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A System for Preclinical Imaging Facility Management and Data Processing

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A System for Preclinical Imaging Facility Management and Data Processing

Ryan Anthony Bozio

A Thesis Submitted to the Graduate Faculty of

GRAND VALLEY STATE UNIVERSITY

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Abstract

Introduction: Preclinical imaging laboratories are unique and specialized facilities that generally operate as service cores within large research institutions. The facilities offer non-invasive imaging to researchers to answer scientific questions. Facilities, such as the one located within the Van Andel Institute, have multiple imaging modalities including PET, CT, SPECT, ultrasound, and optical. These modalities often times come from different manufacturers involving various image formats. Imaging facility managers are responsible for managing collaborative projects, coordinating different groups, scheduling machine and technician time, billing customers, as well as providing meaningful and reliable results to the researchers. These challenges underscore the need for a management system that provides automated tools for designing, scheduling and overseeing the efficient completion of studies. We have developed a system for managing most aspects of an imaging facility to optimize efficiency, decrease errors, provide reliable results and to potentially lay the foundation and framework for other preclinical imaging facilities.

Methods: An entirely web-based architecture was chosen for the system to allow for ease of access from any location. The system includes tools for managing projects, data management and finance management. Project management using the system includes scheduling longitudinal studies and personnel coordination such as automated emailing services for tasks and next steps in the project. Data management within the system allows for DICOM image storage, backup, retrieval and post analysis. Post analysis techniques include region of interest (ROI) drawing, image manipulation and SUV for PET data. To evaluate the system for efficiency, PET/CT studies were completed using
the system as well as without the system. Scheduling, billing, and post analysis was timed for both scenarios.

**Results:** It was found that the designed system increased scheduling efficiency by 93%, billing by 87.3% and post analysis by 75%. Manual intervention from the SAIF manager and SAIF members for PET/CT studies was also decreased by 82%.

**Conclusions:** The system increased efficiency within a preclinical imaging facility and can be used to promote a new concept of managing for other facilities as well. As a web-based system it is open architecture allowing for continual expansion as needs grow more complex.
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1. Introduction

1.1. Preclinical Imaging

Preclinical small animal imaging is an integral part of translational cancer research. Imaging modalities have been created to allow a researcher to observe changes in organs, tissues, or cells in animals responding to physiological or environmental changes. These imaging modalities can be categorized into two main categories: anatomical and functional. The anatomical modalities include: micro-ultrasound, magnetic resonance imaging (MRI) and computed tomography (CT). The functional modalities include: optical imaging (fluorescence and bioluminescence), fMRI, positron emission tomography (PET) and single photon emission computed tomography (SPECT). These imaging modalities provide images that are of the highest quality as any of those in clinical studies. The modalities outlined above are all non-invasive and can be used in vivo, which make them well suited for use in longitudinal studies such as those commonly done in research institutions focused on drug development, and studying diseases such as cancer and Parkinson’s. Small animal imaging facilities (SAIF) are unique and specialized facilities that generally operate as service cores within large research institutions. The SAIF is responsible for assisting researchers by providing images of anatomy and function using any of the imaging modalities at their disposal. The complexity and variety of applications for preclinical imaging creates a significant administrative burden for managing an imaging facility. SAIF managers are responsible for managing collaborative projects, coordinating different groups, scheduling machine and technician time, billing customers, implementing procedures
for quality control, as well as providing meaningful and reliable results to the researchers. There challenges underscore the need for a management system that provides automated tools for designing, scheduling and overseeing the efficient completion of studies.

1.2. Focus: Improving Efficiency in the SAIF

Laboratory managers of SAIFs are responsible for all imaging studies performed at the research institutions whether these are in R&D divisions of large companies, at universities, or in private research facilities such as the Van Andel Institute, Grand Rapids. Specific items of responsibility include, but are not limited to: scheduling studies, scheduling imaging scanners, ordering the isotopes, coordinating the study, billing the customer, and providing the customer with the analysis results for their research. With all of these responsibilities, errors and issues commonly occur and lead to wasted time and/or money.

The Van Andel Research Institute in Grand Rapids, MI has a state-of-the-art SAIF. This facility is a core laboratory, meaning it provides imaging services for the principal investigators at the institute who submit study requests that are then performed by the SAIF members. Along with the core studies from other principal investigators, the SAIF also has an internal research focus developing new molecular probes with better imaging properties. Currently, there are over twenty-five principal investigators at the institute and scheduling studies, scanners, SAIF members, and billing is a time consuming process requiring many hours of the SAIF manager’s time and affecting the facilities productivity.
Members within the SAIF are responsible for various tasks within a study as requested by the Principal Investigator (PI) request the study. The type of study dictates the tasks that need to be completed by each SAIF member. The variation in tasks per study puts a lot of pressure on the SAIF coordinator to make sure everybody is doing their tasks at the proper time and in the proper fashion. The various tasks include: ordering the isotope, checking anesthetic and oxygen levels, weighing the animals, administering the isotope, performing the scans, fasting the mice, to name a few. With the large number of studies and the quick turnaround required on results, the SAIF manager must spend a significant number of hours ensuring that all the components of each study occur at the right time and in the right order. All of these challenges underscore the need for an automated system to keep the SAIF organized, on schedule and efficient during studies.

1.3. Summary

The popularity of utilizing preclinical imaging for research purposes allows for conducting longitudinal studies to track progression of disease in small animal models. With the growing number of researchers conducting longitudinal studies on disease progression, the need for an automated system to manage a SAIF is becoming necessary. An automated system will increase efficiency in the SAIF, reduce technician time and labor on administrative tasks, and can allow for human error to be less of a factor in the overall performance of a study. Various systems exist, currently, but are not specifically geared towards a SAIF.
2. Background

2.1. Management Systems

There are many aspects of management systems, that depend on their application but most management systems have the same platform. The basic tasks or activities of management systems include – but are not limited to – scheduling, timelines, alert system for tasks, cost control, and budgeting. These tasks of a management system are used as the starting point when creating a custom management system for a specific application.

