Tensile Behavior and Mechanical Anisotropy of Branched Cerebral Vasculature within Gray Matter

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ABSTRACT OF THE THESIS

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With increasing effort to prevent, diagnose, and treat traumatic brain injury (TBI), a large amount of research has been dedicated to the investigation of axon-containing white matter for the study of TBI onset and progression, as well as the elastographic techniques used for diagnoses. However, the mechanical response of gray matter with embedded vasculature has not been thoroughly studied. The cerebral vessels play a vital role not only in the mechanical stiffening of the structure of the brain but also in supplying it with the oxygen and nutrients. By incorporating a multiscale approach to the finite element (FE) models, it is possible to determine the transfer of loads from macroscale to microscale and study the progression of traumatic injury in the brain. In the present thesis, an FE representative volume element (RVE) model of the gray matter is developed that incorporates a branching tree structure composed of arteries. Both the gray matter and the vasculature are represented with hyperelastic material models aiming at capturing the complex response of the biological materials under large strains. The RVE model of the composite material results in anisotropy stemming from not only the different material properties, but also attributed to the complex microstructure. Tensile stretches are applied to illustrate the stiffening effect of the vasculature as well as to determine the anisotropic material properties. The response of the whole volume is monitored under various external loadings. In this thesis, a general Fung-type constitutive model is adopted, which is one of the most widely used types of anisotropic material to describe the response behavior of the composites. By implementing a scriptable geometry generation routine, different vasculature geometries are investigated to elucidate the effect of the vascular geometry on the response of the gray matter RVE. By integrating an accurate geometry of the underlying vasculature, and the micromechanical response of the composite material consisting of the gray matter and the vasculature, the study of potential mechanisms of injury and the development of a micro architecture based RVE used in TBI multiscale simulations becomes feasible.

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Dedications

To my mom and dad, Mrs. Ping Xu and Mr. Zhao Xing.

Contents

Chapter 1
Introduction

1.1 Background and Motivation

1.1.1 Traumatic Brain Injury

Traumatic brain injury (TBI) attracts attention throughout the world. As revealed from demographic studies, TBI is among one of most deadly diseases threatening human life. According to Centers for Disease Control and Prevention (CDC) [1], "An estimated 1.7 million people sustain a TBI annually, among who 52,000 die, 275,000 are hospitalized, and 1.365 million, nearly 80%, are treated and released from an emergency department. Also, TBI is a contributing factor to a third (30.5%) of all injury-related deaths in the United States." Understanding the fundamental damage mechanism and developing viable methods for prevention is the ultimate goal for researchers in biomechanics and biomedical engineering. Although there is a long way to go, there have been major advances in the field. For instance, axonal injury in white matter, which is considered to be a primary cause for dysfunction following TBI, has been explored in different approaches [2]–[5]. However, gray matter with vasculature has been explored much less [6], [7]. The cerebral vasculature plays a vital role in supplying oxygen and nutrients to various brain cells. The percentage of cerebral oxygen consumption in white matter is 6%

while the percentage of cerebral oxygen consumption in gray matter is up to 94%. Few studies have focused on investigating the concussion mechanisms in gray matter with vasculature [3]. To this end, mechanical responses of quasi-static processes occurring during brain trauma should be thoroughly investigated in order to develop diagnostic and predictive tools applicable to neuropathology and neurosurgery [2] as well as in designing protective equipment for military and recreational purposes.

1.1.2 Motivation

While TBI attracts attention world-wide and countless studies have been dedicated to explore its injury mechanism, efforts for investigating cerebral vasculature embedded in gray matter is insufficient. Most of these studies focus on the mechanical response of a composite material model consisting of cerebral vasculature and gray matter under dynamic impact. The present study is aiming to fill the gaps by simulating the stretch stress-strain behavior of the composite material model for quasi-static loading. Accurate material characterization will result in improved diagnostic tools and predictive techniques, so it is important that the material properties are determined appropriately for the simulation.

1.2 Research Goal

1.2.1 Representative Volume Element Model

One of the assumptions made in this study is the composite brain structure can be homogenized, thus considering it as homogeneous medium with properties reflecting those of its composite structure. This guarantees that the macroscale model can be repeatedly divided into infinitesimal elements. This pseudo-homogeneous effect allows the micromechanics to be reliable at a multiscale level. A representative volume element (RVE) model is incorporated, which contains the properties of the composite material dictated by its microstructure.

The purpose of an RVE model is that its effective properties can represent the composite material as a whole. In the present study, the RVE model contains the essentials of the composite microstructure so that a reliable response of the whole material can be acquired through the response of RVEs subjected to traction or loadings [3].

Owing to the limited number of samples and technical challenges, experiments in *vivo* or even in *vitro* are difficult to perform. An alternative way is set up an RVE model. Furnished with accurate material properties, an RVE model can predict the results effectively and efficiently. The simulation accuracy largely depends on the accurate material characterization and realistic depiction of the tissue microstructure.

Building the structure of the human brain used to be regarded as unachievable due to the technical difficulties associated with introducing an arterial tree into a 3-D mesh [6]. However, in the last decade, significant achievements have taken place in computational biomechanics and biomedical studies. Investigations in the mechanical response and axial mechanical properties of human cerebral blood vessels have been conducted [11], [12], exploration of the tortuosity of intracerebral vasculature [13], [14] have been performed and different material properties between gray and white matters have been determined [15]. In the present thesis, an RVE model is combined with FE analysis. The RVE model is generated at the microscale. Similar to how axons are investigated individually in white matter, cerebral vessels are also analyzed individually in gray matter. By employing RVEs, it is possible to generate the geometrically branched cerebral vasculature and incorporate the vessels in a extracellular matrix.

1.2.2 Anisotropic Constitutive Equations

Most biomedical soft tissues display both high degrees anisotropic and nonlinear elastic behavior. General hyperelastic material models can encompass the nonlinear elastic behavior with large strain but are not able to deal with anisotropy.

To date, there are two dominant constitutive equations for hyperelastic anisotropic incompressible material: the generalized Fung-type constitutive model (including fully anisotropic and orthotropic cases) and the model proposed by Holzapfel, Gasser, and Ogden for arterial walls. The distinction between the two anisotropic models is that Fung-type constitutive model is purely phenomenological, while the Holzapfel- Gasser-Ogden model is micromechanically based. In the present study, the Fung-type constitutive model is more suitable for the simulations.

1.3 Review of Relevant Previous Work

Models used in the earlier simulations were treated as isotropic for simplicity. However, since vasculature is slim and oriented soft tubes, vessels could approximately determine the properties of local gray matter. Even though several studies were conducted into vasculature and gray matter, almost all of them studied the brain at a macroscopic level and focused on dynamic loading [6], [7].

