

Model for Pre-Surgical Intracerebral Hemorrhage Planning

The University of Wisconsin-Madison
Department of Biomedical Engineering
BME Design 400

October 7, 2020

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Abstract

Intracerebral brain hemorrhaging (ICH) is a dangerous condition that affects thousands of Americans annually. Previously, doctors were only able to stabilize these patients, but with new advancements, surgeons are able to remove blood clots formed from ICH. These clots have a wide range of material properties that impacts the surgical method of choice for removing them. Currently, there is no way to determine the stiffness of clots prior to surgery. Our project aims to design a phantom that will eventually be incorporated into a large database that surgeons can utilize to compare the MR images of their patients to MR images of the phantoms in the database, allowing them to determine the stiffness of their patients' clots. Over the year, the imaging capabilities of the model will be examined and a threshold stiffness difference and size of "clot" gels will be identified. After that, the phantom will be changed from a box to a brain structure to make the model more anatomically relevant and therefore more useful. Testing will be mostly visual; the images will be analyzed to compare "brain" gel to "clot" gel rigidities. Additionally, some mechanical testing on the gels may be done to add numerical meaning to the images.

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Introduction

Our project works with intracerebral hemorrhaging (ICH). ICH affects between 40,000 and 67,000 Americans each year with an expected 10 year survival rate of 24.1% [1]. Hypertension and old age both increase a person's risk of experiencing ICH. ICH also occurs more frequently in African Americans, Japanese people, and men [2].

Clots can form as a result of ICH. Clots form when a blood vessel bursts, releasing blood into the brain [2]. The influx of blood results in damage to the surrounding brain cells. The arteries near the clot lack oxygen-rich blood, causing the patient to experience strokes [3]. Immediate actions need to be taken for ICH patients since blood shears white matter, resulting in brain damage. Over time, the red blood cells from the blood released in the bursting of the vessel coagulate and separate from the plasma. This separation makes individual clots very heterogeneous (see Figure 1) which complicates the decision of which method of evacuation to utilize since the best method is dependent on the stiffness of the clot [4]. Currently, it is difficult for surgeons to assess the stiffness of clots prior to surgery.

When a patient displays symptoms of ICH, it is standard for that patient to undergo diagnostic tests such as an MRI and a CT scan. These tests allow doctors to determine the location of the clot, but do not provide information about the stiffness of the clot [2]. Without knowing the characteristics of clots, it is difficult for neurosurgeons to decide on a surgical approach prior to surgery.

Until recently, doctors were only able to stabilize patients. Now, multiple surgical methods have been developed that allow doctors to evacuate clots before brain damage occurs. Removal of the clot is critical since clots can cause cells in the brain to necrose. The cells going through necrosis have the potential to act as harmful biological cues in the brain [5]. There are two types of clots commonly found as a cause of ICH. The first type are clots that are fluid or gel-like. The best method for evacuation of this clot is using a vacuum attached to a catheter to irrigate the clot. The second type of clot is much stiffer. Stiffer clots require a drug-based approach that dissolves the clot before it is evacuated. Once the clot is less viscous, surgeons can remove it with the catheter-vacuum method used for fluid clots.

Our client's long-term goal is to develop a database for neurosurgeons to know the stiffnesses of clots prior to surgery which will allow them to decide on the best method to evacuate clots and increase the success of removal surgeries. Professor Block, our client, aims to

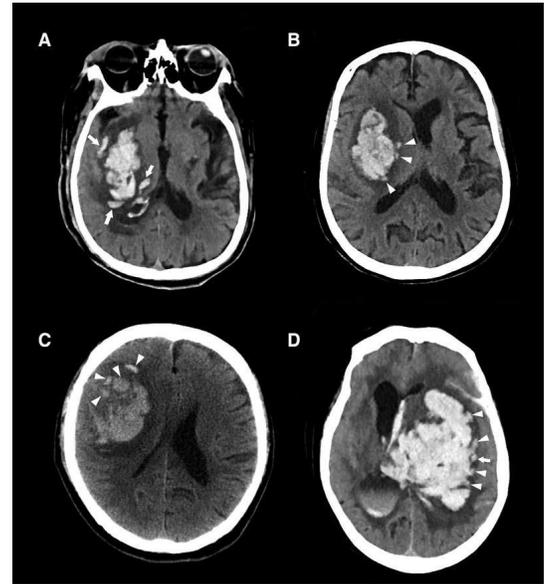


Figure 1. T1 Scan of Heterogeneous ICH Clots [4].

create a large database containing images of brain phantoms with known stiffnesses. Surgeons will be able to compare the images of their patients to the phantom images and deduce the stiffness of the patient's clot.

