Enhancing PET Functionalities with Novel Geometries and Multimodal Imaging Techniques

Suranjana Samanta
Washington University in St. Louis

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Enhancing PET Functionalities with Novel Geometries and Multimodal Imaging Techniques

by

Suranjana Samanta

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requirements for the degree
of Doctor of Philosophy

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Dedicated to my family for their unconditional love and support.
ABSTRACT OF THE DISSERTATION

Enhancing PET Functionalities with Novel Geometries and Multimodal Imaging Techniques

by

Suranjana Samanta

Doctor of Philosophy in Electrical Engineering

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Professor Joseph A. O’Sullivan, Chair
Professor Yuan-Chuan Tai, Co-Chair

Positron emission tomography (PET) is a highly sensitive imaging modality that can provide in vivo quantitative information of biological processes at a biochemical level. The majority of PET systems have a ring geometry where the detectors fully encircle an axial section of a patient to provide whole-body imaging capability using multiple bed positions. However, these clinical whole-body PET systems are limited in terms of both image resolution and system sensitivity. To achieve a high resolution, customized geometries which trade global utility for application specific performance (breast, small animals etc.) imaging probes may be utilized. In some cases, an application-specific PET system can also significantly improve the system sensitivity, while in other cases new imaging capabilities are the main focus of a system design. Since these systems may have non-cylindrical geometries, they require a generalized reconstruction framework which is system geometry independent.
To support the implementation of such PET systems with unconventional geometries, we have developed a fully 3D list-mode GPU based image reconstruction framework using maximum-likelihood expectation-maximization (ML-EM) algorithm. We have implemented correction procedures like normalization, attenuation correction and scatter correction for this image reconstruction framework to support arbitrary system geometry and interactive imaging using the PET/US system. We compare the performance of our framework with a clinical reconstruction framework. For all the systems investigated in our work, we have used this reconstruction framework. We also modified the framework to support continuous patient bed motion acquisition. Appropriate correction techniques (attenuation, scatter, normalization) for continuous bed motion need to be explored in future.

We propose a high-performance dedicated breast PET imaging device concept which will scan both breasts simultaneously and have high sensitivity and resolution; fine temporal resolution; complete visualization of both breasts, mediastinum and axilla; and a modular design that can be inserted into a body MR scanner to provide dual-modality imaging (PET and MRI) allowing for MRI guided biopsy access. The volumetric geometry is illustrated along with GATE Monte Carlo simulations of various sized lesions (4-6mm) of differing lesion: background ratios (6:1 to 4:1) mimicking different biological uptake. We finally compare this dedicated breast PET imager to a state-of-the-art clinical PET/CT scanner.

In another direction, we propose a novel PET/Ultrasound imaging system that will bring both these modalities to patient bedside to support point-of-care applications with near real-time interactive imaging capability. It consists of a movable hybrid imaging probe consisting of PET detector arrays and an ultrasound transducer. The PET detectors are in coincidence with a detector array.
behind a patient. The movable detectors make it possible for the operator to control the scanning trajectory freely to achieve optimal coverage and sensitivity for patient specific imaging tasks.

The initial application is to detect vulnerable plaque in carotid artery using $[^{64}\text{Cu}]\text{DOTA-ECL1i}$, a PET tracer targeting C-C chemokine receptor type 2 (CCR2) developed at Washington University which may identify high-risk plaques with inflammation. We present Monte Carlo simulation studies to test the feasibility of the system. We further optimize the system design, develop time-of-flight (TOF) PET detectors and develop a proof-of-concept POC PET/Ultrasound prototype. We perform phantom studies using this prototype and demonstrate the feasibility of this system to provide adequate anatomic, functional and molecular imaging information for carotid artery imaging. We also investigate another application of the POC PET technology to image lungs. Since, this is a stand-alone system targeted for imaging larger patient volumes, non-uniform tissue attenuation is a challenge. We implement a transmission-scan based attenuation correction and perform simulations to test this correction method with a known analytical $\mu$-map based correction. We also report sensitivity and reconstructed phantom images as well as demonstrate an interactive scanning strategy.

Finally, we discuss additional works needed to extend this list-mode reconstruction framework to support continuous-bed-motion acquisition in the future.
Chapter 1: Introduction

1.1 Positron Emission Tomography

Positron Emission Tomography (PET) is a widely used non-invasive medical imaging technique which generates three-dimensional images based on the detection of photons emitted by a positron-emitting radionuclide within a volume or body. It is a form of nuclear imaging used to acquire images of molecular probes rather than physical anatomy. This molecular imaging capability has the advantage that it may detect molecular or functional changes such as the onset of cancer or neurodegenerative diseases before any anatomical changes are evident in structural imaging such as X-ray CT or MRI.

1.1.1 Applications of PET

The main areas of clinical applications of PET include:

Neurology: PET allows quantification of cerebral blood flow, metabolism, oxygen consumption in different parts of the brain and receptor binding for initial diagnosis and assessment of brain tumors, epilepsy, Parkinson's disease [1], Alzheimer disease, dementia [2], [3], and movement disorders [4].

Oncology: The measurement of the rate of consumption of the radiolabeled glucose analogue or $^{18}$F-fluorodeoxyglucose ($^{18}$FDG) allows the quantification of metabolic activity for cancer diagnosis, staging, differentiation between malignant and benign tumors and treatment response [5], [6]. PET can be used in patient management by assessing the response towards the therapy.
This can help in the decision to continue or discontinue the therapy by measuring tumor aggressiveness in the scanned images. Malignant tumors have higher metabolic activity rates than benign tumors [5]. PET is not only helpful in disease diagnosis and patient management, but its applications extend to oncological drug development for lung, lymphoma, prostate, sarcoma, ovary, breast and colorectal cancers.

**Cardiology:** In ischemic heart failure, there is a metabolic shift that is reported from fatty acid consumption to glucose utilization. Since PET can measure the myocardial glucose metabolism, it can be used as a diagnostic and patient management tool for myocardial ischemia. PET also allows the quantification and assessment of the myocardial perfusion and viability [7]. Myocardial perfusion indicates reduced PET blood flow through the heart vessels, which is localized using PET. This can provide a test for the narrowed or blocked heart vessels [7]. Cardiac viability scans can further clinically indicate if there is a possibility of the heart muscles to go back to normal after placement of a coronary stent or surgically operating to reroute the blood flow along the coronary arteries [7]. Inflammation has been shown to be linked to many chronic diseases [8]. Therefore, there is increasing interest to image acute and chronic inflammatory response in a body using molecular imaging like PET. FDG has been used to image inflammation. [9][10].

### 1.1.2 History of PET

The early medical application of the positron can be traced back to 1951. The first brain probe using positron data was reported by William Sweet at Massachusetts General Hospital (MGH) [11]. The patient was positioned between two opposing sodium iodide (NaI(T1)) detectors, and
the results were printed as a 2-D image of the positron source. In the same year, Frank Wrenn published the study of the localization of brain tumors by detecting the coincidence scintillation of annihilation pairs [12]. In 1973, the first PET tomography (PETT I) was built by Michael Phelps, Michel Ter-Pogossian and Edward Hoffman at Washington University. Phelps named it as Positron Emission Transaxial Tomography (PETT), and later reduced the name to PET [13]. Although this first tomography marks the beginning of modern PET technology, it was failed in producing proper reconstructed images due to the lack of attenuation correction, etc. In the following years, refinement of PET devices were being developed very fast, mainly by Phelps, Hoffman and Ter-Pogossian et al., such as PETT II and PETT III [14]–[16]. The PETT III system consisted a hexagonal array with eight NaI(T1) detectors on each side and detected the coincidences with the detectors on the opposing sides. Another step in the development of the PET technique was the use of ring systems instead of hexagonal array of detectors [17], this ring system has become the prototype of the current shape of PET. The first generation of TOF PET scanners was developed in the early 1980s at Washington University pioneered by Donald Snyder and David Politte [18]. The early TOF PET systems used CsF and later BaF2 as the scintillator, and achieved system timing resolution in the range of 450–750 ps. These early systems used 1-1 coupling of the scintillator to a single photomultiplier tube (PMT), and hence the timing resolution was determined primarily by the intrinsic scintillator timing properties and the scintillator size, which was in turn defined by the PMT size. Due to the 1-1 coupling nature of these detectors the system spatial resolution was also determined by the scintillator and PMT size. Attempts were made using light sharing techniques in the detector design [19], but these were limited by the low light output of these scintillators. Hence, these early TOF PET systems suffered from reduced sensitivity and poor spatial resolution of these detectors relative to detectors utilizing BGO, which
became the standard crystal used in Non-TOF PET. With the subsequent transition of PET imaging to primarily $^{18}$F-FDG oncology studies, the benefit of TOF PET with these early scintillators could not help overcome the reduced sensitivity and worse spatial resolution. Hence, the 1990s saw PET system design dominated by Non-TOF scanners primarily using BGO crystals with septa for 2D data acquisition [20], or alternately using large NaI(Tl) crystals without septa for fully-3D data acquisition [21]. During the period from 1987 to 1990, some major imaging companies, such as Siemens and General Electric (GE), started to distribute commercial PET devices. Ever since, PET has been validated for clinical applications and not just research oriented. Lutetium oxyorthosilicate ($\text{Lu}_2\text{SiO}_5(Ce)$, or LSO(Ce)) was first introduced as a PET scintillator in the early to mid 1990s [22], providing faster decay times and higher light output compared to BGO, which was the primary scintillator being used in commercial PET at that time. LSO was first used in a small animal PET scanner (MicroPET) [23] and subsequently incorporated into a brain scanner [24] and finally a whole-body PET scanner (ECAT Accel) [25]. The improved properties of LSO provided higher sensitivity, improved spatial resolution, reduced deadtime and random coincidences, and also helped facilitate the use of fully-3D PET (no septa) as the standard design for modern PET systems [26]. Soon it was also recognized that the very good timing resolution of LSO and another similar scintillator lutetium–yttrium oxy-orthosilicate ($\text{Lu}_{1.8}\text{Y}_{0.2}\text{SiO}_5(Ce)$, or LYSO(Ce)) could be utilized in the development of TOF PET systems [27] without the limiting design trade-offs present in the first generation TOF PET systems of the 1980s.
1.1.3 PET Radiotracers

A PET radioactive tracer or commonly known as radiotracer is a synthetic chemical compound comprising of a specific biomolecule (the molecule which is targeted to be taken up by a specific tissue or organ so that its subsequent distribution can be readily followed) where one or more of its atoms are replaced by a radioisotope. The radioisotopes are commonly produced by accelerating and bombarding the protons or deuterons onto a stable target using a cyclotron. When the radiolabeled biomolecule is taken up by the target tissue or organ, the radioisotope which decays naturally and contributes to the detected activity. Over the past decades, there has been an observed increase in the number of $[^{11}\text{C}]$-labelled, $[^{64}\text{Cu}]$-labelled and $[^{18}\text{F}]$-labelled radiotracers. These radiotracers are used to image a wide range of molecular abnormalities that are present in the normal or diseased tissues. The most widely used example is fluorodeoxyglucose ($^{18}\text{F}$-FDG), which has significantly contributed towards the success of PET imaging and has helped to launch PET as a viable modality clinically. $^{18}\text{F}$-FDG is a glucose analog created by replacing a hydroxyl group with a positron-emitting fluorine-18 isotope. This compound is taken up by cells as they consume glucose. In oncology, fast growing cancerous lesions will consume the $^{18}$FDG more readily than surrounding tissues (except brain). As a result, FDG-PET for oncologic imaging accounts for the majority of clinical PET imaging utilization.

1.2 Physics of PET

1.2.1 Radioactive Decay:

Radioactive isotopes are atoms whose inner core, their nucleus, is unstable, in a state with extra energy above ground state. Nuclei consist of a densely packed arrangement of protons and
neutrons. By undergoing decay, the nuclei change their composition and properties to arrive in a less energetic and more stable state. The different modes associated with radioactive decay include beta decay, gamma decay, electron capture, positron decay and alpha decay, etc. just to name a few. In case of PET imaging, positron decay is involved. The radioactive decay process follows an exponential law: the number of decays per second is always proportional to the number of undecayed nuclei present. The same is true for the rate of decay, also called activity, which is determined by the half-life of the particular nuclide—the time it takes for half of the original nuclei to decay. Most common in PET is fluorine-18 ($^{18}$F), which has a half-life of 109 minutes. After some time, $t$, the activity left, $A(t)$, is proportional to the initial number, $A(0)$, and an exponential term involving the half-life, $\tau$, of the nuclide:

$$A(t) = A(0)e^{-t(\ln 2)/\tau}$$  \hspace{1cm} (1.1)

Radioactive rates (or activity) are measured in units of becquerel (1 Bq = 1 decay/s) in the International System of Units (SI) or the traditional curie (1 Ci = $3.7 \times 10^{10}$ decay/s).

### 1.2.2 Positron Emission and Annihilation

In $\beta^+$ (positron) decay (Figure 1.1), a nuclide transforms one of its core protons (p) into a neutron (n) and emits a positron ($\beta^+$), essentially a positively charged electron, and a neutrino ($\nu$): $p \rightarrow n + \beta^+ + \nu$. After ejection from the nucleus, the positron loses its kinetic energy in collision with atoms of the surrounding matter; this usually happens within a few millimeters from the site of its origin in body tissue. This distance is called positron range. The average positron range in matter depends on the positron’s energy (typically in the range of 0.5-2 MeV) and material characteristics, such
as the density and the atomic number. If the positron range is large then, this will degrade the spatial resolution of the image.

At the end of its path, the positron, being antimatter to electrons, will annihilate (re-combine) with an atomic electron. In the annihilation, electron and positron convert their mass into energy and produce a pair of 511 keV annihilation photons traveling in opposite directions. This annihilation radiation is what is detected in PET and what is used to form images of tracer concentration in the body. From the conservation of momentum, the two photons or gamma rays are 180 degree back to back if the electron and positron are initially at rest. In reality, the gamma rays are at a slight angle from exactly back to back as a result of the initial momentum of the annihilating photons.

This deviation in angle from 180 degrees is known as photon acollinearity. The average angular deviation is about 0.25° from 180° which causes a small error in event positioning, thus decreasing spatial resolution. Photon acollinearity is a crucial factor of image degradation for scanners with large diameter since it introduces more displacement from the actual event location.
Figure 1.1: General principle of positron emission tomography imaging: decay of radionuclide, positron ($\beta^+$) emission, multiple scatter in tissue, annihilation with electron, and production of two back-to-back 511 keV annihilation photons.

### 1.3 PET data acquisition

The general purpose of photon detection is to choose proper material that can effectively stop the gamma ray and measure its energy and arrival time. For highest sensitivity and accuracy, the preferred mode of interaction is photoelectric absorption where all of the photon’s energy is deposited in the detector crystal, but in practice this is not always possible when the photon undergoes other interaction modes like Compton scattering. In most PET scanners today, scintillation detectors are used as detection elements. They couple inorganic scintillation crystals that emit visible or near ultraviolet light after interaction with an incident high-energy (511 keV)
photon to photo detectors that detect and measure the scintillation photons. In scintillation crystals, the incident annihilation photon (nominally 511 keV energy) interacts and creates tens of thousands of visible wavelength photons (~1 eV energy each) in a very short flash, or “scintillation.” The number of scintillation photons produced in the crystal is proportional to the energy deposited by the annihilation photon.

The most commonly used photodetectors for PET are photomultiplier tubes (PMTs). PMTs are vacuum tubes with a photocathode, which produce electrons from incoming light photons that are accelerated and amplified. The resulting electrical current is proportional to the number of initial scintillation photons and therefore to the energy deposited in the scintillation crystal by the annihilation photon. The most commonly used setup today is the block detector. Here, small individual scintillation crystals, a few millimeters in size, are tightly packed into blocks, which are typically coupled to four or more small photo-multiplier tubes. To determine the interaction position of the annihilation photon from the spread-out scintillation photon signals, the relative outputs from the PMT signals are compared. The calculated location then determines the crystal element that the photon interaction is assigned to. When two photons are detected by a pair of detectors within a specified timing (for e.g. 4-10ns) and energy window (for e.g. 450-560 keV), they are determined to have come from the same annihilation event. This forms a coincidence detection along a given line-of-response (LOR) between two individual crystals in the scanner. Modern detection electronics are fast enough to measure the time difference between the two photon detections and this is used to narrow the location of an event into the most likely segment along the LOR using this time-of-flight (TOF) information. In modern TOF PET scanners, coincidence timing resolution can be as small as 213 ps [28] or about 3.19 centimeters.
Coincidence detection technique described above records three types of coincidence events:

1. **True events** are those where the two detected photons come from the same annihilation without having undergone any interaction in the object from the point of annihilation to the crystals (Figure 1.2(a)).

2. **Scattered events** occur when one or both of the detected photons have interacted with surrounding tissue and therefore changed direction resulting in mis-positioning of the event (Figure 1.2(b)).

3. **Random coincidence** is when two photons from different annihilation processes are detected within the coincidence window (Figure 1.2(c)).

![Figure 1.2: Illustration of the three different kinds of coincidences that can occur.](image)

These scatter and random coincidence events along with many factors including attenuation effects, crystal efficiencies, parallax effects, acollinearity, inter-crystal scatter, detector dead time, geometric limitations contribute to degradation in image quality (image resolution, signal-to-noise-ratio etc.) and quantitative accuracy of PET images. To reconstruct PET images from coincidence events, the general assumption is that the number of coincidences between any two
detector crystals is proportional to the distribution of tracer along the LOR between them. The expected value of the true coincidence data can be represented by a system matrix $H \in \mathbb{R}^{M \times N}$ with $M$ LORs and $N$ image voxels with element $H_{ij}$ representing the probability of detecting an annihilation event from voxel $j$ along LOR $i$. With the addition of random events $r$ and scatter events $s$, a PET system with $y$ representing the measured data and $x$ the real distribution of the tracer can be described as:

$$y = Hx + s + r$$  \quad (1.2)

1.4 Image Reconstruction in PET

Image reconstruction involves solving the inverse problem of Eq. 1.2 associated with estimating the tracer distribution from the noisy measurement data. Reconstruction methods have either analytical or statistical approach. Analytic reconstruction offers a direct and simple mathematical solution for the reconstruction problem such as filtered-back-projection (FBP). Statistical reconstruction methods can model the complicated detection process and provide more accurate solution such as expectation maximization (EM) method.

