BI-DIRECTIONAL FATIGUE LIFE BEHAVIOR OF BOVINE MENISCUS

by

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The following individuals read and discussed the thesis submitted by student Jaremy Creechley, and they evaluated his presentation and response to questions during the final oral examination. They found that the student passed the final oral examination.

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Dedicated to Lynniesue Allen, my mother who has always encouraged me to continue forward.

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AUTOBIOGRAPHICAL SKETCH

Jaremy Creechley was born in Coeur d'Alene Idaho and has since travelled the world, but claims Wyoming and Idaho as home.

ABSTRACT

Meniscal injuries due to tissue tearing are prevalent in the U.S. yet the failure behavior of the meniscus is poorly understood. Clinical studies indicate that fatigue failure causes many of these tears. The highly circumferentially aligned fibers result in transversely isotropic material properties. Tears preferentially align bi-directionally to the fiber orientation. The aim of this study is to present the bi-directional fatigue life behavior of meniscal fibrocartilage. A novel fatigue life approach was developed to achieve this aim. Forty-eight bovine specimens were subjected to cyclic sinusoidal tension-tension stress at 2 Hz until rupture. Normalized peak tensile stresses were determined at prescribed stress levels (SL) from 60-90% of ultimate tensile stress. A novel method was developed to estimate the ultimate tensile stress (UTS) per specimen from tangent modulus of an 8% precondition strain wave. UTS standard errors were reduced from 6.96/1.09 (LG/TR) to 1.96/0.48 (LG/TR) based on a correlation from a set of 64 UTS tests. In total 32 fatigue specimens were tested. The Weibull distribution was used to determine 50% mean lifetimes for each SL. S-N plots followed a linear-log form SL = -5.9 N_0 + 108 (LG) and SL = -5.2 N_0 + 112 (TR) for mean cycles to failure (N_0) with an average fit of R^2 = 0.800.18. Fatigue life results yielded a four-fold increase of mean cycles to failure between LG and TR orientations, but were not able to be shown statistically significant (p = 0.12). The slope of the damage rate decreased by 11% from LG to TR orientations, supporting the hypothesis that bi-directional material properties affect fatigue life behavior of the meniscus.

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CHAPTER 1

INTRODUCTION

Catastrophic failure is pervasive in the soft tissues that connect the musculoskeletal system. This tissue group includes ligaments, tendons, cartilages, and fibrocartilages all primarily comprised of collagen fibers and present structure similar to man-made fibrous composites [31]. Injuries to soft tissues result in over $80 billion in annual surgical costs [50]. The meniscus located in the knee joint (Figure 1.2) is particularly prone to failure with over 850,000 surgeries per year involving [38]. Meniscus tears commonly lead to pain and in some cases result in loss of function [38, 36]. Research indicates that up to one third of meniscus tears are the result of fatigue damage not related to degenerative diseases or traumatic injury [12, 42]. However, to our knowledge, no research has been reported on the bulk fatigue life behavior of meniscal soft tissue. Despite the clear clinical significance of meniscal tears, there is a fundamental lack of knowledge of failure behavior of meniscal fibrocartilage and particularly of fatigue failure behavior.

Similar to many fiber reinforced composite materials, the fibrocartilage of the meniscus has highly directional material properties and failure behaviors. The directionality is due to highly aligned collagen fibers that provide structural support along the fiber orientation resulting in bi-directional material properties. Such material variations affect the etiology of meniscal injuries which predominately align either with or against the primary fiber direction (Figure 1.2-B) [43]. Fatigue behavior of fibrous composites has proven difficult to model in man-made composites. Modeling soft tissues are further complicated by anisotropy and complex interactions betweens fibers and the ground substance [31, 10, 8, 46]. Fatigue behavior experiments of soft tissue have also proved challenging due to issues ranging from specimen clamping to dynamic biological environments [62, 25, 74].

Soft tissues fatigue research has predominately focused on biological and microstructural analysis with limited experimental data on fatigue damage leading catastrophic failure. Most damage modeling has relied on softening parameters derived from static failure properties [52, 27, 73]. Lack of experimental data for the anisotropic fatigue failure behavior in soft tissues will hinder many possible advancements in these models.

This research aims to fill this knowledge gap and provide bi-directional soft tissue fatigue life data. The first goal of this research is to develop a novel fatigue characterization technique that accounts for heterogeneity in soft tissue and reduces errors and requisite large sample sizes. The second goal is to present characterization of bi-directional fatigue behavior in meniscus fibrocartilage. This study is the first to characterize meniscus fatigue life of meniscus and to characterize bi-directional fatigue life in any soft tissue. These data points will enable anisotropic fatigue modeling and will provide crucial mechanical material properties of meniscus fibrocartilage.

1.1 Meniscus Structure

The menisci are two semi-lunar discs of soft tissue located in the knee joint between the femur and the tibia. They have a complex geometrical structure comprised of

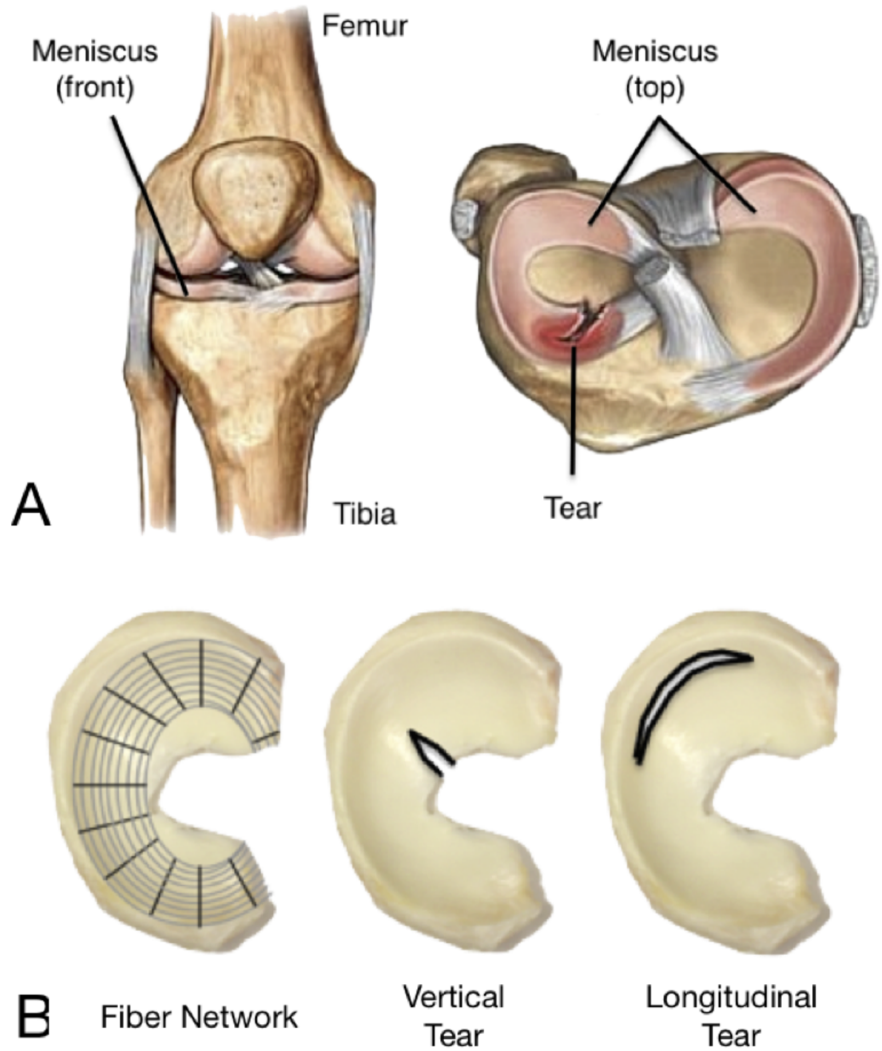

Figure 1.1: Knee Joint Overview. Knee joint with lateral and medial meniscus.

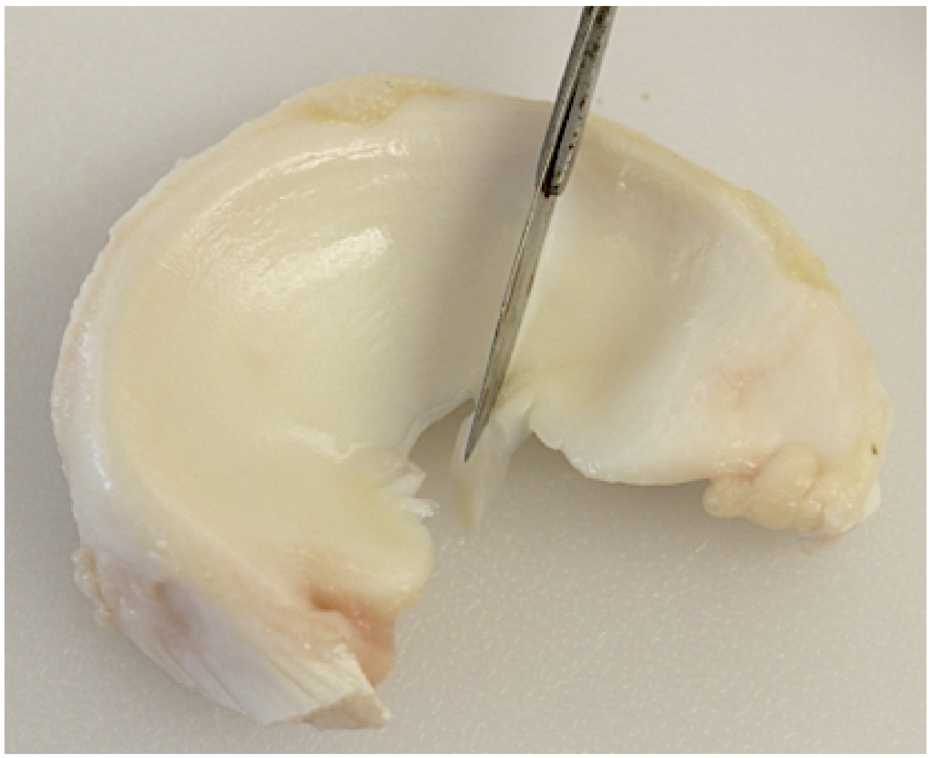

Figure 1.2: Whole Meniscus. Overview of a whole meniscus meniscus.

fibrocartilage interposed with cells. Fibrocartilage exists primarily in joint menisci and intervertebral discs, and it is the only cartilage that normally contains type-I collagen. The extracellular matrix (ECM) primarily consists of type-I collagen fibers embedded in a ground substance made of various proteoglycans and glycoproteins [55]. The ground substance performs a role analogous to the laminate of fiber composite materials and provides both elasticity and compressive strength. The ECM composition is 78% collagen (type-I, type-II, and type-III) with proteoglycans, glycoproteins, and elastin comprising another 8% by dry weight. Normal meniscal tissue consists of 72% water by gross weight [42]. It's collagen structure is grouped into bundles of fibers called fibrils and in the meniscus is predominately circumferentially oriented (Figure 1.3) [42, 61].

