Experimental, Analytical, and Numerical Evaluation of the Mechanical Properties of the Brain Tissue

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EXPERIMENTAL, ANALYTICAL, AND NUMERICAL EVALUATION OF
THE MECHANICAL PROPERTIES OF THE BRAIN TISSUE

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Civil and Environmental Engineering

by

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B.Sc., Sharif University of Technology, 2009
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TO

MY BELOVED PARENTS ALIJAN AND RAZIEH, FOR GIVING ME THE BEST GIFT,
BELIEVING IN ME;
MY WIFE LEILA, FOR BEING MY BEST FRIEND;
AND
MY DAUGHTER LEAH ROSE, FOR GIVING MEANING AND PURPOSE TO MY LIFE.
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ABSTRACT

A true understanding of the mechanisms behind most of the brain diseases is still out of reach. For several years, the interest of scientists has been focused on the genetic and biological causes, however, recent studies unraveled the importance of the biomechanics of the brain growth, folding, impact resistance, and deformation on its pathological conditions. While, a wide range of different methods have been used for characterization of the mechanical properties of the brain at the tissue level, the obtained results from different studies are extremely scattered and sometimes in contrast to one another. Since the brain tissue is extremely soft, its mechanical properties are quite a challenge to be obtained. In this study, the accurate analysis of the mechanical heterogeneity of the brain tissue is performed through dynamic and pseudo-static indentation techniques to evaluate the viscoelastic response of the brain and presenting its anisotropy, inhomogeneity, and rate dependence. In addition, this research provides a detailed reference for modeling the nonlinear mechanical behavior of soft tissues, in general, and the brain tissue, in particular, with addressing important considerations for mechanical modeling in uniaxial loading conditions. With thoroughly presenting the physical basis of the modeling procedure, it is shown that if such considerations are neglected, a considerable inaccurate evaluation of the mechanical properties of the tissue can be expected, although the results might mathematically be correct. Moreover, a new model is developed for the mechanical behavior of the brain tissue that addresses the tension-compression asymmetry with taking into account the compressibility of the tissue in different loading conditions. This model is implemented by utilizing a combined analytical and numerical scheme. The results of this research could be used as input variables for computer simulations of the brain tissue in studying the traumatic brain injury, malformation of the brain folds, and other pathobiological conditions associated with the mechanical behavior of the brain.
1. INTRODUCTION

The aim of the current research is to introduce, calibrate, and rationalize novel experimental and analytical methods to mechanically characterize the brain tissue. This introduction chapter presents the motivation and the importance of this work, while the details are presented in the subsequent chapters.

1.1. Problem Statement

Diseases pertaining to the brain tissue have always been considered to be within the most degenerative and life threatening pathobiological conditions with severe and long term impacts on human life cycle. In particular, traumatic brain injury (TBI) and developmental brain disorders (DBDs) cause enormous burdens in both human suffering and economic costs. Traumatic brain injury, which is a result of severe linear or rotational acceleration and strain experienced by the brain, is among the leading causes of death in the United States with an average of 52,000 annual fatalities (Faul et al., 2010). In addition, normal brain fold development is thought to be mechanically driven and is considered as the basis for having a healthy brain (Budday et al., 2015b). Malformation of these folds has been demonstrated to be an important factor for DBDs such as autism, schizophrenia, and mental retardation. More interestingly, recent studies suggest a downgrade of the mechanical properties of the human brains suffering from neurodegenerative and neuroinflammatory diseases like multiple sclerosis (Streitberger et al., 2012), Alzheimer’s disease (Murphy et al., 2011), normal pressure hydrocephalus (Streitberger et al., 2011), etc. All of these observations demonstrate a significant role for mechanics in pathological condition of the brain tissue.

Recently, studying the biomechanics of the brain tissue has become an emerging field within the biomedical and mechanical engineering disciplines. While most of these biomechanical studies
are based on the computer simulations of the brain, they require valid input data for the mechanical properties of the brain tissue. As an extremely soft material, the mechanical properties of the brain have always been challenging to determine. Although conventional methods for characterizing the mechanical properties of solid materials have been used for the brain, they seem to be inappropriate for this tissue because of two main reasons: firstly, they are not well calibrated for characterizing the elastic properties of soft matters in general. The different numbers presented in the literature for the same mechanical properties of the brain show how inconsistent the used methods are. The second and more important reason is the amount of tissue required to be tested in order to obtain a statistically reasonable result with acceptable standard deviation.

From the constitutive modeling point of view, the field of biomechanics of the brain tissue is still at its infancy stage. The multi-phasic nature of the tissue and its heterogeneous micro and macro structures bring about considerable difficulties in introducing a generic model for its behavior. Most of the constitutive models developed for the brain tissue suffer from mathematical complexities and mostly calibrated for one loading mode only. In addition, many of such models lack physical basis with respect to the principal of continuum mechanics.

1.2. Objectives and Outline

The goal of the current research is to shed light on various aspects of the mechanical properties of the brain tissue. In this way, the indentation experimental technique is used in parallel with analytical modeling and numerical simulation to create a reliable methodology for quantifying the mechanical behavior of this tissue. It is of primary importance in this research to measure the effect of both external environment and internal microstructure on the mechanical response of the brain tissue. The external parameters that affect the mechanical response of the brain include the loading mode and rate, temperature, tissue preservation method, and boundary conditions, and the internal
microstructure that determines the response of this tissue to external stimuli consist of the myelin content, axonal fiber orientation, and fluid content. Accordingly, this research investigates the mechanical properties of the brain tissue with considering the aforementioned influential parameters in experiments, modeling, and simulation.

This dissertation is organized as follows:

In chapter 2, a novel experimental technique is proposed for mechanical testing of the brain tissue. This technique which is called the “indirect indentation method” is based on a modified nanoindentation technique which is developed to minimize the effect of the interaction between the tip and the tissue with high fluid content which has a limiting effect in use of the indentation technique for the brain. This method is first validated and then is used for unraveling the regional and directional dependence of the mechanical properties of the brain tissue in the frequency domain. The rate and postmortem time dependence of the viscoelastic properties of the brain tissue are also investigated with the proposed method.

Chapter 3 includes the viscoelastic characterization of the white matter brain tissue in the time domain. This study includes utilizing of the results of the proposed indirect indentation method in the time domain at different rates to calibrate different viscoelastic solid models and mathematically securitize their appropriateness for the brain tissue. The results of the modal calibrations are further validated and corrected by using the finite element simulation and incorporated for predicting the behavior of the tissue in more complex indentation loading conditions.

Chapter 4 is devoted to the constitutive modeling of the brain tissue. Accordingly, use is made of the results of the previously performed uniaxial testing for different regions of the brain tissue. The concept of hyperelasticity is first described and it is shown that using different elastic fields
has physical implications in material behavior that needs to be considered during modeling and simulation. In addition, it is shown that the boundary conditions have important effects on the mechanical response of this soft tissue, hence, a novel combined analytical and numerical scheme is proposed to consider the effect of the deviation from the perfect boundary conditions during modeling and to obtain appropriate model parameters. More importantly, a new constitutive model is proposed which is aimed at describing the role of compressibility of the tissue in tension-compression asymmetric behavior of the brain during uniaxial loading.

Lastly, Chapter 5 includes the summary, conclusions, and future perspectives of this research.
2. VISCOELASTIC CHARACTERIZATION OF THE BRAIN IN THE FREQUENCY DOMAIN

2.1. Introduction

The role of mechanics in growth, traumatic conditions, and remodeling of human bodies, from sub-cell to tissue and organ levels, has been well recognized and documented by the scientists in the field of biomechanics (Cowin and Doty, 2007; Fung, 2013; Humphrey and O’Rourke, 2015). Among different organs of human bodies, brain is one of the most important and yet least well understood units. Although the electrical characteristics of the brain tissue had overshadowed studying its other aspects for a long time, recent investigations have demonstrated the contribution of the mechanics to the healthy lifecycle of the brain tissue (Chatelin et al., 2010). For example, traumatic brain injury (TBI), which is among the leading causes of death in the United States with an average of 52,000 annual fatalities (Faul et al., 2010), is termed as a damage resulted by the severe linear or rotational acceleration and strain experienced by this tissue during impact or blast loadings. In addition, normal brain fold development is thought to be mechanically driven (Budday et al., 2014a; Budday et al., 2014b; Kuhl, 2016) and is considered as the basis for having a healthy brain (Budday et al., 2015b). Malformation of these folds has been demonstrated to be an important factor for developmental brain disorders (DBDs) such as autism, schizophrenia, mental retardation, etc. (see, e.g., Bayly et al. (2014) and references cited therein). Moreover, recent studies suggest a weakening of the mechanical properties of the human brain suffering from neurodegenerative and neuroinflammatory diseases like multiple sclerosis (Streitberger et al., 2012), Alzheimer’s disease (Murphy et al., 2011), normal pressure hydrocephalus (Streitberger et al., 2011), etc. While all of these diseases are considered to be within the most degenerative and

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life threatening pathobiological conditions with severe and long term impacts on human life, their thorough understanding yet entails further developments in mechanical characterization and modeling of the brain.

Recently, computer simulation has become an excellent replacement for in vivo testing of the brain, especially for studying TBI (Ahmadzadeh et al., 2014; Zhang et al., 2001) and brain folding (Bayly et al., 2014; Razavi et al., 2015; Tallinen et al., 2016a). These models, however, significantly rely on the material properties and the constitutive relations for deformation of the brain tissue as input parameters. Hence, determination of the mechanical properties map of this tissue is of essential importance for such studies. The mechanical characterization of the brain was launched more than half a century ago (Chatelin et al., 2010), nevertheless, being extremely soft, embedded perfectly in the skull, and composed of different subunits have put brain among the most challenging materials to be mechanically quantifiable.

Different methods have been used for evaluating the biomechanics of the brain such as tensile (Miller and Chinzei, 2002; Velardi et al., 2006), compressive (Pervin and Chen, 2009; Prevost et al., 2011a; Rashid et al., 2012), shear (Arbogast and Margulies, 1998, 1999; Feng et al., 2013; Hrapko et al., 2008; Nicolle et al., 2004; Prange and Margulies, 2002; Takhounts et al., 2003), and indentation (Budday et al., 2015a; Chen et al., 2015; Elkin et al., 2011a; Elkin et al., 2011b; Feng et al., 2013; Kaster et al., 2011; MacManus et al., 2015a; MacManus et al., 2016; Prevost et al., 2011b; Van Dommelen et al., 2010; Weickenmeier et al., 2016a) experiments. The results, however, show a wide range of variation and sometimes are in contrast to one another. For example, while some studies suggest that the white matter (WM) of the brain is stiffer than its gray matter (GM) (Budday et al., 2015a; Kaster et al., 2011; Pervin and Chen, 2009; Van Dommelen et al., 2010; Velardi et al., 2006), others have found the GM to be stiffer than the WM (Elkin et al.,
2011a; Elkin et al., 2011b; Nicolle et al., 2004; Prange and Margulies, 2002). Nevertheless, there are still some common conclusions between the experiments like: (i) mechanical response of the brain tissue is extremely rate dependent (Budday et al., 2015a; MacManus et al., 2015a; Miller and Chinzei, 2002; Pervin and Chen, 2009; Rashid et al., 2012; Van Dommelen et al., 2010); (ii) mechanical properties of the cortical GM reveals no significant directional and regional dependence (MacManus et al., 2015a; Pervin and Chen, 2009; Prange and Margulies, 2002; Prevost et al., 2011b), whereas (iii) those of the WM are directional and regional dependent (Chen et al., 2015; Feng et al., 2013; Hrapko et al., 2008; Nicolle et al., 2004; Prange and Margulies, 2002; Van Dommelen et al., 2010; Velardi et al., 2006). It is also worth noting that a proper implication of the experimental observations is limited by the facts that most of these experiments have been performed on animal samples according to the limited availability of human tissues and regulations for using them in research studies. Furthermore, such experiments are mostly performed in vitro which result in information that might be different from the tissue behavior in vivo. Nevertheless, recent studies have demonstrated an acceptable level of similarity between the mechanical behavior of the bovine and human brain tissues (Takhounts et al., 2003). Moreover, with testing the brain tissue in vivo, in situ, and in vitro, Prevost et al. (2011b) have found that only in situ testing condition results in a significantly stiffer response of the tissue, while their observation suggests similar behavior for in vivo and in vitro experiments.

The indentation technique has become a popular method for investigating the mechanical behavior of the brain tissue during recent years (see aforementioned references). It offers a reliable and repeatable measuring method which can minimize the required tissue and maximize the number of the tests within a short postmortem time. Nonetheless, its use has been mostly limited to monotonic loading conditions like pseudo-static loading-unloading or stress relaxation tests.
The limited use of the indentation technique for brain tissue is mainly associated with the tip-tissue interaction, and not the testing instrument itself. For example, the surface detection, which triggers the data recording, is essentially based on a jump in the stiffness measured by the instrument. Due to the extremely soft nature of this tissue, contact might be falsely detected before tip-surface engagement (for a highly sensitive contact detection setting), or might not be detected at all (for low sensitive settings). This difficulty has made some researchers to trigger the data recording manually by visually deciding the contact or starting the tests at a position above the surface (Budday et al., 2015a; Prevost et al., 2011b). In addition, the hydrophilic interaction between the tip and the tissue (which has a considerable moisture content) can rise to a negative force at the onset of the tip-surface engagement (Budday et al., 2015a). This phenomenon not only results in loss of some information at the small deformation range, but also reduces the range of the overall tip travel distance during which the force is measured. Bearing in mind that for most of the indentation instruments, the force measurement calibration is valid for a limited tip travel distance, the latter can further restrict the use of the indentation technique for the brain tissue.

To resolve the aforementioned problems associated with the indentation experiments of the brain tissue, an indirect indentation scheme is proposed in this study during which the imposed deformation is transferred from a sharp tip to the surface of the brain tissue slices through a rigid circular coverslip which is not adhered to either the tip or the sample surface. The proposed testing method, which is employed for a cyclic testing procedure to obtain the linear viscoelastic properties of the brain tissue, is first validated with scrutinizing the loading and response displacement fields. After calibrating the method, the rate, directional, regional, and postmortem time dependence of the dynamic mechanical behavior of the bovine brain samples are evaluated and compared with the previous experimental findings. While this study reveals the advantage of
the indirect indentation over the conventional one, it also demonstrates some interesting aspects of the linear viscoelasticity of the brain tissue, e.g., the evolution of the anisotropy of the white and gray matters with loading frequency.

2.2. Animals and Sample Preparation

Louisiana State University (LSU) endorses practices that may replace, reduce or refine the use of animals. As such, unused animal tissues from an IACUC approved protocol may be utilized by investigators in other studies. Brains for this study were obtained as unused tissues from an approved animal care and use protocol. Four brains from 6 month old calves were obtained from the School of Veterinary Medicine of LSU. Humane euthanasia was performed via overdose of pentobarbital (Fatal-Plus®, Vortech Pharmaceuticals, Dearborn Mi.) at 90 mg/kg intravenously, and brains were removed immediately following the euthanasia and placed in physiological saline solution to maintain moisture and retard the tissue degradation. The brains, in their respective containers, were then transported to testing location in an ice-cooled box within 15 minutes and placed in a refrigerator at 4 °C. Prior to testing, samples were allowed to warm to the room temperature for 10 minutes. Sagittal, horizontal, and coronal section slices of 3-4 mm thickness were made from both hemispheres of the cerebrum (Figure 2.1-a). To minimize the effect of the tissue degradation, samples were randomly tested within 10 hours postmortem, except one coronal slice which was re-tested after 48 hours to study the postmortem time effect.
Figure 2.1. (a) Slicing directions for testing the anisotropy of the mechanical properties of the brain tissue and (b) sagittal section of the brain indicating 1: anterior, 2: superior, 3: posterior, and 4: thalamus regions based on Van Dommelen et al. (2010).
2.3. Dynamic Indentation

2.3.1. Viscoelastic Formalism of the Indentation System

The indentation experiments have been performed using the Dynamic Contact Modulus (DCM) actuator head of an MTS Nanoindenter® machine which has the displacement and loading resolutions of 0.0002 nm and 1 nN, respectively. For applying the cyclic displacement, the “Flat Punch Complex Modulus” method which was developed for measuring the linear viscoelastic properties of “gel-like” materials have been used.

The complex modulus ($E^*$) of a viscoelastic material has real and imaginary components as:

$$E^* = E' + iE''$$  \hspace{1cm} (2.1)

in which $i$ is the imaginary unit, and $E'$ and $E''$ are the storage and loss moduli, respectively. While $E'$ represents the capacity of the material to store portion of the applied energy, $E''$ manifests its energy dissipation capacity. Figure 2.2-a illustrates the generalized viscoelastic model for the internal stiffness ($K_i$) and damping ($C_i$) of the nanoindenter. The response of the viscoelastic material subjected to the indent might also be modeled in parallel with the mechanical model of the machine according to Herbert et al. (2008), as demonstrated in Figure 2.2-b, with $K_c$ and $C_c$ representing the contact stiffness and damping coefficients, respectively. The governing differential equation for describing the motion of the viscoelastic system of Figure 2.2-b is:

$$F = Kh + Ch + m\ddot{h}$$  \hspace{1cm} (2.2)

in which $F$ is the force applied to the mass $m$, and $h$ is its displacement response. Constants $K$ and $C$ are the overall stiffness and damping coefficients of the system, respectively. Since the mass of the moving indented material is small compared to that of the indenter, the inertial contribution of the indented sample can be neglected (Herbert et al., 2009; Herbert et al., 2008).
Figure 2.2. A pictorial representation of the viscoelasticity of the (a) Nanoindenter instrument, and (b) the whole indentation and contact system, based on Oliver and Pharr (1992) and Herbert et al. (2008).

For a load controlled test, the applied oscillatory force may be presented as:

\[ F = F_0 \exp(i\omega t) \]  

(2.3)

in which \( F_0 \) and \( \omega \) are the amplitude and angular frequency of the applied load, respectively, and \( t \) is the time. Since the imposed load and the resulting displacement are required to have the same frequency, the general solution for the displacement field based on Eqs. (2.2) and (2.3) can be assumed to be:

\[ h = h_0 \exp(i\omega t - \phi) \]  

(2.4)

where \( h_0 \) is the displacement amplitude, and \( \phi \) is the phase change between the force and the displacement, which is imposed by the viscoelastic nature of the motion. Considering Eqs. (2.2-2.4), one can express the apparent stiffness of the system as follow:

\[ \frac{F}{h} = \frac{F_0}{h_0} \exp(i\phi) = (K - m\omega^2) + i(C\omega) \]  

(2.5)

Employing the Euler notation for complex variables (\( \exp(i\phi) = \cos \phi + i \sin \phi \)), the equivalent stiffness and damping of the system can be obtained by equating the real and imaginary components of the two sides of Eq. (2.5), which gives:
\[ K - m \omega^2 = \frac{F_0}{h_0} \cos \phi \quad (2.6) \]

\[ C \omega = \frac{F_0}{h_0} \sin \phi \quad (2.7) \]

The values of the load magnitude \( F_0 \) and frequency \( \omega \), as inputs, and also the mass of the moving shaft and the tip, are known parameters; and those for the displacement magnitude \( h_0 \) and the phase lag \( \phi \) are measured during the test. Hence, the equivalent spring and dashpot constants of the system (\( K \) and \( C \), respectively) can be readily obtained. With subtracting the instruments internal stiffness and viscosity constants from the obtained values, the contact properties can be obtained as:

\[ K_c = K - K_i \quad (2.8) \]

\[ C_c = C - C_i \quad (2.9) \]

2.3.2. Determining the Viscoelastic Moduli

Sneddon (1965) presented the closed form solution for the force-displacement fields of an elastic half-space subjected to indentation with different probe shapes. Accordingly, for a cylindrical flat punch, the elastic contact stiffness is related to the isotropic elasticity constants as:

\[ \frac{F}{h} = \frac{2Er}{1 - v^2} \quad (2.10) \]

in which \( E \) is the Young’s modulus, \( v \) is the Poisson’s ratio, and \( r \) is the punch radius. Since the contact area remains constant during deformation, in light of the correspondence principle (Liu et al., 2009), the contact stiffness and Young’s modulus in Eq. (2.10) can be replaced by their corresponding viscoelastic counterparts using Eqs. (2.1) and (2.5), as:

\[ \frac{F_0}{h_0} (\cos \phi + i \sin \phi) = \frac{2(E' + iE'')r}{1 - v^2} \quad (2.11) \]
For obtaining this equation, it is assumed that the Poisson’s ratio is a constant which is not affected by elastic-viscoelastic solution transition. This assumption is valid for incompressible materials in which $\nu=0.5$ (Liu et al., 2009). The assumption of the incompressibility condition for the brain tissue is due to its high liquid content, and is supported by experimental observations (Franceschini et al., 2006; Laksari et al., 2012; Taylor and Miller, 2004). The storage and loss moduli can be obtained with equating the real and imaginary parts of the two sides of Eq. (2.11) as:

\[
\frac{2E' r}{(1 - \nu^2)} = \frac{F_0}{h_0} \cos \phi \tag{2.12}
\]

\[
\frac{2E'' r}{(1 - \nu^2)} = \frac{F_0}{h_0} \sin \phi \tag{2.13}
\]

It is worth noting that in light of Eqs. (2.6-2.9), the right hand side of Eqs. (2.12) and (2.13) should be replaced by $K_c$ and $C_c \omega$, respectively, for eliminating the effect of instrument's internal resistance.

