PRELIMINARY EVALUATION OF X-RAY FLUORESCENCE IMAGING AND ULTRA-HIGH RESOLUTION CDTE PET: THE PROGRESSION TOWARD BROADER SPECTRUM MULTI-MODALITY TOOLS FOR SMALL ANIMAL NEUROSCIENTIFIC INVESTIGATION

BY

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THESIS

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ABSTRACT

The United States Food and Drug Administration (FDA) describes the development of medications to be a five step process which entails three direct steps located in the laboratory environment. These laboratory investigations include exploring the fundamental mechanisms governing the disease of interest as well as testing any drugs in the preclinical environment for a preliminary assessment of the potential impact of humans. The maximum preliminary assessment potential is in part constrained by the instruments available for exploring the small animals, generally mice, involved in the experiments. Nuclear instruments such X-ray, Positron Emission Tomography (PET), and Single Photon Emission Computed Tomography (SPECT) are often implemented due to their ability to identify either the anatomical or physical features of interest. In this thesis, two state of the art nuclear modalities, X-Ray Fluorescence Emission Tomography (XFET) and CdTe Hybrid Pixel-Waveform (HPWF) PET, are evaluated as potentially complementary experimental preclinical instruments due to their combined ability to reveal biological information through the utilization of a broader portion of the electromagnetic spectrum with discussion directly focused on neurological applications.

The two independent experimental systems were evaluated for proof of concept in order to establish the potential viability of imaging small transgenic animals. The first modality, a benchtop XFET system, used an incident monochromatic 17.4 keV beam with a slit mounted Andor Ikon-L Charge Coupled Device (CCD) with a featured pixelated element size of 13.5 µm x 13.5 µm. Samples for the XFET system were mounted on a 4-D stage capable of X-Y-Z translation with full rotation. Fluorescent emissions were measured from a triple tube capillary phantom composed of various chemical compositions in addition to a resin encased osmium stained zebrafish. Spectral results and imaging results are presented.

The second modality was explored with an intent to better understand the maximum achievable spatial resolution. A dual HWPF detector coincidence system composed of CdTe energy resolvable photon counting (ERPC) detectors was implemented with a field programmable gate array (FPGA) modifiable readout sequence of an 8 application specific integrated circuit (ASIC) layout per detector. Each ASIC
featured 64 x 32 pixelated elements of size 350 \(\mu\text{m} \times 350 \mu\text{m}\) bump bonded to the under size of a 2 mm thick CdTe crystal with an area of 11 mm x 22 mm. The unique readout scheme of the HPWF detector design uses an external digitizer sampling at 200 Ms/s to save the cathode waveform and the anode waveform for each individual event for post processing. Experiments were performed using (A) a 10 \(\mu\text{Ci}\) Na-22 source with a diameter of 250 \(\mu\text{m}\), and (B) a set of 3 microcapillary tubes with sub 1 mm inner diameter.

Keywords: XFET, CdTe, PET, Hybrid Pixel-Waveform, Energy Resolvable Photon Counting Detectors, Imaging, Transgenic Animals
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CHAPTER 1. INTRODUCTION

The present mentality for broad spectrum nuclear imaging explores the integration of modalities such as PET and SPECT with magnetic resonance imaging (MRI). Substantial effort has been put into the integration due to the desire to obtain the high soft tissue contrast achievable with MRI with the functional imaging provided by PET and SPECT [1-3]. These efforts assist in the link between a function and anatomy. However, this integration serves only to provide a topical insight into any biology in question. This current state of the art correlates biological function to anatomical position rather than exploring the elements which could explain a function. Therefore, further efforts should explore the integration of modalities which can identify the fundamental function to the elements which govern the function. In this capacity, X-ray fluorescence (XRF), and PET or SPECT could serve as an ideal integration. This work describes the potential contributions each modality could provide to small animal neurological imaging while establishing the proof of concept for each individual instrument.

1.1 Trace Metal Identification Using X-ray Fluorescence

Naturally occurring metal ions are well known to be critical in both disease, and physiological function [4-7]. The degree of our understanding would benefit greatly from imaging methods that could provide high resolution mapping of select metals in biological tissue. Efforts in imaging trace metals initially required the use of high flux source such as those only attainable at synchrotron facilities. Synchrotron-based X-ray fluorescence computed tomography (XFCT) typically employs a pencil beam of highly intense and monochromatic X-ray beam to illuminate the object. Among other interactions, the incident X-rays undergo photoelectric interactions with metal atoms, which will emit characteristic X-rays in response. The characteristic X-rays are collected by a non-spatially capable detector, and, in the absence of significant attenuation, the area of the measured characteristic X-ray peak can be directly related to the line integral through the elemental distribution map. The object is then scanned and rotated through the illumination beam in order to acquire a complete sinogram of line integrals in a first-generation tomographic
acquisition [8-14]. A standard analytic or iterative CT algorithm can then be used for image reconstruction, although in the presence of attenuation, alternative models and methods are needed.

In recent years, several groups have begun to study the potential of developing a benchtop version of XFCT using conventional sources [15], [10], [16]. The initial work has focused largely on organism-scale imaging of metal-based nanoparticles at multi-millimeter resolutions. Most of these approaches also use a variation of the first-generation CT geometry, with measurement of one line integral at a time. We have been exploring an alternative geometry aimed at achieving 100 μm resolution in ex vivo biological specimens [12], [13]. We call the approach X-ray fluorescence emission tomography (XFET), and it couples apertures typically seen in emission tomography with position-sensitive X-ray imaging spectrometers. It still employs a pencil beam of X-rays to excite the metal atoms in the object, but now the fluorescence X-rays are detected by an imaging detector placed behind a slit aperture. The emissions from a small segment of the illumination line are thus imaged onto a column of the detector, and direct image “reconstruction” is possible without the need for solving an inverse problem.

1.2 Semiconductor Positron Emission Tomography for Small Animal Neurological Imaging

PET and SPECT have served as very successful modalities for functional imaging over last many years. The modalities both utilize nuclear decay but differ due the mechanism of decay. SPECT relies on the use of a single gamma ray emitter and physical collimator to determine the projection path from the object space to the detector. PET exploits the use of the near co-linear annihilation gamma events to determine the projection path from the detector space to the object space, which is referred to as electronic collimation. The fundamental selection of the mean of decay results in the limitation and benefits of both modalities. SPECT, lacking the need for positron decay and thus the challenge of positron range, is identified as a higher spatial resolution modality, and, due to the lack of electronic collimation, is capable of resolving multiple tracers based on the emission energy of the characteristic gamma rays. PET benefits from having a higher sensitivity than SPECT and positron emitters better match the naturally occurring atoms within biology making the created radiotracers more chemically compatible. Currently, there are
many PET tracers developed for neurodegenerative applications, while the development of relevant SPECT tracers remains to be very limited [17-22].