A medical phantom is a device that is used to calibrate imaging devices and to develop methods to better analyze the images. Phantoms often seek to mimic the material characteristics of human tissue. Researchers are able to manipulate and analyze phantoms with greater ease than they are able to manipulate human tissue due to ethical reasons and some secondary characteristics. This allows imaging machinery's resolution and accuracy to be tested and calibrated [6]. Our phantom has a gel-gel interface which when imaged using MRE, will show how different stiffnesses will appear on MRI. The gel-gel interface is meant to mimic the interface between clots and native brain tissue such as white and gray matter. Currently, there are no phantoms that mimic clot-tissue in a gel-gel interface like our design does, however other phantoms have been designed that analyze the appearances of different stiffnesses on various diagnostic images. Researchers from Switzerland designed an anatomically correct phantom that modeled white matter and gray matter. They were able to mimic the material properties of these tissues using agar gel [7]. Other phantoms have explored the idea of gel interfaces. Hydrophobic sprays and wax barriers were used to create thermostable gels-gel interfaces [8].

Background

A brain phantom is used by neurosurgeons to compare the MR scans of the phantom with a scan of their patients' brains. The phantom's purpose is to illustrate the stiffness of the patient's brain [9]. Characteristics 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 precise replication of the brain's 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 [10]. 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 to represent the human brain closely.

The composition of the phantom is therefore the most important part of our design and fabrication. Our focus thus leads to the research of different biomaterials to make up our phantom. One biomaterial used in other brain phantoms, gelatin, is used due to its ease of fabrication. It is relatively simple to change gelatin's stiffness by manipulating the concentration [11]. Gelatin's linear elastic behavior makes it hard to mimic the complexity of the brain's makeup [12]. Gelatin has a low activation energy barrier and thereby melts quicker and at lower temperatures (25-40 °C) compared to other gels [12]. However, a crosslinker can be used in order to render the resulting gel thermostable. Another commonly used biomaterial in phantom research is agarose. Agarose is thermoreversible, meaning that the gel is able to transition well from a gel to a liquid at different temperatures [13]. However, Agarose is another gel that cannot

handle high temperatures [13]. Finally, a biomaterial used for its structure, thermostability, and biomimicry is alginate. Alginate is used for phantoms due to it being structurally similar to human tissue [14]. Alginate is also unique due to its thermostability [14], meaning that the phantom is able to best be tested in different environments and is durable.

The chemistry behind how the alginate gels is important to the design of our phantom. Our alginate gel will use ionic cross-linking in order to gel. Ionic cross-linking is done by combining divalent cations with a solution of alginate dissolved in pure water. This happens when the gel forms its structure when the guluronate blocks of adjacent polymer chains form bonds to one another. The reason why the divalent cations bind to the guluronate blocks is because the blocks allow for a high amount of linking with the ions [15]. This process is known as the egg-box model of cross-linking which is illustrated in Figure 2. In the egg-box model of cross linking, the divalent compound forms bonds with the guluronic acid, giving the gel an egg-box structure [15]. For our specific case, we used calcium as our divalent compound. For our phantom we decided to use CaCO_3 as our specific cross-linker since, due to its lower stability, it

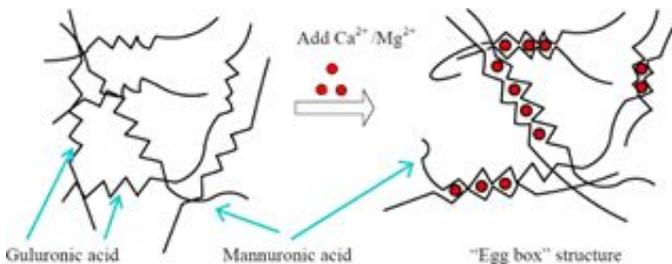


Figure 2. Egg-box model cross-linking [15].

it

our gel, we were able to come up with different percentages of alginate just by changing the concentration of the alginate we used.

Our client, Professor Block, proposed a project to design a brain phantom that will be inputted into a database which will be used by physicians to compare the rigidity of their patient's 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, sinus air space and cerebrospinal fluid. Professor Block highlighted the importance of the shelf life of our phantom, as he hoped to be able to image the phantom multiple times. The current phantoms that are utilized in his lab deteriorate quickly, so not only did he want a durable phantom, but a detailed protocol of our gel making procedure so that he was able to recreate the phantom when needed. Another important feature of the phantom is that it must handle powerful magnetic fields since it must go through MRI. Professor Block consistently emphasized that our phantom would not be used in a clinical setting, instead it was going to be used to create a database of images of clots of different rigidities.

slows the gelation rate. In accordance to our cross-linker, we also added our buffer Glucono- δ -lactone which dissociated our divalent compound from our cross linker. This is done by our buffer decreasing the pH of the solution. The buffer also helps in that it helps slow the gelation in order to make

more gradual [15]. Finally, for the stiffness of

Design Updates

This semester the team built on the design that was completed last semester. This design consists of a large 3D printed outer shell, made out of Polylactic Acid (PLA), that has an internal cavity of size 15 cm x 15 cm x 6 cm with walls that are 1 cm thick (see Figure 3). This will be filled partially with a base alginate gel, and then the fillers seen in Figure 4 will be placed in the gel to create cavities. The fillers are each 5 cm x 5 cm x 3 cm and are also 3D printed with PLA. After the base gel is solidified, “clot” gels will be fabricated inside the sample holder that was printed and used last semester. These gels will be placed inside the cavities, then more base gel will be poured on top. This allows there to be no gel-air interface with the clot gels, which was outlined to be avoided per Professor Block. After all gels are set, the entire box will be sent through MRI and the results will be analyzed.

