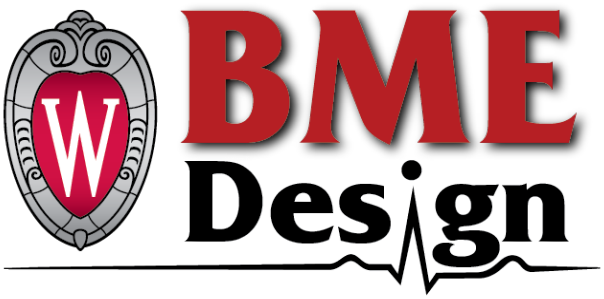

Model for Pre-Surgical Intracerebral Hemorrhage Planning

The University of Wisconsin-Madison
Department of Biomedical Engineering
BME Design 200/300

October 9, 2019

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Abstract:

In the past, the only course of treatment for Intracerebral Hemorrhaging (ICH) was stabilization. However, recent developments in the medical community have developed new ways of actively treating the clot and the internal hemorrhaging. These new treatments are not without their setbacks. No two clots are the same, and choosing the right treatment option can be difficult. Clots vary in stiffness and different stiffnesses can drastically affect the course of treatment. Presently, there is no way for Doctors to discern the stiffness of the clot within the brain. However, new technology is being developed to acquire a database of imaged clots of known stiffness to be used to compare against real patients. This project seeks to assist in the very beginning stages of this process. The imaging software needs to be developed and tested against "clots" of varying stiffnesses. This can be accomplished with a Brain Phantom model. The Brain Phantom models the brain while providing an opportunity to test the imaging software against materials of known stiffness. Mock clots of known stiffness can be placed within the brain model and imaged by MRI or Ultrasound. Using the generated images and the Brain Phantom, researchers can begin to create the Gold-Standard of imaging for Brain clots in order to enhance the course of treatment for ICH.

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Introduction

In the past there was very little that could be done for patients experiencing Intracerebral Hemorrhaging. Intracerebral hemorrhaging occurs when blood vessels burst in the brain, resulting in blood clots. As a result of an influx of blood, pressure builds in the brain resulting in damage to brain cells surrounding the burst. The arteries around the burst lack oxygen rich blood, causing the patient to experience strokes [1]. When a blood vessel ruptures in the brain, action needs to be taken immediately before other brain cells are damaged. Blood shears white matter, so once it enters the brain, immediate damage is done. However, choosing a treatment for a patient can be difficult based on the characteristics of the blood clot. Properties of clots vary widely and the differences in these clots alters the approach that surgeons use to remove it.

There are two main approaches that are used to remove blood clots. The first approach, the drug-mediated procedure, is a drug based process where a catheter is guided into the clotted area, and a clot buster drug is released. This method attempts to dissolve the clot [2]. In this process the white matter damage is not reversed, however, pressure in the brain is decreased resulting in more manageable symptoms for the patient. The second type of treatment, evacuation, attempts to remove the clot through irrigation or suction, based on the rigidity of the clot. This process puts the patient under general anesthesia. A surgical drill is used to perforate the skull, and the removal of the clot is performed [2]. If the clot has a liquid or gel-like consistency, it can be sucked up and removed through a catheter. If the clot has a tough, and more stiff structure, it will need to be cut and scraped out of the brain. Because of this, understanding the rigidity of blood clots is extremely significant because it alters the approach that is used during removal.

As a result, surgeons need a model that can be imaged with an MRI and ultrasound to create a standard of measurement that can help determine the surgical approach before entering the brain. A solution to this would be creating a gel model that mimics the interior of the brain that includes blood clots of different rigidities and elasticities. This would create a range of measurements of clots of different characteristics that would be a standard of comparison for surgeons to predict a surgical approach. Research is being done to map the rigidity of clots pre-op. A physical, gel model that simulates the interior of the brain with various clots would allow researchers to validate whether or not their mapping techniques are functional.

Currently, brain phantoms and models are being used for medical practice. They are used because they are great stand-ins for human tissues and are able to ensure that imaging systems are working properly. Although brain phantoms are common in imaging, no current phantom has ventured into research with blood clot rigidities. Our group is hoping to take the first-step in this new field by combining blood clot properties with phantoms and imaging.

