Rodent Rotation and Translation Stage

BME 200/300 October 9, 2019

Client:

Prof. Jeremy Rogers and Dr. Ben Sadjak

Advisor:

Aaron Suminski

Team:

Kyle Schmidt (*Communicator*)
Riley Pieper(*BSAC*)

Nolan Thole (*BPAG*)
Kurt Vanderheyden (*Team Leader*)
Kevin Tan (*BWIG*)

Abstract

Millions of Americans suffer from blinding diseases such as macular degeneration and glaucoma [1]. In an effort to develop information that will contribute to the treatment of such diseases, extensive research is conducted, often involving the imaging of retinal tissue [1, 2]. In the case of client Dr. Rogers' research, imaging of rodent eyes creates valuable data that can be used to develop conclusions relevant to conditions in the human eye [2]. The process of imaging the retinas of rodent eyes involves prevision alignment of the specimen eye within the field of view of the imaging device and requires the ability to adjust the angular position of the eye to image across the spherical shape of the retina. Current products used to hold and position the imaged specimen, be it a living rodent or an individual orbital, provide rotational and translational degrees of freedom, but fail to provide alignment of the specimen within the rotating elements [3, 4]. This makes adjustment throughout the imaging process cumbersome due to the fact that the eye changes translational position as it is rotated because it is not aligned at the intersection of the rotational axes. Therefore, the aim of this design project is to develop a device providing pitch and yaw rotational freedom as well as a mechanism for the alignment of the pupil of the specimen at the intersection of these rotational axes. The device will ultimately be tested to determine the attainable precision of the various adjustments available as well as the accuracy of aligning the pupil of a specimen at the intersection of the rotational axes. The results will evaluate the effectiveness of the design in streamlining the imaging of rodent eyes for research contributing to the study and treatment of critical ocular diseases.

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I. Introduction

Motivation

Our goal is to create a device that will aid our client in the imaging of photoreceptors in the eye of a rodent. Rodents are commonly used as imaging subjects because of their frequent reproduction, genetic purity, and biological similarity to humans. Ocular imaging of rodents is used to study glaucoma, macular degeneration, cell replacement therapy and gene therapy in humans. By studying these diseases, we hope to better understand the cause of these diseases and develop treatments for humans. In our client's research, the device that currently supports the rodents requires him to adjust the rodent frequently to image the entire eye. Our goal is to create a design that provides 5 degrees of freedom, 3 translational (x, y, z) and 2 rotational (pitch and yaw), that will allow our client to image the entire eye without the need for repositioning. To do this, the center of the rotational axes must be at the center of the eye.

