A transverse isotropic constitutive model for the aortic valve tissue incorporating rate-dependency and fibre dispersion: application to biaxial deformation

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Abstract

This paper presents a continuum-based transverse isotropic model incorporating rate-dependency and fibre dispersion, applied to the planar biaxial deformation of aortic valve (AV) specimens under various stretch rates. The rate dependency of the mechanical behaviour of the AV tissue under biaxial deformation, the (pseudo-) invariants of the right Cauchy-Green deformation-rate tensor $\mathcal{C}$ associated with fibre dispersion, and a new fibre orientation density function motivated by fibre kinematics are presented for the first time. It is shown that the model captures the experimentally observed deformation of the specimens, and characterises a shear-thinning behaviour associated with the dissipative (viscous) kinematics of the matrix and the fibres. The application of the model for predicting the deformation behaviour of the AV under physiological rates is illustrated and an example of the predicted $\sigma - \lambda$ curves is presented. While the development of the model was principally motivated by the AV biomechanics requisites, the comprehensive theoretical approach employed in the study renders the model suitable for application to other fibrous soft tissues that possess similar rate-dependent and structural attributes.

Keywords: Aortic valve, modelling, fibre dispersion, rate-dependency, biaxial deformation.

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1. Introduction

The structural composition of the aortic valve (AV) may be viewed as arrangements of elastin and collagen fibres embedded within the glycosaminoglycans (GAGs) ground matrix - see for example Anssari-Benam et al. (2011a) and Anssari-Benam et al. (2016). This structure endows the AV tissue with marked directional- and rate-dependency in its mechanical properties, i.e. anisotropy and viscoelasticity (Anssari-Benam et al., 2017). In our previous study we devised a new continuum-based model to capture these attributes by considering the mechanical contribution of the ‘*isotropic matrix*’, the circumferentially aligned collagen fibres and the viscous effects of GAGs (Anssari-Benam et al., 2017). The viscous term was introduced as an explicit function of the stretch rate, while the elastic contribution was accounted for using a *Holzappel-type* additive split of the elastic energy functions pertaining to the matrix and the fibres, respectively. In order to characterise the contribution of the ‘*isotropic matrix*’ more accurately, we recently proposed a structurally motivated energy function for the mechanical contribution of the elastin network to the overall load-bearing capacity of the AV and its non-linear mechanical behaviour attributes under tensile deformation (Anssari-Benam and Bucci, 2017). However, as with other collagenous soft tissues, collagen fibres are the principal structural elements that confer anisotropy and augmented mechanical strength to the AV matrix. Therefore, continuum-based models of the mechanical behaviour of the AV should properly incorporate how the collagen fibres are embedded within the tissue structure and correctly account for the ensuing material symmetry.

Macroscopic (see, e.g., Rock et al., 2014) and microscopic (see, e.g., Billiar and Sacks, 1997; Sacks et al., 1998) studies of the AV structure have well established that collagen fibres are principally aligned along the circumferential direction in relation to each AV leaflet. The circumferential and radial loading directions are defined in Figure 1. Therefore, a suitable class of anisotropy to model the mechanical behaviour of the AV may be considered as ‘*transverse isotropy*’ (Freed et al., 2005; Anssari-Benam et al., 2017). From a continuum mechanics point of view, this structural attribute of the AV tissue is rather convenient, because in-plane uniaxial and biaxial tensile tests do provide the required datasets that facilitate validation of models of

transverse isotropy. Those tests, however, do not provide enough independent datasets that are required to characterise models with higher class of anisotropy, e.g. two preferred directions of fibre families, as a function of invariants I_1 , I_4 and I_6 (see Holzapfel and Ogden (2009) and Ogden (2009)). However, the circumferential alignment of collagen fibres in AV tissue is not a perfect alignment, with a degree of fibre dispersion around the circumferential direction (Billiar and Sacks, 1997; Sacks et al., 1998). It is therefore important to incorporate this structural feature into the continuum-based models of the AV, for a more accurate characterisation of the biomechanical behaviour of the tissue.

The pioneering work of Freed et al. (2005) introduced the incorporation of fibre dispersion into the formulation of a continuum-based transverse isotropic model of the AV by devising a material tensor. This work was preceded by that of Sacks (2003), where the angular distribution of the collagen fibres within the AV tissue was accounted for via an ‘*angular integration*’ directly incorporating a probability density function into the second Piola-Kirchhoff stress tensor. However, those models did not include the (‘*viscoelastic*’) rate effects. To our knowledge, Anssari-Benam et al. (2017) presented the first continuum-based rate-dependent transverse isotropic model for application to the AV. That work, however, assumed perfect alignment of the fibres along the circumferential direction and did not account for fibre dispersion.

In this paper, we extend the model presented by Anssari-Benam et al. (2017) to incorporate fibre dispersion into rate-dependent continuum-based modelling of the AV. In doing so, we derive and introduce a new fibre orientation density function which is motivated based on the kinematics of fibres in tissue deformation. We show how the introduced measure of fibre dispersion into the model formulation may be treated as a *phenomenological* concept that is characterised by fitting the stress-stretch data to the model, without having direct structural data on the distribution of fibres within the specimens. We also define and present the invariants of the right Cauchy-Green deformation-rate tensor $\mathcal{E}$ associated with fibre dispersion. The model is then applied to the experimental data obtained from porcine AV specimens under planar biaxial tensile tests at two different displacement ratios and four stretch rates covering a range of 1000-fold. The rate-dependency of the tensile biaxial deformation of the AV specimens is presented, and it will be shown that the model successfully captures and characterises this behaviour.