2.4. Testing Procedure

For testing the WM tissue, sagittal and horizontal sections and coronal sections from posterior and anterior parts of the brain were cut using surgical scalpel (see Figure 2.1-a and b for the definition of the directions and regions, respectively). The cutting directions for GM of the superior part of the brain were such that tests could be performed on sagittal and coronal cut slices as well as indentation in the radial direction. In previous studies GM has been tested in one (MacManus et al., 2015a; Pervin and Chen, 2009; Prevost et al., 2011b) or two perpendicular (Prange and Margulies, 2002) directions with observing no significant anisotropy. In this study, three mutually orthogonal directions have been selected to further study the anisotropy of this component of the brain.

---

2 Indentation in the radial direction in the superior region is the same as indenting on a section with horizontal cut in this region. The only difference is that to obtain a horizontal direction, the tissue needs to be cut, instead, the radial direction of cortical GM is tested without cutting the tissue and only with removing the pia matter (see Figure 3-a).
brain. For indentation in radial direction, the pia matter was carefully removed from the top of the tissue (see Figure 2.3-a). To study the inhomogeneity of the cortical GM, the results from the coronal plane of the superior part have been compared to those in the same plane of the anterior region. Samples were mounted in cylindrical cups with an inner diameter of 25 mm (Figure 2.3) for stabilizing, confining, and preventing the slippage of the tissue. A 3 mm diameter coverslip disk, 0.15 mm thick (Warner Instruments catalogue #CS-3R), was used to transfer the load from a sharp indenter tip, which was selected in order to avoid the coverslip slippage during the test, to the tissue surface. The considerably big size of the coverslip allows the assumption of the local homogenous response of the tissue with neglecting the microscale inhomogeneities caused by cell-cell and cell-ECM interactions (Samadi-Dooki et al., 2015) or the presence of the vasculatures (Buday et al., 2015b). On the other hand, care has been taken to avoid recording the combined response of the gray and white matters in the transition areas with ensuring that the tested area under the coverslip consists of either of them only. This task is convenient since the calf brains used in this study are large enough to have distinguishable white and gray matters. Nevertheless, the big size of the disk might cause violations of the half-space assumption for the generated stress underneath it (Finan et al., 2014). Accordingly, the correction factor of $\frac{2}{3}$ based on the work by Finan et al. (2014) is used to offset such violations. Due to the assumption of the correspondence principle for obtaining the viscoelastic constants and also the linearity of the solution, the viscoelastic moduli might be directly adjusted by multiplying them by appropriate correction factors for the elastic solution (Finan et al., 2014).
Figure 2.3. Samples mounted in cylindrical cups for tests on (a) cortical GM in radial direction and (b) WM and GM of a sagittal slice.

The loading segment of the test cycle is performed by setting the tip to sinusoidally push the coverslip whose center point was marked under a scaled Brinell scope prior to the tests (Figure 2.4). The machine was calibrated prior to the experiments and cyclic tests were performed at frequencies ranging from 1 to 120 Hz which are well below the 180 Hz resonance frequency of the load cell. At the beginning of each test cycle, the pure response of the instrument was measured automatically by free oscillation of the tip. Next, the vibrating tip with the raw load amplitude of 20 μN and frequency of 110 Hz started moving downward and the surface was detected with recording a 1 Deg. of phase change. A precompression of known value was then applied to ensure a full contact between the tip and the coverslip during the loading. Afterwards, the tip started indenting the surface cyclically with the input frequency and displacement amplitude values. The combined dynamic response of the sample and the instrument was recorded and used to find the linear viscoelastic properties of the brain as mentioned before. To avoid the outliers in the data

---

3 It is important to note that the machine operates under load controlled mode testing. Since the users have a better understanding of the right displacement, the displacement amplitude is used as the input parameter. However, once the tip is brought into contact with the sample, a certain force is applied to the surface and the corresponding displacement is measured. Since the system is linear, the initial force amplitude is adjusted such that the input displacement amplitude is achieved. All these happen automatically “behind the scenes” prior to the experiment. Once the right force amplitude is determined, it is fixed for the remainder of the experiment, and the displacement amplitude is measured.
sets, at least 3 tests were performed for each measurement, and the mean values are presented as data points in the graphs.

Figure 2.4. Indirect application of the load from the indenter tip to the tissue surface thorough a rigid coverslip.

To adjust the input values for displacement amplitude and precompression parameters, first, a series of tests have been performed to investigate the consistency of the results. After finding the appropriate input parameter values, the cyclic indentation tests on WM, cortical GM, and GM from the thalamus are performed and the results for storage modulus $E'$, loss modulus $E''$, and the absolute complex modulus $|E^*| = \sqrt{(E')^2 + (E'')^2}$ are obtained. The obtained moduli are converted to shear values with dividing them by $2(1 + \nu)$, where $\nu$ represents the Poisson’s ratio, so the results become comparable with those from the shear dynamic tests. For the brain tissue as an almost incompressible material, the Poisson’s ratio can be satisfactorily assumed to be equal to 0.5 (Franceschini et al., 2006). Although the results are presented as shear viscoelastic moduli, they should be perceived as viscoelastic properties in the direction along the tested plane rather than in-plane shear values. It is also worth noting that to ensure the coverslip does not slip on the tissue surface during the test, the initial and final position of its center were investigated under a microscope which is located at a fixed distance from the indenter.
2.5. Input Parameters Calibration and Test Validation

As it was mentioned before, a precompression is applied on the glass disk in order to ensure the full contact condition during the cyclic loading of the samples. There are two key factors that need to be considered for adjusting the precompression. First, it should be selected such that the linearity of the viscoelastic response of the material is not compromised. Previous studies show that the strain values below 1% can guarantee the linear behavior of the brain tissue (Feng et al., 2013; Nicolle et al., 2004). The “average” indentation strain under a flat rigid punch can be obtained as (Elkin et al., 2011b):

\[ \varepsilon_{\text{ind}} = \frac{2h}{\pi r} \]  

(2.14)

thus, it is expected that for the 3 mm diameter (=2r) circular loading coverslip if the total displacement (precompression plus the displacement amplitude) is below \( \frac{\pi r}{200} = 23.6 \ \mu m \), the response of the material would remain within the linear range. With a maximum total compression of less than this value, the effect of the substrate can be neglected on the elastic field generated under a sharp tip (Suresh et al., 1999). However, the values of the linear viscoelastic moduli need to be corrected due to the relatively big size of the coverslip as it was mentioned before. Accordingly, a correction factor of \( \frac{2}{3} \) is selected based on the study by Finan et al. (2014) for cylindrical punch with neglecting the friction effects.

To experimentally confirm the linearity of the viscoelastic response of the brain tissue, tests were performed on the horizontal WM in the posterior region with the frequency of 110 Hz, the displacement amplitude of 1 \( \mu m \), and the precompression values ranging from 3 to 10 microns. As the results in Figure 2.5 demonstrate, the storage, loss, and absolute complex shear modulus values are independent of the precompression values which confirms the linearity of the tissue response.
Figure 2.5. Effect of the precompression on dynamic shear moduli of the posterior WM brain tissue in horizontal plane. The frequency and oscillation amplitude are set to 110 Hz and 1 μm, respectively.

The second important point is the full contact condition between the tip and the coverslip during the cyclic loading. If the tip detaches from the coverslip at any stage of the test, a zero force will be recorded which results in an underestimation of the mechanical response of the underlying tested tissue. If the material is elastic only, a precompression equal to the amplitude of the oscillation would be adequate for guaranteeing the full contact during the test. However, since the brain tissue is viscoelastic and the phase angle shift between the load and the displacement is about 30-50 degrees (as shown in the forthcoming sections), balanced values for precompression and oscillation amplitude need to be found to ensure the full contact condition during the test. Figure 2.6 shows the storage, loss, and absolute complex shear moduli of the posterior WM in the horizontal direction at the frequency of 110 Hz, the precompression of 5 μm, and the oscillation amplitudes varying from 200 nm to 5 μm. While the viscoelastic response values remain unvaried at small oscillation amplitudes up to 1 μm, they drop sharply at amplitudes of 2 μm and higher. This trend suggests that for a 5 μm precompression, an oscillation amplitude beyond 2 μm violates the full contact condition. Hence, for the rest of the experiments a precompression of 5 μm and an
oscillation amplitude of 1 μm are selected to ensure both the linearity of the viscoelastic response and the full contact condition.

Figure 2.6. Effect of the oscillation amplitude on dynamic shear moduli of the posterior WM brain tissue in horizontal plane. The frequency and precompression are set at 110 Hz and 5 μm, respectively.

To further inspect the full contact condition between the tip and the coverslip, the symmetricity of the load and displacement curves during the cyclic indentation of the sample surface are also investigated. If any detachment occurs during the test, a sudden reduction of the load would be recorded which perturbs the symmetry of the load and/or displacement curves. As an example, a part the load and displacement curves of the loading segment of a test on WM tissue at the frequency of 2 Hz are shown below in Figure 2.7. The curves are symmetric with no sudden changes, and since the phase angle shift is about 30° at this frequency, it could be concluded that the applied precompression is adequate for preventing the tip-coverslip dissociation.
2.6. Dynamic Response of the White Matter

To investigate the degree of the anisotropy and inhomogeneity of the white matter brain tissue, tests were performed on sagittal, coronal, and horizontal direction slices of the anterior and posterior regions of the WM of bovine brains, and results are presented in Figure 2.8. The obtained values suggest that the WM brain tissue is strongly rate dependent with stiffening behavior at elevated frequencies for its elastic ($G'$), viscous ($G''$), and absolute viscoelastic ($|G^*|$) responses. More importantly, they reveal that the WM brain tissue is anisotropic, with the horizontal plane as the stiffest and the sagittal one as the softest, and its mechanical properties are region dependent, with the posterior part showing a slightly higher stiffness compared to the anterior one.

![Figure 2.7. Analyzing the symmetricity of cyclic (a) displacement, and (b) load response graphs of a test for WM at the frequency of 2 Hz.](attachment:image.png)
Figure 2.8. Variation of the: shear storage modulus in anterior (a) and posterior (b) regions, shear loss modulus in anterior (c) and posterior (d) regions, and absolute shear complex modulus in anterior (e) and posterior (f) regions of the WM brain tissue with loading frequency at different directions. Panel (g) shows the variation of the phase shift angle of the WM brain tissue (average of all directions and regions) with loading frequency. Abbreviations used are defined as: first character: “W” ⇒ white matter; second character: “C” ⇒ coronal direction, “H” ⇒ horizontal direction, and “S” ⇒ sagittal direction; third character: “A” ⇒ anterior region and “P” ⇒ posterior region.

(fig. cont’d.)
2.7. Dynamic Response of the Cortical Gray Matter

To thoroughly investigate the anisotropy of the cortical GM, indentation experiments were performed on slices in the sagittal and coronal directions of the superior region of the brain, as well as direct indentation in the radial direction in this region. In addition, to study the homogeneity of this tissue, tests were also performed on GM of the coronal slices of the anterior region. As the results of Figure 2.9 present, the response of the cortical GM is almost identical in anterior and superior parts in the coronal plane which is in consonance with several other studies (MacManus et al., 2015a; Pervin and Chen, 2009; Prevost et al., 2011b). Moreover, the tissue responses in coronal and sagittal directions of the superior region are very similar which suggests that these two planes are mechanically identical. However, the viscoelastic responses of the cortical GM in indentation in radial direction are observed to be smaller than that in the other two tested directions. Hence, the cortical gray matter also shows some degrees of anisotropy, similar to the white matter.
Figure 2.9. Variation of the (a) shear storage modulus, (b) shear loss modulus, (c) absolute shear complex modulus, and (d) average phase shift angle of the cortical GM brain tissue with loading frequency at different regions and directions. Abbreviations used are defined as: first character: “G” ⇒ cortical gray matter; second character: “C” ⇒ coronal direction, “R” ⇒ radial direction, and “S” ⇒ sagittal direction; third character: “A” ⇒ anterior region and “S” ⇒ superior region.

2.8. Effect of the Postmortem Time

To study the effect of the postmortem time on the viscoelastic properties of the brain tissue, coronal slices of the anterior WM bovine brain tissue were kept in physiological saline solution at 4 °C in a refrigerator and tested after 48 hrs. The percentage of the reduction of the absolute viscoelastic shear modulus of the tissue at different tested frequencies are obtained and presented in Figure 2.10. As these results suggest, with keeping it cool and adequately hydrated, the WM
brain tissue loses only a small fraction (about 9% in average) of its load resistance capacity within 48 hrs. postmortem.

Figure 2.10. Average reduction of the absolute complex shear modulus of the coronal slices of anterior WM tissue tested 48 hrs. postmortem.

2.9. General Considerations and Data Analysis

As a new approach for applying the load on the surface of the sample, an indirect indentation scheme is utilized in this study. Despite the thinness of the coverslip, the difference between the stiffness of the glass and the brain tissue (about 7 orders of magnitude) allows the assumption of its rigid behavior in the analyses (see Appendix I). The indirect loading of the sample has at least three major advantages over the direct indentation. Firstly, the full contact condition between the loading part (the glass disk) and the sample is guaranteed. For direct indentation, since the sample surface is not completely flat, partial touch between the tip and the tissue surface might be recognized as a full contact which triggers the test procedure. This would result in an underestimation of the mechanical properties of the tested material. Since the coverslip sits perfectly on the tissue surface, there is no risk for partial contact condition in indirect indentation. Secondly, the interaction between the tip and moisture on top of the sample, which causes a negative force at the beginning of the test, is eliminated. This negative force in dynamic testing
can result in the test termination at the first stage. With indirectly applying the load, the tip is engaged with the top of the coverslip which is dry, hence, no hydro-mediated-interaction takes place (see Figure 2.4). Lastly, since the instrument tip does not come into direct contact with the tissue, no tip cleaning is required between the tests. This would save a considerable amount of time which allows the increased number of the tests within the short acceptable postmortem time for obtaining meaningful data. In addition to these major advantages, the surface detection in this dynamic testing module is based on the tip vibration phase change rather than the stiffness alteration detection. Despite the stiffness sensitive surface detection method the problems associated with which for soft materials have been stated before, triggering the test cycle with detecting a phase change between the load and the displacement offers a very efficient and accurate contact detection for soft materials. The criterion of 1 degree of phase change at the frequency of 110 Hz ensures a proper surface detection since the phase lag angle for this frequency for various parts of the brain tissues is in the order of 30-50 degrees based on the experiments. In addition, since the load amplitude in surface detection stage is very small (20 μN), it corresponds to the deformation amplitude of less than 1 μm in sample surface with a 3 mm punch diameter. Hence, any error in surface detection would be within less than a micrometer range, which is appropriately suppressed by the application of 5 μm precompression in the testing procedure. This method of surface detection, which is the integrated surface detection procedure of the “Flat Punch Complex Modulus” of the DCM option, is not specific to the indirect indentation and can be used for direct indentation of all types of soft viscoelastic materials.

In the forthcoming subsections, the obtained results are discussed. For the statistical analyses, ANOVA with Tukey post hoc test is performed for studying the significance of the differences using the IBM® SPSS® Statistics software.
2.9.1. Anisotropy and Inhomogeneity of the White Matter

Statistical analyses were performed to investigate the significance of the observed differences in viscoelastic response of the WM in different regions. It is observed that although the posterior region is consistently stiffer than the anterior one for all of the tested directions, this difference is not of statistical significance ($P > 0.05$). In addition, the statistical analysis indicates that the elastic response ($G'$) of the horizontal and coronal directions are significantly stiffer than the sagittal direction for the whole tested frequency range. This difference for viscous ($G''$) and absolute viscoelastic ($|G^*|$) responses is only significant at small loading frequencies (below 10 Hz) and the difference is insignificant at higher rates. These results are in consonance with the observations of Hrapko et al. (2008) for cyclic shear tests. This finding suggests that for the phenomena with short timescales, like TBI, the viscoelastic response of the WM can be assumed to be isotropic; however, in a long-term or low rate deformations, it should be modeled as an anisotropic material. In addition, if the WM is modeled as an elastic material with neglecting the viscous part of the response, its anisotropy needs to be considered regardless of the deformation rate. The average of the obtained values for the viscoelastic properties of the WM fall well within the range of those reported in dynamic frequency sweep tests in shear as presented in Figure 2.11, which confirms the validity of the results based on the indirect cyclic indentation experiment.
Figure 2.11. Comparison of the average WM brain tissue storage (circles) and loss (triangles) moduli based on: 1 Bilston et al. (Bilston et al., 1997), 2 Shuck and Advani (1972), 3 Nicolle et al. (Nicolle et al., 2004), 4 Arbogast and Margulies (1998), and 5 Hrapko et al. (Hrapko et al., 2006) with the current study 6.

The WM brain tissue is generally composed of myelinated axons which form bundles with local directional alignment. While in some regions like corpus callosum, the axonal bundles are uniaxially oriented (lateral direction for interconnecting the brain hemispheres), in other parts like corona radiata the pattern of the arrangement is less ordered with regional dependent preferred axes. The fiber-like effect of the axons within the cellular matrix of the brain tissue is similar to the fiber reinforced composites (Arbogast and Margulies, 1999), and the reinforcing effect would be more pronounced with considering the strengthening effect of the myelin for the axons (Weickenmeier et al., 2016a). While the axonal bundles are oriented in a “fan-shape” within the corona radiata (Prange and Margulies, 2002), the observed directional dependence of the viscoelastic properties can be readily justified. According to Figure 2.1-b and 2.12, the horizontal plane in the posterior region is a section which is almost perpendicular to the axonal bundles direction. Hence, the mechanical properties are measured in parallel to the preferred direction of
the fibers in the indentation tests which show a stiffer response. In the anterior region, the fibers are generally more inclined to anteroposterior direction compared to the posterior region, hence, the coronal section also benefits from the reinforcing effect of the fibers and showing the stiffness close to that of the horizontal direction. On the other hand, the sagittal plane is almost parallel to the direction of the fibers in corona radiata, hence, the indentation tests in a direction perpendicular to the fibers in this plane are minimally affected by the reinforcing effect of the axonal tracts (see also Figures 6, 9, and 10 of Catani and De Schotten (2008)). Moreover, the small difference between the viscoelastic properties of the anterior and posterior regions are in agreement with the findings of Chen et al. (2015) and Weickenmeier et al. (2016a) from indentation tests. Besides the fiber orientation difference in these regions, with evaluating the interrelation between the myelin content of the WM tissue and its stiffness, Weickenmeier et al. (2016a) attributed this difference in the mechanical properties to the higher myelination degree of the axons in the posterior region compared to that in the anterior one in bovine brain samples. The conformity of these observations from two different testing protocols (monotonic and cyclic) additionally supports the role of underlying microstructure on the macroscopic response of the tissue.

