Movement Detection
In
Small Animal Gamma-Ray Imaging

Sam Dunn

Senior Project, Undergraduate in Physics

May 2, 2002

Table of Contents

Abstract

A Single Photon Emission Computed Tomography (SPECT) system is being developed for small animal *in vivo* imaging. Gamma-ray detectors are used to image the uptake of a ligand tagged with ^{125}I through the bloodstream and organs of a mouse. Small fiducial markers on the animal bed permit the 2-D image of the gamma-rays to be overlaid on an x-ray image of the mouse in order to locate closely where the tagged ligands traveled with respect to the mouse's bone structure. One important problem has been involuntarily movement of the anesthetized mouse during the imaging process. We investigate ways to detect and correct for this movement.

I. Introduction

There has been an expanding interest in the study of small animals to investigate disease and biological processes [1]. Among the various imaging techniques in the medical industry are Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Single Photon Emission Computed Tomography (SPECT) all of which are described in greater detail below. Each of these systems utilizes *in vivo* imaging as opposed to *in vitro* imaging. There are advantages to both *in vivo* and *in vitro* techniques, but one of the biggest advantages of *in vivo* detection systems is the ability to evaluate data in a subject for an extended period (days to even weeks), whereas an animal must be sacrificed in *in vitro* studies which essentially yield only a single snapshot in time [2]. Although SPECT resolution is often less than that of PET, the practical and economic aspects of SPECT instrumentation make this mode of emission tomography attractive for a small lab [3]. Another advantage to the SPECT system is that one can collect data event by event which allows the investigator the ability to recreate any of the data in any chosen timed sequence.

A SPECT imaging system is being developed by members of the William and Mary physics and biology departments in conjunction with Thomas Jefferson National Accelerator Facility (Jefferson Lab). SPECT imaging allows multiple 2-D images to be taken from different angles then recreated using a SPECT computer program to produce a 3-D image. Thus, this technique can be of interest to biologists as well as doctors using SPECT with patients. In particular, a study of diabetes is one target application of the detection system described in this paper.

II. The Apparatus

Scintillators

Scintillators are used to detect the energy given off by a radioactive isotope, which for this project is ^{125}I. A scintillator is a material that has the ability to absorb a photon and convert that energy into light. In our case, the energy striking the scintillator is of the form of gamma-rays and x-rays. A good scintillator should be able to convert much of the incident energy to light [4]. Scintillators can be either organic or inorganic with each having their own benefits depending on the intended use. We used an inorganic crystal scintillator CsI(Na) in this work because it is able to detect the low energy gamma-rays from ^{125}I [5].

Collimators

Collimators are used to limit the direction of photons as they approach up the scintillator. They can be made out of lead, tungsten, or in the case of our project, copper-beryllium [6]. There are two principal types of collimators used in medical imaging [7]. The pinhole collimator is primarily used in studying very localized objects such as a mouse brain or other organ. It consists of a dense material with a single small hole drilled in the middle. Pinhole collimators offer the benefit of high magnification of a single object, but lose resolution and sensitivity as the field of view gets wider [8]. On the other hand, a parallel-hole collimator consists of hundreds of holes drilled or etched into the material that accept photons only moving perpendicular to the scintillator. For this project a parallel hole collimator was used because it offers reasonable resolution without sacrificing the spatial field of view as is the case with a pinhole collimator. This is important in examining a whole mouse rather than one of its organs.
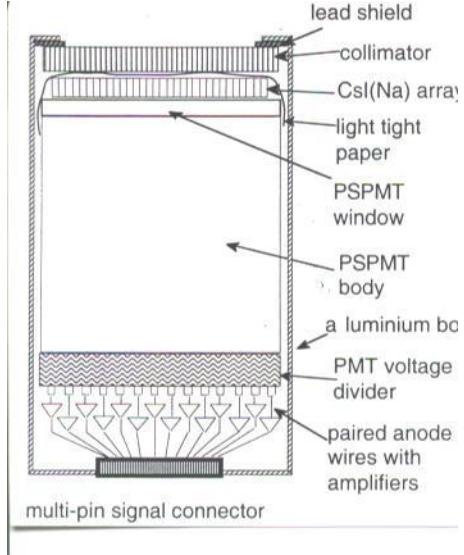
Figure 1: Position Sensitive Photomultiplier Tube

PSPMT

   Once the light pulse is created by the scintillator it hits the Position Sensitive Photomultiplier

Tube (PSPMT) (Fig. 1) which converts the incoming light pulse into an amplified electronic

signal. A photomultiplier tube contains a photocathode which emits electrons through the

photoelectric effect when photons strike [9].   An electric potential accelerates such an electron

to the first dynode in the vacuum tube where it hits the dynode and releases several additional

electrons which are then accelerated to the next dynode. The process is repeated several times

with each electron releasing three or four additional electrons until the resulting cloud reaches an

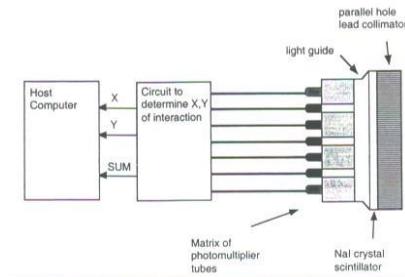anode which creates an output signal.

