MODELING FATIGUE FAILURE IN SOFT TISSUE USING A VISCO-HYPERELASTIC MODEL WITH DISCONTINUOUS DAMAGE

Bradley S. Henderson[1], Katelyn F. Cudworth[1], Estefania Peña[2,3], Trevor J. Lujan[1]

[1]Department of Mechanical & Biomedical Engineering, Boise State University, Boise ID, USA

[2]Department of Mechanical Engineering, University of Zaragoza, Zaragoza, Spain

[3]CIBER-BBN, Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicina, Zaragoza, Spain

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Corresponding Author

Trevor J. Lujan, PhD.

1910 University Drive

Boise, ID 83725-2085

trevorlujan@boisestate.edu

Phone: (+1) 208-426-2857

Fax: (+1) 208-392-1589

Abstract (< 250 words)

Soft tissue is susceptible to injury from single high-magnitude static loads and from repetitive low-magnitude fatigue loads. While many constitutive formulations have been developed and validated to model static failure in soft tissue, a modeling framework is not well-established for fatigue failure. Here we determined the feasibility of using a visco-hyperelastic damage model with discontinuous damage (strain energy-based failure criterion) to simulate low- and high-cycle fatigue failure in soft fibrous tissue. Cyclic creep data from six uniaxial tensile fatigue experiments of human medial meniscus were used to calibrate the specimen-specific material parameters. The model was able to successfully simulate all three characteristic stages of cyclic creep, and predict the number of cycles until tissue rupture. Mathematically, damage propagated under constant cyclic stress due to time-dependent viscoelastic increases in tensile stretch that in turn increased strain energy. Our results implicate solid viscoelasticity as a fundamental regulator of fatigue failure in soft tissue, where tissue with slow relaxation times will be more resistant to fatigue injury. In a validation study, the visco-hyperelastic damage model was able to simulate characteristic stress-strain curves of pull to failure experiments (static failure) when using material parameters curve fit to the fatigue experiments. For the first time, we've shown that a visco-hyperelastic discontinuous damage framework can model cyclic creep and predict material rupture in soft tissue, and may enable the reliable simulation of both fatigue and static failure behavior from a single constitutive formulation.

Keywords: continuum damage mechanics; viscoelasticity; constitutive modeling; connective tissue; uniaxial tensile testing

1. Introduction

Soft fibrous tissues in musculoskeletal joints, including menisci, ligaments and tendons, are frequently torn, leading to pain, joint instability, and increased risk of joint disease (D. D. Anderson et al. 2011). Tissue tears are most commonly associated with single high-magnitude loading events, known as static failures; but tears may also develop from repeated exposure to low-magnitude loads, known as fatigue failures. For example, adult human menisci are subjected to thousands of daily loading cycles, which combined with the limited ability of menisci to remodel (Våben et al. 2020a), make them susceptible to high-cycle fatigue failures (Demange, Gobbi, and Camanho 2016; Henderson et al. 2022). Material damage caused by static and fatigue loading can be mathematically described and predicted through constitutive models. Constitutive frameworks that have had success in simulating the damage processes of soft biological tissue include continuum damage mechanics (CDM) (Holzapfel G. and Fereidoonnezhad B. 2017; Calvo et al. 2007; Nims et al. 2016; Estefanía Peña 2011), pseudoelasticity (Franceschini et al. 2006; E. Peña and Doblaré 2009), and elasto-viscoplasticity (Zhu 2018) where most of these models have been developed to simulate experiments that apply loads to a constant displacement (displacement-control). A loading condition that is more physiological to fatigue injury is the repeated application of a constant cyclic stress (force-control). Prior soft tissue studies have developed constitutive formulations that can model force-control fatigue behavior at low cycles (< 1000 cycles)(Maria C. P. Vila Pouca et al. 2022; M. C. P. Vila Pouca et al. 2022), but to our knowledge, no soft tissue study has previously simulated force-control fatigue failure under high-cycle loading (> 1000 cycles). The identification of constitutive frameworks that can model low- and high-cycle fatigue failure in soft fibrous tissue could help explain this poorly understood failure phenomena and advance the prevention and treatment of fatigue injuries

(Martin and Sun 2015).

A successful constitutive framework for soft tissue fatigue must account for cyclic creep. Cyclic creep occurs from the repetitive application of tensile loads to a constant maximum stress (Fig. 1A), and in soft tissue, results in three characteristic creep stages (I, II, III; Fig. 1B)(Shepherd and Screen 2013; Henderson et al. 2022). Stage I exhibits a rapid increase in strain over a short cycle period until stage II, where cyclic creep stabilizes over a long cycle period. In stage III, cyclic creep becomes unstable and rapidly increases until material rupture.

A novel and elegant solution for modeling cyclic creep behavior in soft tissue may be possible by combining discontinuous CDM with a visco-hyperelastic model. Discontinuous CDM can be physically described as the deterioration of mechanical properties due to broken bonds, such as collagen denaturation at the molecular level (Zitnay et al. 2017). Mathematically, damage evolves (i.e. increases) when the previous maximum of a specified scalar variable (i.e. failure criteria) is exceeded. Previous work has determined that discontinuous CDM with strain energy-based failure criteria can model static failure in soft tissue (Martin and Sun 2015) but has intrinsic limitations in modeling steady state creep, since damage evolution is restricted under a constant load. Conversely, time-dependent viscoelastic models can represent steady state creep (stage II) (Sopakayang and De Vita 2011), but are unable to model the propagation of damage to material rupture (stage III). By pairing a discontinuous, strain-energy based, CDM model with a viscoelastic model, it may be possible for damage to propagate in response to viscoelastic creep during a force-controlled experiment. In this way, the individual limitations of viscoelasticity and discontinuous damage could be overcome, and both fatigue and static failure behavior could potentially be modeled using a single formulation.

