Modelling the growth and stabilization of cerebral aneurysms

PAUL N. WATTON† AND YIANNIS VENTIKOS

Institute of Biomedical Engineering, Department of Engineering Science, University of Oxford, Parks Road, OX1 3PJ Oxford, UK

AND

GERHARD A. HOLZAPFEL

Institute of Biomechanics, Center of Biomedical Engineering, Graz University of Technology, Kronesgasse 5-1, 8010 Graz, Austria and Royal Institute of Technology (KTH), Department of Solid Mechanics, School of Engineering Sciences, Osquars Backe 1, 100 44 Stockholm, Sweden

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Experimental and theoretical guidance is needed to understand how the collagen fabric evolves during the development of aneurysms. In this paper, we model the development of an aneurysm as a cylindrical/spherical membrane subject to 1D enlargement; these conceptual models reflect the development of fusiform and saccular cerebral aneurysms. The mechanical response is attributed to the elastin and collagen. We introduce variables which define the elastin and collagen fibre concentration; these evolve to simulate growth/atrophy of the constituents. A hypothetical aneurysm model is analysed: collagen stretch is constant, elastin degrades and collagen fibre concentration can adapt to maintain mechanical equilibrium. An analytic expression for the rate of evolution of the fibre concentration is derived. The functional form is dependent on (i) the current collagen fibre concentration, (ii) the deviations in the collagen fibre stretch from the attachment stretch, (iii) the rate of change of fibre stretch, (iv) the rate of loss of elastin and (v) the ratio of load borne by elastinous and collagenous constituents. Finally, numerical examples of aneurysm development are considered. Suitable candidates for the fibre concentration evolution equations are identified that yield stabilization of the aneurysm even when there is complete loss of elastin. This theoretical analysis provides the basis for the development of physiologically realistic models of aneurysm development.

Keywords: aneurysm; artery; cerebral; collagen; elastin; growth; remodelling.

1. Introduction

An aneurysm is a localized dilatation of the arterial wall. Aneurysms primarily form in the abdominal and thoracic sections of the aorta and in the cerebral arteries surrounding the circle of Willis. Cerebral aneurysms are present in 2–5% of the population, 90% of which are of saccular type, having berry-like, spherical sacs connected to the vessel by a neck (Lasheras, 2007). The precise cause for cerebral aneurysm is still not known, but it is associated with endogenous factors such as elevated arterial blood pressure and complex flow conditions (Resnick et al., 2003; Chatziprodromou et al., 2007a,b;
Tateshima et al., 2007); genetic factors also seem to play a role (Krex et al., 2001). It is envisaged that theoretical models of aneurysm growth may yield insight into the aetiology of the disease.

The healthy cerebral artery consists of three layers. The innermost layer is the intima, this consists of a basement membrane and a lining of endothelial cells. An internal elastic laminae separates the intima from the media. The media consists of a network of elastin fibres and (approximately) circumferentially orientated smooth muscle cells and collagen fibres. The adventitia is an outer sheath with bundles of collagen fibres arranged in helical pitches around the artery. The collagen provides high tensile strength while elastin gives rise to the compliant response of an artery. Development of a cerebral aneurysm is associated with apoptosis of the medial smooth muscle cells (Kondo et al., 1997, 1998; Sakaki et al., 1997), the breakage and elimination of the elastin fibers within the aneurysmal wall (Mimata et al., 1997; Gaetani et al., 1998; Humphrey & Canham, 2000; Frösen et al., 2004) and the growth and remodelling of the collagen fabric.

The extracellular matrix (ECM) determines the mechanical strength of the artery and acts as an attachment site for cell surface receptors and as a reservoir for many signalling molecules that modulate various cellular functions. The function of fibroblast cells is the production and homeostatic maintenance of the tissue. This is achieved by the synthesis of new ECM, e.g. collagen, elastin and proteoglycans, and the degradation of ECM by matrix metalloproteinases (MMPs) (Gupta & Grande-Allen, 2006). Each fibroblast can synthesize approximately 3.5 million procollagen molecules per day. However, the amount a fibroblast secretes is regulated: between 10% and 90% of all procollagen molecules are degraded intracellularly prior to secretion. This provides a mechanism for rapid adaptation of the amount of collagen secreted (McAnulty, 2007) and thus enables the artery to rapidly adapt in response to altered environmental conditions.

Fibroblasts adhere to the ECM via specialized cell surface receptors, in particular integrins (Wang & Thampatty, 2006). The integrins physically link the ECM to the cytoskeleton of the fibroblast. They transduce mechanical signals to the fibroblast interior. There is increasing evidence that integrins act as stretch sensors (Chiquet et al., 2003). They enable fibroblasts to sense changes in the mechanical strains/stretches applied to them and subsequently the fibroblasts may respond by adjusting their expression and synthesis of ECM molecules in order to adapt their mechanical environment. Given that the developed aneurysm consists of a network of collagen fibres maintained by fibroblasts, the functionality of the fibroblasts must play a critical role in determining whether the aneurysm stabilizes in size or continues to enlarge. Indeed, Mimata et al. (1997) conclude that fibroblasts in the aneurysmal wall may step up the synthesis of collagen to strengthen the aneurysmal wall against hemodynamic stress. However, while it is well recognized that mechanical forces are essential for tissue homeostasis, the molecular signalling and regulatory mechanisms remain incompletely understood (Chiquet et al., 2003).

The continual maintenance of the ECM gives rise to a continual turnover of the collagen fibres within the arterial wall. For example, Nissen et al. (1978) determined the collagen half-life of the aorta and mesenteric arteries of a rat to be 60–70 days in normotensive animals and reduced to 17 days in hypertensive conditions. This physiological process enables the arterial wall to quickly adapt its structure to altered mechanical conditions, e.g. altered flow rates (Gleason & Humphrey, 2004). Fibroblast cells attach and configure the fibres in a state of stretch (Alberts et al., 2008), hereon referred to as the ‘attachment stretch’. Humphrey (1999) hypothesized that the attachment stretch is invariant of the current configuration of the artery, this approach has served the basis for many subsequent models of arterial growth and remodelling (Humphrey & Wilson, 2003; Gleason & Humphrey, 2004, 2007; Watton et al., 2004; Baek et al., 2005, 2006; Gleason et al., 2007; Kroon & Holzapfel, 2007, 2009; Watton & Hill, 2009).
Fibroblasts may be stimulated to increase (decrease) the mass of the collagenous constituents via up (down)-regulation of collagen synthesis and down (up)-regulation of MMP synthesis. Guidance is needed to understand how the mass of the collagenous constituents evolves. This is of particular importance for predicting the growth and the remodelling that occurs in the development of cerebral aneurysms.

It is observed that cerebral aneurysms may stabilize in size. Koffijberg et al. (2008) concluded that a constant, time-independent growth rate of intracranial aneurysms is unlikely. Instead, growth is much more likely to be irregular and discontinuous, which leads to periods with and without growth. The periods without growth can be long. Indeed, over a mean follow-up period of 8.9 years, Wermer et al. (2005) observed lesion growth in only 10 of 40 aneurysms. Computational models should be able to predict such stabilization: theoretical analysis may yield more insight into the underlying physiological mechanisms that give rise to such remodelling.

The geometry of an aneurysm may change significantly as it develops. Although initially it may appear as a small bleb-like outpouching of the arterial wall, it may develop into a saccular form, i.e. a berry-shaped aneurysm, with a well-defined neck. This implies that a region of tissue which originally conformed to cylindrical geometry may remodel into a region with spherical geometry. Consequently, it is of interest to gain insight into requirements of the physiological adaptive mechanisms that act to stabilize the growth of the tissue for these different geometries. Hence, in this paper, we model the artery as a cylindrical membrane subject to a constant internal pressure and a constant axial stretch, and, additionally, we model an evolving aneurysm as a spherical membrane subject to a constant internal pressure. The mechanical response of the membrane is attributed to the additive sum of the mechanical responses of the individual constituents. We introduce (non-dimensional) concentration variables which define the ratio of the mass density of the individual constituents with respect to that of the initial configuration of the artery. The concentrations can evolve to simulate elastin degradation and growth/atrophy of the collagen. To simulate the development of a cerebral aneurysm, conceptual 1D models of aneurysm enlargement are considered. For the purposes of the mathematical analysis, a hypothetical example is considered in which the collagen stretch is always constant and equal to the attachment stretch. The elastinous constituents are prescribed to degrade and the collagen fibre concentration can adapt to maintain mechanical equilibrium. The growth and remodelling is such that the membrane maintains cylindrical or spherical geometry; these conceptual models reflect the development of fusiform and saccular cerebral aneurysms.

We introduce the terminology ‘material equilibrium’ to denote that fibres throughout the tissue have stretches equal to the attachment stretch. Thus, for the conceptual model considered, the collagen fabric is in ‘material’ and ‘mechanical’ equilibrium. Note that if the collagen was in ‘mechanical equilibrium’ but the collagen fabric had fibres with stretches not equal to the attachment stretch, the natural process of fibre deposition and degradation would act to restore fibre stretches to the attachment stretch, and during this process, the structure and geometry of the collagen fabric would change.

Explicit expressions for mechanical equilibrium of the membranes, while the elastin concentration degrades and the fibre concentration adapts, are derived. This enables an analytic expression for the rate of evolution of the fibre concentration to be derived. The functional form is dependent on the current collagen fibre concentration, the deviations in the collagen fibre stretch from the attachment stretch, the rate of change of fibre stretch, the rate of loss of elastin and the ratio of load borne by elastinous and collagenous constituents. For an aneurysm to stabilize in size, the fibre stretch must converge towards the attachment stretch, hence our analysis guides the selection of suitable functional forms for the fibre concentration evolution equations.
The structure of this paper is as follows. In Section 2, we detail the general theoretical framework to describe the deformation and remodelling of a membrane. Sections 3 and 4 consider the governing equations for the mechanical equilibrium of elastinous/collagenous cylindrical and spherical membranes, respectively. We analyse the evolution (and rate of evolution) of the fibre concentration that is necessary to maintain mechanical equilibrium, while the elastin degrades, under the assumption that the fibre stretch is always equal to the attachment stretch. Section 5 compares the fibre concentration evolution equations for the membranes. Finally, in Section 6, representative numerical examples of aneurysm development are considered. Suitable candidates for the fibre concentration evolution equations are identified that yield stabilization of the aneurysm even when there is complete loss of elastinous constituents.

2. Continuum basis

The basilar and internal carotid arteries have diameters in the range 3–5 mm (Kroon & Holzapfel, 2007) and the wall thickness of a (loaded) artery is approximately 1/10 of the radius (Monson et al., 2005). The developed cerebral aneurysm is a thin collagenous structure with diameter typically in the range of 3–25 mm and the thickness typically ranges from 30 to 500 μm (Baek et al., 2005). Thus, for the purposes of studying the deformations that arise as the artery remodels, it is a reasonable approximation to model the developing aneurysm as a membrane (Baek et al., 2005; Kroon & Holzapfel, 2007, 2009), and this is also the approach we adopt here; we have used a geometric non-linear membrane theory to model the membraneous structure (see, e.g. Wempner, 1973; Heil, 1996). The general mathematical formulation to analyse the deformation of a membrane is detailed in Appendices A.1 and A.2. Here, we present SEFs for elastin and collagen, introduce the attachment stretch and discuss the remodelling of the collagen recruitment configuration.

2.1 Strain energy function

The passive mechanical responses of vascular membranes are assumed to be governed by their elastinous and collagenous constituents. In addition, it is assumed that the gross mechanical response can be represented by the additive decomposition of the SEF with respect to the individual constituents (Holzapfel & Weizsäcker, 1998). Thus, Ψ, defined per unit volume in the unloaded configuration Ω₀, may be expressed as

\[ \Psi = \Psi^E + \Psi^C, \tag{1} \]

where Ψ^E and Ψ^C are the SEFs for the elastinous and collagenous constituents, respectively.

2.1.1 Elastin. The SEF Ψ^E for the elastin is expressed as the product of a constitutive function which represents the potential energy of elastin per unit volume, say ˆΨ^E, and a (non-dimensional) elastin concentration m^E, i.e.

\[ \Psi^E = m^E \hat{\Psi}^E, \tag{2} \]

where m^E denotes the ratio of the mass density of elastinous constituents at time t to the mass density at time t = 0. In general, m^E can be spatially and temporally dependent. However, for the purpose of this study, m^E = m^E(t), where \( m^E \big|_{t=0} = 1 \) and m^E(t) ≤ 1, ∀ t ≥ 0.
2.1.2 Collagen. Collagen fibres are distributed with a certain range of orientation within arterial tissues. We define the fibre orientations $\gamma$ with respect to some reference coordinate axis in $\Omega_0$ (see Fig. 1). Furthermore, each collagen fibre consists of a population of collagen fibrils of varying undulation. It is assumed that the mechanical response of the population of the fibrils can be defined with respect to the ‘onset of recruitment’ of the fibrils to load bearing, i.e. with respect to those fibrils of minimum undulation. To simplify the material representation, we visualize a ‘hypothetical fibre’, hereon referred to simply as ‘fibre’, whose mechanical response represents the gross mechanical response of the population of fibrils as they are recruited to load bearing.