Figure 2: Gamma Camera

As seen in Fig. 2, an array of PSPMT's together with a disk of scintillating material, collimator, location circuitry, and computer make up one basic type of detector used in SPECT imaging called a gamma camera [7].
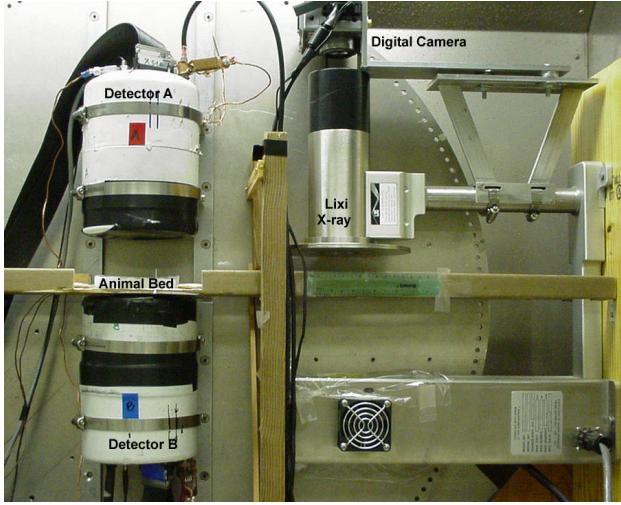

Figure 3: picture of the support gantry with two 110 mm PSPMT's and Lixi X-ray system.

III. Setup

<u>The Support Gantry</u>

Figure 3 shows the system originally used in taking these data. Detectors A and B are two 110 mm PSPMT's. The balsa wood animal bed runs from the detectors to the X-ray device that employs a digital camera. The data are processed using analog-to-digital converters coupled to the PSPMT's and gated by dynode signals from the appropriate tube [7]. A Macintosh G3 computer takes the data and stores the time, position, and energy of each event. The images are processed with computer software and give the biological researcher information concerning the organs of interest.

A. Gamma-Ray Detectors

The system is comprised of two Hamamatsu 125 mm PSPMTs coupled to pixilated scintillators of CsI(Na). Collimators are placed between the scintillators and the animal. In a basic arrangement of the two, a parallel-hole collimator of high spatial resolution and low sensitivity is used on one PSPMT along with a high sensitivity and low resolution collimator on the other. Respectively the two collimators have 0.2 mm openings with 0.05 mm septa and 0.75 mm openings with 0.16 mm septa. Both collimators are 125 mm in diameter and 5 mm thick [12]. In some cases, a pinhole collimator was employed on the second detector.

B. X-Ray Imaging

The x-ray system used consists of a Lixi, Inc. fluoroscope that takes a 5 cm diameter image.
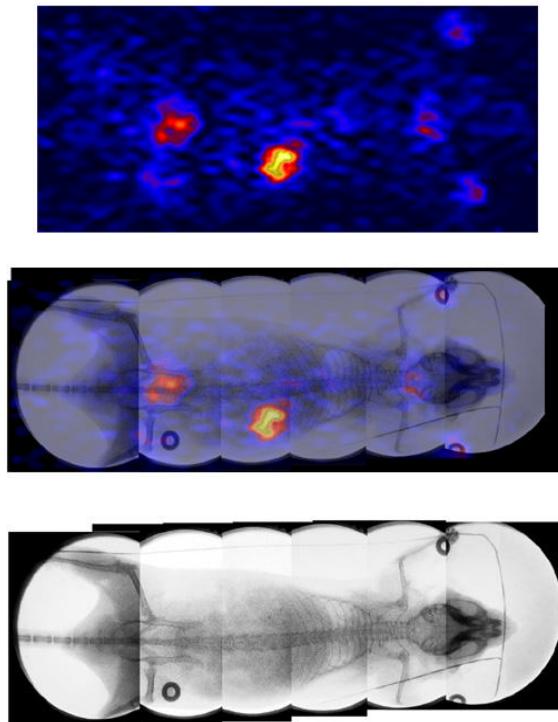

Figure 4: The top picture is created using a high-resolution collimator to create the image of gamma rays from ^{125}I. The bottom image is the x-ray of the whole mouse. The middle image is the overlay of the top and bottom. The black rings line up to achieve an accurate overlay.

