A structural multi-mechanism constitutive equation for cerebral arterial tissue

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1. Introduction

The long range objective of this research is to develop a constitutive model for cerebral arteries which can model changes in the mechanical properties due to the degradation/damage of elastin, one of the central load bearing components of the arterial wall. Constitutive equations of this type are important for biomechanical studies of clinical treatments such as balloon angioplasty which may result in mechanical loading to the point of elastin failure and diseases such as intracranial aneurysm (ICA) formation, which are believed to involve large scale elastin degradation as well as tissue remodeling. In this work, we introduce a structural multi-mechanism model which can describe the nonlinear, anisotropic, inelastic behavior of cerebral arteries.

In an earlier work, Wulandana and Robertson (2005) developed a dual-mechanism, inelastic constitutive equation for the initiation and early development stages of ICA formation. The collagen mechanism in Wulandana and Robertson (1972), the collagen mechanism in Wulandana and Robertson (2005) was chosen to be isotropic. The current study, generalizes this work by including the fibrous nature of the collagen mechanism, leading to an anisotropic model for the arterial wall. Lanir appears to be one of the first to take a structural approach in modeling the anisotropy arising from fiber distribution in connective tissues. Here, the anisotropic material response is increased the number of fiber families, they introduced an orientation density function to represent collagen fiber distribution with collagen recruitment and elastin failure are included as discrete events, initiated when kinematic based criteria are met. Using this approach, the failure/degradation of elastin can be modeled separately from the overall material failure. To our knowledge, this work is the first to model early stage aneurysm formation including these two important characteristics. In the interest of simplicity, and because only uniaxial data were reported in Spencer et al. (1972), the collagen mechanism in Wulandana and Robertson (2005) was chosen to be isotropic. The current study, generalizes this work by including the fibrous nature of the collagen mechanism, leading to an anisotropic model for the arterial wall.

Lanir appears to be one of the first to take a structural approach in modeling the anisotropy arising from fiber distribution in connective tissues (Lanir, 1983; Lanir et al., 1996). In his model, the total strain energy is the sum of strain energies from individual fibers. Fiber orientation is prescribed using statistical distributions obtained from experimental data. Building on Lanir's earlier work as well as that of Spencer (1984, 1992), Holzapfel et al. (2000) introduced a fiber-reinforced structural model for arteries with families of discrete collagen fibers symmetrically arranged with respect to the vessel axis. Gasser et al. (2006) generalized this approach to include the disperse nature of collagen fiber orientations in the adventitial and intimal layers of the wall. Rather than increasing the number of fiber families, they introduced an orientation density function to represent collagen fiber distribution with...
In the current work, an anisotropic, structural, multi-mechanism constitutive model is developed to describe the passive mechanical behavior of cerebral arteries. The orientation of collagen has been found to be nearly circumferential in the media layer and more dispersed in the intima and adventitia layers (Finlay et al., 1995). We model the material anisotropy arising from the collagen fiber orientation using the approach of Lanir (1983), Spencer (1984, 1992), Holzapfel et al. (2000), Gasser et al. (2006). The collagen mechanism is modeled as both (i) a finite number of fiber families and (ii) a distribution of fiber families. A new parameter for collagen recruitment based on local collagen stretch is used. Published inelastic pressure inflation data (Scott et al., 1972) are used to select specific forms for the strain energy functions.

2. Anisotropic multi-mechanism model

2.1. Qualitative features of the multi-mechanism model in cylindrical inflation

To clarify the qualitative features of the anisotropic multi-mechanism model, we first consider quasi-static inflation of an idealized homogeneous, cylindrical arterial segment. It is composed of an isotropic mechanism (grey background) largely controlled by the response of elastin and the surrounding matrix as well as an anisotropic mechanism arising from a helical network of crimped collagen fibers (black curves) (Fig. 1). We will refer to these mechanisms as the elastin and collagen mechanisms, though it should be understood that other structural components may contribute to the passive mechanical behavior. The deformation is divided into seven possible stages in order to emphasize the changing roles of the two mechanisms.

Stage A denotes the stress-free configuration \( \kappa_0 \) (unloaded). By way of illustration, one pair of helically wound fibers for which \( g_{1,0} \) and \( g_{2,0} \) make an angle \( \beta_1 = \beta, \beta_2 = -\beta \) with respect to \( \varphi \) are considered (Fig. 1). The mean fiber angle of family \( i \) of helical fibers is identified by a unit vector \( \hat{g}_{i,0} \) in \( \kappa_0 \) for \( i = 1, 2 \).

During Stage B, the deformation is sufficiently small that collagen fibers show diminishing waviness and change their orientation without contributing significantly to load bearing. The elastin mechanism is responsible for all load bearing, corresponding to the toe region in a typical stress/stretch curve (Busby and Burton, 1965). The symmetry of unloaded fiber orientation and symmetric form of the deformation are such that the two families of fibers undergo the same fiber stretch \( \lambda_f \). The subscript \( f \) is used to emphasize that, in general, the fiber and circumferential stretch are different.

At Stage C, a critical level of \( \lambda_f \) is reached, denoted as \( \lambda_{f,c} \) when the waviness has diminished to the point that under further stretch, the fibers will bear load. Hence, \( \lambda_{f,c} \) reflects the degree of waviness of the collagen fibers in the unloaded material. The subscript \( a \) is used to emphasize the activation of the collagen mechanism in this configuration.

Upon further loading, Stage D, both the collagen and elastin mechanisms contribute to load bearing. The contribution of the elastin mechanism continues to depend on the deformation relative to \( \kappa_0 \), while the stress within the collagen fibers is a function of the fiber stretch relative to stretch \( \lambda_{f,c} \). The addition of the stiffer collagen fibers leads to the steep increase in stiffness in the stress/stretch curve in Stage D, ending the shallow toe region of Stage B (Busby and Burton, 1965; Hoffman et al., 1977; Samila and Carter, 1981).

Upon further loading, Stage E, a critical membrane stretch is reached where the elastin mechanism ceases to contribute to load bearing. In a purely mechanical theory, this disruption is entirely due to an increase in mechanical loading and the criterion for disruption is purely a function of a kinematic measure of the deformation. In some cerebral arteries, for example during early stages of aneurysm formation, this critical level of stretch may be reached under fixed pressure due to a degradation of the IEL arising from a combination of factors such as fatigue, extended periods of exposure to elevated hemodynamic loading such as wall shear stress and wall shear stress gradient, damage due to environment factors, and aging (Busby and Burton, 1965; Samila and Carter, 1981). In clinical treatments such as angioplasty, disruption of the IEL may arise from purely mechanical loading (Zollikofer et al., 1984).

Upon further loading (or unloading), Stage F, only collagen will contribute to load bearing. Unloading during this stage will return the fibers to stretch \( \lambda_{f,c} \) with an increased unloaded radius, relative to the original material. If the arterial segment without a functioning elastin mechanism is considered as a second material, it will appear stiffer than the original artery, and will not display a toe region. This behavior is consistent with mechanical data from Scott et al. (1972) and Roach and Burton (1957).

