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Experimental and Computational Investigation of Correlates of Diffusion Tensor Imaging Changes and Mechanical Strain

OUNIOL AKLILU
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Reviewed and approved* by the following:

Reuben Kraft, PhD
Associate Professor, Mechanical Engineering,
Biomedical Engineering,
Institute for Computational and Data Sciences
Thesis Supervisor

Justin Brown, PhD
Associate Professor, Biomedical Engineering
Honors Adviser

* Electronic approvals are on file.

ABSTRACT

Traumatic brain injury (TBI) and related disability affects more than 2% of the U.S. population.[1] Diffuse axonal injury (DAI) is a common pathology associated with TBI in which deformation of axonal cells leads to rupture and axonal degeneration.[2] DAI can be observed in white matter tissue in the brain,[3] which consists largely of bundles of aligned, myelin-sheathed axons. State-of-the-art imaging techniques (magnetic resonance diffusion tensor imaging, or MR-DTI) can be used to visualize these fibrous structures. However, sensitive measures of structural changes due to injury that can be detected with MR-DTI, notably fractional anisotropy (FA), show conflicting trends in how FA changes in response to injury. Some studies have shown FA values increase within brain fibers inflicted by compressive forces while other studies exhibit increase of FA inside the brain fibers due to tensile force.[4,5]

To better understand how injuries such as TBI affect the brain, computational and experimental investigation was conducted on phantom fibers, a polyester fiber that mimics the white matter of the brain, to learn the impact strain has on fibers and how the FA values changes in response. The hypothesis is that areas of tensile strain will depict increased values of FA while areas of compressive strain depict decreased values of FA. The results from this work will help develop a computational tool that will predict the primary and secondary effects of axonal injury over time and expand the capabilities in the emerging field of computational medicine.

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Chapter 1

INTRODUCTION TO TRAUMATIC BRAIN INJURY

Traumatic Brain Injury (TBI) can be defined as the disruption of normal brain functions due to an inflicted head injury.[6] Brain Trauma is a problem believed to affect everyone regardless of age, ethnicity, gender, or occupations. It is estimated that in the United States only, over 27 million children, aged between 6-18 years, participate in a team sport every year which exposes them to mild yet cumulative head trauma.[1,8] Computational tools such as Digital Brain along with the insights from this work can contribute a significant impact towards minimizing the risk of TBI among society.

Over the years, new advancements have been made and new approaches have been developed to understand how neuroimaging, biomechanics, and computation can help to explain the changes in brain tissue structure in response to injury. In the future, monitoring of structural changes over time could be crucial to help better understand the effects of TBI on the brain. Developing a history-dependent damage model will help further advance the computational medicine field and widen the potential benefits to understanding the human body especially the brain. In addition, this type of model will help clear up contradictory results seen in neuroimaging and validate numerical diagnostics.

Section 1.1 – Why is Traumatic Brain Injury important to study?

As mentioned before, more than 2% of the population are affected by Traumatic brain injury (TBI) and related disability.[1] It is essential to develop a computational method to better

understand how TBI impacts the internal and external brain structure. However, in order to develop methods to understand TBI, sensitive measures of structural changes such as Fractional Anisotropy (FA) must clearly be investigated, and once validated the results can be an input to develop a method. Fractional Anisotropy is a scalar value which describes how restrictive the diffusivity is within the brain. Zero FA value means isotropic and that the diffusion is unrestricted while an FA value of one means a diffusion along a single axis.[7] Some studies have shown increased values of measured FA in regions where tensile force have been applied to the material while other studies depict conflicting result stating an increase in measured FA values in regions where compressive force has been applied.[4,5] This conflicting trend of the FA measurement makes it unreliable to be used to assess the impact of force on the brain. In this work, it is suggested that FA values tend to increase as the fibers are in tension since the tissue is being pulled which aligns the fiber in one direction restricting the diffusion to fewer directions and the opposite would be that the compression will decrease the FA value resulting in unrestricted diffusion.

It is currently unknown why there is a discrepancy in FA values between the various studies but solving the conflict is a step forward towards understanding how external impacts such as a blow are translated inside the brain. The brain is a complex organ with various roles and disruption of normal brain activity can result in numerous severe effects.[9] This work will help advance the development of image-based modeling to learn and predict the potential effects before it actually happens. TBI affects everyone and as such learning more about how to predict or assess the potential damage to the brain is a big step forward towards the prevention of TBI within society. People will be capable of evaluating their risk level and understand what steps

they need to take to avoid TBI with the assistance of their medical provider. The majority of the society will benefit from this especially military personnel, sports players, and senior citizens.

According to recent studies, part of the brain that is most susceptible to damage is the white matter tissue.[10] Scientists believe that damage inflicted on fiber tracts present within the brain can cause neurologic and cognitive deficits after multiple impacts.[9] Perhaps, understanding how the fiber tissue within the white matter responds to an impact could pave the way to quantitively diagnose mild TBI. The white matter is a crucial part of the brain responsible for connecting the different lobes and so learning how white matter is affected might hold the key to help solve the current problems people face with TBI. A common pathology associated with TBI is Diffuse Axonal Injury (DAI). DAI deforms the axonal cells present in the white matter which leads to rupture and axonal degeneration.[2] To learn more about the impact of TBI and DAI on the brain, Magnetic Resonance Diffusion Tensor Imaging (MR-DTI) is used to visualize the fiber tract[11] which will then help assess the structural integrity of normal and diseased white matter in the brain.[12] Once the structure has been defined, a physical quantity can be measured using MR-DTI parameters which include FA and mean diffusivity to learn more about the displacement of diffusing water. Such reports and analysis of the brain structure are possible using MR-DTI but due to the conflicting FA trends observed in several studies, the sensitive measure must be validated in order to be used in history dependent damage model. And so, this work tries to understand how the acute changes in FA are correlated to the type of strain imposed on a tissue whether it is stress or compressive. Once this work is completed, it will provide the possibility to computational model and provide image-based diagnostics.

Furthermore, this work will help expand on the opportunity to model fiber tracts of the brain and learn the quick procedures that could be used to get a quick 3D brain fiber image for

analysis. History dependent damage model is one of the upcoming diagnostics methods within computational medicine that could be used to help medical providers quickly assess a patient's brain fiber structure and overall brain health in 3D. This work will go towards validating the measurement values for accurate assessment and quick treatment.

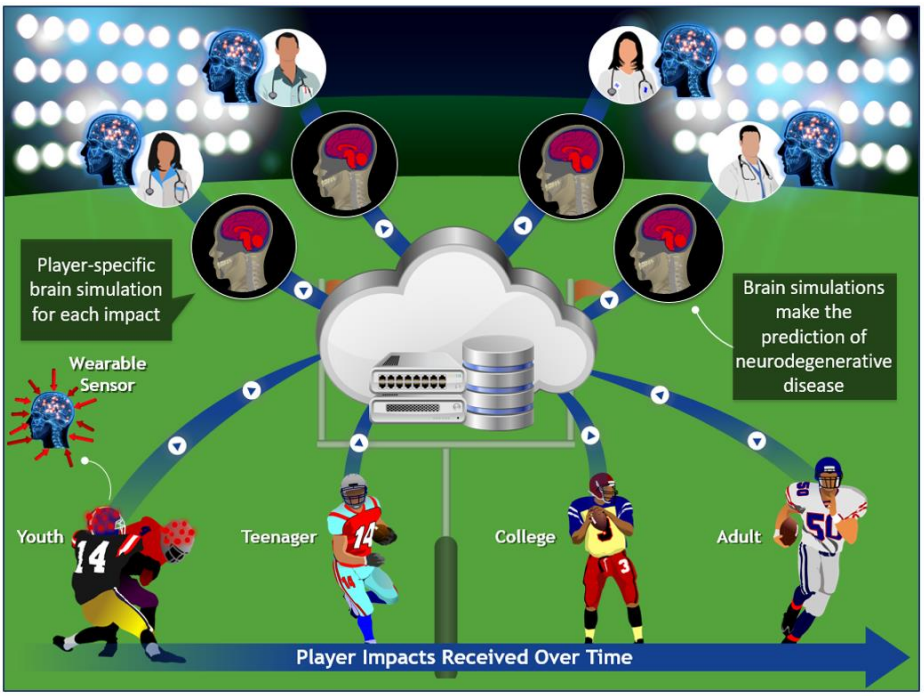

Figure 1: History-dependent analysis of brain tissue structural and functional changes through the Digital Brain and wearable sensor

