A Continuous Fiber Distribution Material Model for Human Cervical Tissue

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Abstract

The uterine cervix during pregnancy is the vital mechanical barrier which resists compressive and tensile loads generated from a growing fetus. Premature cervical remodeling and softening is hypothesized to result in the shortening of the cervix, which is known to increase a woman's risk of preterm birth. To understand the role of cervical material properties in preventing preterm birth, we derive a cervical material model based on previous mechanical, biochemical and histological experiments conducted on nonpregnant and pregnant human hysterectomy cervical tissue samples. In this study we present a three-dimensional fiber composite model that captures the equilibrium material behavior of the tissue in tension and compression. Cervical tissue is modeled as a fibrous composite material, where a single family of preferentially aligned and continuously distributed collagen fibers are embedded in a compressible neo-Hookean ground substance. The total stress in the collagen solid network is calculated by integrating the fiber stresses, and the shape of the fiber distribution is described by an ellipsoid where semi-principal axis lengths are fit to optical coherence tomography measurements. The composite material model is fit to averaged mechanical testing data from uni-axial compression and tension experiments,

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and averaged material parameters are reported for nonpregnant and term pregnant human cervical tissue. The model is then evaluated by investigating the stress and strain state of a uniform thick-walled cylinder under a compressive stress with collagen fibers preferentially aligned in the circumferential direction. This material modeling framework for the equilibrium behavior of human cervical tissue serves as a basis to determine the role of preferentially-aligned cervical collagen fibers in preventing cervical deformation during pregnancy.

Keywords: constitutive modeling, cervix, pregnancy, collagen fibers

1. Introduction

During pregnancy, a closed firm cervix is required to maintain the developing fetus *in utero*. Towards the end of gestation, a normal cervix significantly deforms, dilates and shortens in preparation for delivery. An early onset of cervical shortening, hypothesized to be caused by premature cervical remodeling, is known to put pregnant patients at risk for preterm birth (PTB) (Iams et al., 2011). The true causes of preterm birth remain to be determined, but the mechanical failure of the cervix is a final common pathway for multiple etiologies (Gravett et al., 2010; Solomon and Iams, 2014). The overall research goal of our work is to quantify the mechanical environment of pregnancy and to determine how the cervix functions as a resistive barrier to prevent PTB. The objectives of this study are to present an equilibrium constitutive material model that captures the tension/compression nonlinearity of previously published uniaxial data of human cervical tissue samples (Myers et al., 2008, 2010) and to describe how to incorporate directionality and dispersion parameters measured by optical coherence tomography (OCT) (Gan et al., 2014) into this material model. The purpose of this paper is to report fiber composite material properties for human cervical tissue and initiate a starting point for a 3-dimensional material model that can capture the salient nonlinear features of the cervical material behavior while accounting for its collagen fiber directionality.

The *in vivo* three-dimensional (3D) deformation and stress state of the cervix

22 during pregnancy is complex due to patient-specific pelvic geometry, pelvic tis-
 23 sue material properties, passive and active external loading, and the contact
 24 and boundary conditions between organs (Fernandez et al., 2015; House et al.,
 25 2009, 2012, 2013; Mahmoud et al., 2013). The stress state of the cervix has
 26 been studied using CAD-based (House et al., 2012; Mahmoud et al., 2013) and
 27 patient-specific MRI-based (Fernandez et al., 2015) finite element models of the
 28 pregnant pelvis. Simulation results reveal that under a constant intrauterine
 29 pressure the stress state of the cervix is a combination of tension and compres-
 30 sion (Fig. 1), where the magnitude and directionality of the principal stress and
 31 strain highly depend on the placement of the cervix within the pelvis, material
 32 characteristics of the cervix, and the interactions between the amniotic sac, the
 33 lower uterine segment, and the internal os (e.g. the opening of the cervix into
 34 the uterus) (Fernandez et al., 2015; House et al., 2012). Generally, there is a
 35 principal compressive stress in the longitudinal axis of the cervix, parallel to
 36 the inner canal, caused by the amniotic sac pushing on the internal os. This
 37 compressive stress translates into prominent tensile principal strains in the cir-
 38 cumferential and radial directions. Taken together these forces cause the cervix
 39 to expand radially and shorten, similar to a thick-walled cylinder resisting a
 40 compressive axial stress.

41 The collagen ultrastructure of the cervix plays a crucial role to withstand
 42 the circumferential, radial, and longitudinal stresses throughout the tissue. A
 43 traditional view of the preferred directionality of the collagen was elucidated by
 44 x-ray diffraction techniques by Aspden from an average of eight nonpregnant
 45 human cervixes (Aspden, 1988). This view details three seamless zones of aligned
 46 collagen with an inner and outer zone of longitudinal fibers and a middle zone
 47 of circumferential fibers. Additionally, this study reports a level of dispersion
 48 around the main fiber direction. More recently, second harmonic generation
 49 (SHG) (Feltovich et al., 2012) and OCT data (Gan et al., 2014) of human cervical
 50 tissue specimens reveal a large band of circumferential fibers that extend to the
 51 outer radial edges of the cervix (Fig. 2A). From these ultrastructure studies,
 52 it is clear that the dense core of the cervix contains bands of collagen fibers

53 circling the inner canal preventing circumferential dilation of the cervix. The
54 width of this band of circumferential collagen and also the amount of dispersion
55 for both nonpregnant and pregnant tissue are still under investigation. As we
56 continue to elucidate these possible regions of preferentially-aligned collagen
57 fibers, we develop here a material model that directly incorporates collagen
58 fiber directionality and dispersion from OCT data (Gan et al., 2014).