Dynamic studies such as Omori *et al.* (2000) [12] treated each component as a viscoelastic material. Finite element models were built as half-circular plates representing a parasagittal section. The section included the skull, dura, cerebrospinal fluid, pia mater and brain tissue. The model was loaded with rotational impulses, simulating dynamic response of brain tissue. In the study of Zhang *et, al* (2002) [6], only 2-D slice models were generated including the skull, dura mater, cerebral spinal fluid, ventricles, brain and pia mater. The two models differed in whether or not they contained the vessels so that the effect of vasculature could be predicted. The vessels were regarded as a linear elastic material, while the neuronal and bony components were regarded as a linear viscoelastic material. The loads were applied in the form of a rotational impulse. Another more complicated study was conducted with more updated information [7], where the neuronal components and the vasculature were treated as a viscoelastic material by using the uniaxial exponential model suggested by Fung [17]. In that study, a 3-D finite element head model was used for simulation. Both rotational and translational accelerations were applied. Even though these studies were focused on the vasculature's effect on the brain's mechanical response and considered elastic or viscoelastic material properties, today, it is widely accepted that the brain tissue is more accurately represented by hyperelastic materials models with regional anisotropy.

In order to analyze different material models, Meaney (2003) [12] applied the structural modeling and hyperelastic material behavior to white matter containing axons. This study explained the hyperelastic formulations and compared the results using the Mooney-Rivlin formulation, the generalized Ogden, and the Fung-type model to conclude that the generalized Ogden and the Fung-type material models are more reasonable.

Chapter 2
Representative Volume Element Generation

2.1 Material Properties

Most studies have demonstrated that living tissues, especially tissues in central nervous system, are generally found to be non-linear, hyperelastic and nearly incompressible materials [9]. The constitutive behavior of a hyperelastic material is defined by a total stress-strain relationship. On the other hand, hyperelastic materials are in general almost incompressible and so is the characteristic of most brain tissues.

Previous studies generally only contain linear elastic elements for simplicity, which may lose accuracy in fully demonstrating material behavior [6]. Hyperelastic materials are defined by a unique expression of the potential strain energy [18]. They exhibit high deformability and nonlinearity when subjected to loads or displacements [19]. Darijani *et al.* (2010) [15] points out that the energy formulas are expressed in terms of polynomial, power law or logarithmic expressions. The key to obtaining the appropriate model for the brain tissues involves properly determining the energy model type and accurately determined the material parameters for the particular region of investigation.

In this study, simulations will focus on the component material properties of the composite gray matter in the brain, the arteries or veins and the surrounding neuronal tissue matrix of gray matter which consists of neurons, neuropil, glial cells, etc.

2.1.1 Material Model for Neuronal Matrix

For gray matter, several types of constitutive models based on strain energy formulas including Arruda-Boyce, Ogden, Yeoh and polynomial strain energy potentials have been obtained [13]. According to Kaster *et al.*(2011) [9] , the Yeoh model and the polynomial model suffer less mean errors since they contain more parameters and require less mean number of iterations. Together with the fact that polynomial model was unstable when applied with the data from [5], in this study, the Yeoh model [16] was chosen for its best fit.

The typical Yeoh formula is:

$$U = \sum_{i=1}^{3} C_{i0} (\overline{I_1} - 3)^i \qquad (1)$$

The three necessary parameters for C_{10}, C_{20}, C_{30} are 185 Pa, 601 Pa, 0.01 Pa for gray matter, respectively, where $\overline{I_1}$ is the first strain invariant. Particularly, C_{10} represents the initial shear modulus, which softens at moderate strains due to the effect of the second coefficient C_{20} and is followed by an upturn at large strains due to the positive third coefficient C_{30}. Therefore, the Yeoh model often provides an accurate fit over a large strain range. Young's modulus is also calculated for gray matter, which is 1195 ± 157 Pa [13].

The uniaxial stress-stretch curve of gray matter is plotted in Fig. 1.

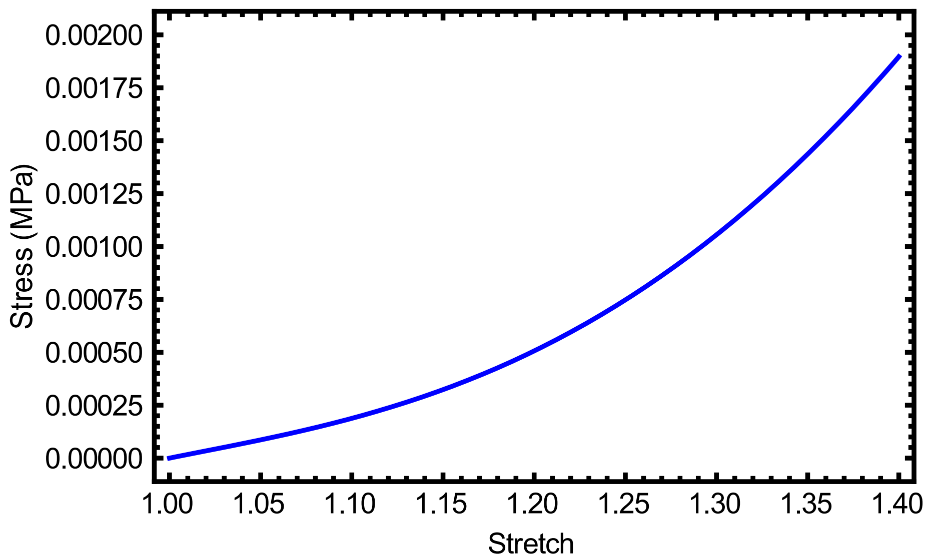

Fig. 1 Tensile behavior of gray matter

In order to better explain the results of the simulations, the slope of the stress–strain curve and the tangent modulus are also determined and plotted.

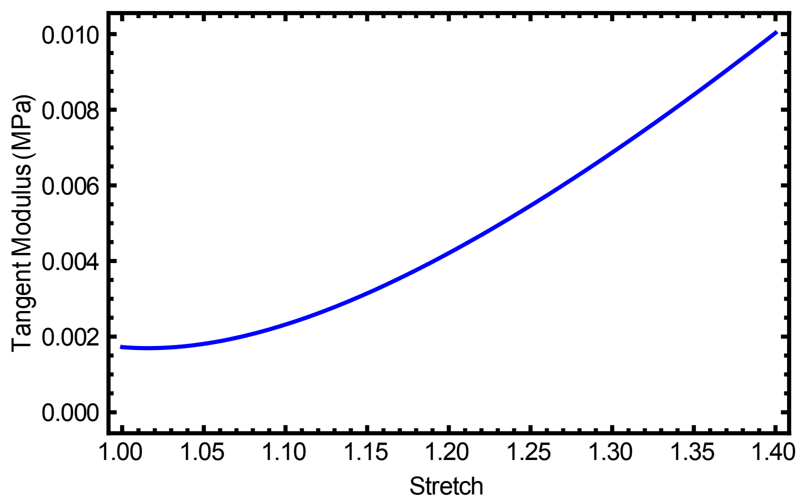

Fig. 2 Tangent modulus with stretch of gray matter

2.1.2. Material Models for Vasculature

Experiments conducted by Monson *et al.* (2003) [6] provide material data cerebral blood vessels with different conditions including different sources and sizes, undergoing quasi-static and dynamic loading [12], [21]. The results from the quasi-static experiments are selected for the current study. Our study aims to provide a microscale approach to simulate the mechanical influence from cerebral vessels in the gray matter under large strain. Whether the soft tissues in the brain should be modeled as a fluid or as solid model has been a controversial discussion over the last two decades. According to Donnelly *et al.* (1997) [15], brain tissues return back to its original shape after deformation, which supports the claim that brain tissue is better treated as solid. For simplicity, all cerebral vasculature are modeled as solid elements because fluid effects in the vessels are not of interest in the present study.