Background

A brain phantom is used by neurosurgeons to compare the MRI scans of the phantom with a scan of their patients' brains. The phantoms purpose is to illustrate the stiffness of the patient's brain [3]. Parts of the patient's brain that are compared to the phantom include the rigidity, structure, clots, and fluids. It is essential for the phantom to have a solid replication of the brains components since its design helps doctors decide how they will treat the patient. For instance, when doctors begin to remove a blood clot from a patient they must decide between using a catheter or creating an incision [4]. They make a decision based on the relationship between the stiffness of the clot in the MRI with the stiffness of the clot in the phantom. Thus, it's very important for brain phantoms in the medical profession to represent the human brain closely.

The make of the phantom is therefore the most important part of our design and fabrication. Our focus thus lead to the research of different biomaterials to make up our phantom. The first of the biomaterials, gelatin, posed a lot of advantages and disadvantages. Gelatin is a biomaterial that is used in many phantoms due to its ease of fabrication. Gelatin is great because we are easily able to change it's stiffness just by manipulating the concentration [5]. We are also able to use a lot of gelatin due to it being very cheap, almost eight dollars per kilogram. Gelatin also made a great biomaterial due to the safety involved in handling it. Unfortunately, Gelatin also had it's disadvantages in many areas. One of these areas is the materials' biomimicry. Gelatin's linear elastic behavior makes it hard to mimic the complexity of the brains makeup [6]. Another issue with gelatin arises with its thermostability. Gelatin has a low activation energy barrier and thereby melts quicker and at lower temperatures than other gels [6]. This isn't good because our client will be putting our phantom in different environments. Another problem with gelatins poor thermal stability is that our client would also like our phantom to last for a long period of time. These factors thereby made gelatin a poor choice for the makeup of the phantom.

The next biomaterial that we did research on was Agarose. Agarose was a candidate for our phantom due to a lot of the gels properties. One of Agarose best properties lies in its strength. Agarose has a high gel strength thereby making it a good candidate to replicate the tissue of the brain [5]. Another great feature of Agarose is that it's thermoreversible. This means that the gel is able to transition well from a gel to a liquid at different temperatures [7]. Like Gelatin, one of the main concerns with Agarose is its thermostability. Agarose is another gel that cannot handle high temperatures well [7]. Although agarose has a lot of good physical properties its poor thermostability made it a poor choice for our phantom.

The third and final biomaterial, Alginate, was a great candidate for our phantom due to its structure, thermostability, and biomimicry. Alginate is a great gel for brain phantoms due to it being structurally similar to human tissue [8]. The biomimicry of the gel means that it will be the best representation of a human brain. Alginate was also unique in that it was the gel with the best

thermostability [8]. This is great for our client since it will meet his requirements of having the phantom go through different environments and last a while.

Our client, Professor Block, proposed a project for us to design a brain phantom that will be used by physicians to compare the rigidity of their patients brain scan with a scan of the phantom. Professor Block set many goals for us to meet for our design. He emphasized the importance for us to mimic the structure and rigidity of the brain. The phantom must also imitate the elasticity of white matter, gray matter, clots, and cerebrospinal fluid. Professor Block also emphasized the importance of the shelf life of our phantom. His current phantoms are a problem since his current phantoms deteriorate very quickly. Another important feature of the phantom is that it must handle powerful magnetic fields since it must go through MRI. Professor Block made it clear to us that the design of the phantom is not as important as the actual composition.

Preliminary Designs

Designs Considered:

Design 1: "Simple Container"

Simple container is appropriately named as this is a very simple and user-friendly design. This container consists of 12 different cavities, each 20mm x 20mm x 60 mm. These can then be filled with the desired biomaterial at different concentrations to image through MRI. The overall dimensions of this container are 180mm x 140mm x 80mm, and the 12 cavities are evenly spaced between each other throughout the center of the container. The overall layout and detailed dimensions of this container can be found in figure #. This is an extremely simple design to fabricate, as it can be 3D printed and used immediately. Biomaterials that are placed in each cavity are easily removed and cleaned out for future use or storage after imaging has taken place. This serves as a great design for proof of concept and ensuring that the biomaterial chosen is able to have its properties altered in order to mimic different stiffnesses.