Existing Devices & Current Method

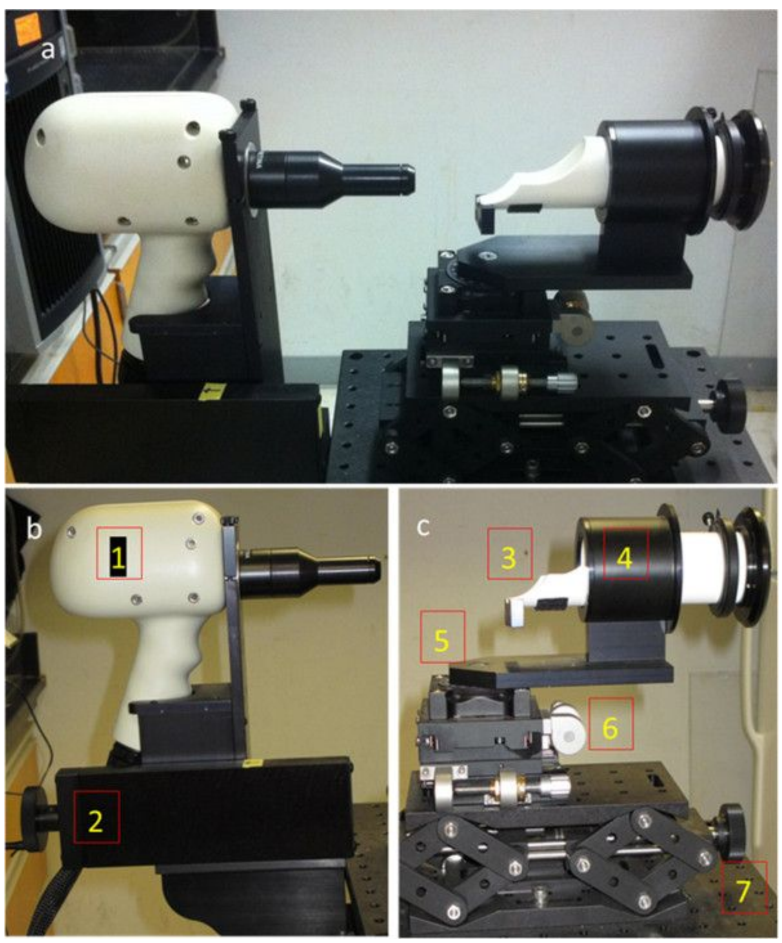


Figure 1: Bioptigen's rodent alignment system (RAS) composed of concentric cylinders presenting pitch and a pivoting joint providing yaw; no element allows for centering of subject pupil [5]

Bioptigen RAS: Device features an alignment stage with two concentric tubes for holding the specimen. It has two degrees of rotation, roll and yaw in the tube. Roll is achieved by rolling the inner tube and yaw is achieved by rotating the tubes side to side. There is one degree of translation within the rotational axes which is the inner tube sliding forwards and backwards. Outside of the rotational axes there are 3 degrees of translational freedom by the whole stage sliding in all directions. This solution was expensive and is no longer on the market.

Figure 2: Past UW Madison BME design team's solution; presents 3 degrees of rotational freedom but limited internal translational freedom; extensive gearing prevents facile sterilizability; prototype 3D printed [6]

Rodent Rotation and Translation Stage: Past design team utilized a 3D printed solution to hold a specimen for imaging of the eye. Device provided 5 degrees of freedom and was built on a gear system for rotation. Device provided an adequate solution to the problem of a device needing 5 degrees of freedom, but failed to keep an eye at the center of rotational axes which is needed to image the eye continuously.

Problem Statement

Research of mammalian retinal photoreceptors, conducted via the imaging of rodent model organisms, requires precise alignment of the specimen. A device providing facile alignment of rodent eyes within the imaging system's field of view as well as rotational freedom for accessibility to a holistic view is called for. This device must provide at least 2 rotational degrees of freedom, pitch and yaw, as well as 3 translational degrees of freedom for the positioning of the eye at the intersection of the rotational axes.

II. Background

Biology & Physiology

According to our client, the rodents that will be used most often in the lab will be a rat. Rat's are typically between 250-500 grams with a length of 17-21 centimeters [7]. Rats generally live in an environment between 20-25 degrees C and humidity of 30%-50% [8]. The current way the client's stage positions the rodent does not allow for rotational and translational freedom as desired by the client. The main priority of our design is the rotational freedom of yaw (side-to-side) and pitch (up-and-down).

Research Required to Design Prototype

To create the prototype and design, research needed to be done on ways to translate and rotate something while keeping the object in the center of the axes. The best way to accomplish the rotation is through friction. Friction allows for something to be rotated without the use of gears and other similar methods. Friction also takes away the need for lubricants, and a large static frictional force will also be very precise in positioning. One negative of using friction as a driving force in rotation is that it requires materials that are heavily wear resistant which would require more expensive materials to be used in assembly [9].

To accomplish the translational requirements, the best options in the x, y, and z components involve a linear translation stage design. Linear stages allow for sliding back in forth in one degree of freedom while constraining the other 5 degrees of freedom in translation and rotation. The linear stage can be translated by using friction, roller bearings, air bearings, belts and pulleys, or by wheels [10]. The linear stage requires a feedback system to be precise and find the exact location desired. Our client has an existing feedback system that could be incorporated into the linear translation stage.

Client Information

Our clients are Prof. Jeremy Rogers and Dr. Ben Sadjak from the University of Wisconsin-Madison. They currently do research and imaging on rodents in the Wisconsin Institute of Medical Research and require a new stage for the rodents. Their research focuses on gaining insight on macular degeneration, glaucoma, and metabolic activity in retinal stem cells in vitro[2].

