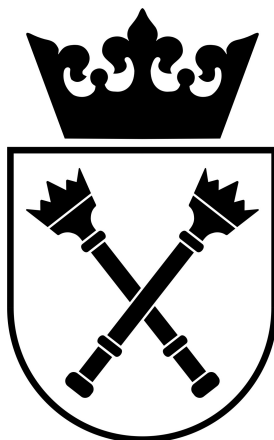


DOCTORAL DISSERTATION  
FACULTY OF PHYSICS, ASTRONOMY AND APPLIED COMPUTER  
SCIENCE  
JAGIELLONIAN UNIVERSITY, KRAKÓW, POLAND



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Development of Metabolic and Positronium Lifetime  
Imaging with the Modular J-PET Scanner

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## Oświadczenie

Ja, niżej podpisany Manish Das (nr indeksu: 1200461), doktorant Wydziału Fizyki Astronomii i Informatyki Stosowanej Uniwersytetu Jagiellońskiego, oświadczam, że przedłożona przeze mnie rozprawa doktorska pt. „Rozwój obrazowania metabolicznego oraz obrazowania czasu życia pozytonium przy użyciu modułowego skanera J-PET” jest oryginalna i przedstawia wyniki badań wykonanych przeze mnie osobiście, pod kierunkiem prof. dr hab. Pawła Moskala oraz dr. Sushil Sharma. Pracę napisałem samodzielnie.

Oświadczam, że moja rozprawa doktorska została opracowana zgodnie z ustawą o prawie autorskim i prawach pokrewnych z dnia 4 lutego 1994 r. (Dz.U. 1994 nr 24 poz. 83 z późn. zm.).

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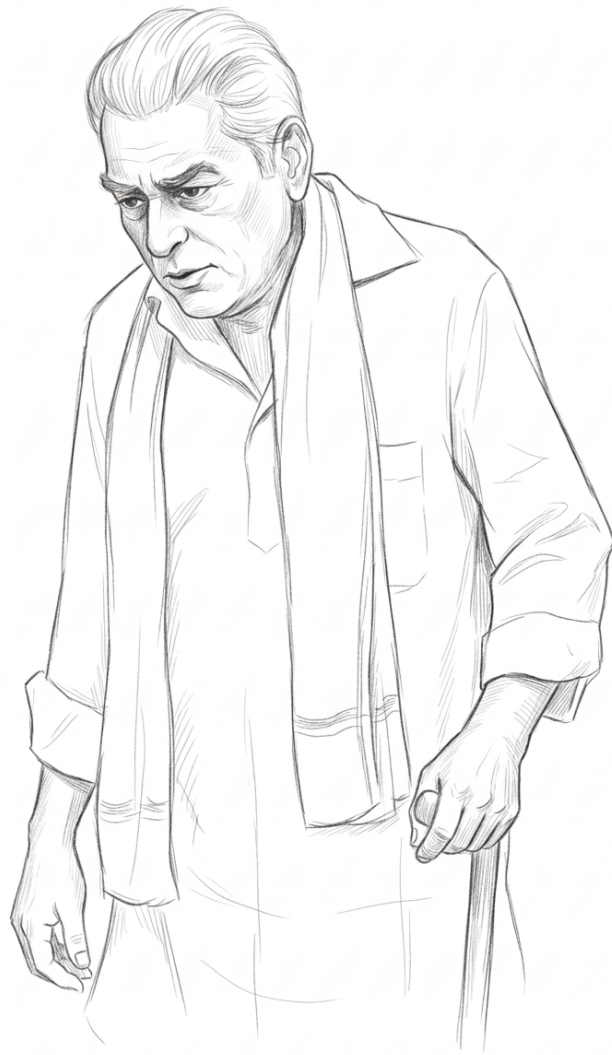
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*In loving memory of my grandfather*

**śp. Krishnachandra Das**

*“Watching our grandchildren study is more fulfilling than visiting a Tirth (pilgrimage site)”*





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# Abstract

This thesis presents the development and evaluation of two-gamma metabolic PET imaging and Positronium Lifetime Imaging (PLI) using the Modular J-PET scanner, the first PET scanner based on plastic scintillator. Its modular, lightweight, and cost-effective design, combined with triggerless data acquisition, enables both conventional metabolic imaging and PLI.

The first part focuses on two-gamma coincidence PET imaging, including the data processing and image reconstruction framework. Three dedicated correction techniques were developed: a CT-based bilinear transformation for attenuation correction, a delayed time-window method for random correction, and a Monte Carlo-based method for scatter correction. These techniques were validated using a NEMA Image Quality (IQ) phantom measurement, where qualitative and quantitative assessments demonstrated comprehensive improvements in background uniformity, shape recovery, and contrast, along with a reduction in residual lung error and material artifacts. The methods were subsequently applied to the first clinical trials at Krakow and Warsaw Medical Hospitals, where semi-quantitative analysis using activity concentration ratios (ACR) showed good agreement between the Modular J-PET and commercial PET/CT scanners.

The second part addresses the development of PLI. PLI exploits the fact that  $\sim 40\%$  of positrons form a positronium (Ps) atom before annihilation and the lifetime shortening of the ortho-positronium (o-Ps) serve as a complementary tissue-microenvironment biomarker. However, implementing PLI requires  $\beta^+$  radionuclides emitting an additional prompt gamma photon as a Ps formation timestamp. However, standard clinically used isotopes ( $^{68}\text{Ga}$ ,  $^{82}\text{Rb}$ , and  $^{124}\text{I}$ ) have low prompt gamma yields. This work presents the first experimental demonstration of PLI using three novel  $\beta^+ + \gamma$  emitters:  $^{44}\text{Sc}$ ,  $^{55}\text{Co}$ , and  $^{52}\text{Mn}$ , in phantom studies.  $^{44}\text{Sc}$  emerges as the optimal candidate due to its high  $\beta^+ + \gamma$  branching ratio ( $\sim 94\%$ ).  $^{55}\text{Co}$  is a strong secondary candidate, yielding a superior peak-to-background ratio ( $\sim 133$ ) compared to  $^{52}\text{Mn}$  ( $\sim 87$ ). Finally, clinical feasibility of PLI was evaluated in patients administered with  $^{68}\text{Ga}$ -DOTA-TATE, revealing organ-specific variations in mean positron lifetime between the patients despite the low prompt gamma yield of  $^{68}\text{Ga}$ .

These studies demonstrate that plastic-scintillator-based J-PET scanner is capable of performing metabolic imaging, which represents an important step toward the next-generation cost effective Total-Body J-PET. The planned 2.5 m long axial field-of-view scanner is expected to enhance sensitivity, enabling faster scans, lower radiation doses, and broader clinical application of PLI as a biomarker for disease assessment and characterization.





# Streszczenie

W niniejszej rozprawie doktorskiej przedstawiono rozwój oraz ewaluację dwukwantowego metabolicznego obrazowania PET oraz obrazowania czasu życia pozytonium (PLI) z wykorzystaniem modularnego skanera J-PET, pierwszego skanera PET opartego na scyntylatorach plastikowych. Jego modułowa, lekka i ekonomiczna konstrukcja, w połączeniu z beztriggerowym systemem zbierania danych, umożliwia zarówno konwencjonalne obrazowanie metaboliczne, jak i PLI.

Pierwsza część pracy skupia się na dwukwantowym obrazowaniu PET w układzie koincydencji, w tym na strukturze przetwarzania danych i rekonstrukcji obrazu. Opracowano trzy dedykowane techniki korekcyjne: transformację dwuliniową opartą na badaniu CT do korekty tłumienia, metodę opóźnionego okna czasowego do korekty koincydencji przypadkowych oraz metodę opartą na symulacjach Monte Carlo do korekty rozproszeń. Techniki te zostały zweryfikowane za pomocą pomiarów fantomu jakości obrazu NEMA (IQ), gdzie ocena jakościowa i ilościowa wykazała wszechstronną poprawę jednorodności tła, odtworzenia kształtu i kontrastu, a także redukcję błędu szczątkowego w obszarze płuc oraz artefaktów materiałowych. Metody te zastosowano następnie w pierwszych badaniach klinicznych w szpitalu medycznym w Krakowie i Warszawie, gdzie analiza półilościowa z wykorzystaniem współczynników stężenia aktywności (ACR) wykazała dobrą zgodność między modularnym skanerem J-PET a komercyjnymi skanerami PET/CT.

Druga część pracy dotyczy rozwoju obrazowania czasu życia pozytonium. Technika PLI wykorzystuje fakt, że  $\sim 40\%$  pozytonów przed anihilacją tworzy atom pozytonium (Ps), a skrócenie czasu życia orto-pozytonium (o-Ps) służy jako komplementarny biomarker mikrośrodowiska tkankowego. Implementacja PLI wymaga jednak użycia radionuklidów  $\beta^+$  emitujących dodatkowy, natychmiastowy kwant gamma, który stanowi znacznik czasu utworzenia pozytonium. Standardowo stosowane w klinice izotopy ( $^{68}\text{Ga}$ ,  $^{82}\text{Rb}$  oraz  $^{124}\text{I}$ ) charakteryzują się niską wydajnością emisji takich kwantów. W niniejszej pracy przedstawiono pierwszą eksperymentalną demonstrację PLI z wykorzystaniem trzech nowych emiterów typu  $\beta^+ + \gamma$ :  $^{44}\text{Sc}$ ,  $^{55}\text{Co}$  oraz  $^{52}\text{Mn}$  w badaniach fantomowych. Izotop  $^{44}\text{Sc}$  okazał się optymalnym kandydatem ze względu na wysoki stosunek rozgałęzienia  $\beta^+ + \gamma$  ( $\sim 94\%$ ).  $^{55}\text{Co}$  stanowił bardzo dobrą alternatywę, osiągając wyższy stosunek sygnału maksymalnego do tła ( $\sim 133$ ) niż  $^{52}\text{Mn}$  ( $\sim 87$ ). Ponadto oceniono kliniczną wykonalność PLI u pacjentów, którym podano radiofarmaceutyk  $^{68}\text{Ga}$ -DOTA-TATE, co ujawniło specyficzne dla poszczególnych narządów różnice w średnim czasie życia pozytonu między pacjentami, pomimo niskiej wydajności emisji natychmiastowych kwantów gamma dla  $^{68}\text{Ga}$ .

Zaprezentowane badania dowodzą, że skaner J-PET oparty na scyntylatorach plastikowych jest zdolny do prowadzenia obrazowania metabolicznego, co stanowi istotny krok w kierunku opracowania opłacalnego ekonomicznie skanera J-PET nowej generacji na całe ciało. Opracowywany skaner o długości osiowego pola widzenia 2,5 m ma na celu zwiększenie czułości, co pozwoli na skrócenie czasu skanowania, obniżenie dawek promieniowania oraz szersze zastosowanie kliniczne PLI jako biomarkera do oceny i charakteryzowania stanów chorobowych.



# Acronyms

**ACR** Activity Concentration Ratio

**BGVar** Background Variability

**CASToR** Customizable and Advanced Software for Tomographic Reconstruction

**CRC** Contrast Recovery Coefficient

**CRMs** Certified Reference Materials

**CT** Computed Tomography

**CTAC** CT based Attenuation Correction

**CTR** Coincidence Time Resolution

**CTW** Coincidence Time Window

**DAQ** Data Acquisition

**DTW** Delayed Time Window

**FBP** Filtered Back Projection

**FDG** Fluoro-deoxy-glucose

**FOV** Field of View

**FPGA** Field-Programmable Gate Array

**FTAB** Front-end TDC Acquisition Boards

**FWHM** Full Width at Half Maximum

**J-PET** Jagiellonian Positron Emission Tomography

**LAFOV** Large Axial Field-of-View

**LOR** Line of Response

**LYSO** lutetium–yttrium oxyorthosilicate

**MLEM** Maximum Likelihood Expectation Maximization

**NECR** Noise Equivalent Count Rate

**NEMA** National Electrical Manufacturers Association

**NETs** Neuroendocrine Tumors

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**o-Ps** ortho-Positronium

**OSEM** Ordered Subsets Expectation Maximization

**p-Ps** para-Positronium

**PALS** Positron Annihilation Lifetime Spectroscopy

**PBR** Peak-to-Background Ratio

**PET** Positron Emission Tomography

**PLI** Positronium Lifetime Imaging

**PMMA** Polymethyl Methacrylate

**PMTs** Photomultipliers

**Ps** Positronium

**PSF** Point Spread Function

**PSMA** Prostate-Specific Membrane Antigen

**ROI** Region of Interest

**SimSET** Simulation System for Emission Tomography

**SiPM** Silicon Photomultiplier

**SiPMs** Silicon Photomultipliers

**SNR** Signal-to-Noise Ratio

**SSRB** Single-Slice Rebinning

**SSS** Single Scatter Simulation

**ST** Scatter Test

**SUV** Standardized Uptake Value

**TOF** Time of Flight

**TOT** Time Over Threshold

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# Introduction

This thesis concerns the development of a cost-effective Positron Emission Tomography (PET) system based on plastic scintillators [1,2] and the development of Positronium Lifetime Imaging (PLI) [3–5].

PET is a well-established nuclear imaging technique used to visualize and measure metabolic and functional activity in the body [6,7]. It has significantly transformed modern medical imaging by enabling the detection of diseases at very early stages, when molecular and cellular alterations occur before measurable functional or structural changes appear [8,9].

Despite its significant clinical value, the broad implementation of PET remains constrained by its high cost. The major contributors to this expense are the raw materials required for detector construction, particularly inorganic scintillation crystals (such as LYSO, LSO, and BGO) and the associated silicon-based readout electronics [10]. As a result, the cost of PET systems cannot be substantially reduced with current technological approaches, restricting access to this diagnostic modality for a large portion of the global population (see Table 1). Significant cost reduction required the development of paradigm-changing technology [2].

Table 1: Global distribution of PET scanners by UN region as of 07-06-2026 [11].

| UN Region    | Countries  | Countries with PET scanners | Population (mil) | Number of PET scanners | PET scanners (per 1 mil) |
|--------------|------------|-----------------------------|------------------|------------------------|--------------------------|
| Africa       | 55         | 16                          | 1,371            | 215                    | 0.16                     |
| Americas     | 42         | 20                          | 1,029            | 2,319                  | 2.25                     |
| Asia         | 50         | 35                          | 4,641            | 1,935                  | 0.42                     |
| Europe       | 44         | 38                          | 743              | 1,387                  | 1.87                     |
| Oceania      | 16         | 3                           | 43               | 107                    | 2.49                     |
| <b>Total</b> | <b>207</b> | <b>108</b>                  | <b>7,827</b>     | <b>5,963</b>           | <b>0.76</b>              |

In addition to the financial cost, current state-of-the-art PET imaging faces clinical limitation regarding diagnostic specificity [12]. Standard molecular tracers operate by mapping altered metabolic activity or targeting specific cellular associated with disease. However, because malignant tissue and inflammatory or infectious processes can exhibit overlapping biological characteristics, conventional metabolic imaging frequently yields confounding signals between active malignancies and benign lesions [13,14]. This diagnostic ambiguity represents a fundamental limitation of Standardized Uptake Value (SUV)-based imaging approaches. Therefore, a novel approach based on PLI can resolve this issue by providing additional diagnostic information regarding the tissue microenvironment. However, currently available clinical isotopes ( $^{68}\text{Ga}$ ,  $^{82}\text{Rb}$ , and  $^{124}\text{I}$ ) are limited due to their low prompt gamma yield. Consequently, the development of novel isotopes specifically optimized for PLI must also be explored.

To address these dual challenges of affordability and specificity, this thesis aims to achieve two primary objectives. First, the aim is to develop and validate a comprehensive framework for data processing, correction techniques, and image reconstruction for a plastic-scintillator-based Jagiellonian Positron Emission Tomography (J-PET) scanner. This is grounded in the hypothesis that a plastic-based J-PET scanner can be used to achieve cost-effective metabolic imaging with a diagnostic performance comparable to state-of-the-art crystal-based PET scanners. Second, the objective is to develop and evaluate PLI using novel  $\beta^+ + \gamma$  emitters ( $^{44}\text{Sc}$ ,  $^{55}\text{Co}$ , and  $^{52}\text{Mn}$ ) selected for their favorable physical properties, and to validate the developed PLI methodology in human subjects using the conventional clinical tracer  $^{68}\text{Ga}$ -DOTA-TATE. This second objective is driven by the hypothesis that utilizing these specific radioisotopes for PLI will provide better statistics for PLI, thereby improving the resolution and leading to enhanced functional tissue characterization, which will ultimately improve diagnostic specificity and enable better differentiation between malignant and inflammatory processes.

The J-PET research group addressed these challenges by building the first PET scanner made of plastic scintillators [1, 15, 16]. The Modular J-PET scanner consists of 312 axially positioned plastic scintillator strips, each read out with silicon photomultiplier (SiPM), making it inexpensive, lightweight (under 60 kg), portable, and equipped with a modular imaging volume which can be reconfigured [4]. The scanner operates in a triggerless data-acquisition mode, in which photons associated with the same annihilation event can be registered [17]. This enables conventional two-photon coincidence metabolic imaging as well as PLI.

Unlike conventional PET detectors that use dense inorganic scintillators to absorb 511 keV photons by the photoelectric effect, the J-PET detector uses low-Z plastic scintillators where the annihilation photons interact by Compton scattering [1, 18]. Two main differences arise from this novel approach: First, the energy deposited by each interaction is only a fraction of 511 keV and thus requires specific signal-identification. Second, the detector geometry of the elongated scintillator strips, each read out from both ends is quite different from the well established pixelated crystal arrays of conventional PET scanners [4]. Thus, all reconstruction as well as all correction techniques, developed for the crystal-based PET detectors, cannot be used directly for the J-PET detector and have to be newly developed.

In this context, the first part of this thesis focuses on the development and validation of a complete two-gamma coincidence imaging pipeline for the Modular J-PET scanner. This includes the implementation of data selection criteria for coincidence identification, a TOF-based iterative reconstruction framework [19–21], and dedicated correction techniques for attenuation, random coincidences, and scatter [22, 23]. To validate the developed methods, a National Electrical Manufacturers Association (NEMA) Image Quality (IQ) phantom measurement was performed, providing the first standardized assessment of image quality for the J-PET system. The results are quantitatively and qualitatively checked against the corresponding NEMA protocols [24]. Furthermore, the developed pipeline was applied to determine the first clinical two-gamma coincidence PET images of human subjects acquired with the Modular J-PET scanner at the Warsaw Medical University and the University Hospital in Krakow. The obtained images were compared in qualitatively as well as semi quantitatively manner to images acquired with a clinical PET/CT scanner at both hospitals.

The second part of the thesis concerns PLI [3–5]. In contrast to conventional two-gamma coincidence PET, the J-PET detector system is able to make use of the multiphoton detection [17] capability for the extraction of additional diagnostic information of the tissue microenvironment. In PLI the lifetime of the bound state of positron and electron, i.e. the positronium, is used as a probe for the molecular surrounding of the tissue. This method, which has stimulated considerable interest in the scientific community following the demonstration of the first *ex-vivo* PLI study [25] and the first *in-vivo* measurement in the human brain [4], is currently being explored in the context of both clinical and preclinical scanners worldwide [4, 25–39].

A primary requirement for PLI is the use of radioisotopes that emit an additional prompt (de-excitation) photon alongside the positron emission ( $\beta^+ + \gamma$  emitters) [40, 41]. The prompt photon carries information on the formation time of the positronium, while the following annihilation photons provide information on the decay time of the positronium. However,  $\beta^+ + \gamma$  emitters currently used in clinical PET imaging ( $^{68}\text{Ga}$ ,  $^{82}\text{Rb}$ ,  $^{124}\text{I}$ ) and in *in-vitro* experiments ( $^{22}\text{Na}$ ) [25, 42–50] are limited either by a low yield of prompt gamma emission or by an unfavourable clinical half-life [5]. Various alternative isotopes have been proposed for PLI [5, 40, 51], but had not been experimentally explored for this purpose prior to this work. Among them,  $^{44}\text{Sc}$  is endorsed as one of the most promising candidates by Moskal et al. [52]. In this thesis, the first experimental demonstration of PLI using  $^{44}\text{Sc}$  is presented, performed with the J-PET scanner using a NEMA IQ phantom [41]. In addition, two novel long-lived  $\beta^+ + \gamma$  emitters, namely  $^{52}\text{Mn}$  and  $^{55}\text{Co}$ , which are of interest for applications requiring extended imaging times (such as immuno-imaging with monoclonal antibodies), have been investigated for PLI for the first time. These measurements were performed using certified reference materials with known mean ortho-positronium lifetime and human tissue samples [53].

Furthermore, given the limited clinical availability of  $\beta^+ + \gamma$  emitters with a high prompt-gamma yield, the feasibility of performing PLI using clinically available radiotracers was also investigated. In this context, PLI studies were conducted in patients injected with  $^{68}\text{Ga}$ -DOTA-TATE radiopharmaceutical.

## Thesis Structure

This thesis is divided into nine chapters. Chapter 1 provides a general overview of two-gamma coincidence imaging, including the principles of iterative reconstruction and correction methods, and introduces the foundations of PLI together with a brief history of the field. Chapter 2 describes the J-PET prototypes, the Modular J-PET scanner and its working principle, as well as the data acquisition and low level data processing methods. Chapter 3 details all measurements conducted for two-gamma coincidence imaging and PLI in the context of this thesis. Chapter 4 presents the development of correction techniques for the J-PET scanner and the complete reconstruction pipeline for two-gamma coincidence imaging. Chapter 5 reports the results of the first phantom and clinical two-gamma coincidence images obtained with the J-PET scanner, together with quantitative and qualitative validation of

the correction techniques. Chapter 6 presents the first PLI study using  $^{44}\text{Sc}$ , one of the most favourable  $\beta^+ + \gamma$  emitters, performed with the J-PET scanner. Chapter 7 presents the first PLI studies with two novel long-lived  $\beta^+ + \gamma$  emitters,  $^{52}\text{Mn}$  and  $^{55}\text{Co}$ . Chapter 8 examines the feasibility of PLI with human subjects in a clinical setting. Chapter 9 concludes the thesis and provides future perspectives on two-gamma coincidence imaging and PLI with the upcoming Total-Body J-PET scanner.

## Author Contribution

In the context of the thesis work, the author actively prepared and conducted the phantom studies with the Modular J-PET scanner following the standard protocols for both two-gamma coincidence imaging and PLI (b)(c)(d). The author also actively participated in clinical trials with the J-PET scanner at the University Hospital of Krakow. The author developed and implemented the analysis criteria for event selection in this study for two-gamma coincidence imaging and PLI (b)(c)(d). Additionally, the author developed the necessary correction techniques for the J-PET scanner: the attenuation correction was based on the Computed Tomography (CT) image, the random correction was developed using a delayed time window method, and most importantly, the scatter correction was developed using a Monte Carlo method (b)(e). The author also performed qualitative and quantitative assessments of image quality for phantom and human studies. Furthermore, the author conducted the first experimental demonstration of PLI using three novel isotopes,  $^{44}\text{Sc}$  (c),  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  (d). These isotopes have not been routinely used in PET but have been of significant interest for a long time.

The author also developed a toy Monte Carlo simulation to estimate purity and efficiency using different  $\beta^+ + \gamma$  isotopes for the J-PET scanner (a).

All figures in this thesis were prepared and conceptualized by the author. Also Figures 3.5, 3.6, 4.2, 6.1, 6.2, 6.4, 6.5, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, and 7.7 (which were already published) were originally prepared and conceptualized by the author.

Throughout the Ph.D. program, the author has presented these results at many international conferences. The author has published five first-author articles relevant to this thesis and has been a main author on three additional articles. The author made significant contributions to the experimental preparation and data analysis for the first *ex-vivo* PLI study with  $^{44}\text{Sc}$  (f). In addition, the author contributed to the preparation of an invited review on PLI (g).

One manuscript has been submitted with the author as the main author concerning the development of iterative reconstruction techniques for PLI (h). Two manuscripts are currently in preparation for the two gamma coincidence imaging (i) and PLI (j) with the patients.

## Publications Related to This Work

The following publications by the author are relevant to this thesis:

- (a) **M. Das**, et al., “Estimating the efficiency and purity for detecting annihilation and prompt photons for positronium imaging with J-PET using toy Monte Carlo simulation,” *Bio-Algorithms and Med-Systems*, vol. 19, no. 1, pp. 87–95, 2023, doi: 10.5604/01.3001.0054.1938.
- (b) **M. Das**, R. Bayerlein, S. Sharma, et al., “Development of correction techniques for the J-PET scanner,” *Bio-Algorithms and Med-Systems*, vol. 20, no. 1, pp. 101–110, 2024, doi: 10.5604/01.3001.0054.9362.
- (c) **M. Das**, S. Sharma, et al., ”First Positronium Imaging Using  $^{44}\text{Sc}$  With the J-PET Scanner: A Case Study on the NEMA-Image Quality Phantom,” *IEEE Transactions*

on *Radiation and Plasma Medical Sciences*, vol. 10, no. 4, pp. 593-602, 2026, doi: 10.1109/TRPMS.2025.3621554.

- (d) **M. Das**, S. Sharma, et al., “First positronium lifetime imaging using  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  with a plastic-scintillator-based PET scanner,” *Scientific Reports* vol. 16, art. no. 16230, 2026, doi: 10.1038/s41598-026-43965-z.
- (e) R. Bayerlein\*, **M. Das**\*, S. Sharma, et al., “Monte Carlo-based scatter correction for the plastic-based modular PET scanner J-PET,” *Physics in Medicine and Biology*, vol. 71, no. 7, p. 075026, Mar. 2026, doi: 10.1088/1361-6560/ae54fb.  
\***Co-first authors.**
- (f) K. Kubat, **M. Das**, S. Sharma, et al., “First ex-vivo positronium imaging of tissues with modular J-PET scanner using  $^{44}\text{Sc}$  radionuclide,” *Zeitschrift Für Medizinische Physik*, Mar. 2026, doi: 10.1016/j.zemedi.2026.03.004.
- (g) P. Moskal, A. Bilewicz, **M. Das**, et al., ”Positronium Imaging: History, Current Status, and Future Perspectives,” *IEEE Transactions on Radiation and Plasma Medical Sciences*, vol. 9, no. 8, pp. 981-1001, Nov. 2025, doi: 10.1109/TRPMS.2025.3583554.
- (h) B. Uluutku, G. Gasparato, **M. Das**, et al., “A Conjugate Bayesian Framework for Fast 3D Positronium Lifetime Estimation with a Partial System Matrix,” *Submitted to EJNMMI Physics*, <https://arxiv.org/abs/2604.09804>.
- (i) P. Moskal, **M. Das**, S. Sharma, et al., “Economical portable PET scanner from plastic scintillators - the first clinical images,” *Under prepration*.
- (j) E. Stepień, **M. Das**, S. Sharma, et al., “Multi-organ evaluation of tissue microenvironment in neuroendocrine tumor patients using Positronium lifetime imaging,” *Under prepration*.

# Chapter 1

## Two-gamma coincidence PET (Metabolic) and Positronium Lifetime Imaging

### 1.1 Two-gamma coincidence PET (Metabolic) imaging

PET is a well-established, non-invasive molecular imaging technique that maps the spatial and temporal distribution of metabolic activity in the body by detecting pairs of gamma photons emitted indirectly from positron-emitting radionuclide. This enables the quantitative visualization of physiological, biochemical, and molecular processes [8, 54]. This capability makes PET a valuable diagnostic tool across multiple areas of medicine, including the diagnosis of cancer, neurological disorders, cardiovascular diseases, and skeletal disorders [8, 9].

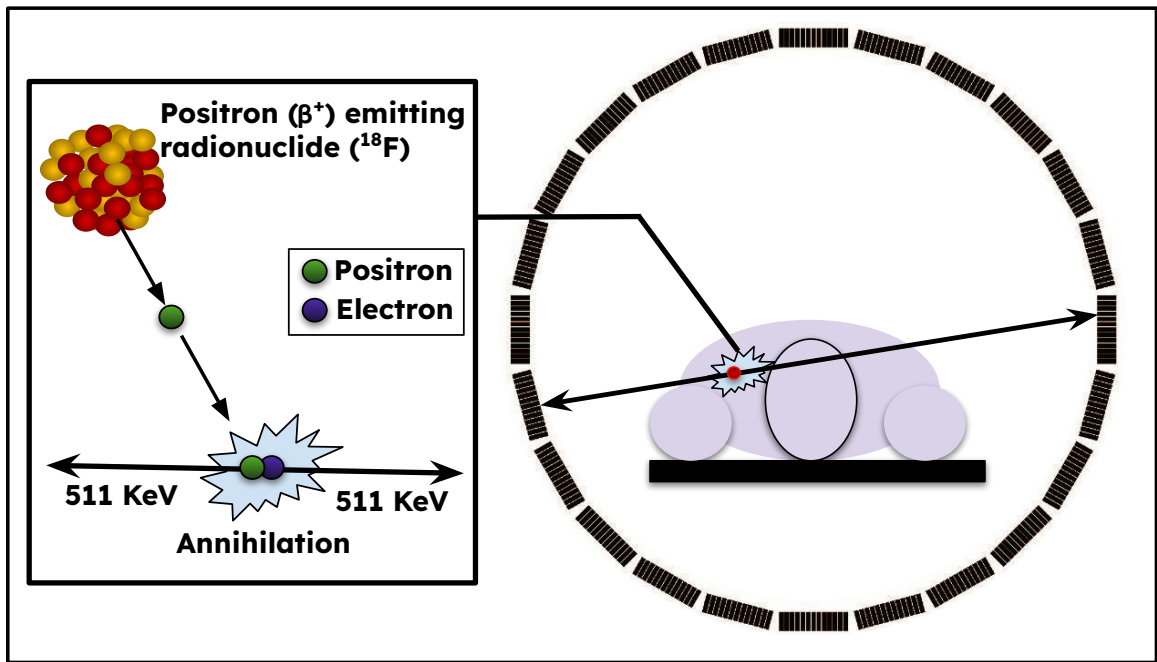


Figure 1.1: Schematic diagram of an annihilation event and the resulting coincidence detection. A positron emitted from a radionuclide annihilates with an electron in the surrounding tissue, producing two 511 keV photons emitted in opposite directions. These coincident photons are registered by detector pairs. The simultaneous detection defines a LOR, enabling localization of the annihilation site.

For diagnostic purposes, the patient is administered a positron-emitting radiotracer intravenously. This radiotracer typically consists of a  $\beta^+$  emitter conjugated to a molecule that targets a specific biological process, known as a radioligand. The choice of radiotracer depends

on the type of tissue or disease under investigation. For example, some of the most commonly used radiotracers in oncology include [ $^{18}\text{F}$ ]-Fluoro-deoxy-glucose (FDG) [55], which is widely used to image tissues with high glucose metabolism. For prostate cancer, a highly specific radiotracer is [ $^{68}\text{Ga}$ ]-Prostate-Specific Membrane Antigen (PSMA), which binds to PSMA receptors that are overexpressed on prostate cancer cells [56]. Similarly, [ $^{68}\text{Ga}$ ]-DOTA-TATE binds to somatostatin receptors in Neuroendocrine Tumors (NETs) [57].

### 1.1.1 Physics of Positron Emission

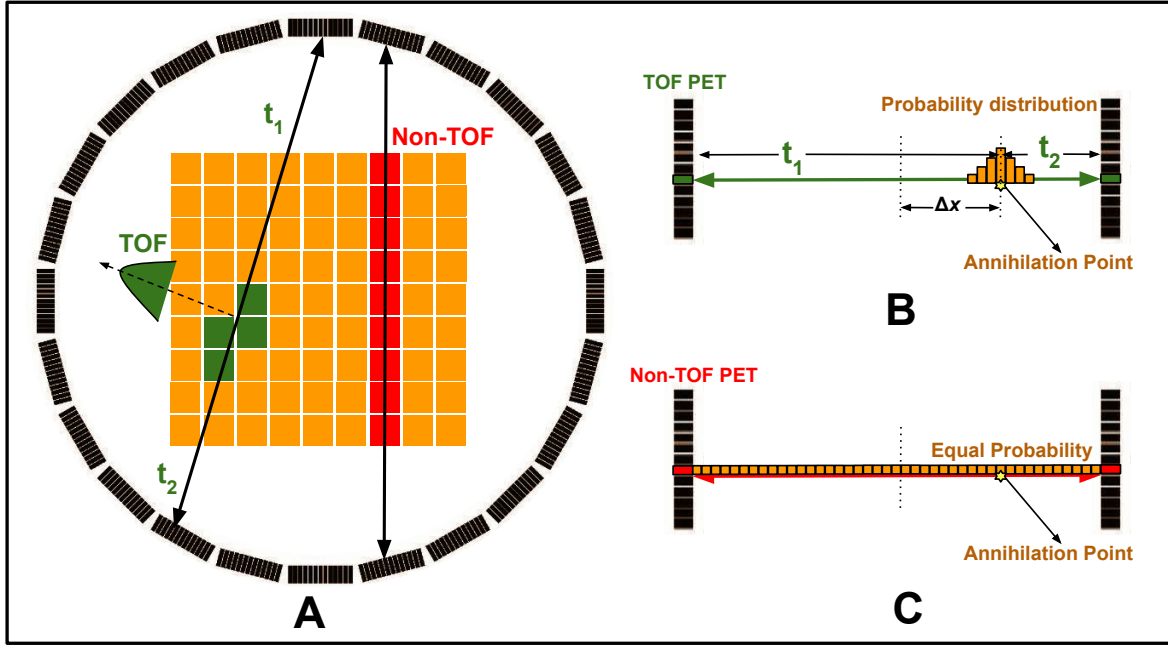


Figure 1.2: (A) Schematic representation of a detector ring registering coincident gamma photon pairs from positron–electron annihilation events, shown for both Time of Flight (TOF)-enabled detection (green) and conventional non-TOF detection (red). (B) Probability distribution of the estimated annihilation location along the LOR in TOF-PET, demonstrating spatial localization provided by timing information. (C) Uniform probability distribution of the annihilation position along the LOR in conventional (non-TOF) PET.

In PET, the radio-tracers undergo the  $\beta^+$  decay in which an unstable nucleus transforms a proton into a neutron, emitting a positron ( $e^+$ ) and an electron neutrino ( $\nu_e$ ):



The emitted positron travels a short distance in tissue. Depending on the isotope the positron range varies typically on the order of a few millimeter. The positron then loses its kinetic energy through interactions with surrounding medium. Eventually, the thermalized positron encounters an electron, resulting in a process known as annihilation. In this process, the mass of the positron and electron is converted into energy, producing two back-to-back photons, each with an energy of 511 keV:



$$e^+ + e^- \rightarrow 2\gamma \text{ (511 keV each)} \quad (1.2)$$

This back-to-back emission of annihilation photons then passing through the human body and is registered by the detector pairs (see Figure 1.1), which is typically made of inorganic crystals such as LYSO, BGO, or LSO due to their high absorption efficiency. These two photons are then sorted by applying a Coincidence Time Window (CTW) (about a few nanoseconds) and an energy window to select the 511 keV photons.

The line connecting the two detected photons is called the Line of Response (LOR), along which the annihilation event is assumed to have occurred as shown in Figure 1.1. In conventional PET scanners, reconstruction algorithms typically assume that the annihilation is likely to occur anywhere along the LOR. This simplification reduces the Signal-to-Noise Ratio (SNR) and leads to lower overall image quality. To enhance PET image quality and improve the SNR, additional TOF information is recorded for each detected photon. TOF is defined as the difference between the interaction times of two photons in the PET detector. TOF measurements allow for more accurate localization of the annihilation point along the LOR (see Figure 1.2) [58, 59].

### 1.1.2 PET Data Formats

In PET, the detected coincidence events (LORs) are stored in raw data formats prior to image reconstruction. The two primary formats for handling this raw data are Sinogram or List-Mode file.

#### Sinogram

In sinogram-based PET data representation, detected coincidence events are organized according to their corresponding LORs, which are parameterized using a pair of variables: the radial distance ( $s$ ) and the projection angle ( $\phi$ ) (see Figure 1.3). The radial coordinate defines the perpendicular distance of the LOR from the center of the Field of View (FOV), while the angular coordinate (projection angle) specifies its orientation.

To construct the sinogram, the continuous radial coordinate is discretized into finite intervals known as radial bins. Each detected event is assigned to a bin based on its calculated radial position, and all events falling within the same radial and angular projection bin are accumulated. Using this information, the projection data can be represented as a sinogram, as shown in Figure 1.3 for a circular object. This discretization process converts the continuous detection geometry into a structured two-dimensional histogram, where each bin represents the number of coincidences recorded for a specific LOR (detector pair).

#### List-Mode Data

List-mode is a PET data acquisition format in which each detected coincidence event is recorded individually. For every event, information such as the event time (time stamp), detector IDs, TOF information, necessary correction factors (**R**andom **F**actors, **S**catter **F**actors,

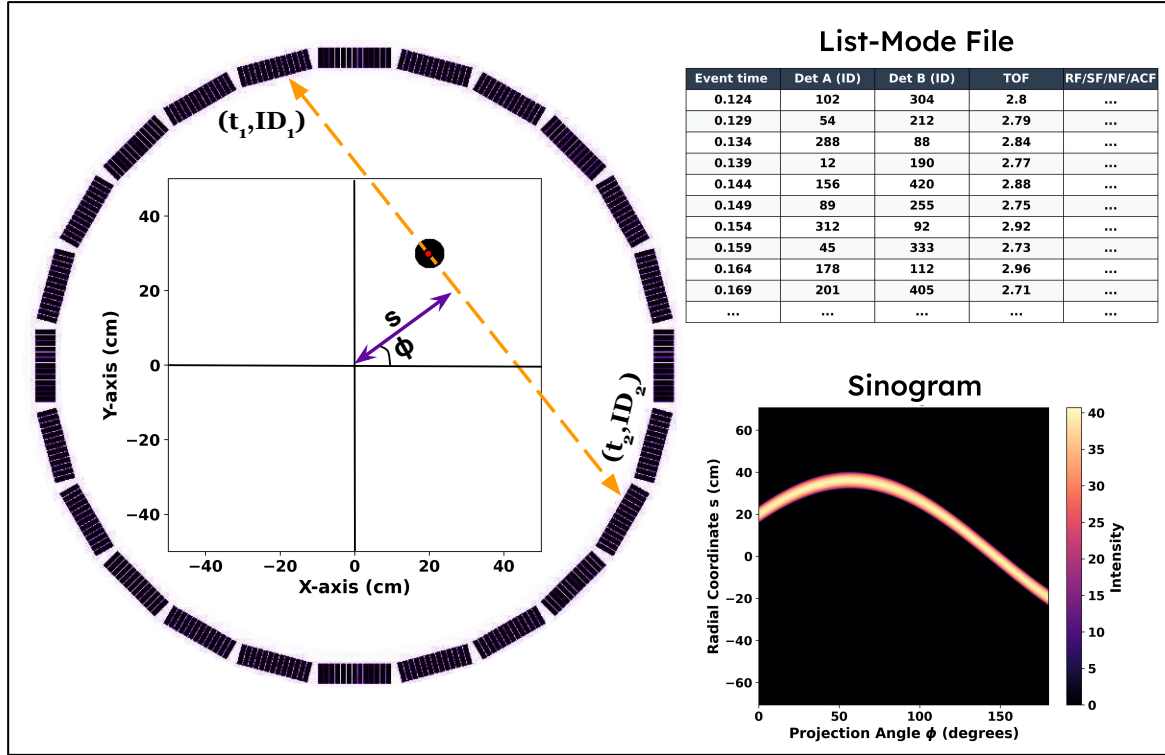


Figure 1.3: The illustration depicts two methods of organizing raw data obtained from a PET scan: the list-mode format and the sinogram format. On the left, an circular object is shown inside the detector, where a coincidence event is recorded as a LOR between two detectors  $(t_1, ID_1)$  and  $(t_2, ID_2)$ , characterized by its radial distance ( $s$ ) and angle ( $\phi$ ). This raw spatial information can be processed into either a list-mode file or a sinogram. The list-mode file (top right) acts as a chronological ledger, recording each individual event’s arrival time, detector IDs, TOF information, and necessary correction factors (RF, SF, NF, ACF, etc.). In contrast, the sinogram (bottom right) organizes these events into a two-dimensional histogram of angular and radial bins.

Normalization Factors, Attenuation Correction Factors, etc.), and energy can be stored. This approach preserves the complete set of measured data without prior grouping or compression, as shown in Figure 1.3.

Because list-mode retains event-level information, it enables flexible post-processing, including rebinning, temporal framing, and the implementation of various reconstruction and correction methods. However, this format requires substantial storage capacity and computational resources due to the large volume of data.

### 1.1.3 Iterative reconstruction in PET

In the context of PET, reconstruction of annihilation points in early PET scanners relied primarily on analytical methods [60], most notably Filtered Back Projection (FBP) [61]. This approach is based on the direct inversion of the Radon transform [62] and was widely adopted in early emission tomography because of its computational efficiency and relatively straightforward implementation. In FBP, projection data are first filtered in the frequency

domain and then backprojected to generate the reconstructed image. However, analytical methods suffer from several important limitations. They tend to amplify high-frequency noise and do not account for the poisson statistical nature of PET data. Moreover, they cannot accurately incorporate key physical effects such as attenuation, scatter, random coincidences, and detector response, all of which are essential for quantitative imaging [63]. These limitations motivated the development of statistical iterative reconstruction methods based on maximum likelihood estimation [20, 21].

The iterative reconstruction process consists of mainly five steps. First, an initial estimate of the image is defined (a guess). Second, forward projections of this estimated image are computed using the system model. Third, the predicted projections are compared with the experimentally measured projection data. Fourth, the differences between the calculated and measured projections are evaluated to quantify the data–model discrepancies, and appropriate correction factors are determined. Finally, the corrected information is backprojected to generate an updated image estimate. This procedure is repeated iteratively until a predefined convergence criterion is satisfied, as illustrated in Figure 1.4.

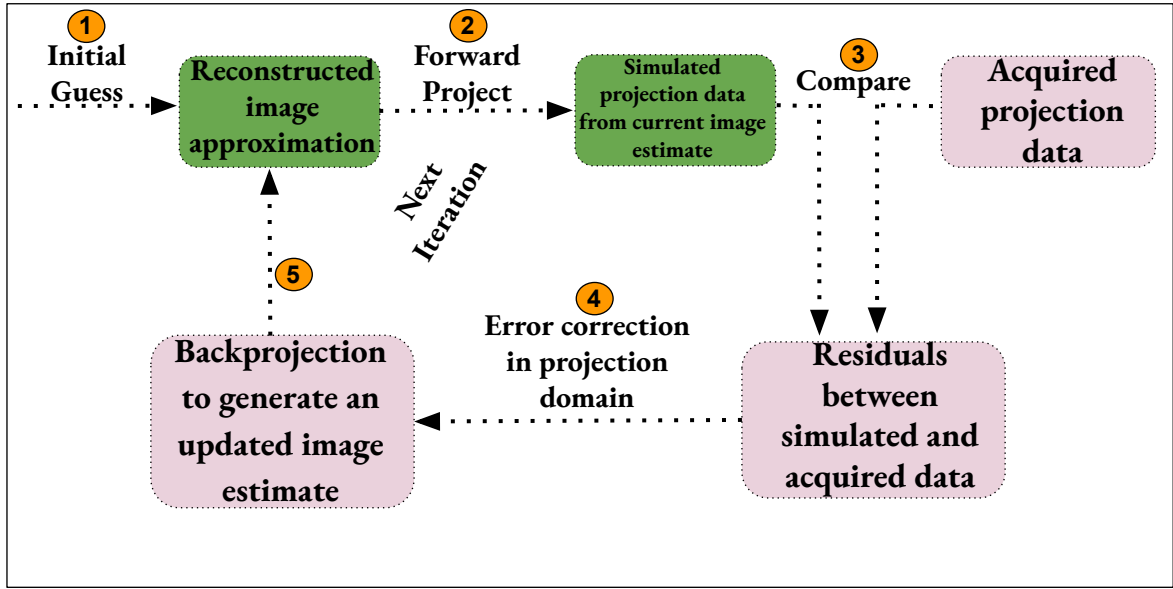


Figure 1.4: Five-step iterative reconstruction process including initialization, forward projection, comparison with measured data, correction, and backprojection with convergence control.

### Maximum Likelihood Expectation Maximization (MLEM)

The Maximum Likelihood Expectation Maximization (MLEM) algorithm is one of the most widely used iterative reconstruction techniques in nuclear medicine imaging, particularly in PET [20]. It aims to find the distribution of radioactivity in a voxel that maximizes the likelihood of producing the observed projection data, while accounting for the statistical (Poisson) nature of the measured data.

Consider an image represented as a matrix of voxels with unknown activity values  $\lambda_j$ , where  $j = 1, \dots, N$  and  $N$  is the total number of voxels. The measured projection value  $p_i$  in

sinogram bin  $i$ , where  $i = 1, \dots, M$ , is modeled as

$$p_i = \sum_{j=1}^N A_{ij} \lambda_j, \quad (1.3)$$

where  $A_{ij}$  is the system matrix element describing the probability that an emission originating from voxel  $j$  is detected in projection bin  $i$ . Assuming Poisson statistics for the measured data, the MLEM update equation for voxel  $j$  at iteration  $k + 1$  is given by

$$\lambda_j^{(k+1)} = \lambda_j^{(k)} \cdot \frac{\sum_{i=1}^M A_{ij} \frac{p_i}{\sum_{j'=1}^N A_{ij'} \lambda_{j'}^{(k)}}}{\sum_{i=1}^M A_{ij}}. \quad (1.4)$$

In a realistic PET system, the measured projection data consist of true, scattered, and random coincidence events, so the forward model can be written as

$$p_i = \sum_{j=1}^N A_{ij} \lambda_j + s_i + r_i, \quad (1.5)$$

where  $s_i$  and  $r_i$  are the expected scatter and random contributions in bin  $i$ , respectively. The corresponding MLEM update becomes

$$\lambda_j^{(k+1)} = \lambda_j^{(k)} \cdot \frac{\sum_{i=1}^M A_{ij} \frac{p_i}{\sum_{j'=1}^N A_{ij'} \lambda_{j'}^{(k)} + s_i + r_i}}{\sum_{i=1}^M A_{ij}}. \quad (1.6)$$

For list-mode data, each detected coincidence event is treated individually and indexed by  $n = 1, \dots, N_{\text{events}}$ , where  $N_{\text{events}}$  is the total number of detected events. The total number of possible LORs in the system is denoted by  $M$ . Including scatter and random contributions, the list-mode MLEM [64, 65] update for voxel  $j$  is

$$\lambda_j^{(k+1)} = \lambda_j^{(k)} \cdot \frac{\sum_{n=1}^{N_{\text{events}}} \frac{A_{nj}}{\sum_{j'=1}^N A_{nj'} \lambda_{j'}^{(k)} + s_n + r_n}}{\epsilon_j}, \quad (1.7)$$

where the voxel sensitivity is

$$\epsilon_j = \sum_{i=1}^M A_{ij}. \quad (1.8)$$

where  $A_{nj}$  is the system matrix element for event  $n$ , and  $s_n$  and  $r_n$  are the scatter and random contributions associated with event  $n$ .

For TOF-PET [58], each detected event  $n$  has an associated TOF coordinate  $t_n$  along its LOR. Including scatter and random contributions, the TOF list-mode MLEM update becomes

$$\lambda_j^{(k+1)} = \lambda_j^{(k)} \cdot \frac{\sum_{n=1}^{N_{\text{events}}} \frac{A_{nj}^{\text{TOF}}}{\sum_{j'=1}^N A_{nj'}^{\text{TOF}} \lambda_{j'}^{(k)} + s_n + r_n}}{\epsilon_j}, \quad (1.9)$$

where  $A_{nj}^{\text{TOF}}$  is the TOF-weighted system matrix element,  $s_n$  is the scatter contribution for event  $n$  (TOF dependent),  $r_n$  is random contribution, and  $\epsilon_j$  is the sensitivity summed over all possible LORs. A schematic breakdown of Eq. 1.9 is presented in Figure 1.5.

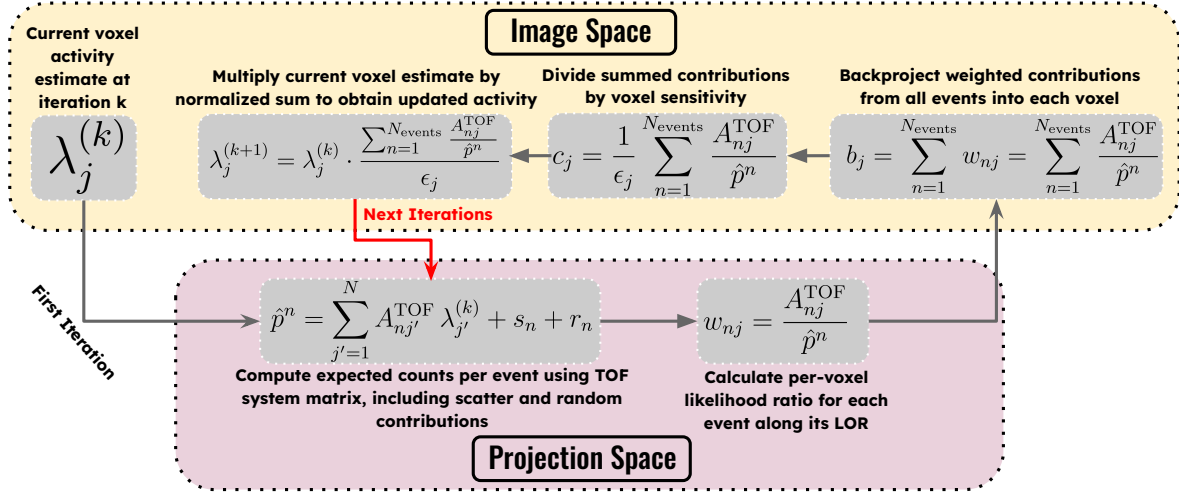


Figure 1.5: Computational scheme of the TOF-MLEM update equation. The current activity estimate is forward projected using the TOF system matrix, corrected for scatter and random contributions, weighted event-wise by the likelihood ratio, backprojected over all detected events, normalized by voxel sensitivity, and multiplicatively applied to obtain the updated image estimate.

As shown in Figure 1.2, the main advantage of TOF-PET is the improved localization of the annihilation point along the LOR. In conventional PET (see Figure 1.2 (C)), the annihilation position is assumed to be uniformly distributed along the LOR, leading to spatial uncertainty. In contrast, TOF-PET (see Figure 1.2 (B)) uses the measured arrival time difference between the two annihilation photons (TOF difference), resulting in a Gaussian-like probability distribution centered at the most likely emission point [58, 59]. This timing constraint reduces spatial uncertainty for each detected event, improves the SNR, and accelerates convergence of the iterative reconstruction. The TOF-weighted system matrix elements  $A_{nj}^{\text{TOF}}$  in Eq. (1.9) explicitly contain this probabilistic localization.

### Ordered Subsets Expectation Maximization (OSEM)

The Ordered Subsets Expectation Maximization (OSEM) algorithm is an accelerated version of the standard MLEM method, designed to reduce the computational time of iterative PET reconstruction [21]. Instead of updating the image using the entire dataset at each iteration, OSEM divides the projection data (or detected events in list-mode PET) into several subsets. Each subset is used sequentially to update the image estimate, and the result from one subset serves as the starting point for the next. A single OSEM iteration is considered complete after all subsets have been processed. By updating the image more frequently, OSEM typically reaches an acceptable reconstruction in fewer iterations compared with standard MLEM, while maintaining the statistical modeling of the measured data.

In list-mode PET data, the OSEM algorithm accelerates convergence by dividing the detected events into  $S$  subsets,  $\mathcal{S}_1, \dots, \mathcal{S}_S$ , and performing an update on each subset sequentially [66]. For each subset, the image estimate is updated using only the events in that subset, while the overall voxel sensitivity remains the same as in standard list-mode MLEM. After all

subsets are processed, one full OSEM iteration is complete, and the resulting image serves as the starting estimate for the next iteration.

Mathematically, for voxel  $j$  and subset  $s$  of iteration  $k$ , the list-mode OSEM update is

$$\lambda_j^{(k,s+1)} = \lambda_j^{(k,s)} \cdot \frac{\sum_{n \in \mathcal{S}_s} \frac{A_{nj}}{\sum_{j'=1}^N A_{nj'} \lambda_{j'}^{(k,s)} + s_n + r_n}}{\epsilon_j}. \quad (1.10)$$

#### 1.1.4 Coincidences in PET

In the context of PET imaging, coincidences are defined as the two photons registered by a detector pair within a defined CTW. These two interactions are used to form an LOR and perform PET reconstruction. However, in reality, several physical processes can influence the detected coincidences. Therefore, coincidences are commonly divided into three types: True, Random, and Scatter, as illustrated in Figure 1.6. The data registered in a PET scanner (prompts) consist of these three types of coincidences:

$$\text{Prompts}(P) = \text{Trues}(T) + \text{Randoms}(R) + \text{Scatters}(S). \quad (1.11)$$

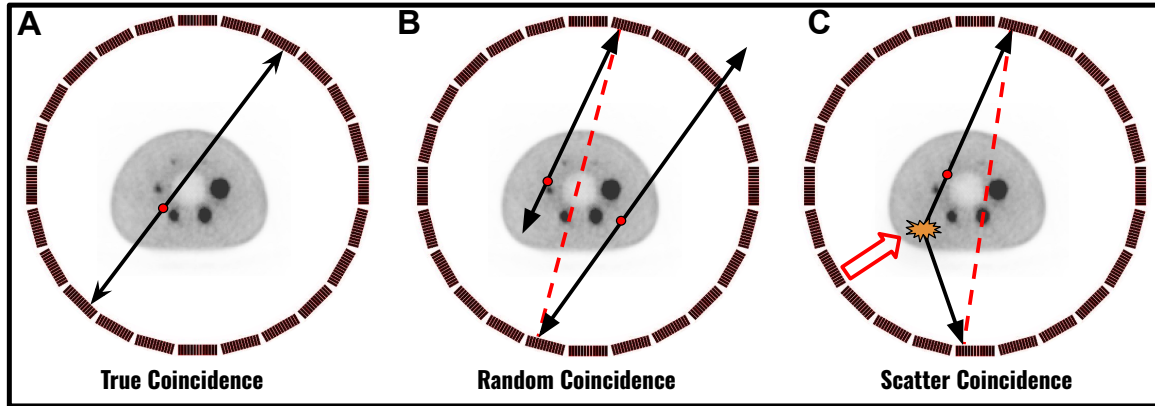


Figure 1.6: Classification of the three primary coincidence events recorded by a PET scanner. (A) True: Simultaneous detection of a photon pair originating from the same annihilation site. (B) Random: A false coincidence created by the coincidental arrival of two unrelated photons from distinct events. (C) Scatter: An event where at least one photon is scattered within the scanned object before reaching the detector (red arrow).

#### True Coincidences

True coincidences occur when both 511 keV photons originating from the same positron–electron annihilation are detected without undergoing any interaction or energy loss before reaching the detectors in the defined CTW, as shown in Figure 1.6(A). These events contain reliable information crucial for the accurate quantification of radiopharmaceutical distribution, contributing to enhanced image quality.

## Random Coincidences

Random coincidences occur when two photons originating from two independent annihilation events are detected within the defined CTW [Figure 1.6(B)]. In such cases, one photon from each annihilation may remain undetected due to attenuation or limited detector efficiency, while the other two photons are registered together as a coincidence event. As a result, a false LOR is formed, leading to an incorrect estimation of the annihilation location. These coincidences introduce uniform noise in the reconstructed image and increase background bias, thereby degrading image quality and quantitative accuracy [67]. Such events must be estimated and corrected during reconstruction.

## Scatter Coincidences

Scattered photons pose a major challenge in PET imaging. As illustrated in Figure 1.6(C), scatter coincidences occur when either one or both photons experience Compton scattering within the patient or nearby objects prior to reaching the detectors. In such cases, the resulting LOR does not correspond to the true source location, thereby introducing noise into the image and reducing contrast. To address this issue, reliable scatter correction techniques are essential.

### 1.1.5 Correction techniques in PET

As discussed in the previous section, various effects contribute to the degradation of image quality in PET imaging and require dedicated correction techniques. In addition to the two effects discussed earlier (randoms and scatters), attenuation of photons also significantly reduces image quality and requires dedicated correction.

## Attenuation Correction

Attenuation of annihilation photons occurs when they are absorbed as they pass through tissue. The degree of attenuation depends on the distance the photons need to travel before reaching the detector. Photons originating near the center of the body experience the highest attenuation due to the longer path length through the surrounding tissue, resulting in an underestimation of tracer distribution in the inner part of the body, whereas photons from peripheral regions are less affected, leading to an apparently higher tracer concentration, as seen in the non-attenuation-corrected image in Figure 1.7(A). To ensure accurate imaging, attenuation correction must be applied to the acquired data during reconstruction.

In stand-alone PET systems, attenuation maps were traditionally obtained from transmission scans using an external radioactive source to measure attenuation along many projection paths around the subject, allowing estimation of attenuation coefficients for correction of emission data [69–73]. Because these transmission measurements were performed at photon energies comparable to those of PET emissions and directly sampled the patient’s attenuation, they have long been considered the gold standard for attenuation correction in PET.

