MUSA SANI MUSA

SIMULATION AND EVALUATION OF A COST-EFFECTIVE HIGH-PERFORMANCE POSITRON EMISSION MAMMOGRAPHY SCANNER

NEU 2021

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A THESIS SUBMITTED TO THE INSTITUE OF GRADUATE STUDIES OF NEAR EAST UNIVERSITY

By
MUSA SANI MUSA

In Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Biomedical Engineering

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Approval of Director of Institute of Graduate Studies

Prof. Dr. K. Hüsnü Can BAŞER

We certify this thesis is satisfactory for the award of the degree of Doctor of Philosophy in Biomedical Engineering

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ACKNOWLEGMENTS

First and foremost, I would want to express my earnest appreciation to my humble supervisor Assoc. Prof. Dr. İlker Özşahin and my Co-supervisor Assoc. Prof. Dr. Dilber Uzun Özşahin for their ceaseless support & guidance, and for providing me with all the required skills and research tools to complete my thesis within the stipulated time. In addition, my gratitude goes to Near East University, Department of Biomedical Engineering and Prof. Dr.Ayse Gunay Kibarer for helping me through my academic journey.

To my Late parents Alh. Sani Musa and Haj. Hauwa Saeed, my Late GrandMa Haj. Aisha Alhassan, words alone can't express how grateful I am for the support you gave me. I miss you so much and love you to the moon and back. May your souls continue to rest in perfect peace.

For bye, my most profound thanks and ardent love goes to my entire family for their consistent support and help amid my thesis writing.

To my Uncle Alh. Auwal Saeed, my Aunties Haj. Hafsat and Haj. Hadiza, my beloved 2nd mother Haj. Halima Sabiu Bako, I thank you for all you have done to me in this life. May Allah reward you abundantly.

Lastly, I would also like to thank Alh. Sani Ibrahim, Alh. Sani Salisu, Haj. Sa'adatu Musa, for their support, including my friends who took their time to share with me their knowledge.

To my parents...

ABSTRACT

Breast cancer causes tumor deaths in women, for this reason, different imaging modalities were introduced to enhance disease diagnoses. There were 246,660 new breast cancer cases diagnosed in 2017, and there were over 40,000 deaths. The key to effective treatment is early diagnosis which helps to minimize the incidences and number of deaths from the disease. PEM scanners detect breast related diseases. They have small FOV to accommodate the breast, and it comes with fewer modules making it cost-efficient. Effective diagnoses are achieved through the use of high spatial resolution scanners with improved sensitivity. Semiconductor based scanners materials are have an excellent intrinsic spatial resolution, whereas those made of scintillators have limited intrinsic resolution. The present work aimed at improving the intrinsic resolution of scintillators by simulating a scanner with 1 × 1 × 10 mm^3 fabricated crystal. GATE software was used to simulate the scanner and NEMA standards to assess the scanner's performance. The scanner has 90 mm and 105 mm transaxial and axial FOV respectively. Results obtained are 10.6% sensitivity, 1.0 mm spatial resolution at CFOV and 2.1mm at the axial position. 1 mm in diameter hot rods were easily resolvable according to image quality test.

Keywords: PEM; GATE; scintillator; semiconductor

ÖZET

Meme kanseri kadınlarda tümör ölümlerine neden olur, bu nedenle hastalık tanılarını arttırmak için farklı görüntüleme yöntemleri uygulanmıştır. 2017 yılında 246.660 yeni meme kanseri vakası teşhis edildi ve 40.000'den fazla ölüm oldu. Etkili tedavinin anahtarı, hastalıktan kaynaklanan ölümlerin ve ölümlerin sayısını en aza indirmeye yardımcı olan erken tanıdır. PEM tarayıcılar memeyle ilişkili hastalıkları tespit eder. Memeyi yerleştirmek için küçük FOV'ları vardır ve daha az modülle birlikte gelir ve bu da maliyeti düşük hale getirir. Etkili teşhisler, gelişmiş duyarlılığa sahip yüksek uzamsal çözünürlüklü tarayıcılar kullanılarak elde edilir. Yarıiletken bazlı tarayıcı malzemeleri mükemmel bir içsel uzaysal çözünürlüğe sahipken, sintilatörlerden yapılanlar sınırlı bir içsel çözünürlüğe sahiptir. Mevcut çalışma, $1 \times 1 \times 10$ mm^3 fabrikasyon kristalli bir tarayıcıyı simüle ederek sintilatörlerin gerçek çözünürlüğünü geliştirmeyi amaçlamıştır. Tarayıcıyı simüle etmek için GATE yazılımı ve tarayıcının performansını değerlendirmek için NEMA standartları kullanıldı. Tarayıcı sırasıyla 90 mm ve 105 mm transaksiyel ve eksenel FOV'ye sahiptir. Elde edilen sonuçlar 10.6% hassasiyet, CFOV'da 1.0 mm uzamsal çözünürlük ve eksenel pozisyonda 2.1mm'dir. 1 mm çapında sıcak çubuklar görüntü kalitesi testine göre kolayca çözülebilirdi.

Anahtar Kelimeler: PEM; GATE; Sintilatör;

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LIST OF ABBREVIATIONS

1D:	One Dimensional
2D:	Two Dimensional
3D:	Three Dimensional
APD:	Avalanche Photo Diodes
BGO:	Bismuth Germanate
Br:	Bromine
C:	Carbon
CdTe:	Cadmium Telluride
CFOV:	Centre Field of View
CNR:	Contrast-Noise-Ratio
CT:	Computed Tomography
CZT:	Cadmium Zinc Telluride
DC:	Direct Current
DOI:	Depth of Interaction
F:	Fluorine
FBP:	Filtered Back Projection
FOV:	Field of View
FT:	Fourier Transform
FWHM:	Full Width at Half Maximum
FWTM:	Full Width at Tenth Maximum
GATE:	Geant4 Application for Emission Tomography
Ge:	Germanium
GSO:	Gadolinium Oxy-Silicate
I:	Iodine
keV:	Kiloelectron Volt
LIOB:	Laser Induced Optical Barrier
LM-OSEM:	List Mode-Ordered Subset Expectation Maximization
LOR:	Line of Response

LSO:	Lutetium Oxyorthosilicate
LuAP:	Lutetium Aluminum Perovskite
LYSO:	Lutetium Yttrium Oxyorthosilicate
MC-PMT:	Multi-Channel-Photo Multiplier Tube
MLEM:	Maximum Likelihood Expectation Maximization
MRI:	Magnetic Resonance Imaging
N:	Nitrogen
NaI:	Sodium Iodide
NEMA:	National Electrical Manufacturers Association
O:	Oxygen
OE:	Origin Ensemble
OSEM:	Ordered Subset Expectation Maximization
PET:	Positron Emission Tomography
PMT:	Photo Multiplier Tube
PSF:	Point Spread Function
PS-PMT:	Position Sensitive-Photo Multiplier Tube
RAMLA:	Raw Action Maximum Likelihood Algorithm
RC:	Recovery Co-efficient
Si:	Silicon
SiPMs:	Silicon Photo Multipliers
SNR:	Signal-Noise- Ratio
SPECT:	Single Photon Emission Computed Tomography
SR:	Spatial Resolution
SSRB:	Single Slice Rebinning
TOF:	Time of Flight
WB:	Whole Body

CHAPTER 1
INTRODUCTION

Breast imaging with gamma rays has been in place for years after scintimammography was introduced in the late 1980s. The earlier devices paved way for the development of current modalities such as breast specific gamma imaging, molecular breast imaging and positron emission mammography (Hruska and O'Connor, 2013). Major problems related to the device performance were addressed, they include spatial resolution and sensitivity, modes of acquisition, radiotracers etc (Hruska and O'Connor, 2013; Ozsahin and Unlu, 2014; Lorenzo et al., 2013).

Nuclear imaging technique gives significant metabolic information as opposed to anatomical information obtained from conventional mammography, ultrasound and magnetic resonance imaging (Histed et al., 2012). The nuclear medicine devices are very good at detecting and characterizing breast tumors because of the ability to outline the behavior of the breast tissue (Histed et al., 2012). In spite of the fact that they have been utilize for decades, they became acknowledged recently because of their limited tumour detectability (Vercher-Conejero, Pelegrí-Martinez, Lopez-Aznar and Cózar-Santiago, 2015). In addition to existing issues, the patient absorbed dose is quite high when compared to organ-dedicated scanners. (Hruska and O'Connor, 2013).

Currently, there is a trend of newer organ dedicated scanners that comes with improved specifications. The latest scanners are capable of detecting tumors at the early stage and also come with dose modulation which helps to reduce the patient absorbed dose (Gonzalez, Sanchez and Benlloch, 2018).

Nuclear breast imaging is now accepted globally as published studies have suggested that it has the ability to detect missing tumors MRI or mammography (Hruska and O'Connor, 2013). Category of patients to benefit from PEM include ductal carcinoma in-situ (DCIS) characterization and high-risk groups where conventional mammography is less effective (O'Connor, Rhodes and Hruska, 2009).

The key requirements for high-speed and high-resolution PET imaging are detectors with fast decay time, high stopping power, light output, spatial and energy resolution (Du et al., 2009).

Semiconductor-based PET detectors such as Cadmium zinc telluride (CZT) and Cadmium telluride (CdTe) have received much attention due to advantages such as high spatial and energy resolutions, high atomic number which means good stopping efficiency for detecting gamma rays (Cherry, Sorenson & Phelps, 2012). Their limitations include difficulty and expense of growing large pieces of CdTe or CZT with the required purity (Cherry, Sorenson & Phelps, 2012). There are also unfavorable cost issues due to the increase in number of readout electronic channels and its associated complexities (Sabet et al., 2016).

Scintillator-based detectors on the other hand, are typically more flexible with lower system cost because they have fewer electronic channels compared to the semiconductor detectors. Nevertheless, they have large spread of light due to the use of non-structured scintillators. The light spread increases with the thickness of the scintillator leading to poor spatial resolution. Therefore, the scintillation light has to be controlled in order to provide high intrinsic spatial resolution (Sabet et al., 2016).

Mechanical fabrication is the traditional technique used to pixelate crystals for various applications. This process leaves inter-pixel gaps and loss of material as the crystals are very hard material and are known to crack under thermal and mechanical stress. The loss of material results in loss of sensitivity (Sabet, Kudrolli, Singh & Nagarkar, 2012).

Laser-induced optical barrier (LIOB) serves as a substitute to mechanical pixelation. It is used to pixelate crystals into submillimetre size, in a crack free manner, thereby increasing the crystal's intrinsic spatial resolution. It is used to form optical barriers (interpixel gaps) without any loss of material. It is profitable as well as efficient because no material will be loss, pixels of varying size with excellent pixel separation can be introduced, intrinsic resolution and sensitivity can be improved. The whole process of LIOB technique is described in (Sabet et al., 2016).

This technique was employed in the present study because of its high efficiency at fabricating crystals with high intrinsic spatial resolution.

The cost-effectiveness of this design is mainly due to the use of scintillator crystal material which is cheaper than semiconductor crystal material and LIOB technique which prevents material lost during the process of fabrication. Detailed explanation of the cost-effectiveness of LIOB technique can be found in Sabet, Bläckberg, Uzun-ozsahin and El-Fakhri, 2016).

In the present study, a Breast scanner (NEU-PEM) employing highly pixelated LSO scintillator detector was simulated with GATE and the detector performance was evaluated according NEMA NU 4-2008. The performance test includes sensitivity, scatter fraction, spatial resolution, uniformity, and image quality.

1.1 Thesis Problems

- Breast cancer is the most frequent cancer among women
- Impacting 2.1 million women each year
- In 2019, an estimated 268,600 new cases of invasive breast cancer are expected to be diagnosed in women in the U.S.
- 62,930 new cases of non-invasive (in situ) breast cancer.

1.2 Aims of the Study

- To simulate a cost-effective PEM scanner
- To simulate a high spatial resolution PEM scanner employing laser processed scintillator crystal
- To simulate a high sensitivity PEM scanner
- To test the scanner's performance following NEMA guidelines

1.3 Significance of the Study

- The findings of the study will lead to a reduction in mortality rates and improve chances of survival (Jemal, Siegel, Xu & Ward, 2010).
- The findings of this study will demonstrate the ability of a cost-effective scintillator-based breast scanner to achieve high spatial resolution.
- The findings of the study will demonstrate the ability of scintillator-based scanners to achieve good sensitivity to detect most of the 511keV photons used in PET scans.
- The findings of the study will serve as reference for future researchers conducting a similar research.

1.4 Limitations of the Study

- The geometry of the simulated scanner is entirely approximate, series of structural changes might be done when developing the true scanner.
- In the simulation, all the voxels work perfectly, but in real life, some might be faulty or not function well.
- The output of one detector connected to a chip is difficult to simulate, but a model of the detector behavior can be created and tested.

1.5 Overview of the Thesis

Chapter 1 introduces the thesis and explains the problems, aims, significance and limitations of the study, while chapter 2 explains the literature review and fundamental physics. In chapter 3, the overview of PET imaging technique and PET in Nuclear medicine is presented. Chapter 4 describes the system specifications, simulation and performance evaluation. Chapter 5 explains the result and lastly, Chapter 6 concludes the study and also includes discussion and recommendations for future studies.

CHAPTER 2
LITERATURE REVIEW AND THEORETICAL PHYSICS

Luo, Anashkin and Matthews (2010) conducted a study in order to assess the NU 4 performance of a positron emission mammography (PEM) system in clinical use. The evaluation included comprises of spatial resolution, sensitivity, and uniformity. They found out that using the NU 4 guidelines, the evaluated system had a Trans-axial spatial resolution 1.8 mm and 2.4 mm FWHM for high resolution reconstruction and standard resolution reconstruction mode respectively. The system uniformity obtained from image quality testing were 3.9% STD and 5.6% at the standard resolution and high-resolution modes respectively. The total system sensitivity was 0.16 cps/Bq. They later concluded that this guideline is a practicable tool to assess PEM scanner performances.