The objective of this study was to determine the feasibility of using a visco-hyperelastic model with discontinuous damage to simulate low- and high-cycle fatigue in human meniscus. A sensitivity study will determine the role of material parameters in resisting fatigue injury, and a validation study will be performed to determine if the model is also predictive of static failure.

2. Materials and Methods

2.1. Overview

Cyclic creep data from six uniaxial tensile fatigue experiments of human meniscus was used to calibrate the specimen-specific material parameters for a visco-hyperelastic damage model (visco-damage) and the quality of the model fits was quantified. The optimization of the calibrated material parameters was performed in a custom MATLAB code that simulated a single volumetric element subjected to force-controlled loading. The sensitivity of the model simulations to changes in material parameter values was assessed, and a validation study was performed by evaluating the model's ability to simulate the stress-strain curve of monotonic uniaxial tensile experiments (static failure).

2.2. Uniaxial Cyclic Fatigue and Pull to Failure Static Experiments

Fatigue experiments were conducted using an electrodynamic test system (Instron, Norwood MA, USA; ElectroPuls E10000) equipped with an acrylic immersion chamber (Fig. 2A). Six dumbbell shaped coupons were extracted from a set of four non-paired medial menisci that were harvested from fresh-frozen human knees (age = 30 ± 6). These coupons were layered, cut, and imaged using previously described methods (Wale et al. 2021; Nelson et al. 2020; Morrill et al. 2016). Specimens were mounted in the mechanical test system and preloaded to 0.1

N. At this position, front and side profile images were taken with a digital camera to measure the initial cross-sectional area (Creechley, Krentz, and Lujan 2017). The specimen was then buckled and the immersion tank was filled with 37°C saline solution (0.9%) containing 0.05 mg/mL of both penicillin and streptomycin. After equilibrating in the bath for 1.5 hours, the specimen was preloaded to 0.1 N, then preconditioned with a 20 cycle triangular wave at 2 Hz to 8% clamp strain. The linear modulus was calculated from the 20^{th} preconditioning cycle to predict the specimen-specific ultimate tensile strength (UTS) by using a linear regression function of UTS vs. linear modulus (Creechley, Krentz, and Lujan 2017). The regression function was developed from monotonic experiments to failure of specimens cut from the same meniscus as specimens used for fatigue testing (Henderson et al. 2022). After preconditioning, the sample was again preloaded to 0.1 N, and the reference specimen length was established from the grip-to-grip displacement after this preload.

Six fatigue experiments were run to a targeted maximum cyclic engineering stress of either 50% (n = 3) or 70% (n = 3) of the predicted ultimate tensile strength (UTS)(Creechley, Krentz, and Lujan 2017). The rationale for selecting these two stress levels (fatigue strengths) was that they resulted in low- and high-cycle fatigue failures and did not exceed the one-million cycle limit of the experiment (Henderson et al. 2022). A 4 Hz tensile-tensile sinusoidal waveform was applied to the targeted stress (minimum = 10% of the targeted stress) until failure (Fig. 2B). Force and displacement data were converted to engineering stress and engineering strain using the reference area and length (Wale et al. 2021). Axial strains were converted to axial stretch and plotted versus cycles (Fig. 2C). The cyclic stress and creep curves for each experiment were generated by taking the maximum values for each stress and strain cycle. Tissue damage was calculated by dividing the dynamic modulus at each cycle by the dynamic modulus measured at the start of fatigue testing. The three stages of cyclic creep (Fig. 1) were automatically delineated using a MATLAB algorithm. This algorithm selected the absolute minimum second derivative (closest to zero), or flex point, which occurred in stage II, and then identified the start and end of stage II as a 10% change in the second derivative from this absolute minima, in both directions (Henderson et al. 2022).

Monotonic uniaxial tensile tests to failure were performed on six dumbbell shaped specimens collected from the same set of human medial menisci used for fatigue testing. The preconditioning, imaging, and preload steps for these tensile tests replicated the fatigue test protocol. After the final preload, the specimen was monotonically pulled to failure at a rate of 1% strain per second. The linear modulus, ultimate tensile strain, and UTS were calculated from the resulting stress-strain curve (Fig. 2D) using previously described methods (Wale et al. 2021; Nesbitt et al. 2023). All static and fatigue failures for the analyzed specimens occurred away from the grips, either near the fillet or in the midsubstance (Fig. 2E).

