A Four-Dimensional Image Reconstruction Framework for PET under Arbitrary Geometries

Aswin John Mathews
Washington University in St. Louis

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A Four-Dimensional Image Reconstruction Framework
for PET under Arbitrary Geometries
by
Aswin John Mathews

A dissertation presented to the Graduate School of Arts and Sciences
of Washington University in partial fulfillment of the
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Washington University in Saint Louis
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Dedicated to my beloved grandparents, loving parents and the pursuit of science.
Positron Emission Tomography (PET) is a functional imaging modality with applications ranging from the treatment of cancer, studying neurological diseases and disease models. Virtual-Pinhole PET technology improves the image quality in terms of resolution and contrast recovery. The technology calls for having a detector with smaller crystals placed near a region of interest in a conventional whole-body PET scanner. The improvement is from the higher spatial sampling of the imaging area near the detector. A prototype half-ring PET insert built to study head-and-neck cancer imaging was extended to breast cancer imaging.

We have built a prototype half-ring PET insert for head-and-neck cancer imaging applications. In the first half of this work, we extend the use of the insert to breast imaging and show that such a system provides high resolution images of breast and axillary lymph nodes while maintaining the full imaging field of view capability of a clinical PET scanner.

We are focused on designing unconventional PET geometries for specific applications. A general purpose 4D PET reconstruction framework was created to estimate the radionuclide...
uptake in the subject. Quantitative estimation in PET requires precise modeling of PET physics. Data acquired in a PET scanner is well modeled as a Poisson counting process. Reconstruction given the forward model is implemented using MAP-OSEM. The framework is capable of reconstructing PET data under arbitrary position of the detector elements and different crystal sizes. A novel symmetry finding algorithm is created to reduce the system matrix size, without loss of resolution. The framework motivates investigation into different PET system geometries for different applications, as well as optimizing the design of PET systems. A generalized normalization procedure was developed to model unknown components. The programs are parallelized using OpenMP and MPI to run on small workstations as well as super-computing clusters. The performance of our reconstruction framework is presented through four novel and unconventional PET systems, each designed specifically for a different geometry. The Virtual-Pinhole half-ring system is a half-ring insert integrated into a Siemens Biograph-40, for head and neck imaging. The Flat-panel system is a modular insert system integrated into the Biograph-40, designed for breast cancer imaging. The MicroInsert II is the second generation full ring insert device, integrated into the MicroPET scanner to improve the resolution and contrast recovery of the MicroPET scanner. The Plant PET system is a PET system designed to image plants vertically, and integrated into a plant growth chamber. The improvement in speed/memory from symmetry finding is as high as a factor of 50 in some cases. Further improvements to the framework and state of the field are also discussed.
Chapter 1

Introduction

The following section briefly introduces Positron Emission Tomography (PET). We discuss some of the applications in PET, followed by an in-depth review of the physics and chemistry underlying the imaging modality. The basic mechanisms of PET instrumentation are covered next. Creating an image from the data requires building a statistical model, and development of inverse algorithms. The principles of image reconstruction for PET are outlined. We end the chapter with a timeline of past developments in PET.

1.1 Positron Emission Tomography and its applications

Positron Emission Tomography (PET) is a functional nuclear imaging technique that produces a volumetric image of the distribution of a positron emitting radionuclide. It is used in the imaging of chemical or biological processes. Positrons emitted during radioactive decay undergo annihilation with its anti-matter counterpart, an electron, to emit two 511 keV back to back gamma rays. These are measured through detectors placed around the target of interest and an image of the radionuclide distribution is build up by passing the data through algorithms on a computing machine.

In medicine, PET is used to quantify a physiological process, by developing radio-pharmaceuticals that target that process. The resulting image is proportional to the biochemical 'activity' in the body. As a result, the image of radionuclide distribution is also called activity distribution.
The major utilization of this modality is in oncology towards cancer imaging, wherein the physiological process that is targeted is glucose metabolism. Cancer is uncontrolled cell growth, and consumes high levels of energy. The observation that cancer cells produce energy by glycolysis forms the foundation of PET imaging for cancer [82, 81, 41]. Fluorodeoxyglucose (FDG) is metabolized similarly to glucose. The radio-pharmaceutical consists of an FDG molecule tagged with a radioactive isotope, commonly $^{18}$F to form Fluorodeoxyglucose $^{18}$F-FDG and it aggregates in regions of high metabolic activity. Although glucose metabolism is the major process targeted by PET, other processes such as oxygen metabolism, amino acid metabolism and DNA synthesis have also been recruited for studying cancer. Specific oncological applications include using PET for head and neck cancer, breast cancer, lung cancer and prostate cancer [63].

PET also finds applications in neuro imaging [13] for studying brain activity, and afflictions such as tumors, strokes or dementia, especially Alzheimer’s disease. These afflictions change the brain metabolism that are detectable on PET images. Radio-pharmaceuticals have been developed that target specific receptors such as 5-HT(1A)-receptor for epilepsy, Benzodiazepine-receptor for schizophrenia and Dopamine receptors for Parkinson’s disease and drug addiction.

In cardiology, PET is used to detect coronary artery disease and myocardial viability [37, 26]. The major processes targeted are blood flow, blood volume, perfusion of the myocardium and fatty acid metabolism. Myocardial perfusion imaging, done in conjunction with a cardiac stress test, evaluates the muscles of heart called myocardium. The viability of the myocardium is identified by either blood flow using $^{13}$N ammonia and $^{15}$O or glucose metabolism. PET is superior to Single Photon Emission Computed Tomography (SPECT) for Myocardial perfusion imaging in image quality and diagnostic accuracy [8].

In pharmacology, PET is used to test the efficacy and mechanism of drugs and in the development of new ones using small animal imaging. The drug is radio-labeled and uptake of the drug in various tissues is monitored. A wide variety of common elements have positron emitting isotopes. The chemical interaction of the element is unchanged by replacement with a positron emitting isotope.
1.2 Physics of positron formation, annihilation and interaction of the resultant gamma photon with matter

A radioactive isotope that forms positrons is introduced into the biological or chemical system whose function has to be characterized. By tagging the isotope with additional molecules, the isotope can be designed to selectively bind to certain function. After introduction, the isotope redistributes in the system following that function.

Radioactive decay follows an exponential law. The number of decay events at any given time within a mass of radioactive material is proportional to the number of atoms of the material. Therefore, the number of decay events as a function of time is exponentially decreasing with a decay constant. The decay constant is a function of the radioactive material.

\[
\frac{\partial N}{\partial t} \propto N, \quad \text{where } N \text{ is the number of atoms in the material}
\]

\[
\frac{\partial N}{N} = -\lambda \partial t
\]

\[
N = N_0 \times e^{-t/\tau}, \quad \tau = \frac{1}{\lambda}
\]
Positrons are emitted by the radioactive isotope as part of its decay process. The positron travels a short distance from its formation point and combines with an electron to form an exotic atom known as positronium. The mean distance traveled by the positron is called \textit{positron range} [43].

Positronium is an electron and positron bound together like a hydrogen atom. The system is unstable and decays after a short period of time by annihilation of the electron and positron and releasing energy in the form of gamma rays. The period of time that a positron remains stable depends on the state of the positronium.

<table>
<thead>
<tr>
<th>$S$</th>
<th>$M_s$</th>
<th>Name</th>
<th>Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>para-positronium</td>
<td>125 ps</td>
</tr>
<tr>
<td>1</td>
<td>-1</td>
<td>ortho-positronium</td>
<td>142 ns</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>ortho-positronium</td>
<td>142 ns</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>ortho-positronium</td>
<td>142 ns</td>
</tr>
</tbody>
</table>

Table 1.1: Positronium and Lifetimes

The mass of both particles has an energy equivalent of 1,022 keV. Therefore, the total energy of the gamma rays produced as a result of the annihilation is 1,022 keV. The highest probability of annihilation is to produce two or three photons. More than three photons is extremely rare. For two photon decay, the energy of the two gamma rays that is produced is 511 keV each. From the conservation of momentum, the two gamma rays are 180 degree back to back if the positronium is initially at rest. More commonly, the gamma rays are at a slight angle from exactly back to back as a result of the initial momentum of the positronium. This deviation in the angle from 180 degrees is known as \textit{photon accolinearity}.

The gamma rays produced has three main modes of interaction with matter, by photoelectric effect, Compton scattering and pair production. The three modes of interaction are described below.

1) \textbf{Pair production} is the creation of another electron-positron pair by the gamma ray. However, from the principle of conservation of energy, the gamma ray must have energy greater than 1,022 keV for this to happen. Under the presence of a third body (nucleus or electron), the gamma photon forms a electron-positron pair. This interaction does not play a role in PET physics.
2) **Photoelectric effect** is when the gamma ray transfers its energy to an atomic electron, causing the electron to leave its atom, resulting in a photoelectron. This is the dominant mode of matter interaction at lower energies. This interaction causes undesirable attenuation of gamma rays in the body being imaged, but is also the process by which gamma rays is detected within the detector crystal.

3) **Compton scattering** is caused by the gamma photon interacting with an atomic electron to eject the electron, with the remaining photon energy being emitted as a lower energy gamma photon with a longer wavelength. The direction of the new gamma photon is distributed around the axis of the original photon. Higher angles from the original axis are more uncommon, with the energy of the emitted gamma photon being much lower. After multiple 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, 

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

Therefore, 

\[ \frac{1}{E_i} = \frac{1}{E_f} + \frac{(1 - \cos(\theta))}{E_0} \]

where \( E_0 = m_e c^2 \) is the rest energy of the electron.

The scattering angle is distributed as defined by the Klein-Nishina formula [38], which gives the cross section of photons scattered from a free electron. The differential cross section is

\[ \frac{d\sigma}{d\Omega} = \alpha^2 r_c^2 \frac{E_f^2}{E_i} \left[ \frac{E_i}{E_f} \left( \frac{E_f}{E_i} - 1 + \cos^2(\theta) \right) \right] / 2 \]

where \( \alpha \) is the fine structure constant, \( r_c = \frac{\hbar}{m_e c} \) is the Compton wavelength of the electron.

The distribution is plotted in Figure 1.2.

The 511 keV gamma emitted during positron annihilation undergoes photoelectric absorption or Compton scattering inside the patient and bed and is known in data correction community.
Figure 1.2: Distribution of scattering angle according to the Klein-Nishina formula.

as *attenuation* and *scattering* respectively. The attenuation coefficient is defined as the probability of gamma photon absorption per unit path length. The scattering coefficient is the probability of photon scatter per unit path length. The unit of both coefficients is cm$^{-1}$. The magnitude of photon flux as a function of depth is determined by Beer-Lambert law. Determination of the coefficients require knowledge of partial interaction cross section of the gamma photon with matter, as well as the density of the medium.

The cross section of photon interaction with matter as a function of photon energy is shown in Figure 1.3. The graph was plotted with data obtained from the NIST XCOM database [9]. Soft tissue and bone composition was determined from ICRU Report 44 [35]. Coherent scattering is Rayleigh scattering and Incoherent scattering is Compton scattering. For high energy levels, Compton scattering dominates Rayleigh scattering by orders of magnitude. Water and Soft Tissue has similar interaction cross sections. The main difference between the two arises from the difference in density (g/cm$^3$), that multiplies with the cross sections to determine the mean attenuation and scattering coefficients. The primary interaction for water, soft tissue and bone for 511 keV gamma photon is scattering. The photoelectric absorption for bone at 511 keV is higher than for tissue. For Lutetium Oxyorthosilicate, photoelectric absorption plays an important role, which partially justifies its use as a detector material.
Figure 1.3: Photon cross sections and attenuation coefficients during interaction with different types of matter, (a) Lutetium Oxyorthosilicate (LSO) (b) Water (c) Bone (d) Soft tissue, as a function of photon energy.
1.3 Data Acquisition for PET

The commonly used block detector for PET comprise of a scintillation crystal, photo multiplier tubes and decoding electronics.

![PET Data Acquisition Diagram]  

Figure 1.4: PET Data Acquisition system

Currently, the commonly used crystal is Lutetium Oxyorthosilicate (LSO) that has high density and atomic number contributing to high efficiency, as well as fast scintillation properties. The crystal detectors, having a high atomic number, interact with the incoming gamma through photoelectric absorption and Compton scattering. The ionizing radiation excite the crystal and cause the re-emission of absorbed energy in the form of light. The amount of light produced is proportional to the energy of the incident radiation.

The common packaging of the crystal is as a block detector, which is a block of the scintillator segmented into an array of crystals by cuts and coupled to photo multiplier tubes (PMT). For good sensitivity, the scintillator has to be of sufficient depth. The cuts on the scintillator control light sharing between adjacent points on the scintillator surface, and maintain resolution. The output of the photomultiplier tubes is an amplification of the light input at its surface. This electrical signal is encoded by a resistive network and fed into an Application Specific Integrated Circuit (ASIC), where the crystal that was excited is decoded. The ASIC also contains a Constant Fraction Discriminator and Time to Digital Converter that measures the time of photon detection.
The data collected from all the crystals are piped into a coincidence unit, which tags two detection events falling within the same coincidence window as a single ’prompt event’. The width of the coincidence window is usually 4 to 12 ns. The output of the coincidence unit is sent to a data acquisition computer and usually stored on disk as list-mode data. List-mode data format is a list of events collected, tagged with time, and ordered in the sequence of their arrival. A prompt event can either be a ‘true event’, which are prompt events comprising of two gamma photon detections from the same nuclear decay, or a ‘random event’, which are prompt events comprising of two gamma photon detections from different nuclear decay.

To statistically correct for random events, the PET system also measures coincident detections with one of the two gamma events delayed by a fixed time window. The delay ensures that there are no detection events belonging to the same nuclear decay. The coincident detections do not have true events, and form background noise whose contribution has to be removed from the prompt event datastream. This method is known as delayed random correction.

### 1.4 Statistical Model of PET

The radionuclide distribution in a human body or phantom is continuous. For reconstruction purposes, we discretize the space on a suitable basis. The basis might be pixels (picture elements) in a two dimensional environment or ‘voxels’ (volumetric elements) in a three dimensional environment. The radionuclide is assumed to be uniformly distributed within a voxel. The value of the element is an integral of the total radionuclide concentration contained by it.

The positron annihilation in voxel occurs at a rate proportional to the activity. We denote the positron annihilation rate across the image space by a lexicographically ordered random vector, $\mathbf{\phi} = \{\phi_0, \phi_1, \phi_2, ... \phi_{N-1}\}$, where $\phi_i$ is the annihilation rate at the $i^{th}$ voxel, $\phi_i : \Omega \to \mathbb{R}$ and $N$ is the total number of voxels. For low rate and large imaging time, the number of back to back gamma rays emitted in a voxel per unit time can be assumed to follow a Poisson distribution, with mean equal to the positron annihilation rate. The Poisson distribution is a discrete probability distribution that encodes the number of events happening in a time
window, given that separate time windows are independent and events appear at a constant rate.

The gamma rays emitted by the voxel over an imaging period can be assumed to follow a Poisson distribution with mean equal to the positron annihilation rate times the imaging time. However, this assumption is not entirely true in the real-world scenario. A radionuclide undergoing decay reduces in concentration exponentially. Rather than correcting for the decay as part of the model, the activity is assumed to be constant over the imaging period, and decay correction is done as a post-process step. Additionally, the PET electronics has a short recovery time, after the detection of a coincidence, termed dead time. Dead time is an issue for imaging a very hot body, where multiple events are expected to arrive within a short time window. For shorter imaging times, in the order of the coincidence time window, the independence assumption between different time windows do not hold either.

Let the detected counts across the data space be represented by another random vector, \( \mathbf{Y} = \{Y_0, Y_1, Y_2, \ldots Y_{M-1}\} \), where \( Y_j \) is the counts detected in \( j^{th} \) detector pair and \( M \) is the number of detector pairs. A detector pair, \( j \), placed in the imaging space detects coincidence events from each image voxel \( X_i \), distributed as Bernoulli, with parameter, \( H(i,j) \). The parameter \( H(i,j) \) is a function of the solid angle coverage of the image voxel by the detector pair, the interaction physics of gamma rays through the medium between the voxel and the detector, as well as angular efficiency of the detector. The interaction physics of the gamma rays through the medium encodes attenuation caused by photo-electric absorption of gamma rays through the body, but not the scattering or random events.

Random and scatter events add a bias to each detector. The expected counts at the detector pair, \( j \), is the sum of \( H(i,j) \) weighted random parameters from every image voxel, along with random events, \( r_j \) and scatter events, \( s_j \). If each image voxel are assumed to be mutually independent, then the counts, \( Y_j \), measured at each detector pair is Poisson with parameter equal to \( \sum_{i=0}^{N-1} H(i,j) \times \phi_i + r_j + s_j \) (For more details, see [69]). The mutual independence of image voxels ensures that the sum of independent Poisson random variables is still Poisson.
Since the measurements across detector pairs are mutually independent, the probability of a measurement, \( k = \{k_0, k_1, k_2, \ldots k_{M-1}\} \), is given by,

\[
Pr(Y = k) = \prod_{j=0}^{M-1} \frac{e^{-\lambda_j} \times \lambda_j^{k_j}}{k_j!} \tag{1.2}
\]

where \( \lambda_j = \sum_{i=0}^{N-1} H_{(i,j)} \times \phi_i + r_j + s_j \).

\[
Pr(Y = k | \phi) = \prod_{j=0}^{M-1} \frac{e^{-(\sum_{i=0}^{N-1} H_{(i,j)} \times \phi_i + r_j + s_j)} \times \left(\sum_{i=0}^{N-1} H_{(i,j)} \times \phi_i + r_j + s_j\right)^{k_j}}{k_j!} \tag{1.3}
\]

Therefore, the log-likelihood of \( Y \), given a full measurement, \( k \), is

\[
L(\phi; Y) = \sum_{j=0}^{M-1} k_j \times \log \left(\sum_{i=0}^{N-1} H_{(i,j)} \times \phi_i + r_j + s_j\right) - \left(\sum_{j=0}^{M-1} \sum_{i=0}^{N-1} H_{(i,j)} \times \phi_i + r_j + s_j\right) - \sum_{j=0}^{M-1} \log(k_j!) \tag{1.4}
\]

### 1.5 Image Reconstruction Techniques

A variety of different methods exist for image reconstruction. As mentioned in the last section, the mean counts at each measurement is distributed as a weighted linear combination of image voxels. The system matrix, \( H = h(i, j) \), has lower rank than unknowns, resulting in an under-determined system. The problem is ill-posed (Hadamard 1917). That is, one of the following conditions is not true.

1. A solution exists
2. The solution is unique

11
3. The solution’s behavior changes continuously with initial conditions.

It is also computationally complicated to invert this matrix. Traditional reconstruction strategies fall into Analytic methods and Iterative methods. Methods that are applicable to this work are described below.

### 1.5.1 Analytic Methods

**Filtered Back Projection**

One approach to reconstructing images from projections is using filtered back-projection. The method was conceived by David Chesler at Massachusetts General Hospital [15]. Let $i^{th}$ image voxel index be $(x_i, y_i)$ and $j^{th}$ data point index $(l_j, \theta_j)$, where $l_j$ is the distance of the line joining the measurement crystals from center and $\theta_j$ is its angle.

That is, $\phi_i = \phi(x_i, y_i)$ and $g(l_j, \theta_j) = y_j$

Filtered Back Projection assumes that each data measurement originates as the integral along a line, with constant efficiency along the line. Therefore,

$$g(l_j, \theta_j) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \phi(x_i, y_i) \delta(x_i \cos \theta_j + y_i \sin \theta_j - l_j) \partial x_i \partial y_i$$

We denote the one-dimensional Fourier Transform of $g(l, \theta)$ across the $l$ dimension be $G(\varphi, \theta)$.

$$G(\varphi, \theta) = \int_{-\infty}^{\infty} g(l, \theta) e^{-j2\pi l \varphi} \partial l$$

Then, $\phi(x, y) = \int_0^\pi \left[ \int_{-\infty}^{\infty} |\varphi| G(\varphi, \theta) e^{j2\pi \varphi \theta} \partial \varphi \right]_{l=x \cos \theta + y \sin \theta} d\theta$ (See Eqn. 6.23 in [59])

That is, the 1-D Fourier Transform is multiplied by a ramp $|\varphi|$ filter, and its inverse Fourier Transform is taken, followed by a summation across all $\theta$.

