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A Phenomenological Model for Mechanically Mediated Growth, Remodeling, Damage, and Plasticity of Gel-Derived Tissue Engineered Blood Vessels

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Abstract

Mechanical stimulation has been shown to dramatically improve mechanical and functional properties of gel-derived tissue engineered blood vessels (TEBVs). Adjusting factors such as cell source, type of extracellular matrix, cross-linking, magnitude, frequency, and time course of mechanical stimuli (among many other factors) make interpretation of experimental results challenging. Interpretation of data from such multifactor experiments requires modeling. We present a modeling framework and simulations for mechanically mediated growth, remodeling, plasticity, and damage of gel-derived TEBVs that merge ideas from classical plasticity, volumetric growth, and continuum damage mechanics. Our results are compared with published data and suggest that this model framework can predict the evolution of geometry and material behavior under common experimental loading scenarios.

Keywords

mechanical conditioning; mechanotransduction; volumetric growth

1 Introduction

There is a great unmet clinical need to develop small diameter tissue engineered blood vessels (TEBVs) with low thrombogenicity and immune response, suitable mechanical properties, and a capacity to adapt to their environment [1–3]. Since the pioneering work by Weinberg and Bell [4], there have been tremendous advances toward this pursuit. Nevertheless, the need for a TEBV suitable as a coronary bypass graft remains unmet. Biomechanical stimuli, such as cyclic strain, have been shown to stimulate remodeling of collagen gel-derived TEBVs to greatly improve their mechanical behavior [5]. It is now becoming clear that tissue engineered constructs adapt synergistically to specific combinations of multidirectional loading [6]. A critical gap remains, however, in understanding the role of multidirectional loading on TEBV remodeling.

Several tissue engineering strategies show great promise for vascular applications, including gel-derived [4], biodegradable scaffold-derived [7], and cell self-assembly-derived [8] TEBVs. Here we focus on the gel-derived approach. Weinberg and Bell [4] pioneered the gel-derived approach by combining collagen gels with a Dacron mesh and showed that the burst pressure increased with increasing collagen concentrations from 2 mg/ml to 5 mg/ml and burst pressure was the maximum at 30 days in culture. Kanda et al. [9] observed that both isometric loading and cyclic dynamical loading of collagen gel rings showed cellular and extracellular matrix alignments in the direction of loading. Seliktar et al. [5] showed that circumferential distension increased modulus, yield stress, ultimate tensile stress, and rates of compaction compared with static cultures. Seliktar et al. [10] reported that these responses can be blocked by inhibiting expression of matrix metalloproteinases; thus this is an active cell-mediated adaptive response.

Isenberg and Tranquillo [11] demonstrated that the amplitude of strain and parameters related to the pulse frequency and shape of the pulse waveform are important parameters regulating these cell-mediated changes in TEBV mechanical properties. Isenberg and Tranquillo [11] said well that “[a]s promising as [gel-derived TEBV] results may be, their interpretation is difficult due to a number of confounding factors;” they cited confounding factors such as degree of compaction prior to mechanical stimulation and plastic deformation due to loading. We agree and submit that interpretation of data from experiments that contain such confounding factors requires a predictive mathematical model. Toward this end, the purpose of this paper is to describe a theoretical framework suitable for quantifying mechanically mediated growth and remodeling of gel-derived TEBVs, while considering that (even under modest loading) the TEBVs experience plastic deformations and damage. Although we admit that a microstructurally motivated model is ultimately required to understand the full complexities for growth, remodeling, damage, and plasticity of gel-derived TEBVs at multiple length scales, we propose that a purely phenomenological model will provide important guidance for designing experiments, interpreting experimental data, and motivating more detailed models. Thus, we describe a theoretical framework that combines the concepts of volumetric growth put forth by Skalak and co-workers [12,13] and extended by many [14–19], with plasticity and continuum damage mechanics, and present several illustrative examples to mimic typical experiments presented in the literature. We use these illustrative simulations to demonstrate the capability of the proposed modeling framework to capture the salient features of growth, remodeling, damage, and plasticity by comparing simulation results to data from the literature; we focus our attention on the results of Seliktar et al. [5], which provide the most comprehensive set of mechanical data currently available. One of the main utilities of theoretical models is to motivate experiments; thus, we also use these illustrative simulations to highlight data that are currently lacking in the literature and to motivate a new experimental approach to mechanical conditioning of gel-derived TEBVs that may be employed to improve mechanical properties and reduce requisite culture times for the development of TEBVs.

2 Theoretical Framework

The major hypothesis of this study is that changes in the geometrical dimensions and mechanical properties of the gel-derived TEBV depend on the magnitude of the local stress experienced by the tissue and the amplitude of the periodic circumferential stretching during dynamic conditioning. To test this hypothesis, some theoretical predictions of a proposed phenomenological model are compared with the available experimental data in the literature. To build the model, we first describe the kinematics of the TEBV and subsequently describe the constitutive formulation of the mechanical response of the TEBV. The derived equations are used in an illustrative example for examining the behavior of a TEBV on a rigid mandrel and on an elastic sleeve of periodically varying diameter.

2.1 Plasticity and Growth (Kinematics)

Consider a stress-free body $\beta_o(0)$ at time $t=0$ that is loaded to the configuration $\beta_\ell(t)$; the deformation gradient for the mapping of points from $\beta_o(0)$ to $\beta_\ell(t)$ is denoted as $\mathbf{F}$ (Fig. 1). The transformation from $\beta_o(0)$ to $\beta_\ell(t)$ results predominately from three processes that can occur simultaneously: (i) an elastic deformation, (ii) a deformation due to plasticity, and (iii) a change in the configuration of an infinitesimal element caused by processes termed generally as growth.

If the applied loads induce stresses beyond the yield stress, *plasticity* will ensue. We define plasticity as a mechanically, but not biologically, mediated change in the stress-free (i.e., natural) configuration. Also, over time, these applied loads can induce a mechanically mediated *growth*. We define growth as the mechanobiologically mediated change in the stress-free configuration, including changes in volume (see Ref. [16]). Growth can occur via cell proliferation or hypertrophy and cell-mediated extracellular matrix production. More specifically the term growth refers to the case when the mass of the element increases, while the case of diminishing mass is considered resorption. A special case of resorption can also occur via cell-mediated compaction, i.e., the rearrangement of cells and collagen or fibrin and the extrusion of water from the construct that result in diminishing of the volume. Thus, growth (or compaction) and plastic deformation may occur in parallel and result in an evolution of the natural configuration.

As plastic deformation and growth proceed in parallel, the traction-free (unloaded) configuration at time t denoted as $\beta_u(t)$ is, in general, not stress-free; it contains residual stresses. We may, however, define $\beta_o(t)$ as the configuration wherein the local neighborhood about every point in the body is stress-free; this configuration consists of discontinuous (and fictitious) elements (see Ref. [16]). The mapping of points from $\beta_o(t)$ to $\beta_u(t)$, thereby assembling the discontinuous elements into the traction-free elements and producing residual stresses, has the deformation gradient $\mathbf{F}_a$. The mapping from the stress-free configuration $\beta_o(t)$ to the loaded configuration $\beta_\ell(t)$ has deformation gradient $\mathbf{F}_e$.

Let us decompose the mapping of points from $\beta_o(0)$ to $\beta_o(t)$, which defines the plastic deformation and the growth, into two deformations: the first accounting for the plastic deformation and the second accounting for the growth. Let the plastic deformation map points from the stress-free configuration $\beta_o(0)$ to an intermediate stress-free configuration $\beta_p(t)$ (which consists of discontinuous (fictitious) elements) have deformation gradient $\mathbf{F}_p$. Let the growth deformation map points from $\beta_p(t)$ to $\beta_o(t)$ have deformation gradient $\mathbf{F}_g$. Finally, we may define $\mathbf{F}_{pg} = \mathbf{F}_g \mathbf{F}_p$, which accounts for the combined effect of growth and plastic deformations; therefore $\mathbf{F} = \mathbf{F}_e \mathbf{F}_g \mathbf{F}_p = \mathbf{F}_e \mathbf{F}_{pg}$.