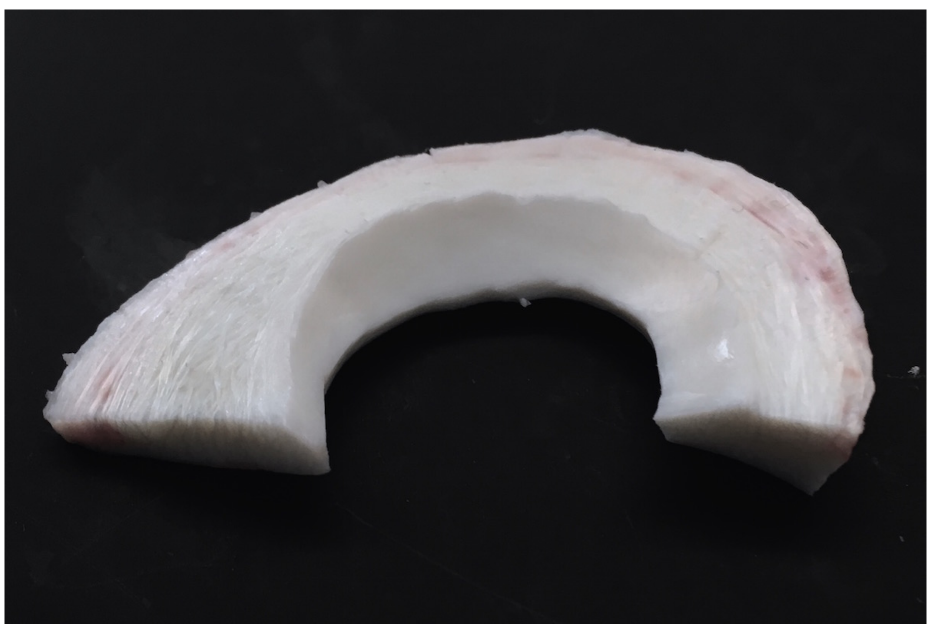

Figure 1.3: Fiber orientation of the meniscus. Fiber orientation of the meniscus. Meniscus fiber are predominantly aligned circumferentially along the shape of the meniscus.

The outer layer of the meniscus forms a sheath that protects the inner meniscus fibers and provides a smooth articulating surface. Fibers in this outer sheath (˜ 1 mm thick) have no preferred orientation. The knee contains an inner medial meniscus and an outer facing lateral meniscus with the lateral being slightly larger. The literature divides the meniscus into three sections or wedges: anterior, middle, and posterior from front to back. These regions have both clinical relevance and variations in properties including Young's and compression moduli [43, 2]. Each meniscus attaches to the knee bones via meniscal attachments to the tibia in humans (bovine lateral posterior attach to the femur) [28, 1]. The knee meniscus in humans and the stifle joint in quadrupeds are similar in structure and composition. Aside from various anatomical differences, the biomechanical properties, and composition of the bovine meniscus are comparable to those in humans and have been used by many researchers as a surrogate for human specimens [58, 2, 69, 41].

1.2 Meniscus Function

Knee joint menisci perform a crucial role in distributing stress in the tibiofemural joints in mammals. In humans, the menisci transfer and distribute approximately 80% of the stresses in the knee joint from the femur (top) to the tibia and fibula (bottom) bones (Figure 1.2) [35, 39]. For many decades the menisci were thought to be non-functional; however, removal of the damaged meniscus (meniscectomies) has been shown to increase the risk of osteoarthritis by 40% over 10 years [38, 51]. The development of hoop stresses has been shown to be crucial to maintaining proper function of the meniscus. For this reason, meniscal tissue structure is highly adapted to perform its function [39, 42, 50]. The collagen fibers are predominately aligned circumferentially to resist concentric strain (Figure 1.3). Circumferential fiber alignment enables the meniscus to generate the large hoop stresses required to distribute stresses in the tibia-femoral joint. Strains vary depending on the knee joint motion including normal gait loading, rotational shifts, and adduction moment [48]. Maximum principal strains calculated using finite element simulation based on experimental contact forces on human meniscus show a combination of stretching both outward and downward (Figure 1.4) [48].

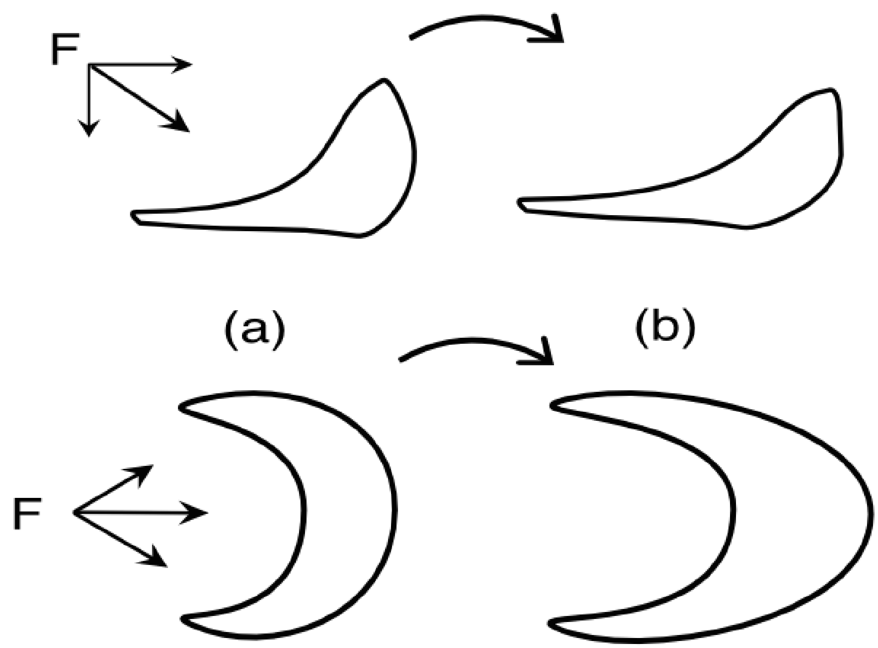

Figure 1.4: Example forces on meniscus. A) Side and top views of undistorted meniscus B) Meniscus shapes after forces from femur are applied.

1.3 Meniscus Failure

Injuries of the meniscus are very common with over 800,000 surgeries performed each year in the US alone [43]. Tears in the meniscus are the most common underlying cause of these injuries and vary in size, orientation, and effect on the structural function of the menisci. Younger populations tend to exhibit radial tears, generally associated with acute injuries. However, the predominate source of meniscal injuries are due to horizontal and complex tears that occur orthogonally to the primary fiber direction of the meniscus [42, 43]. There is still much debate regarding how these tears affect meniscus function since many tears exist without being symptomatic [12]. Improving our knowledge of meniscus tear locations requires a better understanding of the fundamental properties of the meniscus fibrocartilage. Tears of human menisci occur in two distinct patterns either aligning longitudinally with the fiber distribution or transversely to it [43, 42]. In many cases, these tears cause significant pain, joint locking, and other symptoms leading to the development of many types of repair techniques including suturing, meniscectomies (full and partial removal of the meniscus), and replacements. Only partial success have been achieved with any of these methods with current research indicating better success with methods that restore meniscal function [42]. Meniscectomies can induce further damage to the joint, with 45% of meniscectomies resulting in osteoarthritis within 10 years [51, 43, 29].

Metals have well-developed literature regarding basic fatigue properties with centuries of research and experimental data. Extensive fatigue data and research exists for polymers as well. Even man-made composite materials, though much more difficult to study, have had decades of research due to interest from the aerospace and other industries. However, research into macrostructural fatigue of soft tissues – such as the meniscus – have only recently started in ernest. Advances in various damage mechanics and macro-structural damage models tailored for the complexities of biological materials have begun to show success in modeling fatigue softening [60, 7, 68, 8]. None of these models have been broadly applied to modeling rupture due to fatigue. Extending these models to predict macroscopic failure from microstructural properties will require mechanical failure data. Catastrophic failure provides a clear experimental baseline for determining the probabilistic lifetimes of specimens, which is necessary for assessing the predictive power of both theoretical and computational fatigue models. Fatigue life characterization has been performed on various tendons [62, 31, 74]and a few comparative studies of fatigue life have been performed on meniscus repair devices [33, 64, 18, 65]. Experiments performed by Schechtman et al. on human tendons provided direct evidence that soft tissues exhibit fatigue life behavior similar to other materials. Even these results were far from conclusive for tendons and left unexplained discrepancy wherein traditional fatigue methods predicted tendon failure would occur after only a month of normal usage [63]. Based on these challenges, it's clear that more experimental data from more researchers will be needed to develop accurate predictive models. In particular, experimental data determining how fiber anisotropy, loading patterns, and environmental factors affect the fatigue life of soft tissues will be needed to discover which properties need to be included in models. Finite element modeling and increased computational power could potentially apply the predictive capacity of fatigue models to medical situations, but such models still need to know which properties are important and how to measure them experimentally. The purpose of this research is to provide understanding of the fatigue life of meniscus, and to provide techniques to experimentally measure the effect of anisotropy.

CHAPTER 2

BACKGROUND

2.1 Failure Theories

Failure theory of materials divides into two general categories: static and fatigue. Static failure occurs when stresses exceed the ultimate tensile strength (UTS) of a material, resulting in plastic deformation (i.e. irreversible damage), generally proceeding to catastrophic failure. Fatigue failure occurs under cyclic loading conditions below a material's maximum strength which accumulate damage over time, leading to weakening (softening), plastic deformation, and eventual fracture. The study of static and fatigue failure requires different mechanical characterization techniques, with a broad range of methods developed for both [11].

Study of fatigue failure in soft tissues has benefitted from the development of failure theories for fibrous composite materials [72, 17]. In this section background information relevant to soft tissue fatigue failure research is presented. A brief section discusses applying fatigue failure techniques, both experimental and modeling, to soft tissues.

2.1.1 Failure Modes

Material failure can occur with varying degrees of deformation before complete rupture. Soft materials that deform significantly before failure are ductile while materials with little deformation before rupture are brittle. Failure type classification depends on the material's ultimate strain limit and material category (e.g. brittle metals fail with $\epsilon_f = 0.05$ while plastics fail at strains often far above $\epsilon_f > 0.05$). Most materials fall somewhere between ductile and brittle and can often change depending on environmental conditions or types of failure loading (including static or fatigue). Fibrous materials are difficult to classify as brittle or ductile due to their multi-material composition that produce a unique frayed failure pattern visible in soft tissues (Figure 2.1-d) [63].

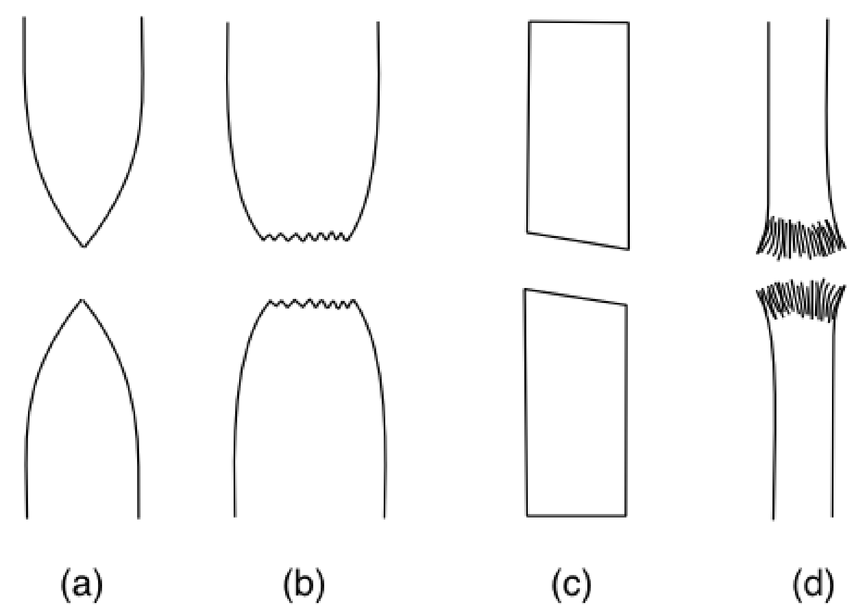

Figure 2.1: Failure modes for various material types. A) Ductile Failure B) Mixed Failure C) Brittle Failure D) Fibrous Failure

2.1.2 Fracture Mechanics

The initiation and formation of cracks underlie many failure theories. Several approaches have been developed to measure and study crack initiation and propagation. These can broadly be broken into three categories to measure crack formation or propagation [11]: Stress/strain, energy, and work methods presented as strain concentrators, K_c, energy release rate, G_c, and work, W_f. These formulations are useful for static strength analysis and have been commonly applied to soft tissues [23, 68, 3, 40]. Review of these results by Taylor et al. [71] has shown inconsistent results with fracture parameters not being independent of specimen or experiment variables. For reliable fatigue results to be obtained direct measurements of fatigue life are necessary.