Analytical Methods

One image reconstruction approach is simplifying the problem and assuming the measurements are produced by the simple Radon transform model while neglecting the noise. The tracer distribution can then be recovered using an inverse method called filtered-back-projection (FBP) that takes advantage of the central slice theorem (also called the Fourier slice theorem). This theorem enables the combination of many one-dimensional measured projections $p(s, \theta)$ through
the tracer distribution in Fourier space to generate the two-dimensional Fourier transform of the tracer distribution. The original tracer distribution is then recovered by performing the two-dimensional inverse Fourier transform on the combined data. Specifically, FBP is calculated by:

\[ f(x, y) = \int_0^\pi p^F(s, \theta) d\theta \]  

(1.3)

Where the filtered projection \( p^F \) is given by:

\[ p^F(s, \theta) = \mathcal{F}^{-1}\{|\nu_s| \{\mathcal{F}\{p(s, \theta)\}\}} \]  

(1.4)

The ramp filter \( \nu_s \) is applied to each projection to compensate for the inherent oversampling in the center of the Fourier space. Additionally, a smoothing function is often added to optimize the noise / resolution tradeoffs. Analytical methods are fast and relatively simple to implement. However, since they don't model the statistical complexity of photon detection physics, other reconstruction techniques were developed to account for these aspects. Specifically, iterative methods based on statistical models arose to accommodate many of these aspects and use a more realistic model of the system in the reconstruction process.

**Statistical Methods**

Statistical reconstruction methods are able to more realistically model the imaging system, such as accounting for noise sources inherent in measurement data, resulting in more accurate images compared to analytic reconstruction methods, but at the cost of significantly more computation. Iterative methods generally contain five common components:

1. **Image model**: A discretization of the image domain into distinct pixels / voxels.
2. **System model:** The system model $H$ has elements $H_{ij}$ that represents the probability that an emission from voxel $j$ is detected in line-of-response (LOR) $i$ and can account for many aspects of the imaging system including attenuation, random events, scatter events, normalization, system geometry etc.

3. **Data model:** This is the relationship between the collected data and the expected value of the collected data. Since radioactive decay is Poisson distributed, which in turn means photon detections are also Poisson distributed, therefore, the Poisson model is used. Following this model, for $M$ LORs the probability $P$ that the random vector of photon counts $Y$ equals the true photon counts $y$ given a vector of positron emission rates $x$, is

$$P(Y = y|x) = \prod_{i=0}^{M} \frac{e^{-n_i} n_i^{y_i}}{y_i!}$$

(1.5)

4. **Objective Function:** Mathematical function that defines the "best" image, with Maximum Likelihood (ML) being the most common choice in PET reconstruction. With a ML objective function, the goal is to arrive at an image estimate $x^*$ that maximizes the likelihood of probability $P$ in equation 1.5. (Since log-likelihood is a monotonic function and simpler to work it, we maximize the log-likelihood function instead.)

5. **Algorithm:** A method that optimizes the cost function to find the "best" image estimate. While numerous algorithms work for this purpose, Expectation Maximization (EM) is the mostly widely used method.

The foundation of most iterative statistical PET reconstruction methods is the Maximum Likelihood Expectation Maximization (MLEM) algorithm applied to image reconstruction by Shepp and Vardi [29] and independently by Lange and Carson [30]. When applied to PET reconstruction this algorithm reduces to this iterative equation:
\[ X_j^{(k+1)} = \frac{X_j^{(k)}}{\sum_i H_{ij}} \left( \sum_l H_{lj} \frac{Y_l}{\sum_m H_{lj} X_j^{(k)}} \right) \] (1.6)

where \( X_j^{(k+1)} \) is the next estimate of voxel \( j \) based on the current estimate. This equation proceeds in logical steps when used in image reconstruction (Figure 1.3). Starting with an initial image guess \( X^0 \), which is typically the entire image set to a constant value (we use all-one image), the image is forward projected into the measurement domain \( \sum_i H_{ij} X_j^{(k)} \) and compared with the measured projections \( Y_l \) creating a correction factor for each projection (the right most fraction in Eq. 1.6). These corrections are then projected back into the image domain with \( \sum_i H_{ij} \) and multiplied by the current image estimate \( X_j^{(k)} \) and divided by a weighting term based on the system model (also called sensitivity image) controlling the strength of the update. The updated image is then used as the starting point for the next iteration of the algorithm and this process continues as the image is optimized towards the maximum likelihood solution. In practice this algorithm is usually terminated prior to convergence (sometimes with the addition of a post-smoothing filter) to limit the high frequency components and resulting image variance (noise) to create a smoother image at the cost of increased image bias. Alternatively, regularization can be implemented by adding a penalty term to the objective function. In this work, all images were reconstructed without regularization. The choice of regularization function and the choice of its parameters can be investigated in the future.
1.5 Monte Carlo simulations

Monte Carlo (MC) simulations, are computer-aided mathematical techniques that rely on repeated random sampling to obtain numerical results. The underlying concept is to use randomness to solve problems that might be deterministic in principle. Whenever there is a chance of different outcomes in a particular process, which cannot be easily predicted due to the presence of random variables, MC simulation can be implemented.

In a Monte Carlo analysis of PET, a computer model is created with characteristics as similar as possible to the real imaging system. In this model the photon and charged particle interactions are simulated based on known probabilities of occurrence, with sampling of the probability density functions (PDFs) using uniformly distributed random numbers. The simulation is similar to a real measurement in that the statistical uncertainty decreases as the number of events increases, and therefore the quality of the reported average behavior improves [31].

We use Monte Carlo simulations throughout our studies to optimize the detector configuration and design of a PET system and to improve the outcome of experiments, because it is easy to change one parameter at a time in the model.
Various simulation packages have been developed for emission tomography applications. SimSET (Simulation System for Emission Tomography) is a dedicated code for PET and SPECT simulations [32]. It uses a simplified physics model that is accurate and fast. It is capable of modeling basic detector design. However, one major drawback of this system is the limited flexibility when simulating different detector geometries apart from the conventional geometry. Also, the number of functions a user can control during simulation is also limited.

Geant4 package [33]–[35], is a more generic Monte Carlo toolkit that simulates the interaction of subatomic particles through matter. It is widely used in high-energy, nuclear, and accelerator physics studies. With Geant4 it is possible to design experimental geometrical construction of different shapes and materials and to choose the particles and physics interactions to be involved in the experiment. But the gain in flexibility comes at a cost of user friendliness and simulation speed.

GATE (Geant4 Application for Emission Tomography) [36] is an object-oriented Monte Carlo simulation toolkit that overcomes all of the limitations mentioned above. GATE is built on top of Geant4 libraries and uses them for simulation of particle transport. GATE simulations employ a Geant4 script language or macro language. Therefore, it does not require the user to have any prior C++ programming skills in order to carry out a GATE simulation. In short, it combines the Geant4 toolkit including its physics models and complex geometry descriptions with powerful 3D visualization to simplify its use and promote research in the field of nuclear imaging.
1.6 Contributions of the dissertation

The key contributions of this dissertation are summarized below:

1. **3D Listmode GPU based reconstruction framework for unconventional geometry**

Since our lab is mainly involved in designing and developing novel PET systems with unconventional geometries, a reconstruction framework that is independent of system geometry is necessary. Before I started working on this project, Dr. Ke Li set the basic workflow of a generalized reconstruction framework. He implemented the Gaussian Tube-of-Response (TOR) forward model in GPU. Building upon his valuable contributions, I started using this framework for a dedicated breast-PET system. However, the reconstructed images had many artifacts which led me to implement a module-based normalization approach. This significantly improved the image quality. There were a couple of issues with the forward model which resulted in underestimating scatter when reconstructed using prompt data and presence of vertical and horizontal artifacts during attenuation correction. I fixed these issues and modified the framework to generate a reconstructed image where intensity of each voxel represents total decays detected in that voxel. This was a crucial step before implementing scatter correction, for which I modified the framework to include estimated scatter values. Dr. Sergey Komarov helped in estimating scatter values using Single Scatter Simulation for Time-of-Flight list mode data. Apart from this, I automated the process of generating a detector geometry file from GATE to give as input to our reconstruction framework, implemented coincidence sorting from GATE singles events to store
trues, scatter and random events separately. The detailed reconstruction framework is discussed in Chapter 2.

I also started extending our current framework, which supports step-and-shoot data acquisition and reconstruction, to support continuous bed motion reconstruction and validated this feature using MC simulations. Correction techniques like attenuation and scatter correction have not yet been implemented for this feature. Chapter 6 contains more details about this framework.

2. Total Breast PET Imager

This was the first project that I started working on. The main motivation behind this project was the lack of a dedicated breast PET system which has high resolution and sensitivity and could image chest wall, axillae and both breasts simultaneously. I conducted multiple GATE simulations to optimize the system geometry. Since this system had an unconventional geometry, I implemented a module-based normalization approach to obtain more uniform images. Finally, I compared the qualitative and quantitative performance of this system with a clinical whole body system and demonstrated the feasibility of the proposed system. This work has been extensively discussed in Chapter 3.

3. Point-of-Care (POC) PET systems and integration with Ultrasound

Our lab previously demonstrated the feasibility of a POC-PET system using a proof-of-concept setup that consists of two planar PET detectors. One detector was mounted to a robotic arm which can position and track the detector at an arbitrary location. The second detector was mounted on a rotational stage and can be rotated around an object. The ideal use case will be that a technician guides this maneuverable PET scanner to cover a scanning contour of a ROI (Region-Of-Interest)
of the patient, with a real time image reconstruction engine that reconstructs the refreshed PET images as the scanning trajectory is being adjusted. This is a very similar concept used in some other imaging modalities such as ultrasound and intraoperative gamma camera. However, in the PET field, there were very few demonstrations of similar concept. Our first generation POC PET system used photomultiplier tubes (PMT) based detector technology that had poor coincidence resolving time (CRT) of 740 ps. Also, the data-acquisition system used was bulky and not optimized for proposed applications. We wanted to use this technology for imaging and detection of atherosclerotic plaque in the carotid artery, which required a better CRT and higher resolution. Ultrasound imaging is the current modality used for carotid artery imaging. I developed a POC PET/Ultrasound prototype using silicon photomultiplier (SiPM) detector technology and PETSys ASICs for PET data acquisition. It consists of a movable hybrid imaging probe which houses both PET detector arrays and a clinical ultrasound transducer. The current system has an improved CRT of 250 ps. I also conducted MC simulation studies to optimize system geometry and interactive scanning strategy. Initial phantom studies using this system shows promising results. This work has been discussed in detail in Chapter 4.

I also proposed a POC lung imager as an alternate application using the above technology. Since this system targeted a larger torso region, attenuation correction was a crucial step. As this system was designed to be a stand-alone system, I implemented and validated a transmission-scan based attenuation correction approach. I also conducted MC simulated phantom studies and demonstrated the feasibility of this system. Chapter 5 contains detailed information about this work.
Chapter 2: List Mode MLEM Image Reconstruction Framework

2.1 Background and Motivation

Since the invention of PET, the majority of the systems have used ring geometry for Whole-Body imaging. The last two decades have seen customization to application specific geometries. A variety of individual reconstruction codes have been developed by investigators for the specific systems. The commonly used underlying algorithm in all systems is the same or a variation. Differences arise due to the data model used. Our lab has been involved with developing accurate reconstruction models for non-cylindrical geometries. We started from 2D linear and iterative algorithms [37] for a ring-shape insert, then 3D statistical iterative method for a half-ring insert [38] and came to a fully 3D statistical iterative algorithm for an arbitrary geometry [39]. Since we mostly work with unconventional system geometries, our basic workflow for validating the feasibility of a system includes a design-simulation-reconstruction loop. This comprises of a design phase when we design a system for a particular application, simulate the design using Monte Carlo tools, and reconstruct the data. Performance characteristics derived from the reconstructed data enable further optimization of the design. The process allows one to trade-off application specific imaging performance vs cost before actual system development. To accelerate this process as well as develop a consistent postproduction reconstruction across different geometries, we have developed a general-purpose image reconstruction framework implemented on Graphics Processing Unit (GPU) that allows for massive parallelism and speedup [40]. By general purpose, we mean that the framework can reconstruct images under different spatial arrangements of the detector blocks of different sizes and materials. This chapter describes the simulation-
2.2 Reconstruction Framework

2.2.1 GATE Simulation and Data Preprocessing

GATE [36] is built based on Geant4 MC code and it uses Geant4 libraries for the simulation of particle transport. GATE simulations employ a Geant4 script language or macro language. Therefore, it does not require the user to have any prior C++ programming skills in order to carry out a GATE simulation[41]. The program has a layered architecture with a core layer that defines the main tools and features of GATE in C++, an application layer with C++ base classes and at the top, a user layer where the simulations are set up using command-based scripts.

A typical GATE simulation is divided in seven steps:

1. The verbosity level is set for each simulation module. This means that it is possible to decide the amount of information about the simulation returned by the program. In the first step, the visualization options are also chosen.

2. The geometries are defined. In this step, the geometry, denoted “world”, in which the simulation is going to take place is initially defined. The user can define the geometry of the PET scanner as accurately as the position and orientation of the LSO crystals. The system definition can be considered as sort of a template described by key components organized in a certain way, what is called a tree level structure, each component having its own specific role or ordering. The different
components of a PET scanner are ‘rsector’, ‘module’, ‘submodule’, ‘crystal’ and ‘layer’. After defining the system geometry, the phantom (i.e. the volume to be scanned) geometry is defined.

3. This step defines the detection parameters in the so-called digitizer module. Here the characteristics of the system are prescribed such as energy and timing resolution. It is also possible to include dead time and other features related to the creation of the image.

4. The physical processes are chosen for the simulation. This includes the choice of interactions library, enabling or disabling interaction effects and setting cut-off energy or range for secondary particle production.

5. The radioactive source is defined. This includes particle type, activity and half-life, source geometry, emission angle and source movement.

6. Output format is chosen. Different output formats are available for different imaging systems. For our simulations, we use the ASCII format.

7. The experiment is initialized and started.

For extracting the geometry information about the detector crystals, we use HepRep (for High Energy Physics REPresentables) file to extract the size, position, and orientation of the detector elements in a hierarchical format. After running the geometry initialization, the following GATE commands are run:

> /vis/open HepRepFile
> /vis/viewer flush

All the geometrical information will be saved in a file with heprep extension. The HepRep file is in XML format and can be displayed by most web browsers with colorful indenting and coding. Geant4 volumes have sub-volumes, etc. For example, a PET system consists of sectors, sectors have modules, modules have crystals, and crystals have LSO (cerium-doped lutetium
oxyorthosilicate) or BGO (bismuth germanate) elements. To read the XML file we utilized the MATLAB® built-in function:

```matlab
DOMnode = xmlread('G4Data0.heprep');
```

This returns a Document Object Model node (DOMnode). In a Document Object Model, every item in an XML file corresponds to a node. The properties and methods for DOM nodes such as `getElementsByTagName('heprep:instance')` and `getChildNodes` are used to extract the geometry information from the scanner all the way down to the LSO elements. We save this information in a text file (which we call the geometry file). In this file, a single crystal information is stored in six consecutive rows. The first row corresponds to the crystal center coordinates, the second, third and fourth rows store the coordinates of the three normal directions of the crystal, the fifth row corresponds to the crystal dimension and the sixth row corresponds to number of depth layers in the crystal. We use this file to define the detector crystal position while doing reconstruction.

Different GATE output formats are available for different systems. The ASCII format, which is the choice in this work, is the simplest. It gives all information about the detected photons in a large text file. Each row corresponds to one event and includes information about event number, time of annihilation, positions of annihilation, scatter, energy deposition, detecting crystal IDs and position where detected. The ASCII format allows us to process our raw data with our own tools. However, this output is not compressed, and the output files are very large. For cases where further analysis of raw data is not required, the ROOT output format can be used to save space and speed up simulation. We used data generated by GATE as singles events from each system since GATE is not capable of generating a coincidence file for the coincidence events between the scanner and
any extra system added to the geometry. We have therefore developed our own sorting code that finds the coincidence events in the individual singles file as well as between different singles file. The coincidence sorting is performed based on two different criteria. The first method uses the time information of each singles event to determine whether they are detected within a certain time window. The coincidence time window we use in our studies is 4.5 ns. Using this method, we get true, scatter and random coincidences. The second method uses event-ID information and if two events have same ID they are written as coincidence event. Using this sorting method, we reject random coincidences and extract only trues and scatter events. Furthermore, the scatter and trues events can also be written as separate files when we use the scatter information from the singles file. After sorting events based on event ID, for each coincidence event, if any of the scatter flags of the two corresponding singles event is non-zero, we write that as a scatter event and vice versa. The scatter and trues coincidence information is used for scatter correction as describe later in this chapter. After coincidence sorting, we get a listmode file (with extension .lst) where each row corresponds to a coincidence event and contains information like event ID, ID of first crystal, ID of second crystal, time of detection for first crystal and difference of detection time between two crystals (time-of-flight). The crystal IDs are ordered in the same way each crystal was built in GATE. Hence, this ordering is the same when we extract crystal information in the geometry file. While doing reconstruction, we read crystal IDs for each coincidence event and look up the corresponding crystal position and orientation coordinates from the geometry file.
2.2.2 List-Mode MLEM Equation

The standard MLEM update equation for emission tomography is given by:

\[ X_j^{(k+1)} = \frac{X_j^{(k)}}{S_j} \sum_i H_{ij} A_i N_i \frac{Y_i}{\sum_{j'} H_{ij'} A_{i} N_i X_{j'}^{(k)} + S_i + R_i} \]  

(2.1)

Where \( S_j = \sum_i H_{ij} A_i N_i \).

\( X_j^{(k)} \) is the intensity value at \( j^{th} \) voxel and \( k^{th} \) iteration for the activity distribution map, \( Y_i \) is the number of prompt events detected at \( i^{th} \) Line-of-Response (LOR), \( S_j \) is the sensitivity value at the \( j^{th} \) voxel denoting the probability of a back-to-back photon pair at the \( j^{th} \) voxel being detected by all possible LORs through that voxel. The term \( S_i + R_i \) is the scatter and random coincidences added to the forward projection of the current image estimate. The system matrix \( H_{ij} \) describes the probability of a back-to-back photon pair emitted at the \( j^{th} \) voxel being detected by the \( i^{th} \) LOR, \( A_i \) is the attenuation correction factor, \( N_i \) is normalization factor.

