The Mechanics of Contusion Spinal Cord Injury: 
Towards Patient-Specific Assessments of Mechanical Loading and Injury

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Abstract

Computational models are becoming an important tool for spinal cord injury (SCI) studies, specifically for transferring in-vivo preclinical achievements to clinical trials and injury prevention design. Despite this, spinal cord tissue properties, constitutive models, and the correlations between tissue mechanics and injury are unclear. Therefore, the anisotropic behaviour of spinal cord tissue was characterized in a human-like animal, constitutive models were employed in SCI computational models, and correlations between SCI model outcomes and tissue injury were evaluated in patient-specific models.

Cervical spinal cords were harvested from nine non-human primates (NHPs). White matter samples were cut from the lateral columns of the spinal cord. Samples were characterized under dynamic compression. The obtained model was combined with published in-vitro tensile responses to capture the anisotropic behaviour of the spinal cord. The model was used to generate subject-specific finite element (FE) models of NHP in-vivo contusion SCI. Several mechanical metrics were assessed for their agreement with tissue damage using logistic analysis.

NHP spinal cord white matter compressive response was sensitive to strain rate and showed substantial stress relaxation. An Ogden model best captured the white matter behaviour in a quasi-linear viscoelastic material model. Rapid relaxation and high strain rate sensitivity of the white matter indicate that incremental movement of the spinal cord during treatment could substantially reduce the risk of ischemic injury. A fiber-reinforced conditional constitutive model best captured white matter anisotropy. Von-Mises and Tresca stresses showed the strongest correlations with damage in the gray matter. FE tissue damage thresholds were subject-specific except for white matter axonal strain and strain energy density.

In summary, the work described herein indicate that measures of mechanical FE outputs correlate with tissue damage both in white and gray matters of spinal cord, and that subject-specific models of human-like animals that include spinal cord anisotropy are able to accurately mimic the biomechanics of contusion impacts.

Keywords: Spinal cord injury; Finite element analysis; Transverse isotropy; Patient-specific modelling; Non-human primate
To Mahin and Baba,

for being such adorable parents

and

to Setareh for all her love and caring …
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To my family, thank you for all the encouragement and support throughout my years at school. Mahin, thank you for going so far beyond the call of a mother duty in everything you did for me and Baba, thank you for all the constitutional support, hope, motivation and encouragement. Thank you both for making such a memorable, valuable and happy life to me; there are no words that sufficiently convey the extent of my gratitude. Setareh, thank you for doing everything in your power to help me succeed, and for all the loving support, kind cooperation and patience. Nazanin, your belief in your brother was encouraging for me all the way through to here and brought me an unveiling self confidence. Thanks to Bledi for his kind and motivative attitude, I learned a lot form you man, and thanks to little Mani, for all the joy he brought to our lives. I would also like to specifically thank two of my mother's siblings, uncle Aliasghar Mohtaj, and aunt Eshrat Mohtaj for their supportive, inspiring attitude since I was a little child. Finally, to my niblings, friends at SFU, those outside of grad school and those in Iran, thank you for balancing my life and bringing this much fun to my life.
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<th>Definition</th>
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<tr>
<td>2D</td>
<td>Two Dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three Dimensional</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under Curve</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>CSF</td>
<td>Cerebral Spinal Fluid</td>
</tr>
<tr>
<td>FE</td>
<td>Finite Element</td>
</tr>
<tr>
<td>GM</td>
<td>Gray Matter</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MRE</td>
<td>Magnetic Resonance Elastography</td>
</tr>
<tr>
<td>MPS</td>
<td>Maximum Principal Strain</td>
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<tr>
<td>NHP</td>
<td>Non-Human Primate</td>
</tr>
<tr>
<td>PNS</td>
<td>peripheral nervous system</td>
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<tr>
<td>QLV</td>
<td>Quasi Linear Viscoelasticity</td>
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<tr>
<td>RMSE</td>
<td>Root Mean Square Error</td>
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<tr>
<td>ROC</td>
<td>Receiver Operator Characteristic</td>
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<tr>
<td>SFU</td>
<td>Simon Fraser University</td>
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<tr>
<td>SCI</td>
<td>Spinal Cord Injury</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>WM</td>
<td>White Matter</td>
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## Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Cranial</td>
<td>Towards the head</td>
</tr>
<tr>
<td>Caudal</td>
<td>Towards the feet or tail</td>
</tr>
<tr>
<td>Medial</td>
<td>Towards the midline of the body</td>
</tr>
<tr>
<td>Lateral</td>
<td>Away from midline of the body</td>
</tr>
<tr>
<td>Ventral</td>
<td>Towards the anterior or lower surface of an animal opposite the back</td>
</tr>
<tr>
<td>Dorsal</td>
<td>Towards the posterior or back of an animal</td>
</tr>
<tr>
<td>Frontal (Coronal) plane</td>
<td>Subdivides the body into ventral and dorsal halves</td>
</tr>
<tr>
<td>Transverse plane</td>
<td>Subdivides the body into cranial and caudal halves</td>
</tr>
<tr>
<td>Sagittal plane</td>
<td>Subdivides the body into two lateral halves</td>
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</tbody>
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Anatomical planes and directions for (left) human and (right) non-human primate.
Preface

A version of Chapter 3 has been published in the journal of biomechanical engineering as a full-length article - Shervin Jannesar, Ben Nadler, and Carolyn J. Sparrey, (2016), “The transverse isotropy of spinal cord white matter under dynamic load,” Journal of Biomechanical Engineering, 138(9), p. 091004, [DOI: 10.1115/1.4034171]. I was responsible for designing the study, analyzing the data, introducing the constitutive model, preparing the codes, generating and running computational models, performing statistical analyses and writing the manuscript.

A version of Chapter 4 has been published in Acta Biomaterialia as a full-length article - Shervin Jannesar, Mark Allen, Sarah Mills, Anne Gibbons, Jacqueline C. Bresnahan, Ernesto A. Salegio, and Carolyn J. Sparrey, (2018), “Compressive mechanical characterization of non-human primate spinal cord white matter,” Acta Biomaterialia, 74, pp. 260-269, [DOI: 10.1016/J.ACTBIO.2018.05.002]. I was responsible for designing the study, analyzing the data, generating and running computational models, performing the statistical analyses, interpreting the results, and writing the manuscript. I received assistance in performing the experiments from a team led by Dr. Carolyn Sparrey.

A version of Chapter 5 will be submitted for publication in the Journal of Neurotrauma as a full-length article – Shervin Jannesar, Ernesto A. Salegio, Michael S. Beattie, Jacqueline C. Bresnahan, Carolyn J. Sparrey., Patient-specific assessment of tissue level finite element outcomes in correlation with spinal cord injury in cervical non-human primates. I was responsible for designing the study, introducing material codes, analyzing magnetic resonance images, generating and running computational models, analyzing the data, performing statistical analyses and writing the manuscript.
Chapter 1.

INTRODUCTION

1.1. Motivation

Spinal cord injury (SCI) affects approximately 1,200 Canadian each year [1]. The catastrophic outcomes together with the high lifetime costs of caring and managing SCI, have encouraged focused attention on SCI to prevent or treat injuries. SCI is usually triggered by a mechanical assault on the spinal cord. The mechanical impact initiates a complex cascade of degenerative cellular and immune system responses that leads to a series of progressive symptoms with functional impairments. There continues to be no effective treatment for SCI.

Several current or planned clinical (i.e. human) and pre-clinical trials are exploring methods for SCI prevention, treatment and rehabilitation strategies [2]. Pre-clinical animal models have been developed to systematically investigate the biological progression of injury, tissue damage patterns, and functional deficits following SCI [3]–[9]. These animal models provide critical assessments of treatment functions and mechanisms before being implemented in humans. However, translating laboratory achievements to beneficial clinical outcomes is not trivial.

Computational models may provide crucial insight into the underlying biomechanical mechanisms contributing to SCI and have the potential to assist in bridging the gap between pre-clinical findings and clinical trials. Ensuring the fidelity of computational models in replicating clinical conditions, will further our understanding of SCI biomechanical mechanisms and facilitate their engagement. Computational finite element (FE) models has been commonly used in studies of SCI [10]–[25], specifically in defining damage thresholds for spinal cord tissue. However, the heterogeneity of the patients is not currently depicted in FE models and single generic models were used with averaged properties.

This study is motivated by the fact that SCI is a mechanical event, and the fundamental hypothesis was that a correlation exists between SCI mechanics and
neurological tissue damage. Characterizing and quantifying this correlation will enable the reliable use of mechanical computational models (FE models) of SCI for SCI prevention, treatment and rehabilitation planning and strategizing. To investigate this hypothesis, the following steps were accomplished in this research: 1) augmenting the transverse isotropic characteristic of the spinal cord white matter to previous SCI models to account for material anisotropy; 2) improving previous SCI models by characterizing spinal cord white matter based on data from a human-like animal (non-human primate (NHP)); 3) integrating the findings from steps (1) and (2) to generate a clinically relevant FE model of SCI, compare the FE model outcomes with in-vivo results, and statistically assess the link between FE model mechanical outcomes and neurological tissue damage quantified by hemorrhage.

By increasing the fidelity of the computational models and the integrity of the link between mechanics and tissue damage, FE models will advance our ability to better understand tissue loading that contributes to injury, gain more accurate insight into parenchymal level interactions and more reliably translate pre-clinical findings to clinical practices.

1.2. Chapter overview

This chapter reviews the spinal cord anatomy and physiological function in humans. The SCI process, mechanisms and specifications will be discussed. Mechanical characterization of the spinal cord and its constituent materials will be reviewed as well as studies that have investigated the sensitivity of predictions of spinal cord damage to the material parameters and characteristics. A section covering FE methods in injury modelling will survey studies of FE modelling of SCI, as well as present an outline of the need for patient-specific modelling and its requirements. Finally, the chapter will conclude by outlining the specific goals, objectives and the scope of this thesis.

1.3. Spinal cord anatomy and function

The nervous system is the external stimuli response regulator of the body and is majorly categorized into central nervous system (CNS), consisting of the brain and spinal cord, and peripheral nervous system (PNS) which links the CNS to the rest of the body. The spinal cord is responsible for a wide range of conductive and reflexive tasks within
the CNS. The primarily role of the spinal cord is to conduct the neural signals from the PNS to and from the brain. However, numerous body reflexes are generated independently in the neural circuits of the spinal cord.

The spinal cord is protected by an osseoligamentous vertebral column and runs through the vertebral foramen in the spine. In humans, the vertebral column is divided into five regions: cervical with 7 segments (C1-C7), thoracic with 12 segments (T1-T12), lumbar with 5 segments (L1-L5), sacrum with 5 segments (S1-S5) and coccyx with 4 segments (Co1-Co4); forming 33 vertebrae in total. The vertebrae differ in size and shape among the regions; however, their basic characteristics are the same (Figure 1-1).

![Organisation of vertebrae in the spinal column](image)

**Figure 1-1**: Organisation of vertebrae in the spinal column; Cervical, thoracic, lumbar, sacral and coccyx regions are shown (figure adapted from Mathison et al. [26])

In a typical vertebra the spinal cord passes through a bony ring in the posterior side of the vertebra called the 'vertebral arch' (Figure 1-2). This bony ring forms the vertebral foramen or the 'spinal canal'. Successive vertebrae are separated with intervertebral discs anteriorly and articular facets on the posterior side. There are foramina on either side of the vertebral body called intervertebral foramen or neural foramen, where the spinal nerve roots diverge from the spinal cord and connect to the PNS.
Figure 1-2: Typical vertebra, represented by cervical vertebra. (A) Superior view. (B) Lateral view. (C) Lateral view of two vertebrae showing intervertebral foramen and annulus fibrosus (Image adapted from Wikipedia https://images.app.goo.gl/7wXUicLNNDTkDXco6)

The spinal cord starts cranially from the caudal section of the brain stem, the medulla oblongata, and extends caudally to the conus medullaris in the lumbar spine (Figure 1-3). Similar to the spinal column, the spinal cord is also divided into five regions; cervical, thoracic, lumbar, sacral and coccygeal. There are two enlargements in the spinal cord at the cervical and lumbar levels, which correspond to innervation of the limbs. The lower regions of the spinal cord do not align with the spinal column regions. The spinal cord occupies the upper two-thirds of the spinal column approximately (the spinal cord ends around the L2 vertebra). Below the L2 level a bundle of nerve roots (the cauda equina) travels from the end of spinal cord to their corresponding vertebral level (Figure 1-3). Nerves from each corresponding part of the body converge together and form a mixed spinal nerve at each vertebral level, and enter the vertebral column through the intervertebral foramen (Figure 1-2 and Figure 1-3). The cervical spinal cord innervates the upper limbs, head, neck and diaphragm. The thoracic spinal cord conducts signals to the chest, abdomen and back. The lumbar cord innervates the lower limbs while the sacral cord conducts signals necessary for bladder, bowel, and sexual functions.
Mixed spinal nerves enter the epidural space and pass through dura and arachnoid maters then split into dorsal roots (sensory nerves) and ventral roots (motor nerves). The split nerve roots pass through the pia mater and synapse on the dorsal and ventral surfaces of the spinal cord respectively (Figure 1-4).

The spinal cord is anchored inside the spinal canal by the rostral and caudal attachments of the dura, nerve roots (covered by dural sheath) and the anterior dural ligaments [27], [28]. The three layers of dura, arachnoid and pia maters encased the spinal...
cord for protection and together are called the “spinal meninges”. The dura mater is the peripheral outermost layer and has a stiff, collagenous structure for protecting the spinal cord. The arachnoid mater covers the inner face of the dura tightly and contains the cerebral spinal fluid (CSF). The spinal cord is wrapped with the pia mater and is submerged in the CSF in the sub-arachnoid space. A pair of denticulate ligaments attach the arachnoid and dura maters and suspend the spinal cord in the CSF (Figure 1-4). The pia mater is an impermeable, thin layer of fibrous tissue that closely covers the spinal cord. The pia mater is elastic in nature and provides constraint for the spinal cord, as well as assisting in restoring the spinal cord to its original shape if it is perturbed [29]. The sub-pial space comprises the spinal cord parenchyma and arteries and veins that circulate the blood to the spinal cord (Figure 1-4).

White and gray matters are the main constituent materials of the spinal cord. Gray matter has a butterfly shape in the middle of the spinal cord and is surrounded by the white matter and the white matter is tethered to the pia mater (Figure 1-4). The spinal cord gray matter contains neuronal cell bodies, neuropil, glial cells, synapses and capillaries and acts as the spinal cord signal processing center. The white matter is comprised of glial cells and myelinated axons and is responsible for transmitting the signals between the cell bodies in the brain, brainstem and spinal cord. Other structures in the CNS such as the brain and brain stem are similarly composed of gray and white matter, in differing ratios and patterns, which leads to many similarities in their tissue behaviors. However, there are some unique feature to the spinal cord white matter structure; it is devoid of an extracellular matrix and is composed of dense packed, longitudinally aligned uniform axonal fibers (myelinated and unmyelinated) embedded in a glial matrix [27]. Due to the structure of axons in the white matter that run longitudinally along the spinal cord, the white matter is anatomically anisotropic [30].

The spinal cord white matter is divided into fasciculi and funiculi and further to the dorsal funiculus, the lateral funiculus and the ventral funiculus (Figure 1-4). Each of these funicular regions contains several sub-divisions of tracts. Each tract is a group of nerve fibers with the same origin, course and termination doing the same function. Tracts are termed ‘ascending’ which convey sensory information to higher centers of the CNS, and ‘descending’ which originate in higher centers and are relay motor signals down to through spinal cord. Additionally, there are several axons that exist to interconnect different levels of the spinal cord (Figure 1-5). It is important to know the location and function of each
tract to understand the functional implications of the location of damage in the spinal cord. The largest descending tract is the corticospinal tract and it is of fundamental importance to motor function. This tract facilitates voluntary, particularly skillful, motor activity by connecting the body to the contralateral (opposite side) portions of the frontal and parietal lobes of the brain. The ascending spinocerebellar tracts carry unconscious proprioception and the ascending anterolateral system in the ventrolateral portion of the cord carries nociceptive (pain), temperature and light touch. The propagation of signals along the spinal cord axons occurs through action potentials. An action potential occurs when the membrane potential of a specific axon location rapidly rises and falls. Damage to the membrane destroys the ability of the cell to generate and conduct action potentials which is one of the cells’ first responses to mechanical insult.

Figure 1-5: Transverse view representation of the spinal cord showing the spinal tracts. Red regions represent ascending tracts which convey sensory signals and the green regions represent descending tracts conveying motor signals.

The spinal cord is a highly vascularized structure with arteries supplying the spinal cord (anterior and posterior spinal arteries) on the outer cord surface (Figure 1-4). Blood supply within the spinal cord arises from sulcal branches. These branches are end arteries that penetrate the cord and end in the medullary capillary bed in the gray matter. Capillaries are less numerous in the white matter than in the gray matter leading to greater
blood flow in the gray matter. Impairment of the vasculature, specifically the breakdown of the blood–spinal cord barrier, leads to hemorrhage and is generally an early response to SCI [31], [32].

1.3.1. Morphology and functional organization of animal and human spinal cords.

By necessity, the majority of the SCI researchers have adopted a rodent model in their studies of SCI [5], [7], [18], [20], [21], [33]–[39]. In rare cases other larger animals (bovine/porcine) have also been used for SCI related investigations [10], [11], [40]. Generally, the anatomical layout of the spine and spinal cord, as well as the neuroanatomy and physiology of the spinal cord, are similar between rodents and humans [38], [41], however, examining a more human-like animal is expected to improve the fidelity of SCI models and their corresponding outcomes. Furthermore, translation of the achievements on a more human-like animal is more reliably transferable to clinical interventions. Highlighting some of the gross anatomy, function, neurophysiology and mechanical behavior differences and similarities between the CNSs of these animals and humans helps to understand the strengths and limitations of the different model systems.

Anatomically, there are obvious differences between human, NHP, and rodent spine and spinal cord regarding the number of vertebrae (57-60 in rats compared to 33 in humans and NHPs), spinal cord diameter (10-17 mm in humans and NHP compared to ~3 mm in rats) and length (~44 cm in humans, ~32 cm in NHP compared to ~9 cm in rats) [42]–[44]. The main consequence of the smaller morphology is that the failure criterion obtained from rodent models requires further scaling to be adapted to humans and the fidelity of this scaling is unclear.

The distribution of functional tracts in the white matter is similar in human, NHP, and rats (Figure 1-6). However, some neuroanatomic features have undergone pronounced evolutionary changes in NHPs and humans [45], [46]. During the evolution of humans and NHPs, the proportion and size of the neocortex increased massively, and a fast-conducting corticospinal tract component evolved. In addition, the corticospinal axons have migrated from the dorsal column in rats to the lateral column in human and NHP (Figure 1-6) [47]. In NHPs and humans the projection patterns of the corticospinal tracts (motor pathways) are much more complex than rats [48]. In humans and NHPs a
significant proportion of CST fibers project to the ventral horns, in contrast to the rats where corticospinal tracts mainly project to dorsal horn neurons.

![Diagram of spinal cord tracts in rat, primate, and human](image)

**Figure 1-6: Approximate location of spinal cord tracts in the rat, primate and human.**
The left and right sides of each section illustrate the general location of the ascending and descending tracts, respectively. (figure adapted from Watson et al. and Courtine et al. [42], [45])

The development of the descending motor pathways has resulted in particular behavioral differences between rodents and NHPs (e.g. precision of the grip between thumb and index finger) [45], [48]. Therefore, any interruption of the cortical projections due to the SCI will cause a major impairment in the fine motor function of the hands and feet in NHPs. This is even more severe in humans, however, such behavioral impairment is not seen in rodents following SCI [48]. Furthermore, lesions in the corticospinal tract had substantial effects on stepping in NHPs and humans (more severe in humans), however, this effect was not significant in rodents [49], [50]. Conclusively, the differences in the anatomical, neurophysiology and behavior of rodents and NHPs suggests that functional deficits due to the damage to corticospinal tracts in rat models may not be representative of outcomes for similar regional injuries in the clinical population. In contrast, similarities between NHPs and humans mean that the NHP models may more reliably, safely and efficiently predict and represent the SCI consequences in humans. It is noteworthy that NHPs are expensive, complex animals that hardly pass the required ethical approvals, therefore, they should only be used for experiments when rodent models fail to provide adequate information.
1.4. Pathophysiology of SCI

SCI initiates by a mechanical assault on the spinal cord and triggers a range of symptoms in the body parts served by the spinal cord below the level of the injury. SCI may be divided into two phases: primary (acute) injury caused by mechanical assault and a subsequent secondary injury of biomolecular origin [51]. The mechanical assault is responsible for the primary phase of the injury while the secondary phase results from the onset of different symptoms such as vascular dysfunction, edema, ischemia, inflammation, electrolyte shifts, and a number of cell-death mechanisms [51]. At clinical admission, the primary injury determines a given patient’s neurologic status and is a strong prognostic indicator [52]. Neurologic deficits are observed in the primary phase of injury, whereas the secondary phase events result in a prolonged period of tissue destruction and possible further loss of neurological function. The cascade of neurological and tissue degradation stabilizes after the secondary phase of the SCI where the injury turns to a chronic lesion. Generally, after the secondary phase of injury, there is substantial tissue destruction in the central part of the cord as well as the formation of cysts, while axons around the peripheral rim of the cord may be spared after injury [53]. It is the primary insult (mechanical assault) to the spinal cord which is the most powerful determinant of long-term neurological deficits [54], [55].

The majority of physical trauma to the spinal cord has their basis in compromise of the osseoligamentous spine with instability. Classification of the spinal column damage and quantifying its correlation to the SCI mechanism is challenging due to the diversity of the causes. However, some common patterns of spinal injury are more likely to cause SCI than others including: minor fractures, fracture dislocation, dislocation only, burst fracture, SCI without obvious radiologic evidence [56]–[58]. Hemorrhage and edema are the earliest clinical indications of damage and help to identify the epicenter of injury [32], [59]. However, the significance of each mechanism to neurological function and the sequence with which they occur following injury has not been clearly established.

1.5. Epidemiology and Etiology of SCI

An overview of the information about the incidence, prevalence and burden of SCI is of value for better understanding the problem’s dimensions and for directing future research. Approximately 4,200 incidences of SCI happens every year in Canada leaving
88,000 individuals currently living with SCI, where almost half of these individuals would have a traumatic SCI (~51%) and the other half suffer from non-traumatic SCI [60], [61]. In the case of traumatic SCI, 66.3% of the SCIs occur at the cervical level of the spinal cord (C1-T1), while 19.3% was reported in thoracic level (T2-T10) and 14.5% in the thoracolumbar (T11-L2) spinal levels [62]. In addition to higher incidence, acute cervical injuries consistently yield more severe neurological deficits for the patients since the injury affects the central nervous system at and below the level of injury [61], [62]. Non-traumatic SCI statistics show that cervical spondylosis is the most common abnormality resulting in SCI in patients [61].

Etiology of adult SCI in North America shows that the traffic accidents including motor vehicle, bicycles and pedestrian were the top causes of SCIs (~47%) [63]. After accidents, falls (~20%), violence (mostly shootings) (~15%), work-related injuries (~14%) and sport-related injuries (~7%) were responsible for acute SCIs [63]. While the mentioned causes of injury are miscellaneous, they do not directly represent the actual mechanism the spinal cord became injured. Generally, the response of the spine during trauma scenarios mentioned above is complex, not identical and specifically do not correlate directly with the type of trauma [64], [65]. However, regardless of the cause of the injury (i.e. car accident, falls, etc.), studies have identified common patterns of spinal injury resulting from different traumas [56]–[58]. Based on the observed patterns, vertebral column injuries resulting in SCI can be categorized as minor fracture (10%), fracture dislocation (40%), dislocation only (5%), burst fracture (30%), SCI without obvious radiologic abnormality (5%) and SCI without obvious radiologic evidence of trauma (10%) with the percentages showing the frequency of the incidence [61]. The majority of acute injuries will have their basis in acute changes in column stiffness (fracture, dislocation, ligamental compromise, etc.) with instability.

1.6. Mechanics and SCI

Since SCI is triggered by a mechanical assault to the spinal cord, and most often the treatments are mechanical (e.g. stabilization, decompression surgery, etc.), deep understanding of the mechanistic characteristics of the SCI is crucial. In addition, the majority of the preventive and protective strategies involve mechanical processes. Therefore, to understand the injury process, plan preventive strategies and to evaluate the efficacy of treatment interventions, the mechanics of the injury process and the
mechanical properties of the spinal cord itself need to be thoroughly explored. Establishing a reliable link between the mechanistic characteristics of the injury and the tissue damage or functional deficiency significantly further our insight of SCI and revolutionize our ability to prevent, treat and rehabilitate injured patients.

Studying the spinal cord tissue response to mechanical loading in the primary phase of SCI is challenging in humans. The primary phase occurs in a matter of seconds to minutes, while the clinical cases arrive at the hospital well beyond this timing. In addition, obviously, systematic experiments on humans are ethically impossible. Therefore, almost all detailed understanding of the primary injury following SCI is based on animal models of SCI.

1.6.1. Animal models of SCI

Although there is debate on how closely animal models can represent the human injury, the overall primary injury events are thought to be similar between animal models and humans [66]. However, the heterogeneous nature of human SCI remains an obstacle for translating the findings across different paradigms and various species to humans.

Rodents are the most common (~92%) species in the animal models of SCI with rats (~72%) at the top of the list [67]. Although the well explored anatomy, established functional analysis techniques, relatively low infectious side effects in the surgery and pathological similarities to humans have attracted researchers to rat models, the most important advantage of rodent models are their low costs and ease of handling compared to larger animals [67]–[69]. Furthermore, obtaining ethical approvals for these species are less challenging. Conversely, there are differences between rats and humans that must be accounted for in interpretation of rat SCI model outcomes. Rats are quadrupeds (in contrast to humans who are bipeds) which has important implications in gait and the reflexive nature of stepping. There is also significantly more redundancy in the NHP/human system and differences in physiology including grasping mechanics. Additionally, anatomical differences between the two species (see section 1.3.1) and the smaller morphology, has limited the clinical translation of treatments established in these species [67]–[69]. Due to these heterogeneities, there continues to be substantial challenges in translating laboratory success in rodent models of SCI to beneficial clinical outcomes [70] and since the larger animal models (NHP models in particular) better
approximate human SCIs [45], [71], the use of these species have been re-examined [3], [45], [72].

Several anatomical characteristics of the spinal cord such as spinal cord diameter, distance between the cell bodies of injured axons and the injury site, relative dedication of the cord to specific ascending and descending pathways, degree of vascularization, size of the sensory and motor neuron populations and white/gray matter composition vary along the length of the spinal cord [67], [73]. Statistically, cervical SCIs are the most common in humans where the white matter disruption often leads to spastic paralysis below the level of injury, sensory loss and chronic pain, as well as gastrointestinal, cardiovascular and sexual dysfunction [8]. Due to these differences and region-specific properties, cervical models may be readily translatable to cervical injury patterns. In recent years, there has been an emphasis on developing cervical models of SCI, and several animal models are now available [3]–[6], [8], [20], [73]–[76].

Based on the pattern of the injury, animal models are categorized to contusion, compression, dislocation, transection, ischemic, excitotoxic and photochemical models [67]. Among these models, the contusion model is most common and best characterized. Contusion SCI models can have varied severities which have been characterized by inflammation, ischemia, hemorrhagic necrosis and central cavitation. In the cervical region, the contusion is mostly applied unilaterally (hemi-contusion) because life-threatening adverse effects could occur after bilateral cervical lesions.

Overall, a cervical unilateral contusion injury model of NHPs without imposing severe functional deficits appears to be an ideal model for investigating SCI in humans and was the basis for the current study.

1.6.2. Impact mechanics

The mechanical insult can cause cells to become dysfunctional or to die in the primary phase of the injury. There are three main mechanisms for cell dysfunction: cell disruption, cell distortion and metabolic derangements [52]. The initial mechanical insult may also disrupt the blood-spinal cord barrier causing normally impermeable molecules and agents flux into the spinal cord [77]. Many experimental studies have tried to calibrate the mechanical assault and correlate it with the tissue dysfunction mechanisms, however,
defining effective mechanical parameters is challenging. A variety of mechanistic parameters of the injury were correlated with injury severity including the impact force [39], [78], the amount of induced strain to the spinal cord [79], [80], height and mass of a dropped weight [35], [43].

The human spinal cord is quite robust to physiological strains (~15%) and physiological strain rates [81], [82]. Experiments on isolated axons showed tensile strains of 0.21 led to morphological damage to the axon while strains of 0.18 disrupted signal conduction along the axon at strain rates of 30-60/sec [83]. Conversely, at low strain rates (0.006–0.008/sec), axons could withstand up to 100% strain, with almost no membrane/structural damage, and retain the majority of their electrophysiological functionality [80]. Also, compression resulting from a degenerative condition such as spinal stenosis, which progresses over several years, can be as high as 45% without causing any neurological symptoms [84]. In rats, the severity of the injury increased when the strain rate increased up to ~100/sec [18].

Efforts have been made to determine the velocity of the canal occlusion (the speed of impact to the spinal cord) as a result of burst fracture injuries in the bovine spine [85]. They concluded that the strain rate at which the bovine canal is occluded (and the cord compressed) during a burst fracture is ~110/sec. In humans, based on the spinal canal diameter, the 110/sec canal occlusion is equivalent to an occlusion velocity of 1.7m/sec. Other studies using human cadavers reported occlusion velocities during SCI of 1.5m/sec-1.87m/sec [86]. Although the results of those studies demonstrated a consistency in the rates at which the spinal cord would be impinged during a burst fracture SCI, the same studies indicate that there is not a clear correlation between the methodology or the energy used to generate the burst fracture and the impinging velocity. Furthermore, because of the complex structure of the spine and the layers of soft tissue surrounding the spine; external velocities (e.g. car speed) have not been correlated with spinal cord compression speed. In brain injury studies, strain rates in the range of 10-100/sec are considered to have direct relevance to impact incidents [87] while a range of 1000-3000/sec are associated with blast injury incidents [88]. However, due to the complex nature of translating external forces to tissue loading, presenting a direct, clinically relevant equivalence for the strain rates used in this study is not possible at this time. However, overall, these studies indicate that mechanical characterization of the spinal cord needs
to be performed to strain rates on the order of 100/sec if the results are to be applied to injury scenarios.

1.7. Computational models of SCI

Computational models of SCI provide crucial insight to the mechanical state of the tissue during and after the impact. Correlating these tissue level mechanics with patterns of tissue damage may help to establish damage thresholds for the tissue [20], [21], [79], [89]. Although understanding the parenchymal level mechanics may provide crucial details of the state of the injury, this information cannot be systematically obtained from *in-vivo* experiments. FE models, also, provide a modality to transfer our findings from *in-vivo* animal SCI models to clinically relevant practices by predicting the impact outcomes and approximating a threshold for SCI. These advanced engineering tools extend our ability to more accurately plan SCI prevention, treatment interventions and rehabilitation strategies with no risk to patients.

FE models of SCI have been generated with different levels of details to simulate injuries in humans [13], [22]–[24], NHPs [76], [90], bovine [10], [11], [91], porcine [17] and rodents [20], [21] for a variety of purposes. Several authors managed to establish a link between the FE model outcomes and neural tissue damage in both acute and chronic SCI such as cervical spondylotic myelopathy. Mechanical factors such as intramedullary stresses were significant to the pathogenesis of cervical spondylotic myelopathy in FE simulations of cervical spinal cord [11], [92]–[94]. Evaluating different SCI mechanisms through FE models showed that the mechanism of injury resulted in different features of stress across the spinal cord and for acute central cord syndrome [20], [95] and hyperextension/flexion [13], [14].

