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A continuous model for an arterial tissue, incorporating remodeling and volumetric growth

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Abstract

A continuum-mechanics approach for the derivation of a model for the behavior, i.e. the growth and remodeling, of an arterial tissue under a mechanical load is presented. This behavior encounters an interplay between two phenomena: continuum mechanics and biology. The tissue is modeled as a continuous mixture of two components: elastin and collagen. Both components are incompressible, but the tissue as a whole can show volumetric growth due to the creation of collagen. Collagen is a fibrous structure, having a strain-induced preferred orientation. Remodeling of the tissue incorporates degradation of elastin and strain-induced creation and degradation of collagen fibers. Both elastin and collagen are considered to be nonlinear elastic media; elastin as a Neo-Hookean and collagen fibers behaving according to an exponential law. The modeling is based on the classical balance laws of mass and momentum.

1 Introduction

An aneurysm is a localized dilatation or ballooning of blood vessels. The size of an aneurysm was considered to be a critical indicator of the rupture potential and need for medical intervention. However, size is no longer considered to be an accurate parameter as there have been incidents of small aneurysms rupturing and large ones remaining intact. It is now believed that aneurysms rupture when the hemodynamically induced wall stress exceeds the wall strength. This necessitates a mechanical analysis of the biological tissue the arterial wall is made of.

In modeling aneurysms and other cardiovascular pathologies, we will encounter the interplay of two phenomena: continuum mechanics and biology. Whereas traditional engineering

materials passively respond to a change in their environment, biological tissues adapt to their environment by changing their configuration and material properties.

In this paper, being a contribution to TRECOP'07 – a conference on COntinuum Physics – we will not aim at a physiological justification of our tissue model, but when needed we will use partial results from existing models from literature. In contrast to many of these models in literature, we will base our model strictly on the basic principles of continuum mechanics. Moreover, we refrain from giving an extensive literature review; for this we refer to forthcoming work as e.g. [1]. Here, we only mention a paper of Humphrey and Rajagopal, [2], one of Kroon and Holzapfel, [3], and two of Baek et al., [4], [5].

We will present a continuous model for a tissue based on the basic laws of continuum mechanics coupled with considerations on the biological behavior of arterial vessels. A tissue of an arterial vessel is mainly built up of two components: elastin and collagen. Elastin behaves as an isotropic nonlinear elastic solid medium, and it has as a special feature that it degrades (vanishes) during the forming of an aneurysm. Collagen has an anisotropic fibrous structure that can take up stresses in a nonlinear elastic way. Collagen remodels in two ways: on one hand collagen fibres weaken, in that they elongate or disappear, on the other hand new collagen is led down or passive fibres become active, by which the collagen as a whole is strengthened. We will propose a continuous mixture model for an arterial tissue in which remodeling is modeled by taking into account degradation of elastin, local changes of mass of collagen and elastin – resulting in volumetric growth of the tissue – and stress- or strain-induced preferred directions for the lay-down of collagen fibres. In order to more basically incorporate the idea of a distributed lay-down of fibers, Muschik et al., introduced in [6] the concept of mesoscopic continuum physics. This is a very elegant concept that also accounts for thermodynamical effects, which, however, are not considered in this paper.

2   Basic model of a tissue

Our basic model for an arterial tissue is a 3-dimensional continuous mixture of two components: *elastin* and *collagen*. These two components are both intrinsically incompressible, but the mixture as a whole can show volumetric growth caused by mass production. This is due to the *degradation* of elastin, modeled as vanishing of elastin particles, and the continuously occurring *creation* (or lay-down) of new collagen fibers and *degradation* (removal) of old ones. By these processes, the total amount, or mass, of elastin and collagen continuously changes in time, which can result in growth or decrease of the volume of the tissue.

Two important state variables for the analysis to come are the *volumetric fractions*, n_e and n_c, of elastin and collagen, respectively. They are defined as the relative amount of elastin or collagen in the mixture; they are dimensionless and they sum up to one, so

$$n_e + n_c = 1. \tag{1}$$

The elastin is modeled as an isotropic nonlinear elastic solid, and its elastic constitutive behavior is described by an incompressible Neo-Hookean model. As elastin can only degrade, the amount of elastin is monotone decreasing once degradation has started.

On the other hand, collagen is an anisotropic fibrous medium. The elastic fibers can only take up stresses in their fiber direction. As constitutive equation for these elastic stresses we will adapt a nonlinear exponential law. Important fiber properties are further their orientation (direction) and pre-stretch. At each moment of time, i.e. at each configuration of the

tissue, the fiber directions are described by a distribution function for the fiber orientations. This distribution function changes continuously in time, governed by the state of stretch of the tissue. A specific choice for this distribution function (see Section 6), which was first introduced by Baek et al., [4], [5], will be given further on.

Initially, in an unloaded state, the collagen fibers are crimped, in which state they do not contribute to the strength of the tissue. When the tissue is loaded, the elastin will be stretched, and there will come a state in which the collagen fibers become uncrimped; the tissue stretch in this state in the direction of a collagen fiber is called the *recruitment stretch*. Here, we will consider the recruitment stretch as a state variable, which in some sense governs the adaptation of the newly created collagen fibers to the state of stretch of the tissue. This adaptation is modeled such that a new laid-down collagen fiber is always in the same state of preferred stretch, called the *attachment stretch*. In contrast to the variable recruitment stretch, the attachment stretch is a constant material parameter in our model.

Before degradation of elastin starts, the tissue is in its *healthy state*. This is a loaded equilibrium state, in which the tisue is stretched and in which the collagen is always stretched to its attachment stretch λ_a. The total amount of neither elastin (no degradation) nor collagen does change, and thus there is no mass production or volumetric growth in this state. However, also in this state there is a continuous turnover (creation and degradation) of collagen, but in such a way that the amount of degraded collagen is always equal to that of newly created collagen, thus keeping the total mass (and volume) of collagen constant.

Finally, for later use, we define the *metabolic equilibrium state* as the state in which the stretch in each collagen fiber is equal to the attachment stretch λ_a.

3   Basics of volumetric growth for a 1-component medium

In this section, we try to explain the peculiar behavior of a medium having internal mass production and volumetric growth by considering as an example a simple or single-component medium (so, not a mixture, as it will be dealt with in the remaining part of this paper). In doing this, we follow the approach of Kuhl et al. in [7].