Another important observation during cyclic testing of the WM (which is also beheld for cortical GM) is the variation of the phase angle at the test frequencies as shown in Figure 2.8-d. Interestingly, the phase shift angle changes from ~30 to 50 degrees for frequencies ranging from 1-10² Hz. This variation, which corresponds to the alteration of the loss factor from below to above 1, is very similar to that of the elastomers with long chains (Gerstl et al., 2010; Nusser et al., 2011). This conclusion from the cyclic tests, is in agreement with that from the monotonic loading condition observed by Franceschini et al. (2006).
Figure 2.12. Projection of the fibers that stem from the *corpus callosum* and extend into the white matter (reproduced from Catani and De Schotten (2008) with permission). The same pattern exists for the fiber orientation of *corona radiata* (see Figure 9 of the same reference).

2.9.2. Anisotropy and Inhomogeneity of the Cortical Gray Matter

In most of the previous studies on the mechanical characterization of cortical GM, this tissue was found to be an isotropic material or its anisotropy was considered to be statistically insignificant. However, those studies have only compared, at most, two different directions. The observations in the current study suggest that the assumption of the isotropic behavior for cortical GM might need to be revisited. The statistical analysis indicates that the elastic response ($G'$) of the radial direction is significantly more compliant than the other two directions for the whole tested frequency range. This difference for viscous ($G''$) and overall viscoelastic ($|G^*|)$ responses is only significant at small loading frequencies (below 10 Hz) and the difference is insignificant at higher rates. This finding is similar to that for the WM brain tissue. In addition, the similarity of the cortical GM in superior and anterior regions suggests the mechanical homogeneity of this tissue.

Among the aforementioned cutting directions for the cortical GM, the mechanical response of the sagittal and coronal direction slices are probably affected by the free boundary condition (edges
of the sample). The free edges cause the material to undergo lateral deformation much easier compared to the ideal indentation situation where the bulk of the material surrounds and confines the indented part. Although this effect is attenuated considering the short distance between the coverslip and the cup edges which restricts the lateral deformation (Figure 2.3-b), the conclusion that the radial direction is softer that the other two directions remains valid since the free boundaries might cause underestimation of the GM resistance in sagittal and coronal directions. Nevertheless, a thorough understanding of the effect of such complicated boundary conditions on the mechanical response of the sample requires a finite element modeling.

The lower mechanical resistance in the radial direction of the cortical GM can be attributed to the pattern of the neural cells layout in the cortex. The cortical GM generally consists of neural cell bodies with no preferred directional orientation. However, the layered structure of this tissue requires the neural cells to be connected closely in the lateral direction, whereas, in the radial direction the elongated dendrites are the dominant components to cover interlayer cortical spaces (Budday et al., 2015b). Hence, the stiffer response of the in-plane mechanical properties of the cortical GM could be attributed to the enlarged pyramidal neural cell bodies, while the elongated dendrites in radial direction can be assumed to be less resistant to the applied load.

2.9.3. White Matter vs Gray Matter

As it was mentioned before, there exists no conclusive agreement between the results of different studies for comparing the mechanical properties of the WM and GM brain tissues. To further investigate the possible differences, the average response of the WM in all tested directions was compared to that of the cortical GM, and the sagittal direction of the thalamic GM as demonstrated in Figure 2.13. From the statistical point of view, for the whole tested frequency range, the overall viscoelastic response of the cortical GM is on average significantly softer than
the WM of the *corona radiata* and the thalamic GM. In addition, the cerebral WM is slightly stiffer than the thalamic GM, but the difference is statistically insignificant. Hence, the structural layout of the cells in the cortex, which is different from the thalamus, seems to have a considerable effect on its mechanical properties.

The conclusion that the white matter is stiffer than the gray matter is in agreement with the findings from indentation and uniaxial tests for bovine and porcine brain tissues (Budday et al., 2015a; Kaster et al., 2011; Pervin and Chen, 2009; Van Dommelen et al., 2010; Velardi et al., 2006); however, it is in contrast to the cyclic shear tests (Nicolle et al., 2004; Prange and Margulies, 2002). Since during the monotonic or cyclic shear tests, the response of the material is only based on the deviatoric component of the applied stress, these observations suggest that the white matter brain tissue has a higher resistance to the hydrostatic pressure component of the applied stress which has a non-zero value in uniaxial or indentation experiments. Whereas, the gray matter shows a higher resistance to the deviatoric component of the applied stress. The interlayer expansion of the neural cells protruding parts in the cortical gray matter might be responsible for its profound response in shear testing conditions with providing a resisting mechanism for sliding of the layers. Whereas, the densely packed structure of the myelinated axons gives the white matter a more fluid like structure with a more pressure resistant nature. Hence, it could be concluded that in comparison with the GM, the behavior of the WM is closer to that of the incompressible materials. This conclusion, however, requires a direct investigation for further validation.
Figure 2.13. Variation of the (a) shear storage modulus, (b) shear loss modulus, and (c) absolute shear complex modulus of the average cortical GM, average WM, and thalamic GM in sagittal direction with loading frequency.

2.9.4. Preserving the Tissue for Long-term Experiments

The mechanical properties of the brain tissue are likely to degrade with increasing postmortem time due to several factors such as protein decay and necrosis (Ferrer et al., 2007). However, previous studies have shown that storing brain tissue in saline solution at 4°C can preserve its mechanical properties up to 5 days postmortem. (Budday et al., 2015a; Nicolle et al., 2004). The current study further supports this conclusion with observing, in average, only 9% reduction of the
mechanical resistance of the WM matter brain tissue 48 hrs. postmortem with preserving it according to the same protocol.

2.10. Conclusions

In this work, the linear viscoelastic properties of the bovine brain samples were obtained using a novel indirect dynamic indentation method. The results indicate that, if considered as pure elastic materials, both white and gray matter brain tissues should be considered as anisotropic materials. For the viscous and overall viscoelastic responses, the anisotropy is more significant at smaller loading rates, and for higher deformation rates, both of these materials can be satisfactorily considered to be isotropic. As an important consideration, it should be noted that the formalism used in this study for extracting the mechanical properties is originally developed for isotropic materials, whereas, the brain tissue is not isotropic in general, as the results demonstrate. Accordingly, a proper analysis of anisotropy of the brain entails development of the model for an anisotropic half-space which is subjected to the flat punch indentation like the one performed by Vlassak and Nix (1993). The analytical solution of such model involves intense mathematics and applying the correspondence theorem for obtaining the viscoelastic model from the elastic one. This increases the complexity of the model, and therefore a finite element simulation might be required to avoid such complexities. This is, however, beyond the scope of the current study, and since the stiffness variation in different directions, especially at higher frequencies, is not very significant, the utilization of the isotropic formalism for analysis might even be more efficient with minimal inaccuracy.

Besides the aforementioned results for the brain tissue, the proposed indirect indentation technique offers great advantages over the conventional direct indentation for obtaining the mechanical properties of soft biological materials. This study indicates that the indirect indentation
can expand the use of the indentation testing for soft materials with considerable moisture content to very small deformation and loads. In addition, despite dynamic shear testing in which the sample fixation between the loading compartments requires applying an adhering glue or axial compression which have unknown effects on the shear response of the specimen, the dynamic indirect indentation proposed in this study does not entail any cumbersome sample preparation, which is a considerable advantage for biological materials with extremely soft nature.
3. VISCOELASTIC CHARACTERIZATION OF THE BRAIN IN THE TIME DOMAIN

3.1. Introduction

Mechanical aspects of the brain tissue, which is regarded as an extremely vulnerable organ during impact and blast loading conditions, have recently attracted researchers in the field of biomechanics (Kuhl, 2016; Prevost et al., 2011a). Besides externally imposed traumatic situations, mechanics has been shown to have a consequential role during growth and folding (Bayly et al., 2014; Budday et al., 2014b; Tallinen et al., 2016a), and also some pathological conditions of the brain tissue (Murphy et al., 2011; Stewart et al., 2017; Streitberger et al., 2012; Streitberger et al., 2011). While the timescale of these phenomena ranges from milliseconds to years, studying the rate dependent mechanical characteristics of the brain is of essential importance in modeling and simulations that seek enhancing design criteria for protective devices like helmets, or understanding the mechanisms involved in pathobiological conditions of the brain.

Brain tissue exhibits a strong rate dependent behavior which can be satisfactorily expressed in terms of viscoelastic models in the realm of small deformation. Accordingly, the viscoelastic characterization of the brain has received considerable attention during recent years. In the direct mechanical testing scheme, viscoelastic characterization can be performed via two different procedures. The first approach is applying cyclic loads (or displacements) at different amplitudes and frequencies which might be termed as the frequency domain viscoelastic characterization. Many researchers have used this approach for examining the frequency and regional dependent viscoelastic properties of the brain tissue. For example, Bilston et al. (1997) reported storage and

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loss moduli of the bovine brain samples via shear rheometry; Arbogast and Margulies (1998) investigated the effect of the orientation of the axonal bundles of the brainstem on its viscoelastic response during oscillatory shear tests; Nicolle et al. (2004) measured the interregional variation of the linear viscoelastic shear modulus of porcine and human brain tissues and also proposed a visco-hyperelastic model for the brain; Hrapko et al. (2008) scrutinized the anisotropy, temperature, and precompression dependence of the dynamic shear response of the brain; and Samadi-Dooki et al. (2017) explored the anisotropy, inhomogeneity, and postmortem time dependence of the viscoelastic moduli through indirect oscillatory flat-punch indentation. Nevertheless, numerical interpretation of the rate dependence of the viscoelastic properties from frequency dependent results is not easy in general. In addition, performing numerical simulation for model calibration and further developments based on frequency dependent parameters is complicated and costly in terms of the required computational resources.

Another approach for viscoelastic characterization of the materials is studying the temporal variation of the mechanical resistance for parametric modeling of the material behavior which is termed as time domain viscoelastic characterization in here. For the brain tissue, use of this method has mostly been limited to investigation of the relaxation behavior of the tissue. For example, Takhounts et al. (2003) examined different linear and nonlinear viscoelastic models to interpret the relaxation behavior of bovine and human brain tissues; Elkin et al. (2011a) utilized microindentation experiments to investigate interregional variation of the relaxation modulus of porcine brains using Prony series fitting scheme; Chen et al. (2015) incorporated the same technique to evaluate the inhomogeneity of the porcine white matter brain tissues using a 5 mm flat circular probe; and Budday et al. (2015a) compared the stress relaxation properties of the bovine brain white and gray matters. The results from the relaxation studies can be conveniently
used in commercial finite element simulation packages, however, the values obtained for viscoelastic constants based on relaxation may not accurately reflect the rate dependent behavior in other loading conditions (load ramp, creep, etc.).

According to the aforementioned limitations of the available information on the viscoelastic characteristics of the brain tissue, physical and numerical parametrization of the viscoelastic response of the brain yet require thorough and in depth investigation to better reflect the overall rate dependent behavior of this tissue. In addition, the extremely soft nature of the brain tissue necessitates considering the effect of the internal response of the testing instrument on the recorded overall load and/or displacement. In fact, the scatteredness of the reported mechanical properties of the brain tissue from different studies (up to 3 orders of magnitude (Chatelin et al., 2010)) implicitly suggests a considerable effect of the testing machine on the obtained results which have been poorly incorporated in the post-test analyses. Moreover, some boundary conditions which are “assumed” for post-test analyses of the experimental information are generally developed for stiff solids and might require to be revisited for soft materials. For example, in instrumented indentation experiments, the effect of the substrate is generally neglected if the total indentation depth is below a certain portion of the total sample thickness, regardless of the impression expansion size. This assumption is valid for indentation of stiff solids which is usually accomplished using a sharp tip. However, for the case of soft materials where a bigger probe size is used, substrate effect might not be negligible, even for shallow indentations (Finan et al., 2014).

This research is aimed at studying different basic viscoelastic models for the white matter brain tissue through presenting an analytical-numerical procedure that can give physical insight into the nature of the rate dependent deformation behavior. Indentation technique is used in this study as a powerful method for mechanical characterization of biological materials with requiring minimal
amount of tissue and sample preparation, and providing fast data acquisition within short postmortem time (Budday et al., 2015a; Feng et al., 2017a; Feng et al., 2017b; Feng et al., 2013; Gefen and Margulies, 2004). Accordingly, experimental observations of the indirect flat-punch indentation during which the indentation load is transferred from a flat end probe to the tissue indirectly via a large circular coverslip, are theoretically and numerically analyzed. In this way, contribution of the internal stiffness of the instrument to the overall load-displacement curves, which is shown here to be significant, is first obtained. Next, different viscoelastic models are parametrized with curve fitting the indentation load and displacement information. While it is demonstrated that the Maxwell and Standard Maxwell models can appropriately interpolate the experimental curves, the accuracy of the numerical values based on the curve fitting process is then investigated with using them as input parameters for a set of dynamic finite element simulations. Since the simulation results show a considerable discrepancy with the experimental values suggesting a violation from the assumptions of the theoretical modeling during experiments, correction factors for adjusting the viscoelastic constants are obtained and presented in this work. Despite the previous trial and error optimization based methods for evaluating the mechanical properties of soft materials (Liu et al., 2009), the correction method presented in this work requires only one set of readjustment of the numerical model parameters which saves considerable amount of time and computing resources. Finally, the appropriateness of the Maxwell model is further investigated and developed with proposing a general Multimode Maxwell model for the brain and comparing the load-hold-unload indentation cycles based on experiments and numerical simulations. Accordingly, the closed-form mathematical solution for the flat-punch indentation force due to the applied piecewise linear displacement field is derived and presented. The model
parameters including springs and dampers, and their associated time constants are analytically obtained and numerically confirmed.

3.2. Animals and Sample Preparation

Seven brains from adult dogs (3-4 years of age) were obtained as byproducts of an IACUC approved study at the School of Veterinary Medicine of LSU. Following the euthanasia via overdose of pentobarbital (Beuthanasia-D Special, Merck & Co. Inc., Madison, NJ) at 90 mg/kg intravenously, brains were removed immediately and placed in physiological saline solution. They were then transported to the testing location in an ice-cooled box within 15 minutes. At the testing location, brains were maintained at 4°C in a refrigerator; and prior to testing, they were allowed to warm to room temperature for 10 minutes. For indentation experiments, sagittal slices of ~10 mm thickness were made using a sharp knife since cuts in this direction expose the maximum apparent white matter area compared to other directions. All of the samples were tested within 5 hours postmortem to reduce tissue degradation due to factors such as protein decay and necrosis (Ferrer et al., 2007).

3.3. Indentation Apparatus

Indentation tests were carried out using an Agilent T-150 UTM instrument (Figure 3.1-a) with the theoretical displacement and load resolutions of less than 0.01 nm and 50 nN, respectively. Indirect monotonic indentation scheme is used in this study during which the indentation load is transferred from the indenter’s tip to the tissue surface via a round coverslip. To ensure the homogenous behavior of the tissue under the indentation loading, a relatively large coverslip (5 mm radius and 0.15 mm thick) is used. This size of the loading part also increases the load range on the sample for a certain displacement, which increases the accuracy of the measurement by significantly surpassing the load resolution of the instrument. Since the stiffness of the glass
coverslip is orders of magnitude larger than that of the brain tissue, it can be assumed as a rigid disk during the analysis. To further assure no localization of the load, the sharp probe of the indenter is also replaced by a 1 mm radius cylindrical one (Figure 3.1-c).

In Figure 3.1-b, the internal configuration of the indentation apparatus, which is fundamentally load controlled, is shown schematically. While the imposed force is controlled electromagnetically by the coil/magnet assembly, the corresponding displacement is measured by the capacitance gauge. The support (leaf) springs, which are very stiff in response to lateral motion, maintain the indenter shaft in a vertical direction during the displacement. However, the stiffness of these springs in the out of plane deformation is substantially low. Since these springs are modeled in parallel with the stiffness of the indented sample (Oliver and Pharr, 1992), their force contribution should be subtracted from the “raw load” (total load exerted by the magnet/coil assembly) for obtaining the “load on sample” (portion of the “raw load” which is applied on the sample) $p$ as:

$$p = f - K_s h$$  \hspace{1cm} (3.1)

in which $K_s$ is the total stiffness of the support springs in vertical direction, and $f$ and $h$ are the raw coil/magnet load and displacement of the shaft, respectively, both measured from onset of the tip-coverslip engagement. It should be noted that the contribution of the frame stiffness to the measured load and displacement is neglected since it is orders of magnitude larger than that of both the soft sample and leaf springs (Oliver and Pharr, 1992).
Figure 3.1. Details of the indentation experiment instrument: (a) visual components of the Agilent T150 UTM which is used in an up-side-down configuration for indentation process, (b) the internal components of the indentation instrument, and (c) the schematic presentation of the indirect indentation process.

3.4. Testing Procedure

The tissue slices were placed in 50 mm diameter petri dish which was mounted on the micropositioner of the instrument’s crosshead (Figure 3.1-a). To minimize the friction between the tissue slices and the petri dish or the coverslip, they were well hydrated with saline solution prior to each experiment. The coverslip, whose center point had been marked under a Brinell scope, was then placed on top of the tissue in the corona radiata area with maximum distance from the surrounding gray matter and corpus callosum. The center point of the coverslip was visually aligned with the cylindrical indenter tip. The crosshead then moved upward at the speed on 0.5 mm/s until the contact between the coverslip and cylindrical tip was detected. Since the surface is detected through alteration of the stiffness sensed by the instrument, a faster crosshead upward movement ensures a more accurate surface detection since the tissue exhibits a stiffer response at higher rates due to its viscoelastic nature. After surface detection, the cylindrical tip moved to zero point of its travel distance at which it was held for 60 s to minimize the thermal drift. The tip then
started “approaching” the speed of 40 $\mu$m/s until it re-engaged with the coverslip. The “loading stage” of the test cycle was then triggered during which the “raw load” increased at a constant rate until the “load on sample” reached a predefined value. At this stage, the sample was “unloaded” either immediately, or after a “raw load hold” segment of 60 s. While the results from the loading segments of the former loading cycle profile were used for parametrizing different viscoelastic models, those from the whole cycle of latter profile were incorporated in investigating the accuracy and generalization of the calibrated models. The magnitude of the “raw load rate” during unloading was the same as that during the loading stage.

