Original research

A micro-mechanical brain model for prediction of neurological disorders

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Abstract

Growing evidence indicate the significant role of Mechanics in neurological disorders such as stroke, dementia, and multiple sclerosis (MS). Previous studies indicate that brain white *matter* is particularly vulnerable to mechanical damage and structural changes. In previous studies on micromechanical behavior of white brain tissue, only axonal fibers and ECM have been employed in the model. Our research takes a unique approach by utilizing the myelin sheath to assess its influence on the mechanical characteristics of axons and the overall behavior of brain tissue. The model is built on electron micrograph data and the probabilistic distribution of axonal fibers within the extracellular matrix (ECM), allowing for qualitative analysis of tensile, compressive, and shear stress distribution on nerve fibers using the finite element method. Additionally, the quantitative analysis of mechanical properties and stress thresholds on nerve fibers was made possible by placing this model in a multi-parameter optimization process. The results showed that, compared to the previous models proposed by other researchers, the present model provides far more accurate hyperelastic material properties for axonal fibers and ECM.

Keywords: White matter; Extracellular matrix; Axons; Brain model; Finite Element

1. Introduction

The brain is affected by many disorders, including infections, stroke, tumors, and neurodegenerative diseases. Fortunately, most cerebral pathologies can be characterized using various advanced imaging techniques. However, neurodegenerative disorders continue to present a significant challenge. These disorders often lead to subtle microstructural alterations in the brain that are usually missed by conventional imaging techniques.

In recent decades, there has been growing evidence indicating the significant role of Mechanics in neurological disorders such as stroke, dementia, and multiple sclerosis (MS). Although microstructural changes in neurodegenerative diseases have been studied, the connection between these changes and the corresponding tissue mechanics or macrostructural properties remains to be fully understood.

Previous research works based on ex-vivo and in-vivo magnetic resonance imaging (MRI) has confirmed the link between white matter impairments and pathological theories in Alzheimer's' Disease by revealing a decrease in white matter volume and changes in the white matter microstructure [1]. Hence, assessing the brain's mechanical properties will provide insights into these structural changes and a method for characterizing focal lesions.

Studies have shown that myelin injury may be closely related to neurodegenerative diseases and may serve as an early diagnostic criterion and therapeutic target. Myelin is a membrane wrapped around axons. Its role is to protect the axon, insulate, and accelerate the transmission of nerve impulses. It can also prevent ion leakage, thus maintaining the electrical potential of axons. Minor changes in myelin thickness could lead to substantial changes in conduction speed and hence can alter neural circuit function.

Myelin, produced by oligodendrocytes around axons, plays a crucial role in maintaining the health and function of white matter. Damage to myelin, such as its degradation in demyelinating diseases like multiple sclerosis, can lead to disrupted neural transmission. This degradation can result from mechanical injury, inflammatory diseases, or aging processes. Myelin vulnerability is recognized as a key factor in the decline of white matter function, and its destruction leads to a significant reduction in the transmission of neural signals [2-4]. The myelin disruption leads to a disturbance in the synchronized timing of neuronal impulses, which is crucial for brain functions. This results in a disconnect between cortical regions, leading to a loss of synchrony that affects more networks and worsens the devastating symptoms we currently refer to as Alzheimer's. Among these neurodegenerative disorders, Alzheimer’s disease has been found to have a significant impact on the destruction and loss of myelin, according to Chu et al. [5].

To assess the impact of Alzheimer's on the viscoelastic properties of the brain, a study was conducted on 28 individuals. This study included 7 individuals with a high probability of developing Alzheimer's, 14 healthy age- and gender-matched individuals without elevated amyloid levels, and 7 healthy individuals with abnormally high amyloid levels [3]. Magnetic Resonance Elastography (MRE) results showed that brain stiffness in individuals with Alzheimer's was significantly lower than in both control groups. These findings suggest that reduced brain stiffness may be associated with the progression of Alzheimer's disease, while abnormal amyloid accumulation alone does not affect brain stiffness.

MRE has been employed as a powerful tool for mapping the biomechanics of the brain, particularly in understanding stiffness changes caused by aging. The development of high-resolution MRE techniques, such as spiral pulse sequences and machine learning-based inversion methods, has enabled the study of specific brain regions such as white matter tracts. These advancements have

allowed MRE to evolve from reporting average brain stiffness to providing precise mechanical properties of different brain regions, which is especially useful in studying aging and neurodegenerative diseases [6-9].

Another challenge in understanding the link between the microstructure and mechanics of brain tissue is the exceptional heterogeneity resulting from differences in local functional demands within the brain. While we can clearly distinguish two tissue types at a macroscopic scale – the gray and white matter–the microstructure of the tissue varies significantly even within those regions. Therefore, understanding the impact of microstructural components on macroscopic mechanical behavior is essential for gaining further insight into the mechanisms of injury and disease in the human brain.