In the reported literature [11], intracranial arteries, cortical veins as well as extra cranial vessels have all demonstrated varying responses. As such, it is necessary to use different material properties for arteries and veins. In previous simulations, vasculature was either treated as linearly elastic or fitted to the uniaxial exponential model proposed by Fung (1980) as non-linear elastic [13], while here it is assumed that intracranial vessels behave as hyperelastic materials. Experiments conducted on brain vessels by Monson *et al.* (2003, 2005) [11], [12] in which tensile stretch test results were reported.

Cerebral vasculature, as with other brain tissues, have the characteristics of non-linear, hyperelastic and nearly incompressible. Therefore, the next critical issue is to determine the appropriate hyperelastic material model for the vessels, including Ogden, Yeoh, polynomial, reduced polynomial and other formulations to choose from. The material models must satisfy two conditions. The first condition is that the model accurately represents the results obtained by Monson, or that the stress-strain curve of the chosen material model should closely match the curve in Monson's experimental data. The second condition is that the constitutive model should satisfy the Drucker stability postulates, which will be discussed later.

This study currently uses Abaqus 6.14 to conduct simulations. Generally, for a certain hyperelastic material model available in Abaqus, Abaqus can automatically determine appropriate values of the coefficients using linear or nonlinear least-square fitting with provided experimental test data. However, the quality of behavior of hyperelastic material must be evaluated. Whether the strain energy potentials determined by Abaqus are acceptable or not, depends on the correlation between the Abaqus predictions and the experimental data.

To fully explain the procedure, stress-stretch curves of 1st-order polynomial (Mooney-rivlin), 5th-order Reduced-polynomial, 1st-order reduced-polynomial, 3rd-order reduced-polynomial (Yeoh), 1st-order Ogden and 3rd-order Ogden for arteries and veins are plotted as follows by Abaqus:

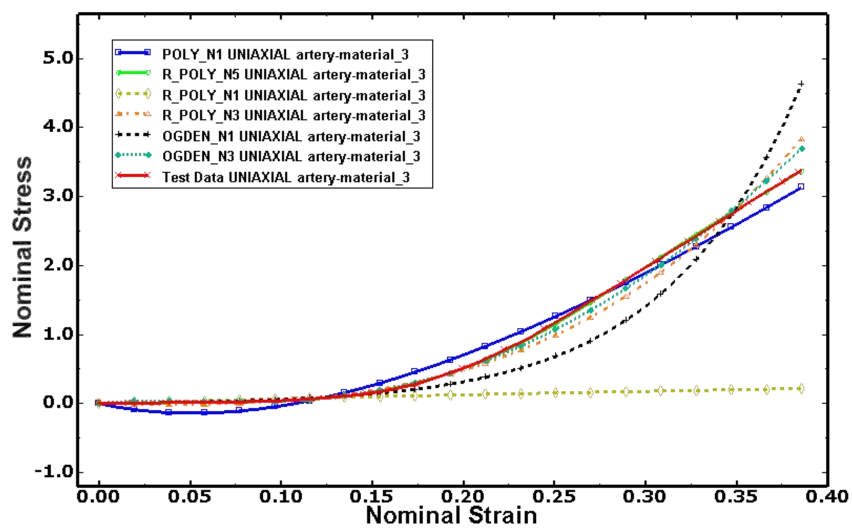

Fig. 3 Hyperelastic material plots for fitting the experimental data of arteries.

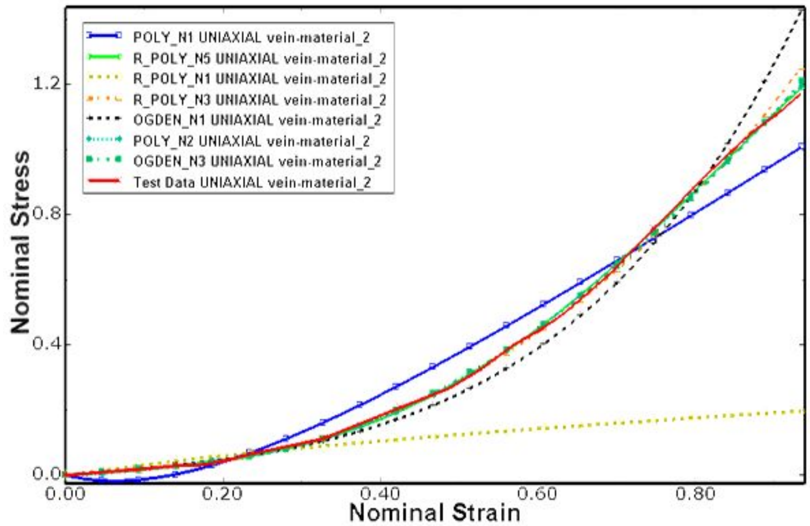

Fig. 4 Different hyperelastic material plots for fitting the experimental data of veins.

For the second material model condition, the Drucker stability postulate is a set of mathematical criteria that restrict the possible nonlinear stress-strain relations that can be satisfied by a solid material [19]. A material that does not satisfy these criteria is often found to be unstable so that the application of a load to a material point can lead to arbitrary deformations. Specifically, the Drucker stability postulate requires that the change in the Kirchhoff stress $d\tau$ following from an infinitesimal change in the logarithmic strain $d\varepsilon$ satisfies the inequality:

$$d\tau : d\varepsilon > 0 \tag{2}$$

With the incompressibility assumption, the Kirchhoff stress is equal to the Cauchy stress:

$$\tau = \sigma \tag{3}$$

Thus:

$$d\sigma : d\varepsilon > 0 \tag{4}$$

Among those satisfying Drucker stability postulate, it is easy to see that the fifth-order reduced-polynomial model best fits the experimental curve for arteries while the third-order Yeoh model exhibits a better fit for veins as illustrated in Fig. 3 and Fig. 4.

The fifth-order reduced-polynomial model is expressed as:

$$U = \sum_{i=1}^{5} C_{i0}(\overline{I_1} - 3)^i \tag{5}$$

where C_{10}, C_{20}, C_{30}, C_{40}, C_{50} are 0.05587 MPa, -0.744 MPa, 26.042 MPa, -65.850 MPa and 54.558 MPa, respectively.

The third-order Yeoh formula is

$$U = \sum_{i=1}^{3} C_{i0}(\overline{I_1} - 3)^i \tag{6}$$

where C_{10}, C_{20}, C_{30} are 26.2 kPa, 93.665 kPa and 1.8157 MPa, respectively.

Figures 5 and 6 depict the selected material models and the relevant experimental data.