Filtered backprojection is very efficient algorithm, and is used as a yard stick to determine image resolution across different systems. However, applying filtered backprojection to general geometries is an open research topic. The images from this algorithm does not have
the resolution as iterative algorithms. Additionally, it is easier to model complicated physics and constraints in iterative methods.

1.5.2 Iterative Methods

Iterative methods are divided into algebraic and statistical. Algebraic methods consist of ART, MART, SMART family of algorithms. Algebraic methods are not discussed in detail due to their limited application in this work.

Maximum Likelihood - Expectation Maximization (ML-EM)

The Maximum Likelihood solution seeks to find a solution that maximizes the log-likelihood equation. The log likelihood equation is given in Equation 1.4 as,

\[
L(\phi; Y) = \sum_{j=0}^{M-1} k_j \times \log \left( \sum_{i=0}^{N-1} H_{(i,j)} \times \phi_i + r_j + s_j \right) - \left( \sum_{i=0}^{N-1} H_{(i,j)} \times \phi_i + r_j + s_j \right) - \log(k_j!)
\]  

(1.5)

The solution we seek is

\[
\hat{\phi}_{ML}(Y = k) = \arg\max_{\phi} Pr(Y = k|\phi)
\]

(1.6)

The data collected from a PET scanner is assumed to be Poisson distributed. There is no closed form analytical solution to the problem. The Expectation-Maximization is an iterative method to find the solution. The algorithm has been proved to converge for exponential families.
The complete EM algorithm is written as ( Appendix B ),

$$
\phi_i^{p+1} = \frac{\phi_i^p}{\sum_{j=0}^{M-1} H_{(i,j)}} \sum_{i=0}^{N-1} \frac{H_{(i,j)} \times k_j}{\sum_{i=0}^{N-1} H_{(i,j)} \times \phi_i^p}
$$

(1.7)

**Maximum APriori - Expectation Maximization (MAP-EM)**

The Maximum-APriori (MAP) estimate incorporates a prior distribution on the estimate. Rather than maximizing the probability of the data given the parameter, the probability of the parameter given the data is maximized.

$$
\hat{\phi}_{ML}(Y = k) = \arg\max_\phi Pr(Y = k|\phi)
$$

$$
\hat{\phi}_{MAP}(Y = k) = \arg\max_\phi Pr(\phi|Y = k)
$$

$$
= \arg\max_\phi \frac{Pr(Y = k|\phi) Pr(\phi)}{\int_{\phi'} Pr(Y = k|\phi') Pr(\phi')} = \arg\max_\phi Pr(Y = k|\phi) Pr(\phi)
$$

(1.8)

$$
Pr(Y = k|\phi) \times Pr(\phi) = \left[\prod_{j=0}^{M-1} e^{-\left(\sum_{i=0}^{N-1} H_{(i,j)} \times \phi_i + r_j + s_j\right)} \times \left(\sum_{i=0}^{N-1} H_{(i,j)} \times \phi_i + r_j + s_j\right)^{k_j} \right] \times Pr(\phi)
$$

(1.9)
The log likelihood is given by

\[ L = \sum_{j=0}^{M-1} k_j \times \log \left( \sum_{i=0}^{N-1} H(i,j) \times \phi_i + r_j + s_j \right) - \left( \sum_{i=0}^{N-1} H(i,j) \times \phi_i + r_j + s_j \right) - \log(k_j!) + \log(Pr(\phi)) \]  \hspace{1cm} (1.10)

The EM algorithm for MAP estimate is,

\[ \phi_{i}^{p+1} = \frac{\phi_{i}^{p} \sum_{j=0}^{M-1} H(i,j) \times k_j}{\sum_{j=0}^{M-1} H(i,j) - \beta \frac{\partial V(\phi)}{\partial \phi_i} \bigg|_{\phi_{old}}} \sum_{j=0}^{M-1} \sum_{i=0}^{N-1} H(i,j) \times \phi_{i}^{p} } \hspace{1cm} (1.11)\]

A generalized version of the MAP estimator is the Penalized Likelihood (PL) estimator. In the MAP estimator, the prior distribution is constrained to a simplex plane, with the probabilities constrained to be positive and summing to one. In the Penalized Likelihood estimator, smoothing of the image is produced by penalizing the Likelihood operator. The penalty is usually a function of the image space variables alone.

The likelihood, \( L = \sum_{j} y_j \times \log \left( \sum_{i} H(i,j) \times \phi_i + r_j + s_j \right) - \left( \sum_{i} H(i,j) \times \phi_i + r_j + s_j \right) - \log(y_j!) + \beta V(\phi) \) \hspace{1cm} (1.12)

The EM algorithm for PL estimate is,

\[ \phi_{i}^{p+1} = \frac{\phi_{i}^{p} \sum_{j} H(i,j) \times y_j}{\sum_{j} H(i,j) - \beta \frac{\partial V(\phi)}{\partial \phi_i} \bigg|_{\phi_{old}}} \sum_{j} \sum_{i} H(i,j) \times \phi_{i}^{p} } \hspace{1cm} (1.13)\]
Ordered Subsets Maximum Likelihood

Ordered Subsets is used to improve the convergence rate of the EM algorithm. At each iteration, only one subset of the data is projected. The algorithm requires the data to be interleaved such that each subset has equal contribution to the image space. The method does not converge. Modifications to the algorithm that converge have been proposed. For OSEM, the algorithm enters a limit cycle, wherein the estimate cycles through each possible solutions of the data subset.

\[
\phi^{p+1} = \frac{\phi_i^p}{\sum_{j \in S(o)} h(y_j | \phi_i)} \sum_{j \in S(o)} \frac{h(y_j | \phi_i) \times y_j}{\sum_i h(y_j | \phi_i) \times \phi_i^p}
\]

(1.14)

1.6 History of PET

PET has a history of over half a century starting in 1951 with a brain probe used to localize brain tumors using coincidence information by William H. Sweet at MGH. A brief history of PET is given below. The material is adapted from [50].

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1951</td>
<td>Probe-counter in diagnosis and treatment of brain tumors using coincidence data [73]</td>
</tr>
<tr>
<td>1951</td>
<td>Using positron emitting isotopes to localize brain tumors [84]</td>
</tr>
<tr>
<td>1963</td>
<td>Image reconstruction for an X-ray system using radon equations [17]</td>
</tr>
<tr>
<td>1971</td>
<td>Examination of body by X or gamma radiation by Hounsfield [28]</td>
</tr>
<tr>
<td>1971</td>
<td>Filtered back projection algorithm is invented [15]</td>
</tr>
<tr>
<td>1973</td>
<td>PETT I, [77]</td>
</tr>
<tr>
<td>1973</td>
<td>PETT II, Michael E Phelps, Ed Hoffman, ORTEC</td>
</tr>
<tr>
<td>1974</td>
<td>PETT III [56]</td>
</tr>
<tr>
<td>1977</td>
<td>Expectation-maximization algorithm [21]</td>
</tr>
<tr>
<td>1978</td>
<td>ECAT: tomographic imaging for radiopharmaceuticals [55]</td>
</tr>
<tr>
<td>1978</td>
<td>(^{18})F-tagged deoxyglucose is first synthesized [34]</td>
</tr>
<tr>
<td>1979</td>
<td>First reported study on FDG-PET [58]</td>
</tr>
<tr>
<td>1981</td>
<td>Time of Flight PET [76, 71]</td>
</tr>
<tr>
<td>1982</td>
<td>Maximum likelihood reconstruction for emission tomography. [66]</td>
</tr>
</tbody>
</table>
1983  Wobbling PET array to increase spatial sampling by Huesman
1983  Image reconstruction from list-mode for Time-Of-Flight PET [70]
1984  PET Medical Cyclotron
1984  Block Detector
1985  CTI, Positron Corporation, PET Electronics Inc
1986  Siemens and CTI establish a joint-venture. CTI PET System, Inc.
1990  General Electric purchases Scanditronix
1990  Institute for Clinical PET
1990  LSO detector is discovered [47]
1994  Ordered-subsets expectation-maximization [31]
1997  MicroPET, a high resolution PET scanner for imaging small animals [14]
2000  Integrated PET/CT [10]
2003  MicroPET II [74]
2003  Virtual Pinhole PET [75]
2004  Pittsburgh compound B (PiB) is shown to image beta-amyloid
      plaque in neuronal tissue [39]
2008  Micro Insert [87]
2009  First commercial PET/MR scanner, Siemens Biograph mMR
2014  Toshiba enters the PET/CT market

Till around mid 1990’s, the main devices in PET were full ring systems. The basis of Time
of Flight, Depth of Interaction and LSO detector was laid down. The early 2000’s saw the
rise of integrated modality with the PET/CT scanner. In addition, there has been work on
building PET devices for particular applications. Some of these applications requires smaller
crystal sizes, enabling higher resolution. The late 2000’s saw the building of the integrated
PET-MR scanner. Currently, there is interest in building small PET devices. This enables
customized imaging for particular patients.

In terms of reconstruction, the general reconstruction method is well established. The
Expectation-maximization algorithm for image reconstruction has been established since
the late 1970’s. The major contribution after the 1970’s has been precise data modeling
and data correction procedures for each system. Mid 1990’s saw the implementation of the
Ordered-subsets version of the algorithm. Fast reconstruction is the goal. Different groups
have approached the problem at different levels. Convergence of the algorithm has remained an academic pursuit. The main push is to deliver acceptable results in a short time. Some groups have opted for faster computing architectures, whereas others have explored using a subset of the image space or data space at each iteration. There has also been work on replacing the original objective function or its gradient by a computationally cheaper alternative.
Chapter 2

Background

This chapter describes the work that was done previously before the author joined the laboratory. It also includes some material that the author has worked on, and published as a supporting author. The chapter ends with specific contributions that the author has made.

2.1 Virtual Pinhole PET

Conventional PET systems are ring systems that provide Whole-Body imaging capability and full angular coverage. The Whole-Body imaging capability for a general class of patients requires positioning the detectors in a circle of large diameter. The image resolution of such a system is limited by the positron range, photon acollinearity and the spatial resolution of the detector. The major loss of resolution in a conventional PET system is the size of the detector. For detectors placed far away, photon acollinearity plays an important role. Positron range is less of a concern for common radionuclides having a short positron range. The increasing error 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 commercial systems to 4-5 mm.

In the Virtual Pinhole PET[75] class of devices, an insert system, containing detectors similar to a conventional PET system, is placed close to the imaging target. The insert system contains detectors smaller than the conventional PET system. The presence of the insert system improves the spatial sampling as well as the contrast recovery of the imaging target.
Figure 2.1: (a) Illustration of the Virtual-Pinole effect (b) Geometric System Matrix of an insert crystal in coincidence with a scanner array.

The detectors in the insert system act as virtual pinholes, similar to the pinhole in a SPECT system.

Figure 2.1 illustrates the idea of Virtual Pinhole PET. An insert detector block of 2x2x5 mm crystal size, having 13x13 crystals is placed in coincidence with scanner modules having 13x13 crystals of 4x4x20 mm crystal size. The geometric system matrix computed using the Siddon’s algorithm and sub-crystal approach is overlaid on the illustration. A small object placed close to the insert is magnified on the scanner crystals by the coincidence Lines of Response. The figure also shows that there is increased contrast recovery at positions close to the insert detector block.

Two insert systems were designed and built by Washington University researchers to prove the Virtual-Pinhole PET concept. The first device, Micro-Insert I [87], was a proof of concept device, meant to improve the imaging capability of small animal imaging. The device was integrated into the MicroPET scanner to improve the resolution at the cost of a reduced field of view. The image resolution was improved between 1.0 and 1.8 mm full width at half maximum from 1.3 and 2 mm full width at half maximum.

The second device is a half-ring device, and intended as an accessory device for a whole-body PET scanner, specifically for head and neck cancer imaging. Investigative studies were
conducted by the author to examine the feasibility of using the device for breast cancer imaging.

## 2.2 Contributions

It is difficult to delineate the contribution of one during a group effort, without seeming assertive but for the purposes of this thesis, it is required to do so. Anyone wishing for further clarification is free to examine my lab record, code repositories and data.

I started my work in October 2009, and was officially in the PhD program from January 2010. In October 2009, Dr. Keesing had already written reconstruction code for the Half-Ring system, and he was graduating then. Dr. Tai asked me to reconstructed some phantoms that he had imaged, using the Half Ring system in the CCIR. Reconstructing images was a multi stage process, involving different pieces of code developed by different people, having different file formats, coding styles and programming languages. The images showed no improvement when going from regular PET/CT to PET/CT with the insert. The code showed artifacts when reconstructing full field of view. It was thought at that time that novel data correction schemes would be necessary to get a reasonable image. However, on checking the reconstruction code, it was clear that the main reconstruction program had bugs in it.

One of the first things I did was to establish an SVN repository for the code to track changes. The program was debugged stage by stage, by manually going through the code as well as reconstructing experimental data. By January 2010, the major bugs in the reconstruction program had been fixed. However, the images reconstructed still had artifacts.

Acquiring data took a long time. Dr. Komarov had written a Monte Carlo program to simulate the half ring PET for studying the effects of scatter. Using data generated by this program, the problem was tracked down to normalization. Reconstruction of Monte Carlo data was correct by May of 2010. The details of the half ring PET reconstruction is given in [36].
For the next three months, we designed and reconstructed a Monte Carlo study of breast cancer. Although the sequence of steps required for full reconstruction took 4 days, the program was run in parallel on the CHPC cluster using batch scripts. The details of the study are included in the Chapter 3.

In August 2010, data was collected from the Half-Ring system in CCIR. The reconstructed images showed artifacts and no improvement in image resolution. I checked reconstruction again and found nothing wrong. It was suggested in the group meetings that the insert alignment was wrong. In December 2010, an experiment was performed by imaging point sources with insert, and reconstructed twice with Scanner-Scanner data only and Insert-Scanner data only. The experiment proved conclusively that the insert was mispositioned.

In January 2011, we fixed the alignment problem and acquired data with and without insert. From January 2011 to August 2011, a variety of experiments, both phantom and human, were designed and the data collected and reconstructed that showed improved imaging with Virtual Pinhole PET. The details of those experiments are clubbed together in Chapter 3.

From September 2011, I started working on a general PET reconstruction code, to reconstruct images for different types of PET systems that we were building. A first version of the program was finished by February 2012. The new program was debugged and cleaned up by May 2012.

The tenuous exercise in debugging Half-Ring Insert reconstruction showed that the particular model of reconstruction requiring extensive bookkeeping in code is flawed. All iterative reconstruction algorithms are simple. To handle large amounts of data, the industry follows certain conventions, such as michelograms, sinograms, etc. Such structures make data easy to visualize, but are unnecessary complications from a programming perspective. Additionally, such structures are tied to ring type geometries, and do not exist for a general reconstruction code. These were probably introduced at a time when computing power was more limited, and certain approximations had to be done on the data before reconstruction. These approximation naturally lend themselves in the sinogram space. Therefore, in the new reconstruction code, none of these structures are handled. The effect is a speed up in programming and debug time.
The program was shown to work and reconstruct preliminary images for the flat panel system in June 2012. Ke Li joined the lab in August 2012. Ke Li and me started establishing the work flow for data acquisition and reconstruction. We applied the reconstruction framework to four novel PET systems developed in the lab, by performing Monte Carlo and experimental studies (when applicable). By mid-2013, we had established the work flow and had preliminary images for all four PET systems. In the fall of 2013, the reconstruction program was modified to perform 4D reconstruction. In addition, the parallelization routines of the code was worked on to enable the program to run in a multiple computer, multi-core setup. The memory usage of the program was also optimized. In December 2013, the first 4D images of radionuclide transport in plants was reconstructed.

Between January and May 2014, the new reconstruction code was checked for accuracy. The symmetry computation component of the framework was re-written to be more transparent. A GUI for the program was also written to enable reliable and user friendly data processing.
Chapter 3

Improving PET imaging for breast cancer using the virtual pinhole PET half-ring system

This chapter describes the full field of view reconstruction for Virtual Pinhole Half Ring system. The work was started by Dan Keesing whose work the author continued. The reconstruction code for the Half Ring system was not complete at the time Keesing graduated. Although most of the data correction framework was already in place, the code as well as the Half Ring system required extensive debugging. Since this project occupied 2 years of the author’s time at Washington University, it forms a chapter in this thesis.

3.1 Introduction

Breast cancer continues to be the second leading cause of mortality due to cancer in women and it will affect 12.29% of women born today [29]. 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 [3, 4]. Positron Emission Tomography (PET) is used in the staging, re-staging and evaluation of response to treatment of the disease. However, currently Fludeoxyglucose (FDG)-PET is not useful for early stages of the disease.

Clinical PET provides quantitative measurement of radionuclide activity concentration in body. Whole body imaging capability provided by clinical PET is useful in detecting distant
metastasis or an unexpected primary tumor. However, clinical PET scanners have limited resolution and hence, the ability to identify tumors that are well differentiated (thus, having low contrast) or having a small volume (such as ductal carcinoma in situ) are limited [5], [6]. Since tumor size correlates with probability of metastasis [27], an improvement in image resolution potentially improves cancer management and patient care.

It is well known that PET resolution is limited by positron range, photon accollinearity and detector intrinsic spatial resolution. Although spatial resolution could possibly be improved by having smaller crystals, the higher cost of detectors for a whole body PET system is prohibitive. Equally important is the fact that even if one uses these high cost higher resolution detectors for a clinical whole body PET scanner, the improvement in resolution will be still limited by photon accollinearity.

Traditional PET systems have detectors arranged in a ring to encompass the object. Various methods to improve the resolution of such systems have been previously explored. For example, the use of depth of interaction detectors can improve image resolution of scanners with small diameter. Wobbling the PET system or the bed can also increase the spatial sampling in PET systems.

The need for higher spatial resolution in breast cancer applications has led to the development of Positron Emission Mammography (PEM) systems. PEM systems achieve higher resolution by using smaller sized crystals, with detector placed around the region of interest. A variety of PEM scanners have been designed with resolution ranging from 2 to 3 mm [79, 64, 22, 23, 1, 11, 90, 45]. Although PEM systems generally have good resolution and have high sensitivity, their field of view (FoV) is often limited to the breast tissues, and cannot detect lesions and lymph nodes behind the chest wall.

We have proposed an innovative class of PET systems, namely Virtual Pinhole PET (VP-PET), whereby a PET insert device is integrated into a conventional PET system to improve its image resolution locally. This PET insert has smaller crystal size than the conventional system and can be positioned closer to the area of interest.

We previously built a micro insert system [87, 86] illustrating the VP-PET concept. The micro insert is a full ring insert device that can be integrated into a MicroPET scanner to increase resolution for small animal imaging. We have shown an improvement in image
resolution from 1.7 mm FWHM without insert to 1.0 mm FWHM with the insert. Other
groups have explored technologies that employ similar magnifying geometry such as Si-Si
ring inside a BGO-BGO ring [54, 16], the Zoom-In system [92, 93], surgical PET imaging
probe [33], time-of-flight PET imaging probe [48] and a prostate imaging probe [20].

Recently, we have built a half ring insert [88] for clinical head and neck imaging. In this
study, we use this prototype device to test our hypothesis that VP-PET technology will
allow imaging of breast tissues and lymph nodes in axilla and mediastinum regions with
high resolution, while at the same time maintaining the whole body imaging capability of a
clinical PET scanner.

The organization of this paper is as follows. We will present a brief introduction of our
prototype VP-PET system and image reconstruction. Then we describe Monte Carlo simu-
alation and experimental approaches that are designed to test our hypothesis. Reconstructed
images followed by quantitative examination are presented in the results section. Some of
the limitations and future directions are outlined in the discussion section.

3.2 Materials and Methods

3.2.1 Prototype System Description

A prototype VP-PET insert with a semicircular geometry was built for clinical research.
This insert, called the VP-PET half ring insert, is shown in Figure 3.3. It consists of 2x2x5
mm Lutetium Oxyorthosilicate (LSO) crystals, with 13x13 crystals in each module. Fourteen
modules are arranged in a half ring format having a radius of 124 mm. Two half ring are
arranged inside a custom made aluminum holder.

The VP-PET half ring insert is integrated into a Siemens Biograph 40 clinical scanner (Figure
5.13), to allow coincidence event detection between the insert and scanner detectors, as well
as within individual systems themselves.

