DEPARTMENT OF BIOMEDICAL ENGINEERING

An Open Source Imaging Platform for Small Animal Imaging and Therapy

Jay Sekhon—Leader
Jon Seaton—Communicator
Whitney Johnson—BSAC
Sarah Springborn—BWIG

Client: Dr. Thomas Rockwell Mackie
Dr. Robert Jeraj
Surendra Prajapati

Advisor: Prof. Willis Tompkins

May 05, 2010

Table of Contents:

Abstract 3
Open Source 3
Computed Tomography Background 3
CT Specifications 7
Positron Emission Tomography 8
PET Specifications 10
Radiation Therapy 11
RT Specifications 12
Combination Systems 13
Combination System Specifications 14
Design Process 14
Device Documentation 17
Regulations and Ethics 18
Conclusion and Future Work 19
References 20
Appendix A: Product Design Specifications 22
Appendix B: Customer Requirements 25

Abstract

An open source medical device has the benefits of a cheaper cost and more collaboration amongst researchers. A combined computer tomography (CT), positron emission tomography (PET) and radiation therapy (RT) system is being developed in the spirit of open source technology. The combination of these systems has the added benefit of correlating data among the imaging systems and using this data for precise radiation therapy treatment. The CT system uses X-ray radiation and detectors to produce 2-D and 3-D cross-sectional images of anatomical structures at high resolution. The PET system uses radioactive tracers to highlight metabolic activity of different biological structures. The RT system uses high intensity X-ray radiation to non-invasively obliterate cancerous cells in the body. A table of specifications for various components of the different systems has been developed with the intention of designing a combined system with the minimal number of components.

Open Source

In collaboration with the Morgridge Institute for Research, the client is developing an Open Source Medical Device (OSMD) program, which would provide researchers around the world free access to a device's design and development. The OSMD program brings researchers together, encouraging cooperation during the design process. Another advantage to open sourcing is that it makes expensive instruments and technology available to research groups with limited funding. As all software and hardware specifications are accessible, researchers can build and design the system for their own use, avoiding buying an expensive unit directly from one manufacturer [11].

Computed Tomography Background

Computed Tomography (CT) is a common technique used to obtain 2-D or 3-D images that display internal structure. CT by itself is not a specific imaging system; instead the term is used to describe the method in which an image is reconstructed. Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT), and x-ray imaging all use CT to create 2-D or 3-D representations from projections. For the purposes of this project, x-ray CT will be the primary technique implemented in the imaging device. In x-ray CT systems, electromagnetic radiation is applied to an object and attenuated as seen in Figure 1. Detectors located opposite the x-ray source measure the remaining radiation, creating a projection of how the objected scattered the energy. The x-ray source is then rotated about the object to create an array of projection data, which can be used to reconstruct a 2-D image. By moving the object in the y-direction as seen in Figure 1, multiple slices can be obtained and used to create a 3-D image.

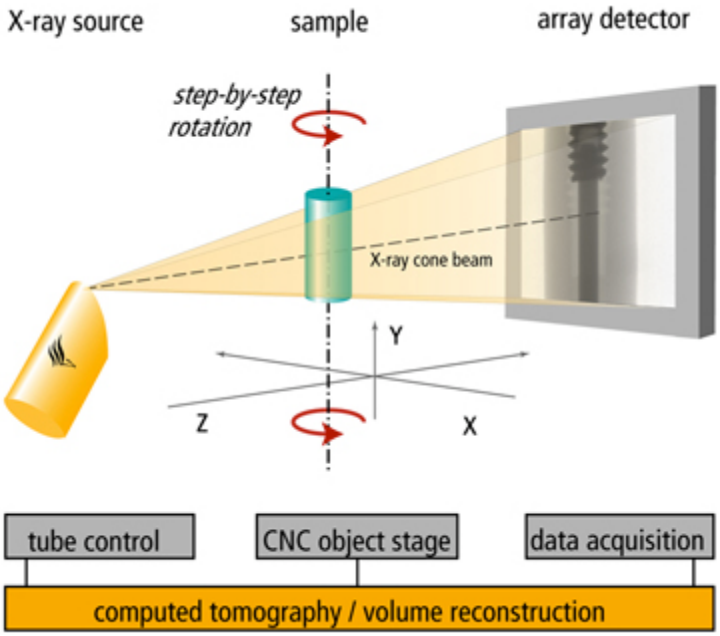

Figure 1. Method of X-Ray CT data collection. [8]

In order to create x-rays, one must first understand the nature of electromagnetic (EM) radiation. X-rays are a subclass of electromagnetic radiation occurring with energies between 20keV to 120keV [6]. Electromagnetic radiation is primarily the result of both an oscillation electric and magnetic field. However, while it can be modeled as a wave, such radiation also has particle properties, the particle being known as a photon. This type of radiation is known as non-ionized radiation since it does not contain a charge. Thus, the energy of EM radiation comes from kinetic energy of photon's motion. The relationship between the energy of the photon and the frequency of its oscillations as a wave is given by:

$$E = hf$$

Where E is the energy, h is Plank's constant, and f is frequency. Thus, in order to create x-rays, one must create an event in which energy is released from the system. A common method is to collide electrons with a target and by conservation of energy. As the electrons slow down, they release energy by conservation, also called Bremsstrahlung radiation [6]. Thus by adjusting the speed in which the electrons hit a target, we can adjust the energy of radiation produced.

Since x-rays can be thought of as a particle, it is clear to understand their interaction with other matter. If an x-ray hits an electron, it can transfer its energy to set that particle in motion, known as the photoelectric effect. Alternatively, an x-ray can come in close contact with an electron or proton and scattered because of the electric field. It is also possible for both events to occur, known as the Compton Effect [6]. Here, an x-ray transfers part of its energy to an electron and then scattered with a reduced energy. These three types of interaction between radiation and matter are exploited with

CT imaging. Since these interactions will be dependent on the electron density of an object, the data collected from x-ray CT represents the contrasts between areas of high density from areas of low density.

Data of how x-rays were attenuated by an object can be collected using photodiodes or photomultiplier tubes. Both methods utilize the photoelectric effect, which converts the x-ray energy to a measurable voltage change. Through the use of an array of these devices, we can discretely measure x-rays after they have passed through an object. After a certain exposure time, the voltage measure by each photodiode represents the sum of x-ray energy in that given period. However, since the object is assumed to be a continuous structure with a continuous distribution of x-rays passing through it, care must be taken when sampling the output. Specifically, the Nyquist criterion states that we must sample the data at twice the spatial frequency to avoid aliasing when reconstructing the image. Once the data is collected, a distribution of the x-rays hitting the detectors can be displayed for that projection.

