 CMES, vol.4, no.3&4, pp.439-455, 2003

Biological Growth and Remodeling: A Uniaxial Example with Possible Application to Tendons and Ligaments

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keywords: mixture theory, kinetics of turnover, evolving natural configurations, hyperelasticity, mass production

Abstract: Recent discoveries in molecular and cell biology reveal that many cell types sense and respond (via altered gene expression) to changes in their mechanical environment. Such mechanotransduction mechanisms are responsible for many changes in structure and function, including the growth and remodeling process. To understand better, and ultimately to use (e.g., in tissue engineering), biological growth and remodeling, there is a need for mathematical models that have predictive and not just descriptive capability. In contrast to prior models based on reaction-diffusion equations or the concept of volumetric growth, we examine here a newly proposed constrained mixture model for growth and remodeling. Specifically, we use this new model to present illustrative computations in a representative, transversely-isotropic soft tissue subjected to homogeneous deformations under uniaxial loading. Consequences of various assumptions for the kinetics of mass production and removal are discussed, as are open problems in this important area of biomechanics.

1 Introduction

D'Arcy Thompson (1917) said it well: "Cell and tissue, shell and bone, leaf and flower, are so many portions of matter, and it is in obedience to the laws of physics that their particles have been moved, moulded, and conformed." Whereas it has long been thought that biological growth and remodeling is governed in large part by physical actions, recent discoveries in molecular and cell biology demonstrate that such regulation occurs at the level of gene expression (Taber, 1995). That is, many cell types sense and convert mechanical stimuli into bioelectrical or biochemical signals that control gene expression and thus biological structure and function, a process now referred to as mechanotransduction. Unfortunately, the fundamental question remains – What does the cell actually sense?

Until, and likely after, the mechanisms of mechanotransduction are elucidated, phenomenological continuum-based models will continue to play an important role in the design of experiments as well as industrial and clinical procedures. Over the years many different classes of models have been suggested. For example, much of the literature on wound healing stems from the pioneering work of Turing (1952) who suggested that morphogenesis (i.e., the development of shape of an organ) can be modeled via reaction-diffusion equations (e.g., Tranquillo and Murray, 1992). In this approach, it is assumed that one should model the diffusion of molecules such as growth factors, proteases, and cytokines as well as the migration of cells, which together play key roles in governing the production and removal of constituents. In contrast, Skalak (1981) introduced the concept of 'volumetric growth' whereby "any finite growth or change of form may be regarded as the integrated result of differential growth, i.e. growth of the infinitesimal elements making up the animal or plant." In this approach, one prescribes growth a priori via kinematics based on assumed constitutive relations for the evolution (growth) of stress-free configurations. See Rodriguez et al. (1994) for an illustrative application. Yet, as noted by Fung (1995), growth necessarily results from the production and removal of constituents, thus there is a need for constitutive relations that relate mass production and stress. Fung did not offer a specific model or approach to accomplish this, however. Recently, Humphrey and Ra-

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jagopal (2002) proposed a constrained mixture model that melds ideas from the continuum theory of mixtures, the concept of evolving natural configurations, and a homogenization for constrained mixtures that allows one to relate mass production/removal to the stress in the continuum – these ideas were presented in general, however, without illustrative examples. The purpose of this paper, therefore, is to illustrate the possible utility of this new constrained mixture model. In particular, we focus on a class of quasi-static uniaxial problems wherein the deformation is homogeneous and the material symmetry group (transverse-isotropy) is preserved throughout growth and remodeling. Allowing growth and remodeling (G&R) to occur over time-dependent deformations reveals consequences of induced material nonuniformities[4] and evolving (local) natural configurations. We suggest that this illustrative example may have important clinical implications for tendons and ligaments, which are often subjected to uniaxial loading and they exhibit a transverse-isotropy.

2 Balance Relations

As we consider G&R within a framework of mechanics, we must conserve mass, linear momentum and energy. By restricting our attention to isothermal processes, however, we shall focus on mass and linear momentum. Because tissues consist of a number of solid constituents, we consider the balance of mass for each constituent as well as that for the whole tissue. As in mixture theory, we allow for co-occupancy of the constituents at each point, thus mass balance for each constituent can be written as

$$\frac{\partial \rho^{(i)}}{\partial t} + div\left(\rho^{(i)}\mathbf{v}^{(i)}\right) = m_{\alpha}^{(i)} - m_{\omega}^{(i)} = m^{(i)}, \;\; i = 1,2,\ldots N, \tag{1}$$

where the index i represents the ith of the N mechanically important constituents comprising the tissue, $m_{\alpha}^{(i)}$ is the rate at which mass of the ith constituent is produced per unit volume of the mixture, and $m_{\omega}^{(i)}$ is the rate at which the mass is removed per unit volume, with the difference between the two being the net production rate. The mass density and velocity of each constituent are denoted by $\rho^{(i)}$ and $\mathbf{v}^{(i)}$, respectively. We assume that none of the constituents, such as elastin or collagen, diffuse with respect to each other. In other words, the constituents are constrained to move together, thus $\mathbf{v}^{(i)} = \mathbf{v}$, the mixture velocity. For such a case, the balance of mass for each constituent reduces to

$$\frac{\partial \rho^{(i)}}{\partial t} + div\left(\rho^{(i)}\mathbf{v}\right) = m_{\alpha}^{(i)} - m_{\omega}^{(i)} = m^{(i)}, \;\; i = 1,2,\ldots N. \tag{2}$$

Total mass balance for the tissue is obtained by summing the mass balances for each constituent and can be written as

$$\frac{\partial \rho}{\partial t} + div(\rho\mathbf{v}) = \sum_{i=1}^{N} m^{(i)} = m, \tag{3}$$

where ρ, the mass density of the tissue, equals the sum of the mass densities of the constituents, namely

$$\rho = \sum_{i=1}^{N} \rho^{(i)}. \tag{4}$$

The net rate at which mass is produced per unit volume of the mixture, m, is the difference between the rate of mass production and the rate of mass removal,

$$m = m_{\alpha} - m_{\omega}. \tag{5}$$

Here a few comments are in order. First, the net mass production rate per unit volume does not have to be identically zero as in most classical mixture theories. This does not mean that matter is being produced or destroyed, however. Rather, we simply do not consider the flux of species such as cells, raw materials, nutrients etc., that lead to the production and removal of collagen in the tissue, which is an open system. Hence, the tacit assumption is that the species fluxing in and out do not have a significant effect on the overall mechanical response. This restriction can be lifted, but we do not add this additional level of complexity herein. Our aim is to formulate a model that accounts for increases or decreases in the

[4] Classical notions of material nonuniformity and homogeneity have to be modified to account for the fact that the body in question is not a fixed set of particles (see Rajagopal (2003) for a discussion of these issues).

primary structural constituents comprising the tissue and their effects on the gross mechanical response. It is clear from Eq. (2) that we need to consider both the rate at which the material is produced and the rate at which it is removed. The manner in which this is done is explained in the next section.

In general, both the size and mass density of the tissue can change with G&R. Yet, it appears that the mass density of the tissue ($\rho \sim 1050$ kg/m^3) does not vary significantly during or after G&R. This simplification has been widely used in previous works on the modeling of growth (see Rodriguez et al., 1994; Taber, 1995). For such a case, Eq. (3) simplifies to

$$div(\mathbf{v}) = \frac{m}{\rho_0}, \tag{6}$$

where ρ_0 is the constant mass density of the tissue. We, too, shall assume that the density of the tissue does not change during the growth and remodeling process.

Following Humphrey and Rajagopal (2002), we invoke a homogenization assumption for the constrained mixture that allows us to use a rule-of-mixtures approach for the total Cauchy stress. Neglecting the effects of inertia and body forces, the balance of linear momentum reduces to a single equation for the mixture,

$$div\mathbf{T} = \mathbf{0}, \tag{7}$$

where $\mathbf{T}$ is the (total or mixture) Cauchy stress. Let us now consider constitutive equations that allow this general approach to be illustrated.

3 Constitutive Model for a Two Constituent Tissue

For materials undergoing biological G&R, there is a need to tie together relations for the stress tensor with those for the production and removal of constituents. Toward this end, consider a tissue of two constituents in which one does not turnover significantly during the G&R process whereas the second does turnover. Such a case may apply to, for example, growth and remodeling in tendons and ligaments wherein the primary constituents are the elastin-dominated amorphous portion of the extracellular matrix, which does not turnover, and the predominant constituent, collagen, which does turnover (note: the fibroblasts are assumed to regulate the matrix but not to contribute to the mechanical integrity of the tissue unlike the myofibroblasts in a healing wound). Here it should be noted that the general methodology is not limited to two constituents; it can be extended in a straightforward manner.

Because the *elastin does not turnover*, its natural configuration κ_n (at each point and each time) remains unchanged, thus $\kappa_n^e \equiv \kappa_o^e$, the 'original' natural configuration[5]. Hence, the mass density for the elastin is given by

$$\det\mathbf{F}_{\kappa_o^e} = \frac{\rho_o^e}{\rho^e(t)}, \tag{8}$$

where $\rho^e(t)$ is the density of elastin (mass per mixture volume). Alternatively, referring to Figure 1, the mass density of the elastin at different times during the G&R process can be computed via the deformation gradient that relates stressed configurations at two different times, τ and t $\quad(0 \le \tau \le t)$, namely

$$\rho^e(t) = \rho^e(\tau)\det\mathbf{F}_t(\tau), \tag{9}$$

where $\mathbf{F}_t(\tau)$ is the deformation gradient associated with a mapping from the current configuration back to the configuration occupied by the tissue at time τ; it is given by

$$\mathbf{F}_t(\tau) := \mathbf{F}_{\kappa(t)\to\kappa(\tau)} = \mathbf{F}_{\kappa_0}(\tau)\mathbf{F}_{\kappa_0}^{-1}(t), \tag{10}$$

where κ_0 is a suitable (local) reference configuration unique for the elastin (Figure 1). Note that $\det\mathbf{F}_t(\tau) = \det\mathbf{F}_\tau(t)^{-1}$. Also, because the density of the tissue does not change appreciably during G&R, overall mass balance for the constrained mixture can be written as

$$div(\mathbf{v}) = tr(\dot{\mathbf{F}}_{\kappa_0}\mathbf{F}_{\kappa_0}^{-1}) = \frac{m}{\rho_0} = \frac{m_\alpha - m_\omega}{\rho_0} = \frac{m_\alpha^c - m_\omega^c}{\rho_0}, \tag{11}$$

where, m_α^c denotes the rate at which collagen is produced per unit volume, m_ω^c is the rate at which collagen is removed per unit volume, and $\mathbf{F}_{\kappa_0}$ is the deformation gradient from a suitably chosen reference configuration κ_0. Thus, *mass is gained or lost solely due to the production and removal of collagen*, i.e., $m_\alpha = m_\alpha^c$ and $m_\omega = m_\omega^c$. Balance of mass for collagen is given by

$$\dot{\rho}^c + \rho^c tr\left(\dot{\mathbf{F}}_{\kappa_0}\mathbf{F}_{\kappa_0}^{-1}\right) = m_\alpha^c - m_\omega^c, \tag{12}$$

[5] A detailed discussion of the concept of natural configuration can be found in Rajagopal (1995), Rajagopal and Srinivasa (1995,1998) and Humphrey and Rajagopal (2002). For our discussion it suffices to think of natural configurations as stress-free configurations with the response of the body being elastic from these configurations.

