Mouse 2”. Reconstructions using FBP-3DRP and 21 iterations of PSF-MLEM are respectively shown at the top and bottom of the figure. Slices through the centre of the heart are shown on the left.
Maximum intensity projections in the sagittal and coronal directions are respectively shown in the centre and right-side of the figure. Because the surface coil could not be repositioned over the abdomen of the mouse between scans, no MR images are available to complement the PET data. The heart is clearly visible in PET images of both types of reconstructions, but is shown with much higher contrast in the PSF-MLEM reconstruction, as expected. The maximum intensity projections show many details such as the heart, spine, and arms.

Fig. 7.16. PET reconstructions of abdomen of "Mouse 2" done with FBP-3DRP (top) and PSF-MLEM (bottom). Images from left to right show a slice through the brain, and maximum intensity projections in the sagittal and coronal directions.

Fig. 7.17 shows slices through the PSF-MLEM reconstructions of the brains of mice 3 to 6. Each zoom-1 reconstruction used 21 iterations and is cropped to a 31×31 mm² (49×49 pixels) image. These images show that the prototype DLO PET system can
consistently produce mouse images showing structure within the brain; these images all show separation between FDG uptake in the cortex and ganglia.

Fig. 7.17. Reconstructions of four mice brains using 21 iterations of PSF-MLEM with zoom-1.

Fig. 7.18 shows PET reconstructions of the rat brain. The rat was imaged with its brain centred in the FOV. Zoom-1 FBP-3DRP and PSF-MLEM (21 iterations) images are presented in the same manner as for “Mouse 2”. Contrast between the cortex and ganglia are visible in both images, albeit with much better contrast in the PSF-MLEM reconstruction. Fig. 7.19 shows the PET/MR fusion. The MR image was once again a HASTE acquisition with 128×128×53 voxels with a size of 0.3175×0.3175×0.635 mm³.
Fig. 7.18. PET reconstructions of the rat brain done with FBP-3DRP (top) and PSF-MLEM (bottom). Images from left to right show a slice through the brain, and maximum intensity projections in the sagittal and coronal directions.

Fig. 7.19. Fused PET and MRI images of the rat brain.
7.7 Discussion and Conclusion

Experiments were performed to characterize the prototype DLO PET system. The average energy and singles timing resolution of the detectors was found to be 12.5% and 5.4 ns FWHM. The spatial resolution, expressed as the width of a reconstructed point source, was quantified throughout the FOV. In the axial centre, the radial resolution varied from 1.17 mm at the radial centre to 1.86 mm at a 15 mm radial offset, while the volumetric resolution varied from 2.15 mm to 4.06 mm. Using an energy window of 300 to 800 keV, a peak sensitivity of 2.2% was measured. The NECR for a mouse-sized phantom was found to peak at 20.8 kcps at an activity of 14.5 MBq. The NECR at 3.7 MBq was found to be 11.1 kcps.

Goertzen et al [139] makes an extensive summary of the characteristics of a number of widely used small animal PET systems: the Siemens microPET family (P4, R4, Focus 120, and Focus 220), the Siemens Inveon, the ClearPET, the Mosaic HP, the Argus, the VrPET, the LabPET 8, and the LabPET 12. His findings will be used for comparison to our PET system. The radial resolution of the prototype DLO PET scanner outperforms all of these scanners at the radial centre of the FOV. As predicted by the simulation data, the reconstructed resolution drops off quickly as one moves off centre, and is outperformed by the Argus, VrPET, and microPET Focus 220 at a 15 mm offset. Resolution degrades off centre in our system much faster than in the other systems because our scanner diameter is much smaller. A smaller diameter means that after a small radial offset, annihilation photons see the detectors at a relatively larger angle compared to other scanners, which results in more severe image parallax. Very recent reports of a small animal MR compatible PET insert from a group at the Seoul National University College of Medicine in Seoul, South Korea, report a volumetric resolution of 1.92 µL at the radial centre of the FOV, degrading to 7.27 µL at a 14 mm offset. The design of the scanner is very similar to the prototype DLO PET system described in this thesis: blocks made from 1 mm long LYSO crystals spaced with a 1.28 mm pitch were repeated around a ring with a diameter of 64 mm and length of 55 mm [140]. The volumetric resolution at the centre of the FOV is not surprisingly very similar to what
we measured (2.15 µL). Because the Seoul group does not use a depth of interaction capable detector block, the resolution degrades much more rapidly than our PET system (which has a volumetric resolution of 4.24 µL at a 15 mm radial offset).