Figure 1 depicts how the Digital Brain would function to help analyze brain tissue structural and functional changes and report insights when needed. In the figure, a football player is depicted receiving several impacts over time during play and the player wears a sensor that records the number and severity of impact over time. The data collected by the wearable sensor then gets transferred to the Digital Brain which sits in the cloud. The Digital Brain presents a report of the players' data including risk after running simulation for every impact. The result from the analysis can then be accessed by medical providers to assess and take quick actions to

prevent the player from facing TBI. The Digital Brain makes it possible to predict neurodegenerative diseases that are currently hard to treat. History-dependent analysis of brain tissue takes on a preventive measure rather than looking at the treatment. Furthermore, the accumulated reports over time can serve as a base to understand how and when TBI, as well as other related disabilities, start to appear among players. In the future, the history-dependent damage model can be extended to assess military personnel and people at high risk of TBI.

Section 1.2 – Causes and Symptoms of Traumatic Brain Injury

Traumatic brain injury (TBI) can be due to a closed head injury or a penetrating injury.[13] These injuries can cause a major blow to the brain which can then result in TBI. Not all injuries cause TBI but when it does, the degree of damage to an individual due to these injuries could vary depending upon the person's physical and mental state, the force of the blow, and location of the injury. While everyone is at risk of getting TBI, children under 4-year-old, young adults between 15 and 24, senior adults above 60 tend to be at a higher risk.[14] Once the damage is inflicted on the brain, there is a possibility for nerve fibers to tear as well as the formation of bruises. Some causes of a closed head injury include falls, vehicle crashes, sport-related injuries, violence (child abuse), and blast-related injuries. Falls from an elevated place are believed to account for the most common cause of TBI in senior adults. Vehicle crashes typically cause varying levels of brain damage depending upon the severity of the crash. The damage also depends on the type of vehicle involved in the crash. Open vehicles such as motorcycles tend to cause more severe damage than closed vehicles such as a car. Violence could consist of wounds and assaults either in a short or long period of time intended to inflict physical injuries which later on could result in

TBI. Another form of violence is child abuse which is the common cause of TBI for children under 4-year-old. For example, child abuse such as violent shaking of an infant can result in a form of TBI called shaken baby syndrome. Another cause of TBI is sport-related injuries and it is usually common in young adults that participate in various sports activities such as soccer, football, and hockey. High impact sports such as football are considered to cause more severe TBI than sports with low impact sports such as walking or yoga. The last and major cause, people typically associate TBI with, is blasts-related injuries. Blast-related injuries are most common in military personnel especially soldiers in war zones. Military personnel are typically exposed to the pressure waves caused by the blast which can then inflict brain damage disrupting the brain from functioning properly. Similar to the close head injury, open head injury is also the infliction of injury that can cause TBI. Unlike close head injury, open head injury results in both external and internal brain damage. Injuries that fall under the open head include damage due to bullet, or blunt weapons. These injuries typically result in bone fractures and in some cases can penetrate through the skull.

The type of TBI symptoms observed depends upon the person and the type of injury they have sustained.[13] In some cases, symptoms may not be observed or the symptoms are present but not distinguishable to the point of diagnosing TBI. Some of the symptoms can arrive within few hours of injury or emerge after few weeks. As such, TBI is hard to clearly assess and point out the signs and symptoms. If not diagnosed early, the condition could worsen and result in permanent physical and psychological damages. The type of effects seen due to TBI can be physical or psychological. As of now, there is still more work to be done to understand the full

impact of TBI on the brain and how the body changes as a result.[14] For now, medical providers diagnose patients using physical and psychological symptoms observed in most TBI patients.

As mentioned before the type of symptoms a TBI patient experiences depends upon many cases and it could result in mild to severe complications. When talking about the physical effects, TBI can result in several physical complications including altered consciousness. These complications at the end can result in brain fiber damages, swelling, fractures, and bruising.

Some of the physical complications that can be observed include seizures, buildup of fluids inside the brain, infections, blood vessel damage, headaches, and vertigo.[14,15] Typically, seizures happen during the early stage of injury but sometimes it can happen later on years after the injury and multiple seizures over time can cause epilepsy. Fluid can also buildup within the brain and it is termed hydrocephalus. The buildup of the fluid more specifically cerebrospinal fluid can result in a greater increase of pressure which can then swell the brain. Infections are common especially when dealing with injuries related to fractures. The layers that surround the brain for protection may be susceptible to tear and opens up a passage for pathogens to enter the brain. If not treated properly, the infection could affect the rest of the nervous system and cause irreversible damages. In addition, blood vessels found in the brain could also get damaged due to TBI and that may lead to stroke and blood clots. One of the most symptoms seen in TBI patients are severe headaches especially within days of injury and it could persist for months.

When specifically talking about severe complications that could result in permanent damages, the consciousness of that person also gets affected. There are many consciousness states that a person could go through if dealing with severe TBI including coma, vegetative state, minimal conscious state, and brain death.[14] People who are in a coma tend to be unaware of their

surroundings and they are unresponsive to any stimulus present. Typically, this state can result in damage to different parts of the brain. Over time a person may regain consciousness and get out of a coma or enter the vegetative state. A vegetative state is what happens when the damage has spread to different parts of the brain. In this state, the person is still unresponsive to their surroundings but regains some of their physical movements including response to reflexes. Patients could incur permanent damage to the brain which could leave them in a vegetative state but typically patients transition to the minimal conscious state in which major alteration has happened in terms of consciousness but the patient is aware of their surroundings and shows progress towards recovery. The last state would be brain death and this typically is irreversible with a record of low brain activity. In this state, a person is incapable of any movements including breathing and that will eventually lead to heart failure. Patients dealing with more than one of the symptoms mentioned above for a long period of time have what is called post-concussive symptoms. Symptoms and the states of TBI typically can linger for days or months depending upon many factors including the person's healthiness and history with TBI.[16]

Furthermore, the base of a skull is a part of the head that is easily susceptible to TBI. The damage to the skull base will result in damage to the cranial nerves found within the brain which will then result in several symptoms including paralysis of the muscles found on the face, loss of smell and taste, hearing loss, and dizziness.[17] Different parts of the brain react differently to TBI and sometimes it is hard to predict what the effect would be. The brain is complex and there is still more work to be done to understand the effect of TBI on the brain but it has been shown that people inflicted with TBI have experienced some sort of symptoms related to it.

In addition, the effect of TBI has also been linked to several degenerative diseases.[14] While there is more work to be done to clear up how TBI is related to degenerative diseases, some research has suggested repeated exposure to TBI increases the risk of being susceptible to degenerative diseases.[14,18] Some of the degenerative diseases include Alzheimer's, Parkinson's, and dementia. Alzheimer's is a loss of memory and thinking skills over time and TBI may further progress the loss. Parkinson's disease is a condition that causes loss of control in body movements due to nerve damages. TBI also affects the nerves and that can further deteriorate body movement capability. Dementia is a loss of memory that usually happens in boxing after a severe blow to the head.

Aside from physical symptoms, TBI can also result in psychological effects. People who have faced severe brain injury would face loss of cognitive skills including the ability to think and process thoughts clearly.[14,19] People with cognitive problems that arise from TBI include loss of memory, learning, and judgment. TBI patients may also face daily functioning problems such as multitasking, planning, or problem-solving. Some of the common problems that arise between families and patients with TBI are communication problems in which the patient will have difficulty understanding speech and at the same time difficulty with speech and writing. This can ultimately affect the ability to participate in conversations and socials skills in general.