To introduce volumetric growth due to mass production, we consider a 1-component intrinsic incompressible medium having as reference configuration: G_r and reference position vector $\mathbf{X}$, and as deformed current configuration: $G = \mathcal{G}(t)$ and current (at time t) position vector $\mathbf{x} = \mathbf{x}(\mathbf{X}, t)$. The density ρ of the medium is contant and uniform. The deformation gradient is $\mathcal{F}(\mathbf{X}, t) = \partial \mathbf{x} / \partial \mathbf{X}$, and the associated Jacobian is $J = \det \mathcal{F} = J(\mathbf{X}, t)$.

A material partial volume b with configuration $g = g(t)$ at the current time t, and reference configuration g_r, is defined as a part of the whole body across the boundary of which no mass flux takes place. However, inside b mass sources can be active causing changes of the total mass contained in b.

The volume of b is

$$V(t) = \int_{g(t)} \mathrm{d}v = \int_{g_r} J(\mathbf{X}, t) \mathrm{d}v_r \ , \tag{2}$$

and its mass is

$$M(t) = \int_{g(t)} \rho \mathrm{d}v = \rho \int_{g_r} J(\mathbf{X}, t) \mathrm{d}v_r \ . \tag{3}$$

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Since this mass $M = M(t)$ is NOT constant, the balance of mass yields

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t} M(t) &= \frac{\mathrm{d}}{\mathrm{d}t} \left[\rho \int_{g_r} J(\mathbf{X}, t) \mathrm{d}v_r \right] \\
&= \rho \int_{g_r} \dot{J}(\mathbf{X}, t) \ \mathrm{d}v_r = \rho \int_{g(t)} \frac{\dot{J}}{J} \ \mathrm{d}v = \int_{g(t)} \dot{m} \ \mathrm{d}v \ ,
\end{aligned}
\tag{4}
$$

where $\dot{m} = \dot{m}(\mathbf{X}, t)$ is the mass source, i.e. the rate of mass production per unit of current volume (in kg/m^{3}sec). The leads to the local mass equation

$$
\rho \frac{\mathrm{d}J}{\mathrm{d}t} = J \ \dot{m} \ .
\tag{5}
$$

The balance of momentum for a medium with volumetric growth reads

$$
\frac{\mathrm{d}}{\mathrm{d}t} \int_{g(t)} \rho \mathbf{v} \mathrm{d}v = \int_{\partial g(t)} \mathbf{t} \mathrm{d}S + \int_{g(t)} \rho \mathbf{b} \mathrm{d}v \ ,
\tag{6}
$$

where, however, now the total body force must be split up into a purely mechanical part, $\rho \ \mathbf{b}_m$, (the external body force) and a part due to the growth of mass, according to

$$
\rho \ \mathbf{b} = \rho \ \mathbf{b}_m + \dot{m} \ \mathbf{v} \ ,
\tag{7}
$$

where $\mathbf{v}$ is the velocity.
Using successively

$$
\begin{aligned}
\frac{\mathrm{d}}{\mathrm{d}t} \int_{g(t)} \rho \mathbf{v} \mathrm{d}v &= \frac{\mathrm{d}}{\mathrm{d}t} \int_{g_r} \rho \mathbf{v} J \mathrm{d}v_r \\
&= \int_{g_r} \rho (\dot{\mathbf{v}} J + \mathbf{v} \dot{J}) \ \mathrm{d}v_r = \int_{g(t)} (\rho \dot{\mathbf{v}} + \dot{m} \mathbf{v}) \ \mathrm{d}v \ ,
\end{aligned}
\tag{8}
$$

Cauchy's stress law, i.e.

$$
\mathbf{t} = \mathcal{T} \mathbf{n} \ ,
\tag{9}
$$

and (7), we obtain the local momentum balance

$$
\rho \dot{\mathbf{v}} + \dot{m} \mathbf{v} = \mathrm{div} \mathcal{T} + \rho \mathbf{b}_m + \dot{m} \mathbf{v} \ ,
\tag{10}
$$

or

$$
\rho \dot{\mathbf{v}} = \mathrm{div} \mathcal{T} + \rho \mathbf{b}_m \ ,
\tag{11}
$$

revealing that the effect of mass production in the local momentum balance has disappeared, and that the local momentum equation takes its classical form.
In (9), $\mathbf{t}$ is the stress vector, or traction, $\mathcal{T}$ is the stress tensor, and $\mathbf{n}$ is the unit outward normal vector on the boundary ∂g of g.
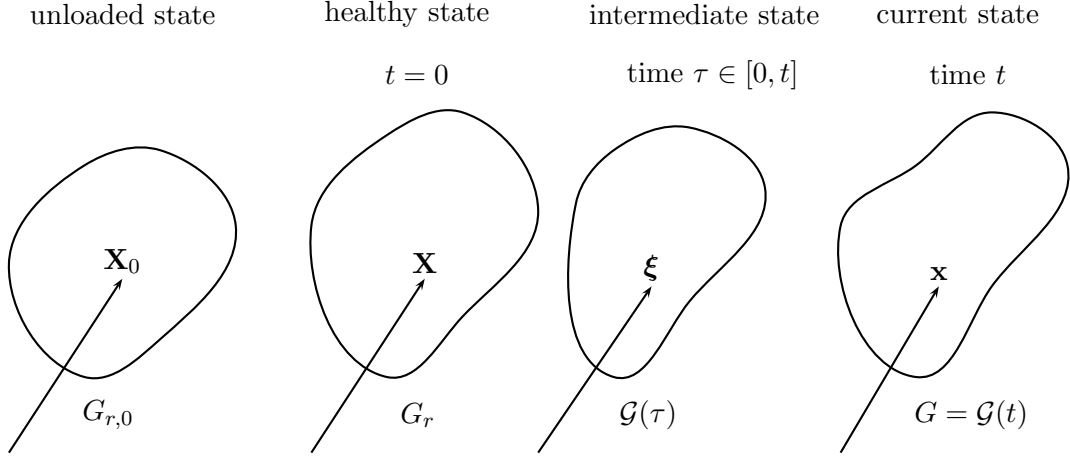
4

Figure 1: Configurations of tissue body $\mathcal{B}$.

4 Configurations and deformations

In this section, we consider the four different configurations depicted in Figure 1:

1. The unloaded state $G_{r,0}$: in this state both the elastin and the collagen are unloaded, but it is assumed that the collagen is not crimped, meaning that $\lambda_{\text{rec},0} = 1$.