The NECR performance of our prototype PET system is very low compared to the scanners in Goertzen et al [139] (direct comparisons are difficult to make, because different energy windows were used). The PET insert built by the group from the Seoul National University College of Medicine, has a peak NECR of 42.41 kcps at 15.03 MBq (although using a slightly different energy window: 250 – 750 keV). The prototype system that we built used only one ring of detector blocks resulting an a relatively short (28 mm) axial FOV, and so NECR is understandably low due to the low solid angle subtended by the detectors. Future versions will use two or three rings of similar detector blocks. The higher solid angle will lead to substantially better count rate performance.

The results presented in this chapter match fairly well the predicted system performance from Monte-Carlo simulations in Chapter 2, although discrepancies exist. Fig. 7.20 shows the resolution in the three orthogonal directions determined from both measured and simulation data. The measured axial resolution is consistently better by approximately 0.1 mm. The general trend in the radial and tangential resolution is the same for both the measured and simulated data and at some radial offsets, the measured and simulated data match very well. Fig. 2.10 and Fig. 7.3 show that the reconstructions of simulated and measured point source data contained streak artefacts. These streak artefacts likely effect the measurement of the point source widths, which could explain part of the discrepancy. These streaks are especially prominent for the point source reconstructions for the measured data (Fig. 7.3).
Fig. 7.20. Comparison between the widths of reconstructed simulated and measured point source data.

The measured and simulated NECR have good agreement in their values at 3.7 MBq (11.1 kcps measured versus 12.2 kcps simulated). The NECR simulations presented here also have good agreement in the peak value and peak activity, but that is because the deadtime model of the simulations was adjusted to match the measurements for that particular count rate. At activities past the peak NECR, the measurements deviate from the simulations. As was stated in §2.5.4, the effects that contribute to detector deadtime in the prototype DLO PET system are quite complicated, and so could not have been adequately modeled in GATE.

A number of factors contribute to detector deadtime. The back-end electronics that readout each detector block take 1.2375 µs to process each single that they read. As soon as that single has been processed they are able to process another event. This creates a block-level non-paralyzable deadtime of 1.2375 µs. Additional deadtime occurs in the front-end of the PET detector blocks. Each block can trigger a readout when one of four analog outputs passes from below to above a predefined threshold (which was configured to 30 mV for the measurements presented in this thesis). The analog signal cannot trigger a second readout until it is allowed the time to drop below the threshold. This should create paralyzable deadtime. These outputs are the four analog outputs used to define an Anger-logic coordinate, as described in §1.5. Because the height of these pulses is proportional to the energy deposited in the detector array, the time over threshold, and therefore the deadtime,
has an energy dependence. To complicate things further, the relative height of each pulse depends on the position within the block where an annihilation photon interacts, as shown in Fig. 7.21. In this example, the block would be able to record the interaction of an annihilation photon in the bottom-right side of the block sooner than it would be able to record the interaction of one in the top-left corner of the block. In this way, regions of the block are paralyzed for variable amounts of time that depend on both the location(s) of interaction and the deposited energy.

Fig. 7.21. Illustration of the four analog outputs following the interaction of an annihilation photon in the detector array. (a) shows the crystal array. The point of interaction is marked with a yellow circle. The four analog outputs are marked with colour-coded lines, which match with plots of the analog outputs from those lines in (b).

The reconstructions of the NEMA image quality phantom show that the spatial resolution is high enough to resolve all five rods (diameters are 1, 2, 3, 4, and 5 mm). No aberrant uniformity artefacts are present in the uniformity region, and the uniformity is 7.6 / 5.6% when using FBP-3DRP / PSF-MLEM reconstruction. It should be noted that the activity in the phantom was much more than 3.7 MBq, which is prescribed by NEMA NU 4-2008, and the scan time was 240 minutes instead of 20 minutes. Because our system is still in the prototype stage and has a very low count rate, it was decided to deviate from the NEMA NU 4-2008 protocol in order to gather sufficient counts to form a good image.
A nanoDerenzo phantom was scanned in the centre of the FOV. Image quality improves significantly by using the PSF-MLEM reconstruction rather than FBP-3DRP. Further improvement is seen when using zoom-2 rather than zoom-1. The zoom-2 PSF-MLEM reconstruction is able to resolve all of the rods in the nanoDerenzo phantom (the smallest of which are 0.7 mm in diameter).

A number of rodents were scanned in the PET scanner. Resolution is sufficient to see organs such as the brain and heart in $^{18}$F-FDG scans of the mice and rat. The PSF-MLEM reconstruction enhances image quality enough so that substructures in the mouse and rat brains (cortex and ganglia) become visible. A number of these acquisitions were made simultaneously with MRI. Where MRI images are available, the PET data are presented fused with the MRI. The MRI provides an excellent anatomical backdrop for the PET data. A detailed study of the interference between the PET and MRI systems is beyond the scope of this thesis. Very little interference was detected, as reported in [141].
Chapter 8: Summary

This thesis has presented work contributing to the design and characterization of a small animal MR compatible PET insert for simultaneous PET/MR imaging. The PET insert was designed to fit within the 114 mm inner diameter of the Bruker BGA-12S gradient coil installed in a 7T Bruker Avance III MRI. The inner diameter of the PET system needed to be large enough to accommodate the 60 mm wide Bruker 35 mm RF volume coil. The insert was built using dual-layer offset detector blocks to mitigate the parallax effect, which is a well-known phenomenon that degrades off-centre spatial resolution in reconstructed PET images.