Due to the rapid pace at which research laboratories operate, laboratory management systems have been developed to accommodate for a laboratory’s needs. These systems are designed to help organize and manage scientific data and information for the user. These systems, however, are not for specific laboratories, but for general laboratory use.

The two main types of architecture for laboratory management systems are thick-client and thin-client. The most popular method of implementation is thin-client architecture. In thin-client architecture, the application functionality is accessed through the user’s web browser. As a web-based architecture, upgrades and modifications are seen by all end-users; no installation is needed by the individual user. Scientific-based management systems have been developed and commercialized, including Quartzy and Labguru.

Labguru is a web-based research and laboratory management system. This system is a collaborative laboratory and research system that helps academic laboratories plan
experiments, track progress on projects and milestones; share results; organize related
documents, protocols, and data; and manage inventories and ordering. Over 35,000
subscribers use Labguru (Anon. 2012a). Quartzy, similarly to Labguru, allows for
online laboratory management and laboratory inventory tracking. In contrast, orders
can be tracked (purchased items externally) and protocols can be shared with
laboratory members. Quartzy also allows laboratory equipment to be scheduled to
alleviate any confusion between laboratory members about equipment availability.
The outstanding feature of Quartzy is its inventory tracking system. This is important
for any setting, especially the scientific field, due to the large quantities of chemicals,
antibodies, etc... (Anon. 2012b)

The Washington University in St. Louis School of Medicine created a system called,
“Small Animal Imaging Center Information Management System”. The system is
web-based and provides the functions of 1) imaging request by the principal
investigator who may be a collaborator to the imaging laboratory, 2) scheduling the
procedures on existing micro PET and micro CT scanners, 3) worklist management
for technologists, 4) image storage/archive and 5) retrieve for processing by
laboratory staff or principal investigator. This system relies heavily on the DICOM
standard for medical images, however each scanner has a proprietary method of
outputting DICOMs, and therefore java authoring tools were created for each scanner
to transfer the data to the main server. This system is limited in the fact that each
computer needs custom software to be able to interface with the main server. The
system also does not provide post analysis tools.
The University Of California Davis College Of Engineering has also developed a management system. Their system provides the functions of 1) internal project management, e.g., collection of patient data records and images; time tracking for billing; session scheduling; data backup, archival; 2) a secure data retrieval system, allowing researchers password-protected access to their study data and images; and 3) a report system to generate summary reports of operations in order to evaluate overall center performance. The limiting factor of this system is its inability to perform post analysis on the stored images.

The architecture, methods, and basic operations of a management system mentioned above will be applied and used as a guide for the SAIF management system to be implemented. In addition, post analysis tools will be deployed in an effort to maximize efficiency.

2.2. Web-Based Image Viewing

Validating and viewing results is a key process in studies performed within a SAIF. The ability to do so using a web-browser from virtually anywhere makes this process much easier with less effort. Pure hypertext markup language (HTML) and JavaScript can be used to construct a virtual slide image viewing system with the aid of HTTP protocol to transmit digital microscopic images. It has been shown that the fundamental requirements of an image viewing system can be accomplished using a pure web-based solution (Lien et al. 2009). For the purpose of viewing medical images on the web, DICOM has defined an HTTP protocol, Web Accessing to DICOM persistent Objects (WADO), for accessing and viewing DICOM images. The
request parameters that HTTP uses include UIDs (study instance UID, series instance UID, and SOP instance UID).

2.3. Popular Imaging Modalities

The following modalities are the most widely used in the small animal imaging community. These modalities will be supported by the management system proposed.

2.3.1. Ultrasound

Ultrasound imaging utilizes the phenomenon of high-frequency sound waves. Small transducers or probes and ultrasound gel is used to expose the body to high-frequency sound waves. Ultrasound is non-invasive and does not require any ionizing radiation to produce the image. Images can be viewed real-time to allow the researcher to visualize the movement of structures and blood flow. The signal from the transducer is sent into the body and reflected back as an echo. The intensity of the echo determines the intensity of the pixel on the image (Hoskins, 2010). Scheduling ultrasound studies involves minimal involvement from the SAIF members due to its lack of occurrence.

2.3.2. Micro Computed Tomography

Micro computed tomography (µCT) is a density based imaging modality, meaning only higher density materials within the body will appear on the scan (bone, metal, some tissues). Many studies, however, involve organs such as the kidney, liver and often times tumors. These organs consist of soft-tissue (lower density), which do not appear on a scan very well. In this case, the researcher can
use a contrast designed for specific organs to increase the density to appear on the scan. In regards to µCT, contrast agents are the only injectable material used. An average mouse CT scan usually takes about 5 minutes depending on the resolution and field of view chosen. The larger the field of view or better the resolution required, the longer a scan will take. The CT scanner is the most operated scanner within a SAIF as it is used for CT, PET/CT and SPECT/CT studies. Thus, scheduling the CT scanner can be very challenging as many studies occur and SAIF technicians are not readily available.

2.3.3. Positron Emission Tomography

Positron emission tomography (PET) is being used increasingly to advance the understanding of cellular and molecular processes that are altered in disease. PET enables highly sensitive and quantitative measurements of biological processes in vivo through labeling of various positron emitters, such as $^{11}$C and $^{18}$F (De Kemp 2010). Biological information is beneficial to a certain extent. Sometimes it is hard to distinguish what is occurring within the PET images. Therefore, a CT or MRI scan is acquired in conjunction with the PET scan. The fusion of the PET and CT/MRI allows the researcher to visualize the PET information with an anatomical reference.