Initial efforts in developing small animal PET were reliant on the use of scintillation detectors due to their good timing ability. However, the basic operation principles of scintillation detectors has limited many commercial small animal imaging systems to above 1 mm [23]. This resolution applied to the brains of mice does not provide adequate spatial resolution for research applications. Efforts have been placed on identifying alternatives to scintillation detectors. This has led to many to explore highly pixelated semiconductor detectors. The challenges of implementing such detectors arise from the material selection used for photoelectric conversion. Works have identified CdTe and CZT as potentially viable options. However, there are still many challenges that need to be addressed within semiconductor devices such as charge trapping, parallax error, timing, and verification of the fundamental spatial resolution of these detectors. This thesis provides a preliminary exploration of the achievable spatial resolution.
2.1 The Appearance of Alzheimer's Disease

In Germany in the early 1900s, a family expressed concern when the wife began to express very odd behavior. At the age of 51 years old, Auguste Deter, wife of Karl Deter, showed significant cognitive impairment. She experienced loss of memory, delusions, sleeping difficulty, and would at times wake her husband in the middle of the night screaming [24]. Given the lack of neurological understanding at the time, Karl Deter admitted his wife to the Institute for the Mentally Ill and Epileptics in Frankfurt Germany in 1901 where the family met Dr. Alois Alzheimer. Dr. Alois Alzheimer had recently begun working very intensely in the hospital to cope with the death of his wife who had left him with their three children behind [25].

The time shared between Dr. Alzheimer and Auguste Deter was brief. However his analysis quickly identified that she had a disease of forgetfulness. Notes rediscovered in showed that he would ask a series of questions in the morning only to return later that day to find Mrs. Deter completely nonsensical [25]. Her condition greatly interested Dr. Alzheimer to such a great extent that even after the doctor left the institute in 1902, he asked that he would be informed of her fate. By 1906, he was informed that she had completely succumbed to dementia and had died by April of that year. Given permission by the family, an autopsy was performed on Auguste. His post autopsy assessment would be the documentation of what has been identified to as the beta-amyloid plaques and neurofibrillary tangles [26].

After presenting his finding to his fellow scientists, Dr. Emil Kraeplin, a coworker and a very prominent psychiatrist in Germany, urged Alzheimer to present his work at the next conference that same year. While the conference committee did not dedicate much text space of to the work, the disease began to garner momentum as more cases quickly followed. The disease remained essentially nameless until the 8th version of Dr. Emil Kraeplin’s textbook was published in 1910 were he acknowledged the importance Dr. Alois Alzheimer’s discovery by publishing the history of Auguste Deter and proposing the name
“Alzheimer’s Disease [26].” Fig. 1 shows Auguste Deter, Dr. Alois Alzheimer, and Dr. Emil Kraeplin. Alzheimer’s disease is now identified as a leading causes of death in the U.S. and has been identified as one of the fastest growing causes of death as there has been an a 71% increase in the percentage change for U.S causes of death from 2000 to 2013 [27]. HIV, heart disease, and stroke have dropped by 52%, 23%, and 14% in the same time frame [27].

![Figure 1](A) Patient Auguste Deter prior to her death in 1906. (B) The famed Dr. Alois Alzheimer. (C) The man who named the discovery as “Alzheimer’s Disease,” Dr. Emil Kraeplin.

### 2.2 Physiological Changes and Metal Ions in Alzheimer’s Disease

After one hundred years of research, Alzheimer’s disease (AD) has yet to be to be cured but significant research has been placed into understanding the governing components. The discussion of AD always covers two major physiological changes: senile plaque formation and neurofibrillary tangle formation. These formations have been identified to be influenced, to some degree, by the concentration of certain metal ions. The potential link of senile plaques and neurofibrillary tangles to metal ions creates an opportunity for the proposed broader spectrum multi-modality. The PET component can and has been capable of imaging the physiological onset of the plaques and tangles but the metal ion concentrations have never been assessed simultaneously in a living subject. The development of an XFET system could provide
this opportunity and the integration of PET and XFET could provide some clarification as to exact role and concentration level metal ions play in vivo. A brief introduction is provided to explain what is currently understood about AD.

The initial indicators of AD are often seen on the behavioral level. Individuals afflicted with AD often exhibit issues with memory, uncertainty of time and place, and agitation in some cases. The numerous post mortem studies performed on symptomatic patients has readily identified the formation of plaque like depositions throughout the grey matter of the brain. These senile plaques have long since been identified as a characteristic physiological marker of AD. The impact of these plaques is assumed negative but there still exists much uncertainty as to the exact role they have.

Senile plaques are the aggregation of a misfolded protein known as β-amyloid (Aβ). To better understand Aβ, researchers have attempted to develop models for the governing formation mechanisms. These models currently point to the transmembrane protein named Amyloid Precursor Protein (APP). Being a transmembrane protein, a portion of the protein exists both within the intracellular environment and in the extracellular environment. APP must be acted upon through enzymatic cleavage to be freed from the cell membrane. Research into the enzymes which execute the cleavage has shown that APP can undergo two different post cleavage pathways as shown in Fig. 2 [28].

APP has three specific cleavage sights and therefore has three cleavage enzymes known as α-secretase, β-secretase, and γ-secretase. Each cleavage enzyme is responsible for specific sight on APP but the initial enzymatic cleavage is critical to the pathway which APP undergoes. When α-secretase acts upon APP, a portion of the protein is freed from the membrane. This protein is named sAPPα and, even if it is not fully understood, is generally assumed to have a positive impact on neuronal growth [28]. This pathway does not produce the aggregation of Aβ resulting in senile plaques. When β-secretase acts instead of α-secretase, the pathway associated with AD is initiated. First, β-secretase cleaves APP and produces sAPPβ in the extracellular environment. Second, γ-secretase cleaves APP’s mid membrane site which frees the Aβ protein chain from the cellular membrane. Now Aβ floats freely in the extracellular fluid with the potential
to aggregate with the process driven by the levels of metal ions such as Cu$^{2+}$, Fe$^{2+}$, and Zn$^{2+}$ [29]. The aggregated form results in plaques which bind to the grey matter of brain tissue.