2.2 Damage and Remodeling (Constitutive Equation)

In addition to growth (or compaction) and plastic deformations, mechanically mediated mechanisms can result in the change in the local material response described by the constitutive equation of the TEBV. It is well documented that mechanical stimuli can increase the effective elastic modulus of collagen gel-derived TEBVs [5,11] through biological mechanisms; thus, let us define *remodeling* as mechanobiologically mediated changes in material properties. In this phenomenological approach, such changes in material properties could be due to altered cellular contraction, altered mechanical properties of cells, extrusion of water leading to increased fraction of load bearing material, synthesis, degradation, or altered cross-linking of extracellular matrix, among many other mechanisms. In addition, if the applied loads produce stresses above some critical stress, local *damage* may occur. We define damage as the non-biologically, but mechanically mediated, change in material properties.

2.3 Anisotropic Damage and Remodeling

With regard to changes in material behavior due to damage, we employ the theoretical framework of Kachonov [20,21] and Rabotnov [22]; we consider anisotropic damage. The Clausius–Duhem equation for isothermal mechanical processes requires that

$$-\frac{\partial W}{\partial t} + \frac{1}{2} \mathbf{S} : \frac{\partial \mathbf{C}_e}{\partial t} = \Phi \geq 0 \quad (1)$$

where t is time, W is the strain energy density function (per unit volume), $\mathbf{S}$ is the second Piola–Kirchhoff stress tensor, $\mathbf{C}_e = \mathbf{F}_e^T \mathbf{F}_e$ is the right Cauchy–Green strain tensor of the elastic deformation, and Φ is the local entropy production. We let $W = W(\mathbf{C}_e, \mathbf{D})$, where $\mathbf{D}$ is a second order damage tensor; thus,

$$\left(-\frac{\partial W}{\partial \mathbf{C}_e} + \frac{1}{2} \mathbf{S} \right) : \frac{\partial \mathbf{C}_e}{\partial t} + \frac{\partial W}{\partial \mathbf{D}} : \frac{\partial \mathbf{D}}{\partial t} = \Phi \geq 0 \quad (2)$$

which is satisfied when

$$\mathbf{S} = 2 \frac{\partial W}{\partial \mathbf{C}_e} \quad \text{and} \quad \frac{\partial W}{\partial \mathbf{D}} : \frac{\partial \mathbf{D}}{\partial t} \geq 0 \quad (3)$$

For $\partial W / \partial \mathbf{D} \geq 0$, Eq. (3) requires that $\partial \mathbf{D} / \partial t$ be non-negative; thus, $\mathbf{D}$ is constant or an increasing function.

With regard to changes in material behavior due to remodeling, we may follow a similar approach and let $W = W(\mathbf{C}_e, \mathbf{M})$, where $\mathbf{M}$ is a second order remodeling tensor; thus,

$$\left(-\frac{\partial W}{\partial \mathbf{C}_e} + \frac{1}{2} \mathbf{S} \right) : \frac{\partial \mathbf{C}_e}{\partial t} + \frac{\partial W}{\partial \mathbf{M}} : \frac{\partial \mathbf{M}}{\partial t} = \Phi \quad (4)$$

since remodeling is a biologically mediated process, the tissue is modeled as an open thermodynamical system. Thus, the local entropy production need not be greater than or equal to zero. We again may let $\mathbf{S} = 2 \partial W / \partial \mathbf{C}_e$ with no constraint on the sign of $\partial \mathbf{M} / \partial t$.

In general, damage and remodeling may occur simultaneously; thus, let us define

$$W = W(\mathbf{C}_e, \mathbf{D}, \mathbf{M}) = W(\mathbf{C}_e, \mathbf{\Gamma}) \quad (5)$$

where $\mathbf{\Gamma}$ is a tensor that accounts for the net effect of damage and remodeling. In this case Eq. (1) becomes

$$\left(-\frac{\partial W}{\partial \mathbf{C}_e} + \frac{1}{2}\mathbf{S}\right) : \frac{\partial \mathbf{C}_e}{\partial t} + \frac{\partial W}{\partial \mathbf{D}} : \frac{\partial \mathbf{D}}{\partial t} + \frac{\partial W}{\partial \mathbf{M}} : \frac{\partial \mathbf{M}}{\partial t} = \Phi \quad (6)$$

which is satisfied with Eq. (3), with no constraint on the sign of $\partial \mathbf{M} / \partial t$. We prescribe an illustrative functional form and material parameters of $W=W(\mathbf{C}_e, \Gamma)$ and $\Gamma(\mathbf{M}, \mathbf{D})$ below.

3 Illustrative Example

Here we consider culture of long, straight, thick-walled, incompressible, cylindrical gel-derived TEBVs under two different loading scenarios; namely, static culture on a rigid mandrel and culture on a distensible tube. There is significant experimental data available in the literature, to which our simulation results are compared. At any moment, the TEBV is considered to be in an axisymmetric state of stress and strain, which produce axisymmetric, but radially variable, plastic, growth, damage, and remodeling responses. We specify the general description of the geometrical and material alterations described above for the case when the introduced configurations $\beta_o(0)$ and $\beta_\ell(t)$ are referred to appropriate cylindrical coordinate systems (Fig. 2).

3.1 Kinematics

We model the TEBV as a thick-walled tube with initial axial length $L(0)$ and initial radius $R(0)$ is in $[A(0), B(0)]$, where $A(0)$ and $B(0)$ are the inner and outer radii. The plastic deformation gradient has components $[\mathbf{F}_p] = \text{diag}[\lambda_{pr}, \lambda_{p\theta}, \lambda_{pz}]$, where

$$\lambda_{pr} = \frac{\partial R_p(t)}{\partial R(0)}, \quad \lambda_{p\theta} = \frac{R_p(t)}{R(0)}, \quad \lambda_{pz} = \frac{L_p(t)}{L(0)} \quad (7)$$

$L_p(t)$ is the length and $R_p(t)$ is the radius in β_p of the infinitesimally thin ring (with thickness $dR_p(t)$) that passes through radial location $R(0)$ in $\beta_o(0)$; since each ring is infinitesimally thin, they cannot support a residual stress. Note that $L_p(t)$ and $R_p(t)$ are functions of $R(0)$. In addition, the plastic deformation is considered isochoric; thus, $\det[\mathbf{F}_p] = 1$. The growth deformation gradient has components $[\mathbf{F}_g] = \text{diag}[\lambda_{gr}, \lambda_{g\theta}, \lambda_{gz}]$, where

$$\lambda_{gr} = \frac{\partial R(t)}{\partial R_p(t)}, \quad \lambda_{g\theta} = \frac{R(t)}{R_p(t)}, \quad \lambda_{gz} = \frac{L(t)}{L_p(t)} \quad (8)$$

where $L(t)$ is the length and $R(t)$ is the radius of the cylindrical shell that passes through radial location $R_p(t)$ in $\beta_p(t)$ and $R(0)$ in $\beta_o(0)$; $L(t)$ and $R(t)$ are functions of $R_p(t)$ and thus functions of $R(0)$. The growth deformation from $\beta_p(0)$ to $\beta_o(t)$ is not isochoric; thus, $\det[\mathbf{F}_g] \neq 1$. By combining Eqs. (7) and (8), the components of the deformation gradient combining plasticity and growth, $[\mathbf{F}_{pg}] = \text{diag}[\lambda_{pgr}, \lambda_{pg\theta}, \lambda_{pgz}]$, are given as

$$\lambda_{pgr} = \frac{\partial R(t)}{\partial R(0)}, \quad \lambda_{pg\theta} = \frac{R(t)}{R(0)}, \quad \lambda_{pgz} = \frac{L(t)}{L(0)} \quad (9)$$