2. Continuum mechanics framework

The framework within which we devise the constitutive relationship between stress and strain tensors is similar to that of our previous work (Anssari-Benam et al., 2017). Accordingly, for an incompressible rate-dependent continuum, the second Piola-Kirchhoff stress tensor $\mathbf{S}$ may be expressed as (Pioletti et al., 1998; Limbert and Middleton, 2004; Vogel et al., 2017)¹:

$$\mathbf{S}(\mathbf{C}, \dot{\mathbf{C}}) = 2 \frac{\partial W_e}{\partial \mathbf{C}} + 2 \frac{\partial W_v}{\partial \dot{\mathbf{C}}} - p \mathbf{C}^{-1}, \quad (1)$$

where $\mathbf{C}$ is the right Cauchy-Green tensor and $\dot{\mathbf{C}}$ is its time derivative, W_e and W_v are two distinct thermodynamics potentials referred to as the elastic strain energy and the (viscous) dissipation functions, respectively, and p is an arbitrary Lagrange multiplier enforcing incompressibility. Note that W_e and W_v may be described as functions of $(\mathbf{C})$ and $(\mathbf{C}, \dot{\mathbf{C}})$, respectively (Limbert and Middleton, 2004), i.e.:

$$\begin{cases} W_e = W_e(\mathbf{C}), \\ W_v = W_v(\mathbf{C}, \dot{\mathbf{C}}), \end{cases} \quad (2)$$

In the case of transverse isotropy, W_e and W_v will be functions of $W_e(\mathbf{C}, \mathbf{M})$ and $W_v(\mathbf{C}, \dot{\mathbf{C}}, \mathbf{M})$, where $\mathbf{M}$ denotes the preferred mean orientation in the reference configuration. It follows that W_e and W_v may be expressed as a function of five and seventeen invariants, respectively:

$$\begin{cases} W_e = W_e(I_1, \dots, I_5), \\ W_v = W_v(I_1, \dots, I_5, J_1, \dots, J_{12}), \end{cases} \quad (3)$$

where $I_i, i = 1, \dots, 5$, and $J_j, j = 1, \dots, 12$ are the respective invariants; the mathematical definition of which is given in Appendix A.

2.1. Incorporation of fibre orientation dispersion

¹ The theoretical underpinning of ‘rate-type’ viscoelastic models, whereby the viscoelastic response is determined by a stored energy function and a rate of dissipation function, has also been extensively examined in a different context through the works of K.R. Rajagopal and co-workers (see, e.g., Rajagopal and Srinivasa, 2000).

In the presence of distributed fibres within the continuum, following the frameworks presented by Gasser et al. (2006) and Holzapfel and Ogden (2010), it is assumed that W_e and W_v are not only functions of $\mathbf{C}$, $\mathcal{C}$ and $\mathbf{M}$, but are indeed also a function of the *structure tensor* $\mathbf{H}$, which accounts for the distribution of fibre orientation around a preferred mean direction. Accordingly, the existence of a fibre orientation density function, say $R(\mathbf{M})$, is postulated such that it characterises the distribution of fibres with respect to $\mathbf{M}$, where $\mathbf{M}$ is a unit vector representing the mean general preferred direction of the fibre family in the Cartesian coordinate system, as depicted in Figure 2. It is given by:

$$\mathbf{M}(\theta, \varphi) = \cos \theta \cos \varphi \mathbf{e}_1 + \cos \theta \sin \varphi \mathbf{e}_2 + \sin \theta \mathbf{e}_3, \quad (4)$$

where $\mathbf{e}_1$, $\mathbf{e}_2$ and $\mathbf{e}_3$ denote the unit vectors of the coordinate system, and the angles θ and φ are defined in Figure 2 (note that $-\pi/2 \leq \theta \leq \pi/2$ and $0 \leq \varphi \leq 2\pi$).

The fibre orientation density function $R(\mathbf{M})$ is defined such that the fraction of fibres oriented within $[(\theta, \theta + d\theta), (\varphi, \varphi + d\varphi)]$ is characterised by $R(\mathbf{M}) \cos \theta d\theta d\varphi$, while satisfying the condition of symmetry $R(\mathbf{M}) = R(-\mathbf{M})$. In addition, $R(\mathbf{M})$ is normalised according to:

$$\frac{1}{4\pi} \int_{\Omega} R(\mathbf{M}) d\omega = 1, \quad (5)$$

where $\Omega = \{\mathbf{M} \in \mathbb{R}^3, |\mathbf{M}| = 1\}$ is a unit sphere and $d\omega$ is the surface area element given by $d\omega = \cos \theta d\theta d\varphi$. Thus:

$$\frac{1}{4\pi} \int_{\varphi=0}^{2\pi} \int_{\theta=-\pi/2}^{\pi/2} R(\mathbf{M}) \cos \theta d\theta d\varphi = 1. \quad (6)$$

Let $\mathbf{N}$ represent the direction of an arbitrary fibre from the fibre family, a unit vector given by:

$$\mathbf{N}(\Theta, \Phi) = \cos \Theta \cos \Phi \mathbf{e}_1 + \cos \Theta \sin \Phi \mathbf{e}_2 + \sin \Theta \mathbf{e}_3, \quad (7)$$

as shown in Figure 2. Note that the angles Θ and Φ are defined in a similar way as θ and φ (Figure 2). The structure tensor $\mathbf{H}$ for the fibre family whose mean direction and position are represented by $\mathbf{M}$ and $\mathbf{N}$, respectively, is thus defined as:

$$\mathbf{H} = \frac{1}{4\pi} \int_{\varphi=0}^{2\pi} \int_{\theta=-\pi/2}^{\pi/2} R(\mathbf{M}(\theta, \varphi)) \mathbf{N}(\Theta, \Phi) \otimes \mathbf{N}(\Theta, \Phi) \cos \theta d\theta d\varphi, \quad (8)$$

where $\otimes$ denotes the dyadic product. Note that $\mathbf{H}$ is a structure tensor involving fibre dispersion, introduced via $R(\mathbf{M}(\theta, \varphi))$, accounting for the dispersion of fibres around a mean direction given by $\mathbf{M}(\theta, \varphi)$.