2.3.4. Single Photon Emission Computed Tomography

Single photon emission computed tomography (SPECT) is similar to PET in that measures of biological processes can be measured and imaged. The most widely used radioisotopes used are technetium-99m and iodine-123 due to their relatively short half-lives.
2.3.5. Optical Imaging

Optical imaging has made it possible to monitor the progression of diseases and biological processes similarly to PET and SPECT. However, there are some advantages over these modalities. Optical markers emit low-energy near-infrared photons that are less harmful than the higher energetic γ-rays emitted from SPECT and PET. Optical imaging provides higher sensitivity and is relatively inexpensive compared to other modalities (Hielscher 2005). Many optical imaging scanners provide high-throughput as well compared to PET and SPECT.

2.4. Post Analysis

As image acquisition is completed, post analysis is required to obtain either qualitative or quantitative results. The following examples are actions researchers and lab technicians take in order to obtain the results they are interested in.

2.4.1. Image Registration

Image registration (image fusion) is the process of overlaying two or more images of the same scene taken at different times, from different viewpoints, and/or by different sensors (Zitová and Flusser 2003). In some cases, studies involve scanning using molecular (PET or SPECT) and anatomical (CT) scans. If the scans are from differing machines (not combined in one machine), image fusion is necessary to overlay the molecular data onto the anatomical data. In these cases, post acquisition algorithms are required to fuse the data together. To accomplish image registration, the rotational and translational transformations must be found, so that the images line-up rotationally and axially. Figure 2.4.1-1 is an example of how image registration is useful.
PET data by itself is difficult to understand what is going on unless an anatomical reference is overlayed. Signals from PET can be confirmed with higher confidence with the CT.

2.4.2. ROI Drawing

Region of interests (ROI) can be drawn on the acquired 3-D scans (SPECT, Ultrasound, PET, and CT) to obtain various measurements of interest. ROI’s drawn on SPECT and PET are to obtain the uptake of the tracer in certain areas of the body. For PET, glucose uptake in a tumor is the most of interest. For SPECT, uptake in the bones (typically fractures) is of interest. ROI’s drawn on CT and Ultrasound is to obtain size measurements. Typically for CT, tumor sizes are of interest. Ultrasound can be used to find the size of many different things. Liver

Figure 2.4.1-1: Image Registration

Images acquired at Van Andel Institute

1 Images acquired at Van Andel Institute
metastases, popliteal lymph nodes, and tumors are a few examples of what Ultrasound can be used for.

Typically ROI’s are drawn slice by slice to create a Volume of Interest (VOI).

Figure 2.4.2-1 shows the ability to select the colon from a 3-D scan.

![Figure 2.4.2-1: Volume of Interest of the Colon](http://bjr.birjournals.org/content/77/suppl_2/S126/F3.expansion.html)

### 2.4.3. Image Filtering

Image enhancement is the processing of an image to enhance certain features of an image. Put simply, image enhancement is improving the interpretability or perception of information in images for human viewers and providing better input for other automated image processing techniques (Lavania and Kumar 2012). Examples of different image filtering techniques include: blurring, edge detection, sharpening, mean and median filtering. Figure 2.4.3-1 shows edge detection of the knee for better visualization.
3. Specific Aims

The purpose of this thesis is to develop a web-based management system for the Small Animal Imaging Facility (SAIF) at the Van Andel Research Institute (VARI). The institute currently houses one micro-ultrasound scanner, one PET scanner, one SPECT scanner, one CT scanner, and one optical imager. The system should allow the SAIF manager to:

1. **Design and schedule longitudinal studies.**

When scheduling a longitudinal study, the SAIF manager should know the following:

- Number of mice
- Number of time points
- Protocol number
- Injection route (Intraperitoneally or Intravenously)
- Isotope and/or contrast used
- SAIF members involved

---

(Heric and Zazula 2007)
The system will use this data to prepare a proposed schedule based on the availability of SAIF members and equipment.

2. **Perform post analysis, view and retrieve data from a database**

Create an extensive database that organizes all of the project, study, member, and imaging data. The database is used to organize the image data by project and study. The study’s analyzer can then view the data and perform image processing transformations on the image to obtain proper results. Some image processing transformations include: brightness/contrast control, color adjust, crop, edge detect, flipping, resizing, and sharpening.

3. **Register and fuse PET and CT data for better visualization and data analysis.**

In regards to only PET/CT studies, the system is capable of registering the CT and PET data so that the images can be fused on any other analysis tool as well as this system. ROI drawing on the CT data can also be accomplished in 3 dimensions to obtain organ volumes and PET tracer uptake.

4. **Evaluating the web-based management system**

   - Develop test studies using each modality at the Van Andel Institute.
   - Measure the amount of time each area of a study takes to perform, with and without the system.
   - Compare results to assess which aspect of a study the system improves the most.
4. Methods

The Van Andel Research Institute’s SAIF houses a Bioscan NanoSPECT/CT scanner, Sofie Biosciences G4 microPET scanner, Visual Sonics Vevo 770 microUltrasound scanner, and a Spectral Instruments Imaging AMI-1000 Optical imager. The other investigators at the institute are all eligible to utilize these resources. Longitudinal studies often times last eight or more weeks and many investigators’ studies can occur at the same time. Coordinating a PET/CT study is the most time intensive and involves many steps in making the study a success. Figure 4-1 displays the steps involved in completing a single PET/CT study. The steps outlined must occur in order and at specific times. A delay or the improper execution of a task may result in an unsuccessful study, thus necessitative repeated studies. The process of beginning any study starts with the investigator contacting the SAIF director or the SAIF manager. When the study details are configured and agreed upon, the scheduling process begins. The SAIF manager must schedule the longitudinal studies based on the availability of the SAIF members and the SAIF scanners. The purpose of this system is to improve efficiency in the SAIF at the Van Andel Research Institute by providing a web-based laboratory management system for use when scheduling different imaging studies for a variety of different research projects being conducted by Principle Investigators in the VARIs large research cohort. To do this the project was divided into a number of phases as detailed below.
Figure 4-1: PET/CT Operations
4.1. Server and Database

To achieve a web-based solution, the system is hosted on a server alongside a database. For performance and speed, an Apple Mac Pro running an Apache web server was selected as the CPU. This CPU hosts the database as well. MySQL was selected as the relational database management system. MySQL is the world’s most used open source database management system with extensive documentation and support. In order for the MySQL database to communicate with the web browser, a suitable programming language must be employed. Hypertext Markup Language (HTML) is suitable for creating web pages and other information that can be displayed on a web browser. Hypertext Preprocessor (PHP) is suitable for server-side scripting to create dynamic web pages. PHP and HTML work together to display information from the database on a web browser. MySQL queries invoked from PHP allow access to and from the database for data display and data storing. The database will be the location for all the SAIF information such as the scan locations, mice details, study information, and project information.