Abreu et al. (2006) conducted a study which aimed at designing and performance testing of an imaging system "Clear-PEM" for positron emission mammography. The system comprises of two parallel heads plana detectors, made of high specs scintillator crystal. The crystal used is of high atomic number, fast, fabricated into smaller voxels with DOI measurement capabilities, and state-of-the-art data acquisition techniques. This novel design is suggested in order to actively diagnosed both breast and axilla lesions. Using detailed simulation, the spatial resolution, detection sensitivity, and count-rates were evaluated by and images were reconstructed by means of an iterative algorithm.

Miyake et al. (2014) developed a novel breast dedicated PET scanner and evaluated its performances according to NEMA NU 4-2008 standards. The scanner was made of LSO crystal and also comprises of a light guide and a photomultiplier tube. Using the NEMA Standards, Spatial resolution, sensitivity, counting rate capabilities, and image quality were evaluated. The result of spatial resolution was 1.6, 1.7, and 2.0 in the Radial, tangential, and axial direction respectively. Scatter fraction was 30.1%, Sensitivity was 11.2%, NECR and peak true rate was 374 kcps at 25 MBq and 603 kcps at 31 MBq, respectively. Recovery coefficients and uniformity of the image-quality phantom study were 0.04–0.82 and 1.9%, respectively. In conclusion, the results showed that the scanner is reasonable enough to be used in breast cancer imaging.

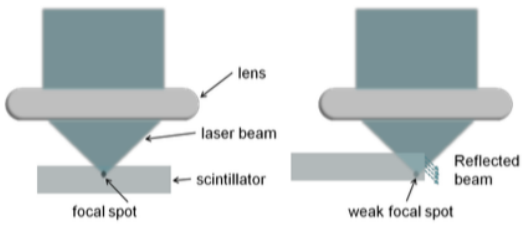
Moliner et al. (2012) developed a dedicated scanner based on LYSO scintillator crystal which was coupled to a PMT. The scanner titled MAMMI is modular in shape comprising of 12 detector modules. It has 40 mm axial FOV and 170mm transaxial FOV. THE scanner's performance was evaluated based on NEMA NU 2-2007 and NU 4-2008. Reported result showed that the system can achieve resolutions of 1.6, 1.8, and 1.9 mm were in the axial, radial, and tangential directions, respectively. Absolute sensitivity measured at the centre FOV was 1.8% and 20.8% scatter fraction and NECR of 25 kcps at 44 MBq.
According to the results obtained, it was concluded that the scanner is able to produce high quality PET images.

Li et al., (2015) developed a new PEM scanner "PEMi" based on LYSO crystal coupled to a PMT and evaluated its performance according to NEMA standards. The goal of this study was to test a small group of patients in order to test its performance and imaging ability. The scanner's specifications are 110 mm transaxial FOV, 166 mm diameter detector ring, and 128mm axial length. The system has 1.67 mm intrinsic resolution and 2.5 mm axial and tangential resolution. It also showed that 1.7 mm hot rods and 1.35-mm diameter rods can be clearly identified. The system has 6.88% peak sensitivity, 110766 cps NECR Using a 6-ns coincidence timing window and a 360 660-keV energy window. The image quality phantom test showed that rods between 1 mm and 5 mm have a recovery coefficient ranging from 0.21 to 0.85. they finally concluded that the PEM scanner is capable of providing detailed structure information than the whole-body PET imaging.

2.1 Laser Induced Optical Barrier

Laser-induced optical barrier (LIOB) is a cost-effective method used to incorporate optical structures into crystals, and a light guide to control the spread of light. This allows for high resolution and depth of interaction measurement.
It is an alternative method to the conventional (mechanical) method of fabricating crystals which involves focusing a laser beam into the bulk of the scintillator crystal. This makes the

crystal structure as well as refractive index changes. Pulse energy, density, wavelength and crystal structure contributes to the size of the damage created on the crystal. Optical barriers serve as reflecting surface that scatters the scintillator photons, they can be constructed in any pattern at numerous depths all over the crystal volume. The simplest pattern is straight walls resembling pixels, which can be used for different materials including hygroscopic scintillators and has the ability to control depth-dependent light spread for depth of DOI measurement. Figure 2.1 shows the concept of the LIOB technique.



(a) (b)

Figure 2.1: Schematics of the concept of LIOB technique (Sabet et al., 2016)

The process involves focusing a high-intensity laser beam into the bulk of crystal via a lens, this introduces intense heat within the crystal. Scintillators are poor heat conductors; therefore, the heat stays within the crystal and causes a regional damage. The size of the area affected by the laser beam can be controlled through optimization of the duration and energy of the laser pulse combined with the delivery optics. Moreover, microstructures with distinct refractive index (RI) with respect to the neighboring medium can be created by optimizing the energy and duration of the laser beam. These microstructures are referred to as optical barriers.

With the optical barriers within the crystal, scintillation light can then be reflected and refracted. The RI of the crystal with respect to the surrounding medium and the angle of incidence of the light photon control the amount of light reflected by a single optical barrier. Having successfully creating the barriers within the crystal, scintillation light can then be effectively redirected and its spread can be controlled leading to improvement in the detector intrinsic spatial resolution.

Furthermore, optical barriers are used to create a reflecting wall that resembles the reflecting material placed between pixels in the conventional mechanical procedure.

NOTE: Apart from creation of pixel-like shapes, the LIOB technique can also be used to create almost any pattern within the crystal. Figure 2.2 shows a picture of scintillator crystal fabricated using the LIOB technique. Optical walls were created using a 140-double pass of laser beam, which was scanned through the scintillator. A second laser scanning followed a little space, that can be of any value (Sabet et al., 2016).

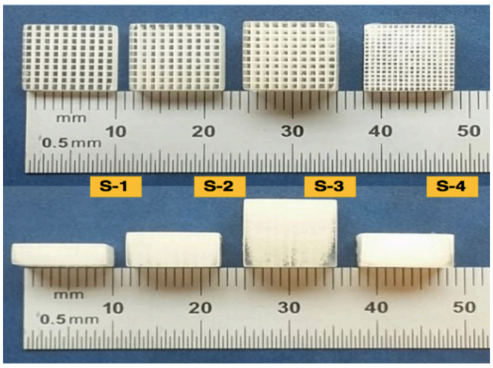


Figure 2.2: Fabricated scintillator arrays using the LIOB technique (Sabet et al., 2016)

2.2 Physics Fundamentals

2.2.1 Discovery of the positron

In the year 1928, Paul Dirac a British scientist wrote down an equation which combines quantum theory and special relativity, while trying to explain the character of an electron that moves at a relativistic speed. Dirac equation appeared to have a problem because two possible solutions could come out of the equation. Paul later interpreted his equation to mean that every existing particle has a corresponding anti-particle with the same mass but opposite charge. In 1931, Dirac forecasted an anti-electron existence having equal mass but of opposite charge with the electron, which he noted that when the two particles interact, they will mutually annihilate. The discovery of Dirac was confirmed in 1933 by Occhialini and Blacket. Another scientist named Anderson proved the existence of this anti-particle and was awarded a Nobel prize in physics in 1936 for discovering the positron. PET imaging got its origin in 1951 when two scientists from Massachusetts General Hospital William Sweet and Gordon Brownell suggested the use of the radiation from Positron-electron annihilation to increase sensitivity and resolution of diagnostic imaging thereby enhancing the quality of brain images. In 1953, these scientists produce the description of the first device for positron-imaging to store 3D brain data ("Discovering the positron", 2017).

2.2.2 Positron production in isotope decays

Positrons were first produced naturally by converting high cosmic-energy radiation into electron-positron pair as observed by Carl Anderson in 1932. Another form of positron production is the famous beta-decay whereby an excess proton is transformed into a neutron, with a positron and electron neutrino emitted as well (Krane, 1987).

$$P \rightarrow n + \beta^{+} + \nu_{e} \tag{2.1}$$

Beta-decay usually takes place in unstable nuclides that have a low atomic number and excess protons. Nowadays, radionuclides that emit positron are often produced in particle accelerators at some major laboratories. A new nucleus (daughter) results from radioactive decay of such unstable nuclides (parent) with short one proton (N) and atomic number (Z). The equation for Beta-decay is as follows:

$$^{A}_{Z}X_{N} \rightarrow {}^{A}_{Z-1}Y_{N+1} + e^{+} + \nu_{e}\ (+\ e^{-}) \tag{2.2}$$

Where X represent unstable nuclide, Y new nucleus and e^{-} stands for an ejected orbital electron so that the total charge can be balanced.

2.2.3 Initial energy and positron range

Initial energy is the energy possessed by a positron after being produced by beta decay. As positron travels through matter, it losses this energy and finally come to rest. Positron range is the term used to describe the distance travelled by a positron before it annihilates with an electron on its path. This range relies upon the emission energy of the positron and the electron density of the neighboring matter. Table 2.1 shows a list of the conventional radionuclides that emit positron and their properties.

Table 2.1: Properties of common positron emitting radionuclides used in PET (Cherry and Dahlbom, 2004)

Radionuclide	E_{max} (Mev)	Half-life	Mean positron range in water
^{13}N	1.20	9.97 min	1.4
^{11}C	0.961	20.4 min	1.1
^{18}F	0.63	109.8 min	1.0
^{15}O	1.73	2.03 min	1.5
^{68}Ga	1.89	67.6 min	1.7
^{82}Rb	2.60, 3.38	1.27 min	1.7

2.2.4 Annihilation photons, energy and non-collinearity

After positron is emitted from an unstable nucleus, it travels a little distance before it interacts with an electron on its path in a reaction known as annihilation. Two gamma photons emerge in opposite direction from such reaction, each with 511 keV (each particle's rest mass equivalent) (Figure 2.3).

Positron interaction with an electron could result to any of these forms, either they give two anti-parallel photons, or they form a positronium. Positronium comprises of a single positron and an electron orbiting at a central position of a system. There are two types of positronium, one is ortho-positronium in which the electron and positron spins are parallel and para-positronium where the spins are anti-parallel. Para-positronium decays further to give two anti-parallel 511 keV photons whereas ortho-positronium decays to emit three photons (Zaidi, 2000).

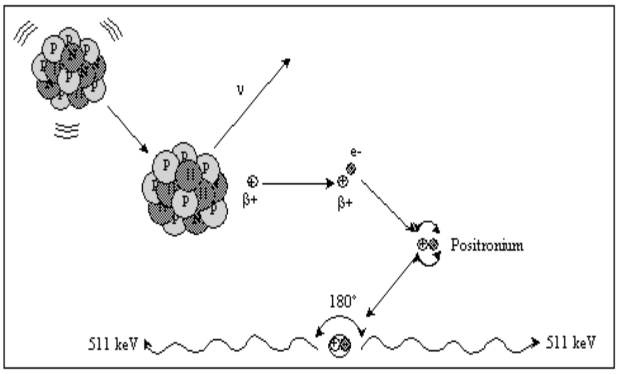


Figure 2.3: Schematic representation of positron emission and annihilation (Zaidi, 2000)

Non-collinearity (Figure 2.4) refers to the slight deviation of annihilation photons from the ideal direction by few tenth of degrees (usually +/- 0.25° with an overall effect of 0.5° on the FWHM). This often happens because the two back-to-back pair of photons are not just stationary rather they are moving at a particular velocity to reach the detectors. This distortion or non-collinearity gets greater with further distance travelled by the photons within the field-of-view of the scanner (Shukla & Utham, 2006).

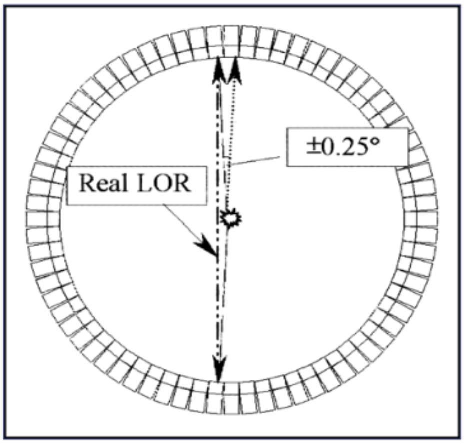


Figure 2.4: Schematic representation of non-collinearity (Shukla & Utham, 2006)

2.3 Photon Interaction with Matter

Photons of electromagnetic radiation undergo a certain form of processes as they pass through matter, which includes, some penetrating the matter without any interaction, some completely absorbed by the matter and some are scattered in several angles, with and without loss of energy. Contrary to photons of charged particles, those from positron-electron annihilation are known to be highly energetic, well-collimated and therefore they tend to be largely absorbed by matter. These nuclear medicine imaging photons are usually involved in three broad processes, namely; coherent (Rayleigh) scattering, photo-electric effect, and Campton (incoherent) scattering. Details are discussed below.

2.3.1 Rayleigh scattering

This is a form of scattering in which an entire atom becomes ionized by an incident photon unlike that seen in Compton scattering whereby only one electron becomes ionized. All the electrons in this atom move in the same direction as a result of the energy released from the photon (Figure 2.5). Note: no electrons ejected from this interaction.

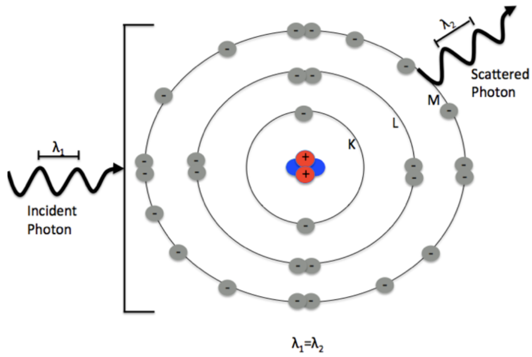


Figure 2.5: Schematic representation of Rayleigh scattering (Imagingkt, 2016)

2.3.2 The photoelectric effect

This is a type of photon-electron interactions that occur in an atom with the photon completely losing its energy, and subsequent ejection of electron from its shell. This effect is achieved when an incoming photon that is having an energy greater than the electron's binding energy, transfers its energy to the electron and removes it from its orbit (Figure 2.6). In this process, the photon is completely absorbed and the electron is now known to be photoelectron. This photoelectron receives energy equal to the energy of the incident photon minus the electron's binding energy. Three things are considered in photoelectric effect, namely; The incident photon's energy (E), Attenuating medium atomic number (Z) and Density of the attenuating medium.