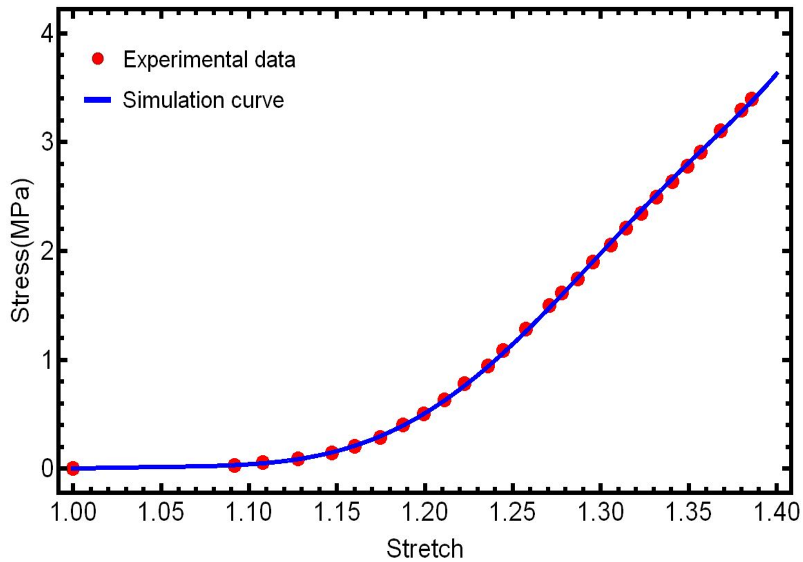

Fig. 5 Comparison of stretch-stress curves of experimental data and simulation curve obtained from the artery model.

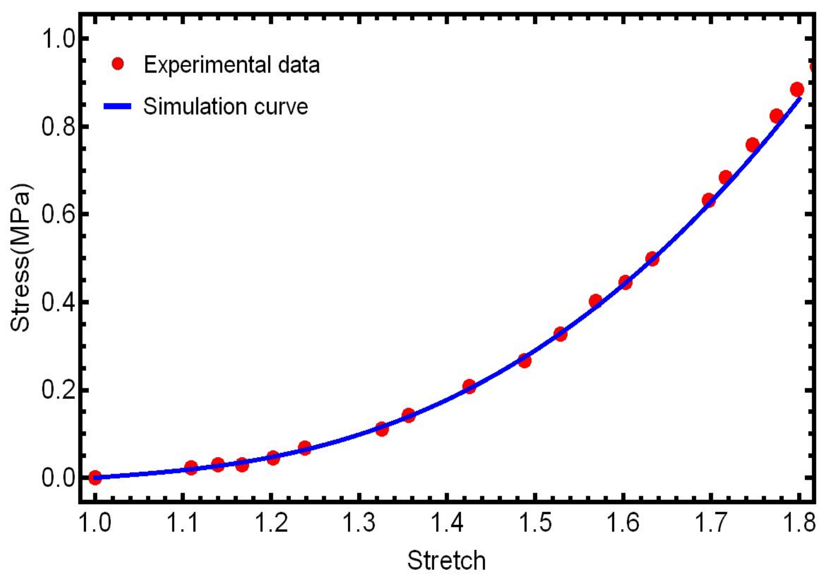

Fig. 6 Comparison of stretch-stress curves of experimental data and simulation curve obtained from the vein model.

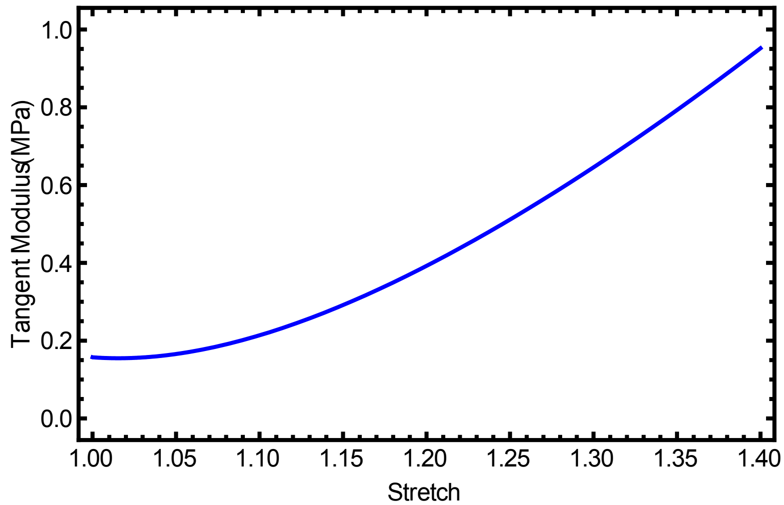

Fig. 7 Tangent modulus of veins.

2.3 Modeling Issues

2.3.1 Finite Element Model of Arteries

Considering the inherent difficulties in incorporating a realistic 3-D model of the cerebral vessel branches into a whole head model, a microscale representative model is generated to obtain the specific the local response in the brain.

Vessels' microstructure and composition have been introduced and analyzed in detail by M. Zamir [24] – [26]. Zamir [24] provides adequate practical details including angle branching, lengths and diameters so that it is easy to construct the vasculature with the help of this data. The length and diameter ratios and the angle between the main and the next two bifurcated vessels are determined by the parameter α. α is the diameter ratio of the branched vessels as seen in Fig. 8. Owing to the inherent variability within biological tissues, α has a range of [0, 1]. When α equals 1, the two bifurcated vessels are totally symmetric. The smaller the α, the larger the difference between the two vessels. The branched model used in this study is kept constant at a value of $\alpha = 0.8$.

The α is defined as

$$\alpha = \frac{d_2}{d_1} \tag{7}$$

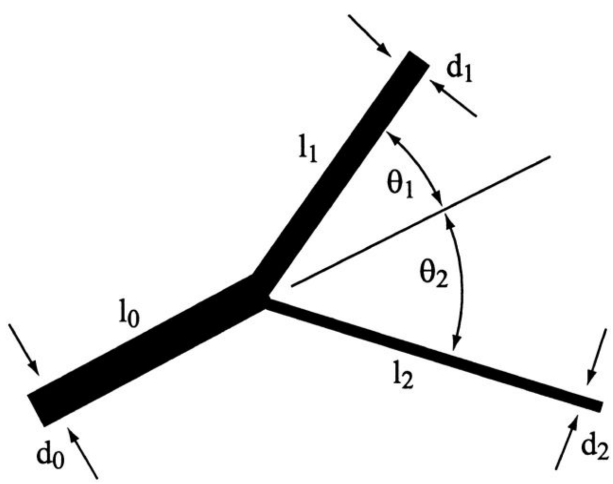

Fig. 8 The basic variables at an arterial bifurcation. The lengths and diameters of three vessel segments are denoted.

The vasculature branches with α equal to 1, 0.8, 0.6, 0.4, 0.2 are generated and displayed in Fig. 9:

Fig. 9 Basic vessels generated with α equals 1, 0.8, 0.6, 0.4, and 0.2, respectively.