In order to get an image of the whole mouse, six or seven 5 cm X-rays are taken and arranged in a linear array by a computer after each image has been processed through a digital camera. This process is relatively simple because the mouse bed lies on a track that runs from the detectors to the X-ray (Fig. 3). An example use of the X-rays can be seen in Fig. 4. The top picture is a gamma ray image taken with one of the PSPMT's. The bottom picture is the mouse image created via several X-ray images. The middle picture is the overlay of the top and bottom pictures. The dark rings are small metal toroids in which ^{125}I was placed and attached to the mouse bed. These fiducial markers permit an accurate overlay of the two images.

The New Gantry

A new detector support gantry under development for this work utilizes an open-barrel shape design and is capable of holding multiple gamma cameras as well as the X-ray system. Figure 5 is a picture of the new gantry. The barrel seen in Fig. 5 is 46 cm in diameter with the support structures made from aluminum. Adjustable mounting plates hold as many as three detectors in place, although the diagram only shows detectors A and B in place. A computer controlled stepper motor drive permits rotation of the gantry in order to obtain the multiple angles for tomographic image reconstruction. Three detector heads can be placed at 120 degree intervals to allow for an efficient 360 degree imaging of the mouse. A stepper motor that interfaces with the G3 Macintosh provides the horizontal translation of the mouse bed along the gantry center.

Figure 5: Picture of the new gantry being developed for SPECT imaging

A. Gamma Ray Detectors

The new gantry utilizes two sets of detection systems. The first is based on the Hamamatsu R5900-M64 PSPMT in which three detector heads are coupled to crystal scintillator arrays as well as high-resolution lead and copper collimators. Adjustable mounting plates hold the three detectors in place (see Fig. 5). Each detector has an active area of 18.1 square mm and produces high imaging resolution. A G3 Macintosh is used to control the incoming data using Kmax data acquisition software from the Sparrow Corporation [10].

The second system utilizes the Hamamatsu R3292-02 based detectors. Two five inch diameter compact gamma-ray imaging detectors are coupled to arrays of CsI(Tl) [10]. Results using this system are reported in "SPECT-CT System for Small Animal Gamma Ray Imaging," by A.G. Weisenberger, et al. [10]

B. X-Ray Imaging

The same fluoroscopic system designed by Lixi, Inc. is used in the new gantry system as in the old system. The anticipated dose per image taken is approximately 5 rads. This value in itself is not excessive, but if several projections are to be taken for X-ray CT a high dose might be administered to a mouse undergoing a complete body scan [5].

IV. Medical Imaging Techniques

Many methods of imaging are available to study biological processes in humans and in animals, such as mice. The degree to which each of them is successful or helpful is dependent upon the goals of the investigator, the biological process studied, and the expense of the imaging method. The methods described below utilize *in vivo* techniques.

PET

Positron Emission Tomography (PET) uses a ligand tagged with a positron emitting isotope such as ^{11}C or ^{13}N. The compound then binds quickly to a certain area of the body. For example, glucose tagged with ^{11}C will bind inside the brain. The isotope will then decay emitting a positron which annihilates a free electron usually no farther than 1 mm away [11].
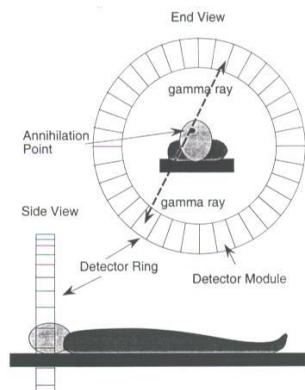

Figure 6: Diagram depicting how a PET scan works

Two co-linear gamma rays, which result from the annihilation, emerge 180 degrees from one another, and can be detected by an array of scintillators that surround the patient (Fig. 6).

When the photons are recorded both simultaneously and 180 degrees apart, the sensors can infer where the annihilation occurred. PET has an advantage over other types of imaging in that it is capable of high resolution. Thus, it can be used, for example, in imaging and studying receptor proteins in the body.

NMR

Nuclear Magnetic Resonance (NMR) is the physical technique that the more commonly known imaging method Magnetic Resonance Imaging (MRI) uses. MRI is mainly used in developing anatomical images, but can also be used to give information about the physical and chemical state of tissues [12].

NMR utilizes the fact that patients are made up mostly of water. A superconducting magnet between 0.5 and 2 Tesla is used to align the protons of the hydrogen atoms. The atoms inside the object that once were pointing in different directions become aligned. Most of the atoms cancel each other out, but one or two in a million do not. A radio frequency is applied to these atoms which absorb the energy and spin at a certain frequency. Once the RF is turned off, the nuclei return to their original states and emit energy at the same frequency as it was absorbed. The signal is picked up by a computer that converts the data into 2-D and 3-D images. Different elements, however, have different resonant frequencies and therefore take longer to get back to the ground state. NMR measures this time which is helpful because certain physical aspects like tumors take longer to get back to ground state [5].