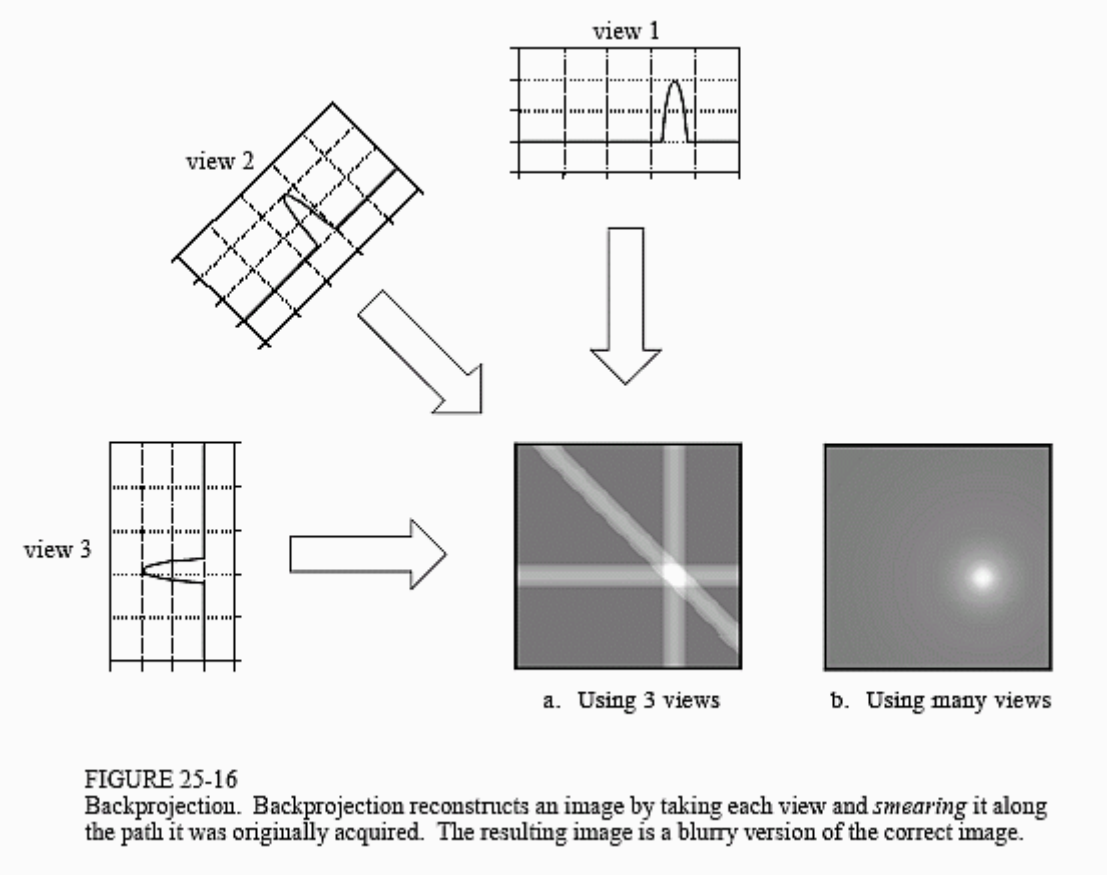

Figure 2. Method of filtered back-projection for reconstructing an image from the response function at different angles. [13]

As seen in Figure 2, projection data of the object is then taken by rotating the gantry at different angles. As seen in diagram, increasing the number of angles used to collect

increases the quality of the image. However, in order to display the original object from the project data, a reconstruction algorithm can be used. One of the most common methods of reconstruction is through filtered back-projection. In this method, a 1-D Fourier transform is taken from the projection data at a given angle. This can then be represented as a 2-D object in spatial frequency space or k-space. A ramp filter is then applied to reduce replication of spatial frequencies in the center of the image. Using the projection angle, the 2-D data is then transformed into the proper coordinates and a 2-D inverse Fourier transform is performed, resulting in the image of the object [6]. An example of an x-ray CT image generated through this method can be seen below in Figure 3.

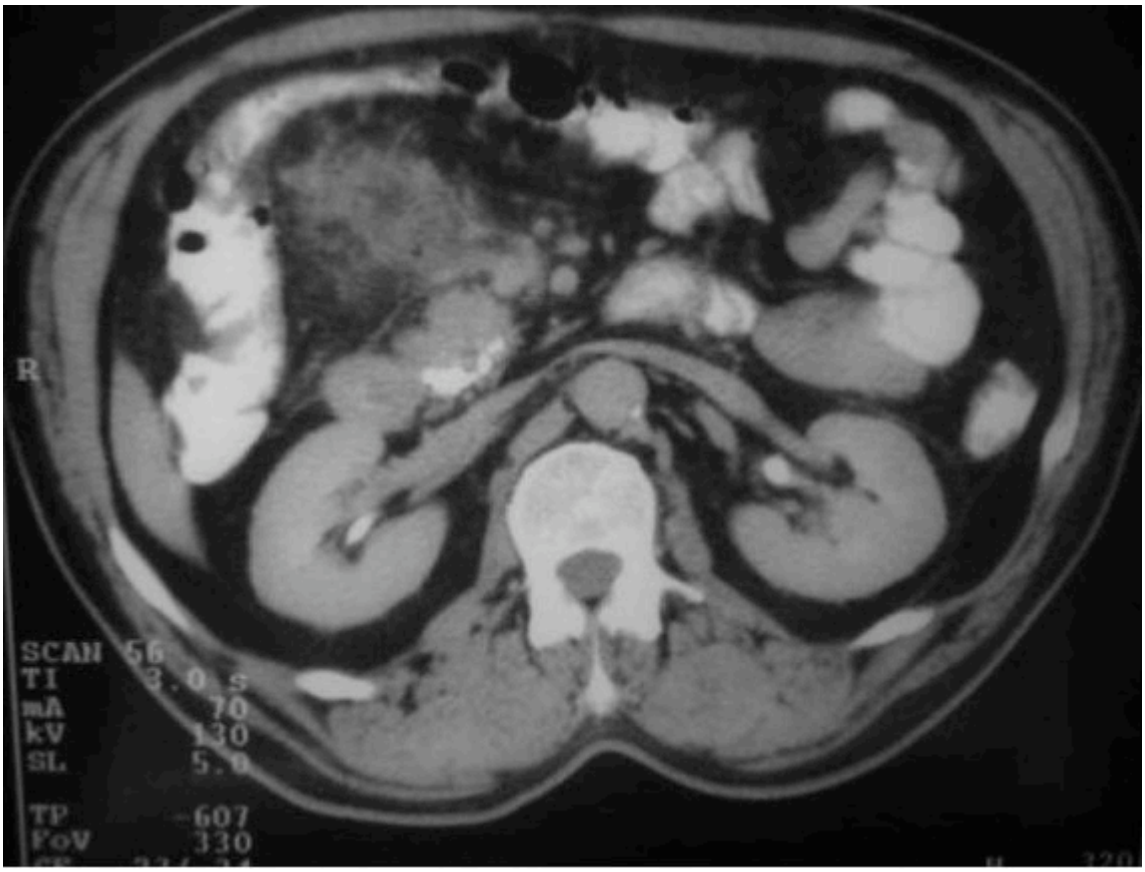

Figure 3. Example of a CT image reconstructed depicting the abdomen of a human patient. [12]

A number of factors affect the quality and resolution of the image. As already discussed, the sampling rate must be in accordance to the Nyquist frequency. If the object is under sampled, the final image will be blurred. Thus it is important to correctly determine the spacing between the photodiodes in the detector. Also, the size of each detector will limit the resolution. Ideally the width of each detector should be zero to obtain maximum resolution, but since this is impossible the image cannot have a spatial density larger than the width of each photodiode. Another factor that affects resolution is the detection scattered x-rays. To reduce this occurrence, a collimator can be added to filter any x-rays not traveling in a straight line. Finally, the x-ray energy used when imaging will affect the quality of an image because high energy x-rays will not be

attenuated as effectively as low energy x-rays since they have much larger forward momentum.

CT Specifications

In order to design an x-ray CT system, a number of specification regarding the x-ray source, detector type, gantry dimensions, collimators, filters, data collection, and reconstruction software. In Figure 4 below, a basic overview of the components in an x-ray CT system can be viewed.