Each approach has strengths and weaknesses in several areas including acquiring experimental values, applying theoretical values, and accuracy of predictions. Approaches based on stress and strain are simple but not as broadly applicable as energy or work methods for multiphase materials or finite element modeling. Energy or work-dissipation methods often present the best method for measuring advanced material properties including tear resistance and fatigue softening.

2.2 Fatigue Failure

Experimental measurements of fatigue failure is performed by repeatedly loading and unloading many specimens at stresses lower than a material's UTS. Despite the loading stresses being below the UTS threshold fatigue, cyclic loading can induce fatigue damage leading to catastrophic rupture. Fatigue damage occurs as micro-cracks accrue with successive loadings (Figure 2.2). Eventually as the micro-cracks increase in size and density they coalesce into larger fractures which accelerate the process until catastrophic failure occurs. This process occurs in all fatigued materials, although some materials resist the formation of micro-cracks below certain stress –

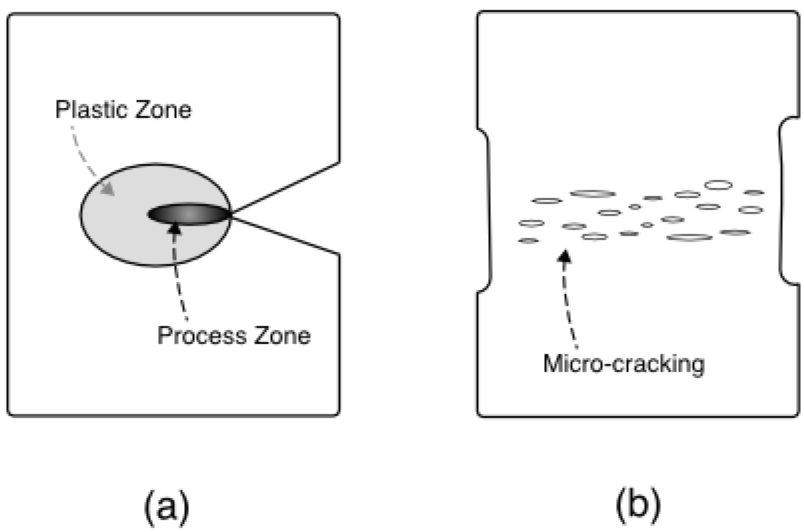

Figure 2.2: Crack Growth Diagrams. Originally developed for glasses then metals but now generalized to all materials. A) Cracked bodies contain a process zone where crack growth occurs. B) Micro-cracking occurs during fatigue resulting in softening and creep.

or strain – thresholds. This phenomena – known as a fatigue endurance limit – has valuable practical implications since these materials will generally not fail due to fatigue loading below their particular threshold (Figure 2.3) [11, 67].

Fatigue life is an inherently statistical measure determined by fitting certain statistical distributions to the number of cycles required to cause rupture as sampled over many specimens. To do this experimental sampling, external specimen loading can be either static or dynamic resulting in a primary driving which is either stress or strain based. Stress based loading methods apply a constant-amplitude stress waveform until failure occurs. Alternatively, strain based loading methods apply constant-displacement waveforms. Many materials exhibit different failure lifes based on the loading method. Specific to this research, studies in tendons have indicated that fatigue failure occurs at relatively consistent strain levels [59].

Eventually fatigue softening or damage effects lead to exponentially decreasing load bearing ability that can be measured empirically at the macroscopic level. These measurements of fatigue damage can be quantitatively expressed as softening factors or by power-law equations relating softening to fatigue life probabilities. The standard empirical formula used to quantify this is known as the Paris Law Equation 2.1 and is based on a power-law formulation deriving from exponential increases in micro-cracks leading to an exponential decrease in specimen survival probability.

2.2.1 Fatigue Life (Stress and Strain)

The most widely applied experimental fatigue method is stress based cyclic loading wherein a constant amplitude force-control waveform is applied to a specimen until failure. Crucial differences arise depending on how the cyclic stresses are applied, however, as the fatigue life can vary greatly depending on the specific stress loadings methods applied. These methods are broadly categorized by the loading configuration (compression, tension, or shear stresses) and the loading profile of the stress waveform employed with sinusoidal, square, or triangle waveforms being the most common. Further variations often include alternating stress types to produce compression-tension loading configurations. Fatigue life experiments are often designed to focus on a specific loading configuration in order to determine the fatigue life under that particular condition. An example would be testing concrete with a compression loading configuration and a sinusoidal waveform to approximate the fatiguing conditions commonly experienced for materials used on highways.

Fatigue testing (also referred to as fatigue life testing) falls into two regimes: low-cycle fatigue (classified as fatigue life experiments below 10^3 cycles), high-cycle fatigue (classified as fatigue life experiments above 10^3 cycles). Types of stress life are tension-tension (specimens cyclically loaded and unloaded to tension), tension-compression (specimens cyclically loaded to tension and then reversed loaded to compression), torsion (specimens cyclically loaded under torsion resulting in tension-compression). Many categorizations exist based on loading patterns seen in the target environments. Our research focuses on tension-tension as a starting point but could be extended to tension-compression loading configurations which are commonly seen in other soft tissues, in particular articular cartilage.

The different cyclic loading configurations can yield very different fatigue lives, especially in composite materials [37]. This can be seen in the next section which demonstrates the fatigue life difference between rotating-bending and fully-reversed torsion loading configurations. Fibrous composites exhibit additional failure modes including fiber buckling and laminate decoupling under different fatigue loadings [37, 22].

Strain-based fatigue life where specimens are cyclically strained to a specified strain is an alternative method for performing fatigue life characterization. Certain materials are well suited to strain life approaches, including low-cycle fatigue experiments [11]. This method is less favored in the research literature in general.

2.2.2 Fatigue Life Curves (S-N Curves)

Fatigue life curves are generally referred to as S-N curves based on the method used to graph experimental fatigue data, but are also known as Wöhler curves after August Wöhler who published the first studies on fatigue behavior [**W**]. These curves provide a straightforward technique for quantitatively fitting the fatigue life behavior of materials. Most materials will exhibit near linear failure curves when plotted against linear stress vs the log of cycles (linear-log scale) although some materials use log scales for both stress and cycles (log-log scales) [11, 67]. Extending on this basic method, various modeling schemes have been introduced over the years to improve the fits. More sophisticated fits first fit multiple data points at a specified stress level to Weibull or Log-Normal distributions. Estimated parameters of these distributions produce mean-lifetimes based on their particular means. More complicated schemes to fit limited numbers of sample sizes common with composite materials include pooling techniques, Bayesian analysis, and stochastic modeling among others [75, 26, 14].

Example S-N curves for steel show the existence of an endurance limit in addition to variations between fatigue loading methods (Figure 2.3) [5]. Different cyclic loading techniques (torsion, tension-tension, tension-compression, and more) can result in varying fatigue life behaviors for the same material. The rightmost S-N curve approches an asymptote where the material will effectively approach an inifinite fatigue life, which is denoted as the endurance limit of a material since under this stress level cyclic loading won't likely result in catastrophic failure (Figure 2.3).

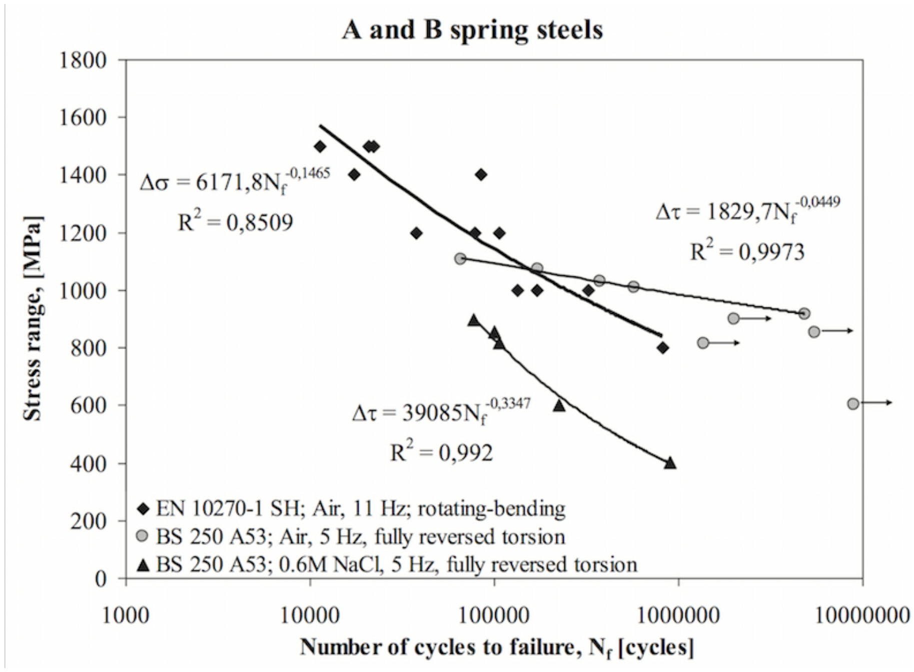

Figure 2.3: S-N Curves for steel. S-N Curves based on rotating-bending, fully reversed torsion, reversed torsion in corrosive environment. Angelova, *On Fatigue Behavior of Two Spring Steels* (Procedia Materials Science, 1997). Used with permission under creative commons license.

2.2.3 Modeling for Fatigue Life (SN Curves)

Many fatigue failure theories build upon the success of fracture mechanics in static failure analysis. The primary assumption in fracture mechanics is that cracking underlies failure. Modeling fatigue life mechanics is handled by assuming the formation of micro-cracks that accumulate during the fatigue process. Over time micro-crack densities reach high enough levels to cause catastrophic failure.

Fatigue life modeling in fracture mechanics can be modeled using Paris' Law:

$$\frac{\mathrm{d}a}{\mathrm{d}N} = C\,(K)^m \tag{2.1}$$

where a is crack length, N is cycles, C and m are material dependent constants. K is the circular stress intensity factor. However, this has not been well generalized to soft tissues. Obtaining accurate measures of ΔK has posed challenging in soft tissue experiments despite many attempts by researchers [70], which unfortunately limits the applicability of Equation 2.1 to empirically estimate soft tissue fatigue lifes based on fracture mechanics theory.