SPECT

Single Photon Emission Computed Tomography is the goal of the experiment described in this paper. SPECT uses one or more gamma cameras that can be rotated around a patient to gather 2-D images from different angles. Whereas PET uses a positron emitting tracer, SPECT uses a photon emitting tracer that is detected by the gamma cameras. The radioactive isotope used in the present experiment is ^{125}I. After injection of the tracer, the PSPMT's are used to detect the gamma-rays given off by the isotope. A SPECT computer system can then recreate three dimensional images of the radioisotope [2].
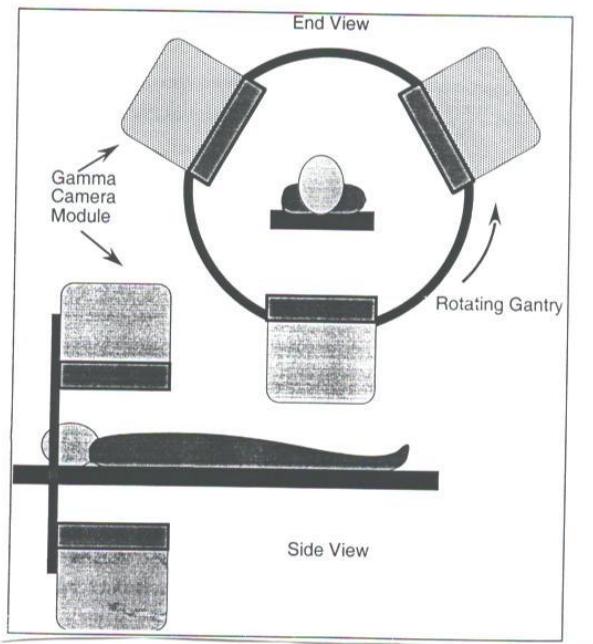

Figure 7: Diagram showing the operation of a clinical SPECT scanner

V. Biological Application to the Study of Diabetes

A major area of interest for the application of this project has been the study of ligands related to diabetes. So far, information has been obtained on the uptake of tagged insulin and

tumor necrosis factor alpha (TNFα). Another goal of the system will be to follow gene expression *in vivo* in small animals and eventually in humans.

Results

In an experiment reported by Welsh, et al. in "An Economical Dual-Modality Small Animal Imaging System With Application to Studies of Diabetes," [13] two different ligands were used that are thought to be essential in the treatment of diabetes. Insulin, which is important in treating diabetes, as well as TNFα, were tagged with ^{125}I. After injections of sodium pentobarbital to anesthetize the mouse, about 4 μCi of the tagged ligand were injected into the mouse. The mouse was then imaged using the support gantry system described above. As seen in the diagrams the labels traveled well into the bladder and stomach by the third hour (Fig. 8).