With the introduction of integrated PET/CT systems [74, 75], CT based Attenuation Correction (CTAC) [76] has rapidly evolved and is considered the clinical gold standard to

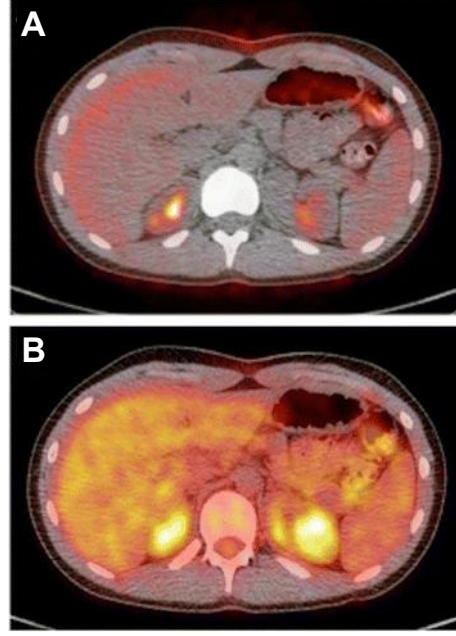


Figure 1.7: CT-based attenuation correction of PET images. (A) Fused CT and non-attenuation-corrected PET data, showing artificially high signals at the edges of the torso and underestimated signals in the central regions. (B) The corresponding attenuation-corrected PET image provides a more accurate representation of the radiopharmaceutical distribution. Figure adapted from [68], licensed under CC BY 4.0.

date. Early methods, as described in [76] and clinically validated in [77], demonstrated the feasibility of using CT images to replace radioactive transmission scans by converting Hounsfield units (HU) into 511 keV attenuation coefficients ( $\mu$ ). However, these early approaches faced significant limitations in accurately modeling bone and high-density materials; because the ratio of photoelectric to Compton interactions differs between bone and soft tissue at CT energies, a single linear scaling factor often led to an underestimation of activity in skeletal structures [77]. Furthermore, these methods were sensitive to variations in CT tube voltage ( $kVp$ ), which could introduce quantitative biases if not specifically calibrated. Carney et al. [78] addressed these issues by introducing a  $kVp$ -dependent bilinear scaling method, which applies distinct linear transformations above and below the density of water. This refinement standardized CTAC as a golden standard in modern PET/CT scanners, enabling fast, low-noise, and reliable attenuation correction in clinical protocols as can be seen in Figure 1.7(A-B). This established method has also been implemented in the J-PET scanner [22], and is described in details in Chapter 4.

Current research in PET attenuation correction focuses on CT-free methods, including deep learning-based map generation, joint activity-attenuation reconstruction (MLAA) and utilization of detector scattered photons for attenuation map reconstruction [79–82]. These approaches aim to reduce radiation dose and improve flexibility, but are still largely in research development and not yet standard in clinical practice.



## Random Correction

Random coincidences in PET scanners can be estimated and corrected using three approaches. The first is the singles rate (SR) method [83–85], a mathematical technique based on the rates of individual photon detections (singles). The rate of random coincidences ( $R_{ij}$ ) between two detectors  $i$  and  $j$  is calculated as

$$R_{ij} = 2\tau \cdot S_i \cdot S_j, \quad (1.12)$$

where  $\tau$  is the CTW, and  $S_i$  and  $S_j$  are the singles rates of detectors  $i$  and  $j$ , respectively.

An extension of this approach is the singles–prompts (SP) method [86], which incorporates both singles and prompt coincidence information to improve random estimation. By modelling pile-up and count-rate effects, the SP method provides more accurate random estimates than the conventional SR method, particularly at high activity levels. However, this method is not currently used in clinical practice.

The third approach is the Delayed Time Window (DTW) method [83, 84], currently regarded the gold standard in clinical PET imaging. It is a hardware-based technique in which coincidences are recorded within a delayed time window shifted with respect to the true CTW. Since true coincidences cannot occur in this delayed window, the measured events represent only random coincidences, which can then be directly subtracted from the prompt coincidence data. This method is also implemented on the J-PET scanner [22] and is described in detail in Chapter 4.

## Scatter Correction

“Scatter is the enemy.” — E. J. Hoffman

Scatter coincidences are one of the major challenges in PET imaging, as scattered coincidences degrade image contrast and quantitative accuracy by mispositioning LORs. One commonly used technique to compensate for scatter coincidences is Single Scatter Simulation (SSS) [87, 88], which analytically estimates the contribution of scatter to every LOR using the Klein–Nishina formula for the Compton scattering cross-section together with attenuation information from the  $\mu$ -map. Although SSS is computationally efficient and widely implemented in clinical systems, it assumes that single scattering dominates. This approximation may become inaccurate for oblique LORs, where the probability of multiple scatter increases, particularly in the context of Large Axial Field-of-View (LAFOV) scanners increasingly introduced into clinical practice.

To address these limitations, Monte Carlo–based techniques have been developed [89] to simulate all possible photon interactions within tissue, including multiple Compton scattering events and detector effects. While these approaches require substantially greater computational power, they may provide improved scatter correction accuracy [90], especially in LAFOV systems such as the uEXPLORER [91] and the upcoming Total-Body J-PET [92]. Monte Carlo–based scatter correction is also developed and applied to the J-PET scanner [22] and is described in detail in Chapter 4.

## 1.2 Positronium Lifetime Imaging

The two-gamma coincidence PET imaging quantifies tracer uptake by detecting two 511 keV photons in coincidence. It relies solely on the spatial and temporal coincidence of annihilation photons to reconstruct the tracer distribution, as described in the previous section, but this approach doesn't provide any insights into the underlying tissue microenvironment. PLI is an emerging [3, 5, 25, 93, 94] extension of PET that complements the capabilities of a conventional PET scanner by exploiting the formation and decay characteristics of Positronium (Ps) atoms, which are bound states of an electron and a positron created prior to annihilation.

### 1.2.1 Principle of Positronium Lifetime Imaging

During a PET examination, approximately 40% of positrons form a Ps atom, within the human body. This phenomenon, which has long remained largely unexplored in clinical imaging, can now be measured and characterized *in-vivo* [4].

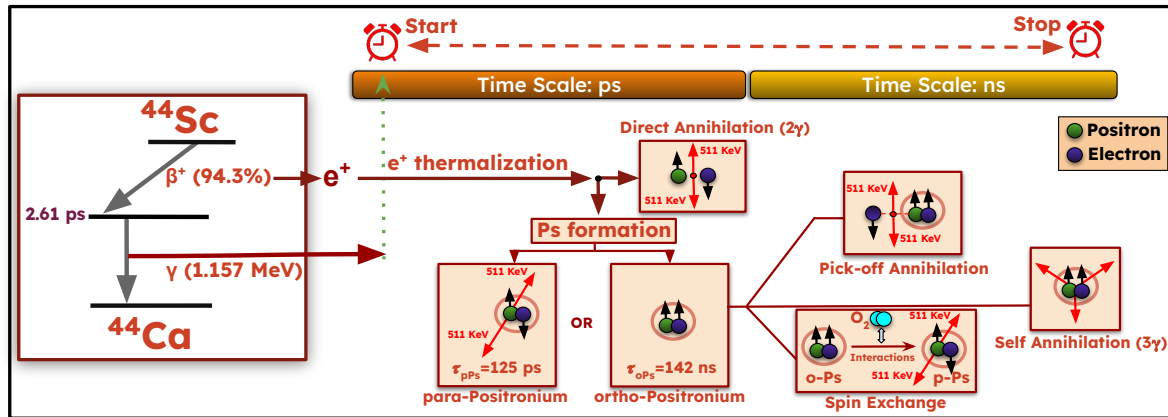


Figure 1.8: Schematic representation of the principle of PLI. A  $\beta^+ + \gamma$  emitter (e.g.,  $^{44}\text{Sc}$ ) emits a prompt gamma photon immediately after positron emission, which serves as the start signal for lifetime estimation. The emitted positron either annihilates directly into two 511 keV photons emitted in opposite directions or forms positronium with an electron in the surrounding medium. Depending on the spin configuration, positronium is formed as para-positronium (p-Ps), which annihilates into two 511 keV photons, or ortho-positronium (o-Ps), whose lifetime in matter is reduced due to pick-off or spin-exchange processes. The registration time of annihilation photons serve as the stop signal for positron lifetime estimation.

A positron emitted from a  $\beta^+$  emitter can either annihilate directly into two back-to-back 511 keV photons, which occurs in roughly 60% of cases, or form a Ps atom by binding with an electron from a nearby molecule. Ps exists in two spin states: para-Positronium (p-Ps), a short-lived state with a mean lifetime of 125 ps in vacuum, and ortho-Positronium (o-Ps), a longer-lived state with a mean lifetime of about 142 ns in vacuum [95]. In materials and biological tissues, the o-Ps lifetime is significantly reduced due to interactions with surrounding molecules [25, 42–49].

There are several processes which are responsible for the shortening of the o-Ps lifetime. One key process is pick-off annihilation, in which the positron in o-Ps annihilates with an electron from nearby molecules, producing predominantly two photons [95, 96]. The pick-off rate depends on the local electron density and cavity size, making the o-Ps lifetime a sensitive indicator of nanoscale free-volume structures. Oxygen concentration is another critical factor; paramagnetic oxygen molecules can collide with o-Ps and convert it to p-Ps, further shortening its lifetime [97, 98]. A third pathway, oxidation, involves chemical quenching of o-Ps via electron transfer to reactive species such as free radicals or certain biomolecules, forming short-lived complexes [95, 99]. The typical scheme showing the formation of Ps atoms and dominant decay channels in medium (e.g., tissue environment) is summarized in Figure 1.8. Measuring the mean o-Ps lifetime in tissues therefore provides a direct and quantitative probe of the microenvironment, including hypoxia (the body or a specific tissue does not receive enough oxygen to function properly), and can enable PLI as a novel biomarker for tissue characterization, early disease detection, assessment of malignancy, and improved differentiation between healthy and pathological tissues [97, 98, 100].

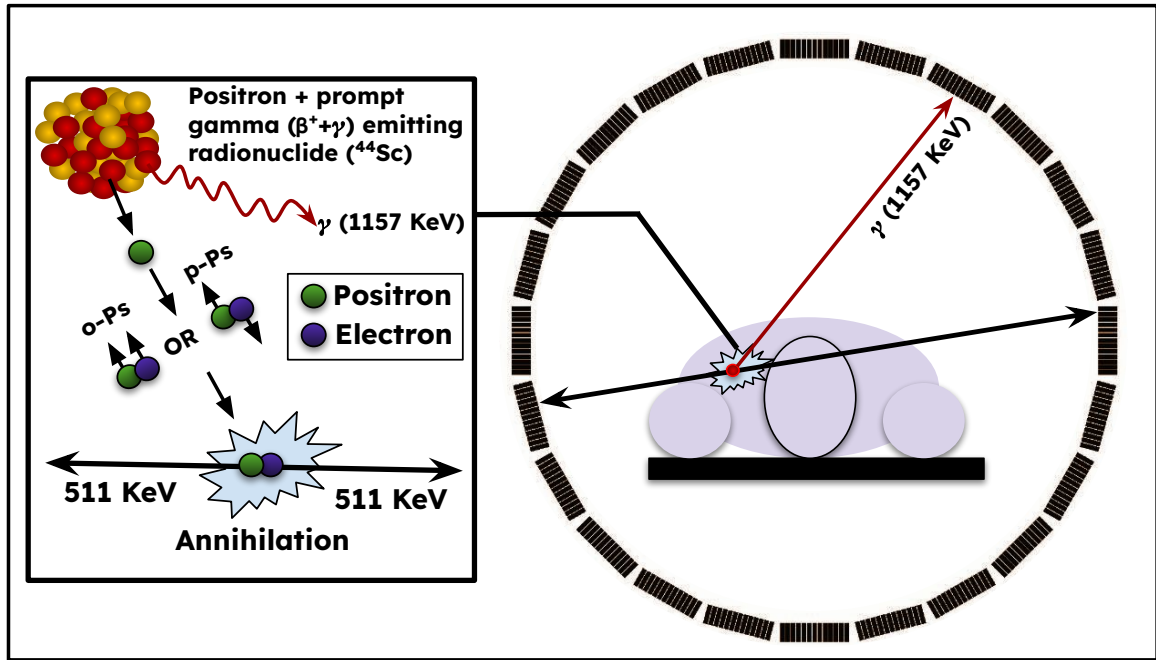


Figure 1.9: Schematic diagram of an event and the resulting coincidence detection for PLI.  $\beta^+ + \gamma$  emitter is shown for PLI studies, emitting one prompt photon immediately after positron emission. The positron then forms Ps with a surrounding electron and subsequently annihilates, producing two 511 keV photons emitted in opposite directions.

### 1.2.2 $\beta^+ + \gamma$ emitters and their Properties for Positronium Lifetime imaging

A key requirement for PLI in PET is the use of an isotope that emits an additional prompt gamma photon ( $\beta^+ + \gamma$  emitters), which serves as a precise timestamp for positron creation and marks the start of the lifetime measurement. Subsequent detection of annihilation photons,

whether from direct positron annihilation or via Ps decay, allows determination of the positron or Ps lifetime respectively, within the tissue.

Table 1.1: Key characteristics of selected  $\beta^+ + \gamma$  radionuclides relevant to PLI. The listed parameters comprise the half-life ( $T_{1/2}$ ), positron emission branching ratio ( $Y_{\beta^+}$ ), maximum positron energy ( $E_{\max}$ ), and mean positron range in water ( $R_{\text{mean}}$ ) [101]. Additionally, the table includes the prompt gamma-ray energy ( $E_\gamma$ ), prompt gamma branching ratio ( $Y_\gamma$ ), branching ratio of pure  $\beta^+ + \gamma$  decays excluding electron-capture contributions ( $Y_{\beta^++\gamma}$ ) [102], the ratio  $Y_{\beta^++\gamma}/Y_{\beta^+}$ , the average delay between positron and prompt gamma emission, and the maximum electron energy resulting from Compton scattering (Comp. E.) [51, 103, 104]. Table, prepared by the author, is adapted from [5, 40], licensed under CC BY 4.0.

| Isotope          | $T_{1/2}$ | $Y_{\beta^+}$<br>(%) | $E_{\max}$<br>(MeV) | $R_{\text{mean}}$<br>(mm) | $E_\gamma$<br>(MeV) | $Y_\gamma$<br>(%) | $Y_{\beta^++\gamma}$<br>(%) | $Y_{\beta^++\gamma}/Y_{\beta^+}$<br>(%) | Delay<br>(ps) | Comp. E.<br>(MeV) |
|------------------|-----------|----------------------|---------------------|---------------------------|---------------------|-------------------|-----------------------------|-----------------------------------------|---------------|-------------------|
| $^{22}\text{Na}$ | 2.60 y    | 89.95                | 0.545               | 0.54                      | 1.275               | 99.94             | 89.90                       | 99.94                                   | 3.6           | 1.062             |
| $^{44}\text{Sc}$ | 4.04 h    | 94.3                 | 1.474               | 1.69                      | 1.157               | 99.9              | 94.3                        | 100                                     | 2.61          | 0.948             |
| $^{68}\text{Ga}$ | 67.71 m   | 88.91                | 1.899               | 2.25                      | 1.077               | 3.22              | 1.19                        | 1.34                                    | 1.57          | 0.870             |
| $^{52}\text{Mn}$ | 5.6 d     | 29.40                | 0.575               | 0.58                      | 1.434               | 100               | 30                          | 100                                     | 0.78          | 1.217             |
|                  |           |                      |                     |                           | 0.936               | 94.5              | 29                          | 98.69                                   | 6.7           | 0.735             |
|                  |           |                      |                     |                           | 0.744               | 90                | 29                          | 98.69                                   | 41            | 0.553             |
| $^{60}\text{Cu}$ | 23.7 m    | 92.59                | 0.653               | 0.67                      | 1.333               | 88                | 81                          | 87.48                                   | 0.735         | 1.118             |
|                  |           |                      |                     |                           | 1.791               | 45.4              | 42                          | 45.36                                   | -             | 1.567             |
|                  |           |                      |                     |                           | 0.826               | 21.7              | 20.4                        | 22.03                                   | 0.59          | 0.631             |
| $^{72}\text{As}$ | 1.1 d     | 87.86                | 3.33                | 4.27                      | 0.834               | 81                | 71                          | 80.81                                   | 3.35          | 0.638             |
| $^{82}\text{Rb}$ | 1.26 m    | 95.36                | 3.382               | 4.34                      | 0.777               | 15.1              | 13.5                        | 14.16                                   | 4.45          | 0.584             |
| $^{55}\text{Co}$ | 17.53 h   | 75.89                | 1.5                 | 1.72                      | 0.931               | 75                | 59                          | 77.74                                   | 8             | 0.731             |
|                  |           |                      |                     |                           | 0.477               | 20.2              | 13.5                        | 17.79                                   | 37.9          | 0.311             |
|                  |           |                      |                     |                           | 1.409               | 16.9              | 11.3                        | 14.89                                   | 37.9          | 1.192             |
| $^{124}\text{I}$ | 4.17 d    | 22.69                | 1.822               | 2.15                      | 0.603               | 62.9              | 12                          | 52.89                                   | 6.2           | 0.423             |
|                  |           |                      |                     |                           | 0.723               | 10.36             | 0.25                        | 4.58                                    | 1.04          | 0.534             |
| $^{10}\text{C}$  | 19.3 s    | 99.97                | 2.93                | 3.69                      | 0.718               | 100               | 99.97                       | 100                                     | 710           | 0.530             |
| $^{14}\text{O}$  | 70.6 s    | 99.89                | 1.808               | 2.13                      | 2.313               | 99.39             | 99.26                       | 99.38                                   | 0.068         | 2.083             |

Several key properties of these isotopes determine their suitability for the clinical translation of PLI. One of the most important factors are the branching ratios for  $\beta^+$  decay ( $Y_{\beta^+}$ ) and for simultaneous  $\beta^+ + \gamma$  emission ( $Y_{\beta^++\gamma}$ ). High values of these branching ratios are essential for maximizing the number of detectable events for PLI, which directly affects the statistical reliability of lifetime measurements and the overall image quality. In addition to branching ratios, the timing of the prompt gamma emission relative to the  $\beta^+$  decay is critical. Prompt gamma rays should be emitted within a very short delay, typically a few picoseconds, for a precise estimate of the positron lifetime. In addition to this, the energy of the prompt gamma ray photons should exceed that of the annihilation photons in order to enable clear distinction from background and high SNR.

The half-life ( $T_{1/2}$ ) of the isotope must be compatible with the imaging protocol [40, 51]. Finally, the isotope should ideally emit only a single prompt gamma. While multiple prompt gamma can increase the intensity of PLI events, they significantly contribute to the background noise and complicate signal analysis. Overall, isotopes suitable for PLI should have a high  $\beta^+$

and  $\beta^+ + \gamma$  branching ratios, short prompt gamma emission delay, favorable photon end-point energy, appropriate half-life, and minimal additional gamma emissions.

Various isotopes that are feasible for PLI are listed in Table 1.1. This table summarizes all relevant physical properties, including half-life, branching ratios, prompt gamma energies, and other key characteristics. The decay schemes of these isotopes are illustrated in Figure 1.10.

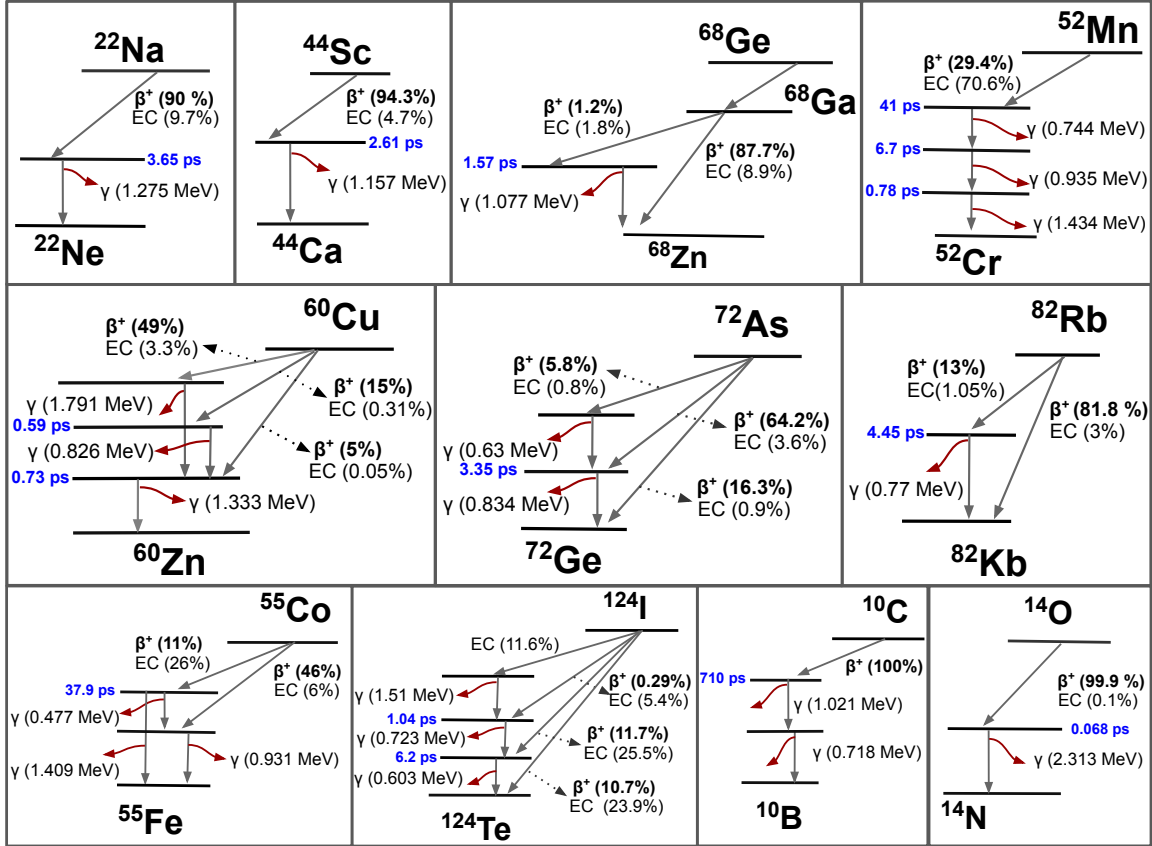


Figure 1.10: The decay schemes of the  $\beta^+ + \gamma$  emitters for the PLI. These decay schemes exclusively highlight the  $\beta^+$  decays followed by the emission of a prompt gamma. As a result, the branching ratios displayed here may not match the total values given in the table. In the decay schemes, the number shown in parentheses next to  $\beta^+$  denotes the positron emission branching ratio, EC indicates Electron Capture contributions, and  $\gamma$  represents the energy of the prompt gamma. Additionally, the blue text represents the delay time, which is the average time between a positron and the prompt gamma emission.

### 1.2.3 History and Current Developments

PLI has been introduced recently [3] and gained considerable recognition and has stimulated significant interest in its implementation in clinical PET imaging [3,5]. This growing interest has also driven new developments in both clinical and preclinical PET scanners worldwide [4,25–37].

Currently, six PET scanners worldwide have been adapted to perform PLI studies. These include the J-PET scanner in Krakow, Poland [4,41]; the Prism-PET scanner in New York City, USA [26]; the Biograph Vision Quadra in Bern, Switzerland [27–29]; the PennPET Explorer in

Philadelphia, USA [30–33]; the NeuroEXPLORER (NX) brain PET scanner in the USA [34]; and the brain-dedicated TOF-PET scanner VRAIN in Chiba, Japan [35,36]. In addition, several reconstruction algorithms for PLI have been proposed in recent years [5,26,31,33,38,105–112].

However, radionuclide selection remains a major challenge limiting the clinical translation of PLI [5,40].

The first proof-of-concept experimental demonstration of spatially resolved PLI in biological tissue was performed by the J-PET research group, using the J-PET tomograph [25]. In this experiment,  $^{22}\text{Na}$  was used as the positron-emitting source. This radionuclide is well suited for *ex-vivo* PLI studies because it emits a 1275 keV prompt gamma photon in 99.94% of  $\beta^+$  decays. For this study, the biological tissues were excised from two patients, including cardiac myxoma and adipose tissue. Each sample was cut into two pieces, and a  $^{22}\text{Na}$  source was placed between two tissue samples. The four samples were then positioned inside the J-PET detector geometry for measurements. A clear difference in the mean lifetime of o-Ps was observed between cardiac myxoma and adipose tissue, with measured values of approximately 1.9 ns and 2.6 ns, respectively [25].

In contrast to earlier studies employing  $^{22}\text{Na}$  in conventional Positron Annihilation Lifetime Spectroscopy (PALS), which provided only bulk-averaged lifetime values for small samples, the J-PET research group demonstrated for the first time spatially resolved imaging of the o-Ps lifetime. This work provided the first proof-of-concept for PLI and directly demonstrated its potential to distinguish tissue types based on differences in their molecular structure. However, the long half-life of  $^{22}\text{Na}$  (2.60 years) and its tendency to accumulate in bone tissue [113] preclude its use for *in-vivo* applications. Therefore,  $^{22}\text{Na}$  remains mainly a source of choice for *in-vitro* and *ex-vivo* PLI studies [25,42–50], as well as for various fundamental physics experiments involving Ps [114–117].

Next, the J-PET research group demonstrated the first *in-vivo* PLI of the human brain in a patient injected with  $^{68}\text{Ga}$ -PSMA and  $^{68}\text{Ga}$ -DOTA-Substance-P [4]. This study was performed using the second generation of the J-PET detector (the Modular J-PET Scanner). However, due to the low branching ratio (1.34%) of  $\beta^+ + \gamma$  emission in  $^{68}\text{Ga}$ , the statistics were limited. Despite the low statistics, the study demonstrated the feasibility of applying PLI in clinical applications by successfully imaging the mean o-Ps lifetime [4]. Later validation studies using a PET/CT system with a LAFOV, the Biograph Vision Quadra in Bern, Switzerland [37,118] and the PennPET Explorer in Philadelphia [33], explored additional clinically available  $\beta^+ + \gamma$  emitters that produce prompt photon emissions suitable for PLI.

Two such isotopes are cyclotron-produced  $^{124}\text{I}$ , frequently used for PET/CT thyroid staging and dosimetry, and  $^{82}\text{Rb}$ , which is obtained from the  $^{82}\text{Sr}/^{82}\text{Rb}$  generator and commonly used for PET perfusion imaging to evaluate coronary artery disease. Phantom measurements and *in-vivo* studies in a thyroid cancer patient [37,118] using the  $^{124}\text{I}$  were conducted with the Biograph Vision Quadra in Bern. Similarly,  $^{82}\text{Rb}$  was used for phantom experiments with the PennPET Explorer in Philadelphia [33] and *in-vivo* imaging in patients [28] was performed with the Biograph Vision Quadra in Bern. Although both isotopes are suitable for initial PLI research, their effective clinical application faces notable challenges. The short half-life of  $^{82}\text{Rb}$  (1.26 minutes) and its relatively low prompt gamma emission probability (13%) in  $\beta^+$  decays

limit the achievable statistics. Similarly, the decay scheme of  $^{124}\text{I}$  produces prompt gamma emission in only about 12% of its  $\beta^+$  decays.

Recently, considerable efforts have been devoted to exploring novel  $\beta^+ + \gamma$  emitters for PLI. Among the ongoing efforts to identify optimal radionuclides,  $^{44}\text{Sc}$  has emerged as a particularly compelling candidate [2]. This interest is primarily driven by its favourable physical decay characteristics, including a clinically suitable half-life of 4.04 hours [119], an extremely short de-excitation time of 2.61 picoseconds, and a high branching fraction of 94.3% for positron emission accompanied by a high-energy prompt gamma of 1157 keV with an emission probability of approximately 100%, as schematically shown in Figure 1.10. Recent phantom investigations carried out using the J-PET scanner in Cracow, Poland [39,41], which constitute a key component of this thesis and are presented in detail in Chapter 6, together with corresponding studies conducted on the PennPET Explorer in Philadelphia [33] and the Biograph Vision Quadra in Bern [120], have collectively highlighted the potential of  $^{44}\text{Sc}$  as a leading radionuclide for future clinical implementation of PLI.

Although  $^{44}\text{Sc}$  meets many of the key requirements for PLI, its relatively short half-life makes it unsuitable for labeling radiopharmaceuticals with slow pharmacokinetics, such as monoclonal antibodies. Additionally, the diversity of production infrastructures across research facilities, including generator and cyclotron-based routes, as well as variations in beam current, can significantly affect the routine availability of particular radionuclides. Therefore, it is necessary to explore alternative  $\beta^+ + \gamma$  emitters.

Several other radionuclides that have not yet been explored for PLI, including  $^{52}\text{Mn}$ ,  $^{55}\text{Co}$ ,  $^{60}\text{Cu}$ ,  $^{72}\text{As}$ ,  $^{14}\text{O}$ , and  $^{10}\text{C}$ , have been proposed due to their physical properties relevant for PLI [5,40]. Among these candidates,  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  are particularly interesting long-lived isotopes that may overcome some of the limitations associated with  $^{44}\text{Sc}$ . The isotope  $^{52}\text{Mn}$  has a half-life of approximately 5.59 days and emits positrons in 29.4% of its decays. The positron emission is followed by a cascade of prompt gamma photons with energies of 744 keV, 935 keV, and 1434 keV. These properties make  $^{52}\text{Mn}$  suitable for delayed imaging studies and for labeling biomolecules with slower biological kinetics. Similarly,  $^{55}\text{Co}$ , with a half-life of about 17.5 hours, emits positrons in approximately 76% of its decays, leading to excited  $^{55}\text{Fe}$  states that subsequently emit prompt gamma photons with energies of 477 keV, 931 keV, and 1409 keV, making  $^{55}\text{Co}$  another promising candidate for PLI. Recently, these two isotopes,  $^{52}\text{Mn}$  and  $^{55}\text{Co}$ , were investigated using the Modular J-PET scanner using phantom studies [53]. These studies constitute a major component of the research presented in this thesis and are discussed in detail in Chapter 7.





## Chapter 2

# J-PET (Jagiellonian Positron Emission Tomography)

The J-PET scanner represents a significant advancement in PET technology, as it is the first scanner constructed using plastic scintillators. It provides a cost-effective and highly versatile alternative to the conventional PET scanners, which rely on inorganic crystal scintillators (such as BGO, LYSO, and LSO). The J-PET scanner is also the first PET system capable of multiphoton detection, which enabled the first ever demonstration of PLI in both *ex-vivo* and *in-vivo* [4, 25]. In addition to PLI, multiphoton detection is used for various studies in fundamental physics [114–117]. The J-PET research group currently maintains two operational prototypes: one based on vacuum Photomultiplier (PMT) tubes (Figure 2.1(A)) and the second generation is based on Silicon Photomultiplier (SiPMs) (Figure 2.1(B)). A Total-Body J-PET scanner is presently under development [92].

### 2.1 Prototypes of the J-PET scanner

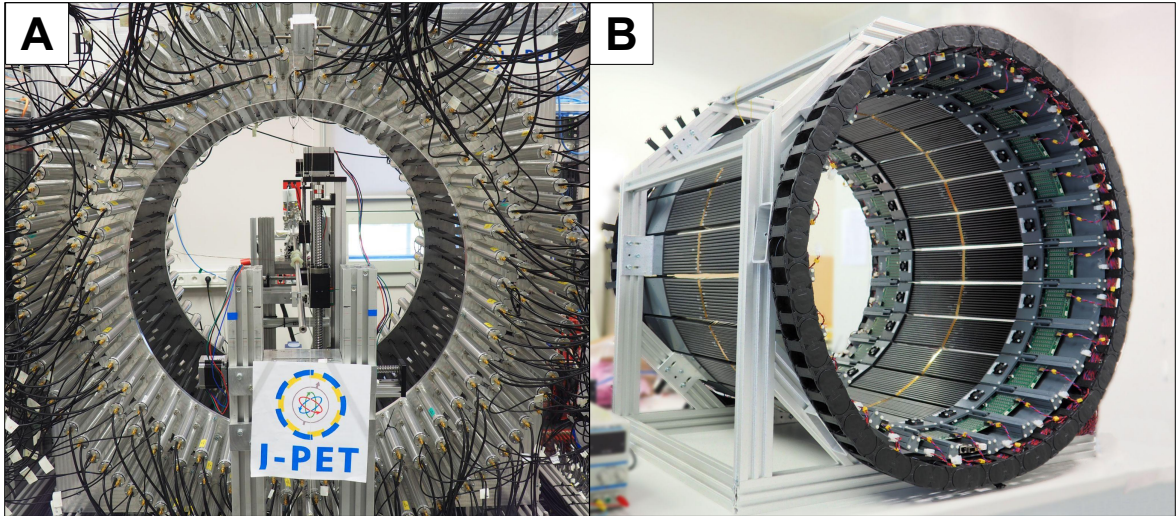


Figure 2.1: Prototype of the J-PET Scanner: (A) The first version of the J-PET prototype consisting of 192 plastic scintillator strips arranged in 3 layers. (B) The second version of the J-PET prototype known as Modular J-PET scanner consisting of 312 plastic scintillator strips forming a single layer of 24 independent detection modules..

The first J-PET scanner was constructed using three cylindrical layers comprising a total of 192 EJ-230 plastic scintillator strips [15], as shown in Figure 2.1(A). Each scintillator strip

has dimensions of  $7 \times 19 \times 500 \text{ mm}^3$ . In this prototype, the scintillators were read out at both ends using Hamamatsu R9800 vacuum tube PMTs [1]. The optical signals produced in the scintillators and converted by the PMTs were processed in the voltage domain using dedicated digital multi-threshold electronics, which sampled the signal at four separate thresholds [17,121]. The Data Acquisition (DAQ) system operates in a triggerless mode, enabling continuous recording of time-stamped data streams. This prototype enabled the demonstration of the first *ex-vivo* positronium images of cardiac myxoma and adipose tissue [25]. Moreover, it has been used to investigate discrete symmetry violations in positronium decays and to study multi-photon quantum entanglement phenomena arising from positronium annihilation [114–117].

This prototype was built with vacuum tube PMTs, resulting in a sparse configuration with large distances between scintillator strips and a non-portable mechanical construction.

The second prototype of the J-PET detector, known as the Modular J-PET Scanner (see Figure 2.1(B)), addresses these limitations by introducing new detection modules in which each scintillator is read out by an array of SiPMs allowing scintillators to be placed adjacent to each other. Furthermore, the detector features a modular design that can be reconfigured in different geometries depending on the application and easily transported to the hospital. The work presented in this thesis is based on this version of the detector. More details about the construction, DAQ, data processing, and the NEMA characteristics of this detector are described in the next section.

## 2.2 Modular J-PET Scanner

The modular J-PET scanner consists of 24 detection modules arranged in a cylindrical geometry. Each module contains 13 tightly packed plastic scintillator strips with a length of 50 cm and a cross-section of  $2.4 \text{ cm} \times 0.6 \text{ cm}$  at the ends [4,22,122–124] (see Figure 2.2). Each module weighs approximately 2 kg with the total detector weighing less than 60 kg.

The detector employs BC-404 plastic scintillators, produced by Saint-Gobain Crystals and Eljen Technology [125], which has been used due to their favorable optical and timing properties. These scintillators provide a light output of approximately 68% relative to anthracene and exhibit a maximum emission wavelength of 408 nm, which is well matched to the spectral sensitivity of SiPMs. Moreover, the fast rise time of 0.7 ns and decay time of 1.8 ns enable precise time measurements, which are crucial for TOF techniques. In addition, the long light attenuation length of approximately 140 cm allows for efficient light propagation along the scintillator, complemented by a relatively low density of  $1.023 \text{ g/cm}^3$ . To enhance light collection efficiency and ensure light-tight operation, each scintillator strip is wrapped with Vikuiti Enhanced Specular Reflector (ESR) foil together with Pokalon 100B foil, providing efficient light reflection and protection from external illumination [126].

To detect the scintillation light, each scintillator strip is read out at both ends using Hamamatsu SiPMs arranged in a  $1 \times 4$  matrix configuration, where each Silicon Photomultiplier (SiPM) has an active area of  $6 \times 6 \text{ mm}^2$ . Optical connection was provided by BC-600 Optical Cement to maintain the same refraction index between scintillators and SiPMs. The signals from each SiPM are processed using a dual-threshold readout scheme, with threshold levels

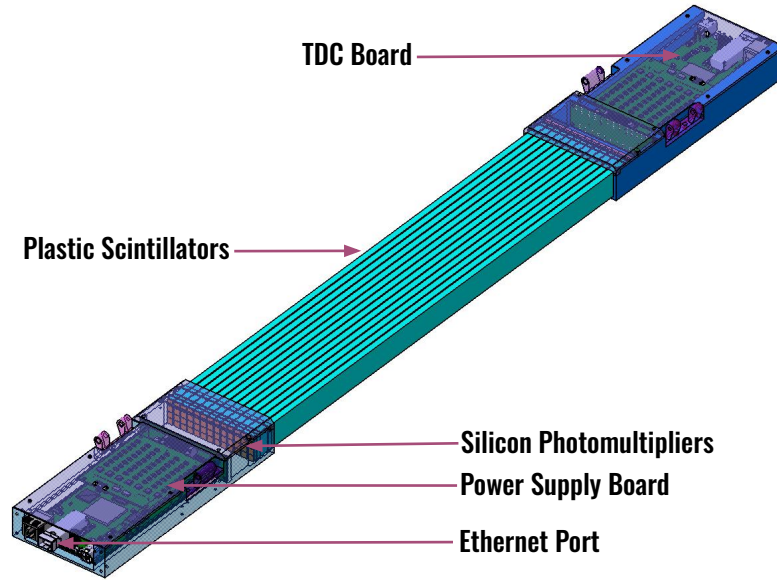


Figure 2.2: Design of one Module of the Modular J-PET scanner with Front End Electronics boards.

set at 30 mV and 70 mV, explained in more detail below.

The total inner diameter of the Modular J-PET detector is 73.9 cm. In the current configuration, it features a split-ring design that can be opened into two halves (see Figure 2.3), which can be easily closed to form a cylindrical geometry for experiments involving patients in a hospitals.

### 2.2.1 Data Acquisition (DAQ)

The DAQ in the Modular J-PET system is based on an Field-Programmable Gate Array (FPGA)-driven architecture designed for efficient real-time processing of multiple data streams [15, 17, 127]. The SiPMs are optically coupled to the scintillators and electrically connected to the front-end electronics through Flexible Flat Cables (FFC). During measurements, the SiPMs were operated at a constant bias voltage of 56.3 V, supplied individually to each SiPM via dedicated Power Supply Boards, which are mounted on top of the Front-end TDC Acquisition Boards (FTAB) on both sides of module (see Figure 2.2). To minimize signal degradation and noise, the front-end electronics are located at the ends of each detector module so that the analog signals are digitized as close to their origin as possible.

The analog signals from the SiPMs are first amplified by Amplifier Boards with a gain factor of approximately 12 and then transferred to the FTAB. On the FTAB, the signals are split into two channels and digitized using the TDC method implemented on FPGA-based electronics built on the TRB3 platform. This setup allows precise measurement of the times at which the analog signal crosses predefined voltage thresholds. During measurements, two constant thresholds of 30 mV and 70 mV were used for each SiPM, enabling the registration of leading and trailing edge timestamps for accurate timing information and calculation of Time Over Threshold (TOT).

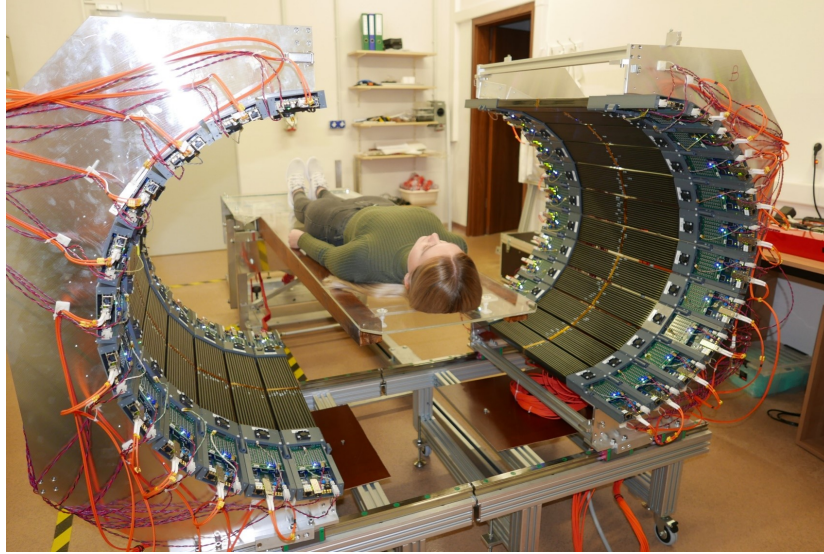


Figure 2.3: Two halves of the Modular J-PET detector surround a student in the J-PET lab. During the scan, these two halves can be easily closed to form a cylindrical PET scanner.

The digitized timing information is temporarily stored in local buffers on the FTAB. Digitized data from each module are then transmitted via optical fiber links using the Xilinx Aurora protocol running at 5 Gbps to the concentrator boards. The Aurora links provide a bidirectional channel that simultaneously transports measurement data, control and monitoring messages, and precise synchronization signals, ensuring all Endpoints receive a common time reference. This allows continuous, triggerless acquisition of multiple photons from the same decay event [17, 128]. A synchronization message generated by the Controller board at a fixed frequency of 20 kHz coordinates the readout process, enabling the Concentrators to collect data from multiple modules and forward it to the DAQ server.

At the system level, the concentrator boards aggregate data from multiple Endpoints, encapsulate it into UDP packets, and transfer it through a high-speed 10 Gigabit Ethernet connection to the DAQ server. Finally, the recorded data are archived onto LTO magnetic tapes for long-term storage and subsequent offline analysis.

### 2.2.2 Low level Data Processing

After DAQ, the initial processing focuses on reconstructing the time, position, and TOT values corresponding to photon interaction and energy depositions in the plastic scintillators. This processing is carried out using the dedicated analysis framework developed for J-PET [124], which is built on ROOT [129], and involves mainly three stages, including signal reconstruction, hit identification, and event formation as showed in Figure 2.4.

#### Signal Reconstruction

A photon interacting via Compton scattering with the plastic scintillator partially deposits its energy in the material, producing a burst of scintillation photons. The light yield of BC-404

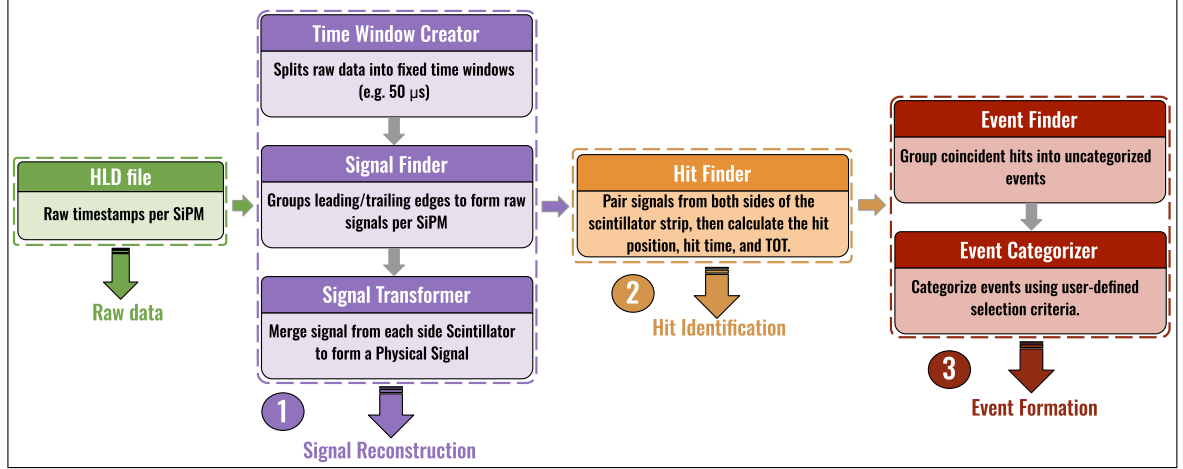


Figure 2.4: The pipeline of the J-PET Framework

is approximately 10,000 photons per MeV [130]. These optical photons propagate along the scintillator strip and are detected by SiPMs mounted on both ends, with four SiPMs coupled to each side (see Figure 2.5(A)). The SiPMs convert the scintillation light into electrical signals, and the leading and trailing edges of these signals are recorded at two predefined thresholds: 30 mV and 70 mV. This data is stored in HLD files as raw timestamps for each SiPM.

In the J-PET framework, the recorded data are first retrieved into fixed time windows of 50  $\mu\text{s}$ . Then, the timestamps recorded at the same threshold are matched within a 250 ns coincidence window between leading and trailing edges. Subsequently, leading-edge times measured at the different thresholds are paired within a 20 ns coincidence window to reconstruct a representation of the SiPM signal, as illustrated in Figure 2.5(B). The measure of the energy deposition is estimated using the TOT technique [18]. For each side of the scintillator, the TOT is calculated using the rectangular method, in which the area under the signal is approximated by a set of rectangles corresponding to the time intervals during which the signal remains above each threshold. The total TOT for one side is obtained by averaging the TOT contributions from all SiPMs on that side. The interaction time of the scintillation event at each end of the scintillator is determined from the average time of the first leading edges of the reconstructed signals, which corresponds to the arrival time of the detected signal (see Figure 2.5(C)).

### Hit Identification

These signal times are then determined for both sides of the scintillator using the method described above. Signals originating from opposite ends of the same scintillator are paired to form a hit if the difference between their arrival times satisfies the condition:

$$|t_A - t_B| \leq 3.8 \text{ ns}, \quad (2.1)$$

where  $t_A$  and  $t_B$  are the reconstructed signal times at sides A and B, respectively. This requirement ensures that only signals originating from the same physical interaction in the scintillator are combined.



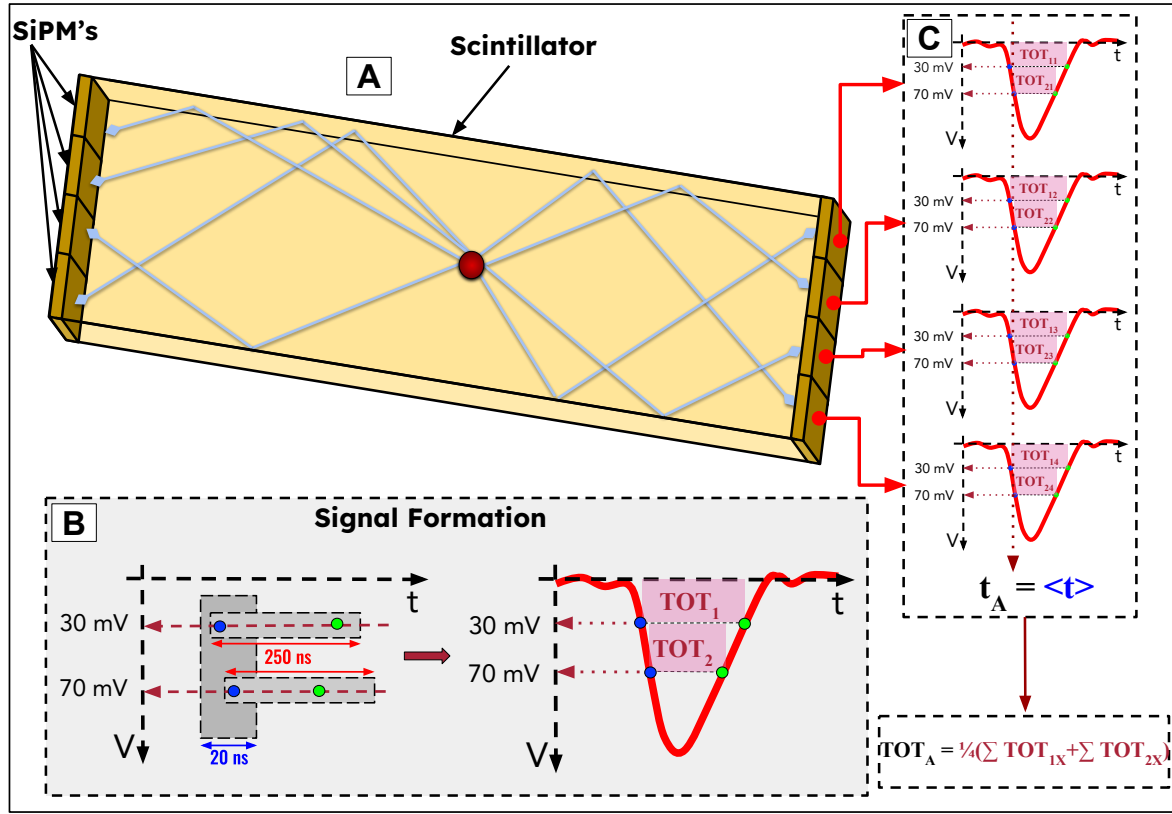


Figure 2.5: (A) Schematic illustration of the scintillation process in a single scintillator, showing how an incoming photon deposits energy and produces scintillation light. (B) Signal formation process, highlighting how the SiPMs detect the scintillation photons and generate electrical signals. (C) Illustration of how the TOT and arrival time of the signal is estimated from one side of the scintillator, using the signals from multiple SiPMs.

For a given interaction (hit), the interaction time of the photon in the scintillator is estimated by taking the average of the times recorded on both sides (denoted as A and B) (see Figure 2.6):

$$t_{\text{hit}} = \frac{t_A + t_B}{2}. \quad (2.2)$$

The interaction position along the scintillator axial length ( $\Delta l$ ) is determined from the difference in arrival times:

$$\Delta l = \frac{v}{2}(t_A - t_B), \quad (2.3)$$

where  $v$  is the effective propagation speed of light in the scintillator material.

The total TOT for the hit is calculated by averaging the contributions from all SiPMs on both sides:

$$TOT_{\text{hit}} = \frac{1}{4} \left( \sum_{i \in A} TOT_i + \sum_{j \in B} TOT_j \right), \quad (2.4)$$

where  $TOT_i$  and  $TOT_j$  are the TOT values measured by the individual SiPMs on sides A and B, respectively. The  $TOT_{hit}$  provides a measure of the deposited energy for one hit in the scintillator, while the combination of hit time and hit position enables precise spatial and temporal reconstruction of the scintillation event.

### Event Formation

After reconstructing hits, the next step in the J-PET Analysis Framework consists of grouping qualified hits into events based on a user-defined CTW. For two-gamma coincidence imaging, for example, events are formed by selecting pairs of nearly back-to-back photons, as illustrated in Figure 2.6. The precise definition of an event and the selection criteria applied at this stage depend on the specific study being performed. Depending on the analysis goals, events may consist of one or several hits, and additional constraints (e.g., angular separation, TOF consistency, or energy windows/TOT-range) can be imposed to select events of interest.

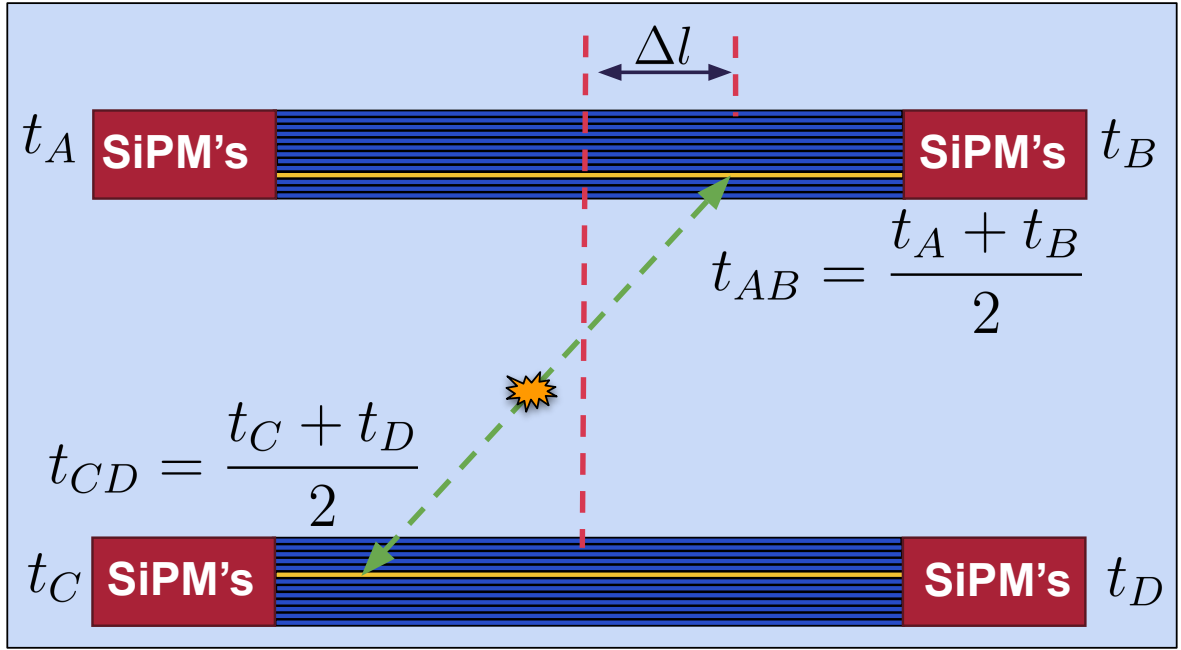


Figure 2.6: Schematic of event reconstruction in the Modular J-PET Scanner.

The experimental parameters required for this stage are loaded from a dedicated JSON configuration file. User-defined selection criteria developed for two different studies in context of this thesis, such as two-gamma coincidence imaging or PLI, are presented in the next chapters.

### 2.2.3 NEMA Characteristics

The standards for PET scanner performance evaluation protocols are established by the NEMA. This standard provides a comprehensive methodology for evaluating the performance of PET scanners with a diameter exceeding 26 cm. It specifies key performance metrics, including spatial resolution, sensitivity, scatter fraction, Noise Equivalent Count Rate (NECR), and image quality. The first version of the standard was published as NU 2-1994 in 1994 and

has been updated in every five years. The most recent version is NU 2–2024 [131]. However, the performance evaluation of the Modular J-PET system was conducted according to the NEMA NU 2–2018 standard [24], as these studies were performed before the release of the 2024 update.

For obtaining the NEMA performance characteristics with the Modular J-PET tomograph, experiments were performed using a  $^{68}\text{Ge}$  line source for sensitivity evaluation,  $^{18}\text{F}$  in the scatter phantom for scatter fraction and count-rate analysis, and a  $^{22}\text{Na}$  point source for spatial resolution determination. Image reconstruction was carried out using the MLEM algorithm [132].

The average system sensitivity was measured to be  $0.768 \pm 0.003$  cps/kBq at the center of the field of view, with a peak sensitivity of 2.1 cps/kBq [123, 132]. The experimentally determined spatial resolution for TOF-MLEM image reconstruction was  $4.92 \pm 0.56$  mm,  $7.38 \pm 0.51$  mm, and  $30.73 \pm 0.52$  mm Full Width at Half Maximum (FWHM) in the radial, tangential, and axial directions, respectively [122]. The radial spatial resolution is comparable to that achieved by commercial PET scanners.

The scatter fraction, calculated using the Single-Slice Rebinning (SSRB) algorithm, was found to be  $41.7 \pm 0.2\%$ . Count-rate performance analysis indicated that at an average activity concentration of 0.342 kBq/cc, the total coincidence count rate was  $31.19 \pm 0.52$  cps, consisting of  $18.18 \pm 0.99$  cps true coincidences and  $13.00 \pm 1.08$  cps scatter coincidences, while the corresponding NECR was  $10.60 \pm 1.17$  cps. In addition, the Coincidence Time Resolution (CTR) of the Modular J-PET scanner was reported to be 628 ps [123, 132], and then improved to 490 ps after precise calibration [124].



## Chapter 3

# Experimental Details

The work presented in this thesis is structured around two principal research directions: two-gamma based metabolic imaging and PLI with the Modular J-PET Scanner. In total, six distinct experimental measurements were conducted across both components. This chapter provides a comprehensive description of the experimental setups, protocols and acquisition details for each of the six measurements. Detailed event selection criteria and the results for each of these experiments are presented and discussed in the subsequent individual chapters (Chapters 5–7).

### 3.1 Experiments for evaluation of Two-gamma coincidence Imaging

The evaluation of two-gamma coincidence imaging was first performed using data acquired with a NEMA IQ phantom. These measurements allowed for a systematic qualitative and quantitative evaluation of image reconstruction accuracy and an assessment of the impact of various correction techniques (attenuation, randoms and scatters) developed for the J-PET scanner.

Following successful validation on the NEMA IQ phantom, the optimized reconstruction framework and correction techniques were applied to clinical patient scans. The measurements were conducted using the modular J-PET scanner at the Medical University of Warsaw Hospital and the Jagiellonian University Medical College Hospital in Kraków.

#### 3.1.1 NEMA Image Quality (IQ) Measurement

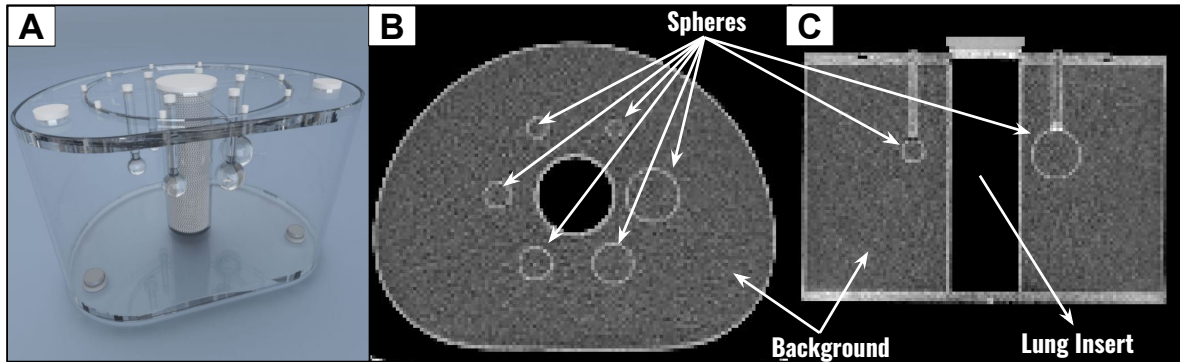


Figure 3.1: (A) Photograph of the NEMA IQ phantom from the vendor's website: <https://www.medipment.pl/produkt/pro-project-pro-nm-nema-nu2-79131>. (B) Transaxial view and (C) coronal view of the CT image, showing the six spheres, background region, and lung insert.