The Siemens Biograph 40 is equipped with 4x4x20 mm LSO crystals with 13x13 crystals in
each block. The clinical scanner has 4 detector rings, each with 48 modules arranged to have
Figure 3.1: VP-PET half ring insert with cover open. The LSO detector module is connected to the Photomultiplier tube (PMT) and the PMT is connected to readout electronics. The back panel has data connectors that allow connection to electronics in Siemens PET/CT.

a radius of 438 mm. One of the detector rings was disabled in order to use its electronics to process the insert detectors.

The VP-PET half ring insert is centered axially and concentrically with the 3 ring scanner rings for maximum symmetry to aid in the reconstruction process.

### 3.2.2 Image Reconstruction and Correction techniques

As described by Pal et al. [53], the addition of the insert into a standard PET scanner gives rise to three different sets of coincidence measurements. The scanner-scanner (SS) coincidences occur between two scanner detectors and are lower resolution. The insert-scanner (IS) coincidences occur between insert and scanner detectors and are of higher resolution. The highest resolution insert-insert (II) data is between insert detectors.

We have developed a fully 3D maximum likelihood reconstruction framework that jointly estimates the radionuclide activity concentration using all 3 types of coincidences. The
Figure 3.2: (a) Front View of insert integrated into a Siemens Biograph 40 scanner; (b) Back View of the PET/CT scanner with insert. The chest phantom with custom breast attachment used for the experiments are mounted on the bed with an aluminum holder.

geometric system matrix is computed through the sub-crystal approach [32], where crystal detectors are divided into sub-crystals, and the tube of response is measured as the average length of intersection of each line joining the sub-crystals with a candidate voxel, divided by the square of the distance between the detectors.

Scatter correction is based on single scatter simulation, where the initial radionuclide distribution is roughly estimated with 10 iterations without scatter. This initial image is down sampled to estimate scatter distribution. The estimate is scaled by fitting the tail to the measured coincidence count and added to the forward model. The application of single scatter simulation to estimate and correct scatter in VP-PET half ring insert has been previously validated [40].

Attenuation correction is based on a composite $\mu$-map, where the body attenuation is calculated by scaling acquired CT images to equivalent 511 keV attenuation. The insert attenuation map was based on a composite attenuation image formed by measuring attenuation coefficients of a single detector module and aluminum using a $^{68}$Ge source, and substituting these values into a CAD model.
Normalization is based on component based normalization [7], and statistically estimated by acquiring coincidence data from a $^{68}$Ge phantom with known activity distribution. All the imaging studies in this work were corrected and reconstructed using the above framework, including scanner images when the VP-PET insert is not in the system. This ensures that the differences observed are solely due to VP-PET insert hardware, instead of software or algorithm.

Keesing et al. [36] provides more details on the reconstruction and correction framework for VP-PET with comparison to standard Siemens PET/CT reconstruction. All the images presented in this paper was reconstructed until the 50th iteration, by which the objective function has converged such that the change in the objective function is less than $10^{-5}$ of the value at iteration 50. The Monte Carlo simulated data is shown with no regularization. Log-cosh regularization using One-Step-Late algorithm was used for reconstructing experimental data. The parameters chosen for the regularization are the same as in [36].
3.2.3 Imaging studies

To compare different imaging studies, we consider a typical 70 kg patient with water density of 1 g/cm$^3$. With a typical injected dose of 10 mCi (370 MBq) of $^{18}$F-FDG uniformly distributed in the patient, the background activity concentration within the body is 0.143 $\mu$Ci/cm$^3$ (5291 Bq/cm$^3$).

Monte Carlo Simulation

To test the suitability of using VP-PET technology for breast cancer imaging, a model of a patient with tumors in the breast was simulated using Monte Carlo simulation techniques and reconstructed. The Monte Carlo package was developed in-house because commonly accepted Monte Carlo packages, such as GATE, do not support the co-existence of multiple types of PET detectors in a system. Furthermore, our Monte Carlo simulation only tracks gamma ray interaction in materials through photoelectric and Compton interactions. Therefore it has a significant speed advantage.
Annihilation sites were randomly distributed based on a given activity distribution. Back-to-back gamma photons were generated isotropically. Photon accollinearity was modeled by pivoting one of the two gamma rays around the axis of the other. The accollinearity angle was randomly sampled, distributed as a Gaussian with FWHM of 0.4 degrees. Positron range was not simulated in this study to reduce simulation time.

The gamma ray photons are tracked through multiple photoelectric and Compton interactions. The deposited energy of a gamma photon within a detector is saved, and a detection event is flagged if the deposited energy is greater than a given threshold. For this simulation, the lower energy threshold was set to 435 keV.

Initial simulation with random events showed that random events were well corrected using the delayed window technique in reconstruction. Therefore, for the simulations presented, random events were not tracked to save simulation time.

A phantom that consists of a chest and a breast was simulated to mimic a patient with breast cancer. An illustration of the phantom is shown in Figure 3.4. The chest was modeled as a box with dimensions 280x180x300 mm, and the breast as a hemisphere with radius 75 mm. A Derenzo-like pattern of spherical tumors with varied diameter was embedded in the breast region. The simulation was performed at tumor-to-background contrast ranging from 3:1 to 12:1 for 5 and 15 minute acquisition times. The tumors in the phantom have diameters of 2, 3, 4, 6, 8 and 12 mm (See Figure 3.7).

**Imaging Setup**

To mimic a patient body, an experiment was assembled with a Data Spectrum Elliptical Lung-Spine Body Phantom as the chest, with a custom acrylic cylindrical phantom as the breast (See Figure 5.13). The space between the chest and breast was filled with a Urethane elastomer, Skinflex (BJB Enterprises Inc, CA). This compound was found to have CT attenuation similar to water. The compound was molded to fill the volume between the two phantoms.

Hollow fillable spherical glass tumors with diameters 3.3, 4.3, 6, 8, 9.6 and 11.4 mm (Pattern "1", Figure 3.5) were arranged inside the breast cylindrical phantom to mimic host lesions.
Another set of glass tumors was embedded within the chest phantom, to measure contrast and resolution for tumors in the axilla/mediastinum region, which was outside the high resolution image FoV. The diameters of these tumors are 3.59, 5, 6.32, 8, 9.6, 10.09 and 11.4 mm (Pattern "2", Figure 3.5). The wall thickness of these glass spheres are less than 0.5 mm. The phantoms were held using a custom-made aluminum frame, attached to the patient bed.

The phantoms were first scanned with the insert for 150, 150, 300, and 600 seconds for a total scan time of 20 minutes. Then, the VP-PET insert was removed, and the phantom was re-scanned in the 3 ring scanner configuration, starting at 30 minutes from the first scan. A CT scan is also performed just prior to PET acquisition in both cases for attenuation correction.

To test the performance of our system, we designed two experiments with distant tumors in two different positions within the chest phantom. In the first experiment, we placed additional tumors on the axilla region of the body. Then, to investigate the possibility of imaging tumors closer to the insert, near the region where artifacts are higher, we placed the tumors in the mediastinum.
Figure 3.6: (a) and (b) Two spherical glass sphere patterns with diameter of the corresponding tumors in mm. The photograph of Pattern “1” can be seen in Figure 3.5 Left). Dotted lines are drawn through the tumors to show the cuts for line profiles in the results section. Illustration of experimental setup for experiments 1 (c) and 2 (d), showing the arrangement of the Data Spectrum Elliptical Lung-Spine Body Phantom with Breast attachment with Skinflex spacer in between is also shown. The glass sphere patterns, ”1” and ”2”, are arranged in different locations and orientations in the breast attachment and chest phantom for both experiments.

The volume of the chest phantom and breast attachment was estimated to be 6535 cm$^3$ and the breast was 1043 cm$^3$ by weighing the empty phantoms before and after they had been filled with water.

For both the experiments, we followed the same dilution plan, described as follows. We targeted an input activity ratio of 6 to 1. To obtain this contrast ratio, we first diluted the activity to 650 ml, to form the main activity volume. A 10 ml sample was taken, diluted to 20 ml to form the tumor volume, and put in glass spherical tumors. 87 ml of the main activity volume was transferred to the breast attachment and 546 ml was filled in the chest phantom. Both phantoms were filled with water, sealed and allowed to mix. The final activity concentration of both breast and chest phantoms are 0.0833 times the activity concentration in the main activity volume. The activity concentration in the tumors is 0.5 times the activity concentration in the original main activity volume. Thus, the final activity ratio is 6 to 1 or the contrast ratio is 5, where

$$\text{Contrast} = \frac{A_{\text{tumor}} - A_{\text{background}}}{A_{\text{background}}}. \quad (3.1)$$
where $A_{\text{tumor}}$ is the mean activity in the tumor and $A_{\text{background}}$ is the mean activity in the background. In Monte Carlo simulation, the centers of the tumors are known. For experimental data, we determine the center of the tumors from registered CT images. The tumor Region-of-Interest (ROI) is defined as a spherical ball around the tumor center with radius equal to 0.75 times the radius of the tumor. For a particular tumor diameter, the value of voxels within the ROI's of those tumors are averaged to obtain $A_{\text{tumor}}$. The background ROI is chosen from a region in the chest or breast depending on the position of the tumor.

In both the experiments, to validate the activity concentration, we took samples of breast, chest and tumor volumes and measured the counts per minute in a well counter.

### 3.3 Results

#### 3.3.1 Monte Carlo Simulation

The background activity concentration that was simulated in Monte Carlo is 0.062486 $\mu$Ci/cm$^3$ (2311 Bq/cm$^3$). The equivalent activity is 0.064598 $\mu$Ci/cm$^3$ (2390 Bq/cm$^3$) in
Figure 3.8: Full field of view of tumor plane slice of reconstructed phantom used in Monte Carlo simulation with 12:1 tumor-to-background ratio for 6.78 minute of $^{18}$F-FDG acquisition at 50 iterations.

$^{18}$F-FDG, considering the branching ratio. Therefore, the activity concentration in a typical human study is 2.211 times that simulated in Monte Carlo. Based on this, 5 minutes of Monte Carlo simulation is equivalent to 2.26 minutes of a typical clinical FDG study and 15 minutes simulation is equivalent to 6.78 minutes of a typical clinical FDG study.

The decay map, shown in Figure 3.7 b) is a recording of positron annihilation during the simulation. The figure is for the lowest acquisition scan time of 2.26 minutes of $^{18}$F-FDG. The input tumor to background ratio in this experiment was 3:1. The decay map was quantized to reconstruction voxel size of 1x1x2 mm. The smallest tumors are clearly delineated. The figure demonstrates that resolution degradation is not due to voxelization of the decay map, but because of the inherent resolution limitation of the PET scanner.

Figure 3.8 shows a full view of the reconstructed images from Monte Carlo simulation, for the 6.78 minute of $^{18}$F-FDG acquisition with 12:1 tumor to background ratio. The Monte Carlo simulation shows that there is potential for improvement in the image resolution in
Figure 3.9: Closeup view of the Derenzo-like pattern in the phantom used in Monte Carlo simulation at 2.26 minute and 6.78 minute acquisition with $^{18}$F-FDG, and 3:1, 6:1, 9:1 and 12:1 tumor to background ratio

the central region, without losing the whole field of view imaging capability of a standard clinical PET scanner.

Figure 3.9 shows a close-up view of the breast region. This axial plane passes through the center of the reconstructed spherical tumors. Figure 3.9 (a) is equivalent to 2.26 minutes of a typical human study scan using $^{18}$F-FDG. The reconstructed images without and with insert are shown in the top and bottom row respectively. There is a clear improvement in resolution when the VP-PET insert is present. With the 2.26 minute acquisition, the scanner without insert can only distinguish tumors with 6 mm diameter when the tumor to background ratio is 12:1. With the VP-PET insert, we are able to detect tumors of the
Figure 3.10: Contrast recovery curves for Monte Carlo simulation with $^{18}$F-FDG acquisition for 2.26 minutes with Tumor/Background ratio of a) 3:1 b) 6:1 c) 9:1 d) 12:1, and 6.78 minutes with Tumor/Background ratio of e) 3:1 f) 6:1 g) 6:1 h) 12:1

Figure 3.11: Line profile through tumors in images reconstructed from Monte Carlo simulation for 6.78 minute acquisition with $^{18}$F-FDG through lines shown in Figure 3.7
same size at lower tumor to background ratios of 6:1. Alternatively, the VP-PET insert can detect 4 mm diameter tumors if the tumor to background ratio is 12:1.

Figure 3.9 (b) is equivalent to 6.78 minutes of a typical human study with $^{18}$F-FDG. Comparing the two separate acquisition times with the same tumor to background ratio of 9:1, 6 mm tumors are distinguishable only in the 6.78 minute scan time set without insert. With the insert, they are easily identifiable at 2.26 minutes. This points to the possibility of reduction of patient scan time or dose reduction when utilizing the VP-PET insert.

Contrast recovery curves are shown for 2.26 and 6.78 minute acquisition for different tumor to background contrast ratios in Figure 3.10, where

$$\text{Contrast Recovery} = \frac{C_{\text{output}}}{C_{\text{input}}} \times 100\%.$$  \hspace{1cm} (3.2)

where $C_{\text{input}}$ is the input contrast and $C_{\text{output}}$ is the output contrast.

Although tumor sizes of 3 mm and 4 mm diameter are unresolvable for 6.78 minute acquisition with contrast ratio 9:1 and below, the contrast recovery curve is unaffected. The 3:1 contrast ratio at 2.26 minutes is severely data limited, causing higher error rates. There is no improvement with insert until the tumor diameter reaches 8 mm.

To better visualize improvement in resolution, line profiles are extracted through the tumor centers as shown in Figure 3.7. The line profiles from the 6.78 minute acquisition and 12:1 tumor to background ratio are shown in Figure 3.11. For these values, the component based normalization procedure during reconstruction is designed such that the background with insert and without insert are scaled to the same background concentration of 1.0. That is, post reconstruction scaling is not done for the Monte Carlo studies. For the largest 3 tumors, of 6, 8 and 12 mm diameter, the profiles from the VP-PET system have higher peak-to-valley ratio. Profile with insert for 12 mm diameter tumor show flat top, while the profile is still spiked without the insert. Profiles in Figure 3.11 b) and f) establish that 3 mm tumors are resolvable with the insert, but not without insert. The smallest 2 mm diameter tumor is not resolvable with or without insert.
Figure 3.9 b) and 3.11 show that the resolution from Monte Carlo simulation without insert on the standard clinical scanner is between 4 and 6 mm, whereas with the insert, the resolution is improved to between 2 and 3 mm. Note that the resolution improvement is for the central region of the system. Away from the center, the improvement has not been validated using Monte Carlo.

### 3.3.2 Experimental Results

**Experiment 0**

Experiment 0, conducted in January 2011, was the first experiment to show improvement in image resolution with the Half-ring insert. The chest phantom was filled with a background activity concentration of 100 $\mu$Ci/cm$^3$ (3.7 mBq/cm$^3$) of $^{64}$Cu. The spherical glass tumors were filled with 6:1 tumor-to-background ratio.

The bottom right of the image shows streaking artifacts with insert. Additionally, there is a slight cupping artifact at the center. Although 4.3 mm diameter tumors are unresolvable without the insert, 3.3 mm diameter tumors are resolvable with 15 minutes of acquisition.

The edge of the insert crystals is bright in the reconstruction with Insert. The insert crystals have sharp edges with high attenuation to 511 keV gamma. Slight mispositioning of the insert and the known location of the insert used in correction can cause such artifacts.

**Experiment 1**

Samples of 1 cm$^3$ were taken from the chest phantom, breast attachment, and tumor volume, and counted in a well counter for 1 minute each. From the results, the tumor to chest background activity ratio is 5.89:1 and tumor to breast background activity ratio is 6.7:1.

For this experiment, the original activity was 3.94 mCi (145.78 MBq) of $^{64}$Cu at the start of the scan with the insert. The activity concentration in the background is approximately 0.5051 $\mu$Ci/cm$^3$ (18688.7 Bq/cm$^3$) of $^{64}$Cu. Correcting for the branching fraction, this is equivalent to 0.0919 $\mu$Ci/cm$^3$ (3400 Bq/cm$^3$) of $^{18}$F. This is approximately 0.6427 times the
activity concentration in a typical patient scan. Another view is that the 5 (or 15) minute acquisition in the phantom imaging experiment is equivalent to 3.2 (or 9.64) minutes of the typical clinical FDG scan.

Figure 3.13 show the reconstructed images in the tumor plane for a 12.85 minute acquisition, reconstructed with 50 iterations. The insert improves image resolution for tumors in both the breast and the axilla. However, the images with the insert show some streaking artifacts
Figure 3.13: Experiment 1: Full field of view of tumor plane, for 12.85 minute acquisition with $^{18}$F-FDG, reconstructed at 50 iterations on the right corner of the phantom. These artifacts are caused by heavy attenuation of Lines-of-Response (LOR) between scanner detectors passing through multiple crystal volumes in the insert. For all image voxels along those LORs, there is no or very low data collected along the direction of the LOR. Additionally, the LOR attenuation varies drastically if it passes through gaps in the insert crystal array as opposed to passing through the crystal. As a result, even a slight misalignment between the expected position of the insert and actual position can cause artifacts.

Figure 3.6 illustrates the locations and the diameters of the tumors in the breast and chest region. Figure 3.14 shows the close-up images of (a) the breast region and (b) the axilla region for different acquisition times.

Figure 3.15 shows contrast recovery curves for tumors in breast and axilla for 3.2, 6.4, 9.64 and 12.85 minutes of acquisition. For breast tumors, the background is chosen to be a uniform region in the breast, and for chest tumors, the background is chosen in the chest. The contrast recovery plots were scaled after reconstruction such that the background is 1.0.
Figure 3.14: Zoomed image of breast and axilla tumors for experiment 1 at a) 3.2 minute b) 6.4 minute c) 9.64 minute d) 12.85 minute ¹⁸F-FDG. Top row is without insert and bottom row is with insert.

For breast tumors, the contrast recovery with the insert is consistently better than without the insert, especially at longer scan times. The contrast recovery for 3.3 mm diameter tumors with the insert is lower than contrast recovery without the insert. These tumors are not resolvable regardless of whether the insert is used.

In the graphs, 6 mm and 11.4 mm diameter tumors have only minimal improvement with the insert. The 6 mm diameter tumors are located near the center of scanner FoV where the scanner image resolution is the highest. For the insert images, these tumors are located in the top of the high resolution region in the FoV where the improvement is due to insert-scanner data only, and not due to insert-insert data. In contrast, the 4.3 mm tumors are located in a region that will have II, IS and SS data, leading to better contrast recovery. For
the 11.4 mm diameter tumors, contrast recovery is almost same for with and without insert as expected since the scanner is adequate for resolving these larger tumors.

For tumors in axilla, there is almost no difference in contrast recovery between the two cases, with or without the insert, especially at long scan times. These tumors are far from the insert high resolution FoV and the performance is determined mostly by scanner-scanner (SS) coincidence data.

Line profiles, as shown by red lines in Figure 3.6, are drawn through the phantom on the axial plane containing all the tumors in Figure 3.16. The profiles are scaled post reconstruction such that the background, as measured in breast and chest, is at 1.0.

In the breast, the larger diameter tumors (especially the 11.4 mm tumor) exhibit matched line profiles regardless of use of the insert, just as in contract recovery (Figure 3.16 c and f). Using the insert provides a slight improvement in resolution for tumors of diameters 8 mm and 9.6 mm. The improvement is markedly better for tumors of 4.3 and 6 mm diameter. For the 6 mm diameter tumor, the line profiles are much better with insert although the contrast recovery is almost the same. For these tumors, images obtained with insert has higher peak-to-valley ratio than images obtained without the insert. The contrast recovery
Figure 3.16: Line profiles in Experiment 1 drawn through tumors located in breast and chest for 12.85 minute acquisition.
curve with insert, computed using mean tumor ROI, is brought down due to the spiky nature of the tumor reconstruction.

For the 3.3 mm diameter tumor, there is little difference with and without the insert, except that the noise with the insert has higher frequency content than without the insert. This is because of the higher spatial frequency sampling from II and IS lines passing through this tumor.

For tumors in the axilla region, the profiles with and without insert are almost similar, although tumor peaks are slightly better resolved than without insert. As already mentioned, this is not surprising because the axilla performance is determined by SS coincidence data which is largely independent of the insert.