We expect an additional stage, Stage G, will be associated with partial collagen disruption and potentially the generation of new collagen in an altered reference configuration as part of a longer time scale process, involving growth and remodeling (Humphrey, 2002). We do not address Stage G in this work.

2.2. Mechanical response of elastin and surrounding matrix

The mechanical response of the isotropic mechanism is identical to that in Wulandana and Robertson (2005) and will only briefly be discussed here. Following classical continuum mechanics, a section of artery will be represented by a three-dimensional body \( \mathcal{B} \) which initially, say at time \( t = t_1 \), is stress free and occupies an undeformed reference configuration \( \kappa_0 \). An arbitrary material particle, labeled in the body \( \mathcal{B} \) will be identified by vector position \( \mathbf{x}_0 \) in configuration \( \kappa_0 \) (Fig. 2). The motion of the material particle is given by \( \mathbf{x} = \mathbf{X}_0(\mathbf{X}_0, t) \) with corresponding deformation gradient tensor \( F_0 = \partial \mathbf{X}_0 / \partial \mathbf{x}_0 \). The associated left and right Cauchy Green tensors are, \( \mathbf{B}_0 = F_0 F_0^T \) and \( \mathbf{C}_0 = F_0^T F_0 \). The isotropic mechanism is assumed to behave as an incompressible, hyperelastic material with strain energy function per unit volume in reference configuration \( \kappa_0 \) defined as \( \psi_0 = \psi_0(\mathbf{F}_0) \). Based on invariance requirements and assuming the elastin mechanism is isotropic with respect to configuration \( \kappa_0 \) and incompressible, \( \psi_0 \) can be written simply as a function of the first and second invariants of \( \mathbf{F}_0 \).
\[ \psi_0 = \psi_0(I_0, I_0), \quad \text{where} \quad I_0 = \text{tr}C_0, \quad I_0 = \frac{1}{2} \left[ (\text{tr}C_0)^2 - \text{tr}C_0^2 \right]. \quad (1) \]

We assume the response of the isotropic mechanism \( \psi_0 \) is dominated by the influence of \( I_0 \) so that \( \psi_0 = \psi_0(I_0) \).

### 2.2.1. Deactivation criterion for elastin

To quantify the disruption of the first mechanism, a measure of deformation level is introduced through the deformation state parameter, \( s_0 \). For the isotropic mechanism, we assume \( s_0 \) like the strain energy function, depends only on \( I_0 \) and furthermore, it is a monotonically increasing function. Without loss in generality, we choose a linear function, \( s_0 = I_0 - 3 \), normalized so that \( s_0 \) is zero in \( K_0 \). The criterion for deactivation of the first mechanism is \( s_0 = s_{00} \) where \( s_{00} \) is a material constant. Once \( s_0 \geq s_{00} \) for some deformation, elastin no longer contributes to load bearing in all further deformations, even when \( s_{00} \) is below \( s_{00} \).

Remark. In earlier studies, activation and deactivation criteria were introduced separately from the deformation state parameter, e.g., Wulandana and Robertson (2005) and Wineman and Huntley (1994). These material functions were defined as independent of the particular choice of deformation state parameter and subsequently used to determine critical values of this parameter. For simplicity, here we directly consider the critical values of the deformation state parameters such as \( s_{00} \).

### 2.3. Mechanical response of the multi-mechanism material with a collagen mechanism composed of N fiber families

In this section, the collagen mechanism is modeled as consisting of \( N \) fiber families each with a different orientation. This approach builds on the classical continuum theory for fiber reinforced composites (see, e.g. Spencer (1984, 1992)) which was applied to arteries by Holzapfel et al. (e.g. Holzapfel et al., 2000; Holzapfel, 2000, Section 6.7) and others. While in these works, a single zero stress state reference configuration was employed for all material constituents, here we introduce additional reference configurations \( K_i \) for each of the \( N \) fibers as well as associated activation criteria. This additional constitutive structure makes it possible to capture the collagen recruitment and the change in unloaded configuration when the first mechanism is disrupted.

#### 2.3.1. Kinematics for \( N \) collagen fiber families

The direction of an arbitrary family \( i \) in \( K_0 \) is characterized by a unit vector \( \bar{g}_{i,0} \) which makes an angle \( \beta_i \) relative to a reference direction in \( K_0 \). Fig. 1. The first subscript on \( g \) is the fiber number and the second is the configuration in which the vector is defined. The fibers are assumed to move affinely with the underlying material during the deformation so that an infinitesimal material element of fiber \( i \), denoted as \( dS_{i,0} = dS_0 \bar{g}_{i,0} \) at point \( X_0 \) in configuration \( K_0 \), will be mapped to \( dx = E_{i} \cdot dS_0 \bar{g}_{i,0} \) at \( x \) in configuration \( K(t) \) (Fig. 2). The stretch of this infinitesimal fiber material element relative to its length in \( K_0 \) is therefore,

\[ s_{i,0} = ds^2/dS^2 = \bar{C}_0 : \bar{g}_{i,0} \otimes \bar{g}_{i,0}, \quad (2) \]

where \( ds = \|dx\| \). In the qualitative discussion in Section 2.1, the critical stretch \( \lambda_{i,0} \) was fiber independent. More generally, \( \lambda_{i,0} \) will be fiber dependent and we will denote the critical stretch for activation of fiber \( i \) as \( \lambda_{i,0} \) and the corresponding configuration as \( K_{i0} \).

The mechanical response of collagen fiber \( i \) will depend on the stretch beyond the uncrimped stretch \( \lambda_{i,0} \) and we therefore turn attention to kinematic quantities defined relative to \( K_{i0} \). The motion of a material particle in configuration \( K(t) \), which has position \( X \) in configuration \( K_0 \) is \( X = \sum_{i=1}^{N} \lambda_{i,0} X_{i}(t) \) and the corresponding deformation gradient tensor relative to \( K_{i0} \) is \( \partial_{X_{i0}}(X_{i}, t) / \partial X \); for \( i = 1, 2, 3, \ldots, N \). The associated left and right Cauchy Green tensors are,

\[ B_i = F_i \cdot F_i^T, \quad C_i = F_i \cdot F_i^T, \quad i = 1, 2, 3, \ldots, N. \quad (3) \]

We can relate the kinematic variables defined relative to \( K_0 \) and \( K_{i0} \) through,

\[ E_i = E_{i0} \cdot F_{i0}^{-1} = E_{i0}^{-1} \cdot E_{i0}, \quad C_i = C_{i0} \cdot F_{i0}^{-1}, \quad i = 1, 2, 3, \ldots, N. \quad (4) \]