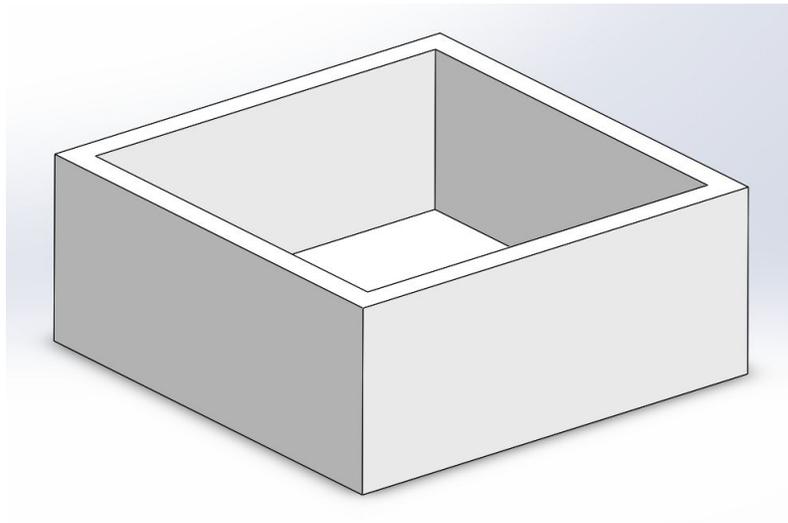


Figure 3. Outside shell to contain base gel and clots.

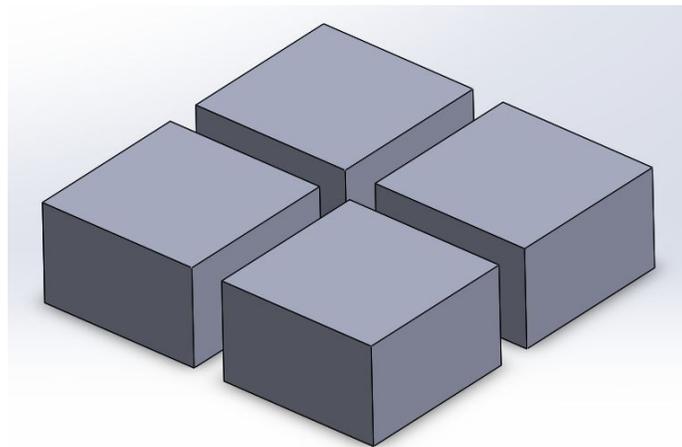


Figure 4. Fillers to create vacancies for clot gels.

Fabrication/Development Process

Materials:

The updated sample container was fabricated via 3D printing using PLA plastic. Within the container, the gels were fabricated using sodium alginate, water, calcium carbonate and glucono δ -lactone.

The Biomaterial Design matrix, which is located in Appendix C, details our material choices for the brain phantom gel. As the matrix shows, we selected alginate as our biomaterial for our phantom gel. Even though gelatin took more categories than alginate, alginate had a much stronger performance across the board than gelatin or agarose. The primary reason alginate was our preferred gel material was due to its biomimicry. Due to the customizability of alginic acid percentage, what cross linker was used, and the buffer used, alginate gels can be tailored to closely resemble the tissues found in an actual human brain. Alginate also has great thermostability and is relatively inexpensive. Due to all of these reasons, mainly the biomimicry, we chose to use alginate as the gel for the brain phantom.

Methods:

The completed solidworks file was brought to the makerspace. At the makerspace the file was uploaded to the CURA 3D-printing software and converted to the appropriate file type. The inside was reduced to a simple lattice design in order to minimize weight and production time. The design holder was then printed using PLA gray material.

In order to make our Alginate gel we first dissolved alginate in water. The water was placed in a beaker of corresponding size and a stir bar was placed in to allow for increased stirring. In order to make our different concentrations of Alginate, we would only alter the amount of Alginate we dissolved in water. Then once the Alginate was dissolved, we added our cross linker and buffer into the solution. For our cross linker and buffer we used Calcium Carbonate and Glucono- δ -lactone respectively. For our cross linker we used a constant 50 mM of Calcium Carbonate for each concentration. A normal base gel was made first to be layered into the bottom of the holder shell. Fillers were taped together and placed into the base gel before gelation could begin. Gels were allowed to gel for a day in the fridge set to 4 °C.

The clot gels were made in a similar procedure as described above. Before gel placement, the fillers were removed to open the gaps created in the initial base gel. Clots were placed into the vacancies. After clot gel placement, another large batch of normal base gel is made. This base gel is then poured over the entire shell holder until the clots are completely encased in gel. This gel-gel interface is then allowed to form in a fridge overnight to promote gellation. .

