Mechanics of blast-induced traumatic brain injury in porcine brain tissue

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Mechanics of blast-induced traumatic brain injury in porcine brain tissue

by

Annastacia Kay McCarty

A thesis submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

Major: Mechanical Engineering

Program of Study Committee:
Sarah A. Bentil, Major Professor
Meng Lu
Pranav Shrotriya

The student author, whose presentation of the scholarship herein was approved by the program of study committee, is solely responsible for the content of this thesis. The Graduate College will ensure this thesis is globally accessible and will not permit alterations after a degree is conferred.

Iowa State University
Ames, Iowa
2020

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DEDICATION

I dedicate this thesis to my family for their love and support. I appreciate all that you do.
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ACKNOWLEDGMENTS

I would like to thank all who assisted in this work. I would like to thank my advisor, Dr. Sarah Bentil, for her guidance and assistance throughout my time working with her, from the process of designing experiments to revising manuscripts. I also would like to thank William Jackson for all of his dedication and assistance through many iterations of designing experiments in order to collect quality data. I would also like to thank my committee members for their time serving on my committee: Dr. Meng Lu and Dr. Pranav Shrotriya.
ABSTRACT

Blast-induced traumatic brain injury (bTBI) often results from the detonation of improvised explosive devices (IEDs) in war settings. However, the material properties of the brain and their changes during and after bTBI are currently not well understood. Characterizing brain tissue is challenging due to the inhomogeneous and anisotropic properties of the tissue and the brain’s enclosure in the skull. Thus, this research is focused on experimentally quantifying the mechanical properties of brain tissues exposed to a blast wave. Specifically, the effects of swelling from storage solution and blast impact were investigated by exposing whole porcine brains to shock waves generated from an air pistol and allowing whole porcine brains to soak in saline solution. The mechanical properties of the brain tissue were quantified in a stress relaxation experiment in which the tissue was compressed to 80% of its original height at a rate of 5 mm/min, 50 mm/min, or 500 mm/min and then held for two minutes. The work from this thesis will increase understanding of the dynamic mechanical behavior of brain tissue. Results describing the brain’s response to shock waves will further knowledge of bTBI mechanisms, which will facilitate the design of effective countermeasures to prevent and protect against blast-induced traumatic brain injury.
CHAPTER 1. INTRODUCTION

Between 2008 and 2018, over 304,000 United States service members were diagnosed with a form of blast-induced traumatic brain injury (bTBI) as a result of the detonation of an IED in a war setting (Defense and Veterans Brain Injury Center, 2018). When an IED is detonated, a shock wave, or a discontinuous increase in pressure and density, travels through the atmosphere (Bass et al., 2012; Ling et al., 2009). The pressure increase lasts less than 100 milliseconds before returning to the ambient pressure (Bass et al., 2012; Greve and Zink, 2009). The wave not only transmits through air or water, but also propagates through objects in its path, including the head of an individual. The resulting injury in the brain from the shock wave is called a primary bTBI (Chen et al., 2009; Gupta and Przekwas, 2013; Kovacs et al., 2014; Nakagawa et al., 2011). The shock wave can cause damage to neuronal and glial cells by breaking and tearing intermolecular bonds and result in inflammation of the tissue (Ahmed et al., 2012; Gupta and Przekwas, 2013; Shively et al., 2016; Sosa et al., 2013).

Even with the current prevalence of brain injury due to blast impact, military helmets in use today are designed to protect the head from penetrating impact, not blast impact (Ling et al., 2009; Gupta and Przekwas, 2013). The Advanced Combat Helmet (ACH), used since 2003, offers increased energy absorption ability relative to its predecessor, yet still only covers the top of the wearer’s head (Gupta and Przekwas, 2013; Kovacs et al., 2014; Moss et al., 2009; Przekwas et al., 2011). As a result, the wearer’s face, sides, and back of the head are left directly exposed to blast waves, the areas most likely to directly transmit load to the brain (Gupta and Przekwas, 2013; Moss et al., 2009; Nyein et al., 2010). During blast wave exposure simulations, when the wave originated perpendicular to a subject’s face, the current military helmet offered only a slight reduction in intracranial stresses relative to no helmet at all (Mott et al., 2008; Nyein et al., 2010). Thus, it would be valuable to design helmets that can protect against primary bTBI. However,
the mechanics of primary bTBI are not currently well understood, limiting the ability to test the efficacy of a helmet.

As a result, this work focuses on experimentally quantifying the behavior of brain tissue during and after bTBIs. Within this goal, the effects of swelling from the storage solution used to preserve the brain and the effect of the blast impact on the mechanical properties of brain tissue were investigated. Whole porcine brains were exposed to shock waves generated from an air pistol connected to a 1/2-in. (12.7 mm) polyvinyl chloride (PVC) pipe which was aimed at the porcine brain. Further, porcine brains were placed in a container with 200 mL of 0.9% saline solution and allowed to soak, and swell, for a varied length of time. Four sets of experiments were performed such that a given brain could either be both exposed to the shock wave and then soaked, only exposed to the shock wave, only soaked, or neither exposed to the shock wave nor soaked before testing the mechanical properties. Once a brain was exposed to the shock wave and/or soaked, as prescribed by the experiment, tissue samples were prepared by coring a 25-mm cylinder of tissue from each hemisphere of the brain. A stress-relaxation experiment was performed on the sample by compressing the tissue to 80% of its original height at a rate of 5 mm/min, 50 mm/min, or 500 mm/min. Once compressed, the 20% strain rate was held for 2 minutes. The mechanical properties of the brain tissue were then quantified using the four-parameter fractional Zener constitutive model, where \( E_\infty \) represents the long-term stiffness, \( E_0 \) the brain’s instantaneous modulus, \( \tau_0 \) the relaxation time, and \( \alpha \) illustrates the brain tissue’s location on the viscoelastic spectrum such that \( \alpha = 0 \) is equivalent to an elastic solid and \( \alpha = 1 \) is equivalent to a Newtonian liquid.

Subsequent chapters in this thesis, describing the progression of this research, are as follows:

- Chapter 2 describes how the mechanical properties of the brain are influenced by saline solution absorption and compressive rate.

- Chapter 3 studies the effect of shock wave exposure on the mechanical properties of brain tissue.

- Chapter 4 summarizes and discusses the conclusions from this thesis.
1.1 References


Defense and Veterans Brain Injury Center (2018). DoD worldwide numbers for TBI. *DVBIC*.


CHAPTER 2. INFLUENCE OF SALINE SOLUTION ABSORPTION AND COMPRESSIVE RATE ON THE MATERIAL PROPERTIES OF BRAIN TISSUE

A paper published in the *Journal of the Mechanical Behavior of Biomedical Materials*
(doi: 10.1016/j.jmbbm.2019.05.028)
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2.1 Abstract

Traumatic brain injuries (TBI) affect millions of people each year and can result in long-term difficulties in thinking or focusing. Due to the number of people affected by these injuries, significant research has been dedicated to determining the mechanical properties of the brain using *postmortem* tissue from animals harvested within 24 hours. The *postmortem* brain tissue is often stored in a solution until a rheological experiment is ready to begin. However, the effect of storage duration on the mechanical behavior of brain tissue is not understood. In this paper, *postmortem* porcine brains were placed in normal saline solution (0.9% NaCl) and refrigerated between 30 minutes and 6.5 hours to allow the brain to absorb the solution. Afterwards, samples from both soaked and freshly extracted brains were subjected to unconfined compression tests at compressive rates of 5, 50, and 500 mm/min. The fractional Zener viscoelastic model was applied to obtain the brain’s mechanical properties. While the results did not show a significant relationship between absorption and the long-term stiffness ($E_\infty$), both the relaxation time ($\tau_0$) and fractional order ($\alpha$) were statistically influenced by both the length of time in the solution and compressive rate. Further,
the instantaneous stiffness \(E_0\) was statistically influenced by the length of time in solution, though not the compressive rate.

### 2.2 Introduction

Each year, millions of people around the world sustain a traumatic brain injury (TBI) due to blunt trauma to the head from contact sports (e.g. football) or vehicle collisions, or blast trauma from detonated improvised explosive devices (IEDs) in a war setting. The United States Department of Defense estimates that 383,947 service members were diagnosed with a form of TBI between January 2008 and March 2018 (Defense and Veterans Brain Injury Center, 2018). Outside of the military, TBIs account for an estimated annual 1.365 million emergency room visits and 275,000 hospitalizations (Daneshvar et al., 2011).

While the severity of a TBI can vary, up to 75% of all TBIs are classified as mild (National Center for Injury Prevention and Control, 2003). The National Center for Injury Prevention and Control (2003) defines a mild TBI as an injury resulting in one or more of the following: a temporary period of confusion or disorientation, memory loss around the time of injury, or a loss of consciousness less than 30 minutes. However, even when the injury is classified as mild, the patient may experience long-term disabilities and have difficulties resuming normal activities and work (National Center for Injury Prevention and Control, 2003). TBIs in a given year are estimated to result in an economic burden exceeding $60 billion dollars when considering direct medical costs and loss of future earnings (Daneshvar et al., 2011). Patients who were employed at the time of a mild TBI experienced unemployment rates of 34% and 9%, three and twelve months after injury, respectively (Rimel et al., 1981; Guthkelch, 1979).

TBIs can not only impact a patient’s cognitive ability, but also their emotional functioning (Centers for Disease Control and Prevention, 2017). The impaired emotional functioning can result in an increased risk of mental illnesses and difficulties regulating emotions. Patients one year post-TBI were 1.8 times more likely to report binge drinking relative to the general population, defined as having five or more drinks on a single occasion (Horner et al., 2005). These impacts also have
the potential to last decades after the original injury. For example, Second World War (WWII) veterans who sustained a head injury in the war were 50% more likely to have depression 50 years later than WWII veterans without a head injury, with the lifetime risk of depression increasing with the severity of the injury (Holsinger et al., 2002).

While the behavioral symptoms of TBI are well recognized, the mechanical behavior of the brain after a TBI is not. Soft biological tissues, like brain tissue, are challenging to model because of their complex structures and the limited signal to noise ratio (Finan et al., 2017). Characterizing the mechanical behavior of an uninjured and injured brain can help researchers predict how the brain will react to blast or blunt head trauma. Predicting the brain’s response will influence (i) the development of protective equipment such as helmets to mitigate TBI and (ii) improvement of diagnostic tools, which will lead to an increase in personalized treatment options for the patient.

Many researchers have utilized experimental methods to evaluate the mechanical response of uninjured brain tissue. Experiments have considered brain tissue subjected to compression, tension, and shear (Bentil and Dupaix, 2014; Budday et al., 2017; Darvish and Crandall, 2001a; Hrapko et al., 2006; Jin et al., 2013; Miller and Chinzei, 2002; Rashid et al., 2013; Velardi et al., 2006; Zhao et al., 2018). Challenges in investigating the properties of the brain are magnified by the heterogeneous and anisotropic nature of the tissue (Boudjema et al., 2015). Previous experiments have been conducted to investigate factors such as the brain’s temperature, region (right vs. left hemisphere), and size (Boudjema et al., 2015; Budday et al., 2015, 2017; Christ et al., 2010; Fallenstein et al., 1969; Jin et al., 2013; Prange and Margulies, 2002; Rashid et al., 2012b; Tirella et al., 2013; Velardi et al., 2006).