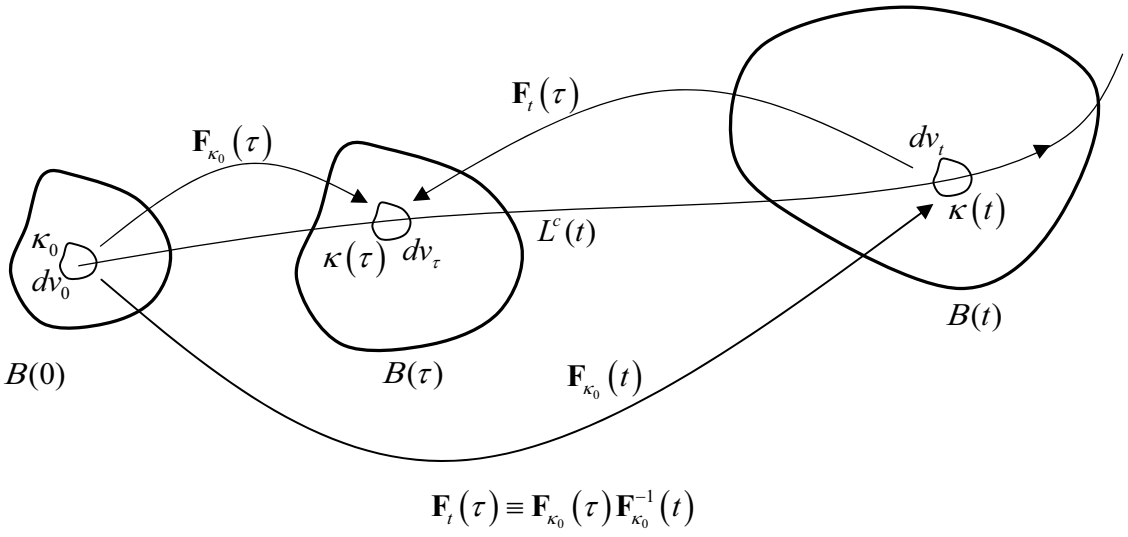

Figure 1 : Kinematics associated with growth

where $\rho^e + \rho^c = \rho_0$. The mass fraction of elastin and collagen at each material point can be taken as

$$\alpha^e = \frac{\rho^e}{\rho_0}, \quad \alpha^c = \frac{\rho^c}{\rho_0}, \quad \alpha^c + \alpha^e = 1. \tag{13}$$

It is possible to use Eq. (12) to calculate ρ^c (and thus α^c) at any instant by prescribing the production and removal rates m^c_α and m^c_ω.

It is not enough to know the total collagen present in the tissue at any given time for collagen produced at different times can exhibit different material symmetries or stiffness. We shall assume, however, that the material symmetry remains the same throughout a specific case of G&R, and so too for the stiffness relative to its updated (evolving) natural configuration.

Rather than track both m^c_α and m^c_ω, let us track the production rate and the time of survival for the collagen that is produced at a particular instant. This is similar, in principle, to tracking the age distribution in population dynamics and is less involved than calculating the net population in terms of births and deaths. Let $m^c_\alpha(\tau)$ be the mass of collagen produced per unit volume (in the configuration occupied by the tissue at time, τ) per unit time and $G^c(\tau,t)$ be the mass fraction of collagen that was produced at time τ that is surviving at current time t. Let dv_t be a differential material volume element at time t that occupied the differential material volume element dv_τ at time τ. These two differential volume elements are related through (cf. Figure 1),

$$dv_\tau = \det(\mathbf{F}_t(\tau))\, dv_t. \tag{14}$$

The mass of collagen produced in the time interval between τ and $\tau + d\tau$, within the volume element dv_τ, is given by $m^c_\alpha(\tau)\, dv_\tau d\tau$. The amount of this mass of collagen surviving at time t, denoted by dM^c is thus given by

$$\begin{aligned} dM^c &= m^c_\alpha(\tau)\, G^c(\tau,t)\, dv_\tau d\tau \\ &= m^c_\alpha(\tau)\, G^c(\tau,t) \det(\mathbf{F}_t(\tau))\, d\tau dv_t. \end{aligned} \tag{15}$$

Note, we have used Eq. (14) to obtain Eq. $(15)_2$. The mass and density of collagen in the current configuration are obtained by integrating Eq. (15) over time and volume $V(t)$, respectively, namely

$$M^c(t) = \int_{V(t)} \int_{-\infty}^{t} m^c_\alpha(\tau) G^c(\tau,t) \det\mathbf{F}_t(\tau)\, d\tau dv_t, \tag{16}$$

$$\rho^c(t) = \int_{-\infty}^{t} m^c_\alpha(\tau)\, G^c(\tau,t) \det\mathbf{F}_t(\tau)\, d\tau. \tag{17}$$

Of course, the equation for the mass of collagen can also

be written as

$$M^c(t) = \int_{-\infty}^{t} \int_{V(\tau)} m_\alpha^c(\tau)\, G^c(\tau,t)\, dv_\tau d\tau, \tag{18}$$

where $V(\tau)$ is the volume occupied by the tissue at time τ. The function $G^c(\tau,t)$ can differ for matter produced at different times and can also depend on local conditions such as stress, deformation, etc., as needed to account for changes in removal rates during periods of G&R. The lower limit of the integral in the above equations, given by negative infinity, can be replaced by some earlier but finite time, t_0, as long as the collagen formed prior to t_0 is either known or it has been removed and hence does not contribute to the mass and density of the tissue. In many cases G&R is initiated from a given basal state; for such a case, the mass and the age distribution of the constituent present in the tissue prior to the commencement of G&R would have to be known. For instance, Eq. (16) and Eq.(17) can be rewritten as

$$\begin{aligned} M^c(t) &= \int_{V(t)} \int_{t_0}^{0} m_\alpha^c(\tau) G^c(\tau,t) \det \mathbf{F}_t(\tau)\, d\tau dv_t \\ &\quad + \int_{V(t)} \int_{0}^{t} m_\alpha^c(\tau) G^c(\tau,t) \det \mathbf{F}_t(\tau)\, d\tau dv_t \\ &= M_0^c(t) + \int_{V(t)} \int_{0}^{t} m_\alpha^c(\tau) G^c(\tau,t) \det \mathbf{F}_t(\tau)\, d\tau dv_t, \end{aligned} \tag{19}$$

$$\begin{aligned} \rho^c(t) &= \int_{t_0}^{0} m_\alpha^c(\tau)\, G^c(\tau,t) \det \mathbf{F}_t(\tau)\, d\tau \\ &\quad + \int_{0}^{t} m_\alpha^c(\tau)\, G^c(\tau,t) \det \mathbf{F}_t(\tau)\, d\tau \\ &= \rho_0^c(t) + \int_{0}^{t} m_\alpha^c(\tau)\, G^c(\tau,t) \det \mathbf{F}_t(\tau)\, d\tau, \end{aligned} \tag{20}$$

where G&R is initiated at time $t = 0$. $M_0^c(t)$ is the contribution to the mass of collagen at current time t, due to collagen originally present in the tissue prior to initiation of G&R, and similarly for $\rho_0^c(t)$.

The total stress in the constrained mixture is modeled using the notion of multiple natural configurations. Following Humphrey and Rajagopal (2002), we assume that the tissue is mechanically incompressible and therefore, with two constituents, the total Cauchy stress tensor takes the form

$$\mathbf{T} = -p\mathbf{I} + \mathbf{T}^E, \quad \mathbf{T}^E = \mathbf{T}^e + \mathbf{T}^c \tag{21}$$

where p is the Lagrange multiplier that arises due to the constraint of incompressibility and $\mathbf{T}^e$ and $\mathbf{T}^c$ are the constituent stresses due to the elastin and collagen, respectively. The form for stress given in Eq. (21) reduces to the usual rule of mixtures approximation under certain conditions as is shown later in this section (cf. Eq. (29)). The motivation to split the stress tensor arises from the observation that each constituent can have separate material properties and symmetries, and most importantly natural configurations that can evolve differently. Splitting the stress tensor in this manner affords us a direct way of connecting the behavior of the whole tissue to the amount and properties of the constituents. Assuming that the natural configuration associated with elastin does not change, and that its functional form for stress remains unchanged during the G&R process, the stress in the elastin is given by

$$\mathbf{T}^e = \mathbf{f}^e_{\kappa_0^e}\left(\mathbf{F}_{\kappa_0^e}(t)\right), \tag{22}$$

where κ_0^e is the natural configuration associated with elastin, $\mathbf{f}^e_{\kappa_0^e}$ is the response function associated with the stress and $\mathbf{F}_{\kappa_0^e}(t)$ is the deformation gradient from the natural configuration, κ_0^e, to the current configuration associated with the tissue, $\kappa(t)$, i.e.,

$$\mathbf{F}_{\kappa_0^e}(t) := \mathbf{F}_{\kappa_0^e \to \kappa(t)}. \tag{23}$$