Previous studies indicate that brain *white matter* is particularly vulnerable to mechanical damage and structural changes. This vulnerability arises from the complex and heterogeneous structure of white matter, the presence of myelinated fibers, and the extracellular matrix (ECM). These factors, along with age-related changes and neurodegenerative diseases, make white matter a critical focus in the study of brain injuries. Research in the biomechanics of brain white matter has advanced significantly by developing accurate micromechanical models that incorporate histological information. These models have improved our understanding of the mechanical behavior of white matter, especially in response to various loading conditions and brain injuries. With the advancement of technologies such as MRE, these modeling efforts have been further enhanced, offering high-resolution insights into the mechanics of brain tissue.

Combining experimental data, histological information, and advanced modeling techniques is essential for a deeper understanding of the structure and function of brain white matter [10-13]. Addressing this issue could improve the potential of early in vivo diagnostics using modern

imaging techniques, such as MRE scans, combined with numerical simulations based on mechanical modeling. Additionally, mechanical models can aid in developing new treatment strategies and plan or detect the need for medical procedures. This temporally expanded model of brain development and its dynamic interaction with brain degeneration creates the possibility of testing its underlying hypotheses through prospective imaging studies focused on areas of active myelination, combined with neurocognitive evaluations and genetic studies targeting proteins and lipids involved in myelination.

In previous studies on micromechanical behavior of white brain tissue, only axonal fibers and ECM have been present. Our research takes a unique approach by utilizing the myelin sheath to assess its influence on the mechanical characteristics of axons and the overall behavior of brain tissue. This approach is supported by several studies such as those conducted by Berg et al. [7] and Budday et al. that have evaluated images from the brain tissue, suggests that in quasi-static loading, myelin can exhibit a positive correlation with tissue stiffness.

2. Materials and methods

2.1. Micromechanical model

The white matter region of the brain, e.g. the corpus callosum and corona radiata, contains anatomical features where long, myelinated axonal fibers are aligned unidirectionally and nearly parallel. Therefore, a three-dimensional transversely isotropic composite model can effectively demonstrate their mechanical properties. In composite materials, the model's representative volume element (RVE) is the smallest volume, and its response is similar to the entire system. This study chooses the corpus callosum (CC) and corona radiata (CR) of white matter as the regions of interest (ROI). Axonal fibers are then embedded in an RVE with a random distribution. The RVE has an optimal size of 5 μm that has shown consistent results [14, 15]. It should also be mentioned

that the model was designed based on a specific axonal volume fraction (AVF). The AVF for corpus callosum and corona radiata were set to $V_f = 0.39$ and $V_f = 0.4$, respectively, reflecting the average volume fraction observed in histological images of the tissue microstructure [7].

To evaluate the differences in the microstructure of different regions of white matter, we first assessed the corresponding response of axonal fibers and extracellular matrices under quasi-static loading. The findings aid in understanding the significance of fiber architecture on the localized responses of white matter substructures. The initial results of our model that solely included axonal fibers and ECM suggested that the presence of other microstructural features including myelin can be very impactful on the accurate prediction of white matter mechanical properties.

The embedded fibers are represented by straight cylinders with an inner radius R_i (axon radius) and an outer radius (myelin sheath radius), as depicted in Figure 1. The diameter of the axon was taken from a study that had found that fiber diameters in human brains range from 0.16 to 9 μm, and have a mean value of 0.6 μm with distributions of diameters being similar in the three systems of cortico-cortical fibers investigated [15].

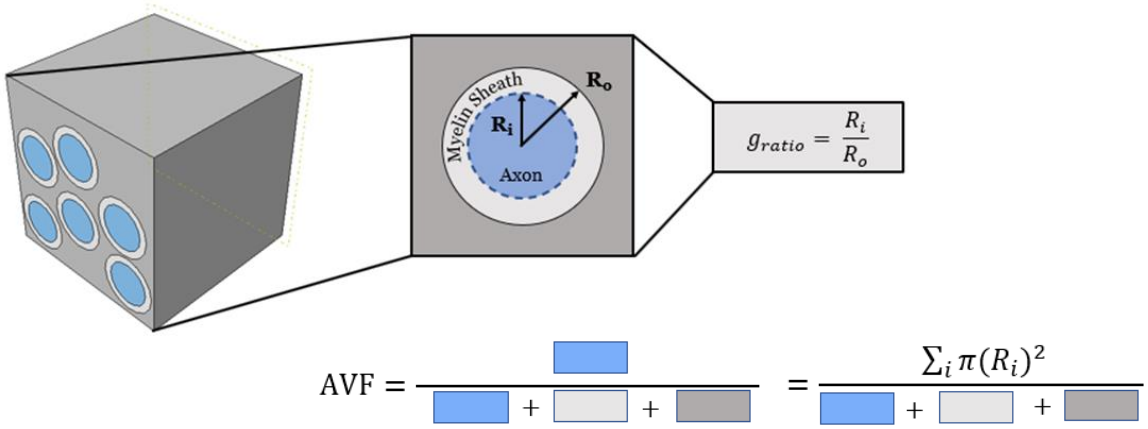

Figure 1: The white matter model. The embedded axonal fibers are represented as straight cylinders, and the g-ratio describes the geometric characteristics of the axons and the surrounding myelin sheath.