We define the stretch of the fibre with respect to the onset of recruitment to load bearing of the population of fibrils. The gross mechanical response of the fibre is thus described by a SEF, say $\Psi^C_\gamma$, defined with respect to the stretch $\lambda^C_\gamma$ that the fibre of orientation $\gamma$ experiences, i.e.

$$\Psi^C_\gamma = G(\lambda^C_\gamma).$$

Note that throughout this paper we use the subscript $\gamma$ to denote a quantity associated with a fibre of orientation $\gamma$. We assume that the undulation distribution of the collagen fibrils does not change and is independent of the configuration in which the collagen is recruited to load bearing, i.e. the functional form of $G$ does not change. Additionally, we assume that the fibres’ mechanical properties are independent of their orientation and thus the functional form of $G$ is not explicitly dependent on the orientation of the fibres. Furthermore, we assume that the collagen fibres do not contribute to load bearing when they are crimped, i.e. $(\lambda^C_\gamma < 1) \Rightarrow G(\lambda^C_\gamma) = 0.$

![Diagram](image.png)

**FIG. 1.** The reference configuration at which the fibres begin to bear load is denoted the ‘recruitment configuration’ $\Omega^R$, while the unloaded and loaded configurations are denoted by $\Omega_0$ and $\Omega^l$, respectively. The stretches in the elastin are defined relative to configuration $\Omega_0$, while the stretches in the collagen are defined relative to $\Omega^R$. In the configuration $\Omega_0$, the stretch in the elastin is $\lambda_\gamma^E = 1$, while in the recruitment configuration $\Omega^R$, the stretch in the collagen fibre is $\lambda^C_\gamma = 1$. Conceptually, the mapping $F$ transforms the position of material points in $\Omega_0$ to their position in $\Omega^l$, the mapping $F^R$ transforms material points from $\Omega_0$ to $\Omega^R$ and the mapping $F^C$ transforms material points in $\Omega^R$ to $\Omega^l$. 
The SEF \( \Psi^C \) of the collagen fabric per unit volume is the summation, over all fibre orientations, of the product of the SEF \( \Psi^\gamma \) of a collagen fibre and the number \( N^C_\gamma \) of collagen fibres of orientation \( \gamma \) per unit volume, i.e.

\[
\Psi^C = \sum_\gamma N^C_\gamma \Psi^\gamma = \sum_\gamma \frac{N^C_\gamma}{N^C_{\gamma 0}} N^C_0 \Psi^\gamma = \sum_\gamma m^C_\gamma \Psi^C_\gamma ,
\]

(4)

where \( \Psi^C_{\gamma} = N^C_{\gamma 0} \Psi^\gamma_{\gamma} \), \( N^C_{\gamma 0} \) denotes the number of fibres per unit volume at \( t = 0 \) and \( m^C_\gamma \in [0, \infty) \) denotes the (non-dimensional) collagen fibre concentration, i.e.

\[
m^C_\gamma = \frac{M^F_{\gamma} N^C_{\gamma}(t)}{M^F_{\gamma} N^C_{\gamma}(t = 0)},
\]

(5)

which is the ratio of the mass density \( M^F_{\gamma} N^C_{\gamma}(t) \) of fibres at time \( t \) to the mass density \( M^F_{\gamma} N^C_{\gamma}(t = 0) \) at \( t = 0 \); \( M^F_{\gamma} \) denotes the mass of a fibre which we assume to be constant, i.e. \( M^F_{\gamma}(t) = M^F_{\gamma}(0) \). Note that \( m^C_\gamma |_{t=0} = 1 \).

Growth of the arterial tissue is associated with increases or decreases of the number of collagen fibres and is thus simulated in this framework by evolving the (collagen) fibre concentration \( m^C_\gamma \). We do not model volume changes to the tissue. However, mathematically, the equilibrium deformation field is dependent on the strain energy stored in the arterial wall. The deformation field for a thickening of the arterial wall would be equivalent to that for an increase in concentration provided that this represented the same number of fibres per unit area of the membrane and the wall remained thin enough for the membrane approximation to be made, i.e. that the strain field across the wall can be taken to be uniform and that the metric of an area segment on the lower surface of the membrane is equal to that of the midplane. Although evolving the fibre concentration relates to the relative change of the number of collagen fibres within the wall for fixed volume, an associated thickness can be inferred (see, e.g. Baek et al., 2006).

In the unloaded reference configuration \( \Omega_0 \), the collagen fibres are crimped and do not bear load. The stretch of the elastin is defined relative to the unloaded configuration \( \Omega_0 \), however, the stretch \( \lambda^C_\gamma \) of the collagen fibres is defined with respect to the reference configuration that they are recruited to load bearing, i.e. the collagen recruitment configuration \( \Omega^R \). The recruitment stretches \( \lambda^R_\gamma \) are variables that define the factor the tissue must be stretched (relative to \( \Omega_0 \)) in the direction of a fibre for it to begin to bear load. Figure 1 illustrates the relationships between the unloaded reference configuration \( \Omega_0 \), the recruitment configuration \( \Omega^R \) and the loaded configuration \( \Omega^t \).

The elastin stretch in the direction of the collagen fibres is simply denoted by \( \lambda_\gamma \). The stretches in the elastin and collagen are related via a decomposition of the stretch according to

\[
\lambda_\gamma = \lambda^R_\gamma \lambda^C_\gamma ,
\]

(6)

where \( \lambda^R_\gamma \), the recruitment stretch, is the stretch in the elastin in the direction of a collagen fibre at its onset to load bearing. In general, \( \lambda^R_\gamma = \lambda^R(X_1, X_2, t) \), however, for the 1D deformation considered in this study, there is no spatial dependence.

The SEF (4) for the collagen per unit volume relative to the unloaded configuration \( \Omega_0 \) can thus be expressed as

\[
\Psi^C = \sum_\gamma m^C_\gamma \Psi^C_\gamma (\lambda^C_\gamma (\lambda_\gamma, \lambda^R_\gamma)) ,
\]

(7)

which is a function of the stretches the fibres experience, i.e. with respect to the reference configuration in which they are recruited to load bearing. Note that for fixed \( t \), \( \lambda^R_\gamma \) is constant, i.e. the recruitment
stretches are not functions of the deformation. However, the recruitment stretches $\lambda^R_\gamma$ may remodel to simulate the remodelling of the collagen fabric, i.e. the consequences of fibre deposition and degradation in altered configurations over time.

### 2.1.3 The attachment stretch $\lambda^C_{AT}$

Collagen fibres are in a state of continual deposition and degradation. The newly deposited collagen fibres are acted on by fibroblast cells to attach them to the ECM in a state of stretch. We define the attachment stretch, denoted $\lambda^C_{AT}$, to be the stretch in the collagen fibres at systole at $t = 0$ (when the artery is in homeostasis) and assume this to be constant. To determine a numerical value for $\lambda^C_{AT}$, we assume that in the initial homeostatic configuration the collagen fibres begin to be recruited to load bearing at diastolic pressure.

### 2.1.4 Remodelling the collagen recruitment configuration

The physiological processes of fibre deposition and degradation and fibres attaching in a state of stretch independent of the current configuration of the tissue imply that the natural reference configuration of the fibres evolves in response to deviations of the stretch of the fibres from equilibrium levels. Phenomenologically, this process can be captured by proposing differential equations to remodel the recruitment configuration such that the fibre stretch is restored to the attachment stretch (Watton et al., 2004).

In this paper, first we consider a theoretical analysis in which the collagen is always in material equilibrium, i.e. the stretch of the collagen fabric is always equal to the attachment stretch. Secondly, we consider numerical examples where the remodelling of the recruitment stretches restores the fibre stretches towards the attachment stretch. To update the reference configuration of the collagen, we follow Watton et al. (2004) and assume that

$$\frac{d\lambda^R_\gamma}{dt} = \mathcal{F}(\lambda^C_\gamma, \lambda^C_{AT}), \quad \mathcal{F}(\lambda^C_\gamma, \lambda^C_{AT}) \equiv a_0(E^C_\gamma - E^C_{AT}),$$

where $E^C_\gamma = [(\lambda^C_\gamma)^2 - 1]/2$, $E^C_{AT} = [(\lambda^C_{AT})^2 - 1]/2$ and $a_0 > 0$ is a remodelling rate parameter which physiologically relates to the turnover rate of the fibres. The faster the turnover rate of the fibres, the larger the value of $a_0$. If there is no turnover of fibres, then $a_0 = 0$ and the recruitment configuration does not remodel. The adoption of this framework enables the remodelling of the collagen fabric during the steady deformation of a membrane to be effectively implemented to model the development of abdominal aortic aneurysms (Watton et al., 2004; Watton & Hill, 2009).

### 3. Deformation and remodelling of a cylindrical membrane

We now apply the introduced framework to analyse the deformation of an elastinous and collagenous cylindrical membrane subject to a constant axial stretch $\lambda_z$ and an inflation with an internal pressure $P$, which yields a circumferential stretch $\lambda$. The unloaded geometry is a cylinder with radius $R$, length $L$ and thickness $H$. The loaded configuration $\Omega'$ is a cylindrical tube of length $\lambda_z L$, radius $\lambda R$ and thickness $h = H/\lambda_z \lambda$ (see Fig. 2). Collagen fibres are assumed to have pitches $\gamma = \pm \beta$ relative to the azimuthal axis, $\lambda^C_\beta$ denotes the stretch of collagen fibres of orientation $\pm \beta$ and $\lambda^E_\beta$ denotes the stretch of the elastin resolved in the direction of the collagen fibres of orientation $\pm \beta$.

The force balance equation for an elastinous and collagenous cylindrical membrane subject to a constant axial stretch $\lambda_z$ and an internal pressure $P$ can be expressed as

$$1 = \frac{1}{P R \lambda_z} \left( m^E S^E + \frac{m^C}{\lambda^2_\beta} \right),$$

(9)
Fig. 2. Maps of a membranous cylinder. In the loaded configuration $\Omega^l$, the cylinder has an axial stretch $\lambda_z$ and a circumferential stretch $\lambda$. The stretch of the elastin is defined relative to the unloaded configuration $\Omega_0$, whereas the stretch of the collagen fibres is defined relative to the configuration that they are recruited to load bearing $\Omega^R$.

where $\hat{S}^E$ is the azimuthal second Piola–Kirchoff stress of the elastin and $\hat{\sigma}^C$ is the azimuthal Cauchy stress due to contributions from the collagen fibres of pitch $\pm \beta$, i.e.

$$\hat{S}^E \equiv \frac{\partial \hat{\Psi}^E}{\partial E_{22}}, \quad \hat{\sigma}^C \equiv (\lambda^C_\beta)^2 \frac{\partial \hat{\Psi}^C_\beta}{\partial E^C_\beta} \cos^2 \beta, \quad (10)$$

and $E_{22}$ is the azimuthal Green–Lagrange strain (see (A.7) and (A.17)). Note that the use of different stress measures to depict the response of the elastin and collagen is convenient to simplify the notation of the theoretical formulation. For derivation of (9), see Appendix A.3.

In the initial loaded configuration, i.e. $\Omega^l$ at $t = 0$, the membrane is assumed to be in mechanical and material equilibrium. The stretch $\lambda^C_\beta$ of the collagen is constant and equal to the attachment stretch $\lambda^C_{AT}$.