The constitutive equation for collagen should account for changes in stress due to the production of collagen in configurations different from those during prior production. Moreover, the model should allow the functional form of the stress tensor for the newly produced collagen to account for changes in material properties and material symmetries during G&R. Both of these features are incorporated into the model by letting the natural configurations and the functional form of the stress for the

newly produced collagen each to depend on local conditions such as stress, strain, etc. Under these conditions the stress in the collagen may be given by

$$\mathbf{T}^c = \int_{-\infty}^{t} \mathbf{f}^c_{\kappa^c_n(\tau)}\left(\mathbf{F}_{\kappa^c_n(\tau)}(t)\right) m^c_\alpha(\tau)\, G^c(\tau,t) \det \mathbf{F}_t(\tau)\, d\tau, \tag{24}$$

where $\kappa^c_n(\tau)$ is the natural configuration associated with the collagen that was produced at time τ and $\mathbf{f}^c_{\kappa^c_n(\tau)}$ is the corresponding response function for the stress. $\mathbf{F}_{\kappa^c_n(\tau)}(t)$ is the deformation gradient from the natural configuration, $\kappa^c_n(\tau)$, to the current configuration occupied by the tissue, $\kappa(t)$, i.e.,

$$\mathbf{F}_{\kappa^c_n(\tau)}(t) := \mathbf{F}_{\kappa^c_n(\tau)\to\kappa(t)}. \tag{25}$$

Hence, to determine the stress, we need to prescribe the natural configuration(s) for the nascent collagen. If, for example, the collagen was produced in a stress-free state, then $\mathbf{F}_{\kappa^c_n(t)}(t) = \mathbf{I}$. A similar approach has been used in a multi-network theory for polymers (Rajagopal and Wineman, 1994) and crystallization in polymers (Rao and Rajagopal, 2000; 2001), wherein it is assumed that the material was converted in a stress-free state. In general, however, $\mathbf{F}_{\kappa^c_n(t)}(t)$ can depend on the stress, mass production rates, mass densities , strains, etc., i.e.,

$$\mathbf{F}_{\kappa^c_n(t)}(t) = \mathbf{g}\left(\mathbf{T}, m^c_\alpha, \rho^c \ldots\right). \tag{26}$$

From Eqs. (21), (22) and (24), the stress in the two-constituent tissue reduces to

$$\mathbf{T} = -p\mathbf{I} + \mathbf{f}^e_{\kappa^e_0}\left(\mathbf{F}_{\kappa^e_0}(t)\right) + \int_{-\infty}^{t} \mathbf{f}^c_{\kappa^c_n(\tau)}\left(\mathbf{F}_{\kappa^c_n(\tau)}(t)\right) m^c_\alpha(\tau)\, G^c(\tau,t) \det \mathbf{F}_t(\tau)\, d\tau. \tag{27}$$

The functional form for $\mathbf{f}^e_{\kappa^e_0}$ and $\mathbf{f}^c_{\kappa^c_n(\tau)}$can be fixed by choosing a specific form of the stored energy function. Assuming hyperelastic responses, Eq. (27) can alternatively be written as

$$\mathbf{T} = -p\mathbf{I} + 2\rho^e \mathbf{F}_{\kappa^e_0} \frac{\partial \psi^e}{\partial \mathbf{C}_{\kappa^e_0}} \mathbf{F}^T_{\kappa^e_0} + \int_{-\infty}^{t} 2\mathbf{F}_{\kappa^c_n(\tau)} \frac{\partial \psi^c}{\partial \mathbf{C}_{\kappa^c_n(\tau)}} \mathbf{F}^T_{\kappa^c_n(\tau)} m^c_\alpha(\tau)\, G^c(\tau,t) \det \mathbf{F}_t(\tau)\, d\tau, \tag{28}$$

where $\mathbf{C}$ is the right Cauchy-Green tensor ($\mathbf{C} = \mathbf{F}^T\mathbf{F}$) and ψ^i are Helmholtz potentials. Note: if the natural configuration and the form of the Helmholtz function for collagen produced at different times remains unchanged, for instance during tissue maintenance, using Eq. (17), the above equation can be simplified to:

$$\begin{aligned}\mathbf{T} &= -p\mathbf{I} + \alpha^e 2\rho_0 \mathbf{F}_{\kappa^e_0} \frac{\partial \psi^e}{\partial \mathbf{C}_{\kappa^e_0}} \mathbf{F}^T_{\kappa^e_0} + \alpha^c 2\rho_0 \mathbf{F}_{\kappa^c_n} \frac{\partial \psi^c}{\partial \mathbf{C}_{\kappa^c_n}} \mathbf{F}^T_{\kappa^c_n} \\ &= -p\mathbf{I} + \alpha^e \hat{\mathbf{T}}_e + \alpha^c \hat{\mathbf{T}}_c,\end{aligned} \tag{29}$$

wherein $\kappa^c_n(\tau)$ has been replaced with κ^c_n to indicate no dependence of the natural configuration of collagen on the time at which it was produced. This shows that for the limiting case of collagen produced in the same state at all times, a simple rule-of-mixtures approximation is recovered, where $\hat{\mathbf{T}}_e$ and $\hat{\mathbf{T}}_c$ can be interpreted as the stresses present in pure elastin and pure collagen, respectively. Of course, for a single constituent tissue, one of the mass fractions vanishes while the other goes to unity, thus recovering the standard result from incompressible finite elasticity.

For illustrative purposes, let us now consider some specific forms for the elastin and collagen. The behavior of amorphous elastin, such as that in a ligament or tendon, can be modeled as a neo-Hookean material (Dorrington and McCrum, 1977). Thus, letting

$$\psi^e = \frac{\mu^e}{2\rho_0}\left(tr\mathbf{C}_{\kappa^e_0} - 3\right), \tag{30}$$

we obtain the following form for the stress due to elastin,

$$\mathbf{T}^e = \rho^e \frac{\mu^e}{\rho_0} \mathbf{B}_{\kappa^e_0} = \alpha^e \mu^e \mathbf{B}_{\kappa^e_0}, \tag{31}$$

where $\mathbf{B}$ is the left Cauchy-Green tensor ($\mathbf{B} = \mathbf{F}\mathbf{F}^T$) and μ^e is the shear modulus (having units of stress) associated with elastin. For type I collagen in a tendon or ligament, we assume that its response can be described by an exponential relation embodying transverse isotropy (with respect to the current natural configuration). A possible form for the Helmholtz potential is thus,

$$\psi^c = \frac{\mu^c_1}{2\rho_0\delta_1}\left\{\exp\left[\delta_1\left(tr\mathbf{C}_{\kappa^c_n(\tau)} - 3\right)\right] - 1\right\} + \frac{\mu^c_2}{4\rho_0\delta_2}\left\{\exp\left[\delta_2\left(\mathbf{N}_{\kappa^c_n(\tau)} \cdot \mathbf{C}_{\kappa^c_n(\tau)}\mathbf{N}_{\kappa^c_n(\tau)} - 1\right)^2\right] - 1\right\}, \tag{32}$$

where μ_c^1 and μ_c^2 are material parameters having units of stress, δ_1 and δ_2 are non-dimensional material parameters, and the unit vector $\mathbf{N}_{\kappa_n^c(\tau)}$ represents the preferred (i.e., collagen fiber) direction, the material being transversely isotropic with respect to this direction. This direction can change, in general, depending on the conditions under which collagen fibers are produced. That is, it is possible for the tissue to have a symmetry different from transverse isotropy if the collagen fibers produced at different instants have different preferred directions $\mathbf{N}_{\kappa_n^c(\tau)}$. For the form of the potential chosen, the stress in the collagen reduces to

$$\mathbf{T}^c = \frac{1}{\rho_0}\int_{-\infty}^{t} m_\alpha^c G^c(\tau,t)\det\mathbf{F}_t(\tau)\left\{\mu_1^c \exp\left[\delta_1\left(tr\mathbf{C}_{\kappa_n^c(\tau)}-3\right)\right]\mathbf{B}_{\kappa_n^c(\tau)} + \mu_2^c\left(\mathbf{N}_{\kappa_n^c(\tau)}\cdot\mathbf{C}_{\kappa_n^c(\tau)}\mathbf{N}_{\kappa_n^c(\tau)}-1\right)\exp\left[\delta_2\left(\mathbf{N}_{\kappa_n^c(\tau)}\cdot\mathbf{C}_{\kappa_n^c(\tau)}\mathbf{N}_{\kappa_n^c(\tau)}-1\right)^2\right]\mathbf{F}_{\kappa_n^c(\tau)}\mathbf{N}_{\kappa_n^c(\tau)}\otimes\mathbf{N}_{\kappa_n^c(\tau)}\mathbf{F}^T_{\kappa_n^c(\tau)}\right\}d\tau. \quad (33)$$

To proceed, we need to prescribe a production rate for the collagen, m_α^c, and the fraction of collagen surviving, i.e., prescribe $G^c(\tau,t)$.