For each specific region of the white matter, the axonal volume fraction (AVF), which indicates the ratio of the axonal volume to the whole tissue volume, was utilized as the axonal content of the RVE:

$$AVF = \frac{\sum_1^N \pi {R_i}^2 a}{a^3} = \frac{\sum_1^N \pi {R_i}^2}{a^2} \quad (1)$$

AVF values of $AVF_{CC} = 33\%$ and $AVF_{CC} = 33\%$ for both regions were chosen from a recent paper by Berg et al. [7], where AVF values were determined based on diffusion-weighted MRI data and combined with MVFs to calculate g-ratio values.

The relationship between axon size and myelin thickness is captured in a parameter called the myelin g-ratio, defined as the ratio of the inner (axon) to the fiber's outer (axon plus myelin) diameter, which provides information on the degree of myelination of nerve fibers. Using MRI, the so-called "aggregate" g-ratio can be determined from the myelin volume fraction (MVF) and the axonal volume fraction (AVF) according to [16]. Here, the values of $g - ratio_{CC} =$

0.82 and $g - ratio_{CR} = 0.72$ were implemented in each model [**Error! Bookmark not defined.**].

In simulations of the corpus callosum and corona radiata models, the axonal volume fraction of CC is higher than that of CR, but a higher g-ratio (myelin thickness) has been reported for CR compared to CC. By considering these differences, we're able to characterize the brain properties in more detail.

In this investigation, we used histological data from a previous study to simulate the distribution of axonal diameters in the brain's anatomical structures. Specifically, we applied data from a study conducted by Liewald et al. [17], where the inner diameters of 762 myelinated axons in cadaveric human brain white matter samples were measured. This study provided continuous cumulative distribution functions (CDFs) for the axonal diameters, which we incorporated within a statistical framework to implement a randomized distribution pattern of axonal fibers in an RVE. This process involved placing axons one by one in the RVE without overlap or insertion while ensuring periodicity at the boundaries of the RVE. Our simulation focused on the corona radiata and the corpus callosum, and the resulting pattern exhibited axonal diameters ranging from 0.5 to 0.7 μm. This methodology enabled us to generate a histology-informed representation of axonal diameters in the brain's anatomical structures.

The axonal fibers were modeled using 4-node tetrahedron linear hybrid elements (C3D10H in ABAQUS 6.14), and the ECM were discretized using 8-node linear brick hybrid elements (C3D8RH), considering the incompressibility assumption. The symmetricity of the mesh on the opposite nodes of the models was maintained by applying face partitioning for the host and guest domains separately.

2.2. Periodic boundary condition and MPC

Periodic boundary conditions were applied as linear constraints in ABAQUS. By introducing the concept of a dummy node, many nodes were constrained using a set of algebraic equations to equalize the deformation on the opposite sides of the RVE:

$$u(x+L) = u(x) + \varepsilon^0 x \qquad \forall x \in B_\delta^2 \tag{2}$$

$$u(x+L) = u(x) \tag{3}$$

$$t(x+L) = -t(x) \qquad \forall x \in B_\delta^1 \tag{4}$$

Each face of the RVE was constrained to an arbitrary reference point as a boundary condition in a fixed direction. The displacement u was then applied to the corresponding arbitrary reference point. The linear homogeneous equation is as follows:

$$A_1 u_i^p + A_2 u_j^Q + \cdots + A_N u_k^R = 0 \tag{5}$$

where u is the strain or displacement value being applied to the model, R, Q, and P represent nodes, and i, j, and k denote the direction of freedom. Applying periodic boundary conditions on the boundary nodes of the RVE ensures the symmetry of stress contours and deformation of the parallel faces of the RVE model.

2.3. Material model

The brain is a viscoelastic material, and under large deformation, brain tissue has been reported to have incompressible hyperelastic behavior. The hyperelastic mechanical behavior of axonal fibers and ECM can be described using the Ogden strain energy material model [32].

$$W(\lambda_1, \lambda_2, \lambda_3) = \sum_{p=1}^{N} \frac{\mu_p}{\alpha_p}\left(\lambda_1^{\alpha_p} + \lambda_2^{\alpha_p} + \lambda_3^{\alpha_p} - 3\right) + \frac{1}{D}(J-1)^2 \quad (6)$$

where $\lambda_1, \lambda_2, \lambda_3$ are the principle stretches, μ represents the shear modulus, D is a material constant representing the bulk modulus, α is a material constant, and J is the determinant of the deformation gradient tensor. By assuming incompressibility, $J = 1$, and the material model for both axonal fibers and ECM can be rewritten as:

$$W_{myelin} = \frac{\mu_{myelin}}{\alpha_{myelin}}\left(\lambda_1^{\alpha_{myelin}} + \lambda_2^{\alpha_{myelin}} + \lambda_3^{\alpha_{myelin}} - 3\right) \quad (7)$$

$$W_{axon} = \frac{\mu_{axon}}{\alpha_{axon}}\left(\lambda_1^{\alpha_{axon}} + \lambda_2^{\alpha_{axon}} + \lambda_3^{\alpha_{axon}} - 3\right) \quad (8)$$

$$W_{ECM} = \frac{\mu_{ECM}}{\alpha_{ECM}}\left(\lambda_1^{\alpha_{ECM}} + \lambda_2^{\alpha_{ECM}} + \lambda_3^{\alpha_{ECM}} - 3\right) \quad (9)$$

respectively.

