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An Open Source Platform for Small Animal Imaging and Therapy

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12/8/2010
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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.

Project Background

The open source imaging platform was started as the initial project in an Open Source Medical Device (OSMD) program. The project began in January 2010 and is expected to be one of the major initiatives within the Wisconsin Institutes of Discovery and Morgridge Institute for Research collaboration. Overall, the project encompasses a wide array of information including the previous work done on the project since January, explanation of the open source concept, and background knowledge of the science behind the device.

Previous Work

From January to May 2010, the project had the goals of ensuring that several key things were accomplished. First, a preliminary set of specifications was developed in conjunction with research into existing systems, current advances in the field, and device design standards for medical devices. Additionally, a preliminary SolidWorks model was started and created to begin modeling parts as part of the whole system. These tasks were accomplished through a BME 301 Design Project.

From June to the beginning of September 2010, the SolidWorks model was further refined. A customer survey was also developed in order to gain information to create a Formal Customer Requirements document which would be further used to improve the system design. Additional market research was carried out to estimate market size and the capability of our product to penetrate the market, which assisted in the creation of a preliminary OSMD business plan. Further research into international design standards and practices was also carried out. These tasks were accomplished through the funding provided by the Tong BME Research and Development Award.

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

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.

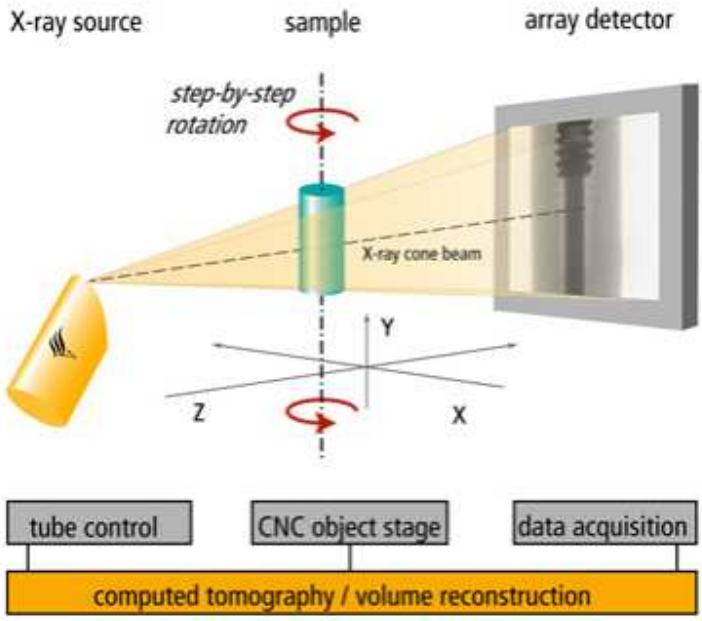

Figure 1. Method of X-Ray CT data collection. [8]

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.

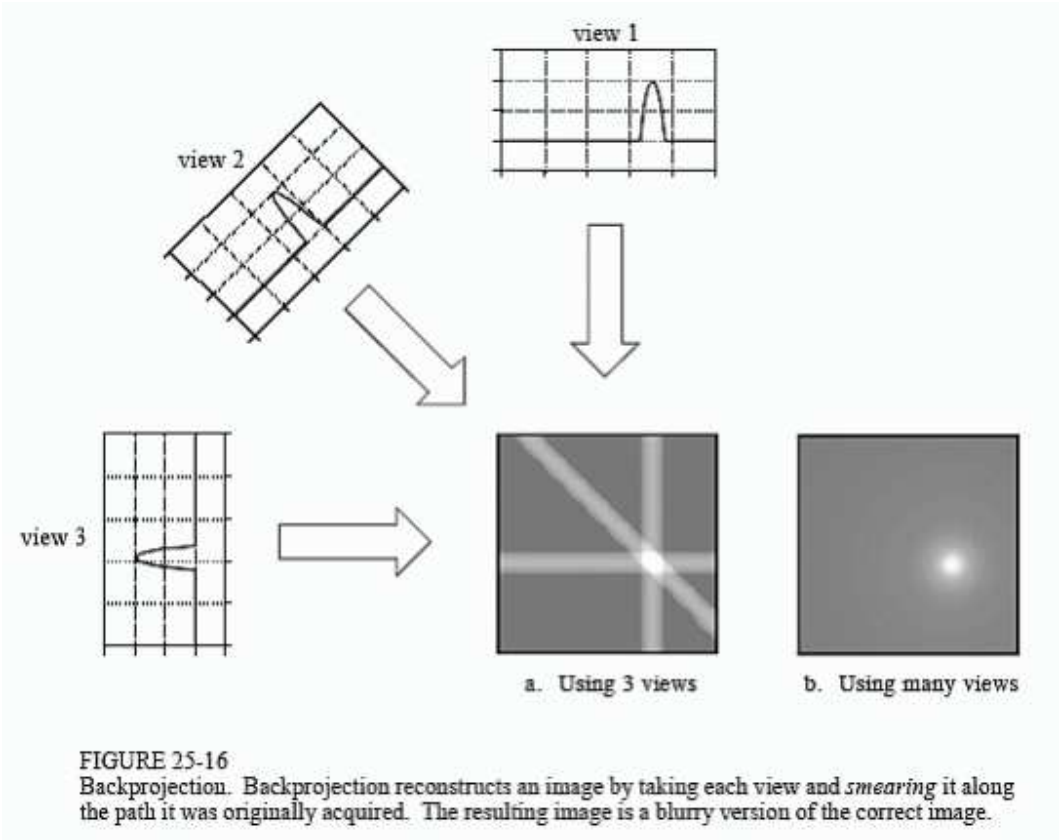

Figure 2. Method of filtered back-projection for reconstructing an image from the response function at different angles. [13]

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.