The formulas are cited here for reference:

$$\lambda_1 = \frac{d_1}{d_0} = \frac{l_1}{l_1} = \frac{1}{(1+\alpha^3)^{1/3}} \tag{8}$$

$$\lambda_2 = \frac{d_2}{d_0} = \frac{l_2}{l_1} = \frac{\alpha}{(1+\alpha^3)^{1/3}} \tag{9}$$

$$\cos\theta_1 = \frac{(1+\alpha^3)^{4/3} + 1 - \alpha^4}{2(1+\alpha^3)^{2/3}} \tag{10}$$

$$\cos\theta_2 = \frac{(1+\alpha^3)^{4/3} + \alpha^4 - 1}{2\alpha^2(1+\alpha^3)^{2/3}} \tag{11}$$

Where subscript 0 represents the parent vessel and subscripts 1, 2 indicate the two children vessels; *d* is used for diameter and *l* for vessels' lengths.

As is noticed, among a unit vessel branch, θ_1, θ_2 are calculated and applied in the plane B where bifurcated vessels lie in [24] , while the main vessel lies in another plane, Plane A. The angle between planes A and B is δ [25]. In most cases, δ is less than 10 degrees.

Fig. 10 Angle δ between the plane with main vessel and the other plane with bifurcated vessels.

VESSEL TYPE	DIAMETER (mm)
Large Arteries	1.0 - 4.0
Small Arteries	0.2 - 1.0
Arterioles	0.01 - 0.20
Venules	0.01 - 0.20
Small Veins	0.2 - 1.0
Large Veins	1.0 - 5.0

The average diameter range for small arteries is 0.01-0.20 mm [27]. Here we set the parent vessel's diameter to be 0.09 mm and length to be 1.8 mm. As presented in Fig. 9, with α changing from 1 to 0.2, five different microstructures are built in order to parametrically investigate the effect of vessel branching.

Figure 10 illustrates the different views of a vessel branch and the associated planes and angles.

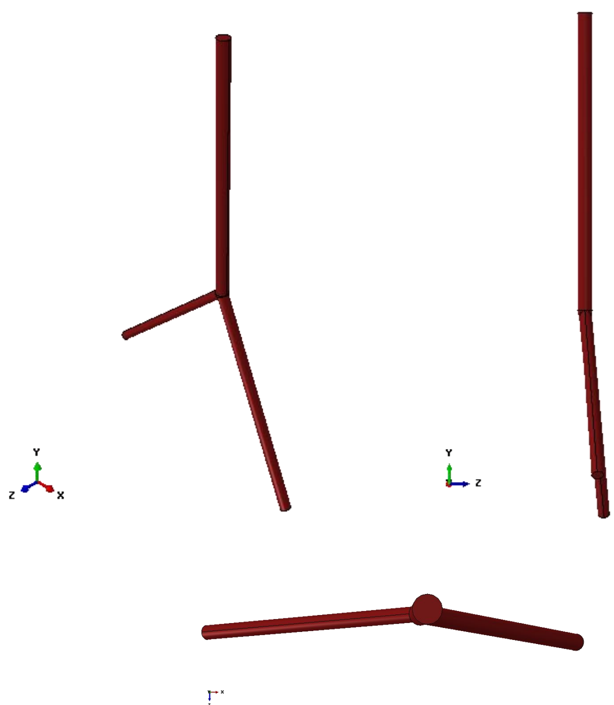

Fig. 11 3D views of vasculature branch.

The current study is a proof of concept that is expected to be furthered in the future with a more advanced numerical model which can be generated using Lindemayer system [24], a parallel rewriting system and a type of formal grammar that can be used to make strings, a collection of production rules, since arteries have recursive nature and lead to self-similarity.

This branched model has vessels with diameters ranging from 13.2 μm to 100 μm [28], containing almost all the possible vessel diameters that can be used to represent real vessels. Furthermore, it is noticed that blood vasculature segment length ranges from 32.206 μm to 51.207 μm [14]. For simplicity, all vessel segments are taken as straight slim cylinders in the current study. Tortuosity of vessels is required to calculate real distances between any two different branch points. The mean value for tortuosity is 1.2 [14], [29]. As a result, the range of vessel segment length used here is from 26.838 μm to 46.673 μm. In order to investigate random vasculature geometries, an elaborate scriptable geometry generation routine is implemented. Moreover, the vasculature geometries also benefit by elucidating the effect of the vascular geometry on the response of the gray matter. The generation routine is written in Python which can be interpreted directly by ABAQUS. The model branch is duplicated in order to fit in the positions of both arteries and veins.

An advanced complex model is also built and demonstrated here.

Fig. 12 A advanced numerical model for arteries using Abaqus.

2.3.2 Numerical Model of Surrounding Matrix

In order to make the RVE as small as possible to represent a homogeneous material and reduce computational demands, and to completely contain a vessel branch in it, the maximum and minimum of coordinate points of the vessel branch were searched by Python code and adopted as sizes of the matrix. We created a cuboid (x = 1717.73 μm, y = 3201.65 μm, z = 209.72 μm) to represent the surrounding matrix of gray matter. Therefore, the size of the cuboid is purposely limited while sufficient to include a cerebral vasculature branch.

2.4 Assembly Issues

A significant problem in simulations of brain tissue is the boundary between two different components. Pan *et al.* [30], [3] made efforts to discover how axons tie to white matter matrix and pointed out a method that could be advantageous to the current study. Since the current study is a proof of concept, our focus is on the mechanical response and intends to provide information about vasculature stiffening in brain tissues. For simpilicity, we assume that the vasculature is directly and completely embedded in the surrounding gray matter. Another assumption made here is that all vessels are fully tied to the surrounding matrix. Further studies towards the interactions are scheduled to be conducted in future work.

As for the most representative and basic case, one neuronal matrix only contains one basis vessel branch. Since vessels are highly directional, they are placed parallel to an edge of the matrix cuboid.

As stated above, the surrounding matrix is purposely built small which on the other hand, gives rise to meet another requirement of volume fraction of vasculature. Generally, the volume fraction of vasculature ranges from 1% to 4%. In RVE, here the volume fraction of vasculature in the neuronal matrix is 1.9%.

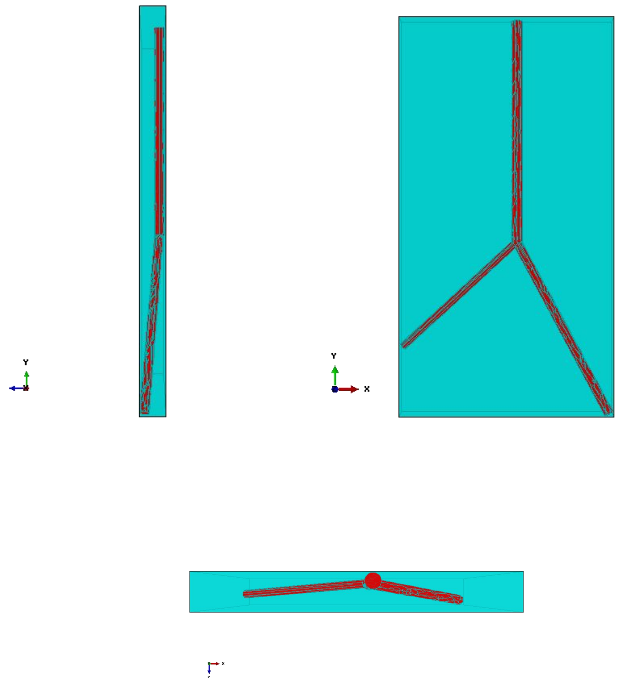

Fig. 13 Finite element model demonstrates the placement of vasculature in the matrix.