2.5. Optimization process/Material characterization

A multi-objective optimization process was used to determine the hyperelastic parameters of axons, myelin sheath, and extracellular matrix. The cost functions were defined as the differences between the experimental data and the tissue's responses. It has been demonstrated that selecting cost functions from different sets of experimental data, conducted for tension, compression, and simple shear, provides more accurate outputs for the hyperelastic material model.

Next, an optimization procedure was utilized to find the optimal hyperelastic material parameters that minimized the cost functions for all three loading cases. The flowchart of the optimization procedure is shown in Figure 2. If the cost function for all models was less than 0.2 and if the optimal parameter fell within the initially assumed range, the process was stopped. If not, a new

set of parameters was set, and the noted process was continued until the stop condition was met. To guarantee that the best possible solution was not influenced by the upper and lower bounds of the parameters or the initial values, a sensitivity analysis was carried out.

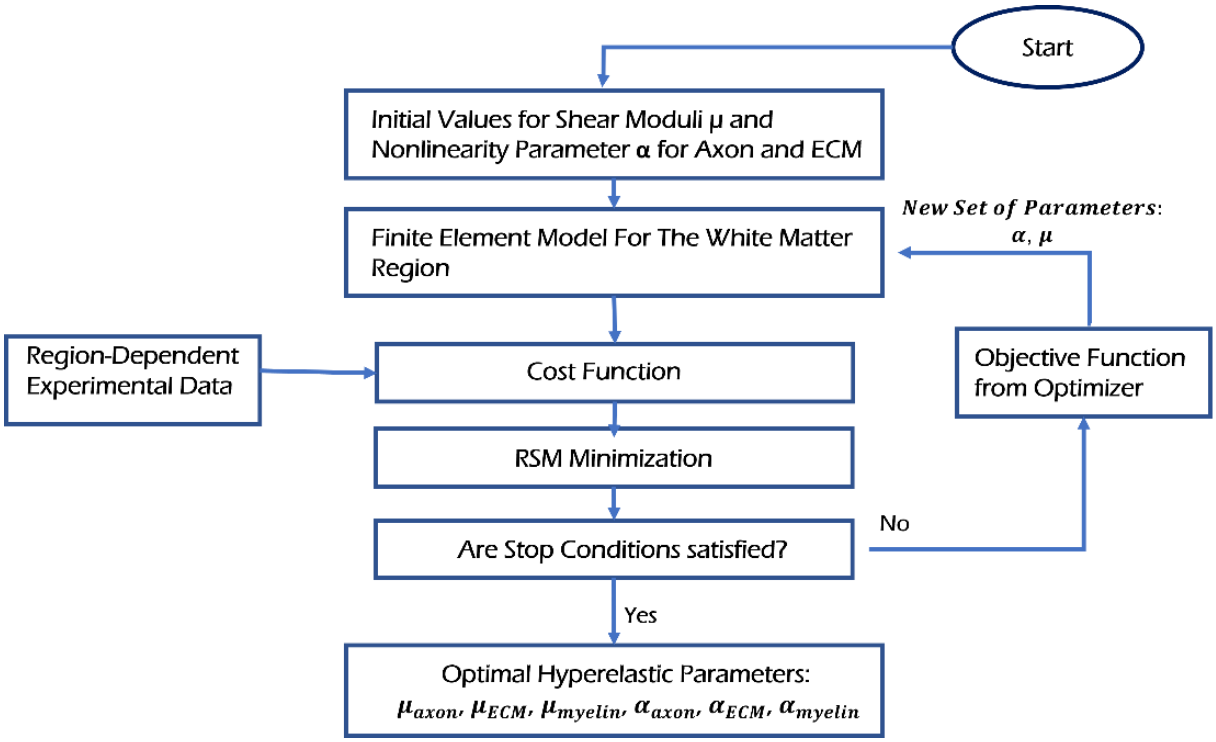

Figure 2 Flowchart of the optimization process for material parameter characterization.

3. Results

3.1. Axonal/ECM models

The derived parameters of the model consisting of axonal fibres and ECM only are listed in Table 1. Table 1 shows that the shear modulus of the axons from the two different regions is significantly different, but the shear modulus of the ECM has remained similar. This indicates that evaluating the axon's microstructure in more depth can help us increase our model's accuracy and create a constitutive model to analyze the significant microstructure difference of different regions of white matter and their impact on the tissues' stiffness.

