A Multiscale Analysis of the White Brain Material with Axons as Bidirectional Orientated Fibers

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Abstract: Axonal injury within the white matter of human brain and spinal cord will lead to sever failure of the central nervous system and traumatic brain injury. In this paper the brain tissue is model with axons distributed with bidirectional orientation within the white matter of the brain. In the modeling procedure a repeating unit cell (RUC) comprising of axons and extracellular matrix is modeled by Abaqus. This micromechanical modeling implements periodic boundary conditions and constraints on the unit cells. Hyperelastic material properties of white matter sheet corona radiata of a porcine brain with bi-directional orientation of axonal fibers within the extracellular matrix are considered as the constitutive materials. Unit cells are modeled by considering different axonal volume fractions. Axial as well as shear loading are applied to the unit cells to study the extent of deformation and stresses in axons and extracellular matrix undergoing large deformations. With the change in axonal volume fraction, the development of stresses in white matter has been witnessed in microscopic level. For this bidirectional orientation modeling of axons, the results are discussed and compared with the experimental data.

Keywords: Brain injury, axons, tissue, bidirectional fibers, multiscale computation

1: Introduction

Head injury can be classified into two types of closed damage and open damage [2]. In case of closed damage, the skull inside the scalp receives a hit but is not injured. Open damage on the other hand occurs when there is an injury to the skull by a rapid moving object which tears through the skull and enters the brain. The open or closed hit causes damage to the brain which is termed as traumatic brain injury (TBI). The injuries might be caused by blasts, falling from heights and mostly by minor or severe road accidents. Gray matter and white matter form the outer and inner layers of the brain. The inner layer, white matter is composed of fibers known as axonal fibers surrounded by extracellular matrix. This paper deals with injury caused to inner portion of the brain, the axons which swell or elongate by a fast moving external source developing shearing forces that cause diffuse axonal injury (DAI) [3], a type of traumatic brain injury.

There have been attempts to model the orientation of axons distributed in the extracellular matrix within the white matter of brain tissue. Work has been done for hexagonal and square arrangement of axons spread in a unidirectional orientation within the extracellular matrix[12] but little has been mentioned about the bi-directional distribution of axonal fibers. The reason for modeling crossed axonal fibers within the base matrix is because the white matter sheet *corona radiata* has a disordered pattern of axons as mentioned by Velardi et al [4]. The researchers have always focused on the white matter sheet *corpus collasum* with uniaxial orientation of axons for developing brain tissue models but bi-directional arrangement of axons in *corona radiata* still remains unexplored.

There have been in vivo and in vitro experiments conducted on the brain tissue but little has been mentioned about the micro-structural damage of the axons within the white matter of the brain tissue. For uniaxial distribution of axons, Arbogast and Margulies [5] proposed an ideal axonal volume fraction of 53%. Experimental works conducted by Prange and Margulies [6] and Velardi et al. [4] on the porcine brain tissue for white matter sheets *corpus collasum* and *corona radiata* has been noteworthy but there has been little work which describes the stresses developed on axons as well as the overall brain tissue for a crossed fiber orientation due to brain injury caused by external forces.

The exact material properties of brain tissue are difficult to find and hence a lot of research is done in this area. There were experiments conducted by Velardi et al. [4] on porcine brain tissues which have properties similar to brain tissue of humans. To understand the non-linearity and anisotropic characteristic of the brain tissue undergoing large deformations, hyper-elastic material has been used. A repeating unit cell (RUC) is modeled using finite element software- Abaqus. The RUC consists of axonal fibers within the base matrix having a bi-directional orientation. Axial as well as shear loads are applied on the unit cell representing the brain tissue and hence the maximum, average normal stresses within the entire brain tissue as well as axons and the extracellular matrix are obtained. Different axonal volume fractions 40%, 53% and 60% are used to model the unit cell. For each respective unit cell, maximum and volume average stresses are obtained by applying loads calculated from stretches (10%, 20%, 30% and 40%) using experimental data by Velardi et al. [4]. The maximum stresses developed in composite brain tissue will be plotted against respective stretches for each volume fraction and compared with the experimental graphs (stress vs. stretch) for *corona radiata.* The computational results obtained will be compared with the experimental data and an ideal axonal volume fraction will be found out.