Project Outline

Stage I.

The initial stage consists of creating a base “brain” gel and then varying gel rigidity on a large scale to analyze the overall imaging capabilities and to ensure that what is expected is what is recorded. The goal is to find the clearest image contrast. The initial expected rigidity ratios compared to the brain gel were approximately 0.5x, 2x, 4x, 6x, 8x, and 10x rigidity, although making an alginate gel of over 5% was not doable in the lab as the subsequent gel was not at all homogenous and fell apart. The updated rigidities in the lab were a 1% “brain” surrounding gel, with 0.5x, 2x, 4x, and 5x rigidity “clots” (see Figure 5 below).

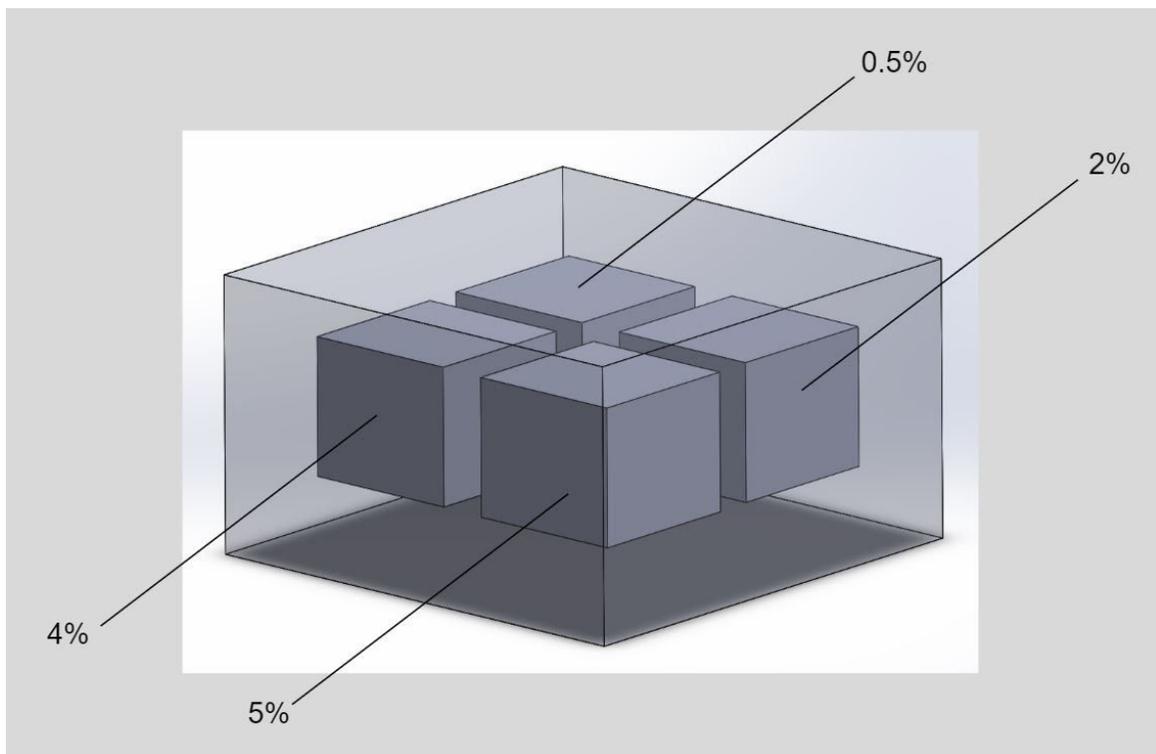


Figure 5. Stage I of project outline, consisting of varying “clot” gel rigidities of the same size. The percentage alginate is labeled for each “clot” gel.

Stage II.

Once a general rigidity of best resolution has been identified and it has been confirmed that the imaging reflects what is being measured, the range will be narrowed to hone in more specifically on how small of a contrast can be measured between the brain base gel and a clot gel. A similar process to the first stage will be used to image, and the rigidities used will be a smaller range that will be determined based on how the first round of imaging went (see Figure 6).