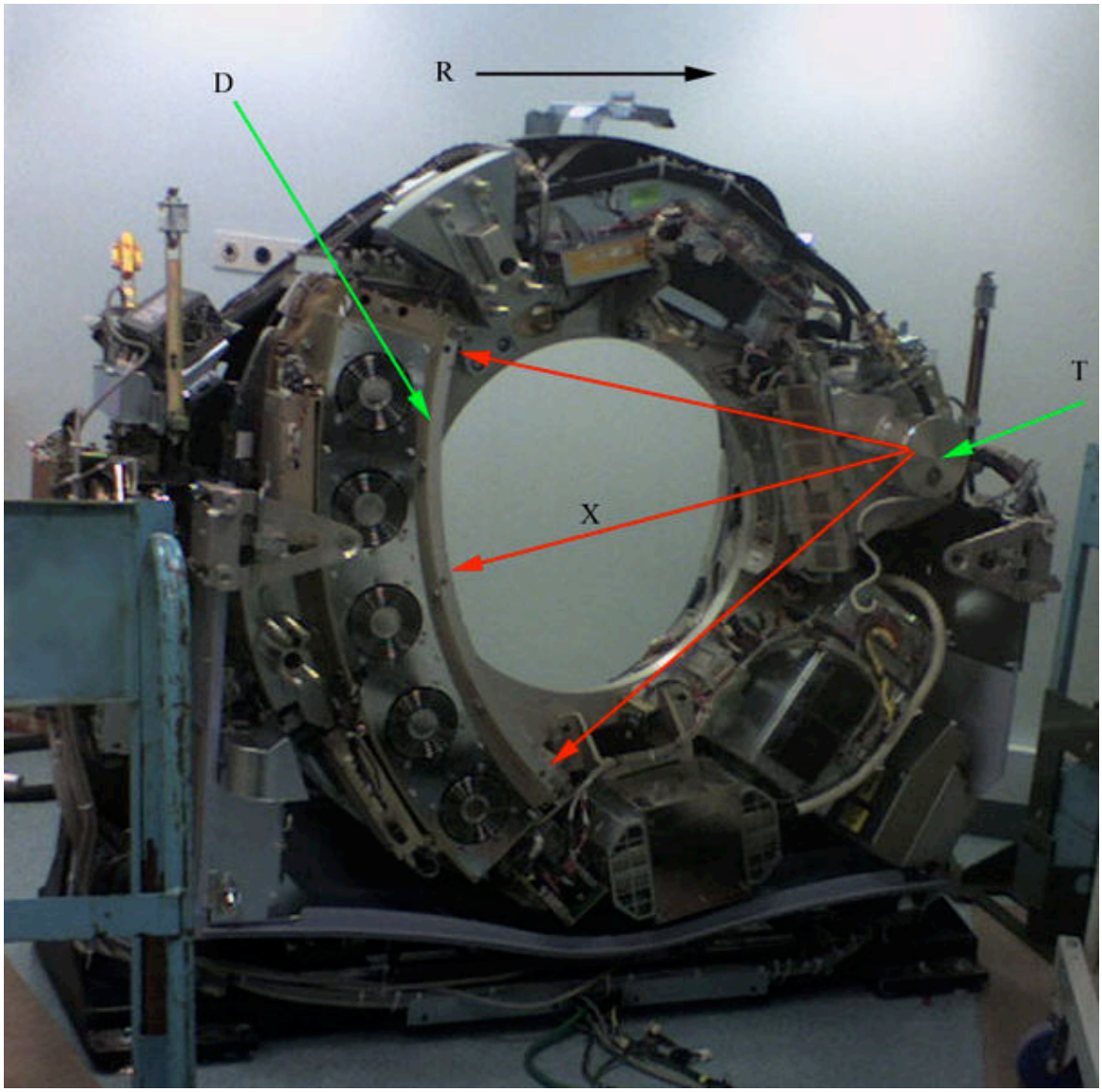

Figure 4. Image displaying the internal components of an x-ray CT machine. T represents the x-ray tube. X are the x-rays produce that travel through the patient. D is the detector array. R is the direction of gantry rotation. Ref: [http://en.wikipedia.org/wiki/File:Ct-internals.jpg].

In Table 1 below, a list of specifications for the CT system are described. Since CT imaging is only one component of the system being designed, specifications

regarding the gantry and cooling system will be discussed elsewhere. It was decided that the x-ray source should output energy between 50-100kVp. This would be enough energy to fully penetrate the object while providing adequate contrast and attenuation. Also, the focal spot of the x-ray source would need to be less than 10 microns to achieve good image resolution. A 0.5 mm copper sheet and a 1mm aluminum sheet were chosen as filters because of their ability to absorb soft x-ray energy. The geometry for data acquisition will be fan beam because of its simplicity and lower cost of production. However, collimators using fan beam geometry require an addition processing to account for changes in the focal position. Silicon photodiodes were chosen as detector elements because of their lower cost, size, and efficiency. Overall, the system designed should have a resolution between 20 to 40 microns.

Table 1. Specification for the CT imaging system.

X-ray Source Energy	50-100kVp
Focal Spot	<10 micron
Filters	0.5mm Cu and 1mm Al
Acquisition Geometry	Fan Beam
Detector	Silicon Photodiodes
Detector Resolution	20-40 micron

Positron Emission Tomography

Positron Emission Tomography (PET) is a nuclear imaging modality that is used to show physiology. The basic principle involves using a radionuclide that decays by positron emission. Positrons are the antiparticle for electrons, and when the particles collide, they annihilate. This produces two gamma rays that travel in opposite directions at 511 keV [6], which is the mass of an electron. For imaging, the radionuclide is attached to a metabolite that is injected into the body. The positron emission and subsequent annihilation can be used to image metabolic activity and physiology. The basics of PET from a systems perspective can be broken down into three major parts—the radionuclide, the detector array, and the imaging reconstruction method.

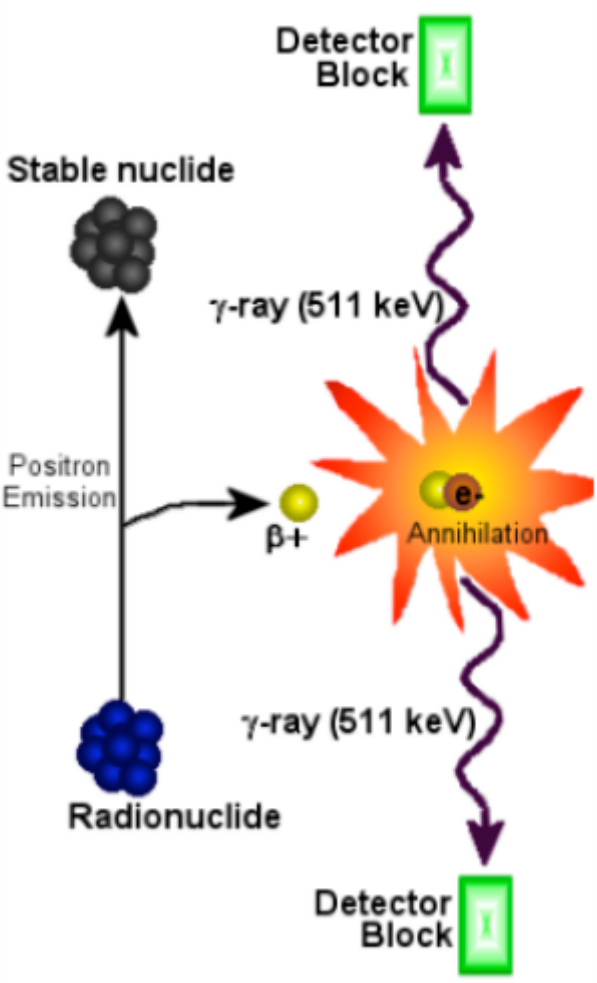

Figure 5. Diagram showing the basics of PET data collection.

The radionuclide that is used for PET varies based upon the system or organ of interest. Commonly used nuclides include C-11, N-13, F-18, Cu-64, I-124 [6], and they can be conjugated with biologically active molecules to determine metabolism. For example, the most commonly used radionuclide, flurodeoxyglucose (FDG) uses F-18 and acts as a glucose analogue [5]. This can be used to image the brain, the heart, and lungs for metabolic activity, or used in oncology to image tumors. The only downside to this method of imaging is that most radionuclides used have short half-lives, usually less than two hours. This requires that it either be made onsite or shipped quickly to clinics that have PET scanners, both of which are very costly.

As mentioned previously, the radionuclides used decay by positron emission—the positrons collide with electrons in the body and produce two gamma rays traveling in opposing directions at 511 keV. These gamma rays are used to indicate an annihilation event when they strike the detector blocks. The detector blocks make up the next major component of the PET imaging system. In the basic block, a scintillation crystal is connected to a photomultiplier tube (PMT). Modern detector blocks have modified this

principle, using a single crystal which has been cut to make a smaller array of crystals. These cuts have an opaque reflector which improves the resolution of detection by controlling the light distribution that reaches the PMTs.

