

Very High Resolution Small Animal PET

Don J. Burdette
Department of Physics
The Ohio State University

April 26, 2005

Abstract

Positron Emission Tomography (PET) is a leading technique in medical diagnostic imaging. PET scanners are used to detect cancerous cells through the use of a positron emitting tracer that is ingested by the patient. The positron annihilates with an electron in the body producing a pair of 511keV gamma rays emitted in opposite directions. The gamma rays are sufficiently energetic to leave the patient's body and to reach an external detector. In conventional PET systems these gamma rays are absorbed by interacting with scintillation crystals that convert the gamma ray's energy into small flashes of light that are collected by an array of photomultiplier tubes. This information gives the energies and positions of the pair of photons and is later used to reconstruct an image with typical system resolution of 10 mm for full body human scans and approximately 1.4mm for small animal scans. The quality of the image is limited both by the spatial resolution and the efficiency of the detectors used. Employing state-of-the-art solid-state silicon detectors developed for use in experimental particle physics significantly higher resolution images can potentially be achieved. In order to test this assumption, we have set-up in collaboration with the University of Michigan a prototype system consisting of a pair of silicon detectors each with 512 channels, 1mm thick, 1.4 mm by 1.4 mm area per pad arranged in a 32x16 array. Using this system to image a Fluorine-18 source we have already obtained a spatial resolution of 0.7 mm FWHM. Further improvements in the system will be achieved by adding an array of secondary detectors to take advantage of the photon from the Compton scattering event in the silicon, thus increasing system efficiency.

1 Introduction to Positron Emission Tomography

Throughout medical history the early detection and prevention of disease has always been a goal. A hundred years ago doctors only had their physical senses and the description of patient's symptoms to determine illness. A dream of doctors throughout the ages has been to see inside patients' bodies in a non-invasive manner in order to diagnose disease before symptoms occur. With the discovery of the X-Ray in 1895 this dream became a reality and the science of medical imaging was born.

The ability to create images of the interior of living organisms has evolved over the latter half of the twentieth century giving medical doctors an invaluable tool for diagnosing disease. The main goal in medical imaging is to identify abnormalities in bodily structures and/or functions. Many different technologies now

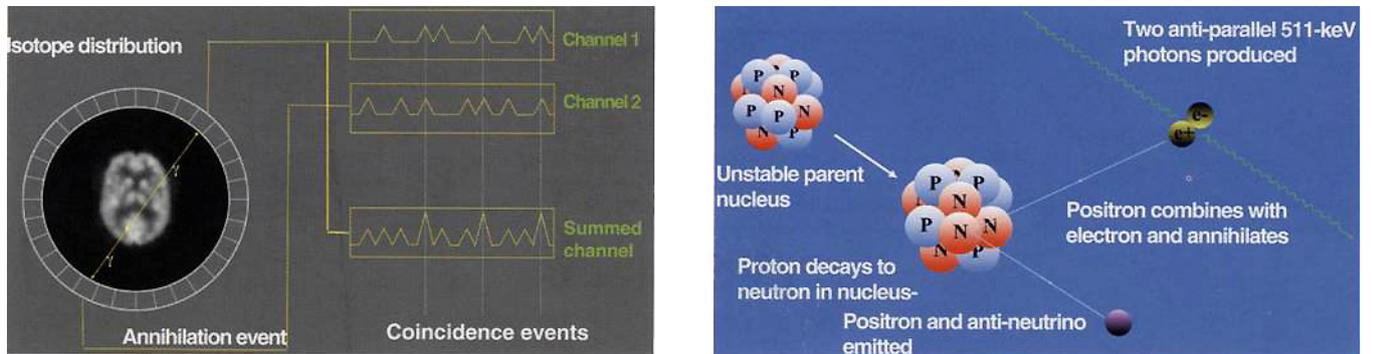


Figure 1: Left: Basic detection principle of PET. Right: The radioactive tracer decays emitting a positron that annihilates with an electron producing two photons traveling in opposite directions [?]

exist including X-Rays, ultrasound, magnetic resonance imaging, and positron emission tomography. Each technique has its advantages and applications and many are used to compliment each other.

Positron Emission Tomography (PET) is a leading imaging technique for the detection of cancer. Unlike other techniques such as XRay and MRI which only image bodily structure, PET creates images of metabolic processes making it an invaluable aid in the detection and understanding of cancer. These PET images are often used to complement the structural images collected via other medical imaging techniques.