2. The healthy state G_r: this state is an equilibrium state under a given external load; equilibrium implies here that the collagen stretch is equal to the attachment stretch λ_a; this healthy state is assumed to be known, and this state is in our further analysis considered as THE reference state (note that this is not an undeformed or stress-free state). At the initial time $t = 0$, the tissue is in its healthy state and then the degradation followed by remodeling and volumetric growth starts.

3. The intermediate state $\mathcal{G}(\tau)$; the intermediate time τ ranges from $t = 0$ to the current time t and at each τ new collagen fibers are laid down.

4. The current state $G = \mathcal{G}(t)$; this is the final deformed state we wish to determine.

To describe the deformation of the tissue $\mathcal{B}$ we consider an infinitesimal material volume element containing the material point $\mathscr{P}$. The position of $\mathscr{P}$ in $G_{r,0}$ is given by its position vector $\mathbf{X}_0$, and further by $\mathbf{X}$ in G_r, by $\boldsymbol{\xi}$ in $\mathcal{G}(\tau)$, and by $\mathbf{x}$ in G. Here, we consider $\boldsymbol{\xi}$ and $\mathbf{x}$ as functions of $\mathbf{X}$ and τ, and of $\mathbf{X}$ and t, respectively,

$$\boldsymbol{\xi} = \boldsymbol{\xi}(\mathbf{X}, t) , \qquad \mathbf{x} = \mathbf{x}(\mathbf{X}, t) . \tag{12}$$

If we call the total deformation gradient of the tissue, or the elastin, from $G_{r,0}$ to G: $\mathcal{F}_{\text{tot}}$, then

$$\mathcal{F}_{\text{tot}} = \frac{\partial \mathbf{x}}{\partial \mathbf{X_0}} = \frac{\partial \mathbf{x}}{\partial \mathbf{X}} \frac{\partial \mathbf{X}}{\partial \mathbf{X_0}} = \mathcal{F} \mathcal{F}_0 , \tag{13}$$

5

where $\mathcal{F} = \mathcal{F}(\mathbf{X}, t)$.

The partial deformation from $\boldsymbol{\xi}$ to $\mathbf{x}$ is described by

$$\hat{\mathcal{F}}(\mathbf{X}, t, \tau) = \frac{\partial \mathbf{x}}{\partial \boldsymbol{\xi}} = \frac{\partial \mathbf{x}}{\partial \mathbf{X}} \frac{\partial \mathbf{X}}{\partial \boldsymbol{\xi}} = \mathcal{F}(\mathbf{X}, t)\mathcal{F}^{-1}(\mathbf{X}, \tau) \ , \tag{14}$$

or

$$\mathcal{F}(\mathbf{X}, t) = \hat{\mathcal{F}}(\mathbf{X}, t, \tau)\mathcal{F}(\mathbf{X}, \tau) \ . \tag{15}$$

Consider a collagen fiber created at time τ in direction γ with initial stretch λ_a, having the initial direction vector

$$\mathbf{e}_c^{(0)}(\mathbf{X}, \tau, \gamma) = \cos\gamma \ \mathbf{v}_1(\mathbf{X}, \tau) + \sin\gamma \ \mathbf{v}_2(\mathbf{X}, \tau) \ , \tag{16}$$

with $\mathbf{v}_{1,2}$ the principal directions of $\mathcal{F}(\mathbf{X}, \tau)$. How the distribution of $\mathbf{e}_c^{(0)}$ depends on the state of deformation at τ, will be explained further on. The unit vectors $\mathbf{v}_1$ and $\mathbf{v}_2$ span a surface in which the main stretching takes place; in the third direction is only shrinking. For instance, for an arterial tissue modeled as a tube under internal pressure and axial stretch, $\mathbf{v}_1$ and $\mathbf{v}_2$ are in the azimuthal and axial direction, while the radial direction is the third direction in which compression takes place.

Let $\mathbf{e}_{c,0}$ be the direction vector representing $\mathbf{e}_c^{(0)}$ in the unloaded state $G_{r,0}$, then

$$\mathbf{e}_{c,0}(\mathbf{X}, \tau, \gamma) = \frac{\mathcal{F}_{\text{tot}}^{-1}(\mathbf{X}, \tau)\mathbf{e}_c^{(0)}(\mathbf{X}, \tau, \gamma)}{||\mathcal{F}_{\text{tot}}^{-1}(\mathbf{X}, \tau)\mathbf{e}_c^{(0)}(\mathbf{X}, \tau, \gamma)||} \ . \tag{17}$$

The elastin stretch λ at time τ in the direction $\mathbf{e}_c^{(0)}$ is

$$\lambda(\mathbf{X}, \tau, \gamma) = ||\mathcal{F}_{\text{tot}}(\mathbf{X}, \tau) \ \mathbf{e}_{c,0}(\mathbf{X}, \tau, \gamma)|| = \frac{1}{||\mathcal{F}_{\text{tot}}^{-1}(\mathbf{X}, \tau)\mathbf{e}_c^{(0)}(\mathbf{X}, \tau, \gamma)||} \ , \tag{18}$$

where in the latter step we have used (17).

Since the collagen stretch λ_c at the moment it is laid down is equal to λ_a, we obtain for the recruitment stretch

$$\lambda_{\text{rec}}(\mathbf{X}, \tau, \gamma) = \frac{\lambda(\mathbf{X}, \tau, \gamma)}{\lambda_a} = \frac{1}{\lambda_a \ ||\mathcal{F}_{\text{tot}}^{-1}(\mathbf{X}, \tau)\mathbf{e}_c^{(0)}(\mathbf{X}, \tau, \gamma)||} \ . \tag{19}$$

Hence, λ_{rec} is not a function of the current time t, and we will use the above relation to eliminate λ_{rec} from our further calculations.