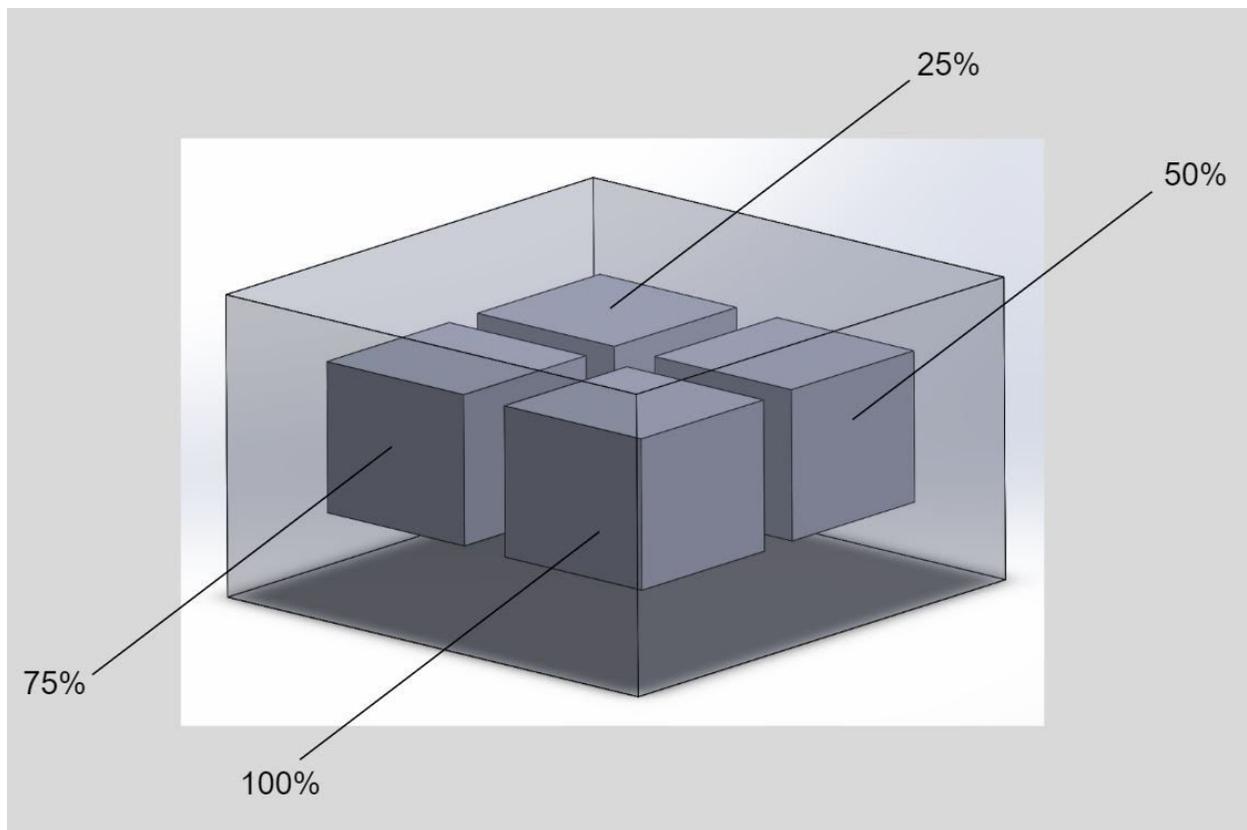


Figure 6. Stage II of project outline, consisting of a much narrower variance of “clot” gel rigidities of the same size. A potential percent alginate in each “clot” relative to the rigidity chosen from Stage I is indicated respectively.

Stage III.

Stage three will consist of testing different sizes of clot gels rather than different stiffnesses. We will test how small we can go in terms of clots to find the spatial imaging resolution limits. The rigidity of the “clot” gels used in this stage will be whatever was found as the confidence level from stage two. This phantom is illustrated in Figure 7 below.

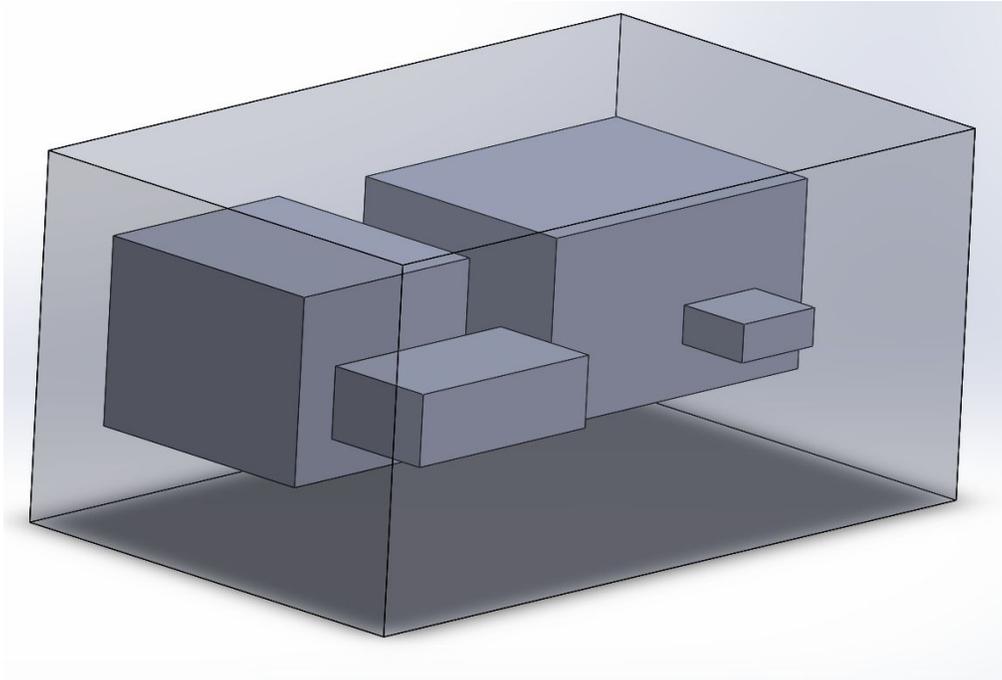


Figure 7. Stage III of project outline, consisting of “clot” gels of one rigidity and varying size.