3.1 Proportion of load borne by the elastinous constituent

The proportion of load borne by the elastinous constituents of a loaded artery may be experimentally determined. Hence, it is natural to represent this with a parameter which we denote as $P^{E:C}$. Consequently, $(1 - P^{E:C})$ represents the proportion of load borne by the collagenous constituents. From inspection of (9), it can be seen that

$$P^{E:C} = \frac{1}{P} \left( \frac{H}{R \lambda_z} m^E \hat{S}^E \right), \quad 1 - P^{E:C} = \frac{1}{P} \left( \frac{H}{R \lambda_z} m^C \hat{\sigma}^C \right), \quad (11)$$

and evaluation of $P^{E:C}$ at $t = 0$, i.e. $P^{E:C}_0$, yields that

$$P^{E:C}_0 = \frac{1}{P} \left( \frac{H}{R \lambda_z} \delta^E_0 \right), \quad 1 - P^{E:C}_0 = \frac{1}{P} \left( \frac{H}{R \lambda_z} \delta^C_{AT} \right), \quad (12)$$
where the subindex 0 denotes a variable evaluated at \( t = 0 \). Note \( \hat{\sigma}^C = \hat{\sigma}^C(\lambda^C) \) and \( \lambda^C_{\beta} \big|_{t=0} = \lambda^C_{\text{AT}} \), hence we have introduced the terminology \( \hat{\sigma}^C_{\text{AT}} = \hat{\sigma}^C(\lambda^C_{\beta} = \lambda^C_{\text{AT}}) \equiv \hat{\sigma}^C \big|_{t=0} \).

We now analyse (9) for two special cases. Firstly, we consider the governing equation for mechanical and material equilibrium for a collagenous membrane (i.e. \( m^E = 0 \)) with \( \lambda^C_{\beta}(t) = \lambda^C_{\text{AT}} = \text{constant} \). This example illustrates the adaption of the collagen fibre concentration necessary to maintain mechanical equilibrium due to geometrical changes. We then consider the mechanical equilibrium equation for an elastinous and collagenous membrane, subject to the condition \( \lambda^C_{\beta}(t) = \lambda^C_{\text{AT}} = \text{constant} \), as the elastin degrades.

### 3.2 Mechanical and material equilibrium for a collagenous cylindrical membrane

The governing equation for mechanical equilibrium for a collagenous cylindrical membrane subject to a constant axial stretch \( \lambda_z \) and constant pressure \( P \) is given by inserting \( m^E = 0 \) into (9), i.e.

\[
P = \frac{H m^C \hat{\sigma}^C}{R \lambda_z \lambda^2_{\beta}}.
\]

(13)

We first consider the solutions of this equation assuming that the ‘collagen is always in material equilibrium’, i.e. \( \lambda^C_{\gamma} = \lambda^C_{\text{AT}} \) and thus \( \hat{\sigma}^C = \hat{\sigma}^C_{\text{AT}} = \text{constant} \), hence for this special case, we have

\[
P = \frac{H \hat{\sigma}^C_{\text{AT}} m^C \left( \frac{\lambda^C_{\beta}}{\lambda^C_{\beta_0}} \right)^2}{R \lambda_z \lambda^2_{\beta_0}}.
\]

(14)

On inspection of (14), it can be seen that if the fibre concentration is constant (i.e. \( m^C(t) = 1, \forall t \geq 0 \)), then the load bearing of the collagenous material decreases (given that it is assumed to remodel to a constant equilibrium attachment stretch) by a factor \( \left( \frac{\lambda^C_{\beta}}{\lambda^C_{\beta_0}} \right)^2 \) as the stretch \( \lambda^C_{\beta} \) resolved in the directions of the fibres increases, i.e. as the circumferential stretch increases. An alternative interpretation is that to maintain mechanical equilibrium for fixed pressure \( P \), for varying diameters, the fibre concentration must evolve according to

\[
m^C = \left( \frac{\lambda^C_{\beta}}{\lambda^C_{\beta_0}} \right)^2.
\]

(15)

### 3.3 Evolution of the fibre concentration to compensate for elastin loss

We now consider the membrane to be comprised of elastinous and collagenous material and investigate the evolution of the collagen concentration that is necessary to maintain mechanical and material equilibrium as the elastin degrades. To assist the analysis, we decompose the collagen fibre concentration \( m^C \) into two additive components \( m^C_1 \) and \( m^C_2 \), i.e.

\[
m^C = m^C_1 + m^C_2
\]

(16)

such that

\[
m^C_1 = \left( \frac{\lambda^C_{\beta}}{\lambda^C_{\beta_0}} \right)^2, \quad m^C_2 \big|_{t=0} = 0.
\]

(17)
This subtle formulation enables a clear interpretation of the evolution of the fibre concentration as the elastin degrades: \( m_1^C \) relates to increases of the fibre concentration to maintain the contribution to load bearing of the original collagenous constituents due to geometrical changes; \( m_2^C \) relates to increases of the fibre concentration to compensate for the loss of the elastinous constituents.

Insertion of (16) into (9) and using definition (17) and the requirement that the collagen is always in material equilibrium (\( \hat{\sigma}^C_{,\beta} = \hat{\sigma}^C_{,\lambda} \)), the governing equation for mechanical equilibrium may be expressed as

\[
1 = \frac{1}{P} \frac{H}{R \lambda_2} \left( m^E \hat{\lambda}^E + m^C_1 \frac{\hat{\sigma}^C_{,\beta}}{\lambda_2^2 \beta_0} + m^C_2 \frac{\hat{\sigma}^C_{,\lambda}}{\lambda_2^2 \beta} \right). \tag{18}
\]

We now suppose that the elastin can degrade and we investigate the evolution of the fibre concentration component \( m^C_2 \) that is necessary to compensate for the loss of elastinous material to maintain mechanical equilibrium. Now, \( \frac{\hat{\sigma}^C_{,\beta}}{\lambda_2^2 \beta_0} \) is constant, hence (18) implies that the summation of the terms \( m^E \hat{\lambda}^E \) and \( m^C_2 \frac{\hat{\sigma}^C_{,\lambda}}{\lambda_2^2 \beta} \) is constant, therefore

\[
\left( m^E \hat{\lambda}^E + m^C_1 \frac{\hat{\sigma}^C_{,\beta}}{\lambda_2^2 \beta_0} \right) \bigg|_t = \left( m^E \hat{\lambda}^E + m^C_2 \frac{\hat{\sigma}^C_{,\lambda}}{\lambda_2^2 \beta} \right) \bigg|_{t=0} = \hat{\lambda}^E \bigg|_{t=0} = \hat{\lambda}^E_0, \tag{19}
\]

given that \( m^C_1 \big|_{t=0} = 0 \) and \( m^E \big|_{t=0} = 1 \). The above expression (19) yields an expression for \( m^C_2(t) \), i.e.

\[
m^C_2 = \left( \frac{\lambda_2^2 \beta_0}{\lambda_2^2 \beta} \right) \left( \frac{P^E_{0^C}}{1 - P^E_{0^C}} \right) \left( 1 - m^E \frac{\hat{\lambda}^E}{\hat{\lambda}^E_0} \right), \tag{20}
\]

where (12) has been used to determine \( P^E_{0^C} / (1 - P^E_{0^C}) \). The decomposition (16) together with (17) and (20) yields an explicit expression for the evolution of the fibre concentration such that the cylindrical membrane is in mechanical equilibrium and, in addition, that the collagen is in material equilibrium:

\[
m^C = m^C_1 + m^C_2 = \left( \frac{\lambda_2 \beta_0}{\lambda_2 \beta} \right)^2 \left[ 1 + \frac{P^E_{0^C}}{1 - P^E_{0^C}} \left( 1 - m^E \frac{\hat{\lambda}^E}{\hat{\lambda}^E_0} \right) \right]. \tag{21}
\]

3.3.1 Calculation of the evolution of \( \frac{dm^C}{dt} \). We now differentiate (21) to obtain an explicit expression for the rate at which the fibre concentration evolves to maintain mechanical and material equilibrium as the elastin degrades. Inspection of the functional form of \( \frac{dm^C}{dt} \) may then give guidance to the appropriate functional forms to adopt for the fibre concentration evolution equations. It is deduced that (for details, see Appendix A.4)

\[
\frac{dm^C}{dr} = \frac{dm^C_1}{dr} + \frac{dm^C_2}{dr} = \frac{1}{\lambda_2^2 \beta_0} 2 \lambda \cos^2 \beta \frac{d\lambda}{dr} + \frac{2m^C_2 \lambda \cos^2 \beta \frac{d\lambda}{dr}}{\lambda_2^2 \beta} \frac{d\lambda}{dr}
\]

\[
- \left( \frac{\lambda_2 \beta_0}{\lambda_2 \beta} \right)^2 \frac{P^E_{0^C}}{1 - P^E_{0^C}} \left( \frac{m^E \hat{\lambda}^E}{\hat{\lambda}^E_0} \frac{d\lambda}{dr} + \hat{\lambda}^E \frac{dm^E}{dr} \right). \tag{22}
\]
The first term on the right-hand side represents the rate of increase in fibre concentration necessary to maintain the magnitude of the load bearing of the original collagen (at \( t = 0 \)) as the circumferential stretch \( \lambda \) changes. The second and third terms represent the increases in fibre concentration to compensate for the loss of load bearing by the elastious constituents. Finally, relations (16) and (17) imply that

\[
m^C = m^C_2 + \left( \frac{\lambda \beta}{\lambda \beta_0} \right)^2.
\]  

so that (22) may be expressed in terms of \( m^C \), i.e.

\[
\frac{dm^C}{dt} = \frac{2\lambda \cos^2 \beta}{\beta^2} \cdot m^C \frac{d\lambda}{dt} - \left( \frac{\lambda \beta}{\lambda \beta_0} \right)^2 \frac{P^E}{1 - P^E^0} \left( \frac{m^E}{S^E_0} \frac{dS^E}{d\lambda} \frac{d\lambda}{dt} + \frac{\dot{S}^E}{S^E_0} \frac{dm^E}{dt} \right).
\]  

(24)

4. Deformation and remodelling of a spherical membrane

A spherical membrane is modelled as a thin structure of undeformed radius \( R \) and thickness \( H \). The collagen is assumed to have an isotropic distribution such that the membrane maintains a spherical geometry when subject to an internal pressure \( P \). For instance, at each point in the tissue fibre, orientations are uniformly distributed in the range \([0, 2\pi)\), e.g. \( \gamma_i = 2i\pi / N, i \in \{0, 1, \ldots, N - 1 : N > 2\} \), and each fibre has identical mechanical properties. Due to the axisymmetry of the deformation, the collagen fibre stretch is independent of its orientation within the membrane and thus may simply be denoted \( \lambda^C \). Similarly, the recruitment stretches are independent of the fibre orientations and are thus denoted \( \lambda^R \).

The SEF (7) for the collagen may be expressed as

\[
\psi^C = \sum_{i=0}^{N-1} m^C_{\gamma_i} \hat{\psi}_{\gamma_i}(\lambda^C_{\gamma_i}, \lambda^R_{\gamma_i})) = \hat{\psi}^f(\lambda^C(\lambda, \lambda^R)) \sum_{i=1}^{N-1} m^C_{\gamma_i},
\]  

(25)

where we have introduced \( \hat{\psi}^f \equiv \hat{\psi}_{\gamma_i} \) given that \( \hat{\psi}_{\gamma_i} = \hat{\psi}_{\gamma_j}, \forall i, j \in \{0, 1, \ldots, N - 1 : N > 2\} \). Now, to achieve axisymmetric deformation, the material must be symmetric, hence the remodelling must be such that

\[
m^C_{\gamma_i} = m^C_{\gamma_j}, \quad \forall i, j \in \{0, \ldots, N - 1 : N > 2\},
\]  

(26)

hence we may define \( m^C_{\gamma_i} = m^C_{\gamma_j} \) and thus subsequently define \( m^C = N m^C_{\gamma_i} = \sum_{i=0}^{N-1} m^C_{\gamma_i} \). Consequently, the SEF (25)2, which models the isotropic mechanical response of the collagen, may simply be expressed as

\[
\psi^C = m^C \hat{\psi}^f(\lambda^C(\lambda, \lambda^R)).
\]  

(27)

Figure 3 illustrates the reference configurations of the spherical membrane. In the unloaded configuration \( \Omega_0 \), the sphere has the radius \( R \). In the loaded configuration \( \Omega^L \), the sphere is subject to a stretch \( \lambda \) (note that the stretch is defined with respect to the reference configuration \( \Omega_0 \)) and thus has radius \( \lambda R \) and thickness \( h = H / \lambda^2 \). The collagen stretch in the configuration \( \Omega^L \) is defined relative to the recruitment configuration \( \Omega^R \).
In the unloaded configuration \( \Omega_0 \), the radius of the sphere is \( R \) and the collagen fibres are crimped. In the loaded configuration \( \Omega^l \), the sphere has a radius \( \lambda R \). In the recruitment configuration \( \Omega^R \), the undulation of the collagen fibres disappears and collagen begins to bear load: \( \lambda = \lambda^R \) and the stretch of a collagen fibre is \( \lambda^C_{AT} = 1 \). The stretch of the elastin is defined relative to \( \Omega_0 \), whereas the stretch of the collagen fibres is defined relative to \( \Omega^R \).