3.5. Viscoelastic Modeling of Flat-Punch Indentation

White matter brain tissue is generally composed of myelinated axons which have regional dependent preferred orientation axes. Although some researchers have proposed that the reinforcing effect of these axonal tracts would cause anisotropic mechanical behavior of the white matter (Chatelin et al., 2013; Feng et al., 2013), recent comprehensive experimental studies suggest that such anisotropies are not of statistical significance and this tissue can be assumed to behave isotopically in small or large deformations (Budday et al., 2017; Jin et al., 2013). In addition, the indentation experiments in the current study were performed on slices from the sagittal direction of the corona radiata within which the axonal tracts are almost parallel to the cutting direction (Catani and De Schotten, 2008). Hence, the mechanical response of the tissue is minimally affected by any strengthening effect of the axon bundles (Samadi-Dooki et al., 2017). Accordingly, the isotropic behavior is assumed for the white matter tissue in this study. Sneddon (1965) presented the load-displacement relation for the flat-punch indentation of a semi-infinite elastic half-space as:
\[ p(t) = \frac{4rG}{1 - \nu} h(t) \]  

(3.2)

with \( p \) and \( h \) represent the load and displacement, respectively, as functions of time \( t \), the parameters \( G \) and \( \nu \) are the shear modulus and Poisson’s ratio of the half-space, respectively, and \( r \) is the radius of the circular punch. In light of the correspondence principle, the load-displacement relation of the flat-punch indentation of a viscoelastic semi-infinite half-space in Laplace space can be obtained from Sneddon’s expression as follows:

\[ \tilde{p}(s) = \frac{4r\tilde{G}}{1 - \tilde{\nu}} \tilde{h}(s) \]  

(3.3)

in which \( s \) is the Laplace space variable, and \( \tilde{\cdot} \) represents the respective parameters in the Laplace space. In general, with assuming the viscoelastic response in shear, and elastic response in volumetric deformation (Liu et al., 2009), the viscoelastic constants \( \tilde{G} \) and \( \tilde{\nu} \) may be expressed as:

\[ \tilde{G} = \frac{\sum_{j=0}^{n} \alpha_j s^j}{1 + \sum_{i=1}^{n} \beta_i s^i} \]  

(3.4)

\[ \tilde{\nu} = \frac{3K - 2\tilde{G}}{6K + 2\tilde{G}} \]  

(3.5)

with \( K \) representing the elastic bulk modulus, \( \alpha_i, \beta_i \) are constants which are determined according to the assumed viscoelastic model, and \( n \) is an integer determined by the number of spring and dashpot elements in the viscoelastic model. It should be noted that in Eq. (3.4), \( i \) and \( j \) designate the subscripts for \( \alpha \) and \( \beta \) and the power for the Laplace space variable \( s \). In Table 3.1, two and three element viscoelastic models used in this study are demonstrated with their respective corresponding values for \( \alpha_i \) and \( \beta_i \).

Replacing Eqs. (3.4) and (3.5) in Eq. (3.3), the generalized load-displacement relation for the flat-punch indentation of a viscoelastic half-space in Laplace space is obtained as:
\[
\bar{p}(s) = \frac{4r \bar{h}(s) \sum_{j=0}^{n} \alpha_j s^j}{1 + \sum_{i=1}^{n} \beta_i s^i} - \frac{6K(1 + \sum_{i=1}^{n} \beta_i s^i) + 2 \sum_{j=0}^{n} \alpha_j s^j}{3K(1 + \sum_{i=1}^{n} \beta_i s^i) + 4 \sum_{j=0}^{n} \alpha_j s^j}
\] (3.6)

Eq. (3.6) can be simplified for an incompressible viscoelastic material to:

\[
\bar{p}(s) = \frac{8r \bar{h}(s) \sum_{j=0}^{n} \alpha_j s^j}{1 + \sum_{i=1}^{n} \beta_i s^i}
\] (3.7)

Equations (3.6) and (3.7) express the governing relations for flat-punch indentation of a viscoelastic solid. The load and displacement can be obtained as functions of time from the indentation experiments. One of these functions can be transformed to the Laplace space, and the load-displacement relation in time space can be found by replacing \( \alpha_i \) and \( \beta_i \) according to the assumed model, and applying the inverse Laplace transformation. The numerical values for the viscoelastic parameters \( G \)'s and \( \eta \)'s can then be obtained by curve fitting either load-time or displacement-time curves, whichever was not used in the Laplace transformation process.

Table 3.1. The model parameters for 2 and 3 element viscoelastic solids.

<table>
<thead>
<tr>
<th>Model</th>
<th>Configuration</th>
<th>( \alpha_0 )</th>
<th>( \alpha_1 )</th>
<th>( \beta_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kelvin</td>
<td>( G_K )</td>
<td>( \eta_K )</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Maxwell</td>
<td>0</td>
<td>( \eta_M )</td>
<td>( \frac{\eta_M}{G_M} )</td>
<td></td>
</tr>
<tr>
<td>Standard Kelvin</td>
<td>( \frac{G_{SK}^1 G_{SK}^2}{G_{SK}^1 + G_{SK}^2} )</td>
<td>( \frac{G_{SK}^1 \eta_{SK}}{G_{SK}^1 + G_{SK}^2} )</td>
<td>( \frac{\eta_{SK}}{G_{SK}^1 + G_{SK}^2} )</td>
<td></td>
</tr>
<tr>
<td>Standard Maxwell</td>
<td>( G_{SM}^1 )</td>
<td>( \left( \frac{G_{SM}^1}{G_{SM}^2} + 1 \right) \eta_{SM} )</td>
<td>( \frac{\eta_{SM}}{G_{SM}^2} )</td>
<td></td>
</tr>
</tbody>
</table>
3.6. Finite Element Simulation

The finite element analysis is used in this study in order to investigate the validity of the half-space assumptions used in obtaining the numerical values for the individual parameters of the aforementioned viscoelastic models. An axisymmetric model was created in ABAQUS™ 2016 (ABAQUS Inc., Providence, RI) including the rigid coverslip, the viscoelastic indented material, and a rigid, fully constrained substrate. The coverslip-tissue and tissue-substrate interactions were modeled as hard normal contact and the corresponding friction in the lateral deformation was neglected. The centerline of the viscoelastic material was also constrained against movement in the lateral direction. To eliminate the singularities in the simulations, the corner edge of the coverslip was modeled as a circular arc with a radius of 50 μm (Figure 3.2). The model consists of 2704 CAX4R and CAX3 elements with a progressively refining mesh pattern towards the coverslip (Figure 3.2). Since only Maxwell and extended Maxwell models show a good correlation in interpolating the experimental observations (see the results section), only these models were validated in the simulations. The instantaneous behavior of the brain tissue was considered as linear elastic, and the viscoelastic effects were introduced to the model as Prony series. The Poisson’s ratio of the material was set at 0.49.
3.7. Out of Plane Stiffness of the Leaf Springs

To measure the stiffness of the leaf springs in vertical motion, the indenter shaft was freely moved from top to bottom of its travel distance range, and the corresponding force was measured. The stiffness was then measured as shown in Figure 3.3. As it is seen in this figure, the leaf springs stiffness in vertical motion is not constant, hence, in calculating the load on the sample using Eq. (3.1), it is important to appropriately consider the variation of $K_s$ considering Figure 3.3 and the position of the tip at the initial contact point.
3.8. Monotonic Indentation

Once the cylindrical tip came into contact with the coverslip during the “approach” segment, the “raw load” was increased at a constant rate until a certain “load on sample” was reached. Accordingly, the “raw load rates” of 1, 1.6, 3.2, and 6.4 mN/s were applied until the “load on sample” of 16 mN was reached, and the load and displacement were recorded. At least two tests on each hemisphere of two different brains were performed at each rate which means a total of at least eight tests for each rate. All of the experiments were performed on the posterior region of the brains to minimize the interregional variation of the mechanical properties (Chen et al., 2015; Samadi-Dooki et al., 2017; Weickenmeier et al., 2016b). Figure 3.4 demonstrates the variation of the load on the sample and displacement with time. As it is perceived from this figure, at higher “raw load rates,” the load and displacement both increase linearly which implies an elastic response of the material in short timescales. At lower “raw load rates,” however, while the displacement is still increasing linearly, the “load on sample rate” decreases as the elapsed
deformation time increases. This observation implies a relaxation mechanism that activates at longer timescales; a phenomenon which is characteristic in viscoelastic materials.

![Graphs showing load on sample and displacement into surface over time, with R^2 values for linear interpolation.](c)

Figure 3.4. Variation of the (a) load on the sample and (b) the displacement into the surface with time during indentation. Part (c) demonstrates the linear interpolation of the displacement with R^2 values of the interpolation.

### 3.9. Viscoelastic Models Fitting

To scrutinize what type of viscoelastic mechanism is appropriate for representing the behavior observed in Figure 3.4, four different models as described in Table 3.1 are numerically parametrized using Eq. (3.7) with assuming incompressibility of the brain tissue (Franceschini et al., 2006). A linear variation of the displacement with time is assumed for modeling according to...
the experimental results of Figure 3.4-c. Accordingly, with considering displacement-time relation as $h(t) = a_1 t$ with $a_1$ representing a constant for each curve in this figure, the load vs time relation for the models in Table 3.1 can be obtained as:

$$p_K(t) = 8r a_1 (\eta_K + G_K t)$$

(3.8)

$$p_M(t) = 8r a_1 \left(1 - e^{-\frac{G_M t}{\eta_M}}\right) \eta_M$$

(3.9)

$$p_{SK}(t) = \frac{8r a_1 G_{SK1}^1}{(G_{SK1}^1 + G_{SK2}^2)^2} \left(\eta_{SK} G_{SK1}^1 \left(1 - e^{-\frac{(G_{SK1}^1 + G_{SK2}^2) t}{\eta_{SK}}}\right) + (G_{SK1}^1 + G_{SK2}^2) G_{SK2}^2 t\right)$$

(3.10)

$$p_{SM}(t) = 8r a_1 \left(\eta_{SM} \left(1 - e^{-\frac{G_{SM1}^2 t}{\eta_{SM}}}\right) + t G_{SM1}^1 \right)$$

(3.11)

for Kelvin, Maxwell, Standard Kelvin, and Standard Maxwell models, respectively. In these equations, all the model parameters are the same as those defined in Table 3.1. Using the FindFit function of Mathematica 10.4 (Wolfram Research Inc., Champaign, IL) with a maximum of 500 iterations, values for the spring and the dashpot element of each viscoelastic model can be obtained in a load curve fitting scheme at each rate. Error! Reference source not found.-a and c demonstrate the interpolation of the curves with Maxwell and Standard Maxwell models, respectively. The numerical values for the parameters of the Maxwell model are $G_M = 2.16 \pm 0.05$ kPa and $\eta_M = 56.84 \pm 6.69$ kPa.s, and those for the Standard Maxwell model are $G_{SM1}^1 = 0.73 \pm 0.04$ kPa, $G_{SM2}^2 = 1.52 \pm 0.05$ kPa and $\eta_{SM} = 18.56 \pm 0.83$ kPa.s. As it is seen in Error! Reference source not found.-b, the Kelvin model cannot appropriately interpolate the load curves. More importantly, the model parameter values obtained for different curves are significantly different from one another which compromises the generality of the model. Numerical values for the model parameter of the Standard Kelvin solid also approach those of the Maxwell model (Error! Reference source not found.-a) with $G_{SK1}^1 \rightarrow G_M$, $\eta_{SK} \rightarrow \eta_M$, and $G_{SK2}^2 \rightarrow$
0. These observations imply that, in general, the Kelvin viscoelastic solid is not appropriate for modeling of the experimental findings.

![Graphs](image)

Figure 3.5. Curve fitting of the load on the sample based on (a) Maxwell, (b) Kelvin and (c) Standard Maxwell viscoelastic models.

3.10. Validation via Finite Element Simulation

In order to determine the accuracy of the numerical values for the Maxwell and Standard Maxwell models based on the curve fitting process, they were used as input parameters for a series of dynamic finite element simulations as described in Materials and Methods section. The coverslip penetration was simulated as linear displacement in the vertical direction, and the
reaction force on the coverslip was measured. In Figure 3.6-a and b, the solid lines demonstrate the results based on the raw input parameters obtained from the curve fitting process, which show a considerable discrepancy with the experimental values. This difference suggests a strong substrate effect on the stress and strain fields generated in the white matter tissue during experiments which causes a violation from semi-infinite half-space assumption for the tissue slices being indented. Interestingly, the ratio between the simulation values and the experimental ones for all curves is a constant close to 1.43. Considering the linear variation of the force with simultaneous proportional variation of the model parameters based on Eqs. (3.8-3.11), the numerical values based on the curve fitting can be adjusted with dividing them by this constant. As such, the raw numerical values for the model parameter were replaced by the corrected one in the simulations. As the results in Figure 3.6 demonstrate (dashed lines), simulations with the corrected values show a good correlation with the experimentally obtained results. The final values of the springs and dashpots in the Maxwell and Standard Maxwell models for the white matter brain tissue are summarized in Table 3.2.

Table 3.2. Corrected numerical values for model parameters of the Maxwell and Standard Maxwell solids representing the white matter brain tissue.

<table>
<thead>
<tr>
<th>Viscoelastic model</th>
<th>$G_M$ kPa</th>
<th>$\eta_M$ kPa.s</th>
<th>$G_{SM}^1$ kPa</th>
<th>$G_{SM}^2$ kPa</th>
<th>$\eta_{SM}$ kPa.s</th>
<th>Average $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxwell</td>
<td>$1.51 \pm 0.03$</td>
<td>$39.75 \pm 4.68$</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.9985</td>
</tr>
<tr>
<td>Standard Maxwell</td>
<td>-</td>
<td>-</td>
<td>$0.51 \pm 0.03$</td>
<td>$1.06 \pm 0.03$</td>
<td>$12.98 \pm 0.58$</td>
<td>0.9968</td>
</tr>
</tbody>
</table>
Figure 3.6. Comparison of the load vs time curves based on experiments and finite element simulation with assuming (a) Maxwell and (b) Standard Maxwell models. Solid lines represent simulations based on numerical values for the model parameters obtained from curve fitting in Mathematica and dashed lines are the simulation with corrected input parameters.

3.11. General Considerations and Data Analysis

3.11.1. Effect of Leaf Springs Stiffness on Data Recording and Analysis

The leaf springs allow the indenter shaft to move in the vertical direction while limiting its lateral motion. Since they are very compliant in the vertical direction (Figure 3.3), their contribution to the total force during indentation of stiff materials is negligible. Nevertheless, for the case of the indentation of soft materials like the brain tissue, whose stiffness is in the range of
leaf springs for the regular flat-punch size (~1 mm), contribution of these springs is not insignificant. More importantly, the vertical stiffness of these springs is not necessarily constant as demonstrated in Figure 3.3. Hence, despite the linear increment of the “raw (total) load” during experiments, the “load on sample” does not increase at a constant rate considering Eq. (3.1) with such behavior of the leaf springs. With increasing the load size using a 5 mm coverslip the stiffness of the sample is expected to be dominant in the total recorded response, however, the varying stiffness of the leaf springs still needs to be considered in the analyses.

The formalism developed for parametrizing the viscoelastic models in this study is very flexible in considering various types of load and displacement inputs, as long as one of them can be interpolated with a function of time which could be transformed into the Laplace space. In this study, the displacement, which can be satisfactorily interpolated linearly (Figure 3.4-c), is selected as input for the Laplace transformation, and the load vs time is curve fitted for finding the viscoelastic constants. This process could have been performed vice versa by considering the Laplace transformation of the load, and interpolating the displacement. However, the complexity of the interpolation function for load-time curves, increases the computation time for both best-fit-finding and finite element simulation.

3.11.2. Effect of the Substrate on the Tissue Behavior

The effect of the substrate on the indentation experiments is usually considered when the indentation depth exceeds 10% of the sample thickness. However, Finan et al. (2014) have recently shown that even at small indentation depth, the substrate effect is considerable for large cylindrical or spherical indentation radii. Their numerical simulations demonstrate that when the tip size increases, the elastic fields under the tip broaden and interfere with the boundaries at the bottom of the sample. Hence, they presented correction factors for different tip radius to thickness and
indentation depth to thickness ratios to adjust the recorded load. This correction factor based on their simulation for indentation depth to thickness ratio of smaller than 0.05, tip radius to thickness ratio of 0.5, and Poisson’s ratio of 0.5 is about 1.9 for elastic materials. A similar correction factor can be obtained based on the earlier analytical study by Hayes et al. (1972). In the current simulations, due to incorporating the correspondence principle and very small indentation depth to thickness ratios (less than 0.037), one expects an almost constant correction factor for simulations at different rates. Accordingly, the general correction factor of 1.43 obtained based on the present work seems to be reasonable. Nevertheless, the obtained value is slightly smaller than those obtained by Finan et al. (2014) and Hayes et al. (1972). The discrepancy is believed to be a result of the difference between the boundary conditions at the bottom of the indented sample in these studies. Finan et al. (2014) constrained the nodes at the lower surface of the sample in both vertical and horizontal directions and Hayes et al. (1972) assumed the perfect bonding condition between the substrate and the tissue, however, the bottom surface of the sample in the current study is allowed to slide in a frictionless manner in the horizontal direction and its vertical displacement is only restrained by defining a hard normal contact with the rigid substrate. Accordingly, less significant substrate effect is expected in the current study compared to those performed by Hayes et al. (1972) and Finan et al. (2014). This conclusion is supported by the study of Dimitriadis et al. (2002) who investigated the substrate effect on spherical indentation of a sample with finite thickness assuming bonded and not-bonded conditions between the sample and the substrate. Based on that study, the correction factor for bonded contact condition is larger than that for the not-bonded condition. The authors believe that the boundary condition considered in the current study is a better model of the current experimental settings since the tissue slices were hydrated with saline solution to minimize the effect of the friction.
3.11.3. Maxwell Model for Load-Hold-Unload Cycle: Generalization to Multimode Maxwell Model

The curve fitting scheme used in this research indicates that the Maxwell model is a more appropriate viscoelastic mechanism for modeling of the indentation of the brain tissue. This result seems reasonable since the relaxation behavior which is activated in the tissue at long term is basically described in terms of the Maxwell model in continuum mechanics. Accordingly, this model can be generalized to a Multimode Maxwell viscoelastic mechanism as shown in Figure 3.7 for the brain tissue. To further investigate the appropriateness of such models, a series of load-hold-unload indentation experiments have been performed on the brain tissue. As such, the “raw load” is increased at a constant rate of 16 mN/s until the “load on sample” reaches 16 mN. The “raw load” is then held at this value for 10 s which is followed by the unloading at the same raw load rate magnitude of the loading stage. Figure 3.8-a demonstrates the test cycle raw load pattern for these experiments. The “displacement into surface” and “load on sample” can be obtained as presented in Figure 3.8-b and c. During the hold segment, the “load on sample” decreases significantly due to the relaxation phenomenon, and to maintain the “raw load” at a constant value, the displacement into surface increases, and hence the contribution of the leaf spring compensates for the relaxation in the tissue.