59 A critical element to evaluating the mechanical loading pattern on the cervix
60 during pregnancy is a micro-structurally inspired constitutive material model
61 for cervical tissue that captures its material response to physiologically-relevant
62 loading patterns. Previous mechanical testing data has found that the material
63 response of human cervical tissue to loading is nonlinear, anisotropic, and time-
64 dependent, where the overall material response for pregnant tissue is orders
65 of magnitude less than nonpregnant tissue (Badir et al., 2013; Fernandez et al.,
66 2013; Hee et al., 2014; Liao et al., 2014; Myers et al., 2008, 2010; Parra-Saavedra
67 et al., 2011; Yao et al., 2014). In both the instantaneous and equilibrium re-
68 sponse, one of the most important features of cervical material behavior is the
69 non-linearity between the tension and compression stress response. Cervical tis-
70 sue is much softer in compression than tension. This asymmetry is due in part
71 to the collagen fiber network, where collagen fibers support loads when they are
72 engaged in a tensile strain.

73 The goal of this modeling study is to determine the simplest form of a mate-
74 rial constitutive equation that describes the salient tension/compression feature
75 of the cervical tissue’s equilibrium stress response, after the transient visco- and
76 poro-elastic effects have subsided. Additionally, the derivation considers the
77 dominant features of the cervical extracellular matrix that are hypothesized to
78 remodel and cause cervical softening during pregnancy, mainly the collagen fiber
79 stiffness, directionality, and dispersion (Akins et al., 2010; Danforth, 1983, 1947;
80 Feltovich et al., 2010; Gan et al., 2014; Myers and Ateshian, 2014; Myers et al.,
81 2009; Read et al., 2007; Yoshida et al., 2014). We model cervical tissue as a
82 composite material where the stress in the tissue is balanced by a continuously-
83 distributed collagen fiber network embedded in an isotropic compressible neo-

84 Hookean ground substance (Lanir, 1983). The model contains a single family of
85 preferentially oriented fibers, where the fibers are dispersed about the main di-
86 rection described by an ellipsoidal orientation density function (Ateshian et al.,
87 2009; Myers and Ateshian, 2014). Both directionality and dispersion are in-
88 formed by OCT collagen fiber measurements of an axial slice of a nonpregnant
89 and pregnant human cervical sample (Gan et al., 2014). We present the tension
90 and compression uni-axial model fits to previously published data (Myers et al.,
91 2008, 2010). We illustrate how the cervical collagen ultrastructure plays a role
92 in preventing cervical deformation by investigating the compression of a thick-
93 walled cylinder with circumferentially aligned fibers, which serves as a simplistic
94 toy model for the stress state of the cervix experienced *in vivo*.

95 2. Methods

96 2.1. Equilibrium Material Model for Human Cervical Tissue

97 A tissue material element of the cervix is modeled as a composite of a
98 preferentially-aligned collagen network embedded within an isotropic, compress-
99 ible neo-Hookean ground substance. Here we assume isothermal and equilibrium
100 conditions, where the transient effects of the interstitial fluid pressurization and
101 the intrinsic viscoelasticity of the collagen network have subsided. Additionally,
102 in the initial form of this model we assume the tissue does not actively contract
103 and that the fixed charge density of the entangled glycosaminoglycans is suf-
104 ficiently low that it does not contribute to the compressive material response
105 of the tissue. The collagen fiber network has a single family of aligned fibers,
106 where the directionality and dispersion are informed by a measure of the ultra-
107 structure of collagen fibers (Gan et al., 2014). The collagen fibers are extensible,
108 deform affinely with the ground substance, and in the current form of the model
109 they do not interact with each other.

110 The total Cauchy stress σ^{TOT} for this equilibrium cervical material model
111 is given by

$$\sigma^{\text{TOT}} = \frac{1}{J} \frac{\partial \Psi^{\text{TOT}}(\mathbf{F}, \hat{\mathbf{a}}_0, \frac{b}{a})}{\partial \mathbf{F}} (\mathbf{F})^T, \quad (1)$$

where Ψ^{TOT} is the total Helmholtz free energy density of the continuously distributed collagen fiber composite, defined per unit reference volume. $\mathbf{F}$ is the deformation gradient given by a standard definition derived from the motion of the material from the reference to the deformed configuration, $J = \det \mathbf{F}$ is the Jacobian, and $\hat{\mathbf{a}}_{\mathbf{o}}$ and $\frac{b}{a}$ are the preferred direction of a single family of collagen fibers and a measure of the fiber dispersion (per Eq. 6) in the reference configuration, respectively. This hyperelastic relation is derived from thermodynamic restrictions imposed by the axiom of entropy inequality (Holzapfel, 2000).

The total Helmholtz free energy density Ψ^{TOT} is the additive contribution from the fibrous collagen network Ψ^{COL} and the neo-Hookean ground substance Ψ^{GS} of non-collagenous ECM components, such as elastin, glycosaminoglycans, and other extracellular proteins, given by

$$\Psi^{\text{TOT}} \left(\mathbf{F}, \hat{\mathbf{a}}_{\mathbf{o}}, \frac{b}{a} \right) = \Psi^{\text{GS}}(\mathbf{F}) + \Psi^{\text{COL}} \left(\mathbf{F}, \hat{\mathbf{a}}_{\mathbf{o}}, \frac{b}{a} \right). \quad (2)$$

The free energy density of the ground substance Ψ^{GS} is given by a standard isotropic, compressible neo-Hookean relation,

$$\Psi^{\text{GS}} = \frac{\mu}{2} (I_1 - 3) - \mu \ln J + \frac{\lambda}{2} (\ln J)^2, \quad (3)$$

where $I_1 = \text{tr} \mathbf{C}$ is the first invariant of the right Cauchy-Green tensor $\mathbf{C} = (\mathbf{F})^T \mathbf{F}$ and μ and λ are the standard lamé constants. These lamé constants combine to form the Young's modulus and Poisson's ratio of the ground substance $E^{\text{GS}} = \frac{\mu(3+\frac{2\mu}{\lambda})}{1+\frac{\mu}{\lambda}}$ and $\nu^{\text{GS}} = \frac{1}{2(1+\frac{\mu}{\lambda})}$, respectively.