2.5 The Finite Element Mesh of the Model

Even though a realistic 3-D model of brain vasculature within gray matter is built in the study, due to the wide range of diameters of vessels and technical complexity associated with the architecture of the branches of the vessels, it is computationally expensive to mesh the model. Moreover, the fewer elements in the model, the faster the FEA calculation. However, the larger size of elements might harm the accuracy of calculations. For instance, if a meshed element is larger than the diameter of a vessel, simulation results would be very inaccurate. Therefore, vasculature are separated by size and proper element seeds applied with sizes as large as possible.

The hexahedral element shape is a recommended and generally used element in FEA. In order to overcome the inherent complexity in the vasculature, in the current study, both components are meshed with tetrahedrons, which are also widely used elements.

The model is meshed in ABAQUS and the RVE has a total of 47842 elements with 23385 nodes using linear tetrahedral elements of type C3D4H as shown in Fig. 14.

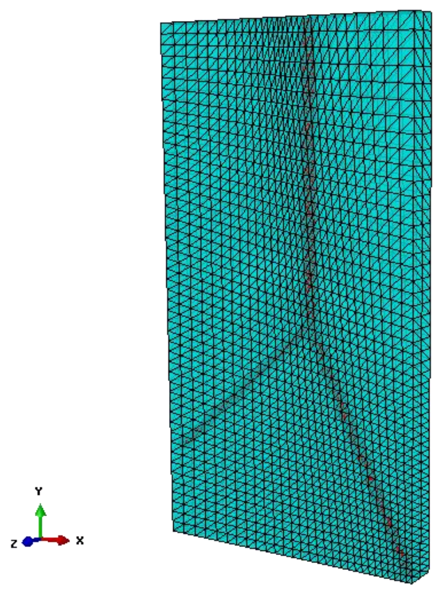

Fig. 14 The vasculature branch embedded within gray matter after meshing.

Chapter 3
Numerical Simulations of Composite Model

3.1 Methods

In continuum mechanics, the large strain theory, or large deformation theory focuses on deformations in which both rotations and strains are arbitrarily large, which invalidates the assumptions inherent in general infinitesimal strain theories. This is generally the case with elastomers, plastically-deforming materials, and other fluids and biological soft tissues [29]–[31].

It is a common practice to use the quasi-static tensile tests to determine material properties. In *vitro* experiments generally glue the specimens at the boundaries (brain/platen interface) for testing brain tissue because of its fragile and tacky nature as an alternative to clamping. In this thesis, the model is fixed $U_x = U_y = U_z = 0$ on x=0, y=0 and z=0 plane in the simulations of x, y, and z direction, respectively.

This thesis conducts typical stretch simulations on biological soft tissue. Compared with infinitesimal strain theory, strains applied are significantly larger. Kaster *et al.* (2011) [8] indicates that for FE analysis, the maximum principle strain can reach as much as 70% in the region so as to be sufficient for probing the tissues' properties. In the measurement of hyperelastic properties of brain tissue, the strain was set to be 50% [9].

In another material property determination applied to CNS white matter, the strain is as much as 50%. Given biological diversity between white matter and gray matter together with the material properties of vasculature, and the experimental data of arteries from Monson for stretch ratio up to 1.42, in this thesis, the whole composite model is stretched with stretch ratio to be 1.4 in x, y and z directions on the opposite face of fixed boundaries planes respectively.

The simulations here work twofold. Firstly, the primary goal is to give a prediction about the stiffening effect of cerebral vasculature on gray matter. In the mean time, the simulation results collected from these simulations could serve as a set of input for calculating parameters in Fung-type strain energy function.

3.2 Results

The von Mises stress contours of the composite model subjected to a stretch ratio of 1.4 in x, y and z direction are shown in Fig. 15, Fig. 16, Fig. 17, respectively. The contours illustrate that the stress is highly localized around the vasculature branch.

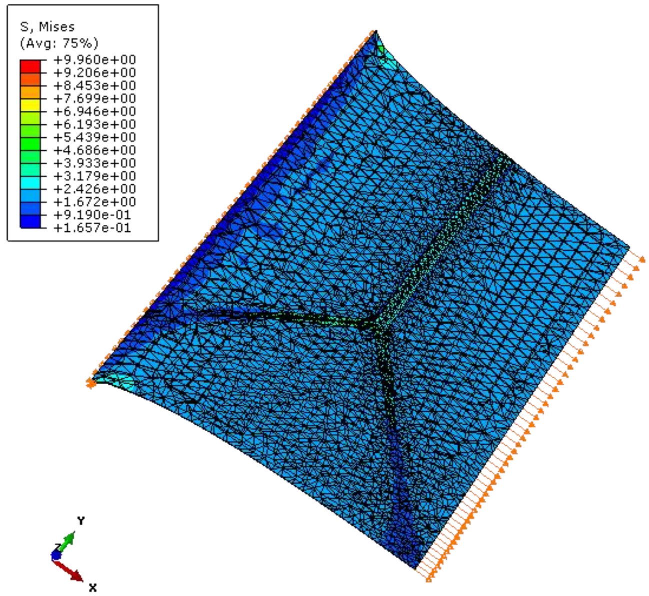

Fig. 15 Deformed FE model of the extracellular matrix and vasculature branch after applying displacement in X-direction.

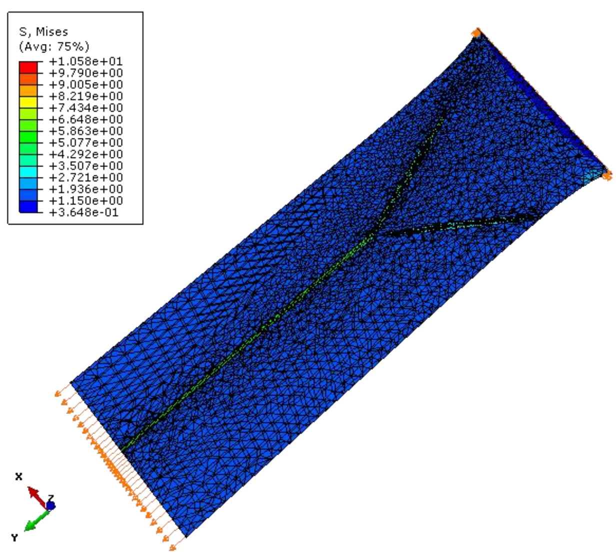

Fig. 16 Deformed FE model of the extracellular matrix and vasculature branch after applying displacement in Y-direction.