The governing equation for a spherical membrane (see Appendix A.5 for details) subject to an internal pressure \( P \) is

\[
1 = \frac{1}{P} \frac{2H}{R} \left[ m^E \frac{\delta^E}{\lambda} + m^C_1 \left( \frac{\lambda_0}{\lambda} \right)^3 \frac{\sigma^C}{\lambda^3_0} + m^C_2 \frac{\sigma^C}{\lambda^3} \right],
\]

where, as for the example of a cylindrical membrane, we have introduced \( m^C = m^C_1 + m^C_2 \) such that \( m^C_2|_{t=0} = 0 \) to facilitate the interpretation of the evolution of the fibre concentration as the elastin degrades.

As before, we denote \( P^{E:C} \) to be the proportion of load borne by the elastinous constituents. From inspection of (28), it can be seen that

\[
P_0^{E:C} \equiv P^{E:C} \bigg|_{t=0} = \frac{2H m^E \delta^E}{PR\lambda} \bigg|_{t=0} = \frac{2H \delta^E}{PR\lambda_0},
\]

\[
1 - P_0^{E:C} \equiv 1 - P^{E:C} \bigg|_{t=0} = \frac{2H m^C \sigma^C}{PR\lambda^3} \bigg|_{t=0} = \frac{2H \sigma^C_{AT}}{PR\lambda_0^3},
\]

given that \( m^E|_{t=0} = 1 \), \( m^C_1|_{t=0} = 1 \) and \( m^C_2|_{t=0} = 0 \).

In the initial loaded configuration of the sphere at \( t = 0 \), the stretch, the radius and the thickness of the loaded membrane are denoted by \( \lambda_0 \), \( \lambda_0 R \) and \( h_0 = H/\lambda_0^2 \), respectively. The collagen fibre stretch \( \lambda^C \) equals the attachment stretch \( \lambda^C_{AT} \). In the initial configuration, the membrane is in mechanical and
material equilibrium. The governing equation for mechanical equilibrium is now analysed under the assumption that the collagen is always in a state of material equilibrium, i.e. $\lambda^C = \lambda^C_{AT}$.

In this special case, the governing equation (28) reduces to

$$1 = \frac{1}{P} \frac{2H}{R} \left[ m^E \frac{\dot{\lambda}}{\lambda} + m^C \left( \frac{\lambda_0}{\lambda} \right)^3 \frac{\dot{\lambda}^C_{AT}}{\lambda_0^3} + m^C \frac{\dot{\sigma}^C_{AT}}{\lambda^3} \right].$$  

(31)

On inspection of (31), it can be seen that if the fibre concentration is constant (i.e. $m^C_1(t) = 1$, $m^C_2(t) = 0, \forall t \geq 0$), then the load bearing of the collagen decreases by a factor $(\lambda/\lambda_0)^3$ as the radius increases by a factor $(\lambda/\lambda_0)$. Alternatively, if we require that the contribution to load bearing of the collagen to be invariant of the configuration it is recruited, we require that the fibre concentration to be a function of the circumferential stretch, i.e.

$$m^C_1 = \left( \frac{\lambda}{\lambda_0} \right)^3.$$

(32)

Thus, for the collagen to maintain its load bearing, it must increase its fibre concentration by the cube of the relative change of the circumferential stretch.

4.1 Evolution of the fibre concentration to compensate for elastin loss

We allow the elastin to degrade and specify that $m^C_1$ remodels according to (32). We investigate the evolution of $m^C_2$ which is necessary to compensate for the loss of elastinous material to maintain equilibrium. First note that (31) implies that

$$\left( m^E \frac{\dot{\lambda}}{\lambda} + m^C_2 \frac{\dot{\sigma}^C_{AT}}{\lambda^3} \right)_{|t=0} = \left( m^E \frac{\dot{\lambda}}{\lambda} + m^C_2 \frac{\dot{\sigma}^C_{AT}}{\lambda^3} \right)_{|t=0} = \frac{\dot{\lambda}}{\lambda_0},$$

(33)

given $m^C_1|_{t=0} = 1, m^C_2|_{t=0} = 0$ and $m^E|_{t=0} = 1$. Consequently, from (29)$_3$, (30)$_3$ and (33), an explicit expression for $m^C_2(t)$ can be derived according to

$$m^C_2 = \frac{P^E_C}{1 - P^E_C} \left( \frac{\lambda}{\lambda_0} \right)^3 \left( 1 - m^E \frac{\dot{\lambda}^C_{AT}}{\dot{\lambda}^C_{AT}^0} \right),$$

(34)

and thus with (32) and (16),

$$m^C = m^C_1 + m^C_2 = \left( \frac{\lambda}{\lambda_0} \right)^3 \left[ 1 + \frac{P^E_C}{1 - P^E_C} \left( 1 - m^E \frac{\dot{\lambda}^C_{AT}}{\dot{\lambda}^C_{AT}^0} \right) \right].$$

(35)

4.1.1 Calculation of the evolution of $d m^C/dt$. An explicit expression for the rate at which the fibre concentration remodels to maintain mechanical and material equilibrium is (see Appendix A.6 for details)

$$\frac{d m^C}{d t} = m^C \frac{3}{\lambda} \frac{d \lambda}{d t} - \frac{P^E_C}{1 - P^E_C} \left( \frac{\lambda}{\lambda_0} \right)^3 \left( m^E \frac{d \dot{\lambda}}{d t} + \frac{\dot{\lambda}^E}{\dot{\lambda}^E_0} \frac{d m^E}{d t} + m^E \frac{d \dot{\lambda}}{d t} \right).$$

(36)
5. Collagen fibre concentration evolution for cylindrical and spherical membranes

We start by discussing the evolution of the collagen fibre concentration for cylindrical and spherical membranes to maintain mechanical and material equilibrium. Intuitively, increases in collagen are necessary to compensate for the loss of load bearing by the elastinous constituents as they degrade. However, we observe (see Sections 3.2 and 4) that additional increases are necessary to maintain mechanical equilibrium due to the enlargement of the geometry. Indeed, for a purely collagenous membrane, the collagen fibre concentration has to increase by a factor \( \left( \frac{\lambda}{\lambda_0} \right)^2 \) for the cylindrical membrane (see, e.g. (15)) and by a factor \( \left( \frac{\lambda}{\lambda_0} \right)^3 \) for the spherical membrane (see, e.g. (31)). These observations are accounted for as follows: suppose the cylindrical membrane enlarges by a factor \( \nu = \frac{\lambda}{\lambda_0} \) and in this new configuration, it is in mechanical and material equilibrium. Assuming incompressibility of arterial tissue implies that the thickness decreases by a factor \( \nu \). The Cauchy stress of the collagen fabric is invariant of the configuration that it is recruited to load bearing (see, e.g. (10)), hence the load bearing of the collagen fabric (Cauchy stress multiplied by deformed thickness) decreases by \( \nu \). Now, the force (pressure multiplied by area) acting on any given cylindrical segment has increased by a factor \( \nu \). Hence, the conclusion follows from a combined effect of the decrease in load bearing of the collagen fabric (at fixed collagen stretch) and the increase in the force acting on the cylindrical membrane.

Similarly, consider the force balance on a hemispherical section of a membrane. It is straightforward to derive that for mechanical equilibrium, \( \sigma^C h l = \pi (\lambda R)^2 P \), where \( h \) is the deformed thickness and \( l = 2\pi \lambda R \) is the circumference of the hemisphere. Now, assume that the hemisphere is initially in mechanical equilibrium when \( \lambda = \lambda_0 \) and consider the conditions for mechanical equilibrium if we suppose that the radius increases by a factor \( \nu = \frac{\lambda}{\lambda_0} \). In this scenario, (i) the membrane will decrease in thickness by a factor \( \nu^2 \), (ii) the force acting on the hemisphere increases by a factor \( \nu^2 \) and (iii) the force due to the collagen decreases by a factor \( \nu \) (this is due to the fact that while the membrane thickness decreases by a factor \( \nu^2 \), the circumference section along which the stress acts increases by a factor \( \nu \)). Hence, the factor \( \left( \frac{\lambda_0}{\lambda} \right)^3 \) appearing in (31) follows.

Next, we compare the increases of \( m^C \) to compensate for complete loss of the elastinous constituents for the cylindrical and spherical membranes, see (21) and (35), respectively. For example, if we suppose that elastin originally bears 80% of the load, the elastin is degraded completely to zero, fibres are arranged azimuthally for the cylindrical membrane (\( \beta = 0 \)) and the diameter enlarges by a factor of 2, then it is straightforward to calculate that the fibre concentration must increase by a factor of 20 to achieve mechanical and material equilibrium for the cylindrical membrane and by a factor of 40 for the spherical membrane. Notably, this is independent of the functional form adopted for the collagen constitutive model due to the assumption that the fibril undulation distribution does not change and the attachment stretch is constant. However, note that if the collagen is not in material equilibrium \( \lambda_C > \lambda_{CA} \), then lower values of \( m^C \) would satisfy the governing equations for mechanical equilibrium, i.e. (9) and (28), assuming that the functional form of the stress response of the collagen is an increasing function of the collagen stretch.

Finally, we compare the collagen fibre concentration evolution for cylindrical and spherical membranes, i.e. (24) and (36), respectively. To simplify the comparison, we suppose an exponential degradation of elastin, i.e.

\[
m^E(t) = \exp(-Bt) \quad \Rightarrow \quad m^E(t) = -\frac{1}{B} \frac{dm^E}{dt}, \tag{37}
\]

where \( m^E(T) = m^{E\text{Min}} < 1 \) and \( m^{E\text{Min}} \) is a specified concentration of elastin at a denoted time \( T \). This implies that \( B = -\ln m^{E\text{Min}} / T > 0 \), thus the fibre concentration evolution equation (24) for the
cylindrical membrane can be expressed as

\[
\frac{dm^C}{dt} = \frac{2\lambda \cos^2 \beta}{\lambda_\beta^2} m^C \frac{d\lambda}{dt} + \left(\frac{\lambda_\beta}{\lambda_\beta^0}\right)^2 \frac{P_0^{E-C}}{1 - P_0^{E-C}} \frac{dm^E}{dt} \left(\frac{\hat{S}^E}{\hat{S}^E_0} - \frac{1}{B \hat{S}^E_0} \frac{d\hat{S}^E}{dt}\right)
\]

(38)

since \(dm^E/dt < 0, \forall t \geq 0\). Similarly, adopting an exponential degradation of elastin for the spherical membrane, (36) becomes

\[
\frac{dm^C}{dt} = \frac{3m^C d\lambda}{\lambda} + \frac{dm^E}{dt} \left(\frac{\lambda}{\lambda_0}\right)^2 \frac{P_0^{E-C}}{1 - P_0^{E-C}} \left(\frac{\hat{S}^E}{\hat{S}^E_0} + \frac{\hat{S}^E}{B \lambda \hat{S}^E_0} \frac{d\lambda}{dt} - \frac{1}{B \hat{S}^E_0} \frac{d\hat{S}^E}{dt}\right)
\]

(39)

If the cylindrical membrane has azimuthally orientated fibres (\(\beta = 0\)), (38) becomes

\[
\frac{dm^C}{dt} = \frac{2m^C d\lambda}{\lambda} + \frac{dm^E}{dt} \left(\frac{\lambda}{\lambda_0}\right)^2 \frac{P_0^{E-C}}{1 - P_0^{E-C}} \left(\frac{\hat{S}^E}{\hat{S}^E_0} + \frac{\hat{S}^E}{B \lambda \hat{S}^E_0} \frac{d\lambda}{dt} - \frac{1}{B \hat{S}^E_0} \frac{d\hat{S}^E}{dt}\right)
\]

(40)

and, based on this assumption, we thus obtain a general differential equation for the rate of evolution of the fibre concentration for the cylindrical and spherical membranes, i.e.

\[
\frac{dm^C}{dt} = a_1 \frac{m^C d\lambda}{\lambda} + \frac{dm^E}{dt} \left(\frac{\lambda}{\lambda_0}\right)^2 \frac{P_0^{E-C}}{1 - P_0^{E-C}} \left(1 + \frac{\alpha_2}{B \lambda} \frac{d\lambda}{dt} - \frac{1}{B \hat{S}^E_0} \frac{d\hat{S}^E}{dt}\right)
\]

(41)

where \((\alpha_1, \alpha_2) = (2, 0)\) for the cylindrical membrane and \((\alpha_1, \alpha_2) = (3, 1)\) for the spherical membrane.