The free energy density of the solid collagen network Ψ^{COL} is an orientation average of the free energy density of a single collagen fiber $\Psi_n^{\text{COL}}(I_n)$ (Eq. 5) weighted by an ellipsoidal distribution $D(\mathbf{n}_{\mathbf{o}}, \frac{b}{a})$ (Eq. 6) and is given by

$$\Psi^{\text{COL}} \left(\mathbf{F}, \hat{\mathbf{a}}_{\mathbf{o}}, \frac{b}{a} \right) = \int_0^{2\pi} \int_0^\pi H(I_n - 1) \Psi_n^{\text{COL}}(I_n) D \left(\mathbf{n}_{\mathbf{o}}, \frac{b}{a} \right) \sin \phi \, d\phi d\theta, \quad (4)$$

where $\mathbf{n}_{\mathbf{o}} = \cos \theta \sin \phi \mathbf{e}_1 + \sin \theta \sin \phi \mathbf{e}_2 + \cos \phi \mathbf{e}_3$ in a local Cartesian basis $\{\mathbf{e}_1, \mathbf{e}_2, \mathbf{e}_3\}$ with spherical coordinates θ , and ϕ and $\hat{\mathbf{a}}_{\mathbf{o}}$ defines the preferred directionality. $I_n = \mathbf{n}_{\mathbf{o}} \cdot \mathbf{C} \cdot \mathbf{n}_{\mathbf{o}}$ is the square of the fiber stretch, and H is the unit step function that enforces collagen fibers sustain only tension. The

137 free energy density of a single fiber bundle Ψ_n^{COL} (i.e. collection of crosslinked
138 collagen fibrils) is constitutively prescribed to be

$$\Psi_n^{\text{COL}} = \xi (\text{I}_n - 1)^\beta, \quad (5)$$

139 where ξ and β represent material properties of the collagen fiber bundle. ξ is
140 the elastic modulus of the collagen fiber, with units of stress, and β is a unitless
141 stiffening parameter giving the shape of tensile nonlinearity of the fiber. (An odd
142 value of β is invalid if the unit step function H is not employed in Equation 4).

143 The distribution of the single family of preferentially aligned collagen fibers
144 is described by an ellipsoidal fiber distribution (Fig. 2E), expressed in a local
145 material element basis $\{\mathbf{e}_i\}$ using spherical coordinates:

$$D\left(\mathbf{n}_o, \frac{b}{a}\right) = \left(\frac{\cos^2 \theta \sin^2 \phi}{a^2} + \frac{\sin^2 \theta \sin^2 \phi}{b^2} + \frac{\cos^2 \phi}{b^2}\right)^{-\frac{1}{2}}, \quad (6)$$

146 where $[a, b]$ are the semi-axes of a planar ellipse fit (Fig. 2D) to the collagen
147 fiber orientation distribution (Fig. 2C) normalized by,

$$1 = \int_0^{2\pi} \int_0^\pi D\left(\mathbf{n}_o, \frac{b}{a}\right) \sin \phi \, d\phi d\theta. \quad (7)$$

148 For the case of the cervix as a thick-walled cylinder, and based on our initial
149 OCT fiber-tracking maps (Fig. 2A&B), $\hat{\mathbf{a}}_o$ aligns with the circumferential di-
150 rection represented by the local coordinate $\mathbf{e}_1$ (Fig. 2F). Considering, the OCT
151 dispersion measurements are taken on the cervical plane perpendicular to the
152 inner canal, we need to make an assumption regarding dispersion in the orthog-
153 onal plane. Therefore, we assume that the dispersion is equal in both orthogonal
154 directions of the main fiber direction. In the case of the circumferential fibers
155 the dispersion is in the longitudinal and radial directions, where the ratio $\frac{b}{a}$ gives
156 the amount of dispersion. When $\frac{b}{a}$ is equal to 1 the fibers are evenly spread
157 around a unit sphere, representing a case with no preferential direction in the
158 reference configuration. When $\frac{b}{a}$ tends towards 0, the fibers are highly aligned,
159 representing a limiting case with no dispersion.

160 2.2. Collagen Fiber Ultrastructure Characterization

161 We recently established a collagen fiber tracking protocol for human cervical
162 tissue using optical coherence tomography (OCT) (Gan et al., 2014). In that
163 work, we describe a methodology to numerically assemble multiple volume sets
164 of OCT data to produce collagen fiber maps of axial cervical slices, and we
165 demonstrate the methodology on specimens from one nonpregnant (age 40)
166 and one pregnant (age 29, 36 weeks of gestation) patient who underwent a
167 hysterectomy. Both samples were taken within 5 mm of the internal os. The
168 OCT signal was conditioned based on a previously published algorithm for heart
169 tissue (Fleming et al., 2008; Gan and Fleming, 2013) and optimized for cervical
170 collagen (Gan et al., 2014).

171 In this paper, fiber orientation distributions (Fig. 2C) were extracted from
172 the OCT data within 12 different 1 mm x 1 mm regions: 3 different radial zones
173 in the anterior, posterior, left, and right of the axial slice (measurement locations
174 indicated in Fig. 2 A & B). Within each measurement location the prominent
175 direction $\hat{\mathbf{a}}_{\mathbf{o}}$ was identified and the planar fiber dispersion was described by an
176 ellipse (Eq. 6), with $\phi = \frac{\pi}{2}$ and θ representing the angle from the preferred
177 direction. The ellipse parameters $[a, b]$ were optimized using a nonlinear least
178 squares optimization routine in Matlab (v 2013b) such that the equation de-
179 scribed OCT dispersion data (Fig. 2D). To extrapolate to a 3D ellipsoid, both
180 the minor axes of the ellipsoid were set equal to $[b]$. Lastly, the major $[a]$
181 and minor $[b]$ semi-principal axes were normalized under the condition in Eq. 7
182 (Fig. 2E).