The collagen stretch $\lambda_c(\mathbf{X}, t, \tau, \gamma)$ at the current time t of the fiber laid down at time τ in the direction $\mathbf{e}_c^{(0)}$ is thus

$$\lambda_c(\mathbf{X}, t, \tau, \gamma) = \frac{\lambda(\mathbf{X}, t, \gamma)}{\lambda_{\text{rec}}(\mathbf{X}, \tau, \gamma)} = \lambda_a \ \frac{||\mathcal{F}_{\text{tot}}^{-1}(\mathbf{X}, \tau)\mathbf{e}_c^{(0)}(\mathbf{X}, \tau, \gamma)||}{||\mathcal{F}_{\text{tot}}^{-1}(\mathbf{X}, t) \ \mathbf{e}_c^{(0)}(\mathbf{X}, \tau, \gamma)||} \ . \tag{20}$$

Let the initial direction at τ: $\mathbf{e}_c^{(0)}(\mathbf{X}, \tau, \gamma)$ deform to the current direction vector $\mathbf{e}_c$ at time t, then

$$\mathbf{e}_c(\mathbf{X}, t, \tau, \gamma) = \frac{\hat{\mathcal{F}}(\mathbf{X}, t, \tau) \ \mathbf{e}_c^{(0)}(\mathbf{X}, \tau, \gamma)}{||\hat{\mathcal{F}}(\mathbf{X}, t, \tau) \ \mathbf{e}_c^{(0)}(\mathbf{X}, \tau, \gamma)||} \ . \tag{21}$$

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5 Mass balances

The tissue is here considered as a mixture of two components: elastin and collagen. Let b be a material partial volume of $\mathscr{B}$ containing both elastin and collagen particles. In a material volume there is no mass flux across the boundaries of the volume, but due to the degradation and production of elastin and collagen, the mass of b is not necessarily conserved. Moreover, although both elastin and collagen are modeled as intrinsic incompressible, also the volume of b is not conserved: there is a volumetric growth due to the mass production. This volumetric growth is represented by the value of the Jacobian $J = \det \mathcal{F}$, being greater than one in case of positive volumetric growth, and less than one in case of tissue resorption. Because J is related to the volumetric growth, we replace J by $J_g = J_g(\mathbf{X}, t)$. Since no volumetric growth takes place in the healthy phase, $J_0 = \det \mathcal{F}_0 = 1$.

Let $g = g(t)$ be the configuration of b at time t, and g_r its reference configuration in G_r. Then the volume of b is given by (compare with Section 3)

$$V(t) = \int_{g(t)} \mathrm{d}v = \int_{g_r} J_g(\mathbf{X}, t)\mathrm{d}v_r \ . \tag{22}$$

The total mass of b consists of the mass of elastin, M_e, and that of collagen, M_c. With ρ_e and ρ_c the constant intrinsic densities of elastin and collagen, respectively, and n_e and n_c their volume fractions, we have for the total mass of b,

$$M(t) = M_e(t) + M_c(t), \tag{23}$$

where

$$M_e(t) = \int_{g(t)} \rho_e n_e(\mathbf{X}, t)\mathrm{d}v = \rho_e \int_{g_r} n_e(\mathbf{X}, t)J_g(\mathbf{X}, t)\mathrm{d}v_r \ , \tag{24}$$

and

$$M_c(t) = \int_{g(t)} \rho_c n_c(\mathbf{X}, t)\mathrm{d}v = \rho_c \int_{g_r} n_c(\mathbf{X}, t)J_g(\mathbf{X}, t)\mathrm{d}v_r \ . \tag{25}$$

We denote the rates of mass production per unit of current volume for elastin and collagen by $\dot{m}_e$ and $\dot{m}_c$ (in kg/m^{3}sec), respectively. The change of elastin mass is only due to degradation, meaning that $\dot{m}_e$ is negative, and is given by

$$\dot{M}_e(t) = \int_{g(t)} \dot{m}_e(\mathbf{X}, t)\mathrm{d}v = \int_{g_r} \dot{m}_e(\mathbf{X}, t)J_g(\mathbf{X}, t)\mathrm{d}v_r \ . \tag{26}$$

For collagen, the situation is somewhat more complex: here, we have collagen production at every time τ from $t = 0$ to the current time t, but meanwhile the collagen produced at τ is monotone decreasing during the period from τ to t, which is described by the monotone decreasing degradation function of collagen $q_c = q_c(t)$. Here, we have assumed that the degradation function q_c is uniform over $\mathscr{B}$.

Let us introduce a new *rate of production of volume fraction of collagen* $\nu_c = \nu_c(\mathbf{X}, t, \tau)$, such that $\nu_c(\mathbf{X}, t, \tau)\mathrm{d}\tau$ is the volume fraction of collagen in $V(t)$ at t produced from τ to $\tau + \mathrm{d}\tau$ in $V(\tau)$ and survived at t. Thus, equating the rate of change of the collagen in $V(t)$ due to the production in $V(\tau)$ from τ to $\tau + \mathrm{d}\tau$ multiplied by the collagen degradation function from τ

to t, we obtain

$$\rho_c \int_{g(t)} \nu_c(\mathbf{X}, t, \tau) \mathrm{d}v \; \mathrm{d}\tau \;\; = \;\; \rho_c \int_{g_r} \nu_c(\mathbf{X}, t, \tau) J_g(\mathbf{X}, t) \mathrm{d}v_r \; \mathrm{d}\tau$$

$$= \int_{g(\tau)} \dot{m}_c(\mathbf{X}, \tau) \mathrm{d}v(\tau) \; \mathrm{d}\tau \; q_c(t - \tau) \;\; = \;\; \int_{g_r} \dot{m}_c(\mathbf{X}, \tau) J_g(\mathbf{X}, \tau) \mathrm{d}v_r \; q_c(t - \tau) \; \mathrm{d}\tau \; , \quad (27)$$

and this yields after localization

$$\nu_c(\mathbf{X}, t, \tau) = \frac{\dot{m}_c(\mathbf{X}, \tau) J_g(\mathbf{X}, \tau)}{\rho_c J_g(\mathbf{X}, t)} \; q_c(t - \tau) \; . \tag{28}$$

The latter relation implies that the total collagen mass of b at the current time t is given by

$$M_c(t) \;\; = \;\; M_{c,r} + \int_0^t \rho_c \int_{g(t)} \nu_c(\mathbf{X}, t, \tau) \mathrm{d}v \; \mathrm{d}\tau$$

$$= \;\; M_{c,r} + \int_0^t \int_{g_r} \dot{m}_c(\mathbf{X}, \tau) q_c(t - \tau) J_g(\mathbf{X}, \tau) \mathrm{d}v_r \; \mathrm{d}\tau \; , \tag{29}$$

where $M_{c,r}$ is the collagen mass in b in the healthy state G_r.
Differentiating this relation with respect to t and using that, by normalization, $q(0) = 1$, we find that the change of the collagen mass in b from $t = 0$ to the current time t is given by

$$\dot{M}_c(t) = \int_{g_r} \dot{m}_c(\mathbf{X}, t) J_g(\mathbf{X}, t) \mathrm{d}v_r + \int_0^t \int_{g_r} \dot{m}_c(\mathbf{X}, \tau) \dot{q}_c(t - \tau) J_g(\mathbf{X}, \tau) \mathrm{d}v_r \; \mathrm{d}\tau \; . \tag{30}$$