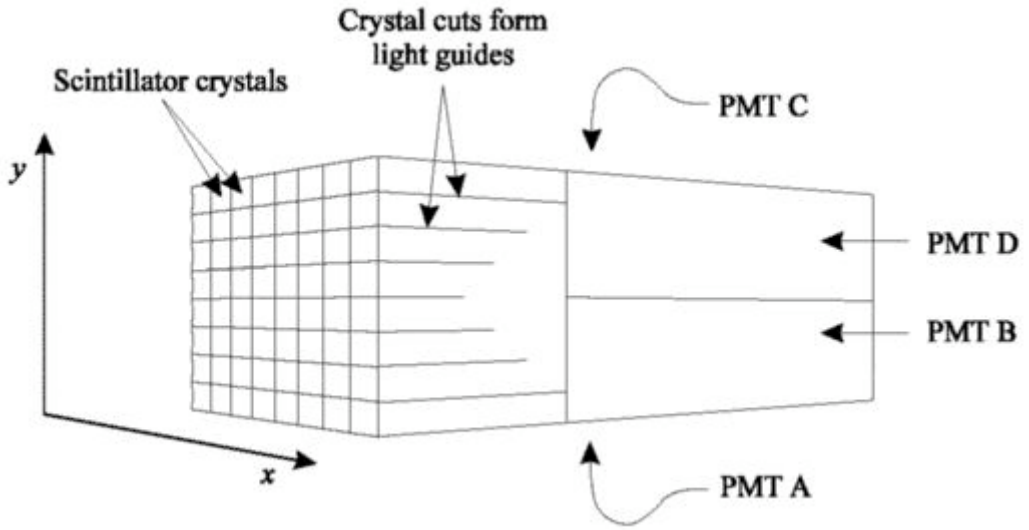

Figure 6. A diagram showing a PET detector block [18].

The choice of scintillator crystal is also important for determining the efficacy of imaging. The detection efficiency is determined by the linear attenuation coefficient of the material as well as the material thickness. The linear attenuation coefficient is given by how easily a beam of light can penetrate the material. As such, a high attenuation is desirable since it indicates that light can penetrate easily. Commonly used materials for detector crystals include BGO (Bismuth germanate), LSO (Lutetium oxyorthosilicate), and BaF_2 (Barium Fluoride) [6]. The PMT is a type of light-detecting vacuum tube and is analogous to an operational amplifier for electric currents. Incoming light is amplified to produce a larger current than would be produced by the incident light, and the resulting current carries the signal of a detection event to the logic system.

In order to produce an image, a few additional characteristics are needed. By noting the time difference between detection events, it is possible to determine the location of the original annihilation event. It is important to note that only events that occur on opposing blocks are recorded—there are scattering gamma rays and random noise that also strike the detector blocks, but these are discarded. A series of opposing detection events over an extended period of time produces enough data to render an image. Similar to CT, the filtered back-projection method is used to create the PET image.

PET Specifications

For our PET system, we need to establish a few basic parameters with which to frame the specifications. It is important to consider that the radionuclide used will be left entirely to the discretion of the clinician or researcher, and as such, all the other equipment must work correctly. The important items to consider are the detector blocks and their components—the scintillation crystals used, the arrangement of the crystals, the

PMTs used, the combination of crystals and PMTs, and how the blocks form a detector array.

For a scintillator crystal, we opted for LSO. LSO has a good linear attenuation coefficient, is fairly inexpensive, and it also came at the recommendation of our client. The crystals will be arranged in a 20 x 20 array with 64 blocks, and each crystal will be 10 mm thick. The size is ideal for a small animal system, and a 20 x 20 array will provide a reasonably good resolution. The 64 block size came suggested from the client as well. The PMT used has yet to be finalized, but we have considered a model from Hamamatsu [17]. Still to be determined is the method of placing PMTs and crystals and the method of arranging the blocks to form the detector ring.

A more detailed list of specifications can be found in Appendix A: Product Design Specifications.

Radiation Therapy

Radiation therapy works by sending ionizing radiation into the body to kill unwanted cells. Commonly, a CT scan is taken of the area to determine the exact size, shape and most importantly location of the tumor. This data can then be fed into a computer and a treatment planning system can be used to develop the most effective treatment. Frequently, intensity modulated ration therapy treatments (IMRT) are used. This involves changing the intensity of the radiation and the collimator size for each beam of radiation [2]. A picture of this type of planning is shown below. High intensity X-rays are then shot into the body. Shape and intensity of the beam are modulated, using components described below, to ensure that only unwanted cells are obliterated. When the x-rays interact with the cells, it changes the genetic make up of the cells, causing them to die instead of proliferate. There are two different types of radiation that cause cellular death: direct and indirect. The direct method enters the cell and directly cuts the DNA and proteins in half. The indirect method enters the cell and ionizes the water molecules. This causes the formation of free radicals, which degrades the cell [3]. This procedure is also effective because cancerous cells divide much faster than healthy cells, so the cancerous cells would die almost immediately. The healthy cells, on the other hand, have time to recover from the radiation and will not be affected so harshly. Overall, radiation therapy has proven to be an effective non-invasive alternative for cancer treatment in humans.

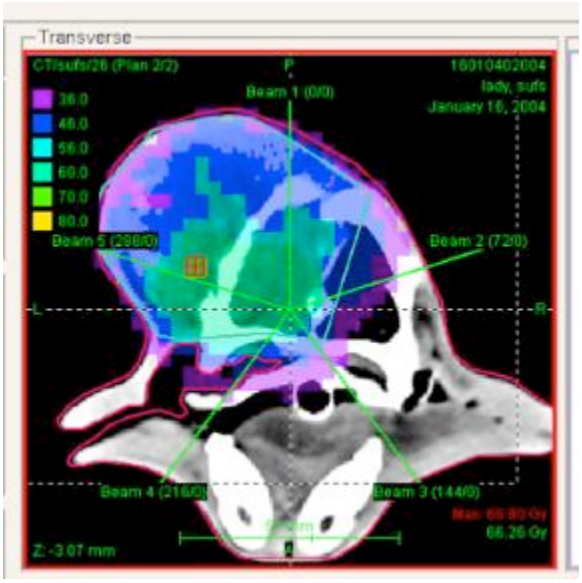

Figure 7 - Image of a IMRT plan showing the exact location and size of the radiation beams [10].

There are three major hardware components involved with the delivery of the radiation: Linear accelerator, collimator and a dosimeter. First, there needs to be some source of radiation to put into the body and this comes from a linear accelerator. A linear accelerator accelerates an electron beam to a very high speed. This beam then strikes a target and X-ray photons are emitted. For radiation therapy purposes, the X-ray photons that are emitted must be of very high intensity and thus are frequently called orthovoltage X-rays. The intensity of the X-ray beam emitted can be modulated through the final speed of the electron beam coming out of the linear accelerator. This is one of the many ways that the treatment can be specialized to each patient. The x-rays are then passed through a collimator, which determines the size of the beam emitted into the body. A collimator is made of metal leaves, frequently lead, that can be moved relative to each other to produce a shape similar to the shape of the tumor. All other X-rays are deflected by the metal leaves and absorbed in the machine. Finally, it is very important to know exactly how much radiation is coming through the collimator at each time, which is where the dosimeter is needed. Most frequently, ion chambers are used as dosimeters in radiation therapy. This system is composed of a small chamber filled with electrically charged gas particles (ions). When X-rays enter the system, the ions dissociate and cause an electric current between the two plates, which are acting as electrodes [3]. This information can be interpreted by a computer to give the exact amount of radiation coming out of the collimator. It is important that the patient not be over radiated, but also that there is enough radiation going into the body to be effective.