The NEMA IQ, often referred to as the NEMA IEC body phantom, is a standard phantom used in PET imaging to assess and compare scanner performance in a consistent and reproducible way. It is made of acrylic and includes a large compartment filled with a radioactive solution, usually  $^{18}\text{F}$ -FDG, to represent uniform background activity. Inside the phantom, there are six spheres of different sizes (ranging from 10 to 37 mm diameter) that simulate lesions (see Figure 3.1). These spheres can be filled with higher activity (hot) or left inactive (cold). It also contains a lung insert filled with low-density material such as styrofoam balls to mimic lung tissue. Imaging this phantom allows evaluation of important quantitative parameters, and the accuracy of the corrections (such as attenuation, randoms, and scatters). Overall, it serves as a simplified but practical model of the human body for testing, validating, and comparing PET scanners and image reconstruction methods.

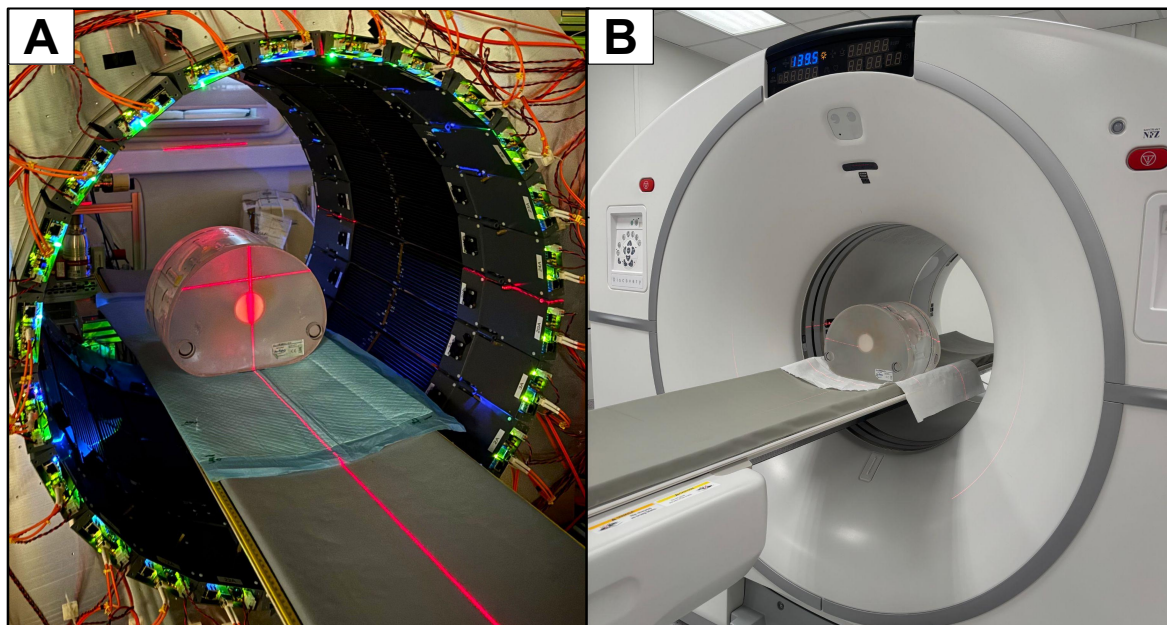


Figure 3.2: (A) Acquisition of the NEMA IQ phantom using the Modular J-PET scanner at Jagiellonian University, where the phantom was positioned on a dedicated patient bed designed for J-PET measurements. (B) Corresponding CT scan of the same NEMA IQ phantom performed on the GE Discovery MI Gen 2 system at the Medical University of Krakow, which was later used to generate the attenuation map for attenuation and scatter correction for J-PET.

### Phantom preparation protocol

For this experiment, the  $^{18}\text{F}$  source was purchased from the commercial company VOXEL. A 100 mL stock solution was prepared containing 281.8 MBq (at the time of phantom preparation). For the sphere preparation, 5.5 mL of the stock solution was mixed with 46.5 mL of water, yielding a total volume of 52 mL, which was then injected into the sphere compartment. The remaining 94.5 mL of the stock solution was transferred to the background compartment and diluted to a total volume of 8796 mL. The resulting sphere-to-background Activity Concentration Ratio (ACR) was 9.85:1.

## Measurement with the J-PET Scanner

At the beginning of the experiment, the activity concentration in the spheres was 42.2 kBq/mL, while the activity concentration in the background volume of the phantom was 4.28 kBq/mL, resulting in an ACR between the hot spheres and the background of approximately 9.85:1. The phantom was placed on the patient bed, as shown in Figure 3.2(A), and scanned for 39 minutes. The same phantom was then scanned using a CT scanner at the University Hospital in Krakow to obtain CT images [Figure 3.2(B)], which was later used for attenuation and scatter correction.

The results of this experiment is detailed in the Chapter 5.

### 3.1.2 First Clinical Trials at Warsaw and Krakow Hospital

Once the reconstruction and correction techniques were validated using phantom studies, the Modular J-PET scanner was transported, in separate measurement campaigns, conducted at two hospitals: the Medical University Hospital in Warsaw and the University Hospital in Krakow. These measurements were performed under clinical conditions to evaluate the performance of the scanner in real patient studies.

In total, four patient studies are presented in this thesis to demonstrate the performance of the scanner using different radiotracers. The measurements were carried out at two independent clinical sites, allowing for a comparison of results across different hospital environments and acquisition conditions.

## Ethics Statement

The clinical imaging studies using the Modular prototype of the J-PET scanner were carried out at two hospitals: the Department of Nuclear Medicine at the Medical University of Warsaw on 2022 and the Chair and Department of Endocrinology at the Jagiellonian University Medical College in Kraków on 2024.

The study conducted in Warsaw took place in March 2022 and received approval from the Ethics Committee of the Medical University of Warsaw (decision dated 21 February 2022, No. KB/16/2022), and is registered at ClinicalTrials.gov (NCT06211803, <https://clinicaltrials.gov/study/NCT06211803>). The studies performed at the University Hospital in Kraków were carried out between March and April 2024, following approval from the appropriate bioethics committees under agreement No. 1072.6120.92.2023 (NCT06242119, <https://clinicaltrials.gov/study/NCT06242119>). All participants were fully informed about the study procedures and provided written informed consent for participation, as well as for the publication of the obtained results.

## Patient Information

A total of four patients were examined to evaluate the performance of the Modular J-PET scanner under clinical conditions. The patient group comprised both male and female subjects

with varying ages and body weights, allowing for the assessment of the scanner across diverse physiological characteristics.

Table 3.1: Summary of patient characteristics for the clinical studies, including hospital site, age, gender, body weight, and administered activity with the corresponding radiotracer. WMU denotes the Medical University of Warsaw, and KMU denotes the Jagiellonian University Medical College in Kraków.

| Pat.No. | Hospital | Age | Gender | Weight (kg) | Act. Inj. (MBq)       |
|---------|----------|-----|--------|-------------|-----------------------|
| 001     | WMU      | 56  | F      | 64          | 156 (Ga-DOTA-TATE)    |
| 002     | KMU      | 62  | F      | 73          | 155.95 (Ga-DOTA-TATE) |
| 003     | KMU      | 70  | M      | 94          | 155.95 (Ga-PSMA)      |
| 004     | KMU      | 50  | M      | 75          | 308 (FDG)             |

The clinical studies were conducted at two centres: the Medical University of Warsaw (WMU) and the Jagiellonian University Medical College in Kraków (KMU). One patient was examined at WMU, while the remaining three were scanned at KMU. Different radiotracers were administered depending on the clinical protocol, including  $^{68}\text{Ga}$ -DOTA-TATE,  $^{68}\text{Ga}$ -PSMA, and  $^{18}\text{F}$ -FDG for imaging NETs, prostate-specific membrane antigen expression, and glucose metabolism, respectively. The administered activity ranged from approximately 155 MBq to 308 MBq, adjusted according to the radiotracer type and clinical protocol. Key patient characteristics, including age, gender, body weight, and injected activity, are summarized in Table 3.1.

### Measurement with the J-PET Scanner

All patients underwent standard clinical PET/CT imaging prior to the J-PET measurement. The timing of the scans varied depending on clinical workflow, with J-PET acquisitions generally performed at later time points after radiotracer injection (except for patient 1 from WMU) as detailed in Table 3.2 and the workflow is shown in Figure 3.4.

Table 3.2: Timing details of the imaging procedures for each patient, including the post-injection time and scan duration for both PET/CT and J-PET acquisitions. Post-injection time refers to the interval between radiotracer administration and the start of the scan, while  $T_{\text{scan}}$  denotes the acquisition duration.

| Pat.No. | Post Inj. (PET-CT) | $T_{\text{scan}}$ (PET-CT) | Post Inj. (J-PET) | $T_{\text{scan}}$ (J-PET) |
|---------|--------------------|----------------------------|-------------------|---------------------------|
| 001     | 85 min             | 23 min                     | 60 min            | 15 min                    |
| 002     | 62 min             | 25 min                     | 97 min            | 16 min                    |
| 003     | 59 min             | 28 min                     | 98 min            | 10 min                    |
| 004     | 56 min             | 16 min                     | 81 min            | 15 min                    |

For Patient 1 ( $^{68}\text{Ga}$ ]Ga-DOTA-TATE, WMU; Figure 3.3(A-C)), imaging was performed using a shared movable bed system. After radiotracer injection and the uptake period, a single-bed-position scan of the abdominal region was first acquired using the Modular J-PET

scanner. The patient was then moved, on the same bed, to the Siemens Biograph 64 PET/CT scanner, where a whole-body examination was performed using eight bed positions.

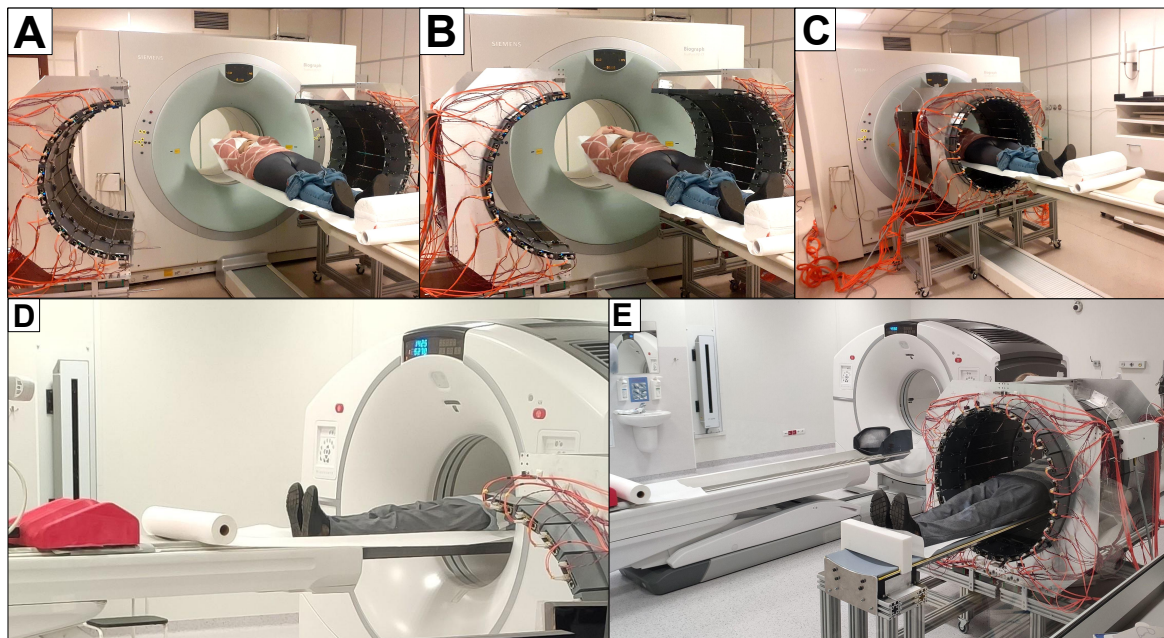


Figure 3.3: (A–C) Photographs from the Warsaw Medical University showing the course of imaging patients with the portable modular J-PET scanner. (A) Before regular diagnostics with the PET/CT Biograph 64 TruePoint, the patient remained on the bed and was surrounded by the J-PET tomograph. (B) Photograph illustrating the positioning of the two halves of the J-PET tomograph around the patient. (C) Final patient positioning within the axial field of view of the J-PET tomograph. (D–E) Photographs from the University Hospital in Krakow showing the course of imaging patients with the portable J-PET scanner. (D) Regular diagnostics of the patient in the GE Discovery MI Gen 2 PET/CT scanner. (E) Photograph of the patient during the scan with the J-PET scanner. The J-PET scan was performed on a separate bed from the PET/CT scanner.

At KMU, a different workflow was applied to Patients 2–4 due to technical limitations that prevented the J-PET scanner from being positioned below the same patient table as the clinical PET/CT system. As a result, PET/CT and J-PET examinations were performed separately using a dedicated patient bed with mechanical properties comparable to those of the PET/CT table (Figure 3.3(D-E)). In all the scans performed in Kraków, patients first underwent imaging on the GE Discovery MI Gen 2 PET/CT scanner. Following completion of the PET/CT acquisition, patients were asked to void their bladder before undergoing imaging with the modular J-PET tomograph.

Patient 2 ( $^{68}\text{Ga}$ ]Ga-DOTA-TATE, KMU), a 62-year-old female was administered 156 MBq of the radiotracer. After a 62-minute uptake period, an eight-bed-position whole-body PET/CT scan was performed over 25 minutes, followed by a 16-minute single-bed-position J-PET acquisition at 97 minutes post-injection.

Patient 3 ( $^{68}\text{Ga}$ ]Ga-PSMA, KMU), a 70-year-old male who was administered 156 MBq of the radiotracer. Following a 59-minute uptake period, a nine-bed-position PET/CT scan was acquired over 28 minutes. This was followed by a 10-minute single-bed-position J-PET



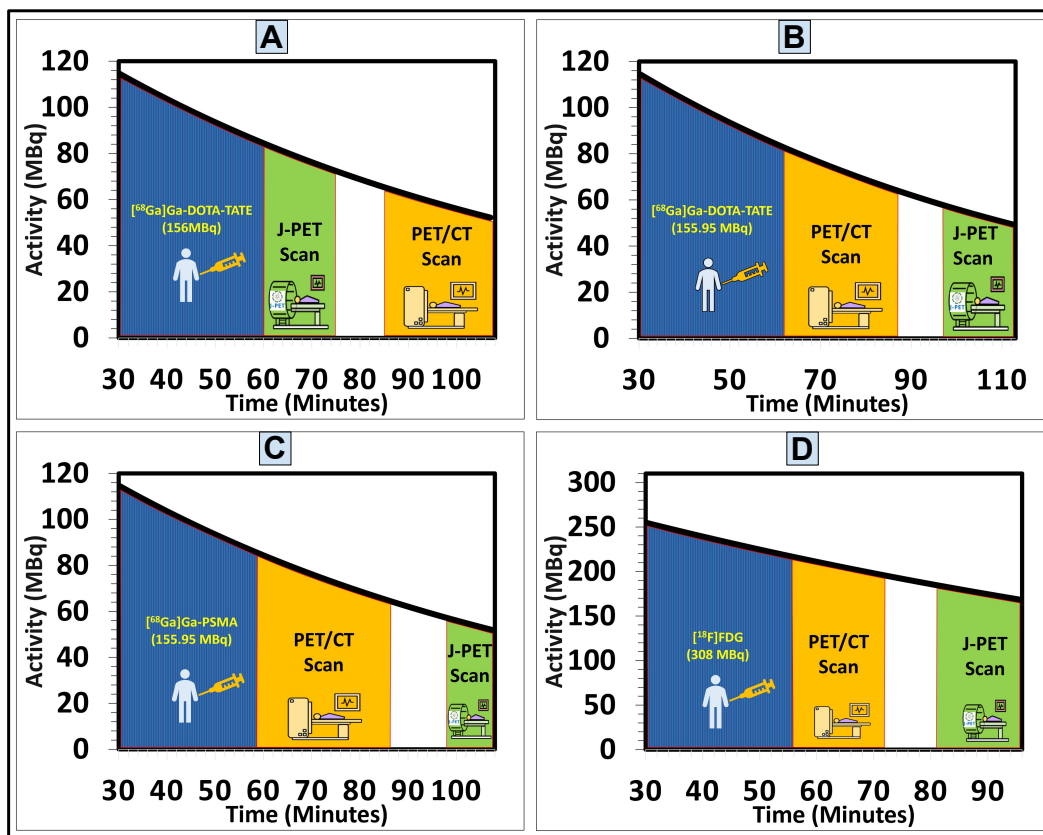


Figure 3.4: Patient-specific acquisition timelines for the first clinical imaging studies performed with the Modular J-PET scanner. The solid black curve represents the decay of radiotracer activity over the course of the imaging procedures. Panels (A–D) correspond to the four examined patients: (A) Patient 1 ([<sup>68</sup>Ga]Ga-DOTA-TATE, Warsaw), (B) Patient 2 ([<sup>68</sup>Ga]Ga-DOTA-TATE, Kraków), (C) Patient 3 ([<sup>68</sup>Ga]Ga-PSMA, Kraków), and (D) Patient 4 ([<sup>18</sup>F]FDG, Kraków). The blue shaded area represents the waiting time after radiopharmaceutical injection, the green shaded area denotes the data acquisition with the modular J-PET scanner, and the orange shaded area corresponds to the imaging performed with the commercial PET/CT scanner.

scan performed at 98 minutes post-injection.

Patient 4 ([<sup>18</sup>F]FDG, KMU), a 50-year-old male who was administered 308 MBq of [<sup>18</sup>F]FDG. After a 56-minute uptake period, a nine-bed-position PET/CT scan was acquired over 16 minutes, followed by a 15-minute single-bed-position J-PET acquisition at 81 minutes post-injection.

The imaging workflow for each patient is summarized in Figure 3.4. In the graphs, the solid black curves represent the physical decay of the administered radiotracer over time, whereas the colored shaded regions indicate the different stages of the imaging procedure: the uptake period after radiopharmaceutical injection (blue), PET/CT acquisition (orange) and J-PET acquisition (green).

The results of the first clinical trials and two gamma coincidence images with the J-PET scanner is detailed in the Chapter 5.

## 3.2 Experiments for Positronium Lifetime Imaging (PLI)

In the second part of thesis, which focuses on PLI, four different measurements were performed. Three of these were phantom studies carried out using novel  $\beta^+ + \gamma$  emitting radionuclides:  $^{44}\text{Sc}$ ,  $^{52}\text{Mn}$ , and  $^{55}\text{Co}$ . These isotopes were selected due to their favorable properties for PLI.

The final measurement was conducted to demonstrate the feasibility of PLI in a clinical setting using patient data. In this case, the analysis was focused on the liver, spleen and kidneys following administration of [ $^{68}\text{Ga}$ ]Ga-DOTA-TATE.

### 3.2.1 Measurement with $^{44}\text{Sc}$ and $^{18}\text{F}$

As described in Chapter 1,  $^{44}\text{Sc}$  emerged as a strong candidate for PLI [5, 40, 41], owing to its favorable decay characteristics. It has a clinically compatible half-life of 4.04 h [119], an ultrashort de-excitation time of 2.61 ps, and a 94.3% probability of decays producing a positron accompanied by a high-energy (1157 keV) prompt gamma [40] with a yield of 100% as shown in the decay scheme (see Figure 1.10). This corresponds to a prompt gamma yield associated with positron emission that is approximately 75 times higher than that of  $^{68}\text{Ga}$  [41].

#### Isotope preparation

In this study, two  $\beta^+$  emitters,  $^{18}\text{F}$  and  $^{44}\text{Sc}$ , were used simultaneously. These isotopes exhibit distinct decay characteristics.  $^{18}\text{F}$  decays predominantly via  $\beta^+$  emission (97%) and, to a lesser extent, through electron capture (3%), without the emission of a prompt gamma photon. In contrast,  $^{44}\text{Sc}$  undergoes  $\beta^+$  decay in approximately 94.3% of cases and is followed by the emission of a high-energy (1157 keV) prompt  $\gamma$ -ray with nearly 100% probability [40]. These fundamental differences, especially the presence or absence of prompt gamma emission, provide a basis for evaluating the effectiveness of the selection criteria developed to identify  $\beta^+ + \gamma$  events for the PLI studies.

The  $^{18}\text{F}$  used in this work was obtained from the commercial supplier VOXEL, while  $^{44}\text{Sc}$  was produced at the Heavy Ion Laboratory of the University of Warsaw via the  $^{44}\text{Ca}(\text{p},\text{n})^{44}\text{Sc}$  nuclear reaction [133–135]. For this purpose, natural calcium carbonate ( $\text{CaCO}_3$ ) targets in the form of pressed tablets were irradiated using a 16.5 MeV proton beam with a current of 15  $\mu\text{A}$  for a duration of 2 hours and 20 minutes. Each tablet, with a mass of 70 mg, was mounted onto a graphite backing, resulting in a total mass of 342 mg per target disc.

Following irradiation, the target material was dissolved in diluted hydrochloric acid (HCl) to extract the scandium. The resulting solution was filtered to remove residual graphite particles, and was subsequently purified, concentrated, and chemically processed. Finally, the solution was buffered to increase the pH from approximately 0.5 to around 4.0, making it suitable for the experimental use.

### Phantom preparation and measurement with the J-PET Scanner

A NEMA-IQ phantom experiment was carried out to demonstrate PLI measurements using  $^{44}\text{Sc}$  with the Modular J-PET scanner. The phantom contains six spherical inserts with diameters of 10, 13, 17, 22, 28, and 37 mm, as well as a lung-equivalent compartment filled with styrofoam beads to mimic low-density tissue. As depicted in the transaxial CT image in Figure 3.5(A), the three smallest spheres (10, 13, and 17 mm) were filled with  $^{18}\text{F}$ , whereas the larger spheres (22, 28, and 37 mm) contained  $^{44}\text{Sc}$ . Both radionuclides were prepared in water solution, with initial activity concentrations of 0.574 MBq/mL for  $^{18}\text{F}$  and 0.185 MBq/mL for  $^{44}\text{Sc}$  at the beginning of the experiment. The background compartment was filled with demineralized water and did not contain any radioactivity. The phantom was positioned inside the scanner as shown in Figure 3.5(B), and data acquisition was performed for 178 minutes. The analysis of the  $^{44}\text{Sc}$  dataset is presented in Chapter 6.

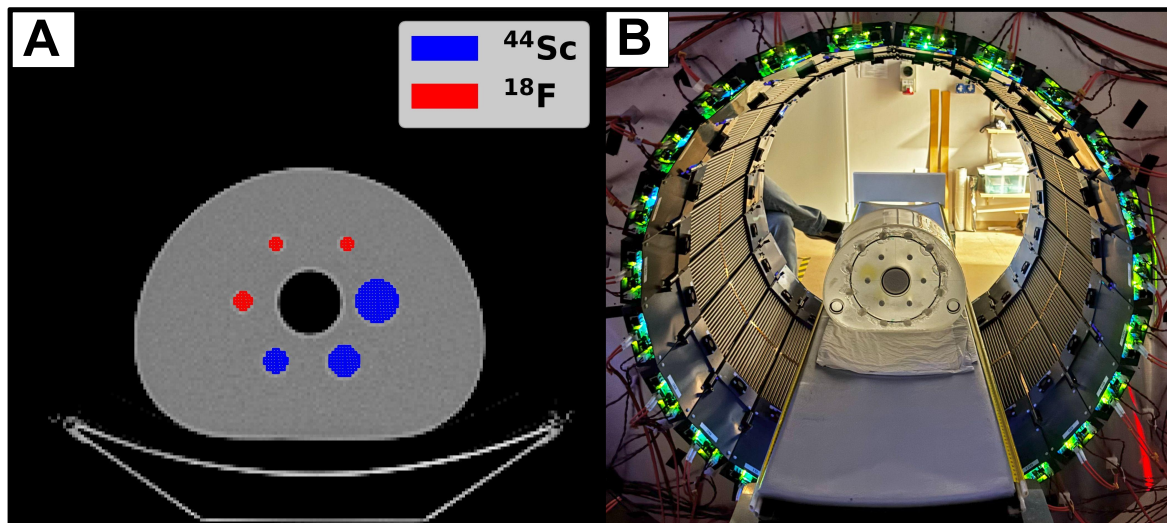


Figure 3.5: (A) Transaxial CT image of the NEMA IQ phantom illustrating the schematic distribution of radiotracers in the spheres, red indicating  $^{18}\text{F}$ -filled spheres and blue indicating  $^{44}\text{Sc}$ -filled spheres. (B) The NEMA IQ phantom positioned inside the modular J-PET detector for the experiment. Figure, prepared by the author, is adapted from [41], licensed under CC BY 4.0.

#### 3.2.2 Measurement with $^{52}\text{Mn}$ and $^{55}\text{Co}$

While  $^{44}\text{Sc}$  satisfies many of the essential requirements for PLI, its short half-life restricts its labelling use in radiopharmaceuticals characterized by slow pharmacokinetics, including monoclonal antibodies. In addition, the availability of specific isotopes may vary across centers depending on available production methods (e.g., generator-based or cyclotron-based approaches). These limitations motivate the search for alternative  $\beta^+ + \gamma$  emitters suitable for PLI. Several candidates, including  $^{52}\text{Mn}$ ,  $^{55}\text{Co}$ ,  $^{60}\text{Cu}$ ,  $^{72}\text{As}$ ,  $^{14}\text{O}$ , and  $^{10}\text{C}$ , have been proposed due to their favorable physical properties [5, 40, 51].

In this work, we investigate for the first time the two promising long-lived radionuclides,  $^{52}\text{Mn}$  and  $^{55}\text{Co}$ , for PLI applications.  $^{52}\text{Mn}$  has a half-life of 5.59 days and emits positrons in



29.4% of decays, followed by a cascade of prompt gamma photons (744 keV, 935 keV, and 1434 keV). This multi-gamma cascade may, in principle, increase the prompt-photon detection efficiency and hence the sensitivity for  $\beta^+ + \gamma$  events suitable for PLI.  $^{55}\text{Co}$ , with a half-life of 17.53 hours, emits positrons in 76% of decays and produces prompt gamma rays (477 keV, 931 keV, and 1409 keV) through de-excitations of  $^{55}\text{Fe}$  states, making it another suitable candidate for PLI.

### Isotope preparation

For this study, two separate experiments were conducted with  $^{52}\text{Mn}$  and  $^{55}\text{Co}$ . The  $^{52}\text{Mn}$  isotope was produced under the PRISMAP – The European Medical Isotope Programme at the Hevesy Laboratory, Department of Health Technology, Technical University of Denmark (DTU). It was produced via the  $^{52}\text{Cr}(p,n)^{52}\text{Mn}$  reaction [136] by irradiating a natural chromium target for 8 hours with a 16.5 MeV proton beam at 40  $\mu\text{A}$  current using a GE PETtrace cyclotron. Following irradiation, the activity was recovered in the form of  $\text{Mn}^{2+}$  cations dissolved in 0.1 M HCl and subsequently transported by air to Warsaw and then by road to Jagiellonian University in Kraków for further experiments.

The  $^{55}\text{Co}$  isotope was produced at the Heavy Ion Laboratory of the University of Warsaw via the  $^{54}\text{Fe}(d,n)^{55}\text{Co}$  reaction [137, 138]. In this case, a metallic  $^{54}\text{Fe}$  target was irradiated for 2 hours with an 8.4 MeV deuteron beam at a current of 14.1  $\mu\text{A}$ . After irradiation, the target material was dissolved in 6 M HCl, filtered, and the  $^{55}\text{Co}$  was chemically separated at the Institute of Nuclear Chemistry and Technology in Warsaw. The resulting solution was then transported to the laboratory in Kraków for experiments.

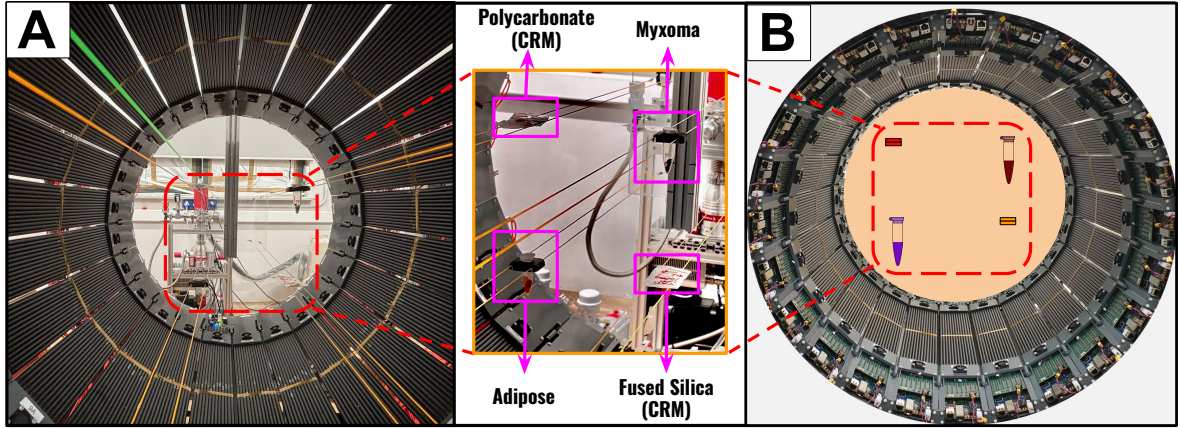


Figure 3.6: (A) Experimental configuration of the four samples inside the Modular J-PET scanner. (B) Schematic representation of the samples relative positioning within the detector FOV. Figure, prepared by the author, is adapted from [53], licensed under CC BY 4.0.

### Phantom preparation and measurement

In both experiments, four types of samples were investigated: human adipose tissue, cardiac myxoma tissue, and two Certified Reference Materials (CRMs), namely fused silica

and polycarbonate, with known mean o-Ps lifetimes. The CRMs were purchased from the National Institute of Advanced Industrial Science and Technology (AIST), Japan, and served as calibration standards to verify the stability and accuracy of the measurements. The biological samples were chosen to represent healthy fatty tissue and tumor tissue, enabling a comparison of the properties of Ps in different tissue types with distinct molecular composition and free-volume structure.

The adipose and cardiac myxoma tissues were collected from a patient at the John Paul II Hospital in Kraków, Poland, under bioethical approval (No. 1072.6120.123.2017). These specimens had previously been used in the first demonstration of *ex-vivo* Ps imaging with the J-PET system [25] and were reused in the present study for measurements with  $^{52}\text{Mn}$  and  $^{55}\text{Co}$ . After the earlier experiments, the tissues were preserved in formaldehyde solution and stored until further use. Prior to the current measurements, the samples were removed from the preservative, immersed in Lugol's solution to enhance soft-tissue contrast for 24 hours at 40 °C, and subsequently drained [39]. The tissues were then stored in the refrigerator. The storage time differed between experiments, of approximately three months for the  $^{52}\text{Mn}$  study and approximately five months for the  $^{55}\text{Co}$  measurements.

For the experimental setup, the adipose and myxoma samples were placed in 5 mL Eppendorf tubes. A separate thin-walled tube (0.2 mL) containing the radioactive solution ( $^{52}\text{Mn}$  or  $^{55}\text{Co}$ ) was positioned between the samples to avoid direct contamination. In the case of the CRMs, fused silica and polycarbonate plates purchased from AIST were used without modification, while the source holder and mounting system were prepared locally. Ten layers of Parafilm, with a total thickness of approximately 1.2 mm, were stacked to form a spacer with a central cavity for the radioactive source. The liquid source was deposited in this cavity and enclosed between two CRM plates. The fused silica plates had dimensions of 15 mm  $\times$  15 mm  $\times$  1.5 mm, while the polycarbonate plates measured 15 mm  $\times$  15 mm  $\times$  2 mm. To ensure proper sealing and prevent leakage, the entire assembly was wrapped with an additional layer of Parafilm.

For the  $^{52}\text{Mn}$  measurements, activities of 1.278 MBq, 1.298 MBq, 1.346 MBq, and 1.354 MBq were used for the cardiac myxoma, adipose tissue, polycarbonate, and fused silica samples, respectively, measured at the start of the experiment. Data acquisition was performed over a period of 19 hours and 44 minutes with all samples placed in the scanner. For the  $^{55}\text{Co}$  study, the corresponding activities were 1.032 MBq, 1.020 MBq, 1.092 MBq, and 1.071 MBq, and the measurement lasted 15 hours and 5 minutes. Apart from the choice of radionuclide and activity levels, the experimental configuration remained identical for both measurements (see Figures 3.6(A–B)). The results of this studies are presented in Chapter 7.

### 3.2.3 Clinical Trials for Positronium Lifetime Imaging at WMU and KMU

Although  $^{68}\text{Ga}$  is characterized by a relatively low  $\beta^+ + \gamma$  yield (approximately 1.19%), it remains widely used in clinical practice, particularly in radiotracers such as PSMA and DOTA-TATE. Despite this limitation for PLI, its clinical availability has enabled the first demonstration of PLI studies of the human brain using [ $^{68}\text{Ga}$ ]Ga-PSMA [4].

In the present work, PLI studies were performed on patients injected with  $[^{68}\text{Ga}]\text{Ga-DOTA-TATE}$  for the assessment of NETs. A total of six patients (3 men and 3 women), aged 33 to 82 years, with suspected NETs of varying stages and locations, were analyzed. Among these patients, five were examined at KMU and one patient at WMU. The patient characteristics are listed in Table 3.3 and the scan workflow with commercial PET/CT and J-PET is summarized in Table 3.4. The primary objective was to evaluate the feasibility of organ-level PLI under routine clinical conditions, with the analysis focused on the liver, spleen, and kidneys.

| Pat.No. | Hospital | Age | Gender | Weight (kg) | Act. Inj. (MBq)      |
|---------|----------|-----|--------|-------------|----------------------|
| 1       | KMU      | 82  | Woman  | 48          | 157.20(Ga-DOTA-TATE) |
| 2       | KMU      | 48  | Man    | 73          | 145.42(Ga-DOTA-TATE) |
| 4       | KMU      | 77  | Man    | 72          | 150.26(Ga-DOTA-TATE) |
| 5       | KMU      | 33  | Man    | 62          | 157.53(Ga-DOTA-TATE) |
| 10      | KMU      | 75  | Woman  | 75          | 147.69(Ga-DOTA-TATE) |
| W       | WMU      | 56  | Woman  | 64          | 156 (Ga-DOTA-TATE)   |

Table 3.3: Summary of patient characteristics for the clinical studies, including hospital site, age, gender, body weight, and administered activity with the corresponding radiotracer. WMU denotes the Medical University of Warsaw, and KMU denotes the Jagiellonian University Medical College in Kraków.

| Pat.No. | Post Inj. (PET-CT) | $T_{\text{scan}}$ (PET-CT) | Post Inj. (J-PET) | $T_{\text{scan}}$ (J-PET) |
|---------|--------------------|----------------------------|-------------------|---------------------------|
| 1       | 60 min             | 25 min                     | 96 min            | 15 min                    |
| 2       | 55 min             | 28 min                     | 91 min            | 20 min                    |
| 4       | 60 min             | 25 min                     | 93 min            | 20 min                    |
| 5       | 61 min             | 28 min                     | 94 min            | 18 min                    |
| 10      | 58 min             | 25 min                     | 90 min            | 15 min                    |
| PW      | 85 min             | 23 min                     | 60 min            | 15 min                    |

Table 3.4: Timing details of the imaging procedures for each patient, including the post-injection time and scan duration for both PET/CT and J-PET acquisitions. Post-injection time refers to the interval between radiotracer administration and the start of the scan, while  $T_{\text{scan}}$  denotes the acquisition duration.



## Chapter 4

# Development of Correction Techniques for the Modular J-PET Scanner

In PET measurements, three physical effects must be corrected in the coincidence data to ensure the quantitative accuracy of a PET scanner: photon attenuation within the object, random coincidences, and scattered coincidences. All three effects introduce both multiplicative and additive contributions to the reconstructed image of the true activity distribution. Consequently, implementing correction methods for the J-PET scanner is essential to mitigate these effects.

The J-PET scanner is composed of elongated plastic scintillator strips. Dominant interaction of photons with 511 keV energy in the scintillator material is Compton scattering. Thus, there is no photopeak in the energy spectra, so that scatter rejection by energy window around 511 keV energy is not applicable. In addition to that, the scanner has an axial strip geometry. Thus, the sampling of the LOR differs from the sampling of the transaxial line in ring-shaped detectors. Therefore, the common correction algorithms, developed for crystal-based PET scanners and based on the assumption of ring-shaped detectors, cannot be used directly. Instead, a dedicated framework for data processing, reconstruction and correction has to be developed and validated for the modular J-PET scanner. In this chapter the implementation of the three correction methods is presented. The work described in this chapter has been published in Ref. [22] where the author of this thesis is the first author.

### 4.1 Attenuation Correction

Attenuation of annihilation photons occurs as they are absorbed or scattered while traversing tissue, leading to a significant underestimation of the activity concentration. The effect is most pronounced for deep anatomical structures, where both 511 keV photons travel a few centimeters in the body tissue before they are detected by the detector. The J-PET scanner utilizes a CTAC method, which is considered the gold standard in PET imaging. This approach involves converting Hounsfield Units (HU) from CT images into linear attenuation coefficients ( $\mu$ ) for 511 keV photons.

Unlike PET imaging, where photon energy is monochromatic at 511 keV, CT imaging utilizes a polychromatic X-ray beam with a spectrum of energies determined by the tube voltage, typically ranging from 80 kVp to 140 kVp. Following the methodology established by Carney et al. [78], the relationship between measured HU and the 511 keV linear attenuation values was modeled using a calibration phantom. A bilinear transformation was established to map HU values to corresponding linear attenuation coefficients ( $\text{cm}^{-1}$ ) using a specific

breakpoint to differentiate between the soft tissue and dense bone. To account for the kVp dependence, the empirical transformation is defined as:

$$\mu = 9.6 \times 10^{-5} \cdot (HU + 1000) \text{ cm}^{-1} \quad \text{for } (HU + 1000) \leq \text{Breakpoint} \quad (4.1)$$

$$\mu = a \cdot (HU + 1000) + b \text{ cm}^{-1} \quad \text{for } (HU + 1000) > \text{Breakpoint} \quad (4.2)$$

For the current J-PET prototype, CT scans were performed using a GE Discovery MI gen 2 PET/CT scanner at the University Hospital in Krakow and the Warsaw Medical University with the Siemens Biograph 64 with a tube voltage of 120 kVp. Based on the 120 kVp settings from Carney et al., the following parameters were applied: a breakpoint  $(HU + 1000) = 1047$  HU,  $a = 5.10 \times 10^{-5} \text{ cm}^{-1}$ , and  $b = 4.71 \times 10^{-2} \text{ cm}^{-1}$ .

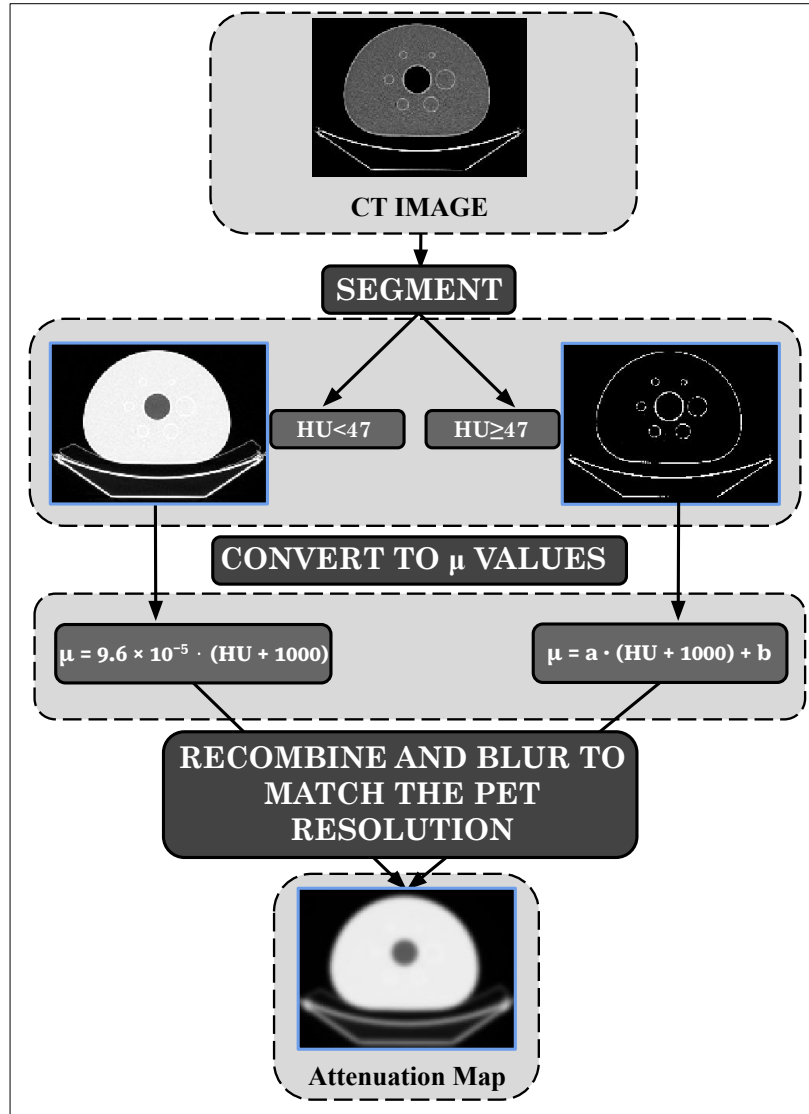


Figure 4.1: Process of obtaining the attenuation map from the CT image

The process begins with the segmentation of the CT image based on the predefined threshold, as illustrated in Figure 4.1 with an example of the CT image of the NEMA IQ phantom obtained with the GE MI gen 2 PET/CT at the University hospital in Krakow. The resulting attenuation map is resampled to a grid of  $200 \times 200 \times 200$  voxels with a voxel size of  $2.5 \text{ mm}^3$ . To align the map with the spatial resolution of the PET system, Gaussian smoothing is applied with a  $2\sigma$  value (quantified in voxels) uniformly in all directions.

Due to the current configuration where J-PET and CT measurements are acquired on separate beds, the isocenters of the two scanners do not coincide. To address this, we performed a spatial registration based on a translational alignment of the isocenters. This ensures that the CT-derived attenuation map is accurately mapped onto the J-PET coordinate system. Following this alignment, the attenuation map is integrated into the reconstruction framework as described in the subsequent section.

## 4.2 Random Correction

Random coincidences occur when two photons originating from independent annihilation events are detected within the same coincidence time window. These events introduce uniform noise and background bias into the reconstructed image, significantly degrading both image quality and quantitative accuracy. Consequently, random coincidences must be accurately estimated and compensated for during the reconstruction process.

The J-PET scanner utilizes the DTW method, which is widely regarded as the reference standard within the PET community. Typically, as described in Chapter 1, this method requires a dedicated delayed coincidence channel to collect random events. However, since the J-PET scanner operates in a triggerless acquisition mode, a physical delayed channel is not required. Instead, the same raw data stream used for two-gamma coincidence imaging can be re-processed to identify random coincidences by applying an offset during the coincidence search, eliminating the need for an additional hardware-level delayed channels.

### 4.2.1 Geometric Considerations

The modular J-PET scanner consists of 312 axially oriented plastic scintillator strips arranged in a transaxial ring. For reconstruction purposes, each scintillator is virtually segmented into 200 axial pseudo-crystals, resulting in a total of 62,400 detection elements. To satisfy geometric constraints, valid coincidences are only defined for pseudo-crystals with a trans-axial separation of at least  $60^\circ$ . At each projection angle, 208 pseudo-crystals are available for coincidence formation. By employing an interleaving strategy, which combines 104 direct parallel lines with 103 cross-pair lines (offset by a half-width), the system achieves 207 radial bins (unique LOR) per projection angle. Across the 156 unique projection angles and  $200 \times 200$  possible axial detector planes, the total number of LORs is calculated as:

$$207 \text{ bins} \times 156 \text{ angles} \times 40,000 \text{ planes} \approx 1.29 \times 10^9 \text{ LORs}$$

Estimating the random coincidence contribution for each of the 1.29 billion LORs individually is statistically impractical under typical clinical count rates, as the majority of bins would contain insufficient data for a reliable estimate.

### 4.2.2 Block-Based Grouping and Sinogram Formation

To address these statistical limitations and improve the SNR of the randoms estimate, a spatial rebining strategy was implemented. Pseudo-crystals were aggregated into larger blocks, significantly increasing the counts per bin. The compression parameters are defined as follows:

- **Axial Grouping:** 8 pseudo-crystals were combined to form 25 axial blocks.
- **Trans-axial Grouping:** 4 scintillators were combined, resulting in 39 angular bins and 51 radial bins.

The resulting 4D data structure for randoms estimation is organized by the parameters  $(s, \phi, z_1, z_2)$ . The axial distribution of these block-based coincidences is organized into a 4D sinogram, where  $z_1$  and  $z_2$  (each consisting of 25 blocks) represent the axial positions of the detector blocks forming a coincidence pair. This grouping reduces the total number of detector combinations to approximately 1,243,125 block pairs ( $51 \times 39 \times 25 \times 25$ ). By performing the correction at the block level, the statistics per bin are increased by three orders of magnitude compared to the pseudo-crystal-based LORs.

### 4.2.3 Implementation of the DTW Algorithm

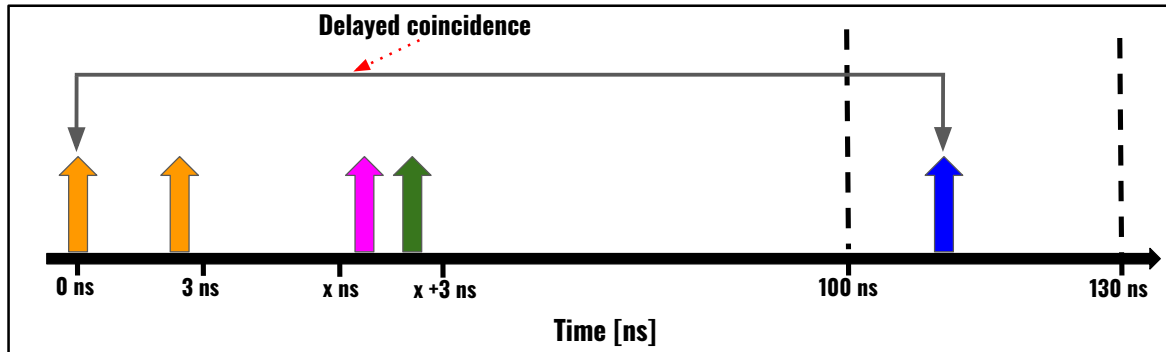


Figure 4.2: Schematic of the DTW method for random coincidence correction. Following an initial interaction, a 100 ns offset is applied to ensure the exclusion of correlated events, after which a 30 ns delayed coincidence window is established to capture random coincidences. The orange arrows denote a true coincidence. The pink and green arrows represent a random coincidence resulting from independent annihilation events where the partner photons were either attenuated or undetected. Time intervals are provided for illustrative purposes and are not to scale. Figure, prepared by the author, is adapted from [22], licensed under CC BY 4.0.

To identify prompt annihilation events, a CTW of 3 ns is used in the modular J-PET Scanner with events containing more than two interactions within this window are excluded. The random coincidence rate was estimated by leveraging the system's triggerless acquisition, introducing a 100 ns temporal offset after each initial interaction. Initially, a 3 ns delayed



CTW was employed to obtain uncorrelated second interactions, ensuring that detected pairs originated from independent annihilation events. However, despite the block-based grouping described previously, the 3 ns delayed CTW resulted in significant statistical variance in the random factors. To mitigate this noise and improve the SNR of the estimation, the delayed CTW was increased to 30 ns, as illustrated in Figure 4.2. This modification increased the obtained statistics by a factor of 10, providing a more stable basis for correction.

Following data processing, random events were binned into the 4D block-based sinograms  $(s, \phi, z_1, z_2)$ . Under the assumption of a uniform distribution of random coincidences across all LORs within a specific block-pair bin, the random rate  $R_i$  for an individual LOR  $i$  belonging to block pair  $b$  was calculated as:

$$R_i = \frac{N_b}{N_{LOR} \times T_{meas} \times 10} \quad (4.3)$$

In this expression,  $N_b$  denotes the total number of entries in the block sinogram bin  $b$ , and  $T_{meas}$  represents the total measurement duration. The term  $N_{LOR} = (8 \times 4)^2 = 1,024$  represents the total number of possible pseudo-crystal-based LORs within the given detector block pair. The scaling factor of 10 is included to normalize the rate, compensating for the deliberate enlargement of the delayed CTW from 3 ns to 30 ns. The resulting LOR-specific random rates were then incorporated as a new column into the Customizable and Advanced Software for Tomographic Reconstruction (CASToR) list-mode data for the reconstruction.

### 4.3 Scatter Correction

Scatter coincidences occur when one or both photons from an annihilation event undergo Compton scattering within the object being imaged. This process results in a change of direction and energy loss, causing the resulting LOR to be mispositioned. Scatter coincidences are a major degradation factor, leading to a significant reduction in image contrast and quantitative accuracy. To compensate for these effects in the modular J-PET scanner, a Monte-Carlo based scatter correction framework was developed and implemented.

#### 4.3.1 Monte-Carlo Simulation with SimSET

Monte-Carlo simulations for scatter estimation were performed using the Simulation System for Emission Tomography (SimSET) (Version 2.9.2). The initial input for the simulation consists of:

- **Emission (Activity) Map:** An initial reconstructed image of the activity distribution, containing all corrections (normalization, attenuation, and randoms) except for scatter.
- **Attenuation Map:** A voxelized map of attenuation coefficients derived from the CT scanner data, as described in the previous section.

SimSET tracks the history of each simulated photon. If a detected coincidence pair involves at least one photon that has undergone a scattering event, it is classified as a scatter coincidence; otherwise, it is recorded as a true coincidence. The simulated true and scattered events are

stored in list-mode format. Since the simulation provides count distributions only relative to the total number of simulated events, proper scaling of the scatter events are required to estimate the scatter contribution in the measured data. After scaling, the scatter correction factors are incorporated into the CASToR list-mode file to perform the final reconstruction.

The complete pipeline is schematically shown in Figure 4.3. More details about the scaling procedure and the estimation of correction factors are provided in the next subsection.

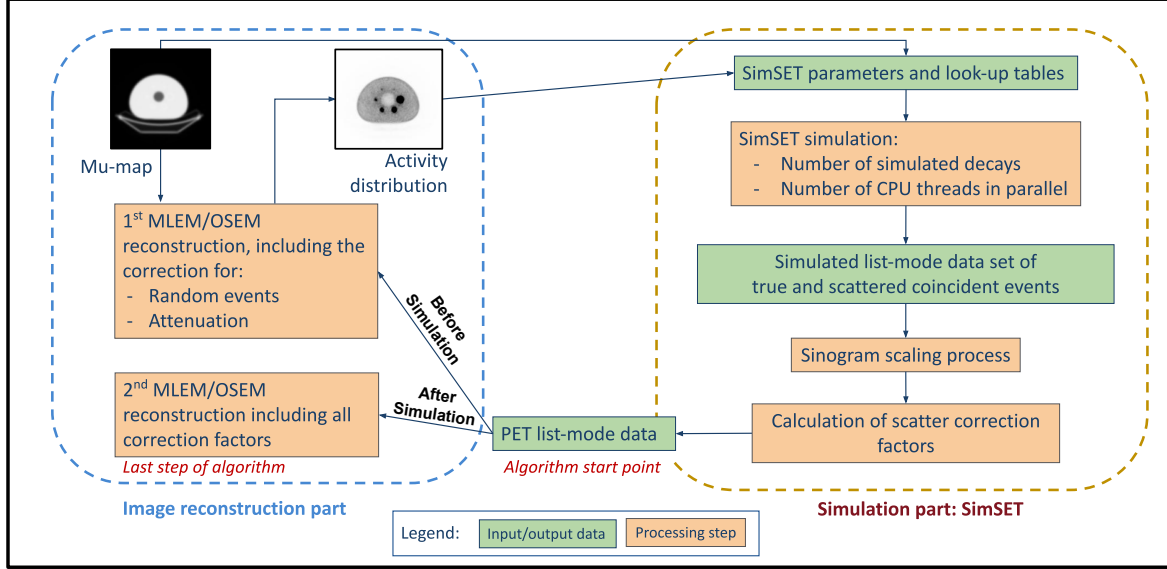


Figure 4.3: Schematic overview of the scatter correction and image reconstruction workflow for the modular J-PET scanner. The process utilizes an initial, uncorrected reconstruction to estimate scatter event rates. These rates are then incorporated into a secondary MLEM/OSEM reconstruction to produce the final, fully corrected PET image

### 4.3.2 TOF-Integrated Binning and Estimation

To estimate the scatter contribution across the large LOR space of the J-PET scanner, a block-based binning approach is used, following the same strategy as in the random coincidence correction. However, unlike the randoms correction, scatter estimation must also account for TOF information. Therefore, the scatter distribution is organized into a 5D sinogram defined by  $(s, \phi, z_1, z_2, \text{TOF})$ . The same block-based grouping as used for randoms (51 radial bins, 39 angular bins and 25 axial blocks) is applied. In addition, the TOF is discretized into 20 bins.

### 4.3.3 Scintillator Material Implementation in SimSET

The J-PET detector is constructed using BC-404 plastic scintillators (Saint-Gobain). This material is a polyvinyltoluene-based compound ( $\text{C}_{10}\text{H}_{11}$ ) with a density of  $1.023 \text{ g/cm}^3$  [139]. These parameters were implemented in the SimSET simulation framework to accurately model the detector response. However, the relatively low attenuation coefficient of plastic scintillators

for 511 keV photons poses a significant challenge, leading to low detection sensitivity and consequently long simulation times detailed in Chapter 5.

To address this limitation, lutetium–yttrium oxyorthosilicate (LYSO) was introduced into the simulation as a high-efficiency surrogate material. Due to its higher density and effective atomic number, LYSO provides significantly improved photon detection efficiency, enabling faster simulations.

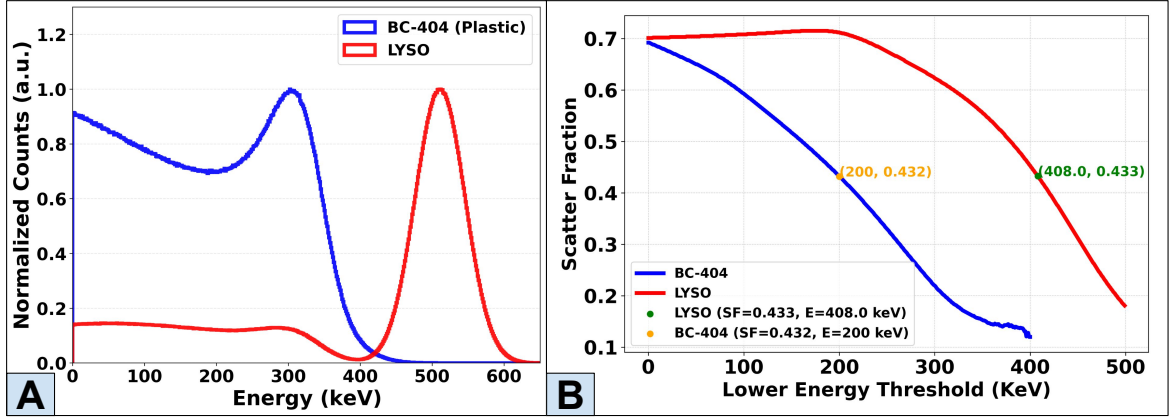


Figure 4.4: (A) Energy spectra of deposited energy for true events simulated with SimSET using BC-404 and LYSO scintillators. (B) Simulated scatter fraction for BC-404 (blue) and LYSO (red) using the NEMA IQ phantom. The markers indicate the lower energy thresholds corresponding to equivalent scatter fractions.

As an initial validation step, the energy spectra for true events simulated with BC-404 and LYSO were compared, assuming 511 keV photon emissions and a detector energy resolution of 16%, as shown in Figure 4.4(A). The BC-404 spectrum is shown in blue, while the LYSO spectrum is shown in red. These simulations were performed using the NEMA IQ phantom. To use LYSO as a surrogate for BC-404, equivalent scatter fraction conditions were established by adjusting the lower energy thresholds. For BC-404, a lower energy threshold of 200 keV resulted in a scatter fraction of 43.2%. To achieve a comparable scatter fraction with LYSO, the corresponding energy threshold was determined to be 408 keV, as illustrated in Figure 4.4(B). A comparison of the reconstructed images and a qualitative evaluation of this approximation are presented in Chapter 5.

#### 4.3.4 Scatter Scaling

Scatter scaling is a critical correction step used to reconcile simulated scatter estimates with actual measured data. The fundamental data representation for this process is based on the relationship in which total prompt events  $P$  consist of true coincidences  $T$ , scattered coincidences  $S$ , and random coincidences  $D$ :

$$P = T + S + D \quad (4.4)$$

$$P - D = T + S \quad (4.5)$$

To perform the scaling, the data are binned into block-sinograms (utilizing  $4 \times 8$  crystals per block), as described previously. The scaling is carried out plane-by-plane, and a separate scaling factor  $f_k$  is computed for each projection plane  $k$  at the block-based sinogram level. This approach relies on the key assumption that the scatter fraction is identical for both measured and simulated block-sinograms within each plane.