4.2. User Interface

A user interface was created in order for the SAIF manager and SAIF members to view and store project, study, schedule and image data. The interface is customized depending on access level. The SAIF manager and director have administrator rights and the SAIF members have user rights. Administrators have the ability to:

- Add/Remove/Alter projects
- Add/Remove/Alter studies
- Add/Remove/Alter member information
- Add/Remove/View Image Data
- Image Analysis
Users have the ability to:

- View Project Data
- View Study Data
- View Image Data
- Image Analysis

The user login information dictates behavior of the user interface. The access rights are stored in the database alongside the user’s login information. The SAIF manager is responsible for managing all projects, studies, SAIF members, SAIF imaging scanners and the image data. The interface to do so is streamlined, easy to understand and easy to use.

4.3. Scheduling and Coordination

Projects within the SAIF often times involve different labs, different researchers, and different imaging technologies to answer different questions. A way to coordinate all of these people with the SAIF is in place through a scheduling system. Microsoft Outlook Exchange Server was utilized to fetch all SAIF member’s and scanner’s schedules to avoid scheduling conflicts. As a result of the study, calendar event creation is automated as well. A custom PHP library was written and used in order to accomplish these tasks.
4.4. Data Storage

Data handling is a key component of the system. The database and server configuration as previously described allows the user to accomplish all tasks via web-browser. The database is responsible for storing all SAIF information. Storing data to the database allows the SAIF manager and the SAIF members to easily access, create and remove information via a web-browser. This information includes:

- SAIF member information
- Project Information
- Study Information
- Time Point Information
- Member Schedules
- Equipment Information
- DICOM Data Information

Database tables and specific information about data storage are provided in the appendices.

Storing data to the database can be accomplished with the use of MySQL queries. To process a query, the table name and its headers must be known.

4.5. DICOM Storage

All images acquired in the clinic are in the Digital Imaging and Communications in Medicine (DICOM) imaging standard. However, in preclinical imaging, this sort of standard has not yet been defined. Since the power of preclinical imaging is in translational research, an efficient communication to the clinic is essential. Each scanner outputs different file formats, therefore converting to DICOM is necessary. These DICOM image files (extension .dcm) are
relatively large and cannot be stored in the database along with all of the information explained above. The files, however, must be stored on the server’s hard drive. A specified folder structure must be used in order to organize the files properly. The location of each DICOM file should be stored to the database for easy access to the server. The folder structure is specified as the following:

“Project Name > Study Name > Time Point Number > Mouse > Modality > Filename”

As DICOMs are uploaded to the server via web-browser, the file location is automated and stored to the proper location based on the project, study, time point, mouse and modality.

The current PET scanner at the Van Andel Institute outputs 208 DICOM files per scan. This is very hard to process; therefore this is something that has been optimized using software by converting all of them into one 3-dimensional DICOM file

4.6. DICOM Image Viewing

DICOM files consist of header information and pixel data. The header data includes vital information about the scan such as image dimensions, patient name, patient position, image origin, and more. To view the DICOM pixel data, it must be extracted from the file. Web programming languages such as PHP, JavaScript, and HTML do not provide built-in DICOM handlers; therefore another route must be taken. Python provides a DICOM library that can extract the proper data from the DICOM file. PHP is capable of calling python scripts. The python script must be able to communicate this information back to the server-side software.
The DICOM handling python script extracts the pixel data from the DICOM file and saves a binary file consisting of the image dimensions and the image data. File format is as follows:

[Image Height][Image Width][Number of Slices][pixel 1]…..[pixel X]

The first 3 bytes describe the image height, width and length. The rest of the bytes describe the image data. The resulting file is a long string of bytes and can be reorganized based on the first 3 bytes of information. At the conclusion of the python script, PHP can then read the binary file and extract that data.

PHP cannot display the data; therefore it is passed to JavaScript for a dynamic image viewing. A user interface to navigate through the slices of the CT and PET, change brightness/contrast was also created for a more qualitative approach on image analysis.

4.7. Post Analysis

Post analysis is accomplished once DICOM image data is uploaded to the server. Analysis techniques employed include the following: ROI drawing, image manipulation, DICOM export, and JPEG export. ROI drawing is the most valuable tool in the system, as it is one of the most time consuming tasks at the SAIF.

4.7.1. ROI Drawing

ROI drawing slice by slice will accomplish a 3-dimensional ROI resulting in organ volume and PET tracer uptake. This information is vital in monitoring disease progression or diagnosing a disease. While some ROI drawing can be automated, at the SAIF, ROIs are typically manually drawn around the mouse tail and the tumor. It is nearly impossible to automate tumor ROI drawing as tumors vary greatly in shape and
location. On the other hand, tails are predominantly in the same position and contain very similar features throughout scans.

Tail ROIs are drawn in order to obtain the PET radiotracer activity that was not metabolized by the body. The residual amount in the tail can be subtracted from the injected amount to obtain more accurate uptake amounts in the tumor or other organs. The process of drawing ROIs around organs and the tail take a considerable amount of time, especially over 1000’s of scans. The goal of our study is to automate a majority of this process such as tail ROI drawing, tail PET activity quantification, tumor (or other organ) PET activity quantification, standard uptake value (SUV) of tumor, and report generation.