183 2.3. Model Fits to Uni-axial Mechanical Testing Data

184 To obtain averaged material parameters $[E_{\text{GS}}, \nu_{\text{GS}}, \xi, \beta]$ the proposed mate-
185 rial model was fit to equilibrium compression and tension data of nonpregnant
186 and pregnant human cervical tissue reported in two previously published studies
187 (Myers et al., 2008, 2010). The detailed mechanical testing protocols were pub-
188 lished in those reports. Briefly, tissue samples were acquired from nonpregnant
189 and term pregnant hysterectomy patients of various obstetric backgrounds and

190 ages. Uni-axial tension and compression samples were taken from axial slices
 191 that were cut perpendicular to the inner canal at various locations throughout
 192 the cervix. Tensile strips (~ 10 mm by 5 mm) (Myers et al., 2010) and com-
 193 pression cylindrical biopsies ($\sim \varnothing 8$ mm by 5 mm) (Myers et al., 2008) were cut
 194 exclusively from the dense mid-stromal region. All samples were tested in a
 195 hydrated environment in a series of ramp-hold tests. Equilibrium data were
 196 averaged here for all nonpregnant and pregnant samples after the transient ma-
 197 terial response has dissipated. The averaged data along with the range in the
 198 stress response are reported in Figure 4. Because it was challenging to obtain
 199 whole cervixes during pregnancy, there was only a single set of pregnant tensile
 200 data reported, and therefore a range of tensile behavior is not reported.

201 Best-fit material parameters for these data were found by informing the ma-
 202 terial model with the collagen directionality $[\hat{\mathbf{a}}_0]$ and averaged dispersion $[\frac{b}{a}]$
 203 measured from our initial OCT results (Figure 2 & Table 1). We assumed that
 204 the preliminary OCT data was representative of typical nonpregnant and preg-
 205 nant collagen fiber orientation and dispersion (This assumption will be tested as
 206 we collect more OCT data, and the limitations of this assumption are discussed
 207 below). Therefore, since tension samples were mechanically tested with the
 208 loading axis aligned with the circumferential direction and compression samples
 209 were tested with the loading axis aligned with the longitudinal axis (i.e. the
 210 inner canal axis), models fits were done such that $\hat{\mathbf{a}}_0$ aligned accordingly. To
 211 get a first approximation of the material properties for the ground substance
 212 $[E_{GS}, \nu_{GS}]$, an analytical form of the material model with no fiber dispersion
 213 was fit to the tension and compression stress response data using a nonlinear
 214 least squares optimization routine in Matlab (v 2013b). Once these parameters
 215 were obtained from the simplified model, the full form of the model with the
 216 collagen dispersion was fit to the data using FEBio (v2.0, <http://febio.org/>),
 217 where the ellipsoidal fiber distribution model is numerically implemented and
 218 documented (Ateshian et al., 2009). In this last step of the fitting, the colla-
 219 gen fiber parameters $[\xi, \beta]$ were optimized by inspection such that the model
 220 calculations matched the experimental data.

221 2.4. Thick-Walled Cylinder Investigation

222 The deformation patterns of a thick-walled cylinder under compressive load-
223 ing were investigated to understand how changes in the material parameters,
224 particularly the fiber ultrastructure, affect the ability of the structure to carry
225 a load. This simplistic boundary value problem attempts to explore the contri-
226 bution of material characteristics as opposed to the complex geometric factors
227 present during pregnancy. The *in vivo* loading conditions of the cervix depend
228 on many interacting geometric and material factors, include anatomical shape,
229 tissue material properties, and contact between the organs. A review of these
230 variables and the current state of pregnancy biomechanics is presented in a
231 companion paper in this special issue (Myers et al., 2015).

232 A thick-walled cylinder was constructed within FEBio using dimensions mea-
233 sured from MRI data of a pregnant patient at 22 weeks of gestation as reported
234 in (Fernandez et al., 2015). The inner canal radius was 8 mm, the outer radius
235 of the cervix was 28 mm, and the length was 38 mm. The model was meshed
236 using 3510 8-node hexahedral elements, where each element was assigned the
237 proposed ellipsoidal dispersion material model. The preferential direction of the
238 collagen fibers $[\hat{\mathbf{a}}_0]$ was aligned with the circumferential direction of the cylin-
239 der, with equal amounts of dispersion in the radial and longitudinal directions
240 (Fig. 2F). A longitudinal 1 kPa compressive stress was applied to the top of the
241 cylinder, with sliding boundary conditions on the bottom and stress-free condi-
242 tions on the outer walls and inner canal (Fig. 2F). These boundary conditions
243 attempt to mimic the stress pattern seen in the posterior part of the cervix
244 in mid-pregnancy (Fig. 1). The longitudinal, radial, and circumferential strains
245 within the cylinder were investigated as a function of cylinder fiber modulus ξ
246 and fiber dispersion $\frac{b}{a}$, where the baseline material parameters for comparison
247 were set equal to the averaged nonpregnant values reported in Table 1.