The patterns of axon damage revealed by histology coincided with higher levels of von Mises stress, which were predicted with FE model of isolated strips of guinea pig spinal cord white matter [79], [89]. These studies suggest that the numerical values of von Mises stress near 2 kPa are required to initiate anatomical tissue injury. Further down, FE simulations of single axons and the surrounding myelin under compression exhibited that von Mises stress was highly concentrated at the paranodal junction. Therefore, the mechanism of myelin retraction during acute demyelination may be associated with stress concentrations that cause debonding at the axoglial interface [96].
Maikos et al. simulated two experimental rat weight drop SCIs with different drop heights in an averaged FE model. They calibrated their FE model by varying mechanical constitutive properties of the spinal cord until the simulations generated similar drop trajectories (i.e. spinal cord displacement under dropped load) to the homogeneous trajectories measured experimentally. There was statistically significant correlations between the distribution patterns of stresses and strains across the cord with patterns of damage to the blood–spinal cord barrier [21]. Their additional parametric studies revealed that differentiating white and gray matter improved the predictive stress-strain patterns across the spinal cord, however, their model did not include the pia mater. Their findings were reinforced by another group who found significant correlations between maximum principal strain in the primary injury patterns and tissue damage measured via axonal permeability to 10-kD fluorescein-dextran within different mechanisms of injury (contusion and dislocation) in rats [20].

Outcomes of FE models are substantially sensitive to the assigned material properties, where principal stresses and pressure were the most sensitive outcomes and strain measures were less sensitive [97]. Distinct modelling of the gray and white matters in the FE models affect the stress-strain distribution patterns [11], [90] and tissue level deformations [10]. Including the pia mater in the FE model explicitly eliminated the need for calibrating the model materials to match the biomechanics of the simulation [90], however, the pia mater material properties had limited (<4% change) effects on stress-strain intensity or distribution outcomes [97]. The CSF had a significant effect on the spinal cord surface deformation during the impact and the type of material models used for the spinal cord and the dura mater were found to be important to the tissue level stress-strain pattern and values [91].

Overall, the fidelity of SCI FE models relies closely on well-defined material constitutive models (and geometries) employed for the spinal cord or its constituent components. Reviewing the body of work done on characterizing the spinal cord constituent materials provides an opportunity to identify, evaluate and implement key factors into the SCI models. The next chapter provides a comprehensive review of the experimental and theoretical efforts made for characterizing the spinal cord parenchyma and its constituents.
1.8. Material Characterization of Spinal Cord Tissue

The majority of biomechanical studies of the CNS are dedicated to brain tissue due to its higher incidence of injury and ease of tissue access. Inherent challenges in acquiring, processing and testing the spinal cord tissue resulted in limited number of experimental studies on the spinal cord tissue. Consequently, deriving appropriate experiment based constitutive models for spinal cord was restricted, and the effects of experimental variables on the constitutive model parameters remained elusive.

Hyperelasticity and material non-linearity has been observed in both tensile and compressive behaviours of the bulk spinal cord and its individual constituents [98]–[101]. Viscoelasticity is demonstrated in spinal cord tissues by increased stiffness with increased strain rate, hysteresis and stress relaxation. More recently, anisotropy of the spinal cord, particularly the white matter has also been identified [11], [90], [102]. Ideally, constitutive models are selected to capture all characteristics of the spinal cord behaviour; however, increased fidelity of the constitutive model requires increasingly complex and computationally costly models. Selecting the appropriate model for each investigation is as important as fitting the experimental data.

Several researchers have used an elastic modulus, or several elastic moduli to represent the intact spinal cord (i.e. gray matter, white matter and pia matter as a single material) behaviour observed in uniaxial tension tests. Early in-vivo research on cat spinal cords observed a nearly linear response to tensile loading [103]. The spinal cord modulus averaged 0.3 MPa at low strains (<5%). Further in-vivo characterization of cat spinal cords found an average modulus of 0.23 MPa for strains up to 10% [99]. Higher cord moduli (1.23±0.5 MPa) were observed for in-vitro human spinal cords for peak strains of 10% [104]. Similar moduli (1.19 ± 0.13 MPa) were observed for in-vitro bovine spinal cords at strains from 6-10% [105]. The bovine cord moduli increased two-fold with increased post mortem time from 3 hours to 72 hours. The elastic moduli for in-vitro lamprey eel spinal cords varied from 0.016 MPa at low strains (0-18%) to 0.5 MPa at higher strains (>18%) [106]. Moduli for the eel spinal cords also varied by region along the cord length at high strain; the tail region of the spinal cord was much less stiff (0.2 MPa) than the head region (0.57 MPa). Overall, the experimentally derived elastic moduli for intact spinal cord shows consistency across species and provide a simple measure for quantifying the intact spinal cord stiffness; however important characteristics of the spinal cord tissue that may affect
injury biomechanics are ignored when the behaviour of the complex spinal cord is represented using a homogeneous linear elastic response.

*In-vitro* experimental results showed significant nonlinearity in the spinal cord response to loading. Although the nonlinear behaviour has been approximated by several elastic moduli; nonlinear functions and hyperelastic models provide a continuous representation of the experimental data in a single model (the reader is referred to Appendices B, C and D for detailed formulations). Human spinal cord was captured by an isotropic, homogeneous and incompressible 1st order Ogden hyperelastic model [104]. Although their model fit their stress-strain experimental data in their range of strain rates, however, no statistically significant trend was observed in their model parameters. The same hyperelastic model was used to capture rat spinal cord behavior, but required further calibration and adjustments when used to simulate weight drop SCIs [21].

Viscoelastic characteristics of the intact spinal cord were observed in several *in-vivo* and *ex-vivo* experiments [12], [99], [104], [107]–[109]. Generally, the strain rate and magnitude have a profound effect on the intact spinal cord properties. A Fung Quasi-Linear Viscoelastic (QLV) model [110] was first used to describe cat spinal cord behavior [111]. Another modified QLV formulation successfully captured the viscoelastic behavior of rat spinal cord [21], [112]. The model fitted the experimental data well, however, over predicted the spinal cord behavior at higher strains. A significant limitation of the modified QLV model was the lack of a unique solution. Later, a nonlinear viscoelastic model was proposed [109] to overcome limitations of the QLV by defining the relaxation modulus being an explicit function of both time and strain magnitude instead of being a separable function of time and strain in QLV. The method was able to perfectly characterize intact porcine lumber spinal cord at physiological loading at different strain magnitudes but was less accurate for cyclic dynamic loading.

### 1.8.1. Constitutive modelling of the spinal cord white matter

Several studies have further explored the mechanical behaviour of the spinal cord in its constituent parts. Since the larger portion of the spinal cord is consisted of white matter, it is expected that the white matter material properties dominantly affect the spinal cord mechanical behaviour. Consequently, white matter modelling was the focus of several constitutive modelling studies [10], [11], [40], [102]. Hyperelasticity or material non-
linearity is observed under both tensile and compressive loads in the spinal cord white matter [10], [11], [40], [102]. More recently, anisotropy of the spinal cord white matter has also been identified [10], [11], [40], [102]. The isolated spinal cord white matter has been characterized statically and quasi-statically using isotropic linear elastic [10] and transversely isotropic reinforced Mooney–Rivlin hyperelastic models [89], [102]. A nonlinear viscoelastic solid model captured the isolated tensile bovine spinal cord white matter behavior at moderate strain rates [10]. Furthermore, a 1st order Ogden strain energy augmented with a QLV model well predicted the porcine white matter at moderate rates [40]. However, none of these studies have presented a model for dynamic transversely isotropic viscoelastic characteristics of the spinal cord white matter.

1.8.2. In-vitro characterization of the spinal cord tissue

Neurological tissue starts to degrade quickly after death for several reasons (e.g. complex enzymatic and microbiological processes, autolytic processes, completion of rigor mortis, osmotic swelling, etc.) [105], [113], [114]; however, measurable effects of this degradation on the tissue mechanical properties may not be as quick [114]. Several studies have explored the deteriorating effects of time post-mortem on the neurological tissue mechanical characteristics [105], [113]. These studies have acknowledged that to minimize the effects of post-mortem on the tissue characteristics, the samples should be tested as quickly as possible after the death of the subject, however, a precise time point for spinal cord tissue has not been established. Most studies using brain tissues, which are similar to the spinal cord, have shown that the tissue degenerates with increasing post-mortem time [113], [115]–[118]. Garo et al. [113], quantified the increase in brain tissue stiffness at approximately 27 Pa/h after 6 h of post-mortem time. They did not report a statistically significant difference in the brain tissue properties before 6 hours, however, their earliest tests started 2 hours post-mortem and therefore the tissue degradation effects before 2-hour post-mortem were not investigated.

Due to inherent difficulties in obtaining and testing spinal cord tissue, only one study has directly investigated the effects of post-mortem time on spinal cord tissue [105]. They tested bovine spinal cord at 3, 24, 48 and 72 hours and reported that the tangent modulus of the tissue increased sharply over a period of 72 h (almost doubled). Generally, the beginning of the post-mortem degradation cannot be definitively stated, however, to
minimize the effect of post mortem degradation, testing must be performed as soon as possible after death.

Other experimental factors, such as age of the subjects, sample preconditioning, sample aspect ratio, preloading the samples and flash freezing of the samples have also been investigated in the studies of the spinal cord. Compared to brain white matter [112], [119]–[121], the reported coefficients of variation in spinal cord white matter experiments [10], [11], [40] were larger. This could be due to the challenges inherent to harvesting the tissue and the small dimensions of spinal cord samples compared to brain tissue samples (1.8±0.6mm for spinal cord compared to 15.5±5.7mm for brain sample diameters). In spinal cord tests, the results from tests with no preconditioning were about one order of magnitude less stiff than their counterparts with preconditioned samples [40], [79], [89], [122]. The effect of preconditioning is clearly highlighted in the large initial plateau region of the stress-strain behavior [89], [102] compared to sloped lines in experiments on samples without preconditioning [10], [11], [40]. Furthermore, a significant increase in the variation of peak stresses have been reported by increasing sample aspect ratio and post mortem time, while applying preload did not reduce the variability [12], [40], [97].

1.9. Patient-Specificity

Individualized models are computational models of the subjects that are generated based on patient-specific data. Developing computational models based on the detailed characteristics of a specific subject provides a more realistic picture of the mechanical behavior of different organs and tissues. Patient-specific modelling has gained more attention recently because of its potential in advancing preventive, diagnostic and rehabilitation interventions, improving clinical treatments by predicting outcomes of therapies and surgical interventions, and providing more reliable platforms for transferring pre-clinical findings [123]–[126]. The majority of research in this field employs modern diagnostic techniques such as high-resolution imaging devices to create an integrated, individualized representation that can become a critical part of the overall understanding of each patient and each treatment decision [127].

Patient-specific modelling approaches have been used in the areas of musculoskeletal biomechanics [128]–[132], cardiovascular biomechanics [133]–[136] and soft tissue biomechanics (e.g. brain, liver, the soft tissues of the pelvic floor, and breast)
An important challenge of these FE methods is that generating the patient-specific model is not trivial, segmentation processes and mesh generating steps are not automatic and require high level experts and is time consuming. The resulting meshes are not flexible, adaptive and straightforward and very difficult to automate. Novel approaches have emerged to overcome these issues, however, many shortcomings remain.

Despite the recognized inter-subject anatomical differences and material characteristic variations, to date, very few studies of SCI have considered patient-specific aspects in their research – none in the field of FE modelling of SCI. The patient-specific hybrid modelling enabled the understanding of neurological problems for spinal cord during complex scoliosis spine deformity correction maneuvers. The patient-specific model of the scoliotic spine was able to predict critical neurologic thresholds qualitatively. Patient-specific FE models are advanced engineering tools enabling computational comparison of the effects of different surgical procedures on the same virtual subject, with no risk to the patient. Sensitivity of SCI FE model outcomes to morphological and anatomical variations suggests that using a generic FE model may imprecisely mediate the analysis results.

Generic FE models are based on either generalizing a single model as the representation of all subjects or averaging data from multiple subjects and presenting an averaged model. None of these methods accounts for the inter-subject variations of their subjects, which mitigates the biofidelity of their results. The anatomy and size variability were in common among small animals such as rodents, however, higher variations were reported in larger animals (e.g. NHPs) and humans. On the other hand, FE analysis results from SCI simulations, such as stress-strain patterns and impactor peak force, were shown to be critically sensitive to variations in model morphology/geometry and injury mechanisms. Altogether, it is expected that generating patient-specific models of SCI are essential for accurate analysis of the SCI and to gain reliable insight into the phenomenon.

1.10. Objectives and Scope

The objective of this dissertation is to determine the correlation between tissue level mechanical measures, determined through computationally simulating SCI, and the
tissue damage. Despite the mechanical nature of both SCIs and most of the treatments, the biomechanics of SCI has not been fully explored. Specifically, the link between recognized mechanical measures and injury indicators and the role of computational model characteristics such as constituent material models, districed constituent modelling and patient-specific variations on this correlation remains unclear. Including detailed constitutive models, characterizing the materials based on in-vivo tests and more human-like animals, and considering patient-specific anatomical variability in SCI models will increase the fidelity of the model outcomes, and will provide a reliable basis for translating pre-clinical findings to clinical practices.

Towards the goals, Chapter 2 explains the required mathematical theories and derives detailed formulations in this thesis. Chapter 3 investigates the spinal cord white matter anisotropy and examines the inclusion of white matter transverse isotropy on whole cord mechanics. The chapter presents a novel constitutive model for the spinal cord white matter which can capture the material's anisotropy under dynamic loading. Using the novel constitutive model, the chapter explores tissue level stress/strain distribution patterns ensuing SCI and highlights the importance of including white matter anisotropy in the SCI computational modelling. Chapter 4 aims to improve the fidelity of existing spinal cord white matter constitutive models by characterizing the material in a more human-like animal (i.e. NHP). In addition, the constitutive model presented in Chapter 4 furthers our insight into spinal cord white matter behavior in high strain rates typical of traumatic SCI for the first time. This is accomplished by utilizing fresh samples being tested under high strain rate loadings. Chapter 5 investigates the correlation between outcome mechanical measures obtained from computational models of SCI and spinal cord tissue injury in the context of patient-specificity. By implementing the achievements from chapters 3 and 4 into the computational SCI model and considering patient-specific variations the white matter constitutive model of Chapter 4 was further upgraded to account for anisotropic behaviour using the methods of chapter 3. Chapter 5 simulates patient-specific unilateral contusion SCI and assesses the link between mechanical measures and tissue injury. Chapter 6 provides an overarching discussion of the studies presented in this dissertation in the context of clinical care and current understanding of SCI. Finally, chapter 7 details concluding remarks and suggests directions for future research based on the findings of this research.
Each chapter in this dissertation represents a unique contribution to the field of SCI mechanics. As outlined in the introduction section, the use of NHPs for testing and experimenting is constrained by ethical issues and costs which resulted in a critical lack of experimental data on such more human-like animals. This study benefits from a unique opportunity in accessing and testing fresh NHP spinal cord white matter tissues and represents the first spinal cord white matter constitutive model characterized at injurious strain rates typical of traumatic SCI.
Chapter 2.

THEORY

Analysis of the mechanistic behavior of the spinal cord is inherently complex due to the highly non-linear behavior of the spinal cord constituent materials. However, there are certain biomechanical behaviors in the spinal cord constituent materials, such as transverse isotropy, that may be employed to simplify their constitutive modelling procedure. Efforts have been made to identify and characterize the spinal cord biomechanical behaviour based on these characteristics. This chapter presents the theoretical foundation for the equations used in this study to derive the required formulations. The source of these equations and the definitions of the variables are important for selecting the appropriate form of the equations for fitting the constitutive models to the experimental results. In addition, the specific implementation of the analytical solution for the finite element simulations depends on further derivation and reduction of the equations presented in this chapter. For more details on the basic assumptions and definitions please refer to Appendices A, B and C.

2.1. Constitutive equations for hyperelastic materials

A hyperelastic material is defined as a subclass of elastic materials in which a Helmholtz free-energy function $\psi$ exists which is solely a function of the deformation gradient $[153]$. The constitutive response of such material is of the form,

$$ P = \frac{\partial \psi(F)}{\partial F} $$  \hspace{1cm} \text{2-1} \\

or,

$$ S = 2 \frac{\partial \psi}{\partial \mathcal{C}} $$  \hspace{1cm} \text{2-2} \\

or,

$$ \sigma = J^{-1} \frac{\partial \psi(F)}{\partial F} F^T $$  \hspace{1cm} \text{2-3}
where $F$ is the deformation gradient, $C$ is the right Cauchy-Green tensor, $P$ is the 1st Piola-Kirchhoff stress tensor, $S$ is the 2nd Piola-Kirchhoff stress tensor, $\sigma$ is the symmetric Cauchy stress tensor and $J$ is the Jacobian determinant or volume ratio (for detailed formulations and derivation see Appendix B).

2.2. **Isotropic hyperelastic materials**

Isotropic materials are defined based on the physical idea that the stress-strain response of the material is the same in all the directions [153], [154]. In isotropic materials, the strain energy may be expressed as a set of independent strain invariants of the symmetric Cauchy-Green tensor $C$ [155],

$$\psi = \psi(I_1(C), I_2(C), I_3(C))$$ \hspace{1cm} 2.4

where the three principal invariants are defined explicitly as [155],

$$I_1 = trC = I: C, \quad I_2 = \frac{1}{2}[(trC)^2 - trC^2], \quad I_3 = detC = J^2$$ \hspace{1cm} 2.5

In addition, the strain energy function (Equation 2-4) may be regarded as function of principal stretches as,

$$\psi = \psi(C) = \psi(\lambda_1, \lambda_2, \lambda_3)$$ \hspace{1cm} 2.6

where $\lambda_1$, $\lambda_2$ and $\lambda_3$ are the principal stretches (for a proof see [153]).

2.3. **Anisotropic hyperelastic materials**

There are two different approaches to formulate the directional dependency in a particular material [155], [156]. One such method for capturing the directionally dependent material is introducing specific symmetry groups in the material. This method has been widely used in modelling living organisms such as cardiac [157], [158], connective [159] and neurological [160], [161] tissues. The symmetric constraint is then included in the strain energy function and the relationship between the resulting strain energy function and the deformation gradient can capture the material non-linearity. These types of materials have strong directional properties and their mechanical responses are regarded
as anisotropic. A material which has one symmetry is regarded as transversely isotopic material.

### 2.3.1. Transverse isotropy

Many biological materials are composed of a matrix material and one or more families of fibers. This type material is generally called a fibre-reinforced material and if the fibers are continuously arranged in the matrix, they impose a directional dependency to the material. The simplest of these materials is when the directional dependency can be described by only one unit vector \( A_0 \) in the undeformed configuration, where the material is called a transversely isotropic material. Examples of transversely isotopic biological materials are arterial walls [157], [162], brain stem [160], brain [161], [163] and spinal cord [102], [164] white matter. The hyperelastic strain energy in transversely isotropic materials may be expressed with a set of independent invariants of the symmetric Cauchy-Green tensor that explicitly incorporates \( A_0 \) [155], [165],

\[
\psi = \psi(I_1(C), I_2(C), I_3(C), I_4(C, A_0), I_5(C, A_0))
\]

where \( I_1, I_2 \) and \( I_3 \) are the standard invariants of the right Cauchy-Green deformation tensor (Equation 2-5) associated with isotropic material behavior; and \( I_4 \) and \( I_5 \) arise directly from the anisotropy (e.g. introduced by the reinforcing fiber family),

\[
I_4 = A_0 \cdot C \cdot A_0 \quad , \quad I_5 = A_0 \cdot C^2 \cdot A_0
\]

### 2.4. Stress response

An objective of this thesis is to develop constitutive expressions for neurological materials and more specifically the spinal cord constituent parts. Many biological tissues are represented as incompressible materials. This means the material can sustain finite strains without noticeable volume changes. Incompressible materials only allow isochoric deformations. Many spinal cord constituent constitutive models have considered the material as incompressible [10], [11], [29], [37].

However, implementing constitutive models into finite element simulations of SCI requires that the constitutive models be defined with an allowance for compressibility.
Purely incompressible constitutive model formulations can confound FE simulations and result in unsolvable models or be prohibitively computationally expensive [154]. Compressible materials undergo volume changes under hydrostatic stress. Porous rubber and foamed elastomers are some examples of compressible materials. For *nearly incompressible* materials like biological soft tissues, a small degree of compressibility can be introduced to expedite the FE model processing.

Constitutive formulations for the fully incompressible assumption (Chapter 3) and the nearly incompressible assumption (Chapter 4 and Chapter 5) are used. Since fully incompressible materials are in fact a sub class of nearly incompressible materials, we first consider nearly incompressible materials.

2.4.1. Nearly incompressible hyperelasticity

In nearly incompressible materials, dilational changes require a much higher external work than volume preserving changes. Since nearly incompressible materials behave quite differently in bulk and shear, constitutive models for these materials often depend on decomposing the deformation tensors into isochoric (deviatoric) and volumetric (dilational) components [153]. Decoupling the volumetric and isochoric behaviour responses is done by introducing a modified deformation gradient matrix [166],

\[
\bar{F} \equiv J^{-1} F
\]

where \( \bar{F} \) characterizes the isochoric deformation and the term,

\[
J^{-1} I
\]

characterizes the volume-changing portion of the deformation and therefore,

\[
det \bar{F} = 1
\]

Using the definition for right Cauchy-Green deformation tensor, and the modified deformation gradient matrix,

\[
\bar{C} = J^{2/3} \bar{F}^T \bar{F} = J^{2/3} \bar{C}
\]

where \( \bar{C} \) is the modified isochoric right Cauchy-Green deformation tensor. The strain energy function (Equations 2-4 and 2-7) can then be defined based on the
decoupling of the deformation. This allows separate exploration of the stresses related to isochoric deformations and those related to volumetric changes.

\[ \psi(C) = \psi_{\text{isochoric}}(\overline{C}) + \psi_{\text{volumetric}}(J) \]  

where \( \psi_{\text{isochoric}} \) is the isochoric strain energy component and \( \psi_{\text{volumetric}} \) is the volumetric strain energy component. Using the decoupled form of strain energy, the 2nd Piola-Kirchhoff stress (Equation 2-2) becomes,

\[ S = 2 \frac{\partial \psi_{\text{isochoric}}(\overline{C})}{\partial \overline{C}} + 2 \frac{\partial \psi_{\text{volumetric}}(J)}{\partial \overline{C}} J = S_{\text{isochoric}} + S_{\text{volumetric}} \]  

Since \( \psi_{\text{volumetric}} \) is a function of \( J \) only, differentiating based on the modified right Cauchy-Green deformation tensor, \( \overline{C} \), and using the chain rule, the right side of the 2nd Piola-Kirchhoff stress formulation (Equation 2-14) becomes,

\[ S = 2 \left( \frac{\partial \psi_{\text{isochoric}}(\overline{C})}{\partial \overline{C}}, \frac{\partial \psi_{\text{volumetric}}(J)}{\partial \overline{C}} J \right) = S_{\text{isochoric}} + S_{\text{volumetric}} \]  

where “:” represents double contraction (see Appendix A. Equations A-7 to A-9). The term \( \frac{\partial J}{\partial \overline{C}} \) may be determined as,

\[ \frac{\partial J}{\partial \overline{C}} = \frac{1}{2} J C^{-1} = \frac{1}{2} J^\frac{1}{2} \overline{C}^{-1} \]

by defining the total dilational stress as the hydrostatic pressure \( p \),

\[ p = \frac{d\psi_{\text{volumetric}}(J)}{dJ} \]

the 2nd Piola-Kirchhoff stress (Equation 2-15) may be represented as,

\[ S = S_{\text{isochoric}} + S_{\text{volumetric}} = 2 \left( \frac{\partial \psi_{\text{isochoric}}(\overline{C})}{\partial \overline{C}}, \frac{\partial \psi_{\text{volumetric}}(J)}{\partial \overline{C}} J \right) + p JC^{-1} \]

the term \( \frac{\partial \overline{C}}{\partial \overline{C}} \) in the isochoric part of the stress may be determined using the derivative formulation for scalar and tensor functions (Equation A-11),

\[ \frac{\partial \overline{C}}{\partial \overline{C}} = J^\frac{1}{2} \left( \frac{1}{3} \overline{C} \otimes \overline{C}^{-1} \right) \]

in which, \( \overline{I} \), is the fourth-order identity tensor (Equation A-6).
Substituting back into the isochoric part of the stress equation (Equation 2-15),

\[ S_{\text{isochoric}} = J^{-2} \bar{S} : \left( \mathbb{I} - \frac{1}{3} \mathbb{C} \otimes \mathbb{C}^{-1} \right) \]  

2-20

where the following definitions were used,

\[ \bar{S} = 2 \frac{\partial \psi_{\text{isochoric}}(\mathbb{C})}{\partial \mathbb{C}} \]  

2-21

and the fourth-order projection tensor is (Equation 2-22),

\[ \mathbb{P} = \mathbb{I} - \frac{1}{3} \mathbb{C}^{-1} \otimes \mathbb{C} \quad ; \quad \mathbb{P}^T = \mathbb{I} - \frac{1}{3} \mathbb{C} \otimes \mathbb{C}^{-1} \]  

2-22

the projection tensor (Equation 2-22) can also be defined as,

\[ \mathbb{P} = \mathbb{I} - \frac{1}{3} \mathbb{C}^{-1} \otimes \mathbb{C} = \mathbb{I} - \frac{1}{3} \left( \mathbb{C} \otimes \mathbb{C}^{-1} \right)^T \]  

2-23

Combined, the isochoric part of the stress (Equation 2-20) may be represented by either of the following two forms, after some algebraic manipulations (see Equations A-12 and A-13),

\[ S_{\text{isochoric}} = J^{-2} \bar{S} : \mathbb{P}^T \quad \text{or} \quad S_{\text{isochoric}} = J^{-2} \bar{S} \]  

2-24

As a result, the 2nd Piola-Kirchhoff stress for a hyperelastic nearly incompressible material is,

\[ S = S_{\text{isochoric}} + S_{\text{volumetric}} = J^{-2} \bar{S} + pJ\mathbb{C}^{-1} \]  

2-25

Based on the obtained 2nd Piola-Kirchhoff and stress relations (Equation B-18), the 1st Piola-Kirchhoff stress or engineering stress may be obtained from the following formulation,

\[ \mathbb{P} = \mathbb{F} : S = J^{-1/3} \mathbb{F} (\mathbb{P} : \bar{S}) + pJ\mathbb{F}^{-T} \]  

2-26

**Isotropic nearly incompressible formulation**

For an isotropic nearly compressible material, the general strain energy function (Equation 2-13) becomes:
\( U_{\text{isotropic}} = U(I_1(C), I_2(C)) + \bar{U}(J) \)  

here, the strain energy for an isotropic material is denoted by \( U \) instead of \( \psi \) for general strain energy, and notations \( \bar{U} \) and \( \bar{U} \) represent the isochoric and volumetric parts of the strain energy respectively.

Based on the isotropic formulation, the term \( \bar{S} \) (Equation 2-21) in the 2\(^{nd} \) Piola-Kirchhoff stress (Equation 2-25) for isotropic nearly incompressible material becomes,

\[
\bar{S}_{\text{isotropic}} = 2 \frac{\partial \bar{U}(I_1(C), I_2(C))}{\partial \bar{C}}
\]

Using the chain rule,

\[
\frac{\partial \bar{U}}{\partial \bar{C}} = \frac{\partial \bar{U}}{\partial I_1} \frac{\partial I_1}{\partial \bar{C}} + \frac{\partial \bar{U}}{\partial I_2} \frac{\partial I_2}{\partial \bar{C}}
\]

and plugging in the formulations for derivatives of the isochoric invariants,

\[
\bar{S}_{\text{isotropic}} = 2 \frac{\partial \bar{U}}{\partial \bar{C}} = 2 \left( \frac{\partial \bar{U}}{\partial I_1} + \frac{\partial \bar{U}}{\partial I_2} \bar{I}_1 \right) I - 2 \frac{\partial \bar{U}}{\partial I_2} \bar{C}
\]

Substituting this formulation for \( \bar{S}_{\text{isotropic}} \) into the 2\(^{nd} \) Piola-Kirchhoff stress (Equation 2-25),

\[
S_{\text{isotropic}} = J^{-2} \bar{S} : \left( 2 \left( \frac{\partial \bar{U}}{\partial I_1} + \frac{\partial \bar{U}}{\partial I_2} \bar{I}_1 \right) I - 2 \frac{\partial \bar{U}}{\partial I_2} \bar{C} \right) + pJC^{-1}
\]

The engineering stress or 1\(^{st} \) Piola-Kirchhoff stress (Equation 2-26) becomes,

\[
P_{\text{isotropic}} = F \cdot S = J^{-1/3} F : \left( 2 \left( \frac{\partial \bar{U}}{\partial I_1} + \frac{\partial \bar{U}}{\partial I_2} \bar{I}_1 \right) I - 2 \frac{\partial \bar{U}}{\partial I_2} \bar{C} \right) + pF^{-T}
\]

If the strain energy function is represented in the form of principal stretches (Equation 2-6), since the principal stretches are functions of the right Cauchy-Green deformation tensor (i.e. \( \lambda_a = \lambda_a(C) \) ) the following relations are valid,

\[
C \hat{N}_a = \lambda_a^2 \hat{N}_a , \quad \frac{\partial \lambda_a^2}{\partial \bar{C}} = \hat{N}_a \otimes \hat{N}_a , \quad \frac{\partial \lambda_a}{\partial \bar{C}} = \frac{1}{2\lambda_a} \hat{N}_a \otimes \hat{N}_a \quad a = 1, 2, 3
\]

where the set of \( \hat{N}_a \)'s are principal referential directions, and eigenvalue characteristics were used for formulation. Using these relations, the 2\(^{nd} \) Piola-Kirchhoff stress may be derived based on the principal stretches and principal referential directions as,
\[ S = 2 \frac{\partial \psi(C)}{\partial C} = 2 \left( \sum_{a=1}^{3} \frac{\partial \psi(C)}{\partial \lambda_a} \frac{\partial \lambda_a}{\partial C} \mathbf{N}_a \otimes \mathbf{N}_a \right) = \sum_{a=1}^{3} \frac{1}{\lambda_a} \frac{\partial \psi(C)}{\partial \lambda_a} \mathbf{N}_a \otimes \mathbf{N}_a \] 2-34

Considering the decoupled structure of the strain energy (Equation 2-13), the 2nd Piola-Kirchhoff stress can be decomposed into purely volumetric and purely isochoric contributions using analogy with (Equation 2-14) and modified principal stretch,

\[ S = S_{isochoric} + S_{volumetric} = 2 \frac{\partial \psi_{isochoric}(\bar{\lambda}_1, \bar{\lambda}_2, \bar{\lambda}_3)}{\partial C} + \frac{\partial \psi_{volumetric}(J)}{\partial C} \] 2-35

To determine the decoupled stress, \( \bar{\lambda}_a = J^{-\frac{1}{3}} \lambda_a \) for the three principal stretches, thus the following useful relation may be obtained,

\[ \frac{\partial \bar{\lambda}_a}{\partial \lambda_a} = J^{-\frac{1}{3}} \left( \frac{1}{3} \bar{\lambda}_a \bar{\lambda}_b^{-1} \right) \quad a, b = 1,2,3 \] 2-36

and using this relation, the decoupled 2nd Piola-Kirchhoff stress (Equation 2-35) becomes,

\[ S = J^2 \sum_{a=1}^{3} \frac{1}{\lambda_a^2} \left( \bar{\lambda}_a \frac{\partial \psi_{isochoric}}{\partial \lambda_a} - \frac{1}{3} \left( \sum_{b=1}^{3} \bar{\lambda}_b \frac{\partial \psi_{isochoric}}{\partial \lambda_b} \right) \right) \mathbf{N}_a \otimes \mathbf{N}_a + pJ^{-1} \] 2-37

where \( p \) is the hydrostatic pressure (Equation 2-17).