4.7.1.1. Standard Uptake Value

Standard uptake value (SUV) is the ratio of the actual radioactivity concentration found in a selected part of the body at a certain time point, and the radioactivity concentration in the hypothetical case of an even distribution of the injected radioactivity across the whole body.

\[
SUV = \frac{TissueActivity(Bq)}{\frac{TissueWeight(g)}{TotalActivityInjected(Bq)} / MouseWeight(g)}
\]

The SUV is primarily useful in the case of the amount metabolized by the body, not the amount of radiation injected in the body. The activity not metabolized by the body is the amount that is contained in the tail. A study was performed was to investigate
the effects of tail residual activity on SUV calculations. Figure 4.7.1.1-1 displays the results.

![SUV Max % Change vs. Tail Residual %](image)

**Figure 4.7.1.1-1: Tail Residual Effects on SUV**

As it can be seen, as the tail residual percent increases, the SUV percent change increases. Therefore, we must consider the tail activity while performing SUV calculations. The TotalActivityInjected/MouseWeight (Bq/g) needs to be adjusted to exclude the tail activity. The SUV of the tumor (or other organ) can be accurately found based on the volume and activity along with the adjusted injected activity/body weight (Bq/g) amount. These steps can be automated and saved to the database for report generation once the appropriate information is in place such as mouse weight and injected dose.
4.7.1.2. Automated Tail ROI

In the SAIF, the mouse’s tail is curled so that the tail is in the entire field of view for both PET and CT. The base of the tail is a user input to the system (clicking notation, see Figure 4.7.1.2-1). The system then can find the entire tail based on that starting position.

![Figure 4.7.1.2-1: Marking the base of tail](image)

Once the base of the tail has been established, the system can automatically segment the tail from the rest of the scan. The method used to segment the tail is the nearest neighbor thresholding that searches for pixel values closely matching the tail’s pixel value (see Figure 4.7.1.2-2). Performing this task slice-by-slice, the tail ROI can be drawn automatically. The resulting data is a 3-dimensional dataset the same size of the CT data; 1’s representing the tail, 0s representing points outside the tail. This 3-dimensional dataset can then be used as a mask for the PET scan to obtain the total tracer activity in the tail for future use.
4.7.1.3. Tumor ROI Drawing

Drawing ROIs around the tumor automatically are nearly impossible due to the variation in size and location of tumors. This process must be a manual step in the analysis process. To create a 3-dimensional ROI around the tumor, the user must analyze the tumor slice-by-slice. Once the user has drawn around the entire tumor, the resulting ROI can be masked the PET data to obtain the tumor tracer uptake.

4.7.2. PET/CT Registration

PET and CT data are acquired consecutively and need to be registered so that information regarding both anatomy (CT) and function (PET) may be obtained. The PET and CT scanners used at the SAIF are from two different manufacturers; therefore the scans are completed at different times using two separate instrumentation systems. Hardware and software solutions were implemented in order to treat them as the same machine. Mechanical adapters and registration software are in place to accomplish this task. The
adapter allows the PET bed to be used in both the PET scanner and the CT scanner. The challenge is aligning the two resulting datasets in all 3 dimensions to view the fused data. The software allows input from the two datasets, aligns the images and produces a new CT file that is registered properly with the PET data. The script is called automatically when the correct PET and CT data are uploaded (from the same mouse).

The bed on which the mouse is placed in the CT scanner is used as a reference due to its straight edges and high density. The bed’s location can be found in all 3 dimensions and based on these measurements the bed can be rotated and shifted in the 3 dimensions (see Figure 4.7.2-1). To obtain a 2-dimensional representation of the entire 3-dimensional volume, the maximum intensity projection was found. An affine transformation was used to accomplish the shifting and rotating. As a result of the translations and transformations, a new CT DICOM image is created and saved to the server.

Figure 4.7.2-1: Rotation of CT Data
Since the CT and PET data are acquired from separate scanners, their centers of origins are unequal; therefore the data must be shifted. Once the CT data has been rotated, it must be shifted to the center of the field of view. See Figure 4.7.2-2 for order of operations to accomplish this shift.

![Diagram of CT data shifting](image)

**Figure 4.7.2-2: Shifting of CT Data**

Zero padding a 2-dimensional dataset will move the data in either rows or columns depending on what is desired. Figure 4.7.2-3 displays a shift of 1 row and 1 column of an example dataset.
To ensure success of this algorithm, a phantom capable of being scanned in both the PET and CT scanners was used. The phantom is shown in Figure 4.7.2-4.

10, 20 and 40 µCi of $^{18}$F-FDG were inserted into each well of the phantom, respectively. The phantom was scanned for 10 minutes in the PET scanner and a
CT reference was recorded shortly after. The pixel difference from PET and CT registration was noted.

4.8. Evaluating the System

To evaluate the web-based system for its ability to increase efficiency in the SAIF, historical PET/CT information was examined. PET/CT studies were completed using the new system to compare to the conventional method. This provides information about how much time was saved in all areas of a study protocol, specifically scheduling, billing, performing the study, and post analysis. Historical datasets were also analyzed by 3 evaluators using conventional manual methods and using the management system.

5. Results

The system was designed in mind to improve efficiency in the Van Andel Research Institute’s SAIF as well as a platform for other SAIFs worldwide. The following is the result of the newly build SAIF management system.