3. Results

3.1. Cervical Collagen Ultrastructure by OCT: Directionality & Dispersion

The detailed OCT methodology and analysis of cervical collagen directionality and dispersion are reported in (Gan et al., 2014), and the preliminary results are used here to demonstrate how to incorporate the OCT data into the continuous fiber distribution material model. OCT fiber maps of axial slices of human cervix indicate a large band of circumferential collagens in nonpregnant (Fig. 2A) and pregnant (Fig. 2B) cervix, where the circumferential fibers exist as far as the outer radial edges of the cervix. Similar to the x-ray data, the collagen fibers are dispersed about the main fiber direction in both the nonpregnant and pregnant tissue (Fig. 3). Averaging the dispersion ($\frac{b}{a}$) data for 12 OCT measurement locations for each of the cervical slices from the internal os, the collagen fiber dispersion is higher in the pregnant tissue slice when compared to the nonpregnant tissue slice (Fig. 3 & Table 1). This result was not statistically significant, and there was also no statistically significant difference between collagen dispersion measured in the different radial zones (Student's t-test, $p > 0.05$; two-tailed power = 0.025 with $p = 0.05$; Fig. 3). An increase in sample size is needed to conclude if collagen fiber dispersion changes throughout pregnancy and if there are distinct zones of fiber families in the human cervix.

3.2. Fiber Composite Model Fit to Uni-axial Data

The proposed fiber composite material model, informed by the averaged OCT directionality and dispersion (Fig. 3), captured the uni-axial tension and compression equilibrium stress behavior of the cervical tissue (Fig. 4). The best-fit material properties for the averaged set of nonpregnant and pregnant data are in Table 1. With a single set of material parameters, one each for the nonpregnant and the pregnant case, the material model describes the averaged tension and compression uni-axial stress response (Fig. 4). The total sums of the squared differences between model calculations and data (calculated in kPa) are 212 and 0.120 for the nonpregnant and pregnant fit, respectively.

278 The range in the collagen fiber modulus ξ reported in Table 1 for the non-
 279 pregnant case captures the highest and lowest tensile stress response reported
 280 (Fig. 4A), while all other material parameters are kept to their averaged value.
 281 Changing ξ alone, however, does not sufficiently capture the highest compressive
 282 stress response for the nonpregnant tissue (Fig. 4B). The range in the material
 283 parameter E_{GS} reported in Table 1 for the pregnant case captures the high-
 284 est and lowest compressive stress response (Fig. 4D), while all other material
 285 parameters are kept to their averaged value.

286 3.3. Compression of a Thick-walled Cylinder with Circumferential Fibers

287 For a thick-walled cylinder under a 1 kPa compressive longitudinal load,
 288 where $\hat{\mathbf{a}}_0$ is aligned circumferentially, and with material properties as listed for
 289 nonpregnant tissue in Table 1, the magnitude of radial strain (Fig. 5A) is larger
 290 than the circumferential strain (Fig. 5B). The collagen fiber modulus ξ influences
 291 the magnitude of the radial and circumferential strain experienced within the
 292 cylinder, but it does not influence the pattern of strain. The radial strain is
 293 mostly uniform throughout the thickness ($<3\%$ change throughout thickness),
 294 whereas the circumferential strain is nonuniform. The radial strain ranges from
 295 0.027 to 0.067, for the highest and lowest measured values of the collagen fiber
 296 modulus ξ , respectively. The corresponding circumferential strain is the smallest
 297 at the inner canal (0.022-0.053) and is the largest at the outer edge (0.025-
 298 0.060). As the fiber modulus ξ increases, and the overall bulk behavior of the
 299 tissue gets stiffer, there is a protective effect of the collagen fibers to maintain
 300 the radius and thickness of the thick-walled structure under a constant load.
 301 Incremental improvements to this protective effect decreases as ξ continues to
 302 increase because of the nonlinear stiffening of the material behavior.

303 Preferentially-aligned fibers in the circumferential direction help maintain
 304 the radius of a thick-walled cylinder under a constant compressive load (Fig. 6).
 305 Decreasing the dispersion such that the collagen fibers become more circumfer-
 306 entially aligned causes a reduction to the circumferential strain and an increase
 307 in the radial strain. In other words, the pattern of circumferential strain evolves

with decreasing fiber dispersion, where an increase in anisotropy creates regions of reduced strain closer to the inner canal. There is an approximately 30% reduction in circumferential strain at the inner canal if all of the collagen fibers within the cylinder have the lowest measured dispersion in the nonpregnant tissue ($b/a=0.58$) as compared to a cylinder with the randomly distributed fibers ($b/a=1$). The level of radial strain, which tends to change the cylinder thickness, only increases by 3% for this level of alignment ($b/a=0.58$).

4. Discussion

Collagen fiber ultrastructure is a key component to the mechanical function of the human cervix during pregnancy. As such, we present a 3D constitutive material model for human cervical tissue that captures its material response to physiologically-relevant loading patterns and is equipped with ultrastructural parameters that describe cervical softening during pregnancy. Experimental uni-axial compression and tension tests reveal that the stress response of the tissue in tension is much higher than in compression and that pregnant tissue is considerably softer than nonpregnant tissue (Myers et al., 2008, 2010), and imaging data of the cervical stroma reveal zones of preferentially-aligned collagen fibers with a level of dispersion (Aspden, 1988; Gan et al., 2014). To describe these known material characteristics of the cervical tissue, we develop here a fiber composite material model with a continuously distributed fiber network, where changes to the collagen fiber stiffness capture the drastic softening that occurs during pregnancy (Fig. 4).