Therefore, an infinitesimal fiber aligned with \( dS_0 = dS_{i0} \) in \( K_{i0} \) is mapped to \( d\bar{X} = dS \bar{g}_{i} \) in \( K_{i0} \) where \( \bar{g}_{i} \) is a unit vector (Fig. 2). The corresponding stretches for the infinitesimal material fibers are,

\[ \lambda_{i,0} = ds/dS_0, \quad \lambda_{i,1} = ds/dS_0^2 = \bar{C}_0 : \bar{g}_{i} \otimes \bar{g}_{i}. \quad (5) \]

Recalling \( \bar{C}_0 : \bar{g}_{i} \otimes \bar{g}_{i} \) is a member of the integrity basis for symmetric tensors \( \bar{C}_0 \) and \( \bar{g}_{i} \otimes \bar{g}_{i} \), we introduce the following notation,

\[ IV_{i0} = \bar{C}_0 : \bar{g}_{i} \otimes \bar{g}_{i}, \quad IV_{i0} = IV_{i0}^{i=0}, \quad IV_{i1} = \bar{C}_0 : \bar{g}_{i} \otimes \bar{g}_{i}, \quad \text{so that from (2)}, \quad (5) \text{and (6),} \]

\[ IV_{i0} = \lambda_{i,0}^2, \quad IV_{i1} = \lambda_{i,1}^2. \quad (7) \]

#### 2.3.2. Activation criterion for N fiber model

It remains to define a constitutive response function to identify the configuration \( K_{i0} \). In Wulandana and Robertson (2005), both the elastin and collagen mechanisms were modeled as isotropic and the deactivation/activation criterion were both functions of \( I_0 \). Here, the fibrous nature of the collagen mechanism is considered and the fiber stretch \( \lambda_{i,0} \) defined in (2) is employed as a measure of the level of uncrimping of collagen fiber \( i \) from the state in \( K_0 \). The deformation state parameter for collagen is defined as a monotonically increasing scalar function of the square of the fiber stretch: \( s_i = \bar{s}_i(\lambda_{i,0}) = \bar{s}_i(IV_{i0}) \). Without loss in generality, we choose a monotonically increasing linear function,

\[ s_i = IV_{i0} - 1 = \lambda_{i,0}^2 - 1, \quad (8) \]

which is normalized so \( s_i \) is zero in \( K_0 \).

Fiber \( i \) will be considered uncrimped when \( s_i \) reaches a critical value, \( s_i = s_{00} \), so that from (7) and (8),

\[ s_{00} = IV_{i0} - 1 = \lambda_{i,0}^2 - 1. \quad (9) \]

#### 2.3.3. Form of the strain energy function for the N fiber model

We assume the collagen mechanism can be modeled as the collective response of \( N \) fiber families, each of which behaves as a hyperelastic, transversely isotropic material. Here, we assume the strain energy function of fiber family \( i \) depends on a measure of strain or stretch of the bulk material as well as the fiber directions in the reference configuration, \( K_i \) which we denote as \( \bar{g}_{i} \).
\[ \psi_{\text{anso}} = \sum_{i=1}^{N} \psi_i(C_i, g_{ij} \otimes g_{ij}). \]  

(10)

Since the material response should not depend on the sign of \( g_{ij} \), the dependence of \( \psi_i \) on \( g_{ij} \) has been assumed to be even. We now assume the only anisotropy in the material is due to families of helically oriented fibers and therefore require,

\[ \psi_i(C_i, g_{ij} \otimes g_{ij}) = \psi_i(Q \cdot C_i \cdot Q^T, g_{ij} \otimes g_{ij} \cdot Q^T), \]

for all proper orthogonal \( Q \). Therefore, without loss in generality, the strain energy for fiber \( i \) can be written with respect to its integrity basis for \( (C_i, g_{ij} \otimes g_{ij}) \) (Spencer, 1984). For lack of extensive data for the anisotropic behavior of cerebral arteries, we reduce the dependence of \( \psi_i \) on these invariants to the simplest form that is consistent with the expected mechanism of collagen load bearing for incompressible materials. In particular, we assume the response of the collagen fibers is dominated by \( \lambda_{ij} \), the stretch of individual collagen fibers relative to \( \lambda_{ij} \), so that \( \psi_i = \psi_i(|V_{ij}|) \). The combined response of all \( N \) fibers is then,

\[ \psi_{\text{anso}} = \sum_{i=1}^{N} \psi_i(|V_{ij}|). \]  

(12)

In writing (12), we have implicitly assumed the response of the fiber families are decoupled. Fiber coupling for the case of two fiber families is considered, for example in Spencer (1984).

2.3.4. Total constitutive response for a structural, multi-mechanism model with a collagen mechanism composed of \( N \) fiber families

Combining the responses of the isotropic and anisotropic mechanisms, we obtain the total strain energy function for the \( N \) fiber multi-mechanism material,

\[ \psi = (1 - d_0)\psi_0(|l_0|a) + \sum_{i=1}^{N} (1 - d_i)\psi_i(|V_{ij}|) \]

(13)

\[ d_0 = \begin{cases} 0 & s_0 < s_{a0}, \\ 1 & s_0 \geq s_{a0}, \end{cases} \quad d_i = \begin{cases} 1 & s_i < s_{ai}, \\ 0 & s_i \geq s_{ai}, \end{cases} \quad i \in [1,N] \]

(14)

where \( s_0 = l_0 - 3, s_i = |V_{ij}| - 1 \) and \( d_0 \) and \( d_i \) are weighting functions for elastin deactivation and collagen activation, respectively. Once the elastin mechanism has been deactivated, it cannot be activated again. This condition is implemented by requiring that once \( d_0 \) has been set to one for a material point, it will remain one at that point for all further deformations.

The Cauchy stress tensor corresponding to (13) is

\[ \mathbf{T} = -p \mathbf{I} + 2(1 - d_0)\frac{\partial \psi_0}{\partial \mathbf{b}} \mathbf{b} + \sum_{i=1}^{N} (1 - d_i) \left[ 2\frac{\partial \psi_i}{\partial |V_{ij}|} |E_i \cdot g_{ij} \otimes E_i \cdot g_{ij}| \right], \]

(15)

where \( p \) is the Lagrange multiplier arising from incompressibility.