**Experiment 2**

Experiment 1 showed artifacts along lines emanating from one corner of the insert. To test the performance of the system when tumors are in that region, we placed tumors in the chest region next to the insert, and repeated the experiment. This is the expected position of mediastinal tumors and lymph nodes.

As in experiment 1, we took samples of 1 cm$^3$ from the breast, chest and tumor volume and measured it in a well counter. The measured ratio of tumor to chest background activity is 7.27:1 and tumor to breast background activity is 6.19:1.

The approximate total activity in breast, chest and tumors at the beginning of scan was 6.5 mCi (240.5 MBq) of $^{64}$Cu. The activity concentration in the background is approximately 0.833 $\mu$Ci/cm$^3$ (30821 Bq/cm$^3$) of $^{64}$Cu. Correcting for the branching fraction, this is equivalent to 0.152 $\mu$Ci/cm$^3$ (5624 Bq/cm$^3$) of $^{18}$F, which is about 1.06 times the activity concentration in a typical patient study of 0.143 $\mu$Ci/cm$^3$ (5291 Bq/cm$^3$) of $^{18}$F. Therefore, a 5 (or 15) minute acquisition of the experiment is equivalent to 5.3 (or 15.9) minutes of a typical patient scan.

The full field of view reconstructed images are shown in Figure 3.17. For this experiment, we were unable to position all the tumors in the same axial plane. Therefore, two slices
Figure 3.17: Experiment 2: Full field of view of tumor plane, for 21.2 minute acquisition, reconstructed at 50 iterations. The top row is a slice centered in Breast tumor plane. The bottom row is a slice centered in Mediastinal tumor plane.
6 mm apart are shown, one centered at tumors in the breast, and the other centered at tumors in the chest region. The half ring insert has one crystal gap at the axial center of the system between two insert half rings, where the insert performance is slightly degraded due to missing in-plane coincidence data. For this experiment, the axial slice with missing in-plane coincidence data lies between the slice with breast tumors and chest tumors that are shown.

Figure 3.18: Zoomed image of breast and mediastinal tumors for experiment 2 at a) 5.3 minute b) 10.6 minute c) 15.9 minute d) 21.2 minute. Top row is without insert and bottom row is with insert.

Figure 3.19 shows contrast recovery curves for breast and chest tumors. The contrast recovery for breast tumors is slightly better with insert than without. However, this is not always true in the chest region due to the location of the tumors.
The 8 mm diameter tumor in breast is above the high resolution imaging region, but is still covered by IS data. IS LORs passing through this region originate from the left corner of the insert and pass through a large portion of the chest phantom. This could explain the lower contrast recovery. In experiment 1, the 6 mm breast tumors are in the same location and show a similar dip in the contrast recovery.

Tumors of diameter 3.3 mm are not resolvable with or without insert. The 4.3 mm diameter tumor is also above the higher resolution region provided by the insert, and further more, close to the chest phantom.

For tumors in the mediastinal region, the tumors have better contrast recovery for sizes between 5 mm and 8 mm. The tumor of diameter 6.32 mm has contrast recovery with the insert almost equal to that without the insert. The largest two tumors of diameter 11.4 mm and 9.6 mm have worse contrast recovery with the insert than without the insert. This could be due to the position of one of the 9.6 mm and the 11.4 mm tumors, at the right most edge of the phantom. The region here is sampled by the side surface of the crystal that is 5 mm long and as such, image reconstruction is expected to be worse in this region.

In Figure 3.20, the line profiles are drawn through lines as depicted in Figure 3.6, for 21.2 minutes of acquisition. Although 3.3 mm tumors are not all resolvable with or without the insert, those tumors along the horizontal direction, are individually distinguishable as seen in line profile Breast (a). This could be attributed to the fact that we have better horizontal resolution in this area due to IS lines of response.

Tumors of 4.3 mm diameter are also distinguishable in the profile plot through Breast a), but not all distinguishable in d). The tumors of 6 mm diameter are clearly distinguishable with the insert in profiles d) and e). The largest tumors of diameter 9.6 mm and 11.4 mm have similar performance with and without the insert.

The line profiles through the mediastinal tumors placed close to the insert edge, in the chest, show that it is possible to obtain good resolution recovery. For the 10.09 mm diameter tumor placed away from the insert, the profile with the insert does not perform as well as without the insert. However, a 5 mm diameter tumor is clearly distinguishable with the insert in profile c), but not without the insert.
Figure 3.19: Contrast recovery curves for Experiment 2 for tumors located in breast and chest at a) 5.3 minute b) 10.6 minute c) 15.9 minute d) 21.2 minute

3.4 Discussion

In this paper, we have extended our existing half ring VP-PET insert for breast cancer imaging applications. The VP-PET insert improves image resolution locally. This enables us to detect smaller tumors and lymph nodes that was unresolvable without insert. The contrast recovery is also improved for tumors close to the insert, which helps in better quantification. Addition of the VP-PET insert is not at the price of whole body imaging capability. Along with proving higher resolution local imaging capability, we have learned additional insights in design of asymmetric PET systems in order to avoid artifacts. This work portends highly flexible and customizable PET imaging.

 Whereas in the past, PET imaging was restricted to factory set design, the new paradigm enables clinicians to customize the acquisition geometry to obtain optimal images based on known data about the disease. Such systems would enable physicians to zoom in to the specific regions by changing the geometry of the scanning system. The main problems that need to be solved for having a flexible system are the automatic or manual positioning of the detectors next to a patient, and precise telemetry to determine the location of the detectors. Our group is investigating the first of such imaging systems, with an adjustable and modular flat panel insert system.
Figure 3.20: Line profiles in Experiment 2 drawn through tumors located in breast and chest for 21.2 minute acquisition.
Building such systems requires redevelopment of detector systems and their associated read out circuitry, along with better data processing electronics. SiPM based detectors offer small packaging and modularity, eliminating the need for bulky PMT’s. Newer electronics technologies such as the Siemens QuickSilver system [49], based on a ring topology for system electronics offers a scalable architecture for such systems.

Having an insert with highly attenuating detectors in the field of view, requires more advanced reconstruction techniques. Certain assumptions, often made in conventional systems, no longer hold. This is the case especially when one line of response overlaps a detector crystal. In our study, we have seen that multiple lines of response attenuated along a certain direction, passing through multiple insert crystals, create artifacts along that direction. Different techniques to correct the artifacts were explored, including using component based normalization from multiple phantom positions, and removing those lines of response completely. They were not successful in reducing the artifacts. Either smarter design of insert systems such that the body being imaged is not affected by such lines or specialized correction techniques in reconstruction such as filling in incomplete data through interpolation in data space is necessary. Despite the presence of artifact in some region of the FoV, the images may still be useful clinically as long as the physicians understand the source of the artifact and limitations of the system.

Although a regularization based on the log-cosh function was chosen, it is not the optimal choice. The parameters that were chosen were 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. Optimization of regularization function is beyond the scope of this work and is left for future study.

Currently, the reconstruction code does not model photon accollinearity or positron range effects. The modeling is important for a more accurate reconstruction code. Another option is to de-blur the final reconstructed image with measured point spread function, as was implemented in Siemens HD-PET technology. Potentially, these improvements would enable even higher resolution.

Further down the chain, strides have to be made in image reconstruction algorithms, which reconstruct PET data for arbitrary systems in a timely fashion. Currently, reconstruction takes approximately 72 hours to complete. To be useful in the clinic, reconstruction time
has to cut down to the order of minutes instead of hours or days. The implementation in this paper does not include an ordered subsets approach. Although the reconstruction algorithms we have used are iterative in nature, the multiply-add nature of the forward and backward projection enable simple parallelization. The current code is parallelized using OpenMP and runs on x86 based systems. The goal of real time image reconstruction might involve taking advantage of newer technological developments such as GPU computing or Intel’s Many Integrated Core architecture.

The weights for the projections are stored in look up tables on the disk. Although compressed for symmetry, the size of the look up table is still substantially large. Future research would involve investigation into on-the-fly computation of the system matrix, compression of the system matrix or a combination of both as was done by Zhou and Qi [94].

3.5 Conclusion

We have proven our hypothesis that placing a high resolution insert in the field of view of a PET scanner can improve its image resolution within a selected FoV without compromising its whole body imaging capability. Although Monte Carlo simulation predicts up to 3 mm tumor detectability with the prototype half-ring insert, the experimental tumor detectability with 6:1 input tumor to background ratio was limited to 4.3 mm. This discrepancy could be the result of imperfect construction of the real system or incomplete physics model used in the Monte Carlo simulation. Nevertheless, resolution improvement can be seen from both types of studies using the insert system.

The addition of the VP-PET half ring insert into the scanner introduces minor artifacts in the reconstructed images. The artifacts could be due to attenuation of coincidence gamma rays along certain lines passing through heavily attenuating regions of the insert or due to slight mismatch between the geometry used in reconstruction and the real system.

The capability of the system to maintain the imaging FoV to include breast tissues as well as axillary and mediastinal lymph nodes has been shown. For tumors in the axilla, there is not significant difference in system performance with or without the insert because the tumors were located far away from the insert due to the system geometry. For mediastinal
tumors, depending on the location, an improvement in contrast recovery and resolution can be seen. The closer the tumor is to the insert, better the resolution and contrast recovery.
Chapter 4

Human study with Half-Ring PET

The VP-PET half ring insert was built for head and neck imaging. We designed and conducted a clinical trial to investigate the feasibility and potential advantages in detecting small lesions and lymph node involvement in head and neck cancers. Of the original five patients that we proposed to image, we imaged four. Although the study was expanded to ten patients, we did not image further patients due to difficulty recruiting suitable candidates.

4.1 Methods

Patients diagnosed with head and neck cancer at the Mallinckrodt Institute of Radiology are recruited on a volunteer basis as test subjects to test the efficacy of the half-ring insert system. It was determined that the insert device has difficulty in imaging tumor growing close to the shoulder region. The difficulty was due to the design of the half-ring system, where the device contacts with the shoulders. The first two patient studies were conducted when the issue in positioning the device became obvious. Further patients were recruited by pre-screening the patients with cancerous growth near or above the jaw region.

Prior to the day of the scan, the insert is setup and aligned to the PET/CT machine. The insert is setup in the scanner room, aligned to the center of the three active rings of the PET/CT bore. The alignment process is performed by scanning a point source along three linear directions using a bislide stage attached to the bed. This enables the registration of the PET/CT system with the point source. The point source is moved to the center of the computed center of the system. Then, the insert is moved in by rough center of the system.
based on previous experiments, and the point source scan is repeated. By comparing IS lines of response with SS lines of response, the position of the insert system in the field of view is computed. Based on the error from the true center of the system, the position of the insert is then corrected. The process takes about four hours.

A normalization scan is acquired using the Ge-68 phantom for 6 hours with and without the insert. The insert is then moved to the back of the scanner and the PET/CT is restored to standard Siemens mode. A Quality Check procedure is run in the morning to test the operation of the PET/CT scanner.

The patient is injected with 10 mCi of FDG. After 30 minutes of uptake and allowing for voiding, the patient is imaged with regular 4 ring PET/CT scan for 10 minutes in a single bed position. CT was acquired for attenuation correction. The patient is positioned and imaged as per standard of care Whole-Body PET/CT.

The patient is then moved out of the PET/CT bore and the tumor region in the patient is aligned with the laser markers outside the scanner. The system is switched to ‘insert’ electronic mode. Then, the insert is moved into the predetermined center of the three ring system. The patient is manually positioned in the PET/CT with the neck in the insert region. Data is acquired for two bed positions with 10 minutes per position. The data acquired is reconstructed using a standard reconstruction protocol. As the patient might have moved between the CT acquisition and With Insert acquisition, a quick reconstruction is done without attenuation correction and used to manually deform the CT using simple linear transformations to obtain the attenuation map. Since two bed positions is acquired with insert, the best axial slices of both sets of reconstruction is used to stitch the two image volumes together.

The images presented below are all manually registered. The patient studies below are referred to by the code assigned to the patients under HIPAA regulation.
Figure 4.1: Axial, Coronal and Sagital views of first patient, imaged on March 08, 2011. The PET images are overlaid on the registered CT images. The top row is Without Insert and the bottom row is With Insert.

4.2 Results

4.2.1 THN01

Patient 1 had a large hypermetabolic tumor with partially necrotic interior on the bottom side of the neck, and near the shoulders, extending to the supraclavicular region. The tumor was just under the skin surface. Figure 4.1 shows the Axial, Coronal and Sagital reconstructions with and without the half-ring insert. The images show the field of view limitation of the Half Ring Insert. The tumor, being in the bottom region of the field of view, and towards the top region of the image in the axial field of view, is outside the high resolution region of the Half Ring.

The reconstructed image with Insert is noisy. This study was the first human study performed and showed the limitations in the design and manufacture of the insert device. The device has a bulky, aluminum hull that is poorly designed for head and neck imaging. The front side of the insert hits the shoulders of the patient, missing most of the neck region. The only viable region of imaging is directly behind the ear region.
In addition, the system has sharp edges and metal corners that make positioning the patient in the insert difficult without injury to the patient. The patient is moved into the PET/CT bore after the insert is moved into the bore. Due to lack of precise control of the patient bed, and safety mechanisms, there is always the danger of the patient hitting the insert device.

4.2.2 THN02

![Axial, Coronal and Sagittal views of first patient, imaged on June 14, 2011. The PET images are overlaid on the registered CT images. The top row is Without Insert and the bottom row is With Insert.](image)

Patient 2 had tumor in the back of the throat, and in the tonsil region. The tumor lies in the high resolution region of the Half Ring Insert. Figure 4.2 shows improvement of the reconstructed images with insert. Both the resolution and contrast recovery improves with the insert device. The tonsil lies at the center of the PET/CT scanner, at the top edge of the field of view of the higher resolution Insert-Insert data. There is potential improvement in the image quality for tumors closer to the insert.
4.2.3 THN03

Patient 3 had tumor in the lower jaw, under the tongue. The tumor was situated above the high resolution field of view offered by the insert device, and is towards the edge of the high resolution field of view. Therefore, there is no or little improvement by using the Half Ring Insert. Some of the structure is better resolved in the PET images with insert.

4.2.4 Conclusion

The majority of patients imaged using the insert device had tumors located far away from the high resolution imaging region. The design of the half-ring insert limits the patients that can be imaged using the device. The bulky nature of the half-ring insert prohibits positioning the device in arbitrary geometries. Of the four patients imaged using the half-ring device, only one subject showed clear improvement in resolution and contrast recovery.

The result of this study motivates a flexible, low-weight, and adaptable insert device for improving the PET image quality. Although some improvement in image quality is obtained
using the half-ring insert device, the design limits the number of patients scannable with the insert device.

Further improvements in the registration and positioning of the insert device is also required. Currently, the time taken to register the insert with the PET/CT gantry limits the imaging to certain times of the day. The positioning mechanism is using a bislide stage that is cumbersome.
Chapter 5

Development of a geometry independent PET reconstruction framework

5.1 Introduction and Background

Since the invention of Positron Emission Tomography (PET) [57], the majority of these systems has used ring geometry for Whole-Body imaging. The last two decade has seen customization to application specific geometries (Breast: [78], [24], [65], [45], [61]; Small Animals: [14], [23], [80]; Imaging Probes: [33]). 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 [60]. Differences arise due to the data model used. Our lab has been involved with developing accurate reconstruction models for challenging geometries [53]. We have previously developed a precise data model, comprising of a randoms and scatter model, normalization approach and geometric system matrix [36].

A design-simulation-reconstruction loop, comprises of a design phase when the PET systems developer designs a system for a particular application, simulates the design using Monte Carlo tools, and reconstructs 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 the design-simulation-reconstruction loop, as well as develop a consistent post-production reconstruction across different geometries, we have developed a general purpose image reconstruction framework. 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 paper describes the framework, as well as shows the applicability of the framework to a variety of PET systems developed within our lab.

Generalizing a design specific reconstruction program to a general reconstruction requires the rethinking of traditional design choices. We have also reworked a variety of data representation and manipulation routines existing in traditional PET reconstruction codes such that the advantage they offered is maintained in the general purpose framework. For instance, the concept of sinogram, which requires thinking in terms of ring systems, is no longer applicable. Although sinograms helped in visualization of the data space before reconstruction, as well as compression in the data space through sinogram binning, they are not necessarily the most generic representation of data. In the proposed platform, the geometry of the PET system is specified in a simple MATLAB script which records the translation/rotation of each detector and its corresponding dimensions. Visualization of the PET system is automatically generated with the geometry specification.

Traditional PET image reconstruction codes has taken advantage of the inherent symmetry in detector arrangement to speed up the processing time. Significant speed up of algorithm and lower storage requirement can be realized by estimating system matrix uniquely for detector pairs symmetrical to each other. To utilize symmetry in a general PET reconstruction, the framework automatically compute the symmetry in the system, given a PET geometry.

Acquiring and reconstructing data at different points in time helps visualize dynamic and complex molecular process. We have adjusted the framework to reconstruct sets of data jointly. In that sense, the framework processes on four dimensional data, binned into time frames. We have assumed that the system matrix is fixed between time frames. When the classic Maximum-Likelihood (ML) algorithm is implemented on such a system, there is no information sharing between the estimated images at different times. Hence, each time frame could be treated as an independent reconstruction. However, a prior distribution across the time dimension could penalize the classic ML equation, to give a maximum a posteriori (MAP) solution that requires information sharing between simultaneous reconstruction of
multiple time frames at every iteration. The framework saves developmental effort, reduces debugging time and accelerates the design-simulation-reconstruction loop. We have optimized the framework through parallelization techniques using the Open Multi-Processing (OpenMP [52]) and Message Passing Interface (MPI [25]) libraries. This framework is a critical component of our overall goal of designing optimal systems. Although current systems are field specific or application specific, the next generation systems are potentially patient specific [93], where prior knowledge of the region of interest or desired image quality dynamically shapes the imaging system design.

The wide types of systems that the framework can reconstruct is shown through the application to each system. Each system to which we apply the framework, investigates a different hypothesis, with PET as the underlying imaging modality. We show that treating Lines of Response having different qualitative properties are unnecessary given that they are quantitatively modeled. Therefore, unlike prior implementations ([53], [36], [91]), we do not group and process the data differently.

The methods section go into details of the framework, starting with defining the image reconstruction task, the algorithm, and data model. Then, we focus on implementation details. We apply our framework to four novel geometries and report on performance of each system. Potential improvements and discussion of the results are in the discussion section.

5.2 Methods

5.2.1 Image reconstruction task

Reconstruction in PET is the task of estimation of radionuclide activity concentration from coincidence 511 KeV gamma detections. The distribution of radionuclide in a patient or phantom is continuous. For computational tractability, the image space is divided into discrete three dimensional voxel regions.

Under further assumption that activity in each voxel is a constant over the imaging period, the positron annihilation in voxel occurs at a rate proportional to the activity. We denote the positron annihilation rate across the image space by a lexicographically ordered random
vector, \( X = \{ X_0, X_1, X_2, \ldots X_N \} \), where \( X_i \) is the annihilation rate at the \( i^{th} \) voxel, \( X_i : \Omega \rightarrow \mathbb{R} \) and \( N \) is the total number of voxels. For low rate and large imaging time, the number of back to back gamma rays emitted in a voxel per unit time can be assumed to follow a Poisson distribution, with mean equal to the positron annihilation rate.

Let the detected counts across the data space be represented by another random vector, \( Y = \{ Y_0, Y_1, Y_2, \ldots Y_M \} \), where \( Y_j \) is the counts detected in \( j^{th} \) detector pair and \( M \) is the number of detector pairs. A detector pair, \( j \), placed in the imaging space detects coincidence events from each image voxel, distributed as Bernoulli, with parameter, \( H(Y_j, X_i) \). The parameter \( H(Y_j, X_i) \) is a function of the solid angle coverage of the image voxel by the detector pair, the interaction physics of gamma rays through the medium between the voxel and the detector, as well as angular efficiency of the detector.

In addition, random and scatter events add a bias to each detector. The expected counts at the detector pair, \( j \), is the sum of \( H(Y_j, X_i) \) weighted random parameters from every image voxel, along with random events, \( r_j \) and scatter events, \( s_j \). If each image voxel are assumed to be mutually independent, then the counts, \( Y_j \), measured at each detector pair is Poisson with parameter equal to \( \sum_i H(Y_j, X_i) \times X_i + r_j + s_j \) (For more details, see [69]).