In addition, while the literature consistently shows differences in the mechanical properties of white and gray matter, the differences are not conclusive. For example, in postmortem human brains, Jin et al. (2013) found white matter from the corpus callosum and corona radiata to be stiffer than gray matter from the cortex and thalamus. In contrast, Budday et al. (2017) found unconditioned gray matter from the cortex and basal ganglia in postmortem human brains to be equally stiff as unconditioned white matter from the corpus callosum and corona radiata. Yet,
when the tissue was conditioned prior to testing, the gray matter was three times stiffer than the white matter (Budday et al., 2017).

However, the reported tissue properties in these studies have varied significantly, up to different orders of magnitude. These differences cannot be entirely due to anisotropy or sample composition, and likely have some origin in the postmortem time and storage of the sampled tissue (Garo et al., 2007). Several studies have focused specifically on the effect of postmortem time on the mechanical properties of brain tissue, with mixed results. On one hand, Darvish and Crandall (2001a) found no correlation between the mechanical behavior of bovine brain tissue and postmortem time up to 16 days. However, Nicolle et al. (2004) found the shear modulus of human and porcine brain tissue increased 6% between 24 and 48 hours postmortem. Notably, in shear experiments, Garo et al. (2007) found that the storage and loss moduli of porcine brain tissue increased 0.45 Pa/min when postmortem times exceeded six hours.

Ayyildiz et al. (2014) examined the effects of postmortem time and storage solution choice, on the shear mechanical properties of bovine liver tissue. In the study, Ayyildiz et al. (2014) tested bovine liver tissue up to 2.5 days postmortem. The samples were stored in one of three different solutions: Lactate Ringer’s, Histidine–Tryptophane–Ketoglutarate, or UW solution (Viaspan). It was found that both the storage and loss moduli of liver tissue increases as the amount of time in the solution increases, regardless of solution choice. However, while all three solutions tested were able to preserve the properties up to 11 hours, only one (Histidine–Tryptophane–Ketoglutarate) was able to preserve the mechanical properties of the tissue for a storage time that was between 29 – 53 hours.

Further, Zhang et al. (2018) used sheep brain tissue to study the effect of postmortem time on engineering stress. The brain tissue was tested either (i) immediately or (ii) after refrigeration for one and four hours, without any preservation solution. They demonstrated a significant decrease in the engineering stress of the tissue with prolonged storage duration. However, it has been shown that tissue gets stiffer as it dries. Thus, tissue is traditionally stored in a solution to prevent dehydration (Hrapko et al., 2006; Nicolle and Palierne, 2010).
Accurate constitutive models are important in order to properly describe the brain’s mechanical behavior. When performing simulations of real-life head injuries, Kleiven (2007) found that the chosen value for the brain tissue’s stiffness significantly affected the calculated strains in the computational model. For example, the peak maximum principal stress values were 40% less and occurred sooner after impact when stiffer tissue properties were considered. As previously mentioned, postmortem time affects the reported stiffness. However, the authors can find no studies that conducted compression experiments with a preservation solution investigating the effect of postmortem time on the mechanical properties of brain tissue. It is important to acknowledge and recognize the effect of storage conditions and duration, on the optimized coefficients of constitutive models. Thus, brain tissue was refrigerated in normal saline (0.9% NaCl) between 30 minutes and 6.5 hours in order to see the effect of postmortem time and solution absorption on the mechanical properties of brain tissue. Tissue samples from both the soaked and freshly extracted (unsoaked) brains underwent unconfined compression tests performed at compressive rates of 5, 50, and 500 mm/min. Following testing, the fractional Zener (FZ) constitutive model was applied to the soaked and unsoaked brain samples, and the FZ coefficients were compared with those found by Bentil and Dupaix (2014) for porcine brains.

The fractional Zener viscoelastic model is a four parameter model that has been used in the literature to describe brain tissue’s stiffness properties, relaxation time, and viscoelasticity (Bentil and Dupaix, 2014, 2018; Davis et al., 2006). The experimental data was fit using the fractional Zener model to quantitatively distinguish the mechanical properties of the soaked and unsoaked brain tissue.

2.3 Method and Theory

2.3.1 Sample Preparation

In this study, 23 fresh porcine skulls from six-month-old pigs were obtained from a local abattoir, equivalent in structure to a four-year-old human (Prange and Margulies, 2002; Thibault and Margulies, 1998). Porcine brain tissue was chosen due to its availability and potential to minimize
the influence of postmortem time on the material response (Bentil and Dupaix, 2014). Although the porcine brains are smaller in size than humans, anatomical similarity of both the vascular system and the gyri and sulci exist when compared with a human brain (Säljö et al., 2008).

Each brain was extracted from the skull and weighed at room temperature (21°C). The extracted brain was either subjected (i) immediately to unconfined compression tests or (ii) placed in a small plastic lidded container, with 200 mL of 0.9% NaCl (i.e. normal saline) solution, and placed in the refrigerator for storage at 12°C before unconfined compression tests.

The saline solution prevented dehydration and deterioration of the tissue in order to accurately measure the stiffness (Hrapko et al., 2006; Nicolle and Palierne, 2010). Normal saline was chosen due to its widespread availability and use with biological tissues. Once the designated time period had elapsed, ranging from 30 minutes to 6.5 hours, the refrigerated brain tissue was removed from the refrigerator and reweighed. The remaining volume of normal saline solution was measured and recorded.

To prepare a sample for testing, the right and left hemispheres of each brain were separated by cutting through the corpus callosum and midbrain (Rashid et al., 2013). A circular steel coring tool with a diameter of 25 mm was used to cut a single cylindrical brain tissue sample from each cerebral hemisphere (Figure 2.1). Coring the brain tissue from the lateral to medial direction resulted in 46 samples for this study. While every effort was made to core samples of consist sizes, brain tissue quickly adheres to the cutting tools. As a result, constant cross-sectional areas of the samples were not always possible (Miller and Chinzei, 2002). Before the unconfined compression tests, the height of the brain sample was recorded.

Each brain sample was extracted and prepared for testing linearly, or one at a time. By doing so, the brain tissue’s stiffness and hydration could be best preserved (Rashid et al., 2013). Less than 20 minutes elapsed between brain extraction and either unconfined compression testing or placement of the tissue in the normal saline solution. When brain samples were removed from the normal saline solution, unconfined compression testing were performed within 10 minutes.
2.3.2 Unconfined Compression Testing

A TA Instruments Discovery Hybrid Rheometer (HR-2) was used to conduct the unconfined compression experiments and was calibrated prior to beginning each test. The normal force sensitivity of the load cell is 0.005 N. Samples were centered on a stainless steel Peltier bottom plate. A 25 mm stainless steel top plate was used to compress the tissue, as shown in the schematic in Figure 2.2. All tests were performed at room temperature (21°C).

At the onset of the test, the height of the rheometer (difference between the plates) was set to the measured height of the sample. This allowed the top plate to just touch the top of the sample, while placing the least possible force (preload) on the sample prior to onset of the experiment.

During the unconfined compression experiments, a ramp-hold loading profile was applied. This loading profile describes a stress relaxation experiment, where a decrease in the brain’s stress response occurs due to application of a constant strain. For the ramp phase, the HR-2’s top plate compressed the sample to 80% of its original height (20% strain) at a constant compressive rate.
of 5 mm/min, 50 mm/min, or 500 mm/min. This correlates to average strain rates of 0.00548/s, 0.0548/s, and 0.548/s, respectively. Once at 20% strain, the hold phase began and consisted of the HR-2 holding the sample at a strain rate of approximately 0/s for two minutes. Stress relaxation occurs during the hold phase. The engineering stress was calculated in response to the ramp-hold loading profile. Due to the limitations of the HR-2, the constant strain rate was conducted by setting the strain rate to $1 \times 10^{-5}$/s, the lowest possible setting allowed by the machine. Each sample was only tested once due to the softness and viscoelastic properties of the tissue (Rashid et al., 2013; Miller and Chinzei, 2002; Bentil and Dupaix, 2014).

### 2.3.3 Fractional Zener Constitutive Model

Brain tissue can be described by a viscoelastic model since the tissue is strain rate dependent and hysteresis applies (Bentil and Dupaix, 2014; Boudjema et al., 2017; Donnelly and Medige, 1997; Finan et al., 2017; Galford and McElhaney, 1970; Green et al., 2008; Jin et al., 2013; Klatt
et al., 2007; Kleiven, 2007; Miller and Chinzei, 1997; Rashid et al., 2012a; Takhounts et al., 1999; Tirella et al., 2013). In order to best describe the brain’s viscoelastic behavior from the unconfined compression experiments, the fractional Zener constitutive model was used to obtain the material properties capturing the stress relaxation behavior. Figure 2.3 and Equation 2.1 represent the FZ model for describing the stress-strain response of brain tissue.

\[
\sigma(t) + \tau_0^\alpha D^\alpha \sigma(t) = E_\infty \epsilon(t) + E_0 \tau_0^\alpha D^\alpha \epsilon(t),
\]

(2.1)

where $\sigma$ is stress, $\epsilon$ is strain, $t$ is time, $D$ is the differintegral operator, $E_\infty = E_1$, $E_0 = E_1 + E_2$, and $\tau_0^\alpha = (E_3/E_2)\tau^\alpha$.

Figure 2.3 Fractional Zener constitutive model using two spring elements and one fractional element.
In the FZ model described by Equation 2.1, the stress-strain relationship is given by solving the rheological system containing two springs, with a modulus of either $E_1$ or $E_2$, and a fractional element (Figure 2.3). $E_\infty$ and $E_0$ describe the stiffness of the brain tissue, where $E_\infty$ represents the long-term stiffness and $E_0$ represents the brain’s instantaneous modulus or initial elastic response. Further, $\tau_0$ describes the relaxation time and $\alpha$ illustrates the brain tissue’s location on the viscoelastic spectrum, where $\alpha = 0$ is an elastic solid (i.e. spring) and $\alpha = 1$ is a Newtonian liquid (i.e. dashpot/damper) (Bentil and Dupaix, 2014). When $\alpha = 1$, the FZ model is equivalent to the traditional Zener model. The fractional Zener model can be implemented in the commercially available finite element software ABAQUS, by writing a user-defined material model (UMAT). The algorithm for the UMAT subroutine is described in Bentil and Dupaix (2018).

Since the lower bound for $\alpha$ is 0, the differintegral operator $D$ results in fractional differentiation. Additionally, since $\alpha$ is between 0 and 1, the fractional derivative results in an interpolation between viscous and elastic elements; therefore, allowing the fractional element to relate stress to a fractional derivative of strain (Davis et al., 2006; Schiessel et al., 1995; Scott Blair, 1947). By using a fractional element, the number of coefficients needed to describe the behavior of the brain tissue can be reduced to four, significantly less than other viscoelastic models (Baley and Torvik, 1983; Davis et al., 2006; Kohandel et al., 2005). Conventional integer-based viscoelastic models can be generalized for materials on the entire viscoelastic range by substituting the viscous elements with a fractional element (Davis et al., 2006; Kohandel et al., 2005; Schiessel et al., 1995).