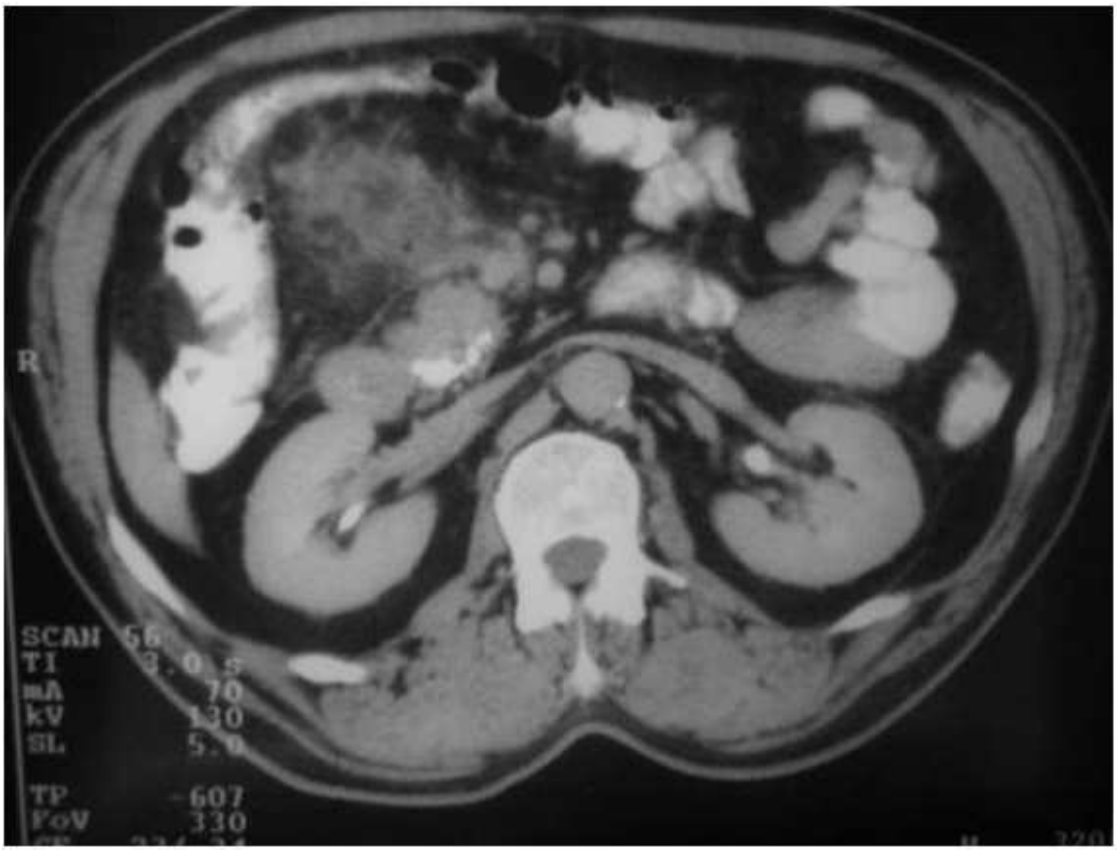

Figure 3. Example of a CT image reconstructed depicting the abdomen of a human patient. [12]

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.

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.

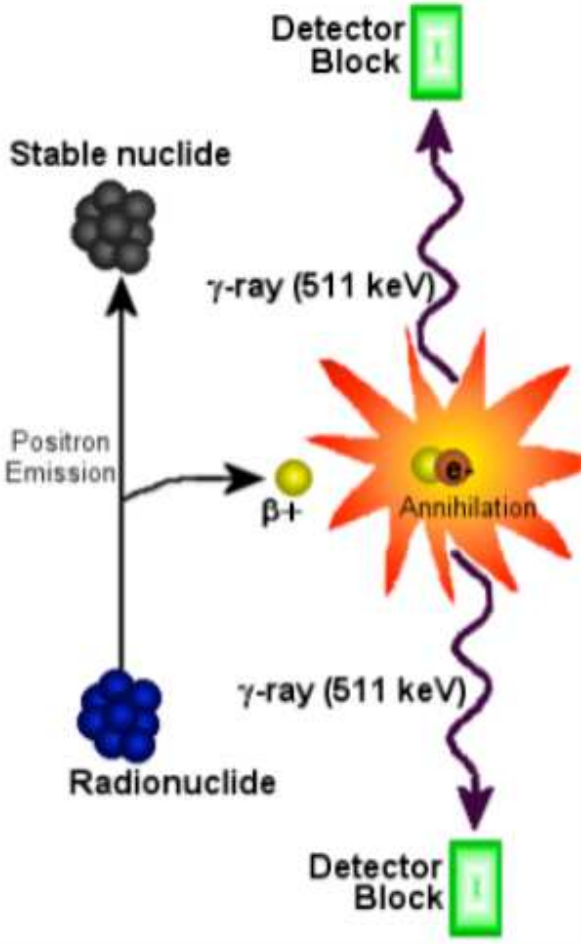

Figure 4. Diagram showing the basics of PET data collection.

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.

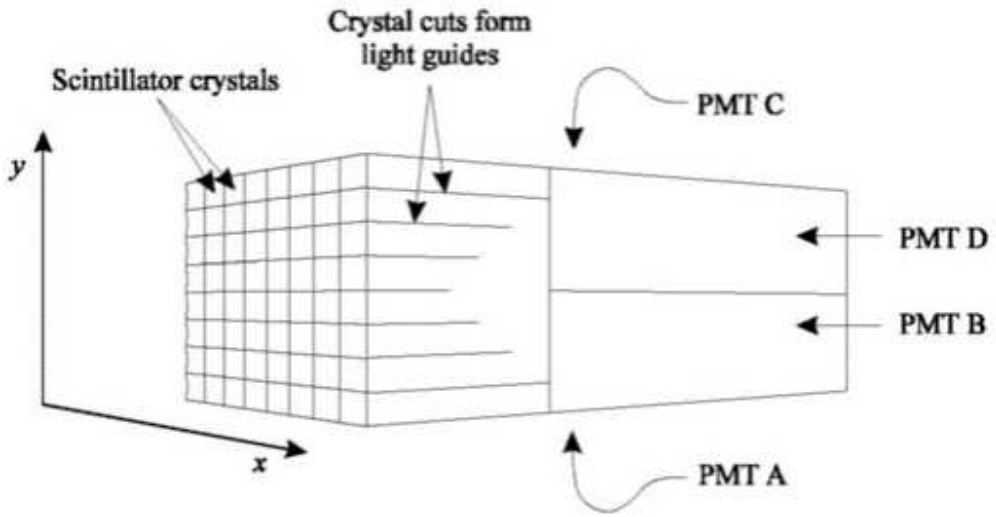

Figure 5. A diagram showing a PET detector block [18].

