SB³C2023
Summer Biomechanics, Bioengineering and Biotransport Conference
June 4-8, Vail, CO, USA

A VALIDATED, DATA-DRIVEN CONSTUTIVE MODEL OF TYPE II COLLAGEN INCLUDING FAILURE

Phoebe Szarek (1), David M. Pierce (1,2)

(1) Biomedical Engineering, University of Connecticut, Storrs, CT, USA
(2) Mechanical Engineering, University of Connecticut, Storrs, CT, USA

INTRODUCTION

Collagen plays a crucial mechanical role in most biological tissues and some biomaterials. Inhomogeneity and anisotropy of the individual constituents, e.g., collagen, within tissues affect mechanics at all scales. Type I collagen (Ø ~ 350 nm – 1 μm) is both the most prevalent type in the mammalian world and the most studied [1]. Type II collagen (Ø ~20 – 200 nm) is next in prevalence and is the primary source of tensile stiffness in some load-bearing soft tissues yet is relatively understudied.

Continuum-level constitutive models of soft tissues often use an exponential function to model the tensile response of type II collagen but these models rely primarily on untested assumptions or phenomenological fits to macroscale experimental data. In this study we aim to: 1) directly measure the stress-stretch response of networked type II collagen, 2) establish a data-driven constitutive model for individual collagen fibers in tension, 3) similarly establish a failure model for individual collagen fibers in tension, and 4) validate the final constitutive model against data from independent mechanical tests.

METHODS

Tensile Testing. We employed our previously established methods to measure the stress-stretch responses of isolated networks of type II collagen to failure [2]. We sourced bovine cartilage from the patellofemoral groove and produced dumbbell-shaped specimens (thickness of 140-160 μm) oriented along the primary fiber orientation (Fig. 1a). We performed quasi-static uniaxial tension tests to failure and converted force-displacement data to Cauchy stress σ and stretch λ.

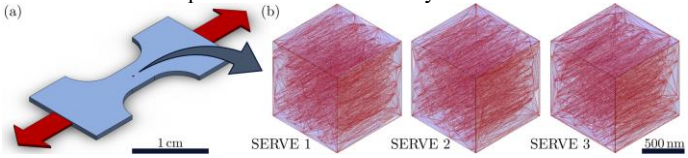

Figure 1. (a) Mechanical test. (b) SERVEs with statistically equivalent orientation, dispersion, and volume fraction of fibers [7].

Constitutive Modeling and Inverse Finite Element Analysis. We created three 1 μm³ cubic statistically equivalent representative volume elements (SERVEs) of the superficial zone of healthy, human articular cartilage (Fig. 1b) using previously quantified data on the morphology of collagen networks in the superficial zone, specifically matching the orientation, dispersion, and volume fraction of fibers [3]. We modeled each collagen fiber as a 1-D spring element with one of ten constitutive models (Table 1, subscript *c* denotes critical). We filled the remaining volume with four-node linear tetrahedra using a biphasic neo-Hookean.

Table 1. Candidate models for individual collagen fibers.

Stress (σ) – Stretch (λ) $\lambda > 1$	*polyI1*	$\sigma = 4\lambda^2 c_1(\lambda^2-1)$
	polyI2	$\sigma = 2\lambda^2[2c_1(\lambda^2-1)+3c_2(\lambda^2-1)^2]$
	polyI3	$\sigma = 6\lambda^2 c_2(\lambda^2-1)^2$
	polyS1	$\sigma = 2\lambda c_1(\lambda-1)$
	polyS2	$\sigma = \lambda[2c_1(\lambda-1)+3c_2(\lambda-1)^2]$
	polyS3	$\sigma = 3\lambda c_2(\lambda-1)^2$
	expI1	$\sigma = 2\lambda^2 c_1(\lambda^2-1)[\exp(c_3(\lambda^2-1)^2)]$
	expS1	$\sigma = 2\lambda c_1(\lambda-1)[\exp(c_3(\lambda-1)^2)]$
	powI1	$\sigma = 2\lambda^2 c_1 c_3(\lambda^2-1)^{c_3-1}$
	powS1	$\sigma = \lambda c_1 c_3(\lambda-1)^{c_3-1}$
Failure $\lambda > \lambda_c$	*Failure stretch*	$\sigma = 0$
	Failure stress	$\sigma = 0$, for $\sigma > \sigma_c$
	Fiber damage [4]	$\sigma = [1-(\lambda-\lambda_f)/(\lambda_c-\lambda_f)]\sigma$
	Fiber softening [5]	$\sigma = \exp[-(\psi_{fib}(\lambda^2)-\psi_{fib}(\lambda_c^2)/m]\sigma$