2.4 Results

2.4.1 Relationship Between Absorption and Time in Solution

Unconfined compression experiments to characterize the brain’s stress relaxation response were performed on samples from 23 different porcine brains. Fifteen (15) of the total brains extracted were placed in normal saline solution and refrigerated between 30 minutes and 6.5 hours. The volume of normal saline solution in the container was recorded both before brain placement and
after brain removal from the solution, in order to quantify the volume of absorbed saline solution by the brain.

![Graph](image)

**Figure 2.4** Volume of normal saline solution absorbed as a function of absorption time (i.e. time in the solution), with the initial mass of the porcine brain denoted by the asterisk.

Figure 2.4 depicts the volume of solution absorbed as a function of time in the solution, while also demonstrating the influence of increased brain mass on solution absorbed given a fixed time in solution. In general, the volume of saline solution that was absorbed by the brain tissue increased the longer it was in the solution. However, the average volume of solution absorbed was lower over the 1 hour period relative to the 30 minute time period. This is most likely due to a small sample
size, as samples from three brains were tested after 1 hour in the solution. Of the three brains tested, one of the samples absorbed just 3.5 mL of solution, less than the other brains in both the 0.5 hour and 1.0 hour cohorts.

Furthermore, while the amount of solution absorbed was still increasing after 6.5 hours, the rate of absorption decreased after 30 minutes. For example, brains with initial masses between 87.3 – 88.9 grams absorbed 6 mL over the first 30 minutes, an additional 1.5 mL between 30 minutes and 4.5 hours, and a final 0.5 mL between 4.5 and 6.5 hours. On average, over 65% of the volume of saline solution absorbed over the 6.5 hour period had already been absorbed after 30 minutes and over 95% after 4.5 hours. As a result, while the brain tissue may not have yet reached saturation after 6.5 hours, it was nearing the saturation point. Regardless of the brain’s time in the solution, the amount of saline solution absorbed was proportional to the unsoaked mass of the brain.

2.4.2 Stress Relaxation Behavior

A correlation exists between the amount of normal saline solution absorbed by the brain and the time in solution. However, there was an inconsistent relationship between the time in the solution and the stress relaxation behavior when isolating individual samples for analysis. For instance, at the 50 mm/min compressive loading rate, the peak stress of the brain generally increases with the time in solution (Figure 2.5). Yet, the brain sample with the second highest magnitude peak stress did not soak in the solution, while the brain samples with the first and third highest stress magnitude were soaked in the normal saline solution for 6.5 hours. Similarly, of all the samples tested at 500 mm/min, the samples that experienced both the highest and lowest magnitude peak stress did not soak in the solution and were tested immediately.

Figure 2.6 highlights the engineering stress-time response of samples extracted from two brains. All samples were tested at 500 mm/min after soaking in the saline solution for 30 minutes. At the fastest tested rate of 500 mm/min, the HR-2 had increased variation in the measured stress across the holding period. This variation (or scatter) was attributed to limitations of the HR-2’s load cell at measuring the normal force at the fastest compressive rate. In Figure 2.6, Brain 1 and Brain
2 weighed 75.904 g and 74.718 g before soaking, respectively. The two samples extracted from each brain had similar stress relaxation curves; yet, the samples extracted from the second brain experienced a higher stress response than samples from the first brain. The experiments occurred on the same day and all four samples were extracted from the same regions of the brain; therefore, minimizing the differences of matter composition between the samples.

Figure 2.5  The average stress relaxation behavior for unsoaked and soaked brains, due to a 50 mm/min compressive rate. The standard deviation is shown by the shaded area.
2.4.3 Fractional Zener Constitutive Model

Using the stress relaxation data from the unconfined compression experiments, the four fractional Zener coefficients \( (E_\infty, E_0, \tau_0, \alpha) \) were calculated for each tissue sample using a nonlinear least squares method in an in-house developed MATLAB program (MATLAB, 2016). 2.9 contains the complete data tables for the averaged FZ coefficient values, along with the standard deviation values. A sample model fit for each of the three compressive rates is shown in Figure 2.7. The FZ model was unable to fit the ramp period for tests at 5 mm/min compressive rate (Figure 2.7a). This was due to the brain exhibiting an increased nonlinear stress response, due to gravitational effects contributing to the tissue deformation. At faster compressive rates (50 mm/min and 500 mm/min), the FZ model was able to capture the stress response from the ramp period, due to minimal time for gravitational effects to contribute to the brain’s deformation. The residual, from the nonlinear least squares method, was used to determine how well the FZ model fit the experimental data from the HR-2. For all compressive rates considered, the FZ model was able to fit the hold period of the experimental data, with an average residual of -0.4907 Pa and standard deviation of 6.30 Pa across all samples. All individual samples had an average hold residual under \(|3 Pa|\). The residual over the hold period was specifically considered because the FZ model aimed to describe the relaxation behavior after the peak stress had been reached (Figure 2.7).

Given the quality fit between the model and FZ model, when considering the residuals, the FZ coefficients were then analyzed statistically using the software JMP (JMP, 2015). Specifically, JMP was used to apply a standard least squares regression to a linear fixed effect model. The linear fixed effects model was used to understand the relationship between two independent variables (i.e. time in the solution and compressive loading rate) on the FZ coefficients (dependent variables). Our analysis showed that the best fit model did not include any binary interactions between the time in the solution and compressive loading rate. Binary interactions resulted in singularities due to the correlation between time in the solution and compressive loading rate.

An analysis of variance (ANOVA) was used to identify the FZ coefficients that were significantly affected by the time in the solution and the compressive rate. The significance level for this
statistical analysis was 0.05, so p-values less than 0.05 were considered significant. Table 2.1 summarizes the significant and non-significant FZ coefficients for the linear fixed effects model comprised of the time in the solution and the compressive loading rate. The relaxation time $\tau_0$ and fractional order $\alpha$ were statistically influenced by both the time in the solution and compressive rate.

<table>
<thead>
<tr>
<th>Linear Fixed Effects Model Parameters</th>
<th>Statistical Significance of Fractional Zener Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in Solution</td>
<td>$E_\infty$ = 0.9499, $E_0$ = 0.0282, $\tau_0$ = 0.0254</td>
</tr>
<tr>
<td>Compressive Rate</td>
<td>$E_\infty$ = 0.6882, $E_0$ = 0.8498, $\tau_0$ = 0.0254</td>
</tr>
</tbody>
</table>

Table 2.1 Parameters influencing FZ coefficients. A p-value less than 0.05 is statistically significant.

Figure 2.8 shows how the average fractional Zener coefficients change as the applied compressive rate and duration of the time in solution increase. For the 500 mm/min compressive loading rate case, soaked brain tissue was only tested after 0.5 hours due to tissue availability. Lack of tissue availability also prevented soaked brains from being tested after a 1 hour soak time at a compressive rate of 5 mm/min, and a 4.5 hour soak time at 50 mm/min. Details describing the number of samples for various combinations of absorption times and compressive rates can be found in 2.10. The results show that $E_\infty$ is unaffected by either the length of time in the solution or the compressive rate, as evidenced in Figure 2.8 and the statistically insignificant result in Table 2.1. Further, while $E_0$ was unaffected by the solution time up to 4.5 hours, the instantaneous elastic response increased 230% between 4.5 and 6.5 hours. However, $E_0$ also had a large standard deviation at 6.5 hours of 4390 Pa.

Figure 2.9 provides the average fractional Zener coefficients with respect to the compressive rate and soaked state of the brain. $E_0$ reduces by 2.2% and 2.9% when comparing the soaked and unsoaked brain samples, as the compressive rate increases from 5 to 50 mm/min, respectively. The soaked and unsoaked brain samples reduce by 24.0% and 10.1%, as the compressive rate
increases from 50 to 500 mm/min, respectively. Further, $\tau_0$ was less influenced by the length of time in the solution when compared with the compressive rate. For instance, among soaked samples, $\tau_0$ decreased 54.3% between 5 and 50 mm/min and then increased 221.8% between 50 and 500 mm/min. Finally, $\alpha$, which measures the brain tissue’s location on the viscoelastic spectrum, was 0.56% larger in value among the soaked brains than the unsoaked brains. The optimized FZ coefficient vary from the values obtained by Bentil (2013) when testing porcine brains at 5 mm/min, where $E_\infty = 442$ Pa, $E_0 = 3520$ Pa, $\tau_0 = 6.62$ s, and $\alpha = 0.624$. At the 5 mm/min compressive rate, while $\alpha$ varies by 1.0%, the percent difference for the other FZ coefficients vary up to 66.9%.
Figure 2.6  Stress relaxation behavior of two brain samples allowed to soak for 30 minutes, before unconfined compression tests at a 500 mm/min compressive rate. Samples of each brain were cored from the “Left” and “Right” hemisphere.
Figure 2.7 A FZ curve with the corresponding experimental data, for a compressive rate of (a) 5 mm/min, (b) 50 mm/min, and (c) 500 mm/min.
Figure 2.8  Compressive rate and time in the solution for the averaged fractional Zener coefficient described by (a) $E_\infty$, (b) $E_0$, (c) $\tau_0$, and (d) $\alpha$. Error bars represent the standard deviation.
Figure 2.9 Compressive rate and soaked state of the brain for the averaged fractional Zener coefficient described by (a) $E_\infty$, (b) $E_0$, (c) $\tau_0$, and (d) $\alpha$. Error bars represent the standard deviation.
2.5 Discussion

Brain tissue samples from both the soaked and unsoaked (freshly extracted brains) cohort were subjected to unconfined compression tests at compressive rates of 5, 50, and 500 mm/min. A fractional Zener viscoelastic model describing the stress response of porcine brain tissue was used to obtain the material properties of the brain. The results did not show a statistically significant result between soaking and the long-term stiffness modulus $E_\infty$. Further, the instantaneous modulus $E_0$ was statistically influenced by the time in solution, though not the compressive rate. In contrast, the relaxation time $\tau_0$ and fractional order $\alpha$ were statistically influenced by both the time in the solution and compressive rate. $E_0$ and $\tau_0$ showed an increase among soaked brains relative to unsoaked brains.

Porcine brain samples tested at the same compressive rate, with the same time in solution, consistently show the same general stress relaxation curve over time. However, the magnitude of the curve varies due to discrepancies in the initial stress applied to each sample, attributed to the magnitude of applied preload. Ideally, each experiment would begin without preloading the sample. However, in order to prevent a gap between the loading head and the sample, and also secure the sample between the top and bottom plates, a preload between 0.01 N and 0.08 N was applied, which translated to an initial stress. For example, consider the samples extracted from two brains highlighted in Figure 2.6. The samples from Brain 2 were tested with initial loads of 0.041 N and 0.036 N, respectively. In contrast, the two samples extracted from Brain 1 underwent initial loads approximately 55% higher, of 0.061 N and 0.064 N. As a result, the samples from the two brains yielded different stress relaxation curves, where the preload correlated to a larger maximum stress, ultimately translating to a larger $E_0$ value.