**Figure 2**: The two pathways for cleaved APP. In the event, that $\alpha$-secretase cleaves the transmembrane protein, plaque formation is currently believed not to be possible. If the other pathway is initiated by the cleaving performed by $\beta$-secretase, and $\gamma$-secretase, then senile plaque formation may occur in the extracellular environment [28].

Fig. 3 shows the general regions of plaque deposition throughout the brain in the three separate stages. Stage A shows low levels of Aβ beginning to form deposits on the neocortical regions of cerebral cortex. The frontal, temporal, and occipital lobe are all potential targets for deposition. The hippocampal formation remains unaffiliated in this initial stage. Stage B shows an increase in aggression of aggregate formation. The majority of neocortex begins to observe medium density Aβ deposits. The only regions of the neocortex which may remain free include sensory and motor sections. Hippocampal formation begins
to observe deposition in the CA1 of the startum. By State C, the neocortex is fully afflicted. The hippocampal formation does not show a significant increase in the number of $A\beta$ [30].

Figure 3: The above shows the 3 stage $A\beta$ onset identified by H. Braak et al. It should be understood that the majority of $A\beta$ aggregation falls upon the neocortical regions of the brain [30].

During the onset of senile plaque formation, an equally important physiological phenomenon is observed. Originally discussed as neurofibrillary tangles (NFTs), NFTs are now understood to be the product of tau proteins and cellular microtubules. Microtubules exist within the cytoplasm of cells and are critical to the cellular function such as mitosis, cell movement, and genetic regulation. Microtubules are stabilized by tau proteins. When AD sets in, the tau proteins become hyperphosphorylated and this results in the destabilization of the microtubule pathways. Tau proteins begin to aggregate causing microtubules to form tangles. Some very early studies hinted at the role of aluminum in tau aggregation but questions still remain regarding the metal’s role [31-33]. In Fig. 4, the onset of NFTs is shown in a three stage onset similar to that of $A\beta$. Unlike $A\beta$, the onset of NFTs does not show equally aggressive onset in the neocortex. Instead, the entorhinal cortex show the initial development of NFTs. This initial region is critical in the
formation of memory, and sleep. It serves as an intermediate connection between the neocortex and the hippocampal formation. The formation of NFTs by the intermediate stage becomes increasingly dense in the entorhinal cortex with some spread toward the neocortex. By late stages, the neocortex shows medium density NFT presence, and high density NFTs in the entorhinal region.

**Figure 4:** From the same publication from H. Braak, NFTs were study and represented in a three stage process. Unlike Aβ, the NFT formation seems to heavily favor the entorhinal cortex until later stages of the disease [30].

### 2.3 The Transgenic Mouse Model and In Vivo Imaging

The birth of non-human small animal experimental subjects was supplied with early interest in understanding deoxyribonucleic acid (DNA) repair mechanism. The exploitation of Non-Homologous End Joining (NHEJ) and the Homologous Recombination (HR) showed great potential for the first attempts at manipulating genes. With various models proposed for HR (the Holliday model, and the Meselson-Radding model), it was not until 1981, when the double strand break model was proposed, that HR began to be considered for transgenic animal generation. Work by many individuals, specifically M. Cappachi, began
the exploration of incorporating genetic material into the embryonic stem cells of animals by HR. This simultaneously showed that genome editing was possible, and that animals could be manipulated to exhibit human disease.

**TABLE 1:** Comparative list of AD based Mouse Models and the Phenotype Timeline

<table>
<thead>
<tr>
<th>Mouse Model - Tg2576</th>
<th>Phenotype Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synonyms:</strong> Tg2576, APP-Swe, APP</td>
<td><strong>Beta-Amyloid:</strong> Numerous parenchymal Aβ plaques by 11-13 months</td>
</tr>
<tr>
<td><strong>Species:</strong> Mouse</td>
<td><strong>Tangles:</strong> Absent of tangles</td>
</tr>
<tr>
<td><strong>Mutations:</strong> APP-KM670/671NL, MAPT-P301L, PSEN1 M146V</td>
<td></td>
</tr>
<tr>
<td><strong>Modification:</strong> APP: Transgenic, PSEN1: Transgenic, MAPT: Transgenic</td>
<td></td>
</tr>
<tr>
<td><strong>Disease Relevance:</strong> Alzheimer’s Disease</td>
<td></td>
</tr>
<tr>
<td><strong>Strain Name:</strong> B6;129-Swe Tg(APPswe, tauP301L)1Jfo/Mmjax</td>
<td></td>
</tr>
<tr>
<td><strong>Genetic Background:</strong> 129X1/SvJ x 129X1/SvJ F1</td>
<td></td>
</tr>
<tr>
<td><strong>Availability:</strong> Jackson Laboratory, available through the Jackson Laboratory #04830; Live</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mouse Model – 3xTg</th>
<th>Phenotype Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synonyms:</strong> 3xTg-AD, The LaFerla mouse</td>
<td><strong>Beta-Amyloid:</strong> Extracellular Aβ by 6 months in the frontal cortex, predominately layers 4 and 5 and progress with age</td>
</tr>
<tr>
<td><strong>Species:</strong> Mouse</td>
<td><strong>Tangles:</strong> By 12 months extensive tau immunoreactivity in CA1 neurons of the hippocampus, particularly pyramidal neurons, later in the cortex. No tau pathology at 6 months.</td>
</tr>
<tr>
<td><strong>Mutations:</strong> APP-KM670/671NL, MAPT-P301L, PSEN1 M146V</td>
<td></td>
</tr>
<tr>
<td><strong>Modification:</strong> APP: Transgenic, PSEN1: Transgenic, MAPT: Transgenic</td>
<td></td>
</tr>
<tr>
<td><strong>Disease Relevance:</strong> Alzheimer’s Disease</td>
<td></td>
</tr>
<tr>
<td><strong>Strain Name:</strong> B6;129-Swe Tg(APPswe, tauP301L)1Jfo/Mmjax</td>
<td></td>
</tr>
<tr>
<td><strong>Genetic Background:</strong> 129X1/SvJ x 129X1/SvJ F1</td>
<td></td>
</tr>
<tr>
<td><strong>Availability:</strong> Jackson Laboratory, available through the Jackson Laboratory #04830; Live</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mouse Model – APPPS1</th>
<th>Phenotype Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synonyms:</strong> APPPS1-S1</td>
<td><strong>Beta-Amyloid:</strong> Aβ deposition arriving at 6 weeks of age in the cortex and by 3-4 months of age in the hippocampus.</td>
</tr>
<tr>
<td><strong>Species:</strong> Mouse</td>
<td><strong>Tangles:</strong> Phosphorylated tau-positive neuritic plaques localized in regions with plaques</td>
</tr>
<tr>
<td><strong>Mutations:</strong> APP-KM670/671NL, PSEN1 L166P</td>
<td></td>
</tr>
<tr>
<td><strong>Modification:</strong> APP: Transgenic, PSEN1: Transgenic</td>
<td></td>
</tr>
<tr>
<td><strong>Disease Relevance:</strong> Alzheimer’s Disease</td>
<td></td>
</tr>
<tr>
<td><strong>Strain Name:</strong> B6-Tg(Thy1 APPswe; Thy1 PS1 L166P)</td>
<td></td>
</tr>
<tr>
<td><strong>Genetic Background:</strong> C57BL/6J</td>
<td></td>
</tr>
<tr>
<td><strong>Availability:</strong> Available through Matthias Jucker.</td>
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</tbody>
</table>