5.1. Scheduling

The SAIF manager must be organized and know the study details prior to scheduling. The process of creating a new study requires the input of a protocol number, number of mice, modality (s), injection route, tracer and number of time points. Using the new management system, the date of each time point is selected to allow the system to query each SAIF member’s Microsoft Outlook calendar for availabilities. All involved members’ availabilities on the selected days will be displayed for ease of scheduling. After selecting dates/times for all time points of a new study, the system will automatically send Microsoft Outlook meeting requests to the involved SAIF members to add to their respective calendars.
When scheduling the study using the conventional method, the SAIF manager needs to query each involved person regarding their availability. Custom Outlook meeting requests also need to be created and sent to the SAIF members based on what the SAIF manager deems most fitting for a study design.

The process in which the SAIF manager schedules a study using the management system starts with he/she initializing the study parameters into the system via web-form, see Figure 5.1-1.

![Figure 5.1-1: Setting up a Study](image)

Once all of the initial parameters are input, the manager can then start to schedule each time point.
When a date has been selected for each time point, the system queries each member’s Microsoft Outlook calendar for their availability on each selected day, see Figure 5.1-2. With a guide for SAIF member’s availability shown, the SAIF manager can then select the start and end times for each time point. Once the times have been selected, the study is added and all involved members receive a Microsoft Outlook meeting request for each time point.

5.2. Billing

There are two phases in the billing process, quoting and final billing. When the customer requests a study be performed, the SAIF manager creates a quote. The customer accepts, denies, or suggests modifications to the study. At the conclusion of the study all participants give the SAIF manager an estimate of hours each spent completing the required tasks. The manager then sends a final bill to the customer, see Figure 5.2-1. With the conventional technique all billing is completed using Microsoft Excel.
For the new management system, at the conclusion of scheduling a study, the SAIF manager can generate a quote based on the input parameters of the study. Such parameters used are hours per time point, tracer, and modality.

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Modality</th>
<th>Date</th>
<th>Scanning (Hours)</th>
<th>Analysis (Hours)</th>
<th>Materials Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timepoint 1</td>
<td>PET CT</td>
<td>2013-04-19</td>
<td>2.5</td>
<td>1</td>
<td>160</td>
</tr>
<tr>
<td>Timepoint 2</td>
<td>PET CT</td>
<td>2013-04-20</td>
<td>2</td>
<td>1</td>
<td>160</td>
</tr>
</tbody>
</table>

Summary:

<table>
<thead>
<tr>
<th>Summary</th>
<th>Hours</th>
<th>Rate</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timepoint 1</td>
<td>3.5</td>
<td>$50</td>
<td>$175</td>
</tr>
<tr>
<td>Timepoint 2</td>
<td>3</td>
<td>$50</td>
<td>$150</td>
</tr>
<tr>
<td>Materials</td>
<td></td>
<td></td>
<td>$20</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>$645</td>
</tr>
</tbody>
</table>

**Figure 5.2-1: Quoting & Billing the Customer**

At the conclusion of a study and when all members have input the hours that they spent on each task in the study, the final bill can be generated and printed. The final bill looks very similar to the quote, except the hours will be based on the members’ input to the system.

### 5.3. Image Analysis

Image analysis is typically completed by SAIF members and is a manual task. For PET/CT studies, the principal investigator is commonly interested in the volume of the tumor and the SUV$\text{max}$ in the tumor. The process to achieve these results is very time consuming, especially for studies involving forty mice. The SAIF member must first manually alter the DICOM header information; this will make the PET/CT data have the same information to allow the data to be open together on analytical software. First, an ROI enclosing the entire tail is drawn; this will quantify the amount of radioactive tracer that is not metabolized by the body
(residual). Next, an ROI that encloses the entire tumor is drawn. Manual calculations must be performed to obtain the $SUV_{\text{max}}$ based on the injected dose, mouse weight, tail residual activity and tumor volume. This entire process takes about 15 minutes per mouse, which means that for a study involving 40 mice the total time is about 10 hours.

In the new management system, the image analysis suite can be accessed after data has been uploaded to the server. The initial tools allow the user to scroll through the slices of the 3-dimensional CT/PET/SPECT data, control brightness/contrast and invert the images, see Figure 5.3-1.

![Figure 5.3-1: Viewing CT Data](image)

The user is then able to perform a full analysis on the dataset. The tail ROI must be found, either manually by the user or automatically by the selection of the base of the tail. This ROI provides the total activity within the tail which can be subtracted from the injected activity for more accurate results of standard uptake value. The organ of interest (typically tumor) must be drawn manually and is by far the most time intensive portion of the post analysis process. The interface which allows the user to perform all of the post analysis is shown in Figure 5.3-2.
Figure 5.3-2: Post Analysis Interface

Three evaluators performed data analysis on the same 18 mice using the conventional manual method and the automated method using the system. The conventional method includes manual PET/CT fusion, and drawing ROI’s around the tail and the tumor. The automated method includes automatic PET/CT fusion, automated tail ROI drawing and manual tumor ROI drawing. The results for the activity in the tail are as follows in Figure 5.3-3.
As it can be seen the activities within the tail for both methods are comparable. The standard deviation errors are lower for the automated method than the conventional method. Figure 5.3-4 displays the results for SUV\textsubscript{max} of each tumor found using conventional and automated methods.

Figure 5.3-3: Tail Activity Comparison
As it can be seen, the SUV\textsubscript{max} found using conventional and automated methods are very comparable, within 3%.

5.4. PET/CT Registration

After recording PET and CT scans of the designed phantom, the pixel difference was recorded. Figure 5.4-1 shows the coronal view of the PET/CT phantom registration.
The difference is very minute and indistinguishable in both the X and Z axes. Figure 5.4-2 shows this registration in the sagittal view.

Figure 5.4-1: Coronal View of PET/CT Registration of Phantom

Figure 5.4-2: Sagittal View of PET/CT Registration of Phantom
As it can be seen, the PET and CT information is slightly off in the sagittal plane (Y axis). The difference in millimeters is 1.42mm. This is approximately 4 pixels (4.85% difference) when accounting for the 0.4mm spatial resolution of the CT scanner.