The mass production rate m_α^c is prescribed through a constitutive equation that may depend on the stress, mass densities, etc. (cf. Eq. (26)). For instance, one could prescribe an equation of the form:

$$m_\alpha^c = f(\mathbf{T},\rho^c,\ldots). \quad (34)$$

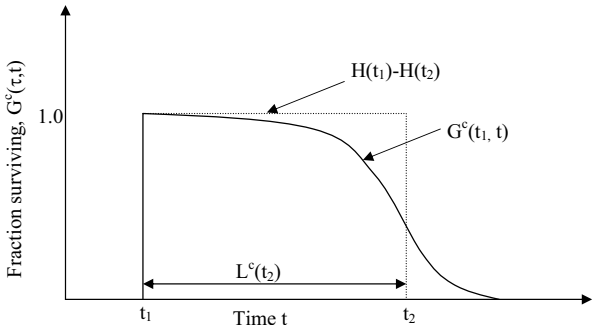

Figure 2 : Fraction of collagen surviving with time

The specific form will be dictated by experimental data, once they are available. In the next section we choose illustrative forms and consider a problem involving homogeneous uniaxial extensions. For $G^c(\tau,t)$, we seek to specify a form that incorporates the main features associated with G&R without being overly complicated. Here we look at a case in which collagen is being produced and removed continuously, i.e., we do not consider the situation in which collagen is produced and removed intermittently even though the current methodology could be so generalized. In this work, we assume that all collagen produced at a specific material point at a given time is removed at a later time; this is tantamount to assuming that collagen produced under identical conditions and experiencing the same environment will have identical life spans. This need not be the case, in general, as collagen that is removed at a specific material point (i.e., in a representative volume element) at a given time can have a distribution of ages. This is illustrated in Figure 2, wherein we show a possible function $G^c(\tau,t)$, with $\tau = t_1$. The collagen produced at a given time (t_1 in the figure) will in general be removed gradually, in contrast with our assumption that the collagen produced at a given time (t_1) is all removed at the same later time (t_2). If the variation in the lifespan is narrow compared to the average lifespan, this assumption is reasonable. For such a case, the function $G^c(\tau,t)$ can be represented using the Heavyside function, H, and has the form

$$G^c(\tau,t) = H(\tau) - H(\tau + L^c), \quad (35)$$

where L^c represents the mean lifespan of the collagen formed at time τ. As a consequence of these assumptions the collagen being removed at current time t was formed at time $t - L^c(t)$, where $L^c(t)$ is the age of the collagen being removed. We also assume that the collagen that is produced earlier is removed earlier, therefore, the collagen formed between $t - L^c(t)$ and t is present in the tissue whereas the collagen formed before $t - L^c(t)$ has already been removed. Thus, the time, τ, at which a specific fraction of collagen was produced is related to the time, t, at which it is removed through

$$\tau = t - L^c(t). \quad (36)$$

Note, at any time, t, we only need to prescribe the age of collagen being removed at that time, i.e., $L^c(t)$ and not the spectrum of lifespans associated with each fraction of collagen comprising the tissue that was produced between $t - L^c(t)$ and t. Recalling that in Figure 1 $\mathbf{F}_t(\tau)$ is

the deformation gradient between the current configuration and the configuration occupied by the tissue at time (i.e., $\mathbf{F}_\tau^{-1}(t)$), Eqs. (16) and (17) can be re-written as

$$\rho^c(t) = \int_{t-L^c}^{t} m_\alpha^c(\tau)\det\mathbf{F}_t(\tau)\,d\tau, \tag{37}$$

$$M^c(t) = \int_V \int_{t-L^c}^{t} m_\alpha^c(\tau)\det\mathbf{F}_t(\tau)\,d\tau dv_\tau. \tag{38}$$

The quantities m_α^c and L^c have to be prescribed; they, too, may depend on local conditions such as the stress, etc.

The rate at which collagen is removed, m_ω^c, is related to m_α^c and L^c because matter removed at a given time was produced at an earlier time. The relationship between these quantities is given by a mass balance for collagen inside an arbitrary material volume for an arbitrary interval of time. We do this by equating the mass of collagen removed in a material volume during a specified period to the period in which it was produced. The mass of collagen removed in an arbitrary material volume for a period $t_2 - t_1$ is given by

$$\int_{t_1}^{t_2}\int_{V(\tau)} m_\omega^c dv_\tau d\tau, \tag{39}$$

where the material volume, $V(\tau)$, over which the integral is evaluated, is a function of time that can change with G&R. The quantity in Eq. (39) was born at an earlier time and is equal to

$$\int_{t_1'}^{t_2'}\int_{V(\tau')} m_\alpha^c dv_{\tau'} d\tau', \tag{40}$$

where the time variables in the above two equations are related through Eq. (36), i.e.,

$$\tau' = \tau - L^c(\tau). \tag{41}$$

Equating Eqs. (39) and (40), we obtain

$$\int_{t_1}^{t_2}\int_{V(\tau)} m_\omega^c dv_\tau d\tau = \int_{t_1'}^{t_2'}\int_{V(\tau')} m_\alpha^c dv_{\tau'} d\tau'. \tag{42}$$

Differentiating Eq. (41), we obtain

$$\frac{d\tau'}{d\tau} = 1 - \frac{dL^c}{d\tau}. \tag{43}$$

Note further that we assume that L^c is a piecewise continuously differentiable function of time. Also, the material volume elements are related through Eq.(14), namely

$$dv_{\tau'} = \det\mathbf{F}_\tau(\tau')\,dv_\tau. \tag{44}$$

Substituting Eq. (41), Eq. (43) and Eq. (44) into Eq. (42), we obtain.

$$\int_{t_1}^{t_2}\int_{V(\tau)}\left(m_\omega^c - m_\alpha^c\det\mathbf{F}_\tau(\tau - L^c(\tau))\left(1 - \frac{dL^c}{d\tau}\right)\right)dv_\tau d\tau = 0. \tag{45}$$

Since both the material volume $V(\tau)$ and the time interval are arbitrary, the integrand must vanish. Hence,

$$m_\omega^c(t) = m_\alpha^c\det\mathbf{F}_t(t - L^c)\left(1 - \frac{dL^c(t)}{dt}\right). \tag{46}$$

For solutions to be physically reasonable L^c cannot take on arbitrary values. For example, the rate of removal, m_ω^c is positive. This condition results in the mathematical restriction,

$$\frac{dL^c}{dt} < 1. \tag{47}$$

In addition, we also require that L^c be positive; if $L^c = 0$, matter disappears the instant it is produced whereas $L^c < 0$ implies that matter is removed before it is produced, which is a physical impossibility. In general, the life span of collagen can be prescribed as a rate equation of the form (cf. Eq. (34)):

$$\frac{dL^c}{dt} = g^c\left(\mathbf{T}, m^c_\alpha, \rho^c, \rho^e .....\right), \tag{48}$$

where the age of collagen being removed can vary with local conditions. Alternatively, a constitutive equation can be prescribed for the removal rate, m^c_ω, and Eq. (46) can be used to derive a form for the $\frac{dL^c}{dt}$. The specific choice between these two methods will be dictated by the problem under consideration and the experimental data available to formulate constitutive equations for m^c_ω or $\frac{dL^c}{dt}$. For the examples considered in this paper, we specify constitutive equations for $\frac{dL^c}{dt}$ by choosing specific forms for the function g^c. With these simplifications, the stress tensor given by Eq. (28) reduces to

$$\begin{aligned}\mathbf{T} &= -p\mathbf{I} + \alpha^e\mu^e\mathbf{B}_{\kappa^e_0} \\ &+ \frac{1}{\rho_0}\int_{t-L^c(\tau)}^{t} m^c_\alpha \det\mathbf{F}_t(\tau)\left\{\mu^c_1 \exp\left[\delta_1\left(tr\mathbf{C}_{\kappa^c_n(\tau)} - 3\right)\right]\mathbf{B}_{\kappa^c_n(\tau)} + \right. \\ &\mu^c_2\left(\mathbf{N}_{\kappa^c_n(\tau)}\cdot\mathbf{C}_{\kappa^c_n(\tau)}\mathbf{N}_{\kappa^c_n(\tau)} - 1\right)\exp\left[\delta_2\left(\mathbf{N}_{\kappa^c_n(\tau)}\cdot\mathbf{C}_{\kappa^c_n(\tau)}\mathbf{N}_{\kappa^c_n(\tau)} - 1\right)^2\right] \\ &\left.\mathbf{F}_{\kappa^c_n(\tau)}\mathbf{N}_{\kappa^c_n(\tau)} \otimes \mathbf{N}_{\kappa^c_n(\tau)}\mathbf{F}^T_{\kappa^c_n(\tau)}\right\} d\tau.\end{aligned} \tag{49}$$

Let us now consider a simple illustration of G&R during uniaxial extensions.

4 Uniaxial Extension

To illustrate the model, consider a uniaxial extension of a cylindrical specimen that is initially in a uniaxially stressed state with its lateral surfaces traction free. G&R is initiated by the application of an additional uniaxial stretch. After applying this additional stretch, the tissue is constrained in the direction of stretch, consequently, the production and removal of collagen only changes the radius of the specimen. Although G&R is initiated by controlling the stretch, it could also be initiated by changing the axial load, i.e., by increasing the stress. For such a case the production and removal of collagen would change both the axial length and radius of the tissue. We do not consider this type of stress-controlled example here, instead we focus our attention on the strain-controlled case.

Consider the cylindrical specimen in a uniaxially stressed equilibrium state. By equilibrium, we imply that in addition to force balance, $m^c_\alpha = m^c_\omega = m^c_{\alpha,eq}$and $L^c = L^c_{eq}$, where $m^c_{\alpha,eq}$ and L^c_{eq} are the equilibrium production rate and the equilibrium life-span associated with collagen in maturity prior to G&R – that is, in a state of tissue maintenance. In addition, let the extant collagen have the same natural configuration because we assume that the tissue is far enough into maturity that all tissue produced during development has been removed. Of course, the elastin and collagen will not have the same natural configurations in general for the elastin was produced during development. Hence, let t =0 be a time during maturity at which G&R starts, which we shall initiate by subjecting the tissue to the additional (e.g., non-physiological) uniaxial extension. See Figure 3. Specifically, we shall study the G&R response for two cases, namely, a constant extension and a quasi-static sinusoidally varying extension. It should be noted that we seek solutions given prescribed homogenous deformations within the context of a standard semi-inverse approach.