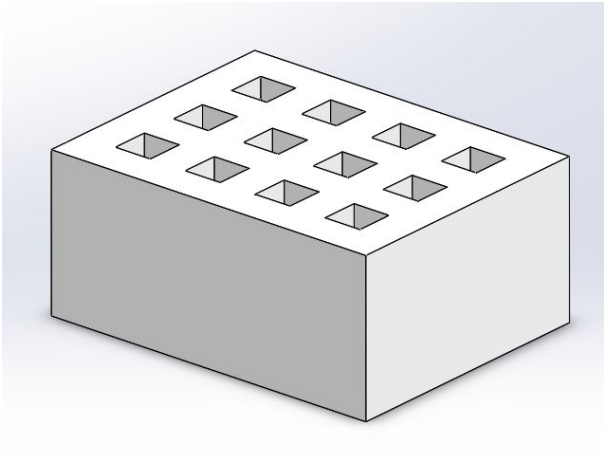

Figure 1: Isometric View of Simple Container

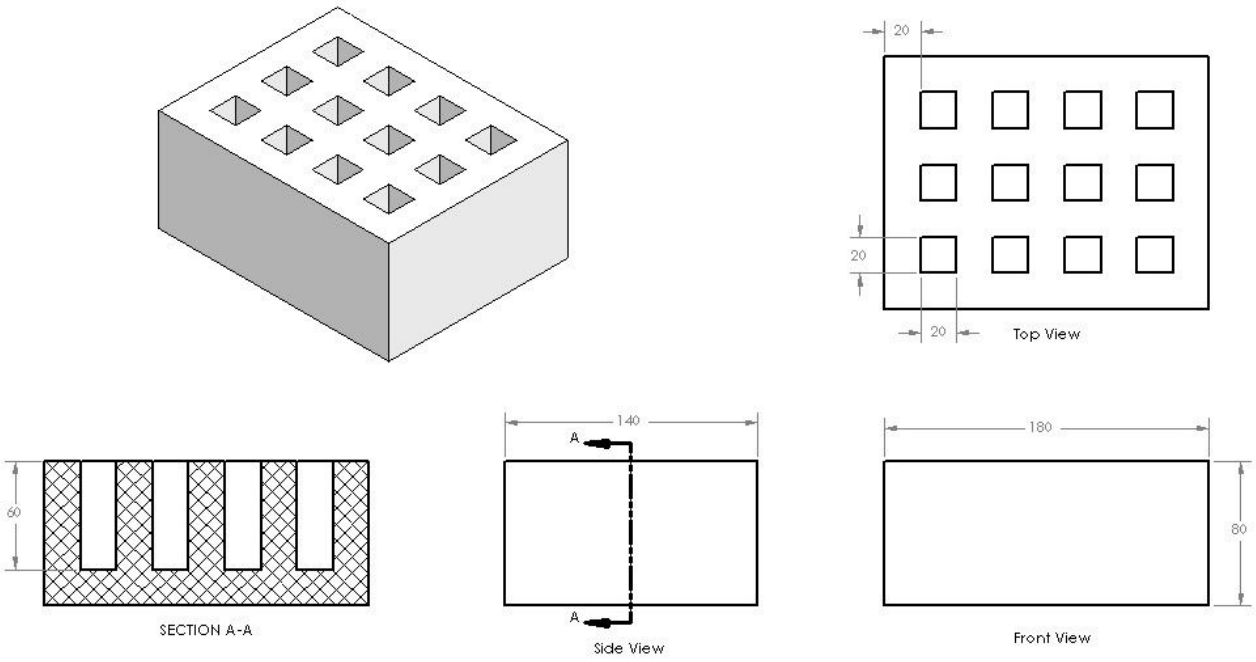

Figure 2: Detailed view of Simple Container

Design 2: Anatomical Model with CSF

This model is much closer to the anatomy of the human brain and contains compartments for white and gray matter, CSF mimicking fluid, as well as clots. In this design, there is room for 4 different clot stiffnesses to be inserted. These clots are surrounded by white matter, which is surrounded by gray matter, which is all surrounded by CSF. This is illustrated clearly in figure # and #. This mimics the anatomy of the brain very closely, however, it doesn't have the ability to

be easily emptied or cleaned. This would be a permanent fabrication with a much longer shelf life as opposed to “Simple Container” whose intention is more for proof of concept than a final anatomically correct brain phantom.