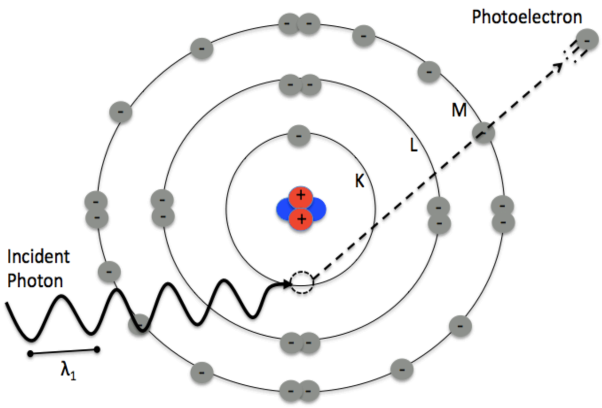


Figure 2.6: Schematic representation of photoelectric effect (Imagingkt, 2016)

A vacant space is left by the ejected electron which becomes occupied by a loosely bound outer electron (Figure 2.7). Such event leads to the emission of energy in the form of characteristic radiation, because each electron level has different binding energy (Radiologykey, 2016).

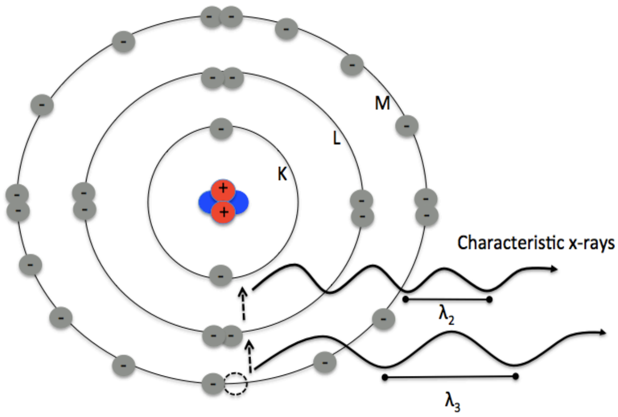


Figure 2.7: Photoelectric effect with X-ray emission (Imagingkt, 2016)

2.3.3 Compton scattering

In Compton interactions, a highly energetic incident photon hits and eject a free electron or loosely bound outer electrons (Figure 2.8). The incident photon changes direction (becomes scattered) and transfers energy to the ejected recoil electron. In this process, there is conservation of both energy and momentum because the scattered photon now has a different energy and wavelength. Note: the transferred energy depends on the number of electrons in the absorbing matter and doesn't depend on the absorbing medium's atomic number. The Compton equation is as follow;

$$E_1 = \frac{E_0}{1+\left(\frac{E_0}{m_0 c^2}\right)\ (1\text{-}\cos\theta)} \tag{2.3}$$

where E_1 represents the scattered photon's energy, E_0 represents the incident photon's energy, m_0 represents the electron's rest mass energy, c^2 represents speed of light and cosθ represent the angle of scattering.

The incident photon's energy and the scattering angle determines the energy gained by the electron or that lost by the photon. As the scattering angle increases, more energy is transferred to the electron. The maximum energy transferred by the photon is observed when the photon is scattered at an angle of 180 degrees (Radiologykey, 2016).

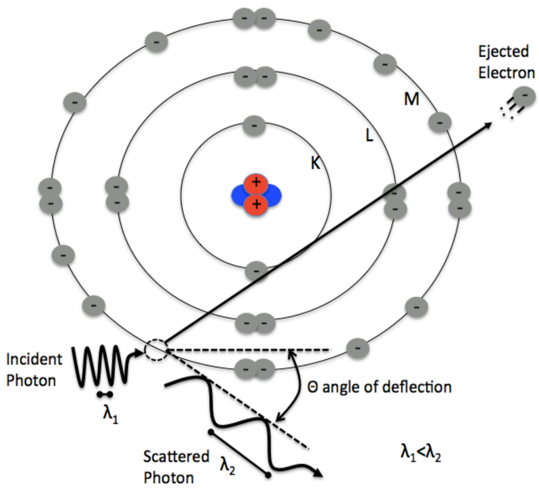


Figure 2.8: Schematic representation of Compton scattering (Imagingkt, 2016)

2.3.4 Pair production

Pair production involves interaction between an incident photon and the nucleus of an atom, alternatively with an orbital electron (in the case of triplet production). This interaction takes place with a high energy (typically greater than 1.02MeV) photon. This energy doubles the electron's rest mass energy, therefore, the interaction results in a transfer of energy to two charged particles, an electron and a positron (Figure 2.9). The energy absorbed by this charged particles is released through ionization and excitation. At rest, positron combines with an electron to produce two photons in opposite direction. These photons are important for nuclear imaging applications. Note: pair production does not occur in X-ray imaging due to the high energy required (Imagingkt, 2016).

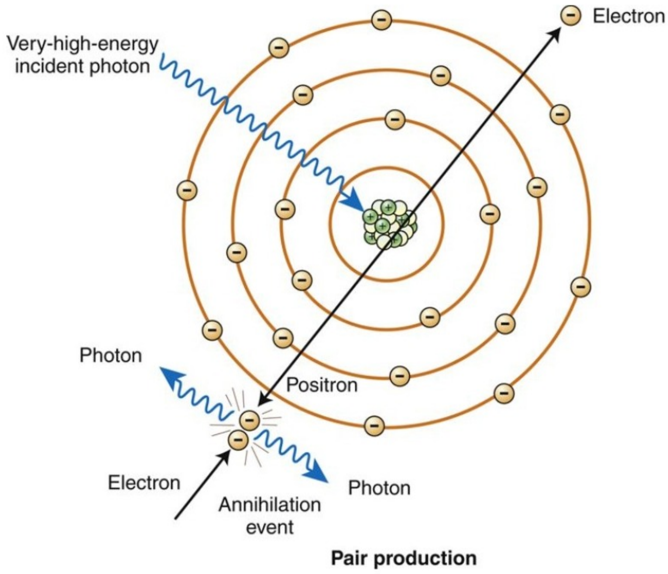


Figure 2.9: Schematic representation of pair production **(**Flickr, 2006)

2.4 Photo-detectors

These are sensing devices that responds to electromagnetic radiation for the purpose of detection and measurement. This is achieved when high energetic photon interacts with the surface of such devices. The main types of photo-detectors are; scintillator detectors, gas-filled detectors and semiconductor detectors. Photo detectors could be used for various purposes such as to measure photon energy, count incoming photons, measure position and arriving time of photons, and also for particle identification. A summary of the different types of photo-detectors is given below.

2.4.1 Gas-filled detectors

They are divided into three namely; Ionization chamber, Proportional counters, and Geiger-Muller counters.

Ionization chamber have been in use for several decades. It is a simple detector which utilizes the produced excitation and ionization of gas molecules when charged particles interact with gas. This photon-gas interaction creates several electron-ion pairs that move in random thermal motion. In the ionization chamber, some sort of collisions occurs between the ions, free electrons and neutral gas molecules. Such collisions include charge transfer as a result of positive ion meeting a neutral molecule leading to the transfer of electron from the neutral molecule to the ion. Another type of collision is recombination, whereby the electron-ion pair try to recombine. This process is stopped by applying an electric field to separate the charge into electron and ion and collecting them on the positive and negative electrode. With strong electric field, all the charges can be collected without loss. Lastly, an electric current called ionization current is measured through. This is the basic principle of DC ion chamber. A simple example of ion chamber is a capacitor with a gas dielectric (Figure 2.10). Inert gas such as argon and xenon are often used to prevent chemical reactions within the gas after ionization.

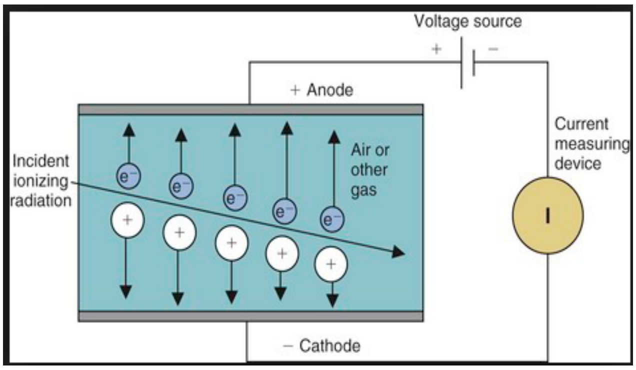


Figure 2.10: Basic principle of gas-filled detectors (Radiologykey, 2016)

When ionizing radiation comes in contact with the gas molecules, electron-ion pair are created. A sufficient electric field is needed to distribute these charges to the plates of the capacitor with the positive plate attracting the electron and negative plate attracting the ion. In the absence of sufficient electric field, a recombination of the charges is likely to occur.

Ion chambers can function in current mode or pulse mode. While operating in current mode, electrons can be obtained as either free electrons or negative ions. Therefore, any filling gas such as air could be used to operate the ion chamber. Whereas pulse mode applications are very limited but sometimes it can be used for fast neutron spectrometry. Ion chamber applications include measurement of gamma ray exposure (Kamal, 2014).

Proportional counters function just like ionization chambers but requires strong electric field. It uses a process called gas multiplication to produce large voltage by multiplying the number of ions produced. The presence of strong electric field makes electrons to have high kinetic energy and therefore can ionize neutral molecules, whereas the ion counterpart gets little energy and low mobility between collision. These pair of electrons are then accelerated to cause further ionizations. The whole of the process takes a cascade form known as Townsend avalanche (Figure 2.11). It is to be noted that in proportional counters, the number of electrons is exponentially increased with distance. These counters are mostly used to differentiate between particle detection and radiation dose measurement. Low efficiency is a major disadvantage of this counters (Kamal, 2014).

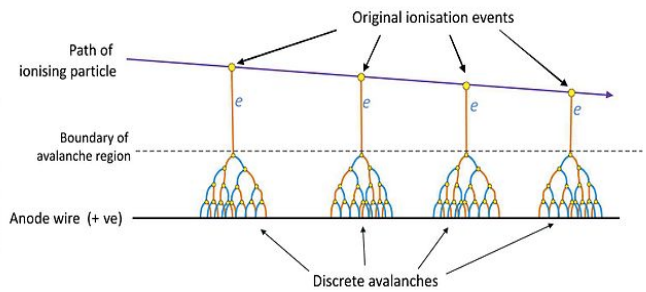


Figure 2.11: Avalanches in proportional counters (“Wikiwand”, 2017)

Geiger-Muller counters are similar to proportional counters but they utilize an electric field strength greater that used by proportional counters. Exponential number of avalanches are produced by these counters which makes them to be used strictly for radiation counting and not for spectroscopy. There is loss of records for the amount of deposited energy by the incident radiation in these counters. Geiger counters are simple and economical radiation counters because they are of low cost and are simple to operate. Their main disadvantage is large dead time, and also, they cannot separate between the time of radiation detection and the energy of the detected radiation. In Townsend avalanche, the excited gas molecules emit photons when they return to their ground state. These photons are likely to be absorbed by the cathode wall or other gas molecules through photoelectric effect. Free electron is created in this process, the electric field inside the detector accelerates this new electron and causes another avalanche. By so doing, Geiger discharge is created (Figure 2.12) leading to a formation of many avalanches throughout the multiplying region that surrounds the anode (Kamal, 2014).

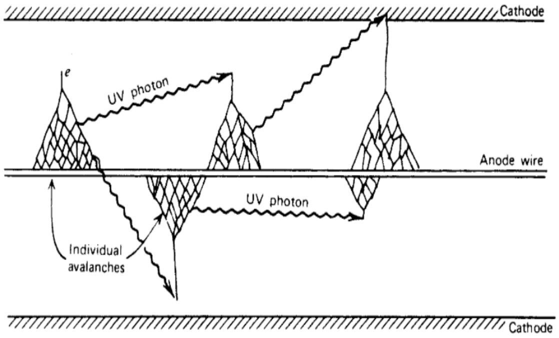


Figure 2.12: Schematic representation of Geiger discharge ("Wikiwand", 2017)

2.4.2 Scintillator detectors

Scintillator detectors are the most widely used radiation detection materials in present day technology. These materials work on the principle of luminescence, a phenomenon whereby a material emits light after being struck by an incoming radiation. The architecture of scintillator detectors (Figure 2.13) is made in such a way that the crystal is attached to a photo sensor (photo-multiplier tubes (PMT) or photo diodes). Incident photons when in contact with the scintillator crystals transfers its energy to the crystal, the crystals absorb the energy and emit it in form of light which is detected by a photosensor attached to the crystal. This light which becomes converted into photoelectrons by the photo-sensors is then amplified at varying potential difference within the photo-sensor and later collected at the anode part of a photo-detector where it becomes transformed into an electric signal (Niki, 2006).

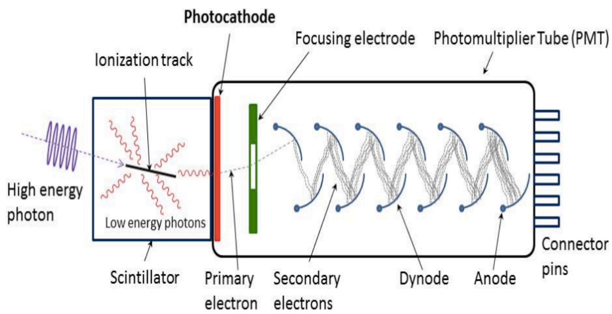


Figure 2.13: Scintillator detector with a scintillation material coupled to a PMT ("Scintillation counter", 2017)

Characteristics of scintillator detectors are as follows:

- Conversion efficiency
- Stopping power

- Light output
- Decay time
- Energy resolution
- Linearity

Conversion efficiency: The number of charged particles converted to light with respect to the absorbed energy of the charged particle. High conversion efficiency is preferred for fast and superior resolution imaging.

Stopping power: Is the ability of the scintillator crystal to attenuate more of the incident photon. It is linearly related to the density and the atomic number of the scintillator crystal. High stopping power is required for good image resolution.