During pregnancy there is a drastic softening that must occur within the cervical tissue to accommodate the delivery of the baby (see cervical mechanics review in this special issue (Myers et al., 2015)). This softening is accomplished through a complex biochemical cascade of events that remodel the ECM components of the tissue (Holt et al., 2011; Read et al., 2007; Word et al., 2007). Our initial evidence from collagen ultrastructure imaging suggests that the overall preferential direction of the collagen fibers remains in the circumferential di-

337 rection, but the level of dispersion increases (Gan et al., 2014). This increase
 338 in dispersion alone cannot capture the substantial softening that occurs during
 339 pregnancy. To capture the difference in the nonpregnant and pregnant material
 340 stress response the collagen fiber ξ modulus must be reduced by approximately
 341 two orders of magnitude (from an average of 190 to 0.7 kPa). Therefore, we
 342 hypothesize this reduction for the individual fiber component indicates that
 343 along with changes to the collagen ultrastructure, the collagen must intrinsi-
 344 cally remodel to accommodate such a level of cervical softening. Evidence of
 345 this collagen remodeling has been found in human and mouse tissue. Previ-
 346 ous studies by our group have shown that the amount of collagen content does
 347 not significantly change in pregnancy, in both human (Myers et al., 2009) and
 348 mouse tissue (Yoshida et al., 2014). Instead tissue solubility increases in human
 349 pregnant tissue, indicating a reduction in collagen crosslinking (Myers et al.,
 350 2009). In mouse tissue we found evidence of a drastic decline in the total ma-
 351 ture crosslink density (moles of pyridinoline and deoxypyridinoline normalized
 352 by moles of collagen) in day 15 pregnant tissue compared to day 6 pregnant
 353 tissue, of a 19 day mouse gestational period (Yoshida et al., 2014). To prove
 354 our hypothesis, we are currently measuring the collagen crosslinking density in
 355 nonpregnant (Zork et al., 2014) and pregnant human cervical tissue.

356 The nonlinearity in the tension/compression stress response is typical for
 357 soft hydrated tissues with a collagen fiber network, where collagen fibers provide
 358 resistance to tension and any preferential alignment will give added deforma-
 359 tion resistance. In the case of the cervix, the collagen fibers have a preferred
 360 circumferential orientation with a level of dispersion, as viewed by x-ray diffrac-
 361 tion (Aspden, 1988) and OCT (Gan et al., 2014) investigations. This collagen
 362 ultrastructure plays a key role in maintaining the mechanical function of the
 363 cervix during pregnancy. In the first form of the model, we ignore the transient
 364 material response of the tissue to investigate the contribution of fiber stiffness,
 365 fiber directionality, and dispersion. We demonstrate this mechanical function
 366 here using a thick-walled cylinder under a compressive load and in patient-
 367 specific finite element models presented in (Fernandez et al., 2015).

368 For the case of the thick-walled cylinder, the circumferential collagen fibers
 369 reduce the amount of circumferential strain, where decreasing levels of disper-
 370 sion increase this resistance to changes in the radius. We hypothesize that this
 371 added resistance to the circumferential strain is a protective feature of the cervix
 372 preventing dilation and over-stretching of interspersed cells that may control cer-
 373 vical remodeling. Additionally, the level of fiber distribution and dispersion aids
 374 in deformation resistance in directions that are not aligned with the main fiber
 375 family. This dispersion plays an important role in resisting deformation for the
 376 non-uniform and asymmetric loading found in the physiologic-loading scenario,
 377 where the geometry of the anatomy and the placement of the cervix within the
 378 pelvis drives patient-specific patterns of cervical stress and strain (Fernandez
 379 et al., 2015). A previous study, by Liao et al., details a three-fiber family model
 380 (with no dispersion) to describe the cervical collagen ultrastructure (Liao et al.,
 381 2014), using a modeling method common in arterial wall mechanics (Gasser
 382 et al., 2006). This material model does a good job of capturing the mechanical
 383 response of the cervical tissue to inflation of the inner canal (Liao et al., 2014).
 384 However, it is unknown if this type of three-fiber family model can capture the
 385 tension/compression behavior seen in the *in-vivo* loading scenario. A full com-
 386 parison of all cervical material models are given in a cervical mechanics review
 387 presented this special issue (Myers et al., 2015).

388 Obtaining and testing human cervical tissue is a challenge, especially for
 389 pregnant tissue specimens. In this modeling study we made simplifying assump-
 390 tions based on the available data sets for human cervical tissue to establish a
 391 framework to study the cervical collagen ultrastructure. These assumptions
 392 create limitations, where components of our model need to be validated and
 393 extended. First, the OCT, tensile, and compression data were not conducted
 394 on the same cervical tissue. Here, we use initial imaging data results coupled
 395 with a database of averaged stress responses from previous studies. Second,
 396 previous mechanical tests reveal that the material response of human cervical
 397 tissue is time-dependent, with stress-relaxation and hysteresis measured during
 398 ramp-hold and load-unload tests (Myers et al., 2008, 2010; Yao et al., 2014).

399 The next iteration of our model will account for this viscoelastic, and possible
 400 poroelastic behavior (Fernandez et al., 2013), by extending a previously explored
 401 one-dimensional nonlinear viscoelastic model (Myers et al., 2010) to 3D. Third,
 402 we have not mechanically tested human cervical tissue in tension in multiple
 403 anatomical directions and we have not taken compression tests to high levels
 404 of strain in which fiber directionality influences the results. We are currently
 405 conducting additional mechanical tests to validate if this fiber dispersion model
 406 can predict tissue behavior in multiple anatomical directions. Lastly, the thick-
 407 walled cylinder is modeled as being homogeneous with even levels of dispersion
 408 and directionality throughout the radius. Here we do not account for the possi-
 409 bility of additional families of fibers directed longitudinally. The heterogeneity
 410 of tissue characteristics and its effect on how the cervix maintain a mechanical
 411 load will be a topic of another study.

412 **5. Conclusion**

413 Here we present a necessary framework for a 3D equilibrium material model
 414 that accounts for the collagen fiber ultrastructure of the tissue. Equipping the
 415 material model with features of the collagen network allows us to explore the
 416 influence of individual collagen fiber properties and network organization to the
 417 overall mechanical response of the tissue. As we continue to collect and me-
 418 chanically test cervical tissue specimens, we will add deformation mechanisms
 419 to the constitutive model as needed to describe the deformation as a result of
 420 physiologically-relevant loading scenarios and to describe the remodeling pro-
 421 cess of the cervix in pregnancy. In this study, we show that a continuously-
 422 distributed fiber network embedded in a compressible ground substance can
 423 represent the stress response of the tissue to uni-axial loading, and we demon-
 424 strate that the collagen directionality and dispersion play a role in resisting
 425 physiological relevant deformation during pregnancy.