The elastic deformation gradient has components $[\mathbf{F}_e] = \text{diag}[\lambda_{er}, \lambda_{e\theta}, \lambda_{ez}]$, where

$$\lambda_{er} = \frac{\partial r(t)}{\partial R(t)}, \quad \lambda_{e\theta} = \frac{r(t)}{R(t)}, \quad \lambda_{ez} = \frac{\ell(t)}{L(t)} \quad (10)$$

where $\ell(t)$ is the loaded length and $r(t)$ is the loaded radius in $\beta_\ell(t)$ of the cylindrical shell that passes through radial location $R(0)$ in $\beta_o(0)$. Finally, we enforce the constraint that the elastic deformation is assumed to be isochoric $\det(\mathbf{F}_e)=1$, i.e., $\lambda_{er}\lambda_{e\theta}\lambda_{ez}=1$. Thus, the overall deformation, from $\beta_o(0)$ to $\beta_\ell(t)$, is $[\mathbf{F}]=\text{diag}[\lambda_r, \lambda_\theta, \lambda_z]$, where

$$\lambda_r = \frac{\lambda_{gr}}{\lambda_{p\theta}\lambda_{pz}\lambda_{e\theta}\lambda_{ez}}, \quad \lambda_\theta = \lambda_{p\theta}\lambda_{g\theta}\lambda_{e\theta}, \quad \lambda_z = \lambda_{pz}\lambda_{gz}\lambda_{ez} \quad (11)$$

which leads to an ordinary differential equation for $r(t)$ having solution

$$r^2 = \frac{2}{\lambda_z} \int_{R_i(0)}^{R(0)} \lambda_{pgr}\lambda_{pg\theta}\lambda_{pgz} R(0) dR(0) + \mu^2 R_i(0)^2 \quad (12)$$

where $R_i(0)$ is the initial stress-free inner radius and $\mu(t) = r_i(t)/R_i(0)$ is the ratio of the inner radii in the current loaded and the original stress-free configurations, respectively. Given Eq. (12), the circumferential elastic stretch is

$$\lambda_{e\theta}^2 = \frac{1}{\lambda_{pg\theta}^2} \frac{r^2(t)}{R(0)^2} = \frac{2}{\lambda_z \lambda_{pg\theta}^2 R(0)^2} \int_{R_i(0)}^{R(0)} \lambda_{pgr}\lambda_{pg\theta}\lambda_{pgz} R(0) dR(0) + \frac{\mu^2 R_i(0)^2}{\lambda_{pg\theta}^2 R(0)^2} \quad (13)$$

Finally, whereas $\beta_o(t)$ is truly stress-free and thus an appropriate configuration for stress analysis, it is not experimentally tractable. Thus, we also consider a nearly stress-free configuration that is experimentally tractable, namely, $\beta_R(t)$, which represents an unloaded ring with a single radial cut that relieves much of the residual stress present in the traction-free configuration. Typically, this configuration is characterized by its axial length $L_R(t)$, the radius of the arch $R_R(t) \in [A_R(t), B_R(t)]$, where $A_R(t)$ and $B_R(t)$ are the inner and outer radii of the open arch, and an opening angle. Let the opening angle be denoted as Φ_o (Fig. 2).

3.2 Constitutive Equation and Equilibrium

For our simulations, at any time, we let the strain energy density function be

$$W(\mathbf{C}_e, \Gamma) = \frac{c}{2} (\Gamma : \mathbf{E}^2) \quad (14)$$

where c is a material parameter and $\mathbf{E} = (\mathbf{C}_e - \mathbf{I})/2$ is the Green strain; thus,

$$W = \frac{c}{2} (\Gamma_{rr} E_{rr}^2 + \Gamma_{\theta\theta} E_{\theta\theta}^2 + \Gamma_{zz} E_{zz}^2) \quad (15)$$

which is similar to the approach proposed by Fung et al. [23]. We let the net effect of damage and remodeling be given as the difference between remodeling and damage:

$$2\Gamma = (\mathbf{M} - \mathbf{D}) \quad (16)$$

At time $t=0$, we let $\mathbf{M}=\mathbf{I}$ and $\mathbf{D}=\mathbf{0}$; thus, $2\Gamma(t=0)=\mathbf{I}$. The components of the Cauchy stress are

$$T_{ii} = -p + \widehat{T}_{ii} \quad (17a)$$

where

$$\widehat{T}_{ii} = 2c_i \Gamma_{ii} (\lambda_{ei})^2 [(\lambda_{ei}^2 - 1)/2] \quad (17b)$$

where $i=r, \theta$, or z , p is a Lagrange multiplier that follows from incompressibility, and $\widehat{p}_{ii}$ are the components of the “extra” stress due to the deformation; no summation is implied in Eq. (17). Thus, let us define

$$c_i = 2c \Gamma_{ii} \quad (18)$$

c_i may be considered as a material parameter that evolves with remodeling and damage. In general, $\Gamma_{ii} \in [0, \Gamma_{\max}]$, where $\Gamma_{ii}=0$ corresponds to completely damaged material and $\Gamma_{\max}$ is an upper limit of Γ_{ii} associated with the maximum possible increase in material parameters.

Given axisymmetry, the linear momentum balance under quasistatic conditions in the absence of body forces requires that $T_{r\theta} = T_{rz} = 0$ (neglecting frictional loads between the mandrel or distensible tube and the vessel wall) and that $\partial T_{rr} / \partial r + (T_{rr} - T_{\theta\theta}) / r = 0$. Noting that $T_{rr}(r_i) = -P$ and $T_{rr}(r_o) = 0$, where P is the luminal pressure, equilibrium requires that

$$P = \int_{r_i}^{r_o} \frac{\widehat{T}_{\theta\theta} - \widehat{T}_{rr}}{e} dr \quad (19a)$$

$$p(r) = \widehat{T}_{rr} + P - \int_{r_i}^r \frac{(\widehat{T}_{\theta\theta} - \widehat{T}_{rr})}{r} dr \quad (19b)$$

where $\widehat{p}_{ii}$ depends on Γ_{ii} according to Eq. (17b). Axial equilibrium requires that the magnitude of the axial force, f , maintaining the in vivo axial extension on a glass mandrel or silicone sleeve in the bioreactor be

$$f = 2\pi \int_{r_i}^{r_o} T_{zz} r dr \quad (20)$$

where $T_{zz} = -p + T_{\text{circ}, zz}$; $p(r)$ is given by Eq. (19b) and $\widehat{p}_{zz}$ is given by Eq. (17). Note that f is the axial force borne by the vessel wall; since we neglect frictional forces between the rigid

mandrel or distensible tube and the vessel, the axial force due to the internal pressure acting on the closed ends of the tube is borne entirely by the silicone sleeve.

3.3 Evolution Equations for Plasticity, Growth, Damage, and Remodeling

As for any objective constitutive law, an evolution equation for the time course of parameters that describe plasticity, growth, damage, or remodeling has to be formulated from the results of simple experiments or based on the comparison between model predictions using a priori postulated equations and available experimental data. In this study, we used the second approach. The analytical form of the postulated equations must satisfy certain conditions that follow from some mechanical and thermodynamical considerations.

In general, the rate of change in the plastic deformation may be a function of many factors, including current growth and plastic deformations $\mathbf{F}_g$ and $\mathbf{F}_p$, the Cauchy stress $\mathbf{T}$ above the yield stress, the rate of change in Cauchy stress $d\mathbf{T}/dt$, and the amplitude of the pulsatile strain $\Delta\mathbf{E}$ (or pulsatile stress), among many others; thus, in general, $\partial\lambda_{pi}/\partial t = f(\mathbf{F}_g, \mathbf{F}_p, \mathbf{T}, \partial\mathbf{T}/\partial t, \dots)$. We assume that there is no axial force applied to the vessel; thus, $f=0$ from Eq. (20). For the case of the silicone sleeve, this requires that all of the axial force associated with mounting the silicone sleeve and internal end cap pressure are borne by the silicone sleeve. This assumption may differ from the experimental case in which the vessel becomes adhered to the mandrel or silicone tube; here we neglect the existence of possible axial traction.