Design Specifications

The purpose of this stage is to employ five degrees of freedom, 3 translational and 2 rotational, while still keeping the rodent's eye in the intersection of the axes. There should be 100 microns of precision in the translational axis and 2° of precision in the rotational axis. The device should be able to support up to a 1 pound organism and be less than 10kg to allow for easy transport around the lab. The stage as a whole should last for 5 years in normal lab conditions while the replaceable sample holders should have a life of service for at least 1 year. The device should be sterilizable and securely hold an anesthetized rodent. There is a flexible budget of $350 for this design project. *See Appendix A for complete list of product design specifications.*

III. Preliminary Designs

Design 1: Bowls

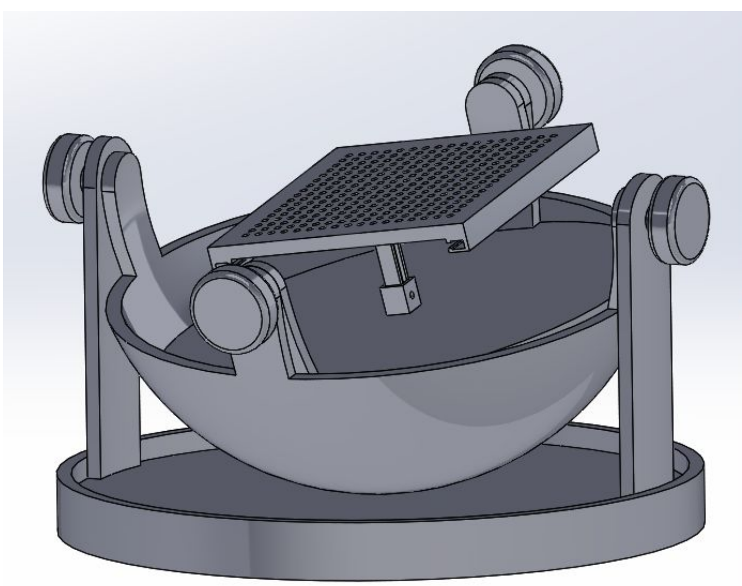


Figure 3: Bowls alternative design; utilizes concentric hemispheres to provide pitch and roll, base spins to provide roll; internal translation provided by stage travelling along rails; all movements are friction based

The Bowls design, shown in Figure 3, provides six degrees of freedom, including three degrees of rotational freedom and three degrees of internal translational freedom. Pitch and roll are achieved via the concentric, partial spheres ("bowls") that slide/pivot across one another. The adjustment dials corresponding to each of these rotational axes are friction based such that the rotational position of the specimen may be adjusted but will hold position afterward. Yaw is available via the pivoting disk that the entire design sits upon. This disk component, again, operates based upon friction. The three degrees of internal translational freedom are achieved via perpendicular tracks along which the rectangular stage within the rotational components may be shifted. This track system is also friction based, with a thumb screw at the base of the vertical rail for extra support of the weight of the specimen. The translating stage is fitted with threaded holes providing extensive flexibility for attachment of a variety of sample or subject holders.