The scatter fraction for a projection plane ( $25 \times 25$  possible projection planes)  $k$  is defined as:

$$SF_k = \frac{\sum_b S_{b,k}^{\text{meas}}}{\sum_b (P_{b,k} - D_{b,k})^{\text{meas}}} = \frac{\sum_b S_{b,k}^{\text{sim}}}{\sum_b (T_{b,k} + S_{b,k})^{\text{sim}}}, \quad (4.6)$$

where  $b$  denotes the block-sinogram bin,  $P_{b,k}^{\text{meas}}$  is the measured prompt coincidence count,  $D_{b,k}^{\text{meas}}$  is the measured delayed coincidence count used for randoms estimation,  $S_{b,k}^{\text{meas}}$  and  $S_{b,k}^{\text{sim}}$  are the measured and simulated scatter coincidence counts, respectively, and  $T_{b,k}^{\text{sim}}$  is the simulated true coincidence count.

From this equality, the plane-dependent scaling factor  $f_k$  is derived, allowing the measured scatter sum for each plane to be estimated by scaling the simulated results:

$$\sum_b S_{b,k}^{\text{meas}} = \sum_b S_{b,k}^{\text{sim}} \cdot \underbrace{\frac{\sum_b (P_{b,k} - D_{b,k})^{\text{meas}}}{\sum_b (T_{b,k} + S_{b,k})^{\text{sim}}}}_{f_k} \quad (4.7)$$

Furthermore, since the distribution of scattered and true events across individual TOF bins is not expected to differ between the simulated and measured data, the entries from all TOF bins are summed for each block bin  $b$  to reduce noise. Consequently, a single scaling factor  $f_k$  (for each plane  $k$ ) is applied uniformly across all TOF bins.

Finally, it is assumed that scatter is, on average, uniformly distributed across all LORs within a block. This assumption allows the estimation of scatter for each LOR  $i$  and TOF bin  $t$  from the scaled block-sinogram entries as described in the next section.

#### 4.3.5 Estimating the Scatter contribution for each LOR and TOF bin

The plane-wise scaling described in the previous section provides the absolute normalization of the simulated scatter distribution with respect to the measured (prompt-random) data. A smoothing procedure was applied to the estimated scatter sinograms prior to their use in subsequent MLEM/OSEM reconstruction updates in order to suppress statistical fluctuations arising from the scatter estimation process. The smoothing was carried out using a Gaussian filter with a FWHM of four bins. Since the smoothing step was performed after the scatter scaling, the overall event counts within each sinogram plane remained unchanged, thereby maintaining the quantitative accuracy of the scatter estimate.

For a given block-sinogram bin  $b$  and TOF bin  $t$ , the total scatter rate  $S_{b,t}$  is calculated by scaling the simulation results:

$$S_{b,t} = \frac{S_{b,t}^{\text{sim,Gauss}} \times f_k}{T_{\text{meas}}}, \quad (4.8)$$

where  $S_{b,t}^{\text{sim,Gauss}}$  represents the entries in the scaled and smoothed simulated scatter sinogram for block bin  $b$  and TOF bin  $t$ , and  $T_{\text{meas}}$  is the measurement duration.

Subsequently, assuming a uniform scatter distribution across all  $N_{\text{LOR}}$  lines of response within that block-sinogram bin, the final scatter rate  $S_{i,t}$  for each individual LOR  $i$  belonging to block  $b$  is given by:

$$S_{i,t} = \frac{S_{b,t}}{N_{\text{LOR}}} \quad \forall \quad i \in b \quad (4.9)$$

where  $N_{\text{LOR}}$  is the number of LORs per block bin. The resulting scatter rates are subsequently integrated into the list-mode data, providing the necessary additive correction term for the CASToR reconstruction framework.

#### 4.4 Establishing the Complete Reconstruction Pipeline

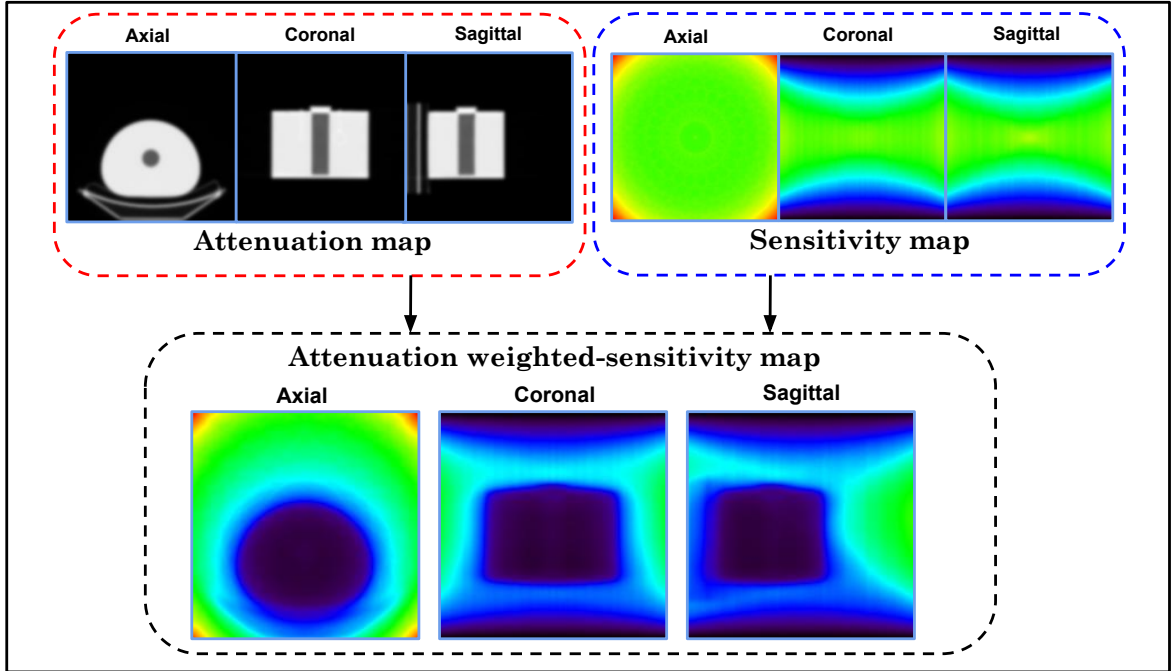


Figure 4.5: Merging the NEMA IQ phantom attenuation map and a Monte Carlo derived sensitivity map using the CASToR SENS optimizer.

Image reconstruction for the modular J-PET scanner is performed using CASToR [19]. In this study, the sensitivity map was derived entirely from Monte Carlo simulations and subsequently applied during the reconstruction process. The Monte Carlo simulation consisted of a high-statistics acquisition of a uniform cylindrical phantom that fully occupied the scanner's FOV.

The sensitivity map computation, along with the incorporation of the attenuation map, was carried out within the CASToR framework using the SENS optimizer, as illustrated in Figure 4.5 for the NEMA IQ phantom. Furthermore, normalization factors were included

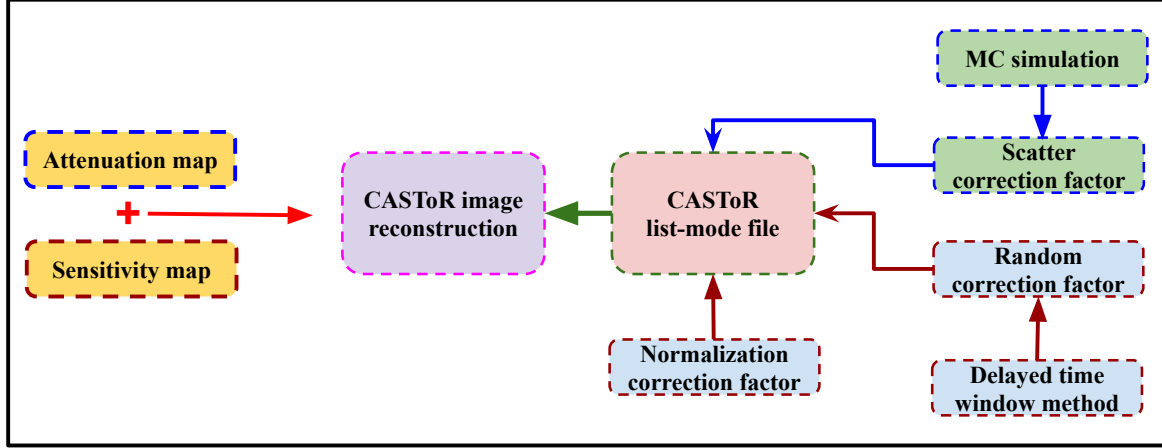


Figure 4.6: Schematic overview of the image reconstruction workflow for the modular J-PET scanner.

during reconstruction using a component-based approach [140, 141]. In addition, correction factors for random coincidences, estimated using the DTW method, and scatter correction factors, derived using a Monte Carlo-based approach, were incorporated into the CASToR list-mode data. A schematic overview of the complete reconstruction pipeline is presented in Figure 4.6.

## Chapter 5

# Evaluation of two-gamma coincidence imaging with J-PET

After establishing the event-selection, correction techniques and reconstruction pipeline in the preceding chapters, this chapter presents the experimental evaluation of two-gamma coincidence imaging with the Modular J-PET scanner. The evaluation was performed in two stages. First, the method is demonstrated using a NEMA IQ phantom measurement, providing the first standardized assessment of image quality for J-PET. Second, the same reconstruction framework was applied to the first clinical PET image of human subjects acquired with the J-PET scanner in a clinical setting. The experimental details for both studies have already been described in Chapter 3. Part of this work has been published in a peer-reviewed manuscript with the author of the thesis as the co-first author [23].

### 5.1 Selection criteria for two gamma coincidence imaging

The triggerless DAQ and low-level data processing described in Chapter 2 provide information on how the raw data are processed with the J-PET framework to obtain the hit-time, hit-position, and total TOT (measure of energy deposition) for each registered photon [18]. In plastic scintillators, photons interact mainly via Compton scattering. This introduces background due to secondary interactions of detector-scattered photons. Additionally, radionuclides that emit high-energy prompt photons can lead to the construction of LORs that contain prompt gamma interactions. Therefore, an event selection is required to suppress events of detector scattered photons, accidental coincidences as well as prompt-gamma interactions that are not spatially correlated with annihilation photons.

For each detected interaction (hit), the TOT value is obtained by averaging the signals recorded by SiPMs coupled to both ends of a scintillator strip [18]. This averaged TOT value serves as a measure for the energy transferred by the Compton-scattered photon. Only interactions with TOT values in the range  $[3, 5]$  ns·V are selected (Figure 5.1(A)). This region, corresponds to the Compton edge for 511 keV photons, enhances the contribution of true annihilation gamma interactions. Prompt photons tend to yield higher TOT values, while secondary scatterings typically result in lower energy deposits. Following the preliminary selection of annihilation-photon candidates, an additional event-selection criterion was applied based on hit multiplicity (Figure 5.1(B)). Events with exactly two hits ( $\mu = 2$ ) within a 3 ns CTW are treated as annihilation candidates. To reduce background from scattered and accidental events, an angular constraint is also applied. The distribution of the relative angle  $\theta_{AA}$  between the two selected annihilation photons with respect to center is shown in

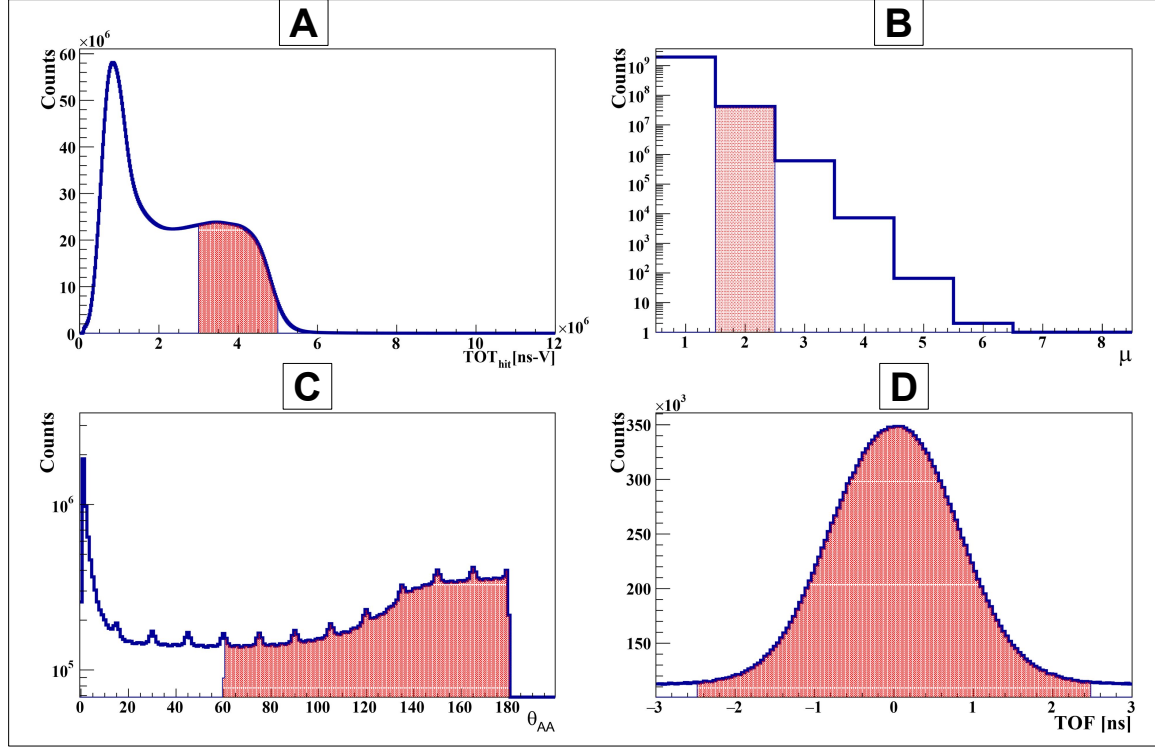


Figure 5.1: Event-selection criteria used for two-gamma coincidence image reconstruction with the Modular J-PET scanner. Any pair of two photon interactions may originate from one of the coincidence types described in previous chapters: true, patient-scattered, detector-scattered, or accidental. Events surviving all selection criteria are used to construct LORs for image reconstruction. **(A)** Distribution of TOT(TOT<sub>hit</sub>) used for photon identification, with annihilation photons selected for further analysis shaded in red. **(B)** Hit multiplicity ( $\mu$ ) distribution for events within a CTW of 3 ns. The red-shaded histogram highlighting selected events containing exactly two annihilation photons. **(C)** Distribution of the relative angle ( $\theta_{AA}$ ) between annihilation-photon direction vectors  $\vec{a}_1$  and  $\vec{a}_2$ , with  $\theta_{AA} \geq 60^\circ$  (red) used as the selection criterion. **(D)** Distribution of the TOF difference  $\Delta t = t_{a1} - t_{a2}$ , with the red-shaded region indicating selected events.

Figure 5.1(C). Only events within the selected angular range ( $\theta_{AA} \geq 60^\circ$ ) are retained.

The TOF difference,  $\Delta t = t_{a1} - t_{a2}$ , is calculated for each event. Events satisfying  $-2.5 \leq \text{TOF} \leq 2.5$  ns (Fig. 5.1(D)) are selected to further suppress background.

Finally, events with exactly two interactions satisfying all selection criteria are used to construct LORs for image reconstruction. The corresponding hit-times, crystal IDs (hit-positions) of the two selected hits, and their TOF difference were then exported in CASToR list-mode format for tomographic reconstruction.

## 5.2 NEMA Image-Quality phantom

This measurement was conducted using a NEMA IQ phantom, with a <sup>18</sup>F source mixed in water, having an ACR of 9.85:1 between the spheres and the background. More details of the measurement has been provided in Section 3.1.1. After low-level data processing and



application of the two gamma event selection criteria described above using J-PET data analysis framework, a total of 32,249,721 coincidence events were obtained.

### 5.2.1 Reconstruction parameters

For the NEMA IQ phantom studies, image reconstruction was performed using the TOF-OSEM algorithm, configured with ten iterations and four subsets. The TOF resolution kernel was modeled as a Gaussian function. For each line of response, a ray-tracing projector based on the incremental Siddon algorithm [142] was employed using 10 rays.

The reconstruction process incorporated image-based Point Spread Function (PSF) modeling within the CASToR framework. The Gaussian kernel size was defined by two standard deviations ( $2\sigma$ ) in both directions. The images were reconstructed into a  $200 \times 200 \times 200$  matrix with an isotropic voxel size of  $2.5 \text{ mm}^3$ .

### 5.2.2 Qualitative assessment of the Correction techniques

This section presents a qualitative evaluation of the attenuation, random-coincidence, and scatter correction techniques developed for the Modular J-PET scanner, using the NEMA IQ phantom measurement.

#### Attenuation correction

Following the merging of the attenuation and sensitivity maps as described in 4.4, image reconstruction was performed using the CASToR framework. Figure 5.2 presents the reconstructed images obtained using only sensitivity correction (top) and with attenuation correction (bottom) applied. It is evident that, without attenuation correction, the tracer distribution in the deeper regions of the phantom is underestimated compared to the edges, resulting in non-uniform signal intensity and reduced quantitative accuracy. In contrast, after applying attenuation correction, the tracer distribution becomes more uniform across the background region of the phantom. Additionally, the overall shape of the phantom is better recovered after applying the correction, with improved delineation of its boundaries and internal structures.

#### Random correction

During this acquisition, 80,420,905 delayed coincidence events were identified using a 100 ns DTW together with a delayed CTW of 30 ns, following the procedure outlined in the previous chapter. To improve the statistical precision of the random coincidence estimate, the delayed coincidence window was intentionally enlarged by a factor of ten. After applying the corresponding normalization, the estimated number of random coincidences contributing to the measurement was approximately 8.04 million events. In comparison, the dataset contained 32,249,721 prompt coincidences, meaning that random events accounted for about 24.9% of all recorded coincidences. The random correction factors were then incorporated into the list-mode file as explained in section 4.2 and the reconstruction was performed.

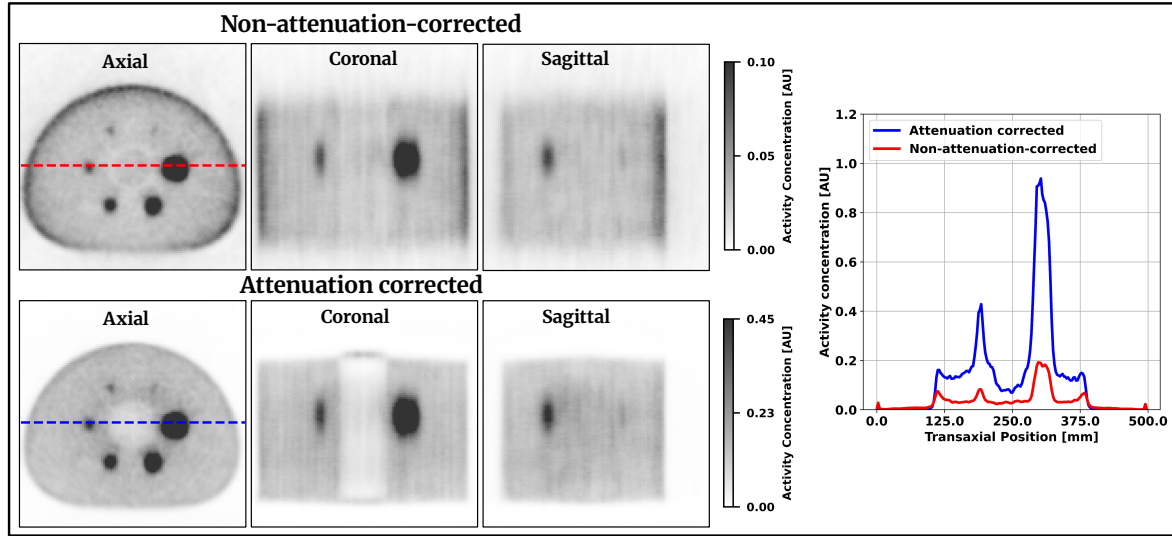


Figure 5.2: Comparison of NEMA IQ phantom images without (top) and with (bottom) attenuation correction, along with the corresponding line profiles. The image reconstructed without attenuation correction exhibits an underestimation of tracer activity in the deeper regions of the phantom, leading to reduced signal intensity in these areas. In contrast, attenuation correction compensates for this effect, resulting in a more quantitatively accurate representation of the tracer distribution throughout the phantom.

To demonstrate the effectiveness of the random correction, Figure 5.3 shows the relative difference between images reconstructed without random correction and those with random correction applied. This metric provides a normalized measure of the degree to which random coincidences have been removed during the correction process.

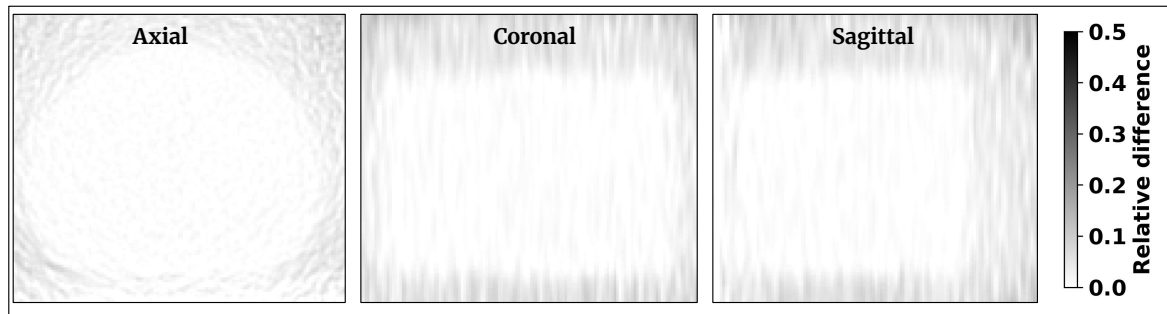


Figure 5.3: Relative difference between non-random corrected (NRC) and random corrected (RC) images of the NEMA IQ phantom scan, showing the proportion (qualitatively a relative difference  $(NRC - RC)/NRC$ ) of random coincidences (contributing to the background) removed by the correction process.

### Scatter correction

Due to the low interaction probability of 511 keV photons in plastic scintillators, the detection efficiency is significantly reduced in the simulation. As a result, simulation run times become impractically long when high-statistics datasets are required for the proper estimation of the scatter correction factors as shown in Table 5.1. To address this, we performed the

simulations using both BC-404 and LYSO materials, to evaluate whether the computational advantages of LYSO can be leveraged without compromising accuracy. In total,  $5 \times 10^9$  radioactive decays of  $^{18}\text{F}$  were simulated for the LYSO, while  $2 \times 10^{11}$  decays were simulated using the BC-404. These values were chosen to yield comparable numbers of detected coincidences, resulting datasets of almost similar size: 49.8 million events for BC-404 and 53.3 million events for LYSO.

Table 5.1: Summary of simulation parameters and results

| Parameter                  | NEMA-IQ    |                  |
|----------------------------|------------|------------------|
|                            | LYSO       | BC-404 (Plastic) |
| Number of simulated decays | 5 Billion  | 200 Billion      |
| Simulation time            | 9 h 40 min | 69 h 22 min      |
| Lower energy threshold     | 408 keV    | 200 keV          |
| Scatter fraction           | 43.27%     | 43.24%           |

The total number of decays in the simulation was distributed across 100 independent instances and executed on AMD EPYC 9754 128-core processors. For the LYSO case, intrinsic radioactivity was not included in the simulation. The same selection criteria as applied to the experimental data were used in the simulation and the TOF resolution was also included in the simulation.

We further evaluated the scatter fraction for both detector materials as a function of the lower energy threshold for photon detection (see Figure 4.4). In the J-PET scanner, photons are typically recorded within an energy window of 200–650 keV. Previous simulation studies have shown that setting the lower energy threshold above 184 keV effectively suppresses detector-scattered coincidences [143]. With a lower energy threshold of 200 keV with the BC-404 as the scintillator material in the Monte Carlo simulation, the obtained scatter fraction was 43.2%. Accordingly, for LYSO, the lower energy threshold was set to 408 keV to obtain a scatter fraction comparable to that of BC-404. Thus, an energy window of 408–650 keV was used for LYSO. In both configurations, the energy resolution was assumed to be 16%.

After estimating the scatter contribution for each LOR and TOF bin, this information was incorporated into the CASToR list-mode data, and image reconstruction was performed using the parameters as described in the image reconstruction section. Figure 5.4 shows both non-scatter-corrected (top) and scatter-corrected images for LYSO (middle) and BC-404 (bottom) scintillators. The results demonstrate that scatter correction significantly reduces the residual activity in the lung insert, as observed in the line profiles. The reduction is 52.5% for plastic and 55.2% for LYSO. This corresponds to a relative difference of approximately 5.1% when taking plastic as the reference. In addition, the correction effectively suppresses the spurious activity observed in the plastic layers above and below the phantom, as clearly visible in the coronal and sagittal views of the reconstructed images.

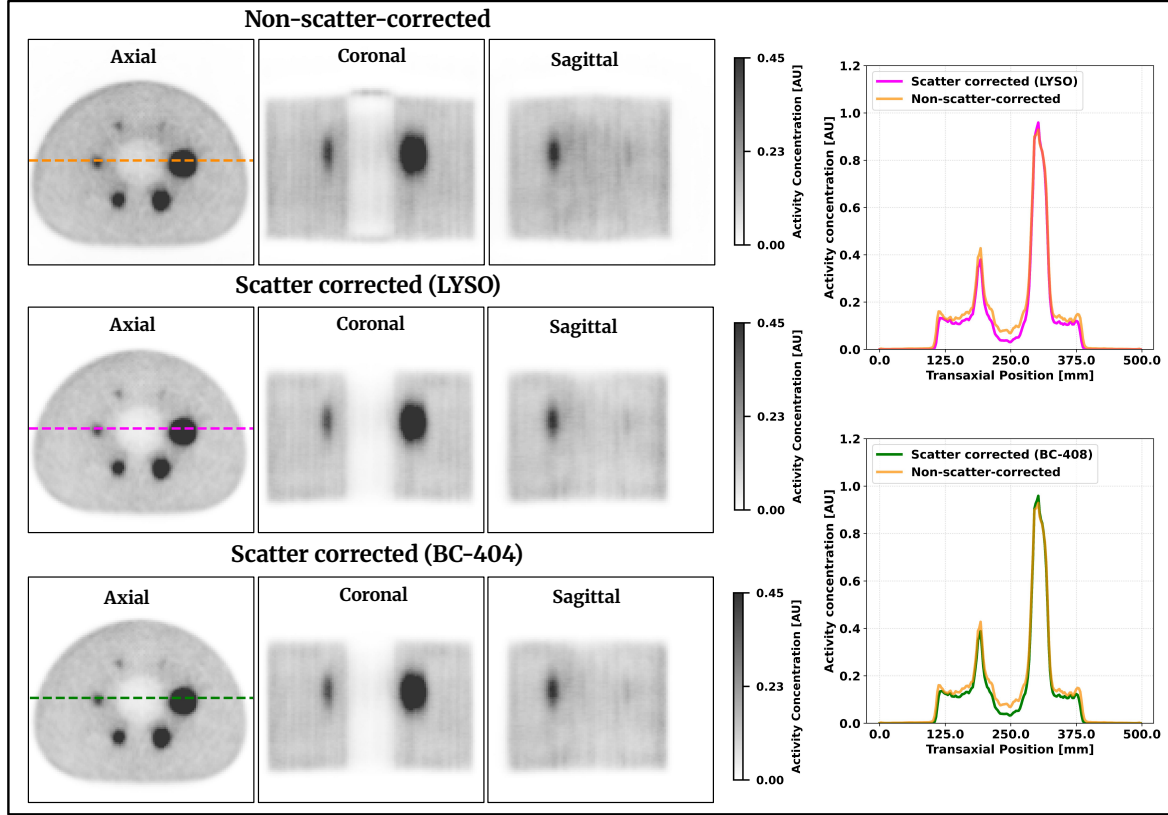


Figure 5.4: Comparison of non-scatter-corrected (top) and scatter-corrected images of the NEMA IQ phantom using LYSO (middle) and BC-404 plastic (bottom) in the Monte Carlo simulation. The corresponding line profiles (right) illustrate the impact of each scatter correction method compared to the uncorrected data. The images without scatter correction show reduced clearance in the lung insert region, with visible residual scattered activity in the plastic layers above and below the phantom in both coronal and sagittal views. In contrast, both scatter-corrected images show a clear improvement, with better suppression of activity in the surrounding plastic and noticeably improved lung insert clearance.

### 5.2.3 Quantitative assessment of Scatter correction and Material Choice

To assess the quantitative accuracy of scatter correction and the material choice in the simulation, an evaluation was performed with the phantom study in accordance with the NEMA NU 2-2018 standard [24]. The analysis focused on three primary metrics: Contrast Recovery Coefficient (CRC), Background Variability (BGVar), and residual lung error.

#### Contrast Recovery Coefficient (CRC)

The CRC quantifies the ability of the scanner to accurately recover the true activity concentration in lesions of different sizes. To evaluate this parameter, circular Region of Interest (ROI)s corresponding to the internal diameters of the six spheres (10, 13, 17, 22, 28, and 37 mm) were defined on the central transaxial slice of the reconstructed image. The CRC ( $CRC_j$ ) of diameter  $j$  are defined as follows:

$$CRC_j = \frac{\left(\frac{C_{H,j}}{C_{B,j}} - 1\right)}{\left(\frac{a_H}{a_B} - 1\right)} \times 100\%,$$

where  $C_{H,j}$  is the mean reconstructed counts in the ROIs for the hot sphere of diameter  $j$ , respectively.  $C_{B,j}$  is the mean background counts for ROIs corresponding to sphere size  $j$ .  $a_H$  and  $a_B$  denote the true activity concentrations in the hot spheres and the background, respectively.

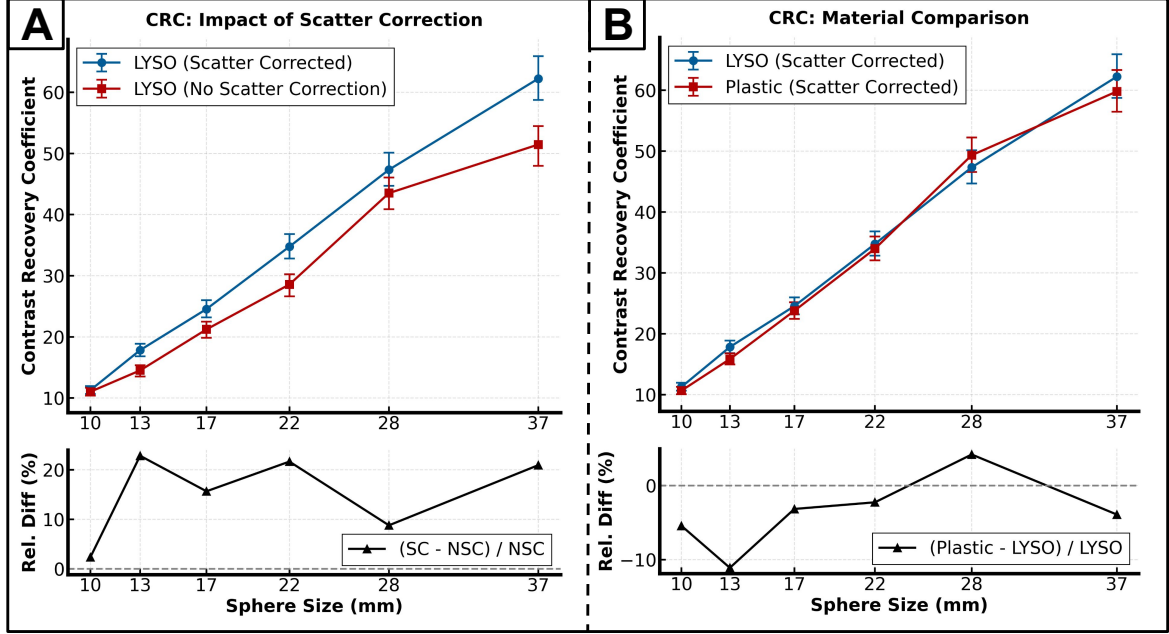


Figure 5.5: Comparison of CRC as a function of sphere size (10–37 mm). (A) Effect of scatter correction, showing CRC values with (blue circles) and without (red squares) correction. (B) Material comparison between scatter-corrected LYSO (blue circles) and scatter-corrected Plastic (BC-404) (red squares). In both panels, the upper plots present absolute CRC values with error bars representing systematic uncertainty in activity concentration. The lower plots show the relative percentage difference (%).

Figure 5.5(A) presents the CRC (top) for uncorrected (red squares) and scatter-corrected (blue circles) images using LYSO as the scintillator material in the Monte Carlo-based scatter correction algorithm. A 5% systematic uncertainty, attributed to possible errors in phantom filling, was considered in the analysis of the CRC values. The relative difference between the scatter corrected and non scatter corrected image (lower panel) for the smallest sphere, shows no significant differences within the uncertainties. However, for larger spheres, scatter correction leads to a clear improvement in CRC. In particular, for the 37 mm sphere, the CRC increases from 51.5% (uncorrected) to 62.2% (corrected), corresponding to a relative improvement of 20.8%.

The comparison of scintillator materials used in the Monte Carlo simulation is shown in Figure 5.5(B) (top), where CRC values obtained using LYSO (blue circles) and plastic (red squares) are presented. The relative differences are shown in the lower panel. The largest deviation is observed for the 13 mm sphere (−11.1%), while the smallest difference is 2.2% for

the 22 mm sphere, with an average deviation of approximately 5.0%.

### Background Variability (BGVar)

The BGVar parameter reflects the statistical noise and uniformity of the reconstructed image in the background region. Therefore, a lower BGVar indicates better image quality. Following the NEMA protocol, for each sphere diameter  $j$ , 12 ROIs of identical size were placed within the background region across five adjacent slices (the central slice, as well as slices at  $\pm 1$  cm and  $\pm 2$  cm relative to the central slice), resulting in a total of 60 background ROIs per sphere size.

Background variability ( $N_j$ ) is defined as:

$$N_j = \frac{SD_j}{C_{B,j}} \times 100\%,$$

where  $SD_j$  is the standard deviation of the mean counts summed over all 60 background ROIs for sphere size  $j$ , and  $C_{B,j}$  is the corresponding mean background count.

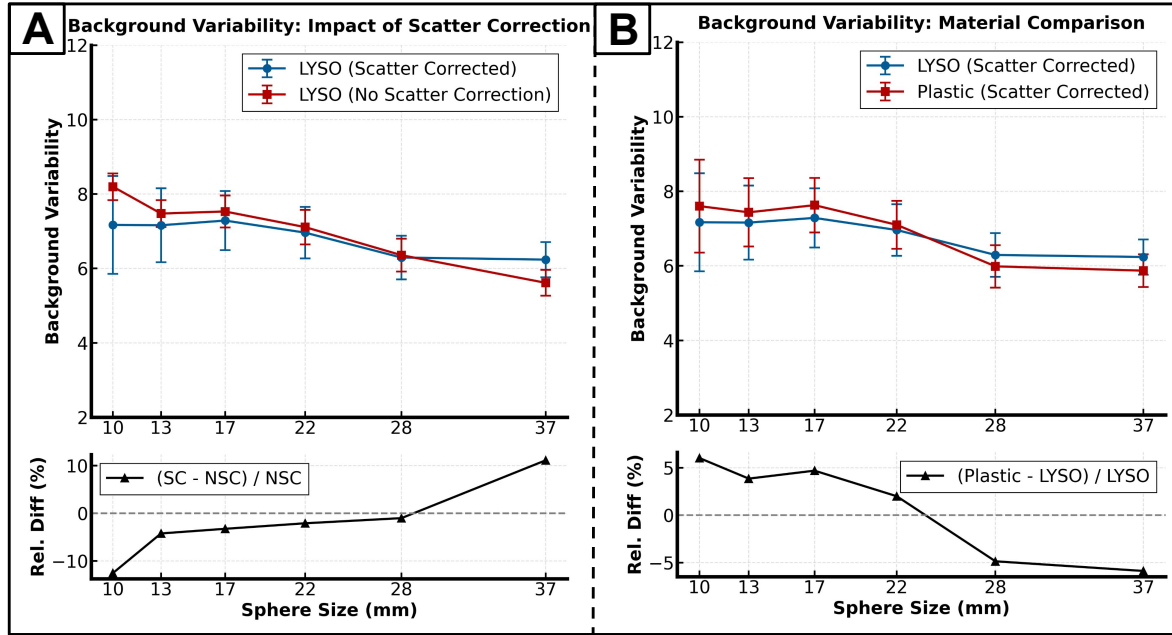


Figure 5.6: (A) The effect of scatter correction, showing results with (blue circles) and without (red squares) correction; (B) a material comparison between scatter-corrected LYSO (blue circles) and scatter-corrected plastic (BC-404) (red squares). The upper plots present absolute background variability values, with error bars representing statistical uncertainties, calculated using Gaussian error propagation. The lower plots show the relative percentage difference (%).

Figure 5.6(A) shows the BGVar for non-scatter-corrected (red squares) and scatter-corrected (blue circles) images. The error bars represent statistical uncertainties, calculated using Gaussian error propagation. Scatter correction improves background uniformity for most sphere sizes. For example, for the smallest sphere, BGVar decreases from 8.2% to 7.2%, corresponding to an improvement of 12.2%. For all sphere sizes except the largest, BGVar is

consistently lower in scatter-corrected images. Although an increase of 11.1% is observed for the largest sphere, this difference is not statistically significant within uncertainties. Overall, these results indicate that the scatter correction algorithm does not introduce additional noise and leads to a more uniform background.

The material comparison is shown in Figure 5.6(B) (top), where the BGVar values for LYSO (blue circles) and plastic (red squares) are presented, with the corresponding relative differences shown in the lower panel. The maximum difference of 6.0% was observed for the smallest sphere, while the minimum difference of 2.0% was found for the 22 mm sphere, resulting in an average difference of 4.6% across all sphere sizes. These small differences indicate that the use of LYSO as a surrogate material does not significantly affect the BGVar and, therefore, has a negligible impact on overall image quality.

### Residual Lung Error

The residual lung error is a quantitative metric which provides an assessment of the accuracy of scatter and attenuation correction in a low-density medium. Since the lung insert is filled with styrofoam balls to mimic the human lung and contains no radioactivity, it should ideally not exhibit measurable activity concentration. To assess this parameter, a circular ROI with a diameter of 30 mm was placed in the center of the lung insert to evaluate the residual activity concentration.

The residual lung error ( $\Delta C_{\text{lung}}$ ) is defined as:

$$\Delta C_{\text{lung}} = \frac{C_{\text{lung}}}{C_B} \times 100\%,$$

where  $C_{\text{lung}}$  is the mean counts within the lung insert ROI, and  $C_B$  is the mean background counts averaged over all ROIs corresponding to the 37 mm sphere background region. A lower value of  $\Delta C_{\text{lung}}$  indicates an improved performance in the scatter and attenuation correction.

The residual error in the lung insert is significantly reduced with scatter correction, from 49.0% (uncorrected) to 14.1%, corresponding to a reduction of 71.2%.

For the material comparison in the Monte Carlo simulation, the residual error is 14.1% for LYSO and 15.1% for plastic, resulting in a relative difference of 6.6%, indicating that the choice of material has not significant impact on the residual lung error.

## 5.3 First Clinical Two-Gamma Imaging of Human Subjects with the J-PET

Following the successful demonstration and validation of the two-gamma coincidence imaging using the NEMA IQ phantom, the same reconstruction framework was applied to the first clinical patient measurements performed with the Modular J-PET scanner. These measurements were done at the Medical University of Warsaw and the University Hospital in Kraków. In total, four representative patient studies are presented in this thesis. These patients were injected with three different radiotracers:  $^{68}\text{Ga}$ -DOTA-TATE,  $^{68}\text{Ga}$ -PSMA, and

$^{18}\text{F}$ -FDG. More details on the patients, the experimental workflow, and the imaging protocols have been provided in Section 3.1.2.

### 5.3.1 Reconstruction parameters

For the human subject study, 10 iterations of TOF-MLEM were performed without subset acceleration. Due to the low count rate in the human dataset, the number of iterations was limited to prevent excessive amplification of image noise. The TOF resolution kernel was modeled as a Gaussian function. For each line of response, a ray-tracing projector based on the incremental Siddon algorithm [142] was employed using 10 rays. The images were reconstructed into a  $200 \times 200 \times 200$  matrix with an isotropic voxel size of  $2.5 \text{ mm}^3$ . A Gaussian post-reconstruction smoothing filter with a 5 mm kernel was applied in all cases.

### 5.3.2 Assessment of Scatter correction with a Human subject image

The effects of attenuation and random corrections are not shown separately for the human subject image because they predominantly affect image quantification and overall count scaling, as already demonstrated with the NEMA IQ phantom. In contrast, scatter correction results in a more visible improvement in image contrast and organ delineation. Figure 5.7 presents transaxial J-PET/CT fusion images of Patient 2 (see Section 3.1.2) reconstructed with and without scatter correction. The arrows indicate residual activity between major organs, such as the liver, spleen, and kidneys, which shows improved delineation after applying scatter correction. A line profile across the torso demonstrates that scatter between the liver and spleen is effectively reduced, with the minimum value decreasing from 0.219 in the uncorrected image to 0.150 after correction (see the green arrow in Figure 5.7). This corresponds to a reduction of 31.4%. Furthermore, correcting for scatter efficiently removed the residual background events from inactive regions, as evident by the steeper drop-off outside the subject.

### 5.3.3 Clinical Two-Gamma images with J-PET

At the Medical University of Warsaw, Patient 1 was scanned with the modular J-PET scanner for approximately 15 minutes, starting 60 minutes post injection. This was followed by routine clinical imaging using the standard Siemens Biograph 64 TruePoint PET/CT scanner at 85 minutes post injection. During both scans, the patient remained on the same movable bed platform. In this measurement, we utilized a key design feature of the Modular J-PET scanner: it can split into two-half geometry, which allows the detector to be positioned around the patient while remaining compatible with an existing clinical PET/CT bed platform. For imaging with the J-PET scanner, the patient was moved on the platform outside the PET/CT gantry, where the patient was surrounded by the two halves of the portable modular J-PET tomograph. It is worth noting that whole-body imaging with the Biograph 64 TruePoint PET/CT scanner was performed using eight bed positions, whereas the J-PET images were acquired using a single bed position scan covering the entire abdomen. Figure 5.8(A-C) demonstrates the two gamma



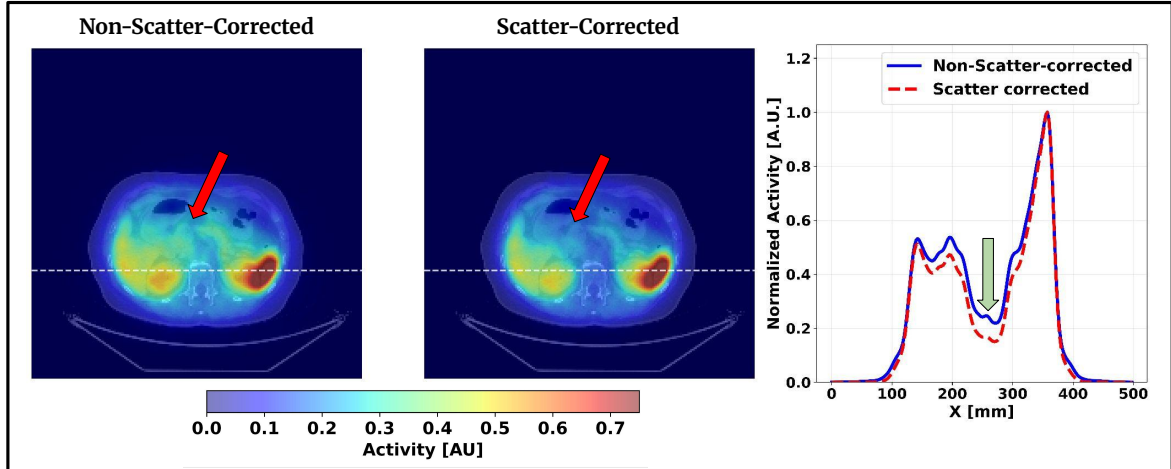


Figure 5.7: Transaxial PET/CT fusion images of Patient 2 without and with scatter correction. The red arrow indicates residual activity between the liver and spleen (left). A line profile across the liver, kidney and spleen is shown on the right. The green arrow shows the reduction of the activity concentration between the spleen and liver.

coincidence PET images obtained with the J-PET showing the physiological accumulation of  $[^{68}\text{Ga}]\text{Ga-DOTA-TATE}$  radio-pharmaceutical in the liver, spleen, and kidney.

At the Jagiellonian University Medical College in Kraków, patients were scanned separately on the commercial PET/CT scanner and the J-PET scanner due to mechanical constraints that prevented positioning the J-PET scanner around the patient on the same PET/CT bed platform. For this purpose, a dedicated bed with properties similar to the PET/CT table was used. Patients were first scanned with the GE Discovery MI Gen 2 PET/CT scanner, after which they were asked to void the urinary bladder in order to reduce bladder activity, followed by imaging with the J-PET scanner. Three patients were scanned with different radiopharmaceuticals.

Figures 5.8(D–F) shows the PET images acquired with the J-PET scanner, showing physiological accumulation of  $[^{68}\text{Ga}]\text{Ga-DOTA-TATE}$  in the liver, spleen, and kidneys. Figures 5.8(G–I) show J-PET images of  $[^{68}\text{Ga}]\text{Ga-PSMA}$  uptake in the kidneys. Finally, Figures 5.8(J–L) show J-PET images of  $[^{18}\text{F}]\text{FDG}$  distribution in the liver, spleen, and bone marrow.

It is worth noting that, in all reconstructed images, the active axial range of the J-PET is 46 cm. A 2 cm region on each side of the scintillator was excluded during the analysis to avoid edge-related effects in hit registration and position reconstruction. The axial range of the commercial scanner corresponds to a whole-body scan acquired with multiple bed positions. However, the images shown here represent only a 50 cm axial section, with the isocentres of the J-PET and the commercial scanner aligned at the same location.

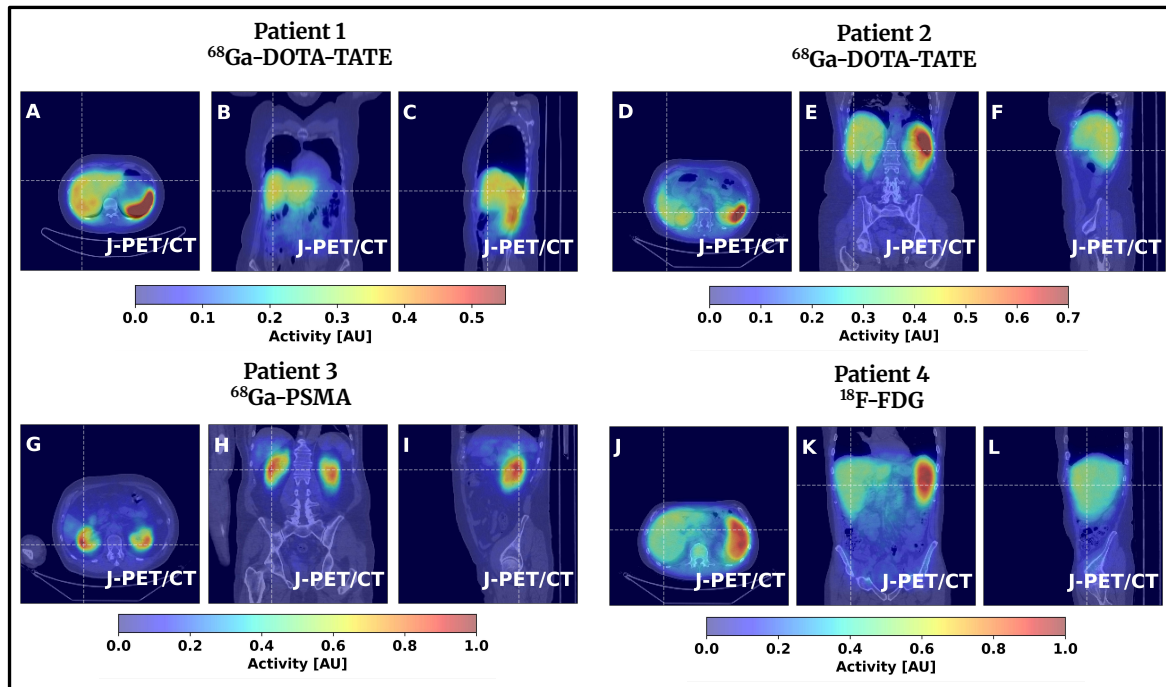


Figure 5.8: First human two-gamma coincidence images acquired with the modular J-PET scanner. Axial (left), coronal (center), and sagittal (right) slices are shown, superimposed on CT images; the corresponding slice positions are indicated by thin white dashed lines. The voxel size is  $2.5 \times 2.5 \times 2.5 \text{ mm}^3$ . The images obtained with the J-PET scanner are corrected for sensitivity, normalization, attenuation, random coincidences, and scatter. (A–C) two-gamma coincidence images acquired with the J-PET scanner of a patient scanned at the Medical University of Warsaw following injection of  $[^{68}\text{Ga}]\text{Ga-DOTA-TATE}$ . (D–F) images of a patient scanned at the Medical University of Krakow after administration of  $[^{68}\text{Ga}]\text{Ga-DOTA-TATE}$ . (G–I) images of a patient scanned at the Medical University of Krakow following injection of  $[^{68}\text{Ga}]\text{Ga-PSMA}$ . (J–L) images of a patient scanned at the Medical University of Krakow after administration of  $[^{18}\text{F}]\text{FDG}$ .

### 5.3.4 Qualitative and semi-quantitative comparison of the J-PET images with the Commercial PET Scanner

To compare the commercial PET/CT scanners with the J-PET scanner, a qualitative assessment was performed using line profiles extracted across image slices in the axial, coronal, and sagittal directions. For consistency, the activity concentration in the reconstructed images from each scanner was normalized to its respective maximum value. Although the J-PET images exhibit higher noise levels and increased residual activity in soft tissues between major organs, the line profiles demonstrate that the overall organ shapes are well preserved, and the normalized intensity distributions are in good agreement with those obtained from the commercial PET/CT Scanner as shown in Figure 5.9 and 5.10.

Several observations can be made from the images. In Patient 1, the activity concentration in the kidneys appears to be underestimated, which could be due to the limited axial resolution of the J-PET Scanner. In Patient 2, as indicated by the red arrow in the coronal view, differences in patient positioning between the J-PET and PET/CT acquisitions—performed on separate

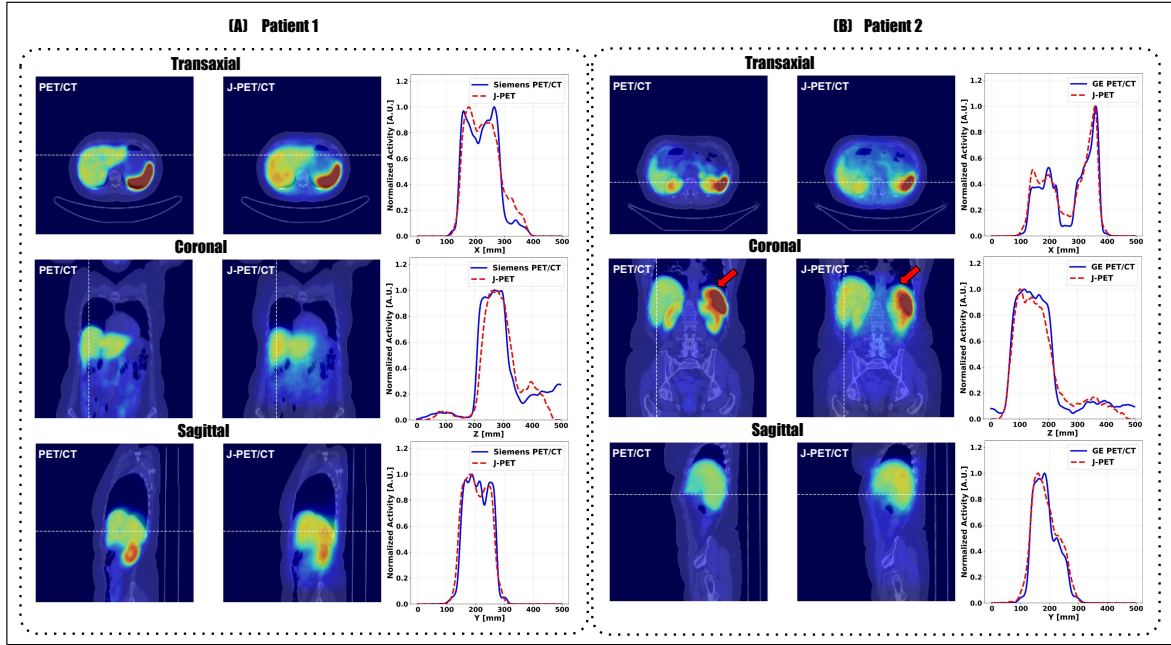


Figure 5.9: Qualitative comparison of images obtained with the J-PET and the commercial PET/CT scanner. The left image is the image obtained from the commercial PET/CT scanner, the middle image is the J-PET reconstructed image, and the right image shows the line profile from the corresponding slice. The dashed lines indicate the position of the line profiles along the transaxial, coronal, and sagittal slices of the images. **(A)** Patient 1 from Warsaw Medical University injected with  $[^{68}\text{Ga}]\text{Ga-DOTA-TATE}$ . **(B)** Patient 2 from University Hospital in Kraków injected with  $[^{68}\text{Ga}]\text{Ga-DOTA-TATE}$ .

beds—result in slight rotational misalignment, particularly noticeable in the region around the spleen. In Patient 3, the right kidney shows edge distortion, which can be attributed to its location near the boundary of the J-PET axial FOV, leading to truncation effects. In Patient 4, a feature visible above the liver in the PET/CT image is not observed in the J-PET image for the same reason. Additionally, no significant activity is visible in the bladder in the J-PET image, as the patient was instructed to void the bladder after the PET/CT.

Additionally, a semi-quantitative analysis was performed by estimating the average ACR between the major organs, such as the liver, spleen, and kidneys. For this analysis, spherical ROIs were drawn in the spleen with a diameter of 35 mm, in both kidneys with a diameter of 20 mm, and in the liver with a diameter of 40 mm. The kidney values were averaged across both kidneys. Figure 5.11 shows a comparison of organ-to-liver ACR measured with the J-PET scanner and Commercial PET/CT scanner. The top panel presents the spleen-to-liver ratios, while the bottom panel shows the kidney-to-liver ratios for four patients scanned with different radiotracers. The ratio's are summarized in Table 5.2.

Overall, J-PET measurements were generally in good agreement with the commercial PET/CT scanner, with minor differences observed, particularly for Patient 3, likely due to liver being located near the edge of the field of view.

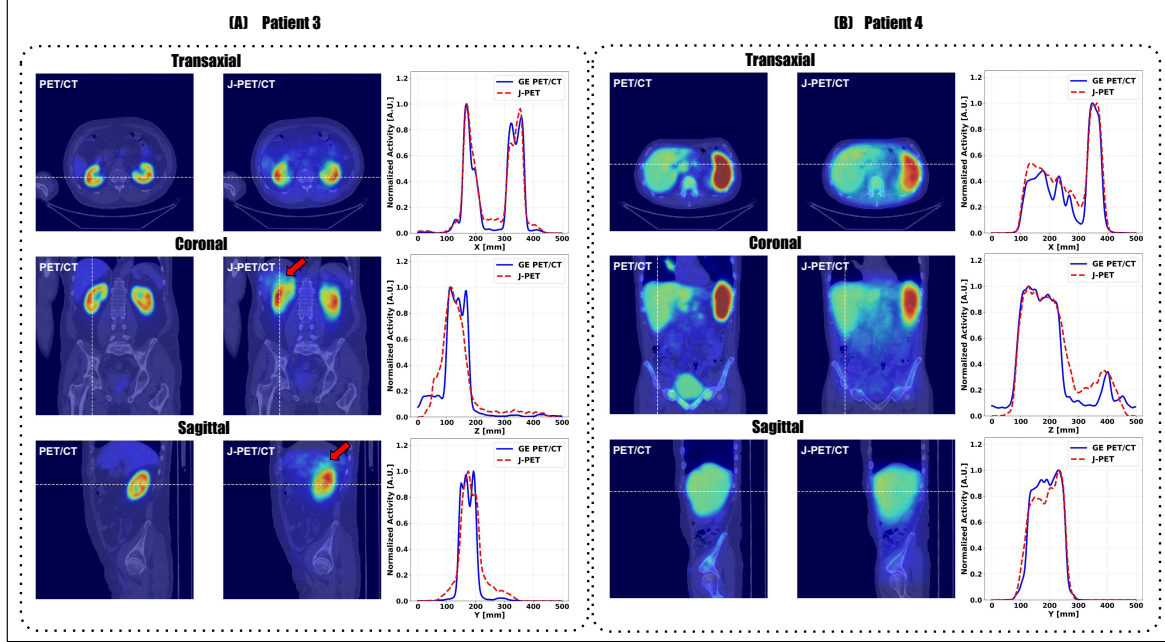


Figure 5.10: Qualitative comparison of images obtained with the J-PET and the commercial PET/CT scanner. The left image is the image obtained from the commercial PET/CT scanner, the middle image is the J-PET reconstructed image, and the right image shows the line profile from the corresponding slice. The dashed lines indicate the position of the line profiles along the transaxial, coronal, and sagittal slices of the images. **(A)** Patient 3 from University Hospital in Kraków injected with  $[^{68}\text{Ga}]\text{Ga-PSMA}$ . **(B)** Patient 4 from University Hospital in Kraków injected with  $[^{18}\text{F}]\text{FDG}$ .