Aside from communication challenges, patients with TBI may also face behavioral changes which include the inability to self-control in certain conditions, showing risky behaviors, and signs of random outbursts. Emotional changes such as depression, anxiety, and anger can also be seen in patients with TBI.[20] The brain has the capacity to process our emotions and keeps our psychological in check but with injuries, the brain can react unpredictably causing the

emotional changes observed. The final effect to be mentioned is problems with sensory with impaired coordination, blind spots, loss of balance, and ringing in the ears. Our head including the brain and the ear function to keep the body in balance and the disruption due to TBI can cause some of the effects mentioned above. There is still more work to be done in order to understand the brain and the effect when impacted with TBI.

Section 1.3 – Current diagnostic techniques and treatment for Traumatic Brain Injury

Currently, there is no one way of diagnosing TBI but rather medical professionals use multiple diagnostic techniques to assess the damage incurred and the severity of the injury. According to CDC, the type of technique used depends on if the person inflicted with injury has mild or severe complications.[21] Typically, the first step in diagnosing a patient for TBI consists of a medical examination which can include a neurological exam in order to assess the person's ability to think clearly, understand and comprehend what someone else is saying at that time. The medical provider could also check if the patient has any damage to the sensory or motor functions. Reflexes are examined to assess if the body is healthy and responding properly. The quick examination can help the medical provider assess the severity to decide whether the patient needs to be taken in for further examination. One of the ways to assess the severity is through the Glasgow Coma Scale which is a point test that medical personnel uses to determine the initial severity. The test checks if the person is capable of following set directions and if they can use move certain parts of the body when instructed. The test is scored between three and fifteen with fifteen stating minimal injuries.

Once the Glasgow Soma Scale test has been concluded, if the person is determined to require further examination, the medical provider may require an imaging test to get more information on the internal damage sustained by the brain. There are a couple of image tests that can be performed including computerized tomography (CT) scan, magnetic resonance imaging (MRI), and intracranial pressure monitor.[22] CT scans are the preferred imaging instrument by doctors when evaluating patients suspected to have TBI. CT scan offers a detailed map of the brain using multiple x-rays. CT scans are typically helpful to identify if there is any hemorrhage or swelling occurring within the brain. It provides clear evidence of the impact area. MRI is used to check the progress of the patient with TBI and track the recovery. The instruments also give a detailed map of the brain using radio waves and magnets. An intracranial pressure monitor is a useful tool to detect if there is any swelling in the brain due to TBI. Swelling can increase the pressure within the skull which could cause more injury to the patient. The instrument will able to monitor the pressure within the skull for any anomalies.

In addition to image tests, recent studies show the benefits of biomarkers in the diagnosis and treatment of TBI.[23] Biomarkers can help in obtaining sensitive information that would have otherwise been neglected. Not only are biomarkers meant to provide additional insights on the severity but also give an idea of the type of treatment as the biomarker expression changes.

Similar to the diagnostic technique, the type of treatment a patient receives also depends on the severity of TBI. When dealing with mild TBI, no treatment is required except to rest and perhaps take over-the-counter medications for any mild symptoms. The rest will help ease the stress on the brain and as such limit, the chance of symptoms worsening. With mild TBI, patients tend to recover fully within a few days.[21] But in the case of severe TBI, the patient may require

emergency care which could consist of prescribing medications and therapy for a full recovery. The first treatment for patients dealing with severe TBI is to provide oxygen, blood supply, and medications to maintain blood pressure. Other medications that could be given to the patient include antiseizure drugs, coma-inducing drugs, and diuretics.[21,22] This medication is typically meant to prevent any secondary damage to the brain after injury. Antiseizure drugs as the name suggests are given to patients diagnosed with severe TBI and meant to prevent the patients from having a seizure during the short period of time after injury. A seizure can cause additional strains to the brain and as such must be avoided at all cost. The coma-inducing drugs are used by doctors to put patients into temporary comas in order to help the brain heal. A normal person requires oxygen for the brain to function properly but when the blood vessels that supply oxygen are constricted due to the built-up pressure that can have severe effects on the patient. And so, the coma-inducing drugs are meant to help in reducing the amount of oxygen required since the patient is in a coma. Diuretics have a similar purpose as coma-inducing drugs i.e. to reduce pressure within the brain by decreasing the fluid within tissues.

In cases that the drugs become ineffective, surgery is required to reduce the damage to the brain tissues. Surgeries have several uses including removing the clotted blood, repairing fractures, opening windows to relieve pressure, stoppage of blood. Surgeries are invasive and patients that require such surgeries may also require time for rehabilitation. Rehabilitation will help fasten their recovery so they are able to perform daily activities.[14,21] The time of rehabilitation depends on each patient and the extent of the damage. Some patients may have to see several therapists to assess their well being and there could be cases when symptoms start showing up. And so being able to analyze and predict when people are at risk of TBI can prevent them from going through invasive surgeries and medications. Tracking the progress and

presenting an output of a person's risk can help reduce the number of people that end up with TBI. It reduces the probability of facing severe symptoms with weeks to recovery.

Chapter 2

METHODS

In order to develop a history-dependent damage model, sensitive measures that are used within the model need to be validated. Currently, MR-DTI parameters such as FA show discrepancy and need to be investigated. The first step in the investigation of the FA is to select a proper material that can mimic the white matter of the brain. It is imperative the material that will be used meet the necessary requirements and have similar properties as the white matter to be used in the study. Few materials will be chosen to be tested and the results will be used to select that one material. Then after selection, the material will be scanned before and after a mechanical test to generate DWI images which will be used to create 3D models, fiber tracts, and FA images. The data will be used to analyze the change in structure and FA values after imposed mechanical strain. FA values will also be obtained from the data for comparison. The results will help gain additional insights on the conflicting FA trend so that it can be used to develop one-of-a-kind damage models to diagnose and monitor brain damage and advance the capability of computational medicine.

Section 2.1 – Material Selection

In order to properly investigate the conflicting FA trends observed in various studies, the first step consisted of selecting the material that will be used for testing. The material needs to

have fibers that can be structurally altered and scanned to observe any deformations. Celery and asparagus were selected as the primary candidate to be used in the study. One reason celery and asparagus were chosen was that they consisted of fibers that run along the whole stem which makes it is easier to see structural changes when various loads are applied to various parts of the sample. The second reason was the affordability and the ability to test as many samples as needed. In order to select which material will be used for the research, an Instron Electro E3000 Static/Fatigue Tester was used at strain rates between 10^{-3}–10^{1} s^{-1} to observe the properties of the samples including the elasticity (ability to revert back to original shape) and how much load the samples can sustain before the breaking point. The main goal was to impose internal fiber damage to mimic what would be observed in a white matter tissue of the brain. The sample was required to handle the applied load without signs of external damage. Once the asparagus and celery were tested, a graph plot of load vs displacement was drawn to better understand which samples were much easier to stop before the breaking point. Furthermore, the celery and asparagus also undergo an MRI scan to assess if the fibers of the sample can be generated using reconstruction and fiber tracking software such as diffusion toolkit. To scan with the MRI, the various samples were embedded in a water bath and positioned parallel to the magnetic field as shown in figure 2.

Figure 2: Two celery samples enclosed in a tube filled with water to mimic the white matter tissue environment and prevent motion artifacts. The celery is placed in an MRI capsule before the scan is started. Additional images of the celery selection experiment can be found in Appendix A.

Preliminary results from the mechanical test showed that both samples had certain limitation which would prevent it from being used in the future. The fatigue tester depicted, during the experiment, that the test was easier to stop before failure for celery compared to the asparagus. Then the MRI was used to scan the celery and asparagus samples shown in figure 3 in order to generate the internal fiber tracts. The result showed that both celery and asparagus did not have long fiber strands running along one direction from top to bottom but rather the fibers were interconnected and stretched in different directions. And so, the samples were no longer being considered for lack of meeting the necessary requirement to clearly visualize the FA changes on different regions of the fiber.