2.4. Mechanical response of multi-mechanism material with distribution model for collagen fibers

2.4.1. Distribution model for collagen fibers

Following Gasser et al. (2006), rather than considering the collagen contribution as being composed of \( N \) fiber families, we consider the collective response of the fibers using a dispersion function for collagen orientation. An orientation density function \( \rho(M)\) characterizes the three-dimensional distribution of fiber angles in \( \kappa_0 \) with respect to a reference orientation \( \mathbf{M}_r \). Fig. 3. In the most general case, \( \mathbf{M}_r \) is an arbitrary unit vector defined using Euler angles \( \Theta \in [0,\pi] \) and \( \Phi \in [0,2\pi] \). The density function is non-negative and defined such that \( \rho(M(\Theta, \Phi)) d\Theta d\Phi \) represents the normalized number of fibers with orientations in the range \( ([\Theta, \Theta + d\Theta], [\Phi, \Phi + d\Phi]) \), where \( d\Theta = \sin \Theta d\Theta d\Phi \). Furthermore, \( \rho \) is symmetric with respect to \( \mathbf{M} \) and normalized through

\[ \rho(M) = \rho(-M) \quad \text{and} \quad \frac{1}{4\pi} \int_{\Theta,\Phi} \rho(M(\Theta, \Phi)) d\Theta d\Phi = 1. \]

(16)

If the fibers have rotational symmetry about some mean referential direction, with unit tangent vector \( \hat{\mathbf{b}}_0 \), \( ^1 \) it is convenient to assume fiber orientation can be captured using a symmetric structure tensor \( \mathbf{H} \).

\[ \mathbf{H} = K_1 \left[ 1 + (1 - 3k)\hat{\mathbf{b}}_0 \otimes \hat{\mathbf{b}}_0 \right], \quad k = \frac{1}{4\pi} \int_{\Theta,\Phi} \rho(\Theta) \sin^2 \Theta d\Theta d\Phi. \]

(17)

Choosing local Cartesian coordinates, such that \( \hat{\mathbf{b}}_0 \) is equal to \( \mathbf{e}_3 \), Fig. 3, it follows that \( \rho \) is independent of \( \Phi \) and \( \mathbf{H} \) takes the simple form,

\[ \mathbf{H} = K_1 \left[ 1 + (1 - 3k)\hat{\mathbf{b}}_0 \otimes \hat{\mathbf{b}}_0 \right], \quad k = \frac{1}{4\pi} \int_{\Theta} \rho(\Theta) \sin^2 \Theta d\Theta. \]

(18)

The dispersion parameter \( k \) represents the fiber distribution in an integral sense and can either be determined directly from experimental data, or if sufficient structural information is known, calculated from (18). If the first approach is taken, it is desirable to know what range of \( k \) are allowable. It can be shown (see Appendix A), that if both (16) and (18) are satisfied then \( k \in (0, 1/2) \).²

When there is an isotropic distribution of collagen fibers, \( \rho \) equals one, so \( k = 1/3 \) and the structure tensor \( \mathbf{H} \) is proportional to the identity tensor. Furthermore, if \( \rho \) is chosen to be proportional to a Dirac delta function, namely, \( \rho = K\delta(\Theta_0) \) where \( K \) is a constant and \( \delta(\Theta_0) \) is the Dirac delta function then for \( \Theta_0 \in (0,\pi), k = 1/2 \sin^2 \Theta_0 \).

Here, we consider arteries in which each layer contains two families of distributed collagen fibers with rotational symmetry about mean direction \( \hat{\mathbf{b}}_{0a} \) in \( \kappa_0(\alpha = 1, 2) \). The structure tensor for the \( \alpha \)th family of fibers relative to its orientation in \( \kappa_0 \) is defined as in (18) and will be denoted as \( \mathbf{H}_{\alpha} \).

\[ \mathbf{H}_{\alpha} = K_1 \left[ 1 + (1 - 3k)\hat{\mathbf{b}}_{0a} \otimes \hat{\mathbf{b}}_{0a} \right]. \]

(19)

For simplicity, both fiber families have the same dispersion parameter, \( k \).

2.4.2. Activation criterion for dispersed collagen fibers

While in Gasser et al. (2006), a single reference configuration was used for all components of the arterial wall. Here, the recruitment of the \( \alpha \)th family of crimped collagen fibers with representative orientation \( \hat{\mathbf{b}}_{0a} \) in \( \kappa_0 \) initiates in a configuration denoted as \( \kappa_{\alpha0} \).

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¹ In the remainder of this work, the over line notation is used to distinguish variables for the distribution model from those for the \( N \) fiber model.
² In Gasser et al. (2006), by way of example, a transversely isotropic and \( \pi \)-periodic von Mises distribution function is considered. For that choice, the maximum value of \( k \) was shown to be \( 1/3 \).
By way of example, we consider two distribution families 
\((\alpha = 1, 2)\).

To identify \(k_{sa}\) and define the constitutive framework for the 
commencement of load bearing, we introduce a metric of deformation 
for each of the fiber families, denoted as, \(s_a\). For the case of \(N\) 
discrete fibers in Section 2.3, this metric was assumed to depend 
on the strain of the specific fiber family under consideration. For 
a dispersed family of fibers, this identification is less clear. We 
assume \(s_a\) is a function of the following scalar measure of strain of 
the \(a\)th family of fibers relative to \(k_0\)
\[
\hat{s}_a = \hat{s}_a(E_{2,0}) \text{ where } E_{2,0} = H_{2,0} : C_0 - 1. \tag{20}
\]

This is the Green–Lagrange-like strain previously used in Gasser et al. (2006) to characterize the strain in the mean direction of a 
fiber family. Using (19), it is clear that for materials with transverse 
isotropy, \(E_{2,0}\) simplifies to
\[
E_{2,0} = k\theta + (1 - 3k)\mathbf{I} \text{ with } \mathbf{I} = C_0 : \mathbf{a}_{0}^{\otimes} \mathbf{a}_{0}^{\otimes}. \tag{21}
\]

for \(\alpha = 1, 2\) with \(\theta\) defined in (1). Without loss in generality, we set 
\(\hat{s}_a(E_{2,0})\) equal to \(E_{2,0}\).
\[
\hat{s}_a(E_{2,0}) = E_{2,0} = k\theta + (1 - 3k)\mathbf{I} \quad \alpha = 1, 2. \tag{22}
\]

We then introduce a material parameter, \(s_{sa}\), such that the \(a\)th fiber 
family will be activated when \(s_a\) reaches the critical value \(s_{sa}\). The 
corresponding configuration is denoted as \(k_{sa}\). In writing (22), we 
assume the fibers in each family are activated simultaneously. We 
can relax this assumption by introducing a gradual recruitment function.

### 2.4.3. Form of the strain energy function for the dispersed collagen fibers

We assume the strain energy function for the collagen mechanism 
depends on the dispersed fiber orientation and the right Cauchy 
Green tensor \(C_{0} = F_{0}^\top \cdot F_{0}\), where \(F_{0}\) is the deformation gradient 
defined relative to \(\mathbf{a}_{0}\). Namely,
\[
\hat{\psi}_a = \hat{\psi}_a(C_{0}, H_{2,0}), \quad \text{with } H_{2,0} = k\theta + (1 - 3k)\mathbf{a}_{0}^{\otimes} \mathbf{a}_{0}^{\otimes}. \tag{23}
\]

where \(\mathbf{a}_{0}\) is the unit vector tangent to \(F_{0} \cdot \mathbf{a}_{0}^{\otimes}\). Following arguments similar to those for the \(N\) fiber family, we reduce this dependence to
\[
\hat{\psi}_a = \hat{\psi}_a(I_a, \mathbf{I}_{2x2}), \quad I_a = \text{tr}C_{0}, \quad \mathbf{I}_{2x2} = C_{0} : \mathbf{a}_{sa}^{\otimes} \mathbf{a}_{sa}^{\otimes}. \tag{24}
\]