Stage IV.

The final stage will be to update the phantom to incorporate anatomical relevance. The sample holder could be a 3D printed skull rather than a plastic bin, and the model could account for gray/white matter (see Figure 8). We can get more into the specifics of this model once we get closer to this stage and our client has more input into what specifically he is looking for.

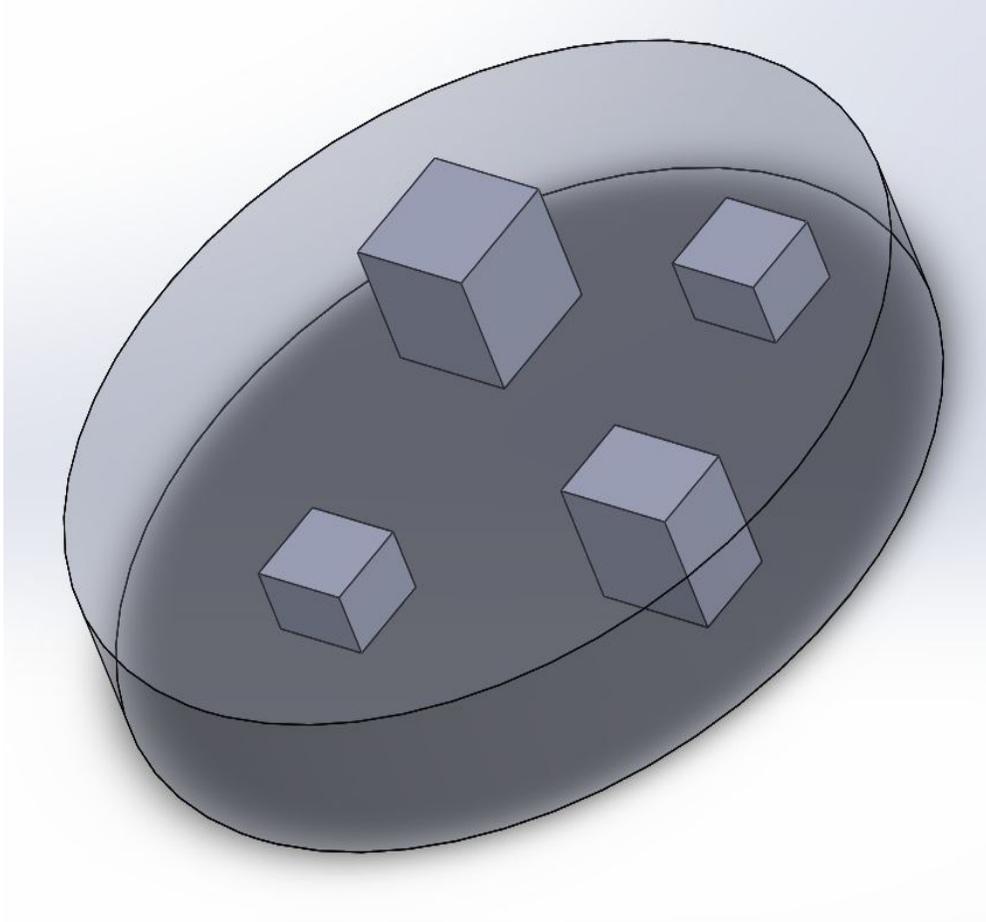


Figure 8. Stage IV of project outline, with an updated anatomical model which will allow for imaging of clots of different sizes, rigidities, depths, etc.

Stage V.

The final stage will be to enhance the anatomical phantom to include different types of geometries in the brain, specifically air and fluid pockets that could be associated with sinuses and ear canals or CSF, respectively. Having fluid or air pockets in the same image as the “brain” and “clot” gels will provide the widest possible range of contrast in one image and will account for all types of geometries found in the brain. An example of what a scan may look like once complete is seen in Figure 9 below.