Taking the time derivatives of $M_e(t)$ and $M_c(t)$ according to (26) and (30) in terms of the integrals over g_r, equating the results to (25) and (26), respectively, and realizing that these results hold for arbitrary b, we arrive at the local mass balance equations

$$\rho_e \frac{\mathrm{d}}{\mathrm{d}t} \left(J_g n_e \right) = J_g \dot{m}_e \; , \tag{31}$$

for elastin, and

$$\rho_c \frac{\mathrm{d}}{\mathrm{d}t} \left(J_g n_c \right) = J_g \dot{m}_c + \int_0^t \dot{m}_c(\mathbf{X}, \tau) \dot{q}_c(t - \tau) J_g(\mathbf{X}, \tau) \mathrm{d}\tau \; , \tag{32}$$

for collagen. Note that $\mathrm{d}/\mathrm{d}t$ stands for the material time derivative, so (for arbitrary f)

$$\frac{\mathrm{d}}{\mathrm{d}t} f = \frac{\partial f(\mathbf{X}, t)}{\partial t} \; . \tag{33}$$

The initial conditions for (31) and (32) are $n_e(\mathbf{X}, 0) = n_{e,r}$ and $n_c(\mathbf{X}, 0) = n_{c,r}$.
Dividing (31) by ρ_e and (32) by ρ_c, adding them together and using the trivial relation

$$n_e(\mathbf{X}, t) + n_c(\mathbf{X}, t) = 1, \tag{34}$$

we obtain the integro-differential equation for J_g:

$$\dot{J}_g = \frac{1}{\rho_e} J_g \dot{m}_e + \frac{1}{\rho_c} J_g \dot{m}_c + \frac{1}{\rho_c} \int_0^t \dot{m}_c(\mathbf{X}, \tau) \dot{q}_c(t - \tau) J_g(\mathbf{X}, \tau) \mathrm{d}\tau \; , \tag{35}$$

with the initial condition $J_g(\mathbf{X}, 0) = 1$.

At this point, we have derived four equations for the four unknowns J_g, n_e, n_c, and ν_c, namely successively (35), (31), (32), and (28), when we for a moment assume that the production rates $\dot{m}_e$ and $\dot{m}_c$ are given. Inspection, especially with use of (30), shows us that

$$n_c(\mathbf{X}, t) = n_{c,r} + \int_0^t \nu_c(\mathbf{X}, t, \tau) \, \mathrm{d}\tau \ . \tag{36}$$

However, in contrast to what we said above, the production rates $\dot{m}_e$ and $\dot{m}_c$ are not explicitly given; we need constitutive equations for these quantities. We will not derive here these constitutive equations, but rather use constitutive equations as we can find them in literature; see specifically Driessen [8] and Baek et al. [4], [5].

The elastin rate we choose here constant and uniform, i.e.

$$\dot{m}_e(\mathbf{X}, t) = -\mu_e, \tag{37}$$

for t running from $t = 0$ to the final time $t = t_f$; before $t = 0$ and after t_f there is no degradation of elastin. Here, μ_e is a given constant material parameter.

The collagen rate we split into two parts as

$$\dot{m}_c(\mathbf{X}, t) = \dot{m}_c^h(\mathbf{X}, t) + \dot{m}_c^e(\mathbf{X}, t), \tag{38}$$

where the superindices 'h' and 'e' stand for 'healthy' and 'extra', respectively.

For the first term we take

$$\dot{m}_c^h(\mathbf{X}, t) = \frac{\rho_c}{Q_c} \, n_c(\mathbf{X}, t) \ , \qquad Q_c = \int_{-\infty}^t q_c(t - \tau) \, \mathrm{d}\tau = \int_0^\infty q_c(\tau) \, \mathrm{d}\tau \ . \tag{39}$$

This term is chosen in such a way that the net collagen mass production in the healthy state is zero.

The 'extra' production term can be related to either the state of stress or stretch of the collagen. In [4, Eq. (16)], Baek et al. use a stress-induced growth-rate relation, while the same authors discuss in [5] three possible cases, the last of which is a stretch-induced growth-rate relation. In this study, we opt for the latter, and we take for this the specific relation

$$\dot{m}_c^e(\mathbf{X}, t) = K_g \left(\bar{\lambda}_c(\mathbf{X}, t) - \lambda_a \right), \tag{40}$$

where $\bar{\lambda}_c$ is a kind of averaged collagen stretch, averaged over the set of collagen fibres in the current state $G = \mathcal{G}(t)$, defined as

$$\bar{\lambda}_c(\mathbf{X}, t) - \lambda_a = \frac{1}{\pi n_c(\mathbf{X}, t)} \int_0^t \nu_c(\mathbf{X}, t, \tau) \int_{-\pi/2}^{\pi/2} \lambda_c(\mathbf{X}, t, \tau, \gamma) \, \mathrm{d}\gamma \, \mathrm{d}\tau \ . \tag{41}$$

We see that the constitutive equation contains the unknown collagen stretch λ_c, which is on its turn related to the unknown deformation gradient $\mathcal{F}$ according to (20). For the determination of $\mathcal{F}$, we need the momentum equation as we did derive it in Section 3. However, we will first discuss how the distribution of the collagen fibers over their different directions can be modeled.

Finally, we make the following choice for the collagen degradation function q_c:
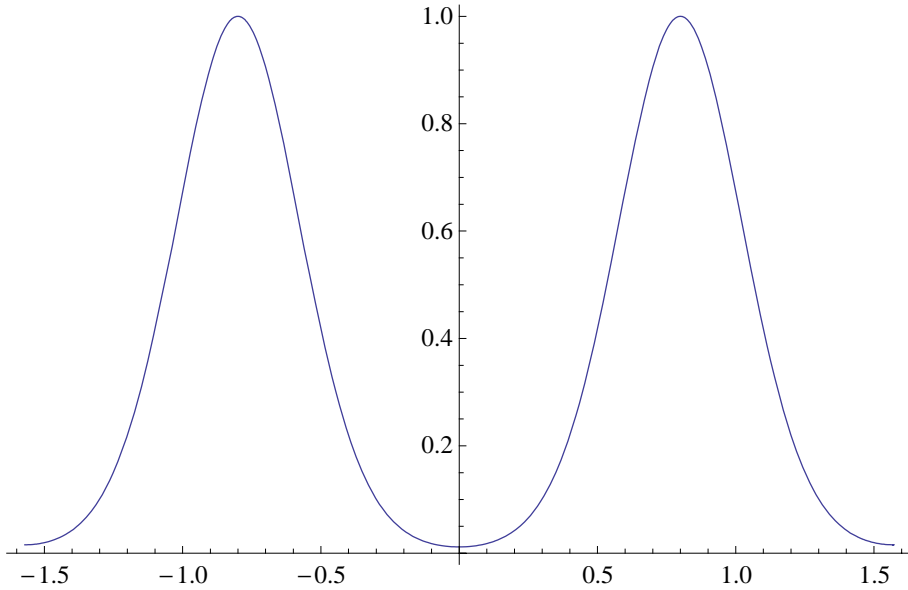
$$q_c(t) = e^{-t/T}, \tag{42}$$