Table 1: Region-specific material coefficient values for axonal fibers and ECM

Region of study	μ_{axon}	α_{axon}	μ_{ECM}	α_{ECM}
Corpus Callosum	0.593	-22.5	0.345	-23
Corona Radiata	0.963	-25.6	0.470	-24.4

3.2. Axonal/ECM/myelin models

The results of the axonal/ECM model (Table 1) showed that, in order to have a model capable of predicting the mechanical characteristics of the brain tissue in different regions, our focus must be on the axons characteristics, and hence we incorporated myelin layers in our next models. An RVE was created to evaluate brain tissue's mechanical properties based on experimental data reported in [18]. The optimization procedure for the representative volume element (RVE) models concluded after 150 iterations with a total runtime of 15 hours. The von Mises stress contour for the RVE model under compression, tension, and simple shear are shown in Figure 3.

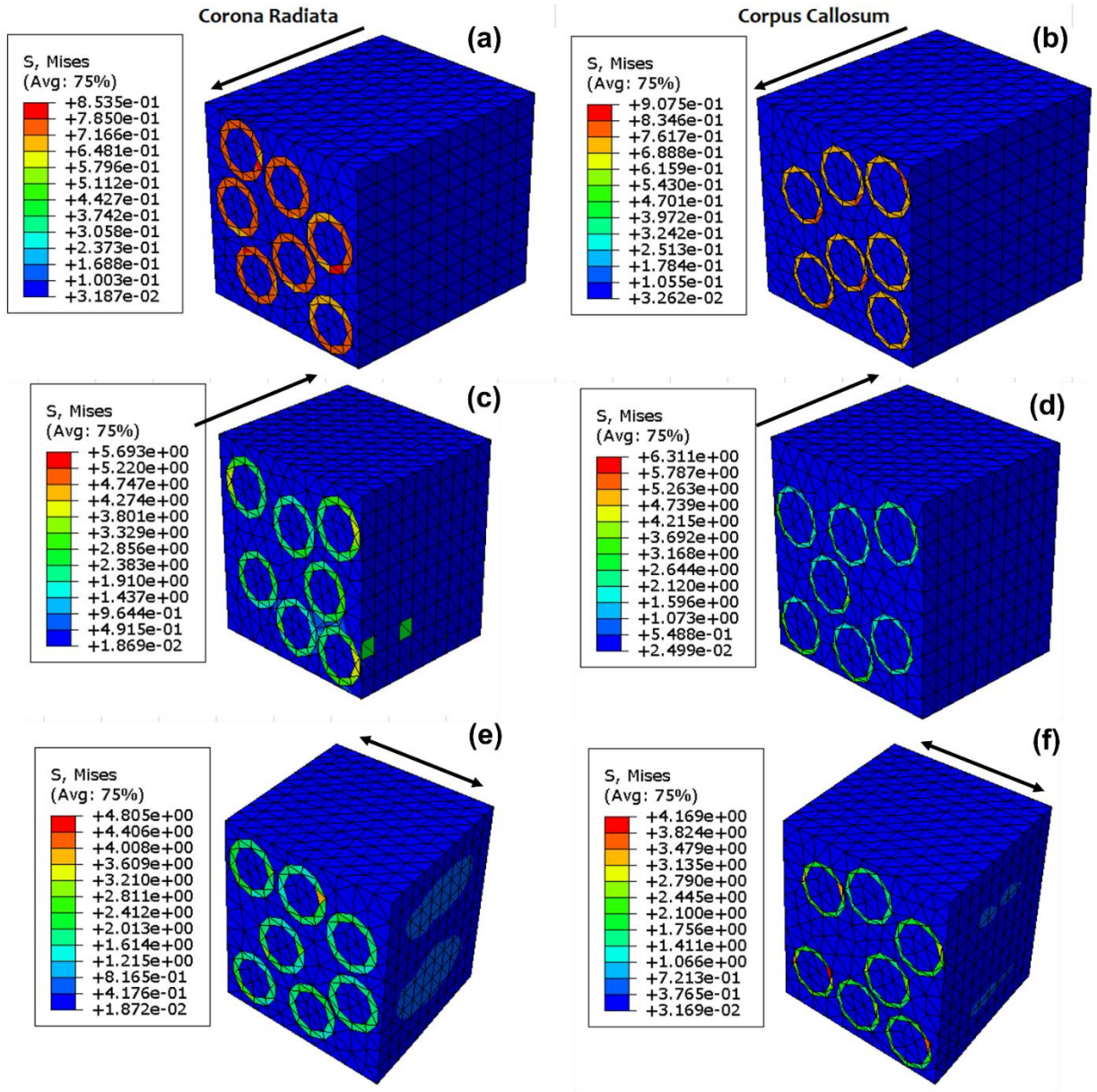

Figure 3 Von Mises stress contour of the RVE model for corona radiata under (a) tension, (c) compression, and (e) simple shear, and for corpus callosum under (b) tension, (d) compression, and (f) simple shear.

A one-term modified Ogden hyperelastic constitutive model can effectively predict the material properties of various regions of white matter under different loadings, such as tension, compression, and simple shear [18]. In our optimization process, to accurately determine the parameters μ_{axon}, α_{axon}, μ_{myelin}, α_{myelin}, μ_{ECM}, and α_{ECM}, we utilized Budday et al.'s three stress-

strain experimental curves [18] for the corpus callosum and corona radiata to predict the hyperelastic material properties.