5.5. SAIF Efficiency

The areas of performing a study that were investigated for efficiency were: scheduling, billing, performing a study, and post analysis. For each area of a study, the conventional method was compared to the method using the system. Figure 5.5-1 describes the total time to perform each task for a 20 mouse PET/CT study.

![Fig 5.5-1](image)

**Figure 5.5-1: Timing Analysis of PET/CT Studies**

As it can be seen, the system appears to improve efficiency in the areas of scheduling, billing and post analysis. The time it takes to schedule studies was decrease by 93% using the system and for billing, 87% decrease. Post analysis time was decreased by 74.8%, also. For a 20 mouse study, the total time saved was 359 minutes (~6 hours).
6. Discussion

Managing and operating a SAIF is a very time consuming process and can lead to errors without the assistance of an automated system. The scope of this thesis was to improve efficiency in the Van Andel Research Institute’s SAIF and to investigate the feasibility of creating a platform for other SAIFs worldwide. The main areas within a study were found to be scheduling, billing, performing the study and post analysis on the data. Each area of a study was investigated for areas of improvement. It was found that scheduling, billing and post analysis can all be completed either automatically or semi-automatically. There are obviously some manual inputs that the system needs in order to operate smoothly.

The automated aspect of scheduling was its integration with Microsoft Outlook. As the manager is setting up the study, he/she can view all involved member’s availabilities based on the days chosen for each time point as well as automatic Microsoft Outlook meeting requests for each time point. The billing portion of the system was completely automated, providing the quote and the final bill with just a click of a button. Image analysis was semi-automatic. The only manual intervention from the SAIF member is drawing an ROI around the tumor or organ of interest. Everything else involved in image analysis is automated and a report is generated at the end that provides SUV_{max} and tumor volume.

The new system greatly improved efficiency by reducing the time it took to schedule a 20 mouse PET/CT study by 6 hours as compared to the conventional technique. Performing a study is deemed as an un-automatable task. Therefore, if the time to perform the study is excluded from efficiency analysis, the efficiency is increased by 90%. The system is designed primarily for PET/CT studies which is the most common type of study at the Van Andel Research Institute’s
SAIF. However, the system can be utilized for a variety of studies using different imaging modalities as well.

### 6.1. Applications of System

The following are some examples of research that is supported by the SAIF management system. The system is not limited to the examples shown.

#### 6.1.1. Apoptosis Imaging

Apoptosis is the process of programmed cell death (PCD). The average adult human has between 50 and 70 billion cells die each day due to apoptosis. Early after therapy, 2'-deoxy-2'-[¹⁸F]-fluoro-D-glucose ([¹⁸F]-FDG) imaging is not always reliable due to the influx of inflammatory cells while apoptosis imaging offers a direct and early measurement of therapy effects. An apoptosis probe, Technetium-99m hydrazinonicotinamide annexin A5 ([⁹⁹mTc]-hAnxA5), in combination with [¹⁸F]-FDG imaging can be used to evaluate therapy response (De Saint-Hubert et al. 2011). This type of research requires the use of SPECT and PET. ⁹⁹mTc-hAnxA5 is a photon emitting tracer, so SPECT is the modality to use in order to visualize it. [¹⁸F]-FDG is a positron emitting tracer, so PET is the modality to use. Figure 6.1.1-1 shows SPECT images before and after treatment.
6.1.2. Early Response of Tyrosine Kinase Inhibitor

Noninvasive PET imaging can be utilized to monitor tumor response to the VEGFR-2 tyrosine kinase (TK) inhibitor ZD4190 during cancer therapy. A previous study evaluated tumor glucose metabolism, tumor cell proliferation, and angiogenesis using $[^{18}\text{F}]-\text{FDG}$, $[^{18}\text{F}]-\text{FLT}$, $[^{18}\text{F}]-\text{FPPRGD2}$, respectively. In this study, mice were treated with ZD4190 three consecutive days, d1, d2, d3. A longitudinal PET study showed that $[^{18}\text{F}]-\text{FDG}$ was not able to tell if ZD4190 was working properly. $[^{18}\text{F}]-\text{FLT}$ showed a significant decrease in uptake in the tumor up until day 3, uptake was similar to the control thereafter. $[^{18}\text{F}]-\text{FPPRGD2}$ showed the greatest decrease in tumor uptake compared to the control mice. The use of different PET probes and longitudinal PET imaging was able to show the researcher the effects of the VEGFR-2 tyrosine kinase inhibitor ZD4190 (Yang et al. 2011). Figure 6.1.2-1 shows PET imaging using the $[^{18}\text{F}]-\text{FPPRGD2}$ tracer.

Figure 6.1.1-1: Apoptosis Imaging\(^4\)

\(^4\) (De Saint-Hubert et al. 2011)
6.1.3. Longitudinal Evaluation of Liver Metastases in Preclinical Models

Liver metastasis is a clinically significant contributor to the mortality associated with melanoma, colon and breast cancer. Preclinical mouse models are essential to the study of liver metastasis. High frequency ultrasound was recently proven to be effective at monitoring metastasis size longitudinally in differing mouse models. A previous study proved the efficacy of using high frequency ultrasound to monitor metastases in breast, colon and melanoma mouse models (Graham et al. 2005). Figure 6.1.3-1 shows the growth of a liver metastasis over a period of time.

Figure 6.1.2-1: 18F-FPPRGD2 Imaging

(Yang et al. 2011)
6.1.4. Anatomical Reference from CT

Computed Tomography (CT) has been used widely for anatomical references for the molecular imaging modalities (PET, SPECT). An anatomical reference provides the researcher with a greater knowledge of what is being visualized in the molecular imaging datasets. CT is a density based modality and relies heavily on high density media within the body (bones). Often times the researcher is interested in softer tissue organs (liver, kidneys). With the use of an injectable contrast agent, CT scans can be recorded to obtain information about the soft tissue organ the researcher is interested in (Peck 2012).