## 5.4 Discussion

This study presents the evaluation of two-gamma metabolic imaging with the plastic-scintillator-based modular J-PET Scanner. Initially, the developed algorithms were validated using the NEMA IQ phantom, which confirmed that the implemented attenuation, random, and scatter corrections significantly improve image quality and quantitative accuracy. Notably, the corrected images showed improved CRC, a reduction in residual lung error by more than 70%, and improvement in BGVar demonstrating the effectiveness of the correction techniques. Furthermore, results from the first human trials using various radiopharmaceuticals ( $^{18}\text{F}$ -FDG,  $^{68}\text{Ga}$ -DOTA-TATE, and  $^{68}\text{Ga}$ -PSMA) provided validation of the developed methods for the Modular J-PET scanner. Both quantitative and semi-quantitative assessments showed good agreement with the commercial PET/CT scanner.

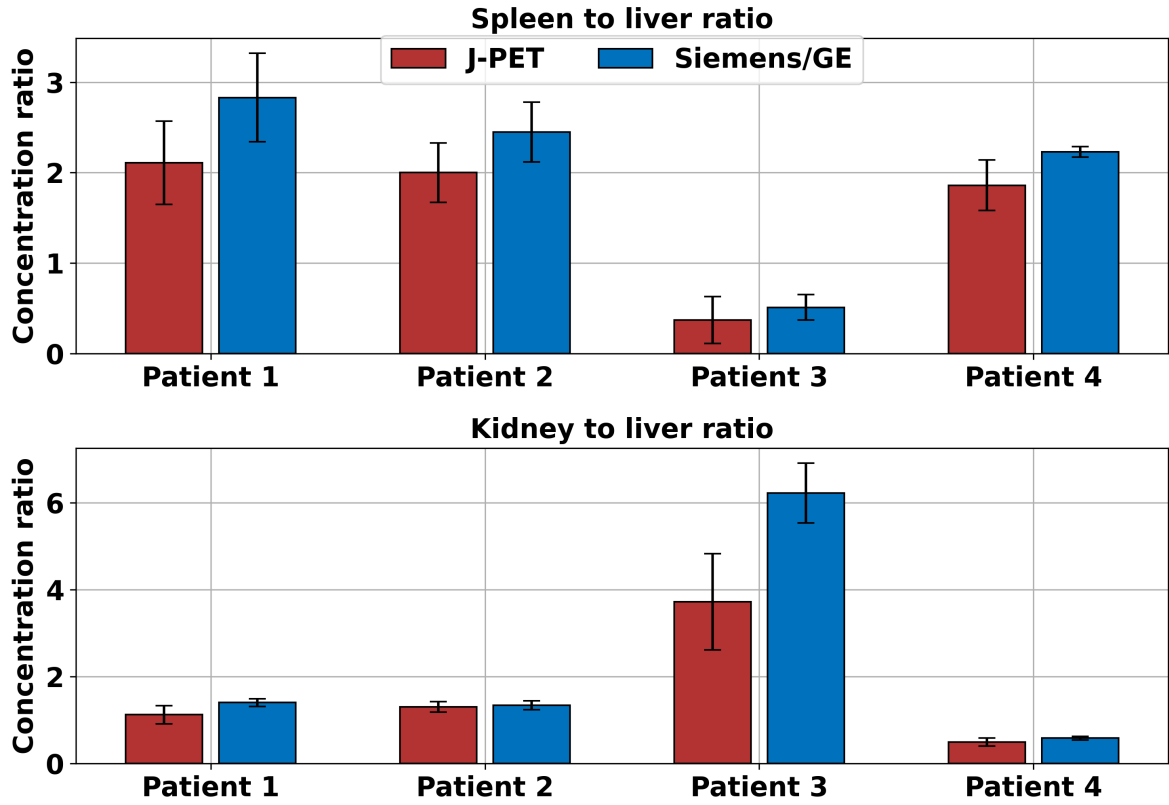


Figure 5.11: Comparison of organ-to-liver ACR with J-PET and Commercial PET/CT scanner. **Top panel:** spleen-to-liver ratio; **Bottom panel:** kidney-to-liver ratio. Bars represent the mean values of ACR for each patient, with the uncertainties calculated using Gaussian error propagation under consideration of the standard deviations on the calculated ROI mean values. J-PET measurements are shown in red, and Commercial PET/CT measurements in blue.

Table 5.2: Spleen-to-liver and kidney-to-liver uptake ratios for J-PET and reference PET/CT systems. The uncertainties were calculated using Gaussian error propagation, taking into account the standard deviations of the mean values within the ROIs.

| Patient | Radiotracer                    | Ratio Type   | J-PET           | Reference PET/CT          |
|---------|--------------------------------|--------------|-----------------|---------------------------|
| 1       | $^{68}\text{Ga}$ ]Ga-DOTA-TATE | Spleen/Liver | $2.11 \pm 0.46$ | $2.83 \pm 0.49$ (Siemens) |
| 1       | $^{68}\text{Ga}$ ]Ga-DOTA-TATE | Kidney/Liver | $1.12 \pm 0.21$ | $1.40 \pm 0.09$ (Siemens) |
| 2       | $^{68}\text{Ga}$ ]Ga-DOTA-TATE | Spleen/Liver | $2.00 \pm 0.33$ | $2.45 \pm 0.33$ (GE)      |
| 2       | $^{68}\text{Ga}$ ]Ga-DOTA-TATE | Kidney/Liver | $1.30 \pm 0.12$ | $1.34 \pm 0.10$ (GE)      |
| 3       | $^{68}\text{Ga}$ ]Ga-PSMA      | Spleen/Liver | $0.37 \pm 0.26$ | $0.51 \pm 0.14$ (GE)      |
| 3       | $^{68}\text{Ga}$ ]Ga-PSMA      | Kidney/Liver | $3.72 \pm 1.11$ | $6.22 \pm 0.69$ (GE)      |
| 4       | $^{18}\text{F}$ ]FDG           | Spleen/Liver | $1.86 \pm 0.28$ | $2.23 \pm 0.06$ (GE)      |
| 4       | $^{18}\text{F}$ ]FDG           | Kidney/Liver | $0.49 \pm 0.09$ | $0.58 \pm 0.04$ (GE)      |





## Chapter 6

# First Positronium Lifetime Imaging with the $^{44}\text{Sc}$ with the J-PET Scanner

Positronium Lifetime Imaging (PLI) is a novel advancement in PET that can provide additional information beyond the standard activity concentration image (two-gamma metabolic imaging) [3,5]. A fundamental prerequisite for PLI is the use of an isotope capable of emitting an additional prompt de-excitation photon. This prompt photon serves as a marker to identify the positron's formation time, whereas the decay time of the Ps is determined from the two 511 keV annihilation photons (see Figure 6.1(B)).

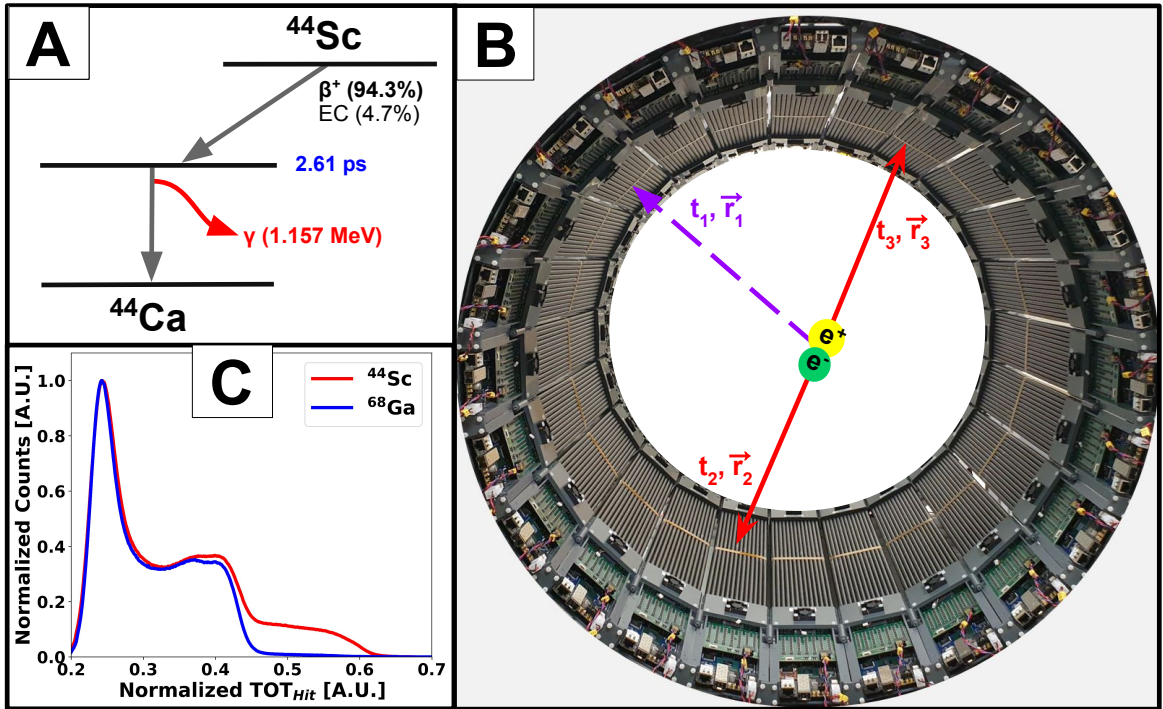


Figure 6.1: (A) The decay schemes for the  $^{44}\text{Sc}$  isotope.  $\beta^+$  denotes the positron yield, EC indicates electron capture contributions, and  $\gamma$  represents the prompt gamma with energy indicated in the parenthesis. (B) The event definition (one prompt gamma ( $t_1, \vec{r}_1$ ) and two annihilation photons ( $(t_2, \vec{r}_2)$  and  $(t_3, \vec{r}_3)$ )) is depicted in the modular J-PET scanner (C) Experimental TOT spectra obtained in the modular J-PET scanner for  $^{68}\text{Ga}$  and  $^{44}\text{Sc}$ , showing an increased prompt gamma yield for  $^{44}\text{Sc}$ . Figure, prepared by the author, is adopted from [41], licensed under CC BY 4.0.

However, the implementation of PLI is limited by the decay characteristics of clinically available isotopes, such as  $^{82}\text{Rb}$ ,  $^{68}\text{Ga}$ , and  $^{124}\text{I}$ . These specific isotopes are characterized by a relatively low  $\beta^+ + \gamma$  coincidence yield, which imposes statistical constraints on their

utility in PLI applications. This limitation is illustrated in Figure 6.1(C), where the high-TOT region, used here as an energy proxy for prompt-gamma candidates, shows a markedly larger contribution for  $^{44}\text{Sc}$  than for  $^{68}\text{Ga}$ .

Due to its advantageous physical characteristics,  $^{44}\text{Sc}$  is considered one of the most suitable candidate for PLI. Specifically, it has a clinically practical half-life of 4.04 hours [119], a minimal de-excitation delay of just 2.61 ps, and an outstanding  $\beta^+ + \gamma$  emission yield. As depicted in Figure 6.1(A), roughly 94.3% of its decays produce a positron alongside a 1157 keV high-energy prompt gamma photon, occurring with an emission probability of almost 100% [144]. More details on PLI has been discussed in Chapter 1.

Although  $^{44}\text{Sc}$  has not yet been established as a standard radionuclide in routine clinical practice, its medical potential has been extensively investigated in both clinical and preclinical settings [119, 145–153]. The efficacy of PET imaging based on  $^{44}\text{Sc}$  has been successfully demonstrated through phantom demonstrations [154], comparative analysis of radionuclides [155], and preclinical radiotheranostic models [156, 157]. Furthermore, initial first-in-human trials have confirmed its viability for visualizing prostate cancer ( $^{44}\text{Sc}$ -PSMA) and NETs ( $^{44}\text{Sc}$ -DOTA-TATE) [158–161], and clinical-grade production techniques have also been optimized [162]. More recently,  $^{44}\text{Sc}$  was found to be potentially relevant for theranostic applications, in particular as PET imaging analogue of targeted radionuclide therapy with therapeutic radionuclides such as  $^{47}\text{Sc}$  or  $^{177}\text{Lu}$  [52, 163].

This chapter presents, to best of our knowledge, the result of the first experimental demonstration of PLI using  $^{44}\text{Sc}$  with the J-PET scanner, performed using a NEMA IQ phantom. Detailed experimental details has been described in Section 3.2.1.

The results presented in this chapter have been published as a peer-reviewed manuscript, with the author of this thesis as the first author [41]. The figures and text included in this chapter are adapted from that manuscript and were originally prepared by the author.

## 6.1 Data Analysis for the PLI with $^{44}\text{Sc}$

The principle of two-gamma coincidence PET imaging is based on the simultaneous detection of two back-to-back 511 keV annihilation photons ( $\gamma_a$ ). In PLI, the two annihilation photons must be detected together with an additional prompt gamma photon ( $\gamma_p$ ), which provides the start-time reference for positron emission. The J-PET scanner operates in a triggerless mode, enabling the simultaneous detection of multiphoton events. The data acquisition and signal processing techniques employed in the modular J-PET scanner are described in Chapter 2.

In this study, event classification is performed according to the radionuclide employed. The isotope  $^{18}\text{F}$  results in the emission of a pair of 511 keV annihilation photons, whereas  $^{44}\text{Sc}$  produces not only the annihilation photon pair but also an additional prompt gamma of 1157 keV ( $\gamma_p$ ). The incident photons in the plastic scintillator interact predominantly via Compton scattering, leading to energy deposition that depends on the scattering kinematics [1]. The deposited energy is inferred indirectly through the TOT technique [18].



The resulting TOT distribution, presented in Figure 6.2(A), exhibits characteristic Compton edges corresponding to different photon energies. The edges associated with 511 keV and 1157 keV photons are observed at approximately  $7.5 \text{ ns} \cdot \text{V}$  and  $11 \text{ ns} \cdot \text{V}$ , respectively, reflecting the maximum possible energy transfer in a single Compton interaction. Based on these features, selection windows are defined: TOT values in the range of  $5.5\text{--}8 \text{ ns} \cdot \text{V}$  are attributed to 511 keV photons (red shaded area), while those between  $8.1$  and  $14 \text{ ns} \cdot \text{V}$  correspond to 1157 keV photons (blue shaded area).

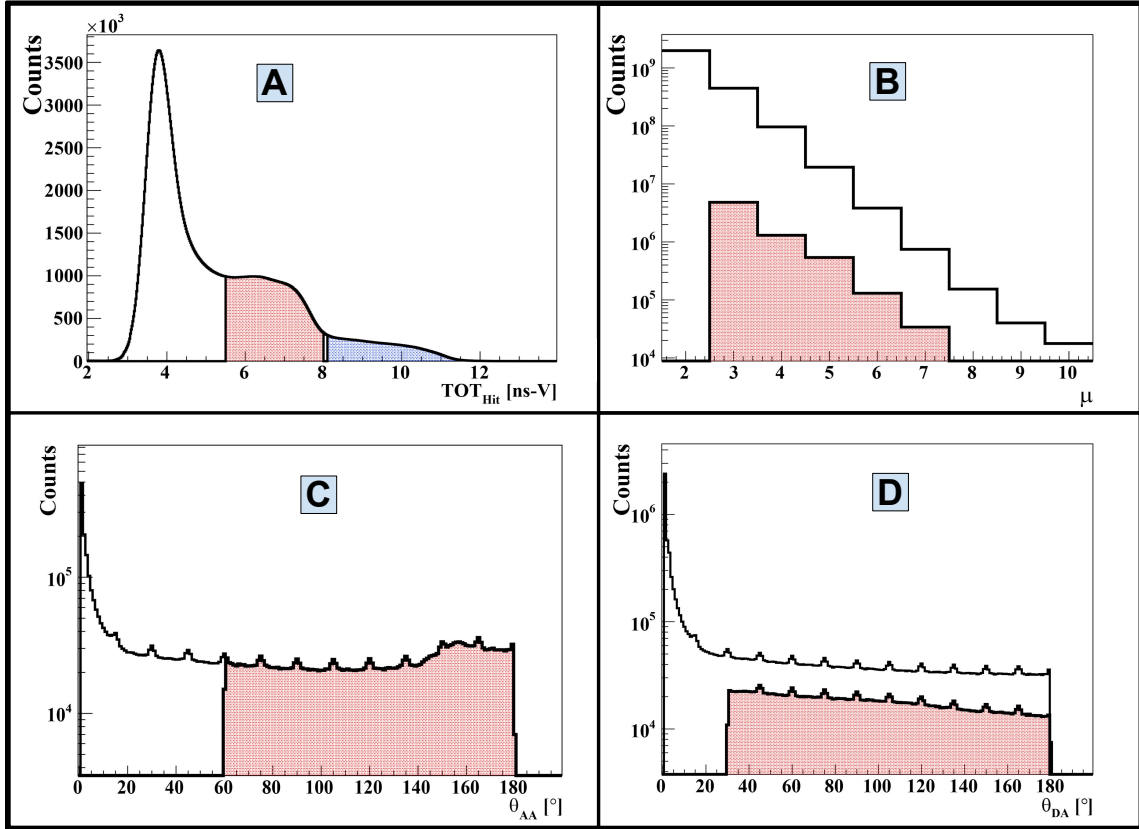


Figure 6.2: (A) Distribution of  $\text{TOT}_{\text{Hit}}$  used for photon identification. Region used to identify annihilation photons is shown in red, while region used to identify prompt gamma is shown in blue, each occupying distinct  $\text{TOT}_{\text{Hit}}$  intervals. (B) Event-wise hit multiplicity ( $\mu$ ) distribution. The red-shaded region indicates the selected topology consisting of two annihilation photons and one prompt gamma. (C) Distribution of the angle  $\theta_{AA}$  between the annihilation photon direction vectors  $\vec{r}_2$  and  $\vec{r}_3$  (as defined in Fig. 6.1B). Events satisfying the condition  $\theta_{AA} \geq 60^\circ$  are marked in red and further selected for analysis. (D) Distribution of the angle  $\theta_{DA}$  between the prompt gamma direction vector  $\vec{r}_1$  and the annihilation photon directions  $\vec{r}_2$  and  $\vec{r}_3$  (see Fig. 6.1B). Events fulfilling  $\theta_{DA} \geq 30^\circ$  (red region) are retained to suppress contributions from misidentified scattered photons. Figure, prepared by the author, is adapted from [41], licensed under CC BY 4.0.

Event building for the PLI is performed by grouping hits that occur within a CTW of 20 ns. The selection and processing of events for the two gamma-coincidence imaging with the J-PET has already been described in Chapter 5. Here we emphasize events involving three coincident interactions, comprising two annihilation photons and one prompt gamma ( $2\gamma_a$

$+\gamma_p$ ), which are of particular relevance for PLI. To assess the effectiveness of the selection criteria, the image reconstructed with 2-hits ( $2\gamma_a$ ) and 3-hits ( $2\gamma_a + \gamma_p$ ) events is presented in the result section.

Event-wise hit multiplicity is used as the next selection criterion. In the case of PLI with  $^{44}\text{Sc}$ , we select events containing exactly three detected hits ( $\mu = 3$ ): two hits corresponding to the 511 keV annihilation photons, identified within  $\text{TOT}_{\text{hit}} \in [5.5, 8] \text{ ns} \cdot \text{V}$ , and one hit corresponding to the 1157 keV prompt gamma, falling within  $\text{TOT}_{\text{hit}} \in [8.1, 14] \text{ ns} \cdot \text{V}$ . The multiplicity distribution is illustrated in Figure 6.2(B), where the red-highlighted region marks events fulfilling this topology, i.e. two annihilation-related hits and one prompt-gamma hit distinguished by their  $\text{TOT}_{\text{hit}}$  values. For events with  $\mu = 3$ , all three recorded hits must satisfy this composition requirement. In cases where the multiplicity exceeds three, events are retained only if they still contain exactly two annihilation-region hits and one prompt-region hit.

To further reduce contamination from scattered photons and random coincidences, angular constraints were introduced based on reconstructed photon emission directions. The distribution of the angle  $\theta_{AA}$  between the two annihilation photons, determined from their interaction positions relative to the detector center, is presented in Figure 6.2(C). Events within the selected angular window ( $\theta_{AA} \geq 60^\circ$ ) are kept for further analysis.

Although the prompt photon  $\gamma_p$  is intrinsically emitted isotropically with respect to the annihilation photon, the measured angular distribution between annihilation photons and the prompt gamma shows a pronounced enhancement at small angles. This effect is attributed to misidentified secondary scatter events being reconstructed as either prompt or annihilation signals. To mitigate this background contribution, an additional angular requirement of  $\theta_{DA} \geq 30^\circ$  is applied, as shown in Figure 6.2(D).

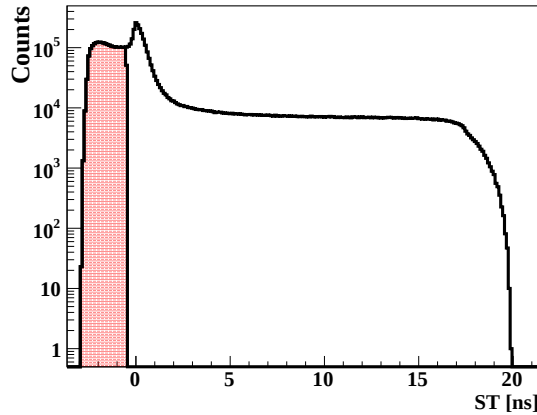


Figure 6.3: Distribution of the ST value used to discriminate true annihilation photon pairs from events contaminated by intra-detector Compton scattering or accidental coincidences. The red-shaded region indicates the selected window for the ST.

Finally, to discriminate true annihilation photon pairs from events contaminated by intra-detector Compton scattering or accidental coincidences, a Scatter Test (ST) was applied. For the annihilation photons registered at times  $t_2$  and  $t_3$ , and positions  $\vec{r}_2$  and  $\vec{r}_3$ , the ST parameter

is defined as

$$\text{ST} = |t_3 - t_2| - \frac{|\vec{r}_3 - \vec{r}_2|}{c}, \quad (6.1)$$

where  $c$  denotes the speed of light.

In the case of ideal direct detection of annihilation photons, the condition  $|t_3 - t_2| \leq |\vec{r}_3 - \vec{r}_2|/c$  is satisfied, resulting in non-positive ST values. When both registered hits originate from primary and secondary interactions of the same photon, the ST value is expected to be approximately zero within the limits of experimental resolution. Conversely, for accidental coincidences, the time difference  $|t_3 - t_2|$  can be larger, leading to positive ST values. To enhance the purity of the selected annihilation events, only pairs satisfying the condition  $\text{ST} < -0.5$  ns were retained in this study (see Figure 6.3).

## 6.2 Image reconstruction

In this study, TOF-MLEM image reconstruction was performed using both  $2\gamma_a$  events and Ps-related  $2\gamma_a + \gamma_p$  events in order to compare the standard two-gamma with the PLI modality. Additionally, this comparison allows the assessment of the impact of the analysis criteria described in the previous section, noting that  $^{18}\text{F}$  does not emit prompt gamma radiation. It is important to emphasize that in both cases only annihilation photon pairs (511 keV) were used for image reconstruction. In the  $2\gamma_a + \gamma_p$  category, the additional prompt gamma photon ( $\gamma_p$ ) was included exclusively for subsequent positronium lifetime estimation.

Furthermore, the annihilation position  $\vec{r}_a$  and annihilation time  $t_a$  can be reconstructed solely from the measured times and positions of the annihilation photons,  $(t_2, \vec{r}_2)$  and  $(t_3, \vec{r}_3)$ , registered by the J-PET scanner:

$$\vec{r}_a = \frac{\vec{r}_2 + \vec{r}_3}{2} + \frac{c(t_3 - t_2)}{2} \cdot \frac{\vec{r}_2 - \vec{r}_3}{|\vec{r}_2 - \vec{r}_3|}, \quad (6.2)$$

and

$$t_a = \frac{t_2 + t_3}{2} - \frac{|\vec{r}_2 - \vec{r}_3|}{2c}. \quad (6.3)$$

To perform the TOF-MLEM reconstruction, the coincidence data for both the  $2\gamma_a$  events and the  $2\gamma_a + \gamma_p$  events acquired with the J-PET scanner were converted to the list-mode format suitable for CASToR reconstruction using the J-PET framework. Image reconstruction was performed with the CASToR package using the TOF-MLEM algorithm with 10 iterations without subset acceleration. The reconstructed volume consisted of  $200 \times 200 \times 200$  voxels, with a voxel size of  $2.5 \times 2.5 \times 2.5$  mm<sup>3</sup>. A Gaussian filter with an FWHM of 5 mm was uniformly applied for post-reconstruction smoothing.

The resulting TOF-MLEM images for the  $2\gamma_a$  and  $2\gamma_a + \gamma_p$  datasets, together with the annihilation position distribution  $\vec{r}_a$  (Eq. 6.2) for the  $2\gamma_a + \gamma_p$  events, are presented in the Results section.

### 6.3 Positronium Lifetime estimation

The lifetime of the positron, defined as  $\Delta T = t_a - t_p$ , represents the time interval between positron emission and annihilation. Here,  $t_a$  denotes the annihilation time, while  $t_p$  is used as an approximation of the emission time. In the decay of  $^{44}\text{Sc}$ , a prompt gamma photon is emitted with an average delay of 2.6 ps relative to the positron emission. Due to this very short delay, the prompt gamma emission time is treated as a reliable estimate of  $t_p$ .

The emission time is obtained by correcting the prompt gamma detection time ( $t_1$ ) for its TOF:

$$t_p = t_1 - \frac{|\vec{r}_1 - \vec{r}_a|}{c}, \quad (6.4)$$

where  $\vec{r}_1$  is the recorded interaction position of the prompt gamma, and  $\vec{r}_a$  is the reconstructed annihilation point (see Equation 6.2). Considering the short positron range in tissue (approximately 1.7 mm [40]), it is reasonable to assume that the prompt gamma originates close to the annihilation site.

The measured  $\Delta T$  spectrum includes contributions from several different annihilation processes. These include direct positron annihilation (p), p-Ps and o-Ps annihilation. Therefore, the spectrum was analyzed by fitting a sum of exponential decay components convoluted with the detector time resolution using the PALS Avalanche software [164–166]. The initial parameters for p-Ps and direct annihilation were set to lifetimes of 125 ps (10% intensity) and 388 ps (60% intensity), respectively. Both lifetimes and intensities were allowed to vary within 200% of their initial values.

The NEMA-IQ phantom used in this experiment was made of Polymethyl Methacrylate (PMMA). The mean lifetime of o-Ps in PMMA falls within the range of 1.7 to 1.9 ns, depending on temperature (20°C–60 °C) [167]. This range is similar to that in water, where the mean o-Ps lifetime is approximately  $1.839 \pm 0.015$  ns at 20°C [168]. Given this similarity, contributions from PMMA and water were treated as a single component during the fitting procedure. The background background from accidental coincidences was estimated by taking the average from the interval between -10 ns and -5 ns and subtracted prior to fit.

To evaluate the reliability of the extracted o-Ps lifetime, three fitting strategies were employed in this study:

**Model 1 (Fixed Background):** the background level was fixed at the estimated value, while the mean o-Ps lifetime ( $\tau_{\text{o-Ps}}$ ) and intensity were treated as free parameters.

**Model 2 (Constrained Background):** the background was allowed to vary within  $\pm 3\sigma$  of its mean value, where  $\sigma$  is the standard deviation of counts in the -10 ns to -5 ns range. The mean o-Ps lifetime ( $\tau_{\text{o-Ps}}$ ) and intensity remained free. This approach improves stability in low-statistics conditions.

**Model 3 (Extended Parameter Range):** the background was fixed, while the mean o-Ps lifetime ( $\tau_{\text{o-Ps}}$ ) and intensity were allowed to vary up to 200% of their initial values (2 ns and 30%, respectively).

In addition to the mean o-Ps lifetime ( $\tau_{\text{o-Ps}}$ ), the mean positron lifetime ( $\Delta T_{\text{mean}}$ ) was

calculated within the 0–5 ns signal region after background subtraction:

$$\Delta T_{\text{mean}} = \frac{\sum_{i=0}^{5 \text{ ns}} (N_i - N_b) \Delta T_i}{\sum_{i=0}^{5 \text{ ns}} (N_i - N_b)}, \quad (6.5)$$

where  $N_i$  is the number of events in bin  $\Delta T_i$ , and  $N_b$  represents the average background estimated from the  $-10$  ns to  $-5$  ns interval. The resulting values of  $\tau_{\text{O-Ps}}$  and  $\Delta T_{\text{mean}}$  from this experiment are presented in the next section.

## 6.4 Result

The transaxial slice of the two gamma coincidence PET image reconstructed using the TOF-MLEM algorithm for  $2\gamma_a$  events is shown in Fig. 6.4(A). The image has been corrected for attenuation and sensitivity.

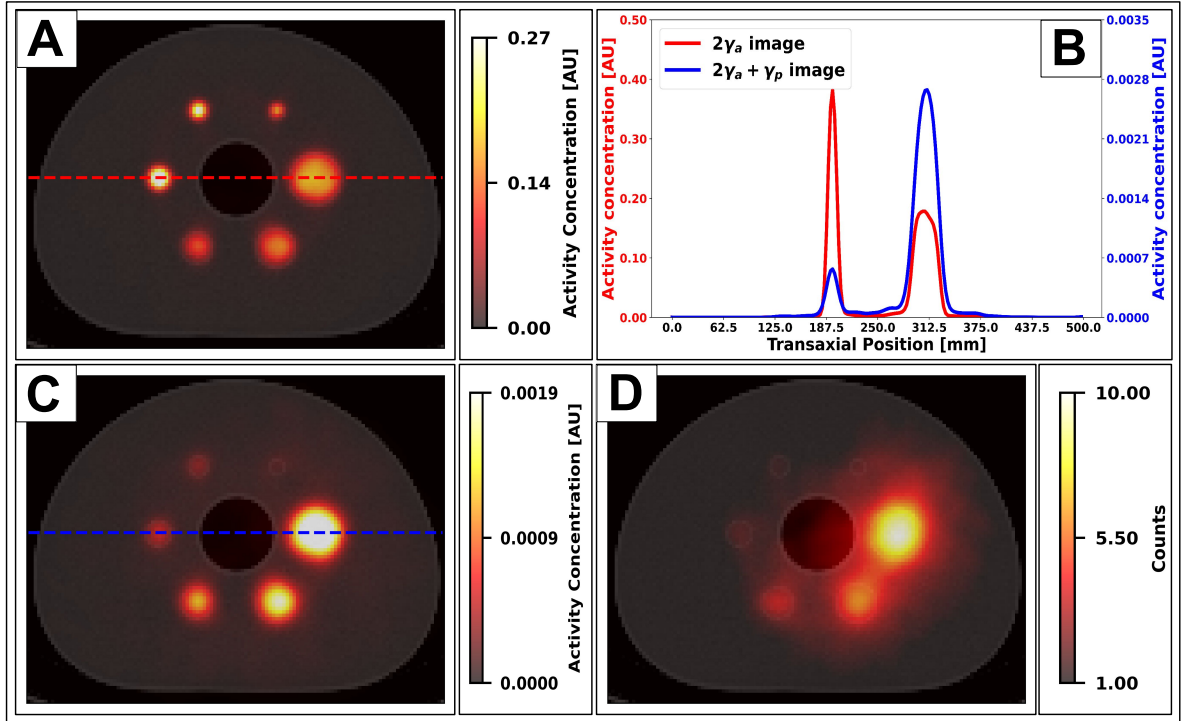


Figure 6.4:  $2\gamma_a$  and  $2\gamma_a + \gamma_p$  image of the NEMA IQ phantom filled with  $^{44}\text{Sc}$  (three largest spheres) and  $^{18}\text{F}$  (three smallest spheres): (A) Transaxial slice of  $2\gamma_a$  acquired with the modular J-PET scanner, reconstructed using CASToR, and overlaid on the corresponding CT image. (B) Line profile extracted along the dashed line indicated in the images. The red line corresponds to the  $2\gamma_a$  image, showing that the activity concentration of  $^{18}\text{F}$  is more than twice that of  $^{44}\text{Sc}$  within the selected slice. The blue curve represents the profile for the  $2\gamma_a + \gamma_p$  image showing reduction in the activity concentration in the region of  $^{18}\text{F}$ . (C) Transaxial slice reconstructed from  $2\gamma_a + \gamma_p$  events using two 511 keV photons in CASToR, overlaid on the CT image. (D) Transaxial distribution of reconstructed annihilation positions distribution ( $\vec{r}_a$ ) for  $2\gamma_a + \gamma_p$  events, overlaid on the CT image. Only voxels with intensities greater than 10% of the maximum are shown. Figure, prepared by the author, is adapted from [41], licensed under CC BY 4.0.

## CHAPTER 6. FIRST POSITRONIUM LIFETIME IMAGING WITH THE $^{44}\text{Sc}$ WITH THE J-PET SCANNER

Table 6.1: Ps lifetime and intensity value estimated from three different fitting-models.  $D$  represents the diameter of the spheres. Here,  $\tau_{\text{o-Ps}}$  represents the mean o-Ps lifetime, while  $I_{\text{o-Ps}}$ ,  $I_{\text{direct}}$ , and  $I_{\text{p-Ps}}$  denote the relative intensities of o-Ps annihilation, direct  $e^+ - e^-$  annihilation, and p-Ps annihilation, respectively. The mean positron lifetime is indicated by  $\Delta T_{\text{mean}}$ . Table, prepared by the author, is adapted from [41], licensed under CC BY 4.0.

| Fitting Model 1 |                           |                       |                         |                       |                               |
|-----------------|---------------------------|-----------------------|-------------------------|-----------------------|-------------------------------|
| $D$ [mm]        | $\tau_{\text{o-Ps}}$ [ns] | $I_{\text{o-Ps}}$ [%] | $I_{\text{direct}}$ [%] | $I_{\text{p-Ps}}$ [%] | $\Delta T_{\text{mean}}$ [ns] |
| 22.00           | $1.413 \pm 0.070$         | $28.46 \pm 1.26$      | $61.11 \pm 1.43$        | $10.43 \pm 1.20$      | $1.099 \pm 0.013$             |
| 28.00           | $1.821 \pm 0.061$         | $25.55 \pm 0.74$      | $63.41 \pm 0.89$        | $11.04 \pm 0.73$      | $1.099 \pm 0.008$             |
| 37.00           | $1.804 \pm 0.042$         | $25.84 \pm 0.52$      | $62.05 \pm 0.63$        | $12.10 \pm 0.52$      | $1.102 \pm 0.005$             |
| Fitting Model 2 |                           |                       |                         |                       |                               |
| $D$ [mm]        | $\tau_{\text{o-Ps}}$ [ns] | $I_{\text{o-Ps}}$ [%] | $I_{\text{direct}}$ [%] | $I_{\text{p-Ps}}$ [%] | $\Delta T_{\text{mean}}$ [ns] |
| 22.00           | $1.693 \pm 0.087$         | $25.68 \pm 1.13$      | $56.96 \pm 1.38$        | $17.36 \pm 1.16$      | $1.122 \pm 0.013$             |
| 28.00           | $2.129 \pm 0.076$         | $23.43 \pm 0.70$      | $63.99 \pm 0.88$        | $12.58 \pm 0.71$      | $1.108 \pm 0.008$             |
| 37.00           | $1.836 \pm 0.044$         | $25.40 \pm 0.51$      | $62.62 \pm 0.62$        | $11.98 \pm 0.51$      | $1.102 \pm 0.005$             |
| Fitting Model 3 |                           |                       |                         |                       |                               |
| $D$ [mm]        | $\tau_{\text{o-Ps}}$ [ns] | $I_{\text{o-Ps}}$ [%] | $I_{\text{direct}}$ [%] | $I_{\text{p-Ps}}$ [%] | $\Delta T_{\text{mean}}$ [ns] |
| 22.00           | $1.398 \pm 0.068$         | $29.13 \pm 1.23$      | $62.85 \pm 1.38$        | $8.02 \pm 1.04$       | $1.099 \pm 0.013$             |
| 28.00           | $1.815 \pm 0.008$         | $25.68 \pm 0.73$      | $65.15 \pm 0.89$        | $9.17 \pm 0.70$       | $1.099 \pm 0.008$             |
| 37.00           | $1.838 \pm 0.044$         | $25.23 \pm 0.50$      | $65.07 \pm 0.60$        | $9.71 \pm 0.43$       | $1.102 \pm 0.005$             |

At the beginning of the measurement, the ACR between  $^{18}\text{F}$  and  $^{44}\text{Sc}$  was 3.10. Due to the distinct decay rates of the two isotopes ( $\lambda_{^{18}\text{F}} = 0.006316 \text{ min}^{-1}$  and  $\lambda_{^{44}\text{Sc}} = 0.002909 \text{ min}^{-1}$ ), this ratio progressively declines during measurement. Following a 178-minute acquisition duration, the time-integrated activity ratio was determined to be approximately 2.38. The  $2\gamma_a$  line profile spanning the 17 and 37 mm spheres (Figure 6.4(B)) shows that within the selected slice, the peak ACR is 2.08, which is in good agreement with the calculated value.

The TOF-MLEM reconstructed image for the  $2\gamma_a + \gamma_p$  events, with the CASToR, is shown in Figure 6.4(C). This image highlights the effectiveness of the applied event selection criteria in selecting the  $2\gamma_a + \gamma_p$  events for PLI. The corresponding line profiles for the 17 and 37 mm diameter spheres [Figure 6.4(B)] show suppression of event contributions from  $^{18}\text{F}$  in the 17 mm sphere. This behavior is expected, as  $^{18}\text{F}$  does not emit prompt gamma. The residual signal associated with  $^{18}\text{F}$  can be explained by coincidences, where a prompt gamma emitted by  $^{44}\text{Sc}$  is detected in coincidence with two annihilation photons originating from  $^{18}\text{F}$  within the coincidence window of 20 ns. Such events lead to misidentified  $2\gamma_a + \gamma_p$  detections and mainly contribute to background.

The spatial distribution of annihilation points ( $\vec{r}_a$ ) reconstructed from  $2\gamma_a + \gamma_p$  events using two 511 keV photons (Equation 6.2) is shown in Figure 6.4(D). The increased intensity of the signal is clearly visible in the spheres with diameters of 22 mm, 28 mm, and 37 mm, which contain  $^{44}\text{Sc}$ . To obtain the positron lifetime ( $\Delta T$ ) from the spheres containing  $^{44}\text{Sc}$ ,

ROIs were defined within each sphere, as illustrated in Fig. 6.5(A), and the corresponding lifetime distributions were plotted with a bin width of 100 ps. The  $\tau_{\text{o-Ps}}$  obtained from the fitting of the lifetime spectra using three different models are summarized in Table 6.1.

In Fitting Model 1, the extracted  $\tau_{\text{o-Ps}}$  values for the 28 mm and 37 mm spheres are consistent with the reference value for water. However, the value obtained for the 22 mm sphere ( $1.413 \pm 0.070$  ns) is noticeably lower. The distribution of the positron lifetime spectra and  $\tau_{\text{o-Ps}}$  image are shown in Figure 6.5(B-E). The deviation in  $\tau_{\text{o-Ps}}$  observed in this model is likely due to low statistics in this sphere, along with a possible overestimation of the background contribution.

To address this issue, Fitting Model 2 was applied, which allows the background level to vary within  $\pm 3\sigma$  of its mean value. With this adjustment, the  $\tau_{\text{o-Ps}}$  in the 22 mm sphere becomes more consistent with the expected value. At the same time, the lifetime in the 28 mm sphere increases, while the result for the 37 mm sphere remains stable and in agreement with the reference value. These observations suggest that further investigation is required, particularly under conditions of limited statistics in PLI. In Fitting Model 3, all the fit parameters were allowed to vary within the bounds of 200%. The resulting  $\tau_{\text{o-Ps}}$  values are in good agreement with those obtained using Model 1.

Notably, the  $\Delta T_{\text{mean}}$  was found to be a more stable observable. This parameter does not depend on choice of the specific fitting model, incorporates the effect of all decay channels, and is mainly influenced by the method used for background estimation. In this study,  $\Delta T_{\text{mean}}$  remains consistent within 10 ps in all models, even when variations are observed in the extracted  $\tau_{\text{o-Ps}}$  (see Figure 6.5(F)).

## 6.5 Discussion

This chapter presents the demonstration of PLI using  $^{44}\text{Sc}$  with the modular J-PET scanner. These results, together with the other studies conducted [33, 39, 120] confirm that  $^{44}\text{Sc}$  is a well-suited radionuclide for PLI. Measurements performed with the modular J-PET scanner shows that the  $\tau_{\text{o-Ps}}$  values in the two largest spheres agree with literature values for water [168], validating the approach. However, results obtained from the smallest sphere reveal limitations driven by low statistics and sensitivity to background estimation.

To address this, multiple fitting strategies were explored. Model 2, which incorporates constrained background estimation, improves the consistency of  $\tau_{\text{o-Ps}}$  under low-statistics conditions (e.g., 22 mm sphere), highlighting the importance of adaptive background treatment. At the same time, its tendency to overestimate  $\tau_{\text{o-Ps}}$  values in higher-statistics regions (28 mm sphere) indicates that increased model flexibility may introduce bias. Therefore, while Model 2 is a valuable tool for assessing background sensitivity, further validation is required before any firm conclusion can be drawn.

By comparison, the  $\Delta T_{\text{mean}}$  was found to be a more stable observable, remaining within a 10 ps variation between different fitting approaches, underscoring its robustness and relevance for PLI.

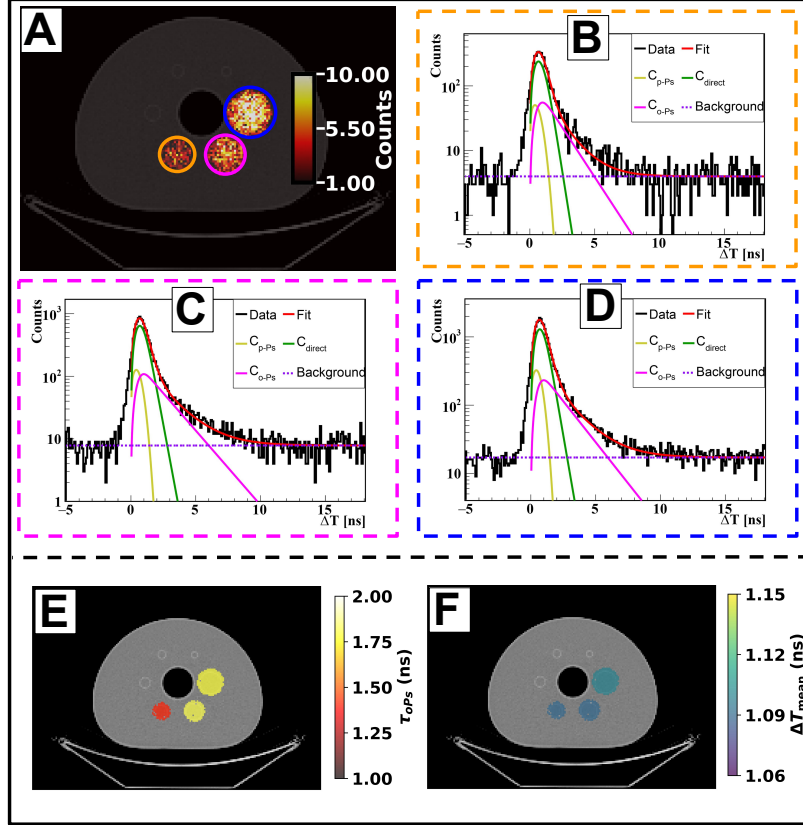


Figure 6.5: **(A)** Transaxial view of the NEMA-IQ phantom showing the selected ROIs, overlaid on the corresponding CT image. **(B–D)** Positron annihilation lifetime ( $\Delta T$ ) distributions for spheres with diameters of 22 mm (B), 28 mm (C), and 37 mm (D). The black histograms represent the measured data, while the superimposed curves indicate the fitted components: p-Ps ( $C_{p-Ps}$ ), direct annihilation ( $C_{direct}$ ), o-Ps ( $C_{o-Ps}$ ), and the background arising from accidental coincidences. The red curve corresponds to the overall fit, given by the sum of all components. **(E–F)** Positronium image of the extracted mean o-Ps lifetime ( $\tau_{o-Ps}$ ) (E) and the mean positron lifetime ( $\Delta T_{mean}$ ) (F) obtained using Fitting Model 1, where voxel intensities within each ROI are replaced by their corresponding lifetime values. Figure, prepared by the author, is adapted from [41], licensed under CC BY 4.0.



## Chapter 7

# First Positronium Lifetime Imaging with Two Novel Long-Lived Isotopes, $^{52}\text{Mn}$ and $^{55}\text{Co}$ , with the J-PET Scanner

In the previous chapter, the demonstration of PLI with ( $^{44}\text{Sc}$ ) established this radionuclide as one of the most favourable candidates for PLI. With high ( $\beta^+ + \gamma$ ) yield, short de-excitation delay and clinically relevant half-life ( $T_{1/2} = 4.04$  h), it is of particular interest for applications where efficient event tagging and pure signal are required. However, there are additional areas where radiopharmaceuticals with slow pharmacokinetics, such as monoclonal antibodies are more suitable. For this reason, it is important to investigate alternative  $\beta^+ + \gamma$  emitters for PLI applications [5, 40].

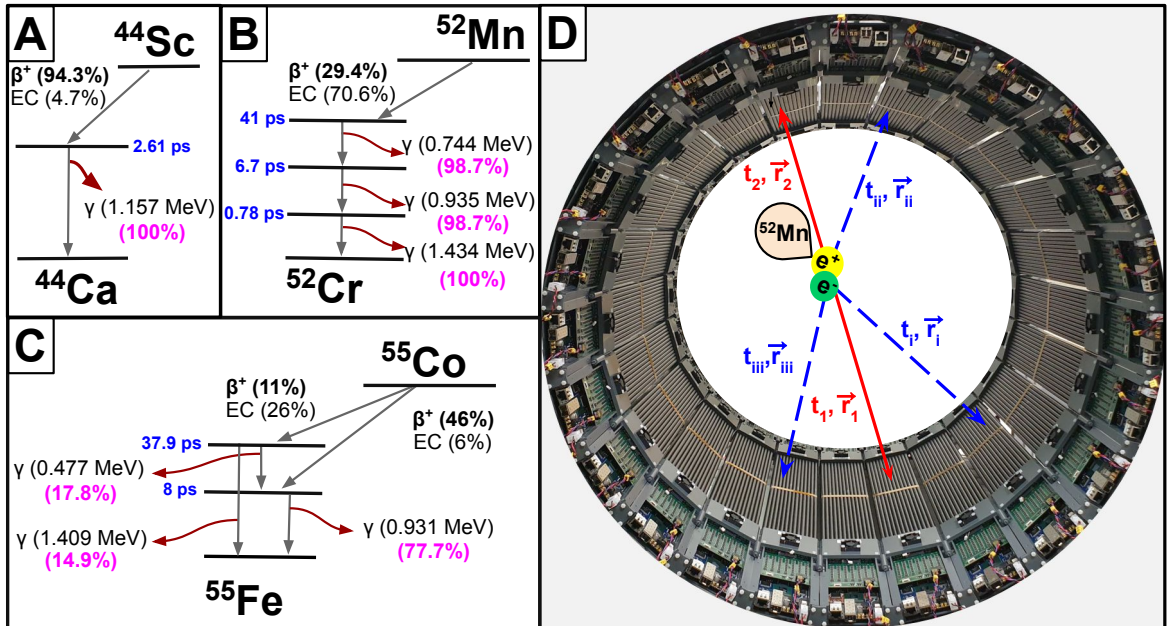


Figure 7.1: (A–C) Decay schemes of  $^{44}\text{Sc}$  (A,  $T_{1/2} = 4.04$  h),  $^{52}\text{Mn}$  (B,  $T_{1/2} = 5.59$  d), and  $^{55}\text{Co}$  (C,  $T_{1/2} = 17.53$  h). (D) Event definition for  $^{52}\text{Mn}$  in the modular J-PET scanner, including two annihilation photons detected at  $(t_1, \vec{r}_1)$  and  $(t_2, \vec{r}_2)$ , together with a possible cascade of three prompt photons detected at  $(t_i, \vec{r}_i)$ ,  $(t_{ii}, \vec{r}_{ii})$ , and  $(t_{iii}, \vec{r}_{iii})$ . Figure, prepared by the author, is adapted from [53], licensed under CC BY 4.0.

Among the other available  $\beta^+ + \gamma$  emitting isotopes,  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  are particularly promising long-lived radionuclides that could overcome some of the limitations associated with  $^{44}\text{Sc}$ . Currently,  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  are not yet included among radionuclides used in routine clinical PET but possess several interesting features. First,  $^{55}\text{Co}$  has a half-life of 17.5 hours, which is significantly longer than that of  $^{68}\text{Ga}$  [169]. Therefore,  $^{55}\text{Co}$  is suitable for immuno-PET using monoclonal antibodies [170] and also allows delayed imaging to increase the tumor-to-background ratio, which is particularly relevant in oncology studies. Initial preclinical studies using  $^{55}\text{Co}$ -based tracers have shown promising results [171, 172]. In addition to applications in oncology,  $^{55}\text{Co}$  has also been proposed for the visualization of neuronal damage in stroke patients [173]. Furthermore, multi-isotope PET imaging has been demonstrated using  $^{55}\text{Co}$  and  $^{18}\text{F}$ -labeled tracers in a single session, where the signals were separated by exploiting the prompt-gamma emission of  $^{55}\text{Co}$  [174, 175].

In contrast,  $^{52}\text{Mn}$  has been investigated in a range of applications. It has been used for *in-vivo* immuno-PET imaging [176]. Due to its properties,  $^{52}\text{Mn}$  is also suitable for combined PET/MR imaging and thus can be used as a PET-analogue for Mn-based MRI contrast agents for distribution and pharmacokinetics studies *in-vivo* [177–180]. Moreover,  $^{52}\text{Mn}$  can serve as a surrogate for  $\text{Ca}^{2+}$  uptake studies, for example in the context of diabetes [181].  $^{52}\text{Mn}$ -labelled liposomes have also been evaluated *in-vivo* [182]. In addition, the radiation effective dose of  $^{52}\text{Mn}$  administered as chloride in humans has been determined [183], and its radiotoxicity has been evaluated in rats [184].

This chapter presents, to best of our knowledge, the first PLI studies with these two long-lived radionuclides ( $^{52}\text{Mn}$  and  $^{55}\text{Co}$ ), performed using CRMs and human tissues (cardiac myxoma and adipose tissue). The experimental details are described in Section 3.2.2.

The results presented in this chapter have been published as a peer-reviewed manuscript, with the author of this thesis as the first author [53]. The figures and text included in this chapter are adapted from that manuscript and were originally prepared by the author.

## 7.1 Data Analysis for the PLI with $^{52}\text{Mn}$ and $^{55}\text{Co}$

The selection procedure follows the methodology already established in our previous studies with  $^{44}\text{Sc}$  (see Chapter 6), including TOT-based photon identification, multiplicity selection, angular constraints, and ST to reduce contribution from detector scattering and accidental coincidences. The measured TOT spectra for  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  are shown in Figure 7.2(A) and Figure 7.3(A), respectively. Unlike  $^{44}\text{Sc}$ , which produces a single prompt photon at 1157 keV well separated from the 511 keV annihilation energy, both  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  emit multiple prompt photons at various energies, resulting in more complex TOT spectra (see Figure 1.10). For  $^{52}\text{Mn}$ , the Compton edges of 511, 744, 935, and 1434 keV photons are clearly visible in the TOT spectrum (Figure 7.2(A)). Similarly, for  $^{55}\text{Co}$ , the Compton edges corresponding to the 477, 511, 931, and 1409 keV photons are observed in Figure 7.3(A). These values correspond to the maximum energy that can be transferred to an electron in a single Compton scattering interaction.

For event selection, TOT windows were applied to identify annihilation photons (511 keV)

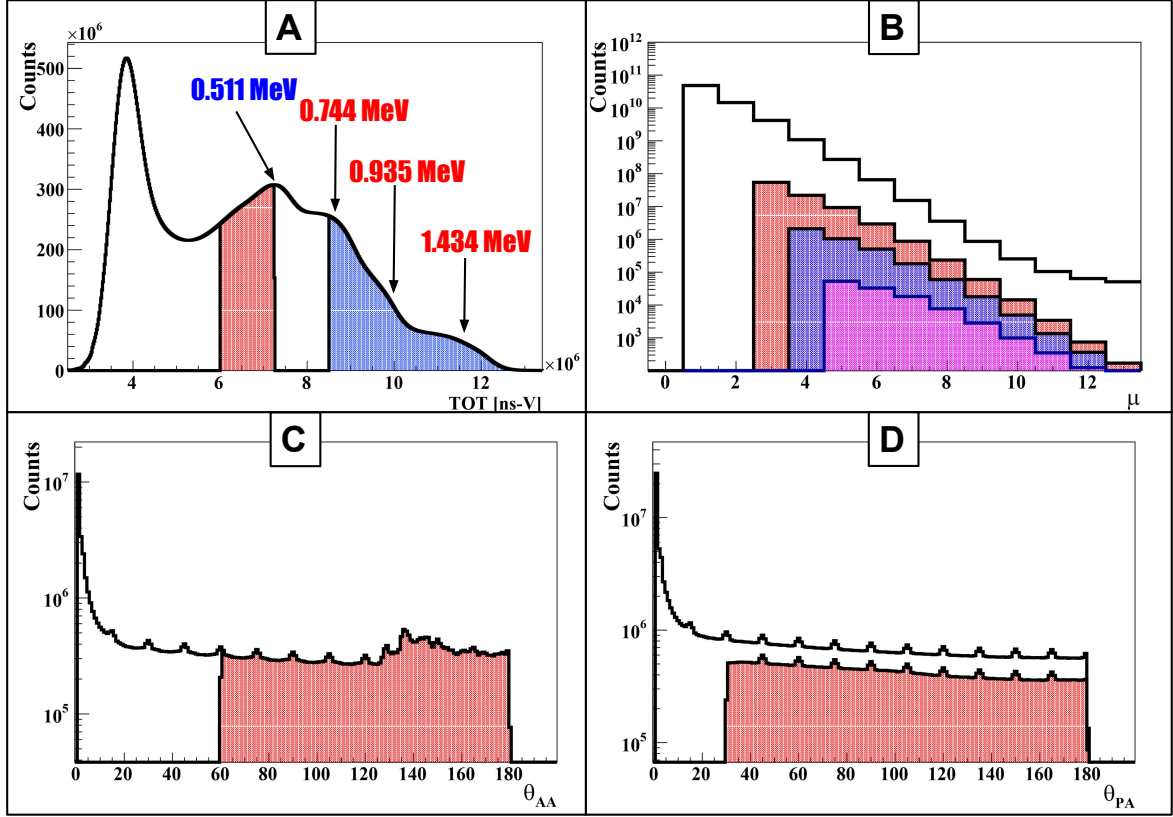


Figure 7.2: Event selection for  $^{52}\text{Mn}$ : (A) Distribution of the  $\text{TOT}_{\text{hit}}$  used for photon identification, where annihilation photons (red) and prompt gamma quanta (blue) are separated by distinct ranges. (B) Hit multiplicity ( $\mu$ ) distribution for registered events, with the red-shaded region shows events with exactly two annihilation photons and one prompt gamma, the blue region shows two annihilation photons and two prompt gammas, and the magenta region shows two annihilation photons and three prompt gammas. (C) Distribution of the relative angle ( $\theta_{AA}$ ) between the annihilation photon vectors  $\vec{r}_1$  and  $\vec{r}_2$  (see Figure 7.1D), where events with  $\theta_{AA} \geq 60^\circ$  (red) are selected. (D) Distribution of the relative angle ( $\theta_{PA}$ ) between the prompt gamma vector  $\vec{r}_i$  and the annihilation photon vectors  $\vec{r}_1, \vec{r}_2$  (see Figure 7.1D), with the requirement  $\theta_{PA} \geq 30^\circ$  (red). Figure, prepared by the author, is adapted from [53], licensed under CC BY 4.0.

and prompt photons. In both figures, the selected annihilation and prompt windows are indicated by the red- and blue-shaded regions, respectively. For  $^{52}\text{Mn}$ , annihilation candidates were selected in the range 6–7.25 ns·V, while prompt photons were selected in 8.5–13.5 ns·V. For  $^{55}\text{Co}$ , the corresponding ranges were 6–7.8 ns·V and 8.8–13.5 ns·V, respectively. The events were then formed based on the multiplicity of hits within a CTW of 20 ns. Next, events with two annihilation photons and one or more prompt photons were considered. For  $^{52}\text{Mn}$ , which emits up to three prompt photons per decay (see Figure 7.1(B)), different multiplicity classes were analyzed containing three hits ( $2\gamma_a + \gamma_p$ ), four hits ( $2\gamma_a + 2\gamma_p$ ), and five hits ( $2\gamma_a + 3\gamma_p$ ), in order to investigate whether the additional prompt photons provide a practical advantage for PLI. For  $^{55}\text{Co}$ , whose decay scheme is simpler, only the single-prompt configuration was considered (see Figure 7.2(B), Figure 7.3(B)). Angular selections on  $\theta_{AA}$  and  $\theta_{PA}$  were applied to suppress misidentified and detector-scattered events (see Figure 7.2(C-D), Figure 7.3(C-D)).