However, from a mathematical point of view, we note that $d\Theta \equiv d\theta$ and $d\Phi \equiv d\varphi$, and thus when performing the integration in equation (8) one shall note that $\cos \Theta \equiv \cos \theta$, $\cos \Phi \equiv \cos \varphi$ and similarly $\sin \Theta \equiv \sin \theta$ and $\sin \Phi \equiv \sin \varphi$. Therefore, components of the tensor $\mathbf{H}$ may be given as:

$$\begin{cases} H_{11} = \frac{1}{4\pi} \int_{\varphi=0}^{2\pi} \int_{\theta=-\pi/2}^{\pi/2} R(\mathbf{M}(\theta, \varphi)) \cos^3 \theta \cos^2 \varphi d\theta d\varphi, \\ H_{12} = \frac{1}{4\pi} \int_{\varphi=0}^{2\pi} \int_{\theta=-\pi/2}^{\pi/2} R(\mathbf{M}(\theta, \varphi)) \cos^3 \theta \sin \varphi \cos \varphi d\theta d\varphi, \\ H_{13} = \frac{1}{4\pi} \int_{\varphi=0}^{2\pi} \int_{\theta=-\pi/2}^{\pi/2} R(\mathbf{M}(\theta, \varphi)) \cos^2 \theta \sin \theta \cos \varphi d\theta d\varphi, \\ H_{22} = \frac{1}{4\pi} \int_{\varphi=0}^{2\pi} \int_{\theta=-\pi/2}^{\pi/2} R(\mathbf{M}(\theta, \varphi)) \cos^3 \theta \sin^2 \varphi d\theta d\varphi, \\ H_{23} = \frac{1}{4\pi} \int_{\varphi=0}^{2\pi} \int_{\theta=-\pi/2}^{\pi/2} R(\mathbf{M}(\theta, \varphi)) \cos^2 \theta \sin \theta \sin \varphi d\theta d\varphi, \\ H_{33} = \frac{1}{4\pi} \int_{\varphi=0}^{2\pi} \int_{\theta=-\pi/2}^{\pi/2} R(\mathbf{M}(\theta, \varphi)) \sin^2 \theta \cos \theta d\theta d\varphi. \end{cases} \quad (9)$$

We note that these equations are similar to those presented by Gasser et al. (2006), barring the differences arising as a result of adopting a different definition for the angle θ .

It may be observed that, by this definition, $\mathbf{H}$ is the weighted mean of the structure tensor $\mathbf{N} \otimes \mathbf{N}$, weighted by the fibre orientation density function $R(\mathbf{M})$ over the unit sphere Ω . It is, therefore, important to incorporate an appropriate and structurally relevant $R(\mathbf{M})$ function in order to compute $\mathbf{H}$. The choice for $R(\mathbf{M})$ will be introduced and developed in §2.3.

As previously demonstrated by Gasser et al. (2006), one may assume, without loss of generality, that the mean direction of the family of fibres in the reference configuration coincides with one of the unit vectors of the Cartesian coordinate system, say, e.g. $\mathbf{e}_3$. It therefore follows that the distribution of the fibres' orientation may be characterised using only one angle, i.e. θ , and thus $R(\mathbf{M}(\theta, \varphi))$ becomes $R(\mathbf{M}(\theta))$, also known as a 'transversely isotropic' distribution (Holzapfel and Ogden, 2010 - see §2.2 for further discussion). In this case, the normalisation condition in equation (6) becomes $\int_{-\pi/2}^{\pi/2} R(\mathbf{M}(\theta)) \cos \theta d\theta = 2$. Adopting the well-established ' κ ' notation, the structure tensor $\mathbf{H}$ may be written as:

$$\mathbf{H} = \kappa \mathbf{I} + (1-3\kappa) \mathbf{M} \otimes \mathbf{M}, \quad (10)$$

where $\mathbf{I}$ is the identity tensor, $\kappa = \frac{1}{4} \int_{-\pi/2}^{\pi/2} R(\mathbf{M}(\theta)) \cos^3 \theta d\theta$ is a measure of fibre dispersion, and $\mathbf{M}$ is pertinent to $\mathbf{e}_3$. Note that $\kappa \in [0, 1/3]$, where $\kappa = 0$ resembles no fibre dispersion, which implies ideal transverse isotropy, and $\kappa = 1/3$ corresponds to a 3D isotropic distribution.

Characterisation of κ may be achieved from experimental data on the distribution of fibre orientation within the tissue of interest, whereby the fibre orientation density function $R(\mathbf{M}(\theta))$ can be established and thus κ can be computed. In the absence of such experimental data, however, κ may also be treated as a phenomenological parameter that is quantified by fitting the experimental stress-stretch data to the continuum-based model of interest that accommodates fibre dispersion (i.e., κ) in its formulation. Both methods have been used to quantify the measure of fibre dispersion within the subject tissues. For examples of structurally driven and phenomenological application of characterising fibre dispersion the interested reader may wish to refer to the contributions by Gasser et al. (2006), Holzapfel and Ogden (2010), Holzapfel et al. (2015) and Schriefl et al. (2012, 2013).

2.2. In-plane fibre distribution

From a tissue structure point of view, the distribution of fibres within a subject tissue is such that the majority of fibres may either lie in a single plane, or are dispersed in a 3D configuration.

The literature suggests that the 3D distribution configurations have mainly been represented within the context of *transversely isotropic* distributions. A *transversely isotropic* distribution is a 3D symmetric configuration of fibre dispersion around a preferred direction $\mathbf{M}$, shown schematically in Figure 3a. This type of distribution was advocated by, and utilised in, the pioneering works of Freed et al. (2005) and Gasser et al. (2006), while an *ellipsoidal distribution* to describe orthotropic symmetries has also been presented by Ateshian et al. (2009) and Holzapfel et al. (2015).

In-plane distributions, however, arise when the fibre family is predominantly dispersed within a single plane. Within the context of a 3D transversely isotropic distribution, a (2D) in-plane distribution may be considered as the projection of the conical 3D transversely isotropic distribution into a plane passing through the centre of the cone, as shown in Figure 3b. The in-plane distribution within the plane and the unit vectors of the 3D Cartesian coordinate system are also shown in Figure 3b. We therefore note that this in-plane distribution describes how the fibres are dispersed within a single plane, and does not reflect any inhibitions for consideration within the general 3D continuum mechanics frameworks. We further note that the adopted definition of an in-plane (2D) distribution here is somewhat different to that proposed and developed in Holzapfel and Ogden (2010). For an overview of other special cases of fibre dispersion the interested reader is referred to Holzapfel et al. (2015).

The mathematical representation of the fibre orientation density function $R(\mathbf{M}(\theta))$ for 3D transversely isotropic distributions is similar to that of the 2D in-plane distributions, in that both distributions are only a function of θ , i.e. $R(\theta)$. The difference, however, is the information they embody. Transversely isotropic distributions represent information on the dispersion of fibre orientations in the transverse directions, characterising the fibre dispersion in both directions with the same distribution. In-plane distributions, however, only contain information on the in-plane dispersion of fibres, representing a single distribution.