2.3. Visco-Damage Constitutive Model

The visco-damage model used a continuum damage mechanics formulation, where the viscoelastic stress response was modulated by a damage variable, D, that ranged from $0 \leq D \leq 1$, with $D = 1$ representing complete rupture. This damage variable scaled the elastic 2nd Piola-Kirchhoff (PK) stress $\mathbf{S}^{\mathrm{e}}$ and the relaxation function G by utilizing a classic quasi-linear viscoelastic formulation (Fung 1973) through the application of a convolution integral:

$$\mathbf{S}(t) = \int_0^t G(t-s)(1-D(t))\frac{\mathrm{d}\mathbf{S}^{\mathrm{e}}}{\mathrm{d}s}\mathrm{d}s \qquad (1)$$

Here, t is the current time and s represents the incremental time points between 0 and t. The 2nd PK elastic stress $\mathbf{S}^{\mathrm{e}}$ was calculated from a hyperelastic strain energy formulation using the right Cauchy-Green deformation tensor $\mathbf{C}$, which is a function of the deformation gradient tensor $\mathbf{F}$.

$$\mathbf{S}^{\mathrm{e}} = 2\frac{\partial W}{\partial \mathbf{C}} \tag{2}$$

Where, strain energy density, W, was modeled using a (nearly) incompressible Neo-Hookean formulation and is comprised of the shear modulus μ and the first scalar invariant I_1 ($I_1 = tr\mathbf{C}$).

$$W = \frac{\mu}{2}(I_1 - 3) \tag{3}$$

The shear modulus is computed using the elastic parameter E (elastic modulus), and a nearly incompressible Poisson's ratio v of 0.499 (μ=0.5E/(1+v)). The relaxation function inside the convolution integral was comprised of six material parameters $\gamma_1, \gamma_2, \gamma_3, \tau_1, \tau_2, \tau_3$ which regulate how quickly the material relaxes to its long-term elastic stress.

$$G(t) = 1 + \gamma_1 \mathrm{e}^{\frac{-t}{\tau_1}} + \gamma_2 \mathrm{e}^{\frac{-t}{\tau_2}} + \gamma_3 \mathrm{e}^{\frac{-t}{\tau_3}} \tag{4}$$

The evolution of the damage parameter D is characterized by an irreversible equation of evolution developed by Simo et al. (Simo 1987) and defined by the following expression

$$\Xi_s := \sqrt{2W(\mathbf{C}(s))} \tag{5}$$

where $\mathbf{C}(s)$ is the Cauchy-Green deformation tensor at time s. We note that W is the "elastic" stored energy function of the undamaged material. Now, let Ξ_t be the maximum value of Ξ over the past history up to the current time:

$$\Xi_t = \max_{s\in(-\infty,t)} \sqrt{2W(\mathbf{C}(s))} \tag{6}$$

The damage evolution function $D(\Xi_t)$ can then be expressed by the energy-based Weibull cumulative distribution function (CDF)(Weibull 1951), which is dependent on two material parameters, the shape parameter β and the scale parameter η:

$$D(\Xi_t) = 1 - \mathrm{e}^{-\frac{{\Xi_t}^{\beta}}{\eta}} \tag{7}$$

This damage function is discontinuous, in that it is characterized by a function of maximum strain energy attained in a loading path that can only evolve when the current maximum strain energy value is exceeded.

2.4. Curve Fitting of Material Parameters

Constitutive model parameters were calibrated to best fit each model to the experimental cyclic creep data. In order to optimize the model material parameters in force-control loading, we developed an optimization program in MATLAB (Mathworks, Natick MA; R2021a) that used a three-dimensional single element material model. This custom program consisted of two nested loops (Fig. 3A). The inner loop used the Levenberg-Marquardt algorithm (LMA; a modified Newton method used for non-linear least-squares optimization) to calculate the axial and lateral stretches at each time point for a given loading profile by minimizing the objective function φ_{stress} (Eq. 8). To ensure that damage was irreversible during fatigue loading, axial stretch was constrained to be either equal or greater than the axial stretch at the prior time step. The outer loop applied LMA to the entire stretch-time profile to select specimen specific material parameters that optimized the fit of the displacement curve by minimizing the objective function $\varphi_{stretch}$ (Eq 9). The optimization program was applied to the visco-damage constitutive model (Eq. 1), where the total stress for each time point (Eq. 10) was calculated by summing the stress at the current time interval (Eq. 11) and all past time intervals (Eq. 12). For this optimization, the derivative of the elastic stress was found numerically using a linear approximation.

$$\varphi_{stress} = \sum_{i=0}^{t}\left[\left(\mathrm{S}_{experiment,axial}(i) - \mathrm{S}_{model,axial}(i)\right)^2 + \mathrm{S}_{model,lateral}(i)^2\right] \tag{8}$$

$$\varphi_{stretch} = \sum_{i=1}^{t}\left[\lambda_{experiment,axial}(i) - \lambda_{model,axial}(i)\right]^2 \tag{9}$$

$$\mathbf{S}_{model}(i) = \mathbf{S}_{current}(i) + \mathbf{S}_{past}(i) \tag{10}$$

$$\mathbf{S}_{current}(i) = G\left(\frac{\Delta t}{2}\right)\left(\mathbf{S}^e(i)\left(1 - D(i)\right) - \mathbf{S}^e(i-1)\left(1 - D(i-1)\right)\right) \tag{11}$$

$$\mathbf{S}_{past}(i) = \sum_{j=1}^{i-1} G\left(i - \left(j - \frac{\Delta t}{2}\right)\right)\Delta\mathbf{S}(j) \tag{12}$$

Prior to inputting the experimental data from the cyclic fatigue experiment into the optimization program, the data was reduced to include only the maximum stress and corresponding stretch to reduce computational cost while still quantifying the tissue's cyclic creep behavior. The stress data was then smoothed and held constant during the second stage of creep to remove any irregularities due to noise. All data used for optimization was interpolated to a set number of points to reduce run time. Curved portions of the input profile were weighted with more data points to improve interpolation accuracy and a visual inspection was made to ensure the interpolated data was representative of all portions of the experimental data. Numerical simulations were run for all six experiments.