In list-mode, which is the processing method used in this work, the detector crystal position, time of arrival and time-of-flight information are stored sequentially in a long list as the scanner records the events. The problem of reconstructing directly from the list-mode data lends itself to a maximum-likelihood formulation based on the EM algorithm. Despite its computational burden, this processing method is popular because it is an efficient format to process sparse data sets, such as dynamic, time-of-flight, or high-resolution studies. It has additional benefits, namely: (1) all the original information can be stored for each event; (2) natural complete subsets can be formed by splitting the events chronologically; (3) Backward and forward projection of LORs can be computed on-the-fly, hence not requiring to store the entire system matrix; (4) image reconstruction can be started as soon as the acquisition begins; (5) events can be positioned
continuously in space and time; and (6) data can be converted to any other format if necessary. The histogram-mode EM update equation can be simply changed into a list-mode EM update equation by changing the backward projection of the counts $Y_i$ into individual backward projection of one count. Since there will be $Y_i$ list-mode events detected by the $i^{th}$ LOR, the addition of their backward projections will be equivalent to the original backward projection of histogram-mode data. Hence, equation (2.1) was changed into a list-mode EM update equation given by:

$$X_j^{(k+1)} = \frac{X_j^{(k)}}{S_j} \sum_m H_{i(m)} j A_{i(m)} N_{i(m)} \frac{1}{\sum_j H_{i(m)} j A_{i(m)} N_{i(m)} X_j^{(k)}} + S_{i(m)} + R_{i(m)}$$

(2.2)

where $m$ denotes the list-mode events and $i(m)$ denotes the corresponding LOR index where the $m^{th}$ event is detected.

The most computationally intensive part is to calculate $S_j$. Calculating $S_j$ requires a full backward projection of system matrix (column sum) including data correction items such as attenuation correction and normalization factors. For systems with large geometry the computation speed of this becomes a limiting factor.

### 2.2.3 GPU Implementation of Projection Kernels

For faster image reconstruction, the forward and backward projection operations were implemented on GPU using Nvidia compute unified device architecture (CUDA) programming model. During forward projection, backward projection, and image update, a group of voxels are simultaneously assigned to different blocks of GPU threads. While within each block, threads loop through all list-mode events. Forward projections of LORs are independent of each other. As a result, LORs are divided into equal-sized groups, each assigned to a thread block. Each thread in
the thread block processes a line independently. The voxel values are projected to be stored sequentially in the same order as list-mode events. This increases the memory access speed because coalesced reading and writing operations are achieved. In backward projection, the matched LOR-driven approach takes advantage of coalesced addressing at the cost of memory writing conflicts in image space since multiple lines may write to the same location in shared memory simultaneously. However, these conflicts are handled by hardware atomic operations in newer generations of GPU devices.

To further improve the image reconstruction speed, a multi-GPU approach is used to simultaneously perform the most computationally intensive projections. List-mode events are divided into different groups and transferred to different GPUs while each GPU keeps a copy of the current iteration of image volume. After one complete forward and backward projection, a global reduction is performed to sum the entire updated image together. After the image update step is finished, the new image volume is then distributed to all GPUs for subsequent iterations of projections.

2.2.4 Calculation of Detector Response Function (System Matrix)

For calculating the geometric detector response function, the Siddon's ray tracing algorithm is a very efficient algorithm to compute the weight along the path of the line-of-response. However, since it relies on a branching operation at the boundary of each voxel, it is not suitable for GPU implementation. Tracing a ray through a large 3D volume involves a large number of branching operations which will cause the threads in the same warp to diverge, significantly increasing the execution time.
To fit the massive parallelism structure of GPU platform, we required a branchless ray-tracing method for calculating the projection kernel on-the-fly. Hence, we have implemented a Gaussian Tube-of-response (TOR) projector [42], [43] to describe the geometric (blurring) component of the system matrix ($H_{ij}$). It is computed for each image space voxel intersected by a particular TOR joining two crystals by weighting the TOR with a Gaussian function. A cylindrical TOR is chosen to include all the voxels whose contribution to the detector response function is above a certain threshold. The intersection of the TOR and a slice is an ellipse. However, for different relative orientations of the TOR and the slice, the width of the bounding rectangle can vary from the diameter of the TOR (when the TOR and the slice are orthogonal) to the size of the slice (when the TOR and the slice are parallel) as shown in Figure 2.1; hence, slice-by-slice processing of the TORs will introduce severe thread divergence, serializing the calculations on the GPU.
Figure 2.1: (a) Intersection of a Tube-of-Response (TOR) with an image slice. The intersection cross-section is an ellipse and the bounding parameter is given by $K$; (b) When TOR is perpendicular to image slice, bounding parameter is diameter of the TOR; (c) When TOR is parallel to the image slice, bounding parameter is given by size of the slice.

To efficiently compute the projection without diverging within thread blocks, we categorize the lines within each subset into two classes according to their predominant direction. More specifically, the predominant direction is the direction selected from $x$ and $y$ (considering our system has smaller axial length and direction $z$ is along the scanner axis) that has the largest absolute value of inner product with the line direction. Here directions $x$ and $y$ span the trans-axial image plane. For each class of lines, the slices are selected to be orthogonal to the predominant line direction. By slicing the image volume orthogonally to the predominant TOR direction, the area of the intersection of the TOR and the slice is bounded. If the bounding parameter is $K$, then we can simply process a fixed square region of $K \times K$ voxels for all TORs without introducing any thread divergence.
The weight of a voxel ($V_j$) depends on the perpendicular distance from the voxel ($V_j$) to the center of the TOR ($T_i$), shown as $d_{ij}$ in Figure 2.2. The width of the Gaussian kernel ($\sigma$) changes for each TOR depending on the cross-section of the two crystals.

If time-of-flight (TOF) information is available, the weighting function is the product of the non-TOF weighting function and a Gaussian function that is centered at the event TOF center and extends along the TOR direction. The event TOF center is calculated as $x = c\Delta t/2$, where $c$ is the speed of light, and $\Delta t$ is the TOF value. The width ($\sigma_{\text{tof}}$) of the weighting function is determined by the system time resolution. The TOF weight for each voxel depends on its distance from the TOF kernel center ($C$), as measured along the TOR. This distance, $d_{ij}^{\text{tof}}$, is shown in Figure 2.2.

Since for this approach, the system matrix was computed on-the-fly, the algorithm does not require the large system matrix to be pre-computed and loaded to memory during reconstruction.

$$K(d_{ij}) = e^{-\frac{d_{ij}^2}{2\sigma^2}}; \quad K(d_{ij}^{\text{tof}}) = e^{-\frac{d_{ij}^{\text{tof}}^2}{2\sigma_{\text{tof}}^2}}; \quad H_{ij} = K(d_{ij})K(d_{ij}^{\text{tof}})$$

Figure 2.2: Gaussian weighted TOR method with TOF information can be implemented using a GPU for on-the-fly calculation of the system matrix.
To approximate the effect of solid angle of a voxel on the two detector crystals, we divide the weighting function by a solid angle ratio (SAR) function. This SAR function has two parts. The first part is $\text{SAR}_{\text{var}}$ which denotes the variation of solid angle along the TOR. The second part is given by the square of the distance between the two crystals. To approximate the effect of solid angle along the TOR, we tried different functions for $\text{SAR}_{\text{var}}$ as shown in Figure 2.3. Each of them is a function of ‘r’ which is the ratio of the projection distance ($x_1$) from voxel center to one of the detectors and the projection distance between two detectors ($x_2$). The plot of each function with respect to ‘r’ is shown in Figure 2.3(b).

![Solid Angle Ratio Approximation](image)

**Figure 2.3:** (a) Solid angle ratio approximation uses the ratio of the projection distance ($x_1$) from voxel center to one of the detectors and the projection distance between two detectors ($x_2$) to compute the $\text{SAR}_{\text{var}}$, this is then multiplied with the square of the distance between two detectors. (b) Three different functions of $\text{SAR}_{\text{var}}$ used to compute solid angle ratio.
We simulate a uniform cylindrical phantom of diameter 30 cm and height 50 cm in air using GATE and acquire data for 5 minutes with a Siemens Biograph Vision scanner. The purpose of this simulation is to test the performance of our framework and system matrix approximation with no attenuation and scatter correction required, since gamma particles in air doesn’t undergo attenuation and scatter. Figure 2.4 shows the reconstructed results for the different solid angle ratio functions (Figure 2.3(b)).

![Central slice of reconstructed images of a cylindrical phantom in air using three different solid angle ratio approximation functions. The corresponding horizontal line plots across the center of the phantom is shown in the bottom row. (Voxel dimension:1.65x1.65x1.65 mm)](image_url)
From Figure 2.4, we observe that case 3 gives the best result among all three cases since it has a uniform profile. From the plots in Figure 2.3 (b), case 3 is almost flat across the central region of the FOV of the scanner, thus it can be approximated as SAR\textsubscript{var} = 1, denoting that there is nearly no change in solid angle ratio across the TOR. For future studies, we use this result to calculate the system matrix.

### 2.2.5 Attenuation Correction

The 511 keV annihilation photons originating from different locations in the body are attenuated by tissue, as they traverse different thicknesses to reach the detector pair in coincidence, thus reducing the number of photons detected in each LOR. These interactions include the photoelectric effect, scattering, and pair production. Attenuation has the largest effect on the central regions of the patient since the rays are more attenuated which makes the radiotracer concentration in these regions appear lower than its true value. Thus, attenuation correction makes the PET images more quantitatively accurate and reduces the visual bright artifacts along the edges. Correcting for attenuation requires knowledge about the attenuation coefficients of different tissues in the body. These attenuation coefficients are stored in a 3-dimensional image called the attenuation map. The probability of photon attenuation depends on the electron density of the tissues, and the attenuation map, therefore, can be easily derived from images acquired with an imaging modality based on the measurement of photon transmission, such as CT. In current PET/CT systems, attenuation correction is typically done by bilinear scaling of CT Hounsfield [44] units. For our studies, since a CT image is not available for the phantoms, we generate analytical attenuation maps with the
corresponding attenuation coefficients of the materials used in the phantoms. The attenuated intensity of radiation is given by:

\[ I_x = I_0 e^{-\int \mu(x) dx} \]  \hspace{1cm} (2.3)

where \( I_x \) and \( I_0 \) are the attenuated and unattenuated intensity of radiation respectively, \( \mu \) is the linear attenuation coefficient (units: cm\(^{-1}\)), and \( x \) is the distance (units: cm) from the source to the detector. Thus, if \( \mu \) values are known for an object, we can calculate the attenuation correction factor (ACF) for a LOR by:

\[ ACF = \frac{I_x}{I_0} = e^{-\int \mu(x) dx} \]  \hspace{1cm} (2.4)

For discretized system, the ACF along LOR \( i \) is given by:

\[ A_i = e^{-\sum \mu_j l_{ij}} \]  \hspace{1cm} (2.5)

Where, \( \mu_j \) is the linear attenuation coefficient value at voxel \( j \), \( l_{ij} \) is the length of intersection of LOR \( i \) with voxel \( j \). The summation is performed for all voxels that lies on the LOR.

Since computing the exact intersection length for each cubic voxel is more computationally expensive in GPU due to many branching operations, we approximate the cubic voxels to spherical voxels (Figure 2.5) which makes the computation of intersection length (2x in Figure 2.5) simpler. The size of the spherical voxel is chosen to fit inside the cube i.e. the diameter of the spherical voxel is equal to the length of the cube.
Using this, we calculate the distance from the center of the voxel to the LOR. This is given by $d$ in Figure 2.5. Since we know both $r$ and $d$, we can calculate $x$ by using $x = \sqrt{r^2 - d^2}$. The intersection length will be given by $2x$. We use this attenuation correction factor in equation 2.5 to get the attenuation corrected reconstructed image.

Using this approximation, we reconstructed a cylindrical phantom filled with water. Figure 2.6 (a) shows the maximum intensity projections of the reconstructed image. We notice vertical and horizontal line artifacts in the image, mostly around the central region. Performing a sub-crystal division (diving each crystal into 4 sub crystals) helped reduce the artifacts (Figure 2.6 (b)) at the cost of increased computation time. We then investigated different sphere radius to cube length ratios so that we can get rid of the artifacts without losing on speed of calculation. We observed that these artifacts are significantly reduced if the radius $r$ of the voxel is such that the volume of the spherical voxel is equal to the volume of the cubic voxel. The reconstructed image is shown in Figure 2.6 (c).
Figure 2.6 Reconstructed images of cylindrical phantom for different attenuation correction approximations. (a) Length of cube equal to diameter of spherical voxel and without sub crystal division, (b) Length of cube equal to diameter of spherical voxel and with sub crystal division, (c) Volume of cube equal to volume of spherical voxel and without sub crystal division.

2.2.6 Normalization

While calculating the system matrix, if some elements in the model are neglected, they eventually cause artifacts in the reconstructed image. This imperfection in the calculation stems either from the incomplete physical model, such as failing to take into account the angle at which a line-of-response (LOR) enters the surface of a crystal, or from the gradual variation in the real system, such as crystal/detector degradation and failing. By scanning an exactly known emission phantom, called normalization phantom, one may estimate the neglected elements in the system matrix by comparing the acquired data from the phantom with the data from the digital phantom being forward projected using the system matrix. This process is called normalization and the neglected elements are compensated for through the multiplicative factors called the normalization factors. Two main requirements for the normalization phantom is (i) the activity distribution of the normalization source must be known: the amount of radioactivity and the map of the normalization source must be known exactly with respect to some standard precision; (ii) the activity distribution
of the normalization source must provide sufficient number of coincidence events to estimate the normalization factors.

Typical PET scanners have detectors with identical crystals, however, if the imaging system consists of more than one type of detector, either crystals of different sizes, or crystals of different materials, then there is more than one type of LORs in terms of detection efficiency. The LORs connecting detectors of the same type, as opposed to LORs connecting detectors of different types, must be properly modeled. If such property is not modeled in the forward model, then it has to be estimated by means of normalization. For example, our total breast PET system discussed in Chapter 3 has different sized crystals across the system with an unconventional geometry. In such cases, normalization becomes a necessary correction.

Normalization can be done using two approaches: direct and component-based. Direct normalization method is designed to be simple to use, as it does not require a model of the individual normalization effects. A uniform normalization source is typically used to illuminate all LORs in the FOV during the direct normalization acquisition. Next, a digital image of the source distribution is created and forward projected using the modeled system matrix factors. Finally, the ratio of the measured data to the forward-projected data is used as the normalization factor. One major drawback of this method is the requirement of a long scan since insufficient count statistics can lead to additional noise and overfitting. In component-based normalization approach, each source of LOR sensitivity variation (other than those already accounted for in system matrix) is modeled as a normalization component. Several component-based normalization methods have been proposed which investigates models of varying complexities[45]–[47].

Our current forward projector model uses the center of the crystal volume to calculate the Gaussian-TOR. It does not take into account differences among individual crystal intrinsic
detection efficiencies, or reduction in effective crystal efficiency due to oblique photon incidence. To account for the differences in crystal detection efficiency among TORs, we start by using a simple normalization approach (Type-0 normalization). For this method, we divide the system into different detector groups based on crystal dimensions. For each group of detectors in coincidence with another group, we compute a single normalization coefficient, thus assuming equal efficiencies for all the detectors in each group pair. The normalization coefficient for each coincidence group pair is calculated by:

\[
c_{g_1g_2} = \frac{N_{g_1g_2}}{\sum_j S_{j}^{g_1g_2}E_j}
\]

(2.6)

Where \(c_{g_1g_2}\) is the coefficient for detector groups \(g_1\) and \(g_2\), \(N_{g_1g_2}\) is the number of coincidence events between \(g_1\) and \(g_2\), \(S_{j}^{g_1g_2}\) is the \(j^{th}\) voxel value of the sensitivity image between \(g_1\) and \(g_2\), \(E_j\) is the \(j^{th}\) voxel value of the normalization image. The final sensitivity image of the whole system is a weighted sum of the individual sensitivity images of each group pair and the weights are given by Equation 2.6. This normalization method works well for a cylindrical PET system which has all crystals of same dimension symmetrically located. To investigate this technique for a system with asymmetric geometry and different crystal sizes, we used this normalization for our total-breast PET system (shown in Figure 2.7(a), also described in chapter 3). We noticed significant artifacts when we reconstructed a torso phantom as shown in Figure 2.7 (b). To avoid these artifacts, we extended the normalization method to estimate the variation in efficiencies between each detector module. Here, a normalization factor needs to be applied to each module pair, taking into account both crystal thickness and photon obliquity. We implement the module-based normalization (Type-1 normalization) as described below.

A module here is defined as a group of neighboring detector crystals. The size of the module can be chosen according to the count statistics of a normalization scan. If a scan has higher count
statistics, a smaller module can be chosen, which will give better normalization factors. If a scan has lower count statistics, a larger module can be chosen to avoid noise. In an ideal situation, a module pair should be equal to one crystal pair. In this case, it is equivalent to direct normalization used in conventional cylindrical PET system which requires large number of counts.

Defining $S_j$ as the total sensitivity value (summed over all TORs) at the $j^{th}$ voxel, $S_j^p$ as the sensitivity image value at $j^{th}$ voxel for the $p^{th}$ module pair and $C_p$ as the normalization factor for $p^{th}$ module pair, the sensitivity image of the total-breast PET system becomes:

$$S_j = \sum_p C_p S_j^p$$  \hspace{1cm} (2.7)

$C_p$ values were empirically determined by comparing the predicted number of coincidences for each module pair, found by forward projection through the non-normalized system matrix, to the actual numbers determined using Monte Carlo simulation. Then the $C_p$ values were defined as:

$$C_p = \frac{\text{Actual} \# \text{ of coincidences for module pair } p}{\text{Predicted} \# \text{ of coincidences for module pair } p}$$  \hspace{1cm} (2.8)

The actual number of coincidence counts for a module pair was computed from Monte Carlo simulation of a known activity distribution in a uniform normalization phantom or from experimental data by scanning a uniform phantom using a real scanner. The predicted number of coincidences calculated by forward projecting a digital representation of the same phantom through the system matrix. After computing $C_p$ for all module pairs, this factor is multiplied while calculating the system matrix during reconstruction (from equation 2.2). We used this approach to the same torso phantom while reconstruction. We noticed significant improvement in uniformity across the torso image as shown in Figure 2.7 (c).
2.2.7 Scatter Correction

In PET, scattering (or Compton scattering) is caused by the gamma photon interacting with an atomic electron to transfers partial energy of the photon to eject the electron. The remaining photon energy is emitted as a lower energy gamma photon with a longer wavelength. The direction of the new gamma photon deviates from the original photon path. Higher angles from the original path are more uncommon, with the energy of the emitted gamma photon being much lower. After Compton scattering, the photon energy decreases, and the probability of photoelectric absorption increases.