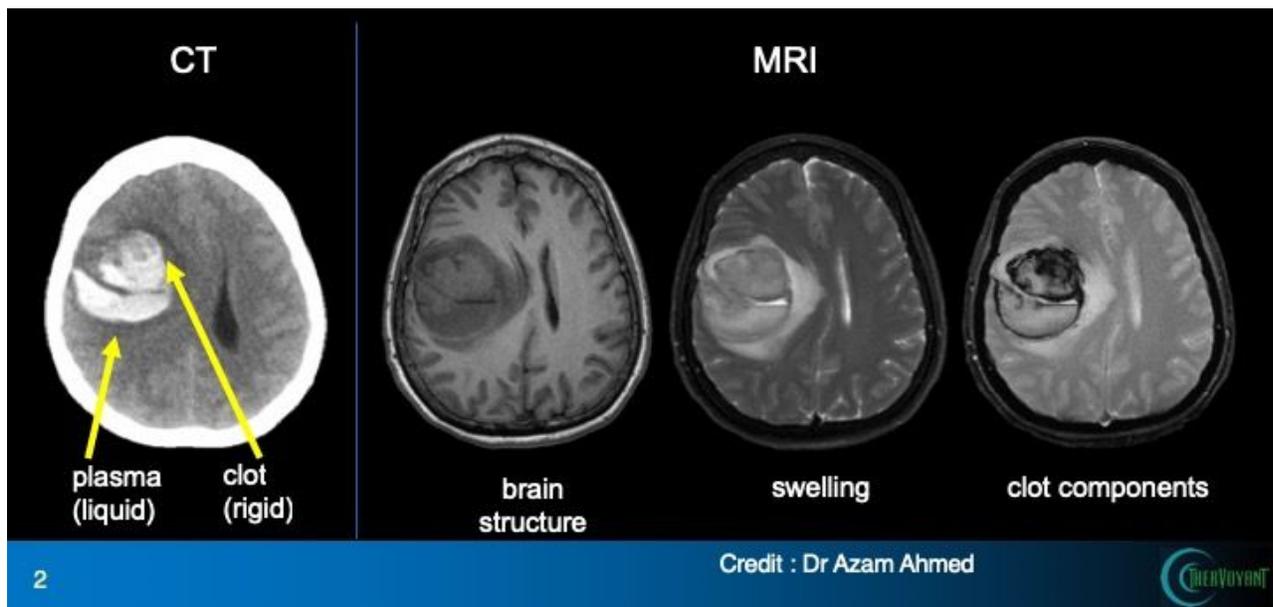


Figure 9. MRI images of actual brain structure with liquid pockets. Shows the specific images of the swelling and the clot components that need to be emulated in stage V.

Future Work

MRI Analysis

Analysis of the gel brain phantom using MRI technology is a critical step in moving the project forward. Using MRE imaging, the relative stiffnesses of the clot gels to the base gels can be obtained and analyzed. MRE imaging uses shear waves sent through the gels to measure their propagation and create stiffness maps in order to compare the relative stiffnesses between the clot gels and the base gels. In order to test the resolution capabilities of using MRE imaging to determine stiffnesses of clots, one stiffness will be chosen from the first batch of MRE images. The phantom for the first round is complete (see Figure 10) and we are waiting on the results of this scan. The resolution will then be tested by changing the size of the clot gels in order to determine the smallest sizes of clots that the stiffness can be accurately obtained using MRE imaging. Moving forward with the project, numerous sizes and stiffnesses of clot gels will be imaged over and over again. The future goal of the MRI analysis is to acquire vast amounts of data on how precise MRE imaging is, MRE images with gels of known stiffnesses for later references when being used with patients, and other important technical limitations or uses for MRE imaging in the field of detecting clots in the brain.

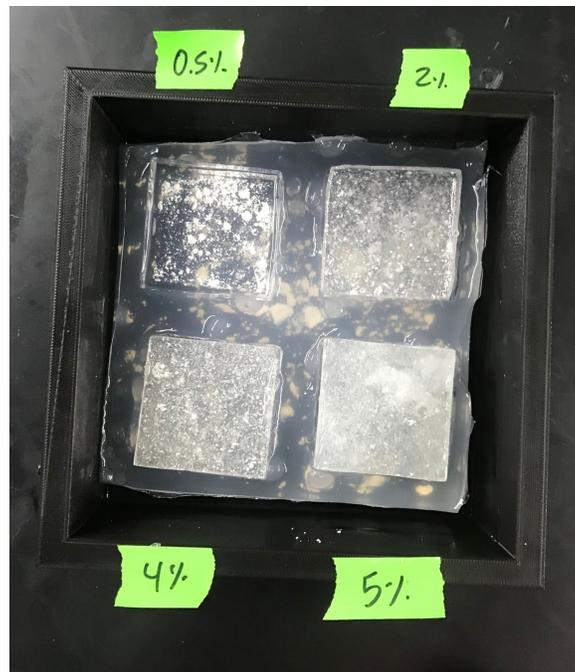


Figure 10. Most recent phantom with four same-size “clot” gels of varying alginate percentage. This was delivered to the client for imaging before campus shutdown.

Mechanical Testing

Since surgeons would be using our image database to find an image that matches their patient's clot in order to quickly obtain the material properties of the clot (and therefore know which surgical method of extraction to use), mechanical testing needs to be done on the alginate "clot" gels to add meaning to the images. The team intends to do compression testing with an MTS machine to calculate the Young's modulus of the gels at different alginate compositions. Specifically, the Young's modulus is a measure of a material's resistance to elastic deformation when under a load. The stiffness of a material is in essence how much it will deform under a specific load. Therefore, the stiffness of a material is dependent upon the Young's modulus of the material. The MTS machine applies increasing compressive force to the material it is measuring. As it slowly increases the applied compressive force, the MTS machine measures the strain and creates a stress-strain graph. The Young's modulus can then be calculated from the slope of the stress vs. strain curve up to the first instance of plastic deformation.