RT Specifications

While there are many specifications relating to the hardware components of the radiation therapy system, there are a few in particular that will be discussed here. The orthovoltage tube (X-ray generator) should reach 250 kVp (peak kilovoltage), which is sufficient to kill any cancerous cells in the body. It should also have two focal spots to increase the maximum amount of power that can be used. A higher power requires a

larger focal spot, this is not always needed, and therefore having two separate focal spots provides the researcher with a choice between the two. The larger of the two focal spots should be 2 mm in diameter while the smaller should be around 0.4 mm. Also dealing with the orthovoltage tube is the problem of maintaining the correct temperature for the linear accelerator. It must be maintained within 2°C and this will be accomplished with a water-cooling system. There are a few different systems commonly used for dosimetry, including quartz fiber, silicone film, thermoluminescence and ion chambers but for this project an ion chamber will be used. Ion chambers give highly reproducible, accurate results and are very accessible. A suitable dosimeter will be selected for use with this project. Finally, the last hardware component that is involved with RT systems is the collimation system. The collimator should be comprised of a type of metal, particularly W, Cu, brass or Pb. The collimator should have a thickness of 2 mm and should be comprised of at least 120 leaves. Programming and movement will be discussed once the software side of the project is worked on. These are the basic specifications for the radiation therapy system in this project.

Combination Systems

The first device in development for this project is an open source small animal research platform that integrates positron emission therapy (PET), computed tomography (CT), and radiation therapy (RT). A system for small animals was chosen because it would face fewer regulatory obstacles when compared to a human system. Also, small animal research serves as important and useful prototype modeling for human medicine [11].

Several RT/CT and CT/PET combination systems currently exist for both human and small animals, although technology in the small animal system area is less advanced. Combination systems are important because images captured from individual systems can be superimposed, allowing their respective information to be correlated [1]. As PET provides relatively low-resolution images of selected metabolic activity and CT provides high resolution images of anatomical structure, a CT/PET system allows researchers to pin-point the location of metabolic activity by fusing the two images. These techniques are used to detect cancers, determine the efficacy of treatment, and map normal organ function [1]. In a similar manner, CT/RT systems are used to find the exact shape and location of treatment areas, such as tumors, in order to coordinate the most appropriate and effective radiation treatment plan.

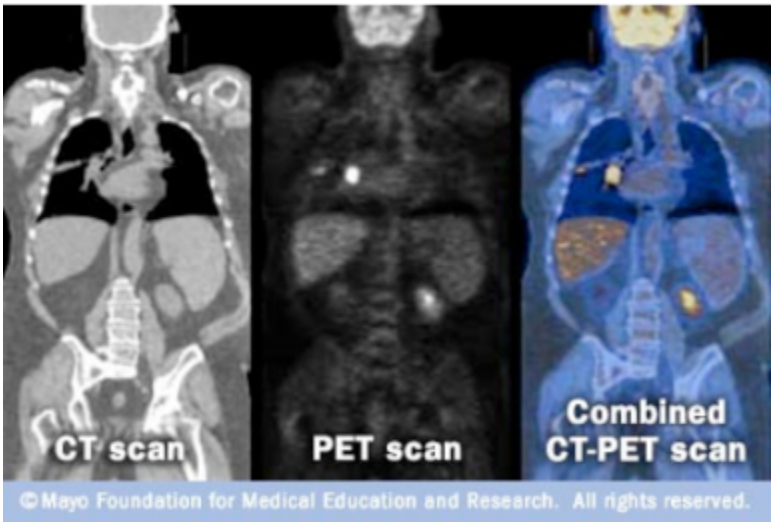

Figure 8 - A comparison of images gathered from CT and PET and the superimposed image showing the increased metabolic activity at anatomical locations.

Combination System Specifications

Although this project involves three separate systems, there are many components that are the same among all of them. These components include the couch, bore, motor, and beam shielding system. The couch system should have linear movement of 0.125 mm in all three planes and should be able to rotate 0.05° for precise positioning of the patient. The bore should have an interior diameter of 12 cm. The majority of the system should be made of plastics, but lead shielding will be needed to block any harmful stray radiation. Although specifications have not been developed for it, the motor is another system that needs to be considered in the future. A motor is required not only for moving the couch in and out of the machine, but also for moving the radiation source around the bore. Finally, a data acquisition system also needs to be considered. There is a great deal of information coming from these systems and it is very important to store and interpret this data. These are some of the more important specifications for the combined systems. This list should grow significantly as the project continues to progress.

Design Process

The design of the small animal imaging device will be done through an open source model. The process involves a determining the systems involved in each imaging modality and then defining the specifications for each system. Once the specifications are determined, vendors are found who can supply the necessary parts. Each part is modeled using SolidWorks and entered into a database, which anyone can access. The catalog will include vendor names and part specifications, which are compatible with the current design. A full model is then assembled in SolidWorks using these parts and tested by physics simulations. If the design is determined to meet its specifications and safety requirements, it will be released to the public—further information on safety and regulatory requirements can be seen in the corresponding sections. Anyone can then purchase the listed parts and assemble the machine themselves or have the machine

preassembled for a small fee. If a client has a specific design requirement, new parts can defined to meet these requirements and the full model recompiled. A basic overview of the current model can be seen below.

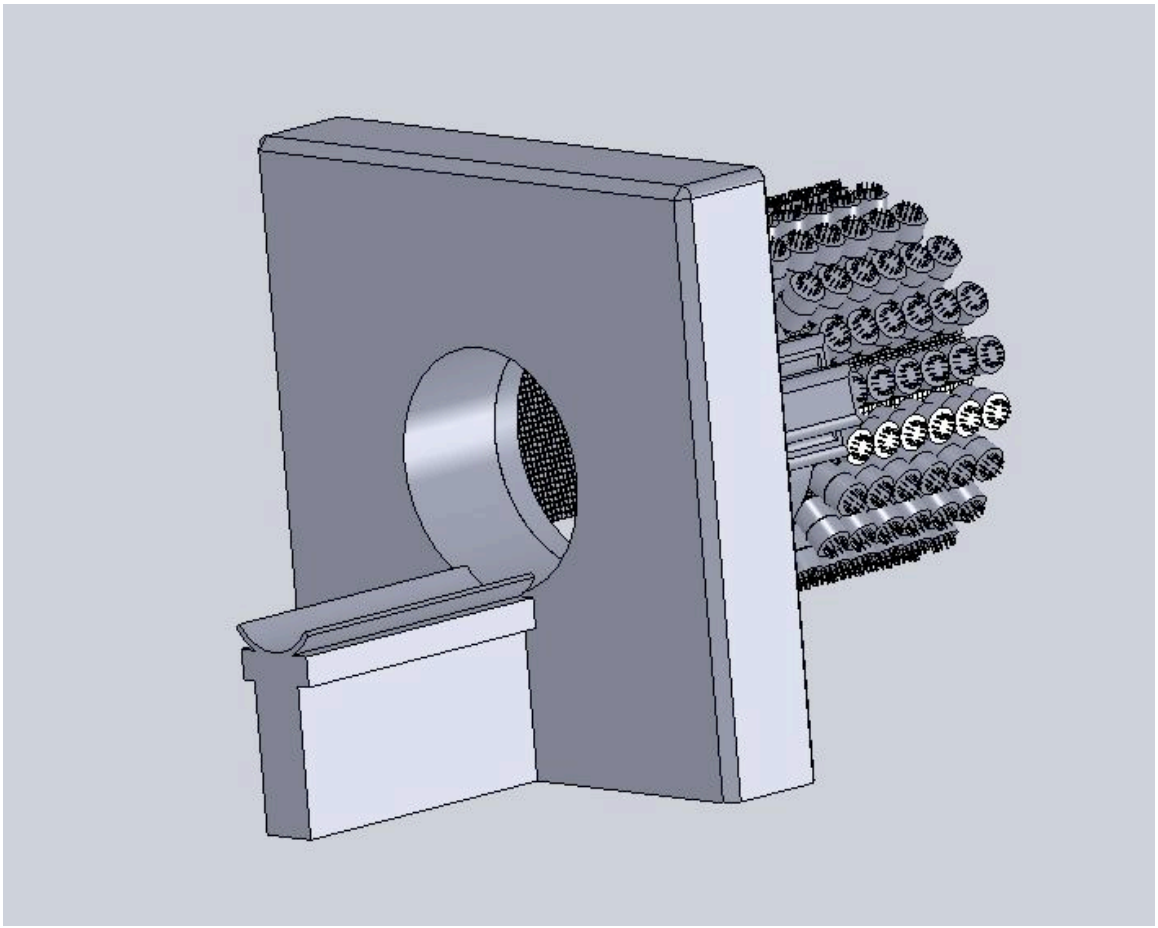

Figure 8 – Preliminary SolidWorks drawing of the total system, incorporating PET, CT, and RT components.