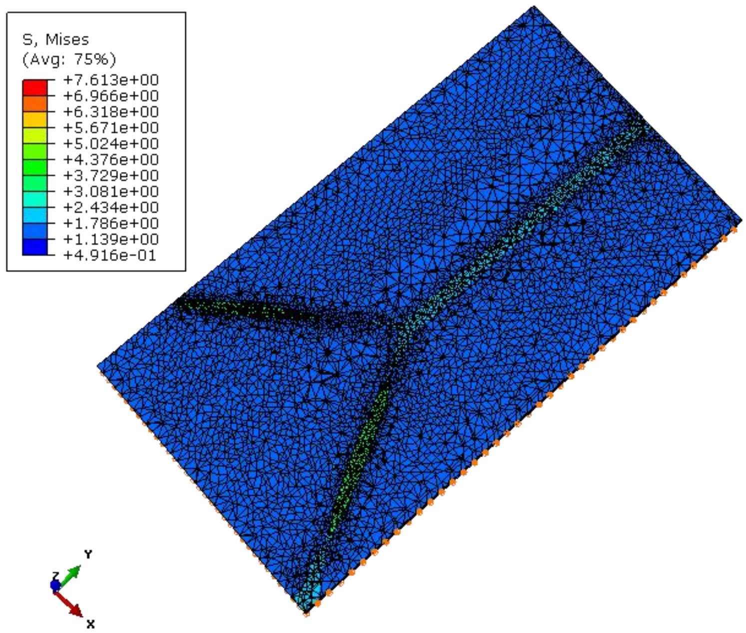

Fig. 17 Deformed FE model of the extracellular matrix and vasculature branch after applying displacement in Z-direction.

In order to clearly determine the cerebral vessels' stiffness effect, the results of tensile simulations of the composite material model are plotted as the overall average uniaxial stress-stretch curves in order to compare with the artery and gray matter in three directions. Force and displacement data obtained from simulations in Abaqus are converted to stress-stretch curves. Figures 18-20 illustrate the stress-stretch curves as well as with stress-stretch behavior of arteries and gray matter in x, y, z direction, respectively. Comparing the stress-stretch curves, the results predict that the arteries do largely stiffen the whole composite material model.

In Fig. 21, stress-stretch curves from the simulations are plotted together in order to demonstrate the anisotropy of the composite material model. The graph indicates the anisotropy of the composite material model. The stress differences between x, y directions and z direction is not as significant as expected. The reason behind this is likely that the volume fraction of arteries is quite small, only 1.9%. A parametric study will be conducted in the future.

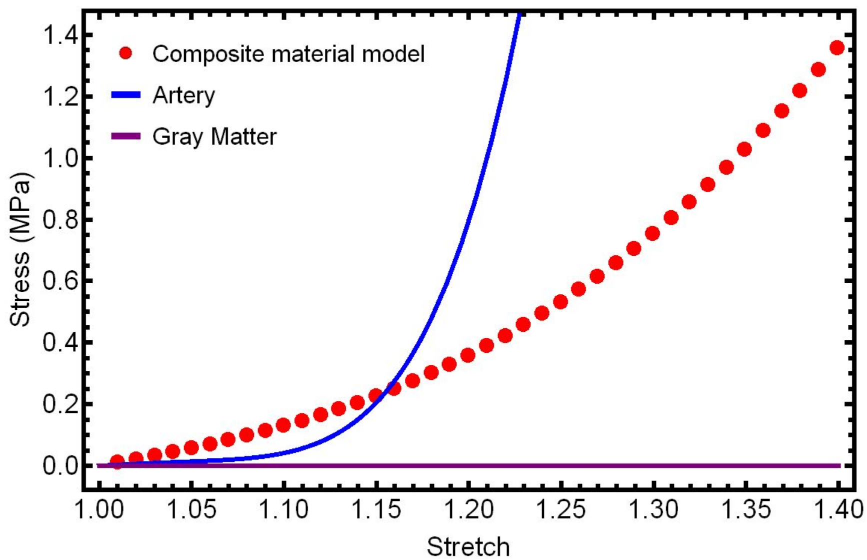

Fig. 18 Stress-stretch curves comparison in x-direction.

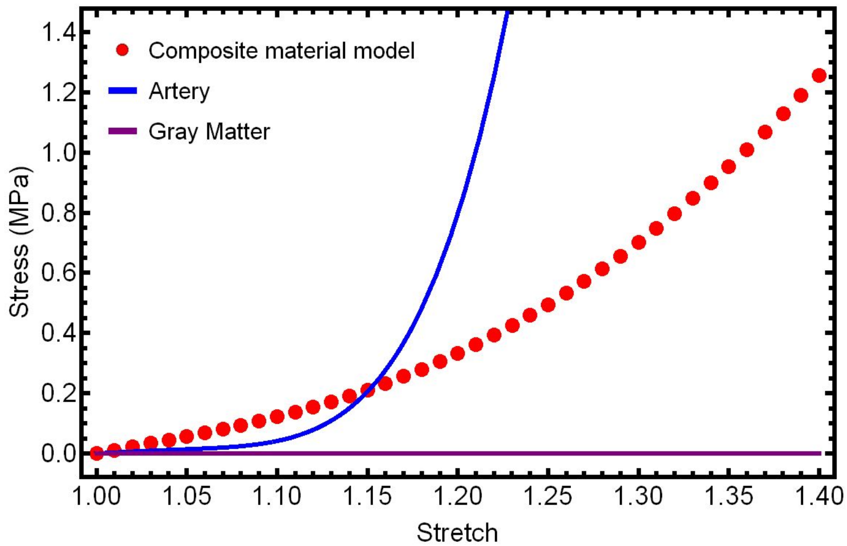

Fig. 19 Stress-stretch curves comparison in y-direction.

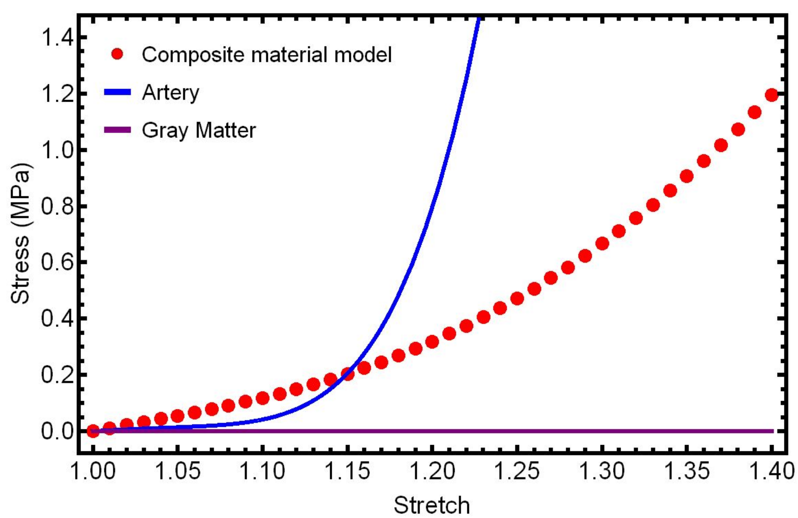

Fig. 20 Stress-stretch curves comparison in stretch z-direction.