Design 2: The Pizza

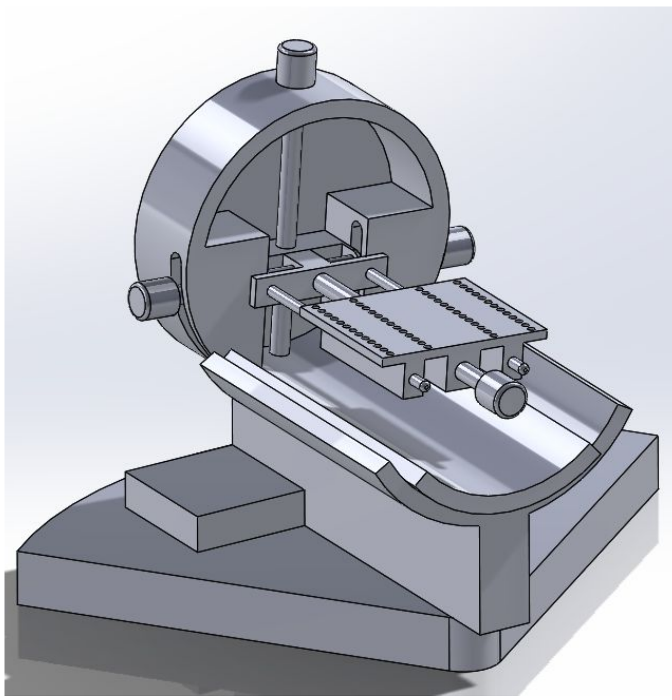


Figure 4: Pizza alternative design; features 5 degrees of freedom: pitch available via turning of the concentric cylinder while yaw via pivoting across triangular base; three degrees of internal translation due to travelling along threaded rods that are turned by dials

The Pizza design, depicted in Figure 4, provides only the five required degrees of freedom - three of internal translation and two of rotation - which eliminates some of the complexity in adjustment that comes with the Bowls design. This design builds on the ideas implemented by Bioptigen's RAS design, specifically relating to the rotational adjustment methods [3]. Yaw is available via a pivot across the triangular base while pitch is manipulated through turning of the large cylinder. The Pizza design improves upon the precision of the Bowls design by including dials for the adjustment of the specimen stage along the three internal degrees of freedom. The translating stage is fitted with threaded holes providing extensive flexibility for attachment of a variety of sample or subject holders. The dials will turn threaded rods to manipulate the position of this stage along the x, y, and z axes such that the pupil of the imaged specimen may be accurately positioned at the intersection of the perpendicular rotational axes. Also of note, unlike the bowls design, this intersection is positioned towards the front of the design, providing more room for the body of potential rodent specimens.

Design 3: The Field Goal

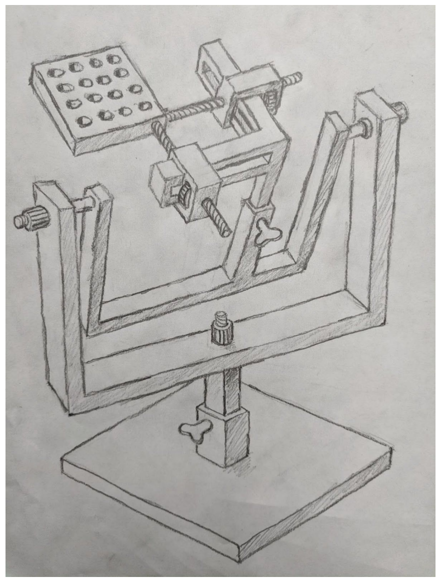


Figure 5: Field Goal alternative design; allows for pitch adjustment via swinging mechanism and yaw as the design spins; three degrees of internal translation via turning dials with threaded rods and vertical adjustments that move stage and whole design up and down

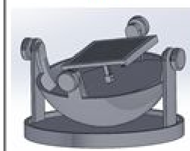
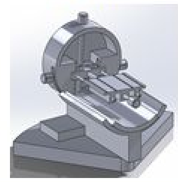
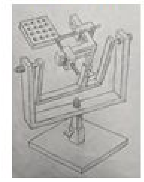
The Field Goal design, depicted in Figure 5, focuses on simplicity and cost efficiency. The base of the design holds the rest of the structure upright with an adjustable, telescoping post. This vertical adjustment along with the horizontal freedom gained from placing this design on a flat surface in front of the microscope, guarantees that the lens of the imaging device can be pointed directly at the center of the two axes of rotation. Above the base, there are two rotating arms which can be adjusted then tightened in place with thumb screws. These arms provide two orthogonal axes of rotation: pitch and yaw. Fixed on the inner of the two rotating arms is a structure that allows for a stage to be translated in three dimensions. Translation is achieved via a telescoping post and threaded knob system. While this knob system is more complicated than simply using more telescoping posts, it provides the user with additional ease of use and potentially finer adjustments. Lastly, the stage itself is covered in threaded holes allowing the user to fix a specimen holder in various positions prior to further adjustment.