Figure 2: Distribution function D as function of γ for $\mu = .8$ and $\sigma = .2$.

where T (in sec) is a time constant, which is characteristic for the rate of degradation of the collagen. We note that the time scale t_f for the elastin degradation is much larger than that of remodeling, so $T \ll t_f$.

For this choice, the coefficient Q_c becomes

$$Q_c = \int_0^\infty e^{-\tau/T} \, \mathrm{d}\tau = T. \tag{43}$$

6 Distribution of collagen fibers

At each intermediate time τ a new generation of collagen fibers is continuously created. These fibers are laid down in a plane spanned by the two unit vectors $\mathbf{v}_1$ and $\mathbf{v}_2$, being the principal directions of the deformation gradient $\mathcal{F} = \mathcal{F}(\mathbf{X}, \tau)$ (see 16), so, for $\lambda \in \mathbb{R}$,

$$\mathcal{F}\mathbf{v} = \lambda\mathbf{v}. \tag{44}$$

The direction of each individual fiber is given by the angle γ, being the angle between the fiber direction and the $\mathbf{v}_1$-axis. The distribution of these directions is assumed to be governed by a kind of double normal distribution $D(\mathbf{X}, \tau, \gamma)$ defined as

$$D(\mathbf{X}, \tau, \gamma) = \mathrm{e}^{-\frac{1}{\sigma}} \left[\exp\left(\frac{\cos[2(\gamma - \mu)]}{\sigma} \right) + \exp\left(\frac{\cos[2(\gamma + \mu)]}{\sigma} \right) \right] , \tag{45}$$

where $\pm\mu = \pm\mu(\mathbf{X}, \tau)$ are the mean fiber directions, and $\sigma = \sigma(\mathbf{X}, \tau)$ is the width of the distribution. The value of γ runs from $-\pi/2$ to $\pi/2$; $\gamma = 0$ corresponds with the $\mathbf{v}_1$-direction, and $\gamma = \pm\pi/2$ with the $\pm\mathbf{v}_2$-direction. A plot of a specific distribution function of the type (45) can be found in Figure 2. Let $N_c(\mathbf{X}, t, \tau, \gamma)\mathrm{d}\tau$ denote the volume fraction of collagen at time t that is created at time τ, from τ to $\tau + \mathrm{d}\tau$, having the direction γ and survived at t (hence, N_c is not so much the volume fraction, but rather the *rate of*). Then, clearly,

$$\nu_c(\mathbf{X}, t, \tau) = \int_{-\pi/2}^{\pi/2} N_c(\mathbf{X}, t, \tau, \gamma) \, \mathrm{d}\gamma . \tag{46}$$

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Since the distribution of N_c is governed by D, the latter relation implies that

$$N_c(\mathbf{X}, t, \tau, \gamma) = \bar{D}(\mathbf{X}, \tau, \gamma)\nu_c(\mathbf{X}, t, \tau) , \tag{47}$$

with

$$\bar{D}(\mathbf{X}, \tau, \gamma) = \frac{D(\mathbf{X}, \tau, \gamma)}{\int_{-\pi/2}^{\pi/2} D(\mathbf{X}, \tau, \gamma) \, \mathrm{d}\gamma} . \tag{48}$$

The mean μ and the width σ are related to the principal stretches of $\mathcal{F}(\mathbf{X}, \tau)$ in the state $\mathcal{G}(\tau)$. The largest principle stretch $\lambda_1 = \lambda_1(\mathbf{X}, \tau)$ corresponds to the first principle direction $\mathbf{v}_1 = \mathbf{v}_1(\mathbf{X}, \tau)$, and the second one λ_2 to $\mathbf{v}_2$; so $\lambda_1 \geq \lambda_2$. Moreover, since we only consider tissues that are principally stretched, we always have $\lambda_1 > 1$. Following Driessen [8, Sect. 8.2.2], we take

$$\mu(\mathbf{X}, \tau) = \arctan\left(\frac{g_2}{g_1}\right), \qquad \text{and} \quad \sigma(\mathbf{X}, \tau) = \frac{k}{g_1/g_2 - 1} , \tag{49}$$

where the so-called stimulus functions g_1 and g_2 are related to their corresponding principle stretches as

$$g_1(\mathbf{X}, \tau) = \lambda_1(\mathbf{X}, \tau) - 1, \qquad \text{and} \quad g_2 = \begin{cases} \lambda_2(\mathbf{X}, \tau) - 1, & \lambda_2 > 1, \\ 0, & \lambda_2 < 1. \end{cases} \tag{50}$$

The volume fraction due to distribution N_c, as given in (47), will turn up in the constitutive equation for the stress that will be given in the next section.

7 Momentum equation and stresses

Following Humphrey and Rajagopal, [2, p.421], and many others in this field, we assume that we may consider the mixture of elastin and collagen as a *constrained mixture* that is homogenized with regard to the stresses. This implies that we only need to satisfy the overall momentum law for the mixture as a whole, and not the two partial momentum laws for the components separately. As we have shown in Section 3, this relation keeps its classical form; see (11). In the following, we shall neglect inertia terms (the deformations we consider are extremely slow) and we exclude external body forces, by which the local momentum equation reduces to the simple equilibrium equation

$$\mathrm{div}\mathcal{T} = 0. \tag{51}$$

We now need a constitutive equation for the stress tensor $\mathcal{T}$. For the constrained mixture we consider here, we may adapt a *rule-of-mixture* relation for the stress, stating that the partial stresses due to elastin or collagen are proportional to their volumetric fractions n_e or n_c, respectively. Accordingly, we assume that the total stress in the tissue in the current configuration at time t is built up of elastin stress and collagen stress according to

$$\mathcal{T}(\mathbf{X}, t) = -p(\mathbf{X}, t)\mathcal{I} + \mathcal{T}_e(\mathbf{X}, t) + \mathcal{T}_c(\mathbf{X}, t) , \tag{52}$$

where p is a pressure term, needed to account for the incompressibility of the elastin and the collagen and $\mathcal{I}$ is the unit tensor. The elastin is modeled as an incompressible isotropic Neo-Hookean material with

$$\mathcal{T}_e(\mathbf{X}, t) = c_e(\mathcal{B}(\mathbf{X}, t) - \mathcal{I}) , \tag{53}$$

where c_e is the elastin shear modulus and $\mathcal{B} = \mathcal{F}\mathcal{F}^T$ is the left Cauchy-Green tensor.