Notably, the functional forms are very similar to achieve stabilization. Naturally, as one would expect, the rate of increase of the fibre concentration necessary for stabilization is larger for the spherical membrane as opposed to \(\alpha_1 = 2\) for the cylindrical membrane. This suggests that during the development of an aneurysm, as the geometry of the arterial tissue evolves from an approximately cylindrical to a saccular topology, the synthesis of collagen may not have to increase significantly to stabilize growth.

Fibroblasts are stimulated with mechanical forces relative to their local mechanical environment, i.e. their local reference configuration. They attempt to reduce their stretch and reach a new equilibrium by restructuring their cytoskeleton and the ECM contacts (see, e.g. Fig. 1 in Chiquet et al. (2003) which illustrates possible responses of fibroblasts on elastic substrates to stretch and relaxation). If it is assumed that the local reference configuration of the fibroblast cell is similar to that of the collagen fabric it is maintaining, then it is natural to express (41) in respect of the reference configuration of the collagen fibres. Now,

\[
\frac{1}{\lambda_\beta} \frac{d\lambda}{dt} = \frac{1}{\lambda_\beta} \frac{d(\lambda R^C \lambda C)}{dt} + \frac{\lambda C}{\lambda_\beta} \frac{d\lambda R}{dt} = \frac{1}{\lambda_\beta} \frac{d\lambda C}{dt} + \frac{\lambda C}{\lambda_\beta} \frac{d\lambda R}{dt}
\]

(42)

and insertion of (8) into (42) yields

\[
\frac{1}{\lambda_\beta} \frac{d\lambda}{dt} = \frac{1}{\lambda_\beta} \frac{d\lambda C}{dt} + \alpha_0 \frac{\lambda C}{\lambda_\beta} (E_C - E_A t).
\]

(43)
Consequently, (41) can be expressed as
\[
\frac{dm^C}{dt} = a_1 m^C \left[ \frac{1}{\lambda} \frac{d\lambda^C}{dt} + a_0 \frac{\lambda^C}{\lambda} (E^C - E^C_{AT}) \right]
\]
\[+ \left( \frac{P_{0}^{EC}}{1 - P_{0}^{EC}} \right) \frac{dm^E}{dt} \left( \frac{\lambda}{\lambda_0} \right)^2 \frac{dS^E}{d\lambda} \left[ 1 + \frac{a_2}{B} \left( \frac{1}{\lambda^C} \frac{d\lambda^C}{dt} + a_0 \frac{\lambda^C}{\lambda} (E^C - E^C_{AT}) \right) - \frac{1}{B \frac{dS^E}{d\lambda}} \right]. \tag{44}
\]

On inspection of (44), it can be seen that the rate of increase of fibre concentration is dependent on the following:

- the current collagen fibre concentration,
- the deviations in the collagen fibre stretch from the attachment stretch,
- the rate of change of fibre stretch,
- the rate of loss of elastin and
- the ratio of load borne by elastinous and collagenous constituents.

The first of these observations would follow from a natural assumption that the number of fibroblast cells (which deposit collagen) increases in proportion with the mass (equivalently concentration) of collagen they have to maintain. Hence, the rate of increase is proportional to the number of fibroblasts and thus proportional to the current collagen concentration. The second observation has physiological support (Chiquet et al., 2003): if the substrate is stretched, a net positive force acts on the cell–ECM contacts and integrin signalling to the nucleus results in an up-regulation of the ECM protein and a down-regulation of collagenase expression; conversely, if the substrate is relaxed or compressed, the cells’ internal cytoskeletal tension is released and it contracts. This can trigger different signals resulting in a reversed pattern of protein expression. Although we do not explicitly model protein synthesis and enzymatic degradation, the net result is to stimulate increases/decreases in the ECM which is accounted for in our framework.

The third observation requires guidance from physiological studies, i.e. it is unclear if fibroblasts are able to detect the rate of change of fibre/substrate stretch; however, this is a reasonable conjecture for experimental investigation. Similarly, the fourth observation requires guidance from physiological studies, i.e. whether fibroblasts can detect the rate of elastin degradation (perhaps by detecting local concentrations of elastase) is questionable, however, again this is a reasonable conjecture for experimental investigation. The fifth observation follows naturally from the consideration of the load bearing requirements of an elastinous and collagenous tissue, i.e. if a greater proportion of load is borne by the elastin and the elastin degrades, then the collagen fabric must adapt more quickly to maintain the mechanical functionality of the tissue; conversely, if the elastin bears negligible load, then from a purely mechanical point of view, the adaptive response of the collagen fabric would not need to be sensitive to the rate of loss of elastin.

6. Numerical examples

In this section, we consider specific numerical examples for the growth and remodelling of membranes. An elastin degradation is prescribed and the collagen concentration evolves to maintain mechanical equilibrium. In contrast to the analysis of sections 3 to 5, we do not impose the condition that the collagen
must be in material equilibrium, i.e. we allow \( \lambda^C \neq \lambda_{AT}^C \). Naturally, a requirement for stabilization of the membrane, i.e. remodelling towards a material equilibrium, is that \( \lambda^C \to \lambda_{AT}^C \).

The theoretical analysis yielded the governing evolution equation (44) for the fibre concentration that would appear to be consistent with the underlying physiology. However, (44) has been derived under the assumption that the collagen is always in material equilibrium (\( \lambda^C = \lambda_{AT}^C \)) and thus only acts as a guide to the functional form to adopt for the fibre concentration evolution equation. More generally, we propose

\[
\frac{d m^C}{dt} = \mathcal{F} \left( m^C, (E^C - E_{AT}^C), \frac{d \lambda^C}{dt}, \left| \frac{dm^E}{dt} \right|, \frac{P^E}{1 - P_{0}^{E,C}} \right)
\]  

(45)

However, for the purposes of the subsequent numerical analysis, we investigate the simpler functional form

\[
\frac{d m^C}{dt} = \left( \xi_1 m^C + \xi_2 \left| \frac{dm^E}{dt} \right| \right) (E^C - E_{AT}^C)
\]  

(46)

with the parameters \( \xi_1, \xi_2 \geq 0 \).

6.1 Specification of constitutive models

For specific numerical examples, the force balance equations (9) and (28) for mechanical equilibrium of the membranes require a specification of the functional forms of \( \hat{S}^E \) and \( \hat{\sigma}^C \). We adopt a neo-Hookean constitutive model for the elastin and a simple non-linear polynomial function for the collagen SEF \( \hat{\Psi}^C \); this simplification enables analytic determination of the collagen material constant.

6.1.1 Cylindrical membrane. We take the governing equation (9) for the mechanical equilibrium of the cylindrical membrane and assume a neo-Hookean model for the elastin of the form

\[
\hat{S}^E = c_E \left( 1 - \frac{1}{\lambda^2 \lambda^4} \right).
\]  

(47)

For ease of analysis, a simple non-linear polynomial function for the strain energy \( \hat{\Psi}^C \) stored in the collagen fabric is adopted as

\[
\hat{\Psi}^C = \frac{E_{AT}^C \kappa_C}{6} \left( \frac{E_C}{E_{AT}^C} \right)^6, \quad E^C \geq 0,
\]  

(48)

and \( \hat{\Psi}^C = 0 \) for \( E_C < 0 \). Note that the exponent must be greater than 2 to give a non-linear response for the collagen, and here, we arbitrarily choose an exponent equal to 6; note that the even power ensures positive definiteness of the SEF. Thus (see (10)\textsubscript{2} and (A.20–A.23)), we have

\[
\hat{\sigma}^C = (\lambda_R^C)^2 \kappa_C \left( \frac{E_C^\beta}{E_{AT}^C} \right)^5 \cos^2 \beta.
\]  

(49)

Insertion of (47) and (49) into (9) yields the governing equation for mechanical equilibrium.

It is assumed that collagen is recruited to load bearing at diastole. The fibres are assumed to be arranged azimuthally (\( \beta = 0 \)). Hence, for azimuthally orientated fibres, the initial value of the recruitment stretch \( \lambda_R^C \) is \( \lambda_R^{R,0} = \lambda_0 / \lambda_{AT}^C \) (see (6)). The material parameters \( c_E \) and \( \kappa_C \) can then be determined explicitly from algebraic manipulation of (11), (47) and (49).
6.1.2 Spherical membrane. The governing equation (28) for the mechanical equilibrium of the spherical membrane is given by

\[ P = \frac{2H}{R} \left( m^E \hat{S}^E + m^C \hat{\sigma}^C \right). \]  

Again, we adopt a neo-Hookean model for the elastin, which implies that

\[ \hat{S}^E = c^E \left( 1 - \frac{1}{\lambda^6} \right), \]  

and we assume a simple non-linear function for the strain energy \( \tilde{\Psi}^f \) stored in the collagen, i.e.

\[ \tilde{\Psi}^f = \frac{E^C \kappa_C}{6 \left( \frac{E^C}{E^C_{AT}} \right)^6}, \]  

which yields with (A.32)

\[ \hat{\sigma}^C = (\lambda^C)^5 \kappa_C \left( \frac{E^C}{E^C_{AT}} \right)^5. \]  

The material parameters \( c^E \) and \( \kappa_C \) can then be determined explicitly from algebraic manipulation of (51), (53), (29)\(_3\) and (30)\(_3\).

6.2 Material parameters

For both geometries (cylindrical and spherical), the material parameters are chosen to be representative for a typical healthy artery. The ratio of the wall thickness to the radius \( H/R \) of an unloaded middle cerebral artery is approximately 0.2 (Monson et al., 2005), the average in vivo axial stretch \( \lambda_z \) of fresh human cerebral blood vessels is 1.31 (Monson et al., 2003) and a typical circumferential stretch \( \lambda_0 \) is 1.3. The relative diameter change during the cardiac cycle for the carotid artery decreases with age: approximately 13% in young adults (aged 15 years) to 5% in the elderly (aged 70 years) and a 10% pulsation is representative for males/females aged 30 years (Hansen et al., 1995). A systolic pressure of 16 kPa is typical for subjects in the supine position.

We assume that the elastinous constituents (internal elastic laminae and passive smooth muscle) bear 80% of the load at systole (Watton & Hill, 2009), i.e. \( P_{E:C} = 0.8 \). The magnitude of the attachment stretch \( \lambda^C_{AT} \) is defined to be the stretch in the collagen fibre at systole at \( t = 0 \). To determine a suitable value for \( \lambda^C_{AT} \), we assume that the medial collagen fibres (with predominant azimuthal orientation) are recruited to load bearing at diastole, i.e. when the circumferential stretch is \( \lambda = \lambda_0/\lambda^S_D \), where \( \lambda^S_D \) denotes the cyclic variation in the circumferential stretch from diastolic to systolic pressure. This assumption implies that the attachment stretch \( \lambda^C_{AT} \) is 1.1. Now, we have the following set of parameters:

\[ H/R = 0.2, \quad P = 16 \text{ kPa}, \quad \lambda_z = 1.3, \quad \lambda_0 = 1.3, \quad \lambda^C_{AT} = 1.1, \quad P_{E:C} = 0.8. \]  

(54)
6.3 Growth and remodelling

6.3.1 Elastin degradation. The functional form of the degradation of the elastinous constituents is unknown. However, aneurysms probably develop over a period of years and their main pathological features are typically characterized by complete disappearance of the internal elastic lamina (Frösén et al., 2004) and thinning of the medial layer (Aoki et al., 2008). For an illustrative example, we assume an exponential degradation of elastin and suppose that after 5 years only 1% of the elastinous constituents remain:

\[ m^E(t) = 0.01^{t/5}, \quad 0 \leq t \leq 5, \]  

(55)

where \( t \) is measured in years. After \( t = 5 \), the elastinous constituents are instantaneously degraded to zero, i.e. \( m^E(t) = 0, \forall t > 5 \).

6.3.2 Collagen remodelling. As the elastin degrades, the stretch in the collagen fibres (and elastin) increases to maintain mechanical equilibrium. In arterial tissue, the collagen fibres are in a continual state of deposition and degradation and we assume that they attach in a state of stretch. To simulate this process, differential equations are utilized to remodel the recruitment stretches to restore the collagen fibre stretch to the attachment stretch (see Section 2.1.4). In the subsequent numerical models, we determine a value for the remodelling parameter \( \alpha_0 \) to be associated with a collagen half-life of 1 month (Watton, 2002; Watton et al., 2004).