The TNFα, which is thought to be involved in the development of diabetes [13], traveled mainly to the liver and bladder regions (see Fig. 9). By studying the binding of this tagged ligand investigators can get an idea of the degree to which the receptors for the ligand are expressed in certain organs (for a more comprehensive description of this experiment see Reference [13]).
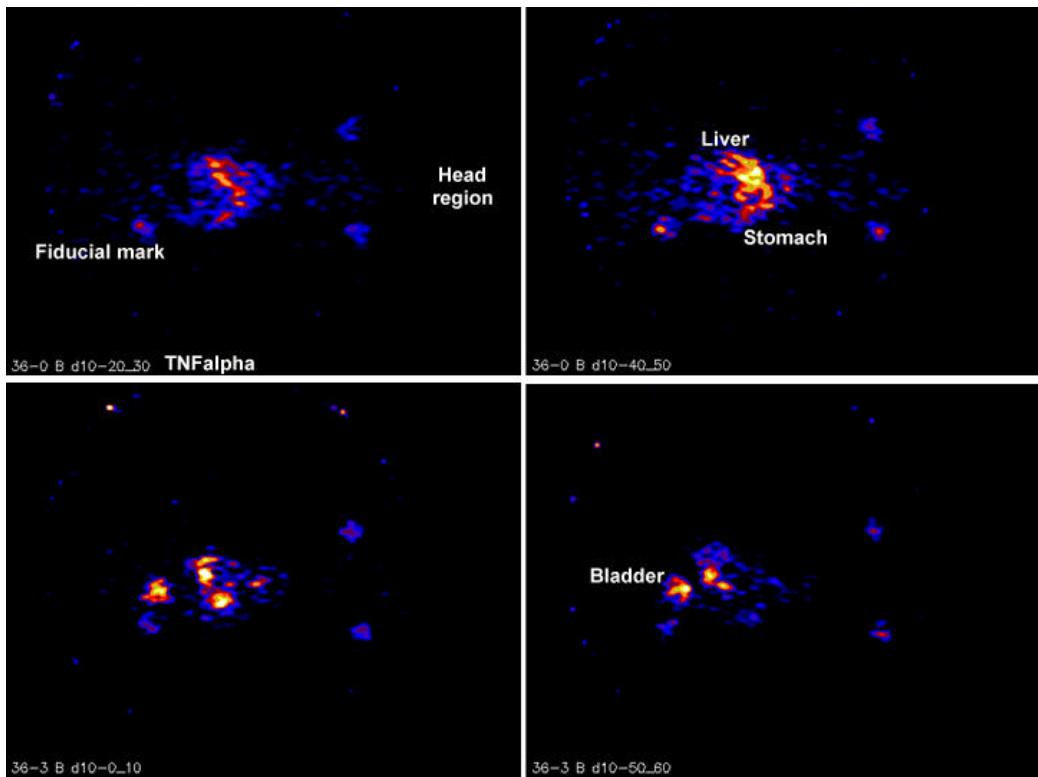
Figure 8: These are four pictures of ten separate time intervals during imaging. The three fiducial markers are apparent in each picture, while the head is to the right in each picture. The top left is an image of the period of 10-20 minutes after injection into the leg. The upper left is 50-60 minutes after injection. The lower left is 3 hours 10-20 minutes. The bottom left is 3 hours 40-50 minutes. By this time the tagged ligand has traveled mainly to the bladder and stomach.
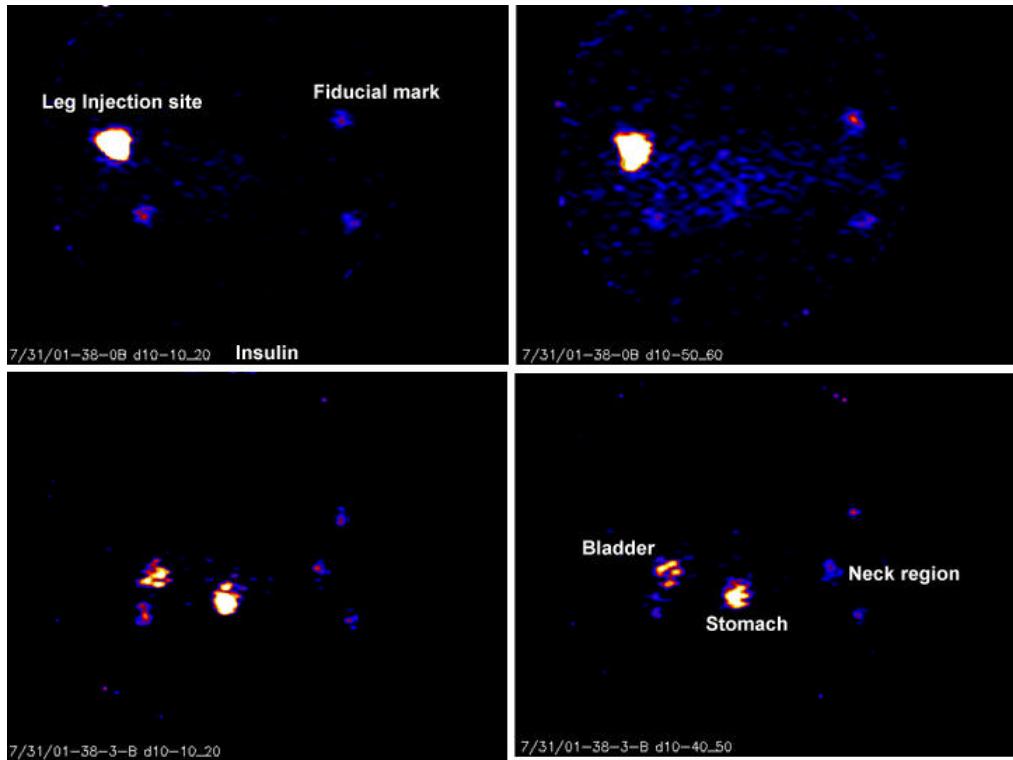
Figure 9: Like the images with the insulin, these images of tagged TNFα are 10 minute intervals. The head is to the right hand side and the three fiducial markers are present as well. The upper left image is of 20-30 minutes. The upper left shows the distribution at 40-50 minutes. The lower left panel is a ten minute study at 3 hours. The lower right image is at 3 hours 50-60 minutes. By this time, the distribution is mainly in the abdominal region, namely the liver and bladder.