Table 2: Optimized hyperelastic parameters for myelin sheath, axons, and ECM.

	μ_{myelin}	α_{myelin}	μ_{axon}	α_{axon}	μ_{ECM}	α_{ECM}
Hyperelastic Parameters	2.35 (kPa)	-36.5	0.139 (kPa)	3.54	0.147 (kPa)	-26.1

Table 3: Coefficient of determination for each region of white matter.

Region of Study	R^2 Tension	Compression	Shear
Corpus Callosum	0.997	0.999	0.999
Corona Radiata	0.998	0.995	0.989

Figure 4 demonstrates the optimized RVE model's performance for both the brain's CC and CR regions. The results show a strong agreement between the characterized RVE model and the experimental data, with a normalized root-mean-square deviation (NRMSD) of less than 1% (Table 1). The model can predict the response of brain tissue under tension, compression, and simple shear simultaneously, reasonably well for both white matter brain regions. The nominal stresses in the RVE are determined by dividing the total reaction force by the initial surface area. These values have been calibrated by minimizing the sum of the root mean squared difference in the stress-strain curve between experimental data and simulations from the RVE model. At each iteration, the optimization algorithm regenerates a new randomized position and selection of diameters within the boundary specified for axonal fibers. This ensures a uniform analysis, evaluating the different possible combinations.

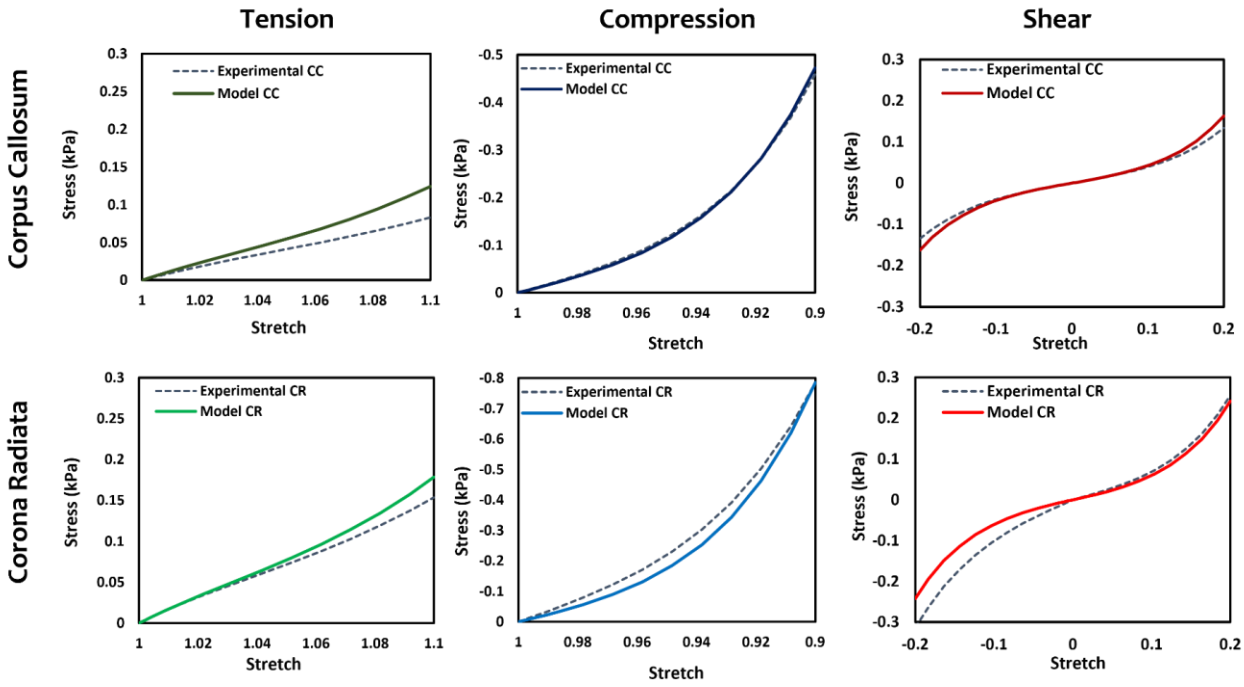

Figure 4 Cauchy stress versus principle stretch curves of brain white matter in corona radiata and corpus callosum under three loadings.

The optimal hyperelastic constants and those proposed by previous studies are presented in Table 4. Previous micromechanical models can predict the mechanical behavior of CC in multiaxial loading. However, they cannot predict tension-compression asymmetry due to their focus on only one or two loading modes of the bulk tissue for model calibration [19]. On the other hand, some models have been calibrated based on only one region of white matter [15]. It is crucial to calibrate models using multiple loading types and to examine the behavior of both the axonal fibers and ECM in different regions of white matter. These parameters may need to vary across different brain regions due to differences in microstructure, cell types, and the varying thickness of myelin sheaths around axons in different areas of white matter. The presence of myelin can significantly impact the stiffness of the axon and the overall stiffness of the region under study.