A better methodology is to fit fatigue data on S-N curves using purely phenomenological fitting functions based on statistical approximations. Whitney et al. developed a general pooling method based on the Weibull failure distribution and tailored for composite materials with limited sample size [75]. A modified form of this pooling method provides a robust phenomenological fit well suited for this experiment. A similar form to that used by Schechtman et al. are used in combination with the pooling method to produce robust fatigue parameters based on the limited data size [63].

$$CNS^b = 1 \tag{2.2}$$

The general form for a power law fit is shown in Equation 2.2. Constants C and b are material-dependent parameters while S and N represent the stress level and cycles to failure respectively. The next equation gives the reliability rate from the desired cycles to failure (N) as scaled by the average cycles to failure (N_0) and a reliability factor α_f. When combined with Equation 2.2, it yields a generalized power law and reliability Equation 2.4 with $K = C^{-\frac{1}{b}}$, $N = N_0$, and $-lnR(N_0) = 1$. Re-arranging these constants allows comparison of the power law formulation Equation 2.2 with the linear-log relation Equation 2.5 used by Schechtman et al.

$$R(N) = \exp\left[-\left(\frac{N}{\mathcal{N}_0}\right)^{\alpha}\right] \tag{2.3}$$

$$S(\mathcal{N}_0) = K\mathcal{N}_0^{-\frac{1}{b}} \tag{2.4}$$

The form found in Equation 2.4 can be fit to a linear-log S-N plot where the parameters can found from a linear slope between S and N. A slightly modified form is used by Schechtman et al. wherein the parameters are reworked to fit the linear-log S-N form directly, seen in Equation 2.5:

$$S = A - B\ln\mathcal{N} \tag{2.5}$$

The parameters A and B are general linear fitting constants that can be used to estimate fatigue life and compare the fatigue life of various materials. Due to the compound nature of fibrous composites are difficult to model phenomenalogically, a general power law formulation based Equation 2.5 is commonly used to empirically fit composite fatigue life data [75]. More advanced models have been developed to better model composite fatigue life data using entropic methods, Bayesian curve fitting, and even machine learning based techniques but these methods are difficult to apply and no consensus has been reached on which techniques work best [32]. A linear-log form of the power law in Equation 2.4 was used to fit the fatigue life data of tendons with good results as reported by both Schechtman et al. and Wang et al. [63, 74]. The parameters from these report can be compared to those of other soft tissues giving researchers clues as to their comparative properties.

Fatigue methods in metals are relatively well researched and understood with first research performed in the 19th century and developed by various scientists including W. Albert, Wöhler, P.C. Paris, among others. Despite this long history, there are still no conclusive and overarching theories that predict fatigue life in all materials. Aspects of fracture mechanics must be developed for each class of materials, and are mostly phenomenologically based (for example refer to a model developed for rubber-like materials [56]).

Weibull Analysis

Each stress level contains a set of fatigue specimens. The Weibull failure distribution is widely used for fitting both continuous and discrete failure events and has well developed and robust fitting methods [24, 75]. Previous research has fit soft tissue fatigue data using the Weibull and log-normal distributions with good results [21, 63], and these two distributions are known to fit the fatigue life of a wide array of materials. The Weibull and log-normal distributions were chosen in part due to their known applicability in other soft tissues in addition to being directly comparable with the results of tendon fatigue data, which given the paucity of data in this field is an important consideration. Weibull is the more common distribution in fatigue literature and the mathematical formulation is described here.

$$N_i \left(N_{i1}, N_{i2}, ..., N_{iN}\right), i = 1, 2, ..., m \tag{2.6}$$

$$f(N;\alpha,\mathcal{N}_{i0}) = \left(\frac{N}{\mathcal{N}_{i0}}\right)^{\alpha} \exp\left[-\left(\frac{N}{\mathcal{N}_{i0}}\right)^{\alpha}\right] \tag{2.7}$$

Each stress level produced contains N specimens with a total of m stress levels. Each stress level is fitted to the Weibull distribution shown in Equation 2.7. The parameters α_i and N_{0i} represent the shape and scaling parameters for each stress level.

Maximum likelihood estimation is a statistical technique for estimating fitting parameters. This is accomplished by maximizing the value of the likelihood function for a distribution:

$$\mathcal{L}(\theta\,;\,x_1,\ldots,x_n) = f(x_1,x_2,\ldots,x_n \mid \theta) = \prod_{i=1}^{n} f(x_i \mid \theta). \tag{2.8}$$

$$\hat{\ell} = \frac{1}{n}\ln\mathcal{L} \tag{2.9}$$

The maximum likelihood estimator (MLE) for the Weibull distribution is derived from Equation 2.8, and is given as:

$$ln(L) = m\,ln(\mathcal{N}) - m\mathcal{N}\,\ln(\alpha) + (\mathcal{N}-1)\sum_{i=1}^{m} ln(n_i) - \sum_{i=1}^{m}\left(\frac{n_i}{\mathcal{N}}\right)^{\alpha} \tag{2.10}$$

For many fatigue experiments, it is common for a subset of specimens not to fail during the time allowed for an experiment to run. These specimens are called run-outs, and their non-failure must be handled specially to account properly for their effect on the failure distribution estimation. In statistical methods, this process is known as type-I censoring, specifically for samples that do not fail during testing. Censoring can be incorporated into MLE by adding additional terms based on the likelihood of samples not failing given α and $\mathcal{N}$ parameters and is shown in

Equation 2.11.

$$ln(L) = m\,ln(\mathcal{N}) - m\mathcal{N}\,\ln(\alpha) + (\mathcal{N}-1)\sum_{i=1}^{m} ln(n_i) - \sum_{i=1}^{m}\left(\frac{n_i}{\mathcal{N}}\right)^{\alpha} - \left[m - r\left(\frac{n_i}{\mathcal{N}}\right)^{\alpha}\right] \tag{2.11}$$

Equation 2.11 introduces several new variables: m number of samples for a stress level (not to be confused with a Weibull modulus), r number of run-out samples, where $\mathcal{N}$, α, and n_i are the scaling, shape, and specimen lifetimes respectively. Numerical optimization of Equation 2.11 is straightforward and yields results comparable to least squares estimation for non-censored data. Overal MLE provides a robust and flexible method to characterize stress level failure probabilities, independent of the particular failure mechanisms. MLE estimation of each stress level combined can be combined with Equation 2.5 to provide a general characterization of the fatigue life based on limited number of samples per stress level. Other methods of modeling fatigue can incorporate UTS and residual strength, but is outside the scope of this study.

2.2.4 Fatigue-Creep

Most materials will begin to plastically deform during fatiguing leading to fatigue creep. This process occurs as materials become more compliant under loading due to the accumulation of damage. Over time, this process can proceed until the specimen geometry can be considered unusable. In mechanical engineering this problem often occurs in environments with extremes in heat or loading cycles, leading to creep-failure, which can be either statically or fatigue induced. Creep related to cyclic loading is an important aspect of fatigue life and provides valuable information on the degree of fatigue occurring in a material. The linear slope of the mode-II region of the fatigue failure provides a basic characterization of the level of creep failure due to fatigue.

2.3 Soft Tissue Failure Analysis

Fatigue behavior of soft tissues has proven to be a difficult topic to research. Experiments must account for both mechanical and biological aspects of these materials. Traditional methods of fatigue failure characterization based on fracture mechanics and static failure properties do not provide reliable methods to model fatigue failure. New experimental techniques must be adopted to find robust material parameters that can eventually describe and predict fatigue failure behavior using mechanistic models. Investigations of tendon fatigue damage have elicited some of the underlying micro-structural mechanisms such as fiber-kinking, however, these failure modes have yet to be incorporated into complete microscopic fatigue models [31] which would require complete macroscopic fatigue life data to validate the models.

Fracture methods broadly relied upon in metals, polymers, and other non-composite materials have shown only limited success in parameterizing soft tissue failure mechanisms (or man-made composite materials). Experiments measuring failure energy or fracture toughness in various tissues show high variation between experiments and tissue types. Based on these variations, one group, Taylor et al. published a paper indicating that reported toughness values of soft tissues (including their own recently published work) were not suitable for modeling soft tissue due in part to their high crack propagation resistance which results in sporadic critical strain energy release rates [23, 70]. Links of fatigue damage and fracture toughness have been studied but not conclusively determined [16]. Since fracture toughness and critical strain energy release rates remain highly dependent on specimen dependent factors including crack length and speed it is impractical to predict general fatigue life based on these parameters. The underlying reasoning is that process zones do not grow with crack size on a power law scale. This limits the applicability of Paris's law (Equation 2.1) for determining fatigue life since it assumes such a relationship between crack growth and the critical strain factor ΔK. Therefore, the research methods in this research rely on phenomenological characterizing techniques including using the Weibull distribution combined with pooling techniques to reduce intra-specimen variability as detailed by Whitney et al. during early research into the fatigue life of composites [75].

Many researchers have begun focusing on advanced computational approaches based damage mechanic theory, to deal with the heterogeneity of soft tissues. This theory extends continuum mechanics to include damage parameters directly into the constitutive equations for materials. Finite element implementations of damage mechanics can model arbitrary specimen geometries, opening the potential to derive intrinsic failure parameters from non-uniform specimens. An early example of this showed that meniscus static failure properties were primarily dependent on their unique geometry [6]. More recent results have not significantly improved upon these early results but have not yet been extended to simulate fatigue life properties [53, 8, 53]. Damage mechanics based on the static failure of soft tissue and has been more researched for a variety of soft tissues and shown interesting results [54, 8, 47]. However, future FEM simulations will need to be extended to incorporate fatigue life predictions. Validations of these models will require experiment characterization results to compare against, which is an intended benefit of this research.

A wide body of research has been conducted on microscopic fatigue damage and even macroscopic fatigue damage but has not resulted in the general ability to model macroscopic fatigue life necessary in engineering applications. Experiments on characterization of macroscopic fatigue life behaviors of soft tissues are notably sparse [63, 31]. Schechtman et al. provided the first fatigue life behavior for human tendons; wherein they noted the difficulty of performing fatigue experiments in soft tissues [63]. The same group later noted the limitations of their earlier research when navely applied without consideration of healing mechanisms. Their calculations predicted that human leg tendons would fail after a month of normal usage [62]; fortunately this does not reflect reality, so they proposed including healing effects into soft tissue fatigue results. Determining healing rates lay outside the scope of this thesis, but the characterization of the failure rate of the bulk tissue sets a lower bound on the required healing rate or ability of the biological environment to reduce fatigue damage. Either of these effects must be present at a rate which prevents the mechanical failure based on the fatigue life of collagen.

Overall, many types of failure theories and techniques have been applied to soft tissues from fracture mechanics to damage mechanics, yet there is still much research needed before the fundamental fatigue failure processes in these materials can be well understood [68, 9, 30]. In vivo studies of tendon fatigue damage provides valuable background on the biological processes influencing damage processes [4, 66]. Factors such as fiber kinking and inflammations both contribute to the micro-structural properties that will be relevant to future investigations. Since these results implicate fiber failure as a key mechanism to fatigue failure, incorporating related research in fibrous composites is becoming an important topic but has yet to be fully embraced by researchers for fatigue research [66, 19, 20, 49].

Fibrous composite research shows strong links between loading directions and fatigue damage [34, 44, 57]. This current research builds on this link and investigates whether fiber directionality will affect fatigue behavior in meniscal specimens. Future research will need to be performed to elicit the unique properties of soft tissues and both fibrous composites and other advanced man-made materials. Their high resistance to crack propagation and self-repair abilities have proven an important source of inspiration for advancements in materials design [45, 76]. Furthering our knowledge of fundamental fatigue properties in biological materials will also benefit the development of future man-made composite materials.