IV. Preliminary Design Evaluation

Criteria Weight

Table 1 presents the design matrix used to evaluate the three preliminary design alternatives. Each design was scored according to weighted criteria to determine an overall score out of 100. The most important criteria included, with a weight of 20, is the ease of adjustment. This is a key feature of the design due to the fact that the motivation behind the project is a need for a means to easily position and adjust the position of ocular specimens being imaged. The translational and rotational components of the stage must be easily manipulated by the researcher for the design to be effective. Other categories of high importance include rotational and translational freedom, with weights of 18 and 15, respectively. The stage to hold the specimen must be easily yet precisely rotated to quickly visualize a wide range of the specimen's retina. Additionally, the stage must be translated within the rotational elements such that the pupil of the imaged eye can be accurately positioned at the intersection of the rotational axes for a variety of specimens. Ease of fabrication and sterilizability received the next highest weight, at 12, due to the importance of developing a prototype to test and the client's wish for smooth surfaces that can easily be cleaned between imaging trials. Finally, the remaining criteria, including strength, safety, simplicity, and cost were considered during the evaluation of designs but held the least weight due to the lack of emphasis put on them by the client.

Table 1: Design matrix evaluating the Bowls, Pizza, Field Goal designs according to weighted criteria; each design scored on a scale from 0-5 for each criteria; total score based on weighted criteria scores and out of 100; Pizza design determined to be the most effective according to evaluation criteria

Criteria	Design 1: Bowls 	Design 2: Pizza 	Design 3: Field Goal 
Ease of Adjustment (20)	3	5	3
Rotational Freedom (18)	5	4	3
Translational Freedom (15)	3	4	2
Ease of Fabrication (12)	3	2	5
Sterilizability (12)	4	3	3
Strength (8)	2	4	2
Safety (5)	4	5	4
Simplicity (5)	3	2	5
Cost (5)	3	1	5
Total (100)	69	72.8	65.2

Evaluation Scores

Ease of Adjustment

The most important characteristic when evaluating potential designs is the ease of adjustment that the stage design provides. For this reason, this criteria is given the highest weight. The purpose of this design project is to develop a product that provides accessible and adjustable alignment of specimens being imaged. In order for a product like this to be useful, it must be easy to use. Primarily, it must be easy to adjust the position of the rat within the rotational components, such that the eye to be imaged is directly at the intersection of the orthogonal rotational axes. This was a key concern of the client. Furthermore, it is clear that this design needs to be easily adjusted during the imaging process in order to access multiple angles and a large area of the retina. Due to its facile, dial-based translational adjustment and biaxial rotational freedom, the Pizza design excelled in this area, receiving a 5. This is compared to the Bowls design, adjusted manually against friction with an unnecessary rotational degree of freedom, and the Field Goal, requiring adjustment and tightening of several components for adjustment/fixation, both receiving a score of 3.

Rotational Freedom

The second most important criteria for evaluation is how freely the device can rotate the eye. The eye must be able to rotate so the imaging device can image different parts of the retina on the rodents eye. For accurate imaging, the eye must remain in the center of the two axes when rotation occurs. The two axes of rotation must intersect at the center and be perpendicular. The device should provide a wide range of degrees of rotation. Because the Bowls design presents three degrees of rotational freedom, it scored the highest with a 5. The Pizza design outscored the Field Goal (3) with a 4 based on the rotational precision that can be achieved through the friction-based design.

Translational Freedom -

Translational Freedom is important in order to locate the rodent's eye in the center of both rotation axes. It is very important that the user is able to achieve this in order to obtain accurate rotations. This translation needs to be adjustable but does not need to achieve as large a range of motion that rotation does. The Pizza design, again, bested the other design alternatives in this criteria due to the potential for a high degree of precision with the threaded internal translation components, scoring a 4. This design does not receive a perfect score due to the fact that improvements may still be made to facilitate the alignment at and locating of the rotational axis intersection point. On the other hand, Bowls scored a 3 because the translating stage can be positioned at many points around the center of the concentric spheres, while the Field Goal's translating stage is slightly offset from the rotating elements, scoring a 2.