With an understanding in hand of the neuropathology and genetic manipulation slowly emerging, the necessity for high resolution in vivo imaging became ever present. Toward the late 1900s, three key modalities saw rise for non-invasive imaging for preclinical and clinical investigation: MRI, SPECT and PET. MRI was hailed for its non-ionizing imaging capability but criticized for its low sensitivity. SPECT and PET varied between high resolution and high sensitivity but generally not ideally selected due to the presence of radiation. However, it was PET that eventually became the prominent imaging modality for AD mouse models due the development of the Pittsburg Compound B radio-imaging radiotracer in 2004 which showed high affinity binding for amyloid plaques [20]. The imaging method was only limited by the
spatial resolution of scintillation crystals being around 1.4 mm. The poor resolution coupled with the size of a mouse brain (~10 mm) resulted in need for further improvements in imaging technology.

Since then, many new models have been developed through the genetic manipulation of small animals. Table I shows three common models now used for nuclear AD imaging studies (Tg2576, 3xTg, and APP/PS1). These models have been highly studied, specifically the promising APP/PS1 model for viability [34]. The phenotype should be noted for each different model because the latency in phenotype onset as well as the degree of the model’s completeness are markers of the model’s quality. For example, the APP/PS1 model requires 6 weeks for plaque formation to be present in the cortex and 6 months for plaque to be seen in the hippocampus. The Tg2576 model requires 11-13 months for plaques to be seen in the brain at all.
CHAPTER 3. GOVERNING PHYSICS IN IMAGING

3.1 X-ray Fluorescence: Photoelectric Absorption, Discrete Orbital Transitions, and Emission Edges

It is possible to force atomic radiation through the use of an external source rather than relying solely on the natural decay of a radioisotope. Using an external source, the incoming radiation can cause the excitation or ionization of a selected material. Electrons orbiting the nucleus of atom exist within discretized shells named K, L, M and N with K being closest to the atom’s nucleus and N being the furthest. It is necessary to create a vacancy within the orbital such that a higher level electron falls to replace the emitted photoelectron. This is possible when photoelectric absorption occurs with an incident energy which exceeds the electron binding energy as shown on the left in Fig. 5. Photoelectric absorption is defined in Equation 1 as,

\[ E_{e^-} = hf - \phi \]  

where \( E_{e^-} \) is the kinetic energy of the photoelectron, \( h \) is Planck’s constant, \( f \) is the frequency of the incident photon and \( \phi \) is the electron binding energy.

When the emitted photoelectron escapes, the vacancy leaves behind a non-preferred energy configuration. Therefore, an electron from a higher orbital falls to replace the vacancy to achieve a stable energy configuration. This transition requires that energy be emitted in the form of an electromagnetic wave. As the orbital shells in an atom have strict configurations, the emission is a discrete characteristic energy for that atom. Therefore, it is possible to force atoms to fluoresce, and identify the atom based on its characteristic emission.

Given multiple orbitals exist within the construct of the atom, it is possible to detect multiple different characteristic emissions based on the allowed shell transitions for a single atom. The probability of interaction, as shown for cortical bone in Figure 5, generally drops as a function of energy but there are spikes in the attenuation curve which are indicative of a sharp increase in the photoelectric absorption for a certain shell of the atom which is called the edge of that shell. This absorption increase is observed at the
X-ray energy just above the level of energy required to cause the excitation of the orbital’s electron. If specific energy of emission is desired, it is best to have an incident source slightly above the edge’s energy.

Figure 5: (LEFT) The Rutherford-Bohr model of the atom representing the discrete nature of electron transitions as a result of photoelectric absorption. (RIGHT) Mass attenuation plot for cortical bone. Two edges can be observed in the plot [35, 36].

3.2 Positron Emission and Annihilation

PET experiments which are carried out require the injection of radioactive substance into the animal or person of interest. This modality specifically exploits the formation of two near co-linear photons to form a line of response (LOR) from the electronic collimation achieved by the 511 keV annihilation photons. When an atom undergoes positron decay, it undergoes a reaction shown in Equation 2,

\[ {^{22}_{11}}Na \rightarrow {^{22}_{11}}Ne + e^+ + \nu_e \]  

(2)

where Na-22 decays to Ne-22 through the emission of a positron $e^+$ and a neutrino $\nu_e$. The positrons produced have a continuous energy spectrum. As the positron passes through a material, inelastic collisions with electrons cause the positron to lose momentum. Upon achieving near zero momentum, the positron will cause a mass to energy conversion with an electron called annihilation. Two annihilation photons will be formed with any access momentum added as a conserved momentum vector to the newly formed 511
keV gamma rays. The production of these gamma rays is explained by Einstein’s mass-energy equivalence shown in Equation 3,

$$E = m_o c^2$$  

(3)

where $E$ is the equivalent energy of the rest mass defined as $m_o$ and the conversion is performed by the multiplication of the speed of light defined as $c$. The annihilation process is shown in Fig. 6.