The energy of the emitted photon is given by Compton scattering equation.

According to the standard Compton equation,

\[ \lambda_f - \lambda_i = \frac{h}{m_e c} (1 - \cos(\theta)) \]  

where \( \lambda_i \) is the wavelength of incident photon, \( \lambda_f \) is the wavelength of the scattered photon, \( h \) is the Planck's constant, \( m_e \) is mass of the electron, \( c \) is the speed of light and \( \theta \) is the
scattering angle.

The energy of the scattered photon,

\[ E_f = h\nu_f = \frac{hc}{\lambda_f} = \frac{1}{E_l} + \frac{1 - \cos(\theta)}{m_e c^2} \]  

(2.10)

As far as scattering is considered the prompt events follow a purely additive model: \( d_0 = d + s \), where \( d \) is the photo-peak (unscattered) events and \( s \) is the scattered events. Several methods have been proposed to correct for scattering in 3D PET. Here we adapted the most widely implemented method for scatter correction using Single Scatter Simulation (SSS) for list mode reconstruction. The original description of the SSS is presented in [48]. Code realization used in our lab is presented in [49].

The goal of the SSS Compton scatter correction is to estimate the fraction of the scatter events in obtained data which is in the form of coincidence detections for every LOR. This estimation is done using known CT/analytically generated attenuation image and preliminary reconstructed image (or activity distribution) using prompt data. Assumptions of this technique include: (i) there is significant fraction of the “true” detections (i.e. none of two detected gammas was scattered) in the prompt data, thus, some preliminary activity distribution can be reconstructed, (ii) most of the scatter events are events with only one scatter for both detected gammas (what is reflected in the name “Single Scatter”), (iii) attenuation image of the object is available, (iv) pre-reconstructed emission image should include proper attenuation and normalization.

Figure 2.8 demonstrates the main approach of SSS. Scatter contribution for crystals A and B is a combination of the two possible scenarios: 1) A detects a scattered gamma (shown in Figure 2.9) while B detects “true” gamma; and 2) B detects scattered gamma while A detects “true” gamma.
Digital implementation of the code is shown on Figure 2.9. Since Compton scatter events are low resolution data, thus, simulations can be done for low resolution images (down-sampled pre-reconstructed images or images reconstructed with large image voxel sizes). Scatter points \( S \) are generated at the center of every “non-empty” image voxel. An image voxel is “non-empty” when the corresponding voxel in attenuation image has non-zero value. Digital integration assumes uniform values of attenuation and activity inside every voxel.
The time-of-flight (TOF) extension of the SSS is presented in [50]. In this SSS TOF extension, the activity line integral is calculated with weighting coefficient \( \varepsilon(x, dT) \) for all voxels along the “scatter path” (ASB on Figure 2.8 or \( C_1S_NC_2 \) on Figure 2.9). Here, \( \varepsilon(x, dT) \) is a normal distribution along scatter path centered in a point that corresponds to the detection time difference \( (dT) \) between detectors \( C_1 \) and \( C_2 \); \( x \) is the distance from the voxel center to the center of distribution (see unfolded path on the bottom in Figure 2.9).

In our SSS TOF, the voxel size was selected to be approximately equal to the detector timing resolution FWHM. This allows to simplify the activity line integral calculation using only one voxel \( V_T \) that corresponds to the given detection time difference between crystals \( C_1 \) and \( C_2 \). Mean (or effective) range will be approximately equal to the voxel size (or less if the detectors FWHM is smaller than voxel size). Thus, we reduce integral to the calculation of the contribution from the most significant voxel. We calculate the activity contribution for all scatter paths joining a detector pair and finally the resultant scatter contribution for that detector pair. For scaling the scatter coefficients with the original scatter data, we calculate a scaling coefficient by comparing the LORs passing through the imaging object from MC scatter data and SSS. A group of LORs are
used to increase the statistics. More details on calculating the scaling coefficient is described below.

To test our scatter correction technique, we simulate uniform cylindrical and elliptical-tube shaped phantoms of different sizes and activity concentrations scanned using Siemens Biograph Vision scanner in GATE. The phantoms were filled with water. Reconstruction of prompt data is performed including attenuation correction and Type-0 normalization using Equation 2.2, assuming scatter and random to be zero. This reconstructed image is then used for scatter estimation using SSS. MC scatter data is used to compute the scaling coefficient between the scatter values and data. In theory, the scaled scatter values for each LOR can be used in the denominator of Equation 2.2 to generate scatter corrected reconstruction image from prompt list mode data. But we had to use an additional scale of 0.1 to the estimated scatter values to get the correct reconstructed image (Figure 2.10). This can be due to different assumptions we made during the process like assuming scatter contribution from the most significant voxel in the scatter path instead of a line integral of all voxels, using a simple global normalization instead of modeling each crystal pair individually etc.
Figure 2.10: Scatter Correction Results for (a), (b), (c) Uniform Cylinder phantom, (d) Elliptical tube phantom. The top left images show the estimated scatter sinograms, bottom left image show the horizontal profile across crystal ID 570. The top row 2nd-4th column show the reconstructed images before scatter correction using prompt data and trues data in air and image after scatter correction. The bottom row show the horizontal line profiles across the center.

Figure 2.10 shows the reconstructed images using prompt events and true events in air, scatter corrected images and histogram plots for computing scaling coefficient for different phantoms and activity concentrations. For the histogram line plots, blue profiles are the MC prompt data, green profiles are MC scatter data and red profiles are scaled SSS TOF data. Estimated scatter sinograms are coincidence matrix for LORs compressed in Z-direction. X and Y coordinates on sinogram are the crystal IDs in a ring. X-projection for Y=570 is obtained by fixing one of the crystals (i.e. a group of crystals that have the same (x,y) coordinates). Thus, profiles presented at the bottom are the projections of the phantom to the scanner from crystal ID 570. Here, the edge of the phantom can be clearly seen and SSS simulated projection can be easily fitted to the “tails” of the simulated
data distribution. From the results in Figure 2.10, we observe that the scaling coefficient computed using tail-fitting is 10 times the coefficient used for reconstruction. This ratio remains constant irrespective of size of phantom and activity concentration. We believe this will also remain constant for different scanners as long as we are using the same system model for calculating scatter and reconstruction. We simulate the phantom both in air and water. In case of air, there is no attenuation and scatter, so we get the ‘trues’ image which we set as the reference standard for comparison. For all the cases, we see the scatter corrected image is more uniform than the prompt image and the voxel values are close to the ‘trues’ image. For the elliptical tube phantom in Figure 2.10 (d), the scatter corrected image is uniform, but the voxel values are a little higher than expected. Figure 2.10 (a) and (b) show results from same sized phantom with different activity concentration (decay/voxel). Here the scaling coefficients are different (150 & 125). Figure 2.10 (c) and (d) have different sizes and shape of phantom but same activity concentration. In this case, the scaling coefficients are same (both 180). This shows that for a certain scanner, the scaling coefficient changes with activity concentration and remains same irrespective of size and shape of the phantom.
2.3 Validation of Image Reconstruction Framework with Clinical Reconstruction Software

2.3.1 Monte Carlo Simulation and Experiment Setup

To validate the quantitative accuracy of our Monte Carlo simulation study and image reconstruction framework, simulation results using the above framework were compared with simulations and experimental results obtained from a Siemens Biograph Vision scanner. A Siemens Biograph Vision PET scanner was simulated using GATE to image a National Electrical Manufacturers Association (NEMA) Image Quality (IQ) phantom placed at the center of the scanner’s imaging FOV. In addition to the six spheres in a standard NEMA IQ phantom (Figure 2.11 (a)), six smaller spheres were also added as shown in Figure 2.11 (b). According to the NEMA NU2–2001 standards[51], the radionuclide to be used in this phantom is $^{18}$F. Activity concentration in the phantom and lesions was 5.3 kBq/cc (143 nCi/cc) and 53 kBq/cc (1430 nCi/cc), respectively, to create a lesion-to-background concentration ratio of 10:1. A 10-minute scan was simulated and the data was reconstructed using our list-mode GPU based framework as described above.

The physical NEMA IQ phantom (with the additional six spheres) was also imaged after filling the spheres with $^{18}$F solution with the activity concentrations specified above in a Siemens Biograph Vision PET/CT scanner. Both simulation and experimental data were reconstructed using the Siemens software (e7 tools) using OP-OSEM-TOF method, with 8 iterations and 5 subsets and no post-reconstruction filter. These reconstruction parameters are chosen to provide high-resolution images. Images were reconstructed on 1x1x1.65 mm$^3$ voxels for Siemens software. For reconstruction using our framework we used 1x1x1 mm$^3$ voxels and 20 iterations. Scatter correction was not implemented for both reconstruction methods.
The contrast recovery coefficient (CRC)\cite{52} (calculation of CRC is explained in section 3.2.5) was measured for the different sized lesions from both simulated and experimental images using standard Siemens software and simulated images using our reconstruction framework for quantitative comparison.

Figure 2.11: NEMA IQ phantom study in GATE. (a,b) NEMA phantom with different lesions’ locations and indicated diameters. (c) GATE implementation of NEMA IQ phantom inside Biograph Vision System

2.3.2 Results

Figure 2.4 shows the experimental and simulated NEMA IQ phantom data reconstructed using three different methods and their corresponding contrast recovery coefficients. Figures 2.12 (a,b) shows the reconstruction of simulated data using Siemens software (E7tools). Figures 2.12 (c,d) shows the reconstruction results of simulated data after 40 iterations using our list-mode MLEM reconstruction framework. Figures 2.12 (e,f) shows the reconstruction of experimental data using Siemens software (E7tools). From the CRC plot (Figure 2.12 (g)), comparable contrast recovery can be observed for all lesions including the three smallest diameters (3.9 mm, 4.94 mm and 6.2
mm). These results suggest that the image reconstruction results from our implementation of list-mode MLEM produces similar image quality as compared to those from simulated and measured phantom data on the Biograph Vision system reconstructed with Siemens provided e7tools software.

Figure 2.12: NEMA IQ phantom reconstructed using (a, b) Siemens software from GATE simulated data, (c,d) list-mode ML-EM framework from GATE simulated data, and (e,f) Siemens software from experimental data. (g) is a CRC plot for lesions of different diameters, as indicated in the plot.
Chapter 3: Development of a Dedicated Total Breast PET System

3.1 Background and Motivation

Breast cancer is one of the leading causes of malignancy and the second leading cause of cancer related death in women in the United States[53]. Worldwide, there are more than 1.6 million newly diagnosed cases[54] and nearly 600,000 deaths from breast cancer per year[55]. Early detection remains a powerful tool in reducing mortality with early intervention. It has been shown that early detection when tumor size is small increases the chances of survival to as high as 98% over a 5-year period[53]. Radiotracer-based molecular imaging can complement conventional breast imaging techniques such as x-ray mammography, x-ray tomosynthesis, ultrasound, and magnetic resonance imaging (MRI) to improve the overall diagnostic accuracy, particularly in patients with dense breasts.

Clinical PET provides quantitative measurement of radionuclide activity concentration in body. Whole body imaging capability provided by clinical PET has been shown to be valuable in detecting loco-regional and distant metastasis for staging both primary and recurrent breast cancer. However, these whole-body PET systems are limited in terms of both spatial resolution and system sensitivity. The increasing uncertainty due to photon acollinearity as a function of PET system diameter, as well as the increased cost of the system when utilizing smaller crystals with their associated hardware limit the resolution of the contemporary whole-body commercial systems to 4-5 mm. Due to low resolution, the ability of these systems to identify tumors that are well-differentiated or small in volume is limited. Since tumor size correlates with probability of
metastasis, an improvement in image resolution potentially improves cancer management and patient care.

PET resolution is limited by positron range and photon acollinearity. Although spatial resolution could possibly be improved by having smaller crystals, the increased cost of the system when utilizing such crystals with their associated hardware can be a constraining factor. Another critical factor is the increasing uncertainty due to photon acollinearity as a function of PET system diameter that limits the overall improvement in PET resolution even if one uses high cost higher resolution detectors for a clinical whole-body PET scanner.

These limitations led to the development of the high-resolution positron emission mammography (PEM) or PEM/CT systems by many groups. PEM systems achieve higher resolution images by using smaller sized scintillation crystals, with detectors closely placed around the region of interest (one or both breasts) to maximize solid angle coverage and thus the overall sensitivity of the system (Figure 3.1). A variety of PEM scanners have been designed with full-width at half maximum (FWHM) resolution ranging from 2 to 3 mm [56]–[86]. However, the current PEM imaging approaches, comprising of either two flat panel detector arrays (stationary/rotating) or a cylindrical arrangement of detectors around the breast, cannot reliably image the chest wall, and miss axilla and beyond due to the system geometry. All are designed to scan only a single breast at a time, except [85],[80] which are comprised of 2 cylinders for scanning each breast individually.
To overcome these limitations, we took a novel approach by first optimizing the overall performance, starting with high annihilation photon detection sensitivity and with all-tissue coverage to increase the FOV for accessing mediastinum and lateral axillary nodes[87][88]. This extended asymmetric PET FOV is meant to provide a view of the breast and all surrounding tissues similar to that from breast-MRI. Having higher sensitivity allows us to exploit detector technology that provides high-resolution images with low statistical noise and/or allow for reduction in patient radiation dose.

3.2 Methods

3.2.1 System Geometry Description

The proposed total-breast PET scanner includes an enclosed “stadium”-shaped detector ring and an anterior panel which together surround both breasts. This is like having endcap detectors on the flat-panel PEM/X box device[68]. The “stadium” ring has increased lateral height to facilitate
axillary lymph node imaging. The system also includes a posterior detector panel working in conjunction with the other two detector groups to enable imaging of the torso (chest wall and axillae). Figure 3.2 shows multiple three-dimensional renderings to illustrate the proposed total-breast PET system concept (using SolidWorks).

![Diagram of detector panels](image)

Figure 3.2: Design includes 3 groups of detectors: anterior panel and “stadium”-shaped ring are Time-of-Flight and Depth-of-Interaction (TOF-DOI) capable high-resolution detector modules while the posterior panel consists of detector modules similar to Siemens Biograph Vision PET/CT system. [Figure Courtesy: Dr. Martin Tornai]

### 3.2.2 Monte Carlo Simulation Study

We have implemented this system geometry in GATE[36] as shown in Figure 3.3 (a). The imaging system is defined by the arrangement of detector modules of different dimensions. The anterior panel and the “stadium”-shaped ring contain a total of 66 high resolution detector modules, each made with a lutetium-oxyorthosilicate (LSO) crystal array of 32x32 elements. Each LSO crystal measures 1.6x1.6x6 mm³ used in a 2-layer DOI configuration (2x6 mm) to increase sensitivity. The choice of small crystal pitches is to provide high image resolution (≤2mm FWHM) below the theoretical limit achievable by a whole-body PET system. The posterior detector panel consists of a total of 88 detector modules. Each detector module contains 20x10 LSO elements measuring
3.2x3.2x20.0 mm³. The specifications of the posterior panel detectors match with those used in the Siemens Biograph Vision PET system. Out of 85,184 crystals in this total-breast PET scanner, the 17,600 crystals in the posterior panel have lower resolution but higher sensitivity compared to the 67,584 crystals of the stadium-shaped ring and anterior panel. Because breast tissues are located near the anterior panel and “stadium”-shaped detectors, this system resembles the virtual-pinhole PET[89] or magnification geometry, where the image resolution in the breast region will be dominated by the intrinsic spatial resolution of the high resolution detector modules placed close to the breasts, with the 1.6x1.6x6 mm³ scintillator pixel cross-section.

To compare the performance of the proposed total-breast PET system against the gold standard – a clinical whole-body PET scanner, we simulated a Siemens Biograph Vision PET scanner as illustrated in Figure 3.3 (b). This scanner represents a state-of-the-art system and consists of a cylindrical arrangement of 38 detector modules. Each module is composed of eight LSO arrays of 20x10 crystals, each crystal measuring 3.2x3.2x20.0 mm³. The geometry described confers axial length of 25.6 cm and a ring diameter of 86.4 cm.

The coincidence resolving time (CRT) of all the detectors for both the systems was assumed conservatively to be 250 ps FWHM based on literature[28]. The energy resolution of all detectors was assumed to be 12.0% for 511 keV gamma rays. The energy window used was from 435 keV to 650 keV. We recorded singles events from all detector volumes and performed coincidence detection offline as a post-processing step using a 4.5 ns coincidence timing window.
3.2.3 Image Reconstruction and Correction Techniques

Since our proposed system has only few symmetries, we have used the general-purpose list mode reconstruction framework developed in our lab, which has been explored in detail in the previous chapter. This framework is particularly useful in systems like this where detector crystals of different sizes have arbitrary spatial arrangements.[77][75][75][74][73].

Normalization corrects for variation in detection efficiency among lines of response (LOR). In theory, any physical effects which are not modeled by the system response function (system matrix) should be corrected for by normalization. These effects may include change of crystal efficiency due to oblique incident angle, inter crystal scattering within a detector block, dead time of detector, etc [45]–[47]. The proposed total-breast PET system employs complex system geometry and two types of detector modules that have different crystal widths and lengths. Thus, accurate normalization is particularly crucial for the proposed total-breast PET system. Also, to maximize the solid angle coverage and overall system sensitivity, the detectors in the anterior panel and the stadium-shaped ring are placed close to breast tissues. Annihilation photons
originating within the imaging FOV may therefore enter those detector units from large oblique angles, thereby reducing the effective crystal thickness and lowering detection efficiency. Our current forward projector model uses the center of the crystal volume to calculate the Gaussian-TOR. It does not take into account differences among individual crystal intrinsic detection efficiencies, or reduction in effective crystal efficiency due to oblique photon incidence. To account for the differences in crystal detection efficiency among TORs, we use a module-based normalization method discussed in Section 2.2.6.

For our highly asymmetric geometry, a non-attenuating normalization phantom of two cuboids of dimensions 37x15x15 cm$^3$ and 30x15.5x10 cm$^3$ with uniform activity concentration was chosen as shown in Figure 3.4 which covers most of the TORs so that a substantial number of counts could be obtained to reduce noise and avoid overfitting. To evaluate the sensitivity of our system relative to a whole-body PET scanner, the sensitivity image of the Siemens Biograph Vision scanner was also computed in a similar fashion using a non-attenuating uniform cylindrical phantom of 40 cm diameter and 30 cm length.