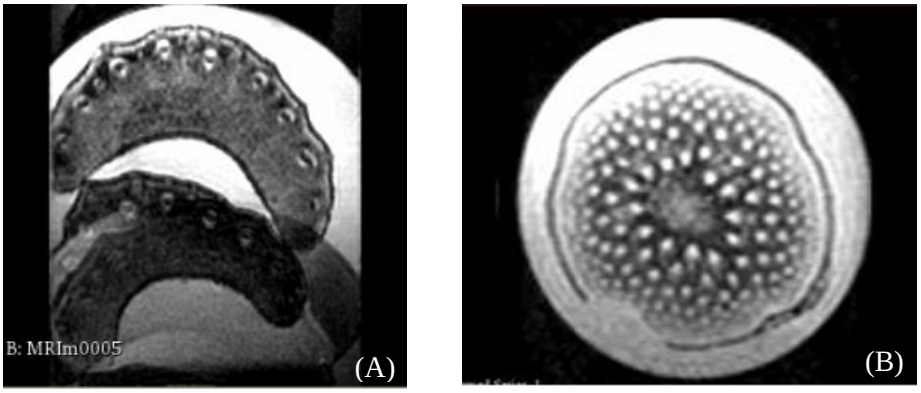

Figure 3: Generated Diffusion Weighted Image (DWI) of Celery (A) and Asparagus (B) to evaluate internal fiber structure. The fiber tracts generated using the DWI image consisted of fiber strands in different directions.

After natural organic fibers were identified as a poor candidate for the study, research was conducted to find artificially manufactured fiber materials. HQ Imaging Diffusion phantoms are made of polyester fiber with a diameter of 15 micrometers embedded in water and bundled in a sleeve.[24] As such there are many fibers within one sample that are completely sealed in order to achieve long-term stability. The process to produce the fiber strands consist of immersing underwater which fills the sample with water. Additionally, the phantom container where the fiber strand is embedded is not designed to remove the fiber strand. HQ Imaging specializes in building different types of strands including circular, circular + crossing, and straight fiber strands.[25,26] In this study, the straight fiber strands were selected since the change of FA can be seen along the straight fibers which simplify the experiment.

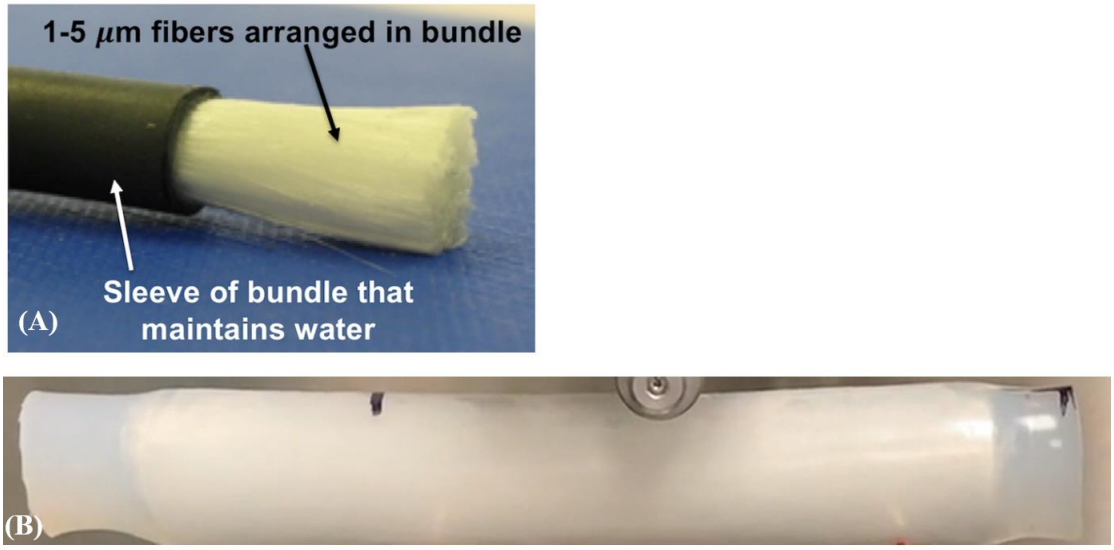

Figure 4: Internal view of the straight Phantom fiber strands in a sleeve of bundle embedded in water to mimic white matter tissue of brain (A) and the enclosed phantom fiber strands used in the mechanical experiment (B)

The setup of the phantom fiber allows for the restricted anisotropic diffusion to be mimicked. The polyester fibers were observed to have long fiber strands as shown in figure 4A and furthermore, the phantom has helped radiologists as well researchers validate MR-DTI sequences, conduct quality assurances and check the proper function of the MRI system. The phantom fiber will be put through a similar process as the celery and asparagus to generate reliable fiber tracts for analysis. A 3 Tesla MRI system will be used to acquire the MR-DTI which will be used to assess changes in FA.

Section 2.2 – Pre and post-test Image Modelling

Once the material is found that best mimics the behavior of white matter in the brain, a pre-test MRI will be conducted using a 3 Tesla MRI to scan and visualize the internal fiber structure. The MRI scan was conducted by an MRI technician here at Penn State (Thomas Neuberger, High Field Magnetic Resonance Imaging Facility) and takes between 6-8 hours for a

complete scan of the whole sample. There is a tradeoff in the quality and resolution of the scanned image when the whole sample needs to be scanned. Careful consideration must be taken to understand how much resolution is lost and at what cost since that could disrupt the quality of the 3D model generated using the scanned image. Furthermore, the position of the phantom fiber must be marked when placing in the MRI so that the data collected after the mechanical experiment does not contain too many errors. The next step after scanning the phantom fiber is to generate a 3D model of the exterior using image processing and 3D visualization software called 3D Slicer (version 4.11.20200930). The 3D Slicer is an open-source software platform available to the public (download.slicer.org) that helps process images and construct 3D models.[27] The scanned DWI image of the phantom fiber is saved as a Neuroimaging Informatics Technology Initiative (nifti) file which becomes the input for the 3D slicer. The software will present sections of the phantom sample in various slices which can be viewed by scrolling the display pane. The software presents a view of the slices in three planes including axial, sagittal, and coronal. The "Segment Editor" tool, shown in figure 5 below, will be used to mask the phantom image which will then segment a 3D model of the external phantom.

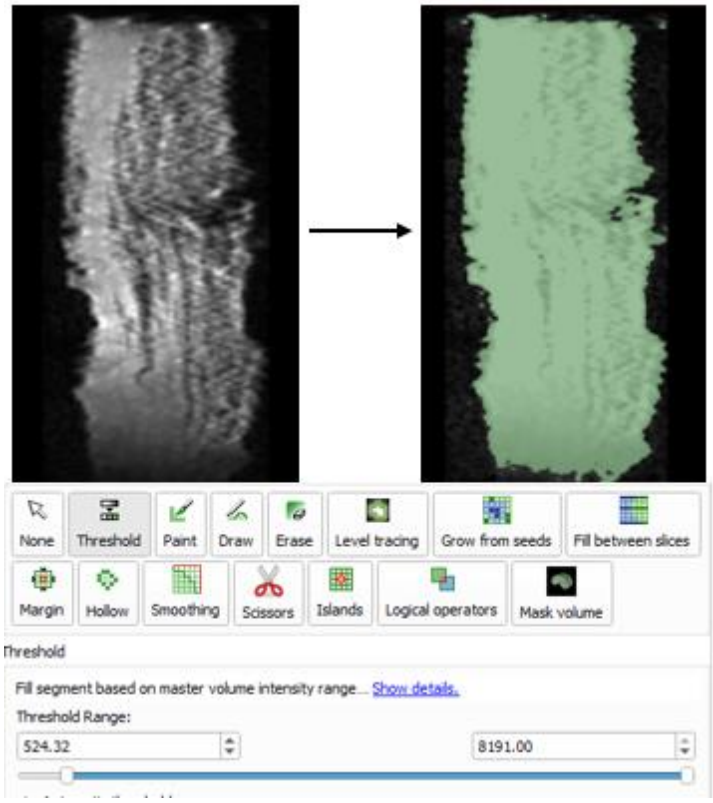

Figure 5: Application of mask on a DWI Image using threshold in segment editor. The threshold range was adjusted to limit background noises due to low scan resolution.