6.1.5. Bioluminescence Imaging of Gene Expression

A rapid and accessible technology for in vivo analysis involves internal biological sources of light emitted from luminescent enzymes, luciferases, to label genes and cells. In vivo bioluminescence imaging (BLI) can be used to view gene function and response to metabolic or pharmacological stimuli in the living animal in real time. The metabolic disease, heme oxygenase-1, was considered as a model in a previous study. The promoter of the gene for HO-1 can be linked with firefly luciferase gene to visualize the light emitted using a BLI scanner. HO-1 is the rate limiting enzyme in the degradation of heme.

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6 (Graham et al. 2005)
to bilirubin. It constitutes an ideal therapeutic target for the prevention of hyperbilirubinemia (Contag and Bachmann 2002).

6.2. Future Work

The new system provides improved efficiency but may be improved by including the following features: in-study warnings/alerts an automated system to record scan record information such as syringe activity, mouse weight, and residual syringe activity. The in-study alert system would be a tool that can be launched at the beginning of a study which directs the study for the SAIF manager and SAIF members from injection times to scan times. Recording values of injected dose, injection time, and scan time manually is a process which could lead to incorrect information. A system to record these values digitally and saved to the database would increase efficiency greatly.
7. Appendix: Relational Database Tables

Table A-1: SAIF Member Information

<table>
<thead>
<tr>
<th>Field Name</th>
<th>Data Type</th>
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</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Username</td>
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</tr>
<tr>
<td>Full Name</td>
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<td>NO</td>
</tr>
<tr>
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<td>NO</td>
</tr>
<tr>
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<td>NO</td>
</tr>
<tr>
<td>Cell Phone Number</td>
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<td>NO</td>
</tr>
<tr>
<td>Email Address</td>
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<td>NO</td>
</tr>
<tr>
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</tr>
<tr>
<td>Title</td>
<td>Enum('DIRECTOR','LAB MANAGER','RESEARCH SCIENTIST','POST-DOC','GUEST STUDENT','GRADUATE STUDENT','STUDENT INTERN','ADJUNCT FACULTY','COLLABORATOR')</td>
<td>NO</td>
</tr>
<tr>
<td>Lab Name</td>
<td>String</td>
<td>NO</td>
</tr>
</tbody>
</table>

Access type associated with each member dictates how the web interface appears to the user logged in. Admins and super users are granted special rights to add, delete, and modify items in the database.

Table A-2: Project Information

<table>
<thead>
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</tr>
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</tr>
<tr>
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<tr>
<td>Description</td>
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<tr>
<td>MTA Status</td>
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<td>NO</td>
</tr>
<tr>
<td>CDA Status</td>
<td>Enum('Complete','In Progress','Not Needed','Needed')</td>
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</table>
Table A-3: Study Information

<table>
<thead>
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<th>Field Name</th>
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<tr>
<td>Project ID</td>
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<td>PARTIAL</td>
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<td>Study Name</td>
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<td>Protocol Number</td>
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<tr>
<td>Description</td>
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<tr>
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<td>Number of Mice</td>
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</tr>
<tr>
<td>Modality</td>
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</tr>
</tbody>
</table>

This information will be known to the SAIF manager prior to scheduling a study and will be input by him or her responsible.

Table A-4: Time Point Information

<table>
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<th>Field Name</th>
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</tr>
<tr>
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<td>PARTIAL</td>
</tr>
<tr>
<td>Date</td>
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</tr>
<tr>
<td>Start Time</td>
<td>Timestamp</td>
<td>NO</td>
</tr>
<tr>
<td>End Time</td>
<td>Timestamp</td>
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</tr>
<tr>
<td>Outlook Event ID</td>
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</tr>
<tr>
<td>Material Cost</td>
<td>Double</td>
<td>NO</td>
</tr>
</tbody>
</table>

When a longitudinal study is scheduled, an Outlook event will be created and added to each member involved personal calendar for each time point. The event ID created automatically by Outlook will be stored to the system to allow for modifications and deletions of the event.

Table A-5: Member Schedules

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<td>PARTIAL</td>
</tr>
<tr>
<td>Study ID</td>
<td>Integer</td>
<td>PARTIAL</td>
</tr>
<tr>
<td>Time Point ID</td>
<td>Integer</td>
<td>PARTIAL</td>
</tr>
<tr>
<td>Task</td>
<td>String</td>
<td>NO</td>
</tr>
<tr>
<td>Hours Worked</td>
<td>Double</td>
<td>NO</td>
</tr>
</tbody>
</table>
As members are selected to participate in a study, the information relating to the task they are assigned, and which time points of the study they are involved in will be saved.

**Table A-6: Equipment Information**

<table>
<thead>
<tr>
<th>Field Name</th>
<th>Data Type</th>
<th>Primary Key</th>
</tr>
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<tbody>
<tr>
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</tr>
<tr>
<td>Equipment Name</td>
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<td>NO</td>
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<tr>
<td>Modality</td>
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<td>NO</td>
</tr>
<tr>
<td>Email Address</td>
<td>String</td>
<td>NO</td>
</tr>
</tbody>
</table>

An email address for each imaging scanner will be created to allow scheduling the scanners on Outlook as well. This allows the scanner’s calendars to be viewable and automated.

**Table A-7: Dicom Data Information**

<table>
<thead>
<tr>
<th>Field Name</th>
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</tr>
<tr>
<td>Time Point ID</td>
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<tr>
<td>Project ID</td>
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<tr>
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</tr>
<tr>
<td>File Name</td>
<td>String</td>
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</tr>
</tbody>
</table>

The mouse name is associated with each mouse involved in a study and tracked by each time point. The data uploaded to a certain mouse’s record will be stored to the server and its location is saved in the database.
8. Bibliography


———. 2012b. “Quartzy Scores $1.2M To Help Life Scientists Stay Organized.”