In what follows, we assume the dependence on \(I_a\) and \(\mathbf{I}_{2x2}\) is such 
that,
\[
\hat{\psi}_a = \hat{\psi}_a(I_a, \mathbf{I}_{2x2}), \quad \text{where } E_{2,0} = k\theta + (1 - 3k)\mathbf{I}_{2x2} - 1. \tag{25}
\]

### 2.4.4. Total constitutive response for multi-mechanism model with 
distributed collagen fibers

The strain energy function for an arterial layer at arbitrary time 
and material point can then be expressed by,
\[
\hat{\psi} = (1 - \bar{d}_a)\hat{\psi}_a(I_0) + \sum_{a=1}^{2}(1 - \bar{d}_a)\hat{\psi}_a(E_{2,0}). \tag{26}
\]

with corresponding Cauchy stress tensor
\[
\mathbf{T} = -pI + 2(1 - \bar{d}_a)\frac{\partial \hat{\psi}_a}{\partial \mathbf{I}} \mathbf{B_0} + 
\sum_{a=1}^{2}(1 - \bar{d}_a)\frac{\partial \hat{\psi}_a}{\partial \mathbf{I}_{2x2}} \left[ k\mathbf{B_0} + (1 - 3k)\mathbf{F}_0 \cdot \mathbf{a}_{sa}^{\otimes} \otimes \mathbf{F}_0 \cdot \mathbf{a}_{sa}^{\otimes} \right]. \tag{27}
\]

where \(d_a\) are weighting functions,
\[
d_a = \begin{cases} 
1 & \hat{s}_a < s_{sa} \\
0 & \hat{s}_a \geq s_{sa} \end{cases} \quad \alpha = (1, 2). \tag{28}
\]

with \(s_{sa} = E_{2,0}\) and \(p\) is a Lagrange multiplier arising from the constraint 
of incompressibility. We have assumed the response of the 
two families of dispersed fibers are decoupled.

In (26) and (27), we used the same weighting function \(d_a\) for 
elastin as given in (14) and introduced a weighting function for 
the dispersed collagen mechanism, \(d_a\). When \(k = 1/3\), the activation 
criterion (22) and Cauchy stress (27) are those given in Wulandana and 
Robertson (2005) for a multi-mechanism material with two 
isotropic mechanisms. In the limit as \(k\) tending to zero, the activation 
criterion and Cauchy stress tensor approach those given in (8) 
and (15) for a single fiber family.

### 3. Application of the structural multi-mechanism model to 
cylindrical inflation

In this section, the structural multi-mechanism model is considered 
in the context of the only relevant inelastic data available for 
cerebral vessels (Scott et al., 1972).

#### 3.1. Inelastic experimental data for quasi-static inflation of cerebral vessels

Scott et al. performed quasi-static pressure inflation studies on 
cerebral vessels (Scott et al., 1972). Their results for tension (product 
of pressure and radius) versus radius data for cyclic loading of an 
anterior cerebral artery (ACA) to 200 mmHg displayed an inelastic 
behavior not previously reported in the literature (Fig. 4). Data from 
the first three loading cycles displayed the typical highly 
nonlinear tension radius curves expected for healthy cerebral 
arterial tissue, characterized by a nearly linear toe region at 
low strain and an exponential like region at high strain. The 
tension/radius data for six subsequent loading cycles were 
qualitatively different. The unloaded radius increased by over 75% 
and the toe region was noticeably absent. Significantly, the second 
set of loading cycles was highly repeatable and no intermediate 
curves were found. Apparently, a second elastic regime was 
created after some irreversible change to the tissue. Similar results 
were found for all three cerebral arteries loaded to this level. No 
shift was seen in control experiments of cyclic loading to a 
maximum pressure of 100 mmHg.

![Fig. 4. Tension versus stretch data from an anterior cerebral artery, reproduced from Fig. 5B in (Scott et al., 1972).](image-url)
3.2. Analytical solution for quasi-static inflation of a cylindrical membrane

We consider the above experimental data in the context of quasi-static inflation of a cylindrical membrane composed of the structural multi-mechanism material. The undeformed arterial segment is modeled as a long cylindrical membrane with half thickness $H_1$ and constant radius $R_0$ that occupies configuration $\kappa_0$ at some initial time $t = t_0$. A uniform normal pressure drop $\Delta P$ is applied across the wall of the membrane to represent the fluid perfusion pressure. It is convenient to employ a cylindrical coordinate system $(r, \theta, z)$ for which the $z$ axis is coincident with the axis of symmetry of the cylindrical vessel. The deformation is assumed to be purely radial and axisymmetric, in which case, a material point located at $x_0 = R_0 e_r + z_0 e_z$ in the unloaded configuration with respect to cylindrical basis $e_r, e_\theta, e_z$, is mapped to position $\mathbf{x} = R(R_0 e_r + z_0 e_z).$ The corresponding circumferential membrane stretch is $\lambda = R/R_0$. It follows from incompressibility, that the half thickness of the wall in the current configuration is $H_1/\lambda$.

The fibers are assumed to have rotational symmetry about the direction $e_\theta$. In the membrane approximation, this reduces to the condition that for every fiber with angle $\beta_i$ relative to $e_\theta$, there exists a second fiber with similar mechanical properties oriented at angle $-\beta_i$. In the remainder of this section, we model the collagen mechanism as (i) $N$ independent fibers, (ii) a distributed fiber model, and (iii) an isotropic material.

For this axisymmetric deformation, the only non-zero cylindrical components of the left and right Cauchy stress tensors relative to the reference configurations $\kappa_0, \kappa_i,$ and $\kappa_s$ are for $(i = 1, \ldots, N),$

$$\text{diag}(R_0) = \text{diag}(C_0) = \begin{bmatrix} 1 & \lambda^2 & 1 \end{bmatrix},$$

$$\text{diag}(B) = \text{diag}(C) = \begin{bmatrix} \frac{1}{\lambda^2} & \lambda^2 & 1 \end{bmatrix},$$

$$\text{diag}(R) = \text{diag}(C) = \begin{bmatrix} \frac{1}{\lambda^2} & \lambda^2 & 1 \end{bmatrix}.$$

(29)

where $\lambda_{sw}$ and $\lambda_{sw}$ are the circumferential stretches in $\kappa_{sw}$, and $\kappa_{sw}$, respectively.