There are various ways to mask the image but the most convenient way is to use the threshold effect which differentiates the image from any background noises and the user has the capacity to vary the level of noise to let in. As discussed previously regarding the quality of resolution versus scanning of the whole sample, eliminating the whole noise will not be possible if the resolution of the image is bad. By eliminating all the noise, the threshold may disregard part of the sample image when masking. As such it is important to weigh the necessary resolution to segment a 3D model without too much noise. In cases, when noises are inevitable, the smoothing tool, shown in figure 6, could be used to either close any open holes within the 3D model or to smooth the hard surface generated by the noise.

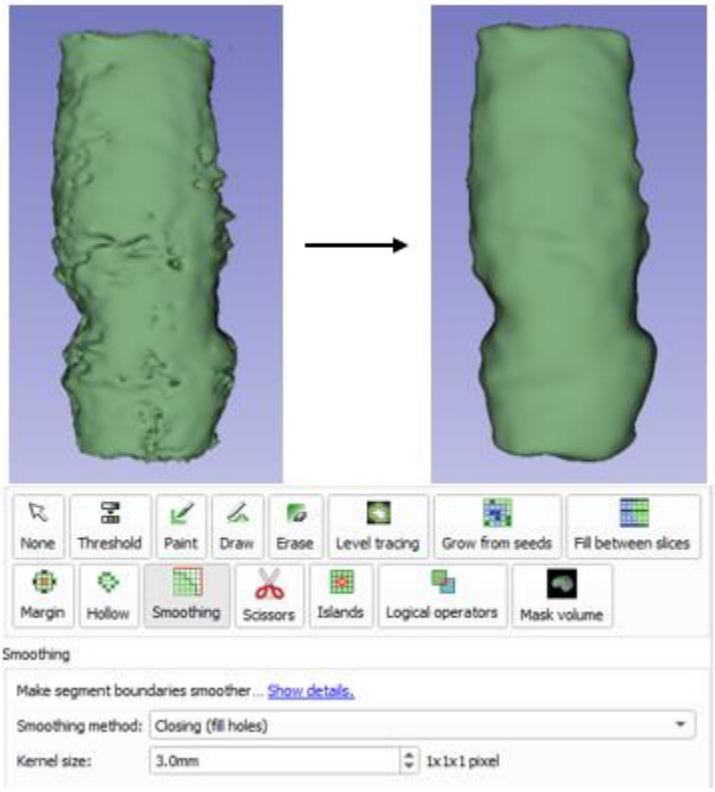

Figure 6: Application of the smoothing tool to fill holes to reduce the impact of noise on the generated 3D model. The smoothing tool helps to fix segmentation errors while preserving all details within the model. The tool resolves the error through the adjustment of the kernel size.

Once the segmentation process is complete, the software will export the 3D model in STL (Standard Triangle Language) format. The next step will consist of generating fiber tracts using diffusion toolkit (command-line tools) software. The software's purpose is to data reconstruct and track fibers in the DWI images.[28] The input files required for the reconstruction include the nifti files used in the 3D segmentation and a set of b-values corresponding to the specific DWI. The software will then output the result in a trk file format which can be viewed using TrackVis Software. High-dynamic-range imaging of the phantom sample can also be added to TrackVis to visualize the DWI and generated fiber tracts on top of each other. Extreme caution must be taken when generating the fiber tracts, especially when designating the orientation since the DWI image and fiber tracts may be out of alignment when viewed on

TrackVis. If misalignment exists, then through an iterative approach the fiber tracts must be generated again by changing the orientation each time. In order to check for misalignment, the hdr file containing the scanned image should be uploaded along with the trk file in TrackVis. Then by selecting a region of interest within the scanned image, the fiber tract specific to that region should appear. If fiber tracts appear in regions where the scanned image is completely dark then that could mean the fiber tract and scanned image is misaligned. To solve the misalignment, as mentioned before, it will require an iterative approach in which the nifti file serves as an input to the diffusion toolkit software, and before generating the fiber tract, the orientation will need to be changed. The diffusion toolkit consists of several image orientation options which include axial, sagittal, and coronal. Once the image orientation is picked, there is an option to invert two of the coordinates and swap two of the coordinates as well. After picking an option, the fiber tract will be run and the trk file produced will be checked for misalignment. If there is a misalignment, the procedures described above will need to be conducted again by changing the image orientation, swapping, and inverting the coordinates until the trk file that aligns with the scanned image is found. And the last step will be to generate the FA values based on the image. The process will include using the bruker 2dseq file generated from the MRI scan and use it as an input into the FMRIB Software Library (FSL) 6.01 software. The FSL software provides image-based statistical analysis by running an automated DTI reconstruction and outputting an FA image as a result.[29] The 2dseq files contain the required b-value and DWI images that are required to create the FA image. Once the FA image is available, the value at a specific region of the phantom sample can be calculated.

After the phantom sample is mechanically tested, the same process above will be followed to generate the 3D model, fiber tracts, and FA images. The images will be visually

analyzed and once the FA values are determined at the specific regions, a comparison can be made.

Section 2.3 – Applied Mechanical Strain Setup

The phantom fibers with an approximate diameter of 15 um and 50 × 5 × 5 mm dimension were mechanically tested to impose strain in the inner fibers so that it results in a certain degree of internal damage which can only be noticed when MR scanned. The materials will be taken up to inelastic (permanent) deformation and the microstructure will be visualized to identify any permanent modification upon unloading. The machine that was used is an MTS EM Flexure (3-Point Bend) machine that loads at 250N with a sample rate of 10Hz and an applied displacement of 2mm/sec until the maximum load. The load was then removed at 2mm/sec. The goal of the mechanical test was to inflict internal damage to the phantom fibers and cause structural change without passing the breaking point to avoid leakage of the water found between the phantom fibers. A 3-point bend machine was chosen to mechanically the phantom fibers since the machine can deliver both tensile and compressive strain to different parts of the sample at the same time. As shown in figure 7B, the upper region of the phantom sample bent inward is under compression while the other side is under tension. By applying different strains on a sample, it is possible to generate fiber tracts to observe the difference in FA values on each side. In addition, the load was intentionally not applied in the middle of the sample so it will be easier, later on, to distinguish which side was on tension or compression. Once the testing is finished, the sample will be scanned again and generate fiber tracts and FA values as mentioned in the previous step.

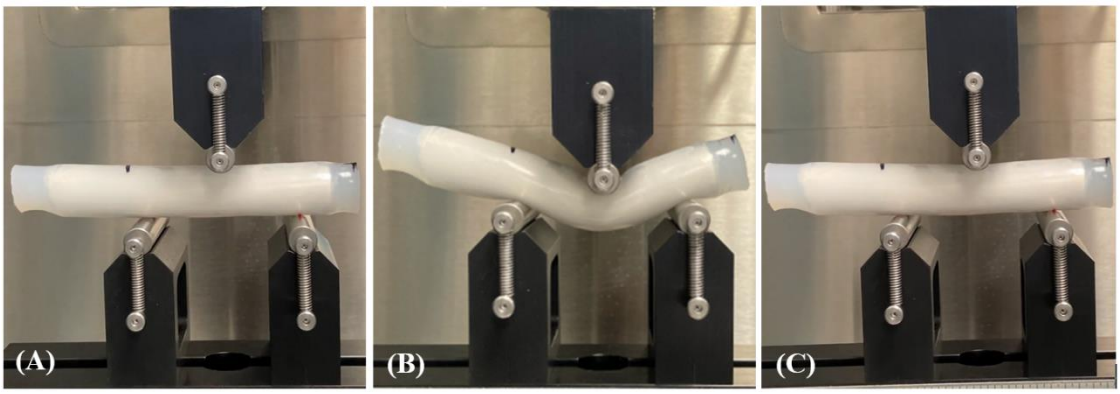

Figure 7: Positions of the phantom samples during 3-point bend testing (at pre-load (A), at maximum load (B), at post-load (C)). The load will apply both tensile and compressive strain at different regions. (Set of coordinates will be used to match the exact spot of applied strain when evaluating the FA).