**Figure 6:** Positron emission results from an unstable parent nucleus which the number of protons to the neutrons is unfavorable. A proton decays to form a neutrino and positron. The positron propagates until enough energy is lost for annihilation to occur. The annihilation of the positron with an electron produces two near co-linear 511 keV gamma events [37].

Ultimately, the spatial resolution of PET imaging is limited by two physical factors. The positron range and the residual moment transfer cause challenges to the overall imaging resolution of a PET system. First, the emission of a positron with a non-zero energy results in a displacement from the point of decay. Given the non-discrete nature of the energy as well, the resulting image resolution is degraded through blurring. The second challenge arises from the small amount of energy that is passed to the annihilation events. As the direction of the momentum is conserved, the annihilation events are not entirely collinear. In application, there is an increasing offset error caused by the non-collinearity as a function of detector ring diameter. This also can result in poorer spatial resolution and increased noise in the reconstructed image.
3.3 Compton and Rayleigh Scattering

When photoelectric absorption or annihilation do not occur, it is not uncommon to observe a scattering event. Scattering can be classified into two different forms: elastic and inelastic. Elastic scattering observes the conservation of the incident and scattered energy, and is common referred to as Rayleigh scattering. Alternatively, inelastic scattering observes a change between the incident and scattered energy of photon and is referred to as Compton scattering. In this case, some of the energy of incident photon is deposited in a recoil electron. Compton scattering is defined in Equation 4,

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

(4)

with the incident wavelength defined as \(\lambda_i\), the scattered wavelength defined as \(\lambda_f\), the angle of scatter as \(\theta\), \(h\) as Planck’s constant, \(m_o\) as the rest mass of an electron, and \(c\) as the value of the speed of light.

Figure 7: An incident photon may undergo inelastic scattering and deposit a portion of its energy into an orbiting electron. The angle of scattering is directly related to the amount of energy the electron will receive. If enough energy is deposited into the electron, the electron can be freed from its orbital, also causing a vacancy [38].
CHAPTER 4. X-RAY EXPERIMENTAL MATERIALS AND METHODS

4.1 Benchtop X-ray Fluorescence Emission Tomography Experimental Design

A prototype benchtop system was developed (as sketched in Fig. 8) for imaging metal content within biological specimens. The lower plane subsystem was for X-ray fluorescence imaging, while the upper plane subsystem allowed for standard radiography and computed tomography imaging, which provides useful information for alignment and attenuation correction. The sample would have to be translated between planes in order to take advantage of each portion of the experiment setup.

![Figure 8: Sketch of the dual planer experimental design for the XFET system. The sample could be translated vertically between the XRF setup and the CT setup. A monochromatic source used on the lower plane with an Andor CCD positioned at 90 degrees to this beam.](image)

The lower plane XFET subsystem contained the primary analytical X-ray source, an X-ray optical systems (XOS) X-beam, whose X-rays were focused and monochromatized with a doublecurved crystal monochromator and then collimated through a pinhole. This led to a circular pencil beam of X-rays of diameter approximately 100 µm. This source generates a flux of $1.55 \times 10^7$ photons/s/mm of 17.4 keV (Mo K X-rays) photons at a focal distance of 20.4 cm, or $1.2 \times 10^5$ photons/s within the 100 µm circular pencil beam. For XFET data acquisition, we used a commercial X-ray CCD detector, Ikon-L (DO-936 N), from
Andor Technology, Belfast, U.K. [38]. The detector has pixels of size 13.5 µm x 13.5 µm, which leads to a total surface area of 2.76 cm x 2.76 cm. For this measurement, the vertical shift speed was set to 76 µs with a horizontal shift frequency of 1 MHz. Pixel binning was used to optimize spectral performance. A single-slit aperture was placed in front of the Andor CCD detector, as shown in Fig. 9. The slit size was set and measured at 50 µm. The upper plane CT subsystem contains a standard polychromatic X-ray source from Oxford Instruments (Apogee 8000 series), which has a maximum tube potential of 50 kVp and a maximum tube current of 1.0 mA. The detector was a flat panel X-ray detector (Varian 1313 [39]) with pixels 127 µm x 127 µm in size. The detector has a total active area of 13 cm x 13 cm. This detector is placed at 36.23 cm from the rotational sample, and the sample is placed 22.55 cm from the source, which yields a source-to-detector distance of 58.78 cm. The sample holder itself is placed on a 5-dimensional scanning system that is composed of two Newport stages, two Velmex stages, and a Micronix rotational stand. The necessity for a 5-dimensional system is derived from the need to control the CT magnification of the sample, the sample alignment with the CT, the rotational scanning during CT, the line-by-line scanning for fluorescence imaging, the fluorescence imaging magnification, and the sample alignment with the emission aperture of our Andor camera.

![Figure 9: (LEFT) Top down view of the XFET system. (RIGHT) Camera, slit and sample positioning.](image-url)
4.2 Benchtop X-ray Fluorescence Emission Tomography Image Formation

The geometry of XFET image formation is shown schematically in Fig. 10 on the left. The pencil beam stimulates emission of characteristic X-rays as it passes through the object, depicted here as three cylindrical tubes corresponding to the physical test object to be described in the next section. The slit collimator creates a mapping between small segments along the pencil beam and vertical columns of the detector. A typical acquired slit image is shown in Fig. 10 on the right, where it can be observed that only a fraction of the detector is actively used. Summing the detected image vertically (i.e., collapsing over the rows) and reversing the resulting vector allows one to directly estimate the elemental distributions along the illuminated line, without the need to solve a tomographic reconstruction problem. By translating the object horizontally through the illumination beam, a 2D image of the slice can be built up, line by line. Vertical translation can allow for the acquisition of additional slices to create a 3-D image.

Figure 10: (LEFT) Conceptual representation of photons from a triple-tube sample propagating through the slit. (RIGHT) Photons generate the expected flipped projection. Photons are only geometrically limited in the horizontal direction and are free to project anywhere along the vertical direction to produce the slit projection.

The achievable spatial resolution for a given slice will be determined by the illumination beam extent (100 μm spatial resolution as determined by the beam size) in one dimension and by the blurring introduced by the finite slit in the other. Due to the selected small sample size, the highly focused and well-collimated beam changes in beam size across the sample are negligible. The specific geometry of the slit,
camera, and tubes is illustrated in Fig. 10 on the left. The magnified extent of the slit in the beam plane is 62.9 µm.