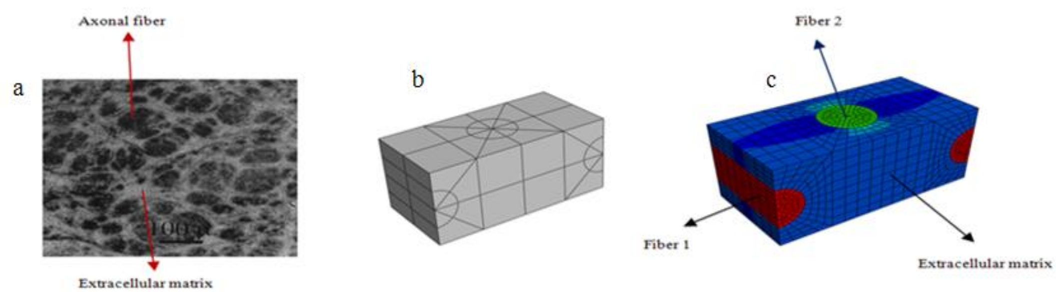

Figure 1. (a) Distribution of axons which are stained dark within the extracellular matrix which are unstained [5] (b) Unit Cell Geometry and (c) Repeating Unit Cell with bi-directional orientation of axons.

2. Experiment on brain tissue of porcine

Velardi et al. [4] tested white matter tissues extracted from *corpus collasum* where axons are distributed longitudinally and *corona radiata* where the fibers are oriented in longitudinal as well as transverse direction. Testing the brain tissue sample strips was not an easy task because of its slippery nature. It was difficult to place the samples on the testing machine but finally the problem was overcome by adopting some techniques. "*The samples were dampened by a physiological solution, covered with a tissue paper before placing it into the grips and the grips to hold the samples were tightened manually"[4]*. The testing machine INSTRON 4301 was used for performing tensile test on the brain tissue strips. Average stresses were calculated by applying loads obtained from porcine tissue strips cross section. CCD camera was placed in front of the testing machine to ensure that the samples did not slip off during the experiment. With the help of the testing machine load versus displacement graphs were generated and were later used to obtain Stress (S) versus Stretch (λ) plots. Force divided by initial sample cross-section area taken as average and displacement between samples divided by initial sample length was used to find Stress and Stretch values. Two plots were obtained for the white matter sheet corona radiata, (a) Stress vs. Stretch plots for axonal fibers oriented in longitudinal direction (Fiber 1) and (b) Stress vs. Stretch plots for fibers oriented in transverse direction (Fiber 2).

2.1 Hyper-elastic model for brain tissue

Hyper-elastic material is a function of strain energy and large displacements. Ogden [7] hyper-elastic model is taken into account where large deformations take place to analyze the stress-strain relations for materials like brain tissue, rubber etc. Unlike visco-elastic material, hyper-elastic materials undergo large deformations and under large strains they exhibit non-linear elastic behavior up to 500%. Ogden [7] hyper-elastic material can undergo a strain till 700% when compared to other models like Mooney Rivilin and Arruda Boyce which have a limit of 200% and 300% strain.

Strain energy equation for Ogden hyper-elastic model can be written as[7]:

$$W = 2\mu/\alpha^2 (\lambda_1^{\alpha} + \lambda_2^{\alpha} + \lambda_3^{\alpha} - 3) + 2k\mu/\beta^2 (I_4^{\beta/2} + 2I_4^{-\beta/4} - 3)$$

$$\lambda_1, \lambda_2, \lambda_3 = 1$$

where, $\lambda_1, \lambda_2, \lambda_3$ are taken as principal stretches, I_4 represent the square of material stretch, μ is the infinitesimal shear modulus, k is the stiffness co-efficient and α and β are material parameters [4,7-9]

2.2 Unit cell modeling using micromechanical principles

The material properties and geometrical parameters of the constituents of a composite must be known in order to analyze the overall behavior of the composite. Here brain tissue is comparable to a composite material whose properties will be evaluated by knowing the properties of its constituents, axons as well as extracellular matrix. The deformation of the axons within the white matter of brain tissue will be measured in the microscopic level and finally characterized in macroscopic level in an average manner. Unit cells which form the representative volume element with known material properties of axons and extracellular matrix will be modeled. The unit cell will undergo large deformations and hence hyper-elastic material will be used.

Unit cells comprising of bi-directional pattern of axonal fibers within extracellular matrix are modeled considering different axonal volume fractions (40%, 53% and 60%). The unit cell will represent a three dimensional brain tissue model and when expanded will cover white matter regions of *corona radiata*. In this paper, the orientation of axons within the base matrix is taken to be 90°. The dimensions for the repeating unit cell are considered to be 20 m, 20 m and 40 m (width, height and length). The unit cell model is meshed in such a manner that the opposite sides of the cell deform symmetrically. Loads in the form of displacements are applied on the unit cell and the corresponding deformations and stresses are found out using finite element software-ABAQUS [1]. The volume average stresses and strains will be obtained.