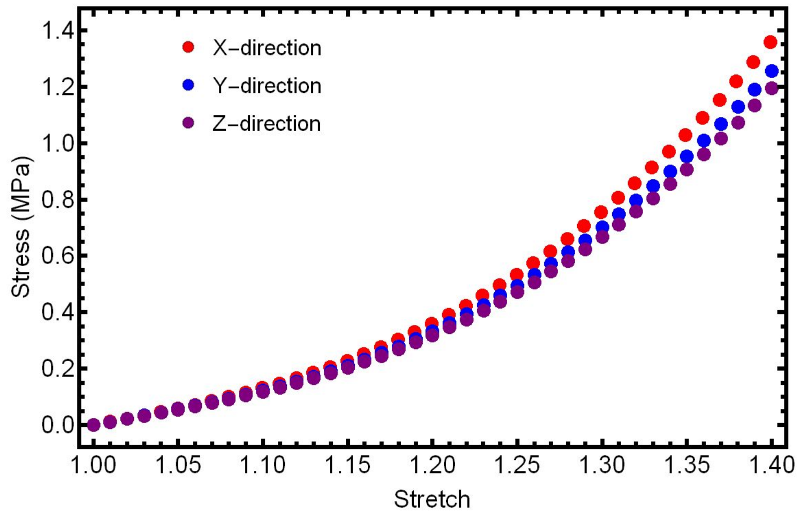

Fig. 21 Stress-stretch curves comparison in three directions showing the anisotropy of the composite model.

Chapter 4
Anisotropic Constitutive Equations

4.1 Generalized Fung-type Formulation without Shear

In this thesis, the whole RVE model contains two unique material models which is not fully explored in previous studies [32]. Prange *et al.* (2000) [32] have demonstrated brain tissue at different regions of the brain, in which the gray matter is shown to be the least anisotropic. This study uses only the axial mechanical properties of vasculature while the gray matter is considered as isotropic material. Therefore, this thesis is limited to tensile behavior of the composite material.

The generalized Fung-type formula after eliminating shear is:

$$U = \frac{1}{2}c(\mathrm{e}^{Q} - 1) \tag{12}$$

where U is the strain energy potential and Q is defined by

$$Q = b_1 E_{11}^2 + b_2 E_{22}^2 + b_3 E_{33}^2 + b_4 E_{11} E_{22} + b_4 E_{11} E_{22} + b_5 E_{11} E_{33} + b_6 E_{22} E_{33} \tag{13}$$

in which E_{ii} is a component of the Green strain tensor, c is a positive stress-like material parameter and b_i, i = 1,...,6, are dimensionless material parameters [26].

4.2 Material Parameter Estimation

4.2.1 Inverse FE Procedure

Inverse finite element procedure has been widely used in many studies to identify material parameters of soft tissue [27], [29]. An inverse finite element analysis method is developed for seeking the parameters in the anisotropic formula by combining uniaxial simulations and FEA using the generated RVE model.

Federico *et al.* (2008) [26] pointed out that the simple fitting of the parameters of a Fung-type formula to experimental stress-strain curves may cause undesirable effects on the reliability of the algorithms used in FE simulations. In the current study, only tensile simulations and normal strains are taken into consideration.

The significant differences in the results of four parameters obtained in the Monson *et al.* (2009) [27] and Shafigh *et al.* (2013) [31] cannot be ignored. Monson began from specimen preparation and conducted the mechanical testings and Shafigh adopted results from Monson and fitted the experimental data to the same formula. Even though the same experimental data are used, they determine diverse coefficient values which differed by several orders of magnitude. Wilber *et al.* (2002) [28] examined the convexity properties and strong ellipticity conditions for the soft-tissue models related to the classical Fung-type constitutive model. They also indicated the mathematical features of those models which were shown by Holzapfel *et al.* (2000) [32] and Humphery *et al.* (2003) [33] are not fully explored and analyzed. Therefore, there is no general theory or method that could validate the obtained material models. More studies towards Fung-type constitutive model are expected to be conducted.

Simulation data is fitted using nonlinear least-squares Levenberg–Marquardt algorithm for the parameters of constitutive model. The coefficients were calculated with Matlab Optimization Toolbox™. Simulation data is fitted to the seven parameters Fung-type hyperelastic constitutive model. Table 1 records the best-fit material parameters.

4.2.2 Results

Table.1 Material Parameters for the Fung-type anisotropic model for composite model.

Parameters	Tensile simulation in x-direction	Tensile simulation in y-direction	Tensile simulation in z-direction
c	17382	18282	12276
b1	-40	615	6264
b2	109	289	2930
b3	65	838	1680
b4	110	-884	4635
b5	89	728	-7313
b6	48	716	-215

Chapter 5
Conclusions and Future Work

5.1 Conclusions

The simulations on the quasi-static mechanical properties of vasculature within gray matter at large strains demonstrate creative steps forward in the investigation of the mechanism of the brain during traumatic injury. Even though brain tissues have been measured in a broad range of testing methods and objectives, it is hard to compare the results and conclusions since the experiments and simulations differ by species, locations, unique material model types, and various range of strains and strain rates. The goal of this thesis is to estimate an effective prediction of the mechanical response of only two brain components, namely the vasculature and gray matter, in the same region.

Instead of using the Ogden model for gray matter which is often the case in previous studies, the suggestions from Kaster *et al.* [7] is adopted to use the Yeoh model for gray matter due to its accuracy, fewer parameters, and shorter computational time requirements. Based on the analysis in the current study, the best fit model for arteries is fifth order reduced-polynomial model.

The stress-stretch curves obtained from the tensile simulations in three directions demonstrate that the vasculature stiffens the gray matter even at a very low volume fraction, i.e. 1.9%.

One of the most expected achievements of this study is that it provides a strain energy potential for an anisotropic composite material model which can be incorporated in large scale studies with less computational cost.

As is mentioned before, cerebral oxygen consumption by gray matter takes up 94% of the whole brain, comparing it with only 4% used by white matter. That means small disruptions or deficit in oxygen supply may cause irreversible damage to neurons in gray matter. Results from this thesis suggest that the fine substructures of the vasculature in brain should not be ignored in traumatic brain injury modeling.

5.2 Limitations and Future Work

This thesis focuses only on vasculature embedded in gray matter in microscopic level and several assumptions are made in order to realize the simulations.

First, for the material property of vasculature, the whole vessel branch was treated as isotropic solid material. Monson *et al.* (2008) [14] indicate that vessels' mechanical behavior vary from tensile stretch to circumferential stretch. With the help of more information explored about vasculature containing fluid blood, an accurate model could result in closer predictions. In addition, this thesis only captures the character of brain tissues' hyperelastic material properties while it did not include their viscous property. A more complex material model needs to be generated in the future.

Second, for the central nervous system, the interaction between two different components is an important issue that needs to be analyzed. In fact, the interfacial contacts could largely affect the whole composite model's behavior. As a preliminary study, the vessels and gray matter are assumed to be fully tied together.

Finally, building the model has inherent difficulties for vessels because of their unpredictable and random development. One limitation is that only one vasculature branch is included without taking the individual variation into consideration. The vessel branch constructed in this thesis has one joint in and does not include the tortuosity of vasculature for simplicity. In order to obtain more information to suffice the prevention and cure of TBI, tortuosity should be included in future investigations.

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