4.3 Imaging Phantom and Osmium-Stained Zebrafish

This hardware was used to perform two separate experimental studies. The first imaging study involved a simple phantom comprising three capillary tubes filled with solutions: one a 25.0% (w/w) aqueous solution of sodium bromide, one a 25.0% (w/w) aqueous solution of iron (II) sulfate, and the last a 25.1% (w/w) aqueous solution of copper (II) nitrate. Each tube had an inner diameter of 0.798 mm and an outer diameter of 1.092 mm. The second sample was a five-day-postfertilization zebrafish embryo that was sacrificed, fixed, and stained with 1% osmium tetroxide and embedded in the resin Embed-812. The sample had been previously prepared for X-ray histology experiments. The zebrafish was approximately 2 mm in diameter and 14 mm tall. The resin encasement was approximately 3.4 mm in diameter. The experiments were performed with 5000 frames per pencil beam illumination position with 2 s of exposure time per frame, yielding a total of 5 hours per line when including readout time. To form a complete 2D image, the tube was translated linearly through 24 positions separated by 100 µm, and the osmium stained zebrafish was translated through 12 positions separated by 100 µm.

4.4 X-Ray Photon Detection and Algorithm for Single-Photon Counting

The Andor detector employed is not natively a photon-counting detector. To obtain energy information about individual events, we operate in a mode in which frames are read out rapidly enough that only a few isolated events are expected in each frame. This allows identification of individual X-ray events and determination of the deposited energy after careful correction and calibration. In order to obtain an accurate energy response from the CCD detector, we have developed a single-photon counting routine to compensate for several physical factors that could degrade the energy information and to determine the energy deposition from each individual X-ray interaction. Given the small pixel size (13.5 µm x 13.5 µm binned to 27 µm x 27 µm) and the very thin depletion layer (15 µm) of the CCD detector used in this
experiment, X-ray photons interacting in the detector could result in a signal charge being shared by multiple adjacent pixels. In addition, long acquisitions could potentially lead the detector response to change with time or temperature. The implemented single X-ray detection algorithm seeks to determine accurate single photon energy information as follows.

1. 200 dark frames are collected from the CCD.

2. From the 200 background frames, a per-pixel average is calculated along with the average over all CCD pixels.

3. In order to minimize the influence of hot pixels, each per pixel average is compared with the overall CCD mean. The per-pixel average is replaced with the CCD mean if the pixel average falls more than three standard deviations outside of the camera’s noise. The resulting mean is used as the first offset subtraction.

4. A second iteration is performed after the initial offset subtraction. Each pixel in every background frame is reanalyzed. Since the noise of the camera follows a known Gaussian distribution, individual background frames for a given pixel with values that do not adhere to the distribution are not considered for just that pixel for that frame as they have either been influenced by background radiation or are hot (per frame behavior is not considered in the first iteration, only average behavior across all frames). A new true background is recalculated per pixel, and this offset is used.

5. Pixels that are constantly identified to not meet the criteria in the first and second iteration are recorded and have their offset calculated and subtracted to account for the hot behavior.

6. 2-D local maximum searching is performed across each data frame to identify single photon events. The sum over a 3 x 3 region around each maximum is computed.

7. The background is then continuously monitored to ensure no baseline drifting and corrected if so. For each local maximum (a single photon event on the detector surface), this method yields the detector
x-position, the detector y-position, the peak energy value, the summed energy value, and the source frame number.

![Diagram showing photon counting and summed energy values](image)

**Figure 11:** The electrons formed from photoelectric absorption repel each other and force spread to occur which may reach out to adjacent pixels. This charge sharing effect can potentially degrade the overall energy resolution achievable with the CCD. In order to correct for this, a fixed region around the peak around the pixel with the highest energy is summed. This summing results in the capture of the majority of the shared charge. The above figure shows an example of intensity and spread difference from two different photoelectric events.

Fig. 11 shows an example of the single photon events on the detector plane. Plotting the spectra using the summed energy values derived from the single-photon counting algorithm reveals that processing is necessary to improve energy resolution. Fig. 12 shows a scatter plot of the summed energy versus the peak energy divided by the summed energy. It can be seen that as the ratio deviates from 1, which represents full energy deposition into a single pixel, the peak shifts downward. The peak shifting needs to be corrected in order to achieve the ideal horizontal alignment visible in the bottom of Fig. 12. The correction is done by partitioning the x-axis into a selected number of bins. In this case, 20 bins were used, and the copper K-alpha peak was selected as the reference peak for the correction. In each bin, the peak maximum position of the copper K-alpha peak was located through Gaussian fitting along the x-axis. As a result of doing this,
the offset from the unity case is known per bin. Therefore, all ratios can be vertically shifted with respect to the unity ratio to align the spectrum, and ultimately correct for charge-sharing.

**Figure 12:** As charge sharing is a challenge in pixelated detectors, correction need to be implemented to account for the fraction loss of charge. The above show the before after vertical shift correction performed to correct to the expected peak charge to summed charged ratio of 1.
CHAPTER 5. PET EXPERIMENTAL MATERIALS AND METHODS

5.1 PET Cathode Waveforms

When energy is deposited within the CdTe detector crystal, electron-holes pairs are produced. In the presence of an electric field, the electrons and holes drift either toward or away from the cathode depending on polarity of bias. When charge moves in an electric field, the displacement of charge results in the formation of a waveform signal on the cathode. Given that both holes and electrons are influenced by the field, multiple components can be measured on the cathode as shown in Fig. 13. It is understood that this waveform can provide additional benefits to our detectors so a design has been developed to incorporate this waveform which is presented in the next section.

![Detector 1 and Detector 2 cathode and anode signal recorded from the HPWF detector.](image)

**Figure 13:** Detector 1 and Detector 2 cathode and anode signal recorded from the HPWF detector. There are three bending points in the cathode. The first (A) represents the generation of electron-hole pairs in the crystal, the second (C) is arrival of the electrons at the anode, and the final (D) is the arrival of the holes at the cathode. The amplitude of the electron contribution (B) is the subtraction of the first and second bending point amplitudes while the hole contribution is the subtraction of the second and third bending point. The total amplitude is shown as (E).