First, consider the specimen in equilibrium prior to G&R. Under these conditions, the natural configurations associated with collagen $\kappa^c_n(\tau)$ do not change and $\det\mathbf{F}_t(\tau) = 1$. From Eq. (50), the stress in normalcy (i.e., the basal state) is given by

$$\begin{aligned}\mathbf{T}_{basal} &= -p\mathbf{I} + \alpha^e_0\mu^e\mathbf{B}_{\kappa^e_0} \\ &+ \alpha^c_0\left\{\mu^c_1 \exp\left[\delta_1\left(tr\mathbf{C}_{\kappa^c_n(\tau)} - 3\right)\right]\mathbf{B}_{\kappa^c_n(\tau)} + \right., \\ &\mu^c_2\left(\mathbf{N}_{\kappa^c_n(\tau)}\cdot\mathbf{C}_{\kappa^c_n(\tau)}\mathbf{N}_{\kappa^c_n(\tau)} - 1\right)\exp\left[\delta_2\left(\mathbf{N}_{\kappa^c_n(\tau)}\cdot\mathbf{C}_{\kappa^c_n(\tau)}\mathbf{N}_{\kappa^c_n(\tau)} - 1\right)^2\right] \\ &\left.\mathbf{F}_{\kappa^c_n(\tau)}\mathbf{N}_{\kappa^c_n(\tau)} \otimes \mathbf{N}_{\kappa^c_n(\tau)}\mathbf{F}^T_{\kappa^c_n(\tau)}\right\} \qquad \text{for } \tau \le t < 0,\end{aligned} \tag{50}$$

where, ρ^e_0 and ρ^c_0 are the mass densities of elastin and collagen in the tissue prior to G&R, and from Eq. (37),

$$\rho^c_0 = m^c_{\alpha,eq}L^c_{eq}. \tag{51}$$

In general, the unit vector $\mathbf{N}_{\kappa^c_n(\tau)}$ can vary with time, but here we consider a uniaxial extension wherein the collagen fibers are oriented in the direction of stretch and the collagen fibers that are subsequently laid down retain this original orientation. The vector $\mathbf{N}_{\kappa^c_n(\tau)}$ for this example problem is thus an unchanging unit vector given by (1,0,0). We choose the natural configurations of elastin and collagen prior to G&R to be such that they are related to the initial configuration of the tissue through uniaxial

stretches (see Figure 3), namely

$$\mathbf{F}_0^e := \mathbf{F}_{\kappa_0^e}(t) = diag\left(\Lambda_0^e, \tfrac{1}{\sqrt{\Lambda_0^e}}, \tfrac{1}{\sqrt{\Lambda_0^e}}\right), \text{ for } t < 0 \quad (52)$$

$$\mathbf{F}_0^c := \mathbf{F}_{\kappa_n^c(\tau)}(t) = diag\left(\Lambda_0^c, \tfrac{1}{\sqrt{\Lambda_0^c}}, \tfrac{1}{\sqrt{\Lambda_0^c}}\right), \text{for } \tau \le t < 0. \quad (53)$$

The basal stress can be obtained by substituting Eqs. (52) and (53) into Eq. (50). If the lateral surfaces are traction free, we obtain

$$\begin{aligned} T_{11})_{basal} &= \alpha_0^e \mu^e \left((\Lambda_0^e)^2 - \frac{1}{\Lambda_0^e}\right) \\ &+ \alpha_0^c \left\{\mu_1^c \exp\left(\delta_1\left[(\Lambda_0^c)^2 + \frac{2}{\Lambda_0^c} - 3\right]\right)\left((\Lambda_0^c)^2 - \frac{1}{\Lambda_0^c}\right)\right. \\ &\left. + \mu_2^c \exp\left(\delta_2\left[(\Lambda_0^c)^2 - 1\right]^2\right)\left((\Lambda_0^c)^2 - 1\right)(\Lambda_0^c)^2\right\}, \end{aligned} \quad (54)$$

all other components of stress being zero. Equilibrium, $div\ \mathbf{T} = \mathbf{0}$, is thus identically satisfied as are the lateral traction boundary conditions.

Given that G&R is initiated by subjecting the tissue to an additional uniaxial extension at t =0, let the deformation gradient from the configuration just prior to the imposition of stretch to the configuration just after the stretch be denoted by $\mathbf{F}_1$ (see Figure 3), where

$$\mathbf{F}_1 = diag\left(\ \Lambda_1, \ \ \tfrac{1}{\sqrt{\Lambda_1}}, \ \ \tfrac{1}{\sqrt{\Lambda_1}}\ \right). \quad (55)$$

The deformation gradients from the natural configurations of elastin and collagen to the configuration occupied by the tissue immediately after the extension are thus given by

$$\mathbf{F}_{\kappa_0^e}(t=0) = diag\left(\Lambda_0^e\Lambda_1, \tfrac{1}{\sqrt{\Lambda_0^e\Lambda_1}}, \tfrac{1}{\sqrt{\Lambda_0^e\Lambda_1}}\right), \quad (56)$$

$$\mathbf{F}_{\kappa_n^c(\tau)}(t=0) = diag\left(\Lambda_0^c\Lambda_1, \tfrac{1}{\sqrt{\Lambda_0^c\Lambda_1}}, \tfrac{1}{\sqrt{\Lambda_0^c\Lambda_1}}\right), \text{for } \tau < 0. \quad (57)$$

The stress in the tissue immediately after this extension is given by

$$\begin{aligned} T_{11} &= \alpha_0^e \mu^e \left((\Lambda_0^e\Lambda_1)^2 - \frac{1}{\Lambda_0^e\Lambda_1}\right) \\ &+ \alpha_0^c \left\{\mu_1^c \exp\left(\delta_1\left[(\Lambda_0^c\Lambda_1)^2 + \frac{2}{\Lambda_0^c\Lambda_1} - 3\right]\right)\left((\Lambda_0^c\Lambda_1)^2 - \frac{1}{\Lambda_0^c\Lambda_1}\right)\right. \\ &\left. + \mu_2^c \exp\left(\delta_2\left[(\Lambda_0^c\Lambda_1)^2 - 1\right]^2\right)\left((\Lambda_0^c\Lambda_1)^2 - 1\right)(\Lambda_0^c\Lambda_1)^2\right\}, \\ &\text{for } t = 0. \end{aligned} \quad (58)$$

Of course, at this instant no new collagen has been produced and consequently the stress is determined only from constituents present prior to the increase in stretch. The increase in stress above the basal value will increase the rate of production of collagen and in addition reduce the life span of the extant collagen, resulting in an increase in the rate of removal. Consequently, the tissue will grow and remodel. Because the tissue is constrained from growing in the direction of stretch, the radius of the cylindrical specimen will increase if there is a net mass production. This is a highly specialized case in that the problem dictates how the material will be laid down. Additional constitutive assumptions will be needed in general, particularly when the material symmetry evolves. Nonetheless, here we denote the deformation gradient from the configuration occupied by the tissue immediately after the application of the stretch to any later (grown) configuration by $\mathbf{F}_2$ (Figure 3) , where

$$\mathbf{F}_2 := \mathbf{F}_{\kappa(0)\to\kappa(t)} = diag\left(\Lambda_2(t), b(t), b(t)\right), \text{ for } t \ge 0, \quad (59)$$

$$\mathbf{F}_2 = \mathbf{I}, \text{ for } t = 0. \quad (60)$$

The value of $\Lambda_2(t)$ is prescribed. For a step change in length, it is

$$\Lambda_2(t) = 1, \text{ for } t \ge 0, \quad (61)$$

whereas for a step change followed by sinusoidal variation in length, it is

$$\Lambda_2(t) = 1 + A\sin(2\pi f_z t), \text{ for } t \ge 0, \quad (62)$$

where f_z is the frequency of the oscillations and A is the amplitude. Again, we emphasize that inertial effects are ignored. The function $b(t)$ represents growth in the radial direction and is obtained as a result of the calculations.

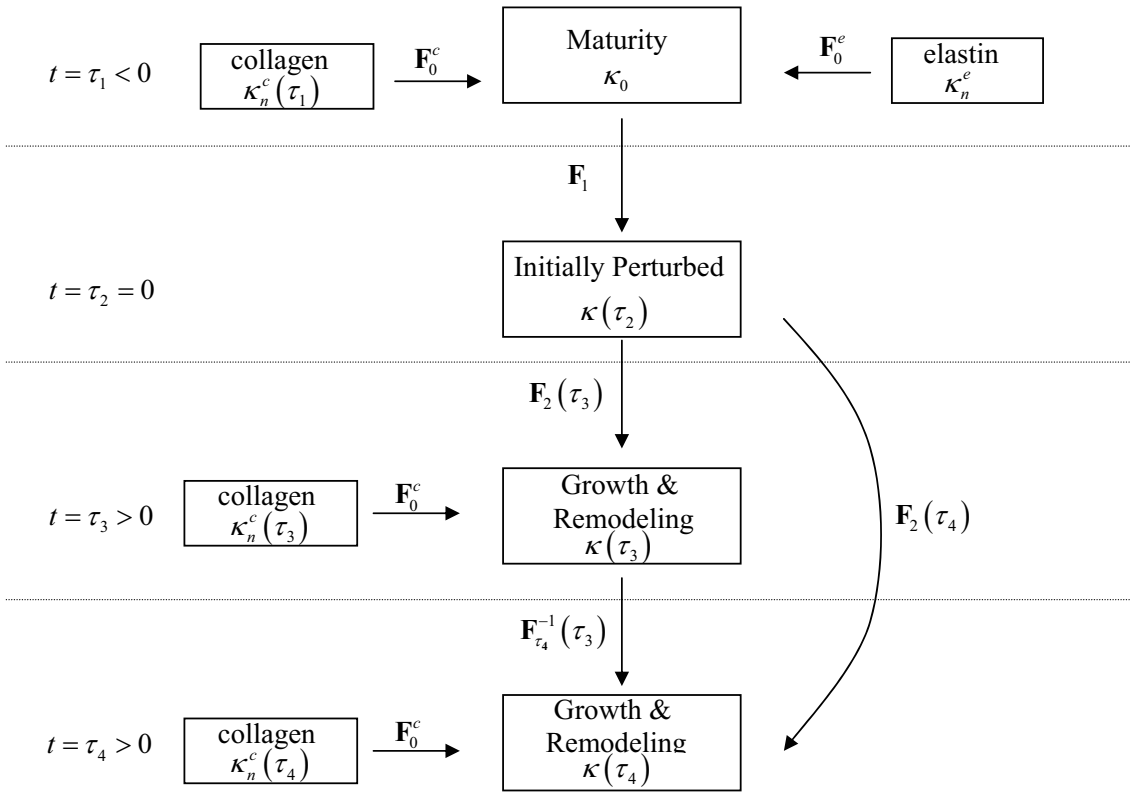

Figure 3 : Schematic of the kinematics associated with G&R

Choosing the initial equilibrium configuration of the tissue to be the reference configuration κ_0, the deformation gradient $\mathbf{F}_{\kappa_0}$ can be expressed in terms of $\mathbf{F}_1$ and $\mathbf{F}_2$ as

$$\mathbf{F}_{\kappa_0} = \mathbf{F}_2\mathbf{F}_1 = diag\left(\Lambda_1\Lambda_2(t), \frac{b(t)}{\sqrt{\Lambda_1}}, \frac{b(t)}{\sqrt{\Lambda_1}}\right), \text{ for } t \geq 0. \tag{63}$$