2.2 Material properties of brain tissue

Finding out the material properties of axonal fibers and extracellular matrix in order to characterize the brain tissue has always been a difficult task. The data available is limited as only a few researchers have conducted experiments on in vivo and in vitro brain tissue. Arbogast and Marguiles [5] used viscoelastic material properties for axonal fibers and extracellular matrix to characterize the brain tissue within the white matter. Meaney [11] carried out experiments on guinea-pig optic nerves which is similar to a human optic nerve and obtained material properties for the axonal fibers. He used hyper-elastic material to represent his model. Velardi et al. [4] performed experiments on porcine brain tissue by applying tensile loads and hence acquired the necessary material parameters for the axon using Ogden [7] hyper-elastic model. Arbogast and Margulies [5] experimentally proposed that axonal fibers are three times stiffer than the extracellular matrix. For axonal fibers, Velardi et al. [4] provided data for infinitesimal shear modulus μ and two other material parameters α and β whose values remain the same for axon as well as the base matrix. Based on these assumptions the material properties of axons and base matrix are considered for the brain white matter *corona radiata*.

Table 1- Hyperelastic material property for axon and extracellular matrix

	μ (Pa)	α	β (Pa^{-1})
Axon	136.82	6.84	1.00 E-08
Extracellular Matrix	45.6	6.84	1.00 E-08

2.3 Periodic and rigid body constraints

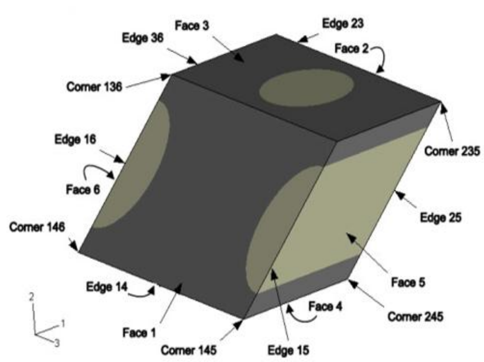

Figure 2 Sample unit cell with faces, edges and corners [10]

Referring to Figure 2, the directions 1, 2 and 3 correspond to longitudinal, transverse and transverse normal. The periodic body constraints must be applied in such a way that the unit cell deforms in a symmetric and identical manner on the reverse sides. To establish the required symmetry, the number and orientation of nodes on reverse sides of the cell must be equal and identical. Figure 2 consists of 12 edges, 6 faces, 6 face center nodes and 8 corner nodes [10]. Here faces 2, 4, 6 are opposite to faces 1, 3 and 5. The degrees of freedom developed due to displacement of the edges, faces and corners of one portion of the unit cell must depend on the other half.

The unit cell must comply with some rigid body constraints in order to avoid unnecessary rotations and translations. In all directions, the center node of the cell is always fixed. Translation movement of the unit cell is prevented by keeping the center node of face 1 fixed along direction 1 and to avoid rotational motion, center node on face 2 is fixed along direction 3. In order to avoid rigid rotation along directions 2 and 3 of the unit cell, a node is fixed on one of the edges of face 1.

2.4 Loading condition

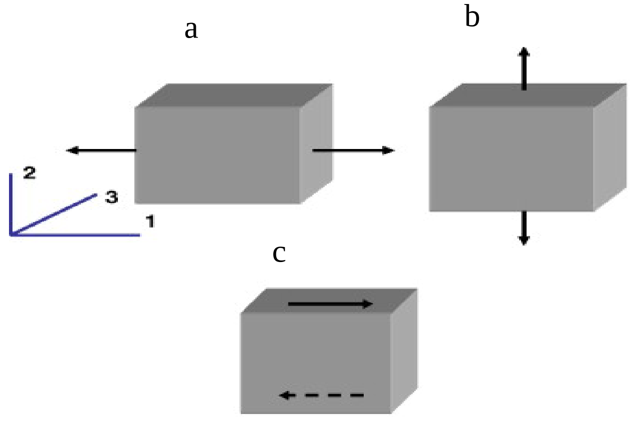

Figure 3. (a) Load case 1 and (b) Load case 2 and (c) Load Case 3 [10]

In Figure 3(a), the applied load 1 is axial and the direction is longitudinal while in 3(b), load 2 is axial and transverse and for 3(c), the applied load 3 is shear. The load 1 on the unit cell is tensile and is applied on face 1 center node along direction 1, load 2 is applied on the center node of face 3 along direction 2 and load 3 is applied in direction 1 on the center node of face 3 as can be seen in Figure 2.