2.5. Verification of Model Implementation

Model verification is a process that ensures the constitutive equations are mathematically implemented correctly (A. E. Anderson, Ellis, and Weiss 2007). This is typically completed through comparison to an analytical solution or an already verified source. The custom MATLAB program was verified by comparing its results to the open-source FE solver FEBio (Maas et al. 2012), using the same constitutive equations and material parameters under a force-control ramp (Fig. 3B). The material within FEBio was selected as viscoelastic (parent) with an elastic damage component. The elastic type was neo-Hookean and the damage type was CDF Weibull with a DC Simo damage criterion, which matches the visco-damage constitutive model (Eq. 1). The FE model included a single element hexahedral model with boundary conditions that replicated the single element model in MATLAB. This was accomplished by connecting a rigid body to the top face of the element and using a sliding elastic contact to allow displacement along the axial load direction. The Poisson's ratio was set to 0.499 to model quasi-incompressibility. For the visco-damage model, the material parameters were selected as $E = 5$, $\gamma_1 = 3, \gamma_2 = 0, \gamma_3 = 0,$ $\tau_1 = 5, \tau_2 = 0, \tau_3 = 0,$ $\beta = 1$, and $\eta = 0.5$ (note: FEBio uses the symbols α and μ to represent β and η, respectively). We also verified a visco-only version of the model by keeping the same material parameters, except the damage parameters β and η were set to 10,000 so that damage effects were negligible. A load curve that ramped and held at 0.5 was input (Fig. 3B) and stretch was output. The stretch curves calculated by FEBio and MATLAB were compared (Fig. 3C), and had RMSE values of 0.013% and 0.002% for the visco-damage and visco-only models, respectively. The nearly identical results between MATLAB and FEBio (Fig. 3B-C) verified the accuracy of our custom numerical algorithm (Fig. 3A).

2.6. Sensitivity Analysis of Material Parameters

The sensitivity of the creep curve to each model parameter was evaluated using the visco-damage model and a representative test case. For this analysis, the elastic and damage terms (E, β, and η) were independently increased and decreased by 10% of their mean curve fitted value, while the set of viscoelastic τ terms (τ_1, τ_2, and τ_3) and the set of viscoelastic γ terms (γ_1, γ_2, and γ_3) were collectively increased and decreased by 10% of their mean curve fitted value and then plotted for comparison. To evaluate the sensitivity of the constitutive formulation to the number of viscoelastic parameters, the number of viscoelastic parameters was reduced to four ($\gamma_1, \gamma_2, \tau_1$, and τ_2) and two (γ_1 and τ_1). The viscoelastic parameters of these two new model formulations were optimized to the experimental data, and the goodness of fit was evaluated using RMSE.

2.7. Model Validation

A validation study determines if a model is able to simulate independent experimental data not used for model calibration (A. E. Anderson, Ellis, and Weiss 2007). A validation study was conducted for the visco-damage model by testing the model's ability to simulate the independent pull to failure experiments (Fig. 4). Using the custom MATLAB program, six single element models were stretched from 1 to 1.5 at increments of 0.0005 to simulate monotonic loading (static failure). Importantly, the sets of material parameters for these six models were calibrated using the cyclic creep data from six fatigue experiments, and therefore model calibration was distinct from model validation (Fig. 4). The resulting stress-stretch responses were plotted, and linear modulus, ultimate strain, and UTS were calculated for comparison to the experimental pull to failure results.

2.8. Statistics

The quality of the model fits to the observed stretch-time behavior (cyclic creep) for the six experiments was quantified using normalized root mean square error (NRMSE). The NRMSE values were calculated by dividing the root mean square error by the mean strain for a specific experiment.

Differences in damage predicted by the visco-damage model and measured by the experiment were determined using a repeated measures ANOVA with stage and test type (model vs experiment) as within-subject variables. Differences between the static material parameters (modulus, UTS, and failure strain) measured in the pull to failure experiment and simulated by the visco-damage model were determined using a MANOVA. All significance levels were set as $p < 0.05$. This statistical analysis was performed using SPSS (Version 25; IBM Corp., Armonk, NY).

3. RESULTS

3.1 Model Curve Fitting to Fatigue Experiments

The six fatigue experiments produced characteristic creep curves (Fig. 5). Under a constant cyclic tensile stress (Fig. 5A), the number of cycles to rupture ranged between approximately 150 to 400,000 cycles, with a median value of approximately 10,000 cycles. The constant cyclic tensile stress for tests #1-6 had a maximum magnitude of 5.7, 18.1, 3.6, 12.2, 2.9, and 5.6 MPa, respectively (Fig. 5A).