Since the measurements across detector pairs are mutually independent, the probability of a measurement is given by,

\[
Pr(Y = y) = \prod_j \frac{e^{-\lambda_j} \times \lambda_j^{y_j}}{y_j!} \tag{5.1}
\]

where \( \lambda_j = \sum_i H(Y_j, X_i) \times X_i + r_j + s_j \). The solution that we seek in this paper is the MAP estimate given by,

\[
\hat{x} = \arg \max_x \sum_j y_j \log \left( \sum_i H(Y_j, X_i) \times X_i + r_j + s_j \right) - \left( \sum_i H(Y_j, X_i) \times X_i + r_j + s_j \right) - \beta U(X) \tag{5.2}
\]

where \( U(X) \) is the penalty with Lagrange multiplier \( \beta \), or equivalently \( e^{-\beta U(x)} \) is the prior distribution in the image space. In this paper, we have implemented the One-Step-Late (OSL) log-cosh penalty, \( U(X) = \sum_{x \in N_X} w_x \log \cosh \left( \frac{X-x}{\delta} \right) \). \( N_X \) is the neighborhood of \( X \),
which is given by 26 voxel connectivity. $w_x$ is the inverse of the $L^2$ distance between $X$ and $x$.

### 5.2.2 Image reconstruction algorithm

We have implemented the ordered-subsets expectation-maximization (OS-EM) algorithm. The expectation-maximization algorithm alternately estimates the complete data, given as the contribution of radionuclide decay from every voxel in the image space to every element in the data space, and the spatial radionuclide activity concentration. In the ordered-subsets version, only part of the data space is used at every sub iteration, with the whole of the data covered after several sub iterations.

For every iteration, $k$, the algorithm is compactly written as

$$
x_{i}^{k+1} = \frac{x_{i}^{k}}{\sum_{j \in O_k} H(Y_j, X_i) + \beta \frac{\partial}{\partial X} U(X)} \times \\
\left[ \sum_{j \in O_k} \frac{H(Y_j, X_i)}{\sum_{i} H(Y_j, X_i)} \times y_j \right] \left[ \sum_{j \in O_k} \frac{H(Y_j, X_i)}{\sum_{i} H(Y_j, X_i)} \times x_{i}^{k} + r_j + s_j \right]$$

where $O_k$ is the subset of data processed at iteration $k$.

The MAP estimate requires computation of the derivative of the penalty function. The derivative for log-cosh penalty is the tanh function.

$$
\frac{\partial}{\partial X} U(X) = \frac{\partial}{\partial X} \sum_{x \in \mathcal{N}_X} w_x \log\cosh\left(\frac{X - x}{\delta}\right) = \sum_{x \in \mathcal{N}_X} \frac{w_x}{\delta} \tanh\left(\frac{X - x}{\delta}\right)
$$

The log-cosh penalty is quadratic less than one, but linear much greater than one. The $\delta$ term controls the scaling of the image voxels to shift the linear and quadratic penalty region.
5.2.3 Data correction techniques

Accurate estimation of the spatial radionuclide distribution requires correction of physical effects, by modeling them in the forward model. The forward model used in this generalized platform is the same as that used in the work by Keesing et. al [36].

Random and scatter events are modeled as additive components. The random event rate at each detector pair is estimated through a delayed-window technique, wherein the events from different detectors are time shifted and fed to the coincidence processor such that no true coincidence is detected. The random event is sparse if acquisition time window is short. In such a case, a mean random model where the singles rate at each detector is estimated and random event is computed from the singles rate forms a smoother approximation over the data space. This mean random model is detailed in [36, 12].

Scatter events are modeled through the Single Scatter Simulation (SSS) mechanism ([83], [40]). The radionuclide activity concentration is estimated without scatter, and used to simulate the scatter component. The simulated scatter component is then used to correct the data.

The attenuation image is computed by obtaining a CT image (when available), registering and scaling it to 511 keV attenuation. This is forward projected through the system matrix weights, negated and exponentiated to obtain attenuation along a LOR. Alternatively, if the shape of the object is known or can be estimated, attenuation coefficients can be calculated [68, 89].

5.3 Image reconstruction framework

The framework for image reconstruction is shown in Figure 5.1. The geometry specific routines are only the Specify Geometry block and Mapping block. All the rest of the programs are written generally so as to be able to process any geometry given the specification files from the first block. The programs in the center block are the main routines for image reconstruction, normalization, projection and sorting. The blocks on the right side are common routines used in the center blocks.
Each block is explained below.

5.3.1 Specify Geometry

In this framework, each system consists of a collection of detector-units. The system designer specifies the geometry using a MATLAB script rather than setting parameters in a text file.

Pairs of detector-units are termed detector-unit-pairs. Each detector-unit is a combination of detector crystals. For instance, the detector-units could potentially be defined as detector blocks. However, in later parts of the framework, when symmetry of detector-unit-pairs is computed, the symmetry is computed only between detector-units and not within crystals belonging to a detector-unit. Ideally, defining detector-units as individual crystals enable the program to obtain the maximum symmetry. In this case, a detector-unit-pair is the same as a Line Of Response. However, this leads to integer overflow for the PET systems that are shown in the application section as well as slows the symmetry computation. Therefore, in
all the PET systems that are discussed in this paper, we group individual crystal elements into detector-units that are smaller than a detector block.

Each detector-unit is treated as a MATLAB struct variable, having a box struct inside it to specify the position and orientation of the unit. It is assumed that the detector-unit is cuboid. The orientation of the detector-unit is specified by storing the eight vertices of the cuboid as well as three face normal vectors. The detector-unit struct variable records the number of crystals along each dimension of the detector-unit. The detector-unit is assumed to be uniformly cut in each of the dimensions by the number of crystals. The sub-crystal approach[32] of computing the system matrix requires further subdivision of the crystals into sub crystals. Three variables denoting the number of sub-crystal cuts in each crystal along each dimension is also stored in the struct variable.

By writing a short MATLAB script, the system designer can generate multiple detector-units and position them using a series of translations and rotations.

The output of this program is a plain text file which records contents of all the detector-units such as the center, vertices, face normals of the detector-unit box as well as number of crystal elements and sub-crystal cuts along each detector-unit dimension. In addition to writing the text file, a visualization of the geometry is generated by MATLAB showing the structure of the system. This generated visualization is shown in Section 5.4 as an illustration for each system.

5.3.2 Compute Symmetry

The Compute Symmetry block find those detector-unit-pairs that are symmetrical to each other on a regular rectilinear grid. This information is used later to compute the system matrix only on a representative detector-unit-pairs of each symmetrical set. This reduces the system matrix size as well as increases the speed of system matrix computation.

The methodology that is undertaken, is to find a set of parameters that define each non symmetrical pair of detector-units uniquely, but have the same value for all detector-unit pairs within a symmetrical group. The symmetry property arises from the interplay between the location of detector-units and the image grid.
For completeness, we introduce the following notation. We operate on a regular cartesian grid of image voxels. Let the global coordinate system be indexed by \((x, y, z)\).

Assuming that all detector-units are right cuboids, the rigid body rotation of a detector-unit with respect to a reference orientation can be represented by a set of 3 Euler rotational angles. All detector-units in the geometry is defined as a rotated, translated version of a reference detector-unit orientation. The reference detector-unit has a fixed frame axes \((X, Y, Z)\). Each detector-unit, \(p\), has a position, \(\overrightarrow{C} = [C_x, C_y, C_z]^\top\) on the global coordinate system.

Let each detector-unit in geometry be indexed and \((p, q)\) define a detector-unit-pair whose first detector-unit has index, \(p\), and second detector-unit has index, \(q\). Since \((p, q)\) pair is same as \((q, p)\), and \(p \neq q\), we consider only \((p, q)\) where \(p < q\).

From this minimalistic set definition, we can uniquely encode all detector-unit-pairs using a 12 element parameter vector, comprising of position of first detector-unit, position of second detector-unit, Euler rotational angles of first detector-unit, and Euler rotational angles of second detector-unit.

**Property of Symmetry**

Symmetry is simply invariance under a transformation. For instance, mirror symmetry implies that the features of object remains same during a mirroring operation. From our previous definition of encoding the state of a detector-unit-pair based on a unique parameter vector, we see that an operation such as mirroring or rotation changes the values of each of the parameters. Therefore, symmetry cannot be inferred from the above parameter vector as it exists. The solution is to convert the original parameter vector into a feature vector, where symmetrical detector-unit-pairs have same feature vector. In effect, the transformation that maps the original parameter vector to the feature vector is an invariant operation of symmetry.

The two properties that must be satisfied by the invariant operation, \(T\), are

1. Property A: \(T(x_1) = T(x_2) \Rightarrow x_1, x_2 \in S_i\)
2. Property B: \(x_1 \in S_i, x_2 \in S_j, i \neq j \Rightarrow T(x_1) \neq T(x_2)\)
where \( x \) is an original parameter vector and \( T(x) \) is a feature vector. \( S_i \) is a single set of symmetrical detector-unit-pairs.

### Types of symmetry

There are five types of symmetrical arrangements that we consider, as shown in Figure 5.2.

1. Translational symmetry
2. Rotational symmetry
3. Reflection symmetry
4. Interchangeability of detector-units forming a detector-unit-pair

5. Interchangeability of a normal face vector of a detector-unit and its reverse

6. Detector-units having equal sides

To find the invariant operation, we could potentially examine candidate functions whose inclusion into the feature vector would maintain property A. We stop once sufficient candidate functions are identified that satisfy property B are found.

Assuming a choice for the first detector-unit, \( p \), and second detector-unit, \( q \), forming the detector-unit-pair, we discuss the candidate functions below.

1. Cartesian distance, \( L_{p,q} \)
   The cartesian distance is the \( L_2 \) norm distance between centers of two detector-units, \((C^p_x, C^p_y, C^p_z)\) and \((C^q_x, C^q_y, C^q_z)\). Any two detector-units, separated by same distance, fall within the same space with this function.

2. Angle between source and destination \( (\overrightarrow{w_{pq}}) \)
   The angle vector is with respect to the global coordinate system. That is, \( \overrightarrow{w_{pq}} = [\overrightarrow{w_x} \overrightarrow{w_y} \overrightarrow{w_z}]^\dagger \).

3. Orthogonal face vectors for \( p \) and \( q \) detectors
   Although there are 6 face vectors for each detector-unit, along \(-X, +X, -Y, +Y, -Z\) and \(+Z\), only 3 of these (say, \(+X, +Y, +Z\)) are necessary to uniquely identify the detector-unit orientation. Each of these vectors have 3 elements, giving the \( x \), \( y \) and \( z \) component in the global coordinate system. Let us denote these \( ^a N^b_c \), where \( a \) is an element of \( \{p, q\} \), \( b \) is an element of \( \{+X, +Y, +Z\} \) and \( c \) is an element of \( \{x, y, z\} \).

It is clear that given a detector-unit pair \((p, q)\),

\[
\left\{ \overrightarrow{C_p}, L_{p,q}, W \right\}
\]

with \( W = \begin{bmatrix} \overrightarrow{w_x} & pN_x & pN_y & pN_z & qN_x & qN_y & qN_z \\ \overrightarrow{w_y} & pN_x & pN_y & pN_z & qN_x & qN_y & qN_z \\ \overrightarrow{w_z} & pN_x & pN_y & pN_z & qN_x & qN_y & qN_z \end{bmatrix} \)
completely describes the geometry of the detector-unit-pair. Let us call this a feature of the detector-unit-pair, $F_1$.

**Group Operations**

We consider each form of symmetry and its effect on the above formulation.

1. Translational symmetry

   Given a detector-unit-pair $(p, q)$, the only component that depends on translation is the center of the first detector-unit, $\overrightarrow{C}_p$. The system matrix for the LOR varies as a function of the vector displacement between the center of the first detector-unit and the image voxel it is located in, along each global axis. The system matrix for the LOR is a copy if this distance is the same as the reference LOR.

   If $\Delta$ is the absolute displacement of $\overrightarrow{C}_p$ from the bounding voxel, and the Hadamard product of $\Delta$ with $\text{sign}(\overrightarrow{w}_{pq})$ indicates the displacement invariance to LOR rotation. All LORs having the different $\Delta \circ \text{sign}(\overrightarrow{w}_{pq})$ fall in different symmetry sets.

   Therefore, we replace $F_1$ by
   
   \[ \{ \Delta \circ \text{sign}(\overrightarrow{w}_{pq}), L_{p,q}, W \} \]

   Since the effect of $\Delta \circ \text{sign}(\overrightarrow{w}_{pq})$ is small if the image voxel is small compared with the length of the LOR, we did not consider this offset in the implementation. However, this is easily added. Without considering the offset, the new feature is $F_2 = \{ L_{i,j}, W \}$

   All LORs having the same $F_2$ feature vectors, are translated versions of each other.

2. Interchangeability of detector-units forming a detector-unit-pair

   For any detector-unit-pair $(p, q)$, the response function remains unchanged if the detector-unit-pair is ordered as $(q, p)$. The effect of interchanging the two detector-units in the feature is that columns 2 to 4 are replaced with columns 5 to 7. Switching the two indices in the feature, $F_2$, would have had the effect of negating the sign of the direction vector such that $\overrightarrow{w}_{qp} = -\overrightarrow{w}_{pq}$. We can model this by a matrix multiplication with a matrix $R$, chosen from a set.
\[ \{L_{p,q}, W \times R\} \]

\[
R_{+1} = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 \\
\end{bmatrix},
\]

\[
R_{-1} = \begin{bmatrix}
-1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 \\
\end{bmatrix}
\]

3. Detector-units having equal sides

There are additional degrees of freedom associated with a square cuboid with at least two faces being equal. This is modeled similarly to detector-unit interchange symmetry, where \( R \) is allowed to take on additional values in the set. For instance, if the first detector-unit is square cuboid with normals 2 and 3 interchangeable, additional \( R \) that should be introduced is,

\[
R_{+2} = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 \\
\end{bmatrix},
\]

\[
R_{-2} = \begin{bmatrix}
-1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 \\
\end{bmatrix}
\]

4. Reflection symmetry
Reflection symmetry is the invariance of the detector-unit-pair to reflection along the axes plane of the global coordinate system. To model this invariance, we examine the effect reflection on yz plane on feature $F_2$.

A reflection operation for a particular detector-unit-pair having this feature vector along $yz$ plane ($x = 0$) uniformly multiplies all the $x$ components in $F_2$ by $-1$. Therefore, the operation can be modeled by introducing a variable, say $g$, which multiplies all the $x$ components by $\pm 1$. Similarly, let us introduce variables, $h$ and $i$ to model reflection along $xz$ and $xy$ planes respectively.

This changes the feature into $F_3 = \{L_{p,q}, T \times W \times R\}$

where $T = \begin{bmatrix} g & 0 & 0 \\ 0 & h & 0 \\ 0 & 0 & i \end{bmatrix}$ and $g, h, i \in \{-1, +1\}$.

5. Interchangeability of a normal face vector of a detector-unit and its reverse

We consider the interchangeability of a normal face vector and its reverse. This property is due to the cuboidal nature of the detector-units. For example, the detector-unit-pair response function is unchanged if a normal face vector $[p \ N_x^p N_y^p N_z^p]^T$ is multiplied by $-1$. We model this effect by the multiplication of $a, b, c, d, e, f$, such that the new feature vector is

$\{L_{p,q}, T \times W \times U \times R\}$

where $U = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & a & 0 & 0 & 0 & 0 \\ 0 & 0 & b & 0 & 0 & 0 \\ 0 & 0 & 0 & c & 0 & 0 \\ 0 & 0 & 0 & 0 & d & 0 \\ 0 & 0 & 0 & 0 & 0 & e \\ 0 & 0 & 0 & 0 & 0 & f \end{bmatrix}$

and $a, b, c, d, e, f \in \{-1, +1\}$.

6. Rotational symmetry

Here we are rotating with respect to the regular rectilinear grid. Hence, there are only finite rotations available. Rotation interchanges all components in $F_3$ belonging to one axis with another one and negates those components along some or all the axis. Row
negation is already modeled in the Reflection symmetry. Therefore, in this section, we only consider the interchanging of coordinate components. We need to make the feature invariant of the ordering of $x, y, z$ components of the direction vector and face normals. We model this symmetry property as pre-multiplication by a matrix, $S$,

$$\{L_{p,q}, S \times T \times W \times U \times R\}$$

$$S_1 = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

$$S_2 = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 1 \\ 0 & 1 & 0 \end{bmatrix}$$

$$S_3 = \begin{bmatrix} 0 & 1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

$$S_4 = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 0 \end{bmatrix}$$

$$S_5 = \begin{bmatrix} 0 & 0 & 1 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix}$$

$$S_6 = \begin{bmatrix} 0 & 0 & 1 \\ 0 & 1 & 0 \\ 1 & 0 & 0 \end{bmatrix}$$

$S \in \{S_1, S_2, S_3, S_4, S_5, S_6\}.$

Hence, all the group operations are modeled as

$$\{L_{p,q}, S \times T \times W \times U \times R\}$$

From the above formulation, it is clear that apart from translational symmetry and detector-units having equal sides, the number of potential members of any one group can be as high as $6 \times 2^9 \times 2 = 6144$. Given any member of a group, we wish to replace by unique element of the group representing that group.

**Algorithm for symmetry computation**

In this algorithm, we attempt to replace the parameter vector of each detector-unit-pair with a representative parameter vector of the symmetry group it belongs to. After this, the array consisting of representative parameter vectors for each detector-unit-pair is sorted, and unique rows of representative parameter vectors are found. These unique rows form the canonical elements of the symmetry table. The mapping between different detector-unit-pair and the canonical element is stored in binary files.
Data: $D, n\text{DetTypes}, S, T, U, R$

Result: $\text{canonicalIndices}, \text{symmetryMap}, \text{lorOrder}$

Initialization; for $p \in D$ do
  for $q \in D$ do
    $l = \text{getPairIndex}(p, q)$;
    if $\text{checkSpurious}(l) == \text{TRUE}$ then
      continue;
    end
  end
  calculate $L_{p,q}$ and $W = 
  \begin{bmatrix}
  w_x p N_x^X & p N_x^Y & p N_x^Z & q N_x^X & q N_x^Y & q N_x^Z \\
  w_y p N_y^X & p N_y^Y & p N_y^Z & q N_y^X & q N_y^Y & q N_y^Z \\
  w_z p N_z^X & p N_z^Y & p N_z^Z & q N_z^X & q N_z^Y & q N_z^Z
  \end{bmatrix}$;
  begin $= \text{TRUE}$;
  for each $S \in S, T \in T, U \in U, R \in R$ do
    Compute $W_{\text{temp}} = S \times T \times W \times U \times R$;
    if $\text{begin} == \text{TRUE}$ then
      $W_{\text{min}} = W_{\text{temp}}$;
      $\text{lorOrder}_{\text{temp}} = (S \times T \times [1 2 3]^T)^T$;
      $\text{switched} = (R[0,0] < 0)$;
      begin $= \text{FALSE}$;
    else
      if $\text{compare}(W_{\text{temp}}, W_{\text{min}}) \leq 0$ then
        $W_{\text{min}} = W_{\text{temp}}$;
        $\text{lorOrder}_{\text{temp}} = (S \times T \times [1 2 3]^T)^T$;
        $\text{switched} = (R[0,0] < 0)$;
      end
    end
  end
  if $\text{switched} == \text{TRUE}$ then
    $p' = p; q' = q$;
  else
    $p' = q; q' = p$;
  end
  $\text{detPairType} = \text{getDetType}(p') \times n\text{DetTypes} + \text{getDetType}(q')$;
  $\text{lParam}[\text{getPairIndex}(p', q'), :] = [L_{p', q'}, \text{makeRow}(W_{\text{min}}), \text{detPairType}]$;
  $\text{lorOrder}[\text{getPairIndex}(p', q'), :] = \text{lorOrder}_{\text{temp}}$;
end

$[\text{lParamSorted}, \text{sortedIndex}] = \text{quicksortRows}(\text{lParam})$;
$[\text{canonicalIndices}, \text{symmetryMap}] = \text{findUniqueRows}(\text{lParamSorted}, \text{sortedIndex})$;

Algorithm 1: Computation of symmetry algorithm
The algorithm takes as input the different types of symmetries possible, and the geometry definition of detector-units and computes the symmetry between detector-unit-pairs.
The method of symmetry computation is given in Algorithm 1. The code was implemented in C. The program reads the output of the Specify Geometry program (Section 5.3.1), as an array of struct variables, $D$ that describes the geometry of each detector-unit. The other inputs required by the algorithm are sets of matrices, $S, T, U, R$, that model symmetrical group operations and the number of detector-unit-pair types, $n_{DetTypes}$.