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 BaF2 (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.

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.

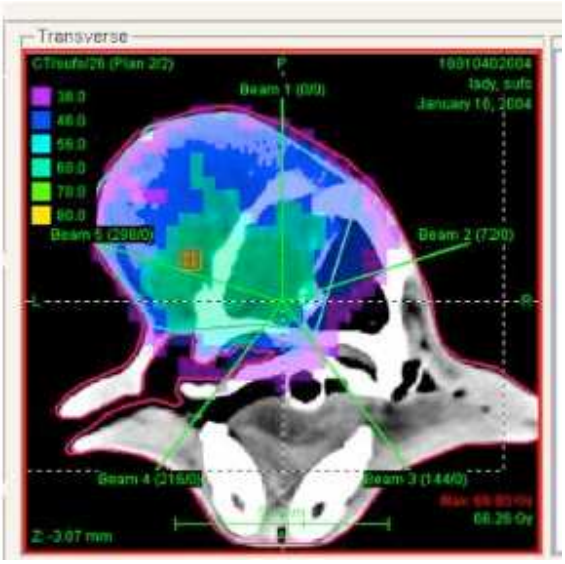

Figure 6. Image of a IMRT plan showing the exact location and size of the radiation beams [10].

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.

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.

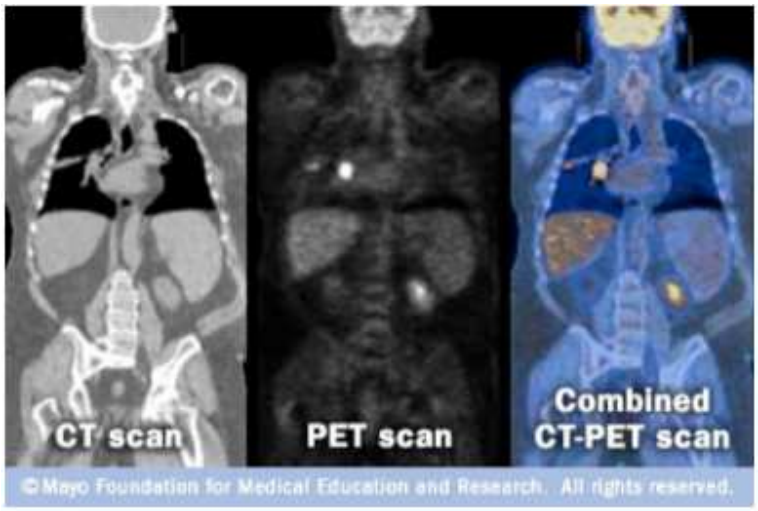

Figure 7. A comparison of images gathered from CT and PET and the superimposed image showing the increased metabolic activity at anatomical locations.

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.

System Design

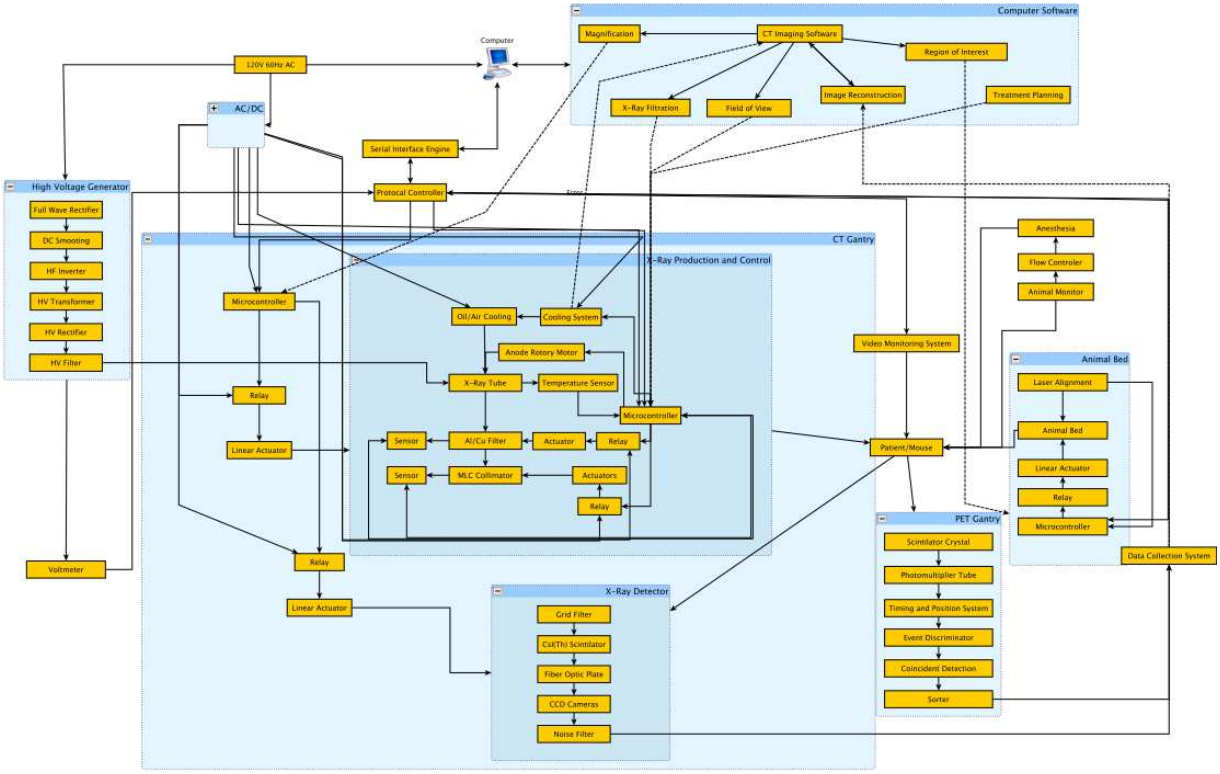

Figure 8. Block diagram describing the overall system design. Black arrows represent directly controlled processes, while dotted arrows represent indirect control. A higher resolution image of Figure 8 can be found in Appendix C.