Loads applied on the periodic unit cell are calculated by considering the displacements resulting due to stretches (λ) as hyper-elastic material is a function of strain energy and strain energy as a function of large displacements. The stretch (λ) values are taken to be 10%, 20%, 30% and 40%.

For each axonal volume fraction (40%, 53% and 60%), displacements were calculated and hence simulations were run for stretches 10%, 20%, 30% and 40% to obtain the axonal deformation and stresses developed in each element which are later utilized to compute the volume average stresses. The overall behavior of the hyper-elastic material can be understood by plotting volume average stresses vs. the stretch.

3. Results

3.1 Computational stress analysis

For different volume fractions 40%, 53% and 60%, stress contour plots for the deformations on the composite brain tissue are obtained but results for only 40% axon volume fraction are shown here. For load cases, 1, 2 and 3 stress contour plots are shown in Figures 4,5,8,9,12,and 13 calculated from the respective stretches 10%, 20%, 30% and 40%. After plotting the stress contours, the values for maximum normal stresses, volume averaged stresses for axon fiber 1, axon fiber 2 and extracellular matrix of the tissue are obtained for load case 1,2 and 3 by using volume average subroutine for different volume fractions. Plots for maximum normal stresses developed on the white matter sheet *corona radiata* for the brain tissue and volume average stresses in its constituents; axonal fiber 1, axonal fiber 2 and extracellular matrix for each volume fraction are obtained considering load cases 1, 2, 3 shown in Figures 6, 7, 10, 11, 14, 15, and 16. In case of maximum normal stresses for each volume fraction considered, stress vs. stretch is obtained and the volume averaged stresses in axon fiber 1, axon fiber 2 and extracellular matrix are plotted against the stretch values to understand the overall effect on the brain tissue. Results for only load case 1 and 2 are compared with the experimental results of Velardi et al [4].

3.2 Tissue unit cell under load case 1 (axial loading-longitudinal)

In Figures 4, and 5, tensile loads are applied on the faces 4 and 6.

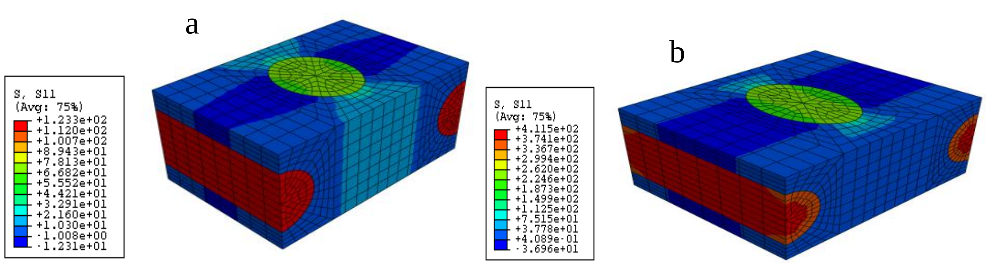

Figure. 4. Contour of normal stress plots for load case 1 with an axonal fiber volume fraction of 40% (a) Stretch 10% and (b) Stretch 20%

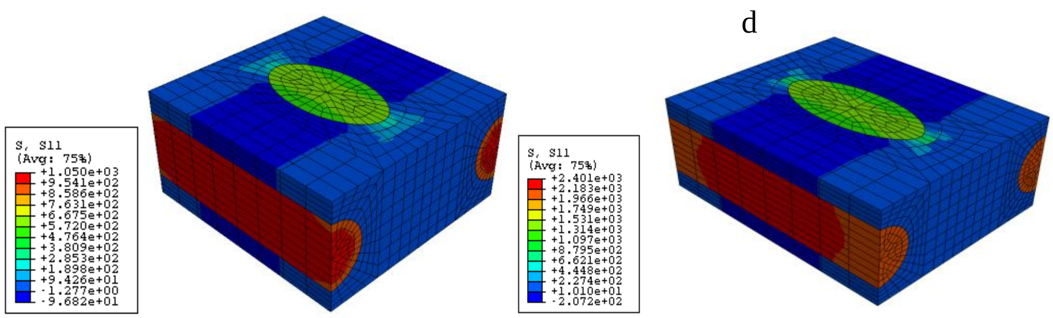

Figure 5. Contour of normal stress plots for load case 1 with an axon volume fraction of 40% (c) Stretch 30% and (d) Stretch 40%.