VI. Mouse Movement

During a recent SPECT scan, it was discovered after looking at the gamma-ray images that the mouse moved during the experiment. Fig. 10 shows four gamma-ray images of the mouse. The images are all ten minute intervals of the third hour post injection.
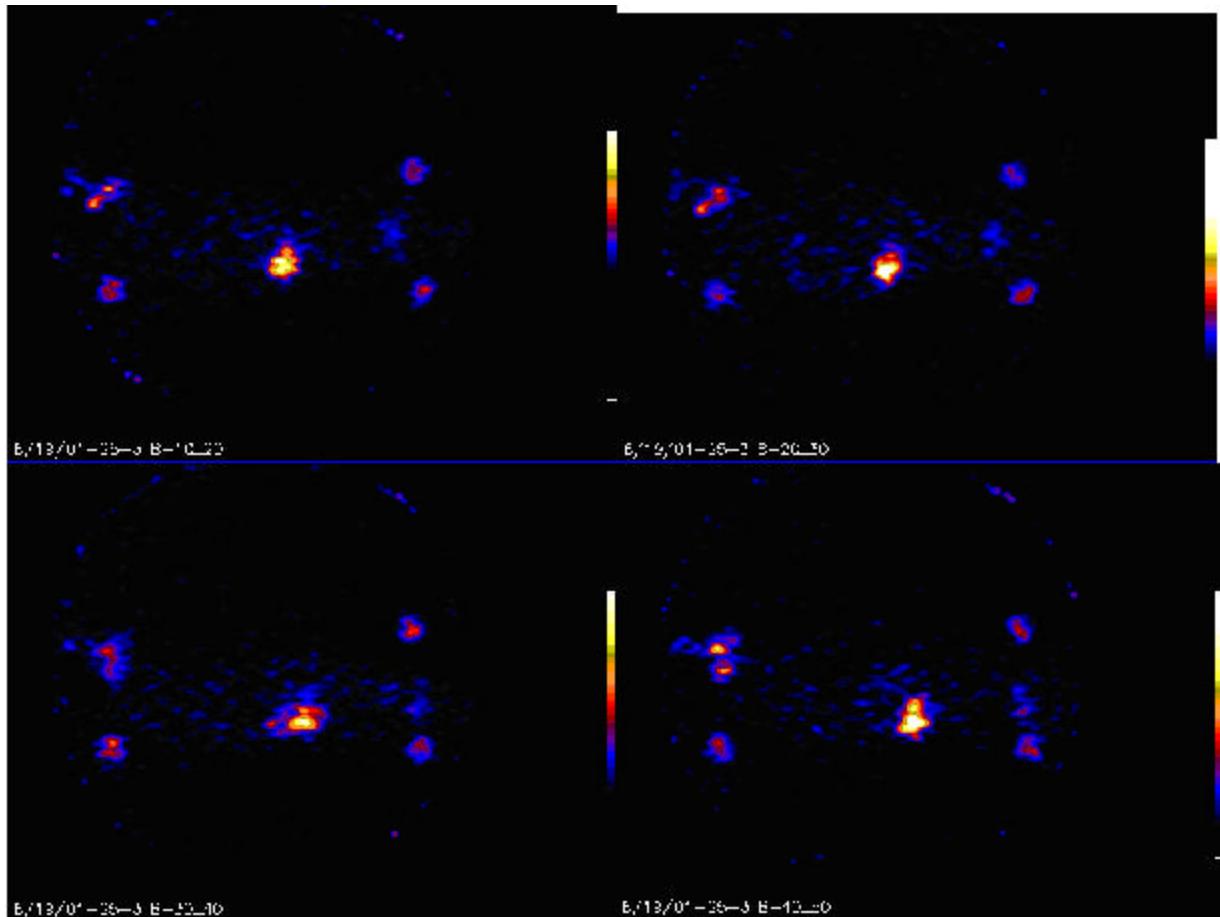

Figure 10: These four pictures show the mouse in the third hour, starting with the upper left image. The upper left picture shows the mouse from 10-20 min.; the upper left shows the mouse from 20-30 min.; the bottom left shows the mouse from 30-40 min.; the bottom right shows the mouse from 40-50 min. It is important to note the shift in the mouse's stomach and paw between 20-30 min. and 30-40 min.

The top left image is of the mouse from 10-20 minutes; the top right is from 20-30 minutes; the bottom left is from 30-40 minutes; and the bottom right is from 40-50 minutes. Notice the shift in the mouse's stomach region and in the upper left paw from the top right picture as compared to the bottom left picture. Not only does this movement blur the gamma-ray imaging, but it also disturbs the overlay of the x-ray images with the gamma-ray images.