Because the inner diameter of the vessel is prescribed by the diameter of the rigid mandrel or silicone tube, as a result of compaction, a compressive radial stress (i.e., a compaction-induced pressure) develops at the inner wall. Note that the radial stress at the outer wall is zero. Therefore, the vessel experiences circumferential tensile stresses, which appear to be the maximum principal stress in the arterial wall. We consider a linear dependence between the rate of change in $\lambda_{p\theta}$ and $T_{\theta\theta}$ as

$$\frac{\partial\lambda_{p\theta}}{\partial t} = a_{p\theta}\lambda_{p\theta}\widehat{p}_{\theta} \quad (21a)$$

where

$$\widehat{p}_{\theta} = \begin{cases} 0 & \text{for } T_{\theta\theta} < T_{\theta\theta}^Y \\ \frac{T_{\theta\theta} - T_{\theta\theta}^Y}{T_{\theta\theta}^Y} & \text{for } T_{\theta\theta} \geq T_{\theta\theta}^Y \end{cases} \quad (21b)$$

where $a_{p\theta}$ is a kinetic parameter and $T_{\theta\theta}^Y$ is the yield stress at which plastic deformation occurs; if $T_{\theta\theta} < T_{\theta\theta}^Y$, then no plastic deformation exists. Given that $T_{rr} \ll T_{\theta\theta}$ and $T_{zz} \ll T_{\theta\theta}$ for this loading, we consider this plastic deformation as in the case of uniaxial loading in the circumferential direction. Thus, incompressibility requires that $\lambda_{pr}\lambda_{pz} = 1/\lambda_{p\theta}$. For the case of a material that plastically deforms isotropically, $\lambda_{pr} = \lambda_{pz} = 1/\sqrt{\lambda_{p\theta}}$. Therefore, in this isotropic case, we may postulate

$$\frac{1}{\lambda_{pr}} \frac{\partial\lambda_{pr}}{\partial t} = \frac{1}{\lambda_{pz}} \frac{\partial\lambda_{pz}}{\partial t} = -\frac{1}{2\lambda_{p\theta}} \frac{\partial\lambda_{p\theta}}{\partial t} \quad (22)$$

In general, however, given that material anisotropies may develop and the applied loading is not truly uniaxial, assuming that the plastic deformation is isotropic may not be justified. Rather, motivated by Eqs. (21) and (22), we prescribe the following

$$\frac{\partial \lambda_{pr}}{\partial t} = -a_{pr} \frac{\lambda_{pr}}{\lambda_{p\theta}} \frac{\partial \lambda_{p\theta}}{\partial t} = \lambda_{pr} (-a_{pr} a_{p\theta} \widehat{p}_{\theta}) \quad (23)$$

and

$$\frac{\partial \lambda_{pz}}{\partial t} = -a_{pz} \frac{\lambda_{pz}}{\lambda_{p\theta}} \frac{\partial \lambda_{p\theta}}{\partial t} = \lambda_{pz} (-a_{pz} a_{p\theta} \widehat{p}_{\theta}) \quad (24)$$

where a_{pr} and a_{pz} are the kinetic parameters and $a_{pr}=a_{pz}=0.5$ corresponds to an isotropic plastic deformation. Note that incompressibility ($\lambda_{pr}\lambda_{p\theta}\lambda_{pz}=1$) requires that $\partial(\lambda_{pr}\lambda_{p\theta}\lambda_{pz})/\partial t=0$, which requires that $a_{pr}+a_{pz}=1$ for incompressible plastic deformations given kinetic equations (21), (23), and (24).

In general, the rate of change in the growth deformation may be a function of many factors including current growth and plastic deformations $\mathbf{F}_g$ and $\mathbf{F}_p$, the Cauchy stress $\mathbf{T}$, the rate of change in Cauchy stress $d\mathbf{T}/dt$, and the amplitude of the pulsatile strain $\Delta\mathbf{E}$ (or pulsatile stress), among many others; thus, in general, $\partial\lambda_{gi}/\partial t = f(\mathbf{F}_g, \mathbf{F}_p, \mathbf{T}, \partial\mathbf{T}/\partial t, \Delta\mathbf{E}, \dots)$. Based on the notion that healthy arteries grow in response to stress- and cyclic strain-mediated enhanced mitosis and synthetic activity of the vascular smooth muscle cells, which are oriented predominantly in the circumferential direction, we assume that the compaction is also circumferential stress and strain mediated and postulate the following evolution equation:

$$\frac{\partial \lambda_{g\theta}}{\partial t} = a_{g\theta} \lambda_{g\theta} \widehat{g}_{\theta} \quad (25a)$$

where

$$\widehat{g}_{\theta} = \left(\frac{T_{\theta\theta} - T_{\theta\theta}^T}{T_{\theta\theta}^T} + b_{g\theta} (\Delta E_{\theta\theta}) \right) \quad (25b)$$

where $a_{g\theta}$ and $b_{g\theta}$ are the kinetic parameters and $T_{\theta\theta}^T$ are the “target” stresses (i.e., the stress at which the tissue is in biological equilibrium (homeostasis)) at which no net growth occurs. The factor $\lambda_{g\theta}$ in Eq. (25) accounts for the fact that as compaction progresses, the smooth muscle cells tend to align in the circumferential direction and the contribution of $T_{\theta\theta}$ as a driving stimulus increases. Similarly, we know that circumferential stress and cyclic strain can mediate changes in vessel wall thickness. Thus, we let

$$\frac{\partial \lambda_{gr}}{\partial t} = a_{gr} \lambda_{gr} \widehat{g}_r \quad (26)$$

where a_{gr} is a kinetic parameter and $\hat{g}_r = \hat{g}_r(T_{\theta\theta}, \dots)$ is a function of the circumferential stress among other factors; we define the functional form for $\hat{g}_r$ later in the text (Eq. (35)).

It is less clear from experimental data what factors control the axial growth. If there is a target axial stress T_{zz}^T and if the vessel remains axially unloaded throughout culture, then one would expect the vessel to continually shorten axially; experimentally, the vessel does shorten axially, both under static and cyclic loading. However, this shortening in the axial directions asymptotically approaches a steady-state value. Indeed, it is argued that much of this axial shortening is due to the plastic deformation associated with circumferential loading. We submit, further, that growth in the circumferential and radial directions necessarily affects growth in the axial direction, e.g., fiber realignment and loss of water due to circumferential stress-mediated remodeling. Thus, for the illustrations herein, we let

$$\frac{\partial \lambda_{gz}}{\partial t} = a_{gz} \lambda_{gz} \hat{g}_z \quad (27)$$

where a_{gz} is a kinetic parameter and $\hat{g}_z = \hat{g}_z(T_{\theta\theta}, \dots)$ is a function of the circumferential stress among other factors; we define the functional form for $\hat{g}_z$ later in the text (Eq. (35)).

Combining Eqs. (21) and (25), the combined plastic and growth deformations, $[\mathbf{F}_{pg}] = \text{diag}\{\lambda_{pgr}, \lambda_{pg\theta}, \lambda_{pgz}\}$ yield the following evolution equations:

$$\frac{\partial \lambda_{pgr}}{\partial t} = \frac{\partial}{\partial t}(\lambda_{pr} \lambda_{gr}) = \lambda_{pgr} [a_{gr} \hat{g}_r + a_{pr} \hat{p}_r] \quad (28)$$

$$\frac{\partial \lambda_{pg\theta}}{\partial t} = \frac{\partial}{\partial t}(\lambda_{p\theta} \lambda_{g\theta}) = \lambda_{pg\theta} [a_{g\theta} \hat{g}_\theta + a_{p\theta} \hat{p}_\theta] \quad (29)$$

$$\frac{\partial \lambda_{pgz}}{\partial t} = \frac{\partial}{\partial t}(\lambda_{pz} \lambda_{gz}) = \lambda_{pgz} [a_{gz} \hat{g}_z + a_{pz} \hat{p}_z] \quad (30)$$

Considering the matter of convergence and the steady-state conditions of growth and plasticity (without damage and remodeling), the kinetic constants and functional forms for $\hat{g}_i$ and $\hat{p}_i$ should be chosen such that as $t \rightarrow \infty$, the evolution equations for $(\partial \lambda_{pgr} / \partial t)$, $(\partial \lambda_{pg\theta} / \partial t)$, and $(\partial \lambda_{pgz} / \partial t)$ approach zero. By setting Eq. (29), with Eqs. (21b) and (25b) to zero, it follows that, at steady state,

$$a_{g\theta} \left(\frac{T_{\theta\theta|ss} - T_{\theta\theta}^T}{T_{\theta\theta}^T} + b_{g\theta} \Delta E_{\theta\theta} \right) + a_{p\theta} \left(\frac{T_{\theta\theta|ss} - T_{\theta\theta}^Y}{T_{\theta\theta}^Y} \right) = 0 \quad (31)$$

where $T_{\theta\theta|ss}$ is the steady-state value for $T_{\theta\theta}$. One way to enforce that $(\partial \lambda_{pgr} / \partial t)$ and $(\partial \lambda_{pgz} / \partial t)$ approach zero as $(\partial \lambda_{pg\theta} / \partial t)$ approaches zero is to require that

$$\frac{\partial \lambda_{pgr}}{\partial t} = a_{pgr} \frac{\lambda_{pgr}}{\lambda_{pg\theta}} \frac{\partial \lambda_{pg\theta}}{\partial t} \quad \text{and} \quad \frac{\partial \lambda_{pgz}}{\partial t} = a_{pgz} \frac{\lambda_{pgz}}{\lambda_{pg\theta}} \frac{\partial \lambda_{pg\theta}}{\partial t}. \quad (32)$$