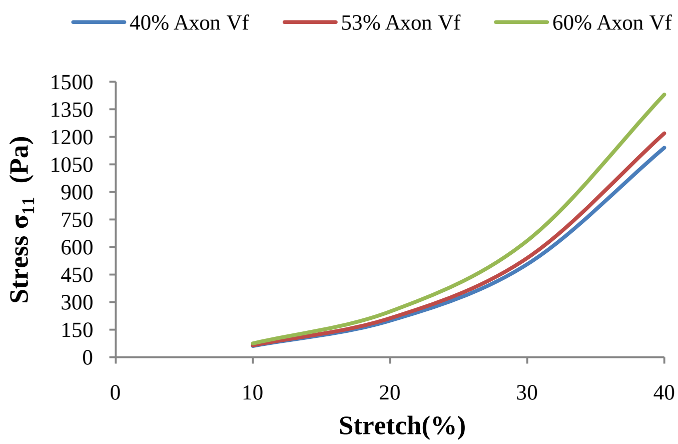

Figure 6. Load Case 1. Maximum Normal Stresses developed in Corona Radiata for 40%, 53% and 60% axon volume fractions with displacement in the form of load applied in direction 1.

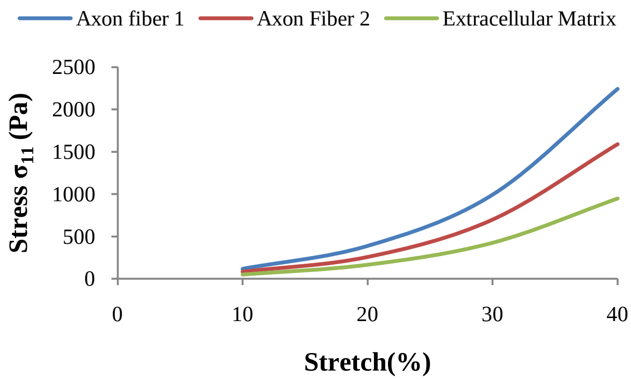

Figure 7. Load Case 1. Average normal stress developed in Axon Fiber 1, 2 and Extracellular Matrix for 60% axon volume fraction with displacement in the form of load applied in direction 1.

3.3 Tissue unit cell under load case 2 (axial loading-transverse direction)

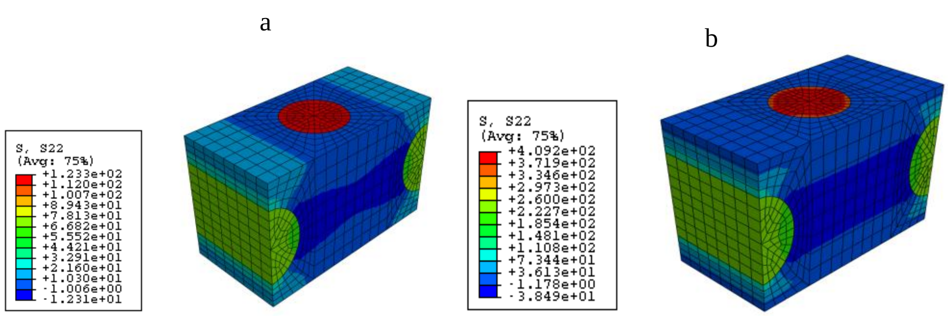

Figure 8. Contour stress plots for load case 2 with an axon volume fraction of 40% (a) Stretch 10% and (b) Stretch 20%

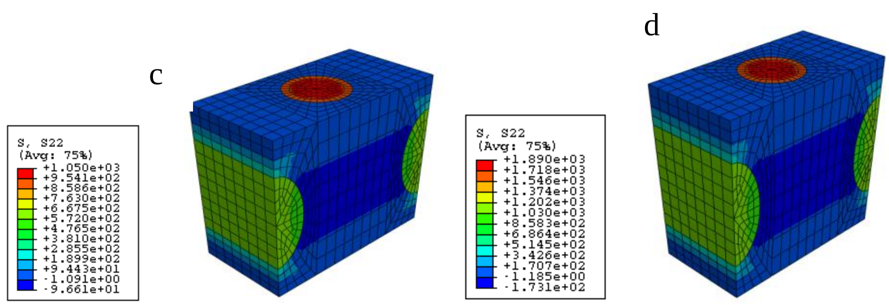

Figure 9. Contour stress plots for load case 2 with an axon volume fraction of 40% (c) Stretch 30% and (d) Stretch 40%