While every effort was taken to minimize the amount of preload, some challenges were inherent to the experimental set-up. The experiments in this paper were completed with smooth stainless steel top and bottom plates. Since the brain tissue exhibits viscous properties, there is a possibility that the top of the tissue did not evenly adhere to the top plate, thus resulting in a small initial
stress (Cheng et al., 2008). Previous studies have used a lubricant to reduce the effect of friction between the plate and sample (Cheng et al., 2008).

Cored brain samples were tested immediately, to minimize the variability of the mechanical response due to the tissue collapsing under the force of gravity. This made the height measurement of the brain challenging, since a measurement taken immediately after coring become obsolete after placement on the bottom plate. Despite these challenges, care was taken to begin each test at the cored brain tissue sample height. The fluctuating height for the brain is reflected in the stress relaxation curves, which produce varying peak engineering stress values for a given compressive rate. Even though the peak engineering stress varied, the trend for the stress relaxation curve was the same for the unsoaked and soaked brain samples regardless of the compressive rate. A future study will investigate whether a consistent height measurement can be attained if compression of the brain sample (placed on the bottom plate) commenced following a 15 second respite.

The differences in the measured material properties may be independent of the preload and instead reflect variances in the distribution of gray and white matter of the cored sample. Since the brain is an inhomogeneous material, the material properties for the white and gray matter are different. As such, any differences in the relative amount of gray and white matter between two brain samples would affect the stress relaxation response (Budden et al., 2017; Boudjema et al., 2017; Finan et al., 2017; Jin et al., 2013; Prange and Margulies, 2002). As a result, when coring the brain samples, care was taken to extract from the same region of the brain for consistency in the anatomical structure. However, variances in the distribution of gray and white matter of the cored sample still occurred.

Additionally, this study showed that the amount of normal saline solution absorbed by a given brain was proportional to its unsoaked, initial mass, regardless of the brain’s time in the solution. While the amount of liquid absorbed was still increasing up to 6.5 hours, over 65% of the amount of liquid had already been absorbed after 30 minutes and the rate of absorption decreased. As a result, while the brain tissue may not have yet reached saturation after 6.5 hours, it was nearing the saturation point. A future study will investigate the time corresponding to the point of saturation.
Since the brains in this study were obtained from 6-month-old porcine, changes in the material properties due to age were not a factor. The difference between infant and adult pig brains is unknown, as studies have reported that adult pig brains are stiffer and also less than half as stiff as infant pig brains (Thibault and Margulies, 1998; Prange and Margulies, 2002). Prange and Margulies (2002) found that fresh human brain tissue is approximately 30% stiffer than porcine brain tissue. The human brain tissue samples acquired in Prange and Margulies (2002)’s study were the result of temporal lobectomies performed on epilepsy patients, leading to the possibility of differences in stiffness between healthy and diseased human brain tissue. In order to apply the FZ coefficients for porcine brains to human brain tissue, the FZ coefficients $E_\infty$ and $E_0$ can increase at most to 30%. The appropriate stiffness values for $E_\infty$ and $E_0$, along with $\tau_0$ and $\alpha$ will be quantified following future experiments with human brain tissue.

2.6 Conclusion

In this paper, whole porcine brains were placed in saline solution and refrigerated between 30 minutes and 6.5 hours. Regardless of the length of time the brain soaked in the solution, the amount of normal saline solution absorbed was proportional to the unsoaked mass of the brain. After soaking, tissue samples from both soaked and freshly extracted brains (unsoaked) were subjected to unconfined compression tests performed at compressive rates of 5, 50, and 500 mm/min. The samples were compressed to 20% strain, at which the strain was held constant to mimic a stress relaxation experiment. Using each experimental data set, a fractional Zener constitutive model was used to obtain the material properties for the brains. While the results did not show a statistically significant relationship between soaking and the long-term stiffness ($E_\infty$), both the relaxation time ($\tau_0$) and fractional order ($\alpha$) were statistically influenced by both the time in the solution and compressive rate. The average value for the instantaneous modulus $E_0$ and relaxation time $\tau_0$ increased by 11.9% and 11.2% among the soaked brains relative to unsoaked brains, respectively.

Further, the instantaneous stiffness ($E_0$) was statistically influenced by the time in solution, though not the compressive rate. Thus, brains soaked in saline solution behave differently than
the unsoaked brains, when considering the instantaneous elastic response \(E_0\) and the viscoelastic response \(\tau_0\) and \(\alpha\). The results of this work will add to the knowledge of the effect of storage duration in saline solution on the material properties of brain tissue. Furthermore, the results show that the viscoelastic response of the brain may be an important factor to consider when modeling edema in brain tissue.

2.7 Acknowledgements

This research was financially supported by the Roy J. Carver Charitable Trust under Grant #18-5021 and is acknowledged gratefully. The research is also financially supported by Iowa State University through start-up funds to SA. Bentil, for which the authors are grateful.

2.8 References


Defense and Veterans Brain Injury Center (2018). DoD worldwide numbers for TBI. *DVBIC*.


### 2.9 Appendix: Average Fractional Zener Coefficients

Tables 2.2 and 2.3 display the average fractional Zener coefficient values (and corresponding standard deviation) for various combinations of compressive rates, time in the saline solution, and soaked state.

**Table 2.2** Average ± standard deviation values for the Fractional Zener coefficients versus compressive rate and soaked state of the brain

<table>
<thead>
<tr>
<th>Compressive Rate</th>
<th>Time in Solution</th>
<th>$E_\infty$ (Pa)</th>
<th>$E_0$ (Pa)</th>
<th>$\tau_0$ (s)</th>
<th>$\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mm/min</td>
<td>0.0 Hours</td>
<td>595 ± 206</td>
<td>6230 ± 1900</td>
<td>3.61 ± 0.29</td>
<td>0.627 ± 0.000</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>0.5 Hours</td>
<td>763 ± 108</td>
<td>5720 ± 665</td>
<td>4.80 ± 0.10</td>
<td>0.635 ± 0.005</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>4.5 Hours</td>
<td>549 ± 204</td>
<td>5050 ± 655</td>
<td>5.06 ± 0.23</td>
<td>0.635 ± 0.003</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>6.5 Hours</td>
<td>585 ± 205</td>
<td>10600 ± 3220</td>
<td>3.76 ± 0.67</td>
<td>0.627 ± 0.015</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>0.0 Hours</td>
<td>631 ± 416</td>
<td>6050 ± 2040</td>
<td>1.77 ± 0.45</td>
<td>0.588 ± 0.011</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>0.5 Hours</td>
<td>883 ± 80.9</td>
<td>4340 ± 390</td>
<td>2.75 ± 0.20</td>
<td>0.602 ± 0.013</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>1.0 Hours</td>
<td>622 ± 187</td>
<td>4540 ± 698</td>
<td>2.34 ± 0.38</td>
<td>0.593 ± 0.007</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>6.5 Hours</td>
<td>686 ± 232</td>
<td>12700 ± 5100</td>
<td>1.27 ± 0.77</td>
<td>0.572 ± 0.008</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>0.0 Hours</td>
<td>678 ± 398</td>
<td>5440 ± 2140</td>
<td>6.29 ± 1.26</td>
<td>0.618 ± 0.010</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>0.5 Hours</td>
<td>590 ± 72.0</td>
<td>5500 ± 912</td>
<td>6.60 ± 0.75</td>
<td>0.624 ± 0.009</td>
</tr>
</tbody>
</table>
Table 2.3  Average ± standard deviation values for the Fractional Zener coefficients versus compressive rate and soaking state of the brain

<table>
<thead>
<tr>
<th>Compressive Rate</th>
<th>State</th>
<th>$E_\infty$ (Pa)</th>
<th>$E_0$ (Pa)</th>
<th>$\tau_0$ (s)</th>
<th>$\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mm/min</td>
<td>Soaked</td>
<td>606 ± 205</td>
<td>7390 ± 3350</td>
<td>4.49 ± 0.75</td>
<td>0.632 ± 0.011</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>Unsoaked</td>
<td>595 ± 206</td>
<td>6230 ± 1900</td>
<td>3.61 ± 0.29</td>
<td>0.627 ± 0.000</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>Soaked</td>
<td>687 ± 212</td>
<td>7230 ± 4890</td>
<td>2.05 ± 0.78</td>
<td>0.587 ± 0.014</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>Unsoaked</td>
<td>631 ± 416</td>
<td>6050 ± 2040</td>
<td>1.77 ± 0.45</td>
<td>0.588 ± 0.011</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>Soaked</td>
<td>590 ± 72</td>
<td>5500 ± 912</td>
<td>6.60 ± 0.75</td>
<td>0.624 ± 0.009</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>Unsoaked</td>
<td>678 ± 398</td>
<td>5440 ± 2140</td>
<td>6.29 ± 1.26</td>
<td>0.618 ± 0.010</td>
</tr>
</tbody>
</table>
### Appendix: Sample Combinations Tested

Table 2.4 Number of samples tested at each compressive rate and time in solution combination.

<table>
<thead>
<tr>
<th>Compressive Rate</th>
<th>Time in Solution</th>
<th>Number of Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mm/min</td>
<td>0.0 Hours</td>
<td>4</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>0.5 Hours</td>
<td>2</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>1.0 Hours</td>
<td>0</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>4.5 Hours</td>
<td>4</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>6.5 Hours</td>
<td>4</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>0.0 Hours</td>
<td>4</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>0.5 Hours</td>
<td>2</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>1.0 Hours</td>
<td>6</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>4.5 Hours</td>
<td>0</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>6.5 Hours</td>
<td>4</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>0.0 Hours</td>
<td>8</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>0.5 Hours</td>
<td>8</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>1.0 Hours</td>
<td>0</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>4.5 Hours</td>
<td>0</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>6.5 Hours</td>
<td>0</td>
</tr>
</tbody>
</table>
2.11 Appendix: Relationship Between Solution Absorbed and Initial Brain Mass

Figure 2.10 Ratio between the volume of normal saline solution absorbed over the initial mass of the porcine brain as a function of absorption time (i.e. time in the solution).
CHAPTER 3. VISCOELASTIC PROPERTIES OF SHOCK WAVE EXPOSED BRAIN TISSUE SUBJECTED TO UNCONFINED COMPRESSION EXPERIMENTS

A paper published in the *Journal of the Mechanical Behavior of Biomedical Materials*


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3.1 Abstract

Traumatic brain injuries (TBI) affect millions of people each year. While research has been dedicated to determining the mechanical properties of the uninjured brain, there has been a lack of investigation on the mechanical properties of the brain after experiencing a primary blast-induced TBI. In this paper, whole porcine brains were exposed to a shock wave to simulate blast-induced TBI. First, ten (10) brains were subjected to unconfined compression experiments immediately following shock wave exposure. In addition, 22 brains exposed to a shock wave were placed in saline solution and refrigerated between 30 minutes and 6.0 hours before undergoing unconfined compression experiments. This study aimed to investigate the effect of a time delay on the viscoelastic properties in the event that an experiment cannot be completed immediately. Samples from both soaked and freshly extracted brains were subjected to compressive rates of 5, 50, and 500 mm/min during the unconfined compression experiments. The fractional Zener (FZ) viscoelastic model was applied to obtain the brain’s material properties. The length of time in the solution statistically influenced three of the four FZ coefficients, $E_0$ (instantaneous elastic response), $\tau_0$ (relaxation time), and $\alpha$ (fractional order). Further, the compressive rate statistically influenced $\tau_0$ and $\alpha$. 
3.2 Introduction

Traumatic brain injury (TBI) occurs when the brain is accelerated or decelerated due to blunt or blast trauma. TBI due to blunt trauma includes injury sustained to the head during American football game play, while blast-induced TBI (bTBI) describes head injury resulting from detonated improvised explosive devices (IEDs) in a war setting. Following detonation of the IEDs, the resulting shock wave travels through the atmosphere and can propagate through the head of an individual in its path. This injury to the brain, classified as primary bTBI, is caused from the shock wave itself (Nakagawa et al., 2011).