5.2 Hybrid Pixel-Waveform CdTe PET Detectors

The transition from the current state of the art in PET system performance has required the exploration of semiconductor detectors with small pixelated elements. It has been anticipated that the use of small pixels
could dramatically improve the intrinsic resolution of detectors of scintillation based systems. Yet, semiconductor detectors are not without challenge. While semiconductor detectors could potentially provide improvement in spatial resolution and energy resolution of the current commercial state of the art, semiconductors suffer from poor timing resolution, charge trapping, and the need for means for DOI. Therefore, to achieve high resolution broad spectrum imaging, the work presented here explores the use of readout system which combines both cathode and anode information. The addition of the cathode waveform opens the possibility of use corrections to be implemented.

The current effort has been focused on developing a CdTe detectors readout with a novel hybrid-pixel waveform readout circuitry shown in Fig. 14. This technique was designed to alleviate several intrinsic hurdles for using highly pixelated semiconductor detectors for PET imaging. This work focuses on the use of a modified 2048-channel 2-D CMOS ASIC for reading out small anode pixels of 350 µm x 350 µm in size, and a high speed digitizer for sampling the cathode and anode waveform induced by each individual event. Several modules were fabricated and tested for coincidence detection of the 511 keV gamma rays produced from annihilation process. Each single module is composed of a CdTe crystal of 1.1 cm x 2.2 cm with a depth of 2 mm. The crystal overlays an anode partitioned into 32 x 64 pixels with each single pixel being 350 µm x 350 µm in size. The HPWF detector approach offers several benefits for PET imaging:

- **Depth of interaction information** can be derived from the cathode waveform acquired using the HPWF method.
- **Improved energy resolution** utilizing the cathode waveform information, which allows for reliable derivation of the total energy deposition regardless any charge loss or sharing on the pixelated anode.
- **Improved timing resolution** by using the cathode signal waveform from initial electron migration through the CdTe crystal.
- **Simplified readout circuitry** due to the reduced burden of extracting all critical information from the small anode pixels. With this technique, the anode readout circuitry only needs to provide spatial position in X-Y directions.
Figure 14: (A) Pixelated elements of the anode. (B) The CdTe crystal bump bonded to the surface of the anode. (C) First generation 4.5 cm x 4.5 cm, 8 ASIC detector design used for the experiments performed in this thesis. (E) Each ASIC can function independently and the electronics for readout are heavily simplified. (F) The total volume occupied by the simplified readout can be reduced to not much more than the area of the CdTe crystal.

5.3 Hybrid Pixel-Waveform CdTe PET Experimental Design

The experimental studies were carried out using two active CdTe hybrids in a benchtop system shown in Fig. 15. The detector firmware was modified to allow coincidence detection, between the two detectors, and a dedicated coincidence control unit was implemented using a Xilinx Spartan FPGA. The readout time per pixel was minimized to 125 ns, and the number of pixels read out on each hybrid was firmware-selectable from 512 to 2048.

The two HPWF detectors were placed around a 4-D (X-Y-Z-Rotation) stage. Three dimensions were for the translation of the axis of rotation, using Newport motors, so that the selected radioactive source was centered in the system field of view (FOV). The final dimension used a Micronex rotational motor in order to simulate a detector ring. Signals induced in the cathode waveform were shaped with a NIM shaper (Ortec FTA 820) and fed into a constant fraction discriminator (Ortec 584). Events exceeding the threshold were sent to the coincidence unit with a resolving time window of 50 ns. For coincidence events, the cathode signals from both detectors were directed to an external ADC running at 200 M samples/sec. This ADC
stored all events in a circular buffer in order to preserve the cathode waveform generated prior to shaped triggering. The schematic of the triggering and readout system are provided in Fig. 16.

Figure 15: System triggering is controlled by the FPGA coincidence control unit (Xilinx Spartan-3E). The 4-D stage used in the experiments allowed source alignment and the simulation of a multi-detector ring through rotation. (B) Ortec analog shaping and CFD electronics were used to process the Amptek A250 preamplifier signals generated from coincidence events.

Figure 16: In the block diagram provided, cathode signals from detector 1 and detector 2 were sent to an Amptek’s A250 preamplifier. The waveform was digitized by our Gage ADC while the timing output was shaped by Ortec’s FTA820. The shaped output was sent to an Ortec 584 constant fraction discriminator (CFD). If the signal arriving at the CFD exceeded 30 mV, a TTL pulse from the CFD would be directed to the Ortec 414a coincident unit. A Xilinx Spartan-3E control FPGA would determine if the coincidence event from the 414a was true or not. Connections between the FPGA and the HPWF PET system were made using P-MOD BNC adapters.

5.4 Hybrid Pixel-Waveform CdTe PET Point Source and Capillary Tubes

The very first PET experiments performed using a design setup relied on the use of a 10 µCi Na-22 point source with a diameter of 250 µm, and three separate microcapillary tubes of approximately ~300
µm inner diameter of a total activity of approximately 18 µCi. The point source was positioned with a 1.305 mm offset, and the capillary tubes were separated approximately by 1.5 mm. Both sets of experiments rotated a full 360 degrees partitioned into 40 positions. Each position was sampled for a full hour. The point source reconstruction was used to provide an early determination of the potential intrinsic spatial resolution of the system while the capillary tubes provided insight into the number counts necessary for a good reconstruction of the data.
CHAPTER 6. EXPERIMENTAL RESULTS

6.1 XFET Single Photon Counting Spectra

The results of the spectral correction algorithms for the tube phantom can be seen in Fig. 17. The raw, uncorrected spectrum is shown in the left panel, and the corrected spectrum is shown in the right panel. For bromine, these comprise a $K_{\alpha}$ peak at about 11.9 keV, and the peak $K_{\beta 1}$ at 13.2 keV. For copper, we see the $K_{\alpha}$ copper peak (a blend of $K_{\alpha 1}$ at 8.048 keV and $K_{\alpha 2}$ at 8.027 keV) and the $K_{\beta 1}$ peak at 8.905 keV. Finally, for iron, only the joint peak is barely visible at 6.4 keV. The tube containing iron, which has the lowest emission energies of the three elements, was inadvertently placed furthest from the detector and thus it suffered tremendous attenuation effects. Therefore, no further mention of iron is made.

In addition to being more distinct after correction, the various peaks are also more quantitatively accurate. The intensity of the bromine $K_{\alpha}$ emissions should be about 7.3 times higher than the $K_{\beta}$ emissions. After correction, the $K_{\alpha}$ peak is about six times higher than the peak, consistent with expectations. Finally, in addition to the characteristic X-ray peaks, there is a distinct single Compton scatter peak at 16–17.5 keV, spanning a relatively broad range of energies because of the range of scattering angles compatible with the system geometry. There is also a broad but low multiple Compton scatter background.