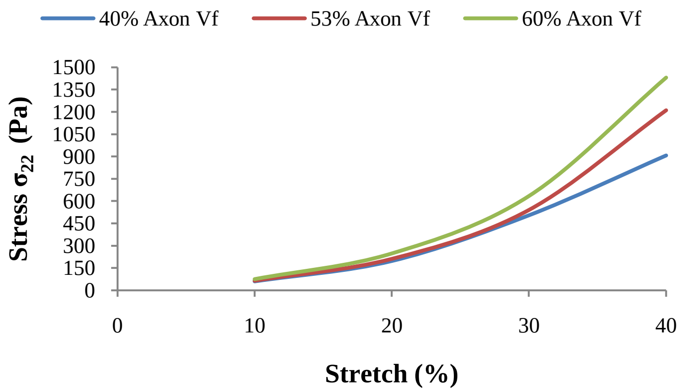

Figure 10. Load Case 2. Maximum normal stresses in Corona Radiata for 40%, 53% and 60% axon volume fractions with displacement in the form of load applied in direction 2.

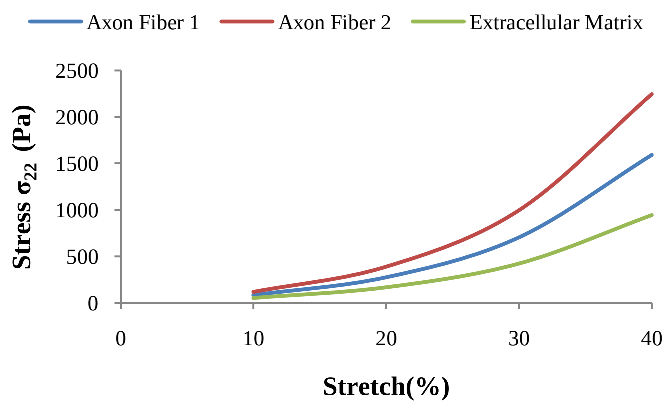

Figure 11. Load Case 2. Average normal stress in Axon Fiber 1, 2 and extracellular matrix for 60% axon volume fraction with displacement in the form of load applied in direction 2.

Axonal injury takes place in case of mishaps like explosions, small and severe accidents, falling from heights causing DAI where axons are elongated and deformed. This deformation and elongation of the axonal fibers can be seen in Figures 4, 5 and 8, 9 for load cases 1 and 2. The stresses developed on white matter sheet *corona radiata* and on axons as well as extra-cellular matrix are reported in Table 2, 3. The plot in Figures 6 and 10 tells about the maximum stress developed in the brain tissue under load conditions 1 and 2.Unit cells with different volume fractions 40%, 53% and 60% were modeled and loads were applied on these unit cells in the form of displacements which were in longitudinal direction (Load Case 1) and the other in transverse direction (Load Case 2). In case of load case 1, the stiffer axons were greater in axons with higher volume fractions because the stresses developed here were larger than the stresses developed in axons with low volume fraction. It was found that average volume normal stress of the tissue for an axon V_f of 60% is 2.7 times greater than 40% V_f and 1.4 times greater than 53% V_f for a given stretch of 40%. When considering load case 2, the average volume normal stress of the tissue for an axon V_f of 60% is 1.7 times greater than 40% V_f and 1.5 times greater than 53% V_f for a given stretch of 40%. Axons with higher volume fractions exhibited higher stress values in case overall tissue as well as axon fiber 1, 2 and the extracellular matrix.

For both load case 1 and load case2, volume average stresses developed in axon fiber 1, 2 and extracellular matrix can be compared. In case of load case 1 for 40% axon V_f, stress in axon fiber 1 is almost 2.5 times greater than the extracellular matrix while for 53% and 60%, the stress developed is 2.5 and 2.35 times greater than the extracellular matrix. Here axon fiber 2 for 40% V_f is about 1.5 times and for 53% and 60%, V_f is 1.5 and 1.67 times larger than the base matrix. In case of load 2 for 40% axonal V_f, stress in axon fiber 1 is 1.5 times more than the extracellular matrix while for 53% and 60%, the stress developed is 1.5 times and 1.67 times greater than the extracellular matrix. Axon fiber 2 for 40% V_f is about 2.5 times and for 53% and 60%, V_f is 2.5 and 2.35 times greater than the base matrix. Considering the stresses developed in Axon Fiber 1 which is the longitudinal direction, load case 2 is more evenly distributed than load case 1. But for Axon Fiber 2 which is the transverse direction, stresses in load case 1 are more evenly distributed than load case 2.