CHAPTER 3

MANUSCRIPT

Fatigue Life of Bovine Meniscus under Longitudinal and Transverse Tensile Loading

Journal of the Mechanical Behavior of Biomedical Materials

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3.1 ABSTRACT

The knee meniscus is composed of a fibrous matrix that protects the tibiofemoral articular cartilage from excessive loads. Consequently, large cyclic stresses on the meniscus result in frequent tearing with uncertain etiology. Fatigue failure is a potential failure mechanism for many of these tears but is poorly characterized. The objective of this study is to measure the fatigue life of bovine meniscus when applying tensile loads either longitudinal or transverse to the principal fiber direction. Fatigue experiments consisted of cyclic loads to 60, 70, 80 or 90% of the predicted ultimate tensile strength until failure occurred or 20,000 cycles was reached with a sample size (N=12) samples in both longitudinal and transverse loading directions.

Results produced S-N curves that had strong negative correlations for both loading directions, where the slope of the transverse S-N curve was 11% less than the longitudinal S-N curve (longitudinal: $S = 108 - 5.9\ln(N)$; transverse: $S = 112 - 5.2\ln(N)$). The Weibull distribution provided adequate fitting of the failure data. Strongly significant differences ($p=0.001$) were found when comparing data from the two fatigue loading directions, with a 2-fold increase in failure strain and a three-fold increase in creep of transverse compared to longitudinal loading directions. This study has measured for the first time the susceptibility of the meniscus fibrocartilage to fatigue failure under tensile loading, and has found that fatigue properties are dependent on fiber

orientation. Collectively, these results suggest that the non-fibrillar matrix is more resistant to fatigue failure than collagen fibers which may be important to meniscal tear etiology.

3.2 Introduction

The knee meniscus is a fibrocartilagenous soft tissue that distributes and dissipates cyclic loads across the tibiofemoral joint. By distributing loads, the meniscus can protect the articular cartilage by reducing the peak stress transmitted across the cartilage surfaces by over two-fold.[41] The meniscus performs this important function in an extreme mechanical environment that experiences sudden and recurring forces, and consequently the meniscus is one of the most frequently torn soft tissues in the body, with over 500,000 acute incidents in the U.S. each year.[16] Tearing of the meniscus can cause pain, swelling, joint instability, and increased risk of developing osteoarthritis.[21, 20, 29] Unfortunately, for most meniscus injuries, there is no effective treatment to fully restore meniscus function.[20, 23, 6] Improvements in the treatment and prevention of meniscus injuries require an understanding of the failure mechanisms that cause tears to develop and propagate.

While meniscal tears are most commonly associated with a single high-magnitude loading event, there is evidence that meniscal tears may also develop from repeated exposure to low-magnitude loads, a phenomenon known as fatigue failure. These fatigue failures occur at stresses below the material strength, as repetitive loads cause microcracks to form and propagate to fracture. A recent study found that a third of patients with acute meniscus tears did not have a traumatic event or degenerative condition, and therefore the tears may be related to fatigue failure,[11] while other studies have designated similar tear etiologies as atraumatic.[40, 36] The existence of fatigue failure in soft fibrous tissue is further supported by numerous studies in tendon, which have demonstrated that low-magnitude repetitive loading will ultimately cause acute tendon failure.[31, 30, 12, 38] Tendon research has also characterized fatigue behavior using a stress-life method, whereby the number of cycles to failure is measured at variable stress levels.[31] This information was used to predict fatigue life in order to identify loading patterns that lead to overuse injuries.[31]

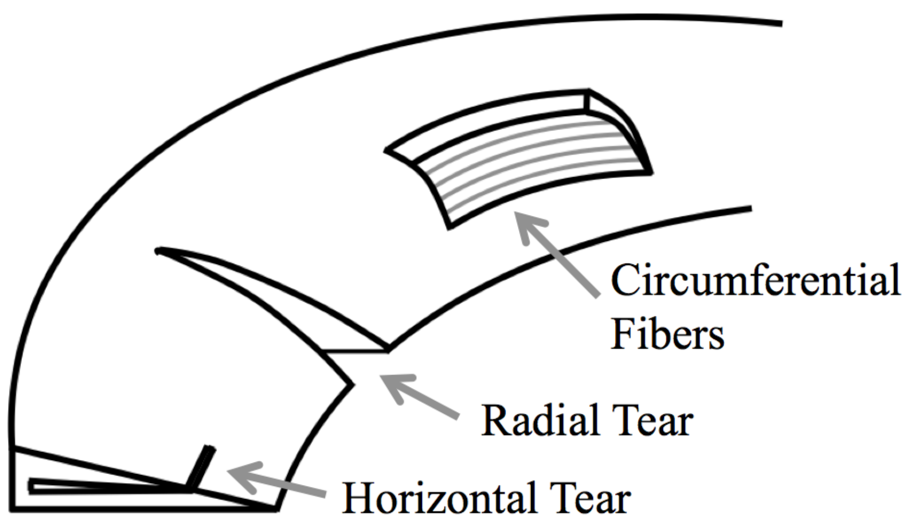

Figure 3.1: Meniscal Tears. Illustration of common meniscal tears and the principal fiber orientation.

To fully characterize meniscus fatigue behavior, it is important to consider the anisotropic extracellular organization that enables the meniscus to support large stresses. The meniscus extracellular matrix is structurally reinforced with a fibrous collagen network that makes up 75% of the dry weight.[19] These collagen fibers are embedded in a ground substance that consists mostly of glycosaminoglycans, glycoproteins, elastin and water.[22] In meniscus, the fibrous architecture displays a distribution of fiber orientations, where the majority of collagen fibers are aligned *longitudinal* to the meniscus circumference Figure 3.1, and a smaller subset of collagen fibers, called tie fibers,[3] are aligned *transverse* to the circumference. The circumferential collagen fibers provide the majority of the load distribution function, as these fibers resist deformation caused by the circumferential tensile stress or hoop stress generated in the semi-circular meniscus during joint compression.[23] The generation of tensile strains during joint compression, both longitudinal and transverse to the circumferential fiber direction, have been experimentally verified using imaging technology and strain transducers.[17, 18]

Failure patterns common to the meniscus relate to the anisotropic nature of the fibrous network. Radial tears account for nearly 10% of all meniscus tears and may occur when stresses longitudinal to the circumferential fiber direction cause tensile strains to exceed a failure limit Figure 3.1.[24] Horizontal tears account for approximately 35% of all meniscal tears and may occur when stresses transverse to the circumferential fiber direction cause tensile strains to exceed a failure limit Figure 3.1.[24] Although the stresses and strains that cause quasi-static failure of human and animal meniscus have been well characterized for quasi-static loading conditions, no study has yet characterized the tensile fatigue behavior of meniscus. Furthermore, to our knowledge, no study on soft connective tissue has directly measured the tensile fatigue behavior transverse to the principal collagen fiber orientation.

The objective of this study is to characterize the fatigue life of bovine meniscus under longitudinal and transverse tensile loading. This study aims to fill a current knowledge gap in the fatigue behavior of meniscus, and will determine if fiber orientation has any influence on fatigue properties.

3.3 Materials and methods

The stress-life fatigue behavior of bovine meniscus was characterized in two stages. In stage one, ultimate tensile stress (UTS) experiments were performed by straining specimens under quasi-static loading to failure. In stage two, fatigue experiments were performed on meniscus specimens by applying cyclic tensile stresses to either 60, 70, 80 or 90% of their predicted ultimate tensile strength (%UTS) until failure occurred or a maximum number of cycles was reached. Specimens were tested with fiber orientations aligned either longitudinal or transverse to the loading direction. This experimental design resulted in eight groups for fatigue testing, with four specimens in each group, for a total of 32 experiments. A Weibull distribution was used to fit the fatigue data in each group, and the mean value from these distributions was used to generate plots of stress level vs. cycles to failure (S-N curves).

3.3.1 Specimen Preparation

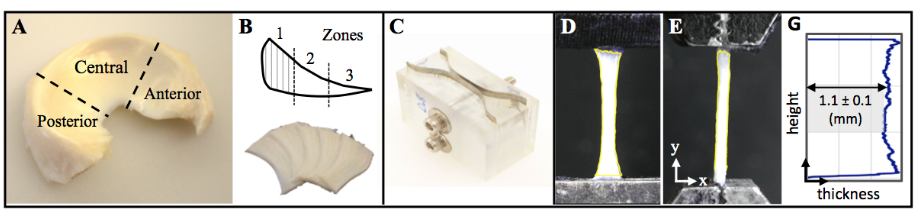

Figure 3.2: Meniscus specimen preparation. A) Bovine meniscus was sectioned into regions, B) then vertically sliced into 1mm thick layers and C) punched using a custom jig. D) Front and E) side dimensions were outlined using image-processing algorithms (yellow line). This protocol produced test specimens with G) consistent dimensions (grey box).

The UTS and fatigue failure experiments were performed using meniscus specimens acquired from left and right bovine knees. Whole knees were obtained 1-2 days after sacrifice from a local abattoir (Greenfield, Meridian ID). They were stored at

-20 C until they were dissected and the medial meniscus was harvested. Each whole meniscus was wrapped in gauze, which was moistened with saline, and was allowed to freeze thoroughly for a minimum of 1 day.

Frozen meniscus specimens were divided into three wedges using a hacksaw (Figure 3.2-A). Individual wedges from the posterior section were embedded in a composite of cellulose and saline and then packed in a small square plastic container (3.0 cm x 3.0 cm). These embedded meniscus wedges were returned to the freezer within 1-3 hours to minimize thawing. The reason for embedding the meniscus is that the cellulose media freezes into a solid cube and thereby provides planar surfaces that improve the slicing of the meniscus tissue into uniform layers.

The meniscus was layered using a commercial deli-slicer that was modified with a customized metal clamp system designed to rigidly hold each specimen cube during slicing (Globe, Bridgeport CT; Model C12). Vertical layers were sliced in Zones 1 and 2 of the posterior meniscus region, parallel to the circumferential fiber direction (Figure 3.2-B). The rationale for testing from this anatomical location, is that the highest incidence of horizontal and radial tears have been shown to occur in the medial meniscus in Zones 1 and 2.[24, 5, 37] Each meniscus wedge was sliced to a nominal thickness of 1.0 mm, and layers were allowed to thaw (Figure 3.2-B). This procedure allowed us to collect 10-15 layers per meniscus from zones 1-2.

The specimens were then cut into dumbbell shapes using custom razor punches (Figure 3.2-C). The long axis of the punches were oriented either longitudinal or transverse to the principal orientation of the visible fiber bundles. The central width of the punches was 1.0 mm, and the tab width for gripping to prevent slipping was set to 3.2 mm. The distance between the tabs, or gauge length, was set to 10.0 and 7.0 mm for longitudinal and transverse punches, respectively. The width to length aspect ratio of the razor punches was selected based on ASTM guidelines for tension-tension fatigue testing of matrix composite materials (ASTM D3479).[33]

The actual dimensions of the meniscus specimens were calculated prior to UTS and fatigue experiments using a custom Python program to analyze digital images of each specimen. Images were taken at side and front profiles of every meniscus specimen using a mounted digital camera (UTS tests: Sony, New York NY, AS100V; Fatigue tests: Cannon, Melville NY, EOS T3i). The Python program used OTSU thresholding from scikit-image libraries to segment the front and side specimen profile (Figure 3.2-D,E).[26] The binary outlines from segmentation were analyzed to determine the average number of pixels that spanned the middle third of the gauge length to calculate specimen width and thickness from the front and side profiles, respectively (Figure 3.2-G). Pixels were converted to metric units using a two-dimensional calibration frame (1 pixel = ˜10 m). This measurement technique enabled us to accurately calculate the inter- and intra-specimen variability of the specimen dimensions Table 3.1.