Each year, TBIs in the United States result in an estimated 1.365 million emergency room visits, 275,000 hospitalizations, and an economic burden exceeding $60 billion dollars (Daneshvar et al., 2011). Approximately 75% of all TBIs in the United States are classified as mild (National Center for Injury Prevention and Control, 2003). Symptoms of mild TBI include temporary confusion or memory loss around the time of injury, or loss of consciousness for less than 30 minutes (National Center for Injury Prevention and Control, 2003). However, the effects of mild TBI on a patient’s behavior and employment can span decades (National Center for Injury Prevention and Control, 2003). In the short term, 34% of patients who were employed at the time of a mild TBI were unemployed three months later (Rimel et al., 1981). A year after a TBI, previously-employed patients reduced their unemployment rate to 9% (Guthkelch, 1979). Even so, TBI patients were 1.8 times more likely to report binge drinking, defined as having five or more drinks on a single occasion, relative to the general population (Horner et al., 2005).

Diffusion tensor imaging (DTI) has been utilized as a method to monitor water diffusion patterns, as a means to track changes in the structure of the brain’s white matter in patients with acute concussions (Bazarian et al., 2012; Lancaster et al., 2016). The DTI technique has been crucial for determining the differences in the brain’s white matter as a result of a sports-related concussion. Bazarian et al. (2012) concluded that the white matter in athletes with concussions underwent three times as much change over a three month period as those of athletes without a concussion. However, the authors of this study could find no previous studies that examined the
mechanical response of brain tissue after a TBI. Instead, the literature shows researchers who have studied brain tissue using both experimental and computational methods to evaluate the mechanical response of uninjured brain tissue subjected to compression, tension, and shear (Bentil and Dupaix, 2014; Budday et al., 2017; Darvish and Crandall, 2001b; Hrapko et al., 2006; Jin et al., 2013; Miller and Chinzei, 2002; Rashid et al., 2013; Velardi et al., 2006; Zhao et al., 2018).

By characterizing the mechanical behavior of the injured brain, researchers will be able to predict the brain’s response to blast or blunt head trauma. Additionally, the injured brain’s mechanical response will ultimately allow for (i) the design of improved protective equipment to prevent TBI and (ii) the development of diagnostic tools to help physicians and clinicians determine if a TBI has occurred, which will in turn allow for (iii) a personalized treatment plan to be designed for the patient.

The study in this paper considered the material properties of brain tissue both immediately after shock wave exposure and after being placed in normal saline (0.9% NaCl) and refrigerated between 30 minutes and 6.0 hours. The refrigerated brains were exposed to a shock wave and placed in the saline solution in order to examine the effect of a time delay on the mechanical response, in the event that researchers cannot immediately conduct experiments after the brains are exposed to a shock wave. Tissue samples from both the soaked and freshly extracted (unsoaked) brains underwent unconfined compression tests performed at compressive rates of 5, 50, and 500 mm/min.

The fractional Zener (FZ) constitutive model coefficients were optimized using the unconfined compression experimental data gathered for the soaked and unsoaked shock wave exposed (SWE) brain samples. The FZ model uses four coefficients/parameters to quantify the brain tissue’s stiffness properties, relaxation time, and viscoelasticity (Bentil and Dupaix, 2014, 2018; Davis et al., 2006). This research will contribute to the understanding of how injured and/or damaged brain tissue behaves under varying compressive loading conditions. Additionally, this work will lay the foundation for the development of improved preventative measures against TBI and treatment strategies for TBI patients.
3.3 Method and Theory

3.3.1 Sample Preparation

This study examined the mechanical properties of 32 fresh porcine brains, which were extracted from the skulls of six-month-old pigs obtained from a local abattoir. The constant age of the pigs limited any developmental differences between the examined brains. Although the porcine brains are smaller in size than humans, the vascular system, gyri, and sulci are anatomically similar to the human brain and structurally equivalent to a four-year-old human (Prange and Margulies, 2002; Säljö et al., 2008; Thibault and Margulies, 1998). Porcine brain tissue was also chosen due to its availability, compared to human brain samples. As a result, all tests were completed within 12 hours postmortem to minimize the influence of postmortem time on the material response (Ayyildiz et al., 2014; Bentil and Dupaix, 2014; Garo et al., 2007).

Each brain was extracted from the skull immediately after the porcine was harvested; therefore, the brain tissue’s stiffness and hydration was best preserved (Rashid et al., 2013). After extraction from the skull, each brain was weighed at room temperature (21°C) and then glued to a base plate, which was in turn secured in a clamp such that the brain was 5 mm away from the end of the shock tube. A 0.177 caliber Crosman Pumpmaster Classic air pistol served as the driver of a small-scale shock tube and was connected to a 64-cm long Schedule 40 polyvinyl chloride (PVC) pipe (driven section), with a nominal size of $\frac{1}{4}$-in. (1.27 cm) (Courtney et al., 2015).

The air pistol and attached pipe, aimed at the temporal lobe of the brain, was pumped ten (10) times before firing a single shock of air (Figure 3.1). A pellet was not used with the air pistol. The reflected shock wave pressure after 10 pumps was 103.5 – 124.2 kPa (15 – 18 psi), which was measured using a pressure transducer (PCB 113B24). The pressure transducer was placed 5 mm away from the end of the pipe. Figure 3.2 shows the reflected shock wave’s pressure history over time, as measured by the pressure transducer. A preliminary study showed that brains exposed to a single shock wave, produced by the air pistol, resulted in a stress response comparable to brains that were not exposed to a shock wave when subjected to unconfined compression tests. Thus,
in order to increase the simulated primary bTBI effect, each pig brain was exposed to the shock wave five (5) times, on either the left or right hemisphere. An example of a scenario involving repeated shock wave exposure is the detonation of IEDs in a confined space (e.g. military vehicle or building) (Agoston, 2017). In conjunction with the propagating shock wave causing injury to an individual, the reflected shock wave pressure off the walls of the confined space would also cause additional bTBI. Exposing the brain to repeated shock waves is a simplification of bTBI resulting from the detonation of IEDs in a confined space. As a result, the variable intensities and waveforms of the reflected shock wave pressures are not considered in the repeated bTBI framework used in this study.

After the shock wave exposure, each brain was prepared for unconfined compression testing either immediately or after being refrigerated for a prescribed amount of time. The refrigerated brains were placed in a small plastic lidded container with 200 mL of normal saline solution (0.9% NaCl), and stored in the refrigerator at 12°C in order to determine the effect of a time delay on the mechanical properties. The brain’s absorption of the saline solution prevented dehydration and deterioration of the tissue (Hrapko et al., 2006; Nicolle and Palierne, 2010). After the designated time period in the refrigerator, ranging from 30 minutes to 6.0 hours, the weight of the refrigerated brain tissue and the remaining volume of normal saline solution was measured. For the 500 mm/min compressive loading rate case, brain tissue was only tested after 0.5 hours due to tissue availability.

Figure 3.1  Schematic diagram of shock wave exposure setup. Brain sample (pink ellipse) is placed on top of the base plate (black rectangle).
Figure 3.2  Pressure history of the reflected shock wave over time, measured 5-mm away from the end of the pipe. Error bars denote standard deviation for 10 runs at the aforementioned location.

To extract samples from each brain, the right and left hemispheres were separated by cutting through the corpus callosum and midbrain (Rashid et al., 2013). A single cylindrical brain tissue sample was then cut with a 25-mm diameter circular steel coring tool from each cerebral hemisphere, coring from the lateral to medial direction (Figure 3.3). The height of the brain sample was recorded. However, due to the brain tissue’s adhesive properties, the tissue quickly adhered to the cutting tool and prevented clean cuts of the tissue. As a result, there was some variation in the cross-sectional areas of the samples (Miller and Chinzei, 2002).

Brain samples underwent unconfined compression testing within 25 minutes of either (i) being exposed to the shock wave, in the case of the unsoaked samples, or (ii) removal from the normal saline solution, in the case of the soaked samples.
Figure 3.3 The black circle, overlaid on the right hemisphere of the porcine brain, illustrates the region cored.

3.3.2 Unconfined Compression Testing

The cored brain samples were centered on a stainless steel Peltier bottom plate of a calibrated TA Instruments Discovery Hybrid Rheometer (HR-2). The load cell’s normal force sensitivity is 0.005 N. A 25-mm stainless steel top plate, approximately equivalent in diameter to the sample, was used to compress the tissue, as shown in Figure 3.4. Prior to beginning each test, the height of the rheometer was set to the measured height of the sample such that the top plate just touched the top of the sample. This procedure minimized the force placed on the sample outside of the duration of the experiment. All tests were performed at room temperature (21°C).

Each sample underwent a single unconfined stress relaxation experiment consisting of an applied ramp-hold displacement input. The experiment was not repeated on samples due to the softness and viscoelastic properties of the tissue (Bentil and Dupaix, 2014; Miller and Chinzei, 2002; Rashid et al., 2013). During the ramp phase, the HR-2’s top plate compressed the sample to 20% strain, or 80% of its original height, at a constant compressive rate of either 5 mm/min, 50 mm/min, or
Figure 3.4 Schematic diagram of test setup.

500 mm/min, correlating to average strain rates of 0.00568/s, 0.0568/s, and 0.568/s, respectively. During the hold phase, the HR-2 held the sample at a strain rate of approximately 0/s for two minutes. Specifically, the constant strain rate was conducted by setting the strain rate to $1 \times 10^{-5}$ s$^{-1}$, the lowest possible strain rate allowed by the HR-2. Stress relaxation occurs during the hold phase, which results in a decrease in the brain’s stress response over the hold period.