![Figure 3.4: Normalization Phantom placed inside the dedicated breast PET system](image)

Attenuation correction was implemented using forward projection of the attenuation coefficient map of the known geometry of the object, which in practice can be either obtained by CT or MR
images. This implies that the proposed total-breast PET scanner can be combined with a second modality to provide anatomic landmarks as well as to support correction techniques that are needed for quantitative total-breast PET images.

3.2.4 Comparison of System Performance

Sensitivity Comparison

The sensitivity image used for image reconstruction also physically describes the probability of detection of a pair of annihilation gamma rays originating in the image space. It was calculated by backward projecting the system matrix along with appropriate normalization. Using the normalized system matrix and equations in section 3.2.3, the normalized sensitivity image of the proposed total-breast PET system was calculated. The sensitivity image of the Siemens Biograph Vision scanner was also computed in a similar fashion.

Phantom Image Comparison

To evaluate the performance of the proposed total-breast PET system for breast cancer detection, a torso-like phantom consisting of three water-equivalent cuboids was simulated to approximate the body and breasts. An illustration of the phantom is shown in Figure 3.5. The dimensions of the torso are 30x20x15 cm$^3$ and the breasts are 10x9x10 cm$^3$ each. Note that while this cuboid phantom is not curvaceous as a normal human torso would be, the edges and corners or the torso and breasts add high frequency features, which can be additionally evaluated for image quality. Furthermore, these simulated breast dimensions are more like the larger breast sizes encountered[90][91], and hence more difficult physical conditions for imaging. The radioactivity concentration was assumed to be $\sim$5.3 kBq/cc ($\sim$143 nCi/cc) in the body and breasts based on the assumption of $\sim$555 MBq ($\sim$15 mCi) of FDG uniformly distributed in a 70kg patient and the scan is acquired one-hour post-
injection. Twenty lesion-like spherical sources were placed at different regions throughout the phantom as shown in Figure 3.5 (c). The lesion diameter was varied from 4 to 6 mm, where, in each acquisition, all the lesions were of the same diameter (i.e. either 4, 5, or 6 mm). The ratio of activity concentration between lesions and the body background was varied from 4:1, 5:1 and 6:1. Imaging the torso phantom was simulated for 200s using the total-breast PET system as well as with the Siemens Biograph Vision scanner. Detector normalization using module-based approach was used for both systems. Attenuation correction used an analytically generated μ-map of the phantom, using the nominal narrow beam μ-value of water at 511 KeV (0.096 cm⁻¹). Scatter correction was not implemented.

Figure 3.5 Volumetric cuboid torso phantom included for visualization in (a) simulated clinical PET system, (b) dedicated breast PET system, and (c) planar distribution of 20 spherical lesions throughout the torso volume. Phantom and inserted lesion sizes are in the text

3.2.5 Quantitative Image Analysis Metrics

Contrast Recovery Coefficient (CRC)

To quantify the performance of the two systems in the detection of small lesions, the contrast recovery coefficient (CRC) for each known lesion in the simulation study was calculated. The
lesions were divided into three categories depending on their physical location inside the torso, namely (i) axilla, (ii) mediastinum, (iii) breast. For each lesion, regions-of-interest (ROI) consisted of concentric spheres drawn around that lesion. The lesion count density, $C_t$, within a ROI for $i^{th}$ lesion was defined as the sum of the counts in voxels that overlap with the ROI. The background count density, $C_b$, for $i^{th}$ lesion was computed as the sum of counts in identically sized annular-shaped ROIs drawn concentric to the lesion centers lying in lesion $i$ from 10 adjacent slices. The inner diameter of the annulus is equal to 1.12 times the diameter of the lesion under evaluation to limit the effect of spillover from the lesion into background measurement. The outer diameter is 40 mm. For ROIs closer to the surface, only the counts from the part that lies inside the torso were considered. The $CRC_i$ for the $i^{th}$ lesion was calculated according to the NEMA NU2–2001 definition[52].

$$CRC_i = \frac{C_t}{C_b}$$

where uptake is the corresponding known lesion-to-background ratio.

**Receiver Operating Characteristics (ROC)**

To quantify the capability of the two scanners for the detection of a lesion with small diameter and low lesion-to-background ratio, receiver operating characteristic (ROC) curves[92] were estimated for reconstructed images of the phantom as described in Section 3.3.2, by plotting the True Positive Fraction (TPF) against the False Positive Fraction (FPF). To acquire more statistics, for each combination of lesion diameter and contrast, both simulation and reconstruction were repeated five times and ROC curves are calculated for five sets of reconstruction image volumes. Similar to the calculation of CRC, the torso was divided into three locations, axilla, mediastinum and breast. Within each location a rectangular grid was drawn comprising spheres of the same diameter as the
lesion under consideration (see ahead to Figure 3.9 (a)). The total voxel count density inside each of these spheres was calculated. If the intensity inside a particular spherical VOI was greater than a chosen threshold, it was considered ‘detected lesion’. Since, the true positions of the lesions were already known, a detected lesion can be classified as either ‘true positive’ or ‘false positive’. This process is repeated for all three locations across all possible threshold values (depending on the image voxel intensities) to calculate the TPF and FPF. Finally, ROC curves were plotted using TPF and FPF.

3.3 Results

3.3.1 Sensitivity Analysis

Figure 3.6 (a,b) show sensitivity images of Biograph Vision PET scanner and the proposed total-breast PET system for an identical FOV within each scanner. Note different ranges of the gray scale for each image. Figure 3.6 (c,d) show Y sensitivity profiles at different horizontal positions (X = 0 and 7 cm). The offset of 7 cm was chosen to compare the sensitivity within the breast (X=7 cm) to that between them (X=0). “Predicted” sensitivity value profiles were obtained from the calculated sensitivity images in Figure 3.6 (a,b). “Measured” sensitivity values were calculated by moving a simulated pure positron point source across the transverse FOV of both the systems in small steps of 1 cm each. From the data in the figures, it can be seen that the profile plots from the two methods share a similar trend. For the total-breast PET system, the torso is sampled non-uniformly by different detector groups. Thus, the sensitivity of the system is spatially variant through-out the entire imaging FOV. The system is configured to achieve maximum sensitivity in the breast region while including the mediastinum (anterior chest wall) and axillary lymph nodes.
in the scanner’s imaging FOV. Figure 3.6 (e) shows a sensitivity ratio image across the torso-like phantom, which is computed by voxel-wise division of the total-breast PET sensitivity values with Biograph Vision sensitivity values within the phantom. The mean and maximum sensitivity across each of the three regions: breast, axilla and mediastinum, as well as the [total-breast PET sensitivity: Biograph Vision sensitivity] ratio, are shown in the table of Figure 3.6 (f). It shows that the total-breast PET system has 3.21 times higher mean sensitivity for imaging breasts, a slightly lower sensitivity in the mediastinum, and a higher sensitivity in the axilla as compared to a whole–body PET scanner.
Figure 3.6: Sensitivity images across the central slice for (a) Biograph Vision Scanner and (b) proposed total-breast PET scanner, along with their corresponding pixel intensity calibration bars. (c,d) Profiles (along red & blue lines in (a,b)) across the calculated sensitivity images in parts (a,b) for two horizontally displaced vertical profiles obtained by stepping a point source across transverse FOV for two horizontal positions. (e) Total-breast PET to Biograph Vision sensitivity ratio image across the central slice of the phantom. (f) Mean and maximum sensitivity values across 3 regions (marked in yellow in (e)) for the two systems along with sensitivity ratio.
3.3.2 Lesion Detectability

The images in Figure 3.7(a) show the source maps of detected coincidence events from the 4 mm diameter lesions detected by (ii) Biograph Vision Scanner and (iii) the total-breast PET system during the simulation study. The lesion-to-background ratio in this experiment was 4:1. The map was sampled on a rectangular grid of $1 \times 1 \times 1 \text{ mm}^3$. All the lesions are clearly delineated despite significant attenuation of signals (i.e. counts) from the torso, particularly in the mediastinum.

Figure 3.7 (b) shows the reconstructed images after the 20th iteration using 200 seconds of coincidence events with TOF information from Biograph Vision Scanner (top), and our proposed total-breast scanner (bottom) for a fixed lesion-to-background ratio (4:1) and varying lesion diameters (4 mm, 5 mm, 6 mm, respectively). Figure 3.7 (c) shows the reconstructed images for fixed lesion diameter (4 mm) and different lesion-to-background ratios (4:1, 5:1, 6:1, respectively). The results in Figure 3.7 (b,c) show that the 4mm diameter lesions are difficult to detect by the whole-body PET scanner imager, especially when the lesion contrast is low (e.g. 4:1 ratio). However, those 4 mm (and larger) lesions are easily seen in the dedicated total-breast PET system images, particularly in the breasts, despite the non-uniformity artifacts in the medial and posterior torso regions due to incomplete sampling of these tissues. The larger (5mm and 6mm) and higher contrast valued (5:1 and 6:1) lesions are more easily detectable by both systems, however, the lesions appear more blurred in images from the whole-body PET system than those from the total-breast PET system.

Contrast recovery coefficient (CRC) values are shown in Figure 3.8 for different lesion-to-background ratios and lesion diameters. It is clear that for all the cases, the total-breast PET system
has higher contrast recovery coefficients in the breast region as compared to the whole-body PET scanner. For the mediastinum and axillary regions, both systems have similar contrast recoveries. The ROC curves in Figure 3.9 help to illustrate the lesion detectability for small lesions with low lesion-to-background ratios. The area under the curve (AUC) values for each case show similar detectability for mediastinum and axilla and a higher detectability for breast regions for the dedicated total-breast PET system as compared to the whole body PET system.
Figure 3.7: (A) Distribution of coincidence events detected by (ii) Biograph Vision PET Scanner and (iii) the total-breast PET imager for lesion diameter 4mm, 4:1 L:B. Lesion placement map shown at left (i). Iteratively reconstructed central-slice images of the torso phantom containing lesions (B) of indicated sizes in each image, along with fixed lesion-to-background concentration ratio of 4:1 imaged by (top row) whole-body scanner and (bottom row) dedicated total-breast PET scanner, (C) with various indicated lesion-to-background activity concentration ratios along with
a fixed lesion diameter of 4 mm imaged by (top row) whole-body scanner and (bottom row) dedicated total-breast PET scanner
3.4 Discussion and Future Work

We have designed a dedicated total-breast PET system with a highly unconventional geometry in order to overcome the fundamental limitations of other previous dedicated breast PET approaches that could not image the chest wall (mediastinum) region nor the axilla. By surrounding both breast volumes with detectors and capturing the posterior breast regions not imaged in previous breast PET designs, our system yields considerably higher sensitivity (3.21 times) than a contemporary clinical whole-body PET system. While there are more detector modules used in our system design than in single-breast PET systems, we have arrived at an asymmetric system geometry that provides comprehensive sampling and imaging in the most relevant regions when evaluating breast
disease: the breast, mediastinum and axilla. Moreover, our system substantially outperforms the contemporary clinical whole-body PET system in breast imaging tasks, indicating that it could be clinically useful in characterizing breast disease, especially at its earliest stages.

All reconstructions used a fast GPU-based list-mode ML-EM framework developed in our WUSTL lab. The ability of this framework to support unconventional scanner geometries has been essential for reconstructing images from our proposed total-breast PET system, which has very few symmetries. This framework can model the system response between any two crystals in coincidence using their location in 3D space. Another aspect of our system is the large variation in geometric efficiencies due to the steep angle of incidence of gamma rays to certain detector crystals. We account for this variation by absorbing it into a normalization factor between coincident detector blocks.

In its current state, the mean sensitivity of our dedicated total-breast PET system is 3.21 times that of a contemporary clinical whole-body PET scanner for the breast region with a similar sensitivity in the mediastinum and axillary lymph nodes. This increased sensitivity has several implications. Firstly, along with significantly improved spatial resolution (largely based on crystal dimensions)\cite{63,80} it will allow depiction of tissue heterogeneity in mid-large sized cancers for targeted biopsies. Secondly, the increased sensitivity will reduce image noise, which is especially important for high spatial resolution systems. Alternatively, under conditions of fixed image noise and scan time, it will permit lower overall injected doses to the patients undergoing diagnostic scans. The lesions in the breasts appear sharper with higher contrast in images from the total-breast PET system in Figure 3.7 (b,c) due to smaller crystal dimensions used in the “stadium” ring and the front panel. From these results, we can conclude that the total-breast PET system shows

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superior lesion detectability in clinically challenging tasks such as small lesions (4 mm diameter) with low lesion-to-background ratio (4:1).

Currently, we are using only 2 DOI layers (2x6 mm) of scintillator crystals for the detectors placed closer to the breast region to increase sensitivity while keeping good spatial resolution. System sensitivity can be further increased by either increasing the number of detectors or by increasing the number of DOI layers, with concomitant increase in the complexity of readout electronics and overall cost.

Since our system has very few geometric symmetries, its sensitivity is spatially variant throughout the entire imaging FOV. Accordingly, it is impossible to assign a single value of sensitivity to the entire system. In order to compare sensitivities between two systems, we positioned the torso so that the breast region lies within the high sensitivity areas of each system. We then divided the torso into three separate regions, axillae, mediastinum and breasts, and found the mean and maximum sensitivity within each region for both systems.

A simplified version of normalization was applied to both systems. It assumes all TORs between a detector module pair have equal detection efficiencies for 511 keV annihilation photons. This does not take into account inter-crystal scattering in a block detector. From the reconstructed total-breast PET images, we can notice some non-uniformity artifacts in the medial and posterior torso regions of the images from the dedicated total-breast PET system. A more accurate component-based normalization that models detection efficiencies for each individual TOR is expected to further improve the image quality and the quantitative accuracy of the total-breast PET system [45]–[47].

To reduce over-fitting due to noisy measured data, we could regularize the MLEM optimization problem. A standard regularization method is to add a penalty function to the original objective
function as a means of discouraging large changes between neighboring voxels. However, choosing the suitable penalty function with optimal regularization parameters is extremely difficult, especially for our system, which has non-uniform spatial resolution throughout the FOV. For commonly used penalty functions such as the ‘log-cosh’ function [38], the parameters that are chosen are global across the image space. The combination of high- and low- resolution regions in the reconstructed image suggest a spatially variant regularization as a better alternative.

We have conducted a simulation study in GATE to analyze Compton scattering events collected by the proposed breast imager versus a standard whole-body PET scanner. The table below shows events statistics (Trues and Scatter coincidences from a phantom) for each system.

<table>
<thead>
<tr>
<th>Region in Phantom</th>
<th>True Event (as a % of total events)</th>
<th>Scatter Event in Phantom (as a % of total events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biograph Vision</td>
<td>Torso</td>
<td>71.3</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>75.2</td>
</tr>
<tr>
<td>Total-Breast PET</td>
<td>Torso</td>
<td>68.4</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>78.3</td>
</tr>
</tbody>
</table>

Table 3.1: Percentage of Trues and Scatter events generated during Monte Carlo simulation across different regions of the body when scanned using different PET systems
For the total-breast PET system, there may be additional scatter events due to interference of the stadium and front panel, as the scatter fraction is slightly higher in the breast imager for events originated from the torso. However, the difference is small (28.7% for the whole-body PET system versus 31.6% for the breast imager), which implies that the scatter events from interference of the stadium and front panel are not significant. A possible explanation for this is that most of these scatter events would not pass the energy discrimination and would be rejected. More importantly, for events originated from the breast regions, the scatter fraction is actually lower in the breast imager than in the whole-body PET scanner. This is because the majority of coincidence events from the breast regions are detected by the stadium and front panel detectors, thus the two gamma rays do not pass through the torso. In contrast, for a significant fraction of coincidence events from the breast regions, one of the two gamma rays must pass through the torso in order to be detected by a whole-body PET scanner. As a result, the lesion contrast in the breast region is significantly higher by the breast imager despite a slightly elevated scatter fraction for the torso region.

To analyze the contribution of scatter events to the non-uniformity artifacts, we have reconstructed the torso phantom using only ‘Trues’ events from the total-breast PET system and can still see the background non-uniformity in the torso region. We have implemented an attenuation correction using an analytically generated attenuation map of the phantom we are reconstructing. The images after attenuation correction improves the image uniformity (removes the bright edge artifacts from the phantom due to attenuation). We have used TOF information (250 ps) for the reconstructed images, which have improved the images from their Non TOF version but did not completely remove the artifact. Thus, we believe this non-uniformity can be attributed to limited angle
tomography and partial geometric sampling of the torso. A more accurate system model and normalization may further improve the image quality.

The proposed breast PET imager has extended imaging FOV that includes the axilla and mediastinum. It provides high resolution images and reasonable uniformity for regions that are critical for breast cancer imaging applications. However, the geometry of the system does not provide complete sampling of the entire torso. Therefore, we do not anticipate the images will be completely uniform for the entire torso. Additionally, for this system we used a TOR-variant solid angle approximation while calculating the system matrix. However, as discussed in Chapter 2, we noticed that a TOR-invariant solid angle approximation works better since it reduces the low intensity artifacts in the central region. Hence, we believe, implementing a TOR-invariant solid angle approximation would make the images more uniform. A combination of the stadium detectors with a regular whole-body scanner could provide better torso image quality than the current system, but that would require a separate scan. The stadium detector could also potentially be used as an insert to a whole-body scanner for simultaneous scanning. That would be a completely different approach requiring a separate feasibility study that can be investigated in the future.

The total-breast PET system can be made MR-compatible using compact detector modules with appropriate shielding. It can be used either as a stand-alone dedicated breast PET device, or as an ‘insert’ inside the bore of an MRI system. One hallmark of our total-breast PET system approach is to image both breasts and torso simultaneously. In fact, our total-breast PET active FOV is virtually identical to the MRI FOV from prone breast MR imaging, leading to straightforward
PET-MR registration. The only other PEM system capable of imaging both breasts, albeit without chest wall or axillary capability, is a dual-cylinder approach that is intended to be integrated with an MR coil[78],[80]. In principle, our system is capable of the same PET-MRI hybridization, but otherwise could be used sequentially with CT or MR imaging.