**Transversely isotropic nearly incompressible hyperelasticity**

For a transverse isotropic nearly incompressible material, the general hyperelastic strain energy (Equation 2-13) will have the form,

\[ U_{transverse isotropic} = \bar{U}(\bar{I}_1(C), \bar{I}_2(C), \bar{I}_4(C, A_0), \bar{I}_5(C, A_0)) + \bar{U}(J) \] 2-38

Similar to the procedure used earlier, using the invariant definitions (Equation 2-8), the 2nd Piola-Kirchhoff stress (Equation 2-25) for a transversely isotropic nearly incompressible material reduces to,

\[ S_{transverse isotropic} = 2J^2 \mathbb{P} : \left( \frac{\partial \bar{U}}{\partial \bar{I}_1} + \frac{\partial \bar{U}}{\partial \bar{I}_2} \bar{I}_1 \right) - \frac{\partial \bar{U}}{\partial \bar{I}_4} A_0 \otimes A_0 + \frac{\partial \bar{U}}{\partial \bar{I}_5} (A_0 \otimes \bar{C} \cdot A_0 + A_0 \otimes A_0) + pJ^{-1} \] 2-39
consequently, the engineering stress (Equation 2-26) for the transverse isotropic compressible material is,

\[ \mathbf{P}_{\text{transverse isotropic}} = 2J^{-1/3} \mathbf{F} \left( \mathbf{P} : \left( \frac{\partial \mathbf{U}}{\partial I_1} + \frac{\partial \mathbf{U}}{\partial I_2} I_1 \right) \mathbf{I} - \frac{\partial \mathbf{U}}{\partial I_2} \bar{\mathbf{C}} + \frac{\partial \mathbf{U}}{\partial I_4} \mathbf{A}_0 \otimes \mathbf{A}_0 + \frac{\partial \mathbf{U}}{\partial I_5} (\mathbf{A}_0 \otimes \bar{\mathbf{C}}. \mathbf{A}_0 + \mathbf{A}_0. \bar{\mathbf{C}} \otimes \mathbf{A}_0) \right) \right) + \mathbf{p} J^{-T} \]

2.4.2. Fully incompressible hyperelasticity

This section provides the foundation for the analytical solutions developed in Chapter 3 of the thesis. An ideal material which keeps it volume constant throughout a motion (isochoric motion) is characterized by an incompressibility constraint (Equation 2-41),

\[ \det \mathbf{F} = J = 1 \]

For this material the strain energy function and stress response formulations are presented and used in Chapter 3.

**Isotropic incompressible formulation**

If the incompressible material is isotropic (such as spinal cord gray matter), the strain energy function (Equation 2-4) is,

\[ \psi = \psi(\bar{\mathbf{C}}) - \mathbf{p}(J - 1) \]

Using the 2\textsuperscript{nd} Piola-Kirchhoff formulation (Equation 2-2) and differentiating the strain energy (Equation 2-42) the stress tensor becomes,

\[ \mathbf{S} = -p \bar{\mathbf{C}}^{-1} + 2 \frac{\partial \psi(\bar{\mathbf{C}})}{\partial \bar{\mathbf{C}}} \]

and the 1\textsuperscript{st} Piola-Kirchhoff stress (Equation 2-1) is obtained as,

\[ \mathbf{P} = -p \mathbf{F}^{-T} + \frac{\partial \psi(\mathbf{F})}{\partial \mathbf{F}} \]
The strain energy can also be represented in terms of the standard invariants of the right Cauchy-Green deformation tensor (Equation 2-5). The 2nd Piola-Kirchhoff formulation (Equation 2-18) is then,

\[
S = -p\tilde{C}^{-1} + 2\left(\frac{\partial \psi}{\partial I_1} + \frac{\partial \psi}{\partial I_2}\tilde{I}_1\right) I - 2\frac{\partial \psi}{\partial I_2} \tilde{C}
\]

where \( I \) represents the identity tensor.

**Transversely isotropic incompressible formulation**

Considering the transversely isotropic material with incompressible condition, the strain energy function (Equation 2-7) may be represented as,

\[
\psi = \psi(\tilde{C}, A_0) - p(J - 1)
\]

The stress response may be determined using the following formulation,

\[
S = -p\tilde{C}^{-1} + 2\left(\frac{\partial \psi}{\partial I_1} + \frac{\partial \psi}{\partial I_2}\tilde{I}_1\right) I - 2\frac{\partial \psi}{\partial I_2} \tilde{C} + 2\frac{\partial \psi}{\partial I_4} A_0 \otimes A_0
\]

\[+2\frac{\partial \psi}{\partial I_5}(A_0 \otimes \tilde{C} A_0 + A_0 \tilde{C} \otimes A_0)\]

where \( I \) represents the identity tensor.

**2.5. Viscoelasticity at large strain**

Viscoelastic theory describes the transient response of the material and presents a time-dependent relationship between stress and strain in the material. In a viscoelastic material the current state of the material depends on previous loading events; that is, the mechanical behavior is dependent upon the loading history (history-dependent behavior). Like most other neurological tissues, the spinal cord constituent parts exhibit viscoelastic behavior [37], [109], [167], [168]. In order to fully describe the spinal cord biomechanical behaviour, the time-dependent behavior of the spinal cord needs to be formulated. The transient response of the spinal cord to the mechanical insult is responsible for the primary SCI and will further affect the secondary SCI as discussed earlier in the introduction. This section develops the viscoelastic formulations required to appropriately represent the spinal cord constituent parts for modelling the SCI phenomena.
2.5.1. Quasi-linear viscoelasticity formulation

Linear viscoelasticity assumes linear behaviour for both the elastic and the viscous components of the material [153], [169]. For large strains typical of SCI, a generalization of the linear viscoelastic formulation may be employed where the elastic component of the viscoelastic formulation is defined by a hyperelastic model. This viscoelastic material model is called the Quasi-Linear viscoelastic (QLV) [110] in the sense that, the material is assumed to have linear viscous behavior and the relaxation function is a function of time only (as in linear viscoelasticity), however, the linear elastic behavior is generalized into a hyperelastic behavior. The reader is referred to sections 3.2.1 and 4.2.4 for more details on the efficacy and appropriateness of the QLV for SCI modelling.

In a QLV hyperelastic material undergoing finite deformation, the relaxation coefficients can be applied to the energy function[154]. Considering an arbitrary energy function,

\[ U(t) = \sum_{i=1}^{n} g(t - \tau_i) \Delta U_i H(t - \tau_i) \]  

where \( U \) is the strain energy at a current time \( t \), \( \Delta U_i \) is the change in strain energy magnitude for the \( i^{th} \) strain applied to the material at time \( \tau_i \), \( g \) is the dimensionless relaxation function, the material is assumed to follow the Boltzman superposition principal [169] and \( H(t) \) is the Heaviside step function. Since a general state consists of infinite steps therefore the strain energy at current time (Equation 2-48) becomes the following hereditary integral [170],

\[ U(t) = \int_{0}^{t} g(t - \tau) H(t - \tau) dU \]  

For a differentiable strain energy function, the strain energy function for a QLV material can be presented in the form of the following convolution integral,

\[ U(t) = \int_{0}^{t} g(t - \tau) \frac{dU}{d\tau} d\tau \]  

The dimensionless relaxation moduli is represented in terms of Prony series,

\[ g(\tau) = g_\infty + \sum_{i=1}^{N} g_i e^{-\tau/\tau_i} \]  

where \( g_i \)'s are the relative moduli of terms \( i \), \( g_\infty \) is the long-term response moduli and,
\[ g_\infty + \sum_{i=1}^{N} g_i = 1 \]

now, substituting 2-51 into 2-50, the energy function, the instantaneous material response becomes,

\[ U(t) = \int_0^t \left( g_\infty + \sum_{i=1}^{N} g_i e^{-(t-\tau)/\tau_i} \right) \frac{du}{d\tau} \, d\tau \]

or, using 2-52 and substituting in 2-53, to eliminate the long-term effect, the strain energy is obtained,

\[ U(t) = \int_0^t (1 - \sum_{i=1}^{N} g_i(1 - e^{-(t-\tau)/\tau_i})) \frac{du}{d\tau} \, d\tau \]

### 2.6. Directory of usage

The formulations derived in this chapter represented details of mathematical formulations used in later sections of this thesis. Briefly, the constitutive models obtained based on the full incompressibility assumption (Equations 2-43, 2-44, 2-45 and 2-47) augmented in QLV formulation (Equations 2-53 and 2-54) were used to capture spinal cord constituent materials’ behaviour in Chapter 3. Constitutive equations derived based on nearly incompressible assumption of the materials (Equations 2-31, 2-32, 2-37, 2-39 and 2-40) were used in combination with the QLV formulation (Equations 2-53 and 2-54) in Chapter 4 and Chapter 5.
Chapter 3.

THE TRANSVERSE ISOTROPY OF SPINAL CORD WHITE MATTER UNDER DYNAMIC LOAD

The rostral-caudally aligned fiber-reinforced structure of spinal cord white matter gives rise to transverse isotropy in the material. Stress and strain patterns generated in the spinal cord parenchyma following SCI are multi-directional and dependent on the mechanism of the injury. Our objective was to develop a white matter constitutive model that captures the material transverse isotropy under dynamic loading. White matter mechanical behavior was extracted from published tensile and compressive experiments. Combinations of isotropic and fiber-reinforcing models were examined in a conditional quasi linear viscoelastic (QLV) formulation to capture the white matter mechanical behavior. The effect of transverse isotropy on SCI model outcomes was evaluated by simulating a NHP contusion injury experiment. A second-order reduced polynomial hyperelastic energy potential conditionally combined with a quadratic reinforcing function in a four term Prony series QLV model best captured the white matter mechanical behavior (0.89< R²<0.99). White matter isotropic and transversely isotropic material models combined with discrete modeling of the pia mater resulted in peak impact forces that matched the experimental outcomes. The transversely isotropic white matter with discrete pia mater resulted in maximum principal strain distributions which effectively captured the combination of ipsilateral peripheral white matter sparing, ipsilateral injury and contralateral sparing, and the rostral/caudal spread of damage observed in in-vivo injuries. The results suggest that white matter transverse isotropy could have an important role in correlating tissue damage with mechanical measures and explaining the directional sensitivity of the spinal cord to injury.

3.1. Introduction

Accurately understanding and quantifying the impact biomechanics of SCI are critical for differentiating injury models [171]–[173] and predicting neurological outcomes [3]. While animal models of injury are useful in developing knowledge of SCI [35], [174]–
the physiological and morphological differences between animals and humans limits the extrapolation of animal injury model results to humans. Computational models provide an additional tool to study SCI biomechanics and to improve the fidelity of human injury modeling. However, computational models rely on accurate material constitutive models as inputs to simulate the tissue response to mechanical loading. Improving the accuracy of these constitutive models is crucial for advancing biofidelic computational models of human SCI.

Most experimental studies have tested the intact spinal cord [12], [99], [103]–[107], [111]; while only a few have separated the tissue into its constituent parts for testing and modelling [10], [11], [40], [102]. Therefore, several FE models of SCI have considered the spinal cord as a uniform material to study injury mechanisms and develop correlations between tissue level stresses and strains and histological damage [20]–[22], [89]. Most of the FE models simulate a contusion impact [38], [177]; however, the resulting stress and strain measures at the tissue level that best correlate with tissue damage are multi-axial [20], [21], [79], [89]. Although FE modelling of the cord as a uniform structure simplifies and expedites computational models, it markedly affects the patterns of stress and strain in the simulations [10], [19]. Discretely and more accurately modeling the constituent tissues of the spinal cord may enable more refined calculation of the stresses and strains in the cord during impact.

None of the previously proposed spinal cord white matter (WM) constitutive models coupled the dynamic (viscoelastic) [11], [40], [106] and anisotropic properties [102], [178] in a single constitutive model [10], [11], [40], [102]. The only study to account for the transverse isotropic properties of white matter assumed quasi-static loading rates (and not viscoelastic) which are not representative of traumatic injury [102]. In addition, reported constitutive models for white matter are based on tissue tests in isolated tension [10], [11], [89], [102] or isolated compression [40], [102]. However, applying a constitutive model obtained from an isolated tension test to compression (or vice versa) neglects material anisotropy.

The goal of this study was to define a constitutive model based on experiments from the literature [11], [40] to accurately capture the transversely isotropic viscoelastic characteristic of the white matter in a single model. The specific objectives were to 1) determine a transversely isotropic, quasi-linear viscoelastic (QLV) constitutive model for
the spinal cord white matter that fits published spinal cord white matter experiments, 2) verify the FE implementation of the conditional QLV model through simulation of published isolated tensile [11] and unconfined compressive [40] experiments and 3) assess the effects of white matter transverse isotropy on the mechanics of impact and the resulting tissue level strains in a FE model of contusion SCI.

3.2. Methods

3.2.1. Anisotropic constitutive model of spinal cord white matter

The axonal fibers in spinal cord white matter are primarily aligned rostral-caudally, resulting in a fiber-reinforced transversely isotropic structure [79], [179]. While there have been limited studies on spinal cord white matter anisotropy; in brain white matter, the mechanical resistance of the fibers to compression in the fiber direction was assumed to be negligible with the bulk material matrix governing the tissue biomechanics [180]. In contrast, the axonal fibers were considered to contribute substantially to the tensile response when the material was stretched in the direction of the fibers [102], [160]. The fiber-reinforced constitutive models create both tension/compression asymmetry in the fiber direction and transverse isotropy in the spinal cord white matter, similar to that observed in brain white matter material testing [160].

A conditional strain energy function that switches from an isotropic to a fiber-reinforced transversely isotropic model was proposed for white matter. The white matter material matrix was modeled with an isotropic hyperelastic strain energy function, $U_{matrix}$. The matrix energy function is augmented with a direction-specific reinforcing strain energy function, $U_{fibers}$, to represent the mechanical contribution of the axons. Previous studies on spinal cord tissue have demonstrated a nearly incompressible material response [10], [11], [40], [181]–[183]. Assuming incompressibility, only the invariants of the isochoric Cauchy-Green strain tensor ($\tilde{C}$) are needed to define the energy functions ($U_{matrix}$ and $U_{fibers}$) (Equation 3-1),

$$U_{WM} = \begin{cases} U_{matrix}(\tilde{I}_1, \tilde{I}_2) & \tilde{I}_5 \leq 1 \quad (Isotropic) \\ U_{matrix}(\tilde{I}_1, \tilde{I}_2) + U_{fibers}(\tilde{I}_4, \tilde{I}_5) & \tilde{I}_5 > 1 \quad (Anisotropic) \end{cases} \quad 3-1$$
where \( U_{WM} \) represents the elastic strain energy of the white matter and \( I_i \) (\( i = 1-5 \)) are the invariants of isochoric Cauchy-Green tensor (Equation 3-2),

\[
\begin{align*}
I_1 &= \text{tr}(\bar{C}); \quad I_2 = \frac{1}{2}[\text{tr}(\bar{C})^2 - \text{tr}(\bar{C})^2]; \quad I_4 = A_0 \cdot \bar{C} \cdot A_0; \quad I_5 = A_0 \cdot \bar{C}^2 \cdot A_0
\end{align*}
\]

\( A_0 \) is a unit vector defined in the direction of the fibers; therefore, the value of \( I_5 \) determines the state of the fibers in the material where \( I_5 > 1 \) indicates stretch and \( I_5 < 1 \) indicates contraction in the fibers.

Combinations of three well-established isotropic hyperelastic strain energy functions \( (U_{\text{matrix}}) \), that have previously been used for modelling brain [112], [184], [185] and spinal cord [21], [40], [102], [107] (Table 3-1), with a series of established reinforcing strain energy functions \( (U_{\text{fibers}}) \) (Table 3-1) were evaluated in a QLV model [160], [181]–[183]. For each combination of strain energy functions, the uniaxial response in the direction of the fibers (Equation 3-3) was solved explicitly (Mathematica, Wolfram Research, Inc., Version 10.0, Champaign, IL) [160], [181]–[183]. Based on the results, a 4-term Prony series was used (N=4).

**Table 3-1:** Hyperelastic isotropic and reinforcing functions evaluated to characterize the white matter. \( C_{ij}, \mu_i, \alpha_i, \text{and } \gamma_i \) are material parameters, \( N \) is the order of the hyperelastic model and \( \bar{\lambda}_i \) are the deviatoric principal stretches.

<table>
<thead>
<tr>
<th>Isotropic model</th>
<th>Incompressible energy function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polynomial</td>
<td>( U_{\text{Matrix}}(I_1, I_2) = \sum_{i+j=1}^{N} C_{ij}(I_1 - 3)^i(I_2 - 3)^j \quad N \geq 1 )</td>
</tr>
<tr>
<td>Reduced polynomial</td>
<td>( U_{\text{Matrix}}(I_1) = \sum_{i=1}^{N} C_{i0}(I_1 - 3)^i \quad N &gt; 1 )</td>
</tr>
<tr>
<td>Ogden</td>
<td>( U_{\text{Matrix}}(\bar{\lambda}_1, \bar{\lambda}_2, \bar{\lambda}<em>3) = \sum</em>{i=1}^{N} \frac{2\mu_i}{\alpha_i^2}(\bar{\lambda}_1^{\alpha_i} + \bar{\lambda}_2^{\alpha_i} + \bar{\lambda}_3^{\alpha_i} - 3) \quad N \geq 2 )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reinforcing model</th>
<th>Incompressible energy function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard ( I_4 )</td>
<td>( U_{\text{fibers}}(I_4) = \frac{1}{2} \gamma_{\text{std}} (I_4 - 1)^2 )</td>
</tr>
<tr>
<td>Quadratic ( I_5 ) [186]</td>
<td>( U_{\text{fibers}}(I_5) = \frac{1}{2} \gamma_{\text{quad}} (I_5 - 1)^2 )</td>
</tr>
</tbody>
</table>
Weiss exponential [165] \[ U_{fibers}(\bar{I}_4) = \gamma \exp \left( e^{I_4 - 1} - \bar{I}_4 \right) \]

The responses were then evaluated by comparing them to the published uniaxial compressive [40] and tensile [11] experimental data (Equation 3-3).

\[
P_U(t) = \int_0^t \left( 1 - \sum_{i=1}^N g_i \left( 1 - e^{-(t-\tau)/\tau_i} \right) \right) \frac{d}{d\tau} \left( \frac{dU_{WM}}{d\lambda_U} \right) d\tau
\]

where \( P_U(t) \) is the rate-dependent first Piola-Kirchhoff stress component in the direction of fibers, \( \lambda_U \) is the principal stretch in the direction of fibers, \( g_i \)'s are the dimensionless Prony series constants, \( \tau_i \)'s are the relaxation times, \( t \) is time, and \( U_{WM} \) is the strain energy function (Equation 3-4).

\[
U_{WM} = c_{10}(\bar{I}_1 - 3) + c_{20}(\bar{I}_1 - 3)^2 + \frac{1}{2} \gamma_1(\bar{I}_5 - 1)^2
\]

where \( \langle \ldots \rangle \) represents Macaulay brackets. The value in the brackets provides a conditional response for the inclusion of the fibers in the material response; \( \langle \ldots \rangle \) is zero when \( \bar{I}_5 < 1 \), showing no contribution of the fibers on the strain energy in compression.

Parameter optimization was performed using two-step non-linear optimization. In the first step, the isotropic portion was alternately fit to the highest strain rate and then the lowest strain rate compressive stress-relaxation data [40], where the optimization constraints were updated after each iteration based on the results from the previous iteration [40], [181]. Following published methods [181], the QLV relaxation function was estimated by a Prony series expansion and the number of terms in the Prony series in (Equation 3-3) were chosen to be equal to the number of compressive strain rates published (four-term [40]). Relaxation times were assumed to be equal to the duration of the compressive loading at different strain rates (\( \tau_1 = 0.1 \) sec, \( \tau_2 = 1.0 \) sec, \( \tau_3 = 10.0 \) sec, \( \tau_4 = 100.0 \) sec [40]). Optimization terminated when the parameters converged to four decimal places and a single set of parameters was determined. In the second step, the optimized isotropic energy function was augmented with different reinforcing models (Table 3-1) and fitted to the tensile experiments at different strain rates [11] to determine the corresponding reinforcing parameter. The best strain energy function for the
conditional QLV model was determined primarily by the best fit to the experimental data; however, the ease of FE implementation was also considered.

3.2.2. Constitutive model FE implementation

The fiber-reinforced constitutive model was implemented as a custom material model in Abaqus using UANISOHYPER_INV subroutine (v6.13 Dassault Systemes Simulia Corp. Providence, RI, USA). Coupling the Ogden model with the reinforcing functions for FE implementation was complicated as the Ogden model is defined by principal stretches while the existing reinforcing models are defined by strain invariants (Table 3-1). In contrast, polynomial strain energy functions (i.e. Mooney-Rivlin, 2nd order polynomial and reduced polynomial) were easily combined with the reinforcing functions as they are both defined using strain invariants.

![Figure 3-1: FE simulation of the experimental studies (a) unconfined compression [40] and (b) uniaxial tension [11]. Axonal fibers are assumed parallel to the loading direction in both cases.](image)

To verify the accuracy of the custom coded user material, the published tensile [11] and compressive [40] experiments were reconstructed in Abaqus (Figure 3-1). Dimensions and boundary conditions were adopted from each corresponding experiment. Fibers were considered rostral-caudal, which was parallel to the loading direction. Compressive loads were applied with two frictionless analytically rigid surfaces at $5.0\frac{1}{\text{sec}}$, $0.5\frac{1}{\text{sec}}$, $0.05\frac{1}{\text{sec}}$ and $0.005\frac{1}{\text{sec}}$ strain rates to a peak strain of 50% [40]. For tensile simulations,
tension was applied with rigid cylindrical grips that bounded the white matter sample in the axial direction but left it free to deform in transverse direction. A peak tensile strain of 32% was applied at deformation rates equal to $5.0 \text{ mm/sec}$, $0.5 \text{ mm/sec}$ and $0.05 \text{ mm/sec}$ [11]. Models were meshed with continuum elements (C3D8R). Mesh refinement analysis (peak force convergence) yielded 2584 and 1922 elements for tensile and compressive models respectively. To avoid numerical problems (as required by Abaqus), a Poisson ratio ($\nu=0.499$) was introduced for white matter to approximate incompressibility in the solution [37]. The experimental and FE stress-strain responses were compared at different strain rates.

3.2.3. Simulation of NHP contusion injury

The significance of considering white matter anisotropy in SCI simulations was analyzed through FE models of unilateral contusion injury of NHP [3].

Model generation

An existing primate SCI FE model [76] was modified to include the new anisotropic, viscoelastic white matter constitutive model developed in this study. Briefly, magnetic resonance image (MRI) scans of primate spinal cords ($n=7$) over the C1-C6 cervical levels were obtained from a previous study (Figure 3-2a) [3]. The spinal cord and spinal column cross sections were measured, averaged rostral-caudally for each animal, and implemented in Abaqus (Figure 3-2b). Gray matter, white matter and cerebrospinal fluid (CSF) were distinguishable in the MRI images; however, the pia and dura maters were not visible and were assumed to be bounded to the white matter and the CSF, respectively. The impactor was modeled as a 4 mm diameter analytically rigid cylinder to match in-vivo experiments [3]. FE simulations of contusion SCI have shown an almost symmetric distribution of stresses and strains in the rostral/caudal directions around the impact epicenter [20], [21], [24]. Therefore, only one half of the spinal cord (from injury epicenter to 10 mm rostral) was simulated to reduce the computational time. The average two dimensional cross section of the spinal cord at C5 was extruded to a length of 10 mm because the MRI scans following in-vivo contusion did not show noticeable defects in distances over 5.2 mm rostral or caudal of the injury epicenter [3].

Following a mesh refinement analysis, the final model was comprised of 18950, 47300 and 36850 continuum elements (C3D8R) in the gray matter, white matter and the
CSF respectively. The pia mater had a thickness of 0.13 mm [187] and was meshed with S4R elements. The CSF was tied to both the pia and dura maters. The dura mater was modeled as a 0.35 mm thick [109] shell surrounding the CSF (S4R elements).

To reduce the computational artifacts associated with reduced integration elements, element distortion control, second order accuracy, and enhanced hourglass control were applied to all the elements in the model. The spinal canal was modeled as a rigid surface constraining the spinal cord during the contusion injury. A 6mm diameter portion of the dorsal spinal canal was removed to simulate the surgical laminectomy. The model was explicitly analyzed including material and geometric nonlinearities.

Figure 3-2: Generating the FE contusion model (a) C5 cross-section of a representing MRI scan of a NHP. Scale bar is 10 mm. (b) Symmetric FE simulation of the unilateral contusion SCI model. (c) Sub-regional areas in the spinal cord cross-section used to analyze the FE model results. (d) Mid-coronal section and one element thick slices in the epicenter (i.e. 0 mm) and 1.6 mm, 3.2 mm and 4.8 mm rostral to the injury, used to investigate strain distribution patterns in the rostro-caudal direction.
**Materials**

Different material properties were used for white matter and gray matter to create four spinal cord models:

**Model A.** Discrete white matter and gray matter, with anisotropic white matter and isotropic gray matter was generated using the developed model for white matter (Table 3-2) and an isotropic model for gray matter (Table 3-3). The gray matter constitutive model was obtained by fitting a QLV hyper-viscoelastic Ogden model with a 3-term Prony series to published gray matter tensile experimental data [11].

**Model B.** Discrete white matter and gray matter with isotropic white matter and gray matter; gray matter was modeled as in A, while white matter was modeled as isotropic by setting the white matter reinforcing parameter to zero.

**Model C.** gray matter and white matter modeled together as a uniform material surrounded by a distinct pia mater. The uniform material (GM and white matter) was modeled as isotropic using material properties of the isotropic white matter, as in model B (Table 3-3).

**Model D.** gray matter, white matter and pia mater modeled together as a single isotropic material using the constitutive model presented by Maikos et al.[21] that have been widely used in computational simulations of SCI (Table 3-3)[18], [20], [21], [24].

The CSF was modeled as a low shear-to-bulk modulus Mooney-Rivlin hyperelastic model combined with viscoelastic parameters (Table 3-3) because a fluid-like CSF constitutive model was shown to best represent the brain behavior during impact experiments for the lowest computational complexity[188]. Dura mater properties were obtained from uniaxial mechanical tests on rats (Table 3-3)[37]. For models including pia mater (models A, B and C) the pia mater was modeled as linear elastic material based on porcine cervical pia mater (Table 3-3)[187].
Table 3-2: QLV optimized coefficients and their relative r-squares fit. Relaxation times were $\tau_1=0.1$, $\tau_2=1.0$, $\tau_3=10.0$, $\tau_4=100.0$.

<table>
<thead>
<tr>
<th>Matrix model</th>
<th>Coefficients</th>
<th>R-square of fit to compressive stress-time</th>
<th>Reinforcing function</th>
<th>Reinforcing coefficient [Pa]</th>
<th>R-square of fit to tensile stress-time (loading)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5.0 s$^{-1}$</td>
<td>0.5 s$^{-1}$</td>
<td>0.05 s$^{-1}$</td>
<td>0.005 s$^{-1}$</td>
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<tr>
<td>Mooney-Rivlin</td>
<td>$c_{10}$ [Pa]</td>
<td>514.94</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>$c_{01}$ [Pa]</td>
<td>277.27</td>
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<td></td>
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<tr>
<td></td>
<td>$g_1$</td>
<td>0.4302</td>
<td></td>
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<td></td>
<td>$g_2$</td>
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<td>$g_3$</td>
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<tr>
<td></td>
<td>$g_4$</td>
<td>0.0672</td>
<td>0.70</td>
<td>0.91</td>
<td>0.74</td>
</tr>
<tr>
<td>Standard $I_4$</td>
<td>$c_{10}$ [Pa]</td>
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<td></td>
<td>$c_{20}$ [Pa]</td>
<td>91.18</td>
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<td></td>
<td>$c_{11}$ [Pa]</td>
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<td></td>
<td>$c_{01}$ [Pa]</td>
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<td></td>
<td>$g_2$</td>
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<td></td>
<td>$g_3$</td>
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<td>0.93</td>
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<tr>
<td>Weiss exponential</td>
<td>$g_4$</td>
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<td>$c_{20}$ [Pa]</td>
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<td>$c_{11}$ [Pa]</td>
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<tr>
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<td>$c_{01}$ [Pa]</td>
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<td>$g_2$</td>
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<td>$g_3$</td>
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<td>$g_4$</td>
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</tr>
</tbody>
</table>
### Table 3-3: Material properties of GM, CSF, Dura and Pia maters used in the unilateral SCI contusion impact simulations.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Hyperelastic constitutive model</th>
<th>Hyperelastic model parameters</th>
<th>Density(^a)</th>
<th>Viscoelastic Prony series parameters</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM</td>
<td>Ogden 1st order</td>
<td>(\mu_0 = 30.57 \text{ [kPa]})</td>
<td>(\mu = 1045\text{ [kg m}^{-3})</td>
<td>(\tau_1 = 0.64 \text{ [sec]})</td>
<td>Derived through fitting to tensile test data[11]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\alpha = 7.52)</td>
<td></td>
<td>(\tau_2 = 6.4 \text{ [sec]})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\nu = 0.45)</td>
<td></td>
<td>(g_2 = 0.2462)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\rho = 1045\text{ [kg m}^{-3})</td>
<td></td>
<td>(g_3 = 0.1163)</td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>Mooney-Rivlin</td>
<td>(C_{10} = 125 \text{ [Pa]})</td>
<td>(\mu = 1007\text{ [kg m}^{-3})</td>
<td>(g_1 = 0.95)</td>
<td>[21], [189]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(C_{01} = 125 \text{ [Pa]})</td>
<td></td>
<td>(\tau_1 = 0.002 \text{ [sec]})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\nu = 0.4999)</td>
<td></td>
<td>(\tau_2 = 0.128)</td>
<td></td>
</tr>
<tr>
<td>Dura</td>
<td>Ogden 1st order</td>
<td>(\mu_0 = 3.25 \text{ [MPa]})</td>
<td>(\mu = 1174\text{ [kg m}^{-3})</td>
<td>(g_2 = 0.086)</td>
<td>[37]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\alpha = 4.7)</td>
<td></td>
<td>(\tau_3 = 0.081 \text{ [sec]})</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>(\nu = 0.45)</td>
<td></td>
<td>(g_3 = 0.086)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>(\rho = 1174\text{ [kg m}^{-3})</td>
<td></td>
<td>(\tau_4 = 0.564 \text{ [sec]})</td>
<td></td>
</tr>
<tr>
<td>Pia</td>
<td>Linear elastic</td>
<td>(E = 39.3 \text{ [MPa]})</td>
<td>(\mu = 1075\text{ [kg m}^{-3})</td>
<td>(g_4 = 0.086)</td>
<td>[187]</td>
</tr>
<tr>
<td>Uniform WM and GM spinal cord (model D)</td>
<td>Ogden 1st order</td>
<td>(\mu_0 = 0.188 \text{ [MPa]})</td>
<td>(\mu = 1045\text{ [kg m}^{-3})</td>
<td>(g_1 = 0.5282)</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\alpha = 4.7)</td>
<td></td>
<td>(\tau_1 = 0.008 \text{ [sec]})</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>(\nu = 0.45)</td>
<td></td>
<td>(g_2 = 0.3018)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>(\rho = 1075\text{ [kg m}^{-3})</td>
<td></td>
<td>(\tau_2 = 0.150 \text{ [sec]})</td>
<td></td>
</tr>
</tbody>
</table>

### Loading and boundary conditions

The impactor was positioned at C5 in contact with the dorsal dural surface with the lateral side of the impactor aligned 0.5 mm over the spinal cord midline. A ventral displacement of 6 mm (measured from dural surface) was prescribed for the impactor with a constant velocity of 0.5 \(\text{m sec}^{-1}\) to approximate NHP experiments[3]. Symmetric boundary conditions were applied to the gray matter, white matter, pia mater (models A, B and C), CSF and dura in the axial direction under the impactor. To simulate the \textit{in-vivo} pre-tension in the spinal cord[108], [190] a longitudinal displacement of 1.5 mm (15%) was applied to the free end (rostral) of the spinal cord[10]. Up to 75% of the pre-tension was allowed to relax before the start of the impact. The spinal canal was fixed and the contacts between the dura mater and the spinal canal and the impactor were assumed to be frictionless.
**Effect of material anisotropy on injury mechanics**

The effects of modelling white matter anisotropy on the contusion SCI simulation biomechanics were assessed by comparing model A with the other models. The effects of discrete modelling and/or including the pia mater in the model were differentiated from the effects of white matter anisotropy by comparing the isotropic models B, C with model D.

The impactor peak force was recorded for each simulation and compared with the average experimental peak forces[3]. Since maximum principal strain (MPS) has been widely used as a mechanical indicator that correlates with injury[20], [37], [83], [191], [192], MPS distribution results were compared in the spinal cord parenchyma in a transverse plane at the injury epicenter for the different models[3]. In addition, to visualize the rostral spread of the injury, one element thick (0.2 mm) white matter and gray matter regions were outlined in transverse plane slices of the model, at the injury epicenter (i.e. 0 mm), 1.6 mm, 3.2 mm and 4.8 mm rostral to the epicenter (Figure 3-2d). The ipsilateral side of the injury was divided into five sub-regions, namely gray matter dorsal and ventral horns, white matter dorsal, lateral and ventral funiculus (Figure 3-2c). MPSs were recorded for all the elements on the sub-region slices throughout the impact. The peaks of MPSs for individual elements were averaged over the elements of each sub-region and were compared across the different models. The selected data regions corresponded to the tissue sections used for post-injury histological analysis in the experimental study[3].