![Multimode Maxwell model](image)

Figure 3.7. Schematic representation of the Multimode Maxwell model for the white matter.
The indentation displacement of the load-hold-unload cycle in Figure 3.8-b can be satisfactorily interpolated as piecewise linear function of time. In general, the displacement may be expressed as \( n \) consecutive piecewise linear functions as:

\[
    h(t) = \begin{cases} 
        a_1 t & t < T_1 \\
        a_2 (t - T_1) + a_1 T_1 & T_1 < t < T_2 \\
        \vdots & \\
        a_n (t - T_{n-1}) + \sum_{i=1}^{n-1} a_i (T_i - T_{i-1}) & T_{n-1} < t < T_n
    \end{cases}
\]

In which \( a_i \) is the slope of the curve in each linear section located within the time interval of \([T_{i-1} - T_i] ; \) and \( a_0 = T_0 = 0 \). For the Multimode Maxwell model of Figure 3.7, the shear modulus in the Laplace space is described as:

\[
    \tilde{G} = G_1 + \sum_{i=2}^{m} \frac{G_i \eta_i s}{G_i + \eta_i s}
\]  

Replacing for \( \tilde{G} \) and \( \tilde{h}(s) \) in Eq. (3.3) with Eq. (3.12) and the Laplace transformation of Eq. (3.13), respectively, and applying the inverse Laplace transformation, the load as a function of time for flat-punch indentation of an incompressible Multimode Maxwell solid with piecewise linear displacement into surface is obtained as:

\[
    p(t) = 8r \left[ G_1 \left( a_j t - \sum_{n=1}^{j} (a_n - a_{n-1}) T_{n-1} \right) + \sum_{i=2}^{m} \eta_i \left( a_j - \sum_{n=1}^{j} (a_n - a_{n-1}) e^{-\frac{T_{n-1} - \theta_i}{\tilde{\eta}_i}} \right) \right]
\]

in which \( \theta_i = \frac{\eta_i}{G_i} \) is the time constant for each individual Maxwell element in the Multimode Maxwell model, \( m \) is determined by the total number of individual Maxwell elements as demonstrated in Figure 3.7, and \( j \) is the time interval within which the load is calculated (between \( T_{j-1} \) and \( T_j \)).
To demonstrate the enhancement of the model results with increasing the number of elements, the numerical values for the model parameters of a Multimode Maxwell solid with five elements (one spring in parallel to two individual Maxwell elements) are obtained by curve fitting in Mathematica. This model, in fact, includes the fewest number of elements for Multimode model beyond those of a Standard Maxwell model. The numerical values were then corrected for the substrate effect with dividing them by the previously found correction factor of 1.43 as shown in Table 3.3 (only the values for \( G_1 \) and \( \eta_i \)’s need to be corrected). These values were used for finite element simulation with inserting the indentation displacement of Figure 3.8-b as input parameter. The load vs time is then obtained as shown in Figure 3.8-d. In this figure, the load curves based on the Maxwell and Standard Maxwell model with the numerical values presented in Table 3.2 are also demonstrated. As can be seen, the Multimode Maxwell model with only 5 elements exhibits a considerably enhanced prediction of the experimental observation, especially during the major relaxation period (second stage of the load curve). Brain tissue has been previously shown to exhibit the mechanical behavior similar to elastomers with long chains (Franceschini et al., 2006). The rate dependent behavior of such polymeric materials have been modeled via Multimode Maxwell model for a long time (Laun, 1978). Hence, the suitability of such a model for the brain tissue seems to be reasonable.

Table 3.3. Corrected numerical values for a 5-element Multimode Maxwell model representing the brain tissue

<table>
<thead>
<tr>
<th>Viscoelastic Model</th>
<th>( G_1 ) (kPa)</th>
<th>( \eta_2 ) (kPa.s)</th>
<th>( \eta_3 ) (kPa.s)</th>
<th>( \theta_2 ) (s)</th>
<th>( \theta_3 ) (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-element Multimode Maxwell</td>
<td>0.76</td>
<td>1.68</td>
<td>6.71</td>
<td>3.33</td>
<td>20</td>
</tr>
</tbody>
</table>
Figure 3.8. (a) Raw load, (b) displacement into surface, and (c) load on sample during load-hold-unload indentation cycle; (d) comparison between the experiments and finite element simulations incorporating different Maxwell viscoelastic solids.

3.12. Conclusions

In this work, experimental, theoretical, and numerical schemes for viscoelastic characterization of the white matter brain tissue are presented for the flat-punch indentation. Due to its high accuracy and resolution in providing spatial mechanical properties map, simple sample preparation procedure, and generating a 3D state of deformation induced elastic fields, the indentation technique has become a popular method for the mechanical characterization of the brain tissue.
during recent years. In general, however, accurate characterization of the internal properties of the testing instrument is shown in this study to play a major role in the validity of the experimentally obtained results. In addition, the accuracy of the assumptions for the boundary conditions of the problem in modeling is also demonstrated to critically affect the correctness of the analysis. Nevertheless, it is made clear that for the case of modeling the flat-punch indentation, the violation from the semi-infinite half-space can be compensated for by adjusting the load or viscoelastic constants with introducing correction factors. Although the model parameters can be directly identified from FE simulations in an iterative loop scheme, the current combined modeling and simulation method significantly reduces the required computational time and resources by reducing the iteration loop counts to one cycle only.

For the brain tissue, it is concluded that the most appropriate viscoelastic model at small deformation range is the Maxwell viscoelastic solid. Hence, generalization to this model for considering more complex deformation states is described with presenting a Multimode Maxwell model.
4. CONSTITUTIVE MODELING OF THE BRAIN TISSUE: ROLE OF COMPRESSIBILITY IN TENSION-COMPRESSION ASSYMMETRY

4.1. Introduction

Mechanical interaction of the human body with its surrounding environment is known to be a major factor in its heath or disease conditions. Due to the hierarchical nature of the living matters, their mechanical investigation entails a multiscale analysis that expands a wide range of length scales from the subcellular to tissue levels (Cowin and Doty, 2007; Fung, 2013; Humphrey and O’Rourke, 2015; Mofrad and Kamm, 2006). Such analyses can be performed via physical/mechanical modeling that give valuable insight into the mechanisms involved in the biomechanics of the tissue deformation and provide predictive patterns that aim at reducing the injuries in traumatic conditions and increasing the remodeling rate during healing (Holzapfel and Ogden, 2017). A proper implementation of such models, however, requires a thorough understanding of the mechanical properties of the tissue and the constitutive relations that govern its deformation behavior.

Among human body organs, brain is arguably the most vulnerable unit during mechanically induced trauma (Ahmadzadeh et al., 2014; Faul et al., 2010; Prabhu et al., 2011). In addition, some aspects of its growth and folding processes have been recently shown to be mechanically driven (Bayly et al., 2014; Kuhl, 2016; Tallinen et al., 2016b). Nevertheless, the extremely soft nature of this tissue has made its mechanical testing a challenging task. Mechanical quantification of the brain tissue was started more than one half a century ago, however, the results for mechanical stiffness of this tissue based on earlier studies are very scattered within a range of several orders

---

of magnitude (Chatelin et al., 2010). With recent developments in experimental techniques and increase in instruments’ accuracy and rate of data acquisition, it seems that the results based on different studies with different testing methods and procedures are demonstrating a better agreement with one another (Budday et al., 2015a; Budday et al., 2017; Huston III, 2014; Johnson et al., 2013; MacManus et al., 2015b; Moran et al., 2014; Rashid et al., 2012, 2013, 2014; Samadi-Dooki et al., 2017, 2018; Van Dommelen et al., 2010; Weickenmeier et al., 2016b). Accordingly, the constitutive models that relate the deformation of the tissue to the force can be confidently calibrated using the recent experimentally obtained data.

Brain tissue exhibits a nonlinear mechanical behavior with notable rate and regional dependency. To address its nonlinearity, hyperelastic constitutive laws have been extensively used for this tissue (Budday et al., 2017; Feng et al., 2013; Kaster et al., 2011; Mihai et al., 2017; Mihai et al., 2015; Moran et al., 2014; Sahoo et al., 2014; Voyiadjis and Samadi-Dooki, 2018). In this way, the stress-strain relations can be obtained with taking partial derivatives of the strain energy function which is assigned to the tissue behavior. Among different hyperelastic energy functions, the Ogden model has been shown to appropriately predict the nonlinear behavior of soft tissues including the brain (Budday et al., 2017; Mihai et al., 2017; Mihai et al., 2015; Ogden, 1997). The generalized energy function of Ogden hyperelastic material may be presented as:

\[
\psi_{Ogda} = \sum_{j=1}^{N} \left[ \frac{2\mu_j}{m_j} I_1 (E^{(m_j)}) + \frac{1}{D_j} (J - 1)^{2j} \right]
\]  

(4.1)

in which \(\mu_j, m_j,\) and \(D_j\) are the material parameters pertaining to the shear modulus, degree of nonlinearity, and compressibility, respectively, \(J\) is the determinant of the deformation gradient,

---

6 There are alternative presentations for the Ogden hyperelastic energy function, however, the authors utilize the one which is used in ABAQUS in order to maintain the consistency between the modeling and the simulation processes.
and \( I_1(E^{(m_j)}) \) represents the first invariant of the \( m_j^{th} \) order Seth-Hill strain tensor \( E^{(m_j)} \). The parameter \( N \) in this equation determines the number of terms required to appropriately fit the material behavior. Obviously, the Ogden hyperelastic energy function depends on the form of the strain that is considered for material behavior. This form depends essentially on the magnitude and sign of the nonlinearity parameter \( m_j \), and as will be discussed later in this chapter, can control the tension-compression asymmetry of the material. More importantly, for a hyperelastic energy function to be physically meaningful in general, there are some mathematical criteria that need to be satisfied as described by Attar and coworkers (Attard, 2003; Attard and Hunt, 2004). The most important conditions which are relevant to the analysis of soft tissues include:

1. The energy function cannot attain a negative value for all deformations.
2. At the undeformed state (zero principal strains), the strain energy function must have a zero value, which according to condition 1, is the minimum value as well.
3. At singularities (zero or very large principal stretches), the strain energy function should approach positive infinity.
4. The stresses derived from such energy functions must approach negative and positive infinity for deformation with zero or very large principal stretches, respectively.

These conditions have been elaborately discussed in a recent publication by Moerman and coworkers (Moerman et al., 2016) in which it has been described how selecting a certain form of the Seth-Hill strain class can affect the validity and appropriateness of the resulting strain energy function. Accordingly, the authors came up with a hybrid form of the strain tensor that satisfies the aforementioned criteria and allows the control over tension-compression asymmetry without altering the nonlinearity degree.
The last term in the right-hand-side of Eq. (4.1) pertains to the compressibility of the material. In most of the publications on the mechanical analysis of the brain, this tissue has been considered to be incompressible (Franceschini et al., 2006; Laksari et al., 2012; Mihai et al., 2017). Accordingly, this term is usually dropped from the mathematical formulation for Ogden hyperelastic modeling of the brain tissue. Since the brain tissue possesses a considerable interstitial and intracellular fluid content (up to 0.8 g/ml (Whittall et al., 1997)), the incompressibility condition seems to be reasonable especially in compression. However, recent numerical analysis of the hyperelasticity of the brain tissue has shown that this assumption is not necessarily correct. For example, Moran et al. (2014) calibrated different hyperelastic models based on the experiments performed by Jin et al. (2013). Although Moran et al. (2014) did not discuss the concept of compressibility in their publication, investigating the volume change during deformation with incorporating their findings for Ogden hyperelastic model reveals a considerable compressibility at large deformations for the brain tissue as demonstrated in Figure 4.1. Although this level of volume changes seems unrealistic (especially in compression), the results indicate that the incompressibility assumption for the brain tissue might need to be revisited.
Figure 4.1. Change of volume for white matter, gray matter, and corona radiata brain tissues based on the Ogden hyperelastic model with parameters presented in Moran et al. (2014). The simulation is performed in ABAQUS with dimensions, mesh properties, and boundary conditions (glued surfaces in tension and free slipping surfaces in compression) adopted from the same reference for a 3D model. To check for the compatibility of the present simulation with (Moran et al., 2014), force-displacement curves based on the current model are compared with those in this reference which found to be basically identical (data not shown here).

Another important consideration in model calibration is to appropriately consider the boundary conditions of the experimental setup and their conformity with the modeling assumptions. For uniaxial experiments on the brain tissue, the size of the samples excised from the tissue is usually small with aspect ratios close to unity (Budday et al., 2017; Jin et al., 2013). For such sample size and shape, one needs to appropriately consider the deviation from a homogeneous deformation. For tensile experiments, top and bottom of the sample are usually glued to the instrument crosshead surfaces which causes a non-even lateral deformation of the sample (see Figure 4.7(a)-(c)). The same scenario happens for samples glued to the crosshead surfaces in compression (Figure 4.7(d)-(f)). Even for non-glued samples in compression, the friction between the tissue and the crosshead faces can cause a level of inhomogeneity in deformation of the sample (Miller, 2005).
appropriately compensate for deviation from a homogeneous elastic field assumption, Miller and coworkers (Miller, 2001, 2005; Miller and Chinzei, 2002) proposed a method in which the shape of the lateral deformation of the sample during no-slip boundary condition uniaxial tension or compression is calculated and incorporated in the deformation function for obtaining the material constants of the brain tissue. Some other researchers have used numerical analysis using finite element method and minimizing the objective function for the difference between simulation results and experimental data in an iterative loop to optimize the model parameter values (Moran et al., 2014). While the former method is mathematically rigorous and valid for cylindrical samples only, the latter is time consuming and might result in numerical outputs for model parameters that are physically unsound as shown in Figure 4.1, although they are mathematically correct.

In this work, the general formalism of the Ogden nonlinear elastic model is first presented and the appropriate forms of the strain for application in the model for tension and compression are briefly discussed. The incompressible and compressible forms of the Ogden hyperelasticity are then used to calibrate the model parameters for the brain tissue based on the experiments conducted by Budday et al. (2017). To find the numerical values of such model constants for different regions of the brain, the mathematical modeling is first utilized followed by finite element simulations to investigate any deviation from homogeneous elastic fields during deformation due to the no-slip boundary condition. It is shown herein how neglecting such deviations can cause huge discrepancy between the results of the mathematical modeling and experiments. Due to the incompressibility of the brain tissue in compression and its slightly compressible behavior in tension, it is proposed in this work that the tension-compression asymmetry might arise from the variation of the tissue compressibility in these testing modes, while the deviatoric part of the strain (or strain energy function) can be assumed to be symmetric and modeled based on the Bažant class of strains.
(Bažant, 1998). This hypothesis is used for calibrating the model which shows satisfying agreement with the experiments. This chapter is concluded with suggestions for future experimental and modeling procedures that can better reflect the nonlinear mechanical behavior of the brain tissue at large deformations.

4.2. Animals and Experimental Procedures

In the current study, the experimental results of Budday et al. (2017) are used to calibrate the Ogden hyperelastic model parameters. The hyperelastic analysis of the experiments has already been included in this reference, however, since the deviation from homogenous uniaxial deformation due to the no-slip boundary conditions was not considered therein, the obtained model parameters overestimates the tissue properties. Introducing a combined modeling-simulation methodology, it is demonstrated in here how tissue compressibility can cause the asymmetric tension-compression behavior; and accordingly, a set of Ogden hyperelastic model parameters are presented for future modeling purposes.

Recently, Budday et al. (2017) conducted a comprehensive set of experiments on human brain tissue samples. They performed uniaxial and shear experiments on samples excised from corona radiata (CR), corpus callosum (CC), cortex (C), and basal ganglia (BG) with different testing protocols and in different directions with respect to the axonal fibers preferred orientation (in CR and CC). For uniaxial testing, they excised $5 \times 5 \times 5 \ mm$ samples, however, due to the soft nature of the tissue, samples deformed under their own weight and their sizes varied from $2 \sim 5 \ mm$ in height and $3 \sim 7 \ mm$ in side length. To properly secure the samples during deformation, they glued the samples at the top and bottom surfaces to the crosshead surfaces of the testing machine using a thin layer of cyanoacrylate adhesive. The samples were loaded at the rate of $v = 2 \ mm/min$ uniaxially and representative stress-stretch curves were obtained by averaging the load and unload
paths to mimic a strain rate that approaches zero, hence, the time dependent behavior (viscoelasticity) can be neglected and hyperelastic models can be used to fit the data. Since no statistically significant anisotropic behavior of the tissue was observed, the authors presented regional dependent stress-stretch curves averaging all the tested directions in each region.

4.3. Generalized Seth-Hill and Bažant Strain Tensors

During a continuum deformation, a material point which is identified by the coordinates \( \mathbf{X} \) in the Cartesian system at time \( t = t_0 \) moves to the coordinates \( \mathbf{x} \) at a time \( t > t_0 \). Hence, the path of motion of this point can be represented as:

\[
\mathbf{x} = \chi(\mathbf{X}, t)
\]

in which \( \chi \) is a uniquely invertible motion function. The spatial (deformed) line element \( d\mathbf{x} \) can be generated from the material (undeformed) line element \( d\mathbf{X} \) using the relation:

\[
d\mathbf{x} = \mathbf{F}(\mathbf{X}, t)d\mathbf{X}
\]

where \( \mathbf{F}(\mathbf{X}, t) \) is a two-point tensor known as the deformation gradient which is mathematically defined as (Holzapfel, 2000):

\[
\mathbf{F}(\mathbf{X}, t) = \frac{\partial \chi(\mathbf{X}, t)}{\partial \mathbf{X}}
\]

The deformation gradient may be decomposed into the stretch and rotation tensors as:

\[
\mathbf{F} = \mathbf{RU} = \mathbf{VR}
\]

in which \( \mathbf{R} \) is a proper orthogonal matrix known as the rotation tensor, and \( \mathbf{U} \) and \( \mathbf{V} \) are positive definite symmetric matrices known as right and left stretch tensors, respectively. The right Cauchy-Green strain tensor \( \mathbf{C} \) can be obtained from the deformation gradient as:

\[
\mathbf{C} = \mathbf{F}^T \mathbf{F} = \mathbf{U}^2
\]
Accordingly, the eigenvalues of the right stretch tensor are equal to the square root of those of the Cauchy-Green strain tensor and are known as the principal stretches $\lambda_i$ ($i = 1, 2, 3$).

The material Seth-Hill class of strain tensors are defined as (Hill, 1968; Seth, 1961):

$$ E^{(m)} = \begin{cases} \frac{1}{m} (U^m - I), & m \neq 0 \\ \ln(U), & m = 0 \end{cases} $$  (4.7)

in which $I$ is the second order $3 \times 3$ identity tensor. While $m$ is designated as a superscript for $E$ in Eq. (4.7), it is the power for $U$ in the right-hand-side of this equation. In terms of the principal stretches, the components of the principal strains can be obtained as:

$$ E^{(m)}_i = \begin{cases} \frac{1}{m} (\lambda^m_i - 1), & m \neq 0 \\ \ln(\lambda_i), & m = 0 \end{cases} $$  (4.8)

with $i = 1, 2, 3$. According to Eq. (4.8), for $m = 0, 1, 2, -1, \text{ and } -2$, the principal values for Hencky, Biot, Green-St. Venant, Swainger, and Almansi-Hamel strain tensors are obtained (Batra, 2006). In general, the Seth-Hill class of strains are asymmetric, i.e. $E_i(\lambda_i) \neq -E_i(\frac{1}{\lambda_i})$ (except for the Hencky strain). For uniaxial deformation, the relation between the axial stretch and strain for different Seth-Hill strain tensors is shown in Figure 4.2. As it is seen in this figure, all of these strain tensors (except for the Hencky strain) demonstrate some unsuitable features at singular deformations. In general, it is expected that the strain measures approach positive and negative infinity for very large or zero stretches, respectively, as described in (Moerman et al., 2016).

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7 It should be noted that this definition is only valid for the principal components of Swainger and Almansi-Hamel strain tensors. In general, the strain tensors associated with the negative values of $m$ in Eq. (4.7) are spatial strain tensors and are formulated based on the left Cauchy-Green strain or the left stretch tensors. However, since the principal components of the left and right Cauchy-Green strain tensors (or alternatively the left and right stretch tensors) are equal, the principal strains can be obtained from the principal stretches regardless of the sign of the parameter $m$ as shown in Eq. (4.8).
Nevertheless, for the positive values of $m$, the respective principal strains ($E_1$ in Figure 4.2) approaches $-\frac{1}{m}$ for $\lambda_1 \rightarrow 0$, and for the negative values of $m$, it approaches $\left|\frac{1}{m}\right|$ as $\lambda_1 \rightarrow +\infty$.

Figure 4.2. Variation of the longitudinal strain vs the longitudinal stretch in uniaxial tension-compression for five different strain tensors.