We applied boundary conditions to the SERVEs to match the tensile experiments on isolated collagen networks. Leveraging the SERVEs we used an inverse finite element scheme (with the Constrained Levenberg-Marquardt method) to fit the candidate stress-stretch models (Table 1) to the experimental data prior to bulk softening. We repeated this process with the complete experimental data, i.e., to failure, to fit the failure models (Table 1). We determined the best fit model using n=6 experiments and then fit this model to all n=27 experiments. We completed all modeling using FEBio (R3.7.0, University of Utah) [6].

Independent Validation. We created finite element (FE) models, i.e., SERVEs, of pristine, healthy human cartilage from the superficial zone and simulated both uniaxial tensile testing [7] and large-strain shear testing [8] to exercise our best-fit fiber model including failure. We modeled intact proteoglycan as a biphasic neo-Hookean (shear stiffness 0.23 MPa and permeability 1×10^{-14} μm^4/Ns [9]). We compared our model predictions in uniaxial tension and shear to experimental measurements from these two independent studies.

Statistical Analyses. We used two-way ANOVAs to assess the variance due to both network models (SERVEs) and experiments, with p=0.05 for significance. We established the best models (stress-stretch and failure) by ranking R^2 regression values for each fit, and by considering the number of model parameters (i.e., penalizing additional parameters). We used the root-mean-squared-error to assess model performance in validation.

RESULTS

Tensile Testing. We performed 27 uniaxial tension tests of networks of collagen to failure. The median failure stretch was 1.51 and the median failure stress was 7.71 MPa.

Constitutive Model. We fit ten individual fiber models with three SERVEs to n=6 experimental bulk responses (Fig. 2a) and found the best-fit parameters for each model (Table 2). Fitting the model to all experiments, we propose the first data-driven constitutive model for individual type II collagen fibers as

$$\sigma = \lambda c_1 c_3 (\lambda - 1)^{c_3 - 1}, \qquad (1)$$

with $c_1 = 0.48$, $c_3 = 4.09$ for $\lambda \geq 1$. We also established that the differences in SERVEs had no effect on the resulting fitted parameters.

Table 2. Best-fit model parameters for individual collagen fibers.

Fiber Model	c_1 [MPa]	c_2 [MPa]	c_3 [-]	R^2	Rank
polyI1	0.011	-	-	0.902	8
polyI2	0*	0.024	-	0.970	4
polyI3	-	0.015	-	0.983	1
polyS1	0.076	-	-	0.836	10
polyS2	0*	0.258	-	0.963	7
polyS3	-	0.255	-	0.961	5
expI1	0.010	-	1.21	0.974	5
expS1	0.048	-	6.59	0.934	8
powI1	0.017	-	3.50	0.992	3
powS1	0.857	-	4.09	0.994	1

** optimization process found the best fit at the lower limit, interpreted as 0*

Failure Model. We fit four fiber failure models with one SERVE to n=6 experimental bulk responses (Fig. 2b). We established the best failure/damage model as

$$\sigma = \begin{cases} \sigma, & \lambda < \lambda_c \\ \exp\left[-\dfrac{\psi_{fib}(\lambda^2) - \psi_{fib}(\lambda_c^2)}{m}\right]\sigma, & \lambda \geq \lambda_c \end{cases}, \qquad (2)$$

with $\lambda_c = 1.39$ and $m = 0.178$, and $\psi_{fib}(\lambda^2) = c_1(\lambda - 1)^{c_3}$.