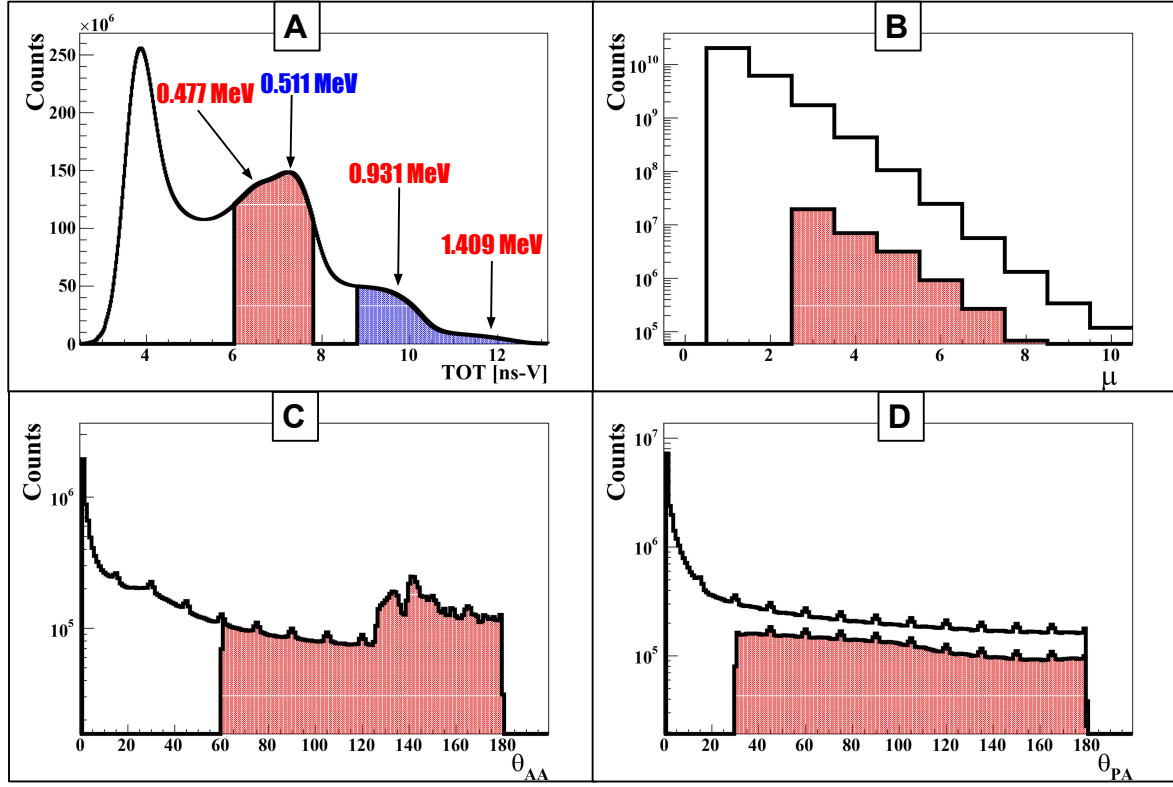


Figure 7.3: Event selection for  $^{55}\text{Co}$ : (A) Distribution of  $\text{TOT}_{\text{hit}}$  used for photon identification, showing a clear separation between annihilation photons (red) and prompt gamma quanta (blue) based on distinct  $\text{TOT}_{\text{hit}}$  ranges. (B) Hit multiplicity ( $\mu$ ) distribution of recorded events, where the red-shaded region highlights the selected subset containing exactly two annihilation photons and one prompt gamma. (C) Distribution of the relative angle ( $\theta_{AA}$ ) between annihilation photon vectors  $\vec{r}_1$  and  $\vec{r}_2$  (see Fig. 7.1D), with events satisfying  $\theta_{AA} \geq 60^\circ$  shown in red. (D) Distribution of the relative angle ( $\theta_{PA}$ ) between the prompt gamma vector  $\vec{r}_i$  and the annihilation photon vectors  $\vec{r}_1, \vec{r}_2$  (see Fig. 7.1D), where the selection criterion  $\theta_{PA} \geq 30^\circ$  is applied (red). Figure, prepared by the author, is adapted from [53], licensed under CC BY 4.0.

As a final step, for a pair of hits with detected hit-times  $t_j$  and  $t_k$ , with corresponding hit-positions  $\vec{r}_j$  and  $\vec{r}_k$ , the ST is defined as:

$$\text{ST} = |t_k - t_j| - \frac{|\vec{r}_k - \vec{r}_j|}{c},$$

was used to reject events consistent with scattering or random coincidences. Ideally, ST will be negative when the two hits come from a pair of photons produced in the same annihilation, and positive when the two hits are just random coincidences as the time interval is not correlated. Only pairs satisfying the previously validated cut ( $\text{ST} < -0.5$  ns, see Chapter 6) were retained. The same criteria were adopted for candidate pairs of prompt photons (with four and five hit multiplicities) in the  $^{52}\text{Mn}$  data set to reduce detector-induced scattering effects from the prompt photons.

After applying all selection criteria, a clean sample of  $2\gamma_a + \gamma_p$  events is obtained for further analysis. However, the purity of the events still depends on the detailed decay schemes

of  $^{52}\text{Mn}$  and  $^{55}\text{Co}$ . Therefore, it is important to identify and quantify the dominant background channels specific to these isotopes, discussed in the next section.

## 7.2 Background contribution

### 7.2.1 $^{52}\text{Mn}$

Among the  $\beta^+ + \gamma$  emitters considered for PLI so far,  $^{52}\text{Mn}$  offers several practical advantages. Its relatively long half-life of approximately 5.6 days is sufficient for production, transport, and multi-step experimental procedures, while still remaining suitable for preclinical studies. Each decay ( $^{52}\text{Mn} \rightarrow ^{52}\text{Cr}^*$ ) is followed by a cascade of three prompt photons (744, 935, and 1434 keV), which are emitted nearly simultaneously on a timescale of tens of picoseconds (see Figure 7.1B). Despite these features for PLI, the complex decay scheme of  $^{52}\text{Mn}$  also introduces specific background contributions that must be carefully addressed.

A single decay can, in principle, provides up to three prompt photons that may be registered in coincidence with the annihilation radiation. This increases the probability of forming valid  $2\gamma_a + \gamma_p$  events by approximately a factor of three compared to isotopes emitting only one prompt photon. A significant limitation of  $^{52}\text{Mn}$ , however, is that in 70.6% of its decays the prompt photons are produced following electron capture rather than positron emission. Such events do not contribute to useful PLI topologies and instead increase the overall level of background. As described in Section 7.1, the annihilation and prompt candidates are selected based on their  $\text{TOT}_{\text{hit}}$  values. Both the 511 keV annihilation photons and the prompt photons from  $^{52}\text{Mn}$  produce distinct structures in the TOT spectra, corresponding to their respective Compton edges. In an ideal case, where photon energies are well separated and only single prompt photons are present, it would be possible to define narrow  $\text{TOT}_{\text{hit}}$  intervals and achieve an unambiguous separation between annihilation and prompt contributions.

However, in plastic scintillators, photon interactions are dominated by Compton scattering, and higher-energy prompt photons are preferentially scattered at small angles, as described by the Klein–Nishina distribution. Consequently, they often deposit only a fraction of their energy in a given strip, resulting in  $\text{TOT}_{\text{hit}}$  values that overlap with the region characteristic of 511 keV photons (see Figure 7.2(A)). This effect is further amplified by the multi-photon cascade of  $^{52}\text{Mn}$ , which increases the number of prompt-related hits in the annihilation energy region and complicates the identification of clean annihilation candidates. To mitigate this contamination, a relatively narrow  $\text{TOT}_{\text{hit}}$  window was chosen around the 511 keV peak. While this improves the purity of the annihilation sample, it also reduces the overall statistics, partially offsetting the efficiency gain expected from the higher prompt multiplicity. In addition, selection criteria based on angular correlations and ST criteria were applied to further suppress misidentified combinations of annihilation and prompt photons. Nevertheless, several background configurations still survive these cuts, as illustrated in Figure 7.4. These contributions can be broadly classified into two categories: those originating from a single decay (Figure 7.4(A–E)) and those arising from accidental coincidences between two independent decays (Figure 7.4(F–I)).

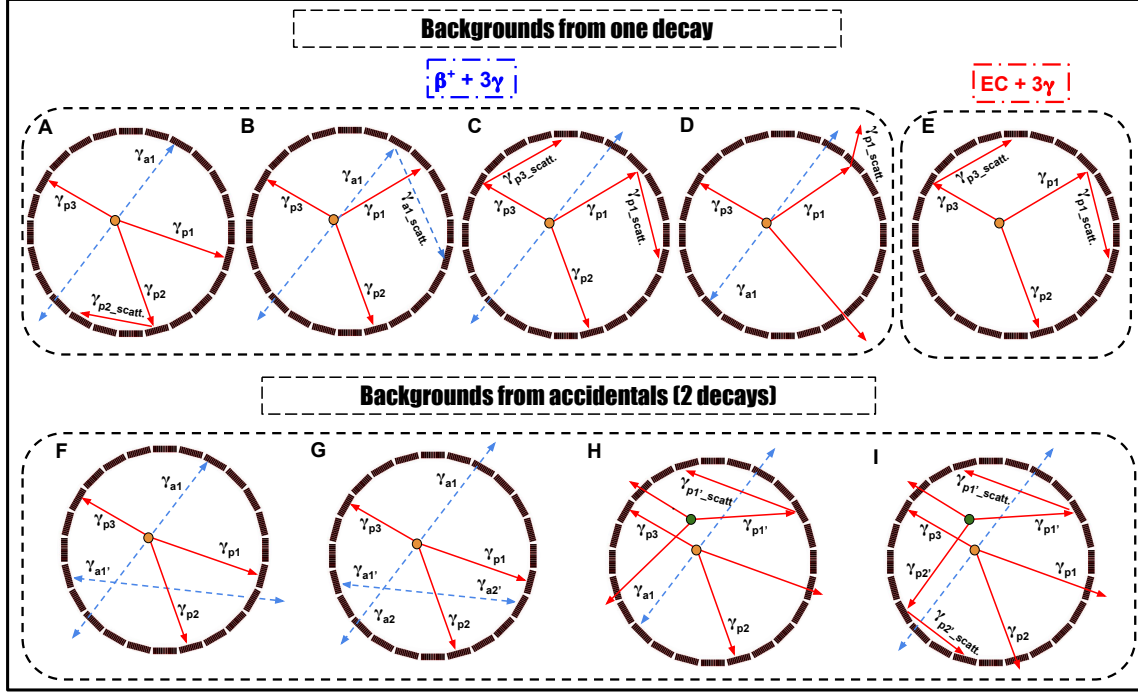


Figure 7.4: Cross-sectional view of the modular J-PET scanner illustrating representative background configurations in  $^{52}\text{Mn}$  data. Primary and scattered prompt photons are shown as red solid arrows, while annihilation photons are indicated by blue dashed arrows. **(A–E)** Backgrounds originating from a single decay: (A) one missing annihilation photon with a double-scattered prompt photon misidentified as annihilation radiation; (B) one missing annihilation photon with a doubly scattered annihilation photon; (C) both annihilation photons are undetected; two scattered prompt photons are misidentified as annihilation candidates; (D) one missing annihilation photon with a low-energy scattered prompt photon misidentified as annihilation radiation; (E) electron capture event without positron emission, where two prompt photons mimic annihilation signatures after scattering. **(F–I)** Backgrounds arising from accidental coincidences between independent decays: (F) coincidence of two annihilation photons from separate decays; (G) coincidence between a prompt photon and an annihilation photon from different decays; (H) mixed coincidence involving prompt photons and misidentified scattered signals from two decays; (I) complex accidental overlap of prompt and scattered photons leading to false annihilation assignment. Figure, prepared by the author, is adapted from [53], licensed under CC BY 4.0.

In the first category, background arises within individual  $^{52}\text{Mn}$  decays. One subset corresponds to 29.4% of decays in which positron emission is followed by prompt photon emission (Figure 7.4(A–D)). A substantial fraction of these events can be suppressed using ST selection between annihilation and prompt photon pairs, combined with angular constraints (see Figure 7.2(D)). The second subset, which accounts for 70.6% of decays, involves electron capture accompanied by prompt emission without positron production (see Figure 7.4(E)). These events can be significantly reduced by applying ST criteria among prompt photon candidates. The second category consists of accidental coincidences between photons originating from different decays (Figure 7.4(F–I)). Some of these contributions can be further suppressed by applying the allowed angular constraint ( $\theta_{AA}$  and  $\theta_{PA}$ ) and ST selections.

After all selection criteria, the data set contains 9,323,325 events classified as  $2\gamma_a + \gamma_p$ , 68,240 events corresponding to  $2\gamma_a + 2\gamma_p$ , and 1,088 events corresponding to  $2\gamma_a + 3\gamma_p$ . The latter two topologies together constitute only 0.74% of the  $2\gamma_a + \gamma_p$  events. Therefore, these higher-multiplicity events were used exclusively for studies of prompt photon multiplicity and were excluded from the Ps lifetime analysis.

### 7.2.2 $^{55}\text{Co}$

The  $^{55}\text{Co}$  isotope exhibits several properties that make it an even more advantageous candidate for PLI. Its half-life of 17.5 h is suitable for preclinical imaging studies, including those involving monoclonal antibodies. Approximately 76% of  $^{55}\text{Co}$  decays proceed via  $\beta^+$  emission, and in most of these events a 931 keV prompt gamma ( $\gamma_p$ ) is emitted with high intensity. This provides a well-defined prompt signal that can be used to construct  $2\gamma_a + \gamma_p$  event topologies. Compared to  $^{52}\text{Mn}$ , the decay scheme is therefore simpler and leads to a cleaner  $2\gamma_a + \gamma_p$  signature. In addition,  $^{55}\text{Co}$  has been used in pre-clinical PET studies using peptides and antibodies, thus establishing the availability of the appropriate chelation chemistry and labeling chemistry to produce targeted molecular imaging agents [171–173, 185]. Nevertheless, its decay scheme leads to additional background contributions that need to be accounted for with respect to PLI based on plastic scintillators.

A specific background arises from the 477 keV prompt photons emitted by  $^{55}\text{Co}$  (with an intensity of approximately 15%), which lie relatively close to the 511 keV annihilation energy. In the  $\text{TOT}_{\text{hit}}$  spectra, these photons often produce signals that fall within the same region as annihilation photons, as illustrated in Figure 7.3(A). As a result, a fraction of 477 keV photons is incorrectly classified as annihilation candidates, contributing to background within the annihilation selection window. Following the same classification as for  $^{52}\text{Mn}$ , the  $^{55}\text{Co}$ -induced background is categorized into two main classes: events originating from a single decay [Figure 7.5(A–B)] and events formed by photons originating from two independent decays [Figure 7.5(C–E)].

In the first category, the background arises from individual  $^{55}\text{Co}$  decays. One possible scenario occurs when one of the annihilation photons is not detected and the 931 keV prompt photon undergoes two interactions within the detector. In such cases, a scattered hit from the prompt photon may be incorrectly identified as an annihilation photon [Figure 7.5(A)].



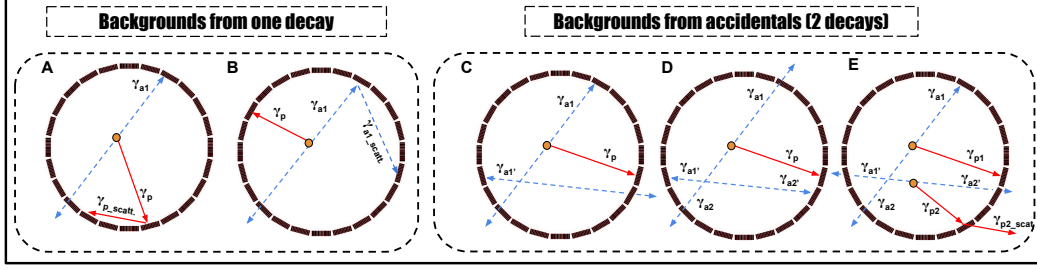


Figure 7.5: Cross-section of the modular J-PET scanner illustrating background events for  $^{55}\text{Co}$  decays. The prompt  $\gamma$  photon is shown as a red solid arrow, while primary and scattered annihilation photons are represented by blue dashed arrows. **(A)** Background event in which one annihilation photon is not detected and the prompt photon undergoes two interactions in the detector, leading to a scattered hit being misidentified as an annihilation photon. **(B)** Background event where one annihilation photon is undetected and the remaining annihilation photon undergoes multiple scattering, resulting in a misidentified second annihilation candidate. **(C)** Accidental coincidence in which a prompt photon from one decay is detected together with an annihilation photon pair originating from another decay. **(D)** Accidental coincidence involving a prompt photon and one annihilation photon from one decay combined with an annihilation photon from a second decay. **(E)** Additional accidental background event in which a prompt photon and one annihilation photon from one decay are recorded together with a low-energy scattered photon from another decay, which is misidentified as an annihilation photon. Figure, prepared by the author, is adapted from [53], licensed under CC BY 4.0.

These events typically tend to cluster at small values of the angle  $\theta_{PA}$  between the prompt and annihilation candidates and can be partially suppressed by applying a lower threshold on  $\theta_{PA}$ , as shown in Figure 7.3(D). Another scenario occurs when one annihilation photon is lost and the remaining photon undergoes multiple scattering, leading to a misidentification of a scattered hit as a second annihilation photon [Figure 7.5(B)]. Such events can be effectively reduced using the ST applied to the annihilation photon pair.

The second category consists of accidental coincidences that involve photons from two independent  $^{55}\text{Co}$  decays. An example is the background in which a prompt photon from one decay is detected together with an annihilation photon pair originating from another decay [Figure 7.5(C)]. A fraction of these events can also be rejected using the ST. Another configuration occurs when a prompt photon and one annihilation photon from one decay are recorded together with an annihilation photon originating from a second decay [Figure 7.5(D)]. In this case, additional suppression is achieved by applying the angular selections on  $\theta_{AA}$  and  $\theta_{PA}$  [Figure 7.3(C–D)], in combination with the ST, which further reduces such accidental coincidences. Another possibility is that a low-energy, scattered prompt photon of another decay could be identified as an annihilation photon as shown in Figure 7.5(E). These events are also suppressed by the TOT-based selection and ST.

### 7.3 Positronium Lifetime estimation

After applying all selection criteria described above, a purified sample of  $2\gamma_a + \gamma_p$  events was obtained and used for Ps lifetime reconstruction. For each selected event, the annihilation



position  $\vec{r}_a$  and annihilation time  $t_a$  were determined from the detection times and positions of the annihilation photons,  $(t_1, \vec{r}_1)$  and  $(t_2, \vec{r}_2)$ , using Equation 6.2 introduced in the previous chapter. Note that the notation for annihilation photons has been modified in this chapter for clarity, due to the presence of prompt photon cascades.

It should be emphasized that the annihilation point distribution was reconstructed exclusively using the 511 keV annihilation photon pair, while the additional prompt gamma photon was used to estimate the positron lifetime. The positron lifetime is defined as  $\Delta T = t_a - t_p$ , representing the time difference between positron emission and annihilation. Here,  $t_p$  serves as an estimator of the positron emission time. Based on the decay schemes shown in Figure 7.1(B–C), in the case of  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  isotopes, the prompt gamma emission occurs, on average, within 45 ps of positron emission. It is significantly shorter than both typical Ps lifetimes and the detector time resolution, which justifies the same approximation of identifying the prompt emission time with the positron emission time.

The emission time  $t_p$  is calculated by correcting the recorded prompt photon time for its time of flight (cf. Equation 6.4, adapted here to the notation of this chapter):

$$t_p = t_i - \frac{|\vec{r}_i - \vec{r}_a|}{c}, \quad (7.1)$$

where  $t_i$  and  $\vec{r}_i$  denote the detection time and position of the prompt gamma, and  $\vec{r}_a$  is the reconstructed annihilation point. Positrons emitted from the decay of  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  have short ranges in tissue, approximately 0.58 mm and 1.72 mm, respectively [101]. Therefore, the positron creation and annihilation points can be assumed to be separated by less than two millimeters. Combined with sub-nanosecond timing resolution, this supports the approximation that the prompt emission point is effectively co-located with the annihilation site.

The resulting  $\Delta T$  spectra include contributions from both direct positron annihilation and annihilation via Ps formation (p-Ps, and o-Ps). Following the same procedure as in Chapter 6, the spectra were analyzed by fitting a sum of exponential decay components convoluted with the detector resolution function, using the PALS Avalanche software [164–166]. Initial parameter values for p-Ps and direct annihilation were set to 125 ps (10% intensity) and 388 ps (60% intensity), respectively. During fitting, both lifetimes and intensities of these components were allowed to vary within a factor of two of their initial values.

For CRMs measurements, an additional fixed component corresponding to Parafilm was included, with a lifetime of 2.35 ns and an intensity of 10%, accounting for the known contribution of the sample mounting material. In contrast, for tissue measurements, no extra components were introduced for the Eppendorf or PCR tubes, as their contribution to the annihilation signal was verified to be negligible [39]. The o-Ps component remained unconstrained in both lifetime and intensity, as its determination constitutes the primary objective of the analysis.

A constant background level was estimated by averaging the counts in the time interval from  $-10$  to  $-5$  ns and subtracted prior to fitting, ensuring that the fit is driven solely by the physical decay components. In addition to the mean o-Ps lifetime  $\tau_{\text{o-Ps}}$  obtained from the multi-component fit, the mean positron lifetime  $\Delta T_{\text{mean}}$  was also evaluated. This quantity is defined as the average value of  $\Delta T$  within the range from 0 to 5 ns after background subtraction,

as described in the previous chapter (see Equation 6.5). It is sensitive to the overall shape of the lifetime spectrum, incorporating both short- and long-lived contributions, and thus provides a complementary metric to  $\tau_{\text{o-Ps}}$ . The extracted values of  $\tau_{\text{o-Ps}}$  and  $\Delta T_{\text{mean}}$  for all samples are presented and discussed in the Results section.

## 7.4 Results

The spatial distribution of annihilation points ( $\vec{r}_a$ ), defined in Equation 6.2, was reconstructed using the 511 keV annihilation photon pairs from the  $2\gamma_a + \gamma_p$  coincidences. The reconstructed annihilation point distributions ( $\vec{r}_a$ ) for  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  are shown in Figure 7.6(A) and Figure 7.7(A), respectively, with a uniform 2.5 mm isotropic voxel grid. After the event selection, a total of 9,323,325 valid  $2\gamma_a + \gamma_p$  coincidences for  $^{52}\text{Mn}$  and 3,706,231 for  $^{55}\text{Co}$  were obtained. The Peak-to-Background Ratio (PBR) was determined from the positron lifetime spectra to evaluate the signal purity, yielding values of 87 for  $^{52}\text{Mn}$  and 133 for  $^{55}\text{Co}$ . The higher PBR observed for  $^{55}\text{Co}$  indicates a cleaner selection of  $2\gamma_a + \gamma_p$  events. This improvement can be attributed to its simpler decay scheme, which has a lower electron-capture fraction and consequently fewer background contributions. For the estimation of positron lifetimes from the individual samples, a spherical ROI with a 33 mm radius was placed at the center of each sample. The average accumulated events across the four measured samples were roughly 239,760 for  $^{52}\text{Mn}$  and 179,450 for  $^{55}\text{Co}$ . The corresponding positron lifetime spectra ( $\Delta T$ ) for each sample are shown in Figure 7.6(D) for  $^{52}\text{Mn}$  and Figure 7.7(D) for  $^{55}\text{Co}$ . Table 7.1 details the extracted mean o-Ps lifetimes ( $\tau_{\text{o-Ps}}$ ), intensities ( $I_{\text{o-Ps}}$ ,  $I_{\text{direct}}$ ,  $I_{\text{p-Ps}}$ ). The mean positron lifetime ( $\Delta T_{\text{mean}}$ ), calculated by averaging  $\Delta T$  over the 0 to 5 ns interval, is also summarized.

### 7.4.1 Validation Using Certified Reference Materials (CRMs)

To validate the accuracy of the PLI technique, CRMs supplied by AIST, namely polycarbonate and fused silica, were investigated. The certified mean o-Ps lifetimes for these CRMs were provided as  $2.10 \pm 0.05$  ns for polycarbonate and  $1.62 \pm 0.05$  ns for fused silica. For polycarbonate, the results obtained using both radioisotopes are consistent with the certified reference values within experimental uncertainties, resulting  $2.069 \pm 0.020$  ns for  $^{52}\text{Mn}$  and  $2.174 \pm 0.024$  ns for  $^{55}\text{Co}$ , as summarized in Table 7.1 and the fitted positron lifetime spectra is shown in Figure 7.6(B) and Figure 7.7(B). In contrast, for fused silica, the measurement using  $^{55}\text{Co}$  accurately reproduces the certified value, giving  $1.607 \pm 0.012$  ns, whereas the result obtained with  $^{52}\text{Mn}$  yields  $1.836 \pm 0.013$  ns, deviating by approximately 200 ps from the certified reference value. The fitted lifetime spectra for fused silica is shown in Figure 7.6(C) and Figure 7.7(C).

As described in Sections 3.2.2 and 7.3, the CRM samples included a Parafilm spacer (1.2 mm) to host the liquid source, whose contribution was modelled as a fixed o-Ps component in the fitting procedure. When the Parafilm intensity was treated as a free parameter in the  $^{52}\text{Mn}$  fused silica dataset, the  $\tau_{\text{o-Ps}}$  shifted closer to the certified reference value. This

CHAPTER 7. FIRST POSITRONIUM LIFETIME IMAGING WITH TWO NOVEL  
LONG-LIVED ISOTOPES,  $^{52}\text{Mn}$  AND  $^{55}\text{Co}$ , WITH THE J-PET SCANNER

Table 7.1: Mean o-Ps lifetimes and relative intensities obtained from the positron lifetime spectra fits. Here,  $\tau_{\text{o-Ps}}$  represents the mean o-Ps lifetime, while  $I_{\text{o-Ps}}$ ,  $I_{\text{direct}}$ , and  $I_{\text{p-Ps}}$  denote the relative yields for o-Ps decay, direct positron-electron annihilation, and p-Ps decay, respectively. The parameter  $\Delta T_{\text{mean}}$  indicates the overall mean positron lifetime. All uncertainties are given at the  $\pm 1\sigma$  level. Note that the  $\tau_{\text{o-Ps}}$  values obtained for the myxoma and adipose samples deviate from earlier reports [25, 48] due to structural and chemical degradation resulting from prolonged refrigerated storage (three months prior to the  $^{52}\text{Mn}$  measurements and five months prior to the  $^{55}\text{Co}$  measurements). Table, prepared by the author, is adapted from [53], licensed under CC BY 4.0.

| $^{52}\text{Mn}$      |                           |                       |                         |                       |                               |
|-----------------------|---------------------------|-----------------------|-------------------------|-----------------------|-------------------------------|
| Sample Name           | $\tau_{\text{o-Ps}}$ [ns] | $I_{\text{o-Ps}}$ [%] | $I_{\text{direct}}$ [%] | $I_{\text{p-Ps}}$ [%] | $\Delta T_{\text{mean}}$ [ns] |
| Polycarbonate         | $2.069 \pm 0.020$         | $21.44 \pm 0.17$      | $54.82 \pm 0.21$        | $13.74 \pm 0.16$      | $1.120 \pm 0.002$             |
| Fused Silica          | $1.836 \pm 0.013$         | $32.45 \pm 0.20$      | $49.46 \pm 0.20$        | $8.10 \pm 0.16$       | $1.223 \pm 0.003$             |
| Myxoma (see caption)  | $2.111 \pm 0.018$         | $24.15 \pm 0.17$      | $64.07 \pm 0.22$        | $11.78 \pm 0.18$      | $1.043 \pm 0.002$             |
| Adipose (see caption) | $2.081 \pm 0.018$         | $23.68 \pm 0.17$      | $63.41 \pm 0.22$        | $12.91 \pm 0.19$      | $1.044 \pm 0.002$             |
| $^{55}\text{Co}$      |                           |                       |                         |                       |                               |
| Sample Name           | $\tau_{\text{o-Ps}}$ [ns] | $I_{\text{o-Ps}}$ [%] | $I_{\text{direct}}$ [%] | $I_{\text{p-Ps}}$ [%] | $\Delta T_{\text{mean}}$ [ns] |
| Polycarbonate         | $2.174 \pm 0.024$         | $20.34 \pm 0.21$      | $59.76 \pm 0.24$        | $9.90 \pm 0.19$       | $1.136 \pm 0.002$             |
| Fused Silica          | $1.607 \pm 0.012$         | $36.30 \pm 0.22$      | $42.54 \pm 0.22$        | $11.15 \pm 0.18$      | $1.240 \pm 0.002$             |
| Myxoma (see caption)  | $2.070 \pm 0.029$         | $13.46 \pm 0.49$      | $72.15 \pm 2.43$        | $14.39 \pm 0.79$      | $0.983 \pm 0.002$             |
| Adipose (see caption) | $1.996 \pm 0.030$         | $11.98 \pm 0.92$      | $71.87 \pm 0.16$        | $16.15 \pm 0.13$      | $0.972 \pm 0.002$             |

observation indicates that small local variations in Parafilm thickness or slight differences in source positioning may have occurred during that particular measurement. Since the  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  experiments were performed at different times, minor differences in the effective thickness of the Parafilm cannot be completely excluded. Therefore, to ensure consistency in the analysis, a fixed 10% Parafilm contribution was used for all datasets, while the remaining deviations were considered as part of the systematic uncertainty.

The spectral decomposition was further validated by analyzing the ratio of o-Ps intensities between the polycarbonate and fused silica samples. A previous interlaboratory study involving 12 independent laboratories reported a intensity ratio of  $I_{\text{poly}}/I_{\text{silica}} \approx 0.56$  for these CRMs [186]. The measurements performed with  $^{55}\text{Co}$  yielded a ratio of  $0.560 \pm 0.006$ , which is in excellent agreement with the reference value reported. In contrast, the  $^{52}\text{Mn}$  data resulted in a slightly higher ratio of  $0.661 \pm 0.007$ , which is consistent with the previously discussed systematic bias introduced by the Parafilm contribution in the fused silica measurement.

Although variations were observed in  $\tau_{\text{o-Ps}}$ , the mean positron lifetimes ( $\Delta T_{\text{mean}}$ ) for both polycarbonate and fused silica remained highly stable and largely independent of the radioisotope used. The differences in  $\Delta T_{\text{mean}}$  between the  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  measurements for both CRMs were below 20 ps, as summarized in Table 7.1. This is consistent with the findings of Chapter 6, where  $\Delta T_{\text{mean}}$  remained stable within 10 ps across different fitting models, and further supports the conclusion that  $\Delta T_{\text{mean}}$ , which reflects contributions from all decay channels, is a particularly robust and isotope-independent parameter for PLI applications [25,

41].

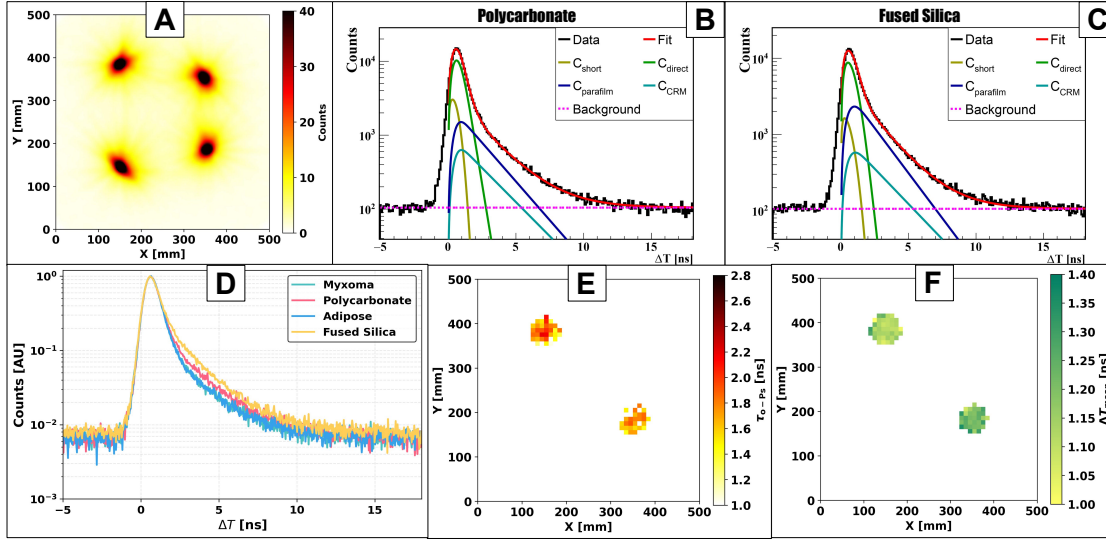


Figure 7.6: Results for  $^{52}\text{Mn}$ : (A) Transverse cross-section of the reconstructed annihilation point distribution ( $\vec{r}_a$ ) obtained from  $2\gamma_a + \gamma_p$  coincidences. (B-C) Positron lifetime ( $\Delta T$ ) spectra for Polycarbonate (B) and Fused Silica (C). Experimental data are shown as black histograms, with individual fitted components overlaid: p-Ps decay ( $C_{\text{short}}$ ), direct annihilation ( $C_{\text{direct}}$ ), Parafilm o-Ps decay ( $C_{\text{parafilm}}$ ), CRM o-Ps decay ( $C_{\text{CRM}}$ ), and the background. The cumulative fit is represented by the solid red line. (D) Comparative  $\Delta T$  spectra of Myxoma, Polycarbonate, Adipose, and Fused Silica samples. (E-F) Voxel-based image of the mean o-Ps lifetime ( $\tau_{\text{o-Ps}}$ ) (E) and the mean positron lifetime ( $\Delta T_{\text{mean}}$ ) (F) for the Polycarbonate and fused-silica. Figure, prepared by the author, is adapted from [53], licensed under CC BY 4.0.

#### 7.4.2 Biological Tissue Assessment and Voxel-based PLI

Results from the cardiac myxoma and adipose tissue samples showed that the obtained  $\tau_{\text{o-Ps}}$  values differed from previously reported *ex-vivo* measurements of fresh tissues, where  $\tau_{\text{o-Ps}}$  was approximately 1.9 ns for myxoma and 2.6–2.7 ns for adipose tissue [25, 48]. In the present study, the measured lifetimes were  $2.111 \pm 0.018$  ns for myxoma and  $2.081 \pm 0.018$  ns for adipose using  $^{52}\text{Mn}$ , and  $2.070 \pm 0.029$  ns for myxoma and  $1.996 \pm 0.030$  ns for adipose using  $^{55}\text{Co}$ , as listed in Table 7.1. The  $\Delta T_{\text{mean}}$  parameter also showed inter-isotope differences, amounting to 60 ps for myxoma and 72 ps for adipose tissue. These deviations strongly indicate that the prolonged storage procedure, including five years in formaldehyde, followed by Lugol's solution staining and several months of refrigerated storage between the  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  measurements, introduced microstructural changes in the tissue samples.

A systematic difference was also observed in the o-Ps intensities ( $I_{\text{o-Ps}}$ ), which were consistently higher in the  $^{52}\text{Mn}$  measurements than in the  $^{55}\text{Co}$  measurements (Table 7.1). The  $^{52}\text{Mn}$  measurements were performed three months after staining, whereas the  $^{55}\text{Co}$  measurements were carried out after five months. The decrease in  $I_{\text{o-Ps}}$  during this additional two-month interval further supports the hypothesis of progressive microstructural degradation under refrigerated conditions.

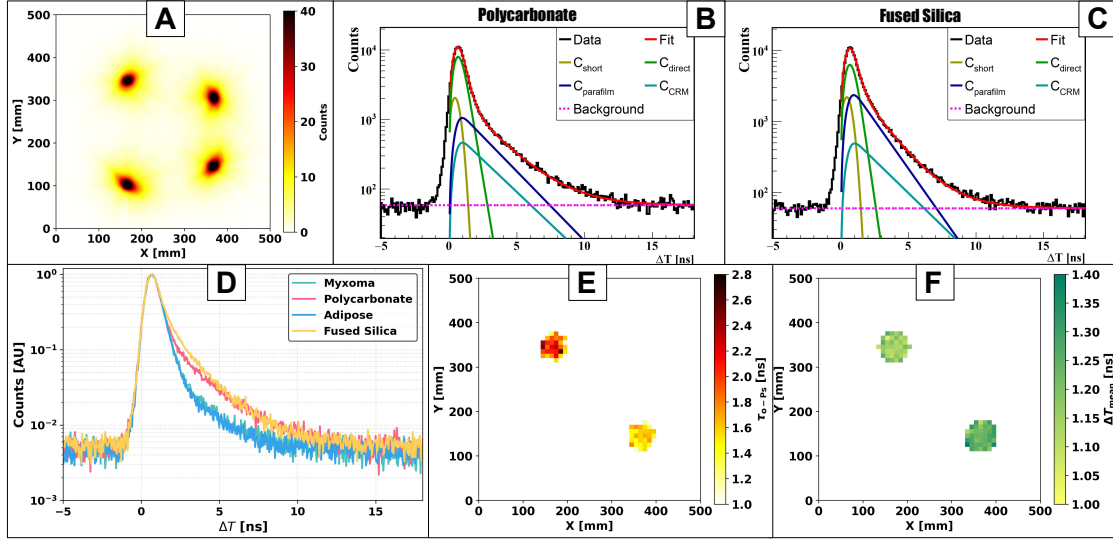


Figure 7.7: Results for  $^{55}\text{Co}$ : (A) Transverse cross-section of the reconstructed annihilation point distribution ( $\vec{r}_a$ ) obtained from  $2\gamma_a + \gamma_p$  coincidences. (B-C) Positron lifetime ( $\Delta T$ ) spectra for Polycarbonate (B) and Fused Silica (C). Experimental data are shown as black histograms, with individual fitted components overlaid: p-Ps decay ( $C_{\text{short}}$ ), direct annihilation ( $C_{\text{direct}}$ ), Parafilm o-Ps decay ( $C_{\text{parafilm}}$ ), CRM o-Ps decay ( $C_{\text{CRM}}$ ), and the background. The cumulative fit is represented by the solid red line. (D) Comparative  $\Delta T$  spectra of Myxoma, Polycarbonate, Adipose, and Fused Silica samples. (E-F) Voxel-based image of the mean o-Ps lifetime ( $\tau_{\text{o-Ps}}$ ) (E) and the mean positron lifetime ( $\Delta T_{\text{mean}}$ ) (F) for the Polycarbonate and fused-silica. Figure, prepared by the author, is adapted from [53], licensed under CC BY 4.0.

To investigate spatial variations in the PLI parameters, voxel-wise reconstructions of the  $\tau_{\text{o-Ps}}$  and  $\Delta T_{\text{mean}}$  were performed. Transverse  $\tau_{\text{o-Ps}}$  images were reconstructed using  $1 \times 1 \text{ cm}^2$  voxels integrated over the full axial field of view of the scanner, as shown in Figure 7.6(E) and Figure 7.7(E). The corresponding  $\Delta T_{\text{mean}}$  images were reconstructed using 1 cm isotropic voxels, presented in Figure 7.6(F) and Figure 7.7(F). For both radioisotopes, fused silica consistently showed lower  $\tau_{\text{o-Ps}}$  values but higher  $\Delta T_{\text{mean}}$  values compared to polycarbonate. This effect results from the significantly higher o-Ps intensity in fused silica, which shifts the effective  $\Delta T_{\text{mean}}$  toward longer overall lifetimes despite its shorter individual  $\tau_{\text{o-Ps}}$ . These spatially resolved distributions confirm that both  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  can provide reliable PLI of heterogeneous samples with the modular J-PET scanner.

For the biological tissue samples, voxel-wise maps were not reconstructed. Due to the limited sample volume, reduced statistics, and the structural degradation caused by long-term storage, only ROI-averaged parameters are reported in Table 7.1 as a stable voxel-wise analysis could not be achieved.

## 7.5 Discussion

This chapter presented PLI studies using  $\beta^+ + \gamma$  emitters  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  with the modular J-PET scanner. For both isotopes  $2\gamma_a + \gamma_p$  events were selected, yielding approximately  $9.3 \times 10^6$

events for  $^{52}\text{Mn}$  and  $3.7 \times 10^6$  for  $^{55}\text{Co}$  after the selection criteria described in Section 7.1.

CRMs (polycarbonate and fused silica) were used for validation of the lifetime analysis. For polycarbonate, the extracted  $\tau_{\text{o-Ps}}$  values for  $^{52}\text{Mn}$  and  $^{55}\text{Co}$ ,  $2.069 \pm 0.020$  ns and  $2.174 \pm 0.024$  ns, agree within uncertainties with the certified value and with each other, indicating isotope-independent performance of the reconstruction for this material. For fused silica, a different behavior was observed:  $^{55}\text{Co}$  reproduced the certified lifetime ( $1.607 \pm 0.012$  ns), whereas  $^{52}\text{Mn}$  was higher by 200 ps. As the Parafilm contribution was treated as a fixed o-Ps component, this shift was attributed to increased sensitivity of the  $^{52}\text{Mn}$  dataset to small variations in Parafilm thickness or positioning. This interpretation is supported by the  $I_{\text{poly}}/I_{\text{silica}}$  ratio [186], which agrees with interlaboratory values for  $^{55}\text{Co}$  but is higher for  $^{52}\text{Mn}$ . The deviation is therefore treated as a mounting-related systematic effect rather than an isotope limitation.

For biological tissues, both myxoma and adipose samples showed significantly reduced  $\tau_{\text{o-Ps}}$  compared to fresh *ex-vivo* PLI measurements with  $^{22}\text{Na}$  [25, 48]. This is consistent with chemical degradation during long-term storage (five years), including macromolecular damage and lipid oxidation in adipose tissue [187]. Additional degradation mechanisms may arise from long-term fixation effects reported for paraformaldehyde “aging” [188]. Iodine-based contrasting (Lugol’s solution) may also alter carbohydrate and glycolipid structure, though its impact cannot be quantified here. The reduction in  $\tau_{\text{o-Ps}}$  demonstrates the sensitivity of PLI observables to structural changes in aged biological material. Tissue shrinkage likely reduced free-volume fractions, which is reflected in the lower  $I_{\text{o-Ps}}$ . Consistently lower  $\tau_{\text{o-Ps}}$ ,  $I_{\text{o-Ps}}$ , and  $\Delta T_{\text{mean}}$  were observed for  $^{55}\text{Co}$ , acquired five months after staining, compared to  $^{52}\text{Mn}$  (three months), the inter-isotope  $\Delta T_{\text{mean}}$  differences amounted to 60–72 ps. Due to limited sample size and reduced statistics, only ROI-averaged values were analyzed, without voxel-wise mapping. Dedicated studies on freshly prepared samples are required before drawing quantitative biological conclusions. In the present work, the tissues were used primarily for isotope performance comparison.

Under identical conditions,  $^{55}\text{Co}$  showed higher PBR ( $\approx 133$ ) than  $^{52}\text{Mn}$  ( $\approx 87$ ), due to its simpler decay scheme with a single dominant prompt photon. In contrast,  $^{52}\text{Mn}$  provides a three-photon cascade that could in principle enhance the prompt detection efficiency, but this advantage is largely offset by its higher electron-capture fraction and increased scattered background. Overall, the combination of all selection criteria (Section 7.1) resulted in cleaner lifetime spectra for  $^{55}\text{Co}$ .

The results indicate that  $^{55}\text{Co}$  can complement  $^{44}\text{Sc}$ , particularly for cobalt-based chemistry or delayed imaging protocols. Although  $^{52}\text{Mn}$  introduces higher background due to its complex decay properties, it remains relevant for applications requiring its longer half-life or specific manganese chemistry.

## Chapter 8

# Positronium Lifetime Imaging in Humans with the J-PET Scanner

The PLI studies conducted with  $^{44}\text{Sc}$  (Chapter 6) and with  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  (Chapter 7) using phantom measurements demonstrated that PLI can provide additional tissue-characterization information beyond conventional metabolic imaging. However, as already discussed in Chapter 1, the clinical implementation of PLI remains challenging because all currently used clinical  $\beta^+ + \gamma$  emitters are limited by a relatively low prompt gamma yield.

One of the most commonly used  $\beta^+ + \gamma$  isotopes in the routine clinical PET imaging is  $^{68}\text{Ga}$ , which has a significantly lower yield of 1.19%. Despite this limitation, its routine clinical availability makes it a suitable choice for feasibility studies of PLI in human subjects. In current clinical practice,  $^{68}\text{Ga}$  is commonly labeled with radiotracers such as PSMA for prostate cancer imaging and DOTA-TATE for NETs imaging, depending on the diagnostic application. Its clinical availability enabled the first *in-vivo* PLI study of the human brain using [ $^{68}\text{Ga}$ ]-Ga-PSMA, performed by the J-PET research group [4].

This chapter presents PLI studies conducted in six patients suspected of NETs who were administered [ $^{68}\text{Ga}$ ]-Ga-DOTA-TATE from two different hospitals. In these patients, the highest tracer uptake was observed in the torso region, particularly in the liver, kidneys, and spleen. Therefore, the study focused only on these organs. Due to the statistical limitations associated with  $^{68}\text{Ga}$ , only the mean positron lifetime ( $\Delta T_{\text{mean}}$ ) was evaluated, as this parameter was found to be less sensitive to statistical fluctuations and fitting model choices, as demonstrated in Chapters 6 and 7. The primary objective of this study is to demonstrate the feasibility of PLI in human subjects using the modular J-PET scanner in a clinical setting. The measurement details of the six patients are described in Chapter 3.

### 8.1 Data Analysis for the PLI with patients

Data analysis for patient studies follows the same methodology as described in the previous chapters for phantom measurements, adapted here for the clinical data acquired with  $^{68}\text{Ga}$ . The first step of the analysis is to identify events corresponding to the detection of two annihilation photons and one prompt gamma ( $2\gamma_a + \gamma_p$ ) based on the  $\text{TOT}_{\text{Hit}}$  parameter. It serves as a measure of the energy deposited in the plastic scintillators. Based on the characteristic Compton edges observed for 511 keV annihilation photons and the prompt gamma (1077 keV) from  $^{68}\text{Ga}$ , appropriate selection windows are defined. Hits with  $\text{TOT}_{\text{Hit}}$  values corresponding to the two annihilation photons (red-shaded region) and the prompt gamma (blue-shaded region) are selected as shown in Figure 8.1(A).

After TOT-based classification, the hits are grouped within a CTW of 10 ns to form individual events. A narrower CTW compared to the phantom studies (20 ns in Chapter 6 and 7) was chosen to reduce the rate of accidental coincidences in the patient data, where the activity distribution is more spatially extended. These events are then sorted according to the multiplicity of hits. As shown in Figure 8.1(B), only events containing exactly three hits are selected from the multiplicity of hits  $\geq 3$ , corresponding to the expected topology of two annihilation photons and one prompt gamma. The red-shaded region indicates the events that satisfy this condition and are retained for further analysis.

To suppress background originating from scattered photons and random coincidences, angular constraints are applied following the same criteria as in Chapters 6 and 7. The angle between the two annihilation photons should be  $\geq 60^\circ$  and the angle between the prompt gamma and each annihilation photon should be  $\geq 30^\circ$ . These angular selections reduce the contribution from misidentified secondary scatter events and improve the purity of the reconstructed dataset. The corresponding angular distributions are presented in Figure 8.1(C-D).

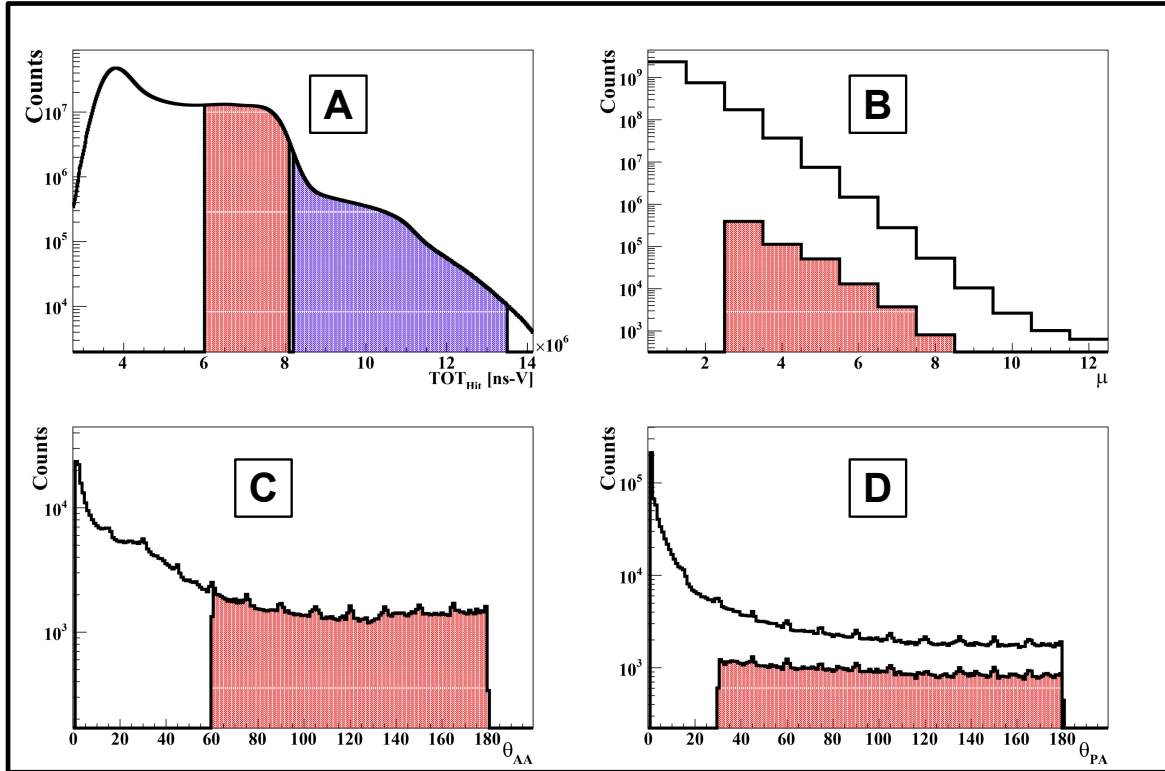


Figure 8.1: **(A)** Distribution of the  $\text{TOT}_{\text{hit}}$  used for photon identification, where annihilation photons (red) and prompt gamma quanta (blue) are separated by distinct ranges. **(B)** Hit multiplicity ( $\mu$ ) distribution for registered events, with the red-shaded region indicating the selected range containing exactly two annihilation photons and one prompt gamma. **(C)** Distribution of the relative angle ( $\theta_{AA}$ ) between the annihilation photon vectors, where events with  $\theta_{AA} \geq 60^\circ$  (red) are selected. **(D)** Distribution of the relative angle ( $\theta_{PA}$ ) between the prompt gamma vector and the annihilation photon vectors, with the requirement  $\theta_{PA} \geq 30^\circ$  (red).

Finally, ST is applied to reject detector-scattered and accidental events. The ST parameter



is calculated using the detection times and reconstructed interaction positions of the two annihilation photons. Only events satisfying the condition  $ST < -0.5$  ns are retained, ensuring that the selected photon pairs are true back-to-back annihilation events rather than intra-detector Compton scattering or accidental coincidences.

The events surviving all selection criteria are then used for reconstruction of the annihilation position ( $\vec{r}_a$ ) [Equation 6.2] and for estimation of the positron lifetime spectra ( $\Delta T$ ) following the method described section 6.3 and 7.3

## 8.2 ROI selection for PLI

In PLI, the annihilation position obtained using Equation 6.2 is reconstructed solely from the TOF information and the interaction positions of the detected photons, the spatial resolution strongly depends on the TOF resolution of the system. As a consequence, the reconstructed annihilation positions are affected by a spatial uncertainty, which can lead to overlap between neighboring anatomical structures. Therefore, when selecting ROIs for PLI analysis in different organs, contamination from organs in the vicinity cannot be neglected.

To evaluate the extent of this spill-over effect, a dedicated simulation study was performed using the activity distribution image obtained from the commercial PET/CT scanner for each patient. The reconstructed PET activity images, originally expressed in Bq/ml, were converted to the expected number of decay events by taking into account the voxel volume and the acquisition time per bed position. This allowed the generation of an event-density map that represents the true spatial distribution of annihilation events in the patient. The resulting event map for one of the patients is presented in Figure 8.2(A).

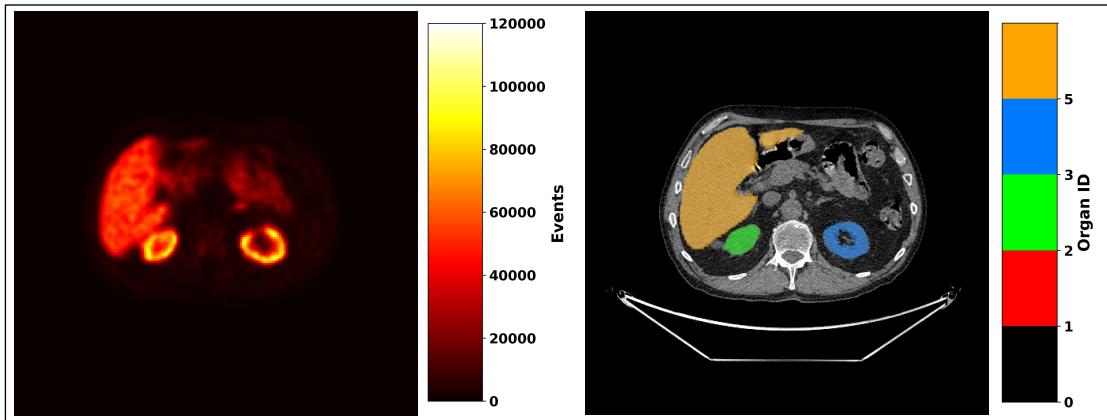


Figure 8.2: (Left) Transaxial PET slice showing the event density (hot colormap). (Right) Corresponding segmentation mask overlaid on CT image. Organ labels are color-coded as follows: 0: Background (Black), 1: Spleen (Red), 2: Right Kidney (Green), 3: Left Kidney (Blue), and 5: Liver (Orange). The spleen is not visible in this image as it is located on a different slice.

To define the anatomical ROIs, the organs of interest: namely the spleen, right kidney, left kidney and liver, were segmented using the corresponding CT images with the TotalSegmentator tool [189]. The resulting segmentation masks for these organs are shown in Figure 8.2(B), each

organ mask is identified by a different ID value.

To investigate the effective spatial resolution of the J-PET system for PLI, events corresponding to each segmented organ were extracted separately from the generated event map, as illustrated in Figure 8.3(A). Subsequently, a uniform Gaussian smoothing with a FWHM of 50 mm was applied to each organ distribution to emulate the experimental spatial resolution of the J-PET scanner for PLI studies. This value was estimated from the CTR of the Modular J-PET scanner [124]. The resulting smeared distributions are shown in Figure 8.3(B) and the line profile in Figure 8.3(C). This allows for the estimation of inter-organ spill-over, which is detailed in Table 8.1. The results demonstrate that event recovery within the original segmented masks remains critically low, approximately 10–34% for the spleen and kidneys and 53–64% for the liver. Therefore, defining the ROI strictly by the original anatomical boundaries will lead to a loss of data due to signal spill-over of that organ.

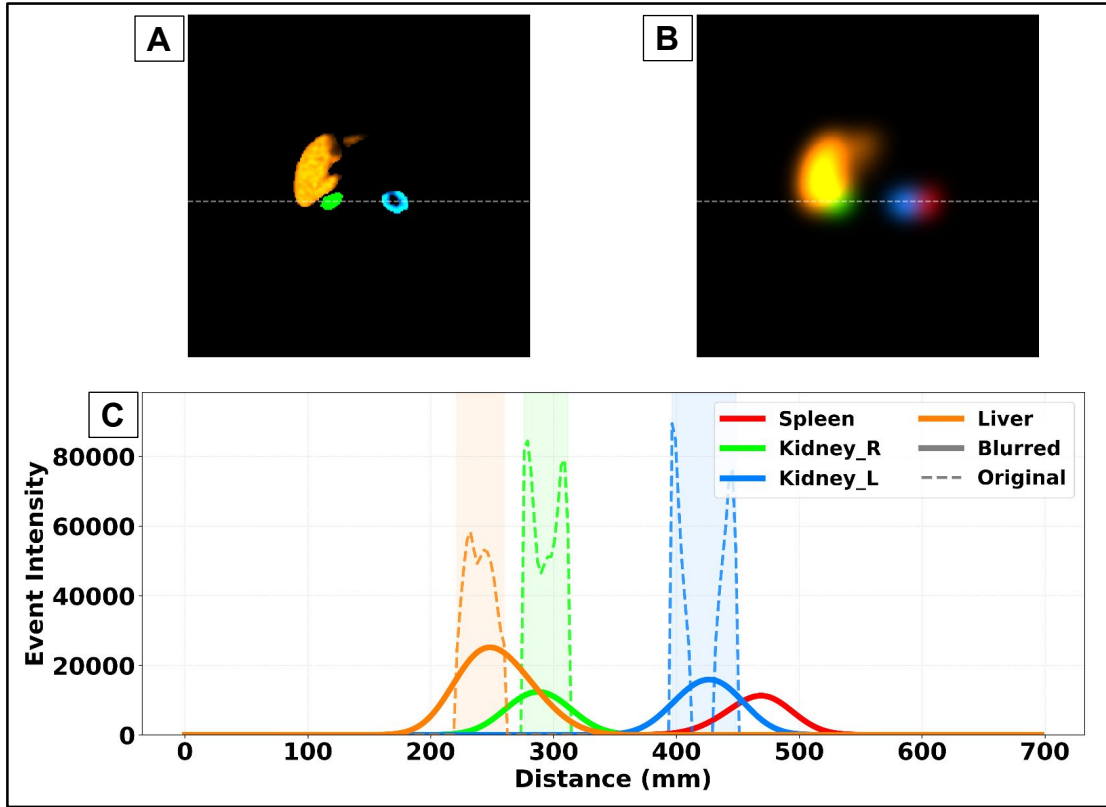


Figure 8.3: (A) Event distribution mapped using organ-specific ROIs. (B) Smeared event distribution after applying Gaussian smoothing with a 50 mm FWHM. For visualization purposes, each organ was locally normalized to its own maximum intensity to clearly illustrate the extent of spatial spillover. (C) Line profile across the liver and kidneys showing the extent of spillover along the white dotted line indicated in images (A) and (B). Solid lines represent the smeared distributions, while dashed lines correspond to the original distributions before smoothing.