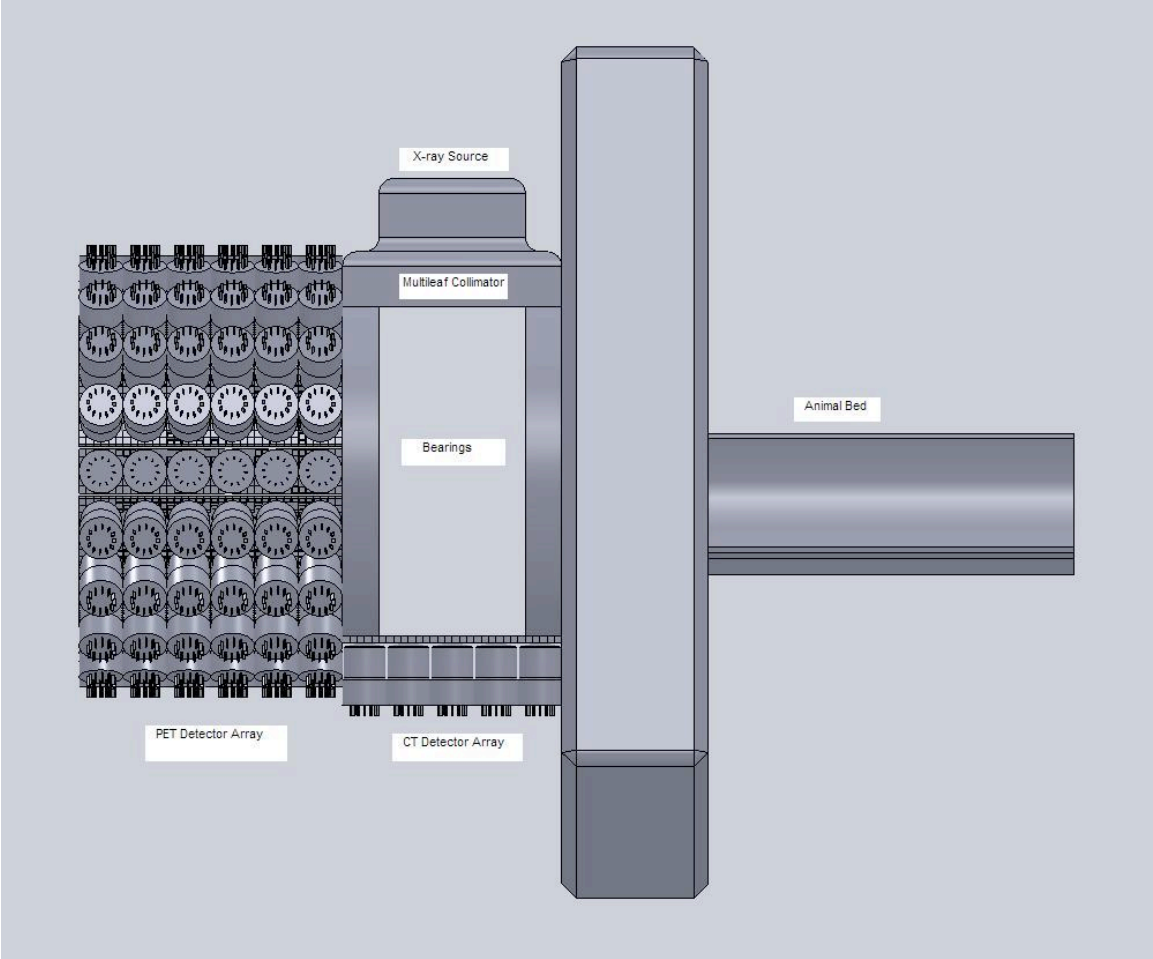

Figure 9 – Top View of SolidWorks Drawing. Specific parts have been labeled.

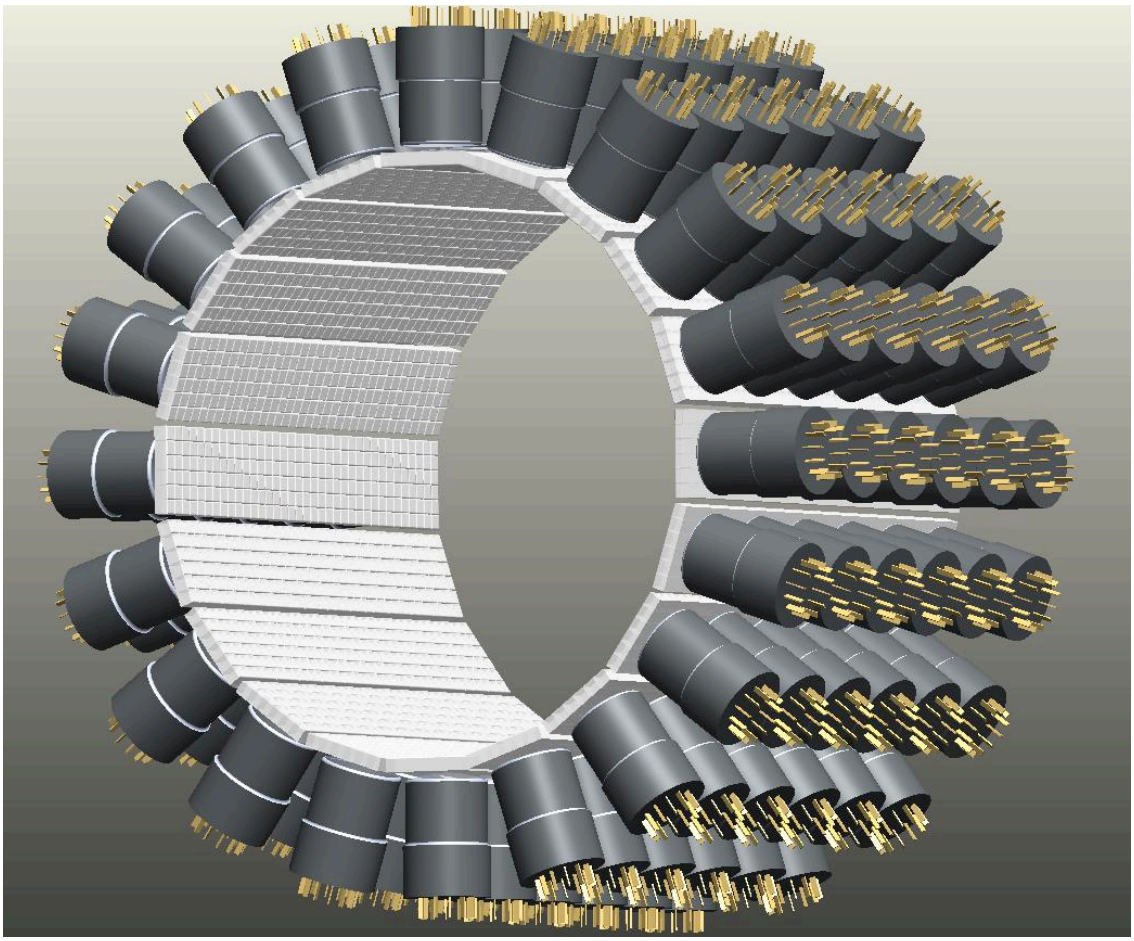

Figure 10 – Color view of the PET detector array. The proposed design will have 3 rings of 32 detectors each, as opposed to the 6 rings of 20 detectors each which is shown above.