The creation of PET images are accomplished through the use of radioactive tracers that are either ingested, inhaled, or injected into a patient. These tracers have two important properties. One, they bond to cancerous cells, thus accumulating into large concentrations where cancer is present. For example, fluorine-18 is a tracer that bonds to common glucose, thus it can be used to measure glucose metabolism. It is now know that malignant tumors have an increased glucose metabolism; therefore, more of the fluorine-18 will accumulate in these cancerous cells. Secondly, as the tracer decays it emits a positron that ultimately allows for the creation of an image. The emitted positron will scatter off of the electrons in the patient's body as it loses its kinetic energy. When the positron reaches thermal energies it will annihilate with one of the electrons in the patient's body producing a pair of 511keV photons traveling in opposite directions. The range of the annihilation event from the source of the positron emission in organic tissue can be up to 1.2mm [?]. The two photons have sufficient energy to pass through the patient undeflected and fall incident to a detector ring where they both are detected in coincidence. The detector ring consists of a coupled scintillator and photomultiplier tube (PMTs) array. The scintillator absorbs the incident energies of the photons and converts it to small flashes of light. The light is collected by the photomultiplier tubes and converted into an

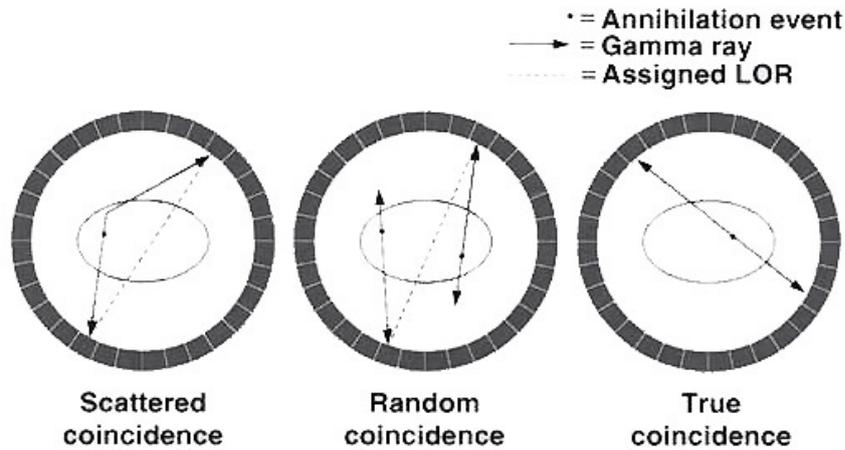


Figure 2: Three types of coincidence events measured in PET [?]

electrical signal. The signal is then amplified, digitized, and readout for later analysis. During reconstruction the data is used to form a line between the two detected photons representing the possible locations where the annihilation event could have occurred. By taking a large number of coincident events many lines can be constructed. An image can then be reconstructed by employing a tomographic algorithm on the data.

2 Conventional PET: System Resolution and Efficiency

There are two important quantities to any imaging system that define its performance: system resolution and efficiency. The resolution refers to the level of detail that can be distinguished in the image while the efficiency refers to the number of recorded events divided by the total number of events. Higher efficiencies correspond to quicker data acquisition times and a lower radiation dose to the patient. The efficiency of the detector can be improved by using more efficient detectors and by increasing the dimensions of the detector in order to capture more of the emitted photons. Lowering the resolution and increasing the efficiency are the goals of ongoing research projects.

For conventional PET the system resolution is on the order of 10 mm for whole body human scans [?]. This resolution is affected by many components of the measurement process including the resolution of the detector ring, noise in the associated readout electronics, and false coincidences.

There are three types of events that are recorded by the detector ring: real, scattered, and random coincidences. Real coincidences correspond to two undeflected photons detected during the coincidence

window originating from the same annihilation event. Scattered coincidences occur when one or both of the photons have scattered in the patient while random coincidences are due to two annihilation events happening nearly simultaneously. Figure 2 depicts the three scenarios. False coincidences due to scattered and random events arriving during the coincidence window degrade the final image resolution. They can not be avoided, but they can be minimized. One way to minimize random coincidences is to decrease the patient dose; however, the trade-off is an increase in the data acquisition time. Longer data acquisition times increase the chance that the patient may move, thus degrading the resolution. However, if the efficiency of the detector can be improved, lower patient doses can be administered without requiring an increased data acquisition time.