For the collagen stress, we follow Oijen [9, Sect. 3.2.4]. The collagen fibers can only take up tensile stress in their fiber direction, and the nonlinear stress-strain behavior of the collagen fibers is captured by an exponential form for the fiber stress. This leads to the following formulation:

$$\mathcal{T}_c(\mathbf{X}, t) = \int_0^t \int_{-\pi/2}^{\pi/2} \left\{ N_c \left[\tau_f(\lambda_c) - \mathbf{e}_c \cdot \mathcal{T}_e \, \mathbf{e}_c \right] \mathbf{e}_c \otimes \mathbf{e}_c \right\} (\mathbf{X}, t, \tau, \gamma) \, \mathrm{d}\gamma \, \mathrm{d}\tau \ , \qquad (54)$$

where

$$\tau_f(\lambda_c) = 2k_1 \lambda_c^2 (\lambda_c^2 - 1) \exp \left[k_2 (\lambda_c^2 - 1)^2 \right] \ , \qquad (55)$$

with k_1 and k_2 material constants, while $\lambda_c = \lambda_c(\mathbf{X}, t, \tau, \gamma)$ is given by (20). For the $\mathcal{T}_e$ in the integral in (54) one must read $\mathcal{T}_e(\mathbf{X}, \tau)$.

In (52)-(54), the contribution of $n_e \mathcal{T}_e$ is split in $\mathcal{T}_e$ and $-n_c \mathcal{T}_e$, with the latter taken up in (54). However, in (54) this is only done in the fiber direction and not in the transverse direction. The reason for this is that the stress perpendicular to the fiber direction is uncoupled from the fiber fraction, which would mean that the transversal properties of the tissue are not affected by the fibers. This is not logic, because then the tissue would become unnaturally weak in transverse direction as then only the elastin would contribute to this stiffness. Oijen [9] compensated for this by taking in the transverse direction the full $\mathcal{T}_e$, and not the partial $n_e \mathcal{T}_e$. Mechanically, this means that he accounts to the collagen fibers a transverse stiffness that is equal to that of the elastin. The stress perpendicular to the fiber direction is uncoupled from the fiber fraction, meaning that the transversal properties of the tissue are not affected by the fibers.

8 One-dimensional example

We consider as a first example a 1-dimensional problem for a slender circular rod loaded by a fixed uniaxial tensile stress. Let $\mathbf{e}_3$ be the axial direction of the rod, then the axial normal stress $T_{33} = S$ is given, while all other stresses are zero, i.e. $T_{ij} = 0$, $(i, j) \neq (3, 3)$. All collagen fibers are in the $\mathbf{e}_3$-direction, so the distribution of the fibers does not play a role here.

In the unloaded state G_0 the tissue is unstretched, whereas in the healthy state the rod is loaded and stretched such that the collagen stretch $\lambda_{c,r}$ is equal to its attachment stretch λ_a. By the (not very relevant) assumption that $\lambda_{\mathrm{rec}} = 1$ in the healthy state, we see then that also the stretch of the tissue, and the elastin, in the $\mathbf{e}_3$-direction is equal to λ_a. Since there is no volumetric growth in the healthy state, $\det \mathcal{F}_0 = 1$ and thus the matrix of $\mathcal{F}_0$ is of the form (also accounting for rotational symmetry of the problem)

$$\mathcal{F}_0 = \begin{pmatrix} \lambda_a^{-1/2} & 0 & 0 \\ 0 & \lambda_a^{-1/2} & 0 \\ 0 & 0 & \lambda_a \end{pmatrix} . \qquad (56)$$

We consider next the current state $G = \mathcal{G}(t)$. This state is here a homogeneous state, so there is no dependence on $\mathbf{X}$ in this example. The total deformation gradient is $\mathcal{F}_{tot}(t) = \mathcal{F}(t)\mathcal{F}_0$, implying that the tissue stretch in the $\mathbf{e}_3$-direction is

$$\lambda(t) = ||\mathcal{F}_{tot}(t)\mathbf{e}_3|| = ||\mathcal{F}(t)\mathcal{F}_0\mathbf{e}_3|| = ||\mathcal{F}(t)\lambda_a\mathbf{e}_3|| = \lambda_a F_{33} \ . \qquad (57)$$

Due to the rotational symmetry: $F_{11} = F_{22}$, and thus the matrix of $\mathcal{F}(t)$ is

$$\mathcal{F}(t) = \begin{pmatrix} F_{11}(t) & 0 & 0 \\ 0 & F_{11}(t) & 0 \\ 0 & 0 & \lambda(t)/\lambda_a \end{pmatrix} . \tag{58}$$

Since $\det \mathcal{F}_0 = 1$, the Jacobian in G is equal to

$$J_g(t) = \det \mathcal{F}(t) = \frac{\lambda(t)}{\lambda_a} F_{11}^2(t) , \tag{59}$$

yielding

$$F_{11}(t) = \sqrt{\frac{\lambda_a}{\lambda(t)} J_g(t)} . \tag{60}$$

In the intermediate state $\mathcal{G}(\tau)$ we have

$$\hat{\mathcal{F}}(t,\tau) = \mathcal{F}(t)\mathcal{F}^{-1}(\tau) = \begin{pmatrix} F_{11}(t)/F_{11}(\tau) & 0 & 0 \\ 0 & F_{11}(t)/F_{11}(\tau) & 0 \\ 0 & 0 & \lambda(t)/\lambda(\tau) \end{pmatrix} . \tag{61}$$