Table 3.1: Bovine Specimens. Physical Dimensions of Bovine Specimens.

Experiment	Fiber Orientation	Length* (mm)	Width (mm)	Thickness (mm)	Intra-Specimen Variability in Thickness (mm)
UTS	Longitudinal	14.5 ± 0.2	1.32 ± 0.13	1.22 ± 0.17	0.18 ± 0.04
	Transverse	8.1 ± 0.8	1.34 ± 0.07	1.03 ± 0.15	0.19 ± 0.04
Fatigue	Longitudinal	14.6 ± 0.2	1.20 ± 0.08	1.05 ± 0.11	0.14 ± 0.03
	Transverse	8.8 ± 1.1	1.08 ± 0.26	0.92 ± 0.19	0.17 ± 0.07

*clamp-to-clamp; all values are mean ± standard deviation

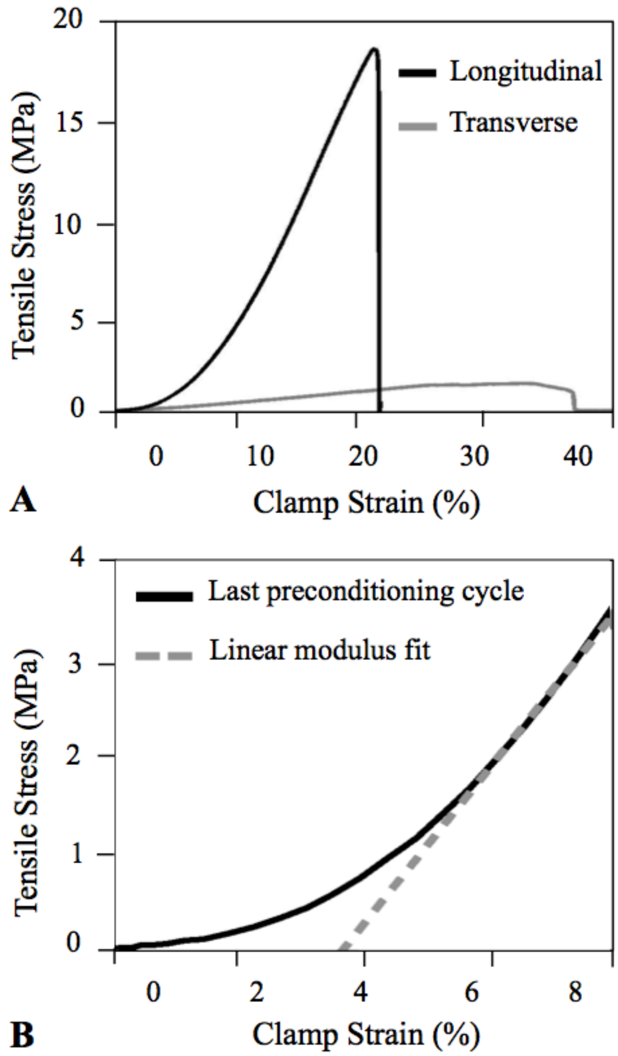

Figure 3.3: Raw data from UTS experiments. A) Stress- strain curves during quasi-static loading to failure for a longitudinal and transverse specimen. B) Prior to failure, specimens were preconditioned and the linear modulus was calculated by fitting a line (dashed gray) to the linear region of the stress-strain curve.

3.3.2 Quasi-Static Failure

The UTS of bovine meniscus was characterized prior to running fatigue experiments. A total of 21 meniscus specimens from six unpaired hind bovine knees were quasi-statically loaded in uniaxial tension. Two UTS groups were tested based on fiber orientation: Longitudinal and transverse. All experiments were conducted using an electrodynamic test system (Instron, Norwood MA; ElectroPuls E10000). Specimens were cut into dumbbell shapes and imaged to measure specimen dimensions Table 3.1 using previously described methods (see section 2.1). Prior to imaging, specimens were preloaded to 0.50 N or 0.10 N for longitudinal and transverse tests, respectively. Specimens were then mechanically preconditioned with a 20 cycle triangular wave and a 20 cycle sinusoidal wave, both at 2Hz and 8% clamp strain. After a 5 second rest, specimens were pulled to failure at 0.2 mm/s (Figure 3.3-A). The location of failure was documented and the stress-strain curve was analyzed to measure UTS and strain at failure. In addition, the linear modulus from preconditioning tests was calculated as the slope of the stress-strain curve from the 19^{th} triangular wave cycle (Figure 3.3-B). The linear modulus was calculated using linear regression to fit a straight line between 6-8% clamp strain ($R^2 > 0.98$ for all tests).

3.3.3 Fatigue Failure

In order to characterize fatigue life using a stress-life method, the UTS of a material must be known to determine the number of cycles to failure as a percentage or UTS (%UTS).[33] A challenge in measuring the stress-life for meniscus, or any soft heterogeneous tissue, is that large variations in UTS exist between specimens. These large inter-specimen variations preclude the reliable prediction of %UTS from a single average UTS value. To overcome this challenge, we correlated a specimen's UTS to its linear modulus, which was measured during preconditioning. Importantly, the resulting linear regression functions had a very strong positive correlation (see results, Fig. 5), and these linear functions allowed us to non-destructively predict the UTS for each specimen by measuring the linear modulus prior to fatigue testing. This key discovery enabled us to conduct fatigue tests based on %UTS, and to generate S-N curves for a highly heterogeneous material.

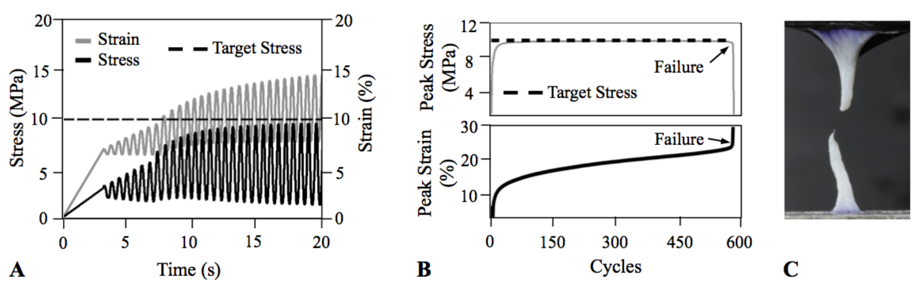

Figure 3.4: Results from a fatigue experiment. A) Stress and strain response during initial fatigue loading to a target stress of 70% predicted UTS. B) Peak stress and peak strain values during cyclic fatigue loading of a transverse specimen. C) Image of a specimen after failure by fatigue loading.

The longitudinal and transverse fatigue life of bovine meniscus was characterized uby testing a total of 32 specimens from 5 unpaired hind bovine knees in uniaxial tension. The posterior wedge from the medial meniscus provided on average 12 test specimens per knee Figure 3.2. Specimens were separated to ensure that all test groups had at least 3 specimens from different animals. Specimens were preloaded, imaged to determine dimensions, and preconditioned using the same methodology described for the UTS tests. The linear modulus was calculated using preconditioning data to predict the specimen-specific UTS, based on linear regression functions of UTS vs. linear modulus from quasi-static testing (see results, Fig. 5). Each specimen's predicted UTS was used to calculate the maximum stress magnitude at a specific %UTS (60, 70, 90 or 90%). This maximum stress magnitude was applied with a 2 Hz tension-tension sine wave that had a ratio of min force to max force set at 0.1 (Figure 3.4-A). To operate in load control, the Instron mechanical test system required an initial ramping of cyclic stress (Figure 3.4-A), and the number of cycles to failure began to be counted once the peak cyclic stress reached 80% of the targeted stress. These cyclic stresses were maintained until specimen failure or a maximum number of 20,000 cycles was reached. The number of cycles to failure and specimen length at failure, l_f, was recorded using a failure criteria determined by a 25% loss of stress resistance (Figure 3.4-B). Failure strain was calculated using $(l_o - l_f) / l_o$, where l_o is initial specimen length and l_f is final specimen length. Creep was calculated by subtracting the length at failure l_f from the specimen length when the number of cycles to failure began to be counted. The location of failure was recorded using a digital camera, and was classified as midsubstance if it failed within the gauge length (Figure 3.4-C). During cyclic testing, tissue hydration was maintained using a drip of 9% saline at room temperature (average drip rate of 73 mL/min).

Results from all tests were reviewed to ensure that the actual maximum stress magnitude during cyclic testing, after reaching steady state, was within 5% of the targeted stress level (average difference between targeted stress and actual stress for all tests = -0.4 2.8%). Due to large temperature fluctuations in the mechanical testing room, which influenced the accuracy of the load sensor during fatigue experiments, a total of sixteen specimens from four test groups were invalidated and new specimens were tested. During retesting, the problem was corrected by constructing an enclosed testing chamber that maintained air temperature to within 0.5 C.

3.3.4 Statistical Analysis

For quasi-static failure testing, the effect of fiber orientation on tangent modulus, UTS, and failure strain was assessed using a MANOVA. For fatigue failure testing, the effect of fiber orientation and maximum stress (%UTS) on tangent modulus, UTS (predicted), max stress (targeted), failure strain, and cycles-to-failure was assessed using a MANOVA, followed by Bonferroni post-hoc tests if significance was detected. The effect of fiber orientation on creep results was determined using an independent t-test.

Fatigue life stress life curves (S-N curves) were produced using a two step process. First a two-parameter Weibull probability distribution was fit to the cycles-to-failure data for each of the four %UTS test groups for both loading directions using SAS analytical software (SAS Institute Inc., Cary NC). The mean, scaling parameter, shape parameter, and goodness of fit of the Weibull probability distribution function were calculated for each group (eight groups total, N=4 per group). Type-I right censoring was automatically applied in SAS software via the built-in maximum-likelihood estimation method on any run-out specimens, which were defined as specimens not failing before the fatigue test stopped at 20,000 cycles. The second step employed the means of the resulting Weibull distributions for each stress level to fit a linear-log stress-life curve (S-N) by least squares fitting. The power-law S-N curve fits and the fatigue life data were used produce to plot the S-N curves for the longitudinal and transverse uniaxial tests, respectively. Regression analysis was performed on the S-N curve fits following the procedure deployed by Schectmann et al for human tendons (Schectmann 1998). This procedure follows the ASTM standard statistical techniques as closely as possible, with an S-N sample size (N=12) sufficient for exploratory research (Standard, ASTM 1997; Sutherland 2000).

3.4 RESULTS

3.4.1 Quasi-Static Failure

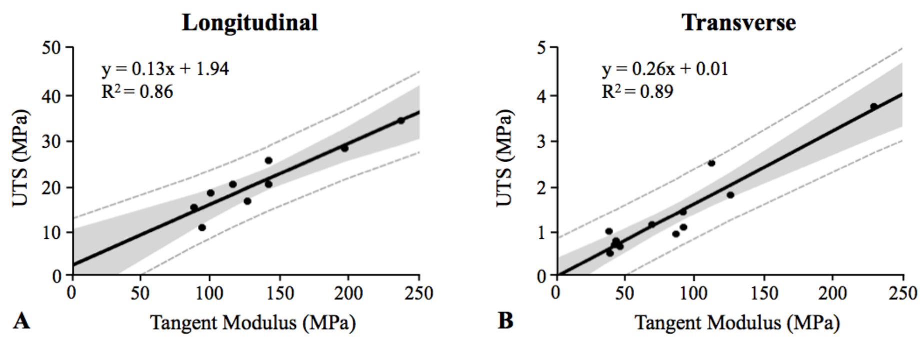

Figure 3.5: UTS vs Tangent Modulus. Plot of ultimate tensile strength vs the linear tangent modulus for bovine specimen from the quasi-static experiments.