The visco-damage model had excellent fits to fatigue experiments (Fig. 5B; Table 1). The overall average error (NRMSE) in simulating stretch at all fatigue stages was 2.4% (Table 1), and the localized average error in simulating stretch in stage I, II, and III was 3.0%, 1.1%, and 5.9%, respectively. The curve fitted material parameters for all tests are listed in Table 1. The overall average error in simulating stretch increased to 17% and 4.2% if either the damage or viscoelastic components from the model were removed prior to curve fitting, respectively (see Appendix A and Supplementary Material).

3.2 Comparison of Fatigue Damage between the Model and Experiment

The damage values calculated from the fatigue experiments and predicted by the visco-damage model were compared (Fig. 6). The model overpredicted damage in each stage by an average of 0.08, but this difference was not significant ($p = 0.052$).

3.3 Sensitivity of the Model to Changes in Material Parameters

The visco-damage model was sensitive to changes in all material parameters (Fig. 7). In general, decreases in material parameter values resulted in fatigue failure at a lower cycle count than the optimized value. The opposite trend was seen when the parameter value was increased, such that fatigue failure did not occur before reaching the cycle limit. The elastic modulus (Fig. 7A) and the viscoelastic parameters (Fig. 7B-C) were found to influence all stages of cyclic creep response, while changes in the damage parameters predominately affected failure propagation (stage III) and had little to no effect on the initial cyclic creep response (Fig. 7D-E).

Increasing the number of viscoelastic parameters in the visco-damage formulation improved the model's fit to the experimental data (Fig. 8). However, increasing the number of parameters from four to six provided only a nominal improvement (Fig. 8; inset). The RMSE values of each case when compared to the experimental stretch values were 0.65%, 0.23%, and 0.19% for the 2 term, 4 term, and 6 term cases, respectively.

3.4 Validation Study using Pull to Failure Experimental Data

Pull to failure experiments were simulated with the visco-damage model using specimen-specific material parameters fit to the six fatigue experiments (Table 1). The simulated stress-strain curves had a characteristic shape for all six sets of parameters (Fig. 9A). The UTS (12 ± 8 MPa) and linear modulus (58 ± 35 MPa) predicted by the model were 21% and 41% less than the experimental results (not significant), while the failure strain predicted by the visco-damage model (29 ± 7%) was 37% greater than the experimental results (21 ± 3%) (p=0.03)(Fig. 9B). When using the mean parameter values from all six curve fits (Table 1), the predicted UTS (14 MPa; Fig. 9A, dashed line) was within 10% of the experimental average.

4. Discussion

This study has demonstrated the feasibility of using a visco-hyperelastic continuum damage constitutive framework (visco-damage) to simulate cyclic creep behavior and fatigue failure of soft fibrous tissue. Impressively, the visco-damage formulation was able to reproduce a broad range of experimental time-dependent, non-linear fatigue behaviors (Fig. 5) when using a relatively low number of elastic and damage material coefficients. Further, the visco-damage model was able to concurrently simulate static failure behavior during monotonic loading (Fig. 9). These results establish a visco-hyperelastic model with discontinuous damage as a desirable framework for modeling fatigue failure in soft tissue.

The visco-damage model was effective at modeling fatigue behavior due to an energy-based damage criterion that enabled viscoelastic creep to drive damage evolution, even during constant cyclic stress. As the material is loaded in stage I, a rapid increase in stress and stretch caused initial material weakening due to the strain-energy damage threshold being exceeded (Fig. 6). Once stretch equilibrated under constant stress, cyclic creep entered stage II, where the time-dependent terms in the solid viscoelastic component regulate the gradual steady-state increase in stretch (mean model creep rate in stage II = 1.1 ± 2.2 μm/cycle). The incremental increases in stretch will continue to evolve damage, creating a feedback loop, where increasing damage generates greater maximum stretch under constant cyclic stress, and increasing maximum stretch generates more damage. Eventually, this interplay leads to a non-linear increase in stretch, marking the start of stage III. Damage then propagates rapidly (mean model creep rate in stage III = 16 ± 35 μm/cycle) until the weakened tissue is stretched to a magnitude that exceeds the experimental rupture strain. This formulation enabled the visco-damage model to successfully fit all stages of creep with an average normalized RMSE of roughly 2.5% for a wide range of fatigue experiments that failed between 150 to 400,000 cycles (Fig. 5). It's worth noting that damage evolution under constant cyclic stress can only evolve with our modeling approach if the damage criterion is a function of time-dependent strain. If we used a stress-based failure criterion (e.g. 1st principal stress), or did not permit time-dependent increases in stretch to influence damage (i.e. damage based purely on elastic strain), then damage would not have evolved under constant cyclic stress. Not surprisingly, removal of either the viscoelastic or damage component resulted in inferior stretch simulations, less physical material parameters, and no mathematical mechanism for damage to evolve during steady-state fatigue loading (see Appendix A). The ability of a visco-damage framework to successfully model cyclic creep suggests that the intrinsic solid viscoelasticity of soft tissue plays a critical role in modulating fatigue damage.