The resolution of the detector ring directly affects the ability to localize the points of absorption of the incident photons. This uncertainty in the photons' positions directly translates into an uncertainty in the source position, hence a degradation of the resolution. It stands to reason that making finer detection units would improve the spatial resolution of the detectors and thus improve the overall system performance. This has been, and continues to be, the trend in PET technology. To first order, the smaller the dimensions of the detector unit, the better the resolution.

The efficiency of any imaging system is mainly due to the efficiency of the detector ring. Ideally, all photons emitted from the source would be collected, and they would all be real coincidence events. Unfortunately, all events that emit photons out of the plane of the detector ring are not recorded. The only way to correct for this is to make a longer detection ring thus increasing the solid angle of detectable events. Using more efficient scintillation crystals with a higher stopping power can also increase the efficiency; however, higher efficiency crystals tend to have poorer spatial resolution. This trade off between resolution and efficiency is a major issue in PET research and development.

3 Small Animal PET Systems

PET technology is obviously an important tool for detecting cancer in humans; however applications other than human imaging exists for PET systems. One area of study that has been the focus of many research groups is the development of PET systems for use in imaging small animals. Dedicated small animal PET systems are important in biomedical, pharmaceutical, and genetic manipulation applications. One important example is in the use of animals as human disease models. Mice have become the choice animal for modeling

and testing treatments on human diseases due to the similarity between our genetic codes (most human genes have a related mouse gene). Geneticists now have the ability to knock out and replace genes suspected to cause disease. These genetically altered mice have offspring, thus passing down their genetically altered state. Conventionally, the disease studies done on these mice demand sacrificing large number of the offsprings at various stages of disease development or treatment. These studies can become expensive due to the number of mice needed. Adding to the equation genetically altered mice, the cost can quickly escalate to over a thousand dollars per mouse [?]. Hence the ability to study the same mouse through the entire development and treatment of a disease without sacrificing the animal would be preferable. A small animal PET system gives us this opportunity.

Unfortunately there are challenges that must be overcome to convert the technology developed for conventional PET into the small animal domain. The main issue that needs to be addressed is the spatial resolution. The spatial resolution needs to be improved over conventional PET due to the large difference in the volume being measured between human full body scans and mice, which represents about a 200 fold decrease in volume. In order to create the same image quality seen in conventional, human imaging PET, an order of magnitude improvement in resolution must be achieved. A typical PET system has a resolution of approximately 10mm for full human body scans, thus for the small animal set-up to have the same image quality a resolution of less than 1mm needs to be achieved [?].

One may think that the efficiency when imaging small animals may not be as large a problem as when imaging humans because there are no radiation exposure limits on animals. This is not the case. One of the fundamental principals of tracer kinetic experiments is that the mass levels of the tracer can not interfere with normal biological functions. Many circumstances exist in which the mass of the tracer will limit the amount of radioactivity that can be injected into the animal, thus an increase in efficiency over conventional PET is desirable.

In order to achieve both better resolution and efficiency new methods and/or detectors must be developed for small animal PET systems.

4 A Different Approach: Using a Silicon Detector

One way to increase the system resolution is to improve the spatial resolution of the detectors. A detector type with better spatial resolution than conventional scintillation/PMT detectors already exists and has

been developed and used in high energy physics experiments since the early 1980s. These devices are known as solid state detectors. The better resolution inherent in solid state detectors is due to their pixellated pads that are on the order of a square millimeter.

Solid state detectors operate by sandwiching an n-type and a p-type semiconductor (in our case silicon) together to form two regions. The n-type region is doped with an impurity such that there are an excess of electrons in the material. These electrons are known as free-charge carriers and are free to move throughout the material. The p-type region is doped with an impurity that leaves a vacancy in one of the bonds it makes between the silicon atoms. This vacancy is referred to as a hole and can be thought of as a positive charge that is not bound to any one atom, but is free to move throughout the material analogous to the electron in the n-type material. A reverse bias voltage is applied across the detector creating an electric field. The electric field separates the free charge carriers creating a charge free region, known as the depletion region. When the incident gamma rays pass through the depletion region they ionize the material causing the creation of approximately 140,000 electron-hole pairs for a fully absorbed gamma ray [?]. The electric field that exists in the depletion region separates the electrons and holes which is detectable as a small impulse of current. This signal can then be amplified and recorded as an event for later analysis.