Mass balance, by substituting Eq. (63) into Eq. (11), requires

$$\frac{\dot{b}(t)}{b(t)} = \frac{1}{2}\left(\frac{m_\alpha^c - m_\omega^c}{\rho_0} - \frac{\dot{\Lambda}_2(t)}{\Lambda_2(t)}\right). \tag{64}$$

The mass density of elastin after G&R begins is

$$\rho^e = \frac{\rho_0^e}{\det(\mathbf{F}_{\kappa_0})} = \frac{\rho_0^e}{\Lambda_2(t)\, b(t)^2}. \tag{65}$$

Since the mass density of the tissue is assumed to be a constant, the density of collagen is given by

$$\rho^c = \rho_0 - \rho^e. \tag{66}$$

Eq. (13) specifies the associated mass fractions. For elastin, $\mathbf{F}_{\kappa_0^e}(t)$ after the initiation of G&R becomes

$$\mathbf{F}_{\kappa_0^e}(t) = \mathbf{F}_2\mathbf{F}_1\mathbf{F}_0^e = diag\left(\Lambda_0^e\Lambda_1\Lambda_2(t), \frac{b(t)}{\sqrt{\Lambda_0^e\Lambda_1}}, \frac{b(t)}{\sqrt{\Lambda_0^e\Lambda_1}}\right), \text{ for } t \geq 0, \tag{67}$$

on which the stress in the elastin depends. For a period after t =0 (until $t - L^c(t) = 0$), a part of the collagen present was produced prior to the initiation of G&R whereas the remainder is produced after G&R begins. For the collagen that was produced prior to the begining of G&R, the deformation gradient is

$$\mathbf{F}_{\kappa_n^c(\tau)}(t) = \mathbf{F}_2\mathbf{F}_1\mathbf{F}_0^c = diag\left(\Lambda_0^c\Lambda_1\Lambda_2(t), \frac{b(t)}{\sqrt{\Lambda_0^c\Lambda_1}}, \frac{b(t)}{\sqrt{\Lambda_0^c\Lambda_1}}\right), \text{ for } \tau < 0 \leq t. \tag{68}$$

Because the newly produced collagen is produced in a stressed state, we need to know the deformation gradient

from the stress-free state to the configuration occupied by the tissue, i.e., $\mathbf{F}_{\kappa_n^c(t)}(t)$ to know the stress in this newly produced material. Here, we assume that the new collagen is laid down with $\mathbf{F}_{\kappa_n^c(t)}(t)$ equal to $\mathbf{F}_0^c$, i.e.,

$$\mathbf{F}_{\kappa_n^c(t)}(t) = \mathbf{F}_0^c = diag\left(\Lambda_0^c,\ \frac{1}{\sqrt{\Lambda_0^c}},\ \frac{1}{\sqrt{\Lambda_0^c}}\right),\ \text{for } t \geq 0. \quad (69)$$

This is tantamount to assuming that collagen produced during G&R is laid down at a stretch equal to the stretch in the collagen prior to G&R. This assumption will allow us to illustrate the potential utility of the overall model; various hypothesis with regard to this issue of natural configurations for tissue produced in stressed states will need to be explored similarly. Moreover, the deformation gradient associated with collagen produced at a previous time following the onset of G&R, i.e., $\mathbf{F}_{\kappa_n^c(\tau)}(t)$ is given by

$$\mathbf{F}_{\kappa_n^c(\tau)}(t) = \mathbf{F}_t(\tau)^{-1}\mathbf{F}_0^c = diag\left(\frac{\Lambda_0^c\Lambda_2(t)}{\Lambda_2(\tau)}, \frac{b(t)}{\sqrt{\Lambda_0^c}b(\tau)}, \frac{b(t)}{\sqrt{\Lambda_0^c}b(\tau)}\right),$$
$$\text{for } 0 \leq \tau < t, \quad (70)$$

In addition, the following relationship holds:

$$\mathbf{F}_t(\tau) = diag\left(\frac{\Lambda_2(\tau)}{\Lambda_2(t)},\ \frac{b(\tau)}{b(t)},\ \frac{b(\tau)}{b(t)}\right),\ \text{for } 0 \leq \tau < t. \quad (71)$$

Utilizing Eq.(50), Eq.(67), Eq.(68), Eq.(70) and Eq.(71) the stress during adaptation when collagen produced prior to the onset of adaptation is still present in the tissue is given by

$$T_{11} = \alpha^e\mu^e\left((\Lambda_0^e\Lambda_1\Lambda_2(t))^2 - \frac{b(t)^2}{\Lambda_0^e\Lambda_1}\right)$$
$$+\int_0^t \mu_1^c \exp\left(\delta_1\left[\left(\frac{\Lambda_0^c\Lambda_2(t)}{\Lambda_2(\tau)}\right)^2 + \frac{2}{\Lambda_0^c}\left(\frac{b(t)}{b(\tau)}\right)^2 - 3\right]\right)$$
$$\left(\left(\frac{\Lambda_0^c\Lambda_2(t)}{\Lambda_2(\tau)}\right)^2 - \frac{1}{\Lambda_0^c}\left(\frac{b(t)}{b(\tau)}\right)^2\right) m_\alpha^c\left(\frac{\Lambda_2(\tau)b(\tau)^2}{\Lambda_2(t)b(t)^2}\right)d\tau$$
$$+\int_0^t \mu_2^c \exp\left(\delta_2\left[\left(\frac{\Lambda_0^c\Lambda_2(t)}{\Lambda_2(\tau)}\right)^2 - 1\right]^2\right)\left[\left(\frac{\Lambda_0^c\Lambda_2(t)}{\Lambda_2(\tau)}\right)^2 - 1\right]$$
$$\left(\frac{\Lambda_0^c\Lambda_2(t)}{\Lambda_2(\tau)}\right)^2 m_\alpha^c\left(\frac{\Lambda_2(\tau)b(\tau)^2}{\Lambda_2(t)b(t)^2}\right)d\tau$$
$$+\int_{t-L^c(t)}^0 \mu_1^c \exp\left(\delta_1\left[(\Lambda_0^c\Lambda_1\Lambda_2(t))^2 + \frac{2b(t)^2}{\Lambda_0^c\Lambda_1} - 3\right]\right)$$
$$\left((\Lambda_0^c\Lambda_1\Lambda_2(t))^2 - \frac{b(t)^2}{\Lambda_0^c\Lambda_1}\right) m_\alpha^c\left(\frac{1}{\Lambda_2(t)b(t)^2}\right)d\tau$$
$$+\int_{t-L^c(t)}^0 \mu_2^c \exp\left(\delta_2\left[(\Lambda_0^c\Lambda_1\Lambda_2(t))^2 - 1\right]^2\right)\left((\Lambda_0^c\Lambda_1\Lambda_2(t))^2 - 1\right)$$
$$(\Lambda_0^c\Lambda_1\Lambda_2(t))^2 m_\alpha^c\left(\frac{1}{\Lambda_2(t)b(t)^2}\right)d\tau,$$
$$\text{for } t - L^c(t) < 0. \quad (72)$$

When all the collagen produced prior to the onset of adaptation has been removed the stress is given by

$$T_{11} = \alpha^e\mu^e\left((\Lambda_0^e\Lambda_1\Lambda_2(t))^2 - \frac{b(t)^2}{\Lambda_0^e\Lambda_1}\right)$$
$$+\int_{t-L^c}^t \mu_1^c \exp\left(\delta_1\left[\left(\frac{\Lambda_0^c\Lambda_2(t)}{\Lambda_2(\tau)}\right)^2 + \frac{2}{\Lambda_0^c}\left(\frac{b(t)}{b(\tau)}\right)^2 - 3\right]\right)$$
$$\left(\left(\frac{\Lambda_0^c\Lambda_2(t)}{\Lambda_2(\tau)}\right)^2 - \frac{1}{\Lambda_0^c}\left(\frac{b(t)}{b(\tau)}\right)^2\right) m_\alpha^c\left(\frac{\Lambda_2(\tau)b(\tau)^2}{\Lambda_2(t)b(t)^2}\right)d\tau$$
$$+\int_{t-L^c}^t \mu_2^c \exp\left(\delta_2\left[\left(\frac{\Lambda_0^c\Lambda_2(t)}{\Lambda_2(\tau)}\right)^2 - 1\right]^2\right)\left[\left(\frac{\Lambda_0^c\Lambda_2(t)}{\Lambda_2(\tau)}\right)^2 - 1\right]$$
$$\left(\frac{\Lambda_0^c\Lambda_2(t)}{\Lambda_2(\tau)}\right)^2 m_\alpha^c\left(\frac{\Lambda_2(\tau)b(\tau)^2}{\Lambda_2(t)b(t)^2}\right)d\tau$$
$$\text{for } t - L^c(t) \geq 0. \quad (73)$$

To illustrate this model, we simulate a G&R process taking place after a uniaxial extension using a mass production rate, m_α^c, given by

$$m_\alpha^c = K_{m_1}\left[T_{11})_{avg} - T_{11})_{basal}\right] + m_{\alpha,eq}^c, \quad (74)$$

where K_{m_1} is a positive constant. $T_{11})_{avg}$ is a measure of time-averaged stress, which could be the stress at the current instant or a value averaged over past times. Here we use

$$T_{11})_{avg} = \frac{1}{L^T}\int_{t-L^T}^t T_{11}d\tau, \quad (75)$$

where L^T is the time over which the value of stress is averaged. For the results presented here we assume that $L^T = L^c$. Hence an increase in stress above the basal value causes an increase in the production of collagen; when the average stress equals the basal value of stress, the collagen production rate equals the basal value of the

production rate. For the lifespan of the collagen, we consider

$$\frac{dL^c}{dt} = -K_{L_1}\left[T_{11})_{avg} - T_{11})_{basal}\right] + K_{L_2}\left(L^c_{eq} - L^c\right), \quad (76)$$

where K_{L_1} and K_{L_2} are positive constants. Hence, an increase in the stress causes the lifespan of collagen to decrease. Note: in the above two equations we have ignored the possible dependence of m^c_α and L^c on other quantities such as mass densities, etc. Given the current lack of experimental data, it is emphasized that the above equations for m^c_α and L^c were simply chosen to illustrate the model; preferred forms will have to come from experimental data. In the calculations that follow, the stress is non-dimensionalized by an average modulus, $\overline{\mu} \equiv \mu^e + \mu^c_1 + \mu^c_2$, time with L^c_{eq}, and the production rate with $m^c_{\alpha,eq}$. The non-dimensional parameters that result from this are $K_{m_1}\overline{\mu}/m^c_{\alpha,eq}$, $K_{L_1}\overline{\mu}$, $K_{L_2}L^c_{eq}$ and $f_z L^c_{eq}$. For the results presented in the next section the value of $K_{L_2}L^c_{eq}$ is set to unity.