That is, it is assumed that the rates of change in λ_{pgr} and λ_{pgz} are proportional to the rate of change of $\lambda_{pg\theta}$. The consequence of this assumption, employing Eqs. (23) and (24), is that

$$\frac{1}{\lambda_{gr}} \frac{\partial \lambda_{gr}}{\partial t} = a_{pgr} \frac{1}{\lambda_{g\theta}} \frac{\partial \lambda_{g\theta}}{\partial t} + (a_{pgr} + a_{pr}) \frac{1}{\lambda_{p\theta}} \frac{\partial \lambda_{p\theta}}{\partial t} \quad (33)$$

$$\frac{1}{\lambda_{gz}} \frac{\partial \lambda_{gz}}{\partial t} = a_{pgz} \frac{1}{\lambda_{g\theta}} \frac{\partial \lambda_{g\theta}}{\partial t} + (a_{pgz} + a_{pz}) \frac{1}{\lambda_{p\theta}} \frac{\partial \lambda_{p\theta}}{\partial t} \quad (34)$$

or that

$$a_{gr} \widehat{g_r} = a_{pgr} a_{g\theta} \widehat{g_\theta} + (a_{pgr} + a_{pr}) a_{p\theta} \widehat{p_\theta} \quad \text{and} \quad a_{gz} \widehat{g_z} = a_{pgz} a_{g\theta} \widehat{g_\theta} + (a_{pgz} + a_{pz}) a_{p\theta} \widehat{p_\theta} \quad (35)$$

Thus, a consequence of prescribing Eq. (32) is that the growth rates in the r and z directions are not only functions of the difference between $T_{\theta\theta}$ and $Y_{\theta\theta}^T$ but also functions of the difference between $T_{\theta\theta}$ and $Y_{\theta\theta}^Y$.

The rate of change in the damage may also be a function of many factors, including the current value of remodeling and damage $\mathbf{M}$ and $\mathbf{D}$, the Cauchy stress $\mathbf{T}$, and the rate of change in Cauchy stress $d\mathbf{T}/dt$, among many others; thus, in general, $\partial D_{ii}/\partial t = f(\mathbf{M}, \mathbf{D}, \mathbf{T}, \partial \mathbf{T}/\partial t, \dots)$. For these illustrative simulations, we consider a linear dependence between D_{ii} and W :

$$\frac{dD_{ii}}{dt} = \alpha_{D1} \left(\frac{W - W_{cr}}{W_{cr}} \right) \quad (36)$$

where α_{D1} is a kinetic parameter and W_{cr} is the critical strain energy above which damage occurs; if $W < W_{cr}$, then no damage occurs and we let $\alpha_{D1} = 0$. Note that Eq. (36) models isotropic damage.

Similarly, in general, $\partial M_{ii}/\partial t = f(\mathbf{M}, \mathbf{D}, \mathbf{T}, \partial \mathbf{T}/\partial t, \Delta \mathbf{E}, \mathbf{F}_{gp}, \dots)$. For these illustrative simulations, we let

$$\frac{dM_{\theta\theta}}{dt} = (a_{R\theta} + b_{R\theta} \Delta E) \frac{\partial \lambda_{gp\theta}}{\partial t} \quad (37)$$

where $a_{R\theta}$ and $b_{R\theta}$ are the kinetic parameters. That is, we assume that the rate of remodeling is linearly related to the rate of compaction of the tissue. We further assume that

$$\frac{dM_{rr}}{dt} = a_{Rr} \frac{dM_{\theta\theta}}{dt} \quad \text{and} \quad \frac{dM_{zz}}{dt} = a_{Rz} \frac{dM_{\theta\theta}}{dt} \quad (38)$$

where a_{Rr} and a_{Rz} are the kinetic parameters. That is, we assume that the material remodels in an orthotropic manner.

Finally, for these illustrative simulations, we let

$$\frac{\partial T_{\theta\theta}^Y}{\partial t} = \frac{a_{Y\theta}}{2} \left(\frac{\partial M_{\theta\theta}}{\partial t} - \frac{\partial D_{\theta\theta}}{\partial t} \right) = a_{Y\theta} \frac{\partial \Gamma_{\theta\theta}}{\partial t} \quad (39)$$

where $a_{Y\theta}$ is a kinetic parameter; thus, the change in yield stress is proportional to the change in the “stiffness” defined by Eq. (18). The rationale for this assumption is that the same structural changes that lead to stiffening of the material most likely elevate the stress level at which the tissue manifests plasticity.

4 Simulation Results

The gel-derived approach to vascular tissue engineering consists of vascular cells embedded in a reconstituted gel matrix, typically of collagen or fibrin. These TEBVs are formed by pouring the solutions of vascular cells, collagen, and/or fibrin, and supplemented cell culture media into a cylindrical mold. The suspension is allowed to polymerize (usually for ~1 h), and then the mandrel with the gel is removed and placed in tissue culture dishes containing supplemented cell culture media. We consider two culture scenarios: (i) culture of the vessel on the rigid mandrel, providing a circumferential constraint and radial loading, and (ii) culture of the vessel on a distensible membrane that allows for displacement control of the inner radius. The goal of this paper is to illustrate that this modeling framework is sufficient to capture many of the salient features of growth, remodeling, damage, and plasticity of gel-derived TEBVs and to highlight data that are currently lacking in the literature.

The governing equations are the kinematic equations (9), (10), and (12), the constitutive Eq. (17), equilibrium equations (19a), (19b), and (20), and the kinetic equations (29), (32), and (36)–(39). We prescribed the initial values: $r_i(0)=R_i(0)=1.775$ mm, $r_o(0)=R_o(0)=5.25$ mm, $\ell(0)=38$ mm, $T_{\theta\theta}^Y(0)=5$ kPa, and $\Gamma_{ii}(0)=1$. We prescribed the following parameters: $a=1.0$, $c=0.5$ kPa, $a_{g\theta}=0.12/\text{day}$, $b_{g\theta}=0.01/\text{day}$, $a_{p\theta}=0.60/\text{day}$, $T_{\theta\theta}^T=150$ kPa, $a_{pgr}=1.4$, $a_{pgr}=0.5$, $a_{R\theta}=100$ kPa, $b_{R\theta}=200$ kPa, $a_{Rz}=0.5$, $a_{Y\theta}=1.5$, and $W_{cr}=10$ kJ/m³. We have solved this system of equations numerically by discretizing the radius and using an implicit time- step, using MATLAB 7.1.

Given our initial values, we calculated the Cauchy stress, employed the evolution equations for growth and plasticity to determine the stress-free configurations for the subsequent time step, and employed the evolution equations for remodeling and damage to determine values for Γ_{ii} at the subsequent time step. For all time steps, we explicitly prescribed the inner radius in the loaded configuration and the axial force $f=0$; thus, Eq. (20) was solved to determine the loaded length $\ell(t)$ and Eq. (13) yielded the loaded radius for the current time step. Given the loaded configuration ($dr(t)$, $r(t)$, $\ell(t)$) and the stress-free configuration ($dR(t)$, $R(t)$, $L(t)$), the elastic stretches and the Cauchy stress were calculated and evolution equations evaluated for the subsequent time step. This iterative procedure was continued for a defined time interval. For the set of selected model functions and parameters, the asymptotic

solution was unique and stable. In addition, results from these numerical simulations showed that small variations in a single input parameter or combinations of parameters cause small changes in the output parameters, proving the necessary requirement for robustness of the model. Note that, for these illustrative parameters and loading scenarios, $W_{cr}=10 \text{ kJ/m}^3$ was not exceeded in any simulations below and therefore mechanical conditioning did not cause tissue damage in our simulations. Nevertheless, we included damage in the general theoretical framework, since damage mechanisms with other parameter sets or under other loading and testing scenarios (e.g., ring tests or burst pressure tests) are critical for interpreting such experimental results.