The second experimental study, with the osmium-stained fish, produced the raw and corrected spectra in Fig. 18. The osmium characteristic X-rays seen in this spectrum are the L-peaks, since the K-edge of osmium is well above the 17.5 keV beam energy, while the L-edges are in the 10–13 keV range. The peaks observed are $L_1$ 7.82 keV, $L_\alpha$ 8.91 keV, $L_\beta$ 10.35 keV, and $L_\gamma$ 12.09 keV. The scattering peak was again observable.
Figure 17: (LEFT) The uncorrected, raw triple-tube spectrum from the CCD detector. (RIGHT) The Gaussian corrected spectrum which shows resolvable peaks.

Figure 18: (LEFT) The uncorrected osmium zebrafish spectrum. (RIGHT) Corrected spectrum. Multiple osmium peaks are visible along with the Compton scattering peak.

6.2 XFET Imaging Results

In Fig. 19, the results obtained from the capillary tube are presented. Iron did not yield a strong signal as the iron did not stay in solution. The results from bromide and copper are shown. The images obtained from copper and bromide without attenuation correction are shown in Fig. 19a and Fig. 19c. The samples appear to have very strong self-attenuation as the emission X-ray photons must pass through the capillary glass and the sample itself. In the provided images the detector is orientated at the bottom of the
image and, due to such a positon, the intensity of Fig. 19a and Fig. 19c can be seen to have a stronger signal toward the bottom of the image. Attenuation corrected images are also provided (work performed by a collaborator) are shown in Fig. 19b and Fig. 19d. These images obviously improve drastically in image uniformity. The applied energy windows are shown in the previous energy spectra.

![Image](image.png)

**Figure 19:** (A) Attenuation uncorrected capillary image of the bromide solution. (B) Attenuation corrected bromide capillary solution. (C) Copper solution with no attenuation, and (D) Attenuation corrected copper solution. An anomaly was visible in the copper data seen as a small streak but the cause was not determined.

In Fig. 20 and Fig. 21, imaging results from the osmium stained zebrafish sample are shown. Again in this image, self-attenuation of the sample is very clearly observed in Fig. 20a. The camera again is located at the bottom of the image and the strongest signal can be observed closest to the CCD camera. The weakest signal can be seen in the top right as both the incident beam (coming from the right side of the figure) and the emission are being attenuated by the sample. The osmium zebrafish attenuation correction is provided in Fig. 20b. The internal structure of the zebrafish can better visualized with the attenuation correction. Fig. 21 shows the results of isolating the Compton scattering of the incident 17.4 keV X-ray beam used for exciting the sample. It was possible to visualize the resin in which the zebrafish was encased within.
Figure 20: (A) Raw count image obtained from the osmium stained zebrafish. (B) Attenuation corrected osmium stained zebrafish.

Figure 21: Image acquired when only energies of the incident beam scattering was isolated. Heavy attenuation of the scattered events was visible in this image.

6.3 HPWF PET Imaging Results

The acquired PET data was considered with and without DOI data. Fig. 22 shows the reconstruction of the point source data with positional separations ranging from 600 µm down to 400 µm. In the absence of DOI, visualization of the point source is not possible and the shape of the point source is clearly distorted. When DOI correction was applied, the shape of the reconstructed point source improved. Initial results shown here indicate that the system may be able to achieve sub 400 µm resolution but further verification is required.
Figure 22: (LEFT) Reconstruction of point source experimental data and varying separations. No DOI correction was performed on the data. (RIGHT) DOI corrected point source reconstruction data.

Fig. 23 shows the reconstruction of the three capillary tubes. Sub-figures A, C, E, and G show the sinogram data and sub-figures B, D, F, and H are the actual images for the capillary tubes for each reconstructed condition. While 400,000 events were collected from the experiment, the data was reconstructed using a subsets of 20,000 events, 40,000 events, 80,000 events, and 200,000 events. The image quality varied directly as a function of the number of events and the minimum events identified for sufficient image quality was 80,000 events.

Figure 23: (A, B) 20,000 event sinogram and reconstruction. (C, D) 40,000 event sinogram and reconstruction. (E, F) 80,000 event sinogram and reconstruction. (G, H) 200,000 sinogram and reconstruction.
CHAPTER 7. SUMMARY AND CONCLUSIONS

The work in this thesis performed preliminary evaluation of two separate modalities for potential integration such that broader spectrum imaging could be achieved for the purpose of extracting more biologically relevant information. The experimental data from that XFET results indicated that the methods implemented could prove that elements such as copper and bromide were visible. These results were further cemented by the ability to visualize the zebrafish staining. The experimental data from the CdTe PET experiments provided an indication of the maximum achievable resolution with the selected pixelated semiconductor detectors. The results seem favorable for a potential integration for small animal neurodegenerative imaging.

Given these results, XFET/PET could potentially serve as dual modality system but many elements would still need to be addressed. The concentrations imaged by the XFET system were far too high to be biology relevant. The concentrations were on the order of 250 mg/ml but biologically relevant concentrations exist on the microgram scale. Additionally, the self-attenuation serves a natural shield against elements deeper in the tissue and this would require the use of higher energy incident and emission X-rays at the potential challenge of causing more dose. While PET did show a good potential achievable resolution, the images provided were under very simple conditions with no real background noise being provided to the experiment. The long acquisition time and minimal number of counts collected for the capillary tubes indicated that the system sensitivity would also need to be addressed.
CHAPTER 8. FUTURE WORK

Given the true complexity of such modalities, the wisest course of action would be to proceed with a single modality. The information and background presented in this thesis does provide reason to pursue the idea of broader spectrum multi-modality development but each modality is not well understood. Therefore, my future work will only focus on understanding only CdTe PET. This includes better understanding the function of HPWF detectors, the potential limitations of semiconductor material in PET, the system timing resolution, the system energy resolution, and depth of interaction. I also currently have great interest in exploring the waveforms in CdTe PET and, from my intuition, feel that much more information can be extracted than what is visible upon initial inspection.
REFERENCES


22. Chen, Chun-Jen, Kazunori Bando, Hiroki Ashino, Kazumi Taguchi, Hideaki Shiraishi, Keiji Shima, Osuke Fujimoto et al. "In vivo SPECT Imaging of Amyloid-β deposition with radioiodinated imidazo [1, 2-a]