High Voltage Production

The x-ray detector for the small animal imaging device will require a high voltage low current power supply. Ideally, it should be able to operate from a standard wall socket with less than 2400 watts of power usage. In order to generate a high voltage from a standard 120V 60Hz outlet, we can use a full wave rectifier and DC smoother. This will produce a constant DC voltage, but with a high degree of ripple, therefore we will then feed the signal into a high frequency inverter to transforming back into an AC voltage. The high frequency AC signal is fed into a high voltage transform to step the voltage from 120V to up to 250kV. This voltage can then be rectified and smoothed again to reduce the ripple in the signal.

X-ray Production and Control
X-rays are produce as previously described by bombarding a target anode with electrons under a high voltage. However, other considerations for this system include dissipating the large amount of heat produced by the x-ray tube. Therefore, a temperature sensor must be attached to the x-ray tube and feed into a microcontroller to monitor the temperature. If the temperature of the x-ray tube is too high, it will trigger the anode to spin to reduce heat as well as activating a oil/air based cooling system. For lower voltage xray tube <150kV air cooling is sufficient, but for higher energy tubes, 250kv, oil based cooling is necessary to prevent the anode from melting. Other components of the x-ray system include Al/Cu filters to shape the output energy distribution as well as an MLC collimator to adjust the beam geometry. When performing radiation therapy, the MLC collimator is used to shape the x-ray beam around the area of interest.

X-ray Detectors
As previously described, the x-rays will be detected using an array of scintillator crystals attached to CCD cameras. A grid filter is used to reduce detected background noise. The output signal from the CCD cameras is filtered and sent to a data collection system to be stored and digitally processed.

CT Gantry
The CT Gantry will hold all of the x-ray production components as well as detectors and power supplies. This part of the machine must be able to rotate a full 360 degrees with low vibration and high accuracy. In addition to the components described above, the CT gantry must contain linear actuators to physically adjust the magnification of the image.

PET Gantry
The PET gantry will be separate from the CT Gantry if a fixed detector is used. As previously described, the PET detectors will be composed of scintillator crystals and PMTs to detected emitted gamma rays. In addition, the PET detectors must contain complex electronics and precise electronics to determine the timing and position of a detected event, as well as a coincidence detection system to determine whether an event was detected on both sides of the gantry at a time resolution of <300 picoseconds. All collected data must be sorted and stored in a data collection system with high bandwidth.

Animal Bed and Monitor System
The animal bed is an important part of the machine that is meant to hold the mouse or other rodent fixed for the duration of the experiment. The bed will move in and out of the machine using linear actuators to allow the user to work on the animals before it enters the machine. Other important parameters for this system include a video monitoring system, an anesthesia system with adjustable flow control, and a vital sign monitor.

Software
All aspects of the small animal imaging machine must be user configurable by an external software package. This package must include a therapy treatment planning system for performing radiation therapy procedures. A variety of image reconstruction algorithms and filters should be included for digitally manipulating CT images. Other important parameters the user will be able to adjust include the image magnification, the field of view, region of interest, filtration parameters, scan time, and image resolution.

First Generation Mechanical Design

The first design, from the Spring 2010 semester, helped visualize relative sizes of the necessary components. From this, it was possible to develop preliminary interpretations as far as how everything needs to be housed.

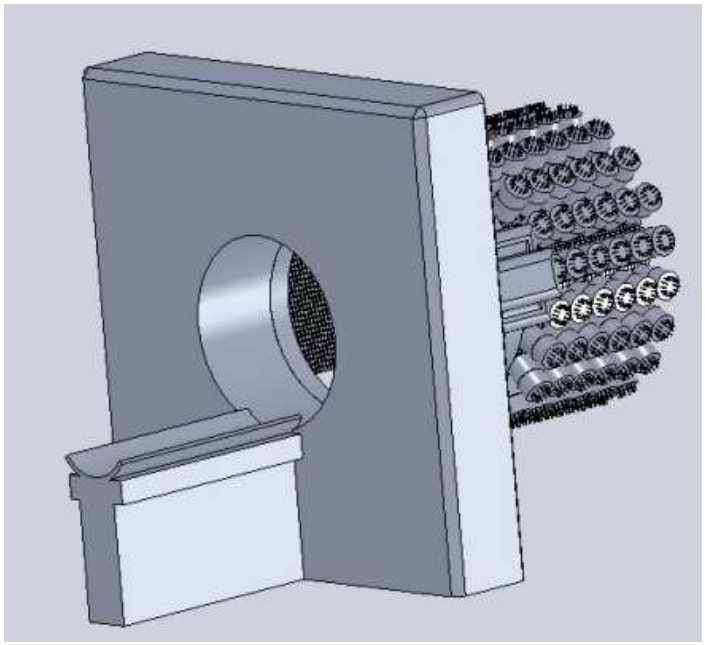

Figure 9. Preliminary SolidWorks drawing of the total system, incorporating PET, CT, and RT components.