Chapter 3

PRELIMINARY RESULTS

The generated fiber tracts, 3D models and FA values of the phantom fiber before and after imposed mechanical strain will be compared to each other to assess if any difference exists. As mentioned previously, various studies had reported conflicting FA trends and behaviors after injury. The analysis will help clear the confusion and validate if the hypothesis that FA values increase in tensile regions and decrease in compressive regions is true. From a biomechanics standpoint, it seems logical that as the tissue is stretched due to tension forces the FA will increase and bring it closer to a scalar value of one since that restricts the anisotropic diffusion. On the other hand, when the tissue is under compression force, the FA decreases and becomes closer to a scalar value of zero since the fiber buckle and becomes unrestricted in every direction. The results talked about in this section are still preliminary and additional experiments will need to be conducted and analyzed to reach any conclusions.

Section 3.1 – Visualization Analysis

After the celery and asparagus were tested, the results showed that the samples were not able to mimic the white matter of the brain. As such, artificially made phantom fibers were considered as the best viable option to be used for the study due to its restricted anisotropic diffusion similar to the brain. The first task after selecting the material was to scan the phantom fiber to see if the images can be used to build a clear 3D model. Using 3D slicer, the scanned DWI was masked and segmented into a 3D phantom model as shown in figure 8A below. Then the phantom fiber was classified in regions such that at the control region no mechanical load will be applied. In the compressive and tensile region, a force of 250N was applied as shown in figure 6 so that section of the phantom fiber is in tension and the other is in compression. Based on figure 7, the phantom sample can be seen to recover shape. After the mechanical strain test, the phantom sample was scanned to generate the DWI image which was then used to create the 3D model as shown in Figure 7B.

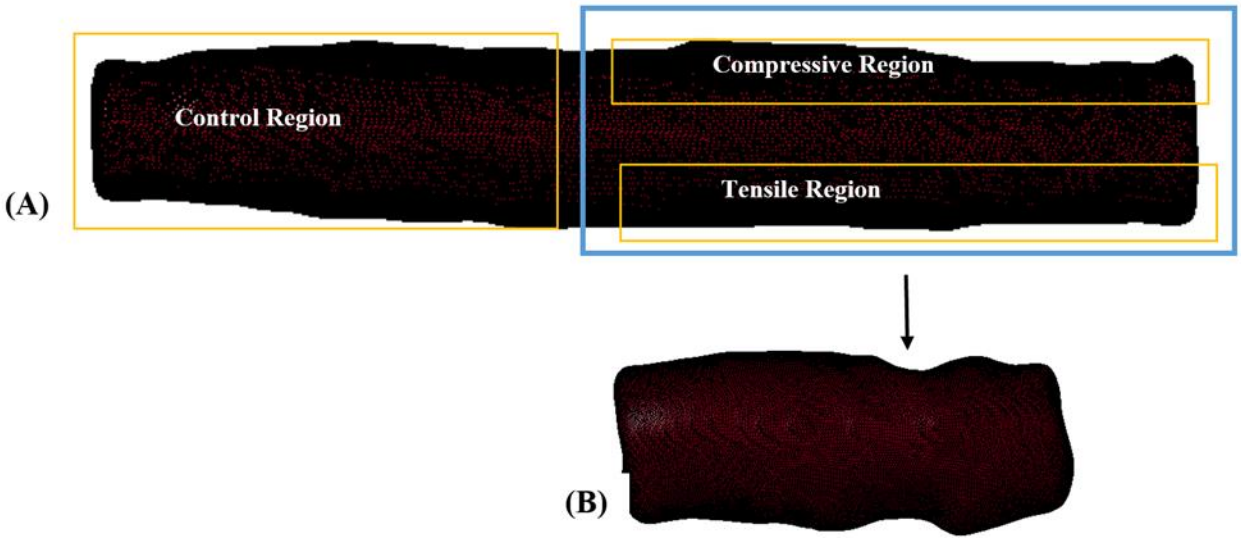

Figure 8: 3D model of the phantom sample before (A) and after (B) imposed mechanical strain with highlighted region of load application. The phantom fiber is classified in regions to study the effect of structural change on the FA value. The control will help validate that no change occurs in that region. The length of the model in (A) is approximately 60mm and the length of the model depicted in (B) is approximately 25mm.

The two models created were visually analyzed and it can be seen there is a clear change in structure within the compressive and tensile region. There are sections of the region where it is bent inwards. The model was able to depict a case when there is a deformation of a brain fiber due to mild TBI. There is some area within the tensile region that depicts a slight bent inward. Based on the observation, it can be concluded that looking only at the changes on the external structure will not give all of the information regarding the deformation of fiber. Additional tests will need to be conducted and more images will need to be scanned in order to generate the exact model that will depict the change in external structure due to the mechanical strain.

Analyzing the 3D model doesn't give a clear picture of the internal deformation and so instead the fiber tracts and FA images of the phantom fiber before and after mechanical strain is looked at to see the internal change. In figures 9 and 10, the fibers in the compressive region seem to be bent inward due to the applied load and agree with the analysis from the 3D model analysis. But the FA image contradicts that the fibers in the tensile region are bent inward as suggested by the 3D model. The 3D model depicts mainly the change in the external structure and images depicted in figures 9 and 10 must be generated to look more closely on the internal change. The FA image contradicts that the fibers in the tensile region are bent inwards and that makes logical sense because when force was applied on one side the other would either bent outward and not significantly change and that is observed in the figure. Furthermore, comparing the two images, the FA around the compressive region seems to be darker. The other side is much more difficult to distinguish with the naked eye and so FSL software was used to get accurate FA values at specific coordinates from various regions. In order to clearly analyze the change, numerical analysis is also required since information gained from the visual analysis is limited.

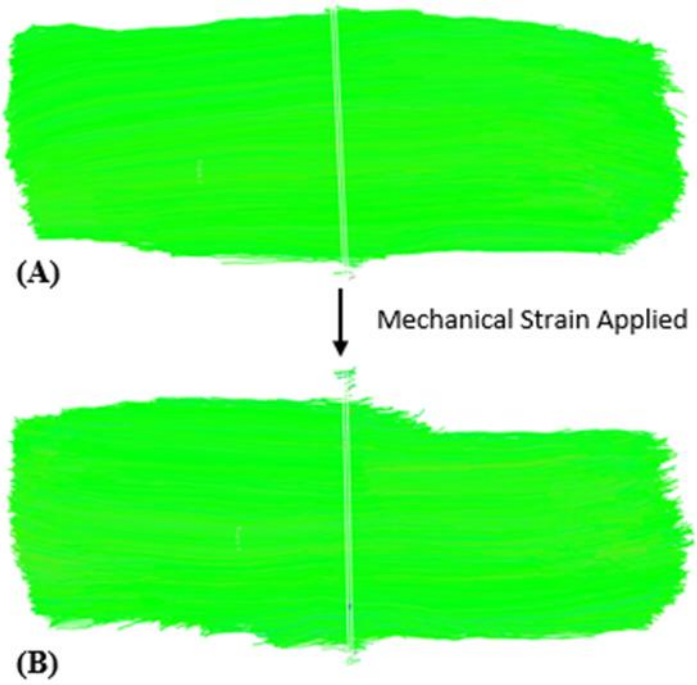

Figure 9: Fiber Tracts of the Phantoms generated before (A) and after (B) mechanical test. The phantom fiber runs in a long strand from one side to the other. The figure presents the damaged fiber regions due to mechanical strain. The compressive region at the top is bent inwards which matches the result seen in the 3D model but depicts a slight outward bend in the tensile region.