The high sensitivity of the proposed breast PET imager can be used for early cancer characterization, tracer kinetic modeling between PET and MRI in breast disease, cancer progression, cancer recurrence and overall therapeutic monitoring. Many possible research avenues could be greatly enhanced by our proposed dedicated total-breast system, such as dynamic imaging with different imaging agents. Moreover, clinical applications exploiting the near-100% sensitivity of MRI can benefit from improved specificity with the functional information from the dedicated breast PET as well as from existing or newly developed radiotracers for breast cancer(s).
Chapter 4: Development of a Point-of-Care PET/Ultrasound System for Carotid Artery Disease Detection

4.1 Background and Motivation

Cardiovascular disease is the leading cause of death in the United States with carotid artery disease being the primary cause of strokes and heart attack [93]. The primary mechanism underlying cerebral ischemia caused by carotid disease is plaque rupture and subsequent embolism to the brain. This has fostered the concept of the vulnerable or high-risk plaque, which is prone to rupture and cause cerebral ischemia [94] Carotid endarterectomy (CEA) or stenting reduces the risk for cerebral ischemia in patients with symptomatic carotid stenosis and to some extent also in patients with asymptomatic carotid stenosis [95], [96]. However, there is no consensus on which patients require surgical therapy and which patients can be safely treated with optimal medical management alone. Current clinical guidelines recommend carotid endarterectomy (CEA) for asymptomatic patients who have 60-99% diameter carotid stenosis and low perioperative risk [97], [98]. However, the average annual risk of stroke in these asymptomatic patients is less than 1.6% [99]–[101]. Thus, the majority of all CEA and carotid artery stenting procedures in asymptomatic patients may be unnecessary, given the high cost of healthcare system in the US. Therefore, identifying patients at high risk for stroke using a less invasive diagnostic tool is of paramount importance and emphasizes the need for individual treatment decisions.
The current imaging method of carotid artery assessment for stenosis is carotid ultrasound imaging with Doppler [102]. Figure 4.1(a) shows an ultrasound image of a patient with a plaque (indicated by a green arrow) in the right internal carotid artery (ICA). Figure 4.1(b) shows the blood flow measured by Doppler ultrasound superimposed with the anatomic image. The peak systolic velocity (PSV) and end diastolic velocity (EDV) are measured from the Doppler ultrasound (Figure 4.1(c)) to assess the severity of carotid stenosis to guide surgical decision. However, standard ultrasound features do not predict the risk of plaque rupture or patient outcomes.

Figure 4.1: (a) An ultrasound image showing a plaque (green arrow) in a patient’s internal carotid artery; (b) Doppler ultrasound signal super-imposed on the anatomic image; (c) Peak systolic velocity (PSV) and the end diastolic velocity (EDV) of the blood flow are used to assess the severity of stenosis
Computed tomography and magnetic resonance angiography (CTA and MRA) can assess morphology and provide higher sensitivity and specificity for the presence of a stenosis, thus are used for confirmation and procedural planning before therapeutic intervention. Yet, these morphology-based image markers cannot predict risk reliably, either.

More advanced techniques such as high-resolution MR imaging of the carotid vessel wall has shown promise in detecting fibrous cap thinning, lipid pool and presence of hemorrhage [103]. Positron emission tomography (PET) imaging with $^{18}$FDG has also been used to assess the metabolic function of plaques [9][10]. With the advances of simultaneous PET/MR scanners, there is increasing interest in assessing carotid artery disease using multi-modal and molecular imaging approaches [7], [104]–[106]. A PET/MR scanner provides anatomic, functional and molecular imaging information simultaneously, making it an ideal imaging tool for diagnosing vascular diseases. However, since it is expensive, its availability is limited to large medical centers.

Our lab previously demonstrated the feasibility of a point-of-care (POC) PET system [107] using a proof-of-concept setup that consists of two planar PET detectors. One detector was mounted to a robotic arm which can position and track the detector at an arbitrary location. The second detector was mounted on a rotational stage and can be rotated around an object. This technology is not meant to compete with clinical PET scanners that are optimized for WB-PET imaging applications. The ideal application of such a system is when a technician guides this maneuverable PET scanner to cover a scanning contour of a ROI (Region-Of-Interest) of the patient, with a real time image reconstruction engine that reconstructs the refreshed PET images as the scanning trajectory is being adjusted. Different from other organ-specific PET scanners that are optimized for a specific body part, the proposed technology is designed to provide maximal flexibility and versatility.
This original POC PET system uses photomultiplier tubes (PMT) based detector technology that has poor coincidence resolving time (CRT) of 740 ps.

To address these challenges and building on our POC PET technology, we propose a portable, low-cost, high-resolution, PET device that can be integrated with a clinical ultrasound system to provide anatomic, functional and molecular imaging capability for vascular diseases. For this prototype system, we redesigned the geometry and use compact data acquisition electronics and SiPM based detector technology to improve CRT and spatial resolution. Such a technology may accelerate the development, validation and dissemination of novel molecular imaging ligands for assessing the risk of plaque rupture in patients with asymptomatic carotid artery disease. It is not only limited to a specific application and can also be used for PET/ultrasound guided biopsy in an operating room and for monitoring disease progression in intensive care units.

4.2 Prototype System Design

When imaging internal carotid artery using an ultrasound device clinically, a patient typically lies down in a supine position, with the front of the neck exposed to permit access by the ultrasound transducer. Considering the space around a patient’s neck and the maneuverability of an imaging probe, we propose to sandwich an ultrasound transducer with 2 compact time-of-flight (TOF) PET detector modules to construct a hybrid imaging probe. This is attached to a robotic arm that can provide mechanical support and precision tracking. Two/Three larger panel detectors are positioned below a patient’s neck to work in conjunction with the 2 PET detector modules in the hybrid imaging probe for coincidence detection. We use a commercial ultrasound transducer in the hybrid imaging probe. Figure 4.2 illustrates a conceptual design of the integrated PET/ultrasound imager.
Figure 4.2: A conceptual interactive PET/ultrasound imager: (A) a hybrid imaging probe containing a) a 2D ultrasound transducer, and b) two high-resolution TOF-PET detector modules; (B) a robotic arm holding and tracking the hybrid imaging probe; (C) two TOF-PET detector panels underneath a patient; (D) a commercial ultrasound system. (Illustration courtesy of Dr. Sergey A. Komarov)

4.3 PET Data Acquisition System

Each PET detector module in the probe comprises of two lutetium-yttrium oxy-orthosilicate (LYSO) arrays each with 8x8 elements, each measuring 3.1mm x 3.1mm x 10mm. The array is fabricated using a 3.2mm crystal pitch to match with the pitch of SiPM (Hamamatsu S14161-3050HS-08). A layer of Enhanced Specular Reflector (ESR) is placed between the crystals for optical isolation. The sizes of the crystals are chosen to make 1:1 coupling between the LYSO crystals and the SiPM elements. The scintillation light from the crystal arrays is collected from one end of the crystal by the SiPM array, meanwhile the other end of the crystal array is covered with an ESR layer.
The SiPM signals is read out by a TOFPET2 ASIC [108] (PETSys Electronics, Portugal), which is a low power ASIC with 64 channels optimized for reading SiPMs for time-of-flight PET applications. Every readout channel in the chip works independently. A block diagram of the internal circuits of the TOFPET2 ASIC has been shown in Figure 4.3.

![Figure 4.3: Block diagram of the functional units in the TOFPET2 ASIC (extracted from the user guide provided by PETSys).](image)

Each TOFPET2 ASIC contains 64 readout channels, each consisting of a low-noise preamplifier, 2 trans-impedance amplifiers, 3 fast discriminators, a quad-buffered charge-to-digital converter (QDC), and a quad-buffered dual ramp time-to-digital converter (TDC). The time-of-arrival (ToA) is measured by a fast discriminator when the amplified signal amplitude (Vth) exceeds a pre-set threshold (T1). T1 can be independently set for each channel, with a resolution of 2.5mV, which corresponds to ~0.1 photoelectrons when using a SiPM of a gain=1.25E10. A second threshold T2 can be set at a higher value to reject background dark counts. A third threshold E can be used for energy discrimination to reject events with lower energy, thereby reducing the event rates processed by the digitization circuits. We use the ASIC test board provided in the PETsys evaluation kit for data acquisition. The crystal arrays are coupled to the SiPM arrays by means of optical grease to form the PET detector module as shown in Figure 4.4, where the detector is housed in a black plastic light-tight box. There is an embedded thermometer inside the PETsys
ASIC, so the temperature of the chip can be monitored. The SiPM arrays are plugged directly in the test board, which integrates TOFPET-2 ASIC allowing the readout of 64 SiPM channels and transmission to a dedicated data acquisition system (DAQ) board through a flat cable. The digitized events from the DAQ board are transmitted to a host computer via a Gbps Ethernet. The ASIC allows 64 independent measurements of event position, energy, and time information when gamma-rays interact within a scintillator array whose scintillation light is read out by a SiPM array of 64 channels.

Figure 4.4: (a) Individual components of a PETsys detector module: SiPM, LYSO crystal separately shown at the top; crystal is optically coupled with SiPM, wrapped with teflon tape and attached to PETsys Front End Board (FEB) shown at bottom; (b) Assembled detector module inside a black light-tight box
4.4 PET Detector Characterization

Setup Calibration

The setup was calibrated using the PETsys calibration routine implemented in the software that came along with the evaluation kit. Depending on SiPM type, a calibration was run once at default ASIC configuration applying an bias voltage that is 4V above the breakdown voltage of the SiPM. The required bias voltages were specified depending on the specifications of the SiPM. The discriminator threshold \( v_{t1} \), \( v_{t2} \) and \( v_E \) were kept at constant values (\( v_{t1} = 20 \), \( v_{t2} = 20 \), \( v_E = 15 \)).

Energy Discrimination

For calibration of the detectors, our test setup includes two detector blocks (each detector block consists of two detector modules), each with 16x16 crystals optically coupled to four 8x8 SiPMs. We house these blocks inside black light-tight boxes. We placed the two PET blocks face-to-face at a distance of 54.6 cm from each other (Figure 4.5) and put a uniform flat sheet Cu-64 source at the center in between them.

Figure 4.5: Test setup with two detector blocks placed face-to-face with a radioactive source in between them
We use the ‘convert_raw_to_coincidences’ method implemented by PETsys. Using this routine, raw data was converted to coincidence event information by applying a 10ns coincidence time window. A table containing timestamps, energy values and the corresponding channel ids for each coincidence event was returned. The energy values are expressed in a QDC number with arbitrary unit, whose amplitude is proportional to the readout signal from SiPM sampled by the ASIC. We plot the energy spectrum for each detector crystal i.e. the histogram plot where each bin represents total number of coincidence events for a particular energy value (expressed in QDC). A sample energy spectrum plot from one SiPM channel is shown in Figure 4.6(a). The signal from each SiPM varies in terms of amplitude, primarily due to differences in light collection by the photodetectors. Therefore, when comparing energy spectra from the individual crystals in a block detector, the location of the photopeak varies depending on the light collection efficiency of that crystal. From each of the energy spectrum plots, we find the energy of the photopeak and create a look-up-table (LUT) with the photopeak energy information for all detector crystals. We then perform an energy discrimination for each detector by selecting only those events which falls within a window of ±10% of the photopeak energy. This is done to eliminate background noise and scatter events since they have much lower energies than the photopeak. This also helps in eliminating higher energy events which may be recorded due to photon pileup. The red window in Figure 4.6(a) denotes the applied energy window.
Timing Calibration

Coincidence time alignment, in which module to module variations in propagation time is corrected for, is an important preprocessing step. This is required since coincidence measurements only accept pairs of events that occur within a narrow time window of each other. In order to ensure that most true coincidences are recorded, it is imperative that all detector signals in the system are adjusted to a common reference time. The general principle is to acquire timing spectra between all detector modules in the system when a positron emitting source is placed at the center of the system by recording differences in the time of detection of annihilation photon pairs. For a non-calibrated system, the timing spectrum has approximately a Gaussian distribution, centered around an arbitrary time. The distribution around the mean is caused by the timing characteristic of scintillation detectors and the associated electronics and the location of centroid caused by variation in time delays in SiPM channels, cables, etc. In the timing calibration, this time delay is measured for each detector, and time adjustments are introduced such that the centroid of all timing spectra is aligned. It is around this centroid where the coincidence time window is placed. For our test setup, we placed a sheet source at the center of the detector modules and used the energy discriminated events for timing calibration. First, we calculate the coincidence timing spectrum for each crystal on the first detector block (reference block) with all the other crystals on the second block. This spectrum is a mixture of Gaussian distributions, but we fit it to a single Gaussian to find the approximate center. Figure 4.6(b) shows the coincidence timing spectrum for one detector crystal w.r.t. all detectors on the opposite block as well as its Gaussian fit. We observe that the mean ($\mu_{ch_1}$) is centered at -188.07 ps and the FWHM is 1639.05 ps. Since our source was placed at center ($t_{ref} = 0$ ps), we have an offset of 188.07 ps for this crystal. Similarly, we calculate the offsets for all the other crystals on the first block and adjust their corresponding arrival times ($\mu_{ch_1}$...
Next, we use the updated times for first block and generate timing spectra for each crystal of the second block w.r.t. all crystals of the first block to get offsets for the second block. We update the arrival times of events for the second block according to the offsets and repeat this process for a few iterations until all the timing spectra are aligned at approximately 0 ps. Figure 4.6(c) shows the timing spectrum of the channel after calibration. The mean is now centered at -0.16 ps and the FWHM reduced to 239.14 ps.

![Energy Spectrum for channel 768](image)

![Fit results: mu = 188.07ps, FWHM = 1639.05ps](image)

![Fit results: mu = -0.16ps, FWHM = 239.14ps](image)

Figure 4.6: Calibration Results; (a) Energy Spectrum plot for a single channel, red window shows the energy discriminated events; (b) Uncorrected timing spectrum for a single channel with corresponding Gaussian fit; (c) Corrected timing spectrum for the same channel with corresponding Gaussian fit after 5 iterations

## 4.5 Integration of Robot-Controlled Hybrid Imaging Probe with Rear Detector Panels

We use the ‘KUKA AGILUSR KR10 R1100 six’ robot for this imaging system. This six axes small robot provides 6 degrees-of-freedom (DOF) control of the device mounted on it. It is capable of handling a 10 kg payload within a range of 1.1 meters. Our high-resolution hybrid imaging probe has a total weight of less than 2 kg. Considering the Force/Torque sensor with some
connection accessories and the extended holder of the detector, the entire package is well within the capability of this robot. The robot itself can achieve repeatability of ±0.03 mm which meets the positioning accuracy requirements of our application. In this section, we use “petus base” (a base coordinate system defined for the robot) to describe the coordinate system of the rear detector panels, which is registered as the base in the robot controller. We use “alignment tool” and “petus tool” (tools that a user can define for the robot) to describe the coordinate system of the corresponding object mounted on the robot, which is registered as different tools in the robot controller.

4.5.1 Hybrid PET/ultrasound Imaging Probe

The hybrid probe consists of an ultrasound transducer with a PET detector module on each side. The PET detector modules are at 15° angle w.r.t. the front surface of the transducer. The PET detector modules consist of two 8x8 LYSO detector arrays coupled with two 8x8 SiPM arrays connected to the TOFPET2 ASIC. We connect two 5V cooling fans near each PET module to prevent overheating. The ultrasound transducer we use is a linear transducer (VF13-5) with a frequency bandwidth of 5-13 MHz which is connected to a clinical Siemens (Acuson Antares Premium Edition) ultrasound system. A light-tight holder housing both the PET modules as well as the ultrasound transducer was designed and printed using a 3D printer (Dremel DigiLab 3D45) with black ABS printing material. One end of the holder is designed in such a way so that it can be connected to the robot via a quick release connector, then a force/torque (F/T) sensor and finally to the flange of the robot. The probe is regarded as a tool (‘petus tool’) of the robot controller. To establish the tool coordinate system with respect to the robot coordinate system, we use direct measurement method to calculate the transform matrix of the robot. We use MicroScribe® as a
coordinate measurement machine. We measure a few characteristic points on the hybrid holder and the adapter plate, which is the surface connected to the robot flange and use these points to calculate the transform matrix of the tool w.r.t the robot center. Figure 4.7 shows the integrated PET/ultrasound probe connected to the KUKA robot.

![Figure 4.7: (a) Front View of the PET-US imaging probe, (b) Top View of the PET-US imaging probe, (c) Assembled probe connected to robot F/T sensor via quick-release connector](image)

### 4.5.2 Rear Detector Panels

Each rear detector panel consists of a detector blocks used in the probe housed together inside a single 3D printed casing. So, each panel has 16x16 LYSO crystals arranged in four 8x8 arrays attached to four Hamamatsu SiPMs using 1:1 coupling. These are then connected to 2 TOFPET2 ASICs. Three such detector panels are attached to a machined T-shaped metal sheet (as shown in Figure 4.8 (a)) with different positioning holes to adjust the degree of rotation of the PET detector panels across 0°, 15° and 45°. Similar to the probe, we use two 5V cooling fans to prevent
overheating of the PET ASICs. For registering the detectors with the robotic coordinate system, we use a customized tool piece and three alignment pins on the T-shaped metal sheet. The alignment tool piece (shown in Figure 4.8 (c)) is a rotatory counterpart of the alignment pins with slight tolerance to allow the F/T sensor to find the right path. After the robot is set to a fixed position, the alignment tool is moved to the roughly estimated positions of the three alignment pins. At each position, the F/T sensor is engaged with searching direction pointing in the tool positive z-axis. The F/T sensor is set to stop if the following conditions are met: 1. The Z-force reaches 5 N and 2. The force on the other two axes are within 0 ± 0.2 N and 3. The torque along all three axes are within 0 ± 0.1 N.m. While searching, the second and third conditions force the robot to correct for its tool position and direction frequently to maintain near zero force and torque. The F/T sensor will finally stop when the tool is pushed hard on the flat surface of the metal sheet, as shown in Figure 4.8 (f). The current coordinate of tool center point (TCP) is recorded for further computations to map the ‘petus’ base to the robot.