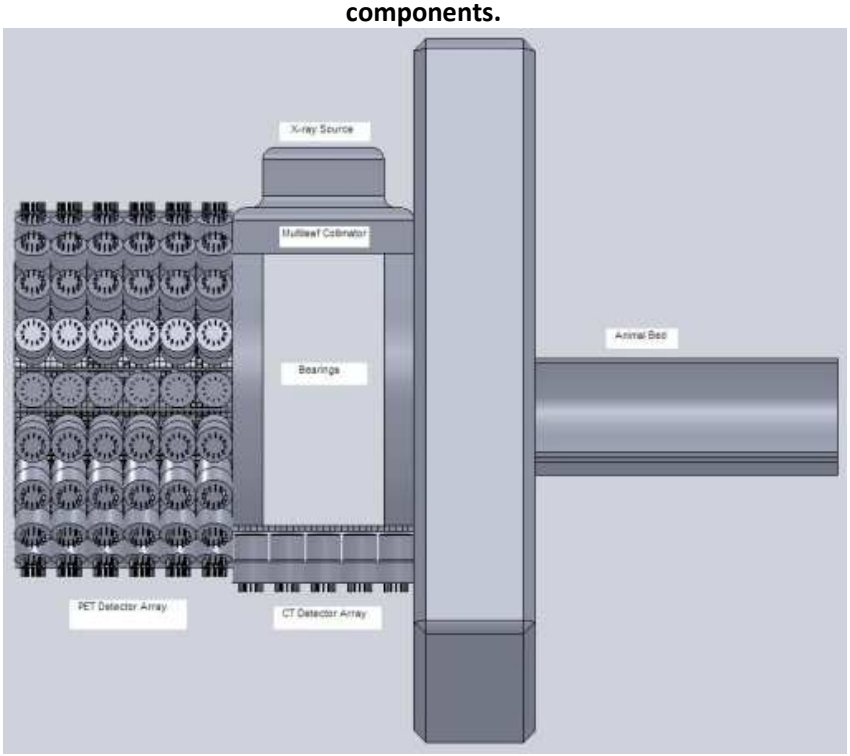

Figure 10. Top View of preliminary SolidWorks Drawing. Specific parts have been labeled.

Current Mechanical Design

The current design features a more detailed layout revolving around a newly constructed shell (Figure 10). The inner diameter of the imaging area is 1.5 m in length, and there is a 1 m diameter gantry wheel to house all of the components. The wheel holds two x-ray tubes, detectors, and the voltage supply. Attached to the imaging center is a custom designed animal bed. The lid is constructed from shielding lead glass, and it is controlled by two linear actuators. There is an opening via a polycarbonate tube, through which the bed may translate into the imaging stations. The structure is placed on locking wheels, and there are adjustable leveling mounts for permanent placement.

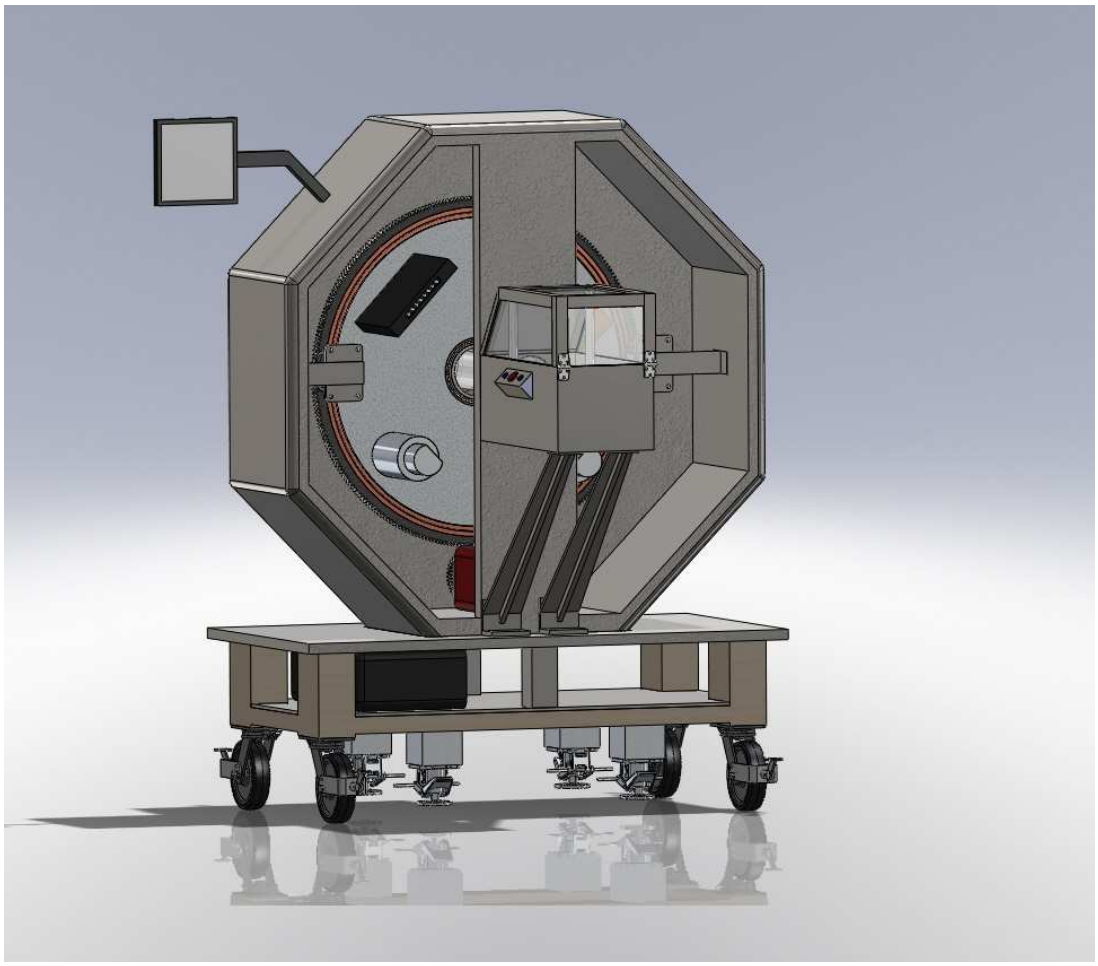

Figure 11. Final design with major components.

The rear of the machine features the PET imaging system (Figure 11). To reach this area, the animal bed translates through the CT section and to the other side of the gantry wheel. It is in this region where the PET array is located. The entire structure is covered in an aesthetic plastic case (Figure 12).