The sensitivity of the simulated cyclic creep response to the material parameters was analyzed to gain insight into the mathematical and physical significance of each parameter. The visco-damage model used a relatively low number of material coefficients, consisting of one elastic parameter (elastic modulus) to scale the response to strain magnitude, two damage parameters that control the initiation and rate of damage, and six viscoelastic parameters that control the response to strain-rate (viscosity) and the subsequent rate of relaxation. The model exhibited sensitivity to changes in all parameters (Fig. 7), although we did determine that the total number of viscoelastic parameters could be reduced to four and still maintain a good fit for the representative case (Fig. 8). The initial creep response was governed by the elastic modulus E and viscosity terms γ. As either of these parameters increase, the material becomes stiffer, and more resistant to fatigue failure (Fig. 7A-B). Similarly, increases to the damage terms and the time rate terms resulted in greater resistance to fatigue failures. Increases in the damage rate terms will effectively delay the initiation and propagation of damage, while increases in the time rate terms will slow stress relaxation and reduce the slope of the creep response. This is a significant finding, as it predicts that tissues exhibiting slow relaxation at long timescales will be more resistant to fatigue injury (Fig. 7C). Interestingly, prior work has shown that relaxation rates decrease as collagen ages (LaCroix et al. 2013), which could explain why human meniscus has a tensile endurance limit (i.e. stress level that can be safely applied for a lifetime of use) that does not decline with aging (Henderson et al. 2022).

This study developed a custom MATLAB program that automated the curve fitting of material parameters in force-controlled loading. The original intent of this study was to optimize the material parameters in an FE solver, however, parameter optimization modules in FE are primarily operated in displacement-control due to the mathematical nature of the underlying stress-strain formulations. Material parameters calibrated in displacement control will not necessarily produce the same solution in force control. For example, in a preliminary study we conducted (data not shown), we optimized the visco-damage parameters by inputting the experimental stretch values (displacement-control) and then selecting material parameters that fit the experimental stress values for a characteristic three stage cyclic creep curve (Fig. 1). However, when we applied those optimized parameters in a force-control simulation (using the same experimental stress data used for parameter optimization) the model calculated a different creep curve that did not advance to tissue rupture in stage III. To overcome this limitation, we coded a single volumetric element in MATLAB that loaded the material to a user-specified stress and then utilized a least-squares optimization approach to minimize the difference between the experimental and predicted stretch values (Fig. 3). In this way, we were able to run force-control simulations with the optimized parameters and get displacement curves that matched the experimental data used for parameter optimization. Moreover, this code was able to iterate towards a solution without the error termination that can prematurely halt optimization routines in FE solvers, and the run-time was very fast relative to FE solvers (less than half the run-time). The accurate implementation of the visco-damage model into MATLAB was verified by having our custom MATLAB code match the FEBio creep solution when using identical materials, parameters, loads, and boundary conditions (Fig. 3C). Conversely, the material parameters optimized in MATLAB (Table 1), can be input into FEBio to simulate cyclic creep curves that match the MATLAB solution (Fig. 10). Importantly, the number of cycles that FEBio terminated only changed by 0.2% if we altered the stress input to run well past the known failure cycle. This suggests that FE error terminations that occur in stage III are indicative of the material being close to fatigue failure. This finding has significant implications, as it can provide a method to estimate fatigue life when the number of cycles to failure is unknown for a user-specified stress amplitude.

A validation study was conducted to test the ability of the visco-damage model to simulate an experiment not used to calibrate the material parameters. Using the same specimen-specific model parameters that were curve fit to the fatigue experiments, we applied a monotonic quasi-static loading profile using our MATLAB code. The visco-damage models were able to simulate characteristic stress-strain curves with mean ultimate strength predictions within about 21% of experimental values (Fig. 9B). However, the corresponding ultimate strain values, predicted by the model, were 37% greater than the experiment ($p = 0.03$). This difference shows that the damage parameters appropriate for modeling fatigue failure create a more “stretched” cumulative distribution function (CDF) that weakens the tissue too gradually to properly model static failure. The longer the number of cycles to failure, the poorer the prediction of static failure strain (Fig. 9A; $R^2 = 0.62$). Another way of explaining is that if we had calibrated the damage parameters to static failure data, and then applied those damage parameters to fatigue loading, the number of cycles to failure would be underpredicted. An explanation for why the CDF for fatigue loading is not ideal for static loading is that, relative to "fast" static failures, the long-term viscoelastic creep occurring during "slow" fatigue failures will decrease the complex modulus, and thereby lesson the damage response for a specific magnitude of elongation. The model therefore predicts that cyclic loading will effectively increase tissue extensibility, and this prediction is supported by our previous experiments that found high-cycle tensile loading to increase failure strains by 41% compared to meniscus specimens only subjected to monotonic loading (Henderson et al. 2022). The increase in extensibility during repetitive loading is likely due to the realignment and sliding of collagen fibers (Xu, Li, and Zhang 2013), which would indicate that collagen realignment serves an important role in protecting the tissue from damage and extending fatigue life.

The dual simulation of static and fatigue failure has given us the ability to assess whether the visco-damage model can predict a reasonable S-N curve. An S-N curve is a diagram of fatigue strength versus fatigue life (number of cycles to failure), where fatigue strength can be expressed as a percent of ultimate tensile strength (UTS). By using the mean parameters (Table 1), and the UTS value predicted using these mean parameters (Fig. 9A, dashed line; 14 MPa), we applied a range of stresses (30%-100% of UTS) in FEBio and recorded the number of cycles until error termination indicated the near onset of fatigue failure. These values were plotted alongside an S-N curve from our previous experimental study of tensile fatigue strength in human meniscus (Fig. 11) (Henderson et al. 2022). This comparison shows that using the mean model parameters results in an overprediction of fatigue life at lower stress levels. In particular, the model prematurely predicted an endurance limit at roughly 40% of UTS, which we did not observe in our previous fatigue experiments with human meniscus. The model prediction of an endurance limit can be explained mathematically from the model's rate of relaxation parameters. Once the number of cycles greatly exceeds the long-term viscoelastic parameter (τ_3), the relaxation rate is nearly zero and damage is no longer able to evolve. Therefore, stretch is predicted to stabilize instead of elongating to stage III rupture. It's worth noting that although the model overestimated the fatigue life, it did successfully replicate the semi-logarithmic response observed in the fatigue experiments (Fig. 11).