### 3.3. Results

#### 3.3.1. White Matter Constitutive Model

Isotropic QLV models predicted the experimental uniaxial compressive response at different strain rates. The isotropic QLV Mooney-Rivlin model with the 4-term Prony series was the weakest fit ($0.70 < R^2 < 0.91$), while isotropic QLV combinations of the Ogden model and second order reduced polynomial with a 4-term Prony series had the best fits ($0.92 < R^2 < 0.99$) (Table 3-2 and Figure 3-3). Higher order strain energy functions (e.g. Ogden $N \geq 2$, polynomial and reduced polynomial $N > 2$) were not evaluated due to the sufficient capability of the lower order functions to predict the experimental data. The fit of the tensile loading data varied from $R^2 = 0.81$ to $R^2 = 0.98$ for different isotropic and
reinforcing model combinations (Table 3-2). For all isotropic models, combinations of the quadratic $I_5$ reinforcing function yielded the best fits to the experimental data at different strain rates ($0.89 < R^2 < 0.99$) (Figure 3-4).

![Graph showing stress relaxation behavior](image)

**Figure 3-3:** Compressive stress-relaxation behavior of different *WM* hyperelastic models for one representative strain rate ($5.0 \text{ \text{[1/sec]}}$) compared with experimental data obtained from Sparrey et al. [40].

The most accurate models for predicting tensile and compressive behaviors were combinations of the 1st order Ogden model or the 2nd order reduced polynomial model with the quadratic $I_5$ reinforcing strain energy function (Table 3-2). However, considering the strain energy *FE* coupling remarks described in the methods, the best fit and most efficiently implemented strain energy function was a 4-term Prony series QLV model, using a 2nd order reduced polynomial energy function conditionally augmented by the quadratic $I_5$ reinforcing function with optimized material parameters (Table 3-2).
3.3.2. Constitutive model FE implementation

The material was effectively simulated by the selected constitutive model in the FE simulations of the isolated tensile and compressive experiments (Figure 3-5). Compared with the available experimental data in tension, the FE model predicted the stress-strain responses for the high (0.5 mm/sec), medium (0.05 mm/sec), and low (0.005 mm/sec) deformation rates accurately ($R^2=0.97$, $R^2=0.97$ and $R^2=0.98$, respectively) (Figure 3-5b). The simulation results were also accurate in compression with $R^2=0.98$, $R^2=0.98$, $R^2=0.93$ and $R^2=0.98$ for the $5.0\frac{1}{\text{sec}}$, $0.5\frac{1}{\text{sec}}$, $0.05\frac{1}{\text{sec}}$ and $0.005\frac{1}{\text{sec}}$ strain rates, respectively (Figure 3-5a).
3.3.3. Unilateral Contusion *FE* Model

The peak impact forces observed in the simulations (model A=17.9 N, model B=16.3N and model C=15.4 N) were in the range of the mean peak force from *in-vivo* unilateral primate contusion experiments (16.1±4.5 N)[3]. Model D overestimated (24.34 N) the peak force during injury.
At maximum compression, the maximum principal strain distribution patterns at the injury epicenter showed substantial differences for each material model (Figure 3-6). The discrete white matter and gray matter models (A and B) had peak MPSs (0.75-0.95) spread across the ipsilateral white matter at the boundary with the ventral horn of the gray matter. In the anisotropic model (model A), the elevated strain zone was more localized under the tip of the impactor. In the uniform white matter and gray matter model with pia mater (model C), the elevated MPS zone was considerably smaller than the other models, and was located directly under the impactor tip.

![Figure 3-6: MPS distribution at 6.5 mm contusion impact in GM and WM over a 0.2 mm thick slice at the injury epicenter. Columns stand for (a) Model A, (b) Model B, (c) Model C, and (d) Model D. MPS is dimensionless and the scale bar is 2 mm.](image)

Simulating anisotropy resulted in less propagated MPSs to the contralateral side of the white matter. Generally, in the white matter, MPSs were the lowest (<0.55) in model D, while the rest of the models showed focal zones of high MPSs (~0.85). There was a general decrease in MPSs with lateral distance from the impactor tip in model D. In the models including the pia mater (Models A, B and C) a narrow rim of low MPS (<0.25) was seen in the periphery of white matter on the impacted side. Within the gray matter, the MPSs were generally higher in model C (0.6-0.8) compared to other models (0.35-0.55) with a focal very high MPS zone at the gray matter ventral horn under the impactor tip. MPS were almost uniform (~0.40) in the gray matter in models A and B with slightly higher MPSs in model A. Generally, for all the models (except model C), within the gray matter
zones, averaged peak MPSs decreased the greater rostral distance they were from the epicenter (Figure 3-7). The simulation of anisotropy (model A) did not noticeably affect the averaged peak MPSs (<5.6% difference from the isotropic models B and D) in the gray matter dorsal and ventral horns over different rostral positions. Dorsal and ventral gray matter horns experienced lower MPSs (up to ~70% lower) at greater rostro-caudal positions in models A, B and D compared to model C.

**Figure 3-7:** Regional variations of the peaks of MPSs for individual elements averaged over the elements of each sub-region, for five sub-regions; dorsal and ventral GM, dorsal, ventral and lateral WM. Data is shown for four transverse slices at the injury epicenter and spaced 1.6 mm, 3.2 mm and 4.8 mm rostral. The x-axis labels indicate the different models. Error bars show the standard deviation of the peak MPSs over the elements in each sub-region.

Within the white matter, models A and D showed a gradual decrease in the MPSs over increased rostral distance from the epicenter (Figure 3-7). Conversely, MPSs were nearly constant over the rostro-caudal distance in the white matter sub-regions in models B or C with an exception of dorsal white matter in model B. When the pia mater was modeled as a uniform material with the gray matter and white matter, the white matter
MPSs were markedly lower (27-66% lower) than the models with distinct pia mater. In the discrete white matter and gray matter models, the MPSs were generally higher in the white matter sub-regions compared to gray matter regions. Within the discrete white matter and gray matter models (A and B), simulation of anisotropy slightly reduced (<7.2% lower) the MPSs in all white matter sub-regions at the epicenter. This decrease was greater for locations further from epicenter.

3.4. Discussion

*In-vivo* studies of SCI mechanics suggest that the injury is a multi-axial event where tissue damage depends on the magnitude and mechanism of loading[174]. This has been reinforced by *FE* simulations of SCI, which have correlated physiological measures of spinal cord damage, such as functional losses and hemorrhage, with multi-axial measures of stresses and strains[20], [21], [24], [89]. We know the stress and strain predictions of *FE* models of SCI are affected by the assumed material properties[10], [97] and that the highly oriented cranio-caudal axonal fibers in the white matter behave as directional reinforcement for the material and result in anisotropic material behavior[10], [102], [109]. However, for computational efficiency and due to a lack of available properties, most studies have represented the spinal cord as a single, isotropic material in their analyses [20], [21], [24]. There are few experimental results that describe the mechanics of spinal cord gray matter and white matter, and characterization of the material behavior is challenging due to the complexity of accessing and testing spinal cord tissue [11], [40], [102]. In this study, a novel constitutive model was developed to capture the transverse isotropy of the spinal cord white matter under dynamic loading.

WM anisotropy has not been fully characterized in previous studies of the spinal cord, especially at high strain rates typical of traumatic SCIs. The spinal cord white matter has been characterized statically and quasi-statically using isotropic linear elastic [10] and transversely isotropic reinforced Mooney-Rivlin hyperelastic models [89], [102]. Isolated tensile and isolated compressive dynamic behavior of spinal cord white matter have also been captured using standard viscoelastic solid [11] and Ogden QLV [40] models, respectively. However, none of the current studies have explored the dynamic transversely isotropic viscoelastic characteristics of the tissue. We presented a QLV constitutive model that was able to predict the highly non-linear white matter material
behavior at high strain rates. Various $I_4$ fiber-reinforced models have been proposed to capture brain and brainstem white matter anisotropy (Fung exponential[185], Weiss exponential[180], standard $I_4$ [160], Ogden type $I_4$ [185], [193] and Holzapfel-Gasser-Ogden[161], [194]). These models were examined in the present study. Although these reinforcing functions sufficiently captured the quasi-static behavior of spinal cord white matter [102]; some of these models were eliminated from our study because the resulting QLV convolution integral was not explicitly solvable [102], [157]. The present study showed that a higher order ($I_5$) fiber-reinforced strain energy function was needed to capture the substantial rostro-caudal tension-compression asymmetry at higher strain rates. This tension-compression asymmetry combined with the previous quasi-static results suggest that the effect of anisotropy becomes more pronounced on the white matter response at the high strain rates typical of traumatic injury. The rate sensitivity of the axonal fibers may explain why in-vivo motion of the cervical spinal cord during controlled head flexion can result in strains of 6-10% with no damage to the tissue[81] while white matter tissue fails at high strain rates with tensile strains of 2-5%[10], [107].

Recent research characterizing white matter properties at the microscopic level using atomic force microscopy also observed white matter transverse isotropy and noted a lower stiffness for compressive loading in the direction of the axonal fibers [178]. This supports our assumption of a negligible contribution of the axonal fibers in compressive loading aligned in the fiber direction, while highlighting the role of axonal fibers in stiffening the tensile response of white matter in the axial direction.

Previous studies[21] adjusted the cord material properties obtained from in-vitro mechanical tests[107] in order to match the impact biomechanics of an in-vivo midline contusion injury model in rats. However, our FE contusion injury models were able to match the in-vivo impact biomechanics of unilateral NHP cervical contusion injuries[3] without recalibrating the constitutive models when the pia mater was modeled explicitly and in-vivo pre-tension was simulated.

Accurately defining the parenchymal materials, their properties and predicting tissue level mechanics are critical for determining tissue damage thresholds to link mechanical measures with tissue damage. While previous studies have correlated tissue damage with MPSs using uniform tissue properties for the spinal cord[20], [21], the FE injury models in the current study revealed that accounting for white matter anisotropy resulted in different
distribution patterns of MPSs that may affect the correlation of tissue level stresses and strains with tissue damage.

Comparing the FE predicted results with histological analyses of NHP unilateral contusion injuries[3] highlights the effects of material model assumptions on predicting patterns of tissue damage (Figure 3-8). Quantitative correlation between the in-vivo test results and the averaged FE model of the NHP developed here without accounting for inter-subject variation is not appropriate. Instead, trends in histological outcomes that were similar across animals were compared with the FE model results. In-vivo histology showed three key characteristics of the tissue damage; 1) the sparing of the peripheral white matter under the impactor, 2) the spread of damage to the contralateral side - including sparing of the ventral white matter and 3) the rostral/caudal spread of damage - showing a rapid decrease in damage away from the injury epicenter. Differentiating the spinal cord gray matter and white matter from the pia mater in the FE models (models A through C) resulted in a peripheral rim of low strains immediately adjacent to areas of high strain under the impactor and a broad rim of low strains in the contralateral white matter. These MPS patterns correspond to the peripheral white matter sparing observed in the ipsilateral white matter and the ventral white matter on the contralateral side of the in-vivo injuries[3]. However, when the white matter was modeled as isotropic (Model B), the strain patterns showed elevated strains in the contralateral white matter where there was no histological damage.

Finally, the size of the in-vivo white matter and gray matter lesions decreased with distance from the injury epicenter[3]. However, only injury simulations using the uniform white matter and gray matter model without pia mater (model D) and the anisotropic model (model A) exhibited similar proportional decreases in MPSs away from the injury epicenter. Therefore, combining material transverse isotropy with discrete modeling of the pia mater (model A) best captured the combination of features observed in the in-vivo unilateral injury. Further work using subject specific FE modeling is required to accurately quantify the relationship between tissue strains and in-vivo damage.
Figure 3-8: The distribution of histological damage at the injury epicenter and rostral to the injury resulting from cervical unilateral contusion SCIs in NHPs (adapted from [3]). Histological sections processed for eriochrome cyanine and neutral red show the spread of the lesion (GM = blue; WM = green; lesion area = red). The four subjects had impact mechanics similar to those modeled in this study. Although there is variation in the histological outcomes for each subject they all show similar characteristics; ipsilateral peripheral WM sparing, ipsilateral injury and contralateral sparing, and decreasing severity of damage in tissue section rostral/caudal to the injury epicenter. Numbers on the left refer to the subject numbers from the in-vivo study.

To definitely determine the material model which best simulates the in-vivo tissue mechanics, paired FE and in-vivo models where localized in-vivo tissue strains are directly recorded is required. A new technique reported in a study by Bhatnagar et al. measured spinal cord strains by using experimental magnetic resonance images (MRIs) before and during contusion SCI in an in-vivo rodent model[34]. Although that study only focused on transverse-plane strains, they observed discontinuous strain distribution patterns across the gray matter/white matter tissue boundary similar to those seen in the discrete white matter and gray matter FE models (Figure 6 models A and B). Previous FE simulation results[20], [21], [24] and those in this study (Figure 6 models C and D) using a uniform constitutive model for gray matter and white matter did not see discontinuous MPSs at the gray matter/white matter tissue boundary. This supports the need for discretely modelling the white matter and gray matter in FE simulations. The differences in the MPS patterns in the spinal cord tissue that resulted from different material model assumptions reinforce
the need for further experimental studies to accurately quantify the properties of each constituent material of the spinal cord and the need to directly validate FE model predictions with in-vivo measures of tissue strains.

**Study Limitations**

Limited experimentally derived material properties for the spinal cord constituent tissues provided some challenges. White matter tensile and compressive mechanical behaviors have not been systematically compared in a single study. Using separate studies for model evaluation may cause artefactual variability in mechanical behavior. However, post-mortem time, specimen size, orientation, temperature, strain rates, and preconditioning, which have been shown to have a significant effect on the experimental results[40], [100] were similar between the two studies. Although the tissues were from different species, the limited experimental data to date suggests there are not significant differences in neurological tissue characteristics between species[100]. Furthermore, the authors are aware that the transverse isotropy captured in this study may not be the only anisotropy in the white matter and there may be other sources of anisotropy in the material. However, distinctly oriented axonal fibers in the rostral-caudal direction of the spinal cord white matter, suggests that the transverse isotropy is the dominant source of observed tension-compression asymmetry in the white matter. Additional mechanical tests are required to fully capture the anisotropy of the white matter. Until the need to systematically explore spinal cord material anisotropy is well established, there is little motivation for researchers to undertake these complex and logistically challenging studies.

The two-step optimization algorithm applied to obtain the viscoelastic material properties required fitting the model to isolated compressive data then applying obtained parameters as constraints in further optimizing the fiber-reinforcing parameter. Although FE implementation of the current optimized material constants sufficiently (R² > 0.93) predicted the experimental results, more complex optimization methods may be employed to yield improved material properties by determining all material parameters, in one step.

Our results predicted the relative effects of material model characteristics on FE-simulated strains during a unilateral contusion injury. Although the efficacy of FE models has been shown by correlating mechanical outcomes (e.g. principal strain) with injury indications (e.g. hemorrhage)[20], [21], histological data are not capable of depicting the strain fields in the spinal cord during the impact. To directly validate the response of the
FE models, the tissue level strains are needed to be visualized, traced and recorded. New MRI-based image registration techniques are being developed that may provide the opportunity to quantify tissue level strains during SCI in the future but are currently limited to approximating two-dimensional strains[195].

3.5. Conclusions

Combined, these observations emphasize that more detailed models of the spinal cord including discrete white matter and gray matter and explicit pia mater, have important effects on the spinal cord response to mechanical impact. In this study, differentiating the pia mater from the spinal cord, simulating cord pretension and using experimentally derived material properties enabled us to simulate the biomechanical outcomes (i.e. peak force) of experimental SCI trials without the need for recalibration of the material properties similar to previous SCI models with uniform white matter, gray matter and pia mater[20], [37]. In addition, the transversely isotropic white matter model resulted in distinct distribution patterns of MPS which better captured the combination of peripheral white matter sparing, ipsilateral injury and contralateral sparing, and the rostral/caudal spread of damage when compared to isotropic materials.

In conclusion, we demonstrated that a fiber-reinforced conditional model based on a reduced polynomial model best fit the highly nonlinear, asymmetric tensile and compressive behaviors of white matter in a single model and could be implemented in FE models. Material properties are crucial inputs for FE models and were shown to affect the strain predictions of the FE models. Integrating this new constitutive model into FE simulations of SCI should increase the biofidelity of the simulated strain patterns and magnitudes. Understanding and quantifying the directional characteristics of spinal cord white matter combined with observations from directional specific injury models[7] may improve our understanding of SCI mechanics and preferential tissue damage during different loading mechanisms.
Chapter 4.

COMPRESSION MECHANICAL CHARACTERISATION OF NHP SPINAL CORD WHITE MATTER

The goal of developing computational models of SCI is to better understand the human injury condition. However, FE models of human SCI have used rodent spinal cord tissue properties due to a lack of experimental data. Central nervous system tissues in NHP closely resemble that of humans and therefore, it is expected that material constitutive models obtained from NHPs will increase the fidelity and the accuracy of human SCI models. Human SCI most often results from compressive loading and spinal cord white matter properties affect FE predicted patterns of injury; therefore, the objectives of this study were to characterize the unconfined compressive response of NHP spinal cord white matter and present an experimentally derived, FE tractable constitutive model for the tissue. Cervical spinal cords were harvested from nine male adult NHPs (*Macaca mulatta*). White matter biopsy samples (3mm in diameter) were taken from both lateral columns of the spinal cord and were divided into four strain rate groups for unconfined dynamic compression and stress relaxation (post-mortem <1-hour). The NHP spinal cord white matter compressive response was sensitive to strain rate and showed substantial stress relaxation confirming the viscoelastic behavior of the material. An Ogden 1st order model best captured the non-linear behavior of NHP white matter in a quasi-linear viscoelastic material model with 4-term Prony series. This study is the first to characterize NHP spinal cord white matter at high (>10/sec) strain rates typical of traumatic injury. The FE derived material constitutive model of this study will increase the fidelity of SCI computational models and provide important insights for transferring pre-clinical findings to clinical treatments.

4.1. Introduction

With recent progresses in SCI pre-clinical trials [3], [70], computational models of SCI have emerged as a powerful platform to bridge pre-clinical findings to humans as well as providing constructive insights into SCI mechanisms [20], [24], [89]. However, the fidelity and the accuracy of these computational models are critically dependent on their
pre-defined material constitutive models [19], [25]. By necessity, the majority of existing SCI computational models have used material constitutive models obtained from rodent [20]–[22], [24], [89] or porcine/bovine [90], [187] tissue characterization. However, due to substantial morphological and physiological heterogeneity between these species and humans, examining a more human-like tissue and quantifying its constitutive properties is expected to improve the fidelity of human injury computational models.

SCI can occur from a range of loading mechanisms [7]. Contusion SCIs are the most common type of injury observed clinically and used experimentally [38], [40]. Characterization of these injuries in-vivo, ex-vivo and mathematically have shown a multiaxial state of strain/stress at the tissue level as a result of the injury [3], [6], [8], [20], [21], [34]. Moreover, differentiating individual tissue characteristics (e.g. gray and white matters and pia mater) is necessary to more accurately predict patterns of injury across the cord structure [90], [102]. There is significant evidence that suggests the spinal cord white matter structure is transversely isotropic due to the rostral-caudal alignment of axonal fibers in the white matter [79], [179]. Therefore, the direction of loading (e.g. mechanical testing) affects the observed material properties of the white matter.

Approaches to modelling transversely isotropic neurological materials include introducing the directional dependency of the material deformation into the strain energy function [155], [156]. A first step in characterizing such materials is to characterize the material’s matrix [157], [165]. The longitudinally aligned axonal fibers in the white matter are embedded in a glial matrix that is devoid of a collagenous, structural extracellular matrix and has isotropic material properties [179]. Since the mechanical resistance of the fibers to compression in the fiber direction is negligible [160], [180], rostro-caudal compressive testing of the white matter determines the isotropic isolated matrix characteristics with a negligible contribution of the fibers. Using more human-like subjects (NHPs) in this study will expand our understanding of the spinal cord white matter glial matrix and provide the opportunity to compare tissue characteristics between species. Further study is required to characterize the axonal fibers to augment the matrix characteristics to fully characterize the transversely isotropic material properties of spinal cord white matter [90], [102], [160], [165]. However, this is a complex challenge due to the scale of available spinal cord white matter tissue samples (< 2 mm).
Unconfined compression tests have been used to characterize spinal cord [40], [102] and brain [114], [120], [121], [170], [196], [197] white matter from a range of species. Despite advances in characterizing the brain tissue, differences in the biological responses of brain and spinal cord [198], [199] and their corresponding structural difference (e.g. fiber orientation, density and alignment) have restricted the use of brain white matter characteristics for the spinal cord. Spinal cord white matter has been characterized using quasi-static [89], [102], 0.5 to 0.005 mm/sec deformation velocities [11] and 0.005/sec to 5.0/sec strain rate test data [40]. More recently, whole cords have been characterized using non-linear viscoelastic models for low strains (<5%) and moderate strain rates (0.1/sec) [200]. However, during a typical traumatic SCI the spinal cord undergoes large deformations at strain rates of approximately 110/sec [85], [86]. Knowing that the impact velocity substantially affects the pattern and severity of the SCI [201], characterizing the tissue at higher strain rates is crucial for more accurate SCI models. Existing computational models of SCI have adopted viscoelastic parameters from brain studies [20], [21], [76], however, applying a constitutive model obtained from combining spinal cord and brain tissues neglects the tissue specific characteristics. Furthermore, the degenerative effects of time post-mortem on the mechanical properties of the neurological tissues have been acknowledged [105], [113]. Tissue degradation starts quickly after animal sacrifice due to complex enzymatic and microbiological processes [105], [113], [114]. However, due to difficulties in accessing the tissue and testing logistics, the time post-mortem has exceeded 3 hours in published spinal cord experiments [10], [11], [40], [104]. The tangent modulus of the spinal cord tissue has been reported to nearly double over the period of 3 to 72 hours post-mortem [105]. To minimize the effect of post mortem degradation on the measured tissue characteristics samples should tested as soon as possible after death. This study aimed to characterize freshly harvested (post-mortem time < 1 hour) NHP spinal cord white matter at high strain rates using unconfined compression testing to better approximate the in-vivo tissue response.

The goal of this study was to characterize the NHP spinal cord white matter mechanical behavior using fresh specimen and at high strain rates (as compared to existing studies). Specific objectives were to: (1) measure the time dependent mechanical response of the NHP spinal cord white matter through unconfined uniaxial compressive tests at strain rates approaching traumatic SCI rates; (2) explore the effects of applied strain rate on the NHP spinal cord white matter mechanical response; and (3) to determine
a time-dependent material model with optimized material parameters capable of capturing
the NHP spinal cord white matter mechanical behavior.

4.2. Methods

4.2.1. Experiment

Spinal cords were collected for unconfined compression testing from the cervical
spines (C1-C7) of nine adolescent (52.6±5.9 months old) male *Macaca mulatta* NHPs
(7.44±1.31kg) immediately (<20minutes) after euthanasia. The spinal cords were
detached from the spinal canal by cutting through denticulate ligaments and the nerve
roots. Dorsal root entry zones of C5 and C6 were used for identification of each spinal
segment. The dura mater was removed, and the spinal cord segments briefly placed in
phosphate-buffered saline (PBS) prior to being tested. Transverse slices of 1.99±0.28mm
height were dissected out from the spinal cords using a 3-mm biopsy punch resulting in
cylindrically shaped portions of white matter collected from the lateral columns. White
matter samples were placed on aluminum platens on the test bench system (linear
actuator Electroforce3200 equipped with a 10N load cell; TA Instruments, New Castel,
DE) and compressed rostro-caudally. The tests were accomplished within one-hour post-
mortem. Each test was recorded using a high-frame rate (120 Hz) camera (GoPro Inc.,
USA) to document the actual sample dimensions (height and diameter) and to monitor
any buckling or bulging at maximum compression. Sample diameter and height were used
to calculate undeformed area and initial length respectively. Test videos were carefully
inspected and samples with any signs of buckling or bulging were removed from further
analysis. To reduce inertia effects during loading, the load cell was mounted on the fixed
side.

A total of 75 tests were performed; however, despite consistent test conditions and
a high precision test system, some samples showed excessive noise (N=4) in the load cell
signal that obscured the test data or buckled/bulged during testing (N=6). These 10
samples were removed from further analysis. Samples were compressed for 1mm in four
pre-set deformation velocities of 0.5mm/sec, 5.0mm/sec, 50.0mm/sec and 150.0mm/sec
where the highest rate was the fastest velocity possible with our test system and other
velocities were set so that the resulting strain rates were comparable with previous spinal
cord [40] and brain [87], [120] white matter studies. The pre-set deformation velocities
resulted in groups with strain rates of (mean standard deviation) 0.32±0.02/sec (ultra-low), 2.83±0.56/sec (low), 25.47±4.06/sec (medium) and 77.22±15.16/sec (high) with 5, 20, 21 and 19 samples respectively. Engineering stress (force over the undeformed area) and strain (machine head displacement over the sample initial height) were calculated for each test. The resulting peak strains varied (0.19 < ε < 0.68) due to variability in the samples’ heights and the machine control protocol. To better mimic in-vivo conditions, samples were not preconditioned in this experiment [40], [112]. To ensure a consistent zero position, all the samples were preloaded to 0.05 N before the test started. The stress-relaxation behavior of the NHP white matter was observed by holding the peak strain for 60 seconds and the force and deformation were recorded (sampling time was 0.0004 seconds).

4.2.2. Statistical analysis

The effect of strain rate on stress was determined using an ANCOVA by comparing stress levels at fixed strain increments (0.1, 0.2, 0.3 and 0.4) between strain rate groups with a Tukey-Kramer post-hoc HSD analysis (α = 0.05). Animal weight and age were included as covariates in the model. To evaluate the effect of strain rate on the amount of stress relaxation, the amount of stress relaxed after 60 seconds was normalized against the peak stress for each test, grouped by strain rate, and compared using an ANCOVA with a Tukey-Kramer HSD post-hoc analysis (α = 0.05). Again, animal weight and age were included as covariates.

4.2.3. Constitutive model definition

To find a FE tractable constitutive model that describes the white matter compressive response for large deformation explicit analysis, a hyperelastic material model that best fit the stress-strain response was required. This hyperelastic model was combined with a Prony series expansion to quantify the viscoelastic response of the material [40], [90], [182], [183]. Loading data of each strain rate group (i.e. ultralow, low, medium and high) samples were pooled to form a point cloud data for each strain rate group in order to find the average response of the experimental tests. Five well established incompressible isotropic hyperelastic constitutive models (Table 4-1) were fit to the pooled data. The strain energy function was formulated as (Equation 4-1),
\[ \psi = \psi(I_1, I_2) - p(J - 1) \quad \text{or} \quad \psi = \psi(\lambda_1, \lambda_2, \lambda_3) - p(J - 1) \]

where \( \lambda_i \) (\( i = 1, 2, 3 \)) are the three principal stretches, \( I_1 \) and \( I_2 \) are the first and second strain invariants, \( J \) is the determinant of the deformation gradient tensor and the \( p \) is identified as a hydrostatic pressure [153]. Model parameters were obtained through constrained nonlinear optimization using fmincon (Matlab R2015b, The MathWorks Inc Natick, MA) with a wide range of randomly generated initial guesses. Drucker stability was imposed in fitting the hyperelastic models while the corresponding constraints (Table 4-1) were also applied to each model [154], [170]. The appropriateness of the model was assessed based on the fit to the data \( (R^2) \) and the complexity of the model (i.e. less complex model was preferred).
Table 4-1: Incompressible strain energy functions and the uniaxial engineering stress response for each strain energy function. \( C_{ij}, \mu \) and \( \alpha \) are the material parameters and \( \lambda_U \) is the principal stretch in the uniaxial loading direction.

Uniaxial response is obtained from \( P_{\text{uniaxial}} = \frac{\partial \psi}{\partial \lambda_U} - \frac{1}{\lambda_U^2} p \), where \( p \) is determined using uniaxial loading boundary conditions.

<table>
<thead>
<tr>
<th>Hyperelastic model</th>
<th>Incompressible energy function</th>
<th>1st Piola-Kirchhoff uniaxial response</th>
<th>Optimization constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mooney-Rivlin</td>
<td>( \psi_1 = C_{10}(I_1 - 3) + C_{01}(I_2 - 3) + p(I - 1) )</td>
<td>( P^1_U = 2(1 - \lambda_U^{-3})(C_{10}\lambda_U + C_{01}) )</td>
<td>( C_{10} + C_{01} &gt; 0; \frac{C_{10}}{C_{01}} &gt; 1 )</td>
</tr>
<tr>
<td>Polynomial (N=2)</td>
<td>( \psi_2 = \sum_{i+j=1}^{2} C_{ij}(I_1 - 3)^i(I_2 - 3)^j + p(I - 1) )</td>
<td>( P^2_U = 2(1 - \lambda_U^{-3}){C_{10}\lambda_U + C_{01} + 2C_{20}\lambda_U(I_1 - 3) + C_{02}(I_1 - 3 + \lambda_U(I_2 - 3)) + 2C_{11}(I_2 - 3)} )</td>
<td>( C_{10} + C_{01} &gt; 0 ); ( \frac{C_{10}}{C_{01}} &gt; 1 ); ( \frac{C_{20}}{C_{02}} &gt; 1 )</td>
</tr>
<tr>
<td>Reduced polynomial</td>
<td>( \psi_3 = C_{10}(I_1 - 3) + C_{20}(I_1 - 3)^2 + p(I - 1) )</td>
<td>( P^3_U = 2(\lambda_U - \lambda_U^{-2})(C_{10}\lambda_U + 2C_{20}(I_2 - 3)) )</td>
<td>( C_{10} + C_{20} &gt; 0; \frac{C_{10}}{C_{20}} &gt; 1 )</td>
</tr>
<tr>
<td>(N=2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeoh</td>
<td>( \psi_4 = \sum_{i=1}^{3} C_{i0}(\bar{I}_1 - 3)^i + p(I - 1) )</td>
<td>( P^4_U = 2(\lambda_U - \lambda_U^{-2})(C_{10}\lambda_U + 2C_{20}(I_1 - 3) + 3C_{30}(I_1 - 3)^2) )</td>
<td>( C_{10} + C_{30} &gt; 0; \frac{C_{10}}{C_{30}} &gt; 1 )</td>
</tr>
<tr>
<td>Ogden (1st order)</td>
<td>( \psi_5 = \frac{2\mu}{\alpha^2} (\lambda_1^\alpha + \lambda_2^\alpha + \lambda_3^\alpha - 3) )</td>
<td>( P^5_U = \frac{2\mu}{\alpha} (\lambda_U^{\alpha-1} + \lambda_U^{-\frac{1}{2}\alpha-1}) )</td>
<td>( \alpha &gt; 1; \alpha &lt; -1; \mu &gt; 0 )</td>
</tr>
</tbody>
</table>


4.2.4. Viscoelastic formulation

Quasi-linear viscoelastic (QLV) theory has provided good fits to our prior high strain experimental data for spinal cord white matter [40], [90] and has been used in several studies modeling the high strains and strain rates of traumatic SCI [20], [21], [40], [90]. QLV models have the benefits of being more easily implemented in commercial software and more computationally cost effective in explicit, large deformation, FE models. In addition, the QLV model has been shown to successfully predict the patterns of injury and tissue level stresses/strains in computational studies of SCI [20], [21], [90]. The QLV model was implemented using the most suitable hyperelastic models identified in the previous section. For the hyperelastic material, the QLV behavior was represented by a Prony series expansion of the dimensionless relaxation modulus applied directly to the strain energy function [154], [170] (Equation 4-2),

\[ W(t) = \int_0^t \left\{ g_R(t - \tau) \frac{d\psi}{d\tau} \right\} d\tau \]  

4-2

where \( W \) denotes the time dependent strain energy, \( t \) is time, \( \psi \) is the hyperelastic strain energy function (Table 4-1) and \( g_R(t) \) is dimensionless relaxation function (Equation 4-3),

\[ g_R(t) = 1 - \sum_{i=1}^{N} g_i(1 - e^{-t/\tau_i}) \]  

4-3

where \( g_i \) is the relative moduli and \( \tau_i \) is the relaxation time of \( i \)th term in the Prony series and \( N \) is the number of terms in the Prony series.