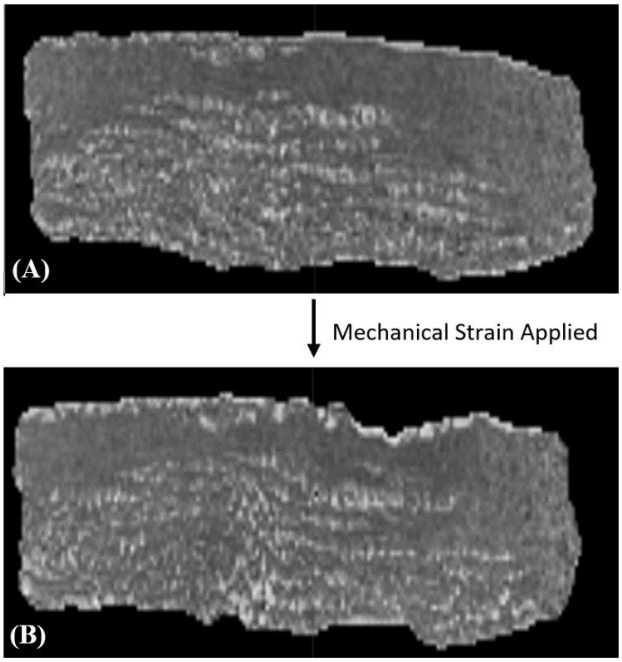

Figure 10: Fractional Anisotropy (FA) images of the phantom before (A) and after (B) mechanical test. The image depicts a clear visual of the internal fiber deformation where the load is applied. The sample is bent inward at the compressive region as was shown in the 3D model. Furthermore, the image shows a clearer image that fibers in the tensile region are not bent inwards

Section 3.2 – Numerical Analysis

Through analyzing the 3D models, fiber tract and FA images, visually, limited information was collected about the structural change and how FA changes in response to strain. Numerical analysis is required to gain more insight, especially on the FA values. After a mechanical test was conducted on the phantom fiber, a plot of load vs displacement to understand more about the properties. From figure 11, it is clear that a load of up to 250N was applied onto the phantom fiber using a 3-point bend machine. Looking at the figure, the phantom fiber reaches the maximum load and then goes down without reaching the breaking point. It is apparent that the application of 250N load had caused some internal fiber damage without failure. One of the aims when selecting the material for the study was that the material should sustain a load similar without severe external damage that would result in leakage of the water among the fibers. After the load went back to zero, there is a displacement occurred within the fibers. This provides evidence that certain internal damage was inflicted.

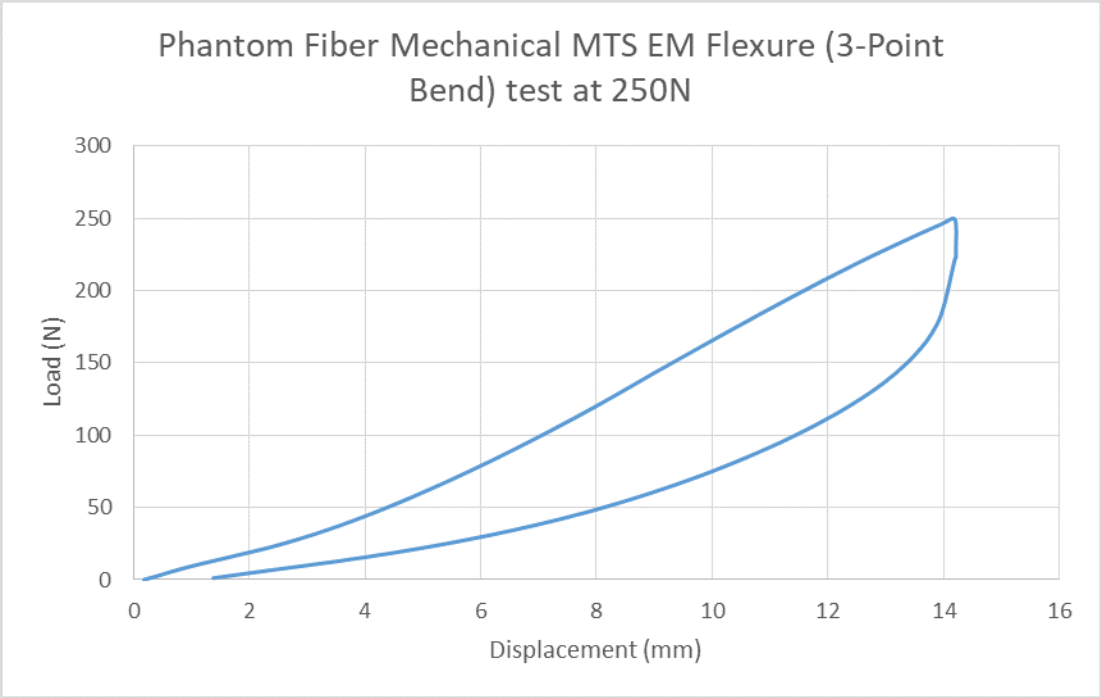

Figure 11: Plot of Load (N) vs displacement (mm) for a phantom fiber mechanically tested with an MTS EM Flexure (3-point Bend) machine at 250N

In order to get more information on the damage and the change in FA, the scanned image data was used to generate FA values in the different regions of the phantom fiber. The FSL software quantifies the FA change within the different regions. Based on the output from the FSL, the FA images before and after the mechanical test was compared. Specific coordinates within each region of the FA images were then chosen to compare the FA values. The specific coordinates were carefully matched in both FA images to make sure the change in FA is viewed for the same spot. Table 1 displays the different regions classified on the phantom sample which includes the control where no load was applied, the compressive region where the fibers around that region had compressive strain imposed due to the load and the tensile region where the fibers are under tensile strain. In the compressive region, it is evident that the FA value had slightly increased between the pre-test and post-test from 0.33185 to 0.36458. In the tensile region, the FA value has also increased but the difference is much bigger and shows a clear

change. In the control, as was expected, the FA value had relatively remained the same. Looking at the table, the data seems to support our hypothesis that the FA value increases in the tensile region but contradicts that FA value decreases in the compressive region. Since this is a preliminary result, more experiments will need to be performed and more data will need to be assessed in order to state any definite conclusions. In addition, factors such as noise or resolution could also have impacted the values obtained.

Table 1: Measured Fractional Anisotropy (FA) values of phantom fiber before and after the mechanical test. The values were calculated for regions in the compressive, tensile, and control region in order to evaluate the difference.

Region (coordinates)	FA value (pre-test)	FA value (post-test)
Compressive	0.33185	0.36458
Tensile	0.54623	0.61697
Control	0.44687	0.445293

Chapter 4

CONCLUSIONS AND FUTURE DIRECTIONS

Investigating the discrepancies found in sensitive measures such as Fractional Anisotropy (FA) is important if the measurements will be aimed to use in the development history dependent models to help people at risk of brain injuries. To better understand and resolve the conflicting FA trends, phantom fibers were selected as the best option due to the ability to mimic the white matter tissue. The phantom fiber was scanned first then tested and scanned again. Analyzing visually, the phantom fiber seemed to recover its shape after the mechanical load was applied and no external structure damage was seen. This means that the 250N load used was the

appropriate amount and will be used in future experiments Since this type of study has not been conducted before, the appropriate amount of load as well as more information about the property had to be learned through trial and error. But looking at the internal structure based on the fiber tracts and FA images generated, deformation caused by the bend was visible which supports our assumption that only the internal structure was damaged. Since this is a preliminary results and conclusion may be hard to draw, the numerical analysis also showed that the FA value increases in both the compressive and tensile region while the FA value stays relatively constant in the control region. But it can be seen from table 1 that the increase in FA value is much wider in the tensile than the compressive region. As such further experiments will need to be conducted in order to better understand the trend and generate statistics from multiple samples. Despite the inconclusive results, the findings were of value as they link mechanical deformation to changes seen in imaging measures which is the overall goal of the study.