The depletion region is where the photons interact with the silicon via ionization events. In order to maximize the efficiency of the silicon detector the depletion region must be made as large as possible (the larger the depletion region; the larger the chance of an interaction). If a sufficiently large reverse bias voltage is applied then the depletion region will encompass the entire detector thickness. The detector is then referred to as being fully depleted. For PET applications the ideal silicon detector would be thick and separated into small detection elements. Thick, fully depleted detectors are ideal for a PET application in order to boost the efficiency. The thicker the detector, the more chance of an interaction, and hence the greater the efficiency. Increasing the resolution is also desired. This can be accomplished by separating the silicon into small sensor pads.

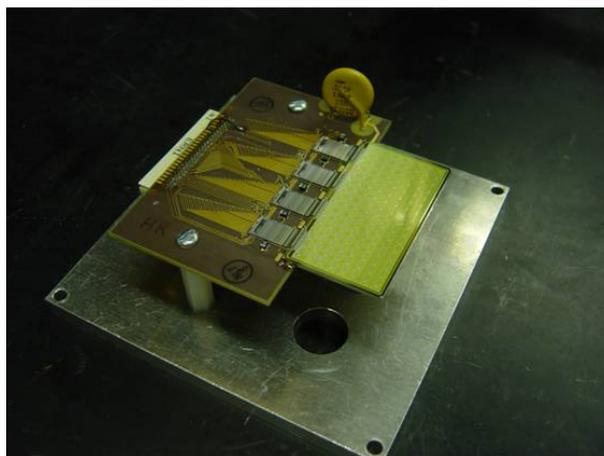


Figure 3: Mounted silicon detector

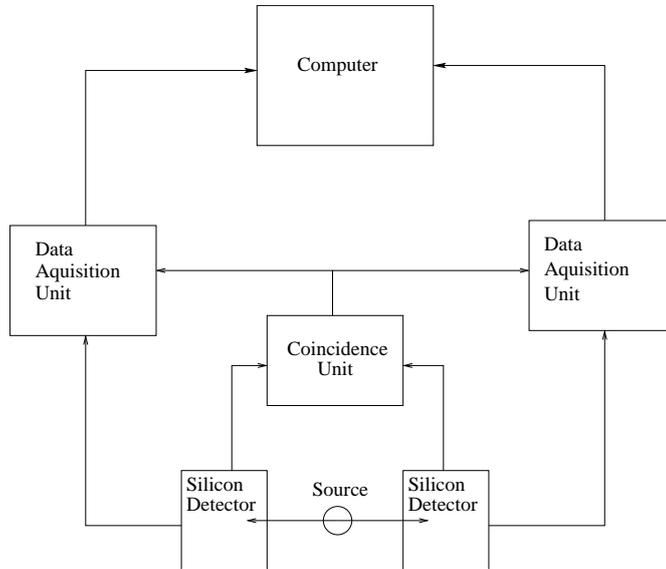


Figure 4: Block diagram of readout electronics

The silicon detectors used in our set-up are composed of 512 pads, 1mm thick by $1.4\text{mm} \times 1.4\text{mm}$ in surface area arranged in a 32×16 array (Figure 3). Typical values of the thickness of silicon detectors used in high energy experiments are on the order of $300\mu\text{m}$. Our 1mm detectors are the result of recent advances in silicon detector growth techniques. The advantage of using a silicon detector over the scintillator/PMT detector is the high spatial resolution that results from the small detection pads. The silicon detectors used in our experiment also have an excellent energy resolution of 1.3keV FWHM (Full Width at Half Max) using a 511keV source. This energy resolution is not exploited in our current small animal PET set-up but will be used in future work.

5 Experimental Set-up and Collection of Data

Our set-up consists of two 512 pixellated pad silicon detectors as described above (Figure 6). They are mounted edge-wise on opposite sides of a Fluorine-18 source collimated into a 1mm thick plane. The source rests on a stand that can be rotated through 360 degrees in 30 degree steps in order to simulate data collected from an entire silicon detector ring. The silicon detectors are mounted on a grounded backplane and wire-bonded to four VATA chips (each chip reads out 128 of the 512 signals from the silicon detector). The VATA chips are ASICs (application-specific integrated circuits) that consists of two main parts. One major