3.3.3 Fractional Zener Constitutive Model

Since brain tissue’s behavior is affected by strain rate and displays hysteresis, it is best described by a viscoelastic model (Bentil and Dupaix, 2014; Boudjema et al., 2017; Donnelly and Medige, 1997; Finan et al., 2017; Galford and McElhaney, 1970; Green et al., 2008; Jin et al., 2013; Klatt et al., 2007; Kleiven, 2007; Miller and Chinzei, 1997; Rashid et al., 2012a; Takhounts et al., 1999; Tirella et al., 2013). In this study, the fractional Zener (FZ) constitutive model was used to quantify
the mechanical behavior of brain tissue during unconfined compression experiments. The FZ model for describing the stress response of brain tissue is represented by Figure 3.5 and Equation 3.1.

\[
\sigma(t) + \tau_0^\alpha D^\alpha \sigma(t) = E_\infty \epsilon(t) + E_0 \tau_0^\alpha D^\alpha \epsilon(t),
\]

(3.1)

where \(\sigma\) is stress, \(\epsilon\) is strain, \(t\) is time, \(D\) is the differintegral operator, \(E_\infty = E_1\), \(E_0 = E_1 + E_2\), and \(\tau_0^\alpha = (E_3/E_2)\tau^\alpha\). \(E_1\), \(E_2\), and \(E_3\) describe the elastic constants, \(\tau\) is the relaxation time, and \(\alpha\) is the fractional order for the single fractional element in the FZ model.

Figure 3.5 Fractional Zener constitutive model. \(E_1\) and \(E_2\) are the elastic constants for the springs. The fractional element’s fractional order, elastic constant, and relaxation time is described by \(\alpha\), \(E_3\), and \(\tau\), respectively.

The rheological system in Figure 3.5, consisting of two springs and a fractional element, can be solved for the stress-strain relationship of brain tissue. In the FZ model, \(E_\infty\) represents the brain’s
long-term stiffness, $E_0$ the instantaneous stiffness of the brain tissue, and $\tau_0$ the relaxation time of the brain tissue after being compressed. Further, $\alpha$ is a parameter of the fractional element that describes the brain tissue’s location on the viscoelastic spectrum, with an elastic solid and viscous liquid as the bounds (Bentil and Dupaix, 2014). When $\alpha = 0$, the fractional element reduces to a spring and describes an elastic solid. In contrast, when $\alpha = 1$, the fractional element reduces to a dashpot and describes a viscous liquid (Bentil and Dupaix, 2014).

The differintegral operator $D$ results in fractional differentiation of order $\alpha$, therefore allowing the model to interpolate between viscous (dashpot) and elastic (spring) elements. As a result, stress is related to a fractional derivative of strain (Davis et al., 2006; Schiessel et al., 1995; Scott Blair, 1947). The use of a fractional element allows the number of coefficients needed to describe the behavior of the brain tissue to be reduced to four, significantly less than other viscoelastic models which need additional parameters to capture the time dependence (Balei and Torvik, 1983; Davis et al., 2006; Kohandel et al., 2005). As a result of this benefit, the FZ model has previously been used to describe the viscoelastic behavior of brain tissue having a short finite cylindrical shape (Bentil and Dupaix, 2014; Davis et al., 2006; Kohandel et al., 2005). In general, conventional integer-based viscoelastic models can be broadened for the entire viscoelastic range by replacing the viscous elements with a fractional element (Davis et al., 2006; Kohandel et al., 2005; Schiessel et al., 1995). Specifically, the FZ model is equivalent to the traditional Zener model when $\alpha = 1$.

The FZ constitutive model can also be implemented in the commercially available finite element software ABAQUS, by writing a user-defined material model (UMAT) subroutine as described in Bentil and Dupaix (2018).

Once the system of springs and dashpot has been solved, the viscosity $\eta$ of the brain tissue can be calculated using Equation 3.2.

$$\eta = \tau_0^\alpha E_0$$  \hspace{1cm} (3.2)
3.3.4 Statistical Analysis

Statistical analysis was conducted using the statistical software JMP (JMP, 2015). The significance level for all statistical tests was 0.05. An Analysis of Variance (ANOVA) was used to determine the effects of the experimental parameters (i.e. time in solution and compressive rate of SWE brains) on the solution absorbed, the peak stress ($\sigma_{\text{max}}$) from the unconfined compression experiments, and the optimized fractional Zener model coefficients. A Tukey Honestly Significant Difference (HSD) test was conducted, as appropriate, to obtain a pairwise comparison of a parameter’s (i.e. factor’s) levels.

3.4 Results

3.4.1 Relationship Between Absorption and Time in Solution

In order to examine the effect of shock wave exposure on the absorptive properties of the brain, 22 of the 32 total brains extracted were placed in normal saline solution before undergoing unconfined compression testing. After being placed in the solution, each brain was refrigerated between 30 minutes and 6.0 hours. The amount of solution was recorded both before and after the refrigeration period to quantify the amount of absorption.

Figure 3.6 illustrates the volume of solution absorbed as a function of time in the solution with the initial mass of the respective brain listed next to each data point. Over the 0.5 hour soaking period, the difference between the initial and final amount of solution in the container varied from 3.2 mL to 7.7 mL. Further, all brains that soaked over 4.5 hours absorbed between 6.5 and 13.0 mL. In general, the volume of normal saline solution that was absorbed by the brain tissue increased the longer it was in the solution.

The amount of solution absorbed was statistically influenced by the time in solution ($p<0.0001$), but not the initial mass of the SWE brain ($p=0.7380$). The Tukey HSD test showed that the solution absorbed was statistically different for SWE brains soaked between 0.5 h and 4.5 h ($p<0.0001$) and 0.5 h and 6.0 h ($p<0.0001$). However, there was not a significant difference in the solution absorbed
for SWE brains soaked between 0.5 h and 1.0 h (p=0.9725), 1.0 h and 4.5 h (p=0.0747), 1.0 h and 6.0 h (p=0.2833), or 4.5 h and 6.0 h (p=0.1697). Further, the binary interaction between the initial mass and the time in solution was not statistically significant (p=0.1339). For example, at the 30 minute time point, a brain weighing 83.950 g absorbed 3.2 mL. However, in the same time period, another brain weighing 84.940 g, less than one gram more, absorbed 7.7 mL, more than twice that of the brain sample weighing 83.950 g. Despite the doubling of the solution absorbed, the initial masses of the two brain samples were not statistically different.

Figure 3.6  Volume of normal saline solution absorbed as a function of time in solution (i.e. absorption time), with the initial mass of the porcine brain denoted next to each asterisk.
3.4.2 Peak Stress Behavior

The peak stress \( (\sigma_{max}) \) for the SWE brain, following the ramp phase of the unconfined compression experiments, increased with the time in solution (Table 3.1). For instance, at the 50 mm/min compressive loading rate, the brain sample with the largest magnitude peak stress soaked in the solution for 6.0 hours, the longest length tested, while the brain sample with the smallest stress magnitude did not soak in the solution and was tested immediately (Figure 3.7). Similarly, at the end of the hold period, the brain samples with the largest stress soaked in the solution for 4.5 hours, while the brain sample with the smallest did not soak. Additionally, the peak stress was statistically influenced by the compressive rate (Table 3.1).

Table 3.1 Parameters influencing the peak stress for SWE brain tissue during unconfined compression experiments. A p-value less than 0.05 is statistically significant.

<table>
<thead>
<tr>
<th>Linear Fixed Effects Model Parameters</th>
<th>Peak Stress ( \sigma_{max} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in Solution</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Compressive Rate</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

3.4.3 Fractional Zener Constitutive Model

The fractional Zener model was applied to each brain tissue sample’s stress relaxation curve to characterize the elastic and viscoelastic properties of the shock wave exposed (SWE) pig brain, due to unconfined compression. The four fractional Zener coefficients \( (E_{\infty}, E_0, \tau_0, \text{ and } \alpha) \) were optimized using a nonlinear least squares method developed from an in-house MATLAB (MATLAB, 2016) program. In the program, the FZ model (Equation 3.1) was first simplified by describing the time-dependent strain \( \epsilon(t) \) using the imposed ramp-hold displacement input applied to the brain by the top compression plate (Figure 3.1). The resulting time-dependent stress \( \sigma(t) \) equation was then used to fit the experimentally obtained stress-time data, for the ramp-hold strain input, to obtain the FZ coefficients’ values. The averaged FZ coefficients and standard deviations can be found in 3.9. Figure 3.8 displays a sample model fit for each of the three compressive rates.
Due to gravitational effects, the brain tissue deforms under its own weight as is typical of compliant materials. Additionally, for materials with viscosity (e.g. brain), the rate of deformation is time dependent. As a result, the brain sample exhibited an increased nonlinear stress response at the 5 mm/min compressive rate due to the increased duration required for the rheometer (HR-2) to compress the tissue to a strain of 20%. This increased duration yielded a nonlinear stress response during the ramp phase, since time was provided for the tissue to relax and deform due to gravity. The FZ model’s ability to fit the ramp period at the slowest compressive rate (5 mm/min)
was limited due to the use of linear springs \((E_1 \text{ and } E_2)\), which were unable to capture the time-
dependent changes resulting in an increased nonlinear (concave up) stress behavior corresponding

to the ramp period. The brain tissue deformation, due to the effects of gravity and relaxation, are

minimized at 50 and 500 mm/min. Therefore, the FZ model is able to better fit the ramp period

at the faster compressive rates.

Regardless of the fit level for the ramp period, the FZ model was able to fit the hold period

at all compressive rates. Since the intent of these experiments was to obtain the stress relaxation

behavior attributed to the hold period, the FZ model results from the 5 mm/min tests were not

excluded since the FZ model is able to account for the time-dependent changes during the hold

period at all compressive rates, regardless of the fit level during the ramp period. The samples

had an average residual of -0.4662 Pa from the fitted model, and a standard deviation of 5.92 Pa

across all samples. All individual samples had an average hold residual under \(|2 \text{ Pa}|\) from the fitted

model. The residual over the hold period was specifically considered because the FZ model aimed

to describe the relaxation behavior after the peak stress had been reached (Figure 3.8).

The optimized FZ coefficients at 5 mm/min for SWE brains are within the same order of

magnitude as the FZ coefficients obtained by Bentil (2013), for non-shock wave exposed (NSWE)

postmortem swine brain tissue. Bentil (2013) subjected NSWE brains in their study to unconfined

compression at 5 mm/min compressive loading rate and 10\% strain, and obtained the following

coefficients: \(E_\infty = 442 \text{ Pa}, \ E_0 = 3520 \text{ Pa}, \ \tau_0 = 7.62 \text{ s}, \ \text{and } \alpha = 0.624\). For the 5 mm/min

compressive rate, the unsoaked SWE brains in this study varied by a percent difference of less

than 5\% for \(E_\infty\) and \(\alpha\), yet differed by 42\% and 85\% for \(E_0\) and \(\tau_0\), respectively, when compared

with the non-shock wave exposed (NSWE) FZ coefficient values provided by Bentil (2013). The

differing values for the instantaneous stiffness \((E_0)\) and relaxation time \((\tau_0)\) may be attributed to

the different strain-level considered (10\% versus 20\%) and shock wave exposure condition (SWE

versus NSWE).