To address the issues with the single-term Seth-Hill class of strains, some hybrid forms of the strain tensor considering positive and negative values of $m$ have been proposed by different authors. Recently, Moerman et al. (2016) presented a strain tensor whose asymmetry is controlled by a weighting factor $q$ as:

$$\epsilon^{(m,q)} = qE^{(m)} + (1 - q)E^{(-m)}$$

with $q \in [0,1]$. For $q \neq 0,1$, this hybrid form eliminates the aforementioned disadvantages of the single-term Seth-Hill class of strains. A special case of Eq. (4.9) is when $q = 0.5$, which results in the symmetric strain tensor introduced by Bažant (1998) and reads as:

$$\Pi^{(m)} = \frac{1}{2}\left(E^{(m)} + E^{(-m)}\right) = \frac{1}{2m}(U^m - U^{-m})$$

and in terms of principal stretches as:
\[ H_i^{(m)} = \frac{1}{2m} (\lambda_i^m - \lambda_i^{-m}) \]  

Figure 4.3 shows the variation of the uniaxial strain with the uniaxial stretch for the Bažant strain tensors with different values of \( m \). As it is demonstrated in this figure \( E_1(\lambda_1) = -E_1 \left( \frac{1}{\lambda_1} \right) \) for each curve that exhibits the symmetricity of the Bažant strain tensor. In addition, this class of strain satisfies the requirements for singularities at zero and large stretches.

![Figure 4.3. Variation of the longitudinal strain vs the longitudinal stretch in uniaxial tension-compression for the Bažant strain tensor with different values of \( m \).](image)

4.4. Compressibility and Poisson’s Ratio

Poisson’s ratio is a material parameter to quantify the induced lateral deformation upon axially forced stretch, and is defined as the negative of the ratio of the lateral “strain” to that in the axial direction for uniaxial testing mode. Accordingly, the relation between the strain and the axial stretch in this testing mode is important in the numerical values of the Poisson’s ratio. Here, it is again noted that “strain” is a mathematical representation of the relative deformation, whereas, “stretch” is a more physical quantity. Commonly, in linear elasticity analysis of small
deformations, a Poisson’s ratio equal to 0.5 is considered to represent an incompressible material. Since this definition is mostly consistent with the engineering (Biot) strain tensor, the concept of compressibility of materials under uniaxial condition for different measures of strain at large deformation and the associated Poisson’s ratio are investigated herein.

One now considers a cube with height \( l_1 \) and equal lateral sides length of \( l_2 \). Upon applying longitudinal deformation in the \( l_1 \) direction, the sides of the specimen start to deform identically according to the Poisson effect and assuming homogeneous and isotropic material behavior. The final volume of the sample can be found by incorporating the definition of the Poisson’s ratio for different measures of the strain. Table 4.1 shows the ratio between the final and initial volumes of the specimen \( \left( \frac{V_f}{V_i} \right) \) in terms of the longitudinal stretch in the \( l_1 \) direction \( (\lambda_1) \) and Poisson’s ratio for four different measures of strain (see also Eqs. (4.8) and (4.11)).

![Table 4.1. Ratio of volume change \( \left( \frac{V_f}{V_i} \right) \) in terms of Poisson’s ratio and the longitudinal stretch for uniaxial deformation of a cuboidal sample with four different measures of strain.](image)

<table>
<thead>
<tr>
<th>Strain Measure</th>
<th>Deformed Height</th>
<th>Deformed Side Length</th>
<th>Volume Ratio ( \frac{V_f}{V_i} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biot</td>
<td>( l_1(1 + E_1^{(1)}) )</td>
<td>( l_2(1 - \nu E_1^{(1)}) )</td>
<td>( \lambda_1(1 + \nu(1 - \lambda_1))^2 )</td>
</tr>
<tr>
<td>Swainger</td>
<td>( \frac{l_1}{1 - E_1^{(-1)}} )</td>
<td>( \frac{l_2}{1 + \nu E_1^{(-1)}} )</td>
<td>( \frac{\lambda_1^2}{(\lambda_1 + \nu(\lambda_1 - 1))^2} )</td>
</tr>
<tr>
<td>Hencky</td>
<td>( l_1 \exp(\varepsilon_1^{(0)}) )</td>
<td>( l_2 \exp(-\nu \varepsilon_1^{(0)}) )</td>
<td>( \lambda_1^{2\nu} )</td>
</tr>
<tr>
<td>Bażant (( m = 1 ))</td>
<td>[ \lambda_1 \left[ \frac{1}{\lambda_1^2} + \left( \frac{1}{\lambda_1^2} \right)^2 \right] ]</td>
<td>[ -\nu \lambda_1 \left[ \frac{1}{\lambda_1^2} + \left( \frac{1}{\lambda_1^2} \right)^2 \right] ]</td>
<td>[ \frac{1}{8\lambda_1^2} \left( -1 + \lambda_1^2 + \lambda_1 \right) \left( 2 + \frac{1}{\lambda_1^2} + \lambda_1 \right) ] [ \times \left( \nu \lambda_1 \left( -\nu \lambda_1 + \frac{4 - 2\nu^2 + \nu^2(1 + \lambda_1^4)}{\lambda_1^2} \right) \right)^2 ]</td>
</tr>
</tbody>
</table>

Figure 4.4 shows the variation of the volume ratio with Poisson’s ratio and the axial stretch. As it is shown in this figure, the Hencky and Bażant (\( m = 1 \)) measures of strain both exhibit volume reduction and increment during compression \( (\lambda_1 < 1) \) and tension \( (\lambda_1 > 1) \), respectively. On the other hand, the volume change for materials with Biot and Swainger strain measures do not
show a uniform variation with stretch: for a small Poisson’s ratio ($\nu < 0.3$), the volume change follows the same routine as the Hencky and Bažant strain measures (reduction in compression and increment in tension), however, for larger Poisson’s ratios the volume reduces for Biot and increases for Swainger measures of strain regardless of the tensile or compressive nature of the axial deformation.

Figure 4.4. Variation of the volume ratio with the Poisson’s ratio and the longitudinal stretch for uniaxial deformation of a cuboidal sample with four different strain measures.

Another important feature of Figure 4.4 is the variation of volume ratio at $\nu = 0.5$ which is depicted in a 2D plot in Figure 4.5. As it is seen in this figure, the assumption of incompressibility for $\nu = 0.5$ is only valid for very small axial stretches for Biot and Swainger strains, whereas, the volume ratio is equal to 1 for the Hencky strain tensor and is very close to 1 for the Bažant strain tensor even at large stretches. Figure 4.6 demonstrates the Poisson’s ratio value required for incompressibility condition at a range of axial stretches in uniaxial loading condition for different measures of strain. The Biot and Swainger strains are used in this section as representatives for the Seth-Hill class of strains with positive and negative values of parameter $m$. According to what is found in here, presenting a single value for Poisson’s ratio of a nonlinear material at large deformations does not seem to be a meaningful terminology. For example, Moran et al. (2014)
presented a single value of the Poisson’s ratio for each region of the brain tissue based on their findings for the shear modulus and the compressibility constants of the Ogden hyperelastic model. Their findings show that this ratio is close to 0.4 for the brain tissue which implies a very small compressible behavior. Nevertheless, the FE analysis shows huge volumetric changes (as shown in Figure 4.1), which in no way is consistent with this value of the Poisson’s ratio. Accordingly, in this chapter presenting a Poisson’s ratio for the brain tissue is avoided and the authors directly calculate the volumetric changes in ABAQUS and present it as a function of the axial stretch during uniaxial testing of the specimens.

Figure 4.5. Variation of the volume ratio with the longitudinal stretch for uniaxial deformation of a cuboidal sample for four different strain measures and a Poisson’s ratio of 0.5.
4.5. Incompressible Ogden Hyperelastic Strain Energy

For an incompressible material, Ogden hyperelastic strain energy function may be presented in terms of the principal stretches as:

$$
\Psi_{Og\text{d}}(\lambda_1, \lambda_2, \lambda_3) = \sum_{j=1}^{N} \left[ \frac{2\mu_j}{m_j^2} \left( \lambda_1^{m_j} + \lambda_2^{m_j} + \lambda_3^{m_j} - 3 \right) \right]
$$

(4.12)

for the Seth-Hill class of strains, and

$$
\Psi_{Og\text{d}}(\lambda_1, \lambda_2, \lambda_3) = \sum_{j=1}^{N} \left[ \frac{\mu_j}{m_j^2} \left( \lambda_1^{m_j} + \lambda_2^{m_j} + \lambda_3^{m_j} + \lambda_1^{-m_j} + \lambda_2^{-m_j} + \lambda_3^{-m_j} - 6 \right) \right]
$$

(4.13)

for the Bažant class of strains. In addition, the incompressibility condition requires the volume size to be preserved during deformation which is mathematically implemented as:

$$
J = \lambda_1 \lambda_2 \lambda_3 = 1
$$

(4.14)

For a uniaxial experiment on a homogeneous and geometrically symmetric sample, this criterion is further specific and reads as:
\[ \lambda_2 = \lambda_3 = \lambda_1^{-1/2} \]  

(4.15)

The principal Cauchy stresses \((t_i)\) can be obtained from the partial derivatives of the strain energy function, and for the incompressible hyperelastic materials are expressed as:

\[ t_i = \lambda_i \frac{\partial \psi}{\partial \lambda_i} - p, \quad i = 1, 2, 3 \]  

(4.16)

in which \(p\) is the Lagrange multiplier. For the uniaxial testing of an Ogden incompressible material in direction-1 and with incorporating the stress-free condition for lateral directions \((t_2 = t_3 = 0)\), the relation between the uniaxial stress and stretch can be obtained using Eq. (4.16) as:

\[
t_1 = \sum_{j=1}^{N} \left[ \frac{2 \mu_j}{m_j} \left( \lambda_1^{m_j} - \lambda_1^{-m_j} \right) \right] \]  

(4.17)

for the Seth-Hill class of strains, and

\[
t_1 = \sum_{j=1}^{N} \left[ \frac{\mu_j}{m_j} \left( \lambda_1^{m_j} - \lambda_1^{-m_j} + \lambda_1^2 - \lambda_1^{-2} \right) \right] \]  

(4.18)

for the Bažant class of strains. The first Piola-Kirchhoff stress tensor \(\mathbf{P}\) can be related to the Cauchy stress tensor using the Piola transformation as (Holzapfel, 2000):

\[ \mathbf{P} = J \mathbf{t} \mathbf{F}^{-T} \]  

(4.19)

For the case of uniaxial testing of an incompressible material, the principal Piola-Kirchhoff stress (the engineering stress) in the loading direction may be simply obtained as:

\[ P_1 = \frac{t_1}{\lambda_1} \]  

(4.20)

with \(t_1\) as presented in Eqs. (4.17) and (4.18).
4.6. Compressible Ogden Hyperelastic Strain Energy

The deformation gradient during finite deformation of a compressible body can be decomposed into distortional and volumetric components, \( \bar{F} \) and \( F_{\text{vol}} \), respectively, as:

\[
F = F_{\text{vol}} \bar{F}
\]

(4.21)

with \( F_{\text{vol}} = J^{1/3} I \) and \( \bar{F} = J^{-1/3} F \). Accordingly, the generalized deviatoric Seth-Hill strains are expressed as follows:

\[
\bar{E}^{(m)} = \begin{cases} \frac{1}{m} (\bar{U}^m - I), & m \neq 0 \\ \ln(\bar{U}), & m = 0 \end{cases}
\]

(4.22)

with \( \bar{U} = J^{-1/3} U \), and for the Bažant class of strains the deviatoric strains read as:

\[
\bar{H}^{(m)} = \frac{1}{2} (\bar{E}^{(m)} + \bar{E}^{(-m)}) = \frac{1}{2m} (\bar{U}^m - \bar{U}^{-m})
\]

(4.23)

The deviatoric principal stretches are also related to \( \lambda_i \)'s as:

\[
\tilde{\lambda}_i = J^{-1/3} \lambda_i
\]

(4.24)

The Ogden decomposed hyperelastic strain energy function for compressible materials is presented in terms of the principal deviatoric stretches and determinant of the deformation gradient \( J \) as:

\[
\Psi_{\text{Ogd}}(\tilde{\lambda}_1, \tilde{\lambda}_2, \tilde{\lambda}_3, J) = \sum_{j=1}^{N} \left[ \frac{2\mu_j}{m_j^2} (\tilde{\lambda}_1^{m_j} + \tilde{\lambda}_2^{m_j} + \tilde{\lambda}_3^{m_j} - 3) + \frac{1}{D_j} (J - 1)^{2j} \right]
\]

(4.25)

for the Seth-Hill class of strains, and
\[ \Psi_{Ogda}(\lambda_1, \lambda_2, \lambda_3, J) = \sum_{j=1}^{N} \left[ \frac{\mu_j}{m_j^2} \left( \lambda_1^{m_j} + \lambda_2^{m_j} + \lambda_3^{m_j} + \lambda_1^{-m_j} + \lambda_2^{-m_j} + \lambda_3^{-m_j} - 6 \right) \right. \\
\left. + \frac{1}{D_j} (J - 1)^{2j} \right] \]

for the Bažant class of strains.

The principal Cauchy stresses for a compressible hyperelastic material can be obtained as (Ogden, 1997):

\[ Jt_i = \tilde{\lambda}_i \frac{\partial \varphi}{\partial \tilde{\lambda}_i} - \left( \frac{1}{3} \sum_{a=1}^{3} \tilde{\lambda}_a \frac{\partial \varphi}{\partial \tilde{\lambda}_a} - f \frac{\partial \varphi}{\partial f} \right), \quad i = 1, 2, 3 \]  \hspace{1cm} (4.27)

For the uniaxial testing of a homogenous compressible Ogden hyperelastic material with laterally symmetric geometry, one can assume \( \lambda_2 = \lambda_3 \), and using Eqs. (4.24) through (4.27), the relation between the uniaxial stress and principal stretch can be obtained as:

\[ Jt_1 = \sum_{j=1}^{N} \left[ \frac{4\mu_j}{3m_j} (\lambda_1^{m_j} - \lambda_2^{m_j})(\lambda_1 \lambda_3^2)^{-m_j/3} + \frac{2j\lambda_1 \lambda_2^2}{D_j} (\lambda_1 \lambda_2^2 - 1)^{2j-1} \right] \]  \hspace{1cm} (4.28)

for the Seth-Hill class of strains, and

\[ Jt_1 = \sum_{j=1}^{N} \left[ \frac{2\mu_j}{3m_j} (\lambda_1^{m_j} - \lambda_2^{m_j})(\lambda_1 \lambda_3^2)^{-m_j/3} - (\lambda_1^{-m_j} - \lambda_2^{-m_j})(\lambda_1 \lambda_3^2)^{m_j/3} \right. \\
\left. + \frac{2j\lambda_1 \lambda_2^2}{D_j} (\lambda_1 \lambda_2^2 - 1)^{2j-1} \right] \]  \hspace{1cm} (4.29)

for the Bažant class of strains. Equations (4.28) and (4.29) depend on the lateral principal stretch \( \lambda_2 \), which, if not measured during experiments, is essentially an unknown variable. Incorporating the stress-free condition for the lateral directions \( (t_2 = t_3 = 0) \), additional relations to find the lateral principal stretch \( \lambda_2 \) are obtained as:
\[ \sum_{j=1}^{N} \left[ \frac{2\mu_j}{3m_j} (\lambda_{2j}^m - \lambda_{1j}^m) (\lambda_1 \lambda_2^2)^{-m_j/3} + \frac{2j\lambda_1 \lambda_2^2}{D_j} (\lambda_1 \lambda_2 - 1)^{2j-1} \right] \equiv 0 \]  

(4.30) for the Seth-Hill class of strains, and

\[ \sum_{j=1}^{N} \left[ \frac{\mu_j}{3m_j} (\lambda_{2j}^m - \lambda_{1j}^m) (\lambda_1 \lambda_2^2)^{-m_j/3} - (\lambda_{2j}^m - \lambda_{1j}^m) (\lambda_1 \lambda_2^2)^{m_j/3} \right. \]

\[ + \frac{2j\lambda_1 \lambda_2^2}{D_j} (\lambda_1 \lambda_2 - 1)^{2j-1} \] \equiv 0

(4.31) for the Bažant class of strains.

The principal Piola-Kirchhoff stress in the loading direction can also be obtained from the Cauchy principal stress as:

\[ P_1 = \frac{Jt_1}{\lambda_1} \]  

(4.32)

4.7. Model Implementation

4.7.1. Incompressible Behavior

Budday et al. (2017) presented the nominal stress vs stretch for different regions of the brain. To obtain the normal stress in the loading direction of the uniaxial testing, they divided vertical force by the initial (undeformed) surface area of the sample. They then calibrated the model parameters of different hyperelastic material models and found that the one-term Ogden model with a negative nonlinearity parameter can acceptably predict the mechanical behavior of the brain tissue. Here, the same procedure is used to model the deformation of the brain tissue based on the experiments conducted by those authors. For the incompressibility assumption, Eqs. (4.17), (4.18), and (20) are used in a curve fitting scheme. The FindFit function of Mathematica 11.2 (Wolfram Research Inc., Champaign, IL) is utilized to find the numerical values of model parameters in
tension and compression. Since the boundary conditions of tension and compression experiments performed by Budday et al. (2017) are different from the ideal uniaxial testing, finite element simulation is used to monitor the accuracy of the values of the model parameters obtained based on the mathematical modeling. Accordingly, a 3D model is created in ABAQUS/CAE™ 2017 (AB AQUS Inc., Providence, RI) including two rigid plates at the top and bottom of a hyperelastic rectangular cube representing the brain tissue sample. The top and bottom plates are tied to the cuboid, and while the bottom one is fixed, the displacement is applied on the top plate at the rate of \( v = 2 \text{ mm/min} \) and up to a stretch value of 0.9 in compression and 1.1 in tension. The dimensions of the deformable sample are set at \( 5 \times 5 \times 3.5 \text{ mm (side \times side \times height)} \) equal to the average size of the sample as reported in Budday et al. (2017), and it includes 11250 linear hexahedral elements of type C3D8H.

4.7.2. Compressible Behavior

The same procedure is used for modeling and simulation by assuming the compressible behavior of the brain tissue. However, in the mathematical modeling, in addition to the model parameters the lateral stretch (\( \lambda_2 \)) is an unknown variable. Since \( \lambda_2 \) is not a constant (and varies with \( \lambda_1 \)), it cannot be directly found using a fitting scheme. Accordingly, an iterative loop is used in Mathematica to find model constants and \( \lambda_2 \). In this way, one may initially “assume” a function for \( \lambda_2 \) in terms of \( \lambda_1 \) (such as \( \lambda_2 = \lambda_1^{-b} \) with \( b \) a constant close but not equal to \( \frac{1}{2} \)). This would eliminate \( \lambda_2 \) from Eqs. (4.28) or (4.29). At the next step, the model parameters can be found utilizing FinFit function in Mathematica using experimental values, similar to what was described for the incompressible model. Next, one needs to study the appropriateness of the assumed values for \( \lambda_2 \). Accordingly, Eq. (4.30) or (4.31) is used to find \( \lambda_2 \) values with the model parameter values found in the previous step. If the “calculated” \( \lambda_2 \) values are significantly different from the
“assumed” ones, they are used as the “assumed” values for the next step. In each step, the engineering stress (or load) vs stretch is also obtained based on the calculated model parameters and $\lambda_2$ values and compared with the experimentally obtained one. The optimum model parameters are found when the differences between $\lambda_2$ values from one step and that of the respective previous step and also between the calculated stress and experimentally obtained stress are simultaneously minimized. The simulation process for validating the findings based on the mathematical model is the same as the one for the incompressible model.

4.8. Homogeneity of the Elastic Fields

In an ideal uniaxial compression experiment, a prismatic (usually cubic or cylindrical) specimen is fixed in the testing device such that its top and bottom surfaces become into full contact with the loading compartments (crossheads). However, the contacting surfaces are allowed to slip laterally with respect to each other in order to avoid generation of any lateral stresses that violate the uniaxial loading condition. A thin layer of lubricant is sometimes placed between the contacting surfaces to minimize the friction that can slightly affect the homogeneity of the stress field. In tension, on the other hand, a dog-bone shape sample is usually fixed between the grips and pulled vertically. Since obtaining homogeneous stress and strain fields is almost impossible in this testing mode due to the boundary effects at the grips, usually a longer specimen is used and an extensometer is hooked to its middle part to record the deformation. Accordingly, the stress and strain within the middle part of the sample can be assumed to fulfill the uniaxial condition.