The optimized parameters were determined through inverse FE analysis by simulating the compressive experiments and fitting the results to the experimental responses (loading portion). The average high and ultralow strain rate group behaviors were each simulated in ABAQUS (v6.14 Dassault Systems Simulia Corp., Providence, RI). The FE models were generated using the average diameter and height of all the samples (h=1.99mm, d=3.59mm) (Figure 4-1).
Figure 4-1: Simulation of the compressive tests in ABAQUS. Undeformed (A) and deformed (B) shapes together with an isometric view (C) are shown.

Models were meshed with 0.15mm continuum elements (C3D8R) following a mesh convergence analysis. The platens were modeled as analytically rigid surfaces. The coefficient of friction (μ) for the contact between the platen and the white matter samples was assumed to be slip rate dependent with μ equal to 0.09, 0.18 and 0.18 at strain rates of 1/sec, 30/sec and 60/sec respectively [202]. ABAQUS linearly interpolates between these values based on the slip rate at the surface to determine the proper coefficient of friction. To avoid numerical ill-conditioning caused by a fully incompressible constitutive model definition in the FE implementation, white matter material compressibility was allowed (𝜐=0.4995) in the simulations [37], [90], [154]. The bottom platen was fixed, and the samples were compressed by displacing the top platen. The force and displacement of the top platen reference point were recorded to calculate the engineering stresses and strains respectively. In this study, the reduced time constants in the Prony series assumed a priori to be approximately equal to the average duration of loading in each strain rate group and our pilot studies showed that a 4-term Prony series was required for this QLV model (i.e. \(\tau_1=0.01\text{sec}, \tau_2=0.02\text{sec}, \tau_3=0.2\text{sec} \) and \(\tau_4=2.0\text{sec}\) ) [181], [182]. A nonlinear constraint optimization algorithm (interior-point, fmincon, MATLAB, R2016b, The MathWorks Inc., Natick, MA), which iteratively invoked a Python code to run the ABAQUS simulations determined the model parameters. The optimization constraints were updated in each iteration based on the previous iteration results. The cyclic procedure continued until the coefficients converged to a single set of coefficients with four decimal accuracy. The corresponding \(R^2\) values were used to quantify the fits.

Once the optimal parameters were determined from optimizing between high and ultralow strain rates, the optimal parameters were implemented to simulate all the four
strain rate experiments (loading and relaxation). To assess the fit of each model, the root mean square error (RMSE) of one standard deviation of the experimental data (loading and relaxation) was compared with the RMSE of the fitted model for each strain rate group [109], [203]. If the RMSE of the fitted model was less than the RMSE of one standard deviation of the experimental data, the model was considered to be a suitable fit. Furthermore, the model was reviewed to ensure the predicted fit stayed within one standard deviation of the mean experimental data at all time points.

4.3. Results

4.3.1. Experimental results

The average peak stresses increased with increased strain rate and peak strain (Figure 4-2). Strain rate had a significant effect on the stress level in all strain increments ($p < 0.0001$), however, animal age, weight and age-weight interaction did not significantly affect the stress levels. At 10% strain, the high rate data was significantly different from the other rates; however, at the other strain increments (i.e. 20%, 30% and 40%) the high and medium rates were significantly different from low and ultralow but not from each other ($p < 0.05$). For the latter increments, the stress levels at the low and ultralow strain rate groups were also not significantly different from each other (Figure 4-3). On average, the percent decrease in stress after 60 seconds was significantly ($p < 0.05$) higher in the high (92.7 ± 3.4 %), medium (91.5 ± 5.3 %) and low (88.6 ± 5.3 %) strain rate groups compared to the ultralow group (77.7 ± 2.2 %). Averaged stress-strain responses showed an increase in the stiffness of the material with increased strain rate except for the high strain rate group where the stiffness increased quickly in low strains (<0.1) then decreased (0.1-0.2) and then increased to reach the peak.
Figure 4-2: NHP spinal cord white matter average compressive stress-strain response grouped by strain rate. Average stress increased by increasing strain rate in all strain rate groups. Error bars show the standard deviation of the stress.

Figure 4-3: Interquartile ranges (boxes) and medians (lines within each box) of stress levels at 10%, 20%, 30% and 40% strain increments for the four strain rate groups. Whiskers are extended to include the range of all data in the sample group. In each strain rate group, stress levels not connected by the same letter are significantly different (Tukey–Kramer HSD). Labels U, L, M and H refer to ultralow, low, medium and high rate groups respectively.
4.3.2. Constitutive model definition

Experimental variability increased with increasing strain rate across the four groups, with stress coefficients of variations between 0.21-0.28, 0.313-0.52, 0.44-0.75 and 0.49-0.66 for the ultralow, low, medium and high strain rate groups respectively. The hyperelastic models fit to all experiments at a single strain rate (point cloud data) showed that the 1st order Ogden, Mooney-Rivlin, and Yeoh models better captured the material behavior (Figure 4-4) in all strain rate groups (0.82<$R^2<$0.86) compared to the reduced polynomial (0.58<$R^2<$0.74) and the 2nd order polynomial (0.14<$R^2<$0.79). Although the Yeoh model was able to predict the tissue behavior, this model contains three invariants (compared to Ogden and Mooney-Rivlin with two invariants) which would increase the complexity of the model in the viscoelastic formulation and FE implementation. Therefore, the Mooney-Rivlin and Ogden hyperelastic models were selected to develop the viscoelastic formulation.

Figure 4-4: Representative pooled stress-strain data points for medium strain rate group. Data for all the samples with same rate group were pooled to form a cloud of data and fit with the hyperelastic models. The fits of the five constitutive models for the medium strain rate compressive response are presented. The average response is also presented in the figure for comparison. Mooney-Rivlin model best fitted the data while polynomial model had the weakest fit in this strain rate group. The Ogden, Mooney-Rivlin and Yeoh model results are coincident for this strain rate group.
4.3.3. Results of the viscoelastic fit

RMSEs of one standard deviation from the experimental mean were 6.66kPa, 5.86kPa, 5.15kPa and 2.54kPa for the high, medium, low and ultralow strain rates respectively. Given the variability of the experimental data, the Ogden QLV model (4-term Prony series) with the optimized parameters (Table 4-2) predicted the material behavior with RMSEs (2.77kPa, 2.60kPa, 2.73kPa and 3.64kPa for high, medium, low and ultralow respectively) that were lower than the experimental RMSEs except for the ultralow rate. The Mooney-Rivlin QLV model (4-term Prony series) also predicted the high, medium and low strain rates with RMSEs of 3.34kPa, 3.02kPa and 3.73kPa respectively, however, was also not able to predict the ultralow rate group (RMSE=5.35kPa compared to experiment RMSE=2.54kPa). For both Ogden and Mooney-Rivlin QLV models, the FE responses well fit within the one standard deviation from the mean for high, medium and low strain rate groups (Figure 4-5-a, b and c). In the ultralow strain rate regime, the Ogden QLV model loading response fit within the one standard deviation lines, however, the Money-Rivlin QLV loading response was softer than the experiments (Figure 4-5-d). The Ogden model better predicted the experimental results in all strain rates compared to the Mooney-Rivlin model. Increasing the number of Prony series terms beyond four did not affect the accuracy of the predictions in the models.

<table>
<thead>
<tr>
<th>QLV model</th>
<th>Model Parameters</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1st order Ogden</td>
<td>$\alpha = 4.63$</td>
<td>$\mu = 8.28$ kPa</td>
<td>$g_1 = 0.5296$</td>
<td>$g_2 = 0.3107$</td>
<td>$g_3 = 0.0141$</td>
</tr>
<tr>
<td>Mooney-Rivlin</td>
<td>$C_{10} = 3.27$ kPa</td>
<td>$C_{01} = 0.91$ kPa</td>
<td>$g_1 = 0.5256$</td>
<td>$g_2 = 0.3163$</td>
<td>$g_3 = 0.1250$</td>
</tr>
</tbody>
</table>

4.4. Discussion

Variations in the mechanical properties of brain across different species [204]–[206] suggest that using spinal cord white matter constitutive models obtained from animal tissue tests in human SCI models may introduce inaccuracies. However, testing human tissue is limited by accessibility and post-mortem time effects [105]. Central nervous system tissues in NHPs closely resemble humans [3] and therefore, it is expected that material constitutive models obtained from NHPs will increase the fidelity and the accuracy.
of human SCI models. As most traumatic SCIs in humans result from compressive loading on the spinal cord, characterizing the compressive response of the spinal cord white matter to traumatic insults is essential. This study is the first to characterize NHP spinal cord white matter mechanical properties; and is the first to test spinal cord white matter at injurious strain rates ($\dot{\varepsilon} > 10$/sec) typical of traumatic SCI, using fresh samples (post-mortem time < 1-hour).

Figure 4-5: Ogden and Mooney QLV model predictions for (a) high, (b) medium, (c) low and (d) ultralow strain rate groups. The mean experimental response (blue line) is shown with one standard deviation of the mean (red and yellow lines) to demonstrate the experimental variability. The horizontal axis represents time [sec] in all of the plots. The number of data points have been reduced from original 0.0004 sec for better visualization of the model results. Figure 6: Ogden and Mooney QLV model predictions for (a) high, (b) medium, (c) low and (d) ultralow strain rate groups. The mean experimental response (blue line) is shown with one standard deviation of the mean (red and yellow lines) to demonstrate the experimental variability. The horizontal axis represents time [sec] in all of the plots. The number of data points have been reduced from original 0.0004 sec for better visualization of the model results.
The primary strength of this study was the use of NHP tissues as NHPs more closely resemble humans. Time post-mortem has been shown to have a significant effect on mechanical response of neurological tissues [105], [113]. Completing the compressive tests within 1-hour post-mortem should reduce tissue degradation and preserve the tissue integrity. During traumatic SCIs, the spinal cord (and its constituents) experience high strains over a short time; however, due to the lack of experimental data at strain rates typical of traumatic impact, existing viscoelastic models were established using low to moderate strain rate tests and the traumatic injury strain rate response was unclear [40], [90], [104], [109]. The high strain rate tests in this study provide critical information on the viscoelastic behavior of the spinal cord white matter immediately after loading which has manifested itself in the Prony series relaxation times ($\tau_i$'s in Equation 4-3), and have enabled a one order of magnitude reduction in relaxation times (i.e. $\tau_1 = 0.01$ sec compared to $0.1$ sec $< \tau_i$'s in previous studies). This new constitutive model will increase the accuracy of spinal cord FE models in predicting the overall in-vivo impact mechanics of traumatic impact injuries and the immediate time after injury. Increased model accuracy may provide important insights into the role and timing of decompression on spinal cord stresses.

The NHP spinal cord white matter average compressive response was slightly stiffer than the porcine spinal cord white matter reported at comparable strain rates (low and ultralow) [40]; however, the stiffness difference increased with increasing strain rate (Figure 4-6). The porcine brain showed a stiffer compressive response at ultralow strain rates [170]; while the bovine brain was much stiffer than NHP spinal cord white matter in ultralow rates [88]. No higher strain rate data (>5.0/sec) for spinal cord white matter exists for comparison to the medium and high rate groups in this study. NHP white matter showed similar behavior to porcine brain results at medium and high strain rates [120]. However, Rashid and colleagues reported stiffer material properties for porcine brain at comparable strain rates [87] (Figure 4-6). Considering the experimental variability in both the previous tests and our tests, our results were within the range of reported values of previous studies. The variability in reported experimental results highlight the difficulties in reliably testing this ultra-compliant tissue and the potential confounding effects of numerous experimental variables such as species, structure, location of tissue sampled, postmortem time, processing and storage parameters. The reliability of the data will continue to improve with large scale testing while controlling for or observing and reporting as many of these experimental variables as possible.
Figure 4-6: Comparison of the compressive behavior of spinal cord and brain white matter in different studies based on the applied strain rate. NHP spinal cord white matter was stiffer than porcine white matter in comparable strain rates and was close to brain white matter at higher strain rates.

The inverse FE modelling method used for optimization in this study has been previously used in brain [160], [184], [188], [207] parameter characterization. However, previous spinal cord viscoelastic modeling efforts have analytically fit the experimental response to constitutive formulations in order to find the material properties [10], [40], [109]. As this method does not replicate the material’s multiaxial (e.g. transverse) state of loading, it inherently hinders the accuracy of the determined material parameters and the model. The advanced optimization method using inverse FE in this study which directly incorporates FE models of the experimental tests in the parameter optimization, considers the off-axis loading responses, and provides a more accurate FE-adoptable constitutive model for the material.
Studies of rat ligaments and the spinal cord suggest that the QLV model is insufficient for predicting these soft tissues’ viscoelastic behavior and that fully nonlinear models are required to capture physiological behavior [109], [208]. However, these studies investigated the material behavior in low strain ranges (<5%) and did not expand their findings for large strains. For the range of peak strains, at the high strains and strain rates explored in this study, the QLV model was able to capture the material’s behavior. A primary strength of the proposed QLV model presented in this study is that the QLV formulation is a built-in model in most commercially available FE software (e.g. ABAQUS) and therefore it is easier to implement in related FE analysis. Further testing of the tissue at a range of peak strains representative of both physiological and injury loading and in both stress relaxation and creep will help to determine if a more complicated material model is required to represent the tissue response more generally. However, the QLV model was able to simulate the high strain and high strain rate loading typical of traumatic injury.

Efforts in reducing the time post-mortem as well as the complexity of the tissue harvesting process introduced different challenges to this study and caused some limitations. Cutting uniform tissue samples in this ultra-soft tissue at the scale needed for these tests is difficult, however, we tried to reduce human error by using a pre-set 3mm biopsy punch. More importantly, relating machine head displacements to each sample’s strain is challenging and may have led to inaccuracies in strain calculations. Our assumption [10], [40], [182], [183] was to consider the machine head displacement as the sample deformation which requires the sample’s transverse sections to remain plane in the loading process. The shear contact force generated between the white matter and the platen may have caused violations from the plane sections assumption. In addition, although the camera system (120Hz, GoPro Inc., USA) used in this study was not fast enough to record the entire high strain rate tests, filtering buckled and bulged tests was enabled by combining the recorded frames with the force readouts and visual inspection of the samples at the end of the procedure. The constitutive models presented in this study were limited to characterizing the mechanical response of the tissue to large strains but did not specifically incorporate damage in the material model. Damage may have occurred in the samples compressed beyond their physiological deformation range. By not accounting for damage accumulation in this model, the authors acknowledge that this limits the generalizability of the model and may not accurately represent stress softening.
or subsequent tissue loading – though these are not typically observed in SCI models. Further work will be required to define the structural and functional failure limits for spinal cord white matter and to derive constitutive models capable of incorporating damage. Finally, the filter settings were changed on the load cell during this series of tests which resulted in a phase lag being introduced in a subset of the data. A correction factor was determined by running similar experiments on surrogate tissue samples to ensure all data was being analyzed on the same timeline [76].

The material constitutive model presented in this study has been characterized based on the compressive behavior of the NHP spinal cord white matter. This material model does not account for the anisotropy of the white matter introduced by the presence of axonal fibers [90], [102]. Therefore, the accuracy of the presented constitute model is limited to compressive loading cases. Extrapolating these results to capture the material’s tensile behavior or to model the multi-axial loading state of the spinal cord during SCI without including anisotropy may hinder the ability of the SCI model to correlate tissue damage to the mechanical outcomes [90]. Further tensile/shear experimental tests are required to determine the anisotropic behavior of NHP white matter and integrate those results to improve the capability of the current constitutive model. However, due to the scale of the NHP spinal cord white matter samples, conducting tensile and shear tests will be highly complex [209].

Directly measuring spinal cord white matter tissue properties in the body would be ideal; however, current technologies are insufficient for isolating white matter tissue properties at the high speeds and high strains typical of injury. While non-invasive magnetic resonance elastography (MRE) methods may have the potential to characterize spinal cord tissue in-vivo; the feasibility of MRE for characterizing spinal cord tissue has not been validated [210]. Although MRE has been used to characterize brain tissue and differentiate in-vivo versus in-vitro responses of brain tissues assuming isotropy [211]–[217] or transverse isotropy [4], current MRE applications are limited to strains that are insufficient for characterizing the large strains associated with the highly nonlinear SCI phenomenon. In addition, isolating spinal cord white matter might be challenging in MRE methods due to the small sizes of the tissue compared to MRE wavelengths [211].

Using NHPs to study SCI has been widely revisited recently [3], [45], [72] since these models increase the fidelity and reliability of SCI models in transferring pre-clinical
findings to humans [72]. However, primates are highly variable morphologically (i.e. weight, skeleton, etc.) and much more expensive than other animal models (e.g. rodents, porcine, etc.). FE models are a critical step in generating a predictable injury foundation as well as improving the repeatability of the models by providing insight to SCI mechanisms and injury mechanics. Similarly, human FE models of SCI are critical for assessing mechanical injury prevention strategies (e.g. helmets, seatbelts, etc.) and may provide insight into the mechanisms of clinical treatments (e.g. decompression surgery). Susceptibility of FE model outcomes (such as patterns of injury) to predefined material constitutive models [18], [21], [90] highlights the need for accurate characteristics for the constituent materials. So far, computational human SCI models have extrapolated their material properties from rodents, pigs and bovine [24], [187]. Our study provides NHP spinal cord material characteristics that eliminate the need for extrapolating these material properties from heterogeneous animals.

4.5. Conclusion

In conclusion, we showed that NHP spinal cord white matter is highly sensitive to loading rate, specifically, it is substantially stiffer at very high loading rates typical of traumatic SCI. In this study we determined the constitutive properties of the isotropic spinal cord white matter glial matrix. Further experiments will be required to quantify the contributions of the embedded axonal fibers to NHP white matter anisotropy. The constitutive model evaluation demonstrated that at large deformations both loading and relaxation regimes of the NHP spinal cord compressive behavior are adequately captured by a QLV model. Importantly, our results showed the NHP spinal cord white matter to have similar properties to those previously reported for porcine spinal cord white matter and brain white matter in compression. This indicates that constitutive models derived from these other tissue sources may provide an adequate representation of spinal cord white matter characteristics without requiring the logistical and ethical complexities of accessing fresh NHP or human tissues.
Chapter 5.

CORRELATING TISSUE MECHANICS AND SCI: PATIENT-SPECIFIC FE MODELS OF UNILATERAL CERVICAL CONTUSION SCI IN NHP

One of the challenges associated with utilizing computational models in SCI research is to interpret the model’s outcomes. Recognized correlations between FE outputs and tissue damage were established based on small animal models where the considerable variations in morphometry of spinal cord and column observed in large animal models and humans do not exist. Here, we examined the correlation between the predicted FE outcomes and tissue damage in an individualized NHP model of unilateral cervical contusion SCI. Subject-specific geometries were obtained from MRI scans of six NHPs to generate FE models of in-vivo NHP contusion experiments. Simulation results were compared to the spread of the lesion obtained from histology slides and the predictive capability of several FE mechanical measures were examined using logit analysis. Generally, stronger correlations were observed between FE predicted outcomes and tissue damage in gray matter compared to white matter with Von-Mises and Tresca stresses showing the strongest correlations in the gray matter (0.55 < Nagelkerke R-square < 0.87). Threshold values for 50% probability of tissue damage were subject-specific for all mechanical measures except axonal strain (0.1) and strain energy density (0.018 mJ/mm3) in the white matter. These results indicate that measures of mechanical FE outputs correlate with tissue damage both in white and gray matters of spinal cord and subject-specific models are able (and necessary) to accurately mimic the biomechanics of NHP cervical contusion impacts that correlate with the tissue damage.

5.1. Introduction

The significant correlation between impact biomechanics and neurological tissue damage after SCI [54], [55] has increasingly motivated the use of computational SCI models as a platform for understanding the SCI tissue level mechanistic behavior. NHP models of contusion SCI provide an important experimental platform for assessing safety and efficacy of pre-clinical therapeutic interventions nearing readiness for translation to
human clinical trials [3], [72]. While contusion injury biomechanics have been shown to closely correlate with histological and function outcomes in rat [8], [75], [171], [218], [219] and mice [5], [176] models, there is greater variability in the links between impact biomechanics and outcomes in large animal models [3], [151]. This may partially be attributed to the greater variability in morphometry of spinal cord, surrounding dural tube and column observed in large animals compared to rodents [151]. There is a need to explore and better define the link between injury mechanics and tissue damage in the NHP contusion SCI model.

Computational models of SCI provide crucial insight into the translation of contusion impacts to tissue level mechanics and corresponding tissue damage. However, establishing reliable correlations between FE model outcomes and neurological tissue damage is critical for clinically relevant interpretations of FE model results. In generic FE models of SCI (where the model geometry and material specifications are generated based on generalizing a single subject [10], [21] or averaging several subjects [24], [90]), FE outputs such as tissue level stress and strain distribution [21], [89], von-Mises stress [79] and maximum principal strain [20] have shown significant correlations with neurological/axonal damage. However, given the sensitivity of FE model outcomes to variations in model geometry [152], predefined constitutive material models [11], [19], [21], [90] and injury mechanisms [20], and the recognized inter-subject variability in spinal cord/column morphometry [147]–[151] and material characteristics [10], [11], [21], [37], [40], [77], [107], [220], it is unclear how these variations affect the correlations between tissue damage and injury mechanics. Consequently, the greater inter-subject variability in morphometric characteristics of spinal cord/column observed in larger animal models such as pigs [151] and NHPs [3] suggests that a more accurate link between FE outcomes and tissue damage may require subject-specific FE analysis of SCI contusion models.

To date, FE methods have been used widely in the studies of SCI to extract the mechanical properties of the spinal cord and its constituent tissues [90], [220], analyze CSF effects and interactions in SCI initiation and propagation [23], [91], [221]–[223], quantify tissue level deformations, stresses or strain patterns [15], [90], [95], assess the sensitivity of tissue level stress/strain patterns to material constitutive models [10], [11], [19], [90], highlight the significance of SCI mechanism on stress/strain patterns [13], [15], [20], [22], [24], [92], and establish correlations between FE measures and structural
damage [20], [21] or lesion [79], [89]; however, none of these studies have accounted for the inter-subject variations of their subjects, which mitigates the biofidelity of their results.

The overall objective of the chapter was to assess the correlation between FE predicted mechanical outcomes and tissue damage in subject-specific FE models of NHP cervical contusion SCI. Our specific objectives were to: (1) generate individualized subject-specific FE models of our recent NHP unilateral cervical contusion SCI experiments based on pre-injury MRIs, (2) validate FE model boundary conditions and assumed material constitutive models using open dura impact experiments, (3) calibrate the individualized FE models by comparing the FE model’s overall biomechanical response with experimental outcomes and adjusting the impactor alignment, and (4) assessing the correlations between FE predicted mechanical outcomes and tissue damage and investigating the effects of subject specificity on those correlations. Improving the definitions of the relationships between impact biomechanics, tissue mechanics and tissue damage are important for better understanding potential sources of variation in both large animal models and the human injury paradigm, and for defining quantitative criteria for injury prevention technologies.

5.2. Materials and Methods

Our recent in-vivo cervical spinal cord contusion experiments on NHPs [3] have provided a unique opportunity to re-evaluate FE predicted tissue damage measures while exploring subject-specific variations in contusion biomechanics. Pre and post-injury MRI scans and post-injury histology data from prior studies [3], [224] were utilized to develop FE models of each test subject. The subject-specific models were then used to simulate the in-vivo cervical unilateral contusion SCIs. Simulations’ biomechanical outcomes were used to calibrate the impact mechanics and chronic lesion histology was evaluated for correlation with FE predicted tissue level mechanics. Statistical analysis of the histology and FE data were used to establish relationships between FE outcomes and spinal cord tissue damage for each subject. Mechanical measures investigated in this study were: maximum/minimum principal logarithmic strain (max/min LEP), axonal logarithmic strain (LEAXON), von-Mises stress (MISES), Tresca stress (TRESCA) and strain energy density (ESEDEN).
5.2.1. NHP unilateral contusion injury experiments

Previously, we conducted a series of in-vivo unilateral cervical contusion tests on six NHPs (adult male *Macaca mulatta*) [76], [224]. All housing and procedures were conducted in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals and were approved by The Institutional Animal Care and Use Committee at the University of California at Davis. The animal care and use program at the University of California at Davis is Association for Assessment and Accreditation of Laboratory Animal Care International accredited.

Briefly, experiments were done in two groups, an open dura contusion group (N=2) where the dura mater was perforated surgically after the laminectomy and contusion impact was applied directly to the spinal cord (open dura) [224], and an intact dura group (N=4) where the dura mater was left intact and contusion impacts were applied to the dura mater (intact dura) [3] (Table 5-1). For all experiments, impacts were applied using a 4 mm diameter lucite tip rod with different mediolateral impounder alignments for each test (Table 5-1). It should be noted that the numbers assigned to the subjects in this study (Table 5-1) are chosen to be the same as the animal numbers in our previous experiments, therefore, are not in order.

**Open dura contusion experiment.** Subjects #14 and #16 were imaged using a 3T MRI scanner approximately one week prior to the contusion surgery to confirm the size of the spinal cord and amount of CSF surrounding spinal cord. On the day of surgery, subjects were sedated, intubated, and maintained at a surgical plane of anesthesia for the duration of the surgery. The surgical approach included a partial laminectomy at the 5th cervical vertebrae (C5), excising the dorsal dura mater, and visualization of the spinal cord midline. The C4 and C6 spinous processes were fixed using vertebral clamps before the impact. Prior to the contusion impact the impactor tip was positioned based on a preset mediolateral alignment with respect to the spinal cord midline (Table 5-1).

A preload touch force of 0.3 N was used to establish a consistent starting position for impact. Blunt contusion impacts were delivered to the cord with parameters of 3.8 mm peak displacement at 1000 mm/s. The resulting impact biomechanics (impactor displacement and force) were recorded for each subject. The contusion lesions were
observed at 3 weeks post-injury using high-resolution 3T MRI T2-weighted isotropic scans oriented in the sagittal plane with a slice thickness of 270 μm.

Table 5-1: Summary of experimental parameters and biomechanical outcomes for the six selected NHPs. The subject numbers are consistent with our previous studies [3], [76].

<table>
<thead>
<tr>
<th>Test type</th>
<th>Open dura</th>
<th>Intact dura</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject number</td>
<td>Subject #14</td>
<td>Subject #16</td>
</tr>
<tr>
<td>Age (Years/Months)</td>
<td>9/4</td>
<td>7/2</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>13.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Laminectomy size AP×ML (mm)</td>
<td>12×9</td>
<td>11×9</td>
</tr>
<tr>
<td>MRI</td>
<td>3T – Pre-and Post-operative</td>
<td>3T – Pre-and Post-operative</td>
</tr>
<tr>
<td><em>in-vivo</em> impactor medio-lateral position (mm)</td>
<td>-0.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>Time of necropsy after impact [Weeks]</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><em>in-vivo</em> pre-load (trapping) data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth from dural surface [mm]</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Pre-load force [N]</td>
<td>-0.16</td>
<td>-0.23</td>
</tr>
<tr>
<td><em>in-vivo</em> impact data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-set velocity [mm/sec]</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>Pre-set displacement [mm]</td>
<td>-3.8</td>
<td>-3.8</td>
</tr>
<tr>
<td>Actual displacement [mm]</td>
<td>-3.54</td>
<td>-3.51</td>
</tr>
<tr>
<td>FE model specification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impactor position (mm)</td>
<td>medio-lateral</td>
<td>0.0</td>
</tr>
</tbody>
</table>
**Intact dura contusion experiment.** Subjects #8 and 9 were scanned approximately a week prior to the injury with 1.5T and 3T MRI scanners respectively (subjects #5 and 6 were not scanned pre-injury). Animals were sedated, intubated, and maintained at a surgical plane of anesthesia for the duration of the surgery. Unilateral contusion impacts were applied after a partial laminectomy at the fifth cervical vertebrae (C5). The C4 and C6 spinous processes were fixed using vertebral clamps before the impact. Prior to the contusion impact the impactor tip was positioned to a preset mediolateral alignment with respect to the spinal cord midline (Table 5-1). To begin each impact, the dorsal dural surface was preloaded to 0.5 N preload to entrap the spinal cord against the vertebral canal, to reduce lateral motion of the spinal cord and establish a consistent starting position for impact. Contusion impact displacements varied slightly for the different test subjects (-4.0 mm for subject #5 and -4.3 mm for subjects #6, 8 and 9) at pre-set impact velocities of 1000 mm/sec (subjects #6, 8 and 9) or 500 mm/sec (subject #5) (Table 5-1). The contusion lesions were observed in subjects #5, 6 and #8 using 1.5T MRI T2-weighted and using a 3T MRI T2-weighted isotropic scanner for subject #9 at 14 weeks post injury to confirm the lesion positioning and volume.

After the contusions, the surgical site was closed in anatomical layers, and animals were allowed to recover in hospital. Subjects were sacrificed after 14-17 weeks and the spinal cords were harvested. Collected spinal cords were sectioned in the transverse plane at 40 µm thickness and co-stained with eriochrome cyanine for myelin and neural red for cell bodies [3]. Lesion and spared tissue borders were outlined on the brightfield images of the selected histology slides (epicenter, ±1.6mm and ±3.2mm rostral to the epicenter lesion).

**5.2.2. FE Model Generation**

The sagittal MRI scans of each NHP subject were registered into isotropic 3-D fused images and were interpolated in Mimics (Mimics Research v19.0, Materialize N.V., Technologielaan 15, 3001 Leuven, Belgium). The isotropic interpolation resulted in images of pixel size 0.3125 mm (intact dura subjects #5, 6, 8 and 9) and 0.2734 mm (open dura subjects #14 and 16). The 3-D images included the full cervical spine for all subjects (Figure 5-1). Based on the post-injury MRI scans, the longitudinal location of the lesion (impact epicenter) was identified for each subject. A three-vertebrae segment was isolated in Mimics using the identified epicenter as the middle vertebrae for each subject. The 3-
vertebrae segments were selected to fully include the injury site while minimizing the size of the model and the resulting computational cost [20]. White matter, gray matter, dural tube and vertebral column structures were segmented using customized image thresholding for open dura subjects (#14 and 16). In the intact dura subjects (#5, 6, 8 and 9) due to the lower resolution of the scans, the gray matter was not distinguishable in the MRI scans. Therefore, for the intact dura models, the spinal cord, dura and the vertebral column geometries were obtained through segmentation in Mimics and the gray matter was manually added by extracting the gray matter profile from each subject from a rostral histological slide (> 4.8 mm from the epicenter). The profile was swept along the spinal cord to create the gray matter 3-D object. The 3-D objects were then exported to Materialise 3-Matic Research (Materialize N.V., Technologielaan 15, 3001 Leuven, Belgium) for geometry edits (e.g. smoothing, rendering, wrapping and cropping to reduce errors in the geometric solid objects before meshing) and meshing. The edited 3-D objects were meshed with tetrahedral elements (prescribed edge of 0.4mm) after being manually partitioned. For intact dura models (#5, 6, 8 and 9) the CSF geometry was obtained by performing a Boolean operation between the spinal cord and the dural tube objects in 3-Matic. Finally, the completed orphan meshes were imported in ABAQUS (AB AQUS/standard/explicit version 6.14, Simulia Inc, Providence RI) to simulate the unilateral contusion impact. We did not include denticulate ligaments or nerve roots in our models since these components have been found to have limited effect on the bulk cord displacement [225].
Figure 5-1: Representative of MRI scans, 3-D segmented mask and FE models. For the subject shown here, the sagittal T2-weighted MRI scans were obtained using a 3T scanner yielding 512×1024 pixel scans with a slice thickness of 270-μm and field of view of 140 mm. Figure illustrates axial view with gray and white matter masks (A), sagittal view showing target spinal cord segment (in between the red lines) for FE modelling and the impact position (red arrow) (B), isometric view of generated 3-D mask showing C2 to C7 vertebrae, white and gray matters cut for illustration (C), a representation of FE model segment and laminectomy site (D), an isometric view of an open dura model (E), and an isometric view of an intact dura FE model.