Light output: Number of photons emitted with respect to the energy absorbed by the scintillators. High light output gives good spatial resolution. Light output is linearly related to conversion efficiency of the scintillator material and also to the energy and type of incident photon.

Decay time: Time interval between excitation and decay back to initial state of the atom within the scintillator material that leads to the emission of light. Short decay time is preferred because it makes the detector to handle more event rate. Furthermore, fast decay time enhances fast light production for a better timing resolution.

Energy resolution: This is an intrinsic property of a detector material which gives it the ability to measure the energy of the deposited particle and also to differentiate between radiations of varying energies.

Linearity: This is the ability of the material to give out light equivalent to the charged particle's deposited energy.

Other qualities to be considered are fast operation speed, low cost, non-hygroscopy and durability. Scintillation materials are classified into organic and inorganic materials. Inorganic materials often require an additional dopant such as thallium (Tl) or cerium (Ce) that produce the scintillation light. The inorganic group are characterized with high densities, high stopping power, high effective atomic number and high conversion efficiency for electrons or photons and are therefore the preferred detectors in nuclear imaging applications (Niki, 2006). Example of inorganic materials are; Lu2Y_2SiO5: Ce (lutetium yttrium oxyorthosilicate doped with cerium), Lu_2SiO_5: Ce (lutetium oxyorthosilicate doped with cerium), NaI:Tl (thallium doped sodium iodide), $Bi_4Ge_3O_{12}$ (bismuth germanate), Gd_2SiO_5: Ce (gadolinium oxyorthosilicate doped with cerium) and BaF2 (barium Fluoride). Properties of scintillator material is shown in Table 2.2. Low energy resolution is the major disadvantage of scintillator detectors.

Table 2.2: Properties of scintillator crystals (Junwei et al., 2009)

Properties	**NaI(Tl)**	**BGO**	**GSO**	**LuAP**	**LSO**	**LYSO**
Effective atomic no. (Z)	71	74	59	65	66	60
Attenuation coeff. (cm^{-1})	0.34	0.92	0.62	0.9	0.87	0.86
Density (g/cm^{-3})	3.67	7.13	6.7	8.34	7.4	7.1
Index of refraction	1.85	2.15	1.85	1.95	1.82	1.81
Light output	100	15	30	16	75	75
Peak wavelength(nm)	410	480	430	365	420	420
Decay time (ns)	230	300	65	18	40	41
Hydroscopic	Yes	No	No	No	No	No

2.4.3 Semiconductor detectors

These detectors work base on the same principle as gas-filled detectors. The basic working principle of this detectors is ionization process which occurs as a result of the interaction between the incident photon and the detector material. The interaction causes absorption of photons by the detector material leading to excitation of the valence band electrons. These electrons move to the conduction band, and the valance band is left with an electron-hole pair. As detector material absorbs more energy, an increasing number of electron pairs is created in the valence band of the detector (Knoll, 2010). A Large number of charges are available because of the incident photon's absorbed energy. These charges need be separated and distributed onto the electrodes of the material so that recombination is prevented. Separation is achieved by applying an electric field usually generated by the electrodes of the material. An electric signal is produced afterward which becomes translated by linked electronics (Cherry, 2004).

Two types of semiconductors are available, a N-type and P-type (Figure 2.14). In the N-type, the materials (Si or Ge) which has 4 valence electrons, are doped with group 5 atoms like Boron (B) or Gallium (Ga). As a result, 5 valence electrons are added to the material lattice, of which 4 will be accommodated and one excess electron will be left. The excess electron serves as a negative charge carrier. In the P-type, the materials are doped with group 3 element, this causes a change in the electron-hole. The dopant donates only 3 valence electrons, hence leaving one excess hole. The hole is regarded as positive charge carrier. A p-n junction is formed when the two semiconductor materials are joined. In-between the charge carrier is a neutral region (depletion zone) that serve as the active region in semiconductor detectors.

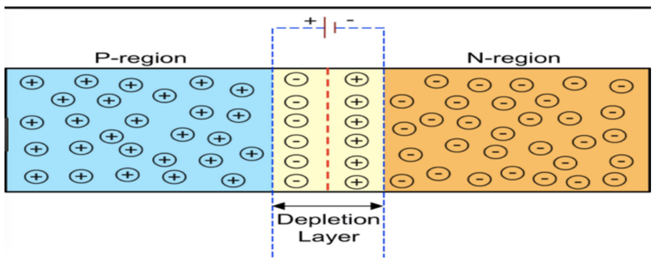


Figure 2.14: Schematic representation of a P-N junction (Cherry, 2004)

An electric field could also be created by reverse bias voltage across the detector, this causes a change in position of the charge carriers in the depletion zone (holes drift from p to n and electron does otherwise). Presence of photons in the material accelerates electrons to the n-region and holes to the p-region, by so doing, an electric field is generated spontaneously.

Semiconductor materials have some known problems which are often created by the bias voltage. They include polarization effect, current leakage and charge trapping (arising from crystal impurities). The major disadvantage of these detectors is low stopping power for 511keV photons and cost. On the other hand, they have good energy resolution (1-4%). For photon detection purpose, the below listed are the most commonly used semiconductor materials with their properties given in Table 2.3.

- Silicon (Si)
- Germanium (Ge)

- Cadmium telluride (CdTe)
- Cadmium zinc telluride (CZT)

Table 2.3: Properties of semiconductor materials (Takahashi and Watanabe, 2000)

Property	Si	Ge	CdTe	CZT
Atomic no. (Z)	14	32	48/52	48/30/52
Density (g/cm^3)	2.33	5.33	5.85	5.81
Band gap at 300K (eV)	1.12	0.663	1.44	1.6
Energy resolution (% at 511keV)	0.1-0.3	0.1-0.3	1	2-3
Electron mobility (cm^2/Vs)	1400	3900	1100	1000
Hole mobility (cm^2/Vs)	450	1900	100	50

2.4.4 Comparison between solid state and scintillator crystals

Solid state crystals:

- They have excellent energy resolution (Avg. 1%)
- They have low atomic number and density ($5.85g/cm^3$), leading to their low quantum detection efficiency for 511keV photons
- They are very expensive

Scintillating crystals

- They have high quantum detection efficiency which is as a result of their large atomic number and density
- They have high light output
- They have fast decay time (short life time of fluorescence)
- They have poor energy resolution (Avg. 10-14%) or higher
- They have good timing resolution
- They are very cheap
- They have high counting rate capabilitie

CHAPTER 3
OVERVIEW OF PET IMAGING TECHNIQUE AND PET IN NUCLEAR MEDICINE

3.1 Annihilation Coincidence Detection

PET is a nuclear imaging technique which involves the use of radiopharmaceutical to provide functional images of the living tissue. A radio-tracer, typically ^{18}F-fluoro-2-deoxy-D-glucose (FDG) is injected into the blood stream, where it travels in the blood stream and by the tissues and cancerous cells. Tumors have higher affinity for glucose than normal healthy cell, therefore they tend to absorb more of the radiotracer. The working principle of PET is based on annihilation coincidence detection, which occurs when the injected radiotracer is subjected to beta-decay and emits a positron (e^+). Positron annihilates mutually with an atomic electron (e^-) to form a positronium which decays and emit a pair of back-to-back 511 keV gamma rays at nearly 180 degrees. These photons are the by-product of the converted rest mass of both positron and electron (Figure 3.1). Prior to annihilation with an electron, the positron travels a small distance (a few mm) depending on its range and energy. The origin of the photons is identified along a line between the PET detectors via simultaneous detections of the two photons. This makes it possible for PET detectors to locate the point where the photons are coming from without the need of a collimator (Cherry, 2012).

The PET scanner is basically a ring of photon detectors surrounding a patient, and it comes with some exclusive integrated circuits that gives it the ability to recognize pairs of annihilation photons. Coincidence detection of a pair of photons by two opposing PET detectors signifies that a decay event happened on a straight line between these detectors. Information obtained from the PET detectors is archived in a computer system inform of sinograms. These sinograms are used to reconstruct positron emitter distribution in 3D format which results to a set of tomographic images (Mikhaylova, 2014).

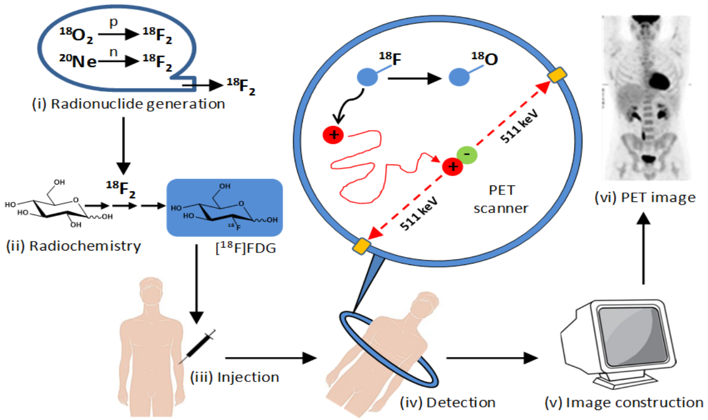


Figure 3.1: PET working principle (Patching, 2015)

3.2 Radiopharmaceuticals in PET

Pharmaceutical refers to any chemical substance designed to be use for diagnosis, treatment, and or prevention of diseases. Radiopharmaceuticals are pharmaceuticals tagged with a radionuclide. In nuclear imaging, these radiopharmaceuticals are used as tracers for the purpose of diagnosis and treatment of several disease conditions. Several tracers are employed in a variety of biochemical, pharmacological and biophysical pharmacological processes in the living organism. Clinical areas to which such tracers are used include; neuroscience cardiology and oncology. Nevertheless, tracers to be used for PET imaging need to meet up with certain criteria such as; high specific activity. The specific activity refers to the reduction in activity of a radionuclide, when a radiopharmaceutical is undergoing chemical synthesis.

Furthermore, tagging of radiopharmaceuticals with radionuclides that has adequate half-life sufficient to examine the selected biologic process, and expectedly to last the same period as the radiopharmaceutical's biological half-life is encouraged. Biologic half-life refers to the time in which the radiopharmaceutical completely leaves the body. Radiopharmaceuticals have different uptake and clearance manners; some their uptake is fast while that of others is slow. Some leave the body earlier while others take longer time. The radionuclide's biologic half-life and physical half-life decides the quantity radioactive decays produced in an area with respect to time. Thus, both parameters ought to be considered when setting the patient radiation dosage. Lastly, Non-toxic radiopharmaceuticals are required so that the patients won't be poisoned.

All radioisotopes from Table 2.1 are used in PET. Another factor to consider when choosing positron emitters for PET exams is the mean energy. Large positron range makes annihilation to occur at a large distance from decay event and this worsens the system's spatial resolution. Radionuclides with short half-life require a cyclotron within the PET environment, whereas those having long half-life present issues regarding disposal and storage. PET radionuclides are required to have physical and chemical properties that makes them suitable for metabolic studies.

Positron emitters like oxygen (^{15}O), nitrogen (^{13}N), and carbon (^{11}C) allow labelling of several organic molecules and this makes them good for use in PET. However, the complexity of the labelled molecules is reduced because of their short half-lives. Likewise, a lot of in- vivo studies is limited with such positron emitters. Another group of positron emitter appropriate for complicated labelling and longstanding biological changes exam due to their relative long half-lives include ^{76}Br with $t_{1/2}$ of 16 hours, or ^{124}I with $t_{1/2}$ of 4.2 days. Flourine-18 (^{18}F, see Table 2.1) happens to be an exception because a great success has been achieved following its use in PET. It has a short positron range which allows it to fit into PET scanners with sub-millimeter spatial resolution. Moreover, its long half-life makes it to be distributed few hundred kilometers away from the production site, rendering cyclotrons needless in the hospitals. FDG is absorbed by cells with high affinity for sugar like cancer cells, kidney, and brain. Among the existing radiopharmaceuticals, it is the most effective one. It is a single tracer with varieties of use such as in brain metabolism study, cardiac function, and cancer detection (Mikhaylova, 2014).

3.3 Acquisition Modes

This section talks about the forms of data acquisition in a PET scanner. The previous section mentioned that PET imaging relies of annihilation coincidence detection of two 511keV gamma photons. There are three ways in which the detected events can be acquired namely: the list mode, frame mode and gated imaging. Different coincidence logics are used in each scanner operation mode.

In list-mode acquisition, there is digitization of information regarding detected events. But sorting of this information into an image grid doesn't occur immediately. The information comprises of energy, coordinates, arriving time of individual event etc. Additional information could be possibly added such as patient movement or position. In this mode data acquisition occurs prior to the coincidence searching and retrospective framing is allowed. In data analysis, this method provides greater simplicity. Nevertheless, it lacks adequate memory usage for conventional imaging acquisition.

For frame-mode acquisition, position signals of individual events are digitized followed by sorting into the right x-y locations inside the digital image matrix. The image data acquisition is halted and the pixel values are saved in the computer storage following an elapsed preset time or following a preset recorded number of counts. A frame refers to an individual image obtained is a series of sequences. Prior to the acquisition process, the image matrix size must be specified.

For gate imaging mode, information is gained simultaneously with the respiratory cycle or pulse. By so-doing, all images are obtained in the meantime amid the movement cycle (Cradduck and Busemann-Sokole, 1985).

3.4 Two-Dimensional (2-D) and Three- Dimensional (3-D) Data Acquisition

2-D data acquisition simply describes a method which is controlled by the action of a septa on the incoming photons. Right from the beginning of its introduction into nuclear medicine, PET designs are made in such a way to accommodate collimators of tungsten or lead materials between detector rings. Presence of such collimators makes incoming photons parallel to the detector to be detected and scattered photons becomes attenuated by the collimator. The septa are also known to minimize single-channel counting rate, as a result random rate are lowered with the true coincidence left to be recorded. The sensitivity of 2-D acquisition can be improved by connecting pairs of detectors in two adjacent rings in a coincidence circuit.