For each combination of two detector-units, $p$ and $q$, the getPairIndex() function returns the index of the detector-unit-pair, $l$. The index value returned by the getPairIndex() function is different for either order of the detector-units. It is important when utilizing the symmetry to differentiate the first detector-unit from the second.

The checkSpurious() routine checks the validity of the detector-unit-pair for that particular geometry. In modern PET systems and reconstruction frameworks, there exists electronic fan-angle limitations that are modeled by this function. Additionally, Lines Of Response that are shorter than a particular length are thrown away. The checkSpurious() routine also throws away one of the permutations of $p$ and $q$. This ensures that the symmetry is computed for only unique combinations of the detector-units. However, later in the code, the order of $p$ and $q$ might be interchanged to encode the symmetry group operation that models detector interchange (Group Operation 2).

The program computes the second part of the feature vector, $W$ for non-spurious detector-unit-pairs. Then, for all combination of symmetrical group operations, we compute $W_{temp} = S \times T \times W \times U \times R$. A unique symmetry invariant $W_{min}$ is identified by finding the minimum after reordering the elements in $W_{temp}$ as a single row. In the current implementation, the matrix $W_{temp}$ is converted to a linear array using column major order. In finding the minimum, each element is compared starting with the first column.

The program is capable of handling different types of detector-unit-pairs. For instance, in a system having crystals of two different dimensions, detector-unit-pairs between crystals of the same dimension and different dimension gives rise to three types of detector-unit-pairs. These different types of detector-unit-pairs must not be mapped to the same canonical element during the symmetry calculation. The function, getDetType() returns the type for each detector-unit. This is encoded for the detector-unit-pair into the $detPairType$ variable.
The invariant found, $W_{min}$, is converted into a linear row using column major format, prefixed with $L_{p,q}$ and suffixed with the detector-unit-pair type. Therefore, detector-unit-pairs having different $L_{p,q}$, detector-unit-pair type or $W_{min}$, do not share the same canonical element.

This is stored as the feature for the particular detector-unit-pair, $l$, in a large two dimensional array, $lParam$.

The $lParam$ array is sorted row-wise using quicksortRows algorithm, operating on rows. The comparison operator within quicksortRows compares rows, in column sequence starting with the first column. The output of the operation is the sorted array as well as a mapping, $sortedIndex$, that maps the original location to the sorted location.

Swapping rows is done by swapping pointer elements to the rows of the array. One characteristic of the operation is that since length of the detector-unit-pair is the first column of all the rows, the detector-unit-pairs are sorted by length after the quicksortRows operation.

The findUniqueRows() routine compares adjacent rows of $lParamSorted$ and finds the unique rows. This operation, combined with converting the original feature to a symmetry invariant feature, finds all the symmetrical detector-unit-pairs. The routine generates two outputs, $canonicalIndices$ and $symmetryMap$. The $canonicalIndices$ records the indices of unique rows in the $lParam$ array. The $symmetryMap$ variable maps each row of the $lParam$ array to a row in the $canonicalIndices$ array.

A two dimensional array, $lorOrder$, which is a 3 element row for every detector-unit-pair that is considered is also stored. The variable tracks the detector-unit-pair through rotation and reflection symmetry and enables quick computation of voxel location for a symmetrical detector-unit-pair in relation to its canonical detector-unit-pair. The decoding is shown in Algorithm 3, that will be described later.

The boolean variable, $switched$, tracks whether the order of the detector-units have to be interchanged during the symmetry computation process. If they are interchanged, the detector-unit-pair index is updated. This ensures that upon computing the system matrix for a unique canonical element in the image space, the symmetrical detector-unit-pairs will have the same relative ordering of their component detector-units.
The program is written in C, and parallelized using OpenMP. When finding the minimum invariant for each detector-unit-pair, the processing is distributed to different cores. Additionally, the quicksortRows() algorithm is a modification of the original QuickSort algorithm to run in a parallel fashion.

5.3.3 Create SEDC Groups

To make the code easy to parallelize, it is advantageous to bin the unique detector-unit-pair into groups. For easy description, we introduce a new name for these groups called Symmetry Encoded Data Clusters (SEDC). During a projection operation, each SEDC is processed using a single core at a time. The number of SEDCs is large enough such that each SEDC has only a few unique detector-unit-pair, enabling us to control the memory footprint of each core at any instant.

The number of SEDCs are on the order of thousands, where the cores on a system are on the order of tens. A set of SEDC are distributed to each core in a dynamic fashion, until all the SEDCs are processed.

After the symmetry computation, the unique detector-unit-pairs are ordered by the first variable of the feature vector, which is the length of the detector-unit-pair. Since computational complexity is roughly proportional to the length, we interleave the detector-unit-pairs across SEDCs so as to balance the computational load. Although taking into account the varying number of detector-unit-pairs that are mapped into each unique detector-unit-pair estimates the computational load more precisely, we do not currently take that into account.

The allocation of unique detector-unit-pairs to SEDCs and the set of all detector-unit-pairs mapped to each unique detector-unit-pair are calculated and stored in binary files.

5.3.4 Data Sorting

The PET data obtained from a regular scanner is in list-mode format. The list-mode data is histogramed into an upper triangular detector-matrix. For faster processing, the data is then presorted using a mapping function into a two dimensional array, with rows being
the SEDC and columns being the LOR in SEDC in the order that they are listed. Within each SEDC row, the data is organized by symmetrical sets. Within each symmetrical set, the data is further organized by detector-unit-pairs and then, by LORs belonging to the detector-unit-pair.

The mapping function maps the detector-unit and crystal index in detector-unit from the MATLAB Specify Geometry script to the index of the crystal in the system. The data is obtained as detector matrices from the real system. The mapping function can be specified in an external, shared C library. The sorting, reconstruction and normalization programs use the mapping function.

The sorting is not trivial as we process the coincidence data in pairs of detector-units. The detector-unit is further cut up into crystals and the sorting code has to take into consideration the relative ordering of the crystals pairs in the detector-unit pair between the symmetric and the unique detector-pair. This is implemented by comparing the normal face vectors of the detector-units forming a detector-unit-pair to normal face vectors of the canonical detector-unit-pair.

5.3.5 LUT generation

Running the framework with an offline system matrix requires pre-computation of the lookup table. The LUT generation code computes the system matrix for each SEDC and stores it as a separate file.

Compute geometric system matrix

We use a compartmentalized system matrix which separates the full matrix given by $H(Y, X)$ into a normalization matrix, an attenuation component and geometric system matrix.

The geometric system matrix is computed using Siddon’s algorithm [67] and sub-crystal approach[32]. The routine generates the system matrix for each SEDC at a time, and only the unique detector-unit-pairs are used. In each Line of Response within the unique detector-unit-pair from the symmetry computation, the two contributing crystals are subdivided into
sub-crystals. Lines joining the sub-crystals are termed sub-LORs and the Siddon’s algorithm is used to compute the length of intersection of sub-LOR’s with voxels of the image space. The values are averaged across sub-LOR’s to obtain weight linking each voxel and LOR and this forms the attenuation system matrix. To equalize the LORs that join detectors of different materials and sizes, it is necessary to model a multiplicative factor to the computed weights. This is taken care of by normalization, where LORs joining crystals of different sizes and materials are grouped separately. To get the emission system matrix that models the detection probability of back to back gamma between a voxel and LOR, the weights of the attenuation system matrix are divided by the square of length of LOR during the projection operation.

![Figure 5.3: System Matrix calculation using the Siddon’s method and Sub-crystal approach. The crystals in a detector block are cut into sub-crystals. Weights are computed for lines joining the sub-crystals to find the system matrix.](image)

$$SM(v) = \sum_{i,j} e^{-\mu \mathcal{L}_i} \times e^{-\mu \mathcal{L}_j} \times l_{i\rightarrow j} \frac{L^2}{L^2}$$

(5.5)

where $\mathcal{L}$ denotes the length of the LOR inside either detector, $L$ denotes the length between the sub-crystals. $i$ and $j$ denotes the sub-crystal index. $l$ is the intersection length of the sub-LOR with the voxel.

These weights can either be stored on disk or computed on the fly. When stored on disk, they are split up based on SEDC ordering into multiple files.
5.3.6 Forward/Backward Projection

The projection routines project the sorted data space into the image space or vice-versa. Projection operation in both directions are implemented together, using a data driven methodology. The algorithm is shown in Algorithm 2. The algorithm processes only a subset of the SEDCs passed as input in SEDCsets. Different SEDCsets are scheduled on different nodes through the MPI parallelization library. The routine is further parallelized using OpenMP such that each core on a node processes a separate SEDC in the SEDCsets. It reads or computes the system matrix, if the system matrix is not already loaded in memory.

The program iterates through each canonicalElement in the SEDC, and then through every LOR within the canonicalElement denoted here as canonicalLOR. Within each canonicalLOR, each symmetrical detector-unit-pair mapped to the canonicalElement is iterated. Within each symmetrical detector-unit-pair, the program moves through image space voxels computed from the system matrix, converts them to correct locations for the symmetrical LOR and increments the value in either the data space or image space depending on the projection direction.

Utilizing representative detector pairs in projection operations

During the system matrix generation, we consider each canonical detector-unit-pair and compute the tube of response of its component LORs. The tube of responses can either be stored on disk or computed on the fly. The computed response function across voxels for each unique LOR has to remapped to correct coordinates for the symmetrical LORs.

To perform this, we first subtract each voxel with canonical detector-unit-pair’s first detector-unit’s center. Note that in the symmetry computation routine, since we record detector-interchange symmetry by reordering the component detector-units, the first detector-unit of the canonical and current detector-unit-pair are equivalent. We later add current detector-unit-pairs source detector center. This is not sufficient as this detector pair has to rotated. The lorOrder variable stored during symmetry calculation is used to reorient the tube of response.
Data: data, img, preloadSystemMatrix, readSystemMatrixFromDisk, projDirection, SEDCsets, D, SM

Result: data, img

for outerFrame ∈ {0...floor(numFrames/framesInParallel)} do
    for SEDC ∈ SEDCsets do
        initialize imgPvt to all zero;
        if preloadSystemMatrix == FALSE then
            if readSystemMatrixFromDisk == TRUE then
                SM = readSystemMatrix(SEDC);
            else
                SM = computeSystemMatrix(SEDC);
            end
        end
        for canonicalElement ∈ SEDC do
            for canonicalLOR ∈ canonicalElement do
                for detectorPair ∈ symmetryMap(canonicalElement) do
                    LOR = getLOR(detectorPair, canonicalLOR);
                    for each voxel do
                        newVoxel = getSymmetricalVoxel(D, voxel, canonicalElement, detectorPair);
                        for frame ∈ innerFrames(OuterFrame) do
                            if projDirection == FORWARD then
                                data[frame, LOR] += SM[canonicalLOR, voxel] × img[frame, newVoxel];
                            else
                                imgPvt[frame, newVoxel] += SM[canonicalLOR, voxel] ×
                                data[frame, LOR];
                            end
                        end
                    end
                end
            end
        end
    end
end

Algorithm 2: Projection algorithm

The algorithm either forward projects the image space into the data space or backward projects the data space into image space.
Data: \( D, \text{voxel}, \text{canonicalElement}, \text{detectorPair} \)

Result: \( \text{newVoxel} \)

initialization;

\[
\text{voxelRelative} = \text{voxel} - D(\text{getFirstDetector(\text{canonicalElement}))}.\text{center};
\]

\[
\text{for } i \in \{0, 1, 2\} \text{ do}
\]

\[
\text{newVoxel}[|\text{lorOrder[detectorPair, i]} - 1|] = \text{sgn(\text{lorOrder[detectorPair, i]})} \times \text{sgn(\text{lorOrder[canonicalElement, i]})} \times \\
\text{voxelRelative}[|\text{lorOrder[canonicalElement, i]} - 1|];
\]

\[
\text{end}
\]

\[
\text{newVoxel} = \text{newVoxel} + D(\text{getFirstDetector(detectorPair)}).\text{center};
\]

Algorithm 3: get Symmetrical Voxel algorithm converts \( \text{voxel} \) in \( \text{canonicalElement} \) to its symmetric location in \( \text{detectorPair} \)

The scheme is to maintain a three element coordinate order vector, whose initial value is a column vector, \([+1 + 2 + 3]^{\top}\) for every detector-unit-pair. The values in the coordinate order vector corresponds to the transformation that was applied to the detector-unit-pair to convert it to the invariant vector. The \( \text{lorOrder} \) parameter is computed during the symmetry computation (See Section 5.3.2).

By knowing the coordinate order vector of the unique LOR which converts it to the invariant parameter vector of the symmetrical set as well as the coordinate order vector of the symmetrical LOR (stored as \( \text{lorOrder} \)), we can re-map a voxel of the unique LOR to a corresponding voxel in the symmetrical LOR. Algorithm 3 describes the conversion operation.

5.3.7 Normalization

Unmodeled factors in the system matrix causes artifacts in the reconstructed image. These factors are unmodeled either due to gaps in our understanding of the physics model or day-to-day variations in a real system, such as detectors fluctuating in efficiency or failing. The
estimation of these unmodeled factors by comparing data collected from a known phantom with the expected data from a digital representation of the phantom projected through the system matrix is called normalization.

We have implemented the Model-based normalization approach [7]. There are a few requirements for successful normalization. The activity distribution of the normalization phantom must be known. Furthermore, the normalization acquisition must have sufficient statistics to estimate all the normalization parameters.

The normalization framework is applied to crystals of different sizes and materials. LORs joining crystals of different types must have different normalization components. Instead of modeling these effects in the system matrix, they are modeled as the components of the normalization matrix and estimated experimentally.

Current framework uses the l-BFGS optimization library [44]. The l-BFGS library is a limited-memory quasi-Newton algorithm implementation and requires only the computation of the gradient. We have a non-negativity constraint on each of the components. The constraint is modeled by estimating the square root of the component values, which makes the problem unconstrained.

Each component is a collection of individual multiplicative variables known as efficiency factors. Each variable multiplies the system matrix weights of certain set of LORs. For instance, the crystal efficiency component has multiplicative variables equal to the number of crystals. Each variable multiplies all LORs containing the corresponding crystal.

Additionally, a LOR might be multiplied by more than one variable of a component. An example is the crystal efficiency component, where the weights of each LOR is multiplied by the multiplicative factors associated with two crystals.

To make the framework general, we estimate a common table of efficiency terms termed the efficiency_matrix. The first dimension of the efficiency_matrix is the component, and the second dimension indexes the multiplicative factors in the component.

We define membership of multiplicative variables to each LOR using a table known as efficiency_index_matrix. Improving the estimated normalization matrix by addition of new components or removing components can be done by changing the table instead of the code.
The table is three dimensional. The first dimension of efficiency_index_matrix is the index of the LOR, the second dimension indexes the component. The third dimension indexes the different multiplicative variables belonging to a component that contribute to the LOR. The number of symbols in the third dimension is variable depending on the component it belongs to. The values stored inside the efficiency_index_matrix are indices of the efficiency_matrix for each component. The concept is illustrated in Figure 5.4.

The Poisson log-likelihood equation is used to estimate the unknown efficiencies. The main difference is that in this problem, the activity distribution in image space is known, and the maximization is over the multiplicative factors to be estimated.

\[
L = \sum_j y_j \log \left( \prod_{k \in S(j)} \eta_k^2 \left[ \sum_i H(Y_j, X_i) \times X_i \right] + r_j + s_j \right) \\
- \left( \prod_{k \in S(j)} \eta_k^2 \left[ \sum_i H(Y_j, X_i) \times X_i \right] + r_j + s_j \right)
\]  
(5.6)
where \( y_j \) is the acquired normalization coincidence data for \( j \)th LOR, \( H(Y_j, X_i) \) is the system matrix values for \( j \)th LOR and \( i \)th voxel in image space, \( X_i \) is the known image, \( r_j \) is normalization randoms data and \( s_j \) is normalization scatter data. \( \eta_k \) is the square root of the efficiency values stored in the \( k \)th location of the efficiency matrix. The set \( S(j) \) maps the index of each LOR to a set of efficiency matrix values through the efficiency index matrix.

The gradient of the likelihood equation is

\[
\frac{\partial L}{\partial \eta_{k'}} = \sum_{j: S(j) \ni k'} 2\eta_{k'} \left[ \prod_{k \in S(j), k \neq k'} \eta_k^2 \right] \left[ \sum_i H(Y_j, X_i) \times X_i \right] \times \left[ \frac{y_j \left[ \prod_k \eta_k^2 \right] \left| \sum_i H(Y_j, X_i) \times X_i \right| + r_j + s_j - 1}{\prod_k \eta_k^2 \sum_i H(Y_j, X_i) \times X_i} \right] \tag{5.7}
\]

During the course of our investigation, we have encountered problems where normalization succeeds in the immediate region of the image space covered by the normalization phantom, but has improper normalization further away from the phantom. For instance, the boundary of the normalization phantom might divide the normalization parameters.

This is true especially when the phantom used for normalization is small, and does not cover enough LORs to normalize them. Therefore, we have a multi position normalization procedure, where the normalization phantom is placed in multiple locations in the imaging field of view. Assuming that each acquisition is independent, we estimate the component efficiencies through a joint objective function which comprises of the sum of the likelihood function at different positions.

\[
L_{\text{joint}} = L_1 + L_2 + ... + L_N \tag{5.8}
\]

where \( N \) is the number of normalization acquisitions. Correspondingly, there are \( N \) sets of \( X \) as well as \( Y \) which denotes known activity distribution as well as acquired data at each
of the $N$ locations. The gradient of $L_{\text{joint}}$ is the sum of the gradients at each $N$ locations with respect to the unknown multiplicative factors.

Our normalization procedure is a two stage process. In the first stage, the forward projection of known activity distribution at each $N$ locations are computed, with corresponding known attenuation and forms $\sum_i H(Y_j, X_i) \times X_i$. In the second stage, the l-BFGS routine is run, with gradients of the likelihood function computed as mentioned above. The second stage of the code is parallelized using OpenMP over the data space, in the computation of the gradient.

Currently, three types of components are modeled for all the geometries, one which separates coincidence data between different types of detectors, another separating crystals and the last which models the angle made subtended by the LOR and the crystal face. The first components are computed in sequence, rather than jointly. Joint estimation requires the addition of further constraints in the code.

<table>
<thead>
<tr>
<th>PET System</th>
<th>LOR Type 0</th>
<th>LOR Type 1</th>
<th>LOR Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-ring</td>
<td>18921.41</td>
<td>191016.8</td>
<td>1668929</td>
</tr>
<tr>
<td>Flat-panel</td>
<td>1.0</td>
<td>111.0478</td>
<td>8663.429</td>
</tr>
<tr>
<td>Micro-insert</td>
<td>86.618</td>
<td>1054.317</td>
<td>12014.71</td>
</tr>
<tr>
<td>Plant PET</td>
<td>79051.31</td>
<td>48068.33</td>
<td>33539.53</td>
</tr>
</tbody>
</table>

Table 5.1: Computed efficiencies between LOR of different types. LOR Type 0 is Insert-Insert data for the Half-ring, Flat-panel and Micro-insert systems, and Inveon-Inveon data for the Plant PET system. LOR Type 1 is Insert-Scanner data for the Half-ring, Flat-panel and Micro-insert systems, and Inveon-R4 data for the Plant PET system. LOR Type 2 is Scanner-Scanner data for the Half-ring, Flat-panel and Micro-insert systems, and R4-R4 data for the Plant PET system. The Flat-panel and Micro-insert are Monte Carlo simulations, while the Half-ring and Plant-PET are experimental systems.

5.3.8 Reconstruction

The reconstruction program is 4D, in that it is capable of reconstructing multiple frames of data simultaneously. The algorithm is OS-EM. Currently in the implementation, the SEDCs are interleaved among the subsets. At each sub-iteration, only one subset is processed.
Figure 5.5: Computed crystal efficiencies for the Half-ring Experimental system

Figure 5.6: Computed crystal efficiencies for the Flat-panel Monte Carlo system

Figure 5.7: Computed crystal efficiencies for the Micro-insert Monte Carlo system
The main reconstruction framework is implemented using a hybrid Open Multi-Processing (OpenMP [52]) and Message Passing Interface (MPI [25]) architecture. Each core processes a set of SEDCs. At the beginning of the program, the task of processing sets of SEDCs are distributed to multiple nodes, by interleaving the SEDCs into different nodes allocation. This is done concurrently with the OS-EM interleaving. Multiple programs are spawned using the Message-Passing Interface (MPI) architecture on different nodes. Within each node, the SEDCs allocated to the node are further split into different cores using the OpenMP shared memory model. The splitting of SEDCs allocated to a node to cores allocation is dynamic.