Ease of Fabrication -

Ease of fabrication is important due to the semester long time constraint. Fabrication must be easily completed to allow time to tweak different aspects of the design according to the needs of the client. The Field Goal design scored the highest in this category due to its simplistic design and lack of complex geometry, with a 5. Due to its several moving mechanical components and cylindrical structure, the Pizza design scored the lowest with a 2 while Bowls received a 3.

Sterilizability -

Sterilizability is important because the easier the stage is to clean, the less time the client would need to spend on cleaning rather than doing the study. The stage needs to be able to be cleaned to prevent the spread of pathogens and other things that a specimen could carry. The easier that a design is to clean, the less likely the lab would need to purchase a new product overtime as well. Although not completely lacking of grooves or spaces, the Bowls design is largely composed of smooth surfaces that would be easily sterilized, earning it a score of 4. Due to their comparatively increased geometry complexity, the Pizza and the Field Goal were given scores of 3 for sterilizability.

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Strength -

The strength of the stage is important because the stronger the design is, the more freedom researchers will be provided in imaging specimens of various weights and sizes. Furthermore, the more durable the product is, the longer it will maintain its integrity and be of use in a laboratory environment. Even though it is difficult to extrapolate strength performance at this stage, it seems that the base and structure of the Pizza design would lend to sturdy operation, even when holding large specimens. For this reason, the Pizza received a 4 for strength, while the seemingly less-supported Field Goal and Bowls each received a 2.

Safety -

Safety is not a primary concern for evaluation of potential designs, specifically because the main risk lies with the rodent specimens being imaged, rather than the humans simply adjusting the imaging stage. This is why the safety criteria has a weight of 5. It remains a concern, nonetheless, as consideration must be taken to ensure that the rats being imaged are not harmed in the process and are properly anesthetized. Furthermore, no components of this design must pose a risk of causing pinching or pain to researchers operating the product. Due to the combination of the sturdiness of the specimen stage and the ease of rotational adjustment, the Pizza design was deemed the most safe for the living imaging subjects with a rating of 5. The other two designs both received a 4 in this area.

Simplicity -

Simplicity is not a big concern for us, although the simpler the device is the easier it will be to use during the imaging of the eyes. The device should be simple enough for the client to use and understand fully in order to achieve necessary images of the rodents eyes. Specifically designed for simplicity, the Field Goal design exceeds in this category with a score of 5. On another hand, the Bowls design was considered to be the next simplest with a score of 3 due to its simplicity of the friction-based adjustment of rotation and translation. As it includes several dials that manipulate threaded components to translate the internal stage, the Pizza design received the lowest simplicity score at 2.

Cost -

The budget for this design is currently $350. A cheaper design would be preferred. However, the budget is flexible since the primary concern for the design is functionality. Due to its simplicity, it seems the Field Goal design will be the most cost effective, so it was awarded a score of 5 for this criteria. Beyond this, it seems that the threaded components required for the Pizza design will increase its price of production, so it was given a score of 1 for cost, while Bowls received a 3.

Proposed Final Design

Based its high evaluation performance, specifically in the areas of adjustment and translational freedom, the Pizza rotation and translation stage design has been deemed most optimal. Therefore, this is the proposed design with which to move forward. Notably, this design implements pitch and yaw for the adjustment of the angular view of the specimen retina as well as three degrees of precisely-adjusted translational freedom of the internal stage. This stage will be movable via turning dials that manipulate threaded rods to move the position of the stage such that the center of the specimen pupil can be aligned. On the same note, moving forward, this design will be optimized for features that facilitate the pupil alignment at the rotational axes intersection by specifically locating this intersection. Furthermore, the selected Pizza design will ultimately be integrated with a cart and a height adjustment component to provide the crude, external degrees of translational freedom.

V. Fabrication/Development Process

Materials

The materials used in the design must be able to withstand direct imaging light and contact with any chemicals used in sterilization and anesthetization of the specimen. Based on the use of friction to manipulate the rotation of the stage, the rotating components must be made out of a smooth material that produces a friction force with itself such as low density polyethylene (LDPE) or PVC. The stage itself will be made out of a metal material such as aluminum while the translating components, including the threaded rods that facilitate the movement and position of the stage, will be made of a strong material such as steel. The threaded rods will be purchased as pre-threaded. The base of the Pizza design will be created from a sheet of material, while the cylindrical rotating component will be fabricated from a cylinder of the necessary material.