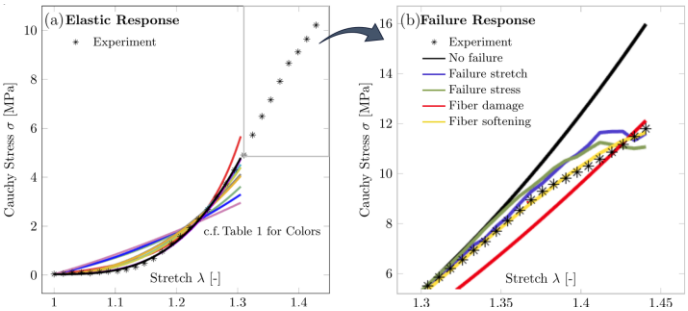

Figure 2. Representative best fits of (a) elastic and (b) failure models to experimental data from a network of type II collagen.

Model Validation. We successfully predicted data from two independent modes of mechanical testing on healthy human cartilage (Fig. 3). Predicted tensile and shear stresses generally lie within one standard deviation of the experiments with a root mean squared error of 0.251 MPa and 40.0 kPa, respectively.

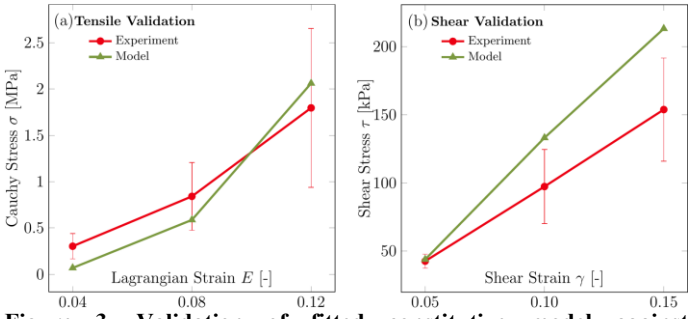

Figure 3. Validation of fitted constitutive model against independent tests on human cartilage: (a) tension [7], (b) shear [8].

DISCUSSION

We established a new validated, data-driven model for networked, type II collagen fibers within cartilage, and potentially within other soft tissues containing type II collagen. Our power-law model for single fibers presents comparable toe and linear regions to those seen in tension testing of soft tissues containing highly aligned networks of collagen. Many of the candidate stress-stretch response models performed equally well at small strains (e.g., *expI1*, *expS1*), but at large strains these models were not able to fit the experimental data. While we tested and modeled tension to rupture, physiological stretches are generally much less extreme, possibly explaining the usability of such models. Introducing fiber failure into our constitutive model, while increasing complexity and computational cost, improved the fit of our model to the gradual bulk softening present in the experimental data.

The data used for validation derived from independent experiments on human cartilage, while our tensile experiments used bovine cartilage. Thus, some discrepancy likely derives from differences in species and location. Our model produced a more non-linear response than the tensile experiments [7]. Our model also predicted higher stresses in the superficial zone under large-strain shear, potentially due to overestimation of the recruitment within the superficial zone [8].

Limitations and Outlook. We assumed that collagen was undamaged in the experimental preparation and was only type II, when collagen within cartilage is heterotypic with small quantities of types IX and XI. We assumed that there was no cross-linking between fibers in our SERVEs and that fibers had no stiffness in bending. We established constitutive models for the stress-stretch and failure responses of individual type II collagen fibers. This novel and fundamental understanding may inform the experimental study and computational modeling of tissues containing type II collagen.

ACKNOWLEDGEMENTS

NSF CAREER 1653358, NSF 1662429, GE Fellowship.

REFERENCES

[1] Sherman, VR et al., *J. Mech. Behav. Biomed. Mater.* 52:22-50, 2015. [2] Szarek, P & Pierce, DM, *J. Mech. Behav. Biomed. Mater.* 136: 105466, 2022. [3] Szarek, P et al., *Osteoarthritis Cartilage Open*, 2:e100086, 2020. [4] Lemaitre, J, *J. Engr. Mater. Technol.,* 1:83-89, 1985. [5] Holzapfel, GA & Ogden RW, *Proc. R. Soc. Lond. A,* 476:17249-17254, 2020. [6] Maas, SA et al., *J Biomech. Eng.,* 134:110005, 2012. [7] Elliot, DM et al., *J. Biomech. Eng.,* 124:223-228, 2002. [8] Maier, F et al., *Osteoarthritis Cartilage,* 27:810-822, 2019. [9] Pierce, DM et al., *Biomech. Model Mechanobiol.,* 15:229-244, 2016.