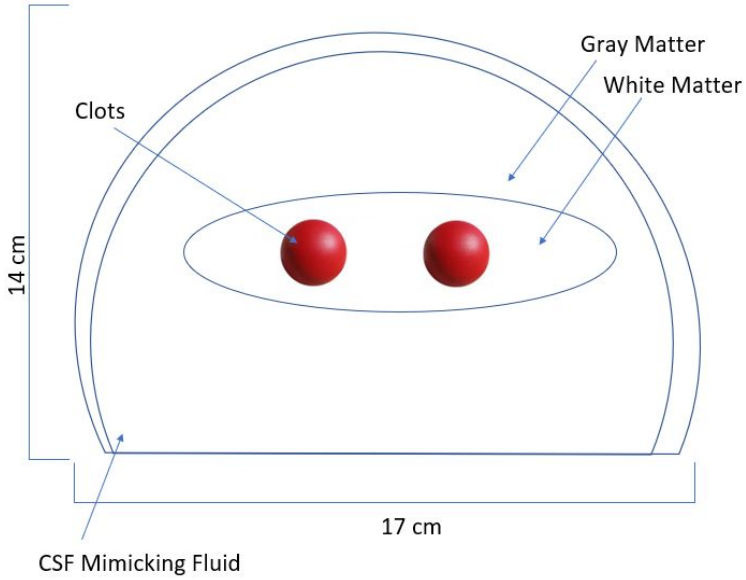

Figure 3 : Side view of Anatomical Model with CSF

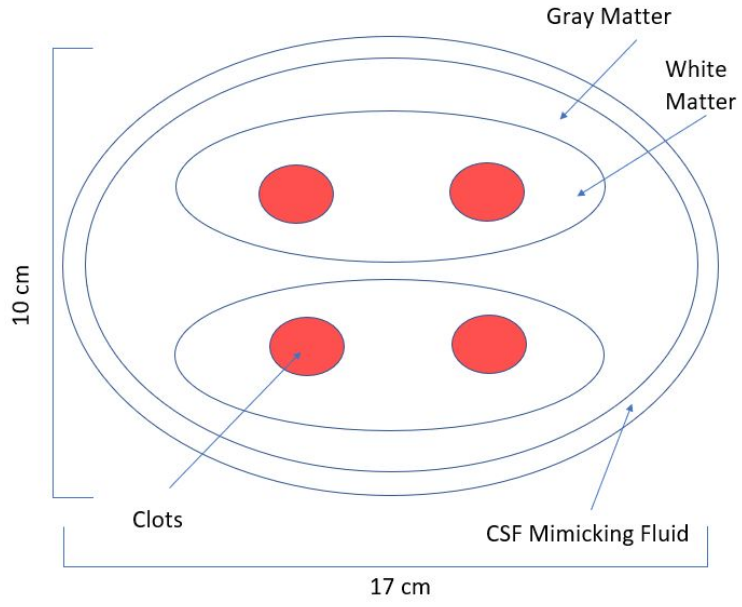

Figure 4 : Top-down view of Anatomical Model with CSF

Design 3: Brain Model with 3D Case

The third and final design considered is named “Brain Model with 3D Case”. This design is very similar to the “Anatomical Model with CSF” as it replicates the anatomy of the human brain. This also has the ability to house 4 different densities of clots as well as white and gray matter. This design does not allow CSF to be incorporated, however, it does feature a sturdy outer shell fabricated from a 3D printed plastic that would loosely mimic the skull.