Methods

Fabrication of the Pizza design prototype will rely largely on machining equipment including a mill, due to its complex geometry and necessity for smooth surface-finishes. Solidworks dimensioned drawings will be drafted for each component part such that independent parts can be fabricated separately and then constructed. If problems arise with the manual fabrication of this design, a minimum viable prototype may be created via 3D printing of the Solidworks drawing, but due to the limits on this fabrication method, it will not result in the necessary materials and finishes required for a product that fully fulfills the requirements of the client.

Testing

To test the accuracy of the device, we will ask to use our client's imaging device. The device must meet the following accuracy requirements: eye alignment within rotational axes must be accurate within 100 microns, rotational alignment must be accurate within 2° and the center of the two axes of rotation must line up with the field of view of the imaging device with an accuracy of under 500 microns. To test the stability and reliability of the device, we will place an object weighing at least 1 pound on the stage of the device and leave it there for at least 1 hour.

VI. Results

There are several aspects of our design that could change depending on our test results. If our device does not keep the eye within the required distance of the center of rotation, we may need to change our stage or method of rotation. If the device does not allow enough alignment in the x, y and z axes, we may need to alter the translational aspect of our design to account for that requirement.

VII. Discussion

After meeting with our advisor and client this week, we will be able to make the necessary judgement of what we are capable of doing with this design. It will most likely come down to feasibility and if the team will be able to fabricate this design, or if it will be too complicated. The team might need to make adjustments to the design based on client and advisor feedback and based on our own expertise if we have the necessary knowledge to fabricate the design. The team also has to research the best materials to use for the needed friction movement that the design requires and the smooth finish that the device will need. The research and testing the team does will help ensure a working product for the client. In researching, ethical considerations had to be taken into account for this project. The specimen to be imaged must not be harmed in any way when on the device or when imaged. The specimen should be comfortable and not in any danger when the device is being used. The team has to make sure to keep these considerations in mind when designing and fabricating the product. The device is ultimately to be used in the aiding of imaging eyes, in order to provide new and advanced treatments for diseases such as glaucoma and macular degeneration.

VIII. Conclusions

The team was asked to develop a solution for the alignment of a rodent's eye for Prof. Jeremy Rogers and Dr. Ben Sajdak. In their research lab, rodent's eyes are imaged in order to better understand the retina and make advances in optics. The center of the pupil has to be in the center of the rotational axes so the eye does not move out of the microscope's view. The team chose to move forward with the Pizza design, which provides the necessary five degrees of freedom, three translational and two rotational. The Pizza provides precise alignment through dials for the three translational components.

Moving forward, the team will meet with the client to go over the proposed design. Once the design is agreed upon, materials need to be ordered in order to begin initial fabrication of the design. Fabrication will be based on the methods described above, and after fabrication meeting with the client is necessary in order to test the initial prototype. After receiving feedback from the client and tests, the team will order new materials if the others weren't sufficient and will make adjustments to the prototype based on the test results. Fabricating a final design will then be needed and more tests will be performed to see if the device successfully solves the problem.

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X. Appendix

A. ProductDesignSpecifications

Rodent Rotation and Translation Stage

Client	Prof. Jeremy Rogers	jdrogers5@wisc.edu	
	Dr. Ben Sajdak	bsajdak@wisc.edu	
Advisor	Aaron Suminski	suminski@neurosurgery.wisc.edu	
Team	Kurt Vanderheyden	kvanderheyde@wisc.edu	Team Leader
	Kyle Schmidt	kjschmidt9@wisc.edu	Communicator
	Nolan Thole	nthole@wisc.edu	BPAG
	Kevin Tan	kktan2@wisc.edu	BWIG
	Riley Pieper	rgpieper@wisc.edu	BSAC

Date: September 20, 2019

Function

Research of mammalian retinal photoreceptors, conducted via the imaging of rodent model organisms, requires precise alignment of the specimen. A device providing facile alignment of rodent eyes within the imaging system's field of view as well as rotational freedom for accessibility to a holistic view is called for. This device must provide at least 2 rotational degrees of freedom, pitch and yaw, as well as 3 translational degrees of freedom for the positioning of the eye at the intersection of the rotational axes.