3-D acquisitions were introduced to improve the sensitivity of PET scanners which was achieved by eliminating the collimators, and acquisition occurs via line of responses (LOR). Compared to 2-D mode, 3-D leads to an increase in sensitivity by a factor of 4 and above. The sensitivity in 3-D mode happens to be high at the center than at the periphery. Full 3-D reconstruction are also done for images from 3-D acquisition mode. Lastly, due to the high sensitivity observed in the 3-D mode, it has now become globally used in state-of-the-art PET systems (Lodge et al., 2006).

3.5 Classification of Detected Events

A valid event must satisfy the following conditions;

- A pair of photons is detected within an established coincidence time window.
- The formed LOR by both photons should be inside a valid acceptance angle of the system.
- The photon energy deposited on the crystal falls inside the chosen energy window.

Events which meet up with the above-mentioned conditions are called prompt events (or “prompts”). Nevertheless, due to photon scattering or coincidence arising from random detection of photon pairs of unrelated annihilation, some of the prompt events become undesired events (Bailey et al., 2005).

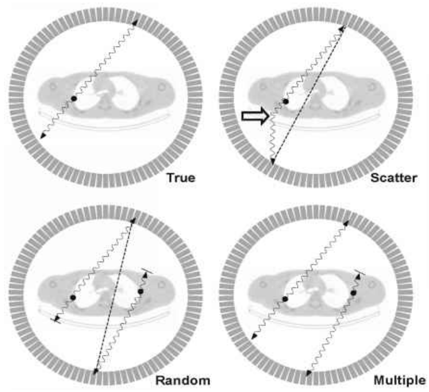


Figure 3.2: Detected events in PET. Dotted lines in the scatter and random events indicate miss-assigned LOR (Bailey et al., 2005)

Description of terms used in PET detected events

True coincidence: This type of event occurs when both annihilated photons coming from the same event arrive at the opposing detectors in a specified time window.

Random coincidence: This event occurs when two different annihilation takes place, giving rise to four photons of which only two (one from each annihilation) are able to arrive the detector and be identified as if they are from the same annihilation. The other two photons are lost. Image artefact and contrast depreciation are noticed when a random event occur.

Multiple (or triple): This involves the detection of three events arising from two annihilations. It often occurs at high count rate whereby more than one detector becomes activated. Multiple events are usually not considered because you can't tell the photons arising from same annihilation.

Scattered events: This usually occur when one or both photons undergoes Compton scattering before being detected. The scattering is often due to a weak photon energy (less than 511 keV). As a result, a false line of response is assigned between the detectors which doesn't correspond to the origin of the annihilation. Causes of scattering include the gantry, patient, and the detector.

3.6 Reconstruction Techniques in Tomographic Imaging

3.6.1 Line of response, projections, and sinograms

Line of response (LOR): This is a line that connects two detectors involved in a coincidence detection of annihilation photons. This line gives an idea of the point where an event took place.

Projection: This is defined as a group of lines of response registered over a detector at a certain angle.

Sinograms: Matrix of projections from several angles. The word sinogram originate from the sine curve shape produced by a point source object placed in a particular position (Figure 3.3).

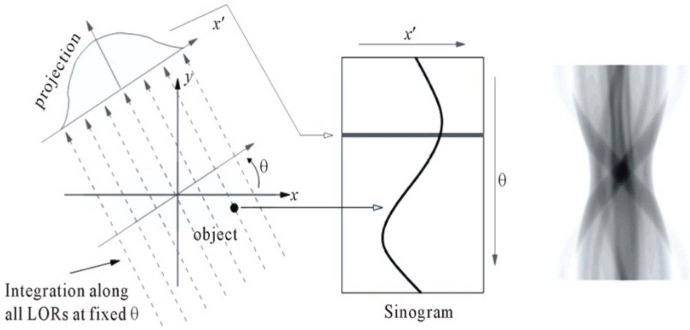


Figure 3.3: 2-D display of projection sets called sinogram (Asl & Sadremomtaz, 2013)

PET coincidence events are often saved as sinogram. These sinograms form the background of image reconstruction in medical imaging.

The combination of PET systems with image reconstruction algorithms are the reason for their success in nuclear imaging, following the production of a 3-D map of radiotracer distribution within the patient. The 3-D images obtained from PET is formed from stacked 2-D reconstructed sections of the object. This image acquisition pattern is termed as tomographic imaging.

Several image reconstruction algorithms exist, which are either analytic or iterative methods. They include Filtered back projection (FBP), Maximum-likelihood expectation-maximization (ML-EM) algorithm, Ordered subset expectation maximization (OSEM), List-mode OSEM (LM-OSEM), and Origin ensemble (OE) algorithms. A brief explanation of these algorithms is given below.

3.6.2 Filtered back projection (FBP)

This is a very fast image reconstruction method due to its analytic nature. It is easy to use in the control of noise correlations and spatial resolution in the reconstruction. It employs projection slice theorem in combination to back projection, in such a way to eliminate image blurring. It works like Fourier transformation but with an addition of a ramp filter before performing the conventional back-projection. The FBP is designed to overcome the limitation of conventional back projection method (Maligs, 2017). The basic steps are shown in Figure 3.4.

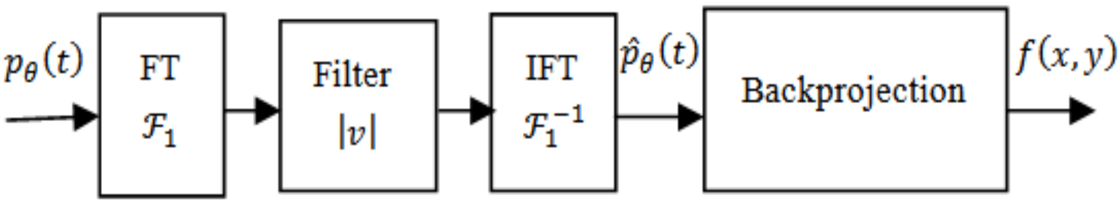


Figure 3.4: FBP concept (Maligs, 2017)

Where Pθ represent the detector function, and is the projection measured along all lines of response at an angle θ. *f(x,y)* represent a 2D object which is defined by the function *(f)*.

First, the image undergoes 1-D Fourier transform (FT), so that filter can be applied to the FT profile. The next step is to compute the inverse FT of each FT profile, by so doing filtered projection profiles are acquired. Lastly, using the filtered profiles, a back projection is performed (Kinahan, Defrise, and Clackdoyle, 2004).

3.6.3 Ordered subset expectation maximization and maximum likelihood expectation maximization (OSEM and MLEM)

These methods are being employed into medical imaging field due to the mass improvement in the processing speed of computer systems. Advantages of such methods include minimized sensitivity to detector imperfections.

The methods involve making an initial image estimate, e.g. a uniform or blank image followed by computation of projections from the image estimate via a process known as forward projection. To achieve this, the intensities along the path of the photons is summed for all the projections through the estimated image. Later on, a comparison is made between the measured and estimated projections. If any difference is observed, then corrections are made to upgrade the estimated image. Convergence between the two projections is evaluated by performing a new iteration. The whole step is repeated several times and solution is achieved through image estimate convergence. Both methods have a lot of similarities and they are the most widely used image reconstruction techniques nowadays.

OSEM was introduced to reduce the reconstruction time of MLEM. It uses subsets of the complete set of data for every image update. Non-overlapping subset is one of the approaches it uses to divide the projection space into subsets. Out of all the subsets, only the projections in a single subset are summed by the back-projection steps. Therefore, image update is done after each sub-iteration. When only one iteration is done, then OSEM is exactly the same as ML-EM (Alessio and Kinahan, 2006).

MLEM is mostly applied to solve incomplete data problems. It is very effective in finding the maximum likelihood estimate. Although this method has advantages like predictable and consistent convergence manner, it also has drawbacks like very noisy images. To solve this, the algorithm is stopped before convergence. In addition to the previous solution, noise suppression is done by smooth filter application on the reconstructed image. The second drawback is its slow convergence. It typically requires many iterations. When compared to FBP, MLEM takes more computation time (Tong et al., 2010).

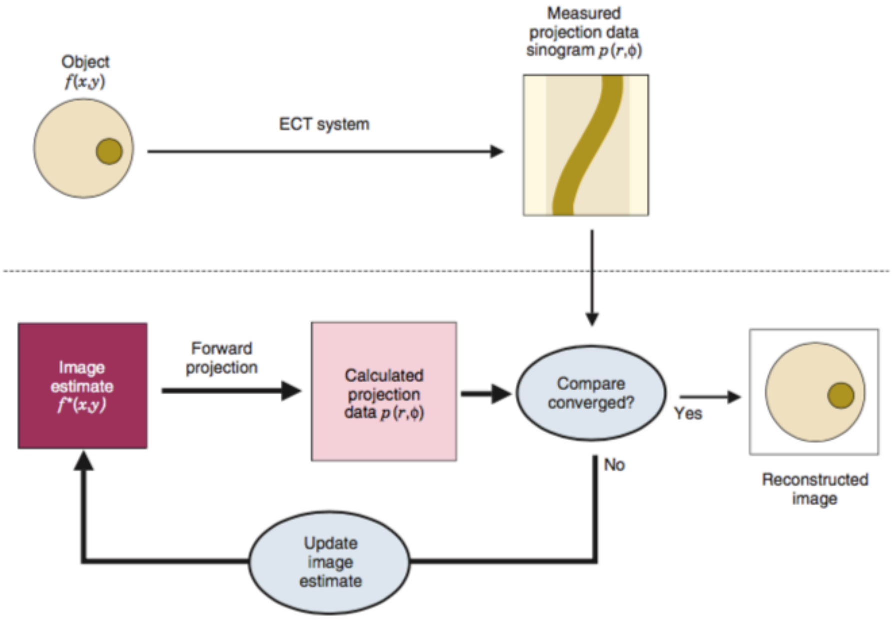


Figure 3.5: Schematic illustration of the steps in iterative reconstruction (Cherry, 2012)

3.6.4 Origin ensemble (OE)

This method is fast converging and its execution is straightforward. It doesn't depend on the number of channels. The initial step involves assigning a random position on the LOR of each event and at each FOV voxel location, the density matrix saves the number of events. During iteration, each event undergoes several steps such as; assigning a new location, accepting the new location with a probability P, and lastly comparing the density at the new location with that at the old. The density matrix is updated immediately when a new event position is accepted, prior to the next event. Several trial runs have to be run because of the stochastic nature of the algorithm and the mean of the trial runs is considered as the final result (Kolstein et al., 2013).

3.6.5 List mode-ordered subset expectation maximization (LM-OSEM)

List-mode (LM) is similar to OSEM only that it uses list mode format of data presentation. There is a replacement of detector bins by detected events in the iterative update function. Nevertheless, because of the numerous pixels in the scanner FOV which are likely to contribute to a specific detected event, this method results in slow convergence and also consume a lot of time (Kolstein et al., 2013).

3.7 Parameters affecting Image Quality

Image quality is the term referring to the accuracy of a reconstructed image of an object with respect to the original object being imaged. Features include:

- Spatial resolution
- Image contrast
- Image noise

Spatial resolution: The ability to differentiate between two closely related objects. It is also related to the number of pixels used to produce a digital image given rise to a sharp image.
Image contrast: This is the intensity variations between areas of an imaged object that has different radioactive uptake.
Image noise: This could be described as the random statistical variations in counting rate, that lead to a spotty appearance on the final image (random noise) or the non-random variations in counting rate that overlap on and obstruct the structures of the object of interest (structured noise).
Factors contributing to the final image quality will be classified into three broad groups: Detector related limitations, intrinsic limitations, and limitations from other sources. Below is a brief review of the above-mentioned factors.

3.7.1 Limitations accompanying detectors

a. Spatial resolution

This can be improved by reducing the pixel size of the elements. An error R_{det} often observed at the center of the detector is d/2 whereas at the edge is d. Therefore, the SR is greatest at the CFOV and slightly decreases towards the periphery. A very fine detector pixelation is needed for good SR to be achieved.
Another detector-related error is parallax or depth-of-interaction effect (DOI). The DOI tells us the exact point of photon-detector interaction (exact point of energy deposition). This type of error occurs when a photon enters the detector element at a slight oblique angle leading to a mismatch between the true and measured line of response because the exact position of interaction is unknown. This effect is mostly noticed in detectors where the distance between opposing detector elements is very small like organ dedicated scanners or where the

annihilation occurs very close to the edge of PET in a circular geometry. Figure 3.6 shows depth of interaction effect. The error become worsen with increasing depth of individual detector, thus the error is minimized using thin crystal with high stopping power (Braem et al., 2004). PET systems with larger diameter are less likely to have parallax error compared to organ dedicated systems, because the photons from annihilation will be more on the central region with less oblique deviation.

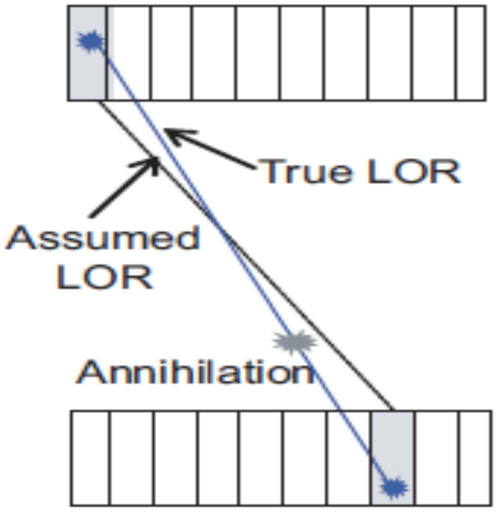


Figure 3.6: Depth of interaction effect (Martins, 2015)

3.7.2 Physics related limitations

a. Spatial resolution

Here, finite positron range is a contributing factor to the limitations of image quality produced by PET systems. The positron range relies on two factors, its energy of emission and the composition of neighboring matter. These two factors make it present some uncertainties with regards to the position where the nuclide decay takes place, leading to a reduction in spatial resolution (Levin et al., 1999). The greatest distance covered by a positron without being scattered and moves on a straight path till the end of its range is known as Actual positron range whereas the mean distance covered from the emitting nucleus to the end of the positron range is known as Effective positron range (R_p) (Figure 3.7). Annihilation photons non-collinearity is another limitation, which is as a result of the remaining energy of the positron at the time of annihilation. This non-collinearity adds up to the uncertainty in locating the annihilation point and therefore, reduce the system's spatial resolution. This effect is most noticeable in systems with larger diameter.