Some possible errors that may have influenced the result include generated motion artifacts during the MRI scans which can add a false image resulting in miscalculation of the FA. Furthermore, more study will be required to study how the orientation of the fiber tracts can be kept aligned with the DWI images for future experiments. Misalignment can also result in false conclusions and as such more work is required to solve it. Aside from further tests, simulations must also be conducted using the generated 3D models and fiber tracts to test multiple scenarios and analyze the numeric findings. Once the experiments have been concluded on phantom fibers, the study will then move on to animal models which will take more complex assumptions into consideration. Non-straight fiber strands can be further studied to produce more conclusive data for the history-dependent damage model.

Appendix A

Additional Image of Scans and Mechanical Test of Celery

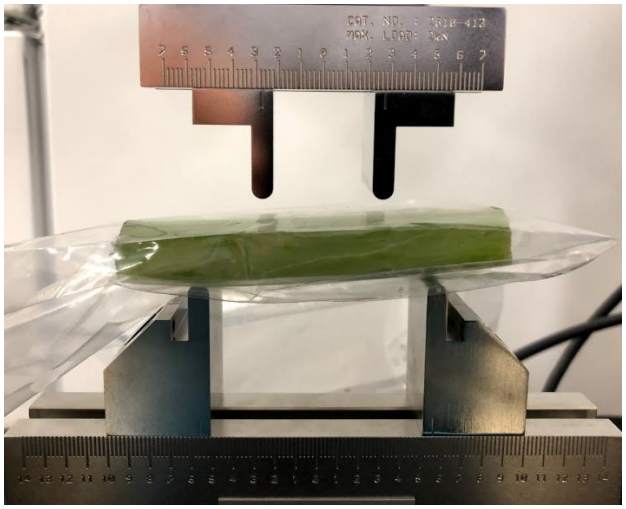

Figure 12: Mechanical test of celery on an Instron Electro E3000 Static/Fatigue Tester at strain rates between 10^{-3}–10^{1} s^{-1}, during the material selection process, to observe the deformation and analyze the property.

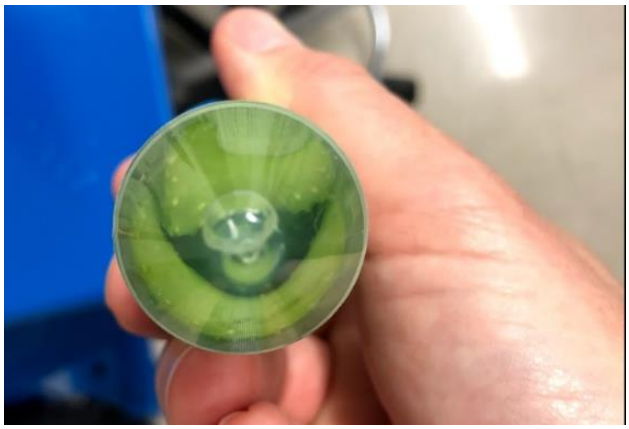

Figure 13: Two celery enclosed in a tube filled with water to observe the deformations that occurred during the mechanical test. The tube is filled with two pieces of celery to prevent the samples from moving during the scan.

Movement of the sample during MRI scan can create motion artifacts which then causes an artificial feature to appear on the DWI image that was not present on the real object. To minimize and if possible prevent motion artifacts, the sample being scanned needs to be enclosed in an item that prevents sudden movements. During the material selection process, two pieces of celery were put in a tube as shown in figure 13 to prevent motion artifacts.

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OUNIOL T. AKLILU

University Park, PA 16802 | ota5043@psu.edu | linkedin.com/in/ouniolaklilu

EDUCATION

The Pennsylvania State University — *University Park, PA*
Bachelor of Science in Biomedical Engineering (Schreyer Honors and Millennium Scholar) — *Expected: May 2021*
Minor in Engineering Leadership and Development

- **Relevant Coursework**: Bio-thermodynamics, Biofluid Mechanics, Mass Transport in Biological Systems, Biomedical Instrumentation and Measurements, Numerical Simulation in BME, Organic Chemistry

École Centrale de Nantes (Study Abroad) — *Nantes, FR*
Study Abroad Program to examine Engineering Design from global perspective — *May 2019 - Jun 2019*

RESEARCH/ INTERNSHIP EXPERIENCE

Pharmaceutical Commercialization Technology | Intern — *West Point, PA*
Manufacturing Division | Merck & Co. — *May 2020 – Aug 2020*

- Designed dashboards in an analytics software to improve process analysis and reporting for various projects
- Evaluated process improvement of analyzing new data using the standard problem-solving methodology
- Collaborated with subject matter experts to apply dashboard templates to other programs

Sellmyer Laboratory | Lab Assistant — *Philadelphia, PA*
Dr. Mark Sellmyer | University of Pennsylvania School of Medicine — *May 2019 – Aug 2019*

- Collaborated with a multi-disciplinary team of graduate students to develop a positron emission tomography probe to distinguish overlapping pathologies
- Designed and conducted experiment to measure the uptake values of [11C] Trimethoprim in a mouse model while determining the resistance and affinity of bacteria to different types of antibiotic drugs.

PSU Computational Biomechanics Laboratory | Undergraduate Researcher — *University Park, PA*
Dr. Reuben H. Kraft | The Pennsylvania State University — *Jan 2018 – Present*

- Designed and conducted experiments to examine the behavior of a synthetic polyester fiber (Phantom Fibers).
- Independently operated a Split-Hopkinson Pressure Bar to measure sensitive changes of Fractional Anisotropy (FA) in response to brain injury.
- Accomplished results leading to co-author of publication in SB3C2019.

Publication: *Menghani, Ritika R[1]., **Aklilu, Ouniol T**[2]., & Kraft, Reuben H[3]. (2019). "History Dependent Damage Modelling for Axonal Fiber Tracts of the Brain." Summer Biomechanics, Bioengineering and Biotransport (SB3C2019).*

LEADERSHIP POSITIONS

SACNAS chapter at Penn State — *University Park, PA*
Vice-President — *Oct 2017 – Present*

- Helped underrepresented minorities pursue advanced degrees in STEM field.
- Redesigned the workshop program that introduces undergraduate students to research programs at Penn State.
- Assisted in organizing and managing the SACNAS Chapter meeting including chapter activities such as outreach programs and fundraisers.

Penn State Student Affairs — *University Park, PA*
Resident Assistant — *Jan 2019 – Present*

- Worked with Co-Resident Assistants to execute creative programs, foster student development socially, and culturally to maximize positive resident interactions. Act as the mediator to resolve roommate conflicts.

Penn State College of Engineering (ENGR 409: Leadership in Organizations) — *University Park, PA*
Teaching Assistant — *Aug 2020 – Present*

- Helped Engineering students develop a deeper understanding of leadership and the fundamentals of business planning and management through facilitating group discussions, clarifying and answering any questions from project teams.

PROJECT PRESENTATIONS

2019 SACNAS - The National Diversity in STEM Conference — *Honolulu, HI*
Investigation of Correlates of Diffusion Tensor Imaging Changes and Mechanical Strain — *Poster Presentation*
2019 Leadership Alliance National Symposium (LANS) — *Hartford, CT*
PET Imaging of bacterial Infection with radiolabelled [11C] Trimethoprim — *Oral Presentation*

ADDITIONAL SKILLS AND CERTIFICATIONS

Skills and Certifications: Proficient in MATLAB, UNIX, SEEQ; Advanced in Microsoft suite; Certified six sigma yellow belt
Languages: Fluent in English, Amharic and French; Conversational Proficiency in Oromo and Arabic
Extracurricular Activities: BMES Society, National Society of Black Engineers, Engineering Leadership Society
Awards: President Freshman Award, Gilman Scholarship, Steve and Artz Engineering Scholarship, Millennium and Schreyer Scholar, CSL Behring Biotechnology Scholarship, Dean's list (6 semesters), Bunton-Waller Scholarship