Client requirements

- Design must provide at least 5 degrees of freedom: pitch, yaw, and triaxial translation.
- Pupil of animal must adjustable to the intersection of the rotational axes.
- Area near head of rodent must be open and accessible for imaging and anesthesiology.
- Degree of translational precision should be within 100 microns.
- Smooth-finished surfaces for facile sterilization between imaging procedures.
- Removable sample holders of different sizes for different specimens.

Design requirements

1. **Physical and Operational Characteristics**

    a. **Performance requirements:** The device should keep the center of the axis at the pupil of the rodent's eye, despite the 5 degrees of freedom it will be available to move in. This device will be used whenever the rat's photoreceptors are being imaged. The top of the device should be open to allow easy access for imaging and loading of the animal as well as anesthesia.

b. **Safety:** This device should be equipped to securely hold an anesthetized rodent model organism in accordance with any animal research treatment guidelines applicable to studies in which this device is used.

c. **Accuracy and Reliability:** The device must provide movement in 5 degrees of freedom, while keeping the middle of the pupil at the intersection of the rotational axes. Internal translational precision must allow positioning of the pupil within 100 microns of this point. Additionally, external position must be within 500 microns while rotational prevision must be within 2°.

d. **Life in Service:** The device must be able to support a specimen of up to 1 pound, keeping it stationary for up to an hour at a time. In addition, the device must remain functional following exposure to direct, imaging light for up to one hour at a time. Furthermore, it must not degrade with cleaning/sterilization after use with each specimen. The body of the device should maintain functionality according to these conditions for 5 years, whereas the easily-replaceable sample holders should have a life in service of at least 1 year.

e. **Shelf Life:** This device should be storable with humidity between 35% - 70% and temperature between 10°C - 30°C and continue to function properly. If electronic components are implemented, the power-source/battery should be functional after at least one year.

f. **Operating Environment:** During operation, the design may be exposed to lighting, necessary for the imaging procedures, that could increase temperature to 35°C for the extent of the imaging process. Furthermore, anesthetized rodents will be held within the design, so the material and ergonomics of the rodent specimen holder must be carefully considered.

g. **Ergonomics:** The device should allow for easy rotation and translation of the specimen on the stage.

h. **Size:** The device should be no bigger than one foot cubed and should be easily portable. The device should implement an open design concept.

i. **Weight:** The device should not exceed 10kg to allow for easy transport and movement around the lab.

j. **Materials:** The device should remain within the budget of $350, so the material cost should not exceed this value. The device should be made of materials that are easy to clean and contain little to no crevices where dirt and other things in a lab can fall into.

k. **Aesthetics, Appearance, and Finish:** Aesthetic appearance of the device is not a primary concern, as functionality takes precedence. The design must have a smooth finish that lends itself to facile cleaning and sterilization.

2. Production Characteristics

a. **Quantity:** 1 unit will be required for use with each imaging system. Requirement for interchangeable specimen holders would limit a requirement for multiple stages as the imaged specimen is changed.

b. **Target Product Cost:** Initial production budget set at $350.

3. Miscellaneous

a. **Standards and Specifications:** There are no international or national standards and this project does not require FDA approval because it will be used in a research setting.

b. **Customer:** The client would like the device to have swappable holders for different sizes of specimens and that the holder should be symmetrical. There should be a cutaway area for a warming blanket for the animals. The design should have an open concept to allow for easy access to the specimen such that eye drops and anesthesia may be administered.

c. **Patient-related concerns:** As the design is intended as a research tool for the study of rodent model subjects and tissue specimens, patients are unrelated.

d. **Competition:** The RAS system, created by Bioptigen (now owned by Leica Microsystems), is the primary competitor in this area. This device utilizes concentric cylinders, as well as a pivoting element, to provide rotational degrees of freedom.