To mitigate this issue, each organ mask was expanded by up to 50 mm to account for spill-over effects arising from the limited spatial resolution of the scanner. However, a uniform expansion of all organ masks results in substantial spatial overlap, particularly between

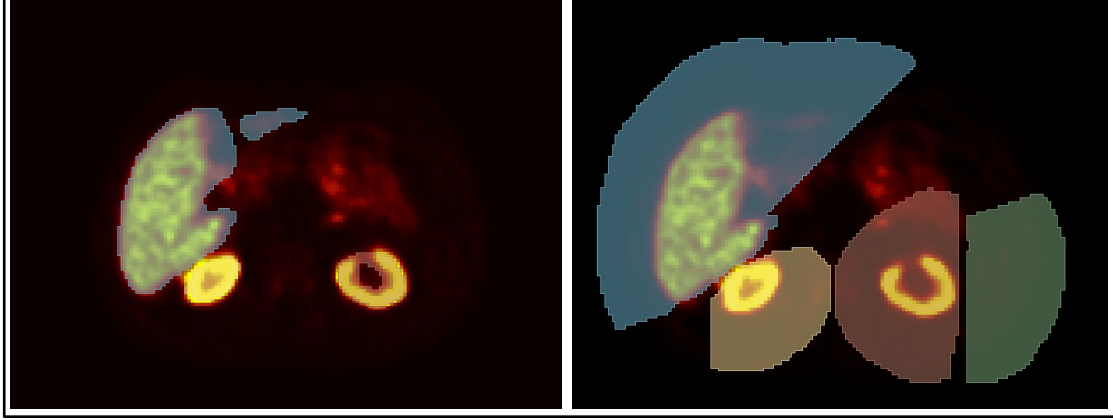


Figure 8.4: Original segmented mask overlaid on the activity image (Left) Extended mask overlaid on the activity image, generated using a geometrically constrained expansion algorithm with a 50 mm limit (Right).

anatomically adjacent structures such as the liver and the right kidney. To prevent this, a geometrically constrained expansion algorithm was applied.

To prevent overlapping boundaries, the closest surface points between each pair of adjacent organ ROIs were identified, and the midpoint between them was calculated. A flat, infinite separation plane was then defined at this midpoint, perpendicular to the vector connecting the two organs, to act as a strict boundary between them during expansion. This ensured that the expansion of one organ did not extend beyond its geometrically assigned territory into a neighbor. The original ROI and the extended ROI are shown in Figure 8.4(A-B).

The expansion of ROIs resulted in an improvement in event recovery in all organs, as detailed in Table 8.1. For smaller organs, the gains were particularly larger: spleen recovery increased from a baseline of 19–34% to as high as 88–91% in several subjects, while left kidney recovery increased from 24% to over 80%. Even liver recovery improved from an average of 58% to more than 80%.

However, the right kidney ROI is contaminated due to its proximity to the liver, resulting low purity. Although its recovery more than doubled, rising from 10.3% to 40.9% in P1 and to 73.9% in P2, this gain in sensitivity came at a significant cost to purity. Across the patients, the purity of the right kidney was low for P1 (47%), while for the other patients it ranged from 67–77%, with liver spill-over accounting for 22–32% of the signal within the extended mask. Despite these limitations, extended ROIs capture a much larger fraction of events and are therefore used for positron lifetime analysis.

### 8.3 Result

These original segmented masks were used to determine organ volumes and were applied to the co-registered two gamma coincidence PET images (from the commercial PET/CT scanner) to calculate the SUV ( $SUV_{max}$  and  $SUV_{mean}$ ) for each respective organ. The resulted values are listed in Table 8.2. These calculations were performed using 3D Slicer software [190].

Table 8.1: Quantitative assessment of event recovery and ROI purity for anatomical organs (Spleen, Kidneys, and Liver) across six patients. The analysis compares the Original anatomical ROIs (derived from CT segmentation via TotalSegmentator) against the Extended ROIs (generated using a geometrically constrained expansion algorithm with a 50 mm limit). Recovery (%) represents the fraction of total organ events captured within the mask after emulating J-PET spatial resolution (50 mm FWHM Gaussian smoothing). Purity (%) indicates the fraction of events within the ROI that truly belong to the target organ. Spill-in (%) details the specific contribution of events from neighboring organs into the target ROI.

| ROI             | Metric (%)       | P1    |       | P2    |       | P4    |       | P5    |       | P10   |       | P(Warsaw) |       |
|-----------------|------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-----------|-------|
|                 |                  | Orig. | Ext.  | Orig. | Ext.  | Orig. | Ext.  | Orig. | Ext.  | Orig. | Ext.  | Orig.     | Ext.  |
| <b>Spleen</b>   | Recovery         | 18.60 | 32.78 | 29.96 | 74.73 | 33.93 | 91.27 | 29.40 | 74.28 | 22.67 | 87.84 | 22.35     | 58.87 |
|                 | Purity           | 65.34 | 63.20 | 94.28 | 94.87 | 96.22 | 95.27 | 93.09 | 94.60 | 96.03 | 93.44 | 92.91     | 93.09 |
|                 | Spill-in: KidL   | 34.66 | 36.80 | 5.68  | 5.00  | 3.78  | 4.67  | 6.91  | 5.36  | 3.97  | 6.39  | 7.08      | 6.56  |
|                 | Spill-in: Liver  | 0.00  | 0.00  | 0.04  | 0.13  | 0.00  | 0.05  | 0.00  | 0.04  | 0.00  | 0.16  | 0.00      | 0.34  |
| <b>Kidney_R</b> | Recovery         | 10.25 | 40.86 | 25.77 | 73.93 | 20.23 | 68.65 | 27.59 | 57.60 | 22.01 | 45.47 | 26.36     | 62.44 |
|                 | Purity           | 39.77 | 47.09 | 70.94 | 77.43 | 67.08 | 72.97 | 66.92 | 70.72 | 63.32 | 67.61 | 69.22     | 76.51 |
|                 | Spill-in: KidL   | 0.00  | 0.36  | 0.00  | 0.02  | 0.00  | 0.09  | 0.00  | 0.23  | 0.00  | 0.04  | 0.02      | 0.23  |
|                 | Spill-in: Liver  | 60.23 | 52.55 | 29.06 | 22.55 | 32.92 | 26.94 | 33.08 | 29.06 | 36.68 | 32.34 | 30.76     | 23.26 |
| <b>Kidney_L</b> | Recovery         | 24.82 | 59.44 | 28.16 | 50.06 | 20.70 | 85.39 | 29.48 | 71.50 | 23.65 | 84.14 | 24.81     | 80.13 |
|                 | Purity           | 90.16 | 90.66 | 69.03 | 70.46 | 88.41 | 87.92 | 66.19 | 72.71 | 96.35 | 94.09 | 79.27     | 76.31 |
|                 | Spill-in: KidR   | 0.00  | 0.07  | 0.00  | 0.05  | 0.00  | 0.06  | 0.00  | 0.07  | 0.00  | 0.03  | 0.04      | 0.58  |
|                 | Spill-in: Liver  | 0.01  | 0.79  | 0.00  | 0.25  | 0.00  | 0.16  | 0.04  | 0.79  | 0.00  | 0.12  | 0.50      | 3.49  |
| <b>Liver</b>    | Spill-in: Spleen | 9.83  | 8.48  | 30.97 | 29.24 | 11.59 | 11.85 | 33.77 | 26.42 | 3.65  | 5.76  | 20.20     | 19.62 |
|                 | Recovery         | 52.80 | 72.53 | 59.05 | 85.55 | 60.34 | 85.86 | 59.10 | 74.44 | 64.22 | 87.09 | 55.41     | 81.27 |
|                 | Purity           | 95.11 | 95.60 | 97.68 | 97.79 | 97.56 | 97.54 | 96.52 | 95.96 | 97.46 | 97.45 | 95.31     | 96.02 |
|                 | Spill-in: KidL   | 0.00  | 0.00  | 0.00  | 0.02  | 0.00  | 0.00  | 0.00  | 0.00  | 0.00  | 0.02  | 0.04      | 0.20  |
| <b>Liver</b>    | Spill-in: KidR   | 4.88  | 4.40  | 2.30  | 1.63  | 2.44  | 2.46  | 3.46  | 4.03  | 2.54  | 2.49  | 4.65      | 3.62  |
|                 | Spill-in: Spleen | 0.00  | 0.00  | 0.02  | 0.56  | 0.00  | 0.00  | 0.00  | 0.00  | 0.00  | 0.03  | 0.00      | 0.16  |

After applying the selection criteria described in Section 8.1, the annihilation point distribution ( $\vec{r}_a$ ) for the  $2\gamma_a + \gamma_p$  events was reconstructed using Equation 6.2. Figure 8.6(A–C) shows the  $\vec{r}_a$  distribution for one of the patients (Patient 2), alongside the two-gamma coincidence images obtained from the J-PET scanner (see Figure 8.6(D–F)) and the commercial PET/CT scanner (see Figure 8.6(G–I)), overlaid with the CT image. The voxel size of the reconstructed  $\vec{r}_a$  distribution image is  $2.5 \times 2.5 \times 2.5 \text{ cm}^3$  (see Figure 8.6(A–C)). A Gaussian smoothing with  $\sigma = 1$  voxel was applied. For visualization, three consecutive voxels were merged along the viewing direction for each plane: along the z-axis for the axial view, along the y-axis for the coronal view, and along the x-axis for the sagittal view.

The obtained positron lifetime distributions ( $\Delta T$ ) for all six patients are overlaid and shown in Figure 8.5. One can observe that for the patient from Warsaw Medical University, the background is higher. This is because this patient was scanned with the J-PET scanner at 60 min post-injection, before the commercial PET/CT scan, whereas the remaining patients were scanned at 90 to 96 min post-injection. Therefore, activity in this patient was higher than in the other patients scanned with J-PET. The extended ROIs (as discussed in the previous section) were applied to the  $\vec{r}_a$  distribution to extract events for each organ. The total number of events and events per organ are summarized in Table 8.3. Due to the low statistics in the right and left kidneys, the events of both were combined for the lifetime analysis.

The mean positron lifetime ( $\Delta T_{mean}$ ) was then estimated within the signal range of 0 to 4.8 ns, with the background determined from the interval -7.5 to -2.5 ns. As demonstrated in the previous chapters (Chapter 6 and 7),  $\Delta T_{mean}$  provides a more robust parameter containing the information from all decay channels. The  $\Delta T_{mean}$  obtained from the different organs in the six patients is summarized in Table 8.4. The mean positron lifetime spectra with the mean lifetime range and the background is shown in Figure 8.7.

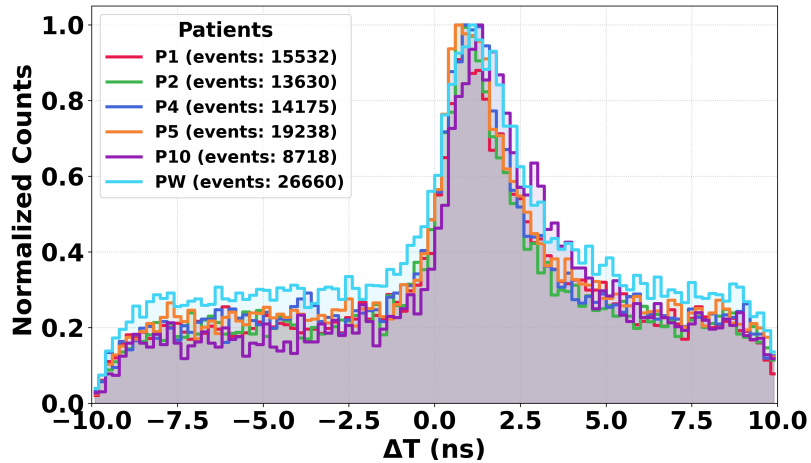


Figure 8.5: Mean positron lifetime distribution ( $\Delta T$ ) from the six patients overlaid, the counts has been normalized to one.

The obtained  $\Delta T_{mean}$  values for the organs show variation between patients. Notably, the differences in organ lifetimes are larger than the statistical uncertainties of the individual

data points. However, establishing any correlation between  $\Delta T_{\text{mean}}$  and disease characteristics would require a comprehensive analysis of patient history and clinical assessment reports before any firm conclusion can be drawn.

Table 8.2: Volume (Vol) of the organs obtained with the segmented mask from the CT image and the  $\text{SUV}_{\text{mean}}$  ( $S_{\text{mean}}$ ) and  $\text{SUV}_{\text{max}}$  ( $S_{\text{max}}$ ) obtained from the PET image from the commercial PET/CT scanner.

| ID  | Spleen |                   |                  | Kidney_R |                   |                  | Kidney_L |                   |      | Liver  |                   |                  |
|-----|--------|-------------------|------------------|----------|-------------------|------------------|----------|-------------------|------|--------|-------------------|------------------|
|     | Vol    | $S_{\text{mean}}$ | $S_{\text{max}}$ | Vol      | $S_{\text{mean}}$ | $S_{\text{max}}$ | Vol      | $S_{\text{mean}}$ | Max  | Vol    | $S_{\text{mean}}$ | $S_{\text{max}}$ |
| P1  | 76.3   | 6.74              | 14.2             | 31.6     | 9.25              | 20.7             | 128.7    | 10.28             | 17.2 | 957.3  | 3.62              | 17.5             |
| P2  | 195.3  | 20.13             | 32.2             | 136.7    | 7.62              | 17.0             | 157.4    | 7.67              | 14.8 | 1279.8 | 7.12              | 22.4             |
| P4  | 180.6  | 15.19             | 30.1             | 102.4    | 12.80             | 21.3             | 106.2    | 12.38             | 22.6 | 1366.6 | 8.49              | 15.4             |
| P5  | 175.7  | 22.74             | 32.9             | 128.9    | 8.35              | 35.1             | 170.1    | 8.51              | 53.9 | 1198.6 | 7.21              | 17.7             |
| P10 | 85.6   | 15.17             | 26.5             | 92.7     | 8.63              | 21.4             | 113.3    | 10.95             | 23.6 | 1627.4 | 5.94              | 21.2             |
| PW  | 97.2   | 23.20             | 39.5             | 141.8    | 8.80              | 19.7             | 125.3    | 8.79              | 19.9 | 1010.4 | 7.64              | 16.2             |

Table 8.3: Total number of PLI events

| Patient Name | Total Events | Spleen | Kidney_R | Kidney_L | Liver |
|--------------|--------------|--------|----------|----------|-------|
| P1           | 15532        | 289    | 220      | 936      | 1740  |
| P2           | 13630        | 863    | 597      | 378      | 1582  |
| P4           | 14175        | 623    | 537      | 713      | 2317  |
| P5           | 19238        | 1535   | 345      | 928      | 2477  |
| P10          | 8718         | 376    | 126      | 288      | 1594  |
| PW           | 26660        | 1239   | 608      | 904      | 3472  |

Table 8.4: Mean positron lifetime ( $\Delta T_{\text{mean}}$ ) values for different organs

| Patient | Spleen (ns)     | Kidneys (ns)    | Liver (ns)      |
|---------|-----------------|-----------------|-----------------|
| P1      | $1.42 \pm 0.12$ | $1.25 \pm 0.07$ | $1.19 \pm 0.05$ |
| P2      | $1.21 \pm 0.07$ | $1.40 \pm 0.07$ | $1.35 \pm 0.06$ |
| P4      | $1.07 \pm 0.08$ | $1.13 \pm 0.04$ | $1.14 \pm 0.04$ |
| P5      | $1.23 \pm 0.06$ | $1.29 \pm 0.07$ | $1.06 \pm 0.04$ |
| P10     | $1.70 \pm 0.14$ | $1.81 \pm 0.14$ | $1.54 \pm 0.06$ |
| P(W)    | $1.45 \pm 0.09$ | $1.41 \pm 0.09$ | $1.32 \pm 0.04$ |

## 8.4 Discussion

The results presented in this chapter demonstrate the feasibility of PLI studies in human subjects using the modular J-PET scanner, with the analysis focused on the torso region, particularly the liver, spleen, and kidneys. Patients were administered  $[^{68}\text{Ga}]\text{-Ga-DOTA-TATE}$  as part of the standard diagnostic procedure for NETs assessment. Since the current

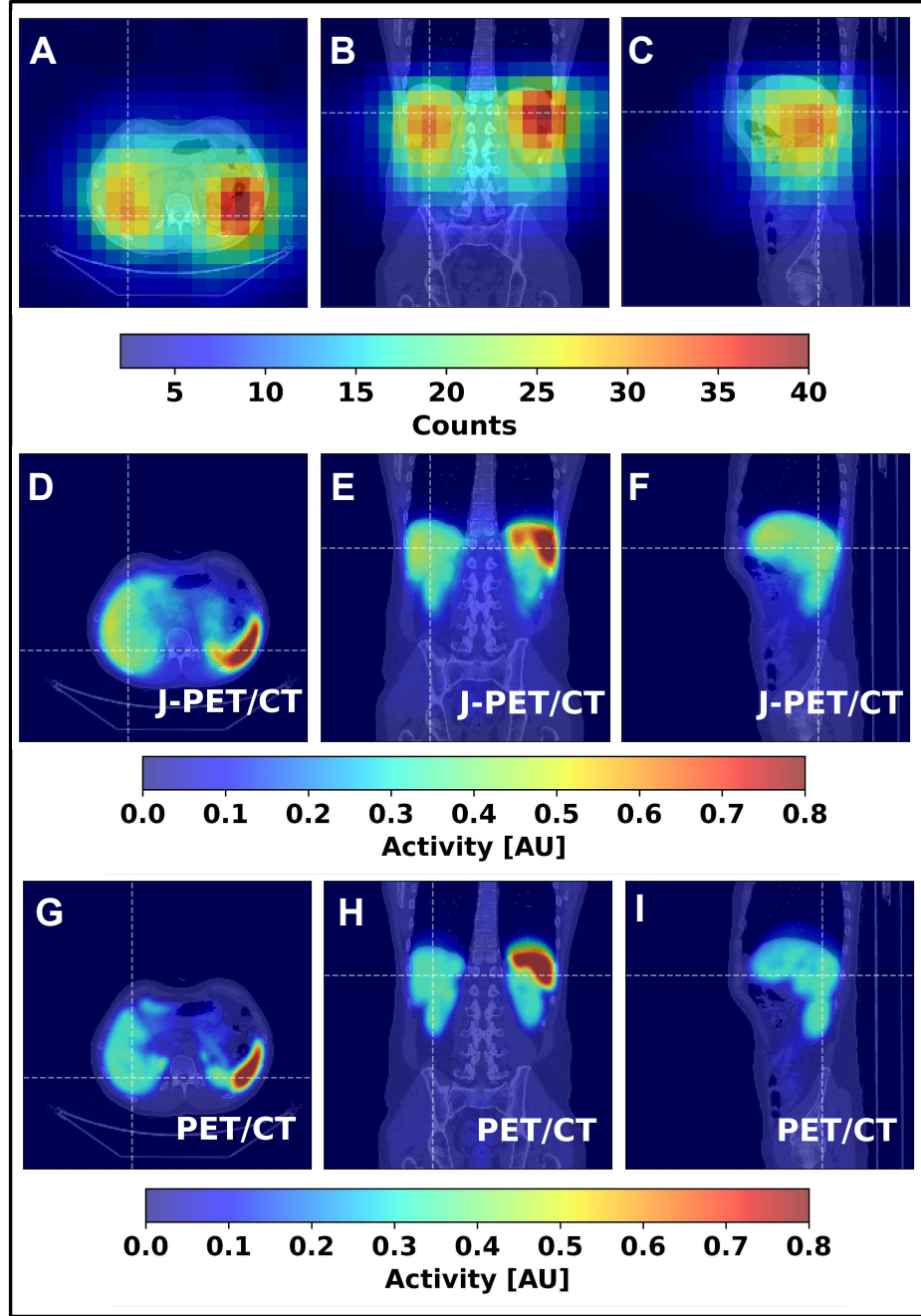


Figure 8.6: (A–C) Annihilation point distribution ( $\vec{r}_a$ ) for  $2\gamma_a + \gamma_p$  events overlaid on the CT image in the axial (A), coronal (B), and sagittal (C) views. (D–F) Two-gamma coincidence images obtained with the J-PET scanner in the corresponding axial (D), coronal (E), and sagittal (F) views. (G–I) Two-gamma coincidence images acquired with the commercial PET/CT scanner in the corresponding axial (G), coronal (H), and sagittal (I) views.



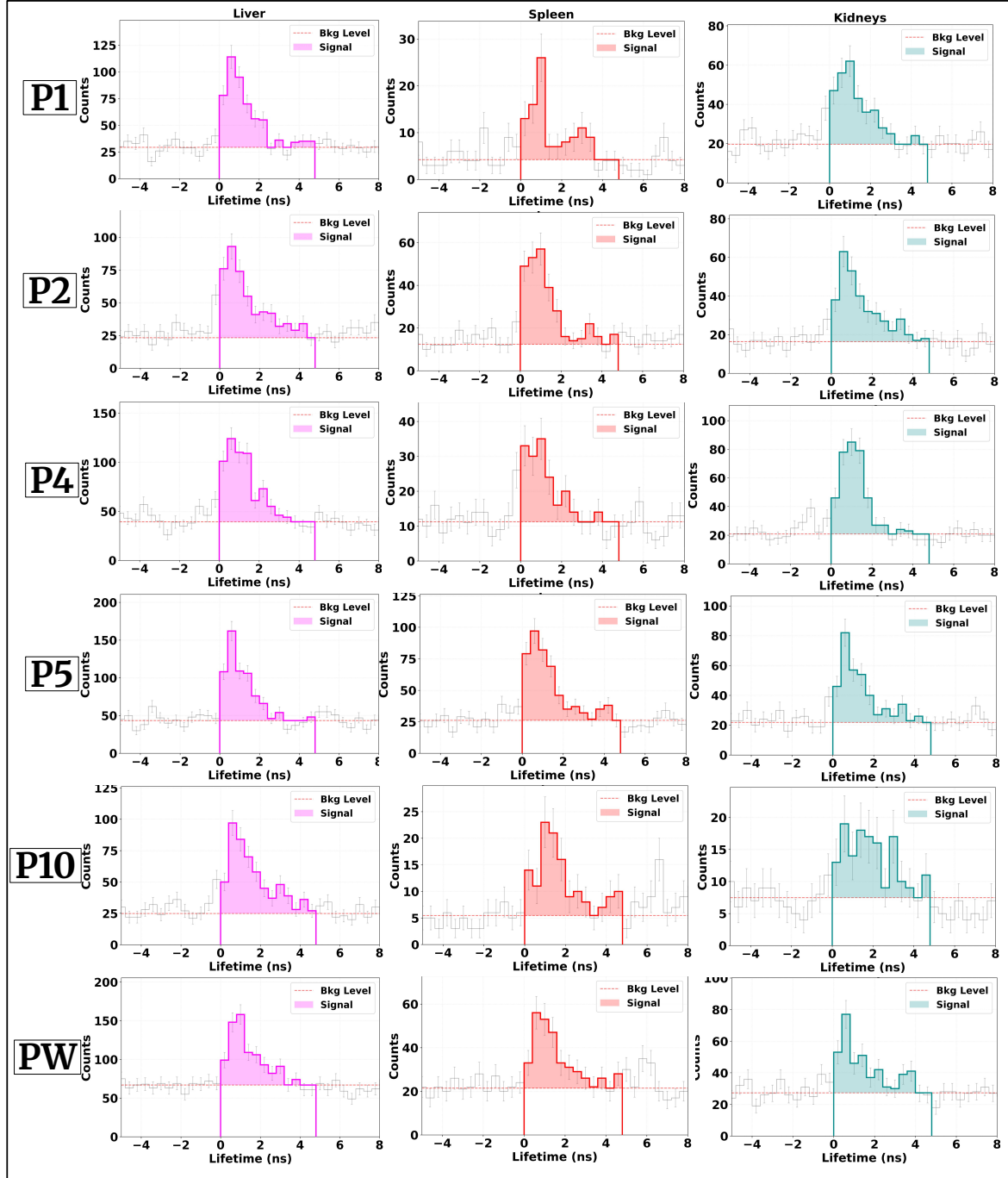


Figure 8.7: Positron lifetime spectra obtained from the liver, spleen, and kidneys for six patients. The shaded regions indicate the signal windows used for the mean positron lifetime calculation: the pink shaded region corresponds to the liver, the red shaded region to the spleen, and the green shaded region to the kidneys. The background was estimated in the time interval from -7.5 ns to -2.5 ns and is indicated by the red dotted lines.



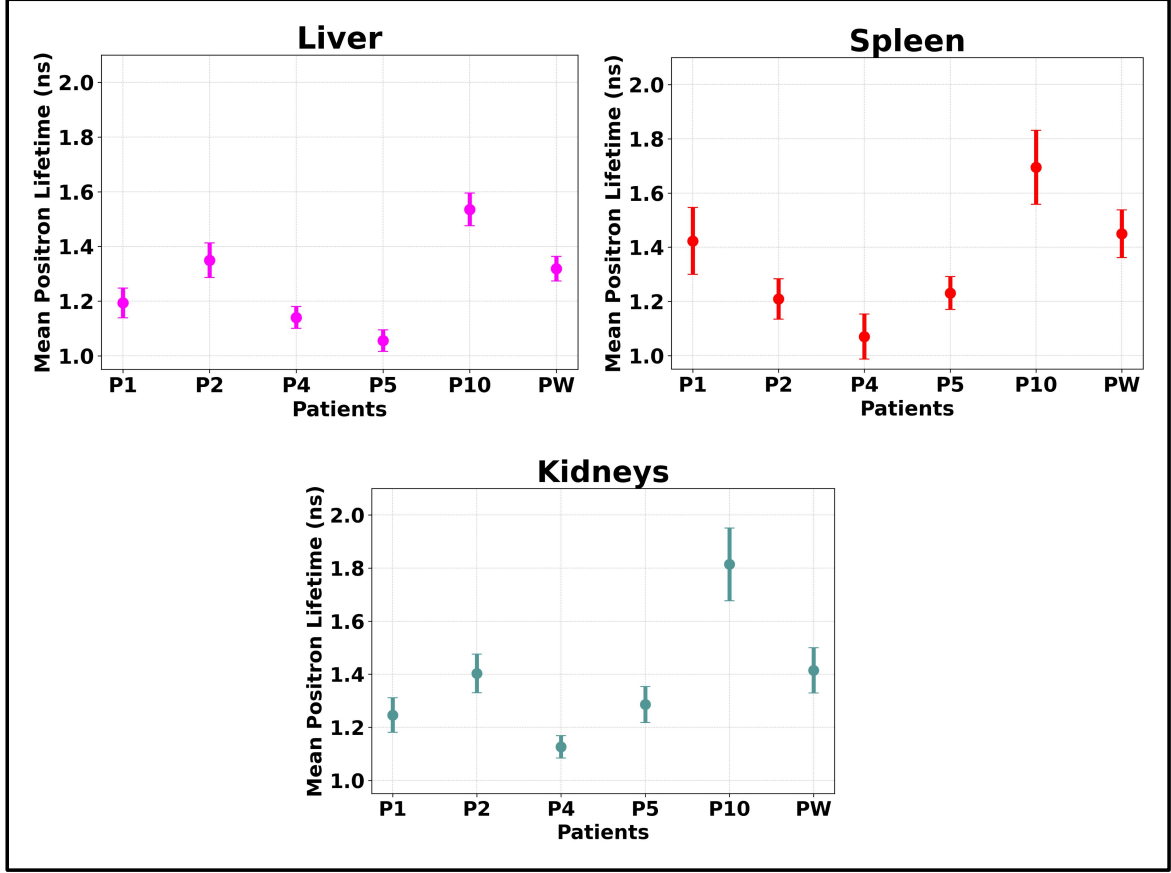


Figure 8.8: The mean positron lifetime ( $\Delta T_{mean}$ ) obtained from the Liver, Spleen and Kidneys.

reconstruction methodology developed for PLI in the J-PET scanner is based primarily on TOF information, the spatial resolution for  $2\gamma_a + \gamma_p$  events remains limited. As a result, activity originating from neighboring organs can contribute to spill-over effects. To assess the extent of the spill-over and recovery, a simulation study was performed using activity concentration images obtained with the commercial PET scanner. This confirmed that event recovery within the original CT-based anatomical masks was significantly low, particularly for smaller organs such as the spleen and kidneys, where recovery remained in the range of 10–34%, while for the liver it reached only 53–64%. This indicates that using strictly anatomical boundaries for ROI definition leads to substantial signal loss. To improve sensitivity and event recovery, the original CT-based ROIs were expanded, which significantly increased the number of recovered events across all studied organs. The improvement was especially pronounced for smaller organs, where spleen recovery increased from 19–34% to as high as 88–91%, and left kidney recovery improved from approximately 24% to over 80%. Liver recovery also increased from an average of 58% to above 80%.

Due to the limited statistics associated with the use of  $^{68}\text{Ga}$ , only the mean positron lifetime ( $\Delta T_{mean}$ ) could be evaluated in this study. The obtained values showed notable variation between patients, and the observed differences were larger than the statistical uncertainties of individual measurements, suggesting potential biological relevance. However, establishing

correlations between  $\Delta T_{mean}$  and disease progression or clinical characteristics would require a detailed analysis of patient history and diagnostic reports, which is beyond the scope of this thesis. Nevertheless, despite the limitations imposed by the low  $\beta^+ + \gamma$  yield of  $^{68}\text{Ga}$ , this study confirms the feasibility of performing PLI in a clinical environment using the modular J-PET scanner.

## Chapter 9

# Discussion and Conclusion

This thesis presents the development of two major imaging modalities for the Modular J-PET scanner: two-gamma coincidence PET imaging and PLI.

The first part focused on the development and implementation of the event selection, reconstruction and correction framework for two-gamma coincidence imaging. The reconstruction framework was developed within the CASToR environment. Three dedicated correction techniques: CT-based attenuation correction, DTW based random correction, and Monte Carlo-based scatter correction, were developed and implemented for the Modular J-PET scanner.

To validate these methods, a qualitative as well as quantitative evaluation was performed using a NEMA IQ phantom following the NEMA NU 2-2018 protocol. The corrected images showed improved CRC, a reduction in residual lung error by more than 70%, and improved BGVar. In addition, LYSO was used as a surrogate material in the Monte Carlo simulations reducing the computational burden by nearly a factor of ten while maintaining the quantitative agreement within an average relative difference of less than 7%. Following the detailed validation, the complete reconstruction and correction pipeline was applied to the first clinical trials involving patients at the University Hospital in Krakow and the Medical University of Warsaw. Since SUV calibration was not available, a semi-quantitative analysis was carried out using organ uptake ratios between the spleen, liver, and kidneys. The results showed good agreement between the J-PET and commercial PET/CT scanners, confirming the viability of the Modular J-PET for clinical metabolic imaging.

The methods developed to perform two-gamma coincidence imaging provided the basis for the second part of this thesis. The data selection criteria, the TOF-based reconstruction framework as well as the detector characterization remained unchanged. However, the TOT-based photon identification, the multiplicity selection, the angular constraints as well as the criteria to test for scattering photons used for two-gamma coincidence imaging were adapted for the identification of  $2\gamma_a + \gamma_p$  events required for PLI.

The second part of the thesis focused on the development of PLI using the modular J-PET scanner. The first PLI study was conducted with  $^{44}\text{Sc}$ , one of the most promising  $\beta^+ + \gamma$  emitters, using a NEMA IQ phantom. The isotope  $^{18}\text{F}$  was included to assess the effectiveness of the selection criteria for identifying the  $2\gamma_a + \gamma_p$  events, required for PLI as it doesn't emit a prompt gamma. The reconstructed images confirmed the robustness of the developed selection criteria, and the mean o-Ps lifetime measured in the two largest spheres was consistent with the reference value for water. However, the smallest sphere containing  $^{44}\text{Sc}$  showed a deviation attributed to low statistics and sensitivity to the background estimation. Across all fitting models, the mean positron lifetime appeared to be a more robust parameter,

remaining consistent within 10 ps, regardless of fluctuations in the mean o-Ps lifetime values.

The next two sets of measurements were performed using two novel long-lived isotopes  $^{52}\text{Mn}$  and  $^{55}\text{Co}$ . These isotopes can provide additional opportunities for applications involving radiopharmaceuticals with slow pharmacokinetics [191], such as monoclonal antibodies, where longer imaging windows are required. Measurements on CRMs with certified mean o-Ps lifetime confirmed that the adopted methodology reproduced the reference lifetime values for both isotopes, demonstrating the reliability of lifetime reconstruction with the J-PET scanner, even for radionuclides characterized by complex decay schemes. Measurements of long-stored tissue samples, including cardiac myxoma and adipose tissue, revealed changes in lifetime and intensity parameters that were most likely influenced by long-term fixation and storage effects, and therefore should not be interpreted solely as biological differences between tissues.

Among the investigated isotopes, measurements with  $^{55}\text{Co}$  resulted in better PBR values and produced spectra with improved lifetime resolution compared to  $^{52}\text{Mn}$ . The longer half-life of  $^{52}\text{Mn}$  makes it particularly suitable for manganese-based tracer applications; however, it is more affected by contamination from scattered background originating from its multiple prompt photons. In comparison with the results obtained for  $^{44}\text{Sc}$ , both  $^{44}\text{Sc}$  and  $^{55}\text{Co}$  appear to be more favorable candidates for PLI, whereas  $^{52}\text{Mn}$  may be better suited for more specialized applications related to its unique radiochemistry and extended half-life. Moreover, the cascade emissions from both  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  enable future studies of inter-photon correlations, as discussed in [192–195].

Finally, PLI studies were performed on six patients with NETs who were administered  $^{68}\text{Ga}$ -DOTA-TATE. Although,  $^{68}\text{Ga}$  has a relatively low prompt gamma yield (1.19%), its routine clinical availability made it a practical choice for this feasibility study of PLI. Since the current PLI reconstruction is based on TOF information, without iterative image reconstruction, spill-over between neighboring organs affects the accuracy of organ-wise analysis. To reduce this effect and improve event recovery, organ-wise PLI analysis was performed using expanded ROIs based on the original CT segmentation. Despite the limited statistics, measurable differences in mean positron lifetime were observed between organs (liver, kidneys and spleen) and among patients, suggesting the potential of PLI as a complementary biomarker for tissue characterization.

The studies of PLI presented in this thesis are complementary to current efforts around the world. LAFOV crystal-based scanners such as the Biograph Vision Quadra [28,118] and the PennPET Explorer [33] have been used for PLI measurements using clinical available isotopes ( $^{124}\text{I}$ ,  $^{82}\text{Rb}$ ). In contrast, the J-PET scanner is the first plastic-scintillator-based system for PLI measurements. Moreover, the J-PET scanner is the first system for experimental studies of  $^{44}\text{Sc}$ ,  $^{55}\text{Co}$ , and  $^{52}\text{Mn}$  for PLI. These isotopes have substantially higher prompt gamma yields than the already clinically used isotopes and the results of the presented studies can serve as a basis for future clinical studies.

In conclusion, this thesis demonstrates the successful development of both two-gamma coincidence PET imaging and PLI with the Modular J-PET scanner, representing an important step toward the next generation of Total-Body plastic-scintillator-based J-PET scanner. The implementation of dedicated reconstruction and correction methods significantly improved

image quality for two-gamma coincidence imaging and enabled the first clinical two gamma coincidence studies using patient data, confirming the potential of the J-PET system for diagnostic imaging. The planned Total-Body J-PET scanner, with a 2.5-meter LAFOV, is expected to further enhance these capabilities. With an expected TOF resolution of about 220 ps, a NEMA sensitivity of 38 cps/kBq at the center of the scanner, and a spatial resolution of 3.7 mm in the transaxial direction and 4.9 mm in the axial direction, its performance is expected to be comparable to state-of-the-art clinical PET systems. Its substantially increased sensitivity and LAFOV will further strengthen its role as a cost-effective Total-Body PET system for conventional two-gamma coincidence imaging, enabling faster scans, lower injected doses, and improved patient throughput without compromising image quality [92, 196].

At the same time, the investigation of novel  $\beta^+ + \gamma$  isotopes highlights the importance of radionuclides that emit prompt gamma photons, such as  $^{44}\text{Sc}$ ,  $^{55}\text{Co}$ , and  $^{52}\text{Mn}$ , for improving PLI performance. Although  $^{68}\text{Ga}$  has a relatively low prompt gamma yield, which limits its efficiency for PLI, its routine clinical availability enabled the feasibility study in patients with NETs. Future studies using isotopes with higher prompt gamma yields, such as  $^{44}\text{Sc}$  and  $^{55}\text{Co}$ , are expected to provide significantly better sensitivity, an improved signal-to-background ratio, and more precise lifetime estimation. For the current Modular J-PET prototype, the sensitivity for standard two-gamma PET imaging is 57 times higher than that for PLI. However, the next-generation Total-Body J-PET is expected to provide nearly 25 times higher sensitivity for  $2\gamma + \gamma_p$  events and substantially improved relative sensitivity, creating much better conditions for PLI [4]. Together with ongoing advancements in LAFOV clinical scanners [27, 29, 92, 197, 198] and dedicated PLI reconstruction methods [26, 31, 33, 38, 105–112], these developments open a promising pathway toward the routine clinical application of PLI as a novel biomarker for cancer diagnosis, treatment monitoring, and tissue characterization.



# Bibliography

- [1] P. Moskal, S. Niedźwiecki, T. Bednarski, E. Czerwiński, Ł. Kapłon, E. Kubicz, I. Moskal, M. Pawlik-Niedźwiecka, N. Sharma, M. Silarski, M. Zieliński, N. Zoń, P. Białas, A. Gajos, A. Kochanowski, G. Korcyl, J. Kowal, P. Kowalski, T. Kozik, W. Krzemień, M. Molenda, M. Pałka, L. Raczyński, Z. Rudy, P. Salabura, A. Słomski, J. Smyrski, A. Strzelecki, A. Wieczorek, and W. Wiślicki, “Test of a single module of the J-PET scanner based on plastic scintillators,” *Nucl. Instr. and Meth. A*, vol. 764, pp. 317–321, 2014.
- [2] P. Moskal and E. Ł. Stępień, “Prospects and clinical perspectives of total-body PET imaging using plastic scintillators,” *PET Clinics*, vol. 15, pp. 439–452, 2020.
- [3] P. Moskal, “Positronium imaging,” in *2019 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC)*, pp. 1–3, 2019.
- [4] P. Moskal, J. Baran, S. Bass, J. Choiński, N. Chug, C. Curceanu, E. Czerwiński, M. Dadgar, M. Das, K. Dulski, K. V. Eliyan, K. Fronczewska, A. Gajos, K. Kacprzak, M. Kajetanowicz, T. Kaplanoglu, Ł. Kapłon, K. Klimaszewski, M. Kobylecka, G. Korcyl, T. Kozik, W. Krzemień, K. Kubat, D. Kumar, J. Kunikowska, J. Mączewska, W. Migdał, G. Moskal, W. Mryka, S. Niedźwiecki, S. Parzych, E. P. del Rio, L. Raczyński, S. Sharma, S. Shivani, R. Y. Shopa, M. Silarski, M. Skurzok, F. Tayefi, K. T. Ardebili, P. Tanty, W. Wiślicki, L. Królicki, and E. Ł. Stępień, “Positronium image of the human brain in vivo,” *Science Advances*, vol. 10, no. 37, p. eadp2840, 2024.
- [5] P. Moskal, A. Bilewicz, M. Das, B. Huang, A. Khreptak, S. Parzych, J. Qi, A. Rominger, R. Seifert, S. Sharma, K. Shi, W. M. Steinberger, R. Walczak, and E. Stępień, “Positronium imaging: History, current status, and future perspectives,” *IEEE Transactions on Radiation and Plasma Medical Sciences*, vol. 9, p. 981–1001, Nov. 2025.
- [6] T. Jones and D. Townsend, “History and future technical innovation in positron emission tomography,” *J. Med. Imag.*, vol. 4, p. 011013, 2017.
- [7] S. R. Cherry, J. Sorenson, M. E. Phelps, and B. M. Methé, “Physics in nuclear medicine,” *Medical Physics*, vol. 31, p. 2370–2371, Aug. 2004.
- [8] A. Alavi, T. J. Werner, E. Ł. Stępień, and P. Moskal, “Unparalleled and revolutionary impact of PET imaging on research and day to day practice of medicine,” *Bio-Algorithms and Med-Systems*, vol. 17, pp. 203–220, 2021.
- [9] A. Alavi, B. Saboury, L. Nardo, V. Zhang, M. Wang, H. Li, W. Y. Raynor, T. J. Werner, P. F. Høilund-Carlsen, and M.-E. Revheim, “Potential and most relevant applications of total body pet/ct imaging,” *Clinical Nuclear Medicine*, vol. 47, p. 43–55, Jan. 2022.
- [10] S. Vandenberghe, N. A. Karakatsanis, M. A. Akl, J. Maebe, S. Surti, R. A. Dierckx, D. A. Pryma, S. A. Nehmeh, O. Bouhali, and J. S. Karp, “The potential of a medium-cost long

- axial fov pet system for nuclear medicine departments,” *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 50, p. 652–660, Sept. 2022.
- [11] “Imagine database,” *International Atomic Energy Agency*, p. <https://humanhealth.iaea.org/HHW/DBStatistics/IMAGINE.html>, 2026.
- [12] C. Wu, F. Li, G. Niu, and X. Chen, “PET Imaging of Inflammation Biomarkers,” *Theranostics*, vol. 3, no. 7, p. 448–466, 2013.
- [13] S. Capitanio, A. J. Nordin, A. R. Noraini, and C. Rossetti, “PET/CT in nononcological lung diseases: current applications and future perspectives,” *European Respiratory Review*, vol. 25, p. 247–258, Aug. 2016.
- [14] M. Motiei, T. Dreifuss, O. Betzer, H. Panet, A. Popovtzer, J. Santana, G. Abourbeh, E. Mishani, and R. Popovtzer, “Differentiating Between Cancer and Inflammation: A Metabolic-Based Method for Functional Computed Tomography Imaging,” *ACS Nano*, vol. 10, p. 3469–3477, Feb. 2016.
- [15] S. Niedźwiecki, P. Białas, C. Curceanu, E. Czerwiński, K. Dulski, A. Gajos, B. Głowacz, M. Gorgol, B. C. Hiesmayr, B. Jasińska, Ł. Kaplon, D. Kisielewska-Kamińska, G. Korcyl, P. Kowalski, T. Kozik, N. Krawczyk, W. Krzemień, E. Kubicz, M. Mohammed, M. Pawlik-Niedźwiecka, M. Pałka, L. Raczyński, Z. Rudy, N. G. Sharma, S. Sharma, R. Y. Shopa, M. Silarski, M. Skurzok, A. Wieczorek, W. Wiślicki, B. Zgardzińska, M. Zieliński, and P. Moskal, “J-PET: a new technology for the whole-body PET imaging,” *Acta Phys. Polon. B*, vol. 48, p. 1567, 2017.
- [16] P. Moskal, M. Silarski, P. Salabura, M. Zieliński, J. Zdebik, and J. Smyrski, “Novel detector systems for the Positron Emission Tomography,” *Bio-Algorithms and Med-Systems*, vol. 7, no. 2, pp. 73–78, 2011.
- [17] G. Korcyl, P. Białas, C. Curceanu, E. Czerwiński, K. Dulski, B. Flak, A. Gajos, B. Głowacz, M. Gorgol, B. C. Hiesmayr, B. Jasińska, K. Kacprzak, M. Kajetanowicz, D. Kisielewska, P. Kowalski, T. Kozik, N. Krawczyk, W. Krzemień, E. Kubicz, M. Mohammed, S. Niedźwiecki, M. Pawlik-Niedźwiecka, M. Pałka, L. Raczyński, P. Rajda, Z. Rudy, P. Salabura, N. G. Sharma, S. Sharma, R. Y. Shopa, M. Skurzok, M. Silarski, P. Strzempek, A. Wieczorek, W. Wiślicki, R. Zaleski, B. Zgardzińska, M. Zieliński, and P. Moskal, “Evaluation of single-chip, real-time tomographic data processing on fpga soc devices,” *IEEE Transactions on Medical Imaging*, vol. 37, no. 11, pp. 2526–2535, 2018.
- [18] S. Sharma, J. Chhokar, C. Curceanu, E. Czerwinski, M. Dadgar, K. Dulski, J. Gajewski, A. Gajos, M. Gorgol, N. Gupta-Sharma, R. D. Grande, B. C. Hiesmayr, B. Jasinska, K. Kacprzak, Ł. Kaplon, H. Karimi, D. Kisielewska, K. Klimaszewski, G. Korcyl, P. Kowalski, T. Kozik, N. Krawczyk, W. Krzemien, E. Kubicz, M. Mohammed, S. Niedzwiecki, M. Palka, M. Pawlik-Niedzwiecka, L. Raczynski, J. Raj, A. Rucinski, Shivani, R. Y. Shopa, M. Silarski, M. Skurzok, E. Ł. Stepień, W. Wislicki, B. Zgardzinska, and P. Moskal,



- “Estimating relationship between the Time Over Threshold and energy loss by photons in plastic scintillators used in the J-PET scanner,” *EJNMMI Phys.*, vol. 7, p. 39, 2020.
- [19] T. Merlin, S. Stute, D. Benoit, J. Bert, T. Carlier, C. Comtat, M. Filipovic, F. Lamare, and D. Visvikis, “CASToR: a generic data organization and processing code framework for multi-modal and multi-dimensional tomographic reconstruction,” *Physics in Medicine & Biology*, vol. 63, no. 18, p. 185005, 2018.
- [20] L. A. Shepp and Y. Vardi, “Maximum Likelihood Reconstruction for Emission Tomography,” *IEEE Transactions on Medical Imaging*, vol. 1, p. 113–122, Oct. 1982.
- [21] H. Hudson and R. Larkin, “Accelerated image reconstruction using ordered subsets of projection data,” *IEEE Transactions on Medical Imaging*, vol. 13, no. 4, p. 601–609, 1994.
- [22] M. Das, R. Bayerlein, S. Sharma, S. Parzych, S. Niedźwiecki, R. Badawi, and E. Y. Beyene, “Development of correction techniques for the J-PET scanner,” *Bio-Algorithms and Med-Systems*, vol. 20, no. 1, pp. 101–110, 2024.
- [23] R. Bayerlein, M. Das, S. Sharma, R. D. Badawi, E. Y. Beyene, N. Chug, C. Curceanu, E. Czerwiński, K. V. Eliyan, J. Hajduga, A. Hubalewska-Dydejczyk, S. Jalali, K. Kacprzak, T. Kaplanoglu, Kapłon, K. Kasperska, A. Khreptak, G. Korcyl, T. Kozik, K. Kubat, S. K. Kundu, A. K. Venadan, D. Kumar, E. Lisowski, F. Lisowski, J. Mędrala-Sowa, S. Moyo, W. Mryka, S. Niedźwiecki, M. Opalińska, P. Pandey, A. Pandey, S. Parzych, A. Porcelli, B. Rachwał, M. Rädler, B. A. Spencer, A. Sowa-Staszczak, M. Skurzok, T. Szumlak, S. Tiwari, P. Tanty, K. Tayefi Ardebili, E. Stępień, and P. Moskał, “Monte Carlo-based scatter correction for the plastic-based modular PET scanner J-PET,” *Physics in Medicine and Biology*, vol. 71, p. 075026, Apr. 2026.
- [24] National Electrical Manufacturers Association, “Performance Measurements of Positron Emission Tomographs (PETs).” NEMA Standards Publication NU 2-2018, oct 2018. Available at: <https://www.makeitelectric.store/us/view-details/performance-measurements-of-positron-emission-tomographs-pet>.
- [25] P. Moskał, K. Dulski, N. Chug, C. Curceanu, E. Czerwiński, M. Dadgar, J. Gajewski, A. Gajos, G. Grudzień, B. C. Hiesmayr, K. Kacprzak, Ł. Kapłon, H. Karimi, K. Klimaszewski, G. Korcyl, P. Kowalski, T. Kozik, N. Krawczyk, W. Krzemień, E. Kubicz, P. Małczak, S. Niedźwiecki, M. Pawlik-Niedźwiecka, M. Pędziwiatr, L. Raczyński, J. Raj, A. Ruciński, S. Sharma, S. null, R. Y. Shopa, M. Silarski, M. Skurzok, E. Ł. Stępień, M. Szczepanek, F. Tayefi, and W. Wiślicki, “Positronium imaging with the novel multi-photon PET scanner,” *Science Advances*, vol. 7, no. 42, p. eabh4394, 2021.
- [26] B. Huang, Z. Wang, X. Zeng, A. H. Goldan, and J. Qi, “Fast high-resolution lifetime image reconstruction for positron lifetime tomography,” *Communications Physics*, vol. 8, no. 181, 2025.

- [27] W. M. Steinberger, L. Mercolli, J. Breuer, G. Prenosil, K. Shi, A. Rominger, U. Fischer, M. Schwyzer, and P. Cumming, “Positronium lifetime validation measurements using a long-axial field-of-view positron emission tomography scanner,” *EJNMMI Physics*, vol. 11, no. 1, p. 76, 2024.
- [28] L. Mercolli, W. M. Steinberger, H. Sari, A. Afshar-Oromieh, F. Caobelli, M. Conti, u. R. F. Cardoso, C. Mingels, P. Moskal, T. Pyka, N. Rathod, R. Schepers, E. Stpień, M. Viscione, A. Rominger, K. Shi, and R. Seifert, “In Vivo Positronium Lifetime Measurements with Intravenous Tracer Administration and a Long Axial Field-of-View PET/CT,” *IEEE Transactions on Radiation and Plasma Medical Sciences*, p. 1–1, 2026.
- [29] G. A. Prenosil, H. Sari, M. Fürstner, A. Afshar-Oromieh, K. Shi, A. Rominger, and M. Hentschel, “Performance characteristics of the biograph vision Quadra PET/CT system with a long axial field of view using the NEMA NU 2-2018 standard,” *J. Nucl. Med.*, vol. 63, p. 476, 2022.
- [30] B. Dai, M. Daube-Witherspoon, S. McDonald, M. Werner, M. Parma, M. Geagan, V. Viswanath, and J. Karp, “Performance evaluation of the PennPET explorer with expanded axial coverage,” *Phys. Med. Biol.*, vol. 68, p. 095007, 2023.
- [31] B. Huang, B. Dai, E. J. Li, J. S. Karp, and J. Qi, “High-resolution Positronium Lifetime Imaging on the PennPET Explorer,” in *2024 IEEE Nuclear Science Symposium (NSS), Medical Imaging Conference (MIC) and Room Temperature Semiconductor Detector Conference (RTSD)*, pp. 1–1, 2024.
- [32] J. S. Karp, V. Viswanath, M. J. Geagan, G. Muehllehner, A. R. Pantel, M. J. Parma, A. E. Perkins, J. P. Schmall, M. E. Werner, and M. E. Daube-Witherspoon, “PennPET Explorer: Design and Preliminary Performance of a Whole-Body Imager,” *Journal of Nuclear Medicine*, vol. 61, no. 1, pp. 136–143, 2020.
- [33] B. Huang, B. Dai, S. E. Lapi, G. Liles, J. S. Karp, and J. Qi, “High-Resolution Positronium Lifetime Tomography at Clinical Activity Levels on the PennPET Explorer,” *Journal of Nuclear Medicine*, vol. 66, p. 1464–1470, Aug. 2025.
- [34] S. Samanta, X. Sun, H. Li, and Y. Li, “Feasibility Study of Positronium Imaging using the NeuroEXPLORER (NX) Brain PET Scanner,” in *2023 IEEE Nuclear Science Symposium, Medical Imaging Conference and International Symposium on Room-Temperature Semiconductor Detectors (NSS MIC RTSD)*, pp. 1–1, IEEE, nov 4 2023.
- [35] S. Takyu, K.-i. Matsumoto, T. Hirade, F. Nishikido, G. Akamatsu, H. Tashima, M. Takahashi, and T. Yamaya, “Quantification of radicals in aqueous solution by positronium lifetime: an experiment using a clinical PET scanner,” *Japanese Journal of Applied Physics*, vol. 63, p. 086003, Aug. 2024.
- [36] S. Takyu, F. Nishikido, H. Tashima, G. Akamatsu, K. ichiro Matsumoto, M. Takahashi, and T. Yamaya, “Positronium lifetime measurement using a clinical PET system for

- tumor hypoxia identification,” *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*, vol. 1065, p. 169514, 2024.
- [37] L. Mercolli, W. M. Steinberger, N. Rathod, M. Conti, P. Moskal, A. Rominger, R. Seifert, K. Shi, E. Stepień, and H. Sari, “Phantom imaging demonstration of positronium lifetime with a long axial field-of-view PET/CT and 124I,” *EJNMMI Physics*, vol. 12, Aug. 2025.
- [38] Uluutku, Berkin and Gasparato, Giuliano and Das, Manish and Choiński, Jarosław and Pandey, Anand and Sharma, Sushil and Moskal, Paweł and Stepień, Ewa and Kao, Chien-Min and Huang, Hsin-Hsiung, “A conjugate bayesian framework for fast 3d positronium lifetime estimation with a partial system matrix,” 2026.
- [39] K. Kubat, M. Das, S. Sharma, E. Y. Beyene, A. Bilewicz, J. Choiński, N. Chug, C. Curceanu, E. Czerwiński, J. Hajduga, S. Jalali, K. Kacprzak, T. Kaplanoglu, Kapłon, K. Kasperska, A. Khreptak, G. Korcyl, T. Kozik, A. K. Venadan, D. Kumar, S. K. Kundu, B. Leszczyński, E. Lisowski, F. Lisowski, J. Mędrala-Sowa, S. Moyo, W. Mryka, S. Niedźwiecki, A. Pandey, P. Pandey, S. Parzych, A. Porcelli, B. Rachwał, M. Rädler, M. Skurzok, A. Stolarz, T. Szumlak, S. Tiwari, P. Tanty, K. T. Ardebili, K. V. Eliyan, R. Walczak, P. Moskal, and E. Stepień, “First ex-vivo positronium imaging of tissues with modular J-PET scanner using 44Sc radionuclide,” *Zeitschrift für Medizinische Physik*, Mar. 2026.
- [40] M. Das, W. Mryka, E. Yitayew, S. Parzych, S. Sharma, E. Stepień, and P. Moskal, “Estimating the efficiency and purity for detecting annihilation and prompt photons for positronium imaging with J-PET using toy monte carlo simulation,” *Bio-Algorithms and Med-Systems*, vol. 19, pp. 87–95, 2023.
- [41] M. Das, S. Sharma, E. Yitayew Beyene, A. Bilewicz, J. Choiński, N. Chug, C. Curceanu, E. Czerwiński, K. Valsan Eliyan, J. Hajduga, S. Jalali, K. Kacprzak, T. Kaplanoglu, Kapłon, K. Kasperska, A. Khreptak, G. Korcyl, T. Kozik, K. Kubat, D. Kumar, A. Kunimall Venadan, E. Lisowski, F. Lisowski, J. Medrala-Sowa, S. Moyo, W. Mryka, S. Niedźwiecki, P. Pandey, S. Parzych, A. Porcelli, B. Rachwał, E. Perez del Rio, M. Rädler, A. Rominger, K. Shi, M. Skurzok, A. Stolarz, T. Szumlak, P. Tanty, K. Tayefi Ardebili, S. Tiwari, R. Walczak, E. Stepień, and P. Moskal, “First Positronium Imaging Using 44Sc With the J-PET Scanner: a Case Study on the NEMA-Image Quality Phantom,” *IEEE Transactions on Radiation and Plasma Medical Sciences*, vol. 10, p. 593–602, Apr. 2026.
- [42] T. Ahn, D. W. Gidley, A. W. Thornton, A. G. Wong-Foy, B. G. Orr, K. M. Kozloff, and M. M. Banaszak Holl, “Hierarchical nature of nanoscale porosity in bone revealed by positron annihilation lifetime spectroscopy,” *ACS Nano*, vol. 15, p. 4321, 2021.