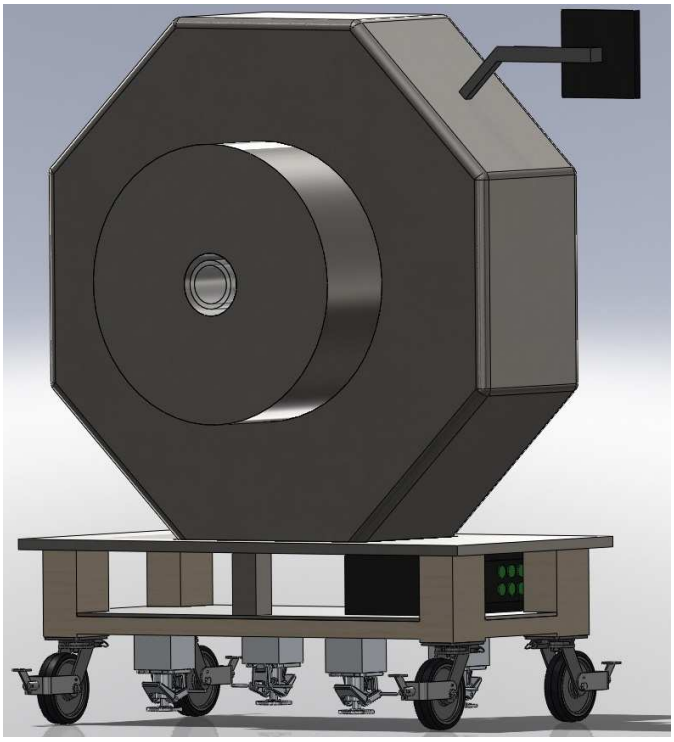

Figure 12. Rear view, showing the enclosed PET system.

Figure 13. Final design featuring the aesthetic cover.

Component Design Matrices

An important component of the small animal imaging machine are the detectors used to register in coming x-rays. The most important considerations when selecting x-ray detectors are their precision, resolution, and dynamic range. Other important factors are cost, durability, ease of use, and frame speed. Old x-ray machines used film based detectors, but for our application, film would not be viable because all of the collected data must be digitally processed by a computer. Another problem with film is its poor dynamic range makes it inconsistent and unreliable. We consider a number of solid state detectors including CCD, CMOS, and photodiode array detectors to include in the CT section of the device. The CCD based detector performed the best based on our design matrix below because CCDs offer superior image quality and flexibility. CMOS imagers have easier integration, better power dissipation, and smaller size, but offer poor image quality especially in reduced light environments such as in CT [25]. Photodiode arrays are difficult to integrate and require many external filters and amplifiers as well as not offering great image quality. However, photodiode arrays can be operated in parallel, giving them high frame rates and bandwidth. One problem with all x-ray detectors is the detection of unwanted background noise. For a small range of magnifications, we plan to use an anti-scatter grid to improve the signal to noise ratio.

Table 1. CT Camera Systems

	Weight	**CCD**	**CMOS**	**Photodiode Array**
Precision	(40)	32	25	20
Cost	(10)	7	5	5
Durability	(25)	20	20	20
Ease of Implementation	(15)	9	13	6
Speed of Operation	(10)	7	8	9
TOTAL	**(100)**	**75**	**71**	**60**

Solid state detectors such as CCDs cannot detect light in the x-ray frequency range. Therefore, we must scintillator crystals to convert the higher energy x-rays into visible light that a CCD camera could detect. This method is highly dependent on the detectable quantum efficiency of crystals, in other words the ratio of the number of the number of photons actually detected versus the total number of incoming photons and the emission spectra of the crystals. Other important considerations include the dead time of the crystal, or the time in which the crystal needs to reset to a detectable state after a photon has cascaded through the crystal, cost, and durability. From the design matrix below, it was determined that the CsI(Th) would perform best when coupled with a CCD detector. This is mainly because its emission spectra peaks at 550nm and CCD detectors have a high detection efficiency over the range from 450nm to 650nm. NaI(Th) has an emission maximum at 415nm, outside of the range of the CCD detector. The CsI(Th) also has a high conversion efficiency and small dead time. The organic plastic scintillator crystal has a much shorter decay constant than any of the other crystals and can be adjusted to emit light in the

detectable range of a CCD camera. However, because of its lower atomic number, it has very poor x-ray conversion efficiency.

Table 2. X-Ray Scintillator Crystals

	Weight	**Csi(Tl)**	**Organic Plastic**	**NaI(Tl)**
Emission Maximum	(25)	23	21	18
Cost	(10)	7	4	7
Durability	(15)	12	14	7
Conversion Efficiency	(25)	20	18	23
Decay Constant	(25)	19	22	17
TOTAL	**(100)**	**81**	**79**	**72**

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), as well as other regulatory agencies internationally. 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.

Project Timeline and Future Work

One of the major difficulties in undertaking such a massive project is the amount of time required to produce the initial prototype. It is frustrating for both workers and supervisors if neither is familiar with the deadlines and milestones associated with the project as well. To mitigate this issue as well as clarify the goals of each project, a timeline was developed (Figure 13).

Figure 14. A timeline of the project from January 2010 to December 2011.

The progress of the project thus far has been following the timeline closely with no major setbacks. However, the complexity and amount of work required in the coming months is greater than before, and the timeline may have to be adjusted accordingly. The major projects in the near future (i.e., next semester) include completion of all vendor searching and beginning ordering of necessary parts, creating testing protocols to validate the mechanical design and hardware, validation of the SolidWorks model, beginning software design, and beginning the construction of the system. The first prototype will ideally be completed and validated by December 2011.

Conclusion

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.

Products to be Purchased

During the current phase of the project, searching for potential vendors was started. Through communications with several company representatives, as well as some site visits, many required products were identified. This led to the creation of a purchase order/parts list, seen below (Table 3).