A limitation of the current implementation program is that the system matrix is assumed to be the same for all frames. Therefore, the program is not for dynamically changing geometries.

There exists a trade-off between accuracy of the system matrix and the speed of system matrix computation. The trade-off is controlled by the number of sub-crystal cuts of a crystal, when computing the system matrix. For very accurate reconstruction for complex non-conventional PET system shown in the application section, the system matrices are of the order of hundreds of gigabytes.

For big system matrices, the matrix can be read from disk. On regular workstations, as there is insufficient Random Access Memory (RAM) to load the entire matrix into memory, the system matrix is read or computed for each SEDC by the thread requiring it. A disadvantage of this is that the entire system matrix is read or computed at each iteration, resulting in heavy I/O traffic or slow program. The alternative, for machines having sufficient memory, is to read or compute the system matrix at beginning of the reconstruction program, before the iterations. Each node only reads or computes the SEDCs that it is required to process. The flexible nature of the current implementation allows the same program to run on a workstation or a distributed cluster.

Limitation in the coincidence processing electronics, such as a fan-angle limitation would cause some LORs to be not measured. Failure to model this effect would introduce artifacts into the reconstructed images. Within the sorted detector matrices, these data points would be zero. Artifacts are introduced through the sensitivity image ( denominator term in Equation (5.3) ). Modeling of this effect is done through the use of masks that zero the contribution of unmeasured LORs to the sensitivity image, as well as randoms and scatter.

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Forward Projection - Ratio - Back Projection

The functional block forward projects the current image estimate, adds randoms and scatter to form the mean data estimate. The ratio of the collected coincidence data to the mean data estimate is found and back projected into the image space. The algorithm for this block is similar to the projection algorithm.

Compute Penalty

At each iteration, the image may be penalized using a One-Step-Late approach. In using this penalty, the gradient of the prior distribution is added to the sensitivity image. To compute the prior distribution, the reconstruction program calls an external shared C library and passes it the current 4D image. The external C library computes the term that needs to be added. Although a variety of different priors in space and time can be modeled using this approach, currently we have only implemented the log-cosh penalty.

Subset Strategy

A geometry independent strategy that divide SEDCs into subsets that balances the contributions of each voxel to every subset is required. The current strategy is to uniformly interleave the SEDCs into every subset. Other strategies can be easily implemented and plugged in.

5.4 Application and Results

Please note that in all the results presented, we are not correcting for randoms or scatter. This was done to keep the computation time low. As the results do not show significant artifacts when these effects are not corrected, we have not attempted to correct for them. For each reconstruction, the iterations are run until the images show satisfactory convergence.
**Data**: data, image, read\_system\_matrix\_from\_disk\_flag, projection\_flag

**Result**: data, image

initialization;

for each SEDC, s, do

initialize image\_private to all zero;

if read\_system\_matrix\_from\_disk\_flag = yes then

\[ \text{system\_matrix} = \text{read\_system\_matrix}(s); \]

else

\[ \text{system\_matrix} = \text{compute\_system\_matrix}(s); \]

end

for each unique\_index in SEDC do

for each symmetry\_index in symmetry\_mapping (unique\_index) do

mean\_data = 0;

for each voxel\_index in system\_matrix(unique\_index, 0) do

\[ \text{new\_voxel\_index} = \text{convert\_to\_symmetrical\_voxel\_index}(\text{voxel\_index}); \]

\[ \text{mean\_data} = \text{system\_matrix}(\text{unique\_index}, 1) \times \text{image}(\text{new\_voxel\_index}); \]

end

mean\_data = mean\_data + \text{randoms}(\text{symmetry\_index}) + \text{scatter}(\text{symmetry\_index});

ratio = \text{measured\_data}/\text{mean\_data};

for each voxel\_index in system\_matrix(unique\_index, 0) do

\[ \text{new\_voxel\_index} = \text{convert\_to\_symmetrical\_voxel\_index}(\text{voxel\_index}); \]

\[ \text{backprojected\_ratio\_private}(\text{new\_voxel\_index}) = \text{system\_matrix}(\text{unique\_index}, 1) \times \text{ratio}; \]

end

end

for each voxel\_index do

\[ \text{backprojected\_ratio}(\text{voxel\_index}) = \text{backprojected\_ratio}(\text{voxel\_index}) + \text{backprojected\_ratio\_private}(\text{voxel\_index}); \]

end

end

**Algorithm 4**: Forward and back projection algorithm
5.4.1 Virtual Pinhole PET half ring system

![Diagram of Virtual Pinhole PET half ring system]

(a) 3D View of Half Ring Insert integrated into a Siemens Biograph 40 scanner; (b) Front View; (c) Top View.

Figure 5.8: **Half Ring system concentric with Siemens Biograph-40** (a) 3D View of Half Ring Insert integrated into a Siemens Biograph 40 scanner; (b) Front View; (c) Top View.

Our lab is focused on new PET geometries, particularly, the Virtual-Pinhole PET technology [75] enhanced devices. The particular technology calls for the addition of smaller sized detectors close to a region of interest in a regular PET scanner.

Our recent work involves the investigation of a device, Half-Ring Virtual-Pinhole PET (VP-PET) Insert, in a clinical PET scanner to improve its imaging quality for head and neck cancers [88]. The functionally complex region within the head and neck region with multiple lymph nodes could benefit from the high resolution capability provided by the insert system. Resolution and contrast recovery were the main metrics that need to be optimized, due to the complex structural anatomy of the region. The higher resolution imaging capacity could also potentially help study neurodegenerative diseases like Alzheimer’s and Parkinson’s disease.

The insert device is a half ring of 28 LSO detector modules in two half rings with radius of 124 mm. Each module comprises of 13x13 LSO crystals of 2x2x5 mm$^3$ size. The insert device is integrated into a Siemens Biograph-40, having 192 detector modules arranged in 4 rings of radius 438 mm. To connect the insert device, we disabled one of the four rings of the Biograph-40 and connected the insert electronics to the coincidence processor.
We have previously shown the design of the Half Ring system [88], data modeling and reconstruction framework [36], and scatter estimation [40]. We have also shown that such a system could improve local image resolution, but still maintain the scanner field of view for imaging whole body [46]. However, the earlier version of the reconstruction program had hard coded symmetry, and was only applicable when the system was at the center of the field of view.

Here, we have re-implemented the geometry within the current framework. Each detector-unit consists of 13 crystals in the same z plane within a detector block. Pairs of detector-units with length lower than a threshold were not used. This corresponds to sinogram trimming by the scanner hardware. Additionally, those detector-unit pairs with direction vector greater than 0.2 in the z component were also not used. This corresponds to a maximum ring difference of 22.

A voxel size of 1x1x2 mm was chosen, with an image size of 600x600x83 voxels. The number of detector-units are 2,236 and number of detector-unit pairs are 2,498,730. Of these, only 1,269,334 are selected after spurious checking. For the Half-Ring in the center, 25,229 unique detector-unit-pairs are computed through the symmetry finding program and the system matrix size is 73 GB. For the Half-Ring positioned 76.20 mm off-center towards the bottom, 27,166 unique detector-unit-pairs are found, with a system matrix size of 85 GB.

**Results**

To investigate the reconstruction performance with the VP-PET half-ring insert, and to show the versatility of the reconstruction framework, we scanned a cylindrical phantom with 5.6 mCi (207.2 MBq) of $^{64}$Cu. The images were acquired with the half-ring insert concentric to the Siemens Biograph 40 and with the half-ring insert moved down 76.20 mm. Moving the half-ring insert down increases the imaging FoV of the system.

For both the configurations, we scanned a cylinder phantom with a Derenzo-like pattern of spherical hollow glass spheres. The glass spheres are 3.3 mm, 4.3 mm, 6 mm, 8 mm, 9.6 mm and 11.4 mm in diameter. The glass spheres were filled with activity with 11.16:1 tumor-to-background ratio. The reconstructed images and line profiles drawn through the tumor plane are presented in Figure 5.9 for the half-ring concentric to the Biograph-40 and
Figure 5.9: **Half Ring system concentric with Siemens Biograph-40** Reconstructed Axial, Coronal and Sagital views of an experimental study consisting of glass spheres of 3.3, 4.3, 6, 8, 9.6, and 11.4 mm diameter, arranged in a Derenzo-like pattern in a cylindrical phantom. The phantom was filled with $^{64}$Cu at 11.16:1 tumor-to-background ratio and scanned for 30 min.
Figure 5.10: **Half Ring system moved 76.20 mm to bottom with Siemens Biograph-40** Reconstructed Axial, Coronal and Sagital views of an experimental study consisting of glass spheres mimicking tumors of 3.3, 4.3, 6, 8, 9.6, and 11.4 mm diameter, arranged in a Derenzo-like pattern in a cylindrical phantom. The phantom was filled with $^{64}$Cu at 11.16:1 tumor-to-background ratio and scanned for 30 min.
in Figure 5.10 for the half-ring moved down. There is a minor artifact at the bottom of
the phantom when the half-ring insert is at the center. The artifact might be due to LORs
that are zeroed due to the limitation of electronics, but are not explicitly modeled in the
reconstruction.

The line profiles indicate that there is a loss in resolution and contrast recovery when the
half-ring insert is moved to the bottom. The half-ring insert at the center has difficulty
imaging parts of the head and neck. The freedom to move the insert down increases the
variety of patients that can benefit from the system.

5.4.2 Flat-Panel system

Figure 5.11: Flat-Panel system concentric with Siemens Biograph-40 (a) 3D View
of the flat-panel insert integrated into a Siemens Biograph 40; (b) Front View; (c) Top View.

Extending the concept of VP-PET to study other organs of interest require development of
a modular and flexible PET insert. We are currently developing a flat-panel VP-PET insert
device [62]. The flexible positioning capability of the insert device allows for patient specific
PET geometries. An initial study investigated the potential application of the technology to
breast cancer using the Half-Ring VP-PET Insert, and showed improved image resolution
without losing Whole-Body imaging capability [46]. Positron Emission Mammography, a
competing technology, also improves image resolution [78] but has difficulty resolving tumors
or secondary lymph node involvement near the chest wall and in medistinum.
The Insert device (See Figure 5.11) has 28 detector modules in a 7x4 panel, with 16x16 LSO crystals per module. Each crystal is 1x1x3 mm$^3$. The scanner is the Siemens Biograph 40 with 192 detector modules in four rings. Each detector module has 13x13 crystals of 4x4x20 mm$^3$ crystals.

Crystals within a detector block with the same z coordinate were grouped together into detector units. For the flat-panel system, all coincidences between detector-units of the flat-panel were not used, as well as detector units separated by less than 641.7 mm between scanner detector units. We also did not use detector-unit pairs with z component of their direction greater than 0.2, similar to the Half ring system.

A voxel size of 1x1x2 mm was chosen, with an image size of 600x600x120 voxels. The number of detector-units are 2,944 and number of detector-unit pairs are 4,332,096. Of these, only 2,494,704 are selected after spurious checking. 50,654 unique detector-unit-pairs are computed through the symmetry finding program and the system matrix size is 102 GB.

**Results**

The reconstructed results of a Monte Carlo study of the new Flat-Panel design with 7x4 detector modules of 16x16 crystals each is shown in Figure 5.12. The phantom that was simulated is a model breast cancer patient with background in the body (box) and breast (sphere). A Derenzo pattern of spherical tumor sources were embedded in the breast region, with 2, 3, 4, 6, 8, 12 mm diameter spherical tumors. The tumor to background ratio is 10:1 or the contrast ratio is 9. For a typical 70 kg patient with water density of 1 gm cm$^{-3}$ and 10 mCi (370 MBq) of $^{18}$F-FDG injected dose, the background activity concentration within body is 0.143 $\mu$Ci/cm$^3$ (5291 Bq/cm$^3$). The background activity concentration simulated is 0.064598 $\mu$Ci/cm$^3$ (2390 Bq/cm$^3$) of $^{18}$F-FDG for 15 minutes. Therefore, the simulation presented is 6.78 minutes of a typical patient scan.

The reconstructed figures may be compared with results presented in [46]. Tumors of 4 mm diameter are resolvable with 6.78 minutes with the flat-panel insert. However, due to the approximations within the Monte Carlo simulation, we do not claim a particular resolution or contrast. We are currently revising the design of the flat-panel insert and construction is only partially complete. Therefore, we do not present any experimental results.
Figure 5.12: **Flat-Panel system concentric with Siemens Biograph-40** Reconstructed Axial, Coronal and Sagital views of a Monte Carlo study consisting of spheres mimicking tumors of 2, 3, 4, 6, 8 and 12 mm diameter, arranged in a Derenzo-like pattern in a cylindrical phantom. The data is equivalent to 6.78 minutes of a typical $^{18}$F-FDG acquisition with 10:1 tumor to background ratio.
5.4.3 Micro-Insert II in MicroPET system

![Micro-Insert II in MicroPET system](image)

Figure 5.13: **MicroInsert II integrated to MicroPET** (a) 3D View of MicroInsert II integrated into a MicroPET scanner; (b) Front View; (c) Top View.

PET imaging of small animals helps study in-vivo disease models, pharmacokinetics and gene expressions. The MicroPET scanner [14] provides for small animal imaging. In the past, we have build a Micro-Insert device to enhance small animal imaging [87]. Currently, we are building the second generation of the device, which is a small complete ring system with sub-millimeter crystals. The Micro-Insert II, when integrated into the Micro-PET scanner, improves the imaging resolution of the scanner and noise level of the MicroPET scanner.

The insert device has 48 detector modules arranged in 4 rings of radius 32.9 mm. Each detector module has 20x20 LSO crystals per module. The crystals are 0.8x0.8x3 mm$^3$ in size. The MicroPET scanner is the Siemens Inveon preclinical microPET/CT, with 64 detector modules in four rings of radius 85.5 mm. Each module has 20x20 LSO crystals with 1.59x1.59x10 mm$^3$ crystals.

For the Micro Insert II in MicroPET, we grouped together crystals having the same z coordinate inside a detector block as a detector-unit. Detector-unit pairs with separation distance less than a threshold was not used. Detector-unit pairs with direction vector greater than 0.2 in the z component were also not used. This corresponds to a maximum ring difference of 16 for insert-insert data, 21 for scanner-scanner data and 29 for insert-scanner data.
A voxel size of 0.4x0.4x0.4 mm was chosen, with an image size of 210x210x320 voxels. The number of detector-units are 2,240 and number of detector-unit pairs are 2,507,680. Of these, only 739,208 are selected after spurious checking. 39,900 unique detector-unit-pairs are computed through the symmetry finding program and the system matrix size is 161 GB.

**Results**

We simulated a Monte Carlo phantom within the new MicroInsert integrated into the MicroPET scanner. The phantom was a cylindrical phantom with spherical tumors embedded in a Derenzo pattern. The diameters of the tumors chosen were 0.6, 1.0, 1.27, 2. 2.6, and 4 mm. The reconstructed image and line profiles drawn through the tumors in the tumor plane is shown in Figure 5.14. The background activity concentration within body is 1 $\mu$Ci/cm$^3$ (37 kBq/cm$^3$), and the tumor-to-background ratio is 14.5, with 30 minutes of simulation time. Line profiles drawn through the tumors on tumor plane indicate a resolution between 0.6 and 1.0 mm.

As the new MicroInsert construction is still underway, we do not report any experimental results.

**5.4.4 Plant PET system**

We are investigating a novel PET system dedicated for plant imaging. The plant imaging system enables plant biologists to study the response of plants under various environmental conditions.

The plant PET imager (See Figure 5.15) is integrated into a plant growth chamber and with horizontal PET detector rings. The system is built of two half rings, having MicroPET R4 modules on one side and Inveon modules on the other. The bigger half ring comprises of MicroPET R4 modules having 84 detector modules in 4 rings. Each module has 8x8 LSO crystals with 2.4x2.4x10 mm$^3$ crystals. Inveon modules form the smaller half ring and has 32 detector modules in 4 rings, with 20x20 LSO crystals per module. Each crystal is 1.59x1.59x10 mm$^3$. 
Figure 5.14: **MicroInsert II integrated to MicroPET** A Monte Carlo study of Derenzo sphere in MicroInsert attached to MicroPET with 0.6, 1.0, 1.27, 2, 2.6 and 4 mm diameter tumors with 14.5:1 tumor-to-background ratio.
Figure 5.15: **Plant PET imaging system** (a) 3D View of the plant imager geometry; (b) Top view of the plant imager; (c) Side view of the plant imager

The plant is placed in between, and the two half rings of the imager are able to move up and down, providing vertical imaging capability of whole plants. The plant imaging system has a dynamic geometry that can be adapted for plants of different widths and height and at different stages of growth. The imaging system enables studying the functional and molecular characteristics of plants and provides a non-invasive mechanism to study plant development.

We grouped together crystals having the same z coordinate and within the same detector block as a detector-unit. Detector-unit pairs with z component of their direction vector greater than 0.8 was ignored. Additionally, there are Inveon-R4 pairs of detector-units that pass through the Inveon module that was also ignored.

A voxel size of 0.8x0.8x0.8 mm was chosen, with an image size of 400x400x160 voxels. The number of detector-units are 1,312 and number of detector-unit pairs are 860,016. Of these, only 661,280 are selected after spurious checking. 128,673 unique detector-unit-pairs are computed through the symmetry finding program and the system matrix size is 345 GB.

**Results**

To characterize the image resolution of the Plant PET system, we simulate a Monte Carlo Derenzo like phantom with 0.84, 1.26, 1.66, 2.5, 3.34 and 5 mm diameter tumors with 6:1 tumor to background ratio. The reconstructed image is shown in Figure 5.16. Line profiles
Figure 5.16: **Plant PET imaging system** An Monte Carlo study of a Derenzo sphere pattern in the Plant PET system with 0.84, 1.26, 1.66, 2.5, 3.34, 5 mm diameter spherical tumors with 11:1 tumor-to-background ratio.
drawn through the tumor pattern shows separation of 1.66 mm diameter tumor, but not the 1.26 mm diameter tumor.

To investigate the performance of the plant imaging system, we simulated the system with the Monte Carlo framework. Figure 5.16 shows reconstruction of a cylindrical phantom with Derenzo-like spherical tumors. A tumor-to-background ratio of 11:1 was simulated for an imaging time of 16 minutes with total activity of 0.13 mCi (4.81 MBq). The tumor diameters are 0.84 mm, 1.26 mm, 1.66 mm, 2.5 mm, 3.34 mm and 5 mm. Line profiles drawn through the tumor are shown in 5.16. From the simulation, the theoretical image resolution is between 1.26 and 1.66 mm. The edge of the imaging field of view is normally noisy in PET, due to lack of data. For the plant imaging system, the edge of the field of view has significant noise due to the angular field of view, cutting the image voxels at an angle. In the experimental images that are presented, this noise has been cropped out.

We conducted an experimental study of a cylindrical phantom of 10 cm diameter with glass spherical spheres. The spheres were filled with $^{64}$Cu with sphere-to-background ratio of 11.16:1. The total activity in the phantom at imaging time was 4.6 mCi (170.20 MBq). Coincidence data was acquired for 30 minutes. The plant imaging system does not have a mechanism to measure attenuation. Figure 5.17 shows the reconstructed images and line profiles without attenuation correction. Lack of attenuation correction in PET images causes a cupping artifact. The image has more noise than the Monte Carlo simulation. We attribute this to the age of the detector modules and lack of randoms correction.

We reconstructed PET images from the plant imaging system using attenuation maps obtained from the CT scan of the phantom and subsequently scaled to 511 keV attenuation. The attenuation map was registered to images reconstructed without attenuation. The reconstructed images and line profiles through the glass spheres are shown in Figure 5.18.