3.4 Tissue unit cell under load case 3 (shear loading)

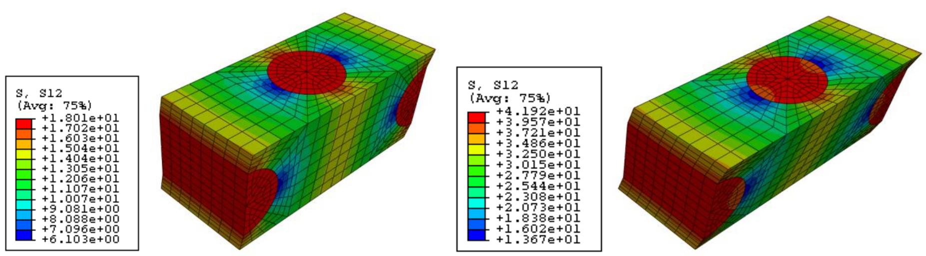

Figure 12. Contour shear stress plots for load case 3 with an axon volume fraction of 40%.

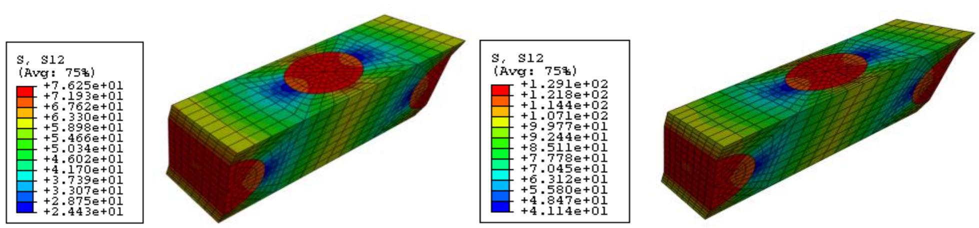

Figure 13. Contour shear stress plots for load case 3 with an axon volume fraction of 40%.

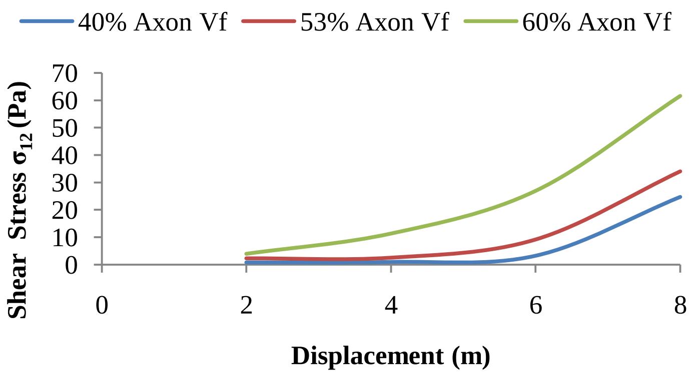

Figure 14. Load case 3. Maximum Normal shear stresses in Corona radiata for 40%, 53% and 60% axon volume fractions with displacements applied in direction 1, 2.

Experiments were conducted on brain tissue by Velardi et al. [4] for loads in longitudinal and transverse direction but shear load must also be considered. The prime reason for DAI is shear forces developing on the axons and hence causing damage to it. Here computational results for development of shear stress are found out by applying displacements in the form of loads at different angles. Considering longitudinal and transverse directions for load case 1 and load case 2, the computational data obtained for maximum normal stress developed in the tissue is almost the same but different when compared to the maximum shear stress developed in the tissue. This indicates that brain tissue under shear loading is affected more when compared to axial loads. In case of load case 3 for 40% axon V_f, stress in axon fiber 1 is almost 1.66 times greater than the extracellular matrix while for 53% and 60%, the stress developed is 1.66 and 1.8 times greater than the extracellular matrix. Here axon fiber 2 for 40% V_f is about 1.9 times and for 53% and 60%, V_f is 1.9 and 2 times larger than the base matrix. The values obtained for average normal shear stress for axon fiber 1 and axon fiber 2 for load case considering different axon volume fractions are almost same thus indicating that stresses are almost equally distributed.

3.5 Verification of the tissue response with experimental data

Experimental results obtained by Velardi et al [4] for different porcine brain samples are in two forms (a) axonal fibers are oriented in longitudinal direction (b) axonal fibers oriented in a transverse direction within the white matter sheet corona radiata.

In the computational analysis, loads created due to displacements in load case 1 and load case 2 with different axon volume fractions (40%, 53% and 60%) are applied and the results for average volume normal stresses developed in the brain tissue are verified experimentally as shown in Figures 15 and 16.