Figure 4.8: (a) T-shaped metal base with three alignment pins and positioning holes to attach detector blocks at three different angles, (b) PET detector blocks attached to the metal base at 15 deg angle, (c) Alignment tool, (d) Alignment tool attached to robot for mapping base coordinate system, (e) Close-up of alignment tool as it starts searching for alignment pin, (f) Alignment tool

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4.6 Imaging Studies

4.6.1 Monte Carlo Simulation Study

In a preliminary design study [109], we ran Monte Carlo simulations using GATE v9.0 package [6] to study the proposed PET/ultrasound imager with a geometry shown in Figure 4.9. The detector modules in the hybrid imaging probe are made of LSO arrays with 24x24 elements of 1x1x10 mm each. The detector modules in the rear panels are made of LSO arrays with 12x12 element of 2x2x20 mm each. Two scanning geometries were considered (Figure 4.9). For stationary geometry, the hybrid probe was placed in position (a) and data was acquired for 10 min. For dynamic scanning geometry, probe was moved sequentially from (a) to (c) with acquisition times of 5 min, 2.5 min, and 2.5 mins respectively. Using these two scanning geometries, we imaged a neck phantom that contains $^{64}$Cu solution (17.4% branching ratio for $\beta^+$ decay). The neck phantom (Figure 4.9d) consists of a cylinder of 15 cm in diameter and 8 cm long, two cylindrical tubes of 1 cm in diameter and 8 cm long to mimic two carotid arteries, and a plaque that is 4 mm in diameter and 15 mm long inside one of the carotid arteries. The radioactivity concentration of the background tissues in the neck phantom, blood inside the internal carotid artery, and the plaque was assumed to be 4500, 10200, and 32000 Bq/mL, respectively. These values are estimated from the MR/PET images of a patient after $[^{64}\text{Cu}]$DOTA-ECL1i injection.
with partial-volume correction applied to the estimated activity concentration in the plaque due to its small size and limited scanner resolution (> 4mm FWHM) from the whole-body PET/MR system. All data were reconstructed using the previously mentioned GPU-based list-mode reconstruction framework using a Gaussian TOF kernel that can model arbitrary geometry. The energy resolution of all detectors was assumed to be 10.0% for 511 keV gamma rays. The energy window used was from 435 keV to 650 keV. The coincidence resolving time (CRT) was assumed to be 200 ps FWHM. We recorded singles events from all detector volumes and performed coincidence detection offline as a post-processing step using a 4.5 ns coincidence timing window.

Figure 4.9: (a) Simulated geometry of the integrated PET/US system when the hybrid imaging probe is placed near a carotid artery (target FOV, as highlighted); (b, c) geometry of the system when probe is moved to 2 adjacent locations; (d) Simulated neck phantom with 2 carotid arteries and one plaque in the artery near the hybrid ultrasound/PET probe

4.6.2 Experimental Phantom Study

We performed imaging studies using the prototype system in Fig. 4.8 with two different phantoms as described below:

Phantom 1 is a cylindrical phantom with 5 groups of Derenzo-patterned rods in it, shown in Figure 4.10 (a). The diameter of the rods in each group are 2.5mm, 2mm, 1.32mm, 0.94mm and 0.62mm. The height of the phantom is 48 mm. The rods were filled with $^{64}\text{Cu}$ solution with a total activity...
of 3 mCi. The choice of $^{64}$Cu over $^{18}$F for this experiment is due to the longer half-life of the $^{64}$Cu (12.7 h) that permits us to image the phantom over a longer period of time. This phantom was used only for PET imaging since the material of the phantom wasn’t compatible with ultrasound imaging.

Phantom 2 is a cylindrical gelatin phantom with plastic tubing embedded inside. Different views of the phantom are shown in Figure 4.10 (c,d). The diameter of the gelatin phantom is 10 cm and the height is 8 cm. The tube inner diameter is 3 mm and it was filled with $^{64}$Cu solution with a total activity of 3 mCi. Since this phantom is made with gelatin, it was used for both PET and ultrasound imaging.

Figure 4.10: (a) Top view of Derenzo phantom, (b) Placement of Derenzo phantom in the prototype system for PET imaging, (c,d) Different views of the gelatin phantom with tubing, (e,f) Placement of gelatin phantom for imaging using PET and ultrasound system
We used the robotic arm to move the hybrid probe detectors around the phantoms and track its location using the robot controller. To demonstrate the interactive imaging feature of this system, we start by imaging the phantoms with the probe at the center (i.e. using position 1 in Figure 4.11(d)). We then move the probe to position 2 (as shown in Figure 4.11(e)) and position 3 (as shown in Figure 4.11(f)) consecutively to acquire additional data. The rear detector panels are kept stationary with the two side panels at 15 deg to the middle panel. Constrained by the reach of the robotic arm and the bench space around the experimental setup, we collected coincidence events from these three sampling angles for 20 min per angle. We used ±10% of photopeak as energy window and a coincidence resolving time (CRT) of 250 ps as calculated in the previous section. PET images were reconstructed from list mode coincidence using our reconstruction framework describe in Chapter 2 with and without time-of-flight information. Scatter and attenuation correction were not implemented. For phantom 2, ultrasound image was acquired only for position 1 using a frequency of 11.43 MHz which provided a depth of 6 cm.
Figure 4.11: (a,b,c) The hybrid probe (green) is moved to three different positions while the rear panels (yellow) are stationary, (d,e,f) Different positions are shown in the real system
4.7 Results

4.7.1 Simulation Results

The sensitivity image of the two scanning geometries mentioned in section 4.5.1 are shown in Figure 4.12 (a, b). The peak sensitivity of the system is ~3% within the targeted imaging FOV. This is comparable to a typical whole-body PET scanner, even though we are using much fewer number of detectors.

![Sensitivity Image](image)

Figure 4.12: Sensitivity image for (a) stationary geometry, (b) 3-step scanning geometry; Yellow circle shows targeted field-of-view of the system; Image scale shows the absolute sensitivity of the systems

Figure 4.13 (a) shows the anatomic image of the neck phantom (assumed to be from an ultrasound system) generated analytically using MATLAB®. Figure 4.13(b) and 4.13(c) show the reconstructed PET images from the stationary geometry and 3-step scanning geometry respectively, fused with the anatomic image of the neck phantom. The results show significant artifact in the background region of the phantom where the activity distribution should be uniform. This is due to under-sampling by limited angle tomography. As we scan across more angles, this artifact reduces as can be seen from Figure 4.13 (b) and (c). However, we can still resolve the elevated radiotracer uptake in a plaque surrounded by blood volume in an artery within the targeted
imaging FOV, despite the artifact in other regions. Also, for the 3-step geometry, the plaque region is better resolved as compared to stationary geometry, as can be observed from the transverse views.

Figure 4.13: (a) Anatomic image of a neck phantom containing 2 arteries and a plaque region (transverse, coronal and sagittal views); Fused PET (red) and anatomic image using (b) stationary geometry (c) 3-step scanning geometry

We validated an interactive PET imaging strategy using the dynamic scanning geometry, where we imaged the phantom sequentially in 3 steps. Figure 4.14 shows the reconstructed images after each step. The results show improvement in image quality progressively as more data is acquired.
and images updated. Since the proposed system has a small number of detectors and small imaging FOV, computation time of a sensitivity image (the most time-consuming step) is < 5 seconds using our current setup. This is significantly shorter than the data acquisition time at each location. Thus, the image reconstruction time does not become a bottleneck during the interactive scanning operation.

Figure 4.14: Illustration of interactive scanning strategy; Updated reconstructed images after (a) step 1 (b) step 1+2 (c) step 1+2+3
4.7.2 Experimental Results

Figure 4.15 (a) shows the sensitivity images for three positions of the imaging probe and combined sensitivity images for position 1+2 and position 1+2+3. The sensitivity images are all on the same color scale, so we notice an increase in sensitivity in the central region of the FOV as we scan multiple angles. Figure 4.15 (b) and (c) shows the reconstructed images for Derenzo-alike phantom and gelatin phantom respectively for position 1,2,3 and the joint reconstructed image with coincidence events from position 1+2 and position 1+2+3. All the reconstructed images are with TOF information. We notice an improvement in image quality as we add counts from more angles consecutively. For the combined image using all three angles, we can resolve the rods with three largest diameters as shown by red arrows (2.5mm, 2mm, 1.32mm).
Figure 4.15: Interactive Scanning Strategy (a) Individual sensitivity images for different positions and combined sensitivity images as we add more angles, (b) Reconstructed images (top view) of derenzo phantom for different positions and combined together (red arrows show the group of rods that are clearly resolved), (c) Reconstructed images (top view) of gelatin phantom for different positions and combined together.

Figure 4.16 (a) and (b) show the combined reconstructed images from all positions of the Derenzo-alike phantom without and with TOF information. Images reconstructed with TOF information clearly show fewer artifacts which allow us to better identify the rods in the phantom. For the gelatin phantom, in theory, we should have a vertical tube in the front view (w.r.t to the probe) and two parallel tubes if looked from the side. But, in our phantom, the tubes were not perfectly parallel and straight, which can be seen from the reconstructed images in Figure 4.16 (c).

Figure 4.17 (a) shows the ultrasound image obtained at position 1 for the gelatin phantom. Figure 4.17 (b) shows the combined PET image of the corresponding slice. Figure 4.17 (c) shows the manually fused PET-ultrasound image.
Figure 4.16: Different views of reconstructed images using data from all positions of (a) Derenzo phantom without TOF information, (B) Derenzo phantom with TOF information, (c) Gelatin phantom with TOF information.

Figure 4.17: (a) Ultrasound image of the gelatin phantom, (b) PET image of the same phantom, (c) Fused PET-ultrasound image.
4.8 Discussion and Future Work

In this work, we propose a new interactive POC PET/Ultrasound imaging system, with near real-time image reconstruction capability, using TOF PET detectors. Our preliminary studies (both experimental and Monte Carlo simulation) demonstrate the feasibility of this system that can provide near real-time visual feedback to an operator who can maneuver a hybrid imaging probe to interactively scan an organ-of-interest in a patient to support POC imaging applications.

Using SiPM based detector technology and PETsys ASIC, we achieved a CRT of 250 ps FWHM. The imaging study of a cylindrical Derenzo phantom experimentally shows that this system can identify rod sources $\geq 1.32$ mm in diameter with 3-position scanning. With TOF information, the reconstructed images have fewer artifacts that are due to limited angle tomography. This system provides higher resolution PET images than a whole-body PET scanner in a user-selected target region without compromising the system sensitivity. Fused PET/Ultrasound images of the gelatin phantom show potential application of the system for providing anatomic, functional and molecular imaging capability to assess vascular diseases at a much lower cost than the current technology based on a PET/MR scanner.

Since the geometry of this system is dynamically changing, this can create additional challenges for scanner normalization. In this preliminary work, all images were reconstructed based on the assumption that all LYSO crystals have the same detection efficiency for 511 keV gamma-rays. Component-based normalization approaches [45], [47], [110] can be used to model various physical factors that may affect detection efficiency of gamma-ray detectors. Since the panel detectors may be placed very close to a patient's body, there will be a large variation in detection...
efficiency. Hence, a normalization that models detector efficiency as a function of incident angle of gamma-rays may be necessary.

In a conventional PET/CT or PET/MRI scanner, attenuation correction is often calculated from the CT or MR images. For our preliminary study, attenuation correction has not been implemented. However, since we have simultaneous PET/Ultrasound scans, we may utilize the structural information obtained by the ultrasound sensor to calculate attenuation correction directly if the tissues in the imaging FOV are primarily soft tissues. Alternatively, the ultrasound images may be used to co-register the POC-PET images with previously acquired CT images of the same patient to calculate attenuation correction factors. Appropriate correction techniques, such as normalization, attenuation, and scatter corrections will need to be developed and validated to ensure the quantitative accuracy of the images from this type of system.

Although we achieved usable images without regularization in our current reconstruction software, proper regularization could further improve the image quality under different imaging conditions, especially when the counting statistics are limited. Optimization of the regularization and its parameters needs to be investigated in the future.

We used 3.2 mm\(^2\) cross-section of LYSO crystals for the system. This can be reduced to 1mm\(^2\) crystals for achieving higher intrinsic spatial resolution. Though we achieved a considerable timing resolution of 250 ps, a better timing resolution will further improve image quality.

As noted, sensitivity image calculation is computationally expensive and will preclude the use of continuous freehand movement to scan a patient if real-time visual feedback is desired. Fortunately, for the current system, the sensitivity image computation takes < 5s/position using a workstation with 4 NVidia GeForce GTX Titan X. This is significantly shorter than the data acquisition time at each location. Thus, the image reconstruction time is not a bottleneck during
the interactive scanning operation. However, for a system with smaller crystals or larger FOV, the sensitivity image computation time may increase. Thus, while optimizing the system geometry, these factors should be taken into consideration.

Currently, we used manual registration for fusing the PET and ultrasound images. However, this process can be automated for future studies. For ultrasound imaging, the images are typically referenced to the front surface of the ultrasound transducer. Since the 2D ultrasound transducer is mounted to the robotic arm’s flange, a transformation matrix that define the front surface of the 2D ultrasound transducer as a “tool” will map any voxel in the ultrasound image volume to the robotic coordinate system. We have already mapped the PET system to the robotic coordinate system. Since both imaging modalities’ coordinate systems are mapped to the same robotic coordinate system, the corresponding PET and ultrasound images can be easily mapped to each other.

With the unconventional geometry of the proposed PET/ultrasound imager, PET detectors are in close proximity to a patient’s body and subject to high singles event rate. This may result in a high random coincidence rate that can degrade PET image quality and affect its quantitative accuracy. To reduce the impact of random coincidences, a small coincidence timing window (e.g., 1 ns) can be used to reduce the randoms. This is possible because our target imaging FOV is only a few cm in diameter and our TOF-PET detectors have 250 ps CRT. Also, applying shielding at the superior and inferior surfaces of the rear detector panels to restrict gamma rays from a patient’s head and torso can be beneficial.

Since, this is a dual-modality system, appropriate shielding is necessary to allow an operator to operate the device and benefit from its interactive imaging feature without excessive radiation exposure. Also, instead of the current robot used for the prototype, a smaller robotic arm (or two
arms) that can be guided by hands or a joystick can be a better choice which will provide higher flexibility. With a compact design, the POC-PET can be moved to the patient's bedside for a variety of applications in point-of-care settings. A low-cost system will permit both a broad installation base and the potential installation of multiple units within a cancer center to support novel molecular theranostic applications. Unlike other special purpose PET systems, this innovative approach affords maximum flexibility – whether the patient is an adult or a child, lying in a bed or sitting in a chair, undergoing a surgical procedure, or receiving radio-immunotherapy.
Chapter 5: Feasibility Study of a Point-of-Care PET Lung Imager

5.1 Background and Motivation

Clinical PET systems are typically installed in a room and patients are transported to the scanner room to get their PET scans. However, transporting patients with highly infectious diseases to these PET/CT facilities can be challenging, since it will increase the risk to cancer patients, many of whom are immunocompromised by their treatments. Additionally, it may be difficult to transport patients with severe acute respiratory distress syndrome (ARDS) out of ICU for radiological examinations. To address this unmet clinical challenge, we propose to develop a PET imager that can be brought to bedside to deliver molecular imaging capability on-demand. This low-cost, compact and mobile PET imager that can be brought to immobilized patients to provide important functional information may be of value. Such a system can measure localized tracer uptake quantitatively in user-selected organ(s) using FDG or disease-targeting novel PET tracers. In this feasibility study, we have used the concept of our POCPET system described in the previous chapter to design and evaluate the interactive and quantitative imaging capability of a POC lung imager [111]. Unlike clinical whole-body PET scanners, this system doesn’t use a full ring of detectors. Hence, cost of such a system becomes less expensive, though incomplete FOV coverage results in limited angle tomography. Hence time-of-flight information is very essential for such a scanner. The lower cost and portability could possibly expand the clinical uses of this system and provide better support for nuclear medicine research and development.
For the proposed lung imaging system, non-uniform tissue attenuation is a challenge. Correcting for attenuation requires knowledge about the attenuation coefficients of different tissues in the body. These attenuation coefficients are stored in a 3-dimensional image called the attenuation map. The probability of photon attenuation depends on the electron density of the tissues, and the attenuation map, therefore, can be easily derived from images acquired with an imaging modality based on the measurement of photon transmission, such as CT. In current PET/CT systems, attenuation correction is typically done by bilinear scaling of CT Hounsfield units[112]. However, for a standalone PET scanner like our proposed system, a transmission-scan based attenuation correction can be used[113]. The main idea behind this correction method is to measure attenuation by acquisition of a transmission scan. Figure 5.1 shows the fundamental difference between an emission and transmission scan. In case of emission scan, the patient is injected with a radioactive tracer, which emits back-to-back γ rays that are detected by PET detectors. On the other hand, during transmission scan, the patient is placed in the scanner before giving the radiotracer injection. An external radioactive positron-emitting source (usually $^{68}$Ge/$^{68}$Ga) is placed very close to the detectors on one side and the γ rays from this source gets transmitted through the patient before getting detected by crystals on the other side of the scanner, thus experiencing attenuation along the LOR. Another scan with the same source is generally performed earlier without the patient. This is called blank scan and serves as a reference scan without attenuation. Attenuation correction factors are calculated from the ratio of the transmission and blank scan data. Since we propose to build a standalone PET imager, we use a transmission-scan based attenuation correction where emission and transmission data are acquired, and a time-of-flight (TOF)–based classification method is used to separate transmission data from emission data.
Fig 5.1 (a) Emission scan where a patient is injected with radioactive tracer; (b) Transmission scan with external radioactive source; representative LORs are shown in both cases

5.2 Methods

5.2.1 System Description

Figure 5.2 illustrates the conceptual design of our proposed POCPET lung imager. Key components in the system include: (i) a maneuverable PET imaging probe that contains TOF-PET detectors, (ii) a robotic arm that is attached to the PET imaging probe for mechanical support and precision tracking (±0.03mm repeatability), (iii) a large rear detector panel that can be slid under a patient’s torso to work in conjunction with detectors in the imaging probe for coincidence detection; (iv) a computer workstation to acquire data from PET detectors, house GPUs for data processing and image reconstruction, control the robotic arm and to log the detector locations.
5.2.2 Monte Carlo Simulation Study

In this study, we ran MC simulations using GATE[36] to study the proposed POC-PET imager with a geometry shown in Figure 5.3 (a). Each detector module in the front and rear detector panel is made of a LYSO crystal array with 16 x 16 elements of 2x2x10 mm³ each. The CRT is considered to be 200 ps FWHM for all detectors. The front maneuverable imaging probe has a total sensing area of 192mm x 128mm. The rear panel detector has a total sensing area of 382 mm x 192 mm. The torso is represented by an elliptical cylinder with a long axis, short axis, and axial length of 36 cm, 26 cm, and 15 cm, respectively. The lung inserts (also elliptical cylinders) in the torso have a long axis, short axis and axial length of 14 cm, 9 cm and 10 cm. A spherical lesion of 3cm diameter is placed inside each lung. The linear attenuation coefficient of the lungs, soft-tissues
and lesions is assumed to 0.025 cm$^{-1}$, 0.096 cm$^{-1}$ and 0.096 cm$^{-1}$, respectively, as shown in the attenuation map (Figure 5.3 (b)) generated using MATLAB.