- [43] Y. Jean, Y. Li, G. Liu, H. Chen, Z. J., and J. Gadzia, “Applications of slow positrons to cancer research: Search for selectivity of positron annihilation to skin cancer,” *Applied Surface Science*, vol. 252, p. 3166, 2006.
- [44] H. Chen, J. van Horn, and Y. Jean, “Applications of positron annihilation spectroscopy to life science,” *Defect Diffusion Forum*, vol. 331, p. 275, 2012.
- [45] B. Jasińska, B. Zgardzińska, G. Chołubek, M. Gorgol, K. Wiktor, K. Wysogład, P. Bi-  
ałas, C. Curceanu, E. Czerwiński, K. Dulski, A. Gajos, B. Głowacz, B. Hiesmayr,  
B. Jodłowska-Jędrych, D. Kamińska, G. Korcyl, P. Kowalski, T. Kozik, N. Krawczyk,  
W. Krzemień, E. Kubicz, M. Mohammed, M. Pawlik-Niedźwiecka, S. Niedźwiecki,  
M. Pałka, L. Raczyński, Z. Rudy, N. Sharma, S. Sharma, R. Shopa, M. Silarski, M. Skur-  
zok, A. Wieczorek, H. Wiktor, W. Wiślicki, M. Zieliński, and P. Moskal, “Human tissues  
investigation using pals technique,” *Acta Phys. Polon. B*, vol. 48, p. 1737, 2017.
- [46] B. Zgardzińska, G. Chołubek, B. Jarosz, K. Wysogład, M. Gorgol, M. Goździuk,  
M. Chołubek, and B. Jasińska, “Studies on healthy and neoplastic tissues using positron  
annihilation lifetime spectroscopy and focused histopathological imaging,” *Sci. Rep.*,  
vol. 10, p. 11890, 2020.
- [47] H. Karimi, P. Moskal, A. Zak, and E. Stepień, “3d melanoma spheroid model for the  
development of positronium biomarker,” *Sci. Rep.*, vol. 13, p. 1648, 2023.
- [48] P. Moskal, E. Kubicz, G. Grudzień, E. Czerwiński, K. Dulski, B. Leszczyński,  
S. Niedźwiecki, and E. Ł. Stępień, “Developing a novel positronium biomarker for  
cardiac myxoma imaging,” *EJNMMI Physics*, vol. 10, no. 1, p. 22, 2023.
- [49] S. Moyo, P. Moskal, and E. Ł. Stępień, “Feasibility study of positronium application  
for blood clots structural characteristics,” *Bio-Algorithms and Med-Systems*, vol. 18,  
pp. 163–167, 12 2022.
- [50] K. Kubat, Ł. Kapłon, P. Moskal, and E. Stępień, “Calibration of PALS System with CRM  
Materials for Biomedical Studies,” *Bio-Algorithms and Med-Systems*, vol. 20, p. 35–39,  
Dec. 2024.
- [51] M. Sitarz, J.-P. Cussonneau, T. Matulewicz, and H. F., “Radionuclide candidates for for  
 $\beta^+\gamma$  coincidence PET: An overview,” *Applied Radiation and Isotopes*, vol. 155, p. 108898,  
2020.
- [52] P. Moskal, E. Stępień, and A. Khreptak, “A vision to increase the availability of PET  
diagnostics in low- and medium-income countries by combining a low-cost modular  
J-PET tomograph with the  $^{44}\text{Ti}/^{44}\text{Sc}$  generator,” *Bio-Algorithms and Med-Systems*,  
vol. 20, pp. 55–62, Dec. 2024.
- [53] M. Das, S. Sharma, E. Y. Beyene, A. Bilewicz, J. Choiński, N. Chug, C. Curceanu,  
E. Czerwiński, J. Hajduga, S. Jalali, K. Kacprzak, T. Kaplanoglu, Kapłon, K. Kasperska,

- A. Khreptak, G. Korcyl, T. Kozik, K. Kubat, D. Kumar, S. K. Kundu, A. K. Venadan, E. Lisowski, F. Lisowski, J. Medrala-Sowa, S. Moyo, W. Mryka, S. Niedźwiecki, A. Pandey, P. Pandey, S. Parzych, A. Porcelli, B. Rachwał, M. Rädler, N. Rathod, N. Razzaq, A. Rominger, K. Shi, M. Skurzok, M. Słotwiński, A. Stolarz, T. Szumlak, P. Tanty, K. T. Ardebili, S. Tiwari, K. V. Eliyan, R. Walczak, E. Stepień, and P. Moskal, “First positronium lifetime imaging using  $^{52}\text{Mn}$  and  $^{55}\text{Co}$  with a plastic-scintillator-based PET scanner,” *Scientific Reports*, vol. 16, Mar. 2026.
- [54] M. E. Phelps, “PET: The Merging of Biology and Imaging into Molecular Imaging,” *Journal of Nuclear Medicine*, vol. 41, no. 4, pp. 661–681, 2000.
- [55] M. Reivich, D. Kuhl, A. Wolf, J. Greenberg, M. Phelps, T. Ido, V. Casella, J. Fowler, E. Hoffman, A. Alavi, P. Som, and L. Sokoloff, “The  $[^{18}\text{F}]$ fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man,” *Circulation Research*, vol. 44, p. 127–137, Jan. 1979.
- [56] A. Afshar-Oromieh, A. Malcher, M. Eder, M. Eisenhut, H. G. Linhart, B. A. Hadaschik, T. Holland-Letz, F. L. Giesel, C. Kratochwil, S. Haufe, U. Haberkorn, and C. M. Zechmann, “PET imaging with a  $[^{68}\text{Ga}]$ gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions,” *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 40, p. 486–495, Nov. 2012.
- [57] A. R. Haug, C. J. Auernhammer, B. Wängler, G. P. Schmidt, C. Uebles, B. Göke, P. Cumming, P. Bartenstein, R. Tiling, and M. Hacker, “ $^{68}\text{Ga}$ -DOTATATE PET/CT for the Early Prediction of Response to Somatostatin Receptor-Mediated Radionuclide Therapy in Patients with Well-Differentiated Neuroendocrine Tumors,” *Journal of Nuclear Medicine*, vol. 51, no. 9, pp. 1349–1356, 2010.
- [58] J. S. Karp, S. Surti, M. E. Daube-Witherspoon, and G. Muehllehner, “Benefit of Time-of-Flight in PET: Experimental and Clinical Results,” *Journal of Nuclear Medicine*, vol. 49, p. 462–470, Feb. 2008.
- [59] C. Lois, B. W. Jakoby, M. J. Long, K. F. Hubner, D. W. Barker, M. E. Casey, M. Conti, V. Y. Panin, D. J. Kadrmas, and D. W. Townsend, “An Assessment of the Impact of Incorporating Time-of-Flight Information into Clinical PET/CT Imaging,” *Journal of Nuclear Medicine*, vol. 51, p. 237–245, Jan. 2010.
- [60] P. E. KINAHAN, M. DEFRISE, and R. CLACKDOYLE, *Analytic Image Reconstruction Methods*, p. 421–442. Elsevier, 2004.
- [61] L. A. Shepp and B. F. Logan, “The Fourier reconstruction of a head section,” *IEEE Transactions on Nuclear Science*, vol. 21, p. 21–43, June 1974.
- [62] J. Radon, “On the determination of functions from their integral values along certain manifolds,” *IEEE Transactions on Medical Imaging*, vol. 5, p. 170–176, Dec. 1986.

- [63] S. Tong, A. M. Alessio, and P. E. Kinahan, "Image reconstruction for PET/CT scanners: past achievements and future challenges," *Imaging in Medicine*, vol. 2, p. 529–545, Oct. 2010.
- [64] L. Parra and H. Barrett, "List-mode likelihood: EM algorithm and image quality estimation demonstrated on 2-D PET," *IEEE Transactions on Medical Imaging*, vol. 17, p. 228–235, Apr. 1998.
- [65] H. H. Barrett, T. White, and L. C. Parra, "List-mode likelihood," *Journal of the Optical Society of America A*, vol. 14, p. 2914, Nov. 1997.
- [66] A. Reader, R. Manavaki, S. Zhao, P. Julyan, D. Hastings, and J. Zweit, "Accelerated list-mode EM algorithm," *IEEE Transactions on Nuclear Science*, vol. 49, p. 42–49, Feb. 2002.
- [67] M. Defrise, P. E. Kinahan, and C. J. Michel, *Image Reconstruction Algorithms in PET*, p. 63–91. Springer London, 2005.
- [68] G. C. Colleran, N. Kwatra, L. Oberg, F. D. Grant, L. Drubach, M. J. Callahan, R. D. MacDougall, F. H. Fahey, and S. D. Voss, "How we read pediatric PET/CT: indications and strategies for image acquisition, interpretation and reporting," *Cancer Imaging*, vol. 17, Nov. 2017.
- [69] R. Smith, J. Karp, G. Muehllehner, E. Gualtieri, and F. Benard, "Singles transmission scans performed post-injection for quantitative whole body PET imaging," *IEEE Transactions on Nuclear Science*, vol. 44, p. 1329–1335, June 1997.
- [70] R. E. Carson, M. E. Daube-Witherspoon, and M. V. Green, "A Method for Postinjection PET Transmission Measurements with a Rotating Source," *Journal of Nuclear Medicine*, vol. 29, no. 9, pp. 1558–1567, 1988.
- [71] R. A. deKemp and C. Nahmias, "Attenuation correction in PET using single photon transmission measurement," *Medical Physics*, vol. 21, p. 771–778, June 1994.
- [72] M. Daube-Witherspoon, R. Carson, and M. Green, "Post-injection transmission attenuation measurements for PET," *IEEE Transactions on Nuclear Science*, vol. 35, p. 757–761, Feb. 1988.
- [73] D. L. Bailey, "Transmission scanning in emission tomography," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 25, p. 774–787, July 1998.
- [74] T. Beyer, D. W. Townsend, T. Brun, P. E. Kinahan, M. Charron, R. Roddy, J. Jerin, J. Young, L. Byars, and R. Nutt, "A Combined PET/CT Scanner for Clinical Oncology," *Journal of Nuclear Medicine*, vol. 41, no. 8, pp. 1369–1379, 2000.
- [75] D. W. Townsend and T. Beyer, "A combined PET/CT scanner: the path to true image fusion," *The British Journal of Radiology*, vol. 75, p. S24–S30, Nov. 2002.

- [76] P. E. Kinahan, D. W. Townsend, T. Beyer, and D. Sashin, "Attenuation correction for a combined 3D PET/CT scanner," *Medical Physics*, vol. 25, p. 2046–2053, Oct. 1998.
- [77] C. Burger, G. Goerres, S. Schoenes, A. Buck, A. Lonn, and G. von Schulthess, "Pet attenuation coefficients from ct images: experimental evaluation of the transformation of ct into pet 511-kev attenuation coefficients," *European Journal of Nuclear Medicine and Molecular Imaging*, vol. 29, p. 922–927, Apr. 2002.
- [78] J. P. J. Carney, D. W. Townsend, V. Rappoport, and B. Bendriem, "Method for transforming CT images for attenuation correction in PET/CT imaging," *Medical Physics*, vol. 33, p. 976–983, Mar. 2006.
- [79] H. Zhang, J. Wang, N. Li, Y. Zhang, J. Cui, L. Huo, and H. Zhang, "A quantitative clinical evaluation of simultaneous reconstruction of attenuation and activity in time-of-flight PET," *BMC Medical Imaging*, vol. 23, Feb. 2023.
- [80] Q. Li, X. Zhu, S. Zou, N. Zhang, X. Liu, Y. Yang, H. Zheng, D. Liang, and Z. Hu, "Eliminating CT radiation for clinical PET examination using deep learning," *European Journal of Radiology*, vol. 154, p. 110422, Sept. 2022.
- [81] F. Liu, H. Jang, R. Kijowski, G. Zhao, T. Bradshaw, and A. B. McMillan, "A deep learning approach for 18F-FDG PET attenuation correction," *EJNMMI Physics*, vol. 5, Nov. 2018.
- [82] S. Tiwari, S. Sharma, and P. Moskal, "Feasibility Study of Using Detector-Scattered Photons for Attenuation Correction in CT-less PET Imaging," *Bio-Algorithms and Med-Systems*, vol. 21, p. 13–20, Dec. 2025.
- [83] R. D. Evans and R. Evans, *The atomic nucleus*, vol. 582. McGraw-Hill New York, 1955.
- [84] E. J. Hoffman, S.-C. Huang, M. E. Phelps, and D. E. Kuhl, "Quantitation in positron emission computed tomography: 4. effect of accidental coincidences," *Journal of Computer Assisted Tomography*, vol. 5, p. 391–400, June 1981.
- [85] G. F. Knoll, *Radiation detection and measurement*. John Wiley & Sons, 2010.
- [86] J. F. Oliver and M. Rafecas, "Modelling Random Coincidences in Positron Emission Tomography by Using Singles and Prompts: A Comparison Study," *PLOS ONE*, vol. 11, p. e0162096, Sept. 2016.
- [87] J. M. Ollinger, "Model-based scatter correction for fully 3D PET," *Physics in Medicine and Biology*, vol. 41, p. 153–176, Jan. 1996.
- [88] C. C. Watson, D. Newport, and M. E. Casey, *A Single Scatter Simulation Technique for Scatter Correction in 3D PET*, p. 255–268. Springer Netherlands, 1996.

- [89] C. Levin, M. Dahlbom, and E. Hoffman, “A Monte Carlo correction for the effect of Compton scattering in 3-D PET brain imaging,” *IEEE Transactions on Nuclear Science*, vol. 42, p. 1181–1185, Aug. 1995.
- [90] R. Bayerlein, B. A. Spencer, E. K. Leung, N. Omidvari, Y. G. Abdelhafez, Q. Wang, L. Nardo, S. R. Cherry, and R. D. Badawi, “Development of a Monte Carlo-based scatter correction method for total-body PET using the uEXPLORER PET/CT scanner,” *Physics in Medicine and Biology*, vol. 69, p. 045033, Feb. 2024.
- [91] X. Zhang, J. Zhou, S. R. Cherry, R. D. Badawi, and J. Qi, “Quantitative image reconstruction for total-body PET imaging using the 2-meter long EXPLORER scanner,” *Physics in Medicine and Biology*, vol. 62, p. 2465–2485, Feb. 2017.
- [92] P. Moskal, P. Kowalski, R. Shopa, L. Raczyński, J. Baran, N. Chug, C. Curceanu, E. Czerwiński, M. Dadgar, K. Dulski, A. Gajos, B. Hiesmayr, K. Kacprzak, Ł. Kapłon, D. Kisielewska, K. Klimaszewski, P. Kopka, G. Korcyl, N. Krawczyk, W. Krzemień, E. Kubicz, S. Niedźwiecki, S. Parzych, J. Raj, S. Sharma, S. Shivani, E. Stępień, F. Tayefi, and W. Wiślicki, “Simulating NEMA characteristics of the modular total-body J-PET scanner — an economic total-body PET from plastic scintillators,” *Phys. Med. Biol.*, vol. 66, p. 175015, 2021.
- [93] P. Moskal, D. Kisielewska, R. Y. Shopa, Z. Bura, J. Chhokar, C. Curceanu, E. Czerwinski, M. Dadgar, K. Dulski, J. Gajewski, A. Gajos, M. Gorgol, R. Del Grande, B. C. Hiesmayr, B. Jasinska, K. Kacprzak, A. Kaminska, L. Kaplon, H. Karimi, G. Korcyl, P. Kowalski, N. Krawczyk, W. Krzemien, T. Kozik, E. Kubicz, P. Malczak, M. Mohammed, S. Niedzwiecki, M. Palka, M. Pawlik-Niedzwiecka, M. Pedziwiatr, L. Raczyński, J. Raj, A. Rucinski, S. Sharma, S. Shivani, M. Silarski, M. Skurzok, E. L. Stepień, S. Vandenberghe, W. Wislicki, and B. Zgardzińska, “Performance assessment of the  $2\gamma$  positronium imaging with the total-body PET scanners,” *EJNMMI Phys.*, vol. 7, p. 44, 2020.
- [94] P. Moskal, D. Kisielewska, C. Curceanu, E. Czerwiński, K. Dulski, A. Gajos, M. Gorgol, B. Hiesmayr, B. Jasińska, K. Kacprzak, Ł. Kapłon, G. Korcyl, P. Kowalski, W. Krzemień, T. Kozik, E. Kubicz, M. Mohammed, S. Niedźwiecki, M. Pałka, M. Pawlik-Niedźwiecka, L. Raczyński, J. Raj, S. Sharma, Shivani, R. Y. Shopa, M. Silarski, M. Skurzok, E. Stępień, W. Wiślicki, and B. Zgardzińska, “Feasibility study of the positronium imaging with the J-PET tomograph,” *Phys. Med. Biol.*, vol. 64, no. 5, p. 055017, 2019.
- [95] S. Bass, S. Mariazzi, P. Moskal, and E. Stepień, “Positronium physics and biomedical applications,” *Rev. Mod. Phys.*, vol. 95, p. 021002, 2023.
- [96] Y. C. Jean, P. E. Mallon, and D. M. Schrader, eds., *Principles and Applications of Positron and Positronium Chemistry*, vol. 12 of *Advanced Series in Physical Chemistry*. World Scientific, 2003.



- [97] K. Shibuya, H. Saito, F. Nishikido, M. Takahashi, and T. Yamaya, “Oxygen sensing ability of positronium atom for tumor hypoxia imaging,” *Commun. Phys.*, vol. 3, p. 173, 2020.
- [98] P. S. Stepanov, F. A. Selim, S. V. Stepanov, A. V. Bokov, O. V. Ilyukhina, G. Duplâtre, and V. M. Byakov, “Interaction of positronium with dissolved oxygen in liquids,” *Physical Chemistry Chemical Physics*, vol. 22, p. 5123, 2020.
- [99] D. W. Gidley, H.-G. Peng, and R. S. Vallery, “Positron annihilation as a method to characterize porous materials,” *Annual Review of Materials Research*, vol. 36, no. Volume 36, 2006, pp. 49–79, 2006.
- [100] P. Moskal and E. Stepień, “Positronium as a biomarker of hypoxia,” *Bio-Algorithms and Med-Systems*, vol. 17, p. 311, 2021.
- [101] W. Mryka, M. Das, E. Y. Beyene, P. Moskal, and E. Stepień, “Estimating influence of positron range in proton-therapy-beam monitoring with PET,” *Bio-Algorithms and Med-Systems*, vol. 19, p. 96–100, Dec. 2023.
- [102] IAEA, “International atomic energy agency (iaea), livechart of nuclides.”
- [103] T. Matulewicz, “Radioactive nuclei for  $\beta^+\gamma$  pet and theranostics: selected candidates,” *Bio-Algorithms and Med-Systems*, vol. 17, p. 235, 2021.
- [104] M. Conti and L. Eriksson, “Physics of pure and non-pure positron emitters for PET: a review and a discussion,” *EJNMMI Physics*, vol. 3, May 2016.
- [105] B. Huang and J. Qi, “High-resolution positronium lifetime tomography by the method of moments,” *Physics in Medicine & Biology*, vol. 69, p. 24NT01, Dec. 2024.
- [106] H.-H. Huang, Z. Zhu, S. Booppasiri, Z. Chen, S. Pang, and C.-M. Kao, “A Statistical Reconstruction Algorithm for Positronium Lifetime Imaging Using Time-of-Flight Positron Emission Tomography,” *IEEE Transactions on Radiation and Plasma Medical Sciences*, vol. 9, pp. 478–486, Apr. 2025.
- [107] L. Berens, I. Hsu, C.-T. Chen, H. Halpern, and C.-M. Kao, “An analytic, moment-based method to estimate orthopositronium lifetimes in positron annihilation lifetime spectroscopy measurements,” *Bio-Algorithms and Med-Systems*, vol. 20, pp. 40–48, Dec. 2024.
- [108] J. Qi and B. Huang, “Positronium lifetime image reconstruction for TOF PET,” *IEEE Transactions on Medical Imaging*, vol. 41, p. 2848, 2022.
- [109] B. Huang, T. Li, G. Ariño-Estrada, K. Dulski, R. Y. Shopa, P. Moskal, E. Stepień, and J. Qi, “SPLIT: Statistical Positronium Lifetime Image Reconstruction via Time-Thresholding,” *IEEE Transactions on Medical Imaging*, vol. 43, no. 6, pp. 2148–2158, 2024.

- [110] Z. Chen, L. An, C.-M. Kao, and H.-H. Huang, “The properties of the positronium lifetime image reconstruction based on maximum likelihood estimation,” *Bio-Algorithms and Med-Systems*, vol. 19, pp. 1–8, Dec. 2023.
- [111] R. Shopa and K. Dulski, “Positronium imaging in J-PET with an iterative activity reconstruction and a multi-stage fitting algorithm,” *Bio-Algorithms and Med-Systems*, vol. 19, no. 1, pp. 54–63, 2023.
- [112] Z. Chen, C.-M. Kao, H.-H. Huang, and L. An, “Enhanced positronium lifetime imaging through two-component reconstruction in time-of-flight positron emission tomography,” *Frontiers in Physics*, vol. 12, p. 1429344, Jul. 2024.
- [113] J. T. Triffitt and W. F. Neuman, “The uptake of sodium-22 by bone and certain soft tissues,” *Calcified Tissue Research*, vol. 6, pp. 70–76, Dec. 1970.
- [114] P. Moskal, A. Gajos, M. Mohammed, J. Chhokar, N. Chug, C. Curceanu, E. Czerwiński, M. Dadgar, K. Dulski, M. Gorgol, J. Goworek, B. C. Hiesmayr, B. Jasińska, K. Kacprzak, Ł. Kapłon, H. Karimi, D. Kisielewska, K. Klimaszewski, G. Korcyl, P. Kowalski, N. Krawczyk, W. Krzemień, T. Kozik, E. Kubicz, S. Niedźwiecki, S. Parzych, M. Pawlik-Niedźwiecka, L. Raczyński, J. Raj, S. Sharma, S. Choudhary, R. Y. Shopa, A. Sienkiewicz, M. Silarski, M. Skurzok, E. Ł. Stępień, F. Tayefi, and W. Wiślicki, “Testing CPT symmetry in ortho-positronium decays with positronium annihilation tomography,” *Nature Communications*, vol. 12, no. 5658, 2021.
- [115] P. Moskal, D. Kumar, S. Sharma, E. Y. Beyene, N. Chug, A. Coussat, C. Curceanu, E. Czerwiński, M. Das, K. Dulski, M. Gorgol, B. Jasińska, K. Kacprzak, T. Kaplanoglu, Łukasz Kapłon, T. Kozik, E. Lisowski, F. Lisowski, W. Mryka, S. Niedźwiecki, S. Parzych, E. P. del Rio, M. Rädler, M. Skurzok, E. Ł. Stępień, P. Tanty, K. T. Ardebili, and K. V. Eliyan, “Nonmaximal entanglement of photons from positron-electron annihilation demonstrated using a plastic PET scanner,” *Science Advances*, vol. 11, no. 18, p. eads3046, 2025.
- [116] P. Moskal, E. Czerwiński, J. Raj, S. D. Bass, E. Y. Beyene, N. Chug, A. Coussat, C. Curceanu, M. Dadgar, M. Das, K. Dulski, A. Gajos, M. Gorgol, B. C. Hiesmayr, B. Jasińska, K. Kacprzak, T. Kaplanoglu, Ł. Kapłon, K. Klimaszewski, P. Konieczka, G. Korcyl, T. Kozik, W. Krzemień, D. Kumar, S. Moyo, W. Mryka, S. Niedźwiecki, S. Parzych, E. P. del Río, L. Raczyński, S. Sharma, S. Choudhary, R. Y. Shopa, M. Silarski, M. Skurzok, E. Ł. Stępień, P. Tanty, F. T. Ardebili, K. T. Ardebili, K. V. Eliyan, and W. Wiślicki, “Discrete symmetries tested at 10–4 precision using linear polarization of photons from positronium annihilations,” *Nature Communications*, vol. 15, no. 78, 2024.
- [117] N. Chug, S. D. Bass, E. Y. Beyene, C. Curceanu, E. Czerwiński, M. Das, K. V. Eliyan, M. Gorgol, J. Hajduga, S. Jalali, B. Jasińska, K. Kacprzak, T. Kaplanoglu, L. Kapłon, K. Kasperska, A. Khreptak, A. Kierys, G. Korcyl, T. Kozik, K. Kubat, D. Kumar, A. K. Venadan, E. Lisowski, F. Lisowski, J. Mędrała Sowa, S. Moyo, W. Mryka, S. Niedźwiecki,

- P. Pandey, S. Parzych, E. P. del Rio, A. Porcelli, B. Rachwał, M. Rädler, A. Sienkiewicz, S. Sharma, M. Skurzok, E. L. Stępień, T. Szumlak, P. Tanty, K. T. Ardebili, S. Tiwari, and P. Moskal, “Studies of  $CPT$  symmetry in positronium decays with the 192 plastic strip J-PET detector,” *Phys. Rev. D*, vol. 113, p. 032003, Feb 2026.
- [118] L. Mercolli, W. M. Steinberger, T. Läppchen, M. Amon, C. Bregenzer, M. Conti, u. R. F. Cardoso, C. Mingels, P. Moskal, N. Rathod, H. Sari, E. Stępień, S. Weidner, A. Rominger, K. Shi, and R. Seifert, “In vivo voxel-wise positronium lifetime imaging of thyroid cancer using clinically routine I-124 PET/CT,” *EANM Innovation*, p. 100017, Dec. 2025.
- [119] M. T. Durán, F. Juget, Y. Nadjadi, C. Bailat, P. V. Grundler, Z. Talip, N. P. van der Meulen, P. Casolaro, G. Dellepiane, and S. Braccini, “Half-life measurement of  $^{44}\text{Sc}$  and  $^{44\text{m}}\text{Sc}$ ,” *Applied Radiation and Isotopes*, vol. 190, p. 110507, Dec. 2022.
- [120] L. Mercolli, W. M. Steinberger, P. V. Grundler, A. Moiseeva, S. Braccini, M. Conti, P. Moskal, N. Rathod, A. Rominger, H. Sari, R. Schibli, R. Seifert, K. Shi, E. Stępień, and N. P. van der Meulen, “First positronium lifetime imaging with scandium-44 on a long axial field-of-view PET/CT,” *Frontiers in Nuclear Medicine*, vol. 5, Nov. 2025.
- [121] M. Palka, P. Strzempek, G. Korcyl, T. Bednarski, S. Niedźwiecki, P. Białas, E. Czerwiński, K. Dulski, A. Gajos, B. Głowacz, M. Gorgol, B. Jasińska, D. Kamińska, M. Kajetanowicz, P. Kowalski, T. Kozik, W. Krzemień, E. Kubicz, M. Mohhamed, L. Raczyński, Z. Rudy, O. Rundel, P. Salabura, N. Sharma, M. Silarski, J. Smyrski, A. Strzelecki, A. Wieczorek, W. Wiślicki, M. Zieliński, B. Zgardzińska, and P. Moskal, “Multichannel FPGA based MVT system for high precision time (20 ps RMS) and charge measurement,” *JINST*, vol. 12, no. 08, p. P08001, 2017.
- [122] F. Tayefi Ardebili and P. Moskal, “Assessing the Spatial Resolution of the Modular J-PET Scanner using the Maximum-Likelihood Expectation-Maximization (MLEM) algorithm,” *Bio-Algorithms and Med-Systems*, vol. 20, pp. 1–9, Nov. 2024.
- [123] F. Tayefi Ardebili, S. Niedźwiecki, and P. Moskal, “Evaluation of Modular J-PET sensitivity,” *Bio-Algorithms and Med-Systems*, vol. 19, p. 132, 2023.
- [124] K. Kacprzak, E. Beyene, J. Choiński, N. Chug, C. Curceanu, E. Czerwiński, J. Hajduga, S. Jalali, T. Kaplanoglu, Kapłan, K. Kasperska, A. Khreptak, G. Korcyl, T. Kozik, K. Kubat, S. K. Kundu, D. Kumar, E. Lisowski, F. Lisowski, J. Mędrala-Sowa, S. Moyo, W. Mryka, S. Niedźwiecki, A. Pandey, P. Pandey, S. Parzych, A. Porcelli, B. Rachwał, M. Rädler, S. Sharma, M. Skurzok, A. Stolarz, T. Szumlak, P. Tanty, K. Tayefi Ardebili, S. Tiwari, A. Venadan, E. Stępień, and P. Moskal, “Methodology for calibrating modular J-PET scanner with prompt gamma emitters  $^{22}\text{Na}$  and  $^{44}\text{Sc}$ ,” *Bio-Algorithms and Med-Systems*, Dec. 2026.
- [125] <https://luxiumsolutions.com/sites/default/files/2021-10/BC400-404-408-412-416-Data-Sheet.pdf>. [Accessed 26-05-2026].

- [126] L. Kaplon, “Technical Attenuation Length Measurement of Plastic Scintillator Strips for the Total-Body J-PET Scanner,” *IEEE Transactions on Nuclear Science*, vol. 67, p. 2286–2289, Oct. 2020.
- [127] M. Pałka, P. Moskal, T. Bednarski, P. Białas, E. Czerwiński, Kaplon, A. Kochanowski, G. Korcyl, J. Kowal, P. Kowalski, T. Kozik, W. Krzemień, M. Molenda, S. Niedźwiecki, M. Pawlik, L. Razyński, Z. Rudy, P. Salabura, N. Gupta-Sharma, M. Silarski, A. Słomski, J. Smyrski, A. Strzelecki, W. Wiślicki, M. Zieliński, and N. Zoń, “A novel method based solely on field programmable gate array (fpga) units enabling measurement of time and charge of analog signals in positron emission tomography (pet),” *Bio-Algorithms and Med-Systems*, vol. 10, p. 41–45, Mar. 2014.
- [128] G. Korcyl, P. Moskal, T. Bednarski, P. Białas, E. Czerwiński, Kaplon, A. Kochanowski, J. Kowal, P. Kowalski, T. Kozik, W. Krzemień, M. Molenda, S. Niedźwiecki, M. Pałka, M. Pawlik, L. Razyński, Z. Rudy, P. Salabura, N. Gupta-Sharma, M. Silarski, A. Słomski, J. Smyrski, A. Strzelecki, W. Wiślicki, M. Zieliński, and N. Zoń, “Trigger-less and reconfigurable data acquisition system for positron emission tomography,” *Bio-Algorithms and Med-Systems*, vol. 10, p. 37–40, Mar. 2014.
- [129] R. Brun *et al.*, “root-project/root: v6.18/02,” Aug. 2019.
- [130] Ł. Kaplon, J. Baran, N. Chug, A. Coussat, C. Curceanu, E. Czerwiński, M. Dadgar, K. Dulski, J. Gajewski, A. Gajos, B. Hiesmayr, E. K. Valsan, K. Klimaszewski, G. Korcyl, T. Kozik, W. Krzemień, D. Kumar, G. Moskal, S. Niedźwiecki, D. Panek, S. Parzych, E. P. del Rio, L. Razyński, A. Ruciński, S. Sharma, S. Shivani, R. Shopa, M. Silarski, M. Skurzok, E. Stepień, F. T. Ardebili, K. T. Ardebili, W. Wiślicki, and P. Moskal, “Comparative studies of plastic scintillator strips with high technical attenuation length for the total-body J-PET scanner,” *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*, vol. 1051, p. 168186, 2023.
- [131] National Electrical Manufacturers Association, “Performance Measurements of Positron Emission Tomographs (PETs).” NEMA Standards Publication NU 2-2024, oct 2024. Available at: <https://www.makeitelectric.store/us/view-details/performance-measurements-of-positron-emission-tomographs-pets>.
- [132] F. T. Ardebili, “Evaluation of the NEMA Characteristics for the Modular J-PET Scanner,” 2024.
- [133] A. Stolarz, J. A. Kowalska, J. Jastrzębski, J. Choiński, M. Sitarz, K. Szkliniarz, A. Trzcińska, and W. Zipper, “Ca targets for sc production by proton or deuteron irradiation,” *HIL Annual Report*, p. 30, 2016.
- [134] A. Stolarz, J. A. Kowalska, J. Jastrzębski, J. Choiński, M. Sitarz, K. Szkliniarz, A. Trzcińska, , and W. Zipper, “Targets for production of the medical radioisotopes with alpha and proton or deuteron beams,” *AIP Conference Proceedings*, vol. 2018, p. 020004, 2018.

- [135] J. Choiński and M. Łyczko, “Prospects for the production of radioisotopes and radiobioconjugates for theranostics,” *Bio-Algorithms and Med-Systems*, vol. 17, p. 241, 2021.
- [136] A. L. Wooten, B. C. Lewis, and S. E. Lapi, “Cross-sections for (p, x) reactions on natural chromium for the production of  $^{52}$ ,  $^{52m}$ ,  $^{54}\text{Mn}$  radioisotopes,” *Applied Radiation and Isotopes*, vol. 96, p. 154–161, Feb. 2015.
- [137] H. Valdovinos, R. Hernandez, S. Graves, P. Ellison, T. Barnhart, C. Theuer, J. Engle, W. Cai, and R. Nickles, “Cyclotron production and radiochemical separation of  $^{55}\text{Co}$  and  $^{58m}\text{Co}$  from  $^{54}\text{Fe}$ ,  $^{58}\text{Ni}$  and  $^{57}\text{Fe}$  targets,” *Applied Radiation and Isotopes*, vol. 130, p. 90–101, Dec. 2017.
- [138] K. E. Barrett, H. A. Houson, W. Lin, S. E. Lapi, and J. W. Engle, “Production, Purification, and Applications of a Potential Theranostic Pair: Cobalt-55 and Cobalt-58m,” *Diagnostics*, vol. 11, p. 1235, July 2021.
- [139] Kaplon, E. Beyene, N. Chug, C. Curceanu, E. Czerwiński, M. Das, K. Eliyan, K. Kacprzak, T. Kaplanoglu, G. Korcyl, K. Kubat, D. Kumar, E. Lisowski, F. Lisowski, J. Mędrala-Sowa, G. Moskal, W. Mryka, S. Niedźwiecki, P. Pandey, S. Parzych, E. Pérez del Rio, S. Sharma, M. Skurzok, P. Tanty, K. Tayefi, A. Venadan, E. Stępień, and P. Moskal, “Quality control of plastic scintillators for the total-body J-PET scanner,” *Journal of Instrumentation*, vol. 20, p. P09019, Sept. 2025.
- [140] R. D. Badawi and P. K. Marsden, “Developments in component-based normalization for 3D PET,” *Physics in Medicine and Biology*, vol. 44, p. 571–594, Jan. 1999.
- [141] A. Pépin, S. Stute, S. Jan, and C. Comtat, “Normalization of Monte Carlo PET data using GATE,” in *2011 IEEE Nuclear Science Symposium Conference Record*, pp. 4196–4200, 2011.
- [142] R. L. Siddon, “Fast calculation of the exact radiological path for a three-dimensional CT array,” *Medical Physics*, vol. 12, p. 252–255, Mar. 1985.
- [143] P. Kowalski, W. Wiślicki, L. Raczyński, D. Alfs, T. Bednarski, P. Białas, E. Czerwiński, A. Gajos, B. Głowacz, J. Jasińska, D. Kamińska, G. Korcyl, T. Kozik, W. Krzemień, E. Kubicz, M. Mohammad, S. Niedźwiecki, M. Pałka, M. Pawlik-Niedźwiecka, Z. Rudy, M. Silarski, A. Wiczorek, B. Zgardzińska, M. Zieliński, and P. Moskal, “Scatter Fraction of the J-PET Tomography Scanner,” *Acta Physica Polonica B*, vol. 47, no. 2, p. 549, 2016.
- [144] P. Moskal, A. Khreptak, J. Choiński, P. Jones, I. Kadenko, A. Majkowska-Pilip, R. Palit, A. Stolarz, R. Walczak, and E. Stępień, “Endorsing titanium–scandium radionuclide generator for pet and positronium imaging,” *Acta Physica Polonica A*, vol. 148, p. S152, Jan. 2025.

- [145] K. A. Domnanich, C. Müller, R. Farkas, R. M. Schmid, B. Ponsard, R. Schibli, A. Türlér, and N. P. van der Meulen, “ $^{44}\text{Sc}$  for labeling of DOTA- and NODAGA-functionalized peptides: preclinical in vitro and in vivo investigations,” *EJNMMI Radiopharmacy and Chemistry*, vol. 1, May 2016.
- [146] E. Koumarianou, N. Loktionova, M. Fellner, F. Roesch, O. Thews, D. Pawlak, S. Archimandritis, and R. Mikolajczak, “ $^{44}\text{Sc}$ -DOTA-BN[2-14] $\text{NH}_2$  in comparison to  $^{68}\text{Ga}$ -DOTA-BN[2-14] $\text{NH}_2$  in pre-clinical investigation. Is  $^{44}\text{Sc}$  a potential radionuclide for PET?,” *Applied Radiation and Isotopes*, vol. 70, pp. 2669–2676, Dec. 2012.
- [147] C. Müller, M. Bunka, J. Reber, C. Fischer, K. Zhernosekov, A. Türlér, and R. Schibli, “Promises of Cyclotron-Produced  $^{44}\text{Sc}$  as a Diagnostic Match for Trivalent  $\beta^-$ -Emitters: In Vitro and In Vivo Study of a  $^{44}\text{Sc}$ -DOTA-Folate Conjugate,” *Journal of Nuclear Medicine*, vol. 54, no. 12, pp. 2168–2174, 2013.
- [148] S. Eigner, D. R. B. Vera, M. Fellner, N. S. Loktionova, M. Piel, O. Lebeda, F. Rösch, T. L. Roß, and K. E. Henke, “Imaging of Protein Synthesis: In Vitro and In Vivo Evaluation of  $^{44}\text{Sc}$ -DOTA-Puromycin,” *Molecular Imaging and Biology*, vol. 15, pp. 79–86, May 2012.
- [149] R. Hernandez, H. F. Valdovinos, Y. Yang, R. Chakravarty, H. Hong, T. E. Barnhart, and W. Cai, “ $^{44}\text{Sc}$ : An Attractive Isotope for Peptide-Based PET Imaging,” *Molecular Pharmaceutics*, vol. 11, pp. 2954–2961, Jul. 2014.
- [150] R. Chakravarty, S. Goel, H. F. Valdovinos, R. Hernandez, H. Hong, R. J. Nickles, and W. Cai, “Matching the Decay Half-Life with the Biological Half-Life: ImmunoPET Imaging with  $^{44}\text{Sc}$ -Labeled Cetuximab Fab Fragment,” *Bioconjugate Chemistry*, vol. 25, pp. 2197–2204, Nov. 2014.
- [151] D. Szücs, T. Csupász, J. P. Szabó, A. Kis, B. Gyuricza, V. Arató, V. Forgács, A. Vágner, G. Nagy, I. Garai, D. Szikra, I. Tóth, G. Trencsényi, G. Tircsó, and A. Fekete, “Synthesis, Physicochemical, Labeling and In Vivo Characterization of  $^{44}\text{Sc}$ -Labeled DO3AM-NI as a Hypoxia-Sensitive PET Probe,” *Pharmaceutics*, vol. 15, p. 666, May 2022.
- [152] A. Majkowska-Pilip and A. Bilewicz, “Macrocyclic complexes of scandium radionuclides as precursors for diagnostic and therapeutic radiopharmaceuticals,” *Journal of Inorganic Biochemistry*, vol. 105, pp. 313–320, Feb. 2011.
- [153] M. Pruszyński, A. Majkowska-Pilip, N. S. Loktionova, E. Eppard, and F. Roesch, “Radiolabeling of DOTATOC with the long-lived positron emitter  $^{44}\text{Sc}$ ,” *Applied Radiation and Isotopes*, vol. 70, pp. 974–979, Jun. 2012.
- [154] T. V. M. Lima, S. Gnesin, E. Nitzsche, P. G. Ortega, C. Müller, and N. P. van der Meulen, “First Phantom-Based Quantitative Assessment of Scandium-44 Using a Commercial PET Device,” *Frontiers in Physics*, vol. 8, Jul. 2020.

- [155] T. V. M. Lima, S. Gnesin, K. Strobel, M. d. S. Pérez, J. E. Roos, C. Müller, and N. P. van der Meulen, “Fifty Shades of Scandium: Comparative Study of PET Capabilities Using Sc-43 and Sc-44 with Respect to Conventional Clinical Radionuclides,” *Diagnostics*, vol. 11, p. 1826, Oct. 2021.
- [156] C. A. Umbricht, M. Benešová, R. M. Schmid, A. Türlér, R. Schibli, N. P. van der Meulen, and C. Müller, “ $^{44}\text{Sc}$ -PSMA-617 for radiotheragnostics in tandem with  $^{177}\text{Lu}$ -PSMA-617—preclinical investigations in comparison with  $^{68}\text{Ga}$ -PSMA-11 and  $^{68}\text{Ga}$ -PSMA-617,” *EJNMMI Research*, vol. 7, Jan. 2017.
- [157] C. Müller, M. Bunka, S. Haller, U. Köster, V. Groehn, P. Bernhardt, N. van der Meulen, A. Türlér, and R. Schibli, “Promising Prospects for  $^{44}\text{Sc}$ -/ $^{47}\text{Sc}$ -Based Theragnostics: Application of  $^{47}\text{Sc}$  for Radionuclide Tumor Therapy in Mice,” *Journal of Nuclear Medicine*, vol. 55, pp. 1658–1664, Jul. 2014.
- [158] J. Zhang, A. Singh, H. R. Kulkarni, C. Schuchardt, D. Müller, H.-J. Wester, T. Maina, F. Rösch, N. P. van der Meulen, C. Müller, H. Mäcke, and R. P. Baum, “From Bench to Bedside—The Bad Berka Experience With First-in-Human Studies,” *Seminars in Nuclear Medicine*, vol. 49, pp. 422–437, Sep. 2019.
- [159] E. Eppard, A. de la Fuente, M. Benešová, A. Khawar, R. A. Bundschuh, F. C. Gärtner, B. Kreppel, K. Kopka, M. Essler, and F. Rösch, “Clinical Translation and First In-Human Use of [ $^{44}\text{Sc}$ ]Sc-PSMA-617 for PET Imaging of Metastasized Castrate-Resistant Prostate Cancer,” *Theranostics*, vol. 7, no. 18, pp. 4359–4369, 2017.
- [160] A. Singh, R. Baum, I. Klette, N. van der Meulen, C. Mueller, A. Tuerler, and R. Schibli, “Scandium-44 DOTATOC PET/CT: First in-human molecular imaging of neuroendocrine tumors and possible perspectives for Theranostics,” *Journal of Nuclear Medicine*, vol. 56, no. supplement 3, pp. 267–267, 2015.
- [161] A. Khawar, E. Eppard, J. P. Sinnes, F. Roesch, H. Ahmadzadehfar, S. Kürpig, M. Meisenheimer, F. C. Gaertner, M. Essler, and R. A. Bundschuh, “[ $^{44}\text{Sc}$ ]Sc-PSMA-617 Biodistribution and Dosimetry in Patients With Metastatic Castration-Resistant Prostate Carcinoma,” *Clinical Nuclear Medicine*, vol. 43, pp. 323–330, May 2018.
- [162] N. P. van der Meulen, R. Hasler, Z. Talip, P. V. Grundler, C. Favaretto, C. A. Umbricht, C. Müller, G. Dellepiane, T. S. Carzaniga, and S. Braccini, “Developments toward the Implementation of  $^{44}\text{Sc}$  Production at a Medical Cyclotron,” *Molecules*, vol. 25, p. 4706, Oct. 2020.
- [163] C. V. Gomes, B. M. Mendes, L. Paixão, S. Gnesin, C. Müller, N. P. van der Meulen, K. Strobel, T. C. F. Fonseca, and T. V. M. Lima, “Comparison of the dosimetry of scandium-43 and scandium-44 patient organ doses in relation to commonly used gallium-68 for imaging neuroendocrine tumours,” *EJNMMI Physics*, vol. 11, 7 2024.

- [164] K. Dulski, B. Zgardzińska, P. Białas, C. Curceanu, E. Czerwiński, A. Gajos, B. Głowacz, M. Gorgol, B. C. Hiesmayr, B. Jasińska, D. Kisielewska-Kamińska, G. Korcyl, P. Kowalski, T. Kozik, N. Krawczyk, W. Krzemień, E. Kubicz, M. Mohammed, M. P.-N. S. Niedźwiecki, M. Pałka, L. Raczyński, J. Raj, Z. Rudy, N. G. Sharma, S. Sharma, Shivani, R. Y. Shopa, M. Silarski, M. Skurzok, A. Wieczorek, W. Wiślicki, M. Zieliński, and P. Moskal, “Analysis procedure of the positronium lifetime spectra for the J-PET detector,” *Acta Phys. Polon. A*, vol. 132, no. 5, pp. 1637–1640, 2017.
- [165] K. Dulski, C. Curceanu, E. Czerwiński, A. Gajos, M. Gorgol, N. Gupta-Sharma, B. C. Hiesmayr, B. Jasińska, K. Kacprzak, Ł. Kapłon, D. Kisielewska, K. Klimaszewski, G. Korcyl, P. Kowalski, N. Krawczyk, W. Krzemień, T. Kozik, E. Kubicz, M. Mohammed, S. Niedźwiecki, M. Pałka, M. Pawlik-Niedźwiecka, L. Raczyński, J. Raj, K. Rakoczy, Z. Rudy, S. Sharma, Shivani, R. Y. Shopa, M. Silarski, M. Skurzok, W. Wiślicki, B. Zgardzińska, and P. Moskal, “Commissioning of the J-PET detector in view of the positron annihilation lifetime spectroscopy,” *Hyperfine Interactions*, vol. 239, no. 1, p. 40, 2020.
- [166] K. Dulski, “PALS avalanche - a new PAL spectra analysis software,” *Acta Phys. Polon. A*, vol. 137, no. 2, pp. 167–170, 2020.
- [167] H. F. Mohamed, A. El-Sayed, and G. G. Abd-Elsadek, “Effect of temperature on ortho-positronium in poly(methyl methacrylate),” *Polymer Degradation and Stability*, vol. 71, no. 1, pp. 93–97, 2000.
- [168] K. Kotera, T. Saito, and T. Yamanaka, “Measurement of positron lifetime to probe the mixed molecular states of liquid water,” *Physics Letters A*, vol. 345, no. 1, pp. 184–190, 2005.
- [169] P. E. N. Braad, S. B. Hansen, H. Thisgaard, and P. F. Høilund-Carlsen, “Pet imaging with the non-pure positron emitters: 55co, 86y and 124i,” *Physics in Medicine & Biology*, vol. 60, p. 3479, apr 2015.
- [170] T. K. Nayak and M. W. Brechbiel, “Radioimmunoimaging with Longer-Lived Positron-Emitting Radionuclides: Potentials and Challenges,” *Bioconjugate Chemistry*, vol. 20, p. 825–841, Jan. 2009.
- [171] J. H. Dam, B. B. Olsen, C. Baun, P. F. Høilund-Carlsen, and H. Thisgaard, “A PSMA Ligand Labeled with Cobalt-55 for PET Imaging of Prostate Cancer,” *Molecular Imaging and Biology*, vol. 19, p. 915–922, Sept. 2017.
- [172] H. A. Houson, V. Tekin, W. Lin, E. Aluicio-Sarduy, J. W. Engle, and S. E. Lapi, “Pet Imaging of the Neurotensin Targeting Peptide NOTA-NT-20.3 Using Cobalt-55, Copper-64 and Gallium-68,” *Pharmaceutics*, vol. 14, p. 2724, dec 6 2022.
- [173] H. Stevens, H. M. Jansen, J. De Reuck, M. Lemmerling, K. Strijckmans, P. Goethals, I. Lemahieu, B. M. de Jong, A. T. Willemsen, and J. Korf, “55cobalt (Co) as a PET-tracer in stroke, compared with blood flow, oxygen metabolism, blood volume and gadolinium-MRI,” *Journal of the Neurological Sciences*, vol. 171, pp. 11–18, 12 1999.



- [174] S. J. Zou, I. Lim, J. W. Foster, G. Chinn, H. A. Houson, S. E. Lapi, J. Rao, and C. S. Levin, “Quantitative imaging of  $^{55}\text{Co}$  and  $^{18}\text{F}$ -labeled tracers in a single “multiplexed” pet imaging session,” 2024.
- [175] S. J. Zou, I. Lim, J. W. Foster, G. Chinn, H. A. Houson, S. E. Lapi, J. Rao, and C. S. Levin, “Quantitative Imaging of  $^{55}\text{CO}$  and  $^{18}\text{F}$ -Labeled Tracers in a Single “Multiplexed” Pet Imaging Session,” in *2025 IEEE 22nd International Symposium on Biomedical Imaging (ISBI)*, p. 1–5, IEEE, Apr. 2025.
- [176] S. A. Graves, R. Hernandez, J. Fonslet, C. G. England, H. F. Valdovinos, P. A. Ellison, T. E. Barnhart, D. R. Elema, C. P. Theuer, W. Cai, R. J. Nickles, and G. W. Severin, “Novel Preparation Methods of  $^{52}\text{Mn}$  for ImmunoPET Imaging,” *Bioconjugate Chemistry*, vol. 26, p. 2118–2124, Sept. 2015.
- [177] G. Saar, C. M. Millo, L. P. Szajek, J. Bacon, P. Herscovitch, and A. P. Koretsky, “Anatomy, Functionality, and Neuronal Connectivity with Manganese Radiotracers for Positron Emission Tomography,” *Molecular Imaging and Biology*, vol. 20, p. 562–574, Feb. 2018.
- [178] I. Y. Zhou, I. A. Ramsay, I. Ay, P. Pantazopoulos, N. J. Rotile, A. Wong, P. Caravan, and E. M. Gale, “Positron Emission Tomography–Magnetic Resonance Imaging Pharmacokinetics, In Vivo Biodistribution, and Whole-Body Elimination of Mn-PyC3A,” *Investigative Radiology*, vol. 56, p. 261–270, Nov. 2020.
- [179] C. M. Lewis, S. A. Graves, R. Hernandez, H. F. Valdovinos, T. E. Barnhart, W. Cai, M. E. Meyerand, R. J. Nickles, and M. Suzuki, “ $^{52}\text{Mn}$  Production for PET/MRI Tracking Of Human Stem Cells Expressing Divalent Metal Transporter 1 (DMT1),” *Theranostics*, vol. 5, no. 3, p. 227–239, 2015.
- [180] C. Vanasschen, M. Brandt, J. Ermert, and H. H. Coenen, “Radiolabelling with isotopic mixtures of  $^{52}\text{g}/^{55}\text{Mn}$  as a straight route to stable manganese complexes for bimodal PET/MR imaging,” *Dalton Transactions*, vol. 45, no. 4, p. 1315–1321, 2016.
- [181] R. Hernandez, S. A. Graves, T. Gregg, H. R. VanDeusen, R. J. Fenske, H. N. Wienkes, C. G. England, H. F. Valdovinos, J. J. Jeffery, T. E. Barnhart, G. W. Severin, R. J. Nickles, M. E. Kimple, M. J. Merrins, and W. Cai, “Radiomanganese PET Detects Changes in Functional  $\beta$ -Cell Mass in Mouse Models of Diabetes,” *Diabetes*, vol. 66, p. 2163–2174, May 2017.
- [182] A. I. Jensen, G. W. Severin, A. E. Hansen, F. P. Flidner, R. Eliassen, L. Parhamifar, A. Kjær, T. L. Andresen, and J. R. Henriksen, “Remote-loading of liposomes with manganese-52 and in vivo evaluation of the stabilities of  $^{52}\text{Mn}$ -DOTA and  $^{64}\text{Cu}$ -DOTA using radiolabelled liposomes and PET imaging,” *Journal of Controlled Release*, vol. 269, p. 100–109, Jan. 2018.
- [183] L. De Nardo, G. Ferro-Flores, C. Bolzati, J. Esposito, and L. Meléndez-Alafort, “Radiation effective dose assessment of  $^{51}\text{Mn}$ - and  $^{52}\text{Mn}$ -chloride,” *Applied Radiation and Isotopes*, vol. 153, p. 108805, Nov. 2019.

- [184] H. Napieczynska, G. W. Severin, J. Fonslet, S. Wiehr, A. Menegakis, B. J. Pichler, and C. Calaminus, “Imaging neuronal pathways with  $^{52}\text{Mn}$  PET: Toxicity evaluation in rats,” *NeuroImage*, vol. 158, p. 112–125, Sept. 2017.
- [185] S. S. Rinne, C. Dahlsson Leitao, Z. Saleh-nihad, B. Mitran, V. Tolmachev, S. Ståhl, J. Löfblom, and A. Orlova, “Benefit of Later-Time-Point PET Imaging of HER3 Expression Using Optimized Radiocobalt-Labeled Affibody Molecules,” *International Journal of Molecular Sciences*, vol. 21, p. 1972, Mar. 2020.
- [186] K. Ito, T. Oka, Y. Kobayashi, Y. Shirai, K. Wada, M. Matsumoto, M. Fujinami, T. Hirade, Y. Honda, H. Hosomi, Y. Nagai, K. Inoue, H. Saito, K. Sakaki, K. Sato, A. Shimazu, and A. Uedono, “Interlaboratory comparison of positron annihilation lifetime measurements for synthetic fused silica and polycarbonate,” *Journal of Applied Physics*, vol. 104, p. 026102, 07 2008.
- [187] H. R. Likhithaswamy, G. S. Madhushankari, M. Selvamani, K. P. Mohan Kumar, G. Kokila, and S. Mahalakshmi, “Assessing the Quality of Long-Term Stored Tissues in Formalin and in Paraffin-Embedded Blocks for Histopathological Analysis,” *Journal of Microscopy and Ultrastructure*, vol. 10, p. 23–29, Jan. 2022.
- [188] S. Moyo, A. Wróbel, B. Leszczyński, M. Skalska, J. Stepniewski, G. Kopeć, P. Moskal, and E. Stepień, “Fresh Paraformaldehyde Preserves Thrombus Biochemistry - Infrared Spectroscopy and Secondary Ion Mass Spectrometry Investigation of Pulmonary Artery Thrombi,” *bioRxiv*, 2025.
- [189] J. Wasserthal, H.-C. Breit, M. T. Meyer, M. Pradella, D. Hinck, A. W. Sauter, T. Heye, D. T. Boll, J. Cyriac, S. Yang, M. Bach, and M. Segeroth, “TotalSegmentator: Robust Segmentation of 104 Anatomic Structures in CT Images,” *Radiology: Artificial Intelligence*, vol. 5, no. 5, 2023.
- [190] R. Kikinis, S. D. Pieper, and K. G. Vosburgh, *3D Slicer: A Platform for Subject-Specific Image Analysis, Visualization, and Clinical Support*, p. 277–289. Springer New York, Nov. 2013.
- [191] N. M. Toàn, A. Vágner, G. Nagy, G. Ország, T. Nagy, C. Csikos, B. Váradi, G. Z. Sajtos, I. Kapus, Z. Szoboszlai, D. Szikra, G. Trencsényi, G. Tircsó, and I. Garai, “[ $^{52}\text{Mn}$ ]Mn-BPPA-Trastuzumab: A Promising HER2-Specific PET Radio-tracer,” *Journal of Medicinal Chemistry*, vol. 67, p. 8261–8270, May 2024.
- [192] D. Kim, T. Ueki, A. N. Rahman, L. Yan, M. Uenomachi, K. Shimazoe, and H. Takahashi, “Improvement of double photon emission Compton imaging using angular and polarization correlations in cascade photons,” *Journal of Instrumentation*, vol. 18, p. C05012, May 2023.
- [193] K. Shimazoe, M. Uenomachi, and H. Takahashi, “Imaging and sensing of pH and chemical state with nuclear-spin-correlated cascade gamma rays via radioactive tracer,” *Communications Physics*, vol. 5, Jan. 2022.

- [194] M. Uenomachi, K. Shimazoe, and H. Takahashi, “A double photon coincidence detection method for medical gamma-ray imaging,” *Bio-Algorithms and Med-Systems*, vol. 18, p. 120–126, Dec. 2022.
- [195] K. Shimazoe and M. Uenomachi, “Multi-molecule imaging and inter-molecular imaging in nuclear medicine,” *Bio-Algorithms and Med-Systems*, vol. 18, p. 127–134, Dec. 2022.
- [196] K. T. Ardebili, E. Y. Beyene, N. Chug, C. Curceanu, E. Czerwiński, M. Das, J. Hajduga, S. Jalali, T. Kaplanoglu, Kapłan, K. Kasperska, A. Khreptak, G. Korcyl, K. Kubat, A. K. Venadan, D. Kumar, E. Lisowski, F. Lisowski, J. Mędrala-Sowa, S. Moyo, W. Mryka, S. Niedźwiecki, P. Pandey, S. Parzych, A. Porcelli, B. Rachwał, E. P. Río, M. Rädler, S. Sharma, M. Skurzok, T. Szumlak, S. Tiwari, P. Tanty, K. V. Eliyan, E. Stępień, and P. Moskal, “Development of a Cost-Effective Total Body J-PET From Plastic Scintillators: Definitive Design,” in *2025 IEEE Nuclear Science Symposium (NSS), Medical Imaging Conference (MIC) and Room Temperature Semiconductor Detector Conference (RTSD)*, p. 1–2, IEEE, Nov. 2025.
- [197] B. A. Spencer, E. Berg, J. P. Schmall, N. Omidvari, E. K. Leung, Y. G. Abdelhafez, S. Tang, Z. Deng, Y. Dong, Y. Lv, J. Bao, W. Liu, H. Li, T. Jones, R. D. Badawi, and S. R. Cherry, “Performance evaluation of the uEXPLORER total-body PET/CT scanner based on NEMA NU 2-2018 with additional tests to characterize PET scanners with a long axial field of view,” *J. Nucl. Med.*, vol. 61, p. 861, 2021.
- [198] G. Li, W. Ma, X. Li, W. Yang, Z. Quan, T. Ma, J. Wang, Y. Wang, F. Kang, and J. Wang, “Performance Evaluation of the uMI Panorama PET/CT System in Accordance with the National Electrical Manufacturers Association NU 2-2018 Standard,” *Journal of Nuclear Medicine*, vol. 65, p. 652–658, Feb. 2024.