Following a procedure similar to that used in Wulandana and Robertson (2005), we can obtain analytical solutions for tension as a function of stretch for general strain energy functions for both the $N$ fiber models given in (13)–(15) and the distributed fiber model given in (26)–(28). For the $N$ fiber model,

$$\mathcal{F} = \frac{4H_1}{\lambda} \left[ (1 - d_0) \left( \frac{1}{\lambda} - 1 \right) \frac{\partial \phi_i}{\partial \lambda} + \sum_{i=1}^{N} \left( 1 - d_i \right) \frac{\partial \phi_i}{\partial \lambda} \right] + \left( 1 - d_0 \right) \frac{\partial \phi_0}{\partial \lambda} \left( \frac{1}{\lambda^2} - 1 \right),$$

(30)

where $d_0 = \begin{cases} 0 & \text{for } \lambda < \lambda_b, \\ 1 & \text{for } \lambda \geq \lambda_b, \end{cases} \quad d_i = \begin{cases} 1 & \text{for } \lambda < \lambda_{sw}, \quad i \in [1,N] \\ 0 & \text{for } \lambda \geq \lambda_{sw}, \quad i \in [1,N]. \end{cases}$

(31)

where $\lambda_b$ is the stretch corresponding to $s_0 = s_{sb}$ and from (1), (7), and (29),

$$I_0 = 1/\lambda^2 + \lambda^2 + 1, \quad \lambda_{sb} = \frac{IV_{sb}}{\lambda_{sb}^2} = \lambda_{sb}^2 \cos^2 \beta_i + \sin^2 \beta_i, \quad I_1 = \lambda_{sw}^2/\lambda^2 + \lambda^2/\lambda_{sw}^2 + 1, \quad IV_{sw} = (\lambda^2 \cos^2 \beta_i + \sin^2 \beta_i)/IV_{sb}. \tag{32}$$

Note, $\lambda_b$ is the stretch corresponding to $s_0 = s_{sb}$ and from (1), (7), and (29),

$$I_0 = 1/\lambda^2 + \lambda^2 + 1, \quad \lambda_{sb} = \frac{IV_{sb}}{\lambda_{sb}^2} = \lambda_{sb}^2 \cos^2 \beta_i + \sin^2 \beta_i, \quad I_1 = \lambda_{sw}^2/\lambda^2 + \lambda^2/\lambda_{sw}^2 + 1, \quad IV_{sw} = (\lambda^2 \cos^2 \beta_i + \sin^2 \beta_i)/IV_{sb}. \tag{32}$$

In cases where the critical fiber stretch $\lambda_{sb}$ is known a priori, $\lambda_b$ can be determined from (32),

$$\lambda_b^2 = \left( \frac{\lambda_{sb}^2 - \sin^2 \beta_i}{\cos^2 \beta_i} \right) \cos^2 \beta_i. \tag{34}$$

For the distributed collagen model, the fibers are taken as symmetrically arranged around $e_\theta$ in $\kappa_0$, so we consider only one dispersion direction $\hat{\beta}_{1,0} = \beta$, and set $\beta = 0$. The direction of the material elements oriented parallel to $\dot{\beta}_{1,0}$ are unchanged during this axisymmetric deformation, so $\dot{\beta}_{1,0} = \beta$. The membrane solution for wall tension is

$$\mathcal{F} = \frac{4H_1}{\lambda} \left[ (1 - d_0) \frac{\partial \phi_0}{\partial \lambda} \left( \frac{1}{\lambda^2} - 1 \right) + \left( 1 - d_0 \right) \frac{\partial \phi_0}{\partial \lambda} \left( \frac{1}{\lambda^2} - 1 \right) + \left( 1 - 3k \right) \frac{\lambda^2}{IV_{1,0}} \right],$$

(35)

where $d_0$ was evaluated in (32), $d_0$ has the same definition given in (31), and

$$d_i = \begin{cases} 1 & \text{for } \lambda < \lambda_{sw}, \quad i \in [1,N] \\ 0 & \text{for } \lambda \geq \lambda_{sw}. \end{cases} \tag{36}$$

In addition, it follows from (24), (25) and (29) that

$$E_{11} = k_l + (1 - 3k) IV_{1,1} - 1, \quad \text{with} \quad l_1 = \lambda_{sw}^2/\lambda^2 + \lambda^2/\lambda_{sw}^2 + 1, \quad IV_{1,0} = \lambda_{sw}^2, \quad IV_{1,1} = \lambda^2/\lambda_{sw}^2. \tag{37}$$

If the material parameter $s_{1a}$ is known, then $\lambda_{sw}$ can be determined using (22) and (37) with the condition $s_i = s_{1a}$. Namely, $\lambda_{sw}$ is the root of the equation,

$$s_{1a} = k_l (\lambda_{sw}^2 + 1/\lambda_{sw}^2) + 1 = (1 - 3k) \lambda_{sw}^2 - 1. \tag{38}$$

The isotropic collagen model used in Wulandana and Robertson (2005) is recovered by setting $k = 1/3$ in (35).

3.3. Application of structural multi-mechanism model to the data of Scott, Ferguson and Roach

We now turn attention to the selection of the material functions for the multi-mechanism models using the data from Scott et al. (1972) and the analytical solutions given above. For the elastin mechanism, the functional form of $\phi_b$ and the value of $s_{sb}$ must be determined. Motivated by the results of Wulandana and Robertson (2005), exponential and Neo-Hookean forms for the isotropic strain energy function are considered for $\phi_b(i_b)$, Table 1. For simplicity, only two fibers are considered in the fiber model for collagen. As mentioned above, we assume fiber symmetry such that $\beta_{sw} = -\beta_i = -\beta$ and assume these fibers have identical material properties. Due to the symmetry of the loading, this implies that $\lambda_{sb} = \lambda_{sw}$. In this case, only the function $\psi_i/IV_{1,1}$ and material parameters $s_{1a}$ or $\lambda_{sw}$ and $\beta_i$ must be determined. Using similar

Table 1

<table>
<thead>
<tr>
<th>Strain energy functions considered for the elastin and collagen mechanisms.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elastin mechanism</strong></td>
</tr>
<tr>
<td>Neo-Hookean (NH): $\psi_b = \frac{1}{2} (s - 3)$</td>
</tr>
<tr>
<td>First order exponential (E-EXP1): $\psi_b = \frac{1}{2} e^{(s-3)/\gamma} - 1$</td>
</tr>
<tr>
<td>Second order exponential (E-EXP2): $\psi_b = \frac{1}{2} e^{(s-3)/\gamma^2} - 1$</td>
</tr>
<tr>
<td><strong>Collagen mechanism</strong></td>
</tr>
<tr>
<td>Isotropic model</td>
</tr>
<tr>
<td>Exponential (E-EXP-iso): $\psi_i = \frac{1}{2} e^{(s-3)/\gamma} - 1$</td>
</tr>
<tr>
<td>Anisotropic 2 fiber model</td>
</tr>
<tr>
<td>Exponential (E-EXP2-fiber): $\psi_i = \frac{1}{2} e^{(s-3)/\gamma^2} - 1$</td>
</tr>
<tr>
<td>Anisotropic dispersion model</td>
</tr>
<tr>
<td>Exponential (E-EXP2-disp): $\psi_i = \frac{1}{2} e^{(s-3)/\gamma^2} - 1$</td>
</tr>
</tbody>
</table>
arguments, only the function $\tilde{y}_1(E_{11})$ and the material parameters $\delta_{1a}$ and $k$ need to be determined for the dispersion model.\(^{2}\) Second order exponential functions are considered for the strain energy functions for both anisotropic collagen mechanisms, Table 1. Exponential strain energy functions with second order terms for arterial tissue have been proposed by Fung et al. (1979) and widely used in the literature.