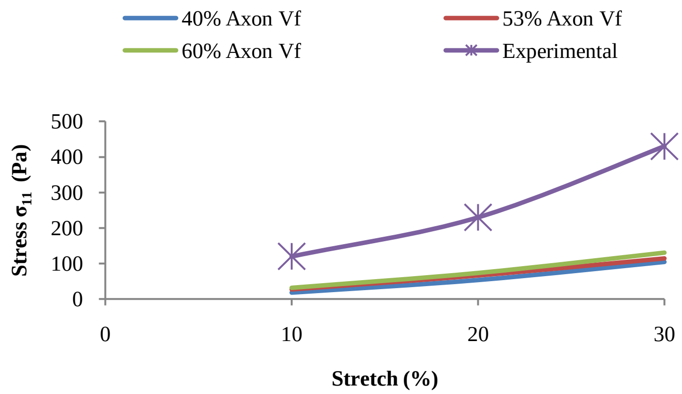

Figure 15. Load case 1. S11 Average Normal stresses in Corona radiata for volume fractions 40%, 53%, 60% and experimental (Levenberg-Marquardt nonlinear fit method [4]) for loading in longitudinal direction 1.

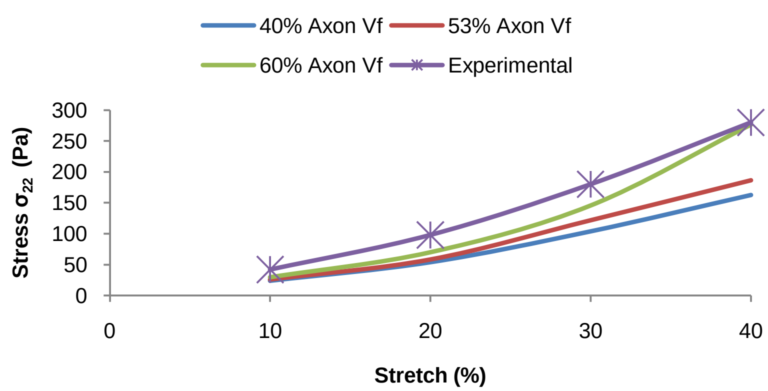

Figure 16. Load case 2. S11 Average Normal stresses in Corona radiata for volume fractions 40%, 53%, 60% and experimental (Levenberg-Marquardt nonlinear fit method [4]) for loading in transverse direction 2, 2.

Arbogast and Margulies [5] reported that for uniaxial orientation of axons within the white matter sheet corpus collasum, the ideal axonal volume fraction is 53%. In case of bi-directional orientation of axonal fibers in corona radiate, results were different. For load case 1, where the loads created due to displacements are applied in longitudinal direction, the computational results were not in agreement with the experimental data. While for load case 2, where loads are applied in transverse direction, the results for 60% axonal volume fraction are in close proximity with the experimental data available.

4: Conclusion

Characterization of brain white matter sheet *corona radiata* consisting of axons oriented in a bi-directional pattern within extracellular matrix is done by making a three dimensional micromechanical model representing a unit cell. Various axon volume fractions (40%, 53% and 60%) are taken into account and for each respective volume fraction; deformation occurring within the axons by applying loads are shown which depicts that how Diffuse Axonal Injury occurs when a fast moving object penetrates through the skull into the human brain. Axial and shear loads were applied on the unit cells to understand the behavior of the brain tissue.

Modeling the unit cells with different axon volume fractions creates an effect on the properties of white matter brain tissue *corona radiata*. As the axonal volume fraction increases, the maximum normal stresses developed in the *corona radiata* increases for each stretch value considered.

The computational results were compared with the experimental results. It can be concluded that when the loads were applied in longitudinal direction the results were slightly conflicting but for loads in transverse direction, the results were in correlation with the experimental data. For Load case 2, it can be inferred that for bi-directional orientation of axon fibers, the ideal volume fraction of axons can be near to 60%. While for load case 1, it might be that axon volume fraction be different with that considered for load case 1.The experiment on brain tissue for shear loading should also be done and verified computationally. The material properties of the brain tissue constituents provided are not sufficient. The model provided must be refined in order to obtain more accurate results by considering bi-directional crossed axonal fibers at different angles.

The bidirectional orientation of axonal fibers as compared to unidirectional arrangement of axons within the white matter sheet of brain tissue is less explored and hence more works needs to be done in this area. The model provided can be further used for micromechanical characterization of brain white matter when accurate experimental results as well as precise material properties of axonal fibers and base matrix are obtained.

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