For the case of the uniaxial testing of soft tissues, implementing a testing procedure that satisfactorily provides a uniaxial testing condition is difficult. In compression, due to the very soft and slippery nature of the samples, they might slide under the crosshead surfaces during deformation; adding fluid to reduce the friction between the tissue and the crosshead surfaces
worsens this situation. More importantly, small amount of friction between the tissue and the crosshead surfaces has a considerable effect on the recorded load for very soft materials (Miller, 2005). For the case of the tensile experiments, there are also limitations in uniaxial testing of soft tissues. In general, clamping a soft tissue specimen between the grips for tension is not feasible. In addition, excising long specimens from the tissue with even thickness and homogeneity is difficult. For example, for the brain tissue, it is impossible to cut a long enough specimen from the cortex tissue that provides uniaxial condition during tensile experiments. Accordingly, instead of attempting to provide ideal uniaxial testing condition, one can fix the specimen in the instrument by gluing its contacting surfaces to the crosshead platens; and to obtain the elastic constants, the method of analysis of the output data needs to be modified. While some researchers developed rigorous mathematical modeling for this purpose (Miller, 2001, 2005; Miller and Chinzei, 2002), others tried to use iterative simulations and correcting the numerical values pertaining to the mechanical model.

In their experimental setup for the brain tissue, Budday et al. (2017) used a thin layer of cyanoacrylate glue to adhere the specimen surfaces to the loading platens of the testing device. However, in the analysis followed the experiment, an ideal uniaxial testing mode was assumed and the numerical values of the hyperelastic model parameters were obtained through a fitting scheme using Matlab. Figure 4.7 shows the axial and lateral nominal strain and stress contours of the cuboid representing the brain tissue at stretches of 1.1 (tension) and 0.9 (compression) with incorporating the Ogden model parameters for the corona radiata as presented in Table 7 of Budday et al. (2017). Obviously, neither longitudinal nor lateral elastic fields are constant at these stretches; a constant elastic field (stress or strain) in principal directions is a requirement for the uniaxial
elasticity analysis. In addition, while the stress field is not constant, presenting a single value of
the axial stress for the whole sample seems not to be suitable.

In the current analysis, the model constants are first obtained through modeling in
Mathematica, similar to what was performed by Budday et al. (2017). The obtained model
parameters are then used for simulation in ABAQUS and the output load is compared with the
experimental values. If any significant difference is observed, the input loads for curve fitting in
Mathematica are adjusted by dividing them by a correction factor which is essentially the ratio
between the simulation results and the experimentally obtained values at each data point. This
procedure is continued until the difference between the results obtained based on the simulation
and the experiments is minimized. In addition, instead of reporting the results as stress-stretch
curves, the load-extension curves are presented. The load values according to the experiments are
artificially constructed by multiplying the reported nominal stresses in (Budday et al., 2017) by
the average cross-section area (25 $mm^2$), and the stretch values are converted to extension by using
\[ \Delta h = (\lambda - 1)h_{\text{undeformed}} \]. Since the stress and strain (stretch) values in principal directions are
not constant according to what is shown in Figure 4.7, the load-displacement curves are more
physically meaningful than the stress-strain (stretch) curves for this setting of experiments. For the
sake of simplicity, one starts with the one-term Ogden model and calibrates the model parameters
in tension and compression separately. To find the values that can simultaneously interpolate the
tension and compression data, the Ogden model with Bažant or Moreman-Simms-Nagel strain
fields are used. Such models are implemented as a two-term Ogden hyperelastic model in
ABAQUS.
Figure 4.7. Contours of (a) nominal strain in “y-y” direction, (b) nominal strain in “x-x” direction, and (c) Cauchy stress in “y-y” direction for uniaxial tension. Ogden hyperelastic model parameters are adopted from Table 7 in Budday et al. (2017) for Corona Radiata. Panels (d), (e), and (f) are the same as (a), (b), and (c), respectively, except for being in compression. The deformation is imposed in “y-y” direction according to the coordinate triad shown in this figure.
4.9. Brain Tissue as an Incompressible Material

Considering Eqs. (4.17) and (4.20), the relation between the applied load and stretch in uniaxial testing of a material with a one-term Ogden hyperelastic incompressible governing behavior reads as:

\[ f = P_1 A = \frac{t_1 A}{\lambda} = \frac{2\mu_1 A}{m_1} \left( \lambda^{(m_1 - 1)} - \lambda^{-\left(\frac{m_1}{2} + 1\right)} \right) \tag{4.33} \]

in which \( A \) is the cross-section area of the sample and \( \lambda \) is the principal stretch in the loading direction. This equation is used for finding model parameters (\( \mu \) and \( m \)) in this section.

4.9.1. Compression

In Table 4.2, the numerical values for the shear modulus and nonlinearity constant for the one-term Ogden model obtained by curve fitting of compressive load-extension experimental results with Eq. (4.33) are presented. These findings are essentially very close to the values obtained by Budday et al. (2017), as expected. These values are employed for simulation in ABAQUS. As it is seen in Figure 4.8, although the curve fitting using Eq. (4.33) with the numerical values of model constants for each region is excellent, the results of simulation considerably overpredict the load values. This deviation (up to 100% of overshooting) is a result of the no-slip boundary conditions at the top and bottom surfaces of the tested specimens. Accordingly, the aforementioned correction procedure is used to refine the model constants which result in a better agreement between the simulation and the experiments.

Table 4.2. Uncorrected model parameters of the one-term incompressible Ogden model for different regions of the brain as obtained from mathematical modeling assuming ideal uniaxial compression.

<table>
<thead>
<tr>
<th>( \mu_1 ) (kPa)</th>
<th>Cortex</th>
<th>Corpus Callosum</th>
<th>Corona Radiata</th>
<th>Basal Ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>( m_1 )</td>
<td>1.625</td>
<td>0.430</td>
<td>0.865</td>
<td>0.831</td>
</tr>
<tr>
<td></td>
<td>-16.32</td>
<td>-22.75</td>
<td>-19.98</td>
<td>-15.34</td>
</tr>
</tbody>
</table>
Figure 4.8. Load vs extension data for compression experiments as reported in Budday et al. (2017) (hollow squares), curve fitting using Eq. (4.33) and model parameters of Table 4.2 (dashed line), and FE simulation in ABAQUS using the same inputs (solid line) for (a) cortex, (b) corpus callosum, (c) corona radiata, and (d) basal ganglia.

Table 4.3 shows the corrected model parameters for the one-term Ogden model for different regions of the brain tissue. The simulation results converge to the experimental ones with only 3 or 4 iterations based on the described procedure. The load-extension results of the simulation using the model constants in Table 4.3 are compared with the experimental ones in Figure 4.9.
Table 4.3. Model parameters of the one-term incompressible Ogden model for different regions of the brain in compression after correction using the iterative simulation and modeling procedure.

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Corpus Callosum</th>
<th>Corona Radiata</th>
<th>Basal Ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_1$ (kPa)</td>
<td>0.954</td>
<td>0.204</td>
<td>0.457</td>
<td>0.499</td>
</tr>
<tr>
<td>$m_1$</td>
<td>-13.53</td>
<td>-19.54</td>
<td>-16.87</td>
<td>-12.67</td>
</tr>
<tr>
<td>$R^2$ (based on the FE simulation)</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Figure 4.9. Comparison of the experimentally obtained data (as reported in Budday et al. (2017)) and the load-extension curves based on the FE simulations (solid lines) using model parameters as shown in Table 4.3 for different regions of the brain tissue in compression.

4.9.2. Tension

Incorporating Eq. (4.33) and the results of the tension experiments as reported in Budday et al. (2017), the numerical values for the one-term incompressible Ogden model are obtained based on the curve fitting as shown in Table 4.4. Not surprisingly, the model parameters for each region are substantially close to the findings of Budday et al. (2017). These values are used for simulation and similar to the results for the case of compression, the load values obtained from simulation
overpredict the actual values, however, in this case the outcome is even worse with up to 1500% of overshooting as shown in Figure 4.10.

Table 4.4. Uncorrected model parameters of one-term incompressible Ogden model for different regions of the brain as obtained from mathematical modeling assuming ideal uniaxial tension.

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Corpus Callosum</th>
<th>Corona Radiata</th>
<th>Basal Ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_1$ (kPa)</td>
<td>1.193</td>
<td>0.350</td>
<td>0.611</td>
<td>0.659</td>
</tr>
<tr>
<td>$m_1$</td>
<td>-44.42</td>
<td>-28.15</td>
<td>-30.70</td>
<td>-32.86</td>
</tr>
</tbody>
</table>

Figure 4.10. Load vs extension data for tension experiments as reported in Budday et al. (2017) (hollow squares), curve fitting using Eq. (4.33) and model parameters of Table 4.4 (dashed line), and FE simulation in ABAQUS using the same inputs (solid line) for (a) cortex, (b) corpus callosum, (c) corona radiata, and (d) basal ganglia.

The authors tried to implement the correction procedure to adjust the model parameters, however, it is found that a one-term incompressible Ogden model with a negative nonlinearity parameter does not converge with a reasonable number of iterative loops. On the other hand, a
model with a positive nonlinearity parameter \( m_1 \) converges after a maximum of 3 iterations and results in an acceptable consonance with the experimental results. The model parameters of the one-term incompressible Ogden hyperelastic model for different regions of the brain tissue in tension are summarized in Table 4.5, and the results of the simulation based on these values are shown in Figure 4.11 besides the experimental data points.

Table 4.5. Model parameters of the one-term incompressible Ogden model for different regions of the brain in tension after correction using the iterative simulation and modeling procedure.

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Corpus Callosum</th>
<th>Corona Radiata</th>
<th>Basal Ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu_1 ) (kPa)</td>
<td>0.563</td>
<td>0.200</td>
<td>0.337</td>
<td>0.353</td>
</tr>
<tr>
<td>( m_1 )</td>
<td>15.44</td>
<td>4.52</td>
<td>6.36</td>
<td>8.12</td>
</tr>
<tr>
<td>( R^2 ) (based on the FE simulation)</td>
<td>0.991</td>
<td>0.990</td>
<td>0.991</td>
<td>0.993</td>
</tr>
</tbody>
</table>

Figure 4.11. Comparison of the experimentally obtained data (as presented in Budday et al. (2017)) and the load-extension curves based on the FE simulations (solid lines) using model parameters as shown in Table 4.5 for different regions of the brain tissue in tension.
4.9.3. Tension-Compression

Findings of the previous subsections demonstrate that it is impossible to interpolate the whole tension-compression uniaxial experiment with one-term Ogden model based on the Seth-Hill class of strains. In fact, while the tissue behavior in compression is well interpolated with a negative nonlinearity constant, the tensile behavior requires a positive nonlinearity constant in hyperelastic modeling. This finding is in consonance with the criteria associated with the strain energy functions for hyperelastic modeling of nonlinear materials proposed by Attard and coworkers (Attard, 2003; Attard and Hunt, 2004). Accordingly, modeling of the whole tension-compression behavior of the brain tissue requires a strain energy function that includes both positive and negative nonlinearity constants. As such, the strain functions proposed by Bažant (1998) and Moerman et al. (2016) are used for hyperelastic modeling of different regions of the brain. It is found that the Ogden hyperelastic model based on the Bažant strain tensors cannot appropriately interpolate the experimental results with a reasonable number of iterations (data not shown here) which demonstrates the tension-compression asymmetric behavior of the brain tissue. On the other hand, the Ogden hyperelastic model based on the Moerman-Simms-Nagel (MSN) definition of strain, which considers the tension-compression asymmetry without altering the nonlinearity constant, can partially predict the tension-compression nonlinear behavior of the brain tissue as shown in Figure 4.12. The results in this figure are obtained based on the corrected numerical values of model parameters as shown in Table 4.6.\(^8\)

\(^8\) It should be noted that the one-term Ogden Hyperelastic model based on the MSN strain is identical to a two-term Ogden model with \(m_2 = -m_1, \mu_1 = q\mu, \mu_2 = (1 - q)\mu\) in ABAQUS.
Table 4.6. Model parameters of the one-term incompressible Ogden model based on MSN hybrid strain for different regions of the brain in tension and compression after correction using the iterative simulation and modeling procedure.

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Corpus Callosum</th>
<th>Corona Radiata</th>
<th>Basal Ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$ (kPa)</td>
<td>0.717</td>
<td>0.142</td>
<td>0.293</td>
<td>0.373</td>
</tr>
<tr>
<td>$m_1$</td>
<td>±18.20</td>
<td>±23.83</td>
<td>±21.55</td>
<td>±16.61</td>
</tr>
<tr>
<td>$q$</td>
<td>0.174</td>
<td>0.141</td>
<td>0.051</td>
<td>0.094</td>
</tr>
<tr>
<td>$R^2$ (based on the FE simulation)</td>
<td>0.998</td>
<td>0.994</td>
<td>0.996</td>
<td>0.998</td>
</tr>
</tbody>
</table>

Figure 4.12. Comparison of the experimentally obtained data (as presented in Budday et al. (2017)) and the load-extension curves based on the FE simulations (solid lines) using Ogden model parameters based on MSN hybrid strain as shown in Table 4.6 for different regions of the brain tissue in tension and compression.

4.10. Brain Tissue as a Compressible Material

For one-term compressible Ogden hyperelastic model, the relation between the load and the principal stretch in the loading direction of the uniaxial testing might be expressed as:

$$f = P_1A = \frac{f t_1A}{\lambda_1} = \left(\frac{4}{3}m_1^2 \left(\lambda_1^{m_1} - \lambda_2^{m_1}\right) - \frac{m_1}{\lambda_1^{m_1}} \right) + \frac{2}{D_1} \left(\lambda_1^{m_2} - 1\right) \frac{A}{\lambda_1}$$

(4.34)

As described before, this equation is coupled with another equality that imposes the stress-free condition in the lateral directions which for the one-term compressible Ogden model reads as:
\[
\lambda_2^{m_1} - \lambda_1^{m_1} + \frac{3m_1(\lambda_1 \lambda_2)(1 + \frac{m_1}{3})}{\mu_1 D_1} (\lambda_1 \lambda_2 - 1) \equiv 0
\] (4.35)

Using the aforementioned iterative scheme, the model parameters can be calibrated based on the available experimental data.

4.10.1. Compression

In Table 4.7 the numerical values of the one-term compressible Ogden model that interpolate the response of different regions of the brain tissue in uniaxial compression are shown. These numbers are the corrected values with considering the inhomogeneous elastic fields due to the no-slip boundary conditions. The results of the simulations based on these numbers are shown in Figure 4.13(a) which demonstrate an acceptable agreement with the experimental ones. In Figure 4.13(b), the variation of the volume ratio during compressive deformation is shown. All the regions of the brain tissue show a very small volume change during 10% compression implying that the mechanical behavior of the brain can be considered as nearly incompressible in compression.

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Corpus Callosum</th>
<th>Corona Radiata</th>
<th>Basal Ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu ) (kPa)</td>
<td>1.012</td>
<td>0.242</td>
<td>0.520</td>
<td>0.523</td>
</tr>
<tr>
<td>( m_1 )</td>
<td>-16.01</td>
<td>-22.81</td>
<td>-19.46</td>
<td>-13.20</td>
</tr>
<tr>
<td>( D_1 ) (kPa(^{-1}))</td>
<td>0.03</td>
<td>0.11</td>
<td>0.06</td>
<td>0.05</td>
</tr>
<tr>
<td>( R^2 ) (based on the FE simulation)</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>
Figure 4.13. (a) Comparison of the experimentally obtained data (as reported in Budday et al. (2017)) and the load-extension curves based on the FE simulations (solid lines) using model parameters as shown in Table 4.7, and (b) variation of the volume ratio with extension based on the FE simulation for different regions of the brain tissue in compression.

4.10.2. Tension

The same procedure as the one described for compression is used to interpolate the experimental data for the case of tension assuming compressibility. In Table 4.8 the numerical values of model parameters of the one-term hyperelastic compressible Ogden model for the case of tensile tests are shown. The results of the FE simulation based on these numbers are also shown in Figure 4.14(a) besides the experimentally obtained values. In addition, in Figure 4.14(b), the volume change ratio during 10% stretch for different regions of the brain are demonstrated. Compared to the case of compression in which the volume change is less than 1.2% at 10% compression, that ratio approaches up to 5% for 10% tension which implies a tension-compression asymmetric compressibility for all regions of the brain tissue.
Table 4.8. Model parameters of the one-term compressible Ogden model for different regions of the brain in tension after correction using the iterative simulation and modeling procedure.

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Corpus Callosum</th>
<th>Corona Radiata</th>
<th>Basal Ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$ (kPa)</td>
<td>0.461</td>
<td>0.248</td>
<td>0.420</td>
<td>0.432</td>
</tr>
<tr>
<td>$m_1$</td>
<td>23.75</td>
<td>10.10</td>
<td>12.24</td>
<td>14.35</td>
</tr>
<tr>
<td>$D_1$ (kPa$^{-1}$)</td>
<td>0.03</td>
<td>0.11</td>
<td>0.06</td>
<td>0.05</td>
</tr>
<tr>
<td>$R^2$ (based on the FE simulation)</td>
<td>0.991</td>
<td>0.991</td>
<td>0.992</td>
<td>0.993</td>
</tr>
</tbody>
</table>

Figure 4.14. (a) Comparison of the experimentally obtained data (as reported in Budday et al. (2017)) and the load-extension curves based on the FE simulations (solid lines) using model parameters as shown in Table 4.8, and (b) variation of the volume ratio with extension based on the FE simulation for different regions of the brain tissue in tension.

4.10.3. Tension-Compression

The findings presented in the previous sections suggest that the tension-compression asymmetry might arise from difference in compressibility of the brain tissue in tension and compression. Accordingly, the compressible Ogden hyperelastic model with the Bažant strain tensor and different compressibility constant ($D$) in tension and compression is considered. For this model, the relation between the load and the principal stretch in the loading direction of the uniaxial testing is expressed as:
\[ f = p_1 A = \frac{J t_1 A}{\lambda_1} \]

\[ = \left( \frac{2\mu_1}{3m_1} \left( (\lambda_1^{m_1} - \lambda_2^{m_1})(\lambda_2^2)^{-\frac{m_1}{3}} - (\lambda_1^{-m_1} - \lambda_2^{-m_1})(\lambda_2^2)^{-\frac{m_1}{3}} \right) \right) + \frac{2\lambda_1 \lambda_2^2}{D_1} (\lambda_1 \lambda_2^2 - 1) \frac{A}{\lambda_1} \]

and the equality that imposes the stress-free condition in lateral directions reads as:

\[ \left( \frac{\lambda_2}{\lambda_1} \right)^{\frac{m_1}{3}} - \left( \frac{\lambda_1}{\lambda_2} \right)^{\frac{m_1}{3}} + \left( \frac{\lambda_2}{\lambda_1} \right)^{\frac{2m_1}{3}} - \left( \frac{\lambda_1}{\lambda_2} \right)^{\frac{2m_1}{3}} + \frac{6m_1 (\lambda_1 \lambda_2^2)(\lambda_1 \lambda_2^2 - 1)}{\mu_1 D_1} = 0 \]

Using the aforementioned iterative scheme, the model parameters can be calibrated based on the available experimental data as shown in Table 4.9. The tissue behavior is assumed to be incompressible in compression and compressible in tension. The results of the FE simulation are also shown in Figure 4.15(a) besides the experimentally obtained values. In addition, in Figure 4.15(b), the volume change ratio during 10\% tension for different regions of the brain are depicted (due to the assumption of the incompressibility in compression, the volume ratio is equal to 1 for all regions in compression, hence, they are not shown in Figure 4.15(b)).