Numerical Results

Λ^c_0	1.2
Λ^3_0	1.3
Λ_1	1.3
δ_1	0.5
δ_2	0.1
$\dfrac{\mu^c_1}{\mu^e+\mu^c_1+\mu^c_2}$	$\dfrac{1}{3}$
$\dfrac{\mu^c_2}{\mu^e+\mu^c_1+\mu^c_2}$	$\dfrac{1}{3}$
$\dfrac{\mu^e}{\mu^e+\mu^c_1+\mu^c_2}$	$\dfrac{1}{3}$

Table 1 : Values of different parameters used for the calculations

In the following calculations, those parameters that remain unchanged are given in table 1. First, consider the case wherein the tissue is subject to a step change in length. Due to this increase in stretch, the stress increases thus causing more collagen to be produced and an increase in the rate at which it is removed. This can result in either an increase or decrease in the radius, i.e., volume of the tissue. The non-dimensional stress is shown in Figure 4 for different values of $K_{m_1}\overline{\mu}/m^c_{\alpha,eq}$, with $K_{L_1}\overline{\mu} = 0.3$. The stress increases immediately after

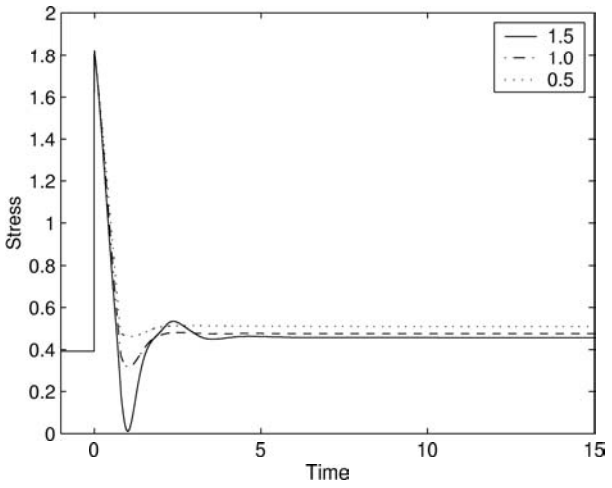

Figure 4 : Stress versus time for different values of $\frac{K_{m_1}\overline{\mu}}{m^c_{\alpha,eq}}$

the increase in stretch, after which it drops because the newly produced collagen, born in a less stressed state, replaces the collagen that is removed. The form of the equations chosen forces the stress to return to a value close to its basal value. For larger values of $K_{m_1}\overline{\mu}/m^c_{\alpha,eq}$ an initial oscillatory response is observed. The normalized radius of the tissue is plotted in Figure 5 for three different values of $K_{m_1}\overline{\mu}/m^c_{\alpha,eq}$. Initially there is a drop

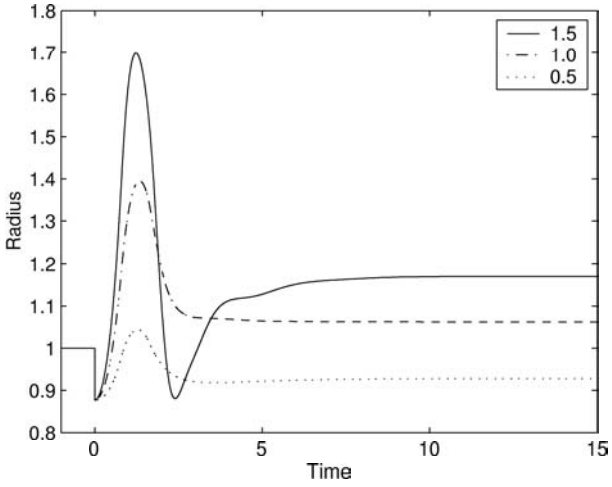

Figure 5 : Radius versus time for different values of $\frac{K_{m_1}\overline{\mu}}{m^c_{\alpha,eq}}$

in the radius due to the applied stretch, after which the radius of the tissue increases due to growth. The rate at which collagen is produced is shown in Figure 6; the increase in stress following the increase in stretch causes an increase in the value of m^c_α. After this transient, it set-

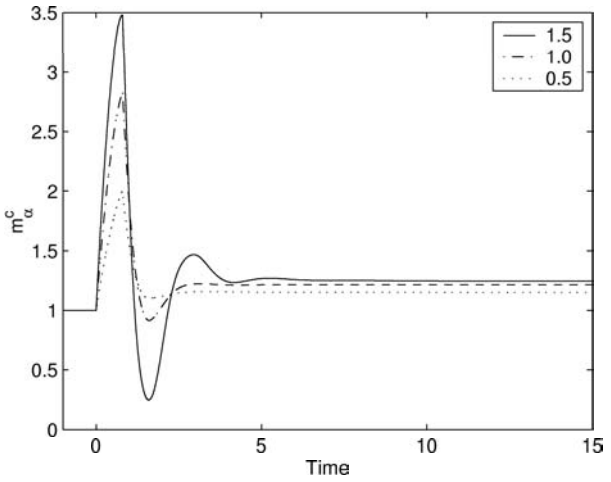

Figure 6 : m_b^c versus time for different values of $\frac{K_{m_1}\overline{\mu}}{m^c_{\alpha,eq}}$

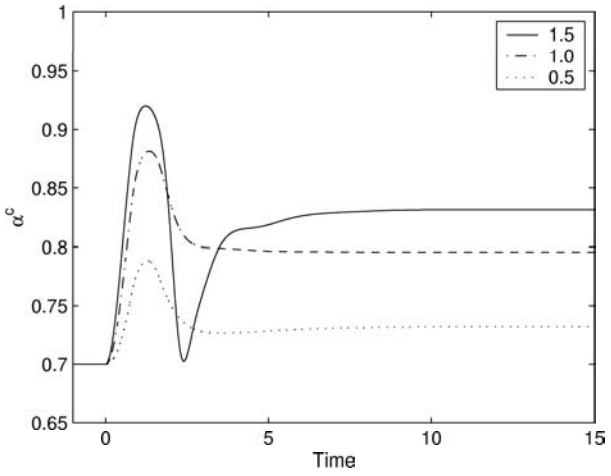

Figure 8 : Mass fraction of collagen versus time for different values of $\frac{K_{m_1}\overline{\mu}}{m^c_{\alpha,eq}}$

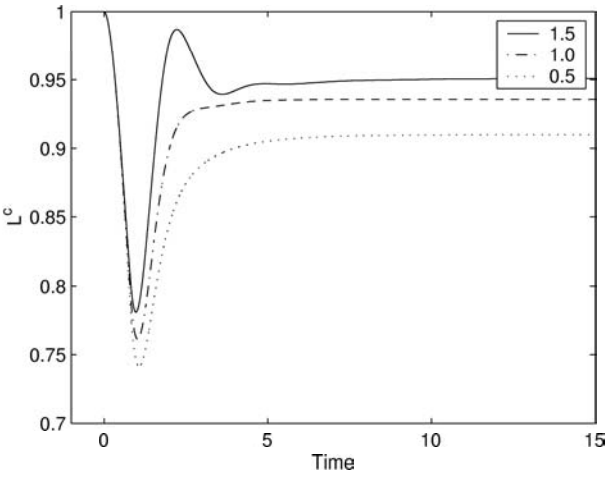

Figure 7 : L^c versus time for different values of $\frac{K_{m_1}\overline{\mu}}{m^c_{\alpha,eq}}$

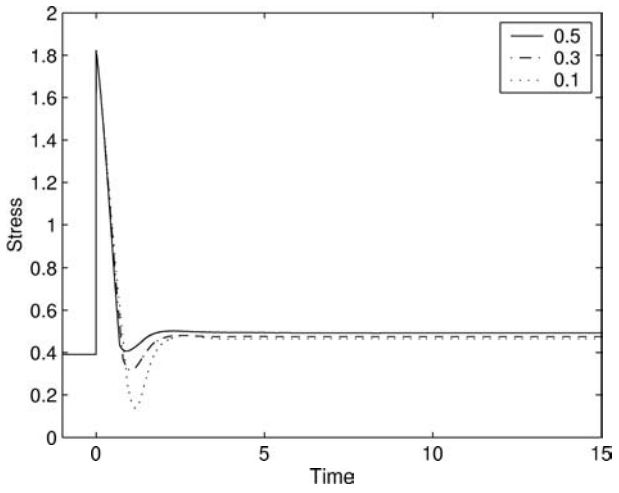

Figure 9 : Stress versus time for different values of $K_{L_1}\overline{\mu}$

tles to a new steady value, higher than the initial value. Figure 7 shows the variation of the assumed life span of collagen over time. The increase in stress causes the life span to drop initially, but after the transient it reaches a new basal value. The mass fraction of collagen is shown as a function of time in Figure 8. As the tissue grows, the invariant elastin is spread over a larger volume while the density of the tissue is constrained to remain constant; this causes the mass fraction of collagen to increase to a new basal value – this is why m^c_α settles to a higher basal value after the transient (see Figure 6). These plots are repeated for different values of $K_{L_1}\overline{\mu}$ (Figures 9 to 13) for a value of $K_{m_1}\overline{\mu}/m^c_{\alpha,eq} = 1.0$. For larger values of $K_{L_1}\overline{\mu}$, the life span decreases rapidly after the initiation of G&R.

For a sinusoidally varying stretch, the stress is plotted for three different values of frequency (Figures 14 and 15). The following values were used: $K_{m_1}\overline{\mu}/m^c_{\alpha,eq} = 1.0$, $K_{L_1}\overline{\mu} = 0.3$ and $A = 0.05$. Note that the stress after adaptation oscillates about the basal value. The radius of the tissue is plotted for these three cases in Figures 16 and 17.