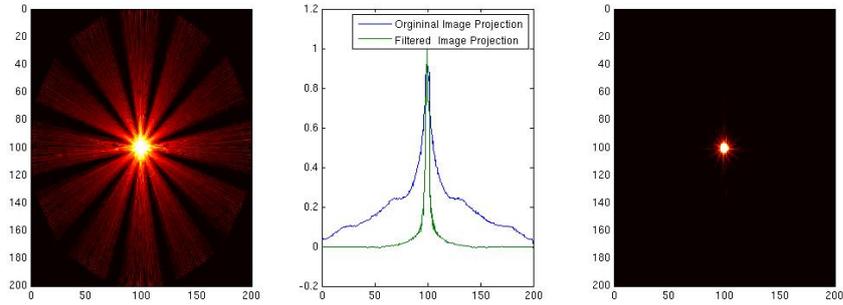


Figure 5: Left: Image created using a simple back-projection of data from a simulated 3mm disk source. Center: Projection of image before filtering process (blue line) and a projection of the image after the filtering process (green line) Left: Image of simulation 3mm disk source after filtering process.

component is the integration of a preamplifier, a shaper, and a sample-and-hold switch. This section of the chip takes the signals given off from the silicon sensor, amplifies, shapes, and holds onto the results until told to readout (a coincidence event) or reset (no coincidence). The second component of the chip implements a self-trigger to determine if a photon was absorbed in the sensor. Without this recently developed feature in the VATA chip the silicon could not trigger itself when a photon interaction in the silicon occurred. Thus, no timing information would be available to determine if two events were in coincidence. This feature of self-triggering in the VATA chip is crucial for the success of our small animal PET set-up.

Whenever one of the detectors detects a signal over the background threshold, it sends out a trigger signal to a coincidence unit which has a delay (equal to the coincidence window) that waits for another trigger signal from the second silicon detector. If this second signal arrives during the coincidence window then the data stored on the VATA chips is readout via a data acquisition module (DAQ) based on the VMEbus standard (Figure 4). The DAQ system was developed at CERN and built at OSU. Each silicon detector has its own DAQ module. This data is recorded as an event and saved for later analysis.

Obviously this experiment set-up is not very efficient due to having only two detectors as opposed to an entire ring. Instead, the aim of this experiment is to demonstrate the high resolution capability of a small animal PET system using silicon detectors.

6 Reconstructing the Image

Once all of the data has been collected an image can be produced by employing a reconstructive algorithm. This is done in a step-by-step procedure. The analysis program must first calculate the pedestals (the electronic signal from a pad sensor when no event is present) so that it is clear when an event in that channel has occurred. Once the pedestals are calculated, a common mode noise calculation is done to take into account electrical noise common to all channels. For each event the signal from each of the 512 pads from both detectors is scanned to find the two pads where the photons' energies were absorbed. A line is then drawn from the center of these two pads representing the possible locations of the positron annihilation event.

Running through the entire data file, lines are constructed for each event and the density of the lines for each point in space is calculated. Using this technique there will be blurring of the image away from the center of the field of view (Figure 5: left). To eliminate this blurring a Fourier transform is applied to the image transforming it into frequency space. The transformed image is then adjusted by a filter that suppresses high frequency contributions (the area with the blurring). The final image is created by transforming the image back to position space via an inverse Fourier transform (Figure 5: right). The center image in figure 5 is a projection of the image through its center before and after the filtering process. Note the substantial improvement in the width of the peak. A narrow peak corresponds to a higher resolution image. It is clear that the filtered image has a superior resolution over the unfiltered image.

7 Experimental Results

We first used a commercially available microPET R4 (Figure 6) at the university of Michigan's PET center to image two 1.1-1.2mm capillary tubes with a wall thickness of 0.2mm filled with a Fluorine-18 source. The microPET R4 consists of an array of 2.1mm \times 2.1mm \times 10mm thick LSO scintillation crystals and associated PMT array. Further details on the microPET R4 can be found in [?]. The resolution of the reconstructed image from the microPET set-up is 1.8mm at the center of the field of view (Figure 8). This is in agreement with the spatial resolution of 1.85mm measured in other independent studies [?].

We then imaged the source with our prototype small animal PET set-up (Figure 7). The resolution of the reconstructed image is 0.7mm at the center of the field of view (Figure 9). The results for the silicon set-up are over a factor of 2 better than the commercially available system and below the 1mm goal for an

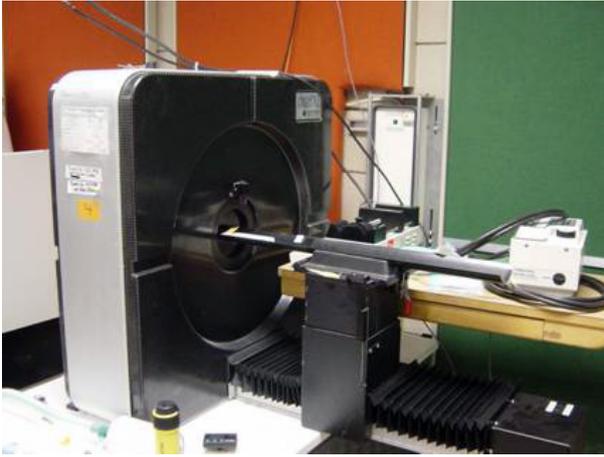


Figure 6: MicroPET experimental set-up.