Table 4.9. Model parameters of the Ogden model (incompressible in compression and compressible in tension) based on the Bažant strain for different regions of the brain in tension and compression after correction using the iterative simulation and modeling procedure.

<table>
<thead>
<tr>
<th></th>
<th>Cortex</th>
<th>Corpus Callosum</th>
<th>Corona Radiata</th>
<th>Basal Ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu ) (kPa)</td>
<td>0.547</td>
<td>0.128</td>
<td>0.275</td>
<td>0.283</td>
</tr>
<tr>
<td>( m_1 )</td>
<td>±16.35</td>
<td>±22.02</td>
<td>±19.53</td>
<td>±15.51</td>
</tr>
<tr>
<td>( D_1 ) (kPa⁻¹) in tension only</td>
<td>0.4</td>
<td>3.0</td>
<td>1.9</td>
<td>1.2</td>
</tr>
<tr>
<td>( R^2 ) (based on the FE simulation)</td>
<td>0.998</td>
<td>0.999</td>
<td>0.999</td>
<td>0.999</td>
</tr>
</tbody>
</table>
Figure 4.15. (a) Comparison of the experimentally obtained data (as reported in Budday et al. (2017)) and the load-extension curves based on the FE simulations (solid lines) using parameters for the Ogden model (incompressible in compression and compressible in tension) based on the one-term Bažant strain for different regions of the brain as shown in Table 4.9, and (b) variation of the volume ratio with extension based on the FE simulation for different regions of the brain tissue in tension.
4.11. General Consideration and Data Analysis

4.11.1. Effect of the Boundary Conditions on Uniaxial Testing

Constraining the lateral expansion or contraction of the specimen during either uniaxial compression or tension experiments causes the generation of inhomogeneous elastic fields. For example, gluing top and bottom surfaces of the cubic soft tissue samples to the loading platens imposes uneven lateral deformation as shown in Figure 4.7 which violates the assumption for uniaxial deformation condition. Accordingly, one needs to consider such effects for modeling purposes to obtain accurate values for the model parameters.

In this study, a combined mathematical modeling and FE simulation approach is used to accurately calibrate the Ogden hyperelastic model for the uniaxial behavior of the brain tissue based on the experiments conducted by Budday et al. (2017). It is shown that neglecting the no-slip boundary effect can generate errors up to 100% in compression and 1500% in tension. More importantly, the nature of the model parameters might also vary significantly if the correct boundary effects are not considered. For instance, for the case of the uniaxial testing, while the initial mathematical analysis with assuming ideal uniaxial condition demonstrates that the experimental results of Budday et al. (2017) can be interpolated by the one-term Ogden hyperelastic model with a negative nonlinearity constant, further investigation using FE simulation suggests that when the proper boundary conditions are considered, only a positive value for such a model can result in an appropriate interpolation of the experiments.

The combined analytical-numerical scheme for correcting the model parameters according to the boundary effect utilized in this study is very efficient. Commonly, the experimental results are interpolated using the FE analysis and the numerical values for the model constants are adjusted at each iteration. In this study, however, instead of adjusting the model constants, the input load
for analytical solution is adjusted based on the results of the FE simulation. The model parameters obtained based on the curve fitting are then used for the next FE simulation and this loop is continued until the difference between the simulation output and experiments is minimized. This approach is very fast and programming in Mathematica is short and simple. It is observed that the current analysis usually converges after 3 to 4 iterations. According to the limited total number of required FE simulations, no advance computational resources are needed.

4.11.2. Role of Compressibility in Tension-Compression Asymmetry

The brain tissue, similar to the other soft tissues, is usually considered as an incompressible material. This tissue possesses a high level of fluid content trapped in the cells, the intercellular spaces, or inside the vasculatures. For the case of uniaxial testing with no control over draining of the fluid, it is likely that the excess interstitial fluid can leave the specimen if the load is applied slowly enough. During the experiments performed by Budday et al. (2017), the authors utilized a procedure for preconditioning the sample with two cycles of loading and unloading prior to recording the data during the third cycle. Since the preconditioning might cause draining of the excess interstitial fluid, for analyzing the results of the third loading cycle one can assume no fluid flow to the outside of the sample. The fluid trapped inside the cells and vasculatures, however, can considerably contribute to the incompressible behavior of the tissue. Nevertheless, this effect is known to be dominant when the “total pressure” value is a positive quantity. This condition in uniaxial testing mode only happens in compression when the first invariant of the stress field is negative. To further investigate the compressibility of the brain tissue, both incompressible and compressible versions of the Ogden hyperelastic model are implemented for uniaxial testing condition. In compression, both compressible and incompressible models are shown to be capable of interpolating data with excellent performance ($R^2$ of close to unity). This is not surprising
because the compressibility constant for the compressible model for all regions in compression is found to be very small and the volume change ratio is less than 1.2% for 10% compression. Hence, the brain tissue can be assumed to behave near incompressible in compression. In tension, on the other hand, although both compressible and incompressible models demonstrate an appropriate performance in interpolating the experimental results, the compressible model exhibits volume changes up to 5% for 10% tension which demonstrates a considerable compressible behavior. From the curve fitting point of view, the compressible model demonstrates a slightly better performance with higher $R^2$ values especially for the case of the white matter (corona radiata and corpus callosum) which shows a higher level of compressibility compared to the gray matter.

To investigate the role of asymmetric compressible behavior in tension and compression on the overall tension-compression asymmetry of the brain tissue, an Ogden hyperelastic model with strain energy that considers the symmetric Bažant class of strain for the deviatoric part is implemented; this model is considered incompressible in compression and compressible in tension. Moreover, for the sake of comparison, a fully incompressible Ogden model is also implemented that incorporates a hybrid asymmetric strain tensor based on the proposal by Moerman et al. (2016) (MSN hybrid strain). Both of these models are used for interpolating the whole tension-compression behavior. While both models show appropriate performance, the one with symmetric isochoric strain and asymmetric compressibility behavior demonstrates a better consonance with the experiments especially at large tension for the white matter brain tissue as shown in Figure 4.16. The correlation with experiments for this model (considering the $R^2$ values) is also slightly better than that for the fully incompressible model with MSN asymmetric strain. This finding supports the idea that the tension-compression asymmetry of the brain tissue might
arise from the variation of the compressible behavior of the tissue with respect to the compressive or tensile nature of the applied stress.

Figure 4.16. Load vs extension data for tension-compression experimental data as reported in Budday et al. (2017) (hollow squares), curve fitting using incompressible Ogden model incorporating MSN isochoric strain tensor (dashed line), and Ogden model incorporating the Bažant isochoric strain tensor with incompressibility in compression and compressibility in tension assumptions (solid line) for (a) cortex, (b) corpus callosum, (c) corona radiata, and (d) basal ganglia.

4.11.3. Interregional Variation of the Mechanical Properties

The interregional variation of the mechanical properties of the brain tissue was thoroughly discussed by Budday et al. (2017) according to their experimental findings. Although the Ogden model parameters obtained in the current study for the same experimental data are substantially different from those reported by Budday and coworkers, the trend of interregional difference is
still the same: while the cortical gray matter and corpus callosum possess the highest and lowest shear modulus, respectively, the tissue of corona radiata and basal ganglia are almost equally stiff. This trend of difference is valid regardless of modeling the brain tissue as a compressible or an incompressible material. The similarity of the mechanical response of the tissue samples excised from the basal ganglia and corona radiata is in well agreement with some other studies (Chatelin et al., 2012; Samadi-Dooki et al., 2017). However, the larger stiffness of the cortical gray matter compared to the white matter is in contrast with the findings for bovine brain tissue (Budday et al., 2015a; Samadi-Dooki et al., 2017). This discrepancy might arise from the considerable postmortem time (up to 60 hours) for running the experiments as reported in Budday et al. (2017). While cortical gray matter has a different microstructure from the white matter and the thalamic gray matter, the paths of variation of the mechanical properties with postmortem time might be different for these regions of the brain tissue. It should, however, be understood that obtaining the human brain samples in a shorter postmortem time than what was carried out by Budday and coworkers is not practical due to the regulations and the required approvals for autopsy.

Another interregional difference observed in this study is the discrepancy between the compressibility of the white and gray matter brain tissues. When a compressible model is utilized, the hypothetical variation of the volume ratio can be mathematically monitored during the deformation. Accordingly, current findings show that the gray matter tissue (cortex and basal ganglia) exhibits a slightly smaller volume change compared to the white matter (corona radiata and corpus callosum). This conclusion, however, requires further investigation with direct measurement of the volume change during the uniaxial deformation.
4.12. Conclusions

This work describes a novel understanding of the tension-compression mechanical asymmetry of the brain tissue due to the variation of the compressible behavior according to the loading direction. The methodology utilized in here provides a comprehensive description for accurate hyperelastic analysis of the soft tissues, in general, and the brain tissue, in particular, with thoroughly considering the physical basis for modeling and the effect of the no-slip boundary condition; nevertheless, some limitations are associated with the current approach. The proposed combined analytical-numerical iterative scheme entails availability of the analytical solution for the specific loading condition. In this study, the uniaxial loading condition is investigated whose analytical solution for a compressible or an incompressible isotropic hyperelastic model is readily available. However, the brain tissue is known to exhibit a level of anisotropic mechanical behavior especially in the white matter region. For example, although the statistical analysis by Budday et al. (2017) demonstrates that the directional dependent behavior of the human brain tissue is not significant, it should be understood that even the results presented in that study show different stress-strain curves for different directions with respect to the pattern of the axonal tracts arrangement (e.g., see Figure 8 of Budday et al. (2017)). On the other hand, if more complex loading conditions (multiaxial, indentation, etc.) or material models (anisotropic behavior) are considered for the brain tissue, finding the analytical solution and the curve fitting process associated with it might be very intense or unavailable. Nevertheless, the general conclusion of the role of compressibility on the tension-compression asymmetric behavior of the tissue is unlikely to be dependent on its anisotropic behavior because the justification for the proposal of such a mechanism is based on the fluid content of the material which is not directional dependent. Another limitation of the current study is unavailability of the information for lateral deformation of the
specimens during the uniaxial loading. The information for variation of this parameter is essential to understanding the actual volume change during the deformation. While the numerical values for the lateral stretch are obtained based on the requirement for traction-free condition in this direction, experimental verification for the shape of the specimen with no-slip boundary condition during the deformation would complement the numerical solution.

While the brain tissue is a biphasic material with the solid and fluid components, its mechanical behavior might be best described by a poroelastic model (Li et al., 2013). Such a model can appropriately account for the tension-compression asymmetry due to the presence of the fluid phase that mediates the alteration of the compressibility behavior according to the pressure component of the applied load. Nevertheless, care should be taken in implementing a porous model with considering the fact that not all the fluid component of the tissue can flow during the deformation since it is mostly trapped inside the cells or vasculatures. A set of confined compression with drained and undrained conditions could shed light on the tissue behavior and the flow of the fluid phase similar to what is usually used in the soil mechanics practices.

Although our understanding of the mechanical behavior of the brain tissue has markedly improved within the last few years, there are still quite a few unraveled aspects of the mechanically driven mechanisms involved in traumatic and pathological conditions of this tissue. The pressing need for quantitative values of the mechanical properties of the brain that supply inputs for computer simulation to model such pathobiological conditions has resulted in numerous experimental studies and novel constitutive models for its deformation. Nevertheless, validity of such measurements sometimes is compromised by accuracy of the measuring device or failing to appropriately analyze the results with considering all the constraints.
This work, as such, demonstrates an easy-to-implement methodology to analyze the mechanical properties of the soft tissues, in general, and the brain tissue, in particular, with incorporating both mathematical modeling and numerical simulation. This study shows that the no-slip boundary condition has a significant effect on the uniaxial behavior of the tissue, and if it is not correctly considered for the modeling purpose, can result in hyperelastic model constants considerably different from actual values. It is also proposed in here that the tension-compression asymmetry of the mechanical response of the brain tissue can arise from the alteration of the compressibility of the tissue in these testing modes. This hypothesis is utilized to model the uniaxial load-deformation behavior of the brain tissue and shows an excellent agreement with the experimental results.
5. SUMMARY, CONCLUSIONS, AND FUTURE PERSPECTIVE

The summary of the research in this dissertation is presented in this Chapter. In addition, the conclusions from this work are deduced. Suggestions and future perspectives based on this research are also presented.

5.1. Summary

In this research, the mechanical behavior of the brain tissue is investigated via experimental, analytical, and numerical methods. The first part of this research is dealing with the development of a novel experimental technique for the brain tissue. This effort includes a modification of the flat punch indentation that considerably enhances the ability of this testing mode for testing soft tissues, in general, and the brain tissue, in particular. Using this novel method, the rate, directional, regional, and postmortem time dependence of the mechanical resistance of the brain tissue at small deformations is investigated. The results demonstrate a statistically significant difference between the mechanical properties of the white matter and the cortical gray matter, whereas, the difference between those of the white matter and thalamic gray matter seems to be insignificant. Moreover, both white and cortical gray matters exhibit a rate dependent directional anisotropy.

The proposed experimental technique is also used for viscoelastic characterization of the brain tissue in the time domain. Different viscoelastic solid models are investigated for their appropriateness for representing the brain tissue. It is concluded that the Maxwell solid is the most suitable model for the rate dependent behavior of the brain tissue in small deformations. The model parameters are calibrated using a combined experimental, analytical, and numerical scheme which is proposed to consider the effect of the violation from the half-space indentation assumption. The proposed scheme is further used to calibrate multimode Maxwell model with higher number of
elements, and its suitability is investigated via investigating the tissue behavior during a more complex load-hold-unload cycle.

The last part of this research deals with the constitutive modeling of the mechanical behavior of the brain tissue in uniaxial loading condition. The concept of hyperelasticity is first described and the physical bases for an appropriate modeling procedure are scrutinized. The experimentally obtained results of the uniaxial behavior of different regions of the brain tissue are used for modeling. It is shown herein how small variations from ideal loading condition can generate huge errors in model calibration. Hence, a combined analytical and numerical method is proposed and utilized for calibration of the compressible and incompressible Ogden hyperelastic model for the brain tissue. Furthermore, it is suggested that the tension-compression asymmetric behavior of the brain during uniaxial loading might arise from the differences in compressible behavior of this tissue in these testing modes. This hypothesis is analytically and numerically investigated, and it is observed to generate reliable results for interpolating the experimentally obtained values.

5.2. Conclusions

The following conclusions and comments are drawn from the work in this dissertation:

- The brain tissue, as an extremely soft material with considerable fluid content, cannot be mechanically quantified with traditional experimental techniques.
- The mechanical response of the brain tissue is extremely rate, regional, and directional dependent.
- If properly preserved at low temperature and kept well hydrated, the brain tissue can be tested within a longer postmortem time without loss of its integrity and resistance.
- The Maxwell viscoelastic model is an appropriate mechanism to predict the viscoelastic behavior of the brain at small deformations.

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• The effect of the boundary conditions need to be thoroughly considered in different testing modes for a reliable analysis of the mechanical behavior of the brain tissue.

• The tension-compression asymmetry of the mechanical response of the brain tissue in uniaxial testing mode might arise from the differences in compressible behavior of this tissue in different testing modes.

5.3. Future Perspective

• While the brain tissue is a biphasic material with the solid and fluid components, its mechanical behavior might be best described by a poroelastic model. Such a model can appropriately account for the tension-compression asymmetry due to the presence of the fluid phase that mediates the alteration of the compressibility behavior according to the pressure component of the applied load. Nevertheless, care should be taken in the implementation of a porous model with considering the fact that not all the fluid components of the tissue can flow during the deformation since it is mostly trapped inside the cells or vasculatures.

• A set of confined compression with drained and undrained conditions could best shed light on the tissue behavior and the flow of the fluid phase similar to what is usually used in soil mechanics practice.

• For a better understanding of the effect of different diseases on the mechanical behavior of the brain tissue, in vivo evaluation of the mechanical properties of the brain tissue would be more appropriate. Such evaluations can be performed via magnetic resonance elastography (MRE). Although this testing mode is currently being used for different soft tissues including the brain, its accuracy has not been well documented yet. The results of the proposed high precision indentation method can be used for investigation of the values
obtained by MRE, hence providing a reliable reference for validity of the elastography method as a replacement for direct mechanical testing of the tissue.

- For a more realistic performance, the proposed compressible hyperelastic model is required to be used in a viscoelastic formulation scheme for modeling the tissue behavior in traumatic conditions. The current model is developed based on the results of pseudo-static experiments.
APPENDIX A. RIGIDITY OF THE COVERSLEEVE

Although the coverslip is considerably stiffer than the brain tissue, its low thickness to radius ratio might cause its flexion during deformation and violation from its rigid behavior which is assumed in the analyses. To investigate the possibility of such a violation, finite element simulation is used for determining the deformation of the coverslip during loading process. In this way, the tissue, coverslip, and the indenter are modeled as axisymmetric solids (Figure A.I.1) in ABAQUS™ 2016 (ABAQUS Inc., Providence, RI). The brain tissue is modeled as an elastic solid with a Young’s modulus of 4 kPa and Poisson’s ratio of 0.49. The coverslip is also considered to be elastic isotropic with the elastic modulus and Poisson’s ratio of 70 GPa and 0.22, respectively, and the indenter is modeled as a rigid triangle with circular head of 50 μm radius. To avoid the singularities in simulation, the corner edge of the coverslip is also rounded with the radius of 50 μm. The simulations results show that for a 10 μm tip penetration, the relative vertical deformation of the middle and corner points of the coverslip (points 1 and 2 in Figure A.I.1 inset) is about 3 Å. Although the input parameters for the brain tissue are simplified and roughly estimated, this illustrative simulation proves the validity of the rigid behavior of the coverslip in indentation at small deformation range (Gladwell and Iyer, 1974).
Figure A.1. Illustrative axisymmetric finite element simulation of the indirect indentation of the brain tissue for investigating the rigid behavior of the coverslip.
APPENDIX B. PERMISSION LETTERS
Title: Hyperelastic modeling of the human brain tissue: Effects of nonslip boundary condition and compressibility on the uniaxial deformation

Author: George Z. Voyiatjis, Arif Samadi-Dooki

Publication: Journal of the Mechanical Behavior of Biomedical Materials

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Prange, M.T., Margulies, S.S., 2002. Regional, directional, and age-dependent properties of the brain undergoing large deformation. Journal of biomechanical engineering 124, 244-252.


VITA

Aref Samadidooki was born in 1986 in the city of Ghaemshahr, Mazandaran Province, Iran. Aref received his primary education in public schools in Ghaemshahr, and his secondary education at a high school affiliated with the National Organization for Development of Exceptional Talents (NODET). He subsequently joined Sharif University of Technology (SUT) in Tehran to pursue a bachelor degree in Civil Engineering in 2004. In 2009, he was admitted to the Master’s program in Structural Engineering at SUT with focus on Theoretical and Applied Mechanics. He graduated from this program in 2012 with receiving the Top Ranked Student Award. In 2013, Aref jointed the doctoral program in Civil Engineering at the Computational Solid Mechanics Laboratory of the Louisiana State University (LSU) under the supervision of Boyd Professor George Z. Voyiadjis. The completed research work in the field of biomechanics of the brain tissue is presented in this dissertation. In addition, during his PhD program Aref Samadidooki has been involved in research in several other areas, such as the constitutive modeling of mechanical behavior of amorphous and semicrystalline polymers, Nanoindentation, Microtension, and AFM experiments, and sample preparation and thermomechanical analysis of solids. He also served as instructor and teaching assistant for several undergraduate level course and a teaching assistant for a number of graduate level course at LSU. His future plans involve continued research on materials characterization with the aid of submicron scale testing, microscopy techniques and multi-scale modeling.