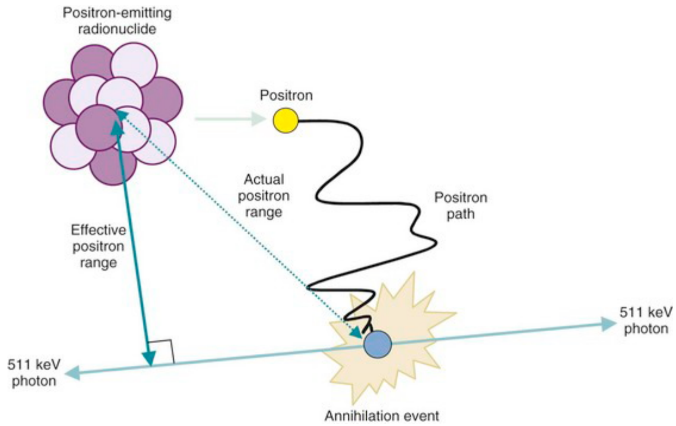


Figure 3.7: Effective and actual positron range ("Positron emission tomography", 2017)

3.7.3 Limitations from other sources

a. Spatial resolution

Factors such as patient motion, reconstruction method, and pixelization effect in the image worsen the system's spatial resolution. The filters used in image reconstruction sometimes results in further degradation of the spatial resolution. Patient motion which include cardiac or breathing-related also affects the final image sharpness. In order to minimize blurring caused by respiratory motion, mechanisms such as breath-holding and special breathing techniques are used. Sometimes, little of patient motion can be solved via special correction algorithms. Pixelation effect usually occur on the reconstruction image, whereby the resolution of the image is being affected by the size of the pixels used to create the image. In a situation whereby, the pixel size happens to be larger than 1/3 of the expected system's spatial resolution, then the image will suffer from loss of details. It should be worthy of note that, smaller pixel size lead to high signal-to-noise ratio (SNR) of the individual pixel.

b. Contrast

High contrast images are being influenced by radiopharmaceutical with high lesion-to-background uptake. Factors like background counting rates which results from sources like random, multiple and scatter could limit the contrast. Contrast is also affected by the number of count density (number of collected coincidences). A noise is usually observed in the image when the count density is small, therefore in order to obtain excellent image contrast certain number of counts must be reached. The required number of coincidences is determined by the organ uptake, dose of radiopharmaceutical administered, the scanner's quantum detection efficiency and the screening time. Another factor that can affect the image contrast is the lesion size with respect to the neighboring tissue and system's spatial resolution. To be more specific, it considers if an activity exists in the lesion (hot) or not (cold). Cold lesions often disappear in higher activity background tissues whereas hot lesions receive high contrast relative to low background.

c. Image noise

Image noise results from varying pixel counts across the image. Most of the parameters affecting the image contrast, affects image noise as well. They include background counting rate and non-uniformity of the imaging system. Increasing the number of total counts in the image is a good solution. But in order to achieve this, certain things need to be done including the use of longer scan time, use of high quantity of radiopharmaceutical and improving the detection efficiency of the scanner. These solutions can affect the patient in a negative way, and can also increase the dead time losses and random coincidence. Therefore, they are not preferred. Noise can be minimized by increasing the noise equivalent count rate (NECR). Noise level assessment can be done by calculating the SNR or contrast-to-noise ratio (CNR. Noise can also arise from the imaging procedure or from the imaging device. For example, an uptake by a particular organ may obscure the lesions in tissues close to it. Artifacts from image reconstruction could also appear as noise in the final image.

3.8 Image Artifacts and Corrective Measures

Photons undergo certain processes such as Compton scattering, photoelectric interaction, pair production, and Rayleigh as they pass through matter and these effects need to be corrected when reconstructing high quality images.

3.8.1 Data normalization

This simply refers to the correction of effects arising from spectral non-uniformities and detector efficiency. Certain factors including detector sensitivity usually varies in a PET scanner. This happens because photons are emitted at different incidence angle, and the detecting medium size varies. Therefore, a non-uniformity in the obtained raw data exist (Badawi and Marsden, 1999). Normalization can simply be achieved by subjecting all detector pairs to same radiation source and recording the number of counts registered by each detector pair. In order to perform this, a blank scan can be done with a source made of water placed inside the FOV of the scanner, and collecting data in either 2D or 3D modes.

3.8.2 Attenuation correction

Attenuation of photons in tissue is one factor that minimizes image quality and the measured effectivity of PET systems (Zaidi and Hasegawa, 2003). Therefore, attenuation corrections need to be done. Photons emerging from the central region of an object happens to be more attenuated than those coming from the periphery of that same object. Non-uniformities from such process is observed due to the reason that most of the coincidence events coming from the center of the object are lost. Thus, a correction is needed for the photon attenuation in that tissue. Methods of attenuation correction include Chang's multiplicative and transmission method (Zaidi and Hasegawa, 2003).

3.8.3 Random coincidences correction

Random coincidences cause artifacts on the final image. Parameters like increased coincidence time window, energy window width and activity make the random coincidence to increase. Reducing the coincidence time window could help reduce the random coincidences. Yet, such window needs to be wide enough in order to accommodate the true coincidences because of the variations in arrival times. Therefore, there is a compromise between minimizing loss of sensitivity for true coincidence and minimizing the acceptance of random coincidences. Methods for random corrections include delayed window method. For dual-head coincidence (DHC) cameras, an alternative method is detector shielding from activity lying outside the FOV of the scanner (Sossi et al., 2000).

3.8.4 Correction for scattered coincidence

Scattering affects, the quality of an image via producing a fog background on the reconstructed image, mostly seen on the central region of the image. Scattering is influenced by the depth and density of body tissue, the activity within the patient, the energy window width and the density of the detecting material of the PET scanner. PET systems usually have high scatter fraction ranging from 10-15% and even up to 40%, mostly seen in 3D mode of scanning where no septa are used. In order to correct for the scatters, a method which involves taking the counts outside the FOV where no true coincidences are expected is employed. The outside counts take in both scattered and randoms, therefore, scattering counts will be left after correcting for randoms. Afterwards, signal intensity is measured and fit to 1-D Gaussian to obtain the corrected image (Cherry and Huang, 1995).

3.8.5 Dead time losses correction and pile-up

The pulse pile-up events refer to a situation whereby the energies of two or more photons get summed when they arrive concurrently. Should these events undergo Compton scattering, their resultant peak is likely to be within the energy acceptance window. These two unrelated events make the event to be counted but wrongly positioned. Image distortion is caused by high count rates and pile-up events.

The dead time refers to a time in which a second event cannot be registered and processed by the PET system, thus it becomes a lost event (Knoll, 2010). Pile-up and dead time effects completely eliminates the relationship between registered coincidence events and the total activity within the FOV. Therefore, at high count rate, there will be a minimized radioactivity concentration.

Sources of dead time include integration time, analogue to digital conversion time and data transmission speed (Bailey et al., 2005).

3.8.6 Image artifact: partial-volume effect

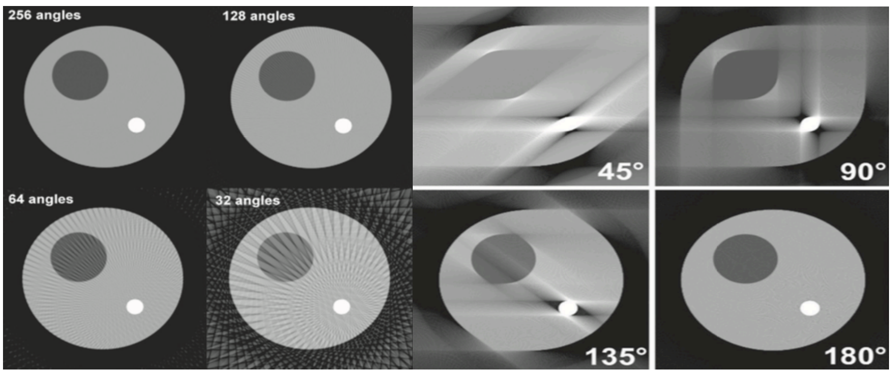
Small structures and regions are usually faced with a diminishing activity due to the limit in spatial resolution of imaging systems. This condition happens in medical imaging particularly in PET and SPECT. In a situation whereby, the region or structure to be imaged is smaller than twice the FWHM resolution in the X-Y- and Z- dimension of the imaging system, the apparent activity of such region or object becomes lower. Systems with higher resolution are able to minimize this effect because they resolve the tissues excellently. This loss of activity arising from the scanners is known as partial-volume effect (Hoffman, Huang & Phelps, 1979). This effect leads to a reduction in contrast among high and low uptake regions.

Recovery coefficient (RC) can be applied to eliminate the partial volume effect. Sometimes, an effect called spill over is noticed in certain scenarios in which an object of interest contains an activity that is low compared to the neighboring structures. The activity from the surrounding structures then spill over onto the object of interest.

3.8.7 Reconstruction related image artifacts

The traditional image reconstruction method (FBP) also creates some artifacts. Conditions such as wrongly choosing the cut-off frequency of the low pass filter and the angular and linear sampling intervals causes the appearance of such artifacts.

For example: Aliasing occurs when too few angular views are used, most noticeable toward the periphery of the image. Filling the sampling requirement is needed to avoid such condition (Cherry, 2003). Ring artifacts are also another set of artifacts that can appear during the reconstruction. They are usually caused by applying a low-pass filter to the FT data. Filters with different parameters can be used to avoid these artifacts (Bracewell, 2000).



(a) (b)

Figure 3.8: Artifacts due to image reconstruction. (a) Number of angular samples effect (b) Angular sampling range effect (Cherry, 2003)

3.9 Nuclear Medicine Imaging (PET)

3.9.1 PET brief history

In the early 1950s, the incorporation of positron emitting isotopes into molecular imaging was recommended for better detection efficiency. This is due to the fact that they could perform better than the traditional techniques employing isotopes that emit a single photon e.g SPECT.

In 1950, Gordon L. Brownell gave the direction to design the first prototype of PET scanner employing two opposite NaI detectors coupled to a PMT. This system uses coincidence detection mechanism and was built within six months in the physics laboratory of Massachusetts General Hospital. Afterwards, brain tumor screening was done with the device, and in 1951 the results were published. In that particular year, an independent exam on annihilation radiation detection was performed and published by Good, Handler and Wrenn. In 1953, an attempt into 3-D data recording was done.

Figure 3.9: First clinical PET **(“**First clinical positron imaging device”, 2017)

In 1952, the first clinical PET device was built (Figure 3.9). It was based on the same concept with that produced in 1950 but it included some transformations. Low resolution images were obtained with such device but it had the sensitivity to suggest the existence of a tumor.

In the middle 1960s, another commercial prototype was developed and the results were published in 1968. This system was a brain dedicated scanner used in the hospital for almost 10years.

The first tomographic imaging PET device known as PC-1 (Figure 3.10) was designed in 1968 and finished in 1969. Tested in 1971 and reports were available in 1972.

David Chesler (1970) designed and tested the FBP through computer simulation. This algorithm was used on the data from PC-1.

In 1971-1976, an improved version of PC-1 the so-called PC-11 was constructed. It employs a rotate-translate mechanism.

In 1973 and 1975, a proposal of systems with ring mechanism was published. They employ several detectors coupled to small PMTs so that good quality images will be reconstructed by means of increasing the number of sampling.

Nowadays, there are several research areas which focus on improving PET systems to achieve high sensitivity and spatial resolution. These areas include scanner geometries, detector materials, image reconstruction techniques and radiopharmaceuticals.

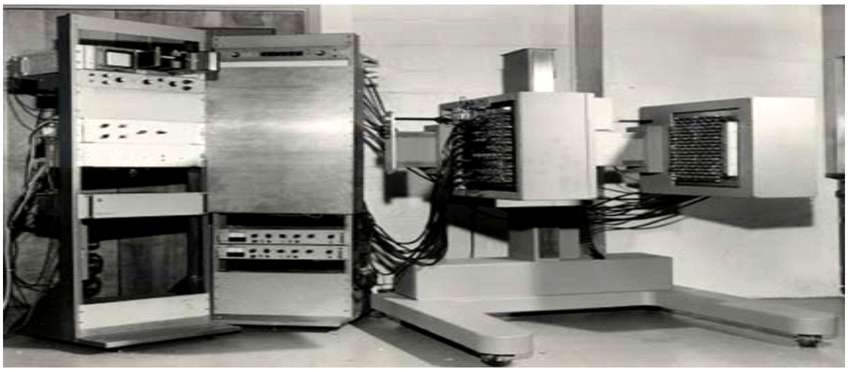


Figure 3.10: First tomographic imaging PET device PC-1 **(**"First clinical positron imaging device", 2017)

3.9.2 State of the art PET scanners

Modern day systems use scintillator detectors due to their low cost and good stopping power. The crystals are arranged in block manner and they are pixelated via mechanical pixelation into smaller elements coupled to PMT (Figure 3.11). An opaque reflective material is used to fill the channels between the elements, this restrict the optical spill over between elements and enhance sharing of light among the PMTs.

Spatial resolution of the scanners is determined by the width of the detector elements and is 3 to 5 mm in modern PET scanners. Very good SNR is achieved through the use of PMTs for low light levels. On the other hand, their disadvantage is low efficiency in emission. Another disadvantage is that as a scintillator photon deposit its energy, a photo-electron escapes from the cathode part of the PMT.