Table 3.2: Quasi-Static Material Properties. Material properties from Quasi-Static Failure Experiments including UTS and Tangent Modulus.

Fiber Orientation	Linear Modulus (MPa)	UTS (MPa)	Failure Strain[a] (%)
Longitudinal	137.5 ± 49.8	19.4 ± 6.8	22.1 ± 3.0
Transverse	5.0 ± 3.3*	1.3 ± 0.9*	30.8 ± 5.6*

*Significantly different than the longitudinal fiber orientation (p<0.001)
[a]Clamp-to-clamp strain

There were significant differences in the experimental UTS results due to fiber orientation ($p < 0.001$). Specimens loaded transverse to the principal fiber orientation had a 93% decrease in UTS, a 96% decrease in linear modulus, and a 40% increase in failure strain Table 3.2, compared to specimens loaded longitudinal to the principal fiber orientation. A strong positive correlation existed between the specimen UTS and linear modulus for specimens loaded longitudinal and transverse to the principal fiber orientation Figure 3.5. Of the twenty-one specimens tested for UTS, 7 failed at the midsubstance (central third), 11 failed between the midsubstance and clamps, and 3 specimens failed at the clamps.

3.4.2 Fatigue Failure

Table 3.3: Fatigue Failure Material Properties. Properties from Fatigue Failure Experiments include Final Failure Strain.

Fiber Orientation	Stress Level (%UTS)	Linear Modulus (MPa)	UTS, Predicted (MPa)	Max Stress, Targeted (MPa)	Failure Strain[a] (%)	Cycles to Failure
Longitudinal	90	82.9 ± 27.9	12.3 ± 3.5	11.1 ± 3.2	20.7 ± 9.4	114 ± 221
	80	101.8 ± 70.9	14.7 ± 9.0	11.8 ± 7.2	18.6 ± 4.1	46 ± 48
	70	112.8 ± 33.6	16.1 ± 4.3	11.3 ± 3.0	21.2 ± 4.6	2155 ± 3851
	60	74.1 ± 23.0	11.2 ± 2.9	6.7 ± 1.7	24.1 ± 11.2	2424 ± 4551
	All	**92.9 ± 41.7**	**13.6 ± 5.3**	**10.2 ± 4.4**	**21.1 ± 7.4**	**1185 ± 2904**
Transverse	90	5.5 ± 0.7	1.4 ± 0.2	1.3 ± 0.2	34.4 ± 14.6	381 ± 759
	80	4.4 ± 1.2	1.2 ± 0.3	0.9 ± 0.3	41.3 ± 7.6	1801 ± 3469
	70	4.0 ± 1.4	1.1 ± 0.4	0.7 ± 0.3	46.6 ± 25.0	5976 ± 10,089
	60	4.0 ± 1.1	1.1 ± 0.3	0.6 ± 0.2	56.2 ± 17.1	10,598 ± 11,974
	All	**4.5 ± 1.2***	**1.2 ± 0.3***	**0.9 ± 0.3***	**32.9 ± 17.8***	**4689 ± 8275**

***Significantly different than longitudinal fiber orientation ($p<0.001$)**
[a]Clamp-to-clamp strain

The fatigue failure behavior of the medial meniscus was influenced by fiber orientation, but not the stress level (%UTS) of the fatigue test (Table 3.3; $p<0.001$ and $p=0.6$, respectively). Compared to specimens loaded longitudinal to the principal fiber direction, transverse specimens had a 2-fold increase in failure strain ($p < 0.001$), and a nearly four-fold increase in cycles to failure (not significant, $p = 0.12$). The transverse specimens also had three-fold greater creep than the longitudinal specimens (transverse creep = 32 17%, longitudinal creep = 11 8%; p=0.001). For transverse specimens, lower stress levels were associated with greater failure strains, but this trend was not significant ($p = 0.4$). There was also not a significant effect of fiber orientation or stress level on cycles to failure ($p = 0.17$ and $p = 0.12$, respectively). Similar to our quasi-static testing results Table 3.2, the linear modulus and UTS (predicted) of the transverse fatigue specimens were 94% and 88% less than the longitudinal fatigue specimens, respectively Table 3.3. Of the thirty-two specimens tested for fatigue failure, 12 failed at the midsubstance (central third), 18 failed between the midsubstance and clamps, and 2 specimens failed at the clamps.

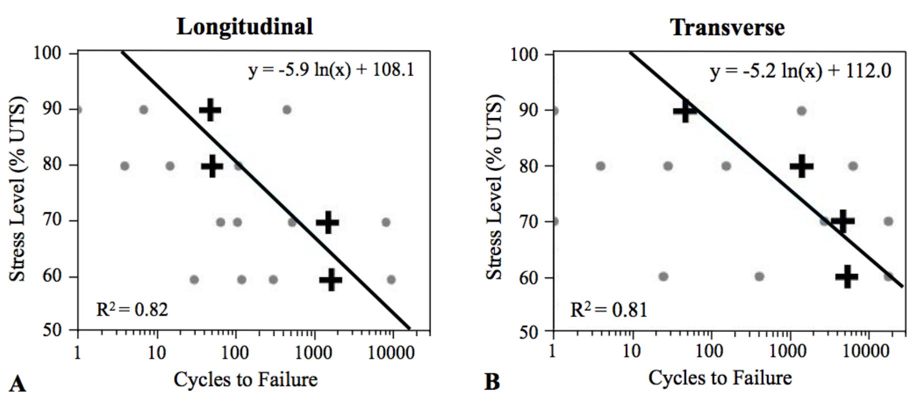

Figure 3.6: Correlation of UTS and linear modulus from specimens tested. A) longitudinal and B) transverse to the preferred fiber direction. Gray dots = cycles to failure for each specimen; Black cross = mean cycles to failure at each stress level (mean values from Weibull fit).

The Weibull probability distribution function produced good correlations to the fatigue failure results. At each stress level, positive linear correlations existed between the number of cycles to failure and failure risk (unreliability), with R^2 values of 0.80

Table 3.4: Weibull Parameters. Parameters from Weibull probability distribution function.

Fiber Orientation	Stress Level (%UTS)	Scale η	Shape β	Mean	R^2
Longitudinal	90	21.8	0.48	47.3	0.72
	80	45.9	0.81	51.7	0.99
	70	977.8	0.60	1482.1	0.82
	60	853.1	0.52	1606.8	0.86
Transverse	90	19.6	0.45	48.6	0.50
	80	413.8	0.38	1536.1	0.92
	70	396	0.28	5097.8	0.61
	60	2332.2	0.45	5845.2	1.0

0.18 Table 3.4. When plotting the S-N curves for longitudinal or transverse groups, strong negative linear-log correlations existed between the stress level and the mean cycles to failure Figure 3.6. The slope for the transverse S-N curve was 11% less than the slope of the longitudinal S-N curve. The y-intercepts of the S-N curves are an estimate of static strength, and therefore the S-N curves gave static strength values within 8% and 12% of the predicted static strength for the longitudinal and transverse specimens, respectively. The correlation of cycles to failure and unreliability was improved using linear and exponential functions, as they both gave fits with R^2 values of 0.83 and 0.93 for the longitudinal and transverse results, respectively.

3.5 Discussion

The characterization of fatigue behavior has been critical to the description and prevention of failures in engineered structures that are subjected to cyclic loading.[7, 28] Despite the fact that the meniscus experiences cyclic loads and a high rate of failure, the fatigue behavior of the meniscus has been poorly characterized. In this study, we have developed a novel methodology to measure the anisotropic fatigue behavior of soft fibrous tissues, and we have reported for the first time the in-vitro fatigue life of meniscus under tensile loading.

A principal finding of this study is that the stress-life fatigue behavior of the meniscus is dependent on fiber orientation. Specimens loaded transverse to the principal fiber orientation had on average 2-fold greater failure strains, 3-fold greater creep, and a 4-fold greater number of cycles-to-failure, although the cycles-to-failure results were not significant ($p=0.12$). These results indicate that the non-fibrillar ground substance is more fatigue resistant than the collagen network, since the non-fibrillar ground substance supports a larger percentage of stress in specimens loaded transverse to the principal fiber orientation. The creep to failure behavior may offer additional insight, as the greater creep in the transverse specimens suggests that the ground substance and tie fibers are able to accrue considerable damage before catastrophic failure. Another possibility is that the transverse meniscus specimens are able to dissipate more energy during cyclic loading, however, viscoelastic tensile testing of ligament found no difference in energy dissipation properties between transverse and longitudinal specimens.[8]

This study may provide insight into meniscal tears that are observed clinically. Common meniscal tear patterns include radial, horizontal, longitudinal (vertical), complex, flap, and bucket handle tears.[24] The longitudinal specimens tested in this study can relate to radial tear patterns, and therefore our fatigue results are relevant to a clinical study that found 32% of 435 patients with isolated meniscus tears, mostly radial, had symptoms consistent with fatigue failure (i.e. atraumatic with acute pain onset).[11] Results from the present study confirm that meniscal tissue is susceptible to radial fatigue failure, and that the circumferential fibers that resist radial tears appear more prone to fatigue than the non-fibrillar matrix. The transverse specimens tested in this study can relate to horizontal and longitudinal tear patterns, which both occur transverse to the principal fiber orientation and are two of the most common meniscal tears. Although horizontal tears are often asymptomatic, they can propagate to debilitating flap tears.[9, 42] Longitudinal tears are associated with traumatic events and can propagate to bucket handle tears that restrict full extension of the knee joint. To our knowledge, no clinical study has yet directly linked horizontal or longitudinal tears to fatigue failure, but considering the high incidence of these tears in older adults and the low level of cyclic stresses that caused fatigue fracture in our transverse specimens (< 1 MPa), fatigue may be a potential failure mechanism.

Results from the fatigue tests can be compared to previous work. First, the fatigue life from our longitudinal and transverse meniscus specimens had a slope that was less than half that of human extensor digitorum longus tendon (meniscus = -5.9, tendon = -14.8). This would indicate that the bovine meniscus is more resistant to fatigue failure than human tendon. Second, the *in vitro* tensile strains applied in the present study are likely much greater than the *in vivo* tensile strains that occur during normal physiological loading. A study by Jones et al. used strain gauges in cadavers to find average circumferential tensile strains to be 2.7% under 3x body weight, while

Kolaczek et al. imaged kinematic markers in cadavers using computed tomography to find that circumferential and superior-inferior strains could reach on average 4% tensile strain in certain locations under 1x body weight.[17] The circumferential and superior-inferior tensile strains measured in these cadaveric studies correspond to the longitudinal and transverse tensile strains measured in the present study, respectively. By using the linear modulus we measured during quasi-static testing, a 4% strain would result in stresses of 3 Mpa and 0.1 Mpa for longitudinal and transverse uniaxial specimens, respectively. Therefore, to model normal physiological loads, fatigue tests would need to be performed at 15% and 8% of the UTS for longitudinal and transverse specimens, respectively. Our fatigue experiments were limited to 20,000 cycles and 60% of the UTS, and therefore our results can only directly address the risk of fatigue failure during elevated loading events. It's important to note that any stress calculations based on previous experimental strain data are just estimates. Not only does the linear modulus over-predict the stress response that occurs in the toe region of the stress-strain curve, but Jones et al. and Kolaczek et al. likely under-predict meniscus strain relative to our study.[14, 17] The reason being that different reference configurations are used to calculate strain, as strains measured in the cadaveric studies are referenced from an unloaded condition that does not account for the in situ stresses that naturally exist in an unloaded state, while strains measured in the present study are referenced after application of only a small preload.