2.3. A fibre orientation density function $R(\theta)$ motivated by fibre kinematics

Most studies to date have either considered a Gaussian (e.g., Freed et al., 2005) or a von Mises (e.g., Gasser et al., 2006; Holzapfel and Ogden, 2010; Holzapfel et al., 2015) distribution function to represent fibre dispersion. The Gaussian distribution function used by Freed et al. (2005)

incorporates an error function term, presented in the form $\frac{1}{\zeta\sqrt{2\pi}\operatorname{erf}\left(\frac{\pi}{2\sqrt{2}\zeta}\right)}\exp\left(-\frac{\theta^2}{2\zeta^2}\right)$. This

choice of function facilitates the change of limits of the integral that appears in the equations for invariants from $\int_{-\infty}^{\infty}$ to $\int_{-\pi/2}^{\pi/2}$ for the angular distribution probability density function. The von

Mises distribution used in the other cited works assumes the form $4\sqrt{\frac{b}{2\pi}}\frac{\exp[b\cos(2\theta)+1]}{\operatorname{erfi}(\sqrt{2b})}$

which is the projection of the normal distribution function onto the unit circle. This choice also facilitates obtaining a closed-form expression in calculating κ .

Alternatively, we derive and present a new distribution function motivated by the kinematics of the fibres within the tissue. Consider the vectors $\mathbf{V}$ and $\mathbf{V}'$ to represent the position vector of a fibre along the preferred direction of the fibre family in the reference and the deformed configurations such that they lie in the direction of unit vectors $\mathbf{N}$ and $\mathbf{N}'$, respectively. A schematic of this configuration is shown in Figure 4. The unit vectors $\mathbf{e}_1$ and $\mathbf{e}_3$ represent the directions of say x and y . Let us assume that the fibres are fixed at one end and may rotate only around that end. The unit vector $\mathbf{N}'$ can therefore be obtained through a rotation of $\mathbf{N}$. Let us also assume that the ensuing rotation is small (we note that, without loss of generality, any rotation may be assumed as a series of infinitely small increments of rotation). Under these assumptions, one may consider that the projections of $\mathbf{V}$ and $\mathbf{V}'$ along the x axis remains unchanged (Figure 4).

In this configuration then: $\tan\theta = y/x \Rightarrow \theta = \arctan(y/x)$. Since the kinematics of the fibres' rotation was assumed such that the projection of the position vectors is negligible along $\mathbf{e}_1$ (i.e., x) direction and is only pronounced in $\mathbf{e}_3$ (i.e., y) direction, the change in the angle θ may be obtained as: $d\theta = \frac{x}{x^2 + y^2} dy$. By dividing both sides by π we obtain:

$$\frac{d\theta}{\pi} = \frac{1}{\pi} \frac{x}{x^2 + y^2} dy.$$

(11)

Interestingly, $d\theta/\pi$ given in equation (11) has the form of a Lorentzian distribution function. The structural interpretation pertaining to this equation is that the mean direction of the family

of fibres as a result of tissue level deformation rotates in such a way that the coordinate variables x and y will have to assume a Lorentzian distribution. Since the sum of two Lorentzian variables also has to vary in a Lorentzian pattern, θ itself would follow a Lorentzian distribution pattern. It may therefore be reasonable to suggest a Lorentzian distribution function affiliated with the dispersion of fibres as

$$R(\theta) = \frac{1}{\pi} \frac{\gamma}{(\theta - \theta_0)^2 + \gamma^2}, \text{ where } \theta_0$$

specifies the location of the peak of the distribution and γ specifies the half-width at half-maximum. For a family of fibres, we note that θ_0 essentially describes the angle along which the majority of the fibres are oriented. Without loss of generality, the direction of one of the unit vectors of the Cartesian coordinate system, say $\mathbf{e}_1$, may be chosen to coincide with the direction described by the angle θ_0 . It would therefore follow that $\theta_0 = 0$ and $R(\theta)$ simplifies to

$$R(\theta) = \frac{1}{\pi} \frac{\gamma}{\theta^2 + \gamma^2}. \text{ However, in order to adjust the domain of } R(\theta) \text{ from } (-\infty, \infty) \text{ to } [-\pi/2, \pi$$

$/2]$, which is necessary to satisfy the normalisation condition and to calculate κ , we choose the projection of $R(\theta)$ onto a unit circle, also known as a wrapped Lorentzian distribution function, to represent the angular distribution density function. This function, subjected to the normalisation condition for transversely isotropic distributions discussed in §2.1, i.e.

$$\int_{-\pi/2}^{\pi/2} R(\mathbf{M}(\theta)) \cos \theta d\theta = 2, \text{ takes the form:}$$

$$R(\theta) = \frac{1 - \rho^2}{\omega \pi (1 + \rho^2 - 2\rho \cos 2\theta)},$$

(12)

where ρ varies from $[0,1)$ and it is a concentration parameter that determines the shape of the distribution, and ω is a normalisation parameter given by:

$$\omega = \frac{1 + \rho}{4\pi\sqrt{\rho}} \left[\arctan\left(\frac{2\sqrt{\rho}}{1 - \rho}\right) - \arctan\left(\frac{-2\sqrt{\rho}}{1 - \rho}\right) \right].$$

(13)

We shall therefore suggest the distribution function in equation (12) for computing the structure tensor $\mathbf{H}$, the dispersion parameter κ and the associated invariants.

Remark: Due to the mathematical nature of $R(\theta)$ in equation (12), we note that the numerical range of the resulting κ as defined in §2.1 is $[1/3, 0.5]$. In order to recover the standard range $[0, 1/3]$, we rescale κ to $(1 - 2\kappa)$ and use the rescaled measure instead. The shape of the distribution function $R(\theta)$ with varying ρ and the corresponding κ is shown in Figure 5.

2.4. The I_i invariants

With the structure tensor $\mathbf{H}$ now available, the five I_i invariants of W_e incorporating fibre dispersion may be redefined. As presented in Appendix A (equation (A.1)), I_1 , I_2 and I_3 are related with the right Cauchy-Green tensor $\mathbf{C}$ and are independent of the fibre orientation. However, the invariants I_4 and I_5 are directly affiliated with the fibre orientation and, therefore, have to be adjusted in order to incorporate fibre dispersion.