Device Documentation

Proper documentation of medical devices throughout design, manufacturing, and testing stages is necessary in order to gain approval from the Food and Drug Administration (FDA). Although very few regulations exist for the testing of small animals, this research platform is currently being designed for components to be scaled to human specifications and applications. The FDA's Center for Devices and Radiological Health requires guidance documents in order to ensure the safety and effectiveness of medical devices. As the design of this platform progresses and human use is being considered, additional documents will be required by the FDA.

For both small animal and human use, a document listing customer requirements must be developed which will list customers' expectations for the device and explain how the project will meet those expectations. Topics covered include hardware specifications, reliability, safety, and cost. The customer requirements document is fluid and should be updated as needed; a current document for this small animal device can be found in Appendix B.

After the device is assembled, extensive testing must be carried out in order to prove its safety. A matrix tabulating the probability of device failure, consequences of each failure, probably of failure going undetected, and possible outcomes will be developed. Mitigation plans for each possible hazard must also be documented.

STED (Summary Technical Document) is a pilot program developed by the Global Harmonization Task Force in order to produce a standardized format for regulatory submissions [24]. Currently, the pilot program has been implemented to test its feasibility for pre-market applications and 510 (k) submissions; both documents are currently required by the FDA for Class II devices and higher. As this device will be used around the world, it is important to note that different locations may require different documentation. Programs such as STED aim to standardize format across jurisdictions and could provide documentation guidelines.

Regulations and Ethics

During the design, production and manufacturing of this product there are many regulations that must be followed before the device can legally be used in an academic, clinical or industrial situation. While this project is aimed for use in small animal laboratory situations, large animal and human regulations must also be considered to ensure that the device can be scaled appropriately and used for human patients.

Animals have been used in testing of medical devices for a very long and thus many regulations for their care and treatment have been developed over the years. In 1966, the Animal Welfare Act was signed into existence. This act has a long set of regulations that ensure that the animals used in research are given humane treatment and care. It also regulates the purchase, housing, care and handling of these animals [19]. Although this act is has the intention of protecting laboratory animals, which is not the primary use of our device, there are many regulations will still need to be considered while designing this machine. Another organization that closely monitors the treatment of animals during laboratory testing is the American Veterinary Medical Association (AVMA). This association has developed a policy, "Use of Animals in Research, Testing and Education," that directs researchers to consider the ethical considerations of using animals for testing. It encourages researchers to minimize the animal pain/distress, reduce the number of animals need for the study and to replace animals with non-animal methods whenever possible without compromising the validity of the study [20]. While the policy is focused on the treatment of the research animals, it does recognize the importance of animal testing in science. A final organization that is committed to the regulation of animals during testing/treatment is the Office of Laboratory Animal Welfare. Although very similar to the AVMA policy, this policy also states that anything causing the animal pain should be done under anesthesia and that researcher or veterinarian should take the animal's health into consideration (Cite OLAW). This policy also stresses the importance of considering ulterior methods before animal testing. While this project has been designed for the benefit of the animals (for diagnostic purposes) the policies and regulations that have been outlined above will still need to be considered during the design process.

In general, animal welfare regulations are much less strict that human regulations. This project involves designing a small animal system that can eventually be scaled up to become a human system. Therefore, it is important to think about human device regulations that will be important in the future. The Food and Drug Administration (FDA) has many regulations for the construction, manufacturing and documentation of medical devices. For example, the Compliance Policy Guides, Section 398.375 outline the documentation that must be done concerning x-ray system failure during manufacture and assembly. This specifically states any defect must be documented and reported to the FDA. If the defect was caused during manufacturing or assembling, the owner must replace or fix the system at no cost [22]. This is just one of many regulations that must be followed for a human system. A further investigation of the documentation needed for FDA approval should be completed before the project has progressed much further.

Ethical considerations are also a huge part of this project. This project will be working directly with animals and the treatment of these animals, therefore it is vital that the comfort and care of the animal is in consideration. The animal should not be in pain during the procedure. Most likely during use of this machine the animal will be anesthetized, which has the effect of eliminating the pain that the animal is feeling and also immobilizing the animal during the imaging. Although the animal should not feel pain at these levels of radiation, there should be a safety factor built in to ensure that the machine cannot cause lasting damage to the animal. The animals should be given humane care and housing between imaging. Their physical and psychological needs should be considered when designing and building a housing structure for the animal [23]. If anything happens to go wrong and the animal needs to be put down, it should be euthanized humanely. During all steps of designing this machine, the animal's welfare and health should be of utmost concern. This project is designed to benefit animals, but these concerns should be highly considered during the design process.

Conclusion and Future Work

In conclusion, open sources medical devices can be used to reduce costs, encourage cooperative research, and expand availability. The first project to be included in the open source medical device organization will be the design of a combination CT, PET, and RT system for small animal imaging. In order to complete this design, a full specification list along with vendors for each component must be created. Additionally, functional 3D models of the system will be made in SolidWorks. All proposed designs will adhere to the rigorous practices specified by the device documentation. Radiation simulation and dosimetry calculations must be performed to assess the dose to the animal and necessary shielding needed to protect people in the surrounding area. Once the final specifications and design are complete, existing parts can be purchased and custom parts such as the gantry can be fabricated. The system will be further rigorously tested and calibrated to ensure the design appropriate for a hospital or research setting. By designing a small animal imaging system, a scaled up version for human use may also be developed in the future.

References

[1] "Positron Emission Tomography – Computed Tomography (PET/CT)." *Nuclear Medicine.* Radiological Society. 2009. Web. 2 March 2010. <http://www.radiologyinfo.org/en/info.cfm?pg=PET>.

[2] Abate, A, M C Pressello, M Benassi and L Strigari. "Comparison of IMRT planning with two-step and one-step optimization: a strategy for improving therapeutic gain and reducing the integral dose." *Phys. Med. Biol.* **54**:7183-7198. 2009.

[3] Attix, F. H. *Introduction to Radiological Physics and Radiation Dosimetry*. Weinhein, Germany: John Wiley & Sons, Inc., 1986.

[4] Barrett, Harrison H. and Myers, Kyle J. *Foundations of Image Science.* Hoboken, NJ: John Wiley & Sons, 2004.

[5] Beyer T, Townsend DW, Brun T, *et al.* "A combined PET/CT scanner for clinical oncology." *J Nucl Med* **41**:1369-1379, 2000.

[6] Cherry, Simon, James Sorenson, and Michael Phelps. *Physics in nuclear medicine*. W B Saunders Co, 2003. Print.

[7] De Graaf, FR. *et. al*. "Clinical Application of CT Coronary Angiography: State of the Art." *Heart Lung Circ*. 2010.

[8] GE Sensing and Inspection Technology. 3D Computed Tomography. 2008. http://www.phoenix-xray.com/images/principles_of_operation/tomography_e.jpg

[9] Kak, Avinash C. and Slaney, Malcolm. "Principles of Computerized Tomographic Imaging." Nov 16, 2006. <http://www.slaney.org/pct/pct-toc.html>

[10] Olsen, R.G. "Experimental Radiation Therapy." *Dept. of Radiation Biol.* Oslo University Hospital. 2009. Web. 28 Feb. 2010. <http://www.rr-research.no/olsen/>.

[11] Prajapati, S, T Mackie, R Jeraj and M Rodriguez. "Initiation of open source medical devices (OSMD) with the development and design of small animal imaging and therapy system." Unpublished Data. 2010.

[12] S. K. Sahu, S. K. Burathoki, D. V. Bahl & P. K. Sachan. "Foreign Body Erosion Of Duodenum." *The Internet Journal of Surgery.* 2007 Volume 13 Number 2. http://www.ispub.com/ispub/ijs/volume_13_number_2/foreign_body_erosion_of_duodenum/erosion-fig2.jpg.