Table 4 Comparison of the hyperelastic parameters with the previous studies.

	Region of Study	μ_{myelin}	α_{myelin}	μ_{axon}	α_{axon}	μ_{ECM}	α_{ECM}
Present Study	Corpus Callosum Corona Radiata	2.35	-36.5	0.139	3.54	0.147	-26.1
Chavoshnejad et al. [15]	Corpus Callosum			0.722	-23	0. 110	-6
Yousefsani et al. [19]	Corpus Callosum			1.1303	4.91	0.0874	4.91
Hoursan (RVE) [20]	Corpus Callosum			1.062	4.89	0.08012	4.89
Hoursan (SVE) [20]	Corpus Callosum			0.738	4.49	0.0994	4.49
Meany [21]	Corpus Callosum			0.291	6.1	0.09694	6.1
Pan et al. [22]	Corpus Callosum			33.28	8.22	11.093	8.22

The observation of negative values for both α_{axon} and α_{ECM} highlights the brain tissue's asymmetric behavior during compression-tension tests. We understand that the parameter α needs to adopt a negative value to represent the effect that stresses are higher in compression than in tension. A positive value for α would yield the opposite trend, which is inappropriate for brain tissue [18]. Comparing the nonlinearity parameter for axon and ECM from Table 1 reveals a similarity consistent with recent tests using the isotropic first-order Ogden formulation. These tests have demonstrated that the material's shear modulus can vary along different shear testing directions. In contrast, the nonlinear behavior of the material (α) remains insensitive to the test direction for fiber-reinforced matrix, i.e. $\alpha_{axon} = \alpha_{ECM} = \alpha$ [21].

4. Discussions

4.1. Comparison with previous research

To understand the mechanism of axonal injury and myelin degeneration in white matter, it is essential to develop complex models of the tissue where the microstructure is precisely examined.

This could help us to model and understand how brain mechanics relate to the underlying microstructure in order to identify biomarkers for neurological diseases or injury. Conditions resulting from trauma or degeneration are frequently linked to the depletion of cellular elements, such as demyelination in Alzheimer's, Parkinson's disease, and Sclerosis [7, 23]. This study, for the first time, presents an RVE model of white matter structures that provides the random architecture of axonal tracts and their surrounding myelin sheaths within the extracellular matrix (ECM). Previous micromechanical models of white matter lacked such precise histological details; in the most detailed model to date [15], only changes in axon diameters were considered. Our more complex hyperelastic micromechanical model enables a more accurate investigation of the homogenized mechanical behavior of white matter structures under various loading types, such as tension, compression, and shear, and provides a more realistic representation of local stresses in different substructures of the tissue to study the effect of myelin on shear modulus and tissue stiffness at the microscopic level.

The optimal hyperelastic parameters and values suggested by previous studies are presented in Table 4. Previous micromechanical models were able to predict the mechanical behavior of the corpus callosum under multiaxial loading. However, they could not predict the tension-compression asymmetry, since they focused on only one or two loading states of the bulk tissue for model calibration [20]. On the other hand, some models have been calibrated based on only one region of the brain's white matter [15, 19, 20]. It is crucial not only to calibrate the models using various types of loading but also to examine the behavior of each element in different regions of the brain's white matter. These parameters may need to change in different brain regions due to differences in microstructure, cell types, and varying thicknesses of myelin sheaths around the

axons in different white matter areas. The presence of myelin can significantly impact axonal stiffness and the overall stiffness of the region under study.

The hyperelastic constants obtained in our study for axons, myelin, and the ECM differ significantly from the values proposed by previous studies (Table 4). The axon's shear modulus is considerably lower than those obtained in other research works. However, this discrepancy is not surprising, given the limitations in the previous studies. First, this difference could be due to the lack of accounting for the myelin sheath. Myelin plays a crucial role in the stiffness of white matter tissue. If it is modeled together with the axon, it overestimates the shear modulus for the axon compared to the actual value.

Many previous studies have described the material properties of axons and the ECM based on data from experiments conducted in a single direction, often the axonal direction, or just one or two types of tests [20, 21]. It has been noted that such characterizations yield unrealistic results due to the large number of parameters introducing redundancy into the problem [24, 25]. As concluded by Latorre et al. [24], hyperelastic material models for fiber-reinforced biomaterials, such as the human brain, should not be determined solely by tensile tests, and additional tests are also necessary.

4.2. Correlation between microstructure and mechanics

According to findings from magnetic resonance imaging (MRI), there is a slightly higher average amount of myelin in the corona radiata compared to the corpus callosum [7]. However, axonal volume fraction is higher in the corpus callosum [7]. Moreover, research using magnetic resonance elastography imaging and brain indentation experiments has indicated a positive correlation between myelin content and tissue stiffness in different white matter regions; higher myelin content is associated with increased stiffness. Our results reveal that the shear modulus of the axons

in the corona radiata is significantly higher than that in the corpus callosum, providing further evidence of the correlation between myelin content and increased stiffness (Table 1). It is important to note that this trend is specific to white matter specimens, as gray matter tissue does not contain myelinated axons.