Depending on the approach employed in developing the material (e.g., Freed et al., 2005) or structure (e.g., Gasser et al., 2006) tensors to incorporate fibre dispersion in a continuum framework, the affiliated invariants have been presented in different forms. For example, Freed et al. (2005) present their ‘fourth invariant’ in the form $\mathbf{C} : \int \int R(\theta) \mathbf{N}(\theta, \varphi) \otimes \mathbf{N}(\theta, \varphi) d\theta d\varphi$, and Holzapfel and Ogden (2010) represent their I_4^* as $I_4^* = \kappa I_1 + (1 - 3\kappa) I_4$. Note that the operator $(:)$ is ‘double contraction’ and is defined as: $\mathbf{A} : \mathbf{B} = \sum_i \sum_j A_{ij} B_{ji}$. The two representations are similar; however, subtle differences emerge when the non-diagonal components of $\mathbf{C}$ and the material/structure tensors are non-zero. To maintain uniformity with the definition of the three principal invariants $I_1, \dots, I_3$ (Appendix A), and in the spirit of Holzapfel and Ogden (2010) we choose:

$$\begin{cases} I_4^* = \mathbf{CH} : \mathbf{I}, \\ I_5^* = \mathbf{C}^2 \mathbf{H} : \mathbf{I}, \end{cases} \quad (14)$$

which results in similar expressions to those presented by Holzapfel and Ogden (2010), i.e.:

$$\begin{cases} I_4^* = \kappa I_1 + (1 - 3\kappa) I_4 , \\ I_5^* = \kappa I_1 + (1 - 3\kappa) I_5 . \end{cases}$$

(15)

The five invariants of W_e may therefore be summarised as:

$$I_1 = \mathbf{C} : \mathbf{I} , \quad I_2 = \frac{1}{2} [(\mathbf{C} : \mathbf{I})^2 - (\mathbf{C}^2 : \mathbf{I})] , \quad I_3 = \det \mathbf{C} , \quad I_4^* = \mathbf{C}\mathbf{H} : \mathbf{I} , \quad I_5^* = \mathbf{C}^2 \mathbf{H} : \mathbf{I}. \quad (16)$$

We note that when there are two families of fibres with two preferred mean directions, I_6^* may be defined as:

$$I_6^* = \kappa I_1 + (1 - 3\kappa) I_6 .$$

(17)

2.5. The J_j invariants

The twelve invariants J_j of W_v , given in Appendix A (equation (A.2)), may also be revisited in light of the structure tensor $\mathbf{H}$. Of the twelve invariants, $J_1, J_2, J_3, J_6, J_7, J_8$ and J_9 are only associated with the tensor $\mathfrak{C}$ and do not accommodate fibre orientation. However, J_4, J_5, J_{10}, J_{11} and J_{12} are directly affiliated with fibre orientation and may therefore require readjustment to account for fibre dispersion. Here, we define these adjusted invariants as:

$$J_4^* = \mathfrak{C}\mathbf{H} : \mathbf{I} , \quad J_5^* = \mathfrak{C}^2 \mathbf{H} : \mathbf{I} , \quad J_{10}^* = \mathbf{C}\mathfrak{C}\mathbf{H} : \mathbf{I} , \quad J_{11}^* = \mathbf{C}\mathfrak{C}^2 \mathbf{H} : \mathbf{I} , \quad J_{12}^* = \mathbf{C}^2 \mathfrak{C}\mathbf{H} : \mathbf{I} , \quad (18)$$

which result in the following relationships:

$$\left\{ \begin{array}{l} J_4^* = \kappa J_1 + (1 - 3\kappa) J_4 , \\ J_5^* = \kappa J_2 + (1 - 3\kappa) J_5 , \\ J_{10}^* = \kappa J_6 + (1 - 3\kappa) J_{10} , \\ J_{11}^* = \kappa J_7 + (1 - 3\kappa) J_{11} , \\ J_{12}^* = \kappa J_8 + (1 - 3\kappa) J_{12} . \end{array} \right. \quad (19)$$

The seventeen invariants of W_v may therefore be summarised as:

$$\begin{aligned} I_1 &= \mathbf{C} : \mathbf{I} , \quad I_2 = \frac{1}{2} [(\mathbf{C} : \mathbf{I})^2 - (\mathbf{C}^2 : \mathbf{I})] , \quad I_3 = \det(\mathbf{C}) , \quad I_4^* = \mathbf{C} \mathbf{H} : \mathbf{I} , \quad I_5^* = \mathbf{C}^2 \mathbf{H} : \mathbf{I} , \\ J_1 &= \mathfrak{C} : \mathbf{I} , \quad J_2 = \mathfrak{C}^2 : \mathbf{I} , \quad J_3 = \det(\mathfrak{C}) , \quad J_4^* = \mathfrak{C} \mathbf{H} : \mathbf{I} , \quad J_5^* = \mathfrak{C}^2 \mathbf{H} : \mathbf{I} , \quad J_6 = \mathbf{C} \mathfrak{C} : \mathbf{I} , \\ J_7 &= \mathbf{C} \mathfrak{C}^2 : \mathbf{I} , \quad J_8 = \mathbf{C}^2 \mathfrak{C} : \mathbf{I} , \quad J_9 = \mathbf{C}^2 \mathfrak{C}^2 : \mathbf{I} , \quad J_{10}^* = \mathbf{C} \mathfrak{C} \mathbf{H} : \mathbf{I} , \quad J_{11}^* = \mathbf{C} \mathfrak{C}^2 \mathbf{H} : \mathbf{I} , \\ J_{12}^* &= \mathbf{C}^2 \mathfrak{C} \mathbf{H} : \mathbf{I} . \end{aligned} \quad (20)$$

2.6. W_e and W_v

In view of the invariants I_i and J_j (note that I_i^* and J_j^* are also functions of I_i and J_j), the second Piola-Kirchhoff stress tensor $\mathbf{S}$ in equation (1) may be re-written as:

$$\mathbf{S} = 2 \frac{\partial W_e}{\partial I_i} \frac{\partial I_i}{\partial \mathbf{C}} + 2 \frac{\partial W_v}{\partial J_j} \frac{\partial J_j}{\partial \mathfrak{C}} - p \mathbf{C}^{-1} \quad (21)$$

The relationships for $\frac{\partial I_i}{\partial \mathbf{C}}$ and $\frac{\partial J_j}{\partial \mathfrak{C}}$ are summarised in Appendix A. Note that functions W_e and W_v are indeed $W_e(\mathbf{C}, \mathbf{H})$ and $W_v(\mathbf{C}, \mathfrak{C}, \mathbf{H})$, whereby the inclusion of $\mathbf{H}$ is accounted for by the invariants I_i^* and J_j^* . We now describe the specific choices for W_e and W_v , as explicit mathematical functions of I_i , I_i^* , J_j and J_j^* .