Conclusions

To address the need for mathematical models capable of predicting mechanically induced G&R, Humphrey and Rajagopal (2002) recently proposed a constrained mixture model. In this paper, we applied this model to a two constituent tissue, of which one constituent continu-

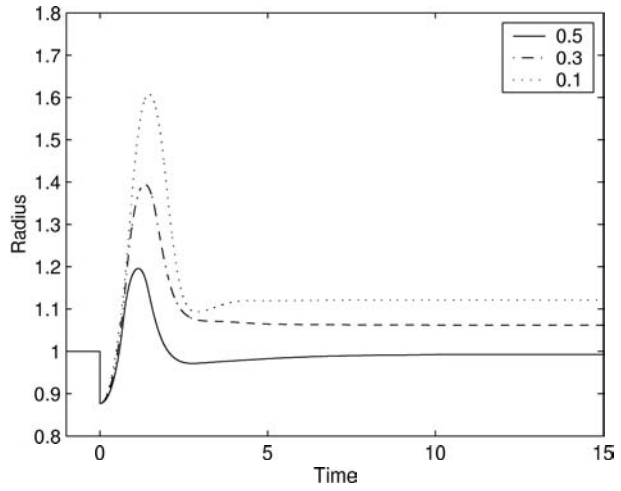

Figure 10 : Radius versus time for different values of $K_{L_1}\overline{\mu}$

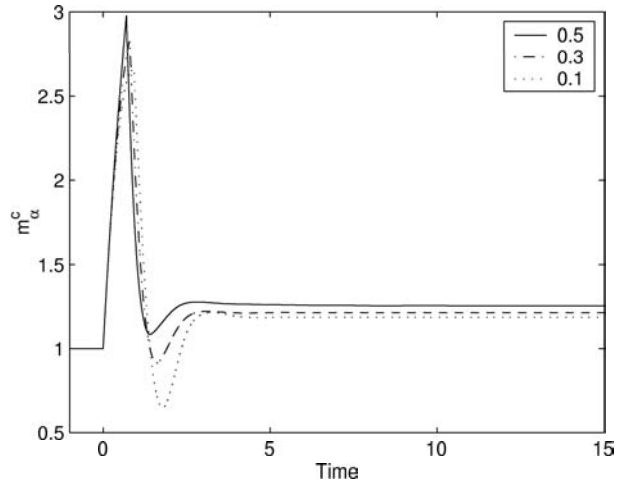

Figure 11 : m_b^c versus time for different values of $K_{L_1}\overline{\mu}$

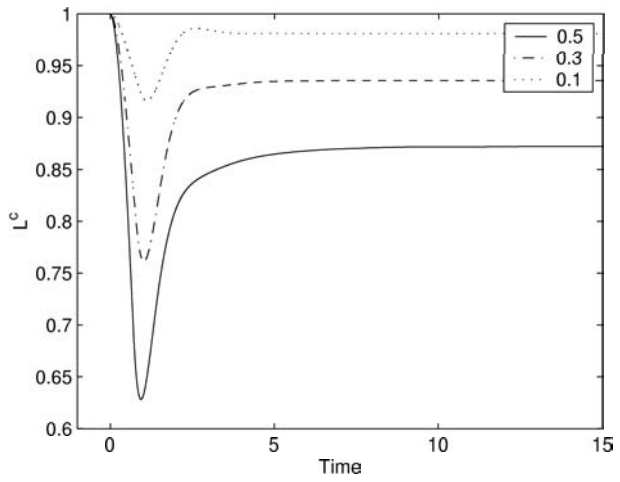

Figure 12 : L^c versus time for different values of $K_{L_1}\overline{\mu}$

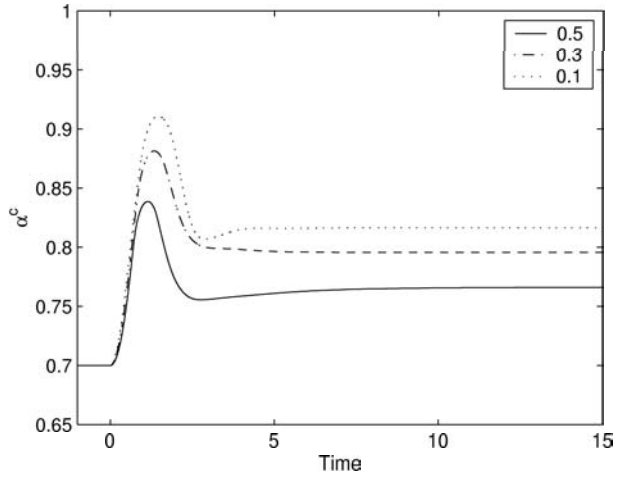

Figure 13 : Mass fraction of collagen versus time for different values of $K_{L_1}\overline{\mu}$

ously turned over (collagen) while the second constituent (elastin) remained unchanged. Collagen was assumed to exhibit a transversely isotropic behavior and elastin an isotropic behavior. The natural configuration(s) of collagen produced at different times during G&R evolve depending on the local conditions. The amount and age of the collagen present at each material point in the tissue was prescribed via mass production rates of collagen per unit volume and the age of the collagen being removed. Both of these quantities depend on local conditions and can vary with stress, mass fractions etc.; illustrative equations were used to model these quantities. The behavior of the model was investigated for two uniaxial extensions: a step change in the length and a step change in length followed by a sinusoidal variation in length about the new value. These types of deformations are commonly encountered in ligaments and tendons. Results showing the evolution of stress, radius, mass fractions, and mass production rates over G&R time were plotted for different values of material constants that arise in the model. These results illustrate the influence of the mass fractions of the different constituents and the kinetics associated with mass production and removal on the stress and shape of the tissue. It is hoped that the results presented in this paper will motivate further work on biological growth and remodeling and in particular aid in identifying the experiments that are needed to formulate

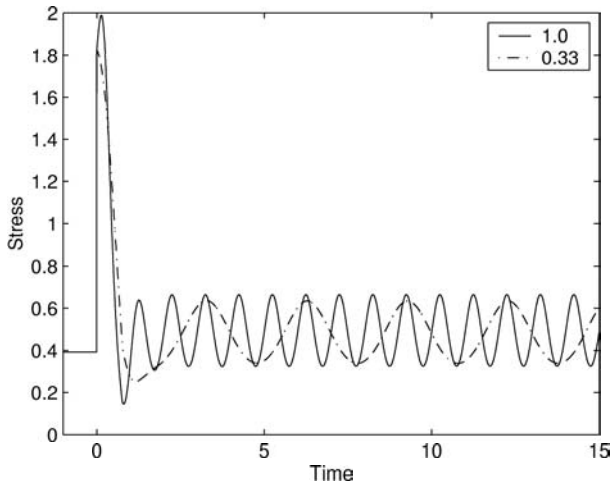

Figure 14 : Stress versus time for different values of $f_z L^c_{eq}$

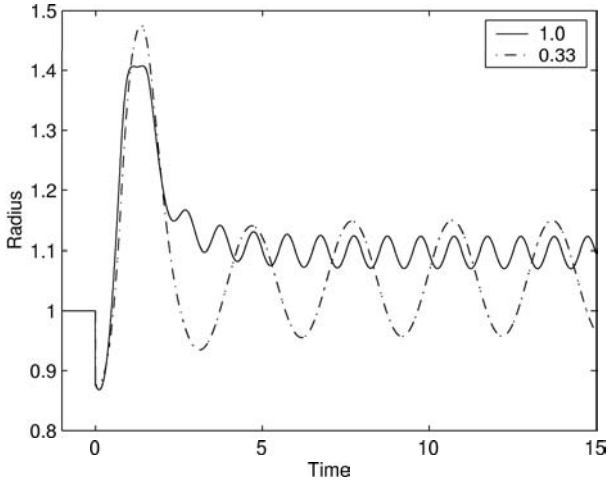

Figure 16 : Radius versus time for different values of $f_z L^c_{eq}$

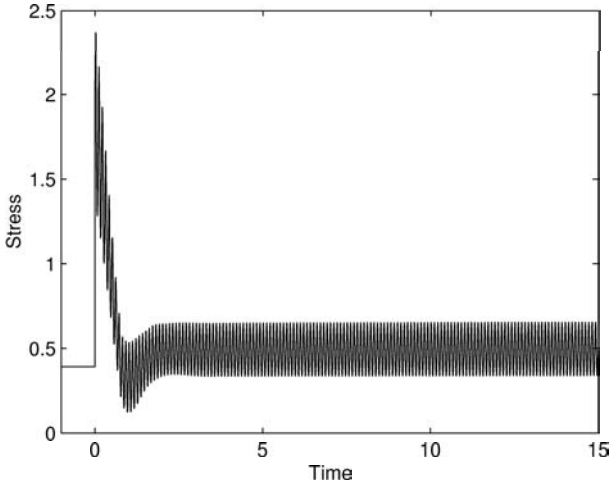

Figure 15 : Stress versus time for $f_z L^c_{eq} = 10$

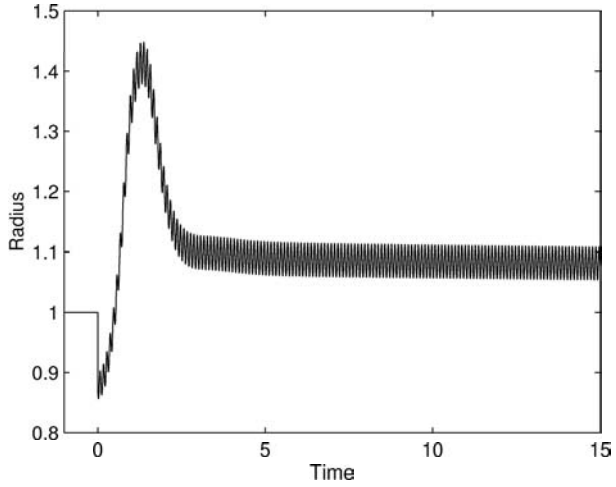

Figure 17 : Radius versus time for $f_z L^c_{eq} = 10$

physiologically meaningful constitutive equations.

Acknowledgement: One of the authors (I. J. Rao) acknowledges support provided by the New Jersey Institute of Technology under Grant No. 421060. This work was also supported, in part, by federal grants from the NIH (HL-58856, HL-64372) and the NSF (BES-0084644).

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