In Chapter 2 Monte-Carlo simulations of the PET system were created using GATE, which is a widely used simulation tool for PET and SPECT. The raw data from the GATE simulations was post-processed to more accurately mimic crystal mispositioning due to intercrystal scatter. The simulations were used to predict the spatial resolution and resolution uniformity, as well as the peak sensitivity and noise equivalent count rate. Comparison to the reconstructed resolution of an otherwise identical system with single-layer detector blocks showed that the dual-layer offset detector design was effective in reducing the off-centre resolution degradation.

In Chapter 3 a prototype PET detector block made from a dual-layer offset crystal block read out by an array of digital photon counters was characterized in terms of its energy resolution, timing resolution and rates of count loss. The characterization was made in terms of device settings such as trigger scheme, inhibit fraction, and use of RTL-refresh. It was found that timing resolution and the rate of count loss from incomplete neighbor-logic varied significantly with trigger scheme, inhibit fraction, and use of RTL-refresh. The opposing behaviour of timing resolution and count loss fraction made it difficult to say what combination of device settings results in the best performance for a small animal PET system such as ours.

In Chapter 4 Monte-Carlo simulations were created to determine what combination of device settings of the DPC PET detector block resulted in the best NECR performance. Monte-Carlo simulations of an acquisition using the NEMA mouse-equivalent NECR phantom were run to collect PET data for 2-ring and 6-ring scanners made using simulated versions of detector block
incorporating the DPC array. The same data set was post-processed many times to mimic the detector characteristics for every combination of device settings explored in the characterization of the DPC array. From these simulated NECR curves, the most appropriate combination of device settings were identified, based on which combination produced NECR curves with both high NECR at 3.7 MBq and high peak NECR.

Chapter 5 described the methods by which raw PET data were prepared for reconstruction with filtered back projection. A method of estimating normalization data using a component based normalization method was described. Following this, it was described how PET data were sorted into sinograms and how gaps in those sinograms, caused by gaps between detector blocks, were filled. Histogramming into a sinogram requires knowledge of the position of each LOR. A novel technique was developed to estimate the position of each LOR using data from a Monte-Carlo simulation was developed. Although this technique did not impact PET image quality for the prototype DLO PET system, it did have a positive impact on images from the Siemens microPET Focus 120 small animal PET scanner.

Chapter 6 described improvements made to a LOR-based PSF-MLEM reconstruction algorithm designed for our prototype DLO PET system. Normalization data were included in such a way as to not account for certain geometric factors inherently modelled by the PSF-MLEM algorithm. To remove non-uniformity artefacts that remained after normalization, further changes were made to increase the accuracy of the system matrix. These changes removed non-uniformity artefacts, but at the cost of extremely long reconstruction time. By exploiting massive symmetry in the system matrix, we were able to create a method to save the system matrix to the hard-drive rather than calculating its values on-the-fly. This allowed image reconstruction to proceed in a more manageable timeframe.

Chapter 7 provided a characterization of the prototype DLO PET system in terms of energy resolution, timing resolution, spatial resolution and resolution uniformity, sensitivity, noise equivalent count rate, and image uniformity. Reconstructed images of the NEMA image quality phantom, a nanoDerenzo phantom, a number of mice, and a rat were also shown. These images
were reconstructed with both filtered back projection and point spread function modelling maximum likelihood / expectation maximization. Rodent imaging was done simultaneously with MRI. Fused PET and MRI images showed good alignment between morphology.

Chapter 7 concludes the project by demonstrating that the system that we built matched our design goals. Measurements of spatial resolution matched very well the predicted spatial resolution described in Chapter 2. The PSF-MLEM reconstruction algorithm originally developed by Zhang et al [128] and further developed as described in Chapter 6 proved to significantly enhance image quality when used on measured phantom and animal PET data as demonstrated in Chapter 7. Most importantly, our rodent studies show that the performance of our PET system does not seem to be affected by the strong magnetic field of the Bruker 7T Avance III MRI system and is thus capable of producing excellent quality simultaneous PET/MR images. Intermodality interference has been further studied in detail by our collaborator J.D. Thiessen, who has shown very minimal detrimental effect of either modality on the other. We believe that once in routine operation, the PET insert system that we have developed will be a valuable contribution to medicine in the context of preclinical research using small animals.
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