4.1 Static Culture on a Rigid Mandrel

The most widely reported experimental data for gel-derived TEBVs involves long-term culture (days to weeks) on a rigid mandrel. Seliktar et al. [5] reported the evolution of compaction and material properties at 2 days, 6 days, and 10 days of static culture. Collagen gels were molded around a glass mandrel covered with a silicone sleeve with an outer radius of 1.775 mm and length of 38 mm; the inner radius of the test tube was 5.75 mm; we assume, however, that the outer radius of the vessel following the initial gelling process, which occurred in $\sim 1 \text{ h}$, was 5.25 mm. Thus, the initial volume of the cells, collagen, and culture media was approximately 3500 mm^3 ; the vessel volume immediately after gelling was approximately 2900 mm^3 .

Seliktar et al. [5] performed two different static cultures: one in which the vessel was allowed to adhere to the silicone sleeve, impairing compaction in the axial direction and one in which the silicone sleeve was coated with Vaseline, allowing the vessel to freely compact in the axial direction. We refer to these experiments as the “constrained static” and “unconstrained static” culture. Since the traction force applied to the vessel on the luminal surface in the axial direction by the adherence to the silicone sleeve in the constrained static culture cannot be measured, below we simulate the unconstrained static culture where this traction force is negligible.

In Ref. [5], the total volume of the TEBVs decreased to approximately 620 mm^3 and 510 mm^3 after 6 days and 10 days, respectively. The length decreased to 23 mm and 25 mm after 6 days and 10 days, respectively; thus, the outer radius decreased to 3.4 mm and 3.1 mm after 6 days and 10 days, respectively. The inner radius was constrained to remain at 1.775 mm throughout culture. Although they did not report the yield stress or modulus for the unconstrained static culture, they reported yield stresses of $\sim 4 \text{ kPa}$ and 8 kPa and material moduli of $\sim 40 \text{ kPa}$ and 63 kPa at 6 days and 10 days for the constrained static case. They also reported that the ultimate tensile stress was 1.24 and 1.55 times higher for the unconstrained versus the constrained static culture at 6 days and 10 days, respectively; thus, it may be reasonable to assume that the yield stress and (perhaps) the modulus for the unconstrained static culture are above that of the constrained static case.

Motivated by these experimental results, for our simulations, we let $r_i(t)=1.775$ and $\Delta E(t)=0$ for all time. As the local stress-free configurations and material parameters evolved, the vessel outer radius, thickness, and axial length were comparable to those reported by Seliktar et al. [5] (Figs. 3(a) and 3(b)). The unloaded radii, thickness, and length in the traction-free configuration β_u decreased monotonically. The opening angle in the reference configuration β_R initially decreased to -22 deg , and then began to increase at time $t=5.3$ days toward a steady-state value of 96 deg (Fig. 3(c)); this is due to unevenly distributed growth at different radial locations across the wall. Note that the experimental values of the unloaded radii and axial length and the stress-free radii, length, and opening angle are not reported Ref. [5], nor are these values typically reported in the literature for TEBVs; the

time course of these values, however, are necessary to quantify the three-dimensional evolution of strain and to predict the evolution of stress throughout culture.

We simulated fixed length pressure-diameter testing results for the model artery at different time points and generated mean nominal stress-engineering strain curves (Fig. 4(a)). These curves were generated by fixing the length at L_u , increasing the pressure at increments of 0.5 mm Hg, and solving for the inner radius via regression. The pressure was increased until the yield stress was reached. The mean nominal stress (defined with respect to the undeformed area) and engineering strain were calculated as

$$\sigma_\theta = \frac{Pr_i}{\lambda_\theta h} \quad \text{and} \quad \varepsilon_{\theta\theta} = \frac{r_{\text{mid}}}{(R_u)_{\text{mid}}} - 1 \quad (40)$$

where r_i is the loaded radius at the inner wall, h is the wall thickness in the loaded configuration, and r_{mid} and $(R_u)_{\text{mid}}$ are the loaded and unloaded radii at the middle of the wall. We calculated an “effective” modulus as the slope of the nominal stress-engineering strain curve over the final five data points. The moduli were comparable to the values reported by Seliktar et al. [5] (Fig. 4(b)). Note that the definition of modulus calculated from these pressure-diameter tests (i.e., slope of the stress-strain curve from a fixed length pressure-diameter test) is quantitatively different from that defined from uniaxial ring testing data by Seliktar et al. [5] (i.e., slope of the stress-strain curve from a uniaxial ring test). One difference is that in the uniaxial ring test, the vessel is free to retract axially, whereas in the pressure-diameter test, the length is held fixed. Nevertheless, these different approaches to measuring modulus may be qualitatively compared. The trends of the effective modulus from our simulations compare well to those of Seliktar et al. [5]. The mean yield stress was initially 0.2 kPa and evolved according to Eq. (39). The trends of the mean yield stress from our simulations compare well to those of Seliktar et al. [5] (Fig. 4(c)).

In addition to predicting measurable quantities such as changes in geometry, residual stress, material response curves, and yield stress, an important utility of modeling is to predict quantities that are not experimentally measurable, such as the *local* stresses and strains and local material properties. Circumferential stress and cyclic circumferential strain are the driving stimuli for the evolution equations; however, since $\Delta E=0$ in this simulation, cyclic strain does not contribute to the evolution equations. The circumferential stress, initially zero at all locations across the wall, began to increase at different rates at each radial location (Figs. 5(a) and 5(b)). The evolution of the circumferential stress is governed by the evolution of the material parameters (c_o , Γ_{rr} , $\Gamma_{\theta\theta}$ (Fig. 5(c)), and Γ_{zz}) and the evolution of the circumferential stretch ($\lambda_{e\theta}$, Fig. 5(d)). The evolution of the circumferential stretch is governed by the evolution of the stress-free and loaded configuration, as governed by the plastic-growth stretches (λ_{pgi} , Figs. 5(e) and 5(f)). The plastic-growth stretches on the inner wall decreased monotonically until $t=4.6$ days. Before $t=4.6$ days, the circumferential stress $T_{\theta\theta}$ was below the yield stress $T_{\theta\theta}^Y$ for all radii (Fig. 4(c)). When the stress on the inner wall reached the yield stress, plastic deformation ensued near the inner wall and the rate of change in λ_{pgi} decreased according to Eq. (28), with Eqs. (21), (25b), and (32). Thus, after $t=4.6$ days, the values $\partial \lambda_{pgi} / \partial t$ at the inner wall decreased and the values for λ_{pgi} at the inner wall asymptotically approached a steady-state value.

Notice that the yield stress varied across the wall; the yield stresses at inner locations were lower than those at outer locations of the wall (Fig. 4(b)). As a result, the steady-state circumferential stress varied across the wall (Figs. 5(a) and 5(b)); the steady-state value of $T_{\theta\theta}$ may be found directly via Eq. (31) and is between $T_{\theta\theta}^Y$ and $T_{\theta\theta}^T$ when $T_{\theta\theta}^Y < T_{\theta\theta}^T$. The

circumferential elastic stretch $\lambda_{e\theta}$, which was initially 1.0 across the wall, increased nonuniformly, but monotonically, across the wall as stress-mediated compaction was initiated via Eq. (28), with Eqs. (21) and (25b); after $t=4.6$ days, however, the elastic stretch varied nonmonotonically across the wall, as inner radial locations experienced plastic deformation, but outer radial locations remained in the elastic regime (below the yield stress). Eventually, as compaction proceeded at outer wall locations, the yield stress was reached at all radial locations and the distribution of elastic stretches became monotonic. Notice, however, that whereas the circumferential stress was highest at the outer wall, the circumferential elastic stretch was highest at the inner wall. The stress was higher at the outer wall because the material properties were highest on the outer wall (Fig. 5(c)).