The study by Budday et al. evaluated the microstructure elements and their effect on the mechanical behavior of brain tissue. Comparing different white matter regions revealed a positive correlation between myelin content and tissue stiffness. The study also suggests that the nonlinearity of the brain tissue response increases with increasing lipid content. Our findings strongly align with these observations. This is evident since the nonlinearity and shear modulus of the axon in CR were reported to be higher than CC (Table 1). Hence, the stiffness of corona radiata is higher than corpus callosum because of the higher myelin content.

4.3. Limitations

There are also several limitations in the current study that should be addressed more thoroughly in future research. First, we have only studied and modeled the myelinated axons and extracellular matrix because, for now, the only component that has shown a positive correlation with the shear modulus in quasi-static loading has been the myelin content [26]. However, this pattern only applies to white matter regions since grey matter does not contain myelinated axons, limiting our model's study to only this region. Second, the experimental data on mechanical testing and the distribution of axons in different regions of white matter have limited us to study and test our model with only two regions: the corpus callosum and corona radiata of the white matter.

Moreover, brain tissue demonstrates viscoelastic properties; however, the present study did not account for viscoelasticity since viscosity has a negligible impact on quasi-static loading conditions [26].

Another limitation of the current study is that the axonal structure in different regions has been considered somewhat uniform. In contrast, the microstructures of the white matter under study, specifically the corpus callosum and corona radiata, often exhibit periodic characteristics. Therefore, developing a more complex model could account for more significant heterogeneity in the arrangement of axonal fibers and better reveal the effects of this heterogeneity. Using fiber orientation distribution data from multi-layer and multi-directional MRI images might be beneficial to construct more precise micromechanical models of white matter structures. This would enable the investigation of axonal distribution and orientation effects at the microscopic level.

In some cases, altering the two parameters of AVF and myelin thickness caused our model to be unable to fit the axons into the designated space appropriately. Since axons were modeled as cylindrical, we could not achieve a FVF higher than 55%. If we can model the axonal cross-section as a free-form shape, a higher FVF could be achieved.

To develop more intricate micromechanical models of white matter structures, we can utilize advanced diffusion MRI data to depict axon orientation distribution. Additionally, microscopic resonance elastography imaging can provide valuable insights into the distribution of myelination and its impact on tissue stiffness. The extracellular matrix (ECM) can be viewed as a complex microstructure comprising glial cells and lipid tissue intertwined with capillaries. A more advanced model could consider the diversity of cells in greater depth.

4.4. Future perspectives

Advanced diffusion MRI data can be used to represent the orientation distribution of axons to develop more complex micromechanical models of white matter structures. Furthermore, the distribution of myelination and its effect on tissue stiffness can be better understood through the

use of microscopic resonance elastography imaging. The extracellular matrix (ECM) is an intricate microstructure containing glial cells and adipose tissue intertwined with capillaries. A more sophisticated model could encompass the variety of cells with more thoroughness. Moreover, models that include subcomponents such as microtubule bundle, neurofilaments network, and axolemma-actin can give a good insight in smaller scales. Beam theories for constant [27-29] and variable cross-sections [30] might then be implemented to analyze the mechanical response of the subcomponents.

5. Conclusion

To understand the complex mechanisms of axonal injury and myelin degeneration's effect on brain tissue stiffness, a sophisticated model of brain white matter is required to accurately represent the tissue's microscopic structure and simulate its mechanical behavior under various loading conditions. This research introduces a hyperelastic micromechanical model designed to comprehensively evaluate the mechanical characteristics of axons and the myelin sheath. The model was built on electron micrograph data and the probabilistic distribution of axonal fibers within the extracellular matrix (ECM), allowing for qualitative analysis of tensile, compressive, and shear stress distribution on nerve fibers using the finite element method. Additionally, the quantitative analysis of mechanical properties and stress thresholds on nerve fibers was made possible by placing this model in a multi-parameter optimization process. The results of this research are as follows:

- The hyperelastic micromechanical model aligned with experimental data and calculated the hyperelastic material properties of neural tissue components. The hyperelastic micromechanical model could predict local axonal strains, making it suitable for studying axonal mechanisms and pathology.

- This study provided far more accurate hyperelastic material properties for axonal fibers and ECM than previous studies. These properties were optimized for three loading conditions: compression, tension, and simple shear, and were calibrated based on two white matter regions. Therefore, the predicted values can be used to improve and update other modeling studies related to traumatic brain injury, deep brain stimulation, and neurodegenerative diseases.
- The hyperelastic material properties for the axon and myelin sheath were obtained separately. This helps investigate the effect of the myelin sheath in different white matter regions and assess its impact on the region's stiffness.
- Furthermore, if data on the shear modulus of neural tissue is available, this model can estimate the thickness of the myelin and the volume fraction of axons in the white matter, which represents an advancement in studying microscopic changes in axonal fibers of individuals with brain disease and injuries. Hence, this model can be used to detect certain neurological diseases, such as Alzheimer's and sclerosis, which represents an innovation in the field.

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