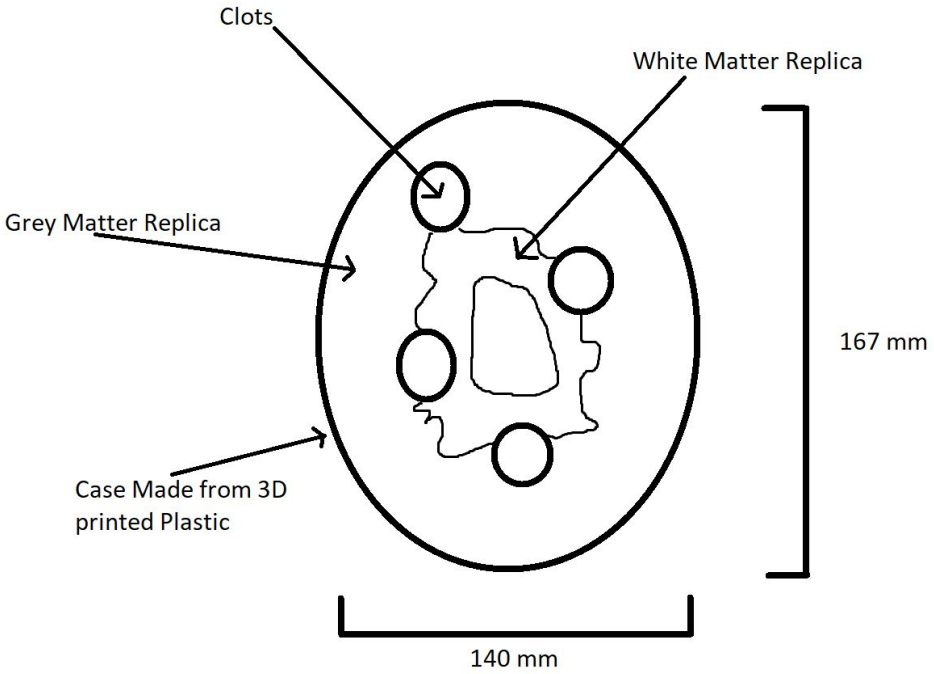

Figure 5: Detailed drawing of brain model with 3D case

Preliminary Design Evaluation

Design Matrices:

Biomaterial Design Matrix:

Criteria	Alginate		Agarose		Gelatin	
Ease of Fabrication (25)	4/5	20	4/5	20	5/5	25
Biomimicry (25)	5/5	25	4/5	20	2/5	10
Cost (15)	4/5	12	4/5	12	5/5	15
Duration (15)	2/5	6	3/5	9	1/5	3
Thermostability (10)	5/5	10	3/5	6	1/5	2
Safety (10)	4/5	8	4/5	8	5/5	10
Total (100)	81		75		65	

Figure 6 : Biomaterial Design Matrix

Container Design Matrix:

Criteria	Brain Model with 3D Case		Anatomically Correct Model with CSF Fluid		Simple Container	
Compatibility with US and MRI (25)	4/5	20	5/5	25	4/5	20
Ease of Fabrication (20)	2/5	8	2/5	8	3/5	12
Accurate Stiffnesses (20)	5/5	20	4/5	16	4/5	16
Ease of Use (15)	4/5	12	2/5	6	5/5	15
Ability to Hold Multiple Clots (10)	4/5	8	4/5	8	5/5	10
Compactness (10)	5/5	10	4/5	8	4/5	8
Total (100)	78		71		81	

Figure 7 : Container Design Matrix

Design Matrices Summaries:

Biomaterial Matrix Summary:

Three different biomaterials were chosen as possible options to mimic the stiffnesses of the clots and brain matter. The three biomaterials were: Alginate, Agarose, and Gelatin. The two most important characteristics of the biomaterial chosen are the "Ease of Fabrication" and the "biomimicry" capability. In order to be fabricated many times over at accurate stiffnesses the biomaterial needs to be easily made. Gelatin won in this category due to the extremely easy method of creation. Biomimicry is extremely important in this situation. The gel chosen needs to accurately represent the stiffnesses and consistencies of the different materials the brain is composed of. Alginate won this category due to its extreme customizability. The next tier of the design matrix has "cost" and "duration of use" at the same rating. Cost must be low due to the probability of remaking the model in the future. Gelatin won in the cost category due to its prevalence and extremely low price. Duration of use was important so that the model could be used for multiple measurements or tests before it begins to deteriorate. The final tier in the matrix had "Thermostability" and "Safety". Thermostability was chosen as a category for a similar reason as duration of use. The model has to be able to not melt or deform during tests at room temperature. Safety was considered but is not extremely important because these models will not be used in a clinical setting.