Results from the quasi-static tests can also be compared to previous work. Our linear modulus values compared well to previous research, as our results were within 5% of the 140 MPa and 5 MPa reported by Proctor et al. for the longitudinal and radial modulus of bovine medial meniscus, respectively.[39] Our UTS results were within 5% of the 18.9 MPa longitudinal UTS reported by Danso et al. for bovine medial meniscus,[10] and were within 40% of the 2.0 MPa transverse UTS reported by Tissakht and Ahmet for human meniscus. Our results were considerably lower than a study by Peloquin et al., which tested bovine medial meniscus and measured the longitudinal and transverse linear modulus to be 215 MPa and 17 MPa, respectively, and the longitudinal and transverse UTS to be 17 MPa and 4 MPa, respectively.[27] The reason for our lower values may be due to differences in specimen geometry and differences in the methodology used to curve fit the linear modulus.

This study may be helpful to scientists and engineers that are designing meniscal replacement devices. An obstacle in the development of functional meniscus implants has been fatigue failure during long duration animal studies.[15, 13] To improve fatigue properties, researchers have begun to evaluate fatigue life of synthetic soft-tissue analogs, typically under compressive loading.[25, 32] The present study will allow research groups to directly compare the tensile fatigue properties of their replacement devices to the tensile fatigue properties of native meniscus. Our evaluation of longitudinal and transverse fatigue life may be particularly useful for research groups that are engineering polymer composites to mimic the anisotropic fibrous matrix of native meniscus.[32]

Another important contribution of this study is that a strong positive correlation was found to exist between the ultimate tensile strength (UTS) and the linear modulus of the meniscus. This correlation influenced the design of our fatigue experiments by allowing us to non-destructively predict the UTS for each specimen, and then to prescribe the peak loading magnitude during fatigue testing based on %UTS. This specimen-specific approach diverged from previous fatigue studies of tendon, which prescribed the peak loading magnitude based on a single average UTS value.[2, 31] Although using an average UTS value would have simplified our fatigue testing protocol, and is recommended by ASTM standards for polymer matrix composites,[33] the high inter-specimen variability of meniscus hindered this global approach. For example, the coefficient of variation of the UTS for tendon specimens used in previous fatigue experiments was 12%,[30] while the coefficient of variation of the UTS for our transverse meniscus specimens was 70%. Consequently, if we used an average UTS value, we would have miscalculated the actual UTS during quasi-static testing by on average 60% per specimen. This large absolute error may explain why our preliminary tests that used an average UTS value for transverse fatigue tests were resulting in either immediate failure or no failure (data not shown). Alternatively, by using the linear correlation between linear modulus and UTS, our error in predicting the actual UTS for transverse quasi-static tests dropped to 19% per specimen, and using this alternative approach, our fatigue tests resulted in an S-N curve with a range of failure durations Figure 3.6. Future fatigue studies could further improve confidence in predicting UTS by only testing specimens with a linear modulus in a range that corresponds to the tightest 95% confidence interval (Figure 3.5, dashed lines). To our knowledge, the correlation between linear modulus and UTS has not been previously reported for meniscus tissue, and it would be interesting to determine if this correlation also exists in other soft connective tissues.

Limitations existed with this study. We only tested the peripheral region of the medial meniscus, and fatigue properties may vary in different regions (e.g. lateral meniscus). Another limitation is the use of bovine meniscus as a surrogate for human tissue. Although bovine and human meniscus have similar structure and mechanical properties,[34, 1] differences may exist in fatigue properties and our results should be interpreted accordingly. For this experiment, we examined fatigue life from tensile loads, as tensile strains occur during joint compression,[4] but fatigue failures may also occur from shear and compressive strains. A sample size of four was used for each test group, which will limit the certainty of mean fatigue life at each stress level Figure 3.6. Despite the small sample size, the Weibull distribution had strong positive correlations in predicting risk of failure in six of the eight test groups, and the sample size of 16 for each S-N curve exceeded ASTM standards for fatigue testing.[33] Finally, there are inherent limitations in using *in-vitro* testing to characterize the fatigue behavior of meniscus, as we do not account for the mechanobiological responses that occur *in-vivo*. Nevertheless, the in-vitro fatigue life reported in this study can serve as a baseline for the fatigue behaviors that may exist *in-vivo*, and this study can benefit researchers that wish to estimate the rate of healing needed to repair microtrauma induced by cyclic loading.[31, 35]

3.6 Conclusions

The anisotropic fatigue life of bovine meniscus was characterized at stress levels between 60% and 90% of the ultimate tensile strength. The meniscus was more resistant to fatigue failure when loaded transverse to the principal fiber direction, as the ground substance and tie fibers withstood very large creeps, of on average 32%, before catastrophic failure. To measure the fatigue life of soft specimens with large variations in UTS, this study developed an experimental methodology to predict a specimen's UTS based on linear modulus. This novel method may be useful for characterizing fatigue life in other soft heterogeneous tissues. Results from this study suggest that repeated loading at stress magnitudes below the material strength is a potential failure mechanism for common meniscal tears (radial and horizontal), and future research is warranted to determine the prevalence of fatigue induced injuries in fibrocartilage, and strategies to prevent structural damage caused by repeated loading.

3.7 ACKNOWLEDGEMENTS

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CHAPTER 4

CONCLUSION

The primary goal was the characterization of the bi-direction fatigue life behavior of bovine meniscus.

Key results include:

- The number of cycles to failure were found to vary four-fold between longitudinal and transverse loading directions using a MANOVA statistical test ($p = 0.12$ not satisfying $p0.05$), justifying future research in this area to obtain statistically significant results.

- This research represents a novel experiment procedure for soft tissue fatigue. Stress life based on a predicted-UTS produced S/N curves with $R^2 = 0.34, 0.70, 0.79, 0.54$ for linear-log fits of stress level to cycles to failure.
- Compared to longitudinal (LG) directions, averaged transverse (TR) UTS values had a 93% decrease UTS ($p < 0.01$), a 96% decrease of tangent modulus ($p < 0.001$), and a 40% longer strain at failure ($p < 0.001$).
- Strong correlation were found between a specimen's UTS and tangent modulus taken during a non-destructive precondition stage ($R^2 = 0.94$ Med/LG, 0.90 Med/TR).

- Accounting for the heterogeneity of specimen UTS reduces the variability of fatigue stress levels in both longitudinal and transverse directions. To our knowledge, this is the first time fatigue life data under transverse loading conditions has been reported for any soft tissue.
- Novel specimen preparation techniques were developed which provided sufficient aspect ratios to meet the ASTM 1395D fatigue standard.
- Machine vision based measurement system enabled precise measurement across specimens and the ability to quantify variability of intra-specimen measurements. Average variation of fatigue specimen thickness was 16%, showing a considerable degree of consistency for biological specimen.

4.1 Limitations

Soft tissue fatigue life research is fraught with challenges, many of which remain open issues. While limitations exist including mimicking *in vivo* conditions, specimen preparation, and accurate modeling materials with multi-scale properties this research provides strong bounds on the underlying fatigue properties of the meniscus that helps narrow down the scope of future studies. Many limitations of this field can be addressed suitably with the application of novel techniques and multi-disciplinary approaches.

The small sample size for each testing configuration limits the certainty of fatigue bounds. The size of the stress level set sizes are due to both the difficulty of testing soft tissue fatigue and the number of testing configurations (4). Despite this small size per stress level, a total of 48 fatigue samples were performed and resulted in S/N fits with errors comparable to tendon fatigue results [63, 25].

Experimental limitations of this study arise from the environmental factors. Similar to past research by Schechtman et al. [63], our experiment used a saline drip system at room temperature. There are known differences between in vivo and in vitro fatigue damage including variations of proteoglycan and mechanical properties in tendinopathies compared to in vitro fatigue testing [66]. Based on these difference, it is possible to speculate that synovial fluid may contain substances that modify the micro-structural properties to protect collagen fibers from fatigue damage accumulation. There are inherent limitations in performing *in vitro* testing on a biological specimen and the interpretation of results. However, the bulk fatigue properties of the meniscus establish a limit on the fatigue behaviors that can exist *in vivo*. Future studies on biological healing processes can benefit from estimating the rate of healing needed to repair mechanical fatigue.

Standard models for fitting bidirectional S/N curves in soft tissue have yet to be established. The methods used in this research relied on the extensive literature for fibrous composites [22, 75, 15]. Methods specifically designed to account for the highly variable nature of biological specimen could provide more robust statistical analysis and comparison of various soft tissues. Similar theoretical advances have already been made in the analysis of fibrous composites including techniques such as the usage of Bayesian analysis or machine learning techniques to derive accurate fatigue data from very sample sizes typical for fibrous composites [13, 15].

An important limitation of this research is the assumption that fatigue properties in human and bovine menisci are similar. This assumption is based on similarity of other mechanical properties including the aggregate modulus (0.09-0.16 vs. 0.11-0.21 MPa), and shear modulus (0.05-0.08 vs. 0.06-0.11 MPa) [2, 69]. Interspecies anatomical differences of menisci [58] have been noted and account for stress differences between knee joints but have not been shown to alter material property characteristics. Bovine menisci have been used as a surrogate for human meniscus previously, based on similar assumptions that bovine and human meniscal tissues share similar mechanical properties despite anatomical differences [2, 1].

4.2 Future Work

Extending the current research into high cycle fatigue testing of the bovine meniscus (stress levels below 60% of the UTS) would provide valuable information regarding long-term fatigue life differences between LG and TR stress orientations. There remains an open question whether the LG and TR orientations would exhibit a difference in fatigue limits although previous tendon fatigue results indicate that collagenous materials do not have a fatigue limit like many plastics.

Quantized polarized light spectroscopy combined with UTS failure and strain precondition to formulate more accurate mappings of meniscus fascicle orientations and specimen failure strengths. A complete mapping survey where high-quality sample layering using the entire meniscus would provide much more complete information for performing finite element modeling to predict failure rates and tear modes. Previous sample preparation methods such as vibratomes require gluing specimen to a sample plate. Several layers of meniscus tissue are rendered unusable for testing, making a whole meniscus survey much more labor intensive. The layering technique presented in Section sec. 3 resolves this problem.

The strong correlation between the tangent modulus and UTS indicates that the elastic moduli of the underlying soft tissue correspond to the quality of the specimens. Additional research has shown a strong correlation between the speed of ultrasound in collagenous samples and their mechanical strength. Building upon this it is likely that ultrasound characterization could be predictive of soft tissue fatigue quality. A non-destructive fatigue characterization method would provide significant potential for both research and clinical applications of fatigue life.

Another possible aspect of this investigation would be the ultimate development of a generalized theory to model and predict fatigue life behavior in a range of soft tissues. New research on the micro-structure of collagen combined with similar advancements from composite fiber materials research will enable the development and experimental validation of structurally based models. Due to the crack resistant nature of soft tissues, this could be valuable to the design of our next-generation composite materials.

Experimental characterization of human menisci would be important for providing validated fatigue life behaviors for clinical research applications. Further work could also extend upon the bovine meniscus providing larger sample sizes and include results for anterior and middle regions. Establishing failure life and damage rates by fatigue and residual UTS strengths in bovine and human meniscus would provide a method for adjusting bovine meniscus fatigue properties to those of human meniscus.

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