For both open and intact dura experiments, we modeled the impactor as a 4 mm analytically rigid cylinder since the bulk modulus of the impactor is several orders of magnitude higher than the soft tissues of the spinal cord. The impactor was meshed with quadrilateral elements (R3D4) [3]. Analytically rigid properties were assigned to the spinal column mesh (R3D3) for the simulations. Imported orphan meshes of white and gray
matters were assigned continuum tetrahedral elements (C3D4) with second order accuracy. The pia mater was modeled as a skin surrounding the white matter with a thickness of 0.13 mm and meshed with linear triangular elements (S3R) [187]. For the intact dura models, the CSF orphan mesh was imported as a solid and was converted to mass particles for further analysis using SPH [226], [227]. In these simulations, the dura was assigned linear triangular shell elements (S3R) and a thickness of 0.35mm [109]. The posterior section of the epicenter vertebrae (lamina and spinous process) was removed to mimic the in-vivo surgical laminectomy [3]. Finalized models were comprised of roughly 24000, 98000, 5000 and 7500 elements for gray matter, white matter, pia mater and dura mater respectively; the CSF contained ~13500 particles in the models (Figure 5-1). To improve the computational efficiency, element distortion control, second-order accuracy, and enhanced hourglass control were applied to all of the elements of the FE models accordingly. The simulations were run on supercomputing clusters (Intel E5-2683 v4 CPUs, running at 2.1 Ghz processors) using ABAQUS/Explicit. The open dura tests were simulated first to validate the model assumptions (structure interactions, contacts, boundary conditions, and material constitutive models). The open dura models were not analyzed for FE outcome-tissue damage correlations as these subjects were used in other experimental protocols and no histology was available.

5.2.3. Material Constitutive Models and properties

**White matter.** The rostral-caudal alignment of axonal fibers in the spinal cord white matter has resulted in a direction specific mechanical response [40], [185]. For these simulations, a conditional quasi-linear viscoelastic (QLV) transversely isotropic model [90] was refined by including our recent NHP white matter compressive characterization results [220] augmented with bovine tensile tests [11] and derived using inverse FE optimization methods [220].

The resulting conditional QLV model is a time dependent strain energy function, \( U_{WM}(t) \), in the form of a Prony series expansion with \( N \) number of terms as (Equation 5-1),

\[
U_{WM}(t) = \int_0^t \left\{ \left( 1 - \sum_{i=1}^N g_i (1 - e^{-(t-\tau)/\tau_i}) \right) \frac{d\psi_{WM}}{d\tau} \right\} d\tau
\]

where \( \psi_{WM} \) represents a conditional hyperelastic strain energy (Equation 5-2),
\[ \psi_{WM} = \begin{cases} \psi_{\text{matrix}} & \lambda_{fibers} \leq 1 \\ \psi_{\text{matrix}} + \psi_{\text{fibers}} & \lambda_{fibers} > 1 \end{cases} \]  

where \( \psi_{\text{matrix}} \) represents the isotropic elastic strain energy of the glial matrix, \( \psi_{\text{fibers}} \) is the contribution of the fibers in the elastic strain energy and \( \lambda_{fibers} \) is the stretch in the fiber direction. Whenever the fibers are not stretched \( (\lambda_{fibers} \leq 1) \) the matrix is governing the strain energy. The matrix response is characterized by a Mooney-Rivlin model with 4-term Prony series \( (\psi_{\text{matrix}}) \) (Table 5-2) [220] and combined with a quadratic reinforcing function \( (\psi_{\text{fibers}}) \) to capture the white matter behavior in the direction of fibers (Equation 5-3) [90],

\[
\psi_{\text{matrix}} = C_{10} (I_1 - 3) + C_{01} (I_2 - 3) + \frac{1}{D} (J - 1)^2 ; \\
\psi_{\text{fibers}} = \frac{\gamma}{2} (I_5 - 1)^2
\]

where \( I_1, I_2 \) and \( I_5 \) are the deviatoric invariants of isochoric Cauchy-Green tensor, \( J \) is the determinant of the deformation gradient tensor, \( C_{10}, C_{01}, D \) and \( \gamma \) are material parameters. In this study, values for \( C_{10}, C_{01}, D \) were assigned from NHP white matter compressive characterization [220] (Table 5-2). \( \gamma \) was determined through an iterative inverse FE optimization method [90], [220] where a series of bovine tensile tests [10], [11] were simulated in ABAQUS/Explicit to determine an optimized \( \gamma \) value. The conditional QLV formulation (Equation 5-2) was implemented as material constitutive model using the user subroutine VUANISOHYPER_INV [90], [154]. The inverse FE optimization includes the off-axis loading responses and provides a more accurate FE-adoptable constitutive model for the material.

**Gray matter.** Unlike the white matter, axonal fibers are oriented more randomly in spinal cord gray matter; therefore, the material was considered to be isotropic. To date, only one study has managed to test isolated spinal cord gray matter, where the strips of bovine spinal cord gray matter were stretched until failure *in-vitro* [11].

The results of these bovine tests were used to determine a 1\textsuperscript{st} order Ogden QLV model with 3-term Prony series (Equation 5-5) for the spinal cord gray matter. The model’s constitutive parameters were identified by an inverse FE optimization method [160], [184], [188], [207], [220], where the bovine gray matter tensile tests were simulated in ABAQUS and the material parameters were iteratively updated by an optimization algorithm [220] to match the FE simulation results to experiments (Table 5-2).
Table 5-2: Material specifications and properties used in modelling the contusion injury. Material density values are obtained from IT’IS website [228].

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Constitutive model</th>
<th>Hyperelastic Constants</th>
<th>Viscoelastic Constants</th>
<th>Density ( \frac{Kg}{m^3} )</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>White matter</td>
<td>Mooney-Rivlin QLV with 4-term Prony series</td>
<td>( C_{10} = 3.27E-3 ) [MPa] ( C_{01} = 0.91E-3 ) [MPa] ( D = 0.2393 ) [MPa] ( v = 0.4995 ) ( y = 6.172E-03 ) [MPa]</td>
<td>( g_1 = 0.5256 ) ( g_2 = 0.3163 ) ( g_3 = 0.1250 ) ( g_4 = 0.0071 )</td>
<td>( \tau_1 = 0.01 ) Sec ( \tau_2 = 0.02 ) Sec ( \tau_3 = 0.2 ) Sec ( \tau_4 = 2.0 ) Sec</td>
<td>( \rho = 1041 )</td>
</tr>
<tr>
<td>Gray matter</td>
<td>1st order Ogden with 3-term Prony series</td>
<td>( \mu_0 = 4.454E-2 ) [MPa] ( \alpha = 10.57 ) ( D = 0.045 ) [MPa] ( v = 0.49 )</td>
<td>( g_1 = 0.4793 ) ( g_2 = 0.2854 ) ( g_3 = 0.0732 )</td>
<td>( \tau_1 = 0.64 ) Sec ( \tau_2 = 0.081 ) 60.4 Sec ( \tau_3 = 64.0 ) Sec</td>
<td>( \rho = 1045 )</td>
</tr>
<tr>
<td>Pia mater</td>
<td>Linear elastic</td>
<td>( E = 39.3 ) MPa ( v = 0.3 )</td>
<td>-</td>
<td>( \rho = 1075 )</td>
<td>Kimpara et al.[187]</td>
</tr>
<tr>
<td>Dura mater</td>
<td>1st order Ogden with 4-term Prony series</td>
<td>( \mu_0 = 1.2 ) MPa ( \alpha = 16.2 ) ( v = 0.45 )</td>
<td>( g_1 = 0.329 ) ( g_2 = 0.128 ) ( g_3 = 0.086 ) ( g_4 = 0.086 )</td>
<td>( \tau_1 = 0.009 ) Sec ( \tau_2 = 0.081 ) ( \tau_3 = 0.564 ) ( \tau_4 = 4.69 ) Sec</td>
<td>( \rho = 1174 )</td>
</tr>
<tr>
<td>CSF</td>
<td>Mie-Gruneisen equation of state</td>
<td>( E = 2.19 ) GPa ( c_0 = 1381.7 \frac{m}{sec} ) ( s = 1.979 ) ( \Gamma_0 = 0.11 )</td>
<td>-</td>
<td>( \rho = 1007 )</td>
<td>Kleiven et al.[229] and Panzer et al.[230]</td>
</tr>
</tbody>
</table>

\[
U_{GM}(t) = \int_0^t \left\{ \left(1 - \sum_{i=1}^3 g_i \left(1 - e^{-\frac{t-\tau}{\tau_i}}\right) \right) \frac{d\Psi_{GM}}{d\tau} \right\} d\tau
\]

where \( U_{GM} \) is the time dependent strain energy function for the gray matter and \( \Psi_{GM} \) is the hyperelastic strain energy defined as (Equation 5-5),

\[
\Psi_{GM} = \frac{2\mu}{a^2} (\bar{\lambda}_1^\alpha + \bar{\lambda}_2^\alpha + \bar{\lambda}_3^\alpha - 3) + \frac{1}{D} (J - 1)^2
\]

with \( \bar{\lambda}_i \)'s defined as the deviatoric principal stretches, \( \alpha, \mu \) and \( D \) are material properties and \( J \) is the determinant of the deformation gradient tensor.
**Pia and dura maters.** Kimpara et al.[187] have performed a series of tensile tests on porcine cervical posterior median septum and observed a linear elastic behavior for the spinal cord pia mater at low strain rates (≤0.5 s⁻¹); based on their findings, a linear elastic behavior for the pia mater was assumed (Table 5-2). For the dura mater, isotropic behavior was assumed and used a 1st order Ogden model with 4-term Prony series [37] (Table 5-2).

**Cerebral Spinal Fluid.** The mesh-free SPH method has been shown to be effective in simulating the large deformation fluid-structure interactions and complex patient-specific geometries [231] for brain [232] and spinal cord [20] injuries. SPH method simulated the CSF behavior in the FE models of this study by assuming a linear Hugoniot form of the Mie-Gruneisen equation of state [154] (Equation 5-6).

\[
p = \frac{\rho_0 c_0^2 \eta}{(1-s \eta)^2} \left(1 - \frac{\Gamma_0 \eta}{2}\right) + \Gamma_0 \rho_0 E_m
\]

where \(p\) is pressure, \(E_m\) is the internal energy of the fluid per unit reference volume, \(c_0\) and \(s\) are material linear Hugoniot constants, \(\eta = 1 - \frac{\rho_0}{\rho}\) is the nominal volumetric compressive strain with \(\rho_0\) and \(\rho\) as the reference and the current densities of the CSF respectively, and \(\Gamma_0\) is also a material constant. The above equation of state, with assigned material properties of water, has been previously used to model brain CSF in FE simulations of blast brain injury [230], [233]. In the current study, the CSF density [228] and bulk modulus (2.19 GPa) [229] were used to determine \(c_0\) while the properties of water were assigned [230] to \(s\) and \(\Gamma_0\) (Table 5-2). Modeling CSF as SPH particles substantially decreased the stable time increments (~1E-8 Sec) in the analysis and eliminated the possibility of parallel domain processing due to convergence difficulties. As a result, the required CPU hours for running intact dura simulations on the supercomputer cluster nodes were substantially higher than that of open dura simulations where no CSF was included in the models (about 55 CPU hours for open dura simulations on average versus more than 220 CPU hours for intact dura impacts).

5.2.4. Loading and Boundary Conditions

To accurately mimic the *in-vivo* experimental conditions for both the intact and open dura impacts, the simulation was performed in two stages of pre-loading and impact. At the first stage (pre-loading), a sensor was defined on the FE impactor using the UAMP
subroutine in ABAQUS to monitor the reaction force of the impactor. The impactor was lowered to touch the pia (open dura) or dura (intact dura) and then continue to trap the spinal cord against the floor of the vertebral canal. This trapping step continued until the force readout from the sensor corresponded to the in-vivo pre-load (Table 5-1). The CSF was not included in the models as the fluid provides negligible resistance at very slow loading rates used in the trapping step and it would result in extremely long simulation times using the SPH method. After the trapping step, the impactor held for 0.2 seconds to let the viscoelastic materials relax, similar to the experimental protocol. During the trapping step, symmetric boundary conditions were applied to the rostral and caudal ends of the spinal cord to restrict the axial movement while allowing unrestricted dorsal/ventral and medial/lateral motion (both open and intact dura simulations). In the intact dura simulations, the rostral and caudal ends of the dura mater were fixed for the pre-loading step to prevent free rotation.

In the second stage, the force sensor was removed from the impactor and the actual in-vivo displacement trajectory of the impactor was prescribed to the FE model impactor [3]. The deformed geometries were imported from the trapping stages. For the intact dura models, CSF particles were added to the model. In our preliminary impact simulations without boundary conditions, the spinal cords rolled over which was not observed during in-vivo impacts. The models best simulated the in-vivo behaviour once the symmetric boundary conditions of the trapping stage were substituted with fixed boundary conditions in the impact stage. The two ends of the dura matter were prescribed axially symmetric boundary conditions for the impact step. To confine CSF particles from escaping the dural tube during the impact, an axial symmetric boundary condition was imposed on the first four superior/inferior rows of CSF particles at either open end of the FE model (Figure 5-1). Applying this condition to less than four rows of particles did not hold the CSF particles in the dural tube during the impact. The spinal canal was fixed in all directions and the impactor was allowed to move only in the impact direction during the entire simulation.

Coefficients of friction were applied at the interacting surfaces. Following rodent contusion SCI simulations [20], [21], the coefficient of contact friction between the outer section of dura and spinal canal was considered 0.15. The friction between the indenter and the dura mater (intact dura simulations) or pia mater (open dura simulations) was assumed to be slip rate dependent with the coefficient of friction equal to 0.09 and 0.18 at...
strain rates of 1/sec and 60/sec respectively [202]. Because of the CSF lubricating effect, a very low friction coefficient was assumed for the contact between the pia-dura (0.01). Although the CSF was removed by excising the dura in open dura tests, there was likely some remaining fluid on the anterior side of the cord and therefore a low contact friction coefficient (0.01) was assumed for pia-column interaction in the open dura simulations.

5.2.5. FE Model Calibration and Validation

The subject-specific FE models were validated by comparing their impactor reaction force outputs against the corresponding in-vivo impactor’s reaction force and trajectory [3], [76]. We know a priori that the constituent spinal cord material properties (white and gray matters and pia mater), boundary conditions and the impactor mediolateral alignment substantially affect the impact force [21], [76], [90]. Material constitutive models for the spinal cord constituents were derived from in-vitro experiments directly and through inverse FE optimization methods. The material properties and constitutive models were not further adjusted in these models. Calibration of the FE model impact mechanics with the experiments was achieved by modifying the boundary conditions and the mediolateral alignment of the impactor (which we know was difficult to precisely determine during surgery). The validity of the assumed material models was confirmed using the open dura simulations. Excising the dura mater and removing the CSF in open dura models provided an opportunity to evaluate the constitutive material models used in the FE model without the uncertainty caused by dissipating effects of CSF [222], [223].

One open dura subject (subject #16) was used as the pilot model to systematically examine the modelling parameters. Six FE models of this subject were generated where combinations of two types of boundary conditions (fixed or axially symmetric) applied to the rostral and caudal free ends of the spinal cord in the FE model and three friction coefficients (frictionless, 0.15 and slip rate dependent) were examined. Biomechanical outputs of each model were observed and compared with the corresponding in-vivo behaviour. In these simulations, if the model with the reported in-vivo mediolateral alignment (0.5 mm - Table 5-1) did not sufficiently match the biomechanical in-vivo results, the mediolateral alignment was incrementally changed to ensure that mediolateral alignment was not the deciding factor. Due to the long runtimes (>55 CPU hours) and to reduce the number of simulations, the mediolateral alignment was varied in increments of
0.1 mm until the output force most closely matched the open dura experiment. The RMSE of the FE predicted impactor force and the impact force recorded during the experiment was determined for each boundary and friction condition for comparison. The boundary conditions and friction coefficients were determined by selecting the conditions which resulted in a predicted impact force that most closely matched the experimental results. To verify the boundary and friction conditions, they were applied to the other open dura subject (subject #14) to examine their performance. Again, the mediolateral alignment of the impactor was varied to calibrate the impact biomechanics to the experimental results.

Boundary conditions, friction coefficients and contact definitions obtained from open dura tests were then applied to simulate intact dura impacts using the same constitutive material models (white matter, gray matter and pia mater). Similar to the open dura experiments, the intact dura models assumed fixed material properties for dura mater and CSF and the mediolateral alignment of the impactor was adjusted in the increments of 0.1 mm to calibrate the impactor output force trajectory with the corresponding in-vivo outcome. RMSE was determined for each simulation and compared to achieve the minimum error.

The effects of spinal cord modelling length were investigated on the initial open dura subject (#16) where additional spinal levels rostral and caudal (C3 to C7 instead of C4 to C6) were simulated. A mesh refinement analysis was also performed with the maximum element edge size decreased to 75% of the pilot model mesh edge (i.e. from 0.4 mm to 0.3 mm) to determine the sensitivity of the predicted outcomes to mesh density.

5.2.6. Tissue damage correlation analysis

Histology slides were processed for eriochrome cyanine and neutral red to show the spread of the chronic lesion [21], [191]. Transverse slices of one element thick (0.4 mm thick) corresponding to the histology slide positions (epicenter and ±1.6 and ±3.2 mm rostral) were outlined in the FE models (Figure 5-2). The injury epicenter was identified as the slice centered under the impactor in the FE model and was used as a reference to locate rostral/caudal FE slices (±1.6 and ±3.2 mm rostral). Based on the histology slides, the selected FE slices were color-coded (Adobe Photoshop) where the lesion area and the spared gray and white matters were outlined accordingly (Figure 5-2) [3]. After the impact simulation, the deformed mesh of the selected slices at each level was
superimposed onto the corresponding color-coded histology slide using an image processing toolbox and a custom code (MATLAB R2018a, The MathWorks Inc Natick, MA). Ventral artery and dorsal median sulcus served as the main reference landmarks together with manually selected points on the perimeter of the gray and white matters. In the composite image, gray and white matter elements overlaying the injured (lesion/red) and uninjured (spared tissue/green for white matter and blue for gray matter) areas were selected accordingly (Figure 5-2). Elements that corresponded to both injured and uninjured tissue were identified as injured.

Following previous studies of brain and spinal cord [11], [20], [21], [89], [191], several tissue level mechanical measures were statistically analyzed to assess their correlation with tissue damage and to determine their corresponding threshold values. As this was the first exploration of NHP contusion injury mechanics, a comprehensive assessment of the mechanical measures (maximum/minimum LEP, LEAXON, MISES, TRESCA and ESEDEN) was performed. These outputs were recorded for all the elements of white and gray matters in the selected slices for the entire impact simulation in each subject. For each element, the corresponding peak value (positive, negative and absolute) experienced through the entire impact was listed together with the element injury status (“1” if detected as injured and “0” if uninjured). This resulted in ten sets of data for each of the subjects (five slices in each subject with two separate sets for gray and white matters) containing element numbers, binary injury status (“1” or “0”) and the corresponding mechanical outcome peak values experienced by the element for the entire duration of impact. In addition to the mechanical metrics listed above, maximum/minimum principal stress and maximum/minimum pressure were investigated in our preliminary studies, however, since these metrics poorly correlated with tissue damage, they were not included in the results presented here. Axons in the white matter were assumed to be predominantly aligned in the rostral-caudal direction prior to the impact. Therefore, a local coordinate system was assigned to each element of the white matter defining the axonal direction. ABAQUS then traced the distortions of each element’s coordinate system spatially during the impact and reported the axon direction accordingly in time intervals. However, axons direction in the gray matter is more random; therefore, no coordinate system was assigned to gray matter elements and LEAXON was always the strain component in initial rostral-caudal direction.
Figure 5-2: (A) Color-coded histology slides of the four intact dura subjects (gray matter = blue; white matter = green; lesion area = red). Sections showing -3.2 mm and -1.6 mm caudal of the epicenter, the epicenter, 3.2 mm and 1.6 mm rostral to the epicenter. (B) Isometric view of an intact dura FE model; one element thick slices corresponding to the selected histology slides are shown. Gray and white matters, dura and pia mater, CSF and spinal column are visible in the figure. (C) Representative of a superimposed FE slice and the corresponding histology section. Injured elements are detected by dark color for both gray and white matters in the section (right).

5.2.7. Statistical Analysis

For each intact dura experiment, numerical output variables were analyzed using Logit analysis (binary logistic regression analysis) in JMP (v13.2.1, SAS Institute Inc., Cary, NC,
USA) to assess their potential capability in predicting spinal cord tissue damage. Random element sets were selected for individual subjects to balance the number of elements selected for the white and gray matter. For each random set, a logistic model (Equation 5-7) was fit to the data of the elements’ binary injury status (injured/uninjured) versus their corresponding peak output variable experienced through the entire simulation.

\[ \pi(X) = \frac{1}{1 + e^{-(\alpha + \sum \beta_i X)}} \]  

5-7

where \( \pi \) is the probability of the tissue being damaged, \( X \) represents a vector of the independent variables (max/min LEP, LEAXON, MISES, TRESCE and ESEDEN), \( \alpha \) is the model intercept and \( \beta_i \)'s are the model parameters associated with \( \alpha \) and the independent variables. JMP uses maximum likelihood estimation method (log-likelihood) to determine the best fit parameters for the regression. A specific likelihood ratio Chi-square test was performed where the observed p-value of the test was judged for model goodness-of-fit assessment (significance was assumed at \( p < 0.05 \)). To determine which candidate output variable provides the best correlation with the occurrence of spinal cord tissue damage, the Nagelkerke R-squared statistic [234] was calculated for each fit [21], [235] (limits are 0 for poor and 1 for perfect correlation).

Moreover, the performance of the binary classifier model at varied thresholds was expressed by plotting receiver operating characteristic (ROC) curves for different output variables and compared [236] (a diagonal ROC curve cannot discriminate between the dichotomous outcomes). The area under the ROC curve (AUC) was another measure of model performance (the output variable with its AUC closest to one was considered the best predictor of tissue damage). Additionally, breakdown values (thresholds) for 50% probability of injury were determined for each variable output by inverse prediction method using confidence interval of 0.9. Finally, a one-way ANOVA with significance level set at \( \alpha = 0.05 \) compared the thresholds obtained for different random sets to analyze the significance of their variations between the subjects.
5.3. Results

5.3.1. Model Validation and Biomechanics

The impactor output force behaviour of the pilot subject (subject #16) best matched the corresponding experimental output (RMSE=0.93) once fixed end boundary conditions and slip rate dependent friction coefficients were applied to the model (Figure 5-3A). This was achieved when the mediolateral alignment of the impactor was adjusted to -0.4 mm (over the midline or a more centered impact) compared to the experimentally reported alignment of 0.5 mm over the midline (Table 5-1). Frictionless contacts or fixed friction coefficient (i.e. $\mu=0.15$) did not result in improved biomechanical outputs when combined with symmetric (RMSE>4.23) or fixed (RMSE>2.61) boundary conditions (Figure 5-3A).

![Figure 5-3: (A) Modelling parameter variations](image)

Using symmetric boundary conditions for rostral and caudal ends of the spinal cord worsened the biomechanical match (RMSE>3.49) for all different contact friction statuses. Increasing the length of spinal cord in the pilot model by one vertebrae rostrally and caudally (i.e. from C4-C6 to C3-C7) did not affect the impactor's peak force, however, it changed the overall force output trajectory (RMSE=2.40) compared with the best fit result.
for the shorter model. Refining the model mesh by 25 percent did not alter the impactor’s biomechanics noticeably (Figure 5-3A). Combined, fixed boundary conditions and slip rate dependent contact definitions best mimicked the biomechanical outcomes of the pilot model. Using these confirmed model conditions, the output force trajectory and peak force of the impactor was still substantially affected by the mediolateral alignment of the impactor in both open dura (Figure 5-3B) and intact dura (Figure 5-3C) models. Accurate predictions of the *in-vivo* impact biomechanics was achieved for each model without the need to alter the material properties of the FE models from their experimentally derived values.

![Figure 5-4](image)

**Figure 5-4:** (A) Impactor force outputs compared for FE simulation and *in-vivo* experiments in open and intact dura simulations. The impactor’s mediolateral alignment was accordingly tuned in each simulation to obtain reasonable match between FE simulation outcome and corresponding experimental output. (B) Superimposed deformed and undeformed configurations of intact dura models showing the ultimate mediolateral positioning of the impactor in each simulation. Spinal canal, gray and white matters, pia mater and the impactor are visible. Deformed configuration is presented at the maximum impactor stroke. Solid lines show the assumed midlines, impactor alignment over the midline (subjects #6 and #8) is defined as negative alignment (Table 5-1), and the scale bar is 4 mm. Open dura subjects are not shown.
In all of the subjects, setting the impactor to the reported *in-vivo* mediolateral alignments overestimated the impactor output force (Table 5-1). The alignments were adjusted in 0.1 mm increments until the FE predicted impact biomechanics mimicked the *in-vivo* results. The peak impact forces observed in each simulation corresponded to the peak force obtained *in-vivo* (less than ±6% difference) (Table 5-1). Applying the validated boundary conditions and contact specifications, the tuned alignment models predicted *in-vivo* biomechanical output accurately in both types of simulations (Figure 5-4). The impacts in subjects #5 and #9 were more lateral and the observed peak force in these models was almost half of subject #6. The fit of the FE predicted output force trajectory to the corresponding *in-vivo* results did not improve by varying the CSF properties or the associated applied boundary conditions.

5.3.2. Subject-Specific Qualitative Analysis of Injury Outcomes

The longitudinal distribution patterns of the investigated metrics (min/max LEP, MISES, TRESERA and ESEDEN) showed elevated levels centered under the impactor that did not spread substantially beyond the impact zone (<2 mm) (Figure 5-5). Studying the distribution patterns in the selected slices (epicenter, ±1.6 mm, ±3.2 mm rostral) also showed the quick damping of stress, strain and strain energy in the spinal cord. The rostral/caudal distribution of the output metrics about the epicenter was not symmetric in the FE simulations. These observations matched the patterns of tissue damage in the corresponding experiments [3] and other *in-vivo* contusion experiments [7], [21]. Subject-specific review of the impact results showed that larger portions of the contralateral spinal cord cross section had elevated levels of output variables in subjects #6 and #8 (Figure 5-6) where the impactor position was more centered (over the midline) compare to other subjects (Figure 5-4). For all of the subjects the zone for peak strain outputs (max/min LEP and LEAXON) was localized under the tip of the impactor with a noticeable short distance directly inferior to the tip of the impactor (Figure 5-6). Ipsilateral ventral gray matter horns showed the greatest stresses and strains in all the subjects. In the white matter, elevated mechanical stresses and strains were located in the lateral funiculus for all subjects. In the white matter, zones of high stresses (MISES, TRESERA), or strains (max/min LEP and LEAXON) were concentrated at the boundary of gray/white matter. Generally, peak output magnitudes in the white matter corresponded with maximum
compression, with the exception of MISES stress in subject #6. Distributions of all output metrics showed a narrow peripheral rim of ipsilateral white matter (adjacent to the pia mater) where magnitudes were lower than the surrounding tissue.

<table>
<thead>
<tr>
<th>Subject #5</th>
<th>Subject #6</th>
<th>Subject #8</th>
<th>Subject #9</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>Max LEP</td>
<td>0.4</td>
<td>0.35</td>
<td>0.3</td>
</tr>
<tr>
<td>Min LEP</td>
<td>-1.5</td>
<td>-0.45</td>
<td>-0.25</td>
</tr>
<tr>
<td>LEAXON</td>
<td>0.3</td>
<td>0.15</td>
<td>0.1</td>
</tr>
<tr>
<td>MISES [kPa]</td>
<td>400</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>TRESCE [MPa]</td>
<td>0.4</td>
<td>0.1</td>
<td>0.075</td>
</tr>
<tr>
<td>ESEDEN [mJ/mm²]</td>
<td>0.35</td>
<td>0.1</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Figure 5-5: Contours representing the distribution of max/min LEP, LEAXON, MISES, TRESCE and ESEDEN at maximum impactor penetration. Values of all output variable dissipates at rostral and caudal ends of the model, demonstrating the minimum effects of end boundary conditions.
Figure 5-6: Distribution of output variables at peak position of the impactor in intact dura subjects. Columns stand for subjects and each row is assigned to an output variable. The cross-sectional slice located under impactor midline is presented (injury epicenter). Deformed gray and white matters, spinal column and the impactor is visible in the cross section. Scale bar is 4 mm.

At maximum compression min LEP, LEAXON and MISES output patterns at the loading epicenter showed the most conformity with the histology results. It is important to
note that the spinal cord tissue may not experience the same patterns of tissue mechanics for the whole duration of the impact. Extracting peak output values from all the elements in the selected slices (epicenter, ±1.6 mm, ±3.2 mm rostral) for the intact dura subjects showed the general distribution of the output variables during the entire contusion simulation (Figure 5-7). Subject specific histograms (not shown) revealed that elements in each of the subjects followed similar patterns as the mixed histograms. Histograms with smallest discontinuity from uninjured to injured elements were observed in min/max LEP in both gray and white matters (suggesting that min/max LEP may be a better predictive metric for the injury). Additionally, on average, gray matter elements experienced almost double the level of stress (i.e. MISES, and TRESCA) of white matter elements. This was opposite to strain levels (i.e. max/min LEP), where white matter elements experienced 24.6 and 12.7 percent higher levels of maximum and minimum LEP respectively compared to gray matter (Figure 5-7).

Figure 5-7: Histograms of peak values of the metrics experienced in injured (red) and uninjured (black) elements (selected slices of all intact dura subjects) for the whole duration of impact. For each metric, the left histogram corresponds to the white matter elements in the slices and the right histogram refers to the gray matter elements. Generally, white matter elements experienced higher strain levels (max/min LEP and LEAXON) compared to gray matter elements; contrarily, higher levels of stress (MISES and TRESCA) were observed in the gray matter elements.
5.3.3. FE Outcome - Lesion Correlation Analysis

Tests of goodness-of-fit resulted in statistically significant values on the chi-square term for logistic regressed curves of all output variables (p<0.0001), meaning the probability of obtaining a fit with greater chi-square value, by chance alone, was less than 0.0001 (Figure 5-8). Considering all the subjects, min LEP presented the highest correlation with the occurrence of tissue damage in white matter with Nagelkerke R-squares greater than 0.5 and AUCs greater than 0.8 (Table 5-3).
Figure 5-8: Typical logistic analysis (min LEP in subject #6 in this case) on a random selected element set. (A) histology slides (white matter in green, gray matter in blue and injured tissue in red) stacked in a 3-D view showing epicenter, ±1.6 mm and ±3.2 rostral with corresponding (B) FE slices at approximately the same anatomical position. Random sets of elements were selected for white and gray matters from all the five slices (elements with light border) comprising approximately the same number of injured and uninjured elements for each set. (C) The peak min LEP experienced by the elements in the element set were plotted against binary status of the element and a logit regression curve was fitted. In this case, the fit was statistically significant with p-value<0.0001 for both gray and white matters, and the Nagelkerke R-square was 0.79 and 0.62 for gray and white matters respectively. (D) ROC curve for the gray matter is more distanced from the diagonal line, tough, min LEP clearly shows better predictive power for gray matter tissue damage compared to the white matter ROC curve. This is confirmed with AUC values equal to 0.95 and 0.88 for gray and white matters respectively.

In subjects #5, #6 and #8, TRESCA and MISES were better injury predictors for white matter (higher Nagelkerke R-squares) compared to min LEP, however, these metrics poorly depicted tissue damage in subject #9 (Nagelkerke R-squares<0.4).
Generally, all metrics presented better potential in predicting gray matter tissue damage compared to white matter considering both the Nagelkerke R-squares and the AUCs. For the gray matter, MISES and TRESCA were the best predictors of tissue damage respectively with Nagelkerke R-squares between 0.55 and 0.87, and AUCs between 0.86 and 0.98. Subject-specific review of the results showed that in white matter, MISES, LEAXON, TRESCA and min LEP were the best predictors of the injury with some variation in the order of best fit across the subjects. Max LEP and ESEDEN showed a comparable predictive capability. Max LEP had very poor results in subjects #6 and #8. Threshold values for each metric parameter were determined at 50% probability of injury (Table 5-3).