Container Design Matrix:

Three different container designs were considered for the container design matrix. The "Simple Container" design was more about testing purposes compared to the other two designs. The most important characteristic for the container design was its "Compatibility with Ultrasound and MRI." In order to assist in developing baseline imaging measurements, the model needs to be able to be imaged by both MRI and US with relative ease. The "Anatomically Correct Model" was by far the easiest design to image due to the lack of any material except for the mock-brain matter. "Ease of Fabrication" and "Accurate Stiffnesses" were rated as the next priorities. Similar to the biomaterials, the designs need to be easily made. There exists a high probability that the design will be made more than once or redesigned and therefore needs to be easy to make. The "Simple Container" design was by far the most easy to make because it is a simple 3D-printed case with gel in slots. Again, the designs need the capacity to accurately represent the varying stiffnesses of the clots and the different components of the brain. The "Brain Model with 3D case" won this category because the whole focus of this design was to create environments with accurate stiffnesses. "Ease of Use" was rated in its own tier of importance. The model needs to be able to easily used and measured by the different imaging softwares. The "Simple Container" design won this category due to its simple design. The final tier of the container design matrix was filled by "Multiple Clots" and "Compactness." The design should be able to hold multiple clots in order to expedite the process during measurement. It would not be efficient to have to take different measurements for each different clot. Finally,

the model must be compact in order to fit onto the MRI pillow. There is only so much space in these imaging systems and our model needs to fit.

Proposed Final Design:

The proposed final design will be the "Simple Container" filled with alginate gel. After consulting our Client and using the design matrices these two choices were obvious. The simple container design gives us an easy way to hold many different "environments" while being completely compatible with both US and MRI and easy to fabricate. The alginate was chosen for its ease of fabrication, relatively low cost, and extreme customizability. The alginate gel is capable of being manipulated into many different stiffnesses in order to simulate different kinds of clots and the differences in brain matter. Together, the proposed container design and the biomaterial give a lot of opportunity to take many measurements at the same time.

Fabrication/Development Process

Materials:

The container will be 3D printed and made from PLA plastic. The clots varying in stiffness will be fabricated from alginate and can be crosslinked in order to vary the stiffnesses.

Methods:

The container solidworks file will be used to 3D print the proof of concept container. Alginate will be fabricated in the tissue engineering laboratory according to the given instructions. Cross-linking will be completed in order to alter the stiffness of the alginate.

Testing:

Preliminary testing to be completed consists of creating a gradient of different stiffnesses and placing them in the simple container. This will then be placed in an MRI machine and an image will be produced. This will test whether or not different stiffnesses will show up differently on MR images.

Conclusions

Future Work

In the future, the main goal is to make the model very-representative of the brain environment. In the short-term this involves becoming adept at controlling the stiffness of alginate. In total, alginate of six different stiffnesses will be needed in the final model. Along with this, clots need to be made mimicking different stiffnesses and consistencies. The clots are

the most important aspect of this imaging model and therefore are the priority of the project. Eventually, the goal is to integrate the clots into and anatomical model of the brain. Once integrated into an accurate model of the brain, the clots will be in a prime environment for the imaging tests the Client wants to run. Beyond this, future work involves fine tuning the model. Adding more depth to our materials such as accurate T2 measurements and enhancing the biomimicry of the model are the ultimate goals.

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Appendices

Appendix A. Product Design Specification

Model for Pre-Surgical Intracerebral Hemorrhage Planning
Product Design Specifications
Date as of: October 9th, 2019

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Function/Abstract:

Professor Walter Block presented the team with the challenge of creating an imaging phantom that can be used to identify the type of intracerebral hemorrhaging prior to brain surgery to evacuate the clot that, without intervention, would likely lead to death. The stiffness of brain clots is very different from patient to patient, which is the most important factor when determining which type of surgery to preform. The phantom will contain biomaterials that mimic grey matter, white matter, CSF and different types of clots. The variance in the material properties of the biomaterials allows for the different types of materials to be distinguished on an MRI scan. Our phantom will be the first step in creating a known standard for brain clots that will be incorporated into a database that allows surgeons to determine the rigidity of brain clots and consequently, choose an appropriate method of evacuation.