6.3.3 Collagen growth. We consider a simple linear differential equation for the evolution of the fibre concentration

\[ \frac{dm^C}{dt} = \xi_0(E^C_C - E^C_{AT}), \]  

(56)

as utilized by Watton et al. (2004) and Watton & Hill (2009), where \( \xi_0 > 0 \), and we consider the newly proposed evolution equation (46) with distinct choices of parameters. Four specific cases are considered:

- growth function 1 (GF 1), i.e. (56), with \( \xi_0 > 0 \);
- growth function 2 (GF 2), i.e. (46), with \( \xi_1 > 0 \) and \( \xi_2 = 0 \);
- growth function 3 (GF 3), i.e. (46), with \( \xi_1 = 0 \) and \( \xi_2 > 0 \);
- growth function 4 (GF 4), i.e. (46), with \( \xi_1, \xi_2 > 0 \).

6.3.4 Summary of the numerical model. Equations (9) and (50) govern the equilibrium deformation field for the cylindrical and spherical membranes, respectively. An elastin degradation is prescribed utilizing (55). As the elastin degrades, the stretches of the elastin and collagen increase. The collagen remodels its reference configuration (see (8)) to simulate the process of fibre deposition and degradation in altered configurations and fibres attaching in a fixed state of stretch. The collagen concentration evolves (see (46) or (56)) to simulate the artery adapting to the loss of elastin and the enlarging geometry.

The parameters \( \xi_0, \xi_1 \) and \( \xi_2 \) for GF 1, GF 2 and GF 3 are chosen such that \( \lambda \approx 3 \) at \( t = 5 \). This is to enable a qualitative comparison of the solutions for each growth function. However, for GF 4, a non-unique set of parameter values exist that satisfy \( \lambda \approx 3 \) at \( t = 5 \). Consequently, as an example, we
utilize the parameter values obtained for GF 2 and GF 3 to illustrate the effect of this functional form on growth. For both membranes, we use $a_0 = 8 \text{ years}^{-1}$ to remodel the reference configuration of the fibres (see, e.g. (8)). For the cylindrical membrane, $\xi_0 = 70$ for GF 1; $(\xi_1, \xi_2)$ is equal to (41, 0), (0, 66), (41, 66) for GF 2, GF 3, GF 4, respectively. For the spherical membrane, $\xi_0 = 165$ for GF 1; $(\xi_1, \xi_2)$ is equal to (70, 0), (0, 150), (70, 150) for GF 2, GF 3, GF 4, respectively.

### 6.4 Results and discussion

Figure 4 illustrates the evolution of (a) the elastin stretch $\lambda$, (b) the collagen fibre stretch $\lambda^C$ and (c) the concentration $m^C$ of collagen fibres with respect to time $t$ for the cylindrical membrane. At $t = 5$, the concentration of elastin is instantaneously reduced from $m^E = 0.01$ to $m^E = 0$, however, this results in negligible change in the circumferential stretch to maintain mechanical equilibrium (see Fig. 4a). This is to be expected as the elastin has negligible contribution to load bearing at $t = 5$. Following complete degradation of the elastinous constituents, it can be seen that if the fibre concentration $m^C$ evolves according to GF 1, the membrane continues to enlarge (approximately linearly), while under GF 2 and GF 4, the membrane stabilizes in size (see Fig. 4a). GF 3 is proportional to the magnitude of the rate of loss of elastin, which decreases with time and is equal to zero for $t > 5$. Therefore, for

![Figure 4](image-url)

**Fig. 4.** Evolution of (a) elastin stretch $\lambda$, (b) collagen fibre stretch $\lambda^C$ and (c) collagen fibre concentration $m^C$ of a cylindrical membrane with time $t$ for four growth functions GF; see (46) and (56).
GF 3, the rate of increase of the $m^C$ decreases and is equal to zero for $t > 5$, and consequently, $m^C$ is constant for $t > 5$ (see Fig. 4c). Hence, the membrane increases non-linearly in size if $m^C$ evolves according to GF 3. On inspection of Fig. 4(b), it can be seen that the collagen fibre stretch $\lambda^C$ increases with time for GF 1 and GF 3, while for GF 2 and GF 4, it can be seen that $\lambda^C \rightarrow \lambda^C_{AT}$. For GF 2 and GF 4, the collagen fibre concentration stabilizes (see Fig. 4c), while for GF 3, it continues to increase since the aneurysm does not stabilize in size. Note that GF 4 prevents the initial rapid increase in fibre stretch which is observed for GF 2 and thus a lower value of $m^C$ is required to stabilize the geometry (see Fig. 4c).

Figure 5 illustrates the evolution of (a) the elastin stretch $\lambda$, (b) the collagen fibre stretch $\lambda^C$ and (c) the collagen fibre concentration $m^C$, with respect to time $t$ for the spherical membrane. As can be seen from Fig. 5(a), GF 2 and GF 4 stabilize the growth of the spherical membrane, while for GF 1 and GF 3, it continues to enlarge. The collagen fibre stretch $\lambda^C$ continues to increase for GF 1, while for GF 2, it undergoes a rapid increase initially but then decreases towards the attachment stretch $\lambda^C_{AT}$. Interestingly, GF 4, which is additionally sensitive to the rate of degradation of elastin, prevents the rapid increase in fibre stretch which is observed for GF 2. Of course, GF 3 alone fails to stabilize the membrane (see Fig. 5a,b).

![Figure 5](image-url)

**Fig. 5.** Evolution of (a) elastin stretch $\lambda$, (b) collagen fibre stretch $\lambda^C$ and (c) collagen fibre concentration $m^C$ of a spherical membrane with time $t$ for four growth functions GF; see (46) and (56).
On inspection of Fig. 5(c), it can be seen that $m_C$ stabilizes for GF 2 and GF 4 as the membrane stabilizes in size and $\lambda_C \rightarrow \lambda_C^{\text{AT}}$. For GF 1, the concentration continues to increase as the increase in collagen fibre concentration is not sufficient to stabilize the growth of the membrane. As for the cylindrical membrane, given that GF 3 is proportional to the magnitude of the rate of loss of elastin, the increase in collagen fibre concentration decreases as a function of time and, therefore, the collagen concentration is constant for $t > 5$ (see Fig. 5c), and thus the membrane increases non-linearly in size (see Fig. 5a).

Finally, we compare the qualitative behaviour of the remodelling for the cylinder and the sphere. Comparing Figs 4(a) and 5(a), it can be seen that when using GF 1, the evolution of the stretch of the sphere has greater non-linearity than for the cylinder; similarly, the fibre stretch increases more rapidly for the sphere (compare Figs 4b and 5b). It is of interest to note how much more rapidly $m_C$ is increasing for the sphere (compare Figs 5c and 4c) under GF 1; however, these increases are insufficient to stabilize the geometry and achieve material equilibrium, i.e. the fibre stretch continues to increase to maintain mechanical equilibrium, and thus it continues to enlarge. Note that GF 4 prevented the rapid increase in the fibre stretch that was observed with GF 2 for both the cylinder and the sphere (compare Figs 4b and 5b) and thus the membranes are stabilizing with smaller geometries than using GF 2 for each case. Hence, lower final increases in the fibre concentration are required to achieve stabilization using GF 4.

### 6.5 Equilibrium stabilization of the membranes

A requirement for equilibrium stabilization of the geometry of the membrane as the elastin is degraded to zero ($\lambda \rightarrow \lambda^{\text{Max}}$ as $m_E(t) \rightarrow 0$) is that the fibre concentration $m_C(t)$ tends to an upper bound $m_{UB}^C$. Insertion of $\lambda = \lambda^{\text{Max}}$ and $m_E = 0$ into (21) and (35) yields

$$m_C \rightarrow m_{UB}^C = \left(\frac{\lambda^{\text{Max}}}{\lambda_0}\right)^n \left(1 + \frac{P_0^{E:C}}{1 - P_0^{E:C}}\right), \quad (57)$$

where the exponent $n$ is equal to 2 for the cylindrical membrane (assuming azimuthally orientated fibres, i.e. $\beta = 0$) and 3 for the spherical membrane. Thus, we can calculate a value of $m_C$ to achieve stabilization of the membrane given complete degradation of elastin. Note that this is invariant of the forms of the stress responses of both the elastin and the collagen. However, it should be appreciated that (57) is derived under the assumption that the functional form of the SEF of the collagen does not change (i.e. the fibre undulation distribution does not change) and that the attachment stretch of the collagen is constant. Table 1 summarizes the elastin stretch $\lambda$, the concentration $m_C$ of collagen fibres at $t = 30$ and the upper bound of $m_C$ given by (57) for the cylindrical and spherical membranes for different growth functions. Since GF 3 clearly does not yield stabilization, we do not show the result in the table. It can be seen that for the growth functions GF 2 and GF 4, the evolved values of $m_C$ are close to (but below) $m_{UB}^C$ for both the cylindrical and the spherical membranes. As $t \rightarrow \infty$, the solutions are such that $m_C \rightarrow m_{UB}^C$.

Note that for the spherical membrane, the simulation using GF 1 has a larger $m_C$ at $t = 30$ compared to GF 4 (see Fig. 5c), however, for GF 1, the geometry continues to enlarge whereas GF 4 yields stabilization (see Fig. 5a). This is due to the fact that the increases of $m_C$ for GF 1 are not sufficient to achieve material equilibrium given the large change in dimensions, i.e. the remodelled value of $m_C$ is well below the required value for $m_{UB}^C$ for material equilibrium at a given stretch: consequently, the membrane continues to enlarge due to the collagen concentration increases being insufficient to stabilize its enlargement.
TABLE 1 Elastin stretch $\lambda$, concentration $m^C$ of collagen fibres for $t = 30$, and $m^C_{UB}$, see (57), for GF 1, GF 2, GF 4 according to (46) and (56). Values are shown for the cylindrical and spherical membranes

<table>
<thead>
<tr>
<th>Growth function</th>
<th>Cylindrical membrane</th>
<th>Spherical membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\lambda</td>
<td>_{t=30}$</td>
</tr>
<tr>
<td>GF 1</td>
<td>23.5</td>
<td>33.5</td>
</tr>
<tr>
<td>GF 2</td>
<td>6.2</td>
<td>100.7</td>
</tr>
<tr>
<td>GF 4</td>
<td>5.0</td>
<td>65.5</td>
</tr>
</tbody>
</table>

The functional form (56) adopted by Watton et al. (2004) for evolving the collagen fibre concentration cannot be obtained as a special case of (46). Although this evolution equation appears well suited to modelling the steady growth of abdominal aortic aneurysms (Watton & Hill, 2009), it does not predict aneurysms that will stabilize in size. Given that cerebral aneurysms may stabilize, alternative functional forms for the evolution of the collagen fibre concentration are required. The limitation of (56) for the evolution of the fibre concentration (assuming complete loss of elastin) is clearly observed in the numerical analysis in this paper. The membranes continue to enlarge and the collagen fibre stretch $\lambda^C$ continues to increase because the fibre concentration does not increase rapidly enough to stabilize the membrane. If stabilization is a requirement, we suggest that the evolution equation (46) is adopted instead: it is a relatively simple and physiologically intuitive relationship that appears well suited to stabilize the membranes.

The proposed computational framework is phenomenologically based. Although it illustrates the functional forms for the rate of increase of collagen concentration to stabilize an aneurysm, the parameters that control the rate of evolution of the fibre concentration do not have a biological interpretation. Further sophistications would be desirable to explicitly represent the cells that deposit the ECM and the signalling pathways that control the maintenance of the ECM. Furthermore, the framework could be developed to consider modifications to the type of the collagen deposited and remodelling of the distribution function for the population of collagen fibrils.

7. Conclusion

The analysis in this paper has highlighted several issues for the remodelling of an elastinous and collagenous membrane. A key result concerned the contribution to load bearing of the collagenous constituents as the membrane enlarges under the assumptions that the collagen is always in material equilibrium, has constant deposition stretch and constant fibril undulation distribution. It was observed for a fixed collagen fibre concentration that the contribution to load bearing decreases by the square (cube) of the relative change in the dimensions of the cylindrical (spherical) membrane. Consequently, a significant increase in fibre concentration is required to maintain the contribution to load bearing of the collagen in addition to the increases necessary to compensate for the loss of elastin.

Explicit expressions were derived for the increase of collagen fibre concentration to maintain material and mechanical equilibrium for the cylindrical and spherical membranes, i.e. (21) and (35), respectively. Differentiation of these expressions yielded explicit expressions for the rate of evolution of the fibre concentration to maintain mechanical and material equilibrium, i.e. (24) and (36). Comparison of the evolution equations of the collagen fibre concentration yields the general evolution equation (44) governing the evolution of the collagen fibre concentration of the membranes. The generalized function
(45) was then stated based on this derived function and from this a suitable novel candidate for the evolution of the collagen fibre concentration was proposed (i.e. (46)).