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433 References

- 434 Akins, M., Luby-Phelps, K., Mahendroo, M., 2010. Second harmonic generation
435 imaging as a potential tool for staging pregnancy and predicting preterm
436 birth. *J Biomed Opt* 15, 026020.
- 437 Aspden, R., 1988. Collagen organization in the cervix and its relation to me-
438 chanical function. *Coll Relat Res* 8, 103–112.
- 439 Ateshian, G., Rajan, V., Chahine, N., Canal, C., Hung, C., 2009. Modeling the
440 Matrix of Articular Cartilage Using a Continuous Fiber Angular Distribution
441 Predicts Many Observed Phenomena. *J Biomech Eng* 131, 061003.
- 442 Badir, S., Bajka, M., Mazza, E., 2013. A novel procedure for the mechani-
443 cal characterization of the uterine cervix during pregnancy. *J Mech Behav*
444 *Biomed Mater* 27, 143–153.
- 445 Danforth, D., 1983. The morphology of the human cervix. *Clin Obstet Gynecol*
446 26, 7–13.
- 447 Danforth, D.N., 1947. The fibrous nature of the human cervix, and its relation
448 to the isthmic segment in gravid and nongravid uteri. *Am J Obstet Gynecol*
449 53, 541–560.
- 450 Feltovich, H., Hall, T., Berghella, V., 2012. Beyond cervical length: emerging
451 technologies for assessing the pregnant cervix. *Am J Obstet Gynecol* , 1–43.
- 452 Feltovich, H., Nam, K., Hall, T.J., 2010. Quantitative ultrasound assessment of
453 cervical microstructure. *Ultrason Imaging* 32, 131–142.
- 454 Fernandez, M., House, M., Jambawalikar, S., Vink, J., Wapner, R., Zweben,
455 N., Myers, K., 2015. Investigating the Mechanical Function of the Cervix
456 during Pregnancy using Finite Element Models derived from High Resolution
457 3D MRI. *in-review Comput Methods Biomech Biomed Engin* .

458 Fernandez, M., Vink, J., Yoshida, K., Wapner, R., Myers, K., 2013. Direct
 459 Measurement of the Permeability of Human Cervical Tissue. *J Biomech Eng*
 460 135, 021024.

461 Fleming, C.P., Ripplinger, C.M., Webb, B., Efimov, I.R., Rollins, A.M., 2008.
 462 Quantification of cardiac fiber orientation using optical coherence tomogra-
 463 phy. *J Biomed Opt* 13, 030505.

464 Gan, Y., Fleming, C.P., 2013. Extracting three-dimensional orientation and
 465 tractography of myofibers using optical coherence tomography. *Biomed Opt*
 466 Express 4, 2150.

467 Gan, Y., Yao, W., Myers, K.M., Hendon, C.P., 2014. An automated 3d reg-
 468 istration method for optical coherence tomography volumes, in: *Engineering*
 469 *in Medicine and Biology Society (EMBC), 2014 36th Annual International*
 470 *Conference of the IEEE, IEEE*. pp. 3873–3876.

471 Gasser, T., Ogden, R., Holzapfel, G., 2006. Hyperelastic modelling of arterial
 472 layers with distributed collagen fibre orientations. *J R Soc Interface* 3, 15–35.

473 Gravett, M.G., Rubens, C.E., Nunes, T.M., GAPPS Review Group, 2010.
 474 Global report on preterm birth and stillbirth (2 of 7): discovery science.
 475 *BMC Pregnancy Childbirth* 10 Suppl 1, S2.

476 Hee, L., Liao, D., Sandager, P., Gregersen, H., Uldbjerg, N., 2014. Cervical
 477 Stiffness Evaluated In Vivo by Endoflip in Pregnant Women. *PLoS ONE* 9,
 478 e91121.

479 Holt, R., Timmons, B., Akgul, Y., Akins, M., Mahendroo, M., 2011. The
 480 molecular mechanisms of cervical ripening differ between term and preterm
 481 birth. *Endocrinology* 152, 1036–1046.

482 Holzapfel, G.A., 2000. *Nonlinear Solid Mechanics: A Continuum Approach for*
 483 *Engineering*. John Wiley & Sons.

484 House, M., Bhadelia, R., Myers, K., Socrate, S., 2009. Magnetic resonance imag-
485 ing of three-dimensional cervical anatomy in the second and third trimester.
486 Eur J Obstet Gynecol Reprod Biol 144 Suppl 1, S65–9.

487 House, M., Feltovich, H., Hall, T., Stack, T., Patels, A., Socrate, S., 2012.
488 Three-dimensional, extended field-of-view ultrasound method for estimating
489 large strain mechanical properties of the cervix during pregnancy. Ultrason
490 Imaging 34, 1–14.

491 House, M., McCabe, R., Socrate, S., 2013. Using imaging-based, three-
492 dimensional models of the cervix and uterus for studies of cervical changes
493 during pregnancy. Clinical anatomy (New York, N.Y.) 26, 97–104.

494 Iams, J.D., Cebrik, D., Lynch, C., Behrendt, N., Das, A., 2011. The rate of
495 cervical change and the phenotype of spontaneous preterm birth. Am J Obstet
496 Gynecol 205, 130.e1–130.e6.

497 Lanir, Y., 1983. Constitutive equations for fibrous connective tissues. J Biomech
498 16, 1–12.

499 Liao, D., Hee, L., Sandager, P., Uldbjerg, N., Gregersen, H., 2014. Identification
500 of biomechanical properties in vivo in human uterine cervix. J Mech Behav
501 Biomed Mater 39, 27–37.