Moreover, the collagen stretch of a fiber created at time τ is

$$\lambda_c(t,\tau) = \lambda_a \frac{\lambda(t)}{\lambda(\tau)} . \tag{62}$$

From (35), we obtain with $\dot{m}_e(t) = -\mu_e$ and $\dot{m}_c(t) = \dot{m}_c^h(t) + \dot{m}_c^e(t)$, where $\dot{m}_c^h(t) = \rho_c n_c(t)/T$, and $\dot{m}_c^e(t) = K_g(\bar{\lambda}_c(t) - \lambda_a)$, the ordinary differential equation for $J_g(t)$:

$$\begin{aligned} \dot{J}_g(t) &= -\frac{\mu_e}{\rho_e} J_g(t) + \frac{1}{T} J_g(t) n_c(t) + \frac{K_g}{\rho_c} (\bar{\lambda}_c(t) - \lambda_a) J_g(t) - \frac{1}{T} J_g(t) n_c(t) \\ &= \left[-\frac{\mu_e}{\rho_e} + \frac{K_g}{\rho_c} (\bar{\lambda}_c(t) - \lambda_a) \right] J_g(t) . \end{aligned} \tag{63}$$

For this 1-dimensional problem, $\bar{\lambda}_c$ follows from (41) as

$$\bar{\lambda}_c(t) - \lambda_a = \frac{1}{n_c(t)} \int_0^t \nu_c(t,\tau)\lambda_c(t,\tau) \, \mathrm{d}\tau , \tag{64}$$

where, according to (28)

$$\nu_c(t,\tau) = \frac{J_g(\tau)}{\rho_c J_g(t)} \left[\frac{\rho_c}{T} n_c(\tau) + K_g(\bar{\lambda}_c(\tau) - \lambda_a) \right] e^{-(t-\tau)/T} . \tag{65}$$

Substituting (65) and (62) into (64), we obtain the following integral equation for $\bar{\lambda}_c(t)$:

$$\bar{\lambda}_c(t) - \lambda_a = \frac{\lambda_a \lambda(t)}{\rho_c J_g(t) n_c(t)} \int_0^t \left[\frac{\rho_c}{T} n_c(\tau) + K_g(\bar{\lambda}_c(\tau) - \lambda_a) \right] \frac{J_g(\tau)}{\lambda(\tau)} e^{-(t-\tau)/T} \, \mathrm{d}\tau . \tag{66}$$

Further, we find from (36)

$$n_c(t) = n_{c,r} + \frac{1}{\rho_c J_g(t)} \int_0^t \left[\frac{\rho_c}{T} n_c(\tau) + K_g(\bar{\lambda}_c(\tau) - \lambda_a) \right] J_g(\tau) e^{-(t-\tau)/T} \, \mathrm{d}\tau . \tag{67}$$

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At this point, we have with (63), (66) and (67) three equations for the four unknowns $\dot{J}_g(t)$, $\bar{\lambda}_c(t)$, $n_c(t)$ and $\lambda(t)$. The missing equation for $\lambda(t)$ will follow from the equations for the stresses. Since we have here a homogeneous stress situation, the equilibrium equations are trivially satisfied. The pressure p will follow from the condition that $T_{11} = T_{22} = 0$, while the remaining equation $T_{33} = S$ will yield the equation for $\lambda(t)$ we are looking for.

The stresses T_{11} and T_{22} do not contain a collagen part, and they are give by

$$T_{11} = T_{22} = -p(t) + c_e(F_{11}^2(t) - 1) = -p(t) + c_e \left(\frac{\lambda_a}{\lambda(t)} \, J_g(t) - 1 \right), \tag{68}$$

Hence, $T_{11} = T_{22} = 0$ yields

$$p(t) = c_e \left(\frac{\lambda_a}{\lambda(t)} \, J_g(t) - 1 \right). \tag{69}$$

Next, T_{33} follows from (52)-(54) as

$$
\begin{aligned}
T_{33}(t) &= -p(t) + c_e(F_{33}^2(t) - 1) + \int_0^t \nu_c(t,\tau) \, [\tau_f(\lambda_c) - T_{e,33}] \, (t,\tau) \, \mathrm{d}\tau \\
&= c_e \left[\frac{\lambda^2(t)}{\lambda_a^2} - \frac{\lambda_a}{\lambda(t)} \, J_g(t) \right] + \int_0^t \nu_c(t,\tau) \, [\tau_f(\lambda_c(t,\tau)) - \tau_e(\tau)] \, \mathrm{d}\tau ,
\end{aligned}
\tag{70}
$$

with ν_c as given by (65), $\tau_f(\lambda_c)$ by (55) and λ_c by (62), while τ_e stands for

$$\tau_e(\tau) = T_{e,33}(t) = c_e \left(\frac{\lambda^2(\tau)}{\lambda_a^2} - 1 \right). \tag{71}$$

The still missing equation for $\lambda(t)$ is the simple one

$$T_{33}(t) = S. \tag{72}$$

Hence, we now have three equations for our three fundamental unknowns: $J_g(t)$, $n_c(t)$ and $\lambda(t)$; the auxiliary variables $\nu_c(t,\tau), \lambda_c(t,\tau)$ and $\bar{\lambda}_c(t)$ are determined by (65), (62), and (66), respectively.

However, even for this most simple example this set of equations is already very complex and can not be solved analytically. Therefore, this set, having only one independent variable: the time t, must be solved by numerical integration. At this stage, we refrain from doing this; it remains an option for further research.

9 Discussion and perspectives

In this paper, we have constructed a model for remodeling and volumetric growth in an arterial tissue, considered as a constrained mixture of elastin and collagen, based on a continuum-mechanics approach. This in contrast to several other approaches, e.g. [1], [8], who built their models in a more discrete way, both in time and place, directly aiming at a finite element implementation. As far as we could compare the present continuous model with the discrete model developed by Machyshyn, [1], we found complete correspondence.

We established here a complete system for the four essential unknowns in a problem for a loaded tissue: the volumetric fraction of collagen, the Jacobian of the deformation (characteristic for the volumetric growth), the stretch of the collagen fibers, and the stretch

of the tissue. The derivation is based on the classical balance laws of mass and momentum. Our model incorporates mass production, volumetric growth, degradation of elastin, strain-induced preferred fiber orientation and collagen creation, isotropic nonlinear (Neo-Hookean) elastic behavior of elastin, and anisotropic (fibrous) nonlinear (exponential) elastic behavior of collagen.

In this paper, we gave the general derivation of the continuous model, but we only applied it to a simple one-dimensional example, and we did not perform explicit numerical calculations. The latter, together with a treatment of more complex examples, was beyond the scope of this article. In near future, we hope to apply this model to more complex (tube-like) structures, and to do the necessary numerical calculations, ultimately amounting in an adequate model for the growth of aneurysms in cerebral blood vessels.

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