Viscoelastic continuum damage frameworks have been previously applied to model various behaviors of engineered materials and soft tissue (E. Peña et al. 2008), but not fatigue failure. The discontinuous damage formulation used in the present study was developed by Simo et al. to model stress-softening behavior (Simo 1987), where discontinuous damage is defined as damage evolving when a specified scalar variable exceeds a previous maximum. This same discontinuous damage formulation has been used to describe stress softening from cyclic loading in collagenous soft tissues of arterial walls (Balzani, Brinkhues, and Holzapfel 2012; E. Peña et al. 2010) and the esophagus (Khajehsaeid, Tehrani, and Alaghehband 2021). Further, a study by Peña et al. used discontinuous damage to simulate stress-softening and permanent set in uniaxial tensile tests of vaginal and vena cava tissue (Estefanía Peña 2011). These studies applied a limited number of cycles (< 20 cycles) and did not investigate high-cycle fatigue behavior. In contrast, two other studies modeled displacement-controlled fatigue by implementing a continuous damage formulation based on equivalent strain and the number of loading cycles (Dong et al. 2020; Martin and Sun 2014a). In continuous damage formulations, damage will always accumulate during cyclic loading, which is advantageous for modeling fatigue behavior, but is unsuitable for modeling static failure. The present study used a more conventional discontinuous damage formulation that we paired with a classic formula for solid viscoelasticity to enable the high-cycle simulation of non-linear cyclic creep. A major benefit of this approach is that constitutive equations for discontinuous damage and viscoelasticity are well established and are available in commercial and open source finite element solvers (e.g. FEBio). To our knowledge, this study is the first to use a viscoelastic continuum damage framework to model high-cycle force-controlled fatigue behavior in soft tissue, and the first time we're aware that this framework has been used to model both fatigue and static failure in any material.

Our results have highlighted some intrinsic limitations of the viscoelastic continuum damage model applied in this study, as well as given us perspective on how the model could be improved in the future. First, in order to limit the number of material coefficients, an incompressible neo-Hookean formulation was selected for the elastic response. While this elastic model was sufficient for simulating the cyclic creep behavior, it is unable to model the toe region of soft tissue during monotonic loading (Fig. 2D). To overcome this deficiency, we'd recommend using a nonlinear elastic formulation (Weiss, Maker, and Govindjee 1996; Holzapfel, Gasser, and Ogden 2000), which would likely improve the model's prediction of modulus and failure strain during monotonic loading (Fig. 9). Second, the model overpredicted damage at each stage of fatigue (Fig. 6). This could potentially be explained by the model not accounting for permanent set, or non-recoverable deformation that is observed in soft tissue after cyclic loading (García et al. 2011). Third, the model overpredicted fatigue life at all levels of applied cyclic stress when using the mean parameters (Fig. 11). This miscalculation is likely related to the large variation in viscoelastic parameters between specimens failing at low and high cycles, and could potentially be improved by implementing viscoelastic formulations that explicitly model the short- and long-term viscoelastic response (Ahsanizadeh and Li 2015; Pioletti and Rakotomanana 2000).

Several other study limitations should be noted. The model used a single volumetric element to describe the material behavior and did not account for specimen geometry or local behavior. Nevertheless, this approach has demonstrated the feasibility of this modeling framework and has provided insight into the mechanisms of fatigue injury. The model also implemented a constraint that axial stretch could not decrease to enforce the condition that damage is irreversible. This contributed to the increase in damage observed in stage III for both the visco-damage and damage-only models due to the sudden reduction in applied force (Appendix A). To efficiently analyze high-cycle fatigue loading, the experimental data set was reduced to a cyclic creep curve, where only the maximum stress values for each cycle were modeled. Therefore, this study was a simplification of the loading and unloading occurring during fatigue testing. We optimized the material parameters using a Levenberg-Marquardt type minimization algorithm (Marquardt 1963) that is often used for experimental data fitting. Convergence to a global minimum with this algorithm is sensitive to the initial guess (Fung 1993), and therefore fits were performed multiple times with different initial guesses. Next, the experiment and model did not account for the anisotropy of fibrous tissue, as this study only investigated fatigue along the principal fiber orientation. The model also did not account for the twenty preconditioning cycles to 8% strain (grip-to-grip) that were applied prior to experimental fatigue testing. These preconditioning cycles may have altered the tissue microstructure (Schatzmann, Brunner, and Stäubli 1998), but relative to the high number of cycles applied during the fatigue tests, any effect from these twenty preconditioning cycles would likely be negligible. Additionally, soft tissue mechanical behavior has been shown to be dependent on strain-rate (Zitnay, Lin, and Weiss 2021) and tissue swelling (Werbner et al. 2022), yet the effect of strain-rate and swelling on fatigue failure was not analyzed with the experiment nor the model. Lastly, the in vitro experiments simulated in this study did not account for cellular remodeling of the extracellular matrix. Collagen remodeling would likely influence fatigue resistance, and although there is evidence that collagen has a limited ability to remodel in adult human meniscus (Våben et al. 2020b), other soft tissues will remodel in response to injury or repetitive exercise (e.g. tendon)(Andarawis-Puri, Flatow, and Soslowsky 2015). Further experimental and modeling work is needed to determine the relationships between biological factors and mechanical fatigue (Martin and Sun 2015).