VII. Movement Detection and Correction Techniques

Phantom and animal studies have shown that movement of as little as 3 mm may lead to artifacts in SPECT images [14]. Axial motion has been seen to cause more artifacts than lateral motion and distortion is accentuated when both types of movement occur simultaneously. Cross-correlation computer techniques and tracking point sources [15] are two of the most frequent ways to detect motion.

Cross-correlation, an efficient process in matching images, utilizes an algorithm called a cross-correlation function to compare the degree to which two series are correlated. Movement is determined by changes in pixel values of successive frames. Motion as small as 1 pixel can be determined using this frame-to-frame correlation technique. Data can then be stored and represented as a curve to display the frame number and the pixel shift [16]. Most often, movement is corrected by shifting images so they conform to the position of a fixed object.

C. Pellot-Barakat, et al. [24], however, propose a different detection and correction system for triple scan SPECT imaging. The total scan acquisition time is divided into three sections of equal length. However instead of traveling 120 degrees, the detector heads move in 3 degree intervals over the full 360 degrees. Three projections per angle are obtained which creates three full sets of SPECT data. By combining certain images from the three sets of data, a motion-free

data set can be made as a function of the angle using a correlation algorithm. The product is a combination of projections that is motion-free [15].

In the medical field however, data acquisition and image processing programs are used to correct for patient movement. HERMES, for example, is a nuclear medicine image acquisition and processing system. HERMES provides a method of motion correction by acquiring a series of dynamic frames every few seconds. The program corrects for motion in the given frames then averages them to form a single, motion corrected, static image.

VIII. Approach to Motion Detection

<u>Procedure</u>

The approach taken for motion detection is based upon a tracking point system. A phantom mouse of 6 cm length was marked with a reflective material on its head, paws, and stomach. Three different materials, 3M Scotchlite reflectors, reflective glass beads, and White Out, were tested to determine how much light they reflected into a digital camera. The setup consists of a Webcam Go digital camera connected to a Macintosh G4 computer. A gif screen capture program was used to capture an image from the screen once every five seconds. The images were then converted into a movie that allowed the investigator to watch the imaging process and determine where and at what time any movement occurred.

<u>Results</u>

After a number of runs testing several types of reflective markers, White Out was seen to reflect the most light to the digital camera.
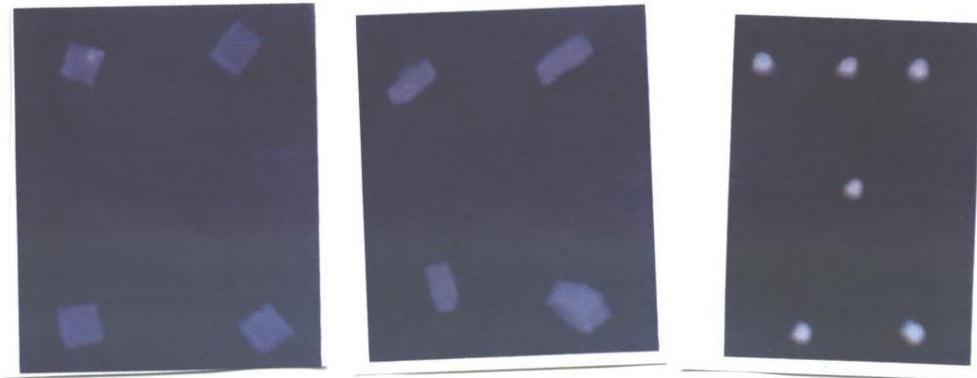
Figure 12: Example of different reflectors. The far left image shows 3M Scotchlite reflectors. The middle image shows glass bead reflectors. The right image shows White Out as a reflector.

A phantom mouse was then imaged for four minutes using the White Out as the reflective marker. Movements were caused by fishing wire tied to the tail to control lateral movement. The series of images were converted into a movie which was played back using Apple Quicktime.

The reflective White Out indicated when motion occurred during the playback of the movie. Once a movement was detected, that particular image was either cut from the movie or taken into Adobe Photoshop where it could be rotated and translated back to its original position using the reflective markers as guides and restored to its position in the movie. An example of a correction is shown in Fig. 13.
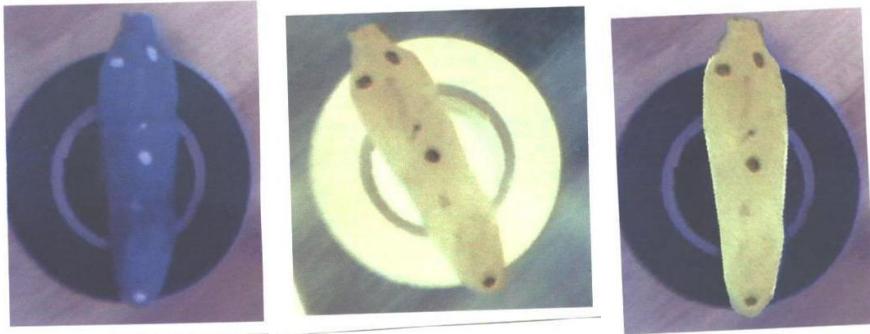
Figure 13: The left image is of a phantom mouse before movement. The middle image is the same phantom after movement. The right image is the correction of the movement back to its original position.