As may be inferred from the number of invariants I_i and J_j (including I_i^* and J_j^*) presented in sections 2.4 and 2.5, a complete characterisation of the W_e and W_v functions requires

mathematical relationships that accommodate 5 and 17 invariants, respectively. From a continuum-mechanics point of view, however, conventional (bio)mechanical tests and equipment to date do not inherently provide enough independent datasets for a complete characterisation of the strain energy and viscous dissipation functions. This may be deduced mathematically, as the number of constitutive functions $\frac{\partial W_e}{\partial I_i}$ and $\frac{\partial W_v}{\partial J_j}$ appearing in equation (21) by far surpasses the number of independent stress-stretch datasets that could possibly be provided via laboratory (bio)mechanical tests. This premise has been discussed and analysed at length by Holzapfel and Ogden (2009) and Ogden (2009). In the case of planar tensile tests, it is therefore important to note that biaxial tensile tests in which only two strain components are varied independently, and uniaxial tensile tests in transverse directions, can only provide two independent stress-stretch datasets, which in turn would only allow consideration and characterisation of energy functions with two invariants. This may be improved by the addition of shear and/or rate-dependent tests and datasets; however, even then the number of available independent datasets would still be substantially below that required for a complete characterisation of W_e and W_v functions.

In order to mitigate the gap between the available experimental datasets and development of a valid continuum mechanics framework, it is admissible to assume *a priori* that W_e and W_v are a function of only certain invariants, i.e. some of the invariants are considered absent from the general forms of W_e and W_v . A standardised theoretical platform that facilitates axiomatic choices of particular functions for W_e and W_v has not been articulated in the literature concerning soft tissues, to the knowledge of the authors, if indeed ever possible to develop. However, Ogden (2009) advocates three baseline factors that provide a sound reference for a valid starting point: (i) W_e must be chosen such that the ensuing stress-stretch relationships are consistent with the experimentally observed behaviour of the subject tissue; (ii) W_e must reflect the relevant material symmetry of the subject tissue; and (iii) W_e must satisfy the condition of convexity. For the viscous dissipation function, thermodynamical requirements enforce W_v to be continuous, positive and convex with respect to $\dot{\mathbf{C}}$, while it must be equal to zero when $\dot{\mathbf{C}} = \mathbf{0}$ (Limbert and Middleton, 2004).

Taking the above considerations into account, a widely acceptable elastic strain-energy function W_e for incompressible transversely isotropic tissues that accounts for fibre dispersion

by incorporating the concept of the structure tensor $\mathbf{H}$ has been devised as (Gasser et al., 2006; Holzapfel and Ogden, 2010):

$$W_e(\mathbf{C}, \mathbf{H}) = W_e(I_1, I_4^*) = W_e^{iso}(I_1) + W_e^{fibres}(I_4^*), \quad (22)$$

where $W_e^{iso}(I_1)$ and W_e^{fibres} represent the contribution of the isotropic matrix and the family of dispersed fibres embedded within that matrix, respectively. For W_e^{iso} , we recently proposed a specialised function based on the structural and mechanical attributes of the elastin network in AV as (Anssari-Benam and Bucci, 2017):

$$W_e^{iso} = n B T N \left[\frac{1}{6N} (I_1 - 3) - \ln \left(\frac{I_1 - 3N}{3 - 3N} \right) \right], \quad (23)$$

where N is the so called Kuhn segment length, B is the Boltzmann constant, T is the absolute temperature, and n is the number of elastin chains per unit volume. For W_e^{fibres} , following Gasser et al. (2006), we choose the following function:

$$W_e^{fibres} = \frac{k_1}{2k_2} \left\{ \exp \left[k_2 (I_4^* - 1)^2 \right] - 1 \right\}, \quad (24)$$

which in view of equation (15)₁ may be re-written as:

$$W_e^{fibres} = \frac{k_1}{2k_2} \left\{ \exp \left[k_2 (\kappa I_1 + (1 - 3\kappa) I_4 - 1)^2 \right] - 1 \right\}, \quad (25)$$

where k_1 and k_2 are positive stress-like and dimensionless parameters, respectively. We note that there are now only two invariants incorporated in the W_e function, namely I_1 and I_4 . Given the fact that in-plane biaxial and uniaxial tensile tests in transverse directions provide two independent stress-stretch equations, the datasets provided via those tests should in principle enable one to characterise the elastic behaviour of the valve, if the elastic response of the tissue specimens is established from the experiments.

For an appropriate choice of W_v , we note that the viscous effects of the bulk AV tissue may stem from the gel-like GAG matrix, as well as the dissipative kinematics of the fibre-matrix and

the fibre-fibre sliding and interaction (Anssari-Benam et al., 2017). Therefore, the overall dissipation function W_v of the valve may be considered as the sum of the contribution of the valve's matrix W_v^{matrix} and the dissipative kinetics of the dispersed fibres within the fibre family W_v^{fibres} . In view of the structure tensor $\mathbf{H}$, we define W_v as:

$$W_v(\mathbf{C}, \mathfrak{E}, \mathbf{H}) = W_v(I_1, J_7, J_{11}^*) = W_v^{matrix}(I_1, J_7) + W_v^{fibres}(I_1, J_{11}^*), \quad (26)$$

where we propose the following functions for W_v^{matrix} and W_v^{fibres} :

$$W_v^{matrix} = \frac{\eta_1}{4} J_7 (I_1 - 3) \quad , \quad W_v^{fibres} = \frac{\eta_2}{4} J_{11}^* (I_1 - 3), \quad (27)$$

Note that η_1 and η_2 are viscosity-like parameters reflecting the dissipative effects of the matrix and the fibre kinematics, respectively, and they are positive. We note that according to the definition of J_7 and J_{11}^* , as given in equation (20), W_v is a quadratic function of $\mathfrak{E}$ (i.e. $W_v = f(\mathfrak{E})$), and therefore it is convex in $\mathfrak{E}$. Moreover, it may be observed that $W_v = 0$ when $\mathfrak{E} = \mathbf{0}$. In view of equation (19), W_v^{fibres} may be re-written as:

$$W_v^{fibres} = \frac{\eta_2}{4} (\kappa J_7 + (1 - 3\kappa) J_{11}) (I_1 - 3). \quad (28)$$

We note that there are now only three invariants incorporated in the W_v function, namely I_1 , J_7 and J_{11} . In the following section, we proceed with deriving the stress-stretch relationships, using the defined W_e and W_v functions.