Conclusions

Intracerebral hemorrhaging causes the formation of blood clots in the brain that can vary in stiffness. Methods of evacuation differ based on the stiffness of the clot. In order to determine stiffness, the clot must be imaged in an MRI. Baseline readings of materials of different stiffnesses are needed to compare to clinical MR images for reference. From a few preliminary scans, the team design of suspending "clot" gels within a "brain" gel seemed to work well and is a good basis to continue the timeline outlined above. The gels will be more thoroughly imaged in an MRI to test both the resolution of the MRI and accuracy of contrast between stiffnesses. We also plan to utilize MTS testing to determine the Young's moduli of the gels made. This would allow for quantitative data to be collected that could relate to actual stiffness of the human brain and make the surgeon comparison of patient images to the database images even more useful. All in all, the goal is to continue to work towards verifying that the imaging software that measures stiffness using shear waves is working correctly and eventually be in a position to create a full database of "clot" gel photos. This would be particularly useful in an anatomically relevant phantom to better simulate the images of a patient's brain where varying textures such as air and fluid pockets can be seen in comparison to the clots.

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Appendices

Appendix A. Product Design Specification

Model for Pre-Surgical Intracerebral Hemorrhage Planning Product Design Specifications Date as of: September 17, 2020

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Function/Abstract:

Intracerebral hemorrhaging (ICH) is an extremely dangerous condition that without intervention can ultimately lead to death. Recently, new methods have been developed for evacuating clots formed as a result of ICH. However, the stiffness of the brain clots can be very different from patient to patient, which complicates the decision of what method of evacuation to utilize. Professor Walter Block presented the team with the challenge of designing a brain phantom that will be used to generate a database that allows neurosurgeons to compare MRE phantom images to MRE images of ICH patients. By comparing the patient's scan to the database of phantom images, a surgeon will be able to determine the stiffness of the clot prior to surgery, and decide on the best method of evacuation. Other brain phantoms have been created, but none target ICH specifically or include a gel-gel interface. Last semester, the team created an alginate phantom with "clots" inside base gels to prove materials of different stiffness can be differentiated in MRE images. This semester, further investigation will be performed to obtain more information on the capabilities of the alginate gel/imaging combination with varying stiffnesses. After that, the resolution quality of decreasing size clots will be researched.

Client Requirements:

- Have a variety of stiffness of gels to create a database of known MR
- Have multiple clots within the phantom that can model varying stiffnesses of clots representing the differences in patients' clots
- Provide mechanical testing of gels to enhance image meaning
- Find smallest clot size that still provides functional image
- 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

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 in MR so that surgeons are more informed before choosing a treatment. The phantom design will allow for imaging of a large array of stiffnesses, with varying resolutions to create a database of known stiffnesses at known resolutions.

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.

c. *Accuracy and Reliability:*

Our phantom is meant to mimic the size and consistency of the human brain. Mechanical testing will be done to compare Young's Moduli of different stiffnesses.

d. *Life in Service:*

The phantom is meant to last for 1 month and be 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 cannot 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 easily so it should not exceed 10 pounds.

j. *Material:*

We need to imitate four 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 using PLA plastic. Both materials are safe for human contact.

k. *Aesthetics:*

For the scope of the project that we will be focusing on, the sample holder can be very simple, as we are just looking for a way to image different stiffnesses of gels at one time. This way we can create a database of known stiffness values and how they are perceived in MR.

2. **Production Characteristics:**

a. *Quantity:*

Our client wants to model different types of clots. Our current design does this in a single phantom.

b. *Target Product Cost:*

Our client notified us that money was not an issue. Additionally, the device will use simple plastic and basic chemicals, so the cost will likely be less than \$100.

3. **Miscellaneous:**

a. *Standards and Specifications:*

The phantom needs to have clots with different stiffnesses, with proportional differences that are clinically relevant. The accuracy of the phantom in terms of imitating the material properties of the native tissues is more important than the design. Compression testing via MTS will provide numerical data to enhance the imaging later in the semester.

b. *Customer:*

According to Professor Block, this device is the first of its kind and is meant to be used in a research setting. The primary focus is to cater to Professor Block and the team's preferences. 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 to mimic varying clot stiffness.

Works Cited

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Appendix B. Materials

Item	Description	Manufacturer	Part Number	Date	Cost	Quantity	Total
Sodium Alginate	250g of sodium alginate	Acros Organics	AC177772500	11/8/2019	\$46.53	1	\$46.53
3D Printed Case	Gel container made of PLA	Makerspace Lab	N/A	10/24/2019	\$28.49	1	\$28.49
Calcium Carbonate	Cross-linker	Dr. Master's Lab	N/A	10/31/2019	\$0.00	1	\$0.00
Glucono- δ -lactone	Buffer	Dr. Master's Lab	N/A	10/31/2019	\$0.00	1	\$0.00
						TOTAL:	\$75.02

Appendix C. Design Matrix

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	