502 Mahmoud, H., Wagoner Johnson, A., Chien, E.K., Poellmann, M.J., McFarlin,
503 B., 2013. System-Level Biomechanical Approach for the Evaluation of Term
504 and Preterm Pregnancy Maintenance. J Biomech Eng 135, 021009.

505 Myers, K., Ateshian, G., 2014. Interstitial growth and remodeling of biological
506 tissues: Tissue composition as state variables. J Mech Behav Biomed Mater
507 29, 544–556.

508 Myers, K., Feltovich, H., Mazza, E., Vink, J., Bajka, M., Wapner, R., Hall, T.,
509 House, M., 2015. The Mechanical Role of the Cervix In Pregnancy. *accepted*
510 *to J of Biomech Special Edition of Reproductive Biomechanics* .

511 Myers, K., Paskaleva, A., House, M., Socrate, S., 2008. Mechanical and bio-
512 chemical properties of human cervical tissue. *Acta Biomater* 4, 104–116.

513 Myers, K., Socrate, S., Paskaleva, A., House, M., 2010. A study of the anisotropy
514 and tension/compression behavior of human cervical tissue. *J Biomech Eng*
515 132, 021003.

516 Myers, K., Socrate, S., Tzeranis, D., House, M., 2009. Changes in the biochem-
517 ical constituents and morphologic appearance of the human cervical stroma
518 during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 144 Suppl 1, S82–9.

519 Parra-Saavedra, M., Gómez, L., Barrero, A., Parra, G., Vergara, F., Navarro,
520 E., 2011. Prediction of preterm birth using the cervical consistency index.
521 *Ultrasound Obstet Gynecol* 38, 44–51.

522 Read, C.P., Word, R.A., Ruscheinsky, M.A., Timmons, B.C., Mahendroo, M.S.,
523 2007. Cervical remodeling during pregnancy and parturition: molecular char-
524 acterization of the softening phase in mice. *Reprod* 134, 327–340.

525 Solomon, C., Iams, J., 2014. Prevention of Preterm Parturition. *N Engl J Med*.
526 370, 254–261.

527 Word, R.A., Li, X., Hnat, M., Carrick, K., 2007. Dynamics of cervical remod-
528 eling during pregnancy and parturition: mechanisms and current concepts.
529 *Semin Reprod Med* 25, 69–79.

530 Yao, W., Yoshida, K., Fernandez, M., Vink, J., Wapner, R., Ananth, C., Oyen,
531 M., Myers, K., 2014. Measuring the compressive viscoelastic mechanical prop-
532 erties of human cervical tissue using indentation. *J Mech Behav Biomed Mater*
533 34, 18–26.

534 Yoshida, K., Jiang, H., Kim, M., Vink, J., Cremers, S., Paik, D., Wapner,
535 R., Mahendroo, M., Myers, K., 2014. Quantitative Evaluation of Collagen
536 Crosslinks and Corresponding Tensile Mechanical Properties in Mouse Cer-
537 vical Tissue during Normal Pregnancy. *PLoS ONE* 9, e112391.

538 Zork, N.M., Myers, K.M., Yoshida, K., Cremers, S., Jiang, H., Ananth, C.V.,
539 Wapner, R.J., Kitajewski, J., Vink, J., 2014. A systematic evaluation of
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541 **List of Tables**

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NP/PG	E_{GS} [kPa]	ν_{GS}	ξ [kPa]	β	$\hat{\mathbf{a}}_{\mathbf{o}}$	$\frac{b}{a}$
NP	2	0.3	190 (40-460)	3	circum	0.77 (0.58-0.90)
PG	0.65 (0.50-0.80)	0.3	0.7	2	circum	0.84 (0.64-0.98)

Table 1: Material model fit parameters. $[\hat{\mathbf{a}}_{\mathbf{o}}$ and $\frac{b}{a}]$ are measured from the OCT analysis of a nonpregnant (NP) and pregnant (PG) cervical axial slice (Gan et al., 2014), where the average and range are reported for the 12 1 mm x 1 mm zones depicted in Fig. 2 A & B. $[E_{\text{GS}}, \nu_{\text{GS}}, \xi, \beta]$ are the best-fit material model parameters, informed by the preliminary OCT data, and fit to uni-axial tension and compression mechanical data reported in (Myers et al., 2008, 2010). The range reported for the material parameters ξ for the nonpregnant data represents the fits to the highest and lowest tensile stress response reported for the tissue. The range reported for the material parameters E_{GS} for the pregnant data represents the fits to the highest and lowest compression stress response reported for the tissue.

Figure 1: Representative principal strain and stress directions depicted for a pregnant patient at 20 weeks of gestation. The intrauterine pressure of 8.6 kPa was applied to the inner surface of the fetal membranes, which are adhered to the lower uterine segment (Fernandez et al., 2015). The mechanical deformation state of the human cervix is a mix of tension and compression. Depending on the placement of the cervix within the pelvis, regions of the cervix experience a longitudinal compressive stress.

Figure 3: Fiber dispersion $\frac{b}{a}$ in the outer, middle, and inner zones for the nonpregnant and pregnant tissue axial slice. There is an increase in dispersion for the pregnant tissue slice compared to the nonpregnant slice. There was no statistically significant difference in fiber dispersion between the zones for each slice.

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Figure 5: Effect of collagen fiber modulus ξ . An increase in ξ decreases the amount of radial and circumferential strain in a thick-walled cylinder that maintains a compressive stress of 1 kPa. The material properties used for this simulation are listed for the nonpregnant tissue in Table 1, where the range represents the material model fit to the highest and lowest tensile stress response measured for nonpregnant human cervical tissue (Myers et al., 2010).

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