2.7. Cauchy stress ($\boldsymbol{\sigma}$) – Stretch (λ) relationship

The Cauchy stress tensor $\boldsymbol{\sigma}$, derived from the second Piola-Kirchhoff stress tensor $\mathbf{S}$, based on the choice of W_e and W_v functions as introduced in §2.6, is presented in Appendix B (equation (B.3)). We shall now expand that equation to obtain a component-by-component relationship between principal stresses and stretches.

Let the notations σ_{11} , σ_{22} , σ_{33} and λ_1 , λ_2 and λ_3 represent the principal stresses and stretches, respectively. In a pure homogenous deformation, which is often achieved by biaxial and uniaxial tensile tests, the deformation gradient $\mathbf{F}$ reduces to a diagonal matrix with components $\text{diag}[\lambda_1, \lambda_2, \lambda_3]$, resulting in:

$$[\mathbf{F}] = \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix}, \quad [\mathbf{C}] = \begin{bmatrix} \lambda_1^2 & 0 & 0 \\ 0 & \lambda_2^2 & 0 \\ 0 & 0 & \lambda_3^2 \end{bmatrix}, \quad [\mathbf{e}] = \begin{bmatrix} 2\lambda_1 \lambda_1^5 & 0 & 0 \\ 0 & 2\lambda_2 \lambda_2^5 & 0 \\ 0 & 0 & 2\lambda_3 \lambda_3^5 \end{bmatrix}, \quad (29)$$

and from §2.1 we further recall:

$$[\mathbf{M} \otimes \mathbf{M}] = [\mathbf{e}_3 \otimes \mathbf{e}_3] = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}. \quad (30)$$

Therefore, the components of the Cauchy stress tensor $\boldsymbol{\sigma}$ may be obtained using equation (C.3) as:

$$\begin{cases} \sigma_{11} = 2(W_e)_1 \lambda_1^2 + 8(W_v)_7 \lambda_1^5 \lambda_1^5 - p, \\ \sigma_{22} = 2(W_e)_1 \lambda_2^2 + 8(W_v)_7 \lambda_2^5 \lambda_2^5 - p, \\ \sigma_{33} = 2\lambda_3^2 [(W_e)_1 + (W_e)_4] + 8\lambda_3^5 \lambda_3^5 [(W_v)_7 + (W_v)_{11}] - p, \end{cases} \quad (31)$$

and the off-diagonal components are zero. In the above equation, p is the Lagrange multiplier and $(W_e)_1$, $(W_e)_4$, $(W_v)_7$ and $(W_v)_{11}$ are defined in Appendix C, i.e. equations (C.3), (C.4), (C.6) and (C.7). Recall that, as illustrated in Figure (3b), $\mathbf{e}_3$ is the direction along which lies the preferred direction of the fibre family, and $\mathbf{e}_2$ and $\mathbf{e}_1$ are the transverse and through-thickness directions, respectively. Therefore, in relation to the AV principal loading directions, σ_{33} and λ_3 represent the stress and stretch along the circumferential direction, while σ_{22} and λ_2 represent the radial stress and stretch, respectively.

Rearranging the relationships in equation (31) to eliminate p yields:

$$\begin{cases} \sigma_{33} - \sigma_{11} = 2(\lambda_3^2 - \lambda_1^2)(W_e)_1 + 2\lambda_3^2(W_e)_4 + 8(\lambda_3^5 \mathcal{E}_3 - \lambda_1^5 \mathcal{E}_1)(W_v)_7 + 8\lambda_3^5 \mathcal{E}_3(W_v)_{11}, \\ \sigma_{22} - \sigma_{11} = 2(\lambda_2^2 - \lambda_1^2)(W_e)_1 + 8(\lambda_2^5 \mathcal{E}_2 - \lambda_1^5 \mathcal{E}_1)(W_v)_7, \end{cases} \quad (32)$$

where the through-thickness (principal) Cauchy stress can be approximated to zero $\sigma_{11} = 0$.

We note that, while W_v by the definition given in equation (26) introduces two additional invariants (J_7 and J_{11}) to stress-stretch equations, only one constitutive component of W_v appears in equation (32)₂, namely $(W_v)_7$. Therefore, theoretically, $(W_v)_7$ may be characterised using an additional set of stress-stretch data obtained from tensile tests performed under a different strain rate compared to that of the elastic response, in the radial direction. Then, the stress-stretch equation in the circumferential direction (equation (32)₁) facilitates the characterisation of $(W_v)_{11}$ using a set of stress-stretch data obtained from tensile tests performed in the same direction but under a different strain rate compared to that of the elastic response. Therefore, from a theoretical point of view, stress-stretch curves obtained from AV specimens under various stretch rates in transverse directions should in principle allow the characterisation of the dissipation function W_v . Equation (32) may now be tailored for application to planar biaxial deformation data.