**Emission Scan**

The activity concentration in the soft tissue, the lungs, and the lesions is assumed to be 143, 143, and 429 nCi/mL, respectively, i.e. the lesion-to-lung contrast ratio is 3:1 (Figure 5.3 (c)). To scan the phantom, the front maneuverable imaging probe is moved sequentially from angle 1 to 3 to collect coincidence events for 3 minutes at each location. The energy resolution of all detectors was assumed to be 10.0% for 511 keV gamma rays. The energy window used was from 435 keV to 650 keV. We recorded singles events from all detector volumes and performed coincidence detection offline as a post-processing step using a 4.5 ns coincidence timing window. The quantitative accuracy was assessed by measuring the uptake-ratio of lesion-to-lung from PET images with (i) no attenuation correction, (ii) measured correction using transmission scan, (iii) analytic correction by known attenuation-coefficient map.

**Transmission Scan**

A transmission source made of a uniform sheet of radioactivity was placed in front of the maneuverable PET imaging probe at a distance of 2 cm from the detector surface. The length, width and height of the source is 200 mm, 135 mm and 5 mm. The total radioactivity inside the transmission source is 1 mCi. As we image the phantom using the maneuverable probe, the system recorded singles events originated from the transmission source. These events are then sorted into coincidence events using a separate post-processing step. A blank reference scan with no phantom
was performed for 30 min at each position and coincidence events from the blank scan was also generated similarly.

Figure 5.3: (a) GATE simulation of POC system with planar transmission source; (b) Attenuation map of phantom where attenuation coefficient of lung and lesion is 30% and 100% of soft tissue; (c) Emission map with 3 times activity in the lesion with respect to lungs and soft tissue

5.2.3 Transmission-scan based Attenuation Correction

The γ rays get attenuated as they pass through tissues within the body which leads to the reduction of the energy of the detected radiation. Attenuation is calculated as:

$$\frac{I_x}{I_0} = e^{-\int \mu(x) dx}$$

(5.1)

where $I_x$ and $I_0$ are the attenuated and un-attenuated intensity of radiation respectively, $\mu$ is the linear attenuation coefficient (units: cm$^{-1}$), and $x$ is the distance (units: cm) from the source to the
detector. Therefore, \( I_x \) and \( I_0 \) are proportional to the transmission scan and blank scan count rates respectively. The attenuation coefficients for the body range from air values (close to zero) in the cranial sinuses, through very low values in the lungs, to fat, tissue and cortical bone, which has the highest value. The attenuation coefficient depends on a number of factors including photon energy, scattering cross-section of the material, and electron density. Typical attenuation coefficient value for water, which is almost the same as soft tissue, is 0.096 cm\(^{-1}\) for 511-keV photons and 0.025 cm\(^{-1}\) for lungs. The linear attenuation coefficient is a measure of the probability of the photon being absorbed per unit length in the object.

The list-mode MLEM update equation we use for reconstruction of this system is given by:

\[
X_j^{(k+1)} = \frac{X_j^{(k)} \sum_i H_{ij} A_i A_{i(m)} \frac{1}{\sum_j H_{ij} A_i A_{i(m)} X_j^{(k)}}}{\sum_{i} H_{ij} A_i}
\]  

(5.2)

Where, \( j \) is the image voxel index, \( i \) is the LOR index, \( i(m) \) is the LOR index where \( m \)th event is detected, \( X_j^{(k)} \) is the reconstructed activity distribution at voxel \( j \) for \( k \)th iteration. \( H_{ij} \) is the probability of detection of an event located at \( j \)th voxel by \( i \)th LOR. \( A_i \) is the attenuation correction factor for \( i \)th LOR. Further, the attenuation correction factor for each LOR \( i \) can be expressed as:

\[
A_i = e^{-\sum_j \mu_j l_{ij}}
\]  

(5.3)

Where, \( \mu_j \) is the linear attenuation coefficient value at voxel \( j \), \( l_{ij} \) is the length of intersection of LOR \( i \) with voxel \( j \). The summation is performed for all voxels that lies on the LOR.

We observe that Eq. (5.3) is the discretized version of Eq (5.1). Thus, the ratio of transmission to blank scan count rates gives the attenuation correction factor for each LOR. We use this ratio to estimate the attenuation for each LOR on-the-fly while reconstructing the emission events. Since our transmission scan is of very short duration, we don’t have enough counts per LOR, leading to improper estimation of the attenuation correction factors. To reduce such statistical variations in
the recorded counts, we group an area covered by 4x4 crystals into a single module and calculate the average counts for this module. So, any LOR that is in that module will have same number of transmission events. We acquire the blank scan data for a longer duration to reduce statistical noise.

5.3 Results

Figure 5.4 (a-c) shows the sensitivity images for three each detector location. The combined sensitivity image is shown in Figure 5.4 (d). Based on this particular system geometry, we estimated the sensitivity of the proposed POC-PET system to be around 1.2% near the center of its imaging field-of-view. This is about half of the sensitivity (2-3%) at the center of FOV of a typical whole-body PET scanner. Using the coincidence events from each angle, the reconstructed images without attenuation correction are shown in Figure 5.4 (e-h). Figure 5.4 (i-l) shows the reconstructed images with transmission-scan based attenuation correction. Even with a single scan at angle #2, we can already detect radiotracer uptake in significant portions of both lungs. Using events from all 3 angles, we can obtain images of the entire torso (Figure. 5.4 (l)) to detect suspicious uptake of PET tracers in the lungs.
Figure 5.4: (a,b,c) Sensitivity images for three detector positions; (d) Combined sensitivity image; (e,f,g) Reconstructed image without attenuation correction for three detector positions; (h) Combined reconstructed image without attenuation correction; (i,j,k) Reconstructed image with transmission-scan based attenuation correction for three detector positions; (l) Combined reconstructed image with transmission-scan based attenuation correction

In the attenuation-corrected images shown in Figure 5.4 (i-l), we observe that the center of the torso and the horizontal edges are more uniform as compared to non-attenuation corrected images in Figure 5.4 (e-h). However, there are still bright artifacts along the vertical edges. In order to make sure this is not caused due to improper attenuation correction; we generate an analytical attenuation map with the exact $\mu$ values of the different regions as shown in Figure 5.3(b). We
calculate the attenuation correction factor for each LOR by forward projecting the attenuation map. We consider this the reference standard. Figure 5.5 (b) shows the combined reconstructed image for all detector locations with analytical attenuation correction and we compare it with image reconstructed with transmission-scan based attenuation correction (Figure 5.5 (c)). For measuring quantitative accuracy between the two different attenuation correction methods, we also calculate the contrast recovery coefficient (CRC) values for the two lesions and plot profiles across the torso for three different horizontal lines as shown in Figure 5.5 (d).

For calculating CRC, first the count density, \( C_{t,i} \) in the \( i^{th} \) lesion was estimated by drawing a spherical ROI over the center of the lesion and then the mean number of counts in the ROI was calculated. The size of each ROI is the same as the corresponding lesion size. The background count density, \( C_{b,i} \) was determined as the mean number of counts in a square ROI drawn over the torso phantom from 10 adjacent slices. The \( CRC_i \) for \( i^{th} \) sphere was calculated according to the NEMA NU2–2001[52] definition:

\[
CRC_i = \frac{C_{t,i}}{C_{b,i}} \frac{1}{\text{uptake}-1}
\]

where uptake is the corresponding known lesion-to-background ratio. In this case the uptake is 3.

The CRC values are shown in Figure 5.5 (e). The three line profiles are shown in Figure 5.5 (f,g,h).
Figure 5.5: Images reconstructed (a) without attenuation correction; (b) analytical attenuation correction with known mu-map; (c) transmission-scan based attenuation correction; (d) Torso map showing the different lines for profile plots; (e) Contrast recovery coefficient values for the two lesions as shown in (d); Profile plots through (f) line 1; (g) line 2, (h) line 3

From both line profiles and CRC values we observe similar quantitative accuracy between measured attenuation correction and reference attenuation correction using μ-map.
To demonstrate the interactive imaging feature of this system, we start imaging the torso with the probe directly above the torso (i.e. using Angle 2 in Figure 5.4). This will provide an image in Figure 5.6 (a) to an operator who can adjust the imaging probe to acquire additional data. If the probe is moved to Angle 1, the updated image will be Figure 5.6 (b). If the probe is moved to Angle 3, the updated image will be Figure 5.6 (c). If using all 3 angles, the update image will be Figure 5.6 (d). As one scans a patient, visual feedback is provided to determine the image quality. If it is sufficient to make diagnostic decision, one can stop the scan. Otherwise, the scan can be continued to further improve the counting statistics and image quality.

Figure 5.6: Demonstration of interactive scanning; (a) Image after first acquisition from angle 2; (b) Updated image after adding data from angle 1; (c) Updated image after adding data from angle 3; (d) Updated image when using data from all three angles

5.4 Discussion and Future Work

We have designed a mobile PET imager that can provide molecular imaging capability at patient bedside and have demonstrated its feasibility to be used as a lung imager. The scanner employs a robotic arm to hold an imaging probe that can be maneuvered by hand to scan a user-selected organ-of-interest. Therefore, the technology is versatile when compared to other organ-specific
PET systems (such as a positron emission mammography machine). We have demonstrated interactive scanning where we see improvement in image quality as we keep adding data from multiple angles. Thus, an operator can scan a patient interactively until the desired image quality and information are acquired. This “interactive scanning” is standard for clinical ultrasound imaging but has never been implemented for PET imaging.

The simulation results shown in Figure 5.4 are significant in several aspects: (i) an initial 3-minute scan taken at angle #2 can reveal the gross distribution of PET radiotracer in the torso; (ii) if there is any region that show suspicious uptake, the probe can be moved to a new location to increase the angular sampling of the targeted area to improve its image quality; (iii) with fast image reconstruction implemented using GPU, we can obtain visual feedback from the reconstructed images in a few minutes (this can be accelerated further using current generation of GPU), adjust the imaging probe location and acquire more counts until the image quality is satisfactory.

Figure 5.5 (a) shows reconstructed images without attenuation correction that show suspicious uptake in lungs using the proposed POC-PET system. However, a closer look reveals attenuation artifact in the reconstructed PET images. This well-known artifact causes the low-density tissues (such as lungs) and the edge of a body to appear with higher uptake than their real values while the center of an object appear to have lower uptake. Although this may not limit the use of POC-PET for the detection of diseases, quantitative imaging is valuable for monitoring disease progression over time. Conventional approaches for attenuation correction include calculated attenuation correction[114], measured attenuation correction using transmission sources[115][116] or CT[117] and hybrid techniques for whole-body PET or MR/PET[118][119]. Several algorithms have been proposed to use data consistency to estimate attenuation coefficients or transmission data from emission data only[120], especially with TOF-PET data[121][122].
However, these methods were all developed for conventional PET scanners that have a ring geometry. In this study, we have implemented a transmission-scan based attenuation correction for our POCPET geometry which has limited angle tomography. This was done to achieve quantitative PET images without the need of a second modality. Our measured attenuation correction method was compared to analytical attenuation correction with known $\mu$ map and both showed similar quantitative accuracy.

In this study, we have acquired emission and transmission data using separate scans. However, a simultaneous acquisition of emission and transmission data is desirable because it reduces acquisition time and improves spatial registration between attenuation correction and the PET image. In our current setup, the CRT is considered to be 200 ps FWHM for all detectors. With this time-of-flight resolution we plot the histogram of the time-difference ($\Delta t$) for emission and transmission events (as shown in Figure 5.7).

![Histogram of $\Delta t$](image)

Figure 5.7: Histogram of $\Delta t$ of arrival time of two detected gamma-rays for emission and transmission events
Results in Figure 5.7 show that the majority of transmission events can be separated from emission events based on the Δt. The separation between the two clusters of events can be further improved if the maneuverable PET detector probe is placed further away from a patient’s body.
Chapter 6: Conclusions and Future Direction

6.1 Summary and Conclusions

In this dissertation, we implemented a generalized GPU-based list mode PET reconstruction framework with appropriate correction techniques (attenuation, scatter and normalization). We used this framework to test the feasibility of novel PET systems with unconventional geometries. We have designed a dedicated total-breast PET system with a highly unconventional geometry in order to overcome the fundamental limitations of other previous dedicated breast PET approaches that could not image the chest wall (mediastinum) region nor the axilla. By surrounding both breast volumes with detectors and capturing the posterior breast regions not imaged in previous breast PET designs, our system yields considerably higher sensitivity (3.21 times) than a contemporary clinical whole-body PET system. While there are more detector modules used in our system design than in single-breast PET systems, we have arrived at an asymmetric system geometry that provides comprehensive sampling and imaging in the most relevant regions when evaluating breast disease: the breast, mediastinum and axilla. Moreover, our system substantially outperforms the contemporary clinical whole-body PET system in breast imaging tasks, indicating that it could be clinically useful in characterizing breast disease, especially at its earliest stages.

We proposed a new interactive POC PET/Ultrasound imaging system, with near real-time image reconstruction capability, using TOF PET detectors. Our preliminary studies (both experimental and Monte Carlo simulation) demonstrate the feasibility of this system that can provide near real-time visual feedback to an operator who can maneuver a hybrid imaging probe to interactively scan an organ-of-interest in a patient to support POC imaging applications.
Using SiPM based detector technology and PETsys ASIC we build a prototype POC PET system and we achieved a CRT of 250 ps FWHM. The imaging study of a cylindrical Derenzo phantom experimentally shows that this system can identify rod sources $\geq 1.32$ mm in diameter with 3-position scanning. With TOF information, the reconstructed images have fewer artifacts that are due to limited angle tomography. This system provides higher resolution PET images than a whole-body PET scanner in a user-selected target region without compromising the system sensitivity. Fused PET/Ultrasound images of the gelatin phantom show potential application of the system for providing anatomic, functional and molecular imaging capability to assess vascular diseases at a much lower cost than the current technology based on a PET/MR scanner.

We have designed a mobile PET imager that can provide molecular imaging capability at patient bedside and have demonstrated its feasibility to be used as a lung imager. The scanner employs a robotic arm to hold an imaging probe that can be maneuvered by hand to scan a user-selected organ-of-interest. Therefore, the technology is versatile when compared to other organ-specific PET systems (such as a positron emission mammography machine). We have demonstrated interactive scanning where we see improvement in image quality as we keep adding data from multiple angles. We have implemented a transmission-scan based attenuation correction for our POCPET geometry which has limited angle tomography. This was done to achieve quantitative PET images without the need of a second modality. Our measured attenuation correction method was compared to analytical attenuation correction with known $\mu$ map and both showed similar quantitative accuracy.
6.2 Continuous Bed Motion Reconstruction

Motivation:

Most PET systems use step-and-shoot (SS) acquisition [123] for whole-body imaging, in which dynamic PET study may be confined to a single-bed position. Recently, continuous-bed-motion (CBM) acquisition of PET has been made commercially available by Siemens [124]. This dynamic whole-body imaging has several advantages over the conventional step-and-shoot bed motion (Fig. 1). Actual field of view is the area of detector field of view in step-and-shoot motion which may show low sensitivity in peripheral areas of view. Thus, some overlap imaging is needed for each step for whole-body imaging. In continuous bed motion, on the other hand, the sensitivity over the axial range is uniform and requires no overlap. Therefore, the whole-body imaging with continuous bed motion permits better uniformity than the conventional whole-body imaging with step-and-shoot motion.

Figure 6.1: Actual field of view on step-and-shoot imaging and continuous-bed-motion imaging. Since sensitivity is low in the peripheral areas of view, and thus, some overlap imaging is needed for whole-body imaging in step-and-shoot imaging. On the other hand, actual field of view is uniform without need for overlap imaging in continuous bed motion. Thus, the sensitivity is higher and uniform for whole-body imaging in the continuous bed motion {Figure Courtesy: [125]}
Methods:

Our existing image reconstruction framework is not readily applicable to CBM due to the constantly moving field-of-view during acquisition. In this study, by taking the bed motion into account, we modified the framework to support CBM acquisition for Siemens Biograph Vision scanner.

During the CBM acquisition, bed position information, is encoded into the list mode data stream. The bed motion can be viewed as rigid axial-direction patient motion. If we consider the patient to be stationary, then during CBM, it is equivalent to the scanner moving in the opposite direction. We use this concept to reposition the detector-pair coordinates of the line-of-response (LOR) for each event in the axial direction using bed position information, to account for bed motion. To test our CBM reconstruction, we simulated a continuous phantom motion in GATE with a speed of 1 mm/s. The phantom we used is a cylindrical phantom filled with water with Derenzo-patterned spherical sources placed across different planes as shown in Figure 6.2. The cylinder has a diameter of 30 cm and height 40 cm. The diameters of the Derenzo spheres are shown in Figure 6.2. The activity concentration in the spheres was 5.3 kBq/cc. There was no background activity. The initial and final position of the phantom is shown in Figure 6.2 (e,f). The total distance moved by the phantom was the length of the phantom i.e. 40 cm. We did not use attenuation correction, scatter correction and normalization while reconstructing.
Figure 6.2: (a) Transverse View of the simulated phantom inside the scanner, (b) Different diameters of spheres, (c,d) Axial views of the phantom, (e) Initial position for CBM, (f) Final position for CBM

Results:

Figure 6.3 (a) and (b) shows the transverse and axial views of the detected coincidence maps for CBM acquisition. The sources are elongated in the axial direction since the phantom is in motion and we didn’t reposition the LORs based on bed position. Figure 6.3 (c) and (d) shows the transverse and axial views of the reconstructed images after LOR repositioning. We can see that the spheres are not elongated in the axial direction, implying that our framework correctly positioned the sources when reconstructing data from CBM acquisition.
Figure 6.3: (a) Transverse and (b) Axial views of detected coincidence map, (c) Transverse and (d) Axial views of reconstructed images using CBM data

**Future Work:**

This was a preliminary study to test our reconstruction framework for CBM acquisition. For quantitative imaging, corrections need to be implemented for scatter, attenuation and normalization. The main challenge that needs to be addressed while implementing these corrections for continuous bed motion is computational complexity since some of these corrections (scatter and attenuation) need to be done for each bed position. Once everything is implemented, this approach can be used for the Augmented Whole-Body Scanning via Magnifying PET (AWSM-PET) [126] prototype system being developed in our lab for full-body imaging.
References


[23] S. R. Cherry et al., “MicroPET: a high resolution PET scanner for imaging small