The FZ coefficients, describing the mechanical properties of SWE brain tissue, were analyzed

using the statistical software JMP (JMP, 2015). As shown in Table 3.2, \(E_0, \tau_0, \) and \(\alpha\) were found to
be statistically influenced by the length of time in the solution. Further, two of the four coefficients, \( \tau_0 \) and \( \alpha \), were statistically influenced by the compressive rate.

Table 3.2 Parameters influencing FZ coefficients for SWE brain tissue. A p-value less than 0.05 is statistically significant.

<table>
<thead>
<tr>
<th>Linear Fixed Effects Model Parameters</th>
<th>( E_\infty )</th>
<th>( E_0 )</th>
<th>( \tau_0 )</th>
<th>( \alpha )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in Solution</td>
<td>0.1704</td>
<td>&lt;0.0001</td>
<td>0.0473</td>
<td>0.0157</td>
</tr>
<tr>
<td>Compressive Rate</td>
<td>0.8321</td>
<td>0.0550</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Figure 3.9 shows how the average fractional Zener coefficients change as the applied compressive rate and duration of the time in solution increase. The results show that \( E_\infty \) is unaffected by either the length of time in the solution or the compressive rate, as evidenced in Figure 3.9 and the statistically insignificant result in Table 3.2. Figure 3.10 provides the average fractional Zener coefficients with respect to the compressive rate and soaked state of the SWE brain. \( E_0 \) decreases as the compressive rate is increased among both soaked and unsoaked brains, as observed from Figure 3.10. Further, \( \tau_0 \) was less influenced by the length of time in the solution when compared with the compressive rate. This is clearly seen in Figure 3.10c by the notably larger values for 500 mm/min than either of the two slower compressive rates. Among soaked brains, \( \tau_0 \) was 2.10 and 3.40 times larger at 500 mm/min than 5 or 50 mm/min, respectively. Similarly, among unsoaked brains, \( \tau_0 \) was 2.16 and 3.59 times larger at 500 mm/min than 5 or 50 mm/min, respectively.

3.4.4 Viscosity of Brain Tissue

Given the FZ coefficients found above, the viscosity of the brain tissue was calculated using Equation 3.2 for the samples that underwent unconfined compression testing at 5 mm/min and 20% strain. The calculated viscosity was compared to the viscosity calculated using the FZ coefficients optimized by McCarty et al. (2019) and Bentil (2013) for unsoaked, non-shock wave exposed (NSWE) brain tissue in similar stress relaxation experiments at 5 mm/min (Table 3.3). McCarty
Figure 3.8 A FZ curve with the corresponding experimental data, for a compressive rate of (a) 5 mm/min, (b) 50 mm/min, and (c) 500 mm/min.

et al. (2019) also provided FZ coefficients for soaked, NSWE brains. Bentil (2013) obtained the following FZ coefficients for the cored NSWE brains with a 15-mm diameter and 12-mm height that were compressed to 10% strain: $E_\infty = 442$ Pa, $E_0 = 3520$ Pa, $\tau_0 = 7.62$ s, and $\alpha = 0.624$. McCarty et al. (2019)’s reported FZ coefficients for 25-mm diameter soaked and unsoaked NSWE brains compressed to 20% strain at 5 mm/min (0.00548/s) were: (i) Soaked: $E_\infty = 606$ Pa, $E_0 = 7390$ Pa, $\tau_0 = 4.49$ s, and $\alpha = 0.632$, and (ii) Unsoaked: $E_\infty = 595$ Pa, $E_0 = 6230$ Pa, $\tau_0 = 3.61$ s, and $\alpha = 0.627$.

For comparison of the calculated viscosity of SWE and NSWE brains, it is noted that the viscosity of coal-tar is 20 billion times the viscosity of water (1 mPa·s at 20°C) (Johnston, 2013). Among the SWE brains, an ANOVA with a post-hoc Student’s t-test analysis and significance level of 0.05 showed that the viscosity for soaked and unsoaked brains are statistically different.
Figure 3.9  Compressive rate and time in the solution for the averaged fractional Zener coefficient described by (a) $E_\infty$, (b) $E_0$, (c) $\tau_0$, and (d) $\alpha$. Error bars represent the standard deviation.

(p=0.0096). The soaked, SWE brains were 47% more viscous than the unsoaked, SWE brains. Further, among soaked tissue, the SWE tissue was 23% more viscous than the NSWE tissue tested by McCarty et al. (2019). Similarly, the unsoaked, SWE tissue was 38% more viscous than the unsoaked, NSWE tissue from the experiments by McCarty et al. (2019). The viscosity calculated for unsoaked, NSWE brain (via the FZ coefficients optimized by McCarty et al. (2019) at 20% strain) is higher than the unsoaked, NSWE brain found by Bentil (2013) at 10% strain. The increased strain level in the experiments by McCarty et al. (2019) led to an increased instantaneous modulus value, and thus the increased value for the calculated viscosity.
Figure 3.10  Compressive rate and soaking state of the brain for the averaged fractional Zener coefficient described by (a) $E_\infty$, (b) $E_0$, (c) $\tau_0$, and (d) $\alpha$. Error bars represent the standard deviation.

Table 3.3  Viscosity of brain tissue during unconfined compression tests at 5 mm/min.

<table>
<thead>
<tr>
<th>Exposure State</th>
<th>Soaked State</th>
<th>Strain Level</th>
<th>Viscosity (Pa · s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWE</td>
<td>Soaked</td>
<td>20%</td>
<td>14690 ± 4581</td>
</tr>
<tr>
<td>SWE</td>
<td>Unsoaked</td>
<td>20%</td>
<td>9995 ± 1706</td>
</tr>
<tr>
<td>NSWE</td>
<td>Soaked</td>
<td>20%</td>
<td>18120 ± 5671 (McCarty et al., 2019)</td>
</tr>
<tr>
<td>NSWE</td>
<td>Unsoaked</td>
<td>20%</td>
<td>13800 ± 3641 (McCarty et al., 2019)</td>
</tr>
<tr>
<td>NSWE</td>
<td>Unsoaked</td>
<td>10%</td>
<td>12500 ± 1054 (Bentil, 2013)</td>
</tr>
</tbody>
</table>
3.5 Discussion

Shock wave exposed (SWE) brain tissue samples from 32 brains were subjected to unconfined compression tests at compressive rates of 5, 50, and 500 mm/min. Samples from 22 porcine brains were placed in normal saline solution and refrigerated for a designated period of time, therefore investigating the effect of a time delay on the mechanical properties in the event that an experiment cannot be completed immediately. A fractional Zener viscoelastic model was used to obtain the material properties of the brain.

For the brains stored in normal saline solution and refrigerated, the results showed a statistically significant relationship between the time in solution and three of the four fractional Zener coefficients \(E_0\), \(\tau_0\), and \(\alpha\) describing the stress response of porcine brain tissue. The compressive rate statistically influenced two of the four FZ coefficients, \(\tau_0\) and \(\alpha\), with the p-value of \(E_0\) \((p=0.055)\) slightly greater than the significance threshold of 0.05. Since the relaxation time and fractional order were statistically influenced by the compressive rate, this may indicate that the fractional Zener model may require modification by including additional time-dependent term(s) to accurately model the brain’s mechanical response across a wide range of strain rates. An additional fractional element(s) will be considered in the future, to introduce more time-dependent term(s) in a modified FZ constitutive model. This modified FZ model is expected to yield stress-time curves that can also capture the influence of gravity and relaxation on the brain’s deformation, during the ramp phase at both low and high strain rates. Ideally, the set of intrinsic material parameters for a constitutive model would hold true for a material’s response, regardless of compressive rate. However, a single set of FZ coefficients were not able to fit the stress response data across all compressive rates considered due to challenges resulting from the unconfined compression experiments with the inhomogeneous brain material.

For instance, porcine brain samples tested at given compressive rates, after similar time in solution, show a consistent stress relaxation curve over time. The peak magnitude of the stress relaxation curve increases as the length of time in the solution increases, as shown in Figure 3.7. Variability among the stress relaxation may be a result of the initial stresses applied to each sample.
before beginning the unconfined compression experiments (Hrapko et al., 2008). In order to secure
the sample between the plates of the rheometer, a preload between 0.01 N and 0.08 N was applied
prior to the beginning of each experiment. The preload translated to an initial stress, which may
have resulted in both a stiffer response during loading and after relaxation (Hrapko et al., 2008).
As a result, the minimum amount of preload was applied while still allowing the brain sample to
touch both plates.

There were inherent challenges to the experimental set-up, such as obtaining an accurate height
measurement of the brain. Measurements taken immediately after coring a brain sample became
obsolete after placement of the sample on the bottom Peltier plate. Therefore, cored brain samples
were tested immediately after coring to minimize the variability of the mechanical response due to
the tissue collapsing under the force of gravity. In addition, the rheometer used in these experiments
was affixed with smooth stainless steel top and bottom plates. Due to the brain tissue’s viscous
properties, there is no guarantee that the tissue evenly adhered to the top plate. If only a section
of the tissue adhered to the top plate, a small initial stress could have resulted (Cheng et al., 2008).
Previous studies have used lubricants to establish uniform boundary and loading conditions (Cheng
et al., 2008).

The differences in the measured material properties may instead be a result of differences in
the ratio of gray and white matter in the cored sample, and be minimally affected by the preload.
Due to the brain’s inhomogeneous structure, the material properties within the brain vary between
anatomical regions and the composition of white or gray matter. For example, white matter from
the corpus callosum and corona radiata has been found to be stiffer than the gray matter of the
cortex and thalamus (Jin et al., 2013). In direct contrast, gray matter from the thalamus has also
been found to be 1.3 times stiffer than the white matter found in the corpus callosum (Prange and
Margulies, 2002). As a result, the proportions of gray and white matter must be consistent in order
to accurately compare the stress relaxation response between different brain tissue samples (Budday
et al., 2017; Boudjema et al., 2017; Finan et al., 2017; Jin et al., 2013; Prange and Margulies, 2002).
In this study, samples were extracted from the same region of the brain while striving for a consistent
anatomical structure. Even so, some variance in the distribution of gray and white matter of the cored sample still existed. Due to the aforementioned challenges (e.g. application of a preload, degree of brain adhesion on the top plate, and composition of white and gray matter) influencing the measured stress response at each compressive rate, the material parameters for the FZ model were provided as an average with a standard deviation.

As shown in Table 3.3, the viscosity of unsoaked, SWE brain tissue was less than the viscosity of unsoaked, NSWE tissue during unconfined compression tests at 5 mm/min. One possibility for the low viscosity of the unsoaked, SWE brain is that the connecting tissue was damaged during the shock wave exposure, therefore resulting in tissue that was more compliant to deformation. The literature reports that neuronal cell damage (e.g. structural, capillary hemorrhages, and vascular leakages from disruption of the blood brain barrier), following blast exposure, can lead to a more compliant brain tissue (Kabu et al., 2015; Laksari et al., 2014; Cernak, 2017). Further, the soaked and unsoaked SWE tissue was 23% and 38% more viscous than the corresponding NSWE tissue found by McCarty et al. (2019), respectively. While the unsoaked, SWE tissue underwent unconfined compression experiments immediately after shock wave exposure, the soaked, SWE brain was placed in saline solution for 0.5 – 6.0 hours between shock wave exposure and undergoing compression experiments. Thus, the high viscosity of the soaked, SWE brain tissue may be due to increased *postmortem* time or the addition of the absorbed saline solution. This observation is supported by the delayed shear experiments conducted on bovine liver tissue by Ayyildiz et al. (2014), where the storage (elastic component) and loss (viscous component) moduli was found to increase as the amount of time stored in a solution increased.