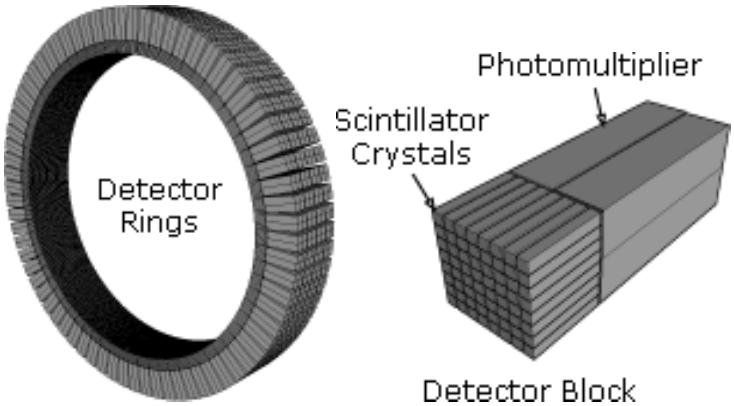


Figure 3.11: Typical geometry of modern PET systems (Valk et al., 2011)

An improvement was made to the PMT used in the scanner, a system known as quadrant sharing where by it covers four quadrants of four detector elements. This is done in order to minimize the number of PMTs used in the scanner. The spatial resolution of such designs is improved, because it allows smaller crystals to be used. Yet, it has a drawback related to dead time because signals from large number of PMT needs to be analyzed.

Good spatial resolution together with short dead time can be achieved by using one-to-one coupling, that is, a single crystal attached to an individual photo-detector. Secondly, small crystals can be coupled to each channel of a Multi-Channel PMT (MC-PMT) or Position Sensitive PMT (PS-PMT).

Instead of PMTs, Avalanche Photo Diodes (APDs) could be an option. The APDs improve SNR by providing an internal amplification of the signal. They can also be employed in hybrid PET/MRI systems because they are not affected by strong magnetic field.

Furthermore, Silicon photomultipliers (SiPMs) can also be used. The SiPMs have ability for input signal amplification (high gain), fast response and low bias voltage. Therefore, they are also good substitute to traditional PMTs.

3.10 PET Clinical Applications

PET plus FDG are used for cancer diagnosis which include the lung, breast, brain etc. They are also used to diagnose brain diseases like Alzheimer's disease, Parkinson's disease and epilepsy. Furthermore, PET has recorded a great success in the diagnosis of cardiovascular diseases and also to determine the extent of damage done to the heart muscles. They can also be used to measure blood circulation.

3.11 PET in Research

Some PET systems design and development are not meant to be used in clinical applications, rather for research purpose. They are the pre-clinical or small-animal PETs characterized by a small FOV, better image quality, high sensitivity, and lower cost. They have certain advantages such as study of disease model and evaluation of radiotracers in animal models. Studies involving animal models permits the development of new radiotracers and assessment of new pharmaceuticals. In order to model human disease and understand mammalian biology, the mouse is a suitable agent. The physiology and genes of mice are similar to that of humans. Furthermore, the rapid reproduction rate of mouse makes the studies more economical, plus mouse colonies maintenance is cheap. Rat models are important in neuroscience because the large rat brain gives ease in surgical procedures, and also during anatomical and developmental studies. Features of Pre-clinical PET systems include narrow timing window, random coincidences minimization, small FOV, high sensitivity and spatial resolution, limited random and scattered coincidences.

3.12 Future PET Generations

Nowadays, developmental trend in PET include: Time-of-fight (TOF) PET, Hybrid imaging (PET/MRI, PET/CT, SPECT/CT) and Semiconductor-based PET systems.

3.12.1 TOF PET

With TOF PET, one can easily locate the position of annihilation without necessarily reconstructing multiple line of responses. This is possible because TOF utilizes the arrival times of annihilation photons and assign greater weight on the photon that arrives first. The difference in arrival times help to identify the point of annihilation between the two detectors.

Annihilation photons need a time in order of hundreds of picoseconds to reach the detector, this timing is far below the timing resolution of available scanners. Scanners that employ fast crystals have the ability to locate the annihilation event along a line section other than the full line. These scanners are referred to as TOF PETs. Improved SNR is an advantage of such systems because annihilation point is estimated rather than gotten from reconstructed images which suffers from noise propagation.

3.12.2 Hybrid imaging

Hybrid imaging is a new technology in the field of nuclear medicine, it involves a combination of a nuclear device and a radiology device using special software. For instance, PET/MRI is a form of hybrid imaging technique that fuses PET and MRI. During a single imaging session, structural and functional information of cells, tissues, as well as information about blood flows in the body could be revealed. Combination of such systems provide both anatomical and metabolic images of diagnostic importance (Harberts & Helvoort, 2014).

PET/CT is a form of hybridization in nuclear medicine that combines CT and PET scanner. In this system, the functional images obtained from PET can be combined with anatomical image from CT scan. A radioactive substance is injected into the patient's body just as explained earlier. After uptake period, the patient is placed on the PET/CT bed. Scanning starts from the CT component of the machine to acquire x-ray tomogram and then subsequently to the PET component to acquire metabolic images. Advantages of these systems are that a better localization and metabolic activity could be determined. Lastly, the acquired data are fused together to form PET/CT image (Beyer et al., 2000).

SPECT/CT is a form of hybrid imaging technique which allows the fusion of structural and functional information. With the aid of SPECT/CT, tumor or lesion localization is enhanced due to the combination of functional image and anatomical image. The sensitivity as well as the specificity of findings is improved by the addition of anatomic information (Andreas et al., 2008).

3.12.3 Semiconductor-based PET systems

These systems use semiconductor crystals like CZT or CdTe unlike the conventional systems based on scintillator crystals. The use of semiconductor crystals provides excellent energy resolution. Few examples of the systems employing this crystal are the dedicated cardiac SPECT scanners developed by Digirad corporation and Spectrum dynamics Israel, and the small animal SPECT systems developed by Gamma Medica and GE healthcare.

CHAPTER 4
SYSTEM SPECIFICATIONS, SIMULATION, AND PERFORMANCE EVALUATION OF THE SCANNER

4.1 System Specifications

This system has a unique specification from other existing scanners. This is done in order to produce a device that is capable of performing excellently at a lower cost. The systems geometry is cylindrical in shape, made from a single module that was highly pixelated and then repeated to obtain a complete ring of detectors. Overcoming certain limitations of scintillator crystals such as large parallax error due to deficiency in information from the depth of interaction (DOI) and poor energy resolution were also put into consideration while simulating the scanner. Some key features of the system include high geometric efficiency from the scintillation crystal used and highly pixelated crystal which results in high intrinsic spatial resolution.

This PEM design can be employed on different types of PEM scanners, whether a small-animal, a whole-body and even a PEM scanner. The design implemented here is dedicated to human brain because of the pathologies associated with the brain and the challenges faced while examining the human brain. It allows scattered events arising from the human skull (high density material in the FOV) to suppressed, of which their presence leads to noisy images and low contrast.

The PEM scanner (Figure 4.1) has a single ring of detector module made from 20×105 mm^2 LSO scintillator crystal material. The surface area and thickness of the individual pixels are 1×1 mm^2 and 10 mm respectively. Each module is highly pixelated into 2,100 channels of $1 \times 1 \times 10$ mm^3. The module was then repeated 14 times to make a complete cylindrical PEM system with 29,400 detector voxels.

The whole detector module faces the center of the cylinder with its active part, thereby allowing 511keV photons to enter from the edge of the crystal. The superb density of LYSO crystal gives it a superior stopping power over other scintillator crystals. The complete scanner has 90 transaxial field of view (FOV) and 105 mm FOV. The system specifications are shown in Table 4.1.

Table 4.1: System specifications

Geometry Design	
Detector size (mm^3)	20 x 10 x 105
Detector voxel size (mm^3)	1 x 1 x 10
Number of detector modules	14
Trans-axial FOV (mm)	90
Axial FOV (mm)	105
Crystal	LSO

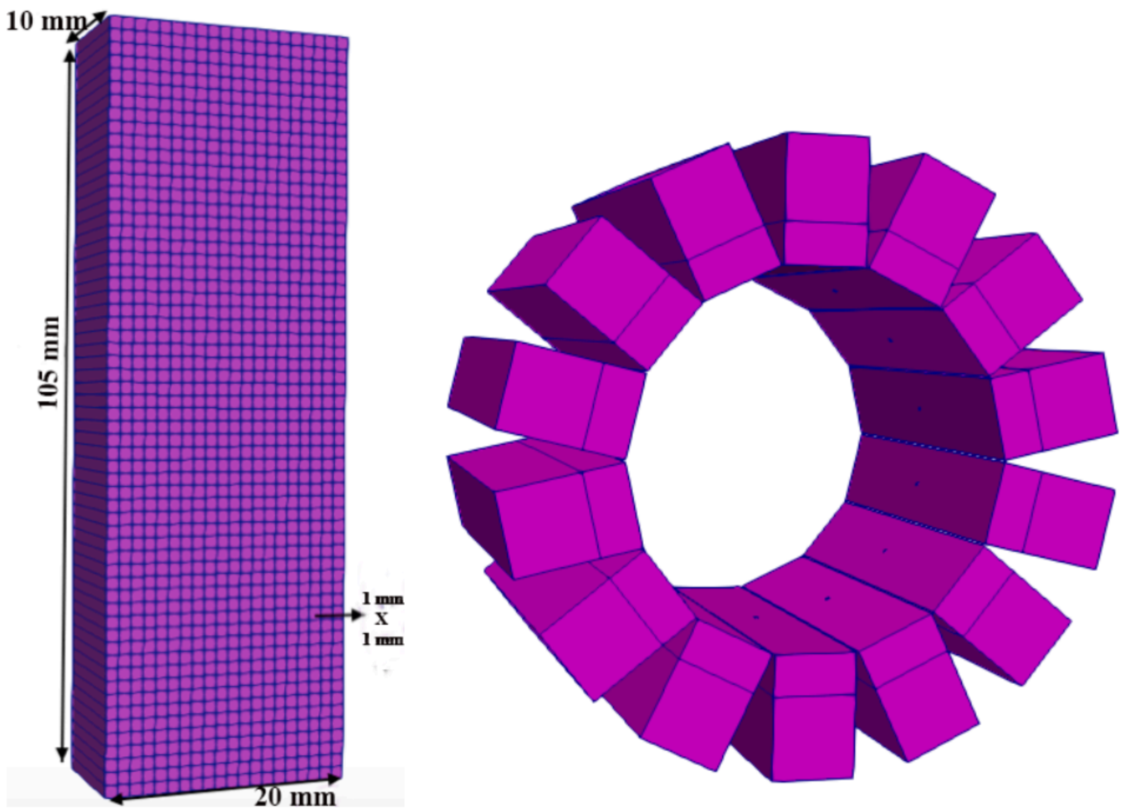


Figure 4.1: GATE render images of module and cylindrical PEM

4.1.1 Advantages and disadvantages

The proposed PET design has several advantages and disadvantages when compared to other PEM systems made from scintillator crystals and solid-state crystals. The advantages include:

Ability to obtain an ideal LOR with DOI measurement due to the use of laser technique to segment the crystal block. Back then, this couldn't be achieved because the conventional method is mechanical pixelation which doesn't permit segmentation down to smaller sized pixel leading to a limitation in the system's spatial resolution.

Another advantage is that the system doesn't need many crystal blocks in the module, a single module can be used and pixelated into the desired size and thickness, and achieve high performance at the same time.

Moreover, organ dedicated scanners improve the tumor detectability of a particular organ, plus a reduced field of view that increases the system sensitivity and minimizes scatter. PEM scanners employing such specifications are often capable of achieving high performance at low cost.

The disadvantage of such PEM system is that, their wide energy window arising from poor energy resolution usually degrades the image quality because weak gamma photons are allowed to be detected by the scanner. This contributes to blurring in the final image.

Another disadvantage is high number of channels, but a technology that handles such numerous channels is available and proposed in (Blanchot et al., 2006).

4.2 Simulations

The scanner was simulated using Geant4 Application for Emission Tomography (GATE version 7.2). GATE is a Monte Carlo simulation that plays an important role in new imaging systems design and acquisition protocol optimization. It can also be used to assess or develop correction techniques and reconstruction algorithms. GATE contains the Geant4 library to actualize a versatile, modular and scripted simulation toolkit suitable for use in the nuclear medicine field. It permits an exact simulation of the interaction between a particle and a material within a prescribed scanner geometry, and it has also played an important role in the characterization of time-dependent processes (Jan et al., 2004).

4.2.1 The GATE simulation tool kit

The simulation toolkit contains the Geant4 libraries and it is dedicated specifically to nuclear medicine field. The software can be used over and over in different context because of the similar concept shared by many nuclear medicine diagnostic techniques.

GATE features include an application layer and the user layer, it also has a developer layer that incorporate the application layer and core layer. There are some base classes in the core layer that are common or compulsory in all Geant4-based simulations, they include the ones in geometry construction, physics interaction etc.

The user layer, provides a platform for running simulations batch-wise or interactively using scripts. Therefore, with the use of script language one can easily define a full set-up of a nuclear medicine experiment.

Systems: The concepts used in the systems includes one or more rings that contains the detector module. Modules to scintillator blocks which are segmented into crystal pixels.

Time dependent processes: Time-dependent process management is a unique feature of GATE (Santin *et al.,* 2003). Simulation of realistic acquisition conditions can be achieved because of the synchronization of the geometry with source kinetics. This include patient movement, cardiac and respiratory motions, changes in activity distribution over time or scanner rotation.

Digitizer: Permits the simulation of the electronics response of a detector within a scanner.

Simulation benchmarks: They provide examples of how to use the main features of GATE to simulate PET or SPECT experiments.

Validation of GATE: To assess the accuracy of GATE, one essential method is to validate the simulated data against real data obtained with PET and SPECT cameras. GATE validation has been done and can be found in (Jan et al., 2004).

In this simulation, we did not provide any specifications for the PMT and the related electronics to be used. In real life conditions, we can decide to use either a quadrant sharing PMT or a pixel readout chip which are capable of handling both the huge number of channels and the fast decay time of the scintillator material. The scanner uses a crystal that is pixelated using LIOB technique.