The negative opening angle (Fig. 3(c)) at early time points indicates that locations near the inner surface were in tension in the traction-free configuration while those close to the outer surface were under compression. The subsequent positive opening angle indicates that the locations near the inner surface were under compression in the traction-free configuration, while those close to the outer surface were in tension. This is in agreement with the predicted time course of the circumferential stretch ratio in the deformed configuration on the mandrel and the time course of the radii of the unloaded vessel. Over time the elastic circumferential stretch ratio increased across the entire thickness, diminishing the stretch gradient from the inner to the outer surface due to development of plastic deformations. When removed from the mandrel, both the inner and outer radii asymptotically decreased and consequently reduced the tensile stretch ratios that existed in the deformed configuration (Fig. 3(a)). This reduction was more pronounced at the inner radius. After 6 days, for example, the elastic circumferential stretch in the loaded configuration was 1.34 at the inner wall but 1.0 at the outer wall (Fig. 5(d)). Thus, when the vessel was removed from the mandrel, the outer wall became compressed, while the inner wall remained in tension. This occurs because the unloaded inner and outer radii are smaller than the inner and outer radii in the loaded configuration. At later time points, the stretch distribution reversed because the reduction in the traction-free inner radius predominated over the extension developed on the mandrel.

4.2 Culture on a Distensible Tube

Seliktar et al. [5] demonstrated that the elastic modulus and rate of compaction increase in response to cyclic strain. In their experimental approach, they cultured collagen gel-derived TEBVs on a distensible elastic membrane that allowed for the cyclic control of the inner radius. Collagen gels were again molded around a glass mandrel covered with a silicone sleeve with an outer radius 1.775 mm and length of 38 mm; the inner radius of the test tube was 5.75 mm; we assume that the outer radius was ~ 5.25 mm after gelling for 1 h. Thus, the initial volume immediately after gelling was ~ 2900 mm³. Vessels were statically cultured on a rigid mandrel for 2 days, and then exposed to 10% cyclic strain for an additional 4 days or 8 days.

Seliktar et al. [5] attempted to culture vessels under cyclic loading both with and without Vaseline to account for the role of adhesion of the gel to the silicone tube. The tests with Vaseline, however, resulted in constructs that were visibly detached from the sleeve throughout the experiment; thus, these vessels did not receive the specified cyclic loading. Thus, we consider the results from the experiments without Vaseline. In their experiment, the total volume of the TEBVs decreased to approximately 295 mm³ and 190 mm³ after 6 days and 10 days (i.e., 2 days under static culture and 4 days and 8 days under cyclic strain), respectively. The length decreased to 23 mm and 10 mm after 6 days and 10 days, respectively; thus, the outer radius decreased to 2.7 mm and 3.0 mm after 6 days and 10 days, respectively. The inner radius was constrained to cycle between 1.775 mm and 1.953

mm throughout culture. The yield stresses were ~8 kPa and 27 kPa and the material moduli were ~40 kPa and 135 kPa at 6 days and 10 days, respectively.

Motivated by these experiments, for our simulations, we let

$$r_i(t) = \begin{cases} 1.775 \text{ mm}, & t \in [0, 2] \text{ days} \\ \frac{R_o^M \Delta \varepsilon}{2} \sin(2\pi \omega t - \pi/2) + \frac{R_o^M(2+\Delta \varepsilon)}{2}, & t \in [2, 10] \text{ days} \end{cases} \quad (41)$$

where $R_o^M = 1.775$ mm is the outer diameter of the silicone sleeve, prior to inflation, $\Delta \varepsilon = 0.10$ is the fractional change in inner radius, and ω is the angular frequency. Note that most experiments were performed at a frequency of 1 Hz, which corresponds to 1.7×10^6 cycles over 20 days. As the local stress-free configurations and material parameters evolve, the outer radius and thickness (when $r_i = 1.775$) evolve to values comparable to those reported by Seliktar et al. [5] (Fig. 6(a)). The axial lengths predicted in our simulations were $\ell(t) = 31, 25, 24$, and 24 mm at 2, 6, 10, and 20 days, respectively, which were significantly higher than their experimental values. The unloaded radii in the traction-free configuration β_u decrease monotonically. The unloaded axial length took values of $L^u = 34, 24, 21$, and 21 mm on 2, 6, 10, and 20 days, respectively (not shown). The opening angle in the reference configuration β_R initially decreased the same as in the static case. After Day 2, cyclic stretching begins and the opening angle decreases at a faster rate until $t = 4.7$ days, after which the opening angle increases toward a steady-state value (Fig. 6(b)). Again, experimental values of the unloaded radii and axial length and the stress-free radii, length, and opening angle are not available in the literature.

The effective modulus increased monotonically from 15 kPa, 170 kPa, 242 kPa, and 242 kPa at 2 days, 6 days, 10 days, and 20 days, respectively (not shown). These trends of the effective modulus from our simulations are qualitatively comparable to those of Seliktar et al. [5]. The mean yield stress was initially 0.2 kPa; the trends of the mean yield stress from our simulations compare well to those of Seliktar et al. [5] (Fig. 7(a)).

The circumferential stress evolved at different rates across the thickness of the vessel (Fig. 7(b)). At 6 days, there was a highly nonuniform distribution of circumferential stress across the wall, including both tensile stresses at inner wall locations and compressive stresses at outer wall locations. By 20 days, however, the transmural circumferential stress was nearly uniform. The cyclic strain is both a function of radius and time (Fig. 7(c)). Notice that, even though the displacement is the same for all time at the inner radius, the cyclic strain evolves with time, since the stress-free reference configuration evolves with time. The circumferential plastic-growth stretch $\lambda_{pg\theta}$ remains uniform across the wall until $t = 2$ days (Fig. 7(d)), when cyclic stretching began the circumferential stress $T_{\theta\theta}$ reached the yield stress $T_{\theta\theta}^Y$ at the inner wall at the highest radius of the cyclic loading (Fig. 7(a)). The yield stress is a function of radial location when cyclic strain is initiated ($t > 2$ days). The circumferential elastic stretch $\lambda_{e\theta}$ evolved from a uniform distribution of $\lambda_{e\theta} = 1.0$ across the wall to a highly non-uniform distribution (Fig. 7(e)). At 6 days, for example, the inner wall experienced tensile elastic stretch, whereas the outer wall experienced compressive elastic stretch. The elastic stretch eventually evolved to a nonuniform distribution. Since the evolution of material properties (e.g., $\Gamma_{\theta\theta}$) is negatively proportional to the evolution of compaction and directly proportional to the local cyclic strain ΔE , the distribution of material parameters versus radius was nearly uniform at steady state (Fig. 7(f)); see Fig. 5(c) for the distribution of $\Gamma_{\theta\theta}$ for the static case at steady state.

5 Discussion

We have proposed a modeling framework and simulations for mechanically mediated growth, remodeling, plasticity, and damage of gel-derived TEBVs. The results obtained suggest that the model framework can qualitatively predict the evolution of geometry and material behavior under common experimental loading scenarios. There remains, however, a need for additional data to identify specific functional forms for constitutive and evolution equations, ultimately leading to a model with predictive capabilities. We used the results from Ref. [5] as a guide for choosing material and evolution equations. Of course many factors can affect these parameters, as well as the functional analytical forms for constitutive and evolution equations; these factors include cell source, extracellular matrix (e.g., collagen versus fibrin), media supplements, and cross-linking [24,25], among many others. Whereas such confounding factors make it difficult to quantify individual and synergistic effects, we submit that modeling can guide the interpretation of data and the design of experiments to optimize vessel geometry and material behavior and minimize requisite culture time.

Toward the end of guiding experimental design, our model framework and simulations illustrate the need to make experimental measurements that are currently lacking in the literature. For example, to quantify the kinematics and perform stress analyses, it is useful to identify the evolution of the traction-free configuration (β_u) and is necessary to identify the evolution of a (at least nearly) stress-free configuration (β_o). Following Chuong and Fung [26], the stress-free configuration may be approximated by quantifying the radius, length, and opening angle of a radially cut vessel ring. These data can provide insight toward the evolution of λ_{pgi} . Also, whereas uniaxial (ring) tests provide information on the material response in the circumferential direction, including an effective modulus, yield stress, and ultimate tensile stress, a predictive model requires a constitutive equation, which is valid for multiaxial loading. Given that these TEBVs are clearly anisotropic, multiaxial mechanical testing is required; see Refs. [27,28].