IX. Conclusion and Future Improvements

The SPECT imaging system described above is being developed in conjunction with Jefferson Lab. It has potential to be very helpful in studying the metabolism of a number of tagged ligands in small animals. It is planned to use this system in studies of diabetes, as well as other diseases and biological processes. A proposed study underway at Jefferson Lab would allow the mouse to run free without anesthetization. Such experiments will put greater demands on the need to correct for movement while the mouse is studied.

The detection system developed now gives investigators the ability to see where motion has occurred. This important information allows the researcher the option of ignoring data depending on when and where the event took place. The next step in the project will be to utilize a cross-correlation function to account for pixel movement in tomographic scans. A mounting unit will be built to hold a camera which can monitor the mouse continually while it is being imaged. Tests will be run using radioactive phantoms to simulate mouse movement. Software using the cross-correlation techniques described in Reference [25] will be designed or obtained to correct for movement during imaging. The goal of the imaging will be to track the mouse to within 2 mm.

References

[1] Mark B. Williams, PhD, Victor Galbis-Reig, Allen R. Goode, MS, Piero U. Simoni, Stan Majewski, PhD, Andrew G. Weisenberger, PhD, Randolf Wojcik, PhD, Walter Phillips, PhD, Martin Stanton, PhD. "Multimodality Imaging of Small Animals."

http://ej.rsna.org/ej3/0107-99.fin/dual99.htm

[2] Andrew G. Weisenberger, "Gamma-Ray Imaging Detector for Small Animal Research," PhD thesis, College of William and Mary, 1998.

[3] "Single Photon Emission Computed Tomography," Medical Imaging Techniques,

http://imasun.lbl.gov/~budinger/medTechdocs/SPECT.html

[4] "Scintillators," Nuclear Medicine Instrumentation

http://oden.nuc.ucla.edu/rs200b/lecture_notes/lecture3/scint1.html

[5] Amorenna Ranck, "Dual Modality Small Animal Imaging," Honors Thesis, College of William and Mary, 2001.

[6] John Feldman, "Small Animal Gamma-Ray Imaging," Senior Research Project, College of William and Mary, 2001.

[7] Andrew G. Weisenberger, "Gamma-Ray Imaging Detector for Small Animal Research," PhD thesis, College of William and Mary, 1998.

[8] John Feldman, "Small Animal Gamma-Ray Imaging," Senior Research Project, College of William and Mary, 2001.

[9] "Scintillators," Nuclear Medicine Instrumentation,

http://oden.nuc.ucla.edu/rs200b/lecture_notes/lecture3/scint15.html

[10]   A. G. Weisenberger, R. Wojcik, E.L. Bradley, P. Brewer, S. Majewski, J. Quan, A. Ranck, M.S. Saha, K. Smith, M.F. Smith, R.E. Welsh, "SPECT-CT System for Small Animal Gamma Ray Imaging."

[11]   "Positron Emission Tomography" Medical Imaging Techniques, http://imasun.lbl.gov/~budinger/medTechdocs/PET.html

[12]   "Nuclear Magnetic Resonance" Medical Imaging Techniques, http://imasun.lbl.gov/~budinger/medTechdocs/NMR.html

[13]   R.E. Welsh, P. Brewer, E.L. Bradley, K.K. Gleason, B. Kross, S. Majewski, v. Popov, J. Qian, A. Ranck, M.S. Saha, K. Smith, M.F. Smith, A. G. Weisenberger, R. Wojcik, "An Economical Dual-Modality Small Animal Imaging System With Application to Studies of Diabetes."

[14]   "Patient Motion," Image Artifacts on Myocardial SPECT http://www.med.harvard.edu/JPNM/TF93_94/Nov23/WriteUpNov23.html

[15]   C. Pellot-Barakat, M. Ivanovic, D.A. Weber, A Herment, D.K. Shelton, "Motion Detection in Triple Scan SPECT Imaging," IEEE Transactions on Nuclear Science vol. 45, No. 4, 2238-2244.

[16]   R.L Eisner, T. Noever, D. Nowak, W. Carlson, D. Dunn, J. Oates, K. Cloninger, H.A. Liberman, and R.E. Patterson, "Use of Cross-Correlation Function to Detect Patient Motion During SPECT Imaging," Journal of Nuclear Medicine vol. 28, 97-101.