For the first time, this study has identified a constitutive equation capable of modeling cyclic creep to failure in meniscus tissue. Moreover, to our knowledge, this is the first study to identify a constitutive formulation that shows promise in modeling the failure behavior of soft tissue under both static (monotonic) and fatigue (cyclic) loading. The findings of this study progress the mechanical knowledge of mechanical fatigue in soft fibrous tissues and are applicable in the prediction and prevention of meniscus tissue injuries.

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APPENDIX A. Modeling Fatigue using either Viscoelasticity or Discontinuous Damage

In this appendix, we demonstrate the importance of pairing a viscoelastic solid with a discontinuous damage model. The viscoelastic solid and discontinuous damage models used in this study (Eq. 1-7) were independently curve fit to the experimental fatigue data by calibrating the specimen-specific material parameters for versions of the visco-damage model without viscoelasticity (damage-only) and without damage (visco-only)(Fig. A.1).

As expected, the damage-only model was unable to simulate steady-state creep behavior, and the visco-only model was unable to simulate failure propagation (Fig. A.1). In comparison, the visco-damage model was able to fit all three stages of cyclic creep. The curve-fitted material parameters and goodness of fits for all six experiments are included in the supplementary material.

FIGURE CAPTIONS

Figure 1. Cyclic creep behavior due to fatigue loading. A) The application of uniform cyclic loads to a maximum stress results in B) three characteristic stages of creep (I, II, and III).

Figure 2. Fatigue and pull to failure experiments of human meniscus. A) Specimens were inserted into a heated saline bath and loaded in uniaxial tension (white arrows). B) For fatigue tests, cyclic loads were applied to a targeted maximum and minimum stress until failure, resulting in C) a characteristic cyclic creep response. D) Pull to failure tests were conducted on coupons from the same human donors as the fatigue tests. E) A dumbbell shaped specimen before and after fatigue testing. All specimens analyzed in this study failed away from the grips.

Figure 3. The custom MATLAB program for force-control parameter optimization. A) Logic flowchart of the custom program, where the inner loop (inner dashed arrow) optimizes the axial and lateral stretch of a single volumetric element using the Levenberg-Marquardt algorithm (LMA) and the outer loop (outer dashed arrow) optimizes the material parameters. B) The custom program was verified by inserting the same materials, boundary conditions, loads, and material parameters into FEBio, and C) getting identical stretch results.

Figure 4. Calibration and validation of the visco-damage model. Model parameters were calibrated to cyclic creep data from fatigue experiments. These parameters were then used in a model validation study to determine if the visco-damage model is able to simulate static failures observed in experiments.

Figure 5. The visco-damage model had excellent fits to the three stages of cyclic creep cyclic creep from all six fatigue experiments. A) The maximum cyclic stress from each experiment was input into the visco-damage model, and B) the material parameters were optimized to simulate tissue stretch from cyclic creep.

Figure 6. The visco-damage model overpredicted damage during fatigue testing. Experimental damage was calculated as a percent reduction in the dynamic modulus at each test cycle.

Figure 7. The visco-damage model was sensitive to 10% changes in material parameters from their optimized value. All stages of cyclic creep were sensitive to A) the elastic parameter, and B-C) the viscoelastic parameters. D-E) The damage parameters most affected the final stage of cyclic creep.

Figure 8. Sensitivity to the number of viscoelastic parameters used in the visco-damage model. Increasing the number of parameters from 4 to 6 resulted in only a nominal benefit (inset).

Figure 9. The visco-damage model can simulate characteristic stress-strain curves for static failure (monotonic loading). A) Using either specimen-specific parameters (solid lines; number = fatigue test) or mean parameters (dashed) from curve fitting the six fatigue experiments, stress-strain curves of static failure were simulated with the visco-damage model and compared to experiments. B) Normalized static material properties calculated from the stress-strain curves. The model

reasonably predicted UTS, but overpredicted the failure strain (*$p < 0.05$; calculated prior to normalizing).

Figure 10. The material parameters optimized in MATLAB can be input into FEBio to simulate a cyclic creep response that matches the MATLAB solution.

Figure 11. The visco-damage model, using average values for the material parameters, overpredicted the number of cycles to failure at various fatigue strengths when compared to our prior fatigue experiments on human meniscus. Unlike the experiments, the model predicted a fatigue limit (endurance limit) at 40% of UTS.

Figure A.1. Compared to the visco-damage model, the visco-only and damage-only models had worse fits to the cyclic creep results from the fatigue experiment. The damage-only model was unable to simulate steady-state cyclic creep (stage Il), while the visco-only model was unable to simulate failure propagation (stage III).

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