In Figure 5.19, we present the change in radionuclide uptake of a maize plant over time to showcase the 4D reconstruction capability of the framework. The maize plant was grown in a 28 cm long glass jar. The plant was labeled with $^{11}$C-CO$_2$, by pumping the gas into the chamber. After a short uptake period, the glass chamber was flushed. A small amount of the gas sticks to the glass wall, as seen in the images. The plant was imaged at 3 bed positions, and the images were stitched together to get the whole plant. Eight time spots are presented. In total, 24 frames of data are reconstructed together to obtain this set of
Figure 5.17: **Plant PET imaging system** Reconstructed Axial, Coronal and Sagital views of an experimental study consisting of glass spheres of 3.3, 4.3, 6, 8, 9.6, and 11.4 mm diameter, arranged in a Derenzo-like pattern in a cylindrical phantom. The phantom was filled with $^{64}$Cu at 11.16:1 tumor-to-background ratio and scanned for 30 min. The image was reconstructed without attenuation correction. Margins of the field-of-view having artifacts due to insufficient data was cropped.
Figure 5.18: **Plant PET imaging system** Reconstructed Axial, Coronal and Sagital views of an experimental study consisting of glass spheres of 3.3, 4.3, 6, 8, 9.6, and 11.4 mm diameter, arranged in a Derenzo-like pattern in a cylindrical phantom. The phantom was filled with $^{64}$Cu at 11.16:1 tumor-to-background ratio and scanned for 30 min. The image was reconstructed with attenuation correction. Margins of the field-of-view having artifacts due to insufficient data was cropped.
images. The carbon absorbed by the plant during photosynthesis is transported to different parts of the plant. The growing tips of the plant root have increased carbon uptake.

5.5 Discussion and Future work

In this work, we have created a reconstruction framework to reconstruct 4D time series images from PET systems of arbitrary geometry. This investigation is a component of the overarching theme of designing application specific PET imaging devices, adaptable to the imaging target and is a precursor to optimizing the design of PET systems.

In developing this framework, we have learned that the expectation-maximization algorithm [21] is robust in its ability to reconstruct artifact free images under various geometrical
arrangements of detectors of varying sizes, provided that there is complete sampling of the basis functions in the image. In the absence of complete sampling, artifacts are introduced. Since these artifacts must be addressed through an external signal or prior understanding that is dependent of system geometry on a case by case basis, we have not attempted to correct for such artifacts.

Another group has helped advance the field along a similar direction [30]. However, their goal requires further investigation such as the optimization of the framework, particularly the automatic computation of symmetries, choice of subsets, and normalization components. These choices are vital for the framework to be adaptable to a large subset of PET geometries, while simultaneously being able to reconstruct in an efficient manner.

We would like to also note that further improvements to such a framework is possible. Although the framework can model a large variety of existing systems with different crystal size and position, we have not accounted for Time of Flight PET or Depth of Interaction (DOI) detectors. Furthermore, more accurate system matrices could potentially provide better quantification accuracy. In this regard, we have not modeled positron range correction or Point Spread Function (PSF) deblurring. These are left as future improvements to the framework.

A major limitation of the current framework is that it is built for static systems with a fixed system matrix. A research direction that we are currently exploring has movable detectors in a dynamic geometry that can be optimized for the subject of interest.

For the OS-EM algorithm, we have chosen a particular subset selection strategy and the log-cosh prior. The general design of the framework allows for studying other subset strategies and better regularizers. Some of the systems have non-uniform image resolution, and could benefit from a spatially varying prior[72]. Choosing a geometry independent subset strategy and prior is beyond the scope of this study.

The current framework can handle very large system matrices and complicated systems. Although memory usage and computational time is high for accurate image reconstruction, Moore’s law predicts faster systems and lower memory cost in the future. Yet, there are advantages to optimizing the memory usage and convergence rate as a function of computational time. There is scope for further research for geometry independent memory/speed
optimization. Other groups have shown progress in these areas, which can be potentially included in our framework. For instance, our approach of reducing the memory requirement is an extension of the existing approach of manual symmetry computation. This is a lossless form of compression. More gains in memory can be made designing a lossy compression scheme, capable of trading of accuracy for memory usage [94]. With respect to computational speed, range-domain decomposition methods[51] and optimization transfer[2, 42] could be potentially explored.

Currently, a significant amount of work has been done by other groups to port reconstruction codes written for x86 architecture to highly parallel Graphic Processor Units (GPU) with simple cores. The approach is justified in the projection process in reconstruction performs the same instructions on multiple data simultaneously. Adapting x86 code to GPU requires simplification and sectioning of the system matrix. In order to maintain the accuracy of the reconstruction, they are not pursued in this work. More importantly, future computing architectures such as the Intel Many Integrated Core (MIC) combines the highly parallel nature of GPUs with the ability to run x86 code. Also, toolkits that convert generic C/C++ code to run on GPU architectures already exist.

5.6 Conclusion

We have developed an accurate image reconstruction framework for four dimensional coincidence data acquired from unconventional positron emission tomography systems. We are focused on designing optimal application-specific PET systems. The reconstruction framework helps validate our hypothesis relating to different application areas, as well as optimize the design of the systems.

Although traditional reconstruction has focused on ring systems and processing data using sinograms, we have moved away from the approach. We have generalized some of the traditional concepts in PET reconstruction to model systems of arbitrary geometry, with crystals of different sizes and materials. Lines of Response between different types of crystals which were treated differently in previous works are approached through the same mechanism.
Modeling of unknown components that are to be estimated using the normalization procedure is made trivial given an understanding of the unknown variables and the lines of response that they affect.
References


[64] Eric L Rosen, Timothy G Turkington, Mary Scott Soo, Jay a Baker, and R Edward Coleman. Detection of primary breast carcinoma with a dedicated, large-field-of-view


Appendix A

Poisson Statistics

A.1 Poisson distribution as an approximation of the Binomial distribution

Acquired coincidence data from a PET scanner is often assumed to be Poisson distributed. A random variable, $Y$, is Poisson distributed if it can take values, $k = 0, 1, 2, \ldots$, with probabilities,

$$P\{Y = k\} = \frac{e^{-\lambda} \lambda^k}{k!}$$

with $\lambda \geq 0$.

Poisson distribution is an approximation of the distribution of measured counts in a time interval when the events arrives with a constant rate, $\lambda$. When the time interval is split into $n$ equally spaced time sub-intervals, the mean rate of event arrival is $\frac{\lambda}{n}$. For each sub-interval, the probability that an event arrives is distributed as a Bernoulli distribution, with parameters $n$ and $\frac{\lambda}{n}$. Then, total number of events over the whole interval is Binomial with parameters, $n$ and $p = \frac{\lambda}{n}$. However, as $n \to \infty$ and $p \ll 0.5$, the Binomial distribution is approximated as a Poisson distribution with parameter, $\lambda$. 

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\[
\lambda = np
\]
\[
P\{Y = k\} = \binom{N}{k} p^k (1 - p)^{(n-k)} = \frac{n(n-1)(n-2)(n-k+1)}{k!} \left(\frac{\lambda}{n}\right)^k \left(\frac{1 - \lambda}{n}\right)^{n-k}
\]
\[
= \left(\frac{\lambda^k}{k!}\right) \left(1 - \frac{\lambda}{n}\right)^n \times \frac{n(n-1)(n-2)(n-k+1)}{n^k} \times \left(\frac{n}{n-\lambda}\right)^k
\]
\[
\approx \left(\frac{\lambda^k}{k!}\right) \left(1 - \frac{\lambda}{n}\right)^n, \text{ if } k \text{ is small relative to } n
\]
\[
\approx \left(\frac{\lambda^k}{k!}\right) e^{-\lambda}, \text{ if } n \text{ is large}
\]

In an experiment involving radionuclide decay, the assumptions are not entirely true. Over the course of an experiment, the total activity decays exponentially. However, for the purpose of reconstruction, we assume that the event rate is a constant.

### A.2 Experimental validation

To experimentally validate the Poisson assumption, we count the number of occurrences of events in multiple disjoint intervals for different mean rates.

The pseudo-code to generate the histogram plots to validate the Poisson statistics is shown in Algorithm 5. Data acquired from a PET scanner in list-mode format is fed into the algorithm. The `num_intervals` denote the number of disjoint time intervals to split the list-mode stream. The algorithm estimates the mean counts in each LOR as the total counts divided by the number of intervals. A histogram is generated for distribution of counts in each sub-interval for a fixed mean rate, across all intervals and LORs.

Five hours of data was acquired with a known Ge-68 phantom of 320 cm$^3$ with total 0.1332 mCi (4.625 uCi/cm$^3$) on the Plant PET imaging system. The total counts for each coincidence Line Of Response (LOR) was calculated. The five hour data was split into 16 independent data streams of 18.75 minutes each. The total counts for each LOR over five hours was divided by 16 to obtain an estimate of the mean event rate for 18.75 time window. The histogram of actual counts in each of the 16 data streams for each mean event rate over all LORs were tabulated. For the experiment, the number of LORs with counts over 100
Data: list_mode_stream, num_intervals
Result: Histogram

initialization;
\[ H = \text{zeros}(\text{max} \_\text{counts}, \text{max} \_\text{counts}) ; \]
for entry \( \in \text{list} \_\text{mode} \_\text{stream} \) do
  \[ \text{TotalCounts}[\text{LOR}(\text{entry})] + = 1; \]
end

for interval \( \in \{1, 2, \ldots, \text{num} \_\text{intervals}\} \) do
  \[ \text{CountsPerInterval} = \text{zeros}(\text{num} \_\text{lors}); \]
  for entry \( \in \text{list} \_\text{mode} \_\text{stream}[\text{interval}] \) do
    \[ \text{CountsPerInterval}[\text{LOR}(\text{entry})] + = 1; \]
  end
  for each LOR do
    \[ \text{Histogram}[\text{TotalCounts}[\text{LOR}], \text{CountsPerInterval}[\text{LOR}]] + = 1; \]
  end
end

for totalcount \( \in \{0, 1, \ldots, \text{max} \_\text{counts}\} \) do
  \[ \text{cumulativecount}[\text{totalcount}] = \text{zeros}(\text{num} \_\text{lors}); \]
  for countperinterval \( \in \{0, 1, \ldots, \text{max} \_\text{counts}\} \) do
    \[ \text{cumulativecount}[\text{totalcount}] + = \text{Histogram}[\text{totalcount}, \text{countperinterval}]; \]
  end
  for countperinterval \( \in \{0, 1, \ldots, \text{max} \_\text{counts}\} \) do
    \[ \text{Histogram}[\text{totalcount}, \text{countperinterval}] / = \text{cumulativecount}[\text{totalcount}]; \]
  end
end

Algorithm 5: Algorithm to validate Poisson statistics

over five hours were zero. Therefore, this test is valid only up to a mean rate of 6.25 for 18.75 minute time interval.

The histogram plot of the experimental results are shown in Figure A.1 with a dot marker. For each mean rate, the histogram of time intervals with experimentally measured count is plotted. The plot was normalized for each mean rate to sum to one. The circular marker indicates the analytically computed value for the Poisson distribution with each mean rate and measured counts.

The analytically computed values of the Poisson distribution matches well with the experimental results for low mean rate. However, for high mean rate, the values are not exactly matched. The mismatch of the analytic and experimental results at high mean rate could be attributed to the fact that we are no longer operating in a Poisson regime, when time of acquisition is short in relation to the high mean rate. The activity concentration for this
study was several times the activity concentration in a regular PET study. Therefore, for typical PET studies, the event rate can be assumed to be Poisson distributed.
Appendix B

Expectation-Maximization Algorithm

The EM method[21, 85] is an iterative method to estimate an unknown parameter, \( \phi \), given measurements \( Y \). The algorithm solves the classic Maximum Likelihood problem,

\[
\phi_{ML} = \arg \max_{\phi} \ g(Y|\phi)
\]

where \( g(Y|\phi) \) corresponds to sampling density of getting \( Y \) given knowledge of \( \phi \).

In the EM formulation, the measurements \( Y \) are 'incomplete'. Incomplete means either the some data is missing, corrupted, or blurred. Often, there is an underlying complete data space \( X \), which is not directly observed, but encodes all the information coming from \( \phi \) and flowing into \( Y \). Therefore, \( \phi \rightarrow X \rightarrow Y \) form a Markov chain.

The dependence of the complete data on the unknown parameter is encoded by the sampling density, \( f(X|\phi) \). The relationship between \( X \) and \( Y \) is \( g(Y|\phi) = \int_{X(Y)} f(X|\phi)d\phi \).

The EM algorithm starts with an initial guess. In the Expectation step, it finds the distribution of the unobserved variables given the observed data and the current estimate of the parameters. In the Maximization step, the parameters are re-evaluated based on the assumption that the distribution of unobserved variables found in the Expectation step is correct. In the Maximization step, the observed data is assumed to be not known.

The generalized EM algorithm is

1. Expectation: Compute \( Q(\phi|\phi^p) = E(\log f(X|\phi)|Y, \phi) \).
2. Maximization: Choose \( \phi^{p+1} = \arg \max_{\phi} Q(\phi|\phi^p) \).

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In the generalized version of the algorithm, the Maximization step need not find the true maximum, but only seeks to improve the value of the function.

For exponential families given by \( f(X|\phi) = b(X) \exp(\phi t(X)^T)/a(\phi) \), the EM algorithm is written as

1. Expectation: \( t^{(p)} = E(t(X)|Y, \phi) \).
2. Maximization: \( \phi^{p+1} : E(t(X)|\phi) = t^{(p)} \).

The sufficient statistic is denoted by \( t(X) \).

**B.1 Expectation-Maximization for Poisson distributions**

In a PET system, the measurements, \( Y \), correspond to measurements on Lines of Response. The unknown parameter, \( \phi \), that is to be estimated is the spatial radionuclide activity concentration. The measurements are independent, and Poisson distributed. For this analysis, we index the measurements by \( j \) and the image space by \( i \).

\[
Pr(Y = y|\phi) = \prod_j \frac{e^{-\left(\sum_i h(y_j|\phi_i) \times \phi_i + r_j + s_j\right)} \times \left(\sum_i h(y_j|\phi_i) \times \phi_i + r_j + s_j\right)^{y_j}}{y_j!} \tag{B.1}
\]

where \( r_j \) denotes random events and \( s_j \) denotes scatter events. Therefore, the log-likelihood of \( Y \), given a full measurement, \( X \), is

\[
L(\phi|Y) = \sum_j y_j \times \log \left( \sum_i h(y_j|\phi_i) \times \phi_i + r_j + s_j \right) - \left( \sum_i h(y_j|\phi_i) \times \phi_i + r_j + s_j \right) - \log(y_j!) \tag{B.2}
\]

Let \( x_{(i,j)} \) be the number of decays emitted by voxel, \( i \), and detected at measurement LOR, \( j \). The measured data consists of a summation over this space, with some decays being never
detected. $X$ denotes the complete data. Neglecting the effect of random events and scatter as additive bias, the number of decays in each voxel, measured at an LOR, is Poisson with mean equal to $h(y_j|\phi_i) \times \phi_i$. Therefore, the likelihood of the complete data, $x_{(i,j)}$, is

$$L(\phi_j|x_{(i,j)}) = \sum_{(i,j)} x_{(i,j)} \times \log (h(y_j|\phi_i) \times \phi_i) - (h(y_j|\phi_i) \times \phi_i) - \log(x_{(i,j)}!) \quad (B.3)$$

The sufficient statistic for Poisson data is the data itself. Since the Poisson distribution is in the exponential family, we apply the EM algorithm as,

**Expectation:** $t^{(p)} = E(t(X)|Y, \phi)$.

$$x_{(i,j)}^{(p+1)} = E(x_{(i,j)}|Y, \phi^p) = E(x_{(i,j)}|\sum_i x_{(i,j)} = y_j, \phi^p) = \frac{y_j \times h(y_j|\phi_i) \times \phi_i^p}{\sum_i h(y_j|\phi_i) \times \phi_i^p} \quad (B.4)$$

**Maximization:** $\phi^{p+1} : E(t(X)|\phi) = t^{(p)}$.

$$\frac{\partial L(\phi_i|x_{(i,j)})}{\partial \phi_i} = \sum_j \frac{x_{(i,j)}}{\phi_i} - h(y_j|\phi_i) = 0 \quad (B.5)$$

$$\phi^{p+1} = \frac{\sum_j x_{(i,j)}}{\sum_j h(y_j|\phi_i)}$$

The complete EM algorithm is written as,

$$\phi^{p+1} = \frac{\phi_i^p}{\sum_j h(y_j|\phi_i)} \sum_j \frac{h(y_j|\phi_i) \times y_j}{\sum_i h(y_j|\phi_i) \times \phi_i^p} \quad (B.6)$$
B.2 The Expectation-Maximization as an Alternating-Minimization algorithm

A different view of the EM algorithm is as a specific case of the Alternating-Minimization (AM) algorithm. Unlike the EM algorithm, the AM algorithm seeks to minimize the cost term in both steps. In this version of the algorithm, we do not assume a Poisson noise model. Rather, a specific distance measure, the Kullback-Liebler Divergence is used. This geometric interpretation of the EM algorithm was proposed by Csiszar and Tusnady [18].

For any convex set of measures, \( P \) and \( Q \), with the Kullback-Leibler information divergence, \( \mathcal{I}(P \parallel Q) \), the AM algorithm is defined as :

1. \( P^{(n+1)} = \arg\min_{P \in P} \mathcal{I}(P \parallel Q^n) \)
2. \( Q^{(n+1)} = \arg\min_{Q \in Q} \mathcal{I}(P^{(n+1)} \parallel Q) \)

B.3 Maximizing Likelihood is the same as minimizing \( \mathcal{I} \)-Divergence

The equation for generalized \( \mathcal{I} \)-Divergence between two families, \( P \) and \( Q \) is

\[
\mathcal{I}(P \parallel Q) = \sum_i p_i \log\left(\frac{p_i}{q_i}\right) - p_i + q_i
\]

As before, the log-likelihood equation is

\[
L(\phi|Y) = \sum_j y_j \times \log \left( \sum_i h(y_j|\phi_i) \times \phi_i + r_j + s_j \right) - \left( \sum_i h(y_j|\phi_i) \times \phi_i + r_j + s_j \right) - \log(y_j!)
\]

Maximizing the log-likelihood equation is equivalent to minimizing the I-Divergence between the measured data and mean projection of the image into the data space.
\[
\min_{\phi} I(y \mid \sum_i h(y_i \mid \phi_i) \times \phi_i + r + s) \\
= \min_{\phi} \sum_j -y_j \times \log \left( \sum_i h(y_j \mid \phi_i) \times \phi_i + r_j + s_j \right) + y_j \log y_j - y_j + \left( \sum_i h(y_j \mid \phi_i) \times \phi_i + r_j + s_j \right) \\
= \max_{\phi} \sum_j y_j \times \log \left( \sum_i h(y_j \mid \phi_i) \times \phi_i + r_j + s_j \right) - \left( \sum_i h(y_j \mid \phi_i) \times \phi_i + r_j + s_j \right) - \log(y_j!) \\
= \max_{\phi} L(\phi \mid Y) \\
\]
Vita
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Degrees
Ph.D. Electrical Engineering, Dec 2014
M.S. Electrical Engineering, May 2013
B.Tech., Electronics and Communication Engineering, June 2006

Professional Societies
Institute of Electrical and Electronic Engineers

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Graduate certification in Imaging Sciences and Engineering, May 2013
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Courses

Skills
Programming C, C++, Java, VHDL, SQL, Latex
Parallel OpenMP, MPI, GPU (CUDA)
Scripting Perl, Python, BASH (Unix)
Simulation MATLAB(+Simulink), Mathematica, ROOT, GATE, GEANT
GUI Development Visual Studio, Netbeans Platform, FLTK
Electronics Analog and Digital Electronics, Microcontrollers, PCB Layout
Other Soldering, Milling, CNC, CAD tools
Employment


Research Asst. 2007–2009

Graduate Technical Asst. 2006–2007, Taught MATLAB, VHDL and C/C++ Laboratory, Coordinating IEEE Distinguished Lecture Program, IEEE Robotics fest, System Administrator and Lab Instructor in Advanced Resources Laboratory and Systems Laboratory, Acted as Instructor and guide for IEEE student branch executive committee and web team.

Extracurricular Activities

Executive Committee BioEntrepreneurship Core, 2013-2014
Treasurer BioEntrepreneurship Core, 2012-2013
Vice President International career development and networking association, 2010-2011
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Vice President Umang, Indian graduate students association, 2008-2009

Conference Publications


Journal Publications


December 2014