[13] Smith, Steve. *The Scientist and Engineers Guides to Digital Signal Processing.* California Technical Pub. 1st edition (1997)

[14] Ter-Pogossian, M.M. ; Phelps, M.E. ; Hoffman, E.J. ; Mullani, N.A. "Positron-emission transaxial tomograph for nuclear imaging (PETT)." *Radiology* Vol. **114**, no. 1, pp. 89-98. 1975.

[15] Visvikis, D; Cheze-Le Rest, C; Jarritt, P. "PET technology: current trends and future developments." *British Journal of Radiology* **(2004) 77**, 906-910

[16] Zhou, Yu and Li, Wu. "Image reconstruction method and X-ray CT apparatus." US Patent 7,656,991. Feb 2, 2010.

[17] "Photomultiplier Tube." Hamamatsu Photonics. <http://sales.hamamatsu.com/assets/pdf/parts_R/R1450.pdf> Feb 2010.

[18] Badawi, R. "Introduction to PET Physics." <http://depts.washington.edu/nucmed/IRL/pet_intro/intro_src/section5.html> 12 Jan 1999.

[19] Animal Welfare. United States Department of Agriculture. 2007. <http://www.aphis.usda.gov/animal_welfare/>.

[20] AVMA Policy: Use of Animals in Research, Testing and Education. American Veterinary Medical Association. Nov. 2007. <http://www.avma.org/issues/policy/animal_welfare/testing.asp>.

[21] Public Health Service Policy on Humane Care and Use of Laboratory Animals. Office of Laboratory Animal Welfare of the National Institutes of Health. Aug. 7, 2002. <http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf>.

[22] CPG Sec. 398.375 Obligations of Factory-based Manufacturers and Assemblers of Diagnostic X-ray Equipment Under the Performance Standard for Diagnostic X-ray Equipment. U.S. Food and Drug Administration. March 1995. <http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073933.htm>.

[23] Guidelines for Ethical Conduct in the Care and Use of Animals. American Psychology Association. 2010. <http://www.apa.org/science/leadership/care/guidelines.aspx>.

[24] Kessler, L. et al. 2008. "Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)." <http://www.ghtf.org/documents/sg1/sg1final-n11.pdf>

Appendix A

Product Design Specifications - V1.5

Date: May 3, 2010
Project Title: An open-source imaging platform for small animals
Team Members:

Jay Sekhon (Leader)
Jon Seaton (Communicator)
Whitney Johnson (BSAC)
Sarah Springborn (BWIG)

Client:

Dr. Robert Jeraj rjeraj@wisc.edu
Dr. Rock Mackie trmackie@facstaff.wisc.edu

Problem Statement:
The overall aim of this project is to develop an open source small animal imaging and therapy platform that integrates imaging (e.g., Computed Tomography (CT), Positron Emission Tomography (PET)) and therapy (e.g., radiotherapy (RT)) together. This system will be designed on a flexible platform, enabling researchers to build their own system according to the available resources and needs. The specific aim for the design project is to provide initial design of such an open source imaging/therapy platform and potentially start prototyping the system at the fast prototyping system at the Morgridge Institute for Research (MIR).

Client Requirements:

- Complete list of specifications necessary for the design of a small animal imaging system
- System should be able to perform PET, CT, and radiation therapy
- Each type of imaging or therapy modality should be independent (e.g., an example device could only incorporate CT or only CT/RT)
- The development should be open source (i.e., all intellectual property is publicly available)
- The final product should have software and hardware completely ready to go in a "plug and play" format

Physical and Operational Characteristics:

- The device is to be used on small animals (e.g., rats and mice)
- The system should be able to incorporate any combination of PET, CT, and RT.
- Couch positioning, data acquisition, and data storage should be independent of any imaging/therapy modality.
- Each imaging/therapy modality will have its own level of specification

Miscellaneous:
Initial specifications for the imaging/therapy modalities and the overall device systems can be found in the tables below.

Table 1. ***Specifications of the micro-RT system***

Components	**Specifications**
X-ray production - orthovoltage tube	2 focal spots, size: 2 mm for RT
X-ray filter	0.5 mm Cu, 2 mm Al
Source treatment dose	200 cGy per min
Dose monitoring system	0.1 cGy accuracy with ion chamber, Radiochromic films
Primary collimation system	Material - W, Cu or Brass, FS < 200 mm x 200 mm
Shutter system	Brass sliding
Secondary and tertiary collimation system	FS = 60 mm x 60 mm to diameter = 0.5 mm
MLC leaves: W or Pb	Thickness - 1 mm, FS < 0.5 mm x 0.5 mm
Beam control system	Charge and time measurement
Target cooling system	Oil to water, oil to air
Motor for positioning	Encoded DC motor
Animal positioning system - table	0.125 mm accuracy, 0.05° rotational
Animal support fixture system	Gas anesthesia, temperature control, stereotactic frames
Laser alignment system	1 mm accuracy for positioning
Physical platform and support	Made with plastics as practicable

Table 2. ***Specifications of the micro-CT system***

Components	**Specifications**
CT system	Cone beam CT or Fan beam CT (FOV = 10 cm x 10 cm)
Bore diameter	120 mm
X-ray source - orthovoltage tube	2 focal spots, size: 0.2 mm for CT
Source imaging dose (whole body scan)	1 cGy
X-ray filters	0.5 mm Cu, 1 mm Al
Flat-panel Si (amorphous) detector	512 x 512 pixel array, 0.25 mm^3 voxel resolution
Detector frame rate	7 Hz
Image reconstruction system	Feldkamp or filtered backprojection
Motor	Encoded DC motor (same as for RT system)
Three dimensional digitzer	MicroScribe3DX
Animal positioning system - table	0.125 accuracy, 0.05° rotational

Table 3. ***Specifications of the micro-PET system***

Components	**Specifications**
LSO detector crystals size	2 mm x 2 mm x 10 mm, 64 channel, 20 x 20 array
Hamamatsu H8500 PS PMT	8 x 8 anodes, pixel = 5.8 mm x 5.8 mm, pitch = 6.08 mm
Photocathode	Bialkali, 300-650 nm spectral response, λ(peak) = 420 nm
Crystal array	64 (8 X 8 crystal/PMT)
Number of detectors	96
Number of crystals	6144
Number of rings	32
Ring diameter	14.8 cm
Time resolution	3 ns
Transmission source	Co-57 or X-ray CT
Image reconstruction system	Filtered backprojection

Table 4. ***List of combined modular sub-systems and other sub-systems***

Software/Hardware	**Management**
Image guided treatment planning	Data acquisition/management
PET and CT image reconstruction	Quality assurance
Fail-safe	Report and Verify
Power control	Picture archiving and communications
Power/Battery Backup	Data base management
Shielding and structural support	Electronic recording and patient scheduling

Appendix B

Customer Requirements

Date: April 21, 2010

The goal of this project is to develop a medical device combining CT, PET, and radiation therapy. As all design plans will be freely available as open source to the public, the customer can choose to purchase individual modular parts and assemble the device or have the device built for them where assembling charge will apply. However, the technology itself will be free of cost.

This product has been designed to promote research in educational and clinical institutions around the world. The system, including all its hardware and software components, can be used for many purposes and in many situations such as academic research, pre-clinical diagnosis, and other commercial uses. Clients for this project include, but are not limited to, physicians, radiology/radiation therapy researchers, oncology researchers, pharmaceutical researchers, and medical physicists. This system will especially benefit researchers from less developed countries that cannot afford expensive equipment from medical device companies.

Requirements:

- Safety
- Reliability
- Easy to construct
    - Include hardware that is easily available for purchase
    - Options to choose quality of parts based on cost
    - Modular systems
- Highly compatible software
- Flexible design (hardware)
- High resolution imaging
- Inexpensive
- Intuitive software user interface
- Repeatability
- Adjustable settings
- Accurate in a variety of environments
- Approved by FDA and AVMA regulations
- Able to complete successive scans and therapy as needed

Future Requirement Considerations:

- Cost Analysis
- Pertinent FDA/AVMA regulations
- Device Longevity