Fresh human brain tissue is approximately 30% stiffer than porcine brain tissue (Prange and Margulies, 2002). However, the human brain tissue samples acquired in Prange and Margulies (2002)’s study were the result of temporal lobectomies performed on epilepsy patients, leading to the possibility of differences in stiffness between healthy and diseased human brain tissue. In order to apply the FZ coefficients for uninjured porcine brains to human brain tissue, the FZ coefficients
and $E_0$ can increase at most to 30%. For SWE human brains, the appropriate stiffness values for $E_\infty$ and $E_0$, along with $\tau_0$ and $\alpha$, will need to be quantified following future experiments.

### 3.6 Conclusion

Whole porcine brains were exposed to a shock wave five times in succession, on either the left or right hemisphere, to investigate the properties of the brain after a bTBI. After exposure, ten (10) brains were tested immediately and the remaining 22 were placed in saline solution and refrigerated between 30 minutes and 6.0 hours to determine the effect of a time delay on the mechanical properties. After the designated time period, tissue samples from both the soaked and freshly extracted brains (unsoaked) were subjected to unconfined compression tests performed at compressive rates of 5, 50, and 500 mm/min. In order to mimic a stress relaxation experiment, the samples were compressed to 20% strain and then allowed to relax at that strain level.

A fractional Zener constitutive model was used to obtain the material properties for the brains. The length of time in the solution statistically influenced three of the four FZ coefficients, $E_0$, $\tau_0$, and $\alpha$. Further, the compressive rate statistically influenced $\tau_0$ and $\alpha$. When the viscosity of the tissue was calculated using the fractional Zener coefficients, the viscosity of the unsoaked, SWE brain tissue was lower than the unsoaked, NSWE brain tissue found by Bentil (2013), potentially due to the tissue damage as result of the shock wave exposure. In contrast, the soaked, SWE brain tissue had higher viscosity than the unsoaked, NSWE brain tissue, which may result from the increased postmortem time as a result of the soaking period. This is the first study the authors are aware of that examined the mechanical response of brain tissue after shock wave exposure. Thus, the results of this study will advance the knowledge of the effect of TBI on the mechanical properties of brain tissue.

### 3.7 Acknowledgements

This research was financially supported by the Roy J. Carver Charitable Trust under Grant #18-5021 and is acknowledged gratefully.
3.8 References


3.9 Appendix: Average Fractional Zener Coefficients

Tables 3.4 and 3.5 display the average fractional Zener coefficient values (and corresponding standard deviation) for various combinations of compressive rates, time in the saline solution, and soaked state.

All values in the tables below describe brain tissue subjected to shock wave impact.

Table 3.4 Average ± Standard Deviation values for the Fractional Zener Coefficients versus Compressive Rate and Soaked State of the Brain

<table>
<thead>
<tr>
<th>Compressive Rate</th>
<th>Time in Solution</th>
<th>$E_{\infty}$ (Pa)</th>
<th>$E_0$ (Pa)</th>
<th>$\tau_0$ (s)</th>
<th>$\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mm/min</td>
<td>0.0 Hours</td>
<td>426 ± 110</td>
<td>5380 ± 520</td>
<td>2.69 ± 0.38</td>
<td>0.623 ± 0.022</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>0.5 Hours</td>
<td>599 ± 289</td>
<td>6690 ± 2570</td>
<td>2.64 ± 0.55</td>
<td>0.603 ± 0.016</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>4.5 Hours</td>
<td>619 ± 122</td>
<td>9100 ± 2440</td>
<td>2.72 ± 0.56</td>
<td>0.599 ± 0.014</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>6.0 Hours</td>
<td>725 ± 144</td>
<td>7770 ± 1590</td>
<td>3.50 ± 0.42</td>
<td>0.619 ± 0.010</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>0.0 Hours</td>
<td>583 ± 230</td>
<td>4770 ± 1440</td>
<td>1.62 ± 0.16</td>
<td>0.567 ± 0.026</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>0.5 Hours</td>
<td>506 ± 50</td>
<td>3980 ± 560</td>
<td>1.96 ± 0.26</td>
<td>0.554 ± 0.027</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>1.0 Hours</td>
<td>390 ± 96</td>
<td>3030 ± 658</td>
<td>2.23 ± 0.41</td>
<td>0.565 ± 0.020</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>4.5 Hours</td>
<td>802 ± 175</td>
<td>8800 ± 2130</td>
<td>1.32 ± 0.28</td>
<td>0.515 ± 0.022</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>6.0 Hours</td>
<td>485 ± 178</td>
<td>6620 ± 2690</td>
<td>1.87 ± 0.83</td>
<td>0.541 ± 0.029</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>0.0 Hours</td>
<td>608 ± 195</td>
<td>4380 ± 1130</td>
<td>5.81 ± 0.99</td>
<td>0.605 ± 0.014</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>0.5 Hours</td>
<td>421 ± 206</td>
<td>4750 ± 1100</td>
<td>6.29 ± 0.72</td>
<td>0.616 ± 0.011</td>
</tr>
</tbody>
</table>
Table 3.5  Average ± Standard Deviation values for the Fractional Zener Coefficients versus Compressive Rate and Soaked State of the Brain

<table>
<thead>
<tr>
<th>Compressive Rate</th>
<th>State</th>
<th>$E_\infty$ (Pa)</th>
<th>$E_0$ (Pa)</th>
<th>$\tau_0$ (s)</th>
<th>$\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mm/min</td>
<td>Soaked</td>
<td>653 ± 220</td>
<td>7610 ± 2370</td>
<td>3.00 ± 0.65</td>
<td>0.608 ± 0.016</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>Unsoaked</td>
<td>426 ± 110</td>
<td>5380 ± 520</td>
<td>2.69 ± 0.38</td>
<td>0.623 ± 0.022</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>Soaked</td>
<td>534 ± 202</td>
<td>5810 ± 2860</td>
<td>1.85 ± 0.65</td>
<td>0.543 ± 0.031</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>Unsoaked</td>
<td>583 ± 230</td>
<td>4770 ± 1440</td>
<td>1.62 ± 0.16</td>
<td>0.567 ± 0.026</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>Soaked</td>
<td>421 ± 206</td>
<td>4750 ± 1100</td>
<td>6.29 ± 0.72</td>
<td>0.616 ± 0.011</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>Unsoaked</td>
<td>608 ± 195</td>
<td>4380 ± 1130</td>
<td>5.81 ± 0.99</td>
<td>0.605 ± 0.014</td>
</tr>
</tbody>
</table>
### 3.10 Appendix: Sample Combinations Tested

Table 3.6  Number of samples tested at each compressive rate and time in solution combination.

<table>
<thead>
<tr>
<th>Compressive Rate</th>
<th>Time in Solution</th>
<th>Number of Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mm/min</td>
<td>0.0 Hours</td>
<td>6</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>0.5 Hours</td>
<td>8</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>1.0 Hours</td>
<td>0</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>4.5 Hours</td>
<td>4</td>
</tr>
<tr>
<td>5 mm/min</td>
<td>6.5 Hours</td>
<td>8</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>0.0 Hours</td>
<td>6</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>0.5 Hours</td>
<td>4</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>1.0 Hours</td>
<td>4</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>4.5 Hours</td>
<td>4</td>
</tr>
<tr>
<td>50 mm/min</td>
<td>6.5 Hours</td>
<td>8</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>0.0 Hours</td>
<td>8</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>0.5 Hours</td>
<td>4</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>1.0 Hours</td>
<td>0</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>4.5 Hours</td>
<td>0</td>
</tr>
<tr>
<td>500 mm/min</td>
<td>6.5 Hours</td>
<td>0</td>
</tr>
</tbody>
</table>
In this thesis, the mechanics of brain tissue exposed to shock waves was explored to yield data that will increase understanding of primary blast-induced traumatic brain injury (bTBI). Currently, the mechanics of primary bTBI are not well understood, therefore hindering the design of personal protective equipment (e.g. helmets) that can adequately prevent and protect against this injury. In order to advance the understanding of the mechanics of the injury, the effects of swelling due to storage solution and the effect of blast impact on the mechanical properties of brain tissue were investigated. To explore the effects of blast impact, whole porcine brains were exposed to a shock wave generated by an air pistol. In addition, to explore the effects of swelling, whole porcine brains were placed in a container with 200 mL of saline solution and allowed to soak between 30 minutes and 6.5 hours in a refrigerator. Experiments were performed such that samples were either both exposed to the shock wave and then soaked, only exposed to the shock wave, only soaked, or neither exposed to the shock wave nor soaked.

Both when the tissue was exposed and not exposed to the shock wave, the results showed a statistically significant relationship between the time in the solution for the instantaneous modulus ($E_0$), relaxation time ($\tau_0$), and fractional order ($\alpha$). When the tissue was not impacted by the shock wave, the average value for the instantaneous modulus ($E_0$) and relaxation time ($\tau_0$) increased by 11.9% and 11.2% among the soaked brains relative to unsoaked brains, respectively. In addition, it was discovered that regardless of the length of time the brain soaked in the solution, the amount of normal saline solution absorbed was proportional to the unsoaked mass of the brain. Thus, brains soaked in saline solution behave differently than the unsoaked brains, when considering the instantaneous elastic response ($E_0$) and the viscoelastic response ($\tau_0$ and $\alpha$). Further, the relaxation time ($\tau_0$) and fractional order ($\alpha$) were statistically influenced by the compressive rate regardless of whether the tissue was exposed to the shock wave.
The viscosity of the unsoaked, shock wave exposed brain tissue, calculated using the fractional Zener coefficients, was lower than the unsoaked, non-shock wave exposed brain tissue found by Bentil (2013). This is potentially due to the tissue damage resulting from the shock wave exposure. In contrast, the soaked, shock wave exposed brain tissue had higher viscosity than the unsoaked, non-shock wave exposed brain tissue, which may result from the increased postmortem time due to the soaking period. The results of this work will add to the knowledge of the effect of storage duration in saline solution on the material properties of brain tissue. Furthermore, the results show that the viscoelastic response of the brain may be an important factor to consider when modeling edema.

Overall, this research has produced contributions that will increase knowledge of the dynamic behavior of brain tissue exposed to shock waves. The data from this work can be used to validate computational models of brains used in bTBI studies such that the results can be used to design effective personal protective equipment. Future work will include investigation of the skull’s effect on the dynamic behavior of brain tissue exposed to the propagating shock wave.