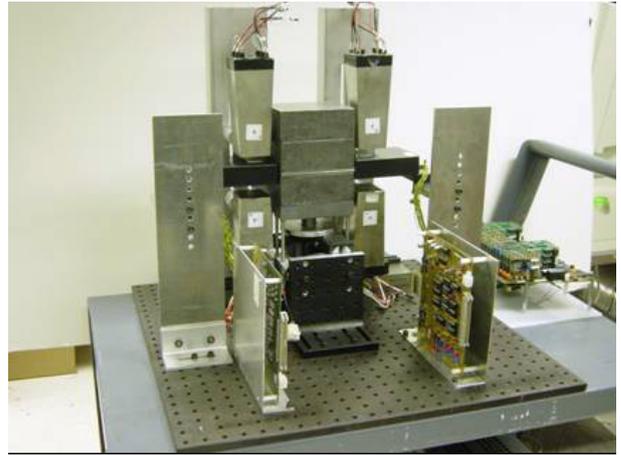


Figure 7: Our Small Animal PET set-up. The silicon detectors are contained in the black boxes.

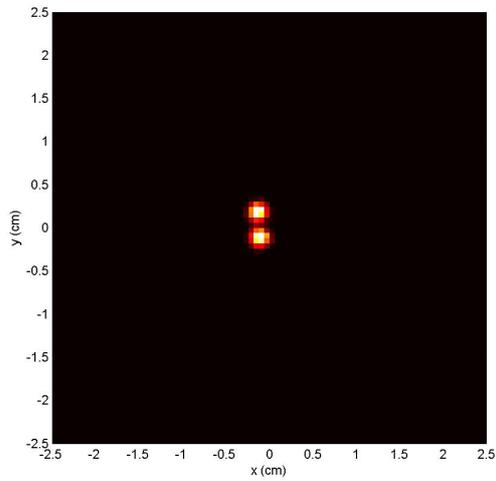


Figure 8: MicroPET image of Fluorine-18 source contained in two 1.1-1.2mm capillary tubes with a wall thickness of 0.2mm.

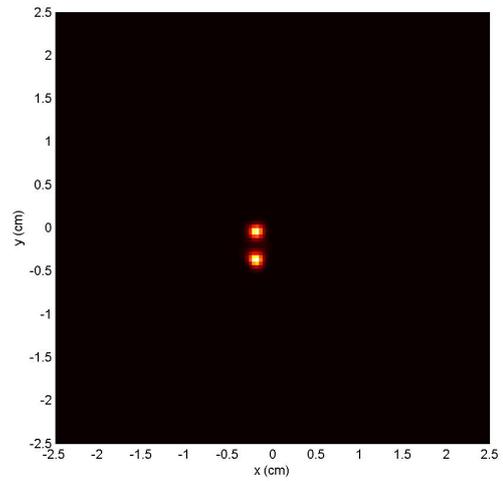


Figure 9: Our Small Animal PET image of Fluorine-18 source contained in two 1.1-1.2mm capillary tubes with a wall thickness of 0.2mm.

ideal comparison between PET image quality of mice and humans desired for human disease modeling in mice.

8 Conclusions and Future Research

It has been shown that using silicon detectors with excellent spatial resolution improves the system resolution of the small animal PET images. Further research is planned for our small animal PET set-up to improve the resolution, rate capability, and efficiency. The resolution can be improved by suppressing the background events by having a smaller coincidence window. This can be accomplished by using a material with faster timing resolution; however, we do not wish to sacrifice the excellent spatial resolution of the silicon detector. Our solution is to use an array of secondary detectors sandwiched around the silicon detectors to take advantage of the Compton scattered photon. The secondary detectors will be composed of a BGO scintillation crystal with fast timing resolution. By using a shorter coincidence window we will not even record many of the random background events that would otherwise degrade the resolution. The efficiency and rate capacity will also improve by having less dead-time in the system. We are also planning on adding a stack of silicon detectors in order to increasing the efficiency.