From one-way ANOVA, only LEAXON and ESEDEN injury thresholds did not vary between subjects in the white matter (0.1 and 0.018 mJ/mm$^3$ for LEAXON and ESEDEN respectively). In gray matter all the metrics had thresholds with significantly different values across subjects.

### Table 5-3: Results of logistic regression analysis comparing potential capability of different mechanical metrics in predicting spinal cord tissue damage computed for the four intact dura subjects. The top and bottom rows of each cell are corresponding to the gray and white matter results respectively. GM denotes gray matter and WM denotes white matter in this table.

<table>
<thead>
<tr>
<th>Metrics</th>
<th>Subjects</th>
<th>Section</th>
<th>Nagelkerke R-square (mean±std)</th>
<th>AUC (mean±std)</th>
<th>Threshold with 50% probability (mean±std)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max LEP</td>
<td>GM</td>
<td>#5</td>
<td>0.86 (±0.69)</td>
<td>0.8 (±0.54)</td>
<td>0.98 (±0.92)</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>#6</td>
<td>0.34 (±0.32)</td>
<td>0.39 (±0.49)</td>
<td>0.78 (±0.78)</td>
</tr>
<tr>
<td>Min LEP</td>
<td>GM</td>
<td>#7</td>
<td>0.71 (±0.73)</td>
<td>0.46 (±0.94)</td>
<td>0.93 (±0.96)</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>#8</td>
<td>0.51 (±0.5)</td>
<td>0.61 (±0.59)</td>
<td>0.85 (±0.85)</td>
</tr>
<tr>
<td>LEAXON</td>
<td>GM</td>
<td>#9</td>
<td>0.75 (±0.73)</td>
<td>0.35 (±0.95)</td>
<td>0.76 (±0.93)</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>#6</td>
<td>0.6 (±0.45)</td>
<td>0.35 (±0.89)</td>
<td>0.83 (±0.94)</td>
</tr>
<tr>
<td>MISES</td>
<td>GM</td>
<td>#6</td>
<td>0.87 (±0.72)</td>
<td>0.55 (±0.98)</td>
<td>0.92 (±0.96)</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>#7</td>
<td>0.67 (±0.56)</td>
<td>0.4 (±0.89)</td>
<td>0.85 (±0.93)</td>
</tr>
<tr>
<td>TRESCA</td>
<td>GM</td>
<td>#8</td>
<td>0.86 (±0.73)</td>
<td>0.55 (±0.98)</td>
<td>0.92 (±0.96)</td>
</tr>
<tr>
<td></td>
<td>WM</td>
<td>#7</td>
<td>0.68 (±0.57)</td>
<td>0.41 (±0.9)</td>
<td>0.85 (±0.93)</td>
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<tr>
<td>ESEDEN</td>
<td>GM</td>
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<td>0.43 (±0.92)</td>
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<tr>
<td></td>
<td>WM</td>
<td>#8</td>
<td>0.49 (±0.37)</td>
<td>0.38 (±0.88)</td>
<td>0.83 (±0.86)</td>
</tr>
</tbody>
</table>
5.4. Discussion

Sensitivity of spinal cord contusion injury models’ outcomes to morphological and anatomical variations [3], [76], [151] suggests that using a generic FE model (commonly generated from averaging specifications) may not appropriately mimic the experimental results. Even in a single species, inter-subject variability was observed in spinal anatomical specifications (spinal column and spinal cord) [147]–[151]; however, higher variations were reported in larger animals (e.g. pigs, NHPs) and humans [148]–[150]. This morphological variability was recently demonstrated to have significant effects on injury variability in a porcine model of contusion SCI [151]. FE analysis results from SCI simulations have been shown to be sensitive to variations in model morphology/geometry [152] and injury mechanisms [20]. Therefore, it is expected that generating patient-specific models of SCI are essential for accurate analysis of large animal SCI mechanics. More specifically, to correlate tissue damage with FE predicted tissue mechanics following contusion SCI, patient-specific approaches should be implemented.

NHP models closely reflect human central nervous system anatomy and physiology [3], [50] and demonstrate morphological heterogeneity more similar to clinical SCI. NHP contusion injury models provide a critical test bed for invasive treatment modalities such as stem cell therapies ahead of human studies. Therefore, understanding and beginning to quantify the link between injury mechanics and tissue damage in the NHP model has important implications for developing standardized injury protocols to minimize experimental variability and provide a reliable foundation to assess treatment efficacy. This study is the first to present NHP subject-specific FE models of contusion SCI and investigate their outcome correlations with tissue damage. The primary contribution of this research was the use of a large-scale animal model in a patient-specific approach to match in-vivo experiments. This allowed for the thorough exploration of the injury biomechanics and the potential correlations between FE mechanics and tissue damage by including inter-subject anatomical and morphological variabilities. In general, the distributions of the output variables matched injury patterns observed at peak point of the impact, although some of the variables (e.g. min LEP and MISES) matched damage patterns better than others. Statistical analysis of the results yielded subject-specific outcomes in terms of the significance of the correlations between different FE predicted mechanical metrics and tissue damage (Table 5-3).
The developed FE models expand the state of the art for computational models of SCI. Working with the larger scale NHP model provided the opportunity to measure tissue mechanics and derive NHP-specific white matter constitutive models [220] to use in the current study. The white matter constitutive model also captured the transverse isotropy of white matter by utilizing an experimentally derived strain energy function [90]. These anisotropic characteristics of the spinal cord have not been included in previous FE models of SCI [20]–[22], [24]. Additionally, the FE models have distinctly modeled the white and gray matters and the pia mater. Discrete modeling of the pia mater has been shown to affect the SCI FE model outcome patterns [90]. Treating white and gray matters as identical materials neglects the complexity of the spinal cord tissue, interactions between the two materials and affect the intraparenchymal mechanics of the model. By integrating these material constitutive models, our open dura simulations closely replicated their in-vivo counterparts without the need to recalibrate the material constitutive models. In fact, the primitive, not modified, constitutive models utilized in the FE models, critically reflect the biofidelity of the FE models in this study. A logit analysis was used to statistically investigate the correlations between FE measures and tissue damage (spread of the lesion) in the histology slides, mainly the corresponding Nagelkerke R-square has been determined for the assessments. The Nagelkerke R-square had the advantage of being bounded between 0 and 1 (similar to R-square in linear regression analysis) and has been utilized previously in studies of spinal cord [21] and brain [191], [235], [237] injury.

Previous midline contusion SCI models have tuned the spinal cord material properties to calibrate their models [20], [21] and reported a marginal effect of off-centered impact on FE outcomes. Unlike those studies, the unilateral experiments of this study showed that submillimeter medio-lateral placement of the impactor substantially affected the in-vivo impact mechanics [3], [76]. This is mainly because of the spinal cord’s bulk lateral shift during these unilateral impacts. However, identifying the spinal cord midline during in-vivo surgery conditions was challenging and impactor alignments reported from the experiment (Table 5-1) were tuned in the FE model to obtain biomechanical outputs from the simulations that were accurately relevant, and closely resembling the in-vivo conditions. We have subsequently developed more advanced positioning devices to detect the spinal cord midline and align the impactor tip especially for intact dura contusion injury experiments.
In a study by Maikos et al. [21], max LEP resulting from midline contusion FE simulations on rats was found to have significant correlation with patterns of blood-spinal cord barrier breakdown (quantified by albumin extravasation) with average Nagelkerke R-squares of 0.84±0.05 for gray matter and 0.56±0.12 for white matter. R-square values determined in our study for max LEP were lower (0.72 for gray matter and 0.39 for white matter). That study did not report other FE measures, however, the correlation significance obtained in our study for min LEP and LEAXON were similar to their reported R-square values (Table 5-3). A potential source of discrepancy may be that we were comparing our tissue level mechanical to chronic lesions while Maikos correlated the FE mechanics to acute injury. The primary damage to the blood–spinal cord barrier that occurs in the acute injury contributes significantly to the overall pathology, including the introduction of reactive species that induce cytotoxicity as well as secondary insults on the blood–spinal cord barrier itself. The chronic lesions that was used to establish correlations with tissue mechanics in this study were mediated by the evolution of secondary injury. However, these chronic lesions are arguable more clinically relevant in representing the long-term implications of the mechanical impact. Furthermore, a stronger correlation was observed between contusion injury impact parameters (impact velocity, cord compression depth, and cord compression rate) and albumin extravasation compared to hemorrhage in rats [77], which suggests albumin extravasation should better correlate with FE predicted tissue mechanics. Using albumin extravasation as injury indicator may yet have another advantage. Using albumin to quantify the disruption of blood-spinal cord barrier is more sensitive than hemorrhage as albumin is an order of magnitude smaller than native red blood cells [77]. This may be particularly relevant for milder injuries, where no primary hemorrhage is observed, however, small albumin species leak across the blood-spinal cord barrier.

Strain in the axon direction (LEAXON) was found to strongly correlate with tissue damage (e.g. 0.78 to 0.94). LEAXON has been proposed by others in the fields of spinal cord [80], [89] and brain [83], [235], [238], [239] injury as a strong correlate with injury. The LEAXON threshold values determined for 50% probability of tissue damage in white matter in our study (between 0.1 and 0.16) agreed with numerical tolerance limits reported for brain diffuse axon injury (0.1465 by Sahoo et al. [235] and 0.13 by Giordano et al. [239]). These threshold results are similar to experimentally derived strain limits of isolated
spinal cord and brain axons (0.18 by Bain et al. [83], 0.2 by Morrison et al. [238] and 0.16 by Sing et al. [240]).

The complexity of NHP in-vivo unilateral contusion injury experiments and FE modeling introduced several challenges to this study and resulted in some limitations. First, in this study, the spinal cord constituent material properties were characterized by direct in-vitro mechanical tests [11], [37], [90], [220] and via FE adaptable methods. The material constitutive models were not further adjusted and the same constitutive material models were used for all of the simulations. A considerable amount of variability has been reported in the spinal cord constituent material mechanical behaviour specifically in larger animals such as porcine [40] and NHPs [220]. Using generic, fixed material constitutive models in the current study may limit the subject-specificity of the output results. However, obtaining individualized accurate material properties for FE models is not trivial and requires advanced, preferably non-invasive, though, complex methods. Total Lagrangian formulation FE analysis methods (instead of updated Lagrangian formulation used in our study) showed the ability to predict the resulting deformation field with a minimal dependency to the predefined constitutive material properties in the studies of brain injury [125], [241]–[243] and the potential to circumvent the need for including material characteristic variations in subject-specific SCI models [244]. However, the method is unreliable for flow-like behavior (e.g. CSF in this case) or topology changes. In addition, description of strains (and stresses) in large strain regimes are complicated due to the initial displacement effects [241].

The histology in this study represents the chronic phase of injury (~20 weeks) which includes the effects of both the mechanical impact and secondary injury cascade. Although this can make the statistical analysis more variable and noisy, it is also more relevant for understanding the link between mechanical impact and long term outcomes (which are most important to the patient). This study did not include a sham group; however, considering the localized nature of contusive SCI[20], [21], preliminary analyses were performed using tissue sections remote from the injury epicenter (±4.8 mm rostral) and the significance of the study statistical results were not changed.

The FE modeling approach also included some limitations. Firstly, our models did not include nerve roots, denticulate ligaments or blood vessels. Adding these exterior structures could restrict the lateral movement of the spinal cord. This is of particular
importance in the simulations of this study since the impact was lateral and unlike previous models of midline impact in rodents [21], the stability of the spinal cord in resistance to bulk lateral shift plays an important role. However, the conformity of the current FE models’ biomechanical behavior with *in-vivo* results, suggests that the roles of these additional structures was minimal, or adequately captured by the assigned boundary conditions. Secondly, the material models used in this study have limitations due to the few available experimental results. The gray matter material model and the viscoelastic material parameters used in the FE models were based on low strain rate experiments (≤ 0.5s⁻¹) [11] and, the material behavior at higher rates was unclear. Further work is needed to characterize these properties directly, though these experiments are exceedingly complex.

The significant correlation of min LEP (compressive strain) and tissue damage observed here both in white and gray matters, suggests that besides the accepted mechanisms of neurological tissue damage such as membrane permeability [245], [246] or axon/myelin disruption [80], [95], [247], that disruption to the spinal cord blood supply needs to be measured in absence not only via hemorrhage. In theory, compressive strain may contribute to blocking the blood circulation. It has been hypothesized that disrupted circulation leads to insufficient blood supply and results in destroyed tissue [248], [249].

High accuracy computational models, such as the ones developed in the current study, could be reliably used in animal model development and testing injury prevention strategies. Translating these models to human injuries have the potential to contribute to clinical decision making and surgical planning where the effects of different surgical interventions may be assessed on the computer first. As an example, these individualized FE models may help in overcoming the challenges in the development of standardized *in-vivo* models of traumatic SCI in large animals such as pigs and NHPs [3], [76], [151]. Inducing a consistent injury in animal models is critically important to establish an injury baseline and to differentiate the efficacy of treatment strategies from normal recovery. Carefully controlled study populations and removing “mishit” animals from analysis have led to tightly correlated impact biomechanical parameters and injury in rats [8], [75], [218] and mice [5], [176], however, these same correlations are not as clear in larger animal models such as pigs or NHPs primarily. The variation in outcomes have been attributed to more variable cord and column morphologies in large animals [3], [151]. Given the extensive housing and experimental costs for large animals (specifically NHPs) and the
desire to minimize the use of animals, establishing methods for reducing experimental variability is critical. The sensitivity of the contusion model outcomes to different parameters observed in the current study suggests that in large animal models of SCI, getting consistent, standardized injury outcomes may require subject-specific impact parameters.

FE predicted injury patterns may also be valuable in further refining our understanding of clinical injuries. Currently, post-injury MRI scanning provides a range of valuable data on the overall extent of the SCI and the involved tissue structures. These patient-specific images are critical in planning strategic treatments based on the individual patient and the injury severity. However, currently, there are some important discrepancies between MRI scans and observed lesion histology, specifically, the MRI scans underestimate the extent of lesion due to the nature of MRI hyperintense signals [3]. Combining MRI scans with patient-specific FE model outcomes may increase the reliability of SCI clinical evaluation since the FE models can provide high-resolution predictions of the lesion location and extent and, perhaps, its ultimate clinical consequences.

Currently, computation times are too large to be clinically feasible (55 to more than 220 CPU hours). This highlights an inherent difficulty in patient-specific modelling of neurological soft tissues (e.g. brain and spinal cord) where the low stiffness of the material substantially reduces the minimum stable time increment required for FE analysis thus extending the run times. In addition, the analysis techniques used here cannot be parallelized and therefore accessing more computing nodes (e.g. a larger super computer) would have limited effect on decreasing simulation run times. Patient-specific models aiming for neurosurgical applications (e.g. image-guided surgeries) require real-time results, therefore, long computation times are a serious obstacle [123], [125], [243], [250]. Total Lagrangian FE analysis methods [241] and emerging meshless techniques [124], [251] have the potential to reduce the required FE analysis timing. In addition, meshless methods have the advantage of reducing the challenges associated with individualized mesh generation in patient-specific approaches. However, these methods require further development and validation; specifically, the capability of these methods in predicting parenchymal level stresses and strains has not been explored. Importantly, these techniques have been limited to simulating low to moderate strain rate phenomenon [123], [125], [243] and the feasibility of applying them to models simulating high strain rates typical of SCI is unclear. Nevertheless, the results of our computational study highly
increased the value of patient-specific SCI results and provide an important first step in justifying further exploration of these emerging methods.

In conclusion, computational modelling of NHP contusion SCI experiments has provided important insight into the subject-specific correlations between FE predicted tissue level mechanics and spinal cord tissue damage. The results have also highlighted the effects of inter-subject morphological variabilities on SCI outcomes. The findings are of particular importance to planning large animal SCI model studies where patient-specific approaches may considerably reduce the variability of the results and, consequently, minimize the costs and the use of animals. These findings also reinforce our understanding of SCI biomechanics, enhance the development of effective injury prevention and therapeutic strategies, and highlight key areas for further investigation.
Chapter 6.

DISCUSSION AND CONCLUSION

6.1. Discussion

Problems associated with transferring pre-clinical findings to clinical trials, have motivated the use of computational models of SCI, where accurate computational models may provide a beneficial platform for non-invasive evaluation of the potential therapies and interventions before clinical trial. Furthermore, the usefulness of these FE models in planning and testing SCI preventive strategies such as car seat belt design and other protective equipment, has gained more attention recently (Chapter 1). While the FE model simulates the process leading to SCI, the FE outputs must be accordingly translated to biological and physiological outcomes. However, the link between FE mechanical outputs and neurological tissue outcomes is unclear. This study aimed to determine and evaluate clinically relevant correlations between SCI computational model biomechanical and tissue level outcomes and spinal cord tissue damage. To achieve this goal, efforts have been made to first, increase the accuracy and fidelity of the FE models by improving material constitutive model definitions (Chapter 3 and Chapter 4), and then to establish a significant link between the model mechanical outcomes and tissue status (Chapter 5).

Constitutive material models of the spinal cord constituents represent fundamental input assumptions in the FE models of SCIs, and material properties have significant effects on FE model outcomes [19]. Including white matter transverse isotropy into the FE models accounts for the anisotropic characteristics of the spinal cord under the impact. A novel QLV strain energy function conditionally augmented with a reinforcing function were able to sufficiently capture the quasi-static behavior of the spinal cord white matter (Chapter 3). Utilizing the transversely isotropic white matter together with discrete modelling of the pia mater in FE simulations of in-vivo contusion SCI, were able to simulate the biomechanical outputs of the in-vivo experiment and captures some remarkable features of the tissue damage patterns (Chapter 3). As such, maximum principal strain distributions in the FE model results effectively captured the combination of the experimentally observed ipsilateral peripheral white matter sparing, ipsilateral injury and contralateral sparing, and the rostral/caudal spread of damage.
The next step in refining the SCI computational models was to utilize a more human-like animal tissue and quantifying its constitutive properties (Chapter 4). Characterizing spinal cord constituent materials based on rodents or porcine/bovine (Chapter 3), may neglect the substantial morphological and physiological heterogeneity between these species and humans when utilized in human SCI simulations. Similarities in the CNS of NHPs and humans suggests that data obtained from these animals may more directly replicate humans. *In-vitro* compressive mechanical tests on fresh NHP white matter samples in high strain rates typical of SCI showed significant sensitivity to strain rate and substantial stress relaxation which confirmed the viscoelasticity of the material (Chapter 4). NHP white matter was substantially stiffer under high strain rates typical of SCI compared to when tested under lower rates (Chapter 4). Characterizing the conditional QLV constitutive model of white matter (Chapter 3) using the new NHP data set increased the fidelity of the model in capturing the white matter behaviour in high strain rates (Chapter 5).

Using the refined constitutive models, a series of individualized computational models of contusion SCI in an NHP model were simulated using the developed material constitutive model (Chapter 5). Models were validated against *in-vivo* counterparts by comparing their biomechanical outcomes and calibrated accordingly. The mechanical outcomes of the validated models investigated several computational mechanical measures statistically to determine their potential capability in predicting spinal cord tissue damage following contusion SCI. Among several FE predicted outputs, minimum and maximum principal strains and von Mises stress showed most significant correlations with tissue damage (Chapter 5). Interestingly, despite the focused effort in this thesis to better characterize white matter material characteristics, the tissue level mechanics in the gray matter better correlated with measures of tissue damage. This could be in part due to the more extensive damage in the gray matter in the subjects analysed. In this study an average of 26.3% of the gray matter was damaged compared with 17.5% of the white matter. Furthermore, as prior work has shown [19], the overall mechanics of injury are sensitive to all material property characteristics, not only the white matter. Therefore, correlations with tissue damage may be improved by more accurate definitions of gray matter and pia mater constitutive properties.

This work comprises an initial effort to link computational mechanical measures of contusive SCI to the ensuing tissue damage in the context of subject-specificity. As recent
research on porcine models of contusion injury have shown, the cord and column morphology play a critical role in injury mechanics and injury outcomes [151]. Therefore, the development of subject-specific models is critical for accurate analysis of large animal contusion SCI. Throughout the different phases of this research, novel observations in the field of SCI, and possible ways to improve the developed models (material constitutive model and the contusion SCI model) were identified. This work demonstrates the usefulness of including white matter anisotropy, discrete models of spinal cord constituents, and utilizing a constitutive model obtained from characterizing fresh white matter tissue from a human-like animal to gain a higher resolution, accurate and clinically relevant outcome in computational modelling of contusion SCI.

6.2. Clinical relevance

Traumatic SCI is a devastating event for individuals. There has been a huge effort towards developing a cure for SCI and reversing the degenerative processes followed by the initial SCI, however, despite beneficial pre-clinical therapies, no clinical progress, or functional recovery has been reported. Potential pre-clinical treatments can not be transferred to the clinical trials without a throughout understanding of the treatment effects and associated outcomes on the patient. Computational models of SCI provide a reliable platform to better understand the outcomes of the therapy without any risk to patients. In addition, scientists working in the field of SCI prevention strategies, may not always use animal surrogates for designing and testing their ideas due to ethical and economical challenges. Computational models of SCI provide a substantial help in this field.

Although several complex mechanisms may directly lead to SCI clinically [62], [70], [252], in most cases, the injury occurs as a result of a contusive load on the spinal cord. In addition, following the initial insult, a portion of the contusive load persist in the spinal cord (residual compression). Hence, contusion-type injury models are considered to be the most clinically relevant models of SCI [3], [76], [151] and, many pre-clinical contusive models have been developed on this basis [253]. In these animal models of SCI, generating a consistent, repeatable injury is critical in order to detect the effects of experimental therapies. In many cases, particularly moderate/incomplete injuries, there is a natural recovery trajectory over time (i.e. the acute injury does not necessary reflect the chronic injury) [3]. Furthermore, if the induced injury is not severe enough, the natural recovery process might be confounded by the therapy results and mislead the
researchers. Hence, understanding the sources, and minimizing the variability in the induced injury has been a major challenge for the researcher in designing, pre-planning and operating large animal contusion SCI studies.

In small animal models of SCI (e.g. rodents), using high accuracy impact devices, large number of animals and tight control of the experimental conditions, has enabled researchers to reduce the variability in the injury outcomes [254], [255]. In addition, in small animal studies, subjects with “mis-hits” or impacts with unusual trajectories can be excluded from further study which further improves the homogeneity of the injury population. However, in larger animal models of SCI, obtaining a consistent, calibrated injury is not trivial and results from every animal must be included due to the high costs and ethical challenges of these studies. Consistency in small animal studies is helped by the number of animals that can be studied because of their modest costs and ethical challenges when compared to high costs associated with testing larger animals such as pigs and NHPs [3], [151]. Furthermore, it is highly likely that the higher inter-species variations in the natural morphometry of the spinal cord and the surrounding dural tube in large animals, is a major obstacle in achieving a repeatable tissue injury in these species [151]. Further insight and advanced methods are required in designing, planning and performing large animal SCI experiments to minimize sources of variability in the experiment.

Access to high resolution MRI scans ahead of contusion experiments provides the opportunity to use the computational models developed in this study to potentially tune the impact parameters to the individual study subject. This could assist with reducing experimental variability in the subjects. In addition, these newly developed computational models provide an ideal testbed for assessing the effect of different experimental parameters such as impactor size and shape, animal posture and positioning, laminectomy size, impactor displacement, etc. on the consistency of impact mechanics and the resulting predicted pattern of injury.

In addition to improving the reliability of large animal models of SCI, which are critical for preclinical validation of potential treatments for human SCI, FE models provide a tool to analyze and better understand the variability in clinical presentations of human injury. MRI scans are typically included in the standard of care for someone suspected of having an SCI. Computational models of SCI developed based on the data provided by
the MRI scans, might eventually enable an accurate and clinically relevant simulation of the injury and related phenomenon. Quantifying the differences in injury mechanics for different human injury scenarios may be important for understanding clinical trajectories for recovery, the role of specific structures in protecting the spinal cord and the mechanisms of spinal loading that lead to varied injury patterns. Computational models of brain injury are in general further advanced in the field of FE modeling of injury. FE models of brain injury have played an important role in differentiating the effects of linear and rotational acceleration on mild traumatic brain injury [118], [187], [256], [257], have highlighted the deep internal structures that are subjected to high strains during these injuries [209], [239], [258] and assisted in evaluating the protective effects of different helmet [259], airbag [260], seatbelt [261] and other safety technology designs.

Currently, injury diagnosis, treatment decisions and prognosis are based on MRIs of the acute injury. However, several studies have demonstrated that MRIs do not reflect the full extent of the lesion [3]. Including FE model predictions of injury may assist in understanding the true extent of injury and areas of mild or moderate injury where spinal cord tissue could be saved with appropriate treatment. However, establishing a meaningful correlation between computational model mechanical outcomes and spinal cord tissue damage is a key component to the fidelity of the model predictions. In addition, the methods of modeling will need to be carefully designed in order to be clinically feasible. Treatment decisions for someone with an SCI are typically made within minutes to hours of presentation at the hospital. FE models that require days or weeks to process will not be effective in a clinical setting. Many researchers are exploring methods for expediting the processing of these models in order to obtain the results in clinical time scale. This includes techniques to morph existing models to new patient morphology [262] developing libraries of computational model results ahead of clinical use and then using optimization methods to best match the clinical case to the existing FE model results [263], or using total Lagrangian FE analysis methods [241] and emerging meshless techniques [124], [251] have the potential to reduce the required FE analysis timing.

In this study, individualized computational models of a set of in-vivo contusion experiments were utilized to establish a statistically significant link between computational model outcomes and tissue damage. Along the way to accomplish this task, efforts have been made to increase the precision of the computational models in the first place, by refining these models to obtain higher resolution outcomes, and then individualizing them.
to include subject-specific morphometric measurements. Although the correlations obtained in the current study were not very strong and were subjected to a variety of limitations, the clinical potential of this approach is positive. These models have already proven valuable in quantifying the relative effect of impactor alignment on both the injury mechanics and predicted patterns of tissue damage. This reinforced the importance of carefully controlling the impactor alignment during the surgical procedures. Furthermore, the model results demonstrated the significance of differentiating the spinal cord constituent materials in accurately capturing the phenomenon of white matter sparing, which is seen in most clinical presentations of SCI but has been lacking in previous computational models. The correlations between impact mechanics and specific tissue damage will likely be strengthened by expanding the study population with new experimental results and further refinement of the computational models using new supercomputing resources. Computational models of SCI, with clearly defined injury thresholds could be critical for developing simulations and physical surrogates (e.g. crash test dummies) which more accurately reflect the injury risk to the spinal cord not just the spinal column. This specific quantitative feedback is critical for assessing the relative effectiveness of different protective equipment designs (e.g. neck braces, augmented helmets, seat belts) in preventing SCI. In addition, these computational models could be used to assess the relative effects of different mechanical treatment measures (e.g. traction, or surgical decompression) on injury outcomes. Finally, developing subject-specific computational models of SCI provides the opportunity to assess the potential contribution of degenerative changes (e.g. canal narrowing and disc herniation) on SCI outcomes. Subject-specific models also provide an opportunity to understand, quantify, and differentiate the specific loading mechanics at the tissue level which most contribute to injury. This could be valuable for more accurately diagnosing patients on clinical presentation, developing more relevant animal models of injury, or establishing tissue culture surrogates of injury on which experimental therapies can more effectively be tested.

6.3. Contributions and novel findings

The overall goal of this thesis was to better understand and define the role of impact mechanics in SCI. By furthering our knowledge about biomechanical factors that contribute to injury outcomes, we hoped to provide a clinically relevant platform that could
be helpful in designing consistent and reproducible large animal contusion SCIs as well as provide a computational tool to assess the design of injury prevention technologies and to better understand the mechanics of the injury process. However, in order to develop a computational model of SCI, critical advances were needed to improve the assumed material properties on which the model was built. To this end, the specific contributions and novel findings of this dissertation were:

1. The development of a novel constitutive material model for spinal cord white matter that captures the transverse isotropy and tension-compression asymmetry of the material in a single model.

2. A new experimental data set of \textit{in-vitro} compressive response of NHP spinal cord white matter, which presents the material behaviour in a wide range of loading rates as well as high loading rates typical of SCI.

3. The development of FE adaptable constitutive material models for NHP spinal cord white matter which were capable of predicting the material response in high loading rates typical of SCI and the ensuing relaxation behaviour.

4. Validated subject-specific FE models of \textit{in-vivo} open and intact dura contusion SCI that were capable to accurately simulate the experimental biomechanical outcomes.

5. Quantified correlations between tissue level mechanics and tissue damage and determining mechanical metrics with significant potential for predicting tissue damage may facilitate the clinically relevant interpretation of the FE predicted outcomes of contusion SCI.

6.4. Future research directions

Due to difficulties in acquiring and testing the spinal cord tissue, tensile, shear and compressive mechanical tests have not been systematically performed in a single study. In the current study, separate studies were used for the evaluation of spinal cord white matter behaviour (Chapter 3). Using separate studies for evaluation of the material behaviour may not be the ideal method and cause artefactual variability in the modelling results. In addition, the mechanical impact loading on the spinal cord results in a multi-axial loading state, where the material undergoes large deformations in different axis. Therefore, using a uniaxial loading mechanical experiment may not sufficiently characterize the spinal cord constituent materials. Accordingly, comparing uniaxial and biaxial (radial and circumferential) characterization results of dura mater showed that the material constitutive model derived from a biaxial test was more accurate in predicting the
dura mater’s behavior [200]. This suggests that volumetric, biaxial or planar experiments may result in more realistic constitutive models for pia mater. Finally, cervical SCI continues to be the most prevalent type of injury [62], thus, the cervical spinal cord was characterized in this study (Chapter 3 and Chapter 4). However, SCI may generally occur in different cord sections (i.e. thoracic and lumbar) and knowing that the whole spinal cord showed uneven longitudinal strain response to tensile tests [107] suggests that there may be different spinal cord properties at different spinal levels. On this basis, the following future research is recommended:

- Developing a protocol and testing spinal cord constituent materials in different loading directions (i.e. compression, tension and shear) in a systematic method all in a single study under preserved environmental, experimental and methodological conditions.

- Expanding the test protocols to include multi-axial loading scenarios where the samples experience loading such as volumetric loading for gray and white matters or biaxial loading for pia mater.

- Future work is required for characterizing different spinal levels of spinal cord tissue (i.e. thoracic and lumbar) where the anisotropic and asymmetric properties should be investigated.

- The effects of sex on spinal cord mechanical properties have not been investigated. This may also be an important topic for future research specifically in larger animals (e.g. NHPs) where greater inter-animal variability in morphometric characteristics have been observed. In addition, there may be sex differences in the material properties of the spinal cord constituents.

The biomechanical behavior of neurological tissues has been confounded by the high variability in the observed mechanical response of the material (Chapter 4). There may be multiple sources contributing to this variability, such as post-mortem time, inconsistent specimen size, inclined test orientation, experiment ambient temperature, subject age and gender, preconditioning and test logistics [40], [100], [122]. Partial flash freezing of the tissue was shown to reduce the variability in mechanical behaviour by up to 20% without changing the mean mechanical behavior and helped in obtaining 40% less variable sample geometries [97]. Hence, the following future research is recommended:

- Using novel techniques such as flash freezing of the tissue to systematically reduce the variability in experimental results. Augmenting these techniques with recent progresses in data acquisition systems may substantially reduce the undesirable variations in tissue characterization studies specifically in higher strain rate regimes.
In addition, since the CNS in NHPs closely resembles humans, these animals are one of the optimal choices for tissue characterization studies. However, these animals are subjected to ethical challenges and high costs of keeping and caring compared to other animal models (e.g. porcine and rodents). In very low strain rates (~0.5/sec), NHP and porcine spinal cord white matter compressive responses were not significantly different (Chapter 4). The same observation was true when comparing NHP spinal cord white matter higher strain rate (~25/sec) response with porcine brain white matter response in separate studies. The observed similarities suggest that it may be possible to substitute NHPs with other animal models with lower costs and ethical challenges under tight control of the test conditions. However, none of these observations were consistent and due to the differences in experimental environments and protocols it is not possible to confirm these similarities overall. On this basis, the following future research is recommended:

- Developing parallel studies on readily accessible large animals (e.g. porcine and bovine) and NHPs with preserved experimental environment to obtain statistical inference on whether NHPs may be substituted by other animal models or not. Positive results of such a study may substantially reduce the burden of experiments and minimize the use of animals.