Table 3. Parts & Vendor List

Part	Purpose	Vendor	Cost	Quantity	Total Cost	Comments
BSM90N-375	Gantry Motor	Baldor	$ 350.00	1	$ 350.00	
2886T88	Heavy Casters	McMaster-Carr	$ 137.00	4	$ 548.00	
22665T620	Light Casters, support for	McMaster-Carr	$ 28.43	4	$ 113.72	
Floor Lifts	Leveling the machine	3D Content Central	Unknown	4		
Frictionless Bearing	Gantry Wheel	Kaydon	$ 490.00	1	$ 490.00	
1549A590	Hinges for animal bed	McMaster-Carr	$ 5.95	2	$ 11.90	
4" x 24" Carbon	Animal Bed	Dragon Plate	$ 179.50	1	$ 179.50	
SLS260*2000 HV	260kV, 7.7mA Power	Spellman	$ 4,995.00	1	$ 4,995.00	
	CT Xray Source <150kv	North Star Imaging	$ 50,000.00	1	$ 50,000.00	estimated
	RT Xray Source 250kv	North Star Imaging	$ 75,000.00	1	$ 75,000.00	estimated
	RT Tube Cooling System		$ 10,000.00	1	$ 10,000.00	estimated
504-22-9430	250kV High Voltage Cable	Okonite	$ 100.00	2	$ 200.00	
J6745-01	XRS-FOP Scintillator	Hamamatsu	$ 2,000.00	2	$ 4,000.00	
MT9M413C36STM	High Speed CCD Sensor	Aptina Imaging	$ 1,000.63	15	$ 15,009.45	
Easy-MCA 8k	Multi-Channel Analyzer	Ortec	$ 1,000.00	1	$ 1,000.00	
ATMEGA128-16AU	Microcontroller	Atmega	$ 18.70	10	$ 187.00	
H8500 PS	PMT*	Hamamatsu	$ 2,500.00	32	$ 80,000.00	
ADIT L13B03W	PMT*	Electron Tubes	$ 300.00	32	$ 9,600.00	
RLMG9x20	Laser Alignment Module	Instapark	$ 4.88	10	$ 48.80	
HS-45HB	MLC Collimator Motors	HiTech	$ 15.99	64	$ 1,023.36	
FA-200-TR-24-20"	Track Actuator for Animal Bed	Firgelli Automations	$ 169.99	1	$ 169.99	
FA-450-TR-24-10"	Track Actuator for X-Ray/CCD magnification	Firgelli Automations	$ 209.99	4	$ 839.96	
Custom Parts						
Machined Al	Octagonal housing	McMaster-Carr	$ 252.51	1	$ 252.51	
Steel structure, lead	Animal Bay	McMaster-Carr	$ 550.00	1	$ 550.00	
PC tube	Animal retainment	McMaster-Carr	$ 48.44	1	$ 48.44	
Steel stock, steel	support table	McMaster-Carr	$ 300.00	1	$ 300.00	
40 cm radius Al	Gantry	McMaster-Carr	$ 108.36	1	$ 108.36	
Steel gear teeth	Gantry	Unknown	Unknown	1		
Steel hollow tube	Support gantry wheel	McMaster-Carr	$ 112.50	1	$ 112.50	
Steel frame	Wheel stabilizers	McMaster-Carr	$ 18.38	1	$ 18.38	
Steel cylindrical	PET enclosure	McMaster-Carr	$ 150.00	1	$ 150.00	
10 cm radius steel	Gantry motor	McMaster-Carr	$ 88.54	1	$ 88.54	
	Computer/Viewing Station		$ 3,000.00	1	$ 3,000.00	
	MLC Collimator Leaves and				$ -	
	Xray detector housing				$ -	
	Lead shielding				$ -	
TOTAL					**$ 178,395.41**	

*Note that only one of the two PMT options is required. The lower price is reflected in the total cost.

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Appendix A: *Product Design Specifications - V2.0*

Date: December 8, 2010
Project Title: An open-source imaging platform for small animals
Team Members:

Jay Sekhon (Leader)
Jon Seaton (BSAC / Communicator)
Ryan Kimmel (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.

Specifications for the Radiation Therapy (RT) System

Components	Specifications
X-ray production - orthovoltage tube	2 focal spots, size: 2 mm for RT, 250 kVp max
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 material	Mainly Pb, hardened with Ca
Jaw system	Brass sliding
Secondary &tertiary collimation system	Max FS = 60 mm x 60 mm
MLC leaves: W or Pb	Thickness - 1 mm, min. FS < 0.5 mm x 0.5 mm
Beam control system	Charge and time measurement
Target cooling system	Either Oil to water or oil to air
Motor for positioning	Absolute 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	0.5 mm accuracy for positioning
Physical platform and support	Made with plastics as practicable

Specifications for the Computed Tomography (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 CCD detector	512 x 512 pixel array, 0.25 mm3 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 mm accuracy, 0.05° rotational
Detector Scintillator Crystal	CsI(Th)

Specifications for the Positron Emission tomography (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	32
Number of crystals	2,048
Number of rings	4
Ring diameter	14.8 cm
Time resolution	3 ns
Transmission source	Co-57 or X-ray CT
Image reconstruction system	Filtered backprojection

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: December 8, 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.

The identified customer is looking for an integrated system that can perform both small animal imaging and radiation therapy. The small animal in question can be size of a medium-sized rat or a small rabbit or ferret. In this document, the animals will be assumed to be a mouse. This customer would like the system to include micro-CT, micro PET and Micro RT in the integrated system.

Ergonomics:

1. The system should be easy to learn to use and user friendly.
2. It should have on-board video in order to be able to the view the animal while scanning.
3. The user should have an easy access to mice at any time while scanning.
4. The system should have design to easily facilitate isofluorane and oxygen supply to the mice.
5. The system should be sanitary, and easy to clean after being used.

System requirements:

1. The system should include micro-CT, micro-PET and micro-RT to image and treat small animals.
2. It should be a modular system so that any sub-system is independent of the other systems present. The user should be able to use them separately or in combination.
3. Hardware should be as integrated as possible.
4. The system should be as cost effective as possible.
5. The system design should be easily available and flexible enough for better design implementations or configurations.
6. The system should be shielded so that the user can stay close to the system while the system is operating.
7. The user should be able to use the system multiple times a day without lag time between each use.
8. The bore diameter should be at least 10 cm and not more than 15 cm.

RT requirements:

1. The treatment beam should be of peak energy 225-250 kV.
2. The system should be able to output at least 200 cGy/min.
3. The system should include dose and time monitoring system to control the treatment.
4. The dose monitoring system should be accurate to at least 0.1 cGy.

5. The maximum treating field size should be 10 cm x 10 cm.
6. The animal positioning system should be accurate to at least 0.5 mm linear motion and 0.5° rotation.
7. The RT should be able to provide intensity modulated (IMRT) type dose delivery and monitoring.
8. It should include Treatment Planning System supporting IMRT.