4.3 Performance Evaluation of the PET Scanner

4.3.1 Sensitivity

Sensitivity is the ability of the PEM scanner to detect coincident photons from inside the FOV of the scanner. The stopping power of the detectors and the geometry of the scanner largely affects the system sensitivity. The common unit is counts per second per Becquerel (cps/Bq). High-sensitivity scanners are those with large axial FOV and small-diameter geometry. In general, higher sensitivity leads to good SNR in the reconstructed image. The sensitivity (S_i) at each axial position i, is determined using:

$$S_i = \left(\frac{R_i - R_{B,i}}{A_{cal}}\right) \tag{4.1}$$

where A is the source activity measured in Bq, R_i represent total counts rate (cps) collected in source position (slice) i, and $R_{B,i}$ represent background event rate obtained with no source in the scanner FOV.

For acquisition i, the relative sensitivity is given by:

$$S_{A,i} = \frac{S_i}{0.9060} \times 100 \tag{4.2}$$

where 0.9060 represent the branching ratio of ^{22}Na. To compute the total system sensitivity, the equation below is used. N represent total number of image slices (source positions).

$$S_{tot} = \frac{1}{\mathrm{N}} \sum_{\substack{all \\ i}} S_i \tag{4.3}$$

$$S_{A,tot} = \frac{1}{\mathrm{N}} \sum_{\substack{all \\ i}} S_{A,i} \tag{4.4}$$

The sensitivity test requires that a ^{22}Na point source of less than 0.3 mm diameter with activity of 1MBq be embedded inside an acrylic cube with sides 10 × 10 × 10 mm (Figure 4.2). Six (6) measurements in total were analyzed. The source was positioned at the CFOV of the system to acquire the first measurement. 10^6 coincidences were obtained at the CFOV. Average of all sensitivities is calculated for each source position using equation 4.1, $R_{B,i}$= 0 in the case of simulation.

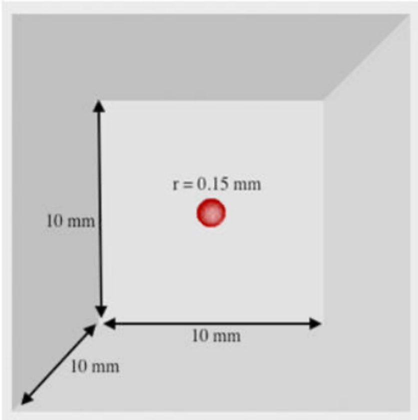


Figure 4.2: Sensitivity measurement phantom

4.3.2 Spatial resolution

The ability to distinguish between two points of radioactivity in an image is known as spatial resolution. This measurement is done on the reconstructed image of compact radioactive sources in order characterize the widths of the point spread function (PSF). Full width at half maximum (FWHM) and full width at tenth maximum (FWTM) are the terms used to describe the spatial resolution of a given system. Measurements are done in the radial and tangential direction of the transverse slice, and also on the axial direction.

The same phantom for sensitivity test was used. Per measurement, minimum of 10^5 coincidences were collected and MLEM algorithm was used to reconstruct the images.

4.3.3 NEMA image quality

The test is performed using a phantom made of polymethylmethacrylate (Figure 4.3). It has five fillable rods of 1 mm, 2 mm, 3 mm, 4 mm, and 5 mm respectively. The chamber of the main body and the rods are filled with ^{18}F radioactive water of 3.7 MBq total activity. It has two chambers at the top section, one is filled with air and the other with water (non-radioactive) so that two cold regions can be formed.

Images were reconstructed from 10 million coincidences as required by NEMA NU 4-2008. MLEM was used to reconstruct the images with no corrections applied. Furthermore, normalization is not required because the data are from simulation. The pixel size and slice thickness are 0.25 mm and 2 mm respectively.

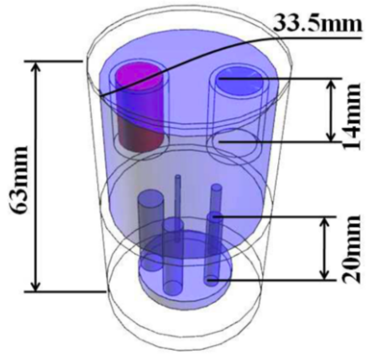


Figure 4.3: NEMA image quality phantom

4.3.4 Derenzo-like phantom study

This phantom is a circular piece of plastic that has several rods drilled through. It has 5 sections, each comprises of rods having different diameters and 12 mm length. The rods are filled with 1 MBq of ^{18}F radioactive isotope. The rods used for this particular test are from 1.2 to 3 mm in diameter (Figure 4.4). The phantom images were reconstructed using MLEM, 10 million coincidences were collected and 0.5 x 0.5 x 1.0 mm^3voxel was used.

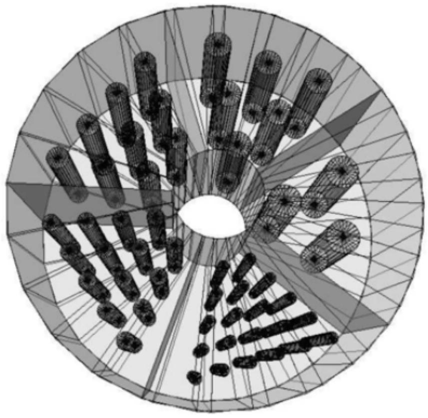


Figure 4.4: Derenzo phantom

CHAPTER 5
RESULTS

5.1: Sensitivity

The result of the scanner's sensitivity to incoming gamma radiation are presented. All coincidences as suggested by NEMA standards were obtained at the scanners centre FOV. Equation (4.1) and (4.2) were used to calculate the presented result.

The absolute system sensitivity is 10.6%, superior to MAMMI PEM (Moliner et al., 2012) and PEMI (Li et al., 2015). The results are shown in Figure 5.1.

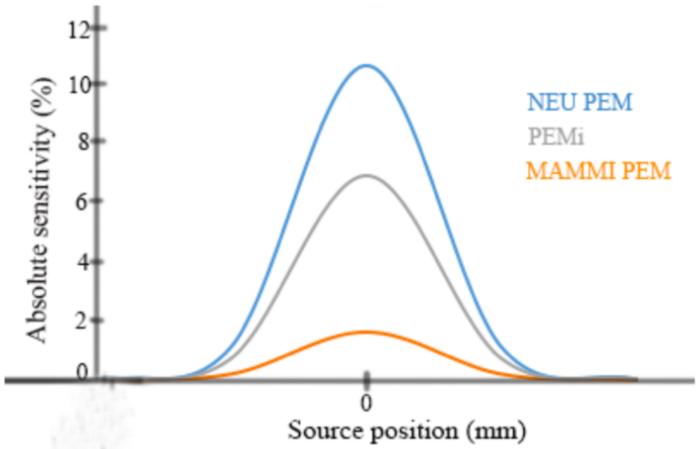


Figure 5.1: Comparison of absolute sensitivity.

The prevalent outcome from our scanner proposes that it will hugely add to the main objective of clinical imaging. Likewise, this will permit little structures and malignancies to be identified. Reduced scan time and low dose scans are also added advantage, yet keeping up with SNR due to sensitivity gain.

Motion artefact from involuntary patient movement affects image quality, this can be reduced with short scan time. Sensitivity gain has made it possible to reduce motion artefact with scan time being reduced by 50% (şın, Ozsahin, Dutta, Haddani and El-Fakhri, 2017).

5.2 Spatial Resolution

Resolutions obtained in three directions are summarized in Table 2, including comparison to existing breast scanners, the proposed scanner's results were superior. This is largely due to smaller pixel size.

Table 5.1: Spatial resolution.

Positions (mm)	NEU-PEM (mm)	PEMi	MAMMI (mm)
Axial	1.0	1.4	1.6
Radial	2.1	2.2	1.8
Tangential	1.0	1.8	1.9

Sub-millitre fabrication were feasible due to LIOB technique, this gave the ability to obtain the present superb spatial resolution which was better than those we compared to. Other parameters that contributed to the improved results were the intrinsic properties of the LSO crystal. There could be significant complexity as a result of the numerous channels within the crystal, a proposed solution is given in (Ballabriga, Campbell, Heijne, Llopart and Tlustos, 2007).

5.3 Image Quality Test

Images of the image quality phantom rods and their line profiles are shown in Figure 5.2.

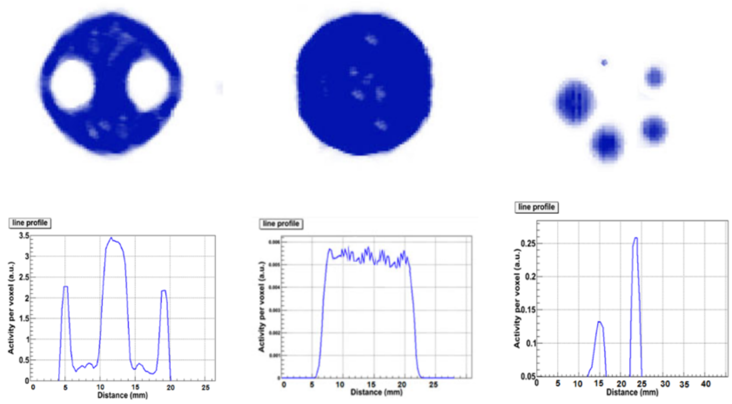


Figure 5.2: Image quality phantom rods
Top: cold regions, uniform region, hot rods. Bottom: corresponding line profiles.

The rods Recovery coefficients (RC), standard deviations (STD) were calculated while assessing Image quality. Other parameters are given in Table 5.2, they include “mean,min,max and uniformity values of phantom’s central region, and the spill-over ratio (SOR) of the two cold regions”.

Table 5.2: Image quality

Rod diameter	1mm	2mm	3mm	4mm	5mm
RC	0.14	0.35	0.60	0.85	0.88
STD (%)	7.0	6.7	5.7	5.5	5.1

5.4 Derenzo-like Phantom Study

According to this phantom test, 1 mm hot rods (Figure 5.3) are visible with no correction applied.

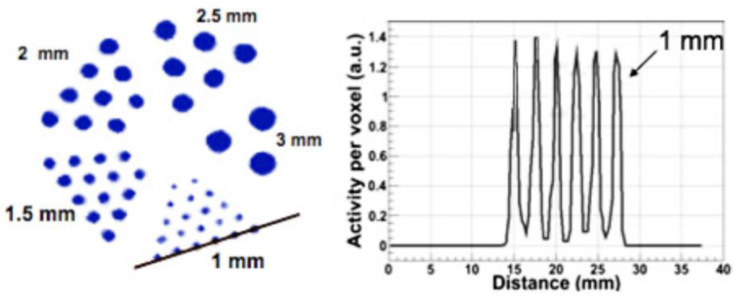


Figure 5.3: Phantom’s image and line profile.

CHAPTER 6
CONCLUSIONS, DISCUSSION AND RECOMMENDATIONS

6.1 Conclusions

The results presented in this thesis are based on GATE simulation. The parameters used to simulate the scanner geometry are from a particular technical design. The concept used to simulate the detector is from a published work on fabricating scintillator crystals using LIOB technique. The image quality, sensitivity, spatial resolution, scatter fraction, uniformity and Derenzo phantom performance evaluation of the simulated scanner were performed with NEMA protocol.

The modelled scanner has a potential clinical use according to the obtained results, the main reason for this suggestion were the sensitivity and resolution results. Previously, such sort of predominant outcomes was gotten by preclinical scanners. The results are superior to some state-of-the-art scanners. The outcomes additionally demonstrated that detection of breast malignancies will be essentially improved, as 1 mm hot rods were visible even without any added correction techniques applied. In addition to this, patient's absorbed dose will be significantly reduced as a result of improved tumour detectability. The images obtained from the quality test suggests that scans can be performed within short duration thereby minimizing motion artefact arising from beating heart, patient movement etc.

This study shows that the scanner is capable of achieving higher spatial resolution and sensitivity at a lower cost. From previous published studies, it was evident that such kind of spatial resolution is only achievable by small animal PET scanners.

LIOB is an automated and cost-effective technique for fabricating scintillator arrays with no material loss. It leaves no inter-pixel gaps in the process of pixelating the scintillator crystal, thus gives rise to a high-resolution and sensitivity detector.

With technological advancement, 1mm x 1 mm pixelated crystal can be coupled to an array of photon counters such as silicon photomultiplier tube (SiPMT). This is a great way of handling complex pixelated crystals with so many voxels. Signals generated from the SiPMT are then read out by electronic systems. In real life application, we could either use a quadrant sharing PMT such as the one listed above or a pixel readout chip which are capable of handling both the huge number of channels and the fast decay time of the scintillator material.

Few of the studies that have used SiPMTs include that of Watanabe et al., 2017 which reported a 1.2 mm finely segmented LYSO array couple to and 8 × 8 array of multi-pixel photon counters.

Another study is that of Borghi, Tabacchini, Bakker & Schaart, 2018 which reported ~1.7 mm detector spatial resolution obtained from a 32 mm × 32 mm × 22 mm LYSO crystal coupled to a digital silicon photomultiplier (dSiPM) array.

Zhang et al., 2019 also reported a finely pixelated detector that was air-coupled to a 4 × 4 array of SiPMs and read out by a custom-designed electronic system.

Peng, Judenhofer & Cherry, 2019 also reported a 1.1 ± 0.1 spatial resolution which was demonstrated from the readout of a complete layered detector with 4 layers coupled to 16 SiPMs.

The above studies were validated by a commercialized molecular imaging PET/CT Si78 scanner. The scanner offers real, homogeneous sub-millimetric 3D PET resolution. This was possible due to SiPM technology and true depth of interaction ("PET/CT | PET System | Preclincal CT | Total Body", 2021)

6.2 Recommendations

For future related study, other crystals and different system design can be adopted to improve the system sensitivity and spatial resolution of PEM scanners. In addition, related studies should be conducted in other to aid accurate diagnosis of breast tumors for better patient health and chances of survival from breast related diseases.

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THESISES

Master

- Musa, S.M. (2018). Simulation and evaluation of a cost-effective high-performance brain PET scanner. Unpublished Master Thesis, Near East University, Biomedical Engineering, Faculty of Engineering, Nicosia, Cyprus.

Bachelors

- Musa, S.M. (2014). Comparison of scan-time and patient dose between two multi-slice CT scanners in Kano Metropoly. Undergraduate Project (B.Sc.), University of Maiduguri, Department of Radiography, College of Medical Sciences, Maiduguri, Borno State, Nigeria.

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