Numerical analysis illustrated that a simple linear differential equation for the evolution of fibre concentration did not stabilize the growth of the aneurysms. Given that some aneurysms may stabilize in size, this questions the general suitability of this evolution law. It was observed that simply using an exponential growth law for the fibre concentration (GF 2) yielded stabilization and incorporating sensitivity to the rate of elastin degradation (GF 4) improved the stability of the growth. Further experimental studies are required to give guidance to the mechanical and chemical sensory mechanisms of the fibroblast cells and how these relate to the increased deposition of collagen fibres to stabilize growth.

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REFERENCES


Appendix A

A.1 Continuum mechanical description of membrane deformation

A body-fitted coordinate system is used to describe the membrane with Lagrangian coordinates $X_\alpha$ ($\alpha = 1, 2$) parallel to the midplane and the $X_3$-coordinate perpendicular to it. The midplane is positioned at $X_3 = 0$; the upper and lower surfaces of the membrane have coordinates $X_3 = \pm H/2$, where $H$ is the thickness of the membrane in the unloaded configuration denoted $\Omega_0$. According to standard notation, upper case letters refer to the unloaded configuration, while lower case to the loaded configuration. The Einstein summation convention is used throughout. The position vector $X = X(X_\alpha)$ of a material point on the midplane of the membrane is expressed as a function of the midplane Lagrangian coordinates. The covariant base vectors, which are tangents to the coordinate lines $X_\alpha$ on the midplane, are given by

$$A_\alpha = \frac{\partial X}{\partial X_\alpha}. \quad (A.1)$$

The unit normal to the two midplane base vectors is chosen as the third midplane base vector, i.e.

$$A_3 = \frac{A_1 \times A_2}{|A_1 \times A_2|}. \quad (A.2)$$

The covariant midplane metric tensors in the unloaded configuration are $A_{ij} = A_i \cdot A_j$ ($i, j = 1, 2, 3$). During the deformation, a material point on the membrane’s midplane, which was at a position $X(X_\alpha)$ in the unloaded configuration, is displaced to a new position $x(X_\alpha)$ in the loaded reference configuration $\Omega^I$:

$$x(X_\alpha) = X(X_\alpha) + u(X_\alpha), \quad (A.3)$$

where $u(X_\alpha)$ is the midplane displacement field. The displacement field may be decomposed into the basis vectors, i.e.

$$u(X_\alpha) = u_i(X_\alpha) A_i(X_\alpha). \quad (A.4)$$

With (A.1), (A.3) and (A.4), the tangent vectors to the loaded midplane are

$$a_\alpha = \frac{\partial x}{\partial X_\alpha} = A_\alpha + \frac{\partial u}{\partial X_\alpha} A_\alpha + \frac{\partial u_i}{\partial X_\alpha} A_i + u_i \frac{\partial A_i}{\partial X_\alpha}. \quad (A.5)$$

The loaded midplane base vector $a_3$ is chosen to be perpendicular to the loaded midplane basis vectors with its magnitude defined such that the incompressibility condition is satisfied on the midplane,

$$a_3 = \frac{(a_1 \times a_2)|A_1 \times A_2|}{|a_1 \times a_2|^2} = \frac{\hat{a}_3|A_1 \times A_2|}{|a_1 \times a_2|}, \quad \hat{a}_3 = \frac{a_1 \times a_2}{|a_1 \times a_2|}. \quad (A.6)$$
Hence, using this definition, the volume metrics $\sqrt{g}$ and $\sqrt{G}$ of the loaded and unloaded midplanes are equal and thus the incompressibility condition is satisfied.

This formulation enables the components $E_{ij}$ of the symmetric Green–Lagrange strain tensor (for the midplane) to be expressed in terms of the difference of the midplane metrics, i.e.

$$E_{ij} = \frac{1}{2}(a_{ij} - A_{ij}), \quad i, j = 1, 2, 3. \tag{A.7}$$

where $a_{ij} = a_i \cdot a_j \,(i, j = 1, 2, 3)$ is the covariant midplane metric tensor of the loaded configuration.

### A.2 Governing equation for mechanical equilibrium

The principle of stationary potential energy requires that the first variation of the total potential energy vanishes (Holzapfel, 2000),

$$\delta \Pi_{\text{int}} - \delta \Pi_{\text{ext}} = 0, \tag{A.8}$$

where $\delta \Pi_{\text{int}}$ denotes the variation of the internal potential energy, while $\delta \Pi_{\text{ext}}$ denotes the variation of the external potential energy caused by the normal pressure $P$ that acts on the membrane. Hence, from (A.8), it can be concluded that the principle of virtual work in material description for the vascular membrane is

$$\int_{\Omega_0} \delta \Psi \, dV - \int_{\partial \Omega_{\sigma}} P(\hat{a}_3 \cdot \delta \mathbf{u}) \, ds = 0, \tag{A.9}$$

where $\partial \Omega_{\sigma}$ is the portion of the boundary surface on which the normal pressure $P$ is applied and $\Psi$ is the SEF per unit volume in the unloaded configuration $\Omega_0$. The infinitesimal volume element in the reference configuration is denoted by

$$dV = \sqrt{G} \, dX_1 \, dX_2 \, dX_3, \tag{A.10}$$

while the infinitesimal area element $ds$ in the plane $X_3 = \text{constant}$ in the loaded configuration is given by $ds = |a_1 \times a_2| \, dX_1 \, dX_2$. Now, with (A.4) and (A.6), the second term in (A.9) can be written as

$$P(\hat{a}_3 \cdot \delta \mathbf{u}) \, ds = P \left( \frac{a_1 \times a_2}{|a_1 \times a_2|} \right) \cdot \left( \delta u_i A_i + u_i \delta A_i \right) |a_1 \times a_2| \, dX_1 \, dX_2$$

$$= P(a_1 \times a_2) \cdot \delta u_i A_i \, dX_1 \, dX_2 \tag{A.11}$$

since $\delta A_i = 0$. Given that the membrane is relatively thin, the approximation is made that the area elements of the upper and lower surfaces are equal to that of the midplane. The assumption that the strain field in the aneurysm tissue is uniform through the thickness of the arterial wall, i.e. the strain field of the off-midplane is equal to that of the midplane, implies that $\Psi$ is independent of $X_3$. This converts the volume integral in (A.9) into a surface integral. Finally, utilizing (A.10) and (A.11), (A.9) becomes

$$\int \int \left[ H \sqrt{G} \delta \Psi - P(a_1 \times a_2) \cdot \delta u_i A_i \right] dX_1 \, dX_2 = 0, \tag{A.12}$$

where $H$ is the membrane thickness.
The 1D deformations of the cylindrical or spherical membranes may be described by one independent stretch variable, here denoted $\lambda$. Due to symmetry of the considered deformations, the function to be integrated is independent of the midplane Lagrangian coordinates $X_\alpha$, thus by considering $\Psi = \Psi(\lambda)$ and the property $a_1 \times a_2 = \sqrt{a_{11}a_{22}}\hat{a}_3$, the governing equation (A.12) for the 1D deformation of cylindrical and spherical membranes reduces to

$$H\sqrt{G}\delta\Psi - P(a_1 \times a_2) \cdot \delta u_i A_i = \left(H\sqrt{G}\frac{\partial\Psi}{\partial \lambda} - P\sqrt{a_{11}a_{22}}\frac{\partial u_i}{\partial \lambda} \hat{a}_3 \cdot A_i\right) \delta \lambda = 0,$$

which must hold for all $\delta \lambda \neq 0$; thus,

$$P = H\sqrt{G} \frac{1}{\sqrt{a_{11}a_{22}}\frac{\partial u_i}{\partial \lambda} \hat{a}_3 \cdot A_i} \frac{\partial\Psi}{\partial \lambda}, \quad \frac{\partial\Psi}{\partial \lambda} = S_{ij} \frac{\partial E_{ij}}{\partial \lambda},$$

where $S_{ij} = \frac{\partial\Psi}{\partial E_{ij}}$ are the components of the second Piola–Kirchhoff stress tensor.

### A.3 Force balance equation for a cylindrical membrane

Cylindrical polar Lagrangian coordinates $X_i (i = 1, 2, 3)$ denote arc lengths in the axial, azimuthal and radial directions, respectively. The collagen fibres are arranged at pitches of $\gamma = \pm \beta$ to the azimuthal axis relative to the unloaded configuration $\Omega_0$. The position vector $X$ of a material point on the midplane before the deformation defined with respect to a Cartesian coordinate system reads in matrix notation as

$$[X] = [R \sin \phi, R \cos \phi, X_1],$$

where $\phi \equiv X_2/R$ and $X_1 \in [0, L]$, $X_2 \in [0, 2\pi R)$. After the deformation, the material point on the midplane is displaced to the new position $x$, i.e.

$$[x] = [(R + u_3) \sin \phi + u_2 \cos \phi, (R + u_3) \cos \phi - u_2 \sin \phi, X_1 + u_1],$$

where the components $u_i$ ($i = 1, 2, 3$) denote the displacements in the axial, azimuthal and radial directions, respectively.

The midplane displacement field for an inflation of the cylindrical membrane subject to constant axial stretch $\lambda_z$ is $u_1 = (\lambda_z - 1)X_1$, $u_2 = 0$, $u_3 = R(\lambda - 1)$. Equations (A.1–A.6) are utilized to determine the metrics of the unloaded and loaded midplanes of the membrane, i.e. $A_{ij} = \delta_{ij}$, $a_{11} = \lambda_z^2$, $a_{22} = \lambda^2$, $a_{33} = (\lambda \lambda_z)^{-2}$ and $a_{ij} = 0, \forall i \neq j$. Utilizing (A.7), it is then straightforward to compute the Green–Lagrange strain components:

$$E_{11} = \frac{1}{2}(\lambda_z^2 - 1), \quad E_{22} = \frac{1}{2}(\lambda^2 - 1), \quad E_{33} = \frac{1}{2}\left(\frac{1}{\lambda_z^2\lambda^2} - 1\right),$$

and $E_{ij} = 0, \forall i \neq j$.

Figure 6 illustrates the relationships between the stretches $\lambda_C^C$ in the collagen fibres and the stretches $\lambda_C$ in the elastin resolved in the direction of the collagen fibres. For the deformation of the cylindrical membrane, the stretch $\lambda_C$ in the elastin resolved in the direction of a collagen fibre of orientation $\gamma$ to the azimuthal axis is given by

$$\lambda_C = \sqrt{\lambda_z^2 \sin^2 \gamma + \lambda^2 \cos^2 \gamma},$$

(A.18)
FIG. 6. Relationships between the elastin stretches $\lambda_\gamma$ resolved in the direction of a collagen fibre of orientation $\gamma$ and the collagen fibre stretches $\lambda_C^\gamma$ for the cylindrical membrane. Note that the fibre orientation is defined relative to the unloaded configuration $\Omega_0$. In the recruitment configuration $\Omega^R$, the stretch in the collagen fibre is $\lambda_C^\gamma = 1$.

and thus the recruitment stretch $\lambda_R^\gamma$ is

$$\lambda_R^\gamma = \sqrt{\lambda^2_\gamma \sin^2 \gamma + \lambda_{\text{rec}}^2 \cos^2 \gamma},$$

where $\lambda_{\text{rec}}$ denotes the magnitude of the circumferential stretch at a configuration in which the fibres begin to be recruited to load bearing. The Green–Lagrange strain $E_\gamma$ in the elastin resolved in the direction of a collagen fibre is $E_\gamma = E_{11} \sin^2 \gamma + E_{22} \cos^2 \gamma$, and the Green–Lagrange strain $E_C^\gamma$ in the collagen fibres is $E_C^\gamma = \frac{1}{2}((\lambda_C^\gamma)^2 - 1)$.