Client Requirements:

- Have models that mimic the stiffness of white matter, grey matter, and cerebrospinal fluid with reasonable T1and T2 values
- Have multiple clots within the phantom that can model varying stiffnesses of clots representing the differences in patients' clots
- Have an in depth fabrication process so that it can be replicated and improved upon for future work
- The phantom should be able to be scanned by MRI and Ultrasound

Design Requirements:

1. **Physical and Operational Characteristics:**
    a. *Performance Requirements:*
    The device must imitate the structure and rigidity of brain tissues to understand the rigidity of blood clots. We need a model that can be imaged with both an MRI and an ultrasound so that surgeons are more informed before choosing a treatment. Our phantom needs to mimic the stiffness, T1 and T2 values of white matter, gray matter, clots, and CSF. The phantom will be scanned multiple times.

    b. *Safety:*
    The device will have an outer casing that must be safe to handle. The materials that mimic the native tissue should also be safe to handle with reasonable personal equipment such as latex gloves. All the materials within the device must be safe to use with MRI and UltraSound.

    c. *Accuracy and Reliability:*
    Our phantom is meant to mimic the size and consistency of the human brain. The margin of error for mimicking the different brain tissues is +/- 10%.

    d. *Life in Service:*
    The phantom is meant to last for 3 months and able to withstand multiple scans. It will be stored in a refrigerator when not in use. Part of the issue with phantom work today is that the old models erode which produces unreliable results. Each scan should take 30-45 minutes, so the device must be able to be outside of a refrigerator for that amount of time.

e. *Shelf Life:*
This phantom must not deteriorate significantly over time. Alginate deterioration is characterized by cloudiness in the gel and an increased liquid character. The client wants to be able to run many tests on the phantom and it must maintain its material properties within the +/- 10% margin of error while being stored in the refrigerator.

f. *Operating Environment:*
This phantom will be exposed to extremely powerful magnetic fields and therefore can not contain any metal, as this will ruin the image that the MRI produces. The outer casing of the phantom must be compatible with Ultrasound as well.

g. *Ergonomics:*
The phantom has to be transported to various imaging machines so ideally it shouldn't weigh more than an average person can carry. A simple case such as a metal box is enough to provide sufficient protection while the phantom is not in use. The case must open to allow users to easily take the phantom out to scan it.

h. *Size:*
The average brain is 14 cm wide and 16.7 cm long. This phantom must adhere to these dimensions in order to fit inside the head coil that goes into the MRI machine.

i. *Weight:*
The average brain weighs about 3 pounds or 1300-1400 grams. The weight of this phantom can be heavier than this, as there is no cause for concern on placing the phantom on an MRI table. An average person should be able to carry the phantom so it should not exceed 10 pounds.

j. *Material:*
We need to imitate 4 different materials found in the brain. This can be achieved by varying the properties of alginate gel. The outer casing of the phantom will be 3D printed out of a plastic and the holder for the phantom will be purchased and made out of a metal.

k. *Aesthetics:*
Ideally the phantom will mimic the anatomy of the brain. However, it is more important to accurately imitate the material properties of the native tissues. Initially, we will focus on the biomaterials aspect, then we will transition to modeling an anatomically correct brain. Our final design should represent a simplified version of the brain. The complex structures in the brain will be simplified to shapes that are easier to work with such as ovoids and spheres.

2. **Production Characteristics:**
   a. *Quantity:*
   Our client wants to model different types of clots. Our current design does this a single phantom.

   b. *Target Product Cost:*
   We were not given a target cost for the phantom.

3. **Miscellaneous:**
   a. *Standards and Specifications:*
   The phantom needs to have a stiffnesses similar to that of the different native tissues in human brain. The phantom also needs to have clots with different stiffnesses. The accuracy of the phantom in terms of imitating the material properties of the native tissues is more important than the design.

   b. *Customer:*
   According to Professor Block, this device is the first of its kind to be used for a brain hemorrhaging application which means there is a possibility that many people will be using the concept of device. They will not use our specific prototype, but they may follow our fabrication process to create a copy. Our main customers are Professor Block and his associates though. It is important that they understand our entire fabrication process and the inner workings of the phantom so they are able to use it as effectively as possible and continue to improve upon the device once the semester is over.

   c. *Patient-related concerns:*
   Since our device will not be used clinically, there aren't many patient related concerns. Each patient's clot has different material properties, so we need mimic varying clot stiffness.

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