Although we focused on the results of Seliktar et al. [5], our modeling framework and illustrative results are consistent with other reports in the literature. For example, Syedain et al. [29] showed that incrementally increasing the amplitude of cyclic distention of gel-derived tissue engineered vessels grown on a distensible elastic sleeve improved mechanical properties beyond that of vessels exposed to an unchanging amplitude of cyclic strain. Our model predicts similar results (not shown). Indeed, our model suggests that one key advantage of incrementally increasing the amplitude of the strain on gel-derived TEBVs is to reduce the overall plastic deformation at early time points (days 2–3); at early time points, the yield stress is low; thus, lower amplitude of cyclic strain causes less plastic deformation. At later time points, the yield stress is higher; thus, higher amplitudes of cyclic strain may be applied without introducing significant plastic deformation. We submit that the current mathematical model could be used to optimize the time course of cyclic strain to maximize growth and remodeling mechanisms and minimize plasticity and damage. Essential data on the evolution of geometry and material properties, however, are currently lacking from the report of Syedain et al. [29] that prevent the direct comparison of simulation results to their experimental data.

We have simulated the common approaches of culture of gel-derived TEBVs, namely, static culture on a rigid mandrel and culture on a distensible tube with cyclic circumferential distension. The advantage of these experimental approaches is the capability to deliver precise cyclic circumferential displacements. In addition, given that the distensible tube is impermeable to fluid, this tube also prevents leakage, a particularly significant challenge for gel-derived constructs at very early time points in culture.

We submit, however, that there are several disadvantages with these approaches as it relates to quantifying mechanically mediated remodeling of TEBVs. First, whereas the change in circumferential distension (i.e., change in inner diameter) is known, the circumferential strain (defined with respect to an appropriate stress-free configuration) is not known and likely changes during culture. Consider the circumferential component of Green strain, $E_{\theta\theta} = (\lambda_\theta^2 - 1)/2$, where $\lambda_\theta(r) = \pi r / ((\pi - \Phi_o)R)$ (in 3D), where r and R are radial locations in the current and stress-free configurations, respectively, and Φ_o is the opening angle (see Ref. [30]), or $\lambda_\theta = r/R$ (in 2D) if we neglect variations across the vessel wall. Although this approach carefully controls r in both the 3D and the 2D cases, the stress-free diameter R of the vessel can change during culture, via growth and plasticity mechanisms, and therefore the circumferential strain can change. In 3D, these changes are more pronounced, for example, as the vessel thickens or compacts, or as the opening angle changes with remodeling.

Second, although the pressure applied to the distensible sleeve is known, the pressure applied to the luminal surface of the TEBV is not known; thus, the circumferential stress is variable and is not known during culture. Third, in most cases the vessels are adhered to the glass or silicone and partially constrained from retracting axially; this applied load, too, is unknown. It is well argued that cells sense and respond to their local mechanical environment (i.e., the local stress and strain); thus, evolution equations for growth and remodeling should be functions of the local stress or strain. In these experimental approaches, however, neither the stress nor the strain is known throughout the experiment. We submit that load controlled (e.g., pressure, flow, and axial force controlled) experiments are better suited for quantifying growth, remodeling, plasticity, and damage of gel-derived TEBVs. Such experiments allow for the control of mean components of the stress tensor, thereby allowing for a more direct comparison between experimental stimuli and the evolution of geometry, reference states, and material behavior.

The evolution equations proposed in this study combine the effects of growth and plasticity into a set of equations and the effects of remodeling and damage into a set of equations. Given that plasticity and damage typically occur over shorter time scales than growth and remodeling, we submit that it is necessary to consider the effects separately. The effect of plasticity and damage can be experimentally quantified independent of those of growth and plasticity by performing acute tests to failure; such tests do not allow enough time for significant growth and remodeling, thereby isolating the noncell-mediated mechanisms of damage and plasticity. Tests such as uniaxial creep, fatigue, and monotonic loading to failure and cylindrical biaxial isobaric, fatigue, and burst pressure testing can be sufficient to quantify evolution equations for damage and plasticity. Once the evolution equations and kinetic parameters are specified for damage and plasticity, culture experiments can be used to identify growth and remodeling equations and parameters.

Limitations of the proposed theoretical approach originate from the adopted assumptions. First, the modeling framework that we have employed combines ideas from volumetric growth, plasticity, and continuum damage mechanics; these frameworks track changes at the tissue level, without quantification of changes in the underlying microstructure. Future refinement of this modeling framework could employ microstructurally motivated constitutive and evolution equations to capture such microstructural changes [31]. Indeed, Feng et al. [32] showed well that even acute mechanical testing, in the absence of growth and remodeling, induced significant realignment of collagen fibrils.

Second, we have chosen evolution equations as linear functions of stress and strain amplitude and a simple quadratic constitutive equation for the stress response; presumably, growth, remodeling, plasticity, and damage are related in some, yet to be determined,

nonlinear manner; data to prescribe such functional forms is currently lacking. Similarly, our damage and plasticity equations are also linear functions of stress and strain amplitude. Literature from native soft tissues [33] and unpublished data from our laboratory on collagen gel-derived TEBVs suggest that plasticity and damage are functions both of stress and rate of change in stress; again, more data are needed to assess their relative contribution and identify appropriate evolution equations. Third, our simulations have focused on compaction of TEBVs in the first 10 days; however, it is more likely that there are two different mechanisms associated with growth of TEBVs: a short-term (0–14 days) compaction response and a long-term (>1 week) growth response, including cell proliferations/apoptosis, and extracellular matrix synthesis/degradation. These different responses will require different sets of evolution equations.

In conclusion, a phenomenological model has been developed for the growth, remodeling, damage, and plasticity of gel-derived tissue engineered blood vessels. Illustrative simulations suggest that this model has the capability of capturing the salient features of mechanically induced changes in TEBV development. Simulations also highlight the need for additional experimental measurements (e.g., evolution of traction-free and stress-free configurations) and the need to perform additional theoretically motivated experiments to quantify analytical forms and parameters for constitutive and evolution equations. Once quantified, use of such a predictive model may be exploited to design loading strategies to improve the mechanical properties of TEBVs and reduce requisite culture times for TEBV development.

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Fig. 1.
General schema for the kinematics of combined plasticity and volumetric growth

Fig. 2. Kinematics of growth and plasticity of a thick-walled axisymmetric tube. Note that the configurations $\beta_p(t)$ and $\beta_o(t)$ consist of infinitesimally thin rings (each with thickness $dR_p(t)$) that pass through radial location $R(0)$ in $\beta_o(0)$; since each ring is infinitesimally thin and cannot support a residual stress.

Fig. 3.

Model predicted evolution of loaded and unloaded radii (a), axial length (b), and opening angle (c) for static culture on a mandrel. Data from Seliktar et al. [5] from constrained (open circles) and unconstrained (solid triangles) static cultures are included for comparison to modeling results.

Fig. 4. Model predicted nominal stress-engineering strain curves that would result from fixed length pressure-diameter testing (a), evolution of modulus (b), and yield stress (c) for static culture on a mandrel. Data from Seliktar et al. [5] from constrained (open circles) static culture are included for comparison to modeling results.

Fig. 5. Evolution of the local circumferential stress ((a) and (b)), circumferential damage and remodeling parameter $\Gamma_\theta(c)$, distribution of the elastic stretch (d), plastic-growth stretches in the radial, circumferential, and axial directions (e), and distribution of the circumferential plastic-growth stretch versus radius at different time points (f) for static culture on a mandrel

Fig. 6. Model predicted evolution of loaded and unloaded radii (a) and opening angle (b) for culture on a distensible tube with 10% cyclic strain. Data from Seliktar et al. [5] from constrained (open circles) and unconstrained (solid triangles) static cultures are included for comparison to modeling results.

Fig. 7.

Evolution of the yield stress (a), local circumferential stress (b), amplitude of cyclic Green strain (c), distribution of the circumferential plastic-growth stretch versus radius (d), distribution of the elastic stretch (e), and the circumferential damage and remodeling parameter Γ_θ (f)