The midplane displacement field for the cylindrical membrane subject to radial inflation implies that $\partial u_1/\partial \lambda = 0$, $\partial u_2/\partial \lambda = 0$, and $\partial u_3/\partial \lambda = R$, and for the radial inflation of a cylinder, the base vector $\hat{a}_3$ has identical direction to unit normal to the midplane of the reference configuration, hence $\hat{a}_3 \cdot A_3 = 1$. The base vectors of the unloaded configuration are orthogonal and thus $\sqrt{G} = 1$. Using these properties, it is straightforward to deduce that (A.14)1 reduces to $P = (H/R\lambda_z)\partial \Psi/\partial E_{22}$. Utilizing (1) and the definitions of the SEFs for the elastin and collagen, i.e. (2) and (4), respectively, the governing equation for the mechanical equilibrium of the cylindrical membrane subject to a constant axial stretch $\lambda_z$ and an internal pressure $P$ is thus

$$P = \frac{H}{R\lambda_z} \left( m_E^E \frac{\partial \Psi^E}{\partial E_{22}} + \sum_{\gamma = \pm \beta} m_C^C \frac{\partial \Psi_C^\gamma}{\partial E_{22}^C} \frac{\partial E_{22}^C}{\partial E_{22}^C} \right).$$

(A.20)
Noting (6), (A.17)\textsubscript{2} and (A.18) implies that
\[
\frac{\partial E^C}{\partial E^{22}} = \frac{\partial E^C}{\partial \lambda^C} \frac{\partial \lambda^C}{\partial \lambda} \frac{\partial \lambda}{\partial E^{22}} = \lambda^C \frac{1}{\lambda} \left( \frac{1}{\lambda^C} \right)^2 \left( \frac{1}{\lambda} \right)^2 \; ;
\] (A.21)
to simplify the expressions appearing in (A.20), we use (10)\textsubscript{1} and define
\[
\hat{\sigma}^C = \left( \frac{1}{\lambda^C} \right)^2 \frac{\partial \hat{\psi}^C}{\partial E^{\gamma^C}} \cos^2 \gamma^C.
\] (A.22)
On inspection of (A.18), it can be seen that \(\lambda_{+\beta} = \lambda_{-\beta}\). We require that the collagen fabric remodels symmetrically to satisfy the assumption of axisymmetric deformations, i.e. \(\lambda_{R\beta} = \lambda_{R-\beta}\). This implies that \(\lambda_{+\beta} = \lambda_{-\beta}\) and similarly \(E_{+\beta} = E_{-\beta}\). These assumptions imply that \(\Psi_{+\beta} = \Psi_{-\beta}\) and \(\partial \Psi^C_{+\beta} \partial E^C_{+\beta} = \partial \Psi^C_{-\beta} \partial E^C_{-\beta}\). Consequently,
\[
\sum_{\gamma = \pm \beta} m^C_{\gamma} \hat{\sigma}^C_{\gamma} = \hat{\sigma}^C \sum_{\gamma = \pm \beta} m^C_{\gamma},
\] (A.23)
where we have introduced the definitions \(\lambda_{\beta} \equiv \lambda_{+\beta} = \lambda_{-\beta}\) and \(\hat{\sigma}^C \equiv \hat{\sigma}^C_{+\beta} = \hat{\sigma}^C_{-\beta}\).

To maintain a symmetrical structure of the collagen during evolution of the fibre concentration, we require that \(m_{+\beta} = m_{-\beta}\), hence we define \(m^C = m_{+\beta} + m_{-\beta}\). Utilizing (A.21)\textsubscript{3}, (10)\textsubscript{1}, (A.22) and (A.23), the force balance equation (A.20) for an elastious and collagenous cylindrical membrane subject to constant axial stretch and internal pressure can be expressed as (9).

### A.4 Derivation of \(\frac{dm^C}{dt}\) for a cylindrical membrane

Relation (20) implies that
\[
\frac{dm^{C}}{dt} = \frac{d}{dt} \left[ \frac{1}{\lambda^C(t)} \left( 1 - m^{E}(t) \frac{\hat{S}^{E}(t)}{\hat{S}^{E}_0} \right) \right], \quad \eta = \left( \frac{1}{\lambda^C(t)} \right)^2 \frac{P^{E:C}_0}{1 - P^{E:C}_0},
\] (A.24)
and hence, by applying the product rule and utilizing (A.18) and (20), we obtain from (A.24) that
\[
\frac{1}{\eta} \frac{dm^{C}}{dt} = \left( 1 - m^{E} \frac{\hat{S}^{E}}{\hat{S}^{E}_0} \right) 2 \lambda \cos^2 \beta \frac{d\lambda}{dt} - \lambda^2 \left( m^{E} \frac{d\hat{S}^{E}}{\hat{S}^{E}_0} \frac{dt}{dt} + \hat{S}^{E} \frac{dm^{E}}{dt} \right)
\]
\[
= m^C \beta \cos^2 \beta \frac{d\lambda}{dt} - \lambda^2 \left( m^{E} \frac{d\hat{S}^{E}}{\hat{S}^{E}_0} \frac{dt}{dt} + \hat{S}^{E} \frac{dm^{E}}{dt} \right).
\] (A.25)
Inserting (A.18) into (17)\textsubscript{1} and differentiating, it can be seen that
\[
\frac{dm^{C}}{dt} = \frac{1}{\lambda_{\beta 0}^2} \frac{d\lambda_{\beta 0}^2}{dt} = \frac{1}{\lambda_{\beta 0}^2} 2 \lambda \cos^2 \beta \frac{d\lambda}{dt},
\] (A.26)
and thus using (A.25)\textsubscript{2}, (A.26) and the definition (A.24)\textsubscript{2}, (16) yields (22).
A.5 Force balance equation for a spherical membrane

Spherical Lagrangian coordinates \( X_i \) \((i = 1, 2, 3)\) are adopted, where \( i \) denotes the arc lengths in the azimuthal, zenithal and radial directions, respectively. The position vector \( \mathbf{X} \), defined with respect to a Cartesian coordinate system, to a material point on the midplane before the deformation is

\[
\mathbf{X} = [ R \sin \theta \cos \varphi, R \sin \theta \sin \varphi, R \cos \theta], \tag{A.27}
\]

where \( \varphi = X_1/R, \theta = X_2/R \) and \( X_1 \in [0, 2\pi R) \) and \( X_2 \in [0, \pi R) \). After the deformation, the material point is displaced to a new position \( \mathbf{x} \) where

\[
\mathbf{x} = [(R + u_3) \sin \theta \cos \varphi, (R + u_3) \sin \theta \sin \varphi, (R + u_3) \cos \theta] \tag{A.28}
\]

and \( u_1 = 0, u_2 = 0, u_3 = R(\lambda - 1) \) denote the displacements in the azimuthal, zenithal and radial directions, respectively. The metrics of the unloaded and loaded midplanes of the membrane are determined using (A.1–A.6): \( A_{ij} = \delta_{ij}, a_{i1} = \lambda^2, a_{22} = \lambda^2, a_{33} = \lambda^{-4} \) and \( a_{ij} = 0 \ \forall \ i \neq j \). The components of the Green–Lagrange strain tensor are then computed using (A.7).

Now, \( \hat{a}_3 \cdot A_3 = 1 \) and \( \hat{a}_3 \cdot A_1 = \hat{a}_3 \cdot A_2 = 0 \). Thus, from (A.14), it can be deduced that the governing equation for the spherical membrane subject to an internal pressure \( P \) is

\[
P = \frac{H}{R\lambda} \left( \frac{\partial \Psi}{\partial E_{11}} + \frac{\partial \Psi}{\partial E_{22}} \right). \tag{A.29}
\]

We introduce the definition \( E = (\lambda^2 - 1)/2 \) such that \( E_{11} = E_{22} = E \) and define the function \( \hat{\Psi}(E) = \Psi(E_{11}(E), E_{22}(E)) \). Consequently, utilizing (2) and (27), (A.29) becomes

\[
P = \frac{2H}{R\lambda} \frac{\partial \hat{\Psi}}{\partial E} = \frac{2H}{R\lambda} \left( m^E \frac{\partial \hat{\Psi}^E}{\partial E} + m^C \frac{\partial \hat{\Psi}^t}{\partial E} \right). \tag{A.30}
\]

where \( \hat{\Psi}^E = \hat{\Psi}^E(E_{11}(E), E_{22}(E)) \) and \( \hat{\Psi}^t = \hat{\Psi}^t(E^C(E)) \), with \( E^C = [(\lambda^C)^2 - 1]/2 \). For the radial inflation of a spherical membrane, the stretch \( \lambda \) in the elastin is related to the stretch \( \lambda^C \) in the collagen simply by \( \lambda = \lambda^R \lambda^C \) and thus, the Green–Lagrange strain of a collagen fibre is \( E^C = [(\lambda^C)^2 - 1]/2 = \{E - \frac{1}{2}[(\lambda^R)^2 - 1]\}/(\lambda^R)^2 \). Consequently, \( \partial E^C/\partial E = (1/\lambda^R)^2 = (\lambda^C/\lambda)^2 \) and thus, (A.30) becomes

\[
P = \frac{2H}{R\lambda^C} \left[ m^E \frac{\partial \hat{\Psi}^E}{\partial E} + m^C \left( \frac{\lambda^C}{\lambda} \right)^2 \frac{\partial \hat{\Psi}^t}{\partial E^C} \right]. \tag{A.31}
\]

By inserting

\[
\hat{S}^E = \frac{\partial \hat{\Psi}^E}{\partial E}, \quad \hat{\sigma}^C = (\lambda^C)^2 \frac{\partial \hat{\Psi}^t}{\partial E^C} \tag{A.32}
\]

into (A.31), (28) is obtained.

A.6 Derivation of \( \text{dm}^C/\text{dt} \) for a spherical membrane

Relation (34) implies that

\[
\frac{\text{dm}^C}{\text{dt}} = \eta \frac{\text{d}}{\text{d}t} \left[ \frac{1}{\lambda^3} \left( 1 - m^E(t) \frac{\hat{S}^E(t) \lambda_0}{\delta \lambda^E(t)} \right) \right], \quad \eta = \left( \frac{1}{\lambda_0} \right)^3 \frac{P_0^{E:C}}{1 - P_0^{E:C}}, \tag{A.33}
\]
and hence, using the product rule,

\[
\frac{1}{\eta} \frac{dm_2^C}{dt} = \left(1 - m^E \frac{\dot{\hat{S}}^E \lambda_0}{\dot{\hat{S}}^E_0 \lambda} \right) \frac{3 \lambda^2 d\lambda}{dt} \\
- \lambda^2 \lambda_0 \left( m^E \frac{d\hat{S}^E}{\dot{\hat{S}}^E_0 \lambda} dt + \frac{\dot{\hat{S}}^E m^E}{\dot{\hat{S}}^E_0 \lambda} dt - \frac{m^E \dot{\hat{S}}^E \lambda d\lambda}{\dot{\hat{S}}^E_0 \lambda} dt \right). 
\] (A.34)

Utilizing (34), it can be identified that

\[
\left(1 - m^E \frac{\dot{\hat{S}}^E \lambda_0}{\dot{\hat{S}}^E_0 \lambda} \right) \lambda^2 = m^C_2 \frac{(1 - P^E:C_0) \lambda_0^3}{P^E:C_0 \lambda}. 
\] (A.35)

and, therefore, (A.34) may be expressed as

\[
\frac{dm_2^C}{dt} = \frac{3 m^C_2}{\lambda} \frac{d\lambda}{dt} - \frac{P^E:C_0}{1 - P^E:C_0} \left( \frac{\lambda}{\lambda_0} \right)^2 \left( \frac{m^E}{\dot{\hat{S}}^E_0 \lambda} \frac{d\hat{S}^E}{dt} + \frac{\dot{\hat{S}}^E}{\dot{\hat{S}}^E_0 \lambda} \frac{dm^E}{dt} - \frac{m^E \dot{\hat{S}}^E \lambda d\lambda}{\dot{\hat{S}}^E_0 \lambda} dt \right). 
\] (A.36)

Now, (32) implies that

\[
\frac{dm_1^C}{dt} = \frac{3 \lambda}{\lambda_0} \frac{1}{\lambda_0} \frac{d\lambda}{dt}, 
\] (A.37)

and thus, from (32), (A.36) and (A.37), we deduce that

\[
\frac{dm^C}{dt} = \frac{dm_1^C}{dt} + \frac{dm_2^C}{dt} \\
= \left[ \left( \frac{\lambda}{\lambda_0} \right)^3 + m^C_2 \right] \frac{3 \lambda d\lambda}{\lambda} \\
- \frac{P^E:C_0}{1 - P^E:C_0} \left( \frac{\lambda}{\lambda_0} \right)^2 \left( \frac{m^E}{\dot{\hat{S}}^E_0 \lambda} \frac{d\hat{S}^E}{dt} + \frac{\dot{\hat{S}}^E}{\dot{\hat{S}}^E_0 \lambda} \frac{dm^E}{dt} - \frac{m^E \dot{\hat{S}}^E \lambda d\lambda}{\dot{\hat{S}}^E_0 \lambda} dt \right). 
\] (A.38)

Finally, with (16) and (32), we obtain (36).