CT requirements:

1. The user wants CT resolution of 100 microns or better.
2. The user should be able to choose and perform different CT reconstruction as desired (with available reconstruction algorithms).

PET requirements:

1. The user wants the PET resolution of 2 mm or better.
2. The user should be able to choose and perform different PET reconstruction as desired (with available reconstruction algorithms).

Software:

1. The system should have onboard dose verification.
2. QA system should be available.
3. The user should be able to access raw data from the scanner and manipulate it.

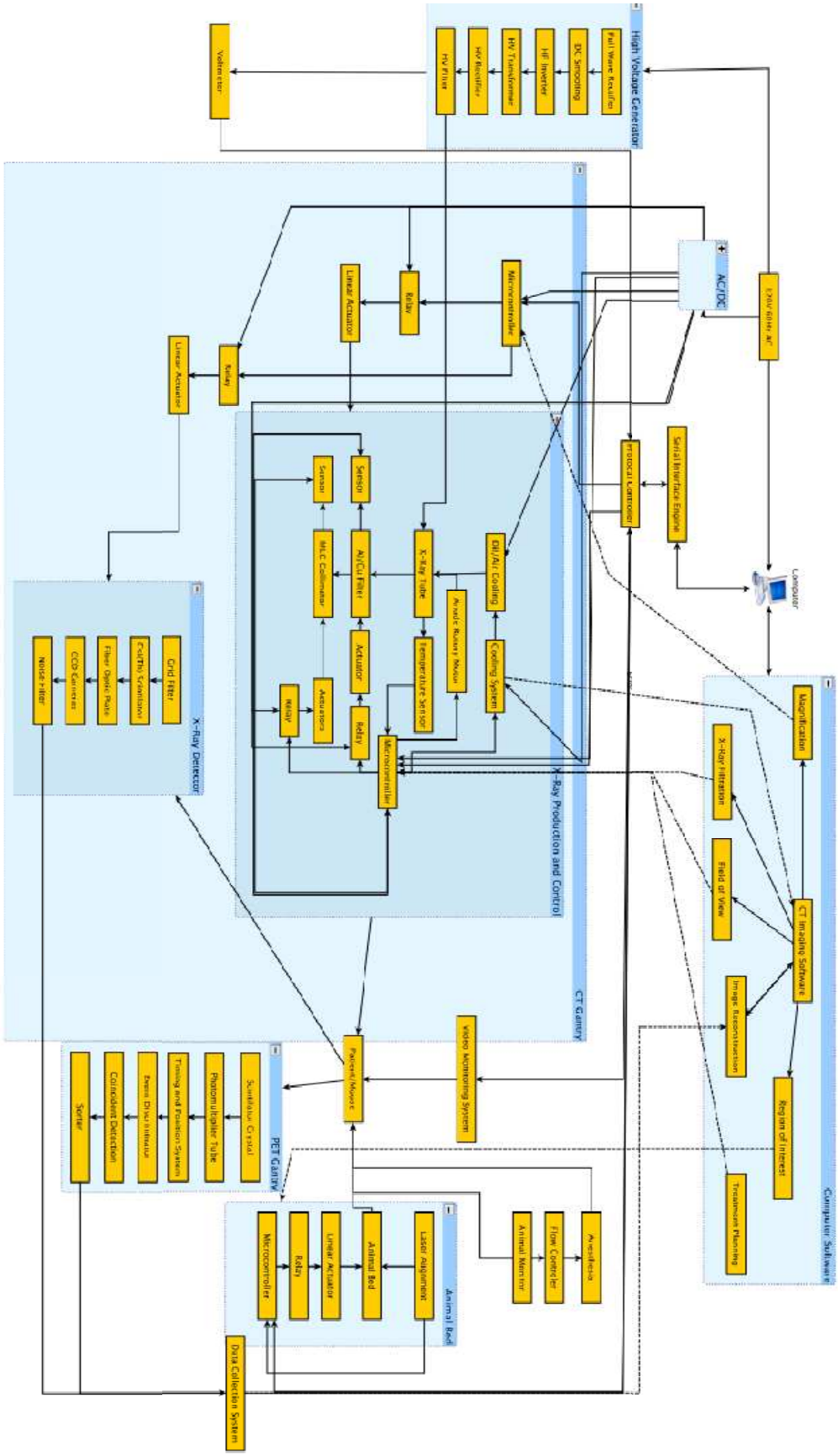
Other Systems:

1. The user should be able to perform biophysiological monitoring while scanning.
2. The system should include laser systems with at least 2 mm positioning accuracy for mice positioning, immobilization and reproducibility of the system.
3. The system should have replacement parts easily available.
4. The system should have electronic recording system.
5. It should include record and verify system.
6. It should include data management system.
7. It should include power controland backup system.
8. It should incorporate PACS.
9. It should include data base management system.

Appendix C: *Other Documentation*

Further information and reports, including SolidWorks files, market research documents, and the preliminary business plan can be found at http://www.formula-database.com/osmd/

Figure 8 is reproduced below at a higher resolution.


High Voltage Generator
Full Wave Rectifier
DC Smoothing
HF Inverter
HV Transformer
HV Rectifier
HV Filter
Voltmeter
AC/DC
Linear Actuator
Relay
Microcontroller
Linear Actuator
Relay
Sensor
Sensor
MLC Collimator
Al/Cu Filter
X-Ray Tube
Oil/Air Cooling
Anodic Rotary Motor
Temperature Sensor
Cooling System
Actuator
Relay
Actuators
Relay
Microcontroller
X-Ray Production and Control
CT Gantry
PROTOCAL Controller
Serial Interface Engine
Computer
Grid Filter
Fiber Optic Plate
CCD Cameras
Noise Filter
X-Ray Detector
Magnification
X-Ray Filtration
Field of View
CT Imaging Software
Image Reconstruction
Region of Interest
Treatment Planning
Computer Software
Patient Mount
Video Monitoring System
Scintillator Crystal
Photomultiplier Tube
Timing and Position System
Coincident Detection
Sorter
PET Gantry
Microcontroller
Relay
Linear Actuator
Animal Bed
Laser Alignment
Animal Bed
Animal Monitor
Flow Controller
Anesthesia
Data Collection System