As in Wulandana and Robertson (2005), it is assumed that only the elastin mechanism is active for $\lambda \in [1, \lambda_{1a}]$ of Runs 1–3, both mechanisms are active for $\lambda \in [\lambda_{1a}, b_0]$ of Runs 1–3, and only the collagen mechanism is active during Runs 4–9. An arterial thickness of 125 $\mu$m was used. Following the approach taken in Wulandana and Robertson (2005), the values for the critical circumferential stretches are $\lambda_{1a} = 1.76$ and $b_0 = 2.3$. Using these values, a nonlinear regression analysis was performed using a modified Levenberg–Marquardt method. All data from the two curves (Runs 1–3 and Runs 4–9) were fit simultaneously using the solutions for tension given in (30) and (35). The quality of the fit was quantified using a modified pseudo $R^2$ value defined by

$$R^2 = 1 - \frac{\sum_n (\mathcal{F}_i - \mathcal{F}_k)^2}{\sum_n (\mathcal{F}_i - \bar{\mathcal{F}}_k)^2},$$

(39)

where $n$ is the number of data points, $\mathcal{F}_i$ is a tension data and $\mathcal{F}_k$ is the average value of the tension data. $\mathcal{F}(\lambda)$ is the tension calculated for stretch ratio $\lambda$, using (30) and (35).

3.3.1. Results of nonlinear regression analysis

To select a strain energy for the elastin mechanism, we compared the results of the regression analysis for the three choices of elastin mechanism given in Table 1 for a 2-fiber collagen model. As will be discussed below, the results for all three collagen models were able to fit the data well. For this reason, when comparing the choices of elastin strain energy functions, we only considered one of the models (the 2-fiber model).

Results of the nonlinear regression analysis are shown in Table 2 and Fig. 5. The choice of the strain energy for the elastin mechanism is most apparent in the toe region of Runs 1–3 where only elastin is active. The Neo-Hookean model has a different concavity than the exponential models and does not fit the data well. The second order exponential model is flatter in this region and gives a slightly better fit than the first order model.

Results for the 2-fiber and distributed collagen fiber models are shown in Table 3 and Fig. 6. In both cases the second order exponential model for elastin is used. All material parameters in Table 3 including fiber orientation variable $\beta$ and $k$ were determined from the regression analysis.

Also shown for comparison are results for the isotropic dual-mechanism model introduced in Wulandana and Robertson (2005). A first order exponential strain energy function was used for both elastin and collagen mechanisms. Due to a typographical error in Wulandana and Robertson (2005), the values reported in Table 3 for $\eta, \eta_0$ differ from those in Wulandana and Robertson (2005) (variables $\xi_1, \xi_2$ in that work). While the anisotropic collagen models introduced here give slightly better fits than the isotropic model, more experimental data is needed to fully appreciate and develop the anisotropic models.

From the results of the regression analysis, it is useful to calculate the material parameters related to the activation of collagen and deactivation of elastin so that these models can be considered for other deformations. From (33) with $b_0 = 2.3$, it follows that $\delta_0 = 3.48$. Evaluating (9) and (32) with $\beta = 48^\circ$ and $\lambda_{1a} = 1.76$, it follows that $\delta_{1a} = 0.94$. Using (38) with $k = 0.298$ it follows that $\delta_{1a} = 0.65$. We emphasize that the values of $\beta$ and $\delta_{1a}$ need to be further explored when inelastic bi-axial data becomes available.

4. Discussion

A structural multi-mechanism constitutive model for cerebral arterial tissue has been developed that builds on a previous multi-mechanism model (Wulandana and Robertson, 2005). In both the earlier and current models, the cerebral arterial tissue is modeled as nonlinear, inelastic and incompressible, with separate mechanisms for elastin and collagen. This splitting is necessary if the failure of the elastin mechanism is possible without failure of the entire wall (such as is found in aneurysm formation and sometimes in balloon angioplasty). In the earlier work, both mechanisms were modeled as isotropic. Structural data on collagen fiber orientation in cerebral arteries provides a motivation for extending this model to include the anisotropy of the cerebral wall. Here the unloaded artery wall is composed of separate mechanisms: an isotropic mechanism controlled by the response of elastin and possibly the surrounding matrix as well as an anisotropic mechanism arising from helical networks of crimped collagen fibers. These fibers require a finite deformation to begin load bearing. Two categories of models are developed for the collagen contribution. In the first, the collagen mechanism is modeled as arising from discrete families of collagen fibers with different orientations, material properties and crimping. In the second, the collective response of fibers is modeled using a distribution function for fiber angle. New activation criteria are introduced for each of these collagen models to designate the beginning of substantial collagen load bearing. This activation criterion is a function of the local stretch of material elements originally tangent to the crimped fiber direction in the unloaded configuration of either the $N$ fiber families or the distribution family.
The proposed model is applied to the inelastic data of Scott et al. (1972) for both collagen mechanism models. The mean fiber angle $\beta$, dispersion parameter $k$ as well as the other material constants, were chosen based on a nonlinear regression analysis of the test data. The value of $k$ was within the required range of $[0, 1/2]$. If tissue specific data on fiber orientation and distribution in cerebral vessels becomes available, $k$ can be directly estimated from this data. A second order exponential strain energy function was found to have the best fit to the data for both the elastin and collagen mechanisms, particularly in the regions of low tension. The current model has a slightly better fit with Scott et al.’s experimental results than the previous isotropic multi-mechanism model (Wulandana and Robertson, 2005). As already discussed, though the data from Scott et al. (1972) is in many ways well suited to developing this multi-mechanism model, it has limited value for determining anisotropic material parameters. Experiments are under way in our laboratory to obtain appropriate data for further refinement of the anisotropic collagen mechanism.

As for most other mechanical models of the arterial wall, we take a continuum approach. It is assumed that the fibers can be approximated as continuously distributed throughout the material (or arterial layer) so that the fiber orientation vector and other quantities have meaning at each point in the material and are continuous functions of position. We do not account for microscopic effects in the composite such as interactions between the fibers and the matrix or coupling between the collagen fibers, or between the fiber families.

In the analysis here, all fiber families at each material point are assumed to have approximately the same level of waviness ($s_f$ is a constant for all fibers at a point). In some soft tissue, the degree of fiber undulation can vary considerably with position Sacks (2003). If warranted by experimental data, it is straightforward to generalize the current model to account for this type of material inhomogeneity. This can be achieved by making $s_f$ a function of position. Furthermore, it is assumed that collagen fibers are completely uncrimped at a discrete loading level $s = s_0$. This can be generalized by introducing an integral model for fiber recruitment.

In the current model, the degradation of elastin is dependent on a local measure of strain, namely it is a purely mechanical model. This will be directly useful for applications such as balloon angioplasty in which the blood vessel is loaded beyond the physiological strain level over a time period much shorter than that for vessel remodeling. In other applications, such as cerebral aneurysms, the degradation of elastin will be dependent on both mechanical and biochemical effects.