Currently, there is an ongoing debate on the effect of timing of surgical decompression on neurological outcome [252], [264], [265]. This lack of agreement among clinicians is particularly due to inability to replicate the high impact velocity with which the human spinal cord is mechanically injured. FE models of SCI may be of great help in this area since they are not restricted to the experimental device limitations. However, to accommodate the proper modeling characteristics, the SCI models critically require spinal cord tissue constituent materials defined at high strain rates typical of SCI. Furthermore, these constitutive models should be capable of accurately capturing long-term behavior of the material. Taken together, the following future research is recommended:

- Characterizing the mechanical viscoelastic behavior of the spinal cord constituent parts (i.e. white and gray matters, pia and dura maters) with the aim of achieving reduced time constants in the range of 0.01-240 seconds.

Recent research suggests that residual compression from the surrounding bone and soft tissues after the initial impact has a noticeable influence on the spinal cord damage [52], [266]. However, in the current state of research most of the studies used simplified SCI models where none of the meninges were included or use linear naive modelling techniques for modelling these tissues [20]. One major difficulty in the
elaborated models is the exponential increase in the computational cost of the simulations when more details are introduced. Though, the following future researches are recommended:

• Devising an effective technique for adding the surrounding meninges such as spinal roots/nerves and fats around spinal canal to FE models without losing computational efficiency. These meninges may be critical in predicting long-term residual compression.

Furthermore, in this study the correlation between FE outcomes and tissue damage were evaluated by assessing the FE results and chronic histology outcomes (Chapter 5). The mechanical impact is mainly responsible for the primary phase of the injury and a cascade of degenerative cellular and immune system responses starts quickly after the impact (secondary injury). The NHP subjects in this study survived for a period of ~20 weeks before the necropsy, which is well beyond the timing of the primary injury (<24 hours). Therefore, the histology slides reflect the contributions of both the primary and secondary injuries. While this makes the FE predictions potentially more clinically relevant, a more accurate evaluation of the direct correlation between tissue mechanics (FE outcomes) and tissue damage requires results of acute SCI. Therefore, the following future research is recommended:

• Performing in-vivo contusion SCI experiments where the subjects are sacrificed quickly after the contusion to ensure minimal confounding effects of secondary injury. Perhaps one optimal method for designing such experiments is using culled animals which will help to reduce the costs and ethical challenges of such experiments. Advanced techniques such as transcardial perfusion of the spinal cords after impact may be considered to minimize the effects of secondary injury in the results (e.g. histology results or post-injury MRIs).

Finally, cervical contusion is the most prevalent pattern of injury in humans [60], [267], however, cervical spinal cord animal models are challenging since the severe lesion caused by a bilateral (complete) contusion can kill the animal or result in severe injuries that are too complex and expensive to care for. As a result, cervical unilateral spinal cord injuries have been developed [3], [76]; however, they are limited by significant variability and bulk cord movement during the contusion impact. For the unilateral contusion injury models to provide a reliable platform for pre-clinical trials, these models are required to be characterized and standardized which requires generating consistent, equivalent, repeatable and reproducible injury on the animals. To achieve this goal, a better
understanding of the contributing factors to experimental variability are essential; therefore, the following study is recommended:

- A comprehensive parametric analysis of the effects of impactor mediolateral alignment, impactor shape, impactor size, angle and rate of approach, spinal cord trapping depth and speed, positioning and preload on the resulting contusion injury in subject-specific FE models of unilateral contusion SCI. The relationship between impact mechanics and the resulting injury outcomes is important for better understanding of the potential sources of variation in contusion model outcomes, and for improving the reproducibility of these animal models.

6.5. Concluding remarks

Traumatic SCI initiates a series of complex irreversible pathophysiological processes that may eventually result in permanent tissue damage, persistent loss of neurologic function and behavioural impairment. Through this work, the significance of accounting for spinal cord anisotropy and distinct modelling of spinal cord constituent parts on tissue level mechanics under contusion SCI were determined. The compressive response of the NHP spinal cord white matter were characterized and the results illustrated substantial stiffening of the material at high loading rates typical of traumatic SCI that has never been visualized before. Finally, utilizing the new constitutive models, subject-specific models of NHP contusion SCI were generated and revealed strong correlations between tissue level stresses and strains and tissue damage. The work described herein provides new experimental data and represents a thorough analysis of the correlation between tissue level mechanics and tissue damage during the SCI that is critical for further development of computational models of SCI that are limited by lack of adequate material characterization. However, the most important message of this study is that generating consistent, reproducible SCIs in large animal models of SCI (pigs, NHPs, etc.), where considerable inter-species variabilities exists, highly likely requires subject-specific modelling and injury parameter characterization. The individualized FE models generated based on pre-injury MRIs provide an invaluable data set that might be used to calibrate the experimental biomechanical parameters and improve pre-surgery planning.
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Appendix A.

TENSOR ALGEBRA

In this appendix mathematical definitions, matrix formulations and notations relevant in this dissertation are defined.

Tensor product. The tensor product or *dyad* is denoted by $\otimes$ and is widely used in matrix calculations. A second order tensor may be represented as the tensor product of basis unit vectors,

\[
\mathbf{A} = A_{ij} e_i \otimes e_j = \begin{bmatrix} A_{11} & A_{12} & A_{13} \\ A_{21} & A_{22} & A_{23} \\ A_{31} & A_{32} & A_{33} \end{bmatrix}
\]

In case of two vectors $\mathbf{u}$ and $\mathbf{v}$, it is convenient to show the tensor product as,

\[
\mathbf{u} \otimes \mathbf{v} = \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix} \begin{bmatrix} v_1 & v_2 & v_3 \end{bmatrix} = \begin{bmatrix} u_1 v_1 & u_1 v_2 & u_1 v_3 \\ u_2 v_1 & u_2 v_2 & u_2 v_3 \\ u_3 v_1 & u_3 v_2 & u_3 v_3 \end{bmatrix}
\]

Similarly, the tensor product of two second order tensors (say $\mathbf{A}$ and $\mathbf{B}$) (Equation A-3), the result is a fourth order tensor (Equation A-4).

\[
\mathbf{A} = \begin{bmatrix} A_{11} & A_{12} & A_{13} \\ A_{21} & A_{22} & A_{23} \\ A_{31} & A_{32} & A_{33} \end{bmatrix} ; \quad \mathbf{B} = \begin{bmatrix} B_{11} & B_{12} & B_{13} \\ B_{21} & B_{22} & B_{23} \\ B_{31} & B_{32} & B_{33} \end{bmatrix}
\]

\[
\mathbf{A} \otimes \mathbf{B} = \begin{bmatrix} A_{11} & A_{12} & A_{13} \\ A_{31} & A_{32} & A_{33} \end{bmatrix} \otimes \begin{bmatrix} B_{11} & B_{12} & B_{13} \\ B_{31} & B_{32} & B_{33} \end{bmatrix}
\]

\[
\rightarrow \quad \mathbf{A} \otimes \mathbf{B} = \begin{bmatrix} A_{11} & B_{11} & B_{21} & B_{31} \\ A_{12} & B_{12} & B_{22} & B_{32} \\ A_{13} & B_{13} & B_{23} & B_{33} \\ A_{21} & B_{21} & B_{31} \\ A_{22} & B_{22} & B_{32} \\ A_{23} & B_{23} \\ A_{31} & B_{31} \\ A_{32} & B_{32} \\ A_{33} & B_{33} \end{bmatrix}
\]

Followin the representation for second order tensor in terms of base unit vectors (Equation A-1), a fourth order tensor ($\mathbb{A}$) may be also represented by tensor product of base units as,
On this basis, the fourth-order identity tensor, \( \mathbb{I} \), is defined and represented as,
\[
\mathbb{I} = \delta_{ij} \delta_{kl} e_i \otimes e_k \otimes e_l = e_l \otimes e_j \otimes e_i \otimes e_j =
\begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}
\]

**Double contraction.** In symbolic notation double contraction is characterized by double dot and is an operation between two tensors (Equation A-3) which yields a scalar,
\[
A : B = \text{tr}(A^T B) = \text{tr}(B^T A) = \text{tr}(BA^T) = \text{tr}(AB^T) = B : A
\]

For the case of second order tensors, the double dot contraction is formulated as,
\[
A : B = \text{tr} \begin{bmatrix}
A_{11}B_{11} + A_{12}B_{12} + A_{13}B_{13} \\
\sim A_{21}B_{21} + A_{22}B_{22} + A_{23}B_{23} \\
\sim A_{31}B_{31} + A_{32}B_{32} + A_{33}B_{33}
\end{bmatrix}
\]

In the special case of double contraction of a second-order tensor by forth-order identity tensor (Equation A-6), the result is,
\[
\mathbb{I} : B = B
\]
Matrix algebra. Some important matrix algebraic formulations are presented in this section, for the detailed derivation of the formulations the reader is referred to[153].

For a smooth scalar function \( \Phi \) and \( A \) smooth tensor value function of \( B \), the following properties hold,

\[
\frac{\partial (\Phi A)}{\partial B} = A \otimes \frac{\partial \Phi}{\partial B} + \Phi \frac{\partial A}{\partial B}
\]

\( (A \otimes B)^T = B \otimes A \)

\( (A \otimes B) : C = A(B : C) = (B : C)A \)

\( A : (B \otimes C) = (A : B)C = C(A : B) \)
Appendix B.

CONTINUUM EQUATIONS

In this appendix, all the assumptions and fundamental equations have been presented. The following assumptions were effective throughout this dissertation unless declared otherwise:

- All tensor quantities were in Cartesian system.
- Whenever indicial notations were employed, the lower-case letters denote the deformed configuration (e.g. \( x \)) and upper-case letters referred to the reference configuration (e.g. \( X \)).
- The bolded letters showed tensors or vectors

All transformations in this dissertation were assumed to happen in the space of linear transformations (Equation B-1),

\[
\text{Lin} = \text{space of all linear transformations from } \mathbb{R}^3 \text{ into } \mathbb{R}^3 \tag{B-1}
\]

**Deformation gradient**

If the initial position of a particle in a structure reference configuration \( \Omega_0 \) is designated by the vector \( X \in \mathbb{R}^3 \), the position of the same particle in the deformed (or current) configuration of the structure, \( \Omega \), may be defined by the mapping function (Equation B-2),

\[
x = \varphi(X, t) \quad \text{with} \quad \varphi : \Omega_0 \to \mathbb{R}^3 \tag{B-2}
\]

where \( x \) is the current position of the particle. The mapping for two neighbouring particles which are initially located at \( X \) and \( X + dX \) gives the current location of the two particles at \( x \) and \( x + dx \) respectively, where the \( dx \) is obtained from the chain rule as (Equation B-3),

\[
dx = \frac{\partial \varphi(X, t)}{\partial X} \, dX \tag{B-3}
\]

By definition, the matrix \( \frac{\partial \varphi}{\partial X} \) is called the deformation gradient tensor, \( F \) (Equation B-4). It is assumed that the deformations of solids are completely described by deformation gradient and it is a primary measure of deformation.
Further, the volume of a parallelepiped in the reference undeformed configuration bounded by three line-elements $dX^{(i)} (i = 1 - 3)$ is determined by,

$$dV = dX^{(1)} . (dX^{(2)} \times dX^{(3)})$$  (B-5)

Right after deformation, the volume element is bounded by the three deformed vectors $dx^{(i)}$. Using matrix calculus and deformation gradient definition (Equation B-4), the deformed volume can be determined (Equation B-6).

$$dv = dx^{(1)} . (dx^{(2)} \times dx^{(3)})$$
$$= FdX^{(1)} . (FdX^{(2)} \times FdX^{(3)})$$
$$= detF \left( dX^{(1)} . (dX^{(2)} \times dX^{(3)}) \right)$$
$$= detFdV$$  (B-6)

where $det$ denotes the determinant of the deformation gradient, known as Jacobian determinant, $J$, or volume ratio (Equation B-7),

$$J \equiv det F ; \quad dv = JdV$$  (B-7)

In general, the tensor $F$ contains rigid body rotations together with deformations of the material. If the displacements at all points on an object are the same, then it is undergoing rigid body displacement and there are no deformations and therefore no strains, stresses, fatigue, etc. However, rigid body rotations are a subset of rigid body displacements that can incorrectly appear as strains if they are not treated properly. The polar decomposition concept was introduced to enable the differentiation of rigid body rotations.

**Polar decomposition and stretch tensors**

A fundamental theorem in continuum mechanics is that any motion characterized by a deformation gradient tensor, $F(X, t)$ (Equation B-4), can uniquely be decomposed into a pure stretch and a pure rotation tensor (Equation B-8).
both $U$ and $v$ are unique, positive definite and symmetric tensors. By definition, $U$ is the right stretch tensor, and $v$ is the left stretch tensor. Using the polar decomposition (Equation B-8) and some math, right and left Cauchy-Green deformation tensors are be defined as follows,

$$\mathbf{C} \triangleq \mathbf{F}^T \mathbf{F} = (\mathbf{RU})^T (\mathbf{RU}) = \mathbf{U}^T \mathbf{R}^T \mathbf{R} \mathbf{U} = \mathbf{U}^T \mathbf{I} \mathbf{U} = \mathbf{U}^T \mathbf{U}$$

and similarly,

$$\mathbf{b} \triangleq \mathbf{F} \mathbf{F}^T = \mathbf{v} \mathbf{v}^T$$

These deformation tensors contain the strain part of the deformation only and the unwanted rigid body rotations are eliminated. Both right and left Cauchy-Green deformation tensors are symmetric and positive definite[268]. The right Cauchy-Green deformation tensor ($\mathbf{C}$) is in the reference configuration and the left Cauchy-Green deformation tensor ($\mathbf{b}$) is in the current configuration.

**Hyperelastic materials**

For a material with a certain symmetry group (e.g. transverse isotropy) the proper constitutive modelling task is to determine how the restriction imposed by the symmetry affects the material response. A hyperelastic material by definition is a grade one elastic material with one additional condition. A first grade elastic material is a material that [165], [269],

- Has a stress response that corresponds to the first gradient of deformation or in other words the stress at a point in the deformed configuration $\mathbf{x} = \varphi(\mathbf{X}, t)$ is only a function of the deformation gradient $\mathbf{F}$ at that point.
- Stress changes are corresponding to configuration changes.
- Is indifferent to the history of the deformation (i.e. time and the manner the deformation was applied).

In addition to the above conditions, a hyperelastic material has a scalar function associated to it from which the stress can be derived at each point of the reference configuration ($\mathbf{X}$),

$$\psi(\mathbf{X}, \mathbf{F}) : \Omega \times Lin^+ \rightarrow \mathbb{R}$$

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where $\text{Lin}^+$ is the space of all linear transformations in $\text{Lin}$ (Equation B-1) where the determinant of the linear transformation is positive. The scalar function is the strain energy function and must be indifferent to the material frame [165]. In this dissertation, the attention is restricted to homogeneous materials and therefore, any orthogonal transformation to the deformation gradient must hold the same strain energy function,

$$\psi(X, F) = \psi(X, QF) \quad \forall (Q, F) \in \text{Orth}^+ \times \text{Lin}^+$$

where $\text{Orth}^+$ is the space of all orthogonal linear transformations in $\text{Lin}^+$.

**Stress measures**

Different measures of stress have been introduced to describe the material stress-strain state. A key discriminator among the different stress tensors is whether they report the stress in a material's undeformed, and unrotated state (reference configuration), or in its deformed and rotated state (current configuration). All stress definitions come in pairs with a corresponding strain tensor such that the product of the two will give the strain energy of the deformation. This does not mean that the corresponding pairs must be used together when performing structural analyses, however, they must be in pairs while computing strain energy density.

Based on Cauchy’s stress theorem the Cauchy or true stress is equal to the traction vector,

$$\mathbf{t} = \mathbf{\sigma} \cdot \mathbf{n} = \lim_{dA \to 0} \frac{d\mathbf{f}_j^{(n)}}{dA}$$

where $\mathbf{t}$ is the traction, $\mathbf{n}$ is the normal to the surface in the deformed configuration, $A$ is the deformed surface and $\mathbf{\sigma}$ is the symmetric Cauchy stress tensor. If the tractions in the deformed body are considered relative to an oriented area vector in the reference configuration, the 1st Piola-Kirchhoff traction vector in the reference configuration is defined (Equation B-14), which is the internal force vector over scalar cross-section area in the reference configuration.

$$\mathbf{T} = \mathbf{P} \cdot \mathbf{N}$$

where $\mathbf{P}$ is the 1st Piola-Kirchhoff stress tensor, and $\mathbf{N}$ is the outward unit normal. The 1st Piola-Kirchhoff stress (Equation B-14) and Cauchy stress tensors (Equation B-13) are related with,
\[ P = J \sigma \cdot F^{-T} \]  

The term \( J \sigma \) is widely used in analysis of incompressible materials and is called the (spatial) Kirchhoff stress,

\[ \tau = J \sigma \]

Another measure to quantify the stress is the 2nd Piola-Kirchhoff tensor. Although there is a lack of straightforward physical interpretation, but the source of this definition is to relate forces and deformations in the reference configuration,

\[ S = J F^{-1} \cdot \sigma \cdot F^{-T} \]

Mathematical relations between the Cauchy stress, 1st Piola-Kirchhoff stress and 2nd Piola-Kirchhoff stress might be useful,

\[ \sigma = J^{-1} P \cdot F^T \quad ; \quad \sigma = J^{-1} F \cdot S \cdot F^T \quad ; \quad P = F \cdot S \]

**Stress-deformation relation**

For a hyperelastic material, the 1st Piola-Kirchhoff stress have expression of the form,

\[ P = \frac{\partial \psi(F)}{\partial F} \]

where \( \psi \) is the strain energy function, and the 2nd Piola-Kirchhoff stress (Equation B-17) is derived based on right Cauchy-Green deformation tensor (Equation B-9) as,

\[ S = 2 \frac{\partial \psi}{\partial \mathcal{C}} \]

The relations obtained above provide an empirical model for approximating the real material behaviour and are called *material constitutive models.*
Appendix C.

UNIAXIAL LOADING MODE

A commonly accepted approach for characterizing materials is to perform uniaxial tensile or compressive tests on them. These experiments provide the material stress-strain behavior which can be used to determine the specific material constants for the material [40], [181], [182], [270]. In this section, detailed formulations of stress components are determined for the specific case of uniaxial loading. These formulations will later be used in fitting algorithms and optimization process for characterizing corresponding materials.

For a transversely isotropic material with directional anisotropy (e.g. bundles of aligned fibres) in direction “1” of an arbitrary cartesian coordinate system, the following unit vector $A_0$ can represent the fibre direction,

$$A_0 = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}$$

C-1

If this material undergoes a uniaxial deformation in the direction of axis “1”, the deformation gradient matrix (Equation B-4) will be,

$$F = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix}$$

C-2

Using definitions for modified deformation gradient and modified principal stretch, the deviatoric part of the deformation gradient (note that the modified deformation gradient represents the deviatoric part of the deformation) is determined as,

$$\bar{F} = J^{-1/3} \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} = \begin{bmatrix} J^{-1/3} \lambda_1 & 0 & 0 \\ 0 & J^{-1/3} \lambda_2 & 0 \\ 0 & 0 & J^{-1/3} \lambda_3 \end{bmatrix} = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix}$$

C-3

where the $\tilde{\lambda}_i$’s ($i = 1,2,3$) are the deviatoric principal stretches (or modified principal stretches). For the case of a transversely isotropic material $\tilde{\lambda}_2 = \tilde{\lambda}_3$, therefore, since $det\bar{F}$ is equal to one, $\tilde{\lambda}_2$ and $\tilde{\lambda}_3$ can be obtained as,
\[ \bar{\lambda}_1 \bar{\lambda}_2 \bar{\lambda}_3 = 1 \Rightarrow \bar{\lambda}_2 = \bar{\lambda}_3 = \bar{\lambda}_1^{-1/2} \]

For the sake of convenience, from now on in this section, the stretch in the uniaxial direction (\(\bar{\lambda}_1\)) will be denoted by \(\bar{\lambda}_U\), so the deformation gradient (Equation C-3) becomes,

\[
\bar{F} = \begin{bmatrix}
\bar{\lambda}_U & 0 & 0 \\
0 & \bar{\lambda}_U^{-1/2} & 0 \\
0 & 0 & \bar{\lambda}_U^{-1/2}
\end{bmatrix}
\]

and simply, the isochoric right Cauchy-Green deformation tensor will be obtained as,

\[
\bar{\mathbf{C}} = \begin{bmatrix}
\bar{\lambda}_U^2 & 0 & 0 \\
0 & \bar{\lambda}_U^{-1} & 0 \\
0 & 0 & \bar{\lambda}_U^{-1}
\end{bmatrix}
\]

The isochoric right Cauchy-Green tensor invariants may then be determined based on the modified right Cauchy-Green tensor (Equation C-6),

\[
\bar{I}_1 = tr \bar{\mathbf{C}} = \bar{\lambda}_U^2 + \frac{2}{\bar{\lambda}_U}
\]

\[
\bar{I}_2 = \frac{1}{2}[(tr \bar{\mathbf{C}})^2 - tr \bar{\mathbf{C}}^2] = 2\bar{\lambda}_U + \frac{1}{\bar{\lambda}_U^2}
\]

\[
\bar{I}_4 = A_0 \cdot \bar{\mathbf{C}} \cdot A_0 = \bar{\lambda}_U^2
\]

\[
\bar{I}_5 = A_0 \cdot \bar{\mathbf{C}}^2 \cdot A_0 = \bar{\lambda}_U^4
\]

In the process of fitting experimental results to find the best fit material parameters, it is useful to calculate the 1\textsuperscript{st} Piola-Kirchhoff stress (or engineering stress) instead of 2\textsuperscript{nd} Piola-Kirchhoff stress since engineering strains are easier to measure in the experimental tests. Therefore, using the relation between different stress measures (Equation B-18) the 1\textsuperscript{st} Piola-Kirchhoff stress can be derived from the 2\textsuperscript{nd} Piola-Kirchhoff stress for an isotropic material,

\[
\bar{P} = \bar{F} \cdot \bar{S} = 2J^{2/3} \bar{F} \left[ \left( \frac{\partial \bar{\mathbf{U}}}{\partial \bar{I}_1} + \frac{\partial \bar{\mathbf{U}}}{\partial \bar{I}_2} \bar{I}_1 \right) \bar{I} - \frac{\partial \bar{\mathbf{U}}}{\partial \bar{I}_2} \bar{C} - \frac{1}{3} \left( \frac{\partial \bar{\mathbf{U}}}{\partial \bar{I}_1} \bar{I}_1 + 2 \frac{\partial \bar{\mathbf{U}}}{\partial \bar{I}_2} \bar{I}_2 \right) \bar{\mathbf{C}}^{-1} \right] + p \bar{F} \cdot \bar{C}^{-1}
\]
knowing that \( F = J^{1/3} \overline{F} \) and \( C^{-1} = J^{-2/3} \overline{C}^{-1} \), the 1st Piola-Kirchhoff stress (Equation C-11) becomes,

\[
P = 2J^{-1/3} \left[ \left( \frac{\partial \overline{U}}{\partial I_1} + \frac{\partial \overline{U}}{\partial I_2} \overline{I}_2 \right) \overline{F} - \frac{\partial \overline{U}}{\partial I_1} \overline{F} \overline{C} - \frac{1}{3} \left( \frac{\partial \overline{U}}{\partial I_1} \overline{I}_1 + 2 \frac{\partial \overline{U}}{\partial I_2} \overline{I}_2 \right) \overline{F} \overline{C} \right] + pJ^{2/3} \overline{F} \overline{C}^{-1} \quad \text{(C-12)}
\]

Derivitives of the strain energy function \( \overline{U} \) with respect to the modified right Cauchy-Green tensor invariants can be obtained using the chain rule and some math as,

\[
\frac{\partial \overline{U}}{\partial I_1} = \frac{\partial \overline{U}}{\partial \lambda_U} \frac{\partial \lambda_U}{\partial I_1} = \frac{1}{2} \frac{\partial \overline{U}}{\partial \lambda_U} \frac{1}{\lambda_U - \lambda_U^{-2}} \quad \text{(C-13)}
\]

\[
\frac{\partial \overline{U}}{\partial I_2} = \frac{\partial \overline{U}}{\partial \lambda_U} \frac{\partial \lambda_U}{\partial I_2} = \frac{1}{2} \frac{\partial \overline{U}}{\partial \lambda_U} \frac{\lambda_U}{\lambda_U - \lambda_U^{-2}} \quad \text{(C-14)}
\]

consequently, if the 1st Piola-Kirchhoff stress (Equation C-12) is divided into four components for detailed derivation,

\[
P = 2J^{-1/3} \left( \frac{\partial \overline{U}}{\partial I_1} + \frac{\partial \overline{U}}{\partial I_2} \overline{I}_2 \right) \overline{F} - 2J^{-1/3} \frac{\partial \overline{U}}{\partial I_2} \overline{F} \overline{C}
\]

\[
-\frac{2}{3} J^{-1/3} \left( \frac{\partial \overline{U}}{\partial I_1} + 2 \frac{\partial \overline{U}}{\partial I_2} \overline{I}_2 \right) \overline{F} \overline{C}^{-1} + pJ^{2/3} \overline{F} \overline{C}^{-1} \quad \text{(C-15)}
\]

each of the components are determined using definitions of modified deformation gradient, isochoric right Cauchy-Green deformation tensor, the invariants and their corresponding derivatives,

\[
I \equiv 2J^{-1/3} \left( \frac{\partial \overline{U}}{\partial I_1} + \frac{\partial \overline{U}}{\partial I_2} \overline{I}_2 \right) \overline{F} = J^{-1/3} \left[ \frac{\partial \overline{U}}{\partial \lambda_U} \frac{\lambda_U^3}{\lambda_U - \lambda_U^{-2}} \right]
\]

\[
0 \quad 0 \quad 0
\]

\[
\boxed{\begin{bmatrix} \hat{\lambda}_U & 0 & 0 \\ 0 & \hat{\lambda}_U^{-1/2} & 0 \\ 0 & 0 & \hat{\lambda}_U^{1/2} \end{bmatrix}} \quad \text{(C-16)}
\]

\[
II \equiv 2J^{-1/3} \frac{\partial \overline{U}}{\partial I_2} \overline{F} \overline{C} = J^{-1/3} \frac{\partial \overline{U}}{\partial \lambda_U} \frac{\lambda_U^3}{\lambda_U - \lambda_U^{-2}} \left[ \hat{\lambda}_U \quad 0 \\ 0 & \hat{\lambda}_U^{-3/2} & 0 \\ 0 & 0 & \hat{\lambda}_U^{-3/2} \right]
\]

\[
\boxed{\begin{bmatrix} \hat{\lambda}_U^3 & 0 & 0 \\ 0 & \hat{\lambda}_U^{-3/2} & 0 \\ 0 & 0 & \hat{\lambda}_U^{-3/2} \end{bmatrix}} \quad \text{(C-17)}
\]
\[ III \equiv \frac{2}{3} J^{-1/3} \left( \frac{\partial \bar{U}}{\partial \bar{x}_1} \bar{I}_1 + 2 \frac{\partial \bar{U}}{\partial \bar{x}_2} \bar{I}_2 \right) \bar{F} \bar{C}^{-1} = J^{-1/3} \frac{\partial \bar{U}}{\partial \bar{\lambda}_U} \frac{5}{3} \bar{\lambda}_U^{2/3} + \frac{2}{3} \bar{\lambda}_U^{-1} \frac{\bar{\lambda}_U^{1/2}}{\bar{\lambda}_U^{1/3}} \begin{bmatrix} \bar{\lambda}_U^{-1} & 0 & 0 \\ 0 & \bar{\lambda}_U^{1/2} & 0 \\ 0 & 0 & \bar{\lambda}_U^{1/2} \end{bmatrix} \]

\[ IV \equiv pj^{2/3} \bar{F} \bar{C}^{-1} = pj^{2/3} \begin{bmatrix} \bar{\lambda}_U^{-1} & 0 & 0 \\ 0 & \bar{\lambda}_U^{1/2} & 0 \\ 0 & 0 & \bar{\lambda}_U^{1/2} \end{bmatrix} \]

summing up the components (Equations C-16 to C-19), the 1\textsuperscript{st} Piola-Kirchhoff stress (Equation C-15) becomes,

\[ P = \begin{bmatrix} \bar{\lambda}_U^{-1} & 0 & 0 \\ 0 & \bar{\lambda}_U^{1/2} & 0 \\ 0 & 0 & \bar{\lambda}_U^{1/2} \end{bmatrix} \begin{bmatrix} \frac{4}{3} & 0 & 0 \\ 0 & \frac{2}{3} \bar{\lambda}_U^{3/2} & 0 \\ 0 & 0 & \frac{2}{3} \bar{\lambda}_U^{3/2} \end{bmatrix} \begin{bmatrix} \bar{\lambda}_U^{-1} & 0 & 0 \\ 0 & \bar{\lambda}_U^{1/2} & 0 \\ 0 & 0 & \bar{\lambda}_U^{1/2} \end{bmatrix} \]

\[ C-20 \]

the reader is noted that in a uniaxial loading mode, the stress components in two off-axis directions are zero,

\[ P_{22} = P_{33} = 0 \]

By determining the stress components from the 1\textsuperscript{st} Piola-Kirchhoff stress formulation (Equation C-20),

\[ P_{22} = P_{33} = -\frac{2}{3} J^{-1/3} \frac{\partial \bar{U}}{\partial \bar{\lambda}_U} \bar{\lambda}_U^{3/2} + pj^{2/3} \bar{\lambda}_U^{1/2} = 0 \]

\[ C-22 \]

and the hydrostatic term, \( p \), in the 1\textsuperscript{st} Piola-Kirchhoff stress formulation (Equation C-20) will be determined as,

\[ p = \frac{2}{3} J^{-1} \frac{\partial \bar{U}}{\partial \bar{\lambda}_U} \bar{\lambda}_U \]

\[ C-23 \]

now, substituting back hydrostatic term (Equation C-23) in the 1\textsuperscript{st} Piola-Kirchhoff stress (Equation C-20), the axial component of the 1\textsuperscript{st} Piola-Kirchhoff stress will be,

\[ P_{11} = 2J^{-1/3} \frac{\partial \bar{U}}{\partial \bar{\lambda}_U} \]

\[ C-24 \]
Transverse isotropy in uniaxial loading mode

Following the same procedure as the one presented for a transversely isotropic strain energy function and applying the uniaxial constraint, the 1\textsuperscript{st} Piola-Kirchhoff stress for a transversely isotropic material becomes,

\[ P_{11} = 4J^{-1/3} \frac{\partial U}{\partial \lambda U} \]  

Uniaxial mode loading viscoelastic formulation

As discussed earlier, uniaxial mode loading is used to serve as a basis for fitting theory and experiments findings and determining the associated material parameters. Using the volumetric-isochoric split for the strain energy function, the axial component of the 1\textsuperscript{st} Piola-Kirchhoff stress for an isotropic material will be,

\[ P_{11}(t) = 2J^{-1/3} \frac{\partial}{\partial \lambda U} \int_0^t (1 - \sum_{i=1}^N g_i (1 - e^{-(t-\tau)/\tau_i})) \frac{dU}{d\tau} d\tau \]  

or,

\[ P_{11}(t) = 2J^{-1/3} \int_0^t \left\{ (1 - \sum_{i=1}^N g_i (1 - e^{-(t-\tau)/\tau_i})) \frac{d}{d\tau} \left[ \frac{\partial U}{\partial \lambda U} \right] \right\} d\tau \]  

and using the same process for transverse isotropic material, the axial component of the 1\textsuperscript{st} Piola-Kirchhoff stress for a transversely isotropic material becomes,

\[ P_{11}(t) = 4J^{-1/3} \int_0^t \left\{ (1 - \sum_{i=1}^N g_i (1 - e^{-(t-\tau)/\tau_i})) \frac{d}{d\tau} \left[ \frac{\partial U}{\partial \lambda U} \right] \right\} d\tau \]