Studies of cerebral aneurysms have shown that the elastin degradation associated with aneurysm initiation can be induced in the presence of unfavorable hemodynamic loads. In particular, it appears that some combination of elevated wall shear stress (WSS), wall shear stress gradient (WSSG) and hemodynamic pressure lead to elastin degradation in native and non-native bifurcations (Fukuta et al., 2000; Morimoto et al., 2002; Gao et al., 2008). It seems likely that the elevated WSS and WSSG play the role of initiating a cascade of biochemical activities that lead to chemical degradation of the wall, rather than directly damaging the elastin. For example, some aspect(s) of the hemodynamic loading may lead to an imbalance in the production of MMP and TIMPs in the wall and thereby to a chemical degradation of the wall.

Since cerebral aneurysms can form in humans in the absence of hypertension, we conjecture the role of elevated hemodynamic pressures in aneurysm formation is to hasten mechanical damage and ultimate failure of an elastin layer previously weakened by biochemical factors. Relatively simple mechanisms can be introduced to extend the current model to include hemodynamically driven degradation of the elastin mechanism such as that introduced in (Robertson et al., 2007). In that work, $\eta_0$, the material constant for elastin in Table 1 is replaced by a parameter $\eta_d$ which depends on the history of WSS and WSSG.

We feel, the next step in modeling aneurysm formation is to develop more sophisticated damage models which include both gradual mechanical and biochemical derived degradation of the elastin (Li and Robertson, 2009). The significant challenge for developing these models is to obtain experimental data to guide the choice of a particular functional form for elastin degradation. This remains an area of active research and will benefit from both animal studies of the kind described above as well as in-vitro studies. Most in-vitro flow chambers are designed for basic studies of response of cellular components of the arterial wall (e.g. endothelial and smooth muscle cells) to homogenous stress fields as well as for inhomogeneous fields of the type associated with atherosclerotic plaque formation. These chambers are not designed for reproducing the salient features of flow found at the apices of bifurcations. Robertson et al. introduced an in-vitro T-chamber, designed to reproduce the WSS and WSSG field identified in numerical simulations of

### Table 3
Results of regression analysis for 2-fiber, dispersion and isotropic collagen models.

<table>
<thead>
<tr>
<th>Model</th>
<th>$\eta_0$ (kPa)</th>
<th>$\gamma$</th>
<th>$\eta$ (kPa)</th>
<th>$\gamma$</th>
<th>$\beta_1 - \beta_2$</th>
<th>$k$</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-EXP2, C-EXP2-2-fiber</td>
<td>5.09</td>
<td>0.677</td>
<td>35.9</td>
<td>0.9917</td>
<td>48.1</td>
<td>0</td>
<td>0.9944</td>
</tr>
<tr>
<td>E-EXP2, C-EXP2-disp</td>
<td>5.67</td>
<td>1.83</td>
<td>380.2</td>
<td>0.9944</td>
<td>0</td>
<td>0</td>
<td>0.9959</td>
</tr>
<tr>
<td>E-EXP2, C-EXP2-2-fiber</td>
<td>5.09</td>
<td>1.84</td>
<td>35.9</td>
<td>0.9944</td>
<td>48.1</td>
<td>0</td>
<td>0.9917</td>
</tr>
<tr>
<td>E-EXP1, C-EXP1-iso</td>
<td>6.45</td>
<td>1.84</td>
<td>35.9</td>
<td>0.9944</td>
<td>48.1</td>
<td>0</td>
<td>0.9917</td>
</tr>
</tbody>
</table>

Fig. 6. Comparison of three choices of the collagen mechanism with an exponential elastin mechanism (i) 2-fiber model (E-EXP2, C-EXP2-2-fiber), (ii) dispersion model (E-EXP2, C-EXP2-disp), and (iii) isotropic model (E-EXP1, C-EXP1-iso) used in Wulandana and Robertson (2005).
flow in cerebral bifurcations (Chung and Robertson, 2003; Chung, 2004). More recently, this chamber was extended to expose cells to a close replication of the WSS and WSSG fields associated with early aneurysm changes in the in-vivo studies of Meng et al. (2007). T-chambers of this kind have recently been used to obtain preliminary data investigating the coupling between MMP production in endothelial cells and exposure to elevated WSS and WSSG fields (Sakamoto et al., 2008; Szymanski et al., 2008). We expect that further work in this direction will provide a strong basis for the extension of the current model to include the mechanobiology of the IEL degradation.

Appendix A. Bounds on the dispersion parameter

In this appendix, we determine bounds on $k$, arising entirely from the definition of $k$ and the normalization condition on $\rho$. For materials with rotational symmetry, the normalization condition (16), simplifies to

$$\int_0^\pi \rho(M(\theta)) \sin \theta d\theta = 2. \quad (A.1)$$

Since the density function is defined as the normalized number of fibers, it is non-negative. With this in mind, let $\mathcal{C}$ be the class of measurable, non-negative functions $\rho(\theta)$ defined for $\theta \in [0, \pi]$ and satisfying (A.1).

**Result 1.** If $\rho$ is a member of $\mathcal{C}$ then necessarily $k \in (0, 1/2)$.

**Proof.** Since $\sin \theta$ is strictly less than one for $\theta \in (0, \pi)$, it follows from (18) and (A.1), that

$$k = \frac{1}{4} \int_0^\pi \rho(\theta) \sin^2 \theta d\theta \leq \frac{1}{4} \int_0^\pi \rho(\theta) \sin \theta d\theta = \frac{1}{2}. \quad (A.2)$$

Therefore, necessarily, $k \leq 1/2$. Furthermore, in order for the normalization condition to be satisfied, $\rho(\theta)$ must be positive on a set of non-zero measure in $\theta \in [0, \pi]$. Therefore, from (18), $k$ is strictly positive. We now show the upper bound on $k$ cannot be smaller than $1/2$, by introducing a $\rho$ such that the corresponding $k$ is arbitrarily close to $1/2$. □

**Result 2.** The supremum of $k(\rho)$ for $\rho \in \mathcal{C}$ is $1/2$.

**Proof.** Consider the density function $\rho = A \sin^n \theta$ where $n$ is a non-negative integer and $A$ is a constant. From the normalization condition (A.1), it follows that, for this choice of $\rho$,

$$A = 2\left(\int_0^\pi \sin^{n+1} \theta d\theta\right). \quad (A.3)$$

It then follows from (18) that,

$$k = A\left(\int_0^\pi \sin^{n+1} \theta d\theta\right) / 4 = \left(\int_0^\pi \sin^{n+1} \theta d\theta\right) / \left(2 \int_0^\pi \sin^{n+1} \theta d\theta\right) = \frac{\pi + 2}{2(\pi + 3)}.$$  

From (A.4), in the limit as $n$ tends to infinity, $k$ tends to $1/2$. □

**References**