3. Modelling the deformation of AV specimens under planar biaxial tension

3.1. Tailoring a model for application to AV planar biaxial tensile tests

For a square AV specimen cut from a leaflet as shown schematically in Figure 1, under planar biaxial tensile deformation, the incompressibility constraint requires $\lambda_1 = \lambda_3^{-1} \lambda_2^{-1}$. Noting that $I_1 = \lambda_1^2 + \lambda_2^2 + \lambda_3^2$, $I_4 = \lambda_3^2$, $J_7 = 4(\lambda_1^4 \mathcal{E}_1 + \lambda_2^4 \mathcal{E}_2 + \lambda_3^4 \mathcal{E}_3)$ and $J_{11} = 4\lambda_3^4 \mathcal{E}_3$, the four invariants may be re-written as: $I_1 = \lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2}$, $I_4 = \lambda_3^2$,

$J_7 = 4[\lambda_3^{-6} \lambda_2^{-6} (\lambda_3^{-2} \mathcal{E}_3 + \lambda_2^{-2} \mathcal{E}_2 + 2\lambda_3^{-1} \lambda_2^{-1} \mathcal{E}_3 \mathcal{E}_2) + \lambda_2^4 \mathcal{E}_2 + \lambda_3^4 \mathcal{E}_3]$ and $J_{11} = 4\lambda_3^4 \mathcal{E}_3$. Therefore, using the relationships in equations (C.3), (C.4), (C.6) and (C.7), the principal in-plane Cauchy stresses may be re-written as:

$$\left\{ \begin{aligned} \sigma_{33} = \sigma_{cric.} &= 2(\lambda_3^2 - \lambda_3^{-2} \lambda_2^{-2}) \left[\frac{1}{6} n B T \frac{9N - (\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2})}{3N - (\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2})} \right. \\ &+ \kappa k_1 [\kappa(\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2}) + (1 - 3\kappa)\lambda_3^2 - 1] \exp \left\{ k_2 [\kappa(\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2}) + (1 - 3\kappa)\lambda_3^2 - 1]^2 \right\} \\ &+ 2\lambda_3^2 k_1 (1 - 3\kappa) [\kappa(\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2}) + (1 - 3\kappa)\lambda_3^2 - 1] \exp \left\{ k_2 [\kappa(\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2}) + (1 - 3\kappa)\lambda_3^2 - 1]^2 \right\} \\ &+ 2(\eta_1 + \kappa\eta_2) [\lambda_3^5 \mathcal{E}_3 + \lambda_3^{-6} \lambda_2^{-6} (\lambda_3^{-1} \mathcal{E}_3 + \lambda_2^{-1} \mathcal{E}_2)] (\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2} - 3) \\ &+ 2\eta_2 (1 - 3\kappa) \lambda_3^5 \mathcal{E}_3 (\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2} - 3), \\ \sigma_{22} = \sigma_{rad.} &= 2(\lambda_2^2 - \lambda_3^{-2} \lambda_2^{-2}) \left[\frac{1}{6} n B T \frac{9N - (\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2})}{3N - (\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2})} \right. \\ &+ \kappa k_1 [\kappa(\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2}) + (1 - 3\kappa)\lambda_3^2 - 1] \exp \left\{ k_2 [\kappa(\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2}) + (1 - 3\kappa)\lambda_3^2 - 1]^2 \right\} \\ &+ 2(\eta_1 + \kappa\eta_2) [\lambda_2^5 \mathcal{E}_2 + \lambda_3^{-6} \lambda_2^{-6} (\lambda_3^{-1} \mathcal{E}_3 + \lambda_2^{-1} \mathcal{E}_2)] (\lambda_3^2 + \lambda_2^2 + \lambda_3^{-2} \lambda_2^{-2} - 3). \end{aligned} \right. \quad (33)$$

Note that subscripts ‘*cric.*’ and ‘*rad.*’ reflect the principal loading directions of the AV leaflet, i.e. circumferential and radial directions, respectively, as shown in Figure 1. Equation (33) may now be applied to the experimental data obtained from planar biaxial tensile tests of AV specimens.

3.2. Experimental data

For the purpose of this study, we used experimental stress-stretch data of porcine AV specimens subjected to in-plane biaxial tensile tests. Porcine hearts were obtained from mature animals, ranging from 18 to 24 months old, within 2 hrs of slaughter from a local abattoir. The three AV leaflets were dissected from the aortic root and maintained in Dulbecco’s Modified Eagle’s Medium (DMEM, Sigma, Poole, UK) at room temperature (20° C). From each leaflet, a 12mm by 12mm square sample was excised from the central region (schematically shown in Figure 1). The square samples were then subjected to biaxial tensile tests.

Two experimental protocols were implemented under displacement control in order to obtain a more comprehensive dataset on the deformation behaviour of the AV specimens: (i) equibiaxial displacement; and (ii) biaxial displacement with a circumferential to radial ratio of 1:3. This ratio was motivated by the deformation of the AV leaflets under physiological condition, as the AV is known to endure *in vivo* strain levels of 10.1% and 30.8% in the circumferential and radial directions, respectively (Sacks and Yoganathan, 2007). The applied stretch rates $\dot{\lambda}$ along the circumferential loading direction in both protocols were 0.001 s^{-1} , 0.01 s^{-1} , 0.1 s^{-1} and 1 s^{-1} , based on which applied radial stretch rates were adjusted to render the designated displacement ratios for each protocol (1:1 or 1:3). Each test was repeated for three samples at each rate, yielding a total of $n = 24$ individual experiments (samples).

Before performing the tests, the thickness of the samples was measured using a non-contact laser micrometer (LSM-501, Mitotuyo - average thickness: $0.56 \pm 0.05 \text{ mm}$). The samples were then secured in an ElectroForce[®] planar biaxial TestBench instrument using BioRake (CellScale[®]) tines (Figure 6a) as part of a custom-designed sample mounting mechanism. Prior to the start of each test, a tare load of 0.05 N was applied to the samples in both loading directions to ensure a consistent starting position. The adjusted position of the grips was then used as the starting point of the tests. Five ink-marker points were printed on the centre of the specimens (Figure 6b) as fiducials and their centroids were tracked over the period of deformation using an in-house video camera, recording at 30 to 240 frames per second depending on the stretch rate at each test, to ascertain the circumferential and radial deformation of the specimens. The recorded frames were then analysed using a custom-developed code in MATLAB[®], devised based on the procedure outlined by Humphrey (2002), and the stretches λ_3 and λ_2 in the central region of the specimens were computed accordingly. Concisely, the four corner markers were considered as the nodes of a linear quadrilateral element, where their positions were recorded during the deformation. Using the standard finite element shape function, the displacement, the referential displacement gradient $\mathbf{G}$ and the deformation gradient $\mathbf{F}$ for each point were calculated ($\mathbf{G} = \mathbf{F} + \mathbf{I}$). The components of the Green-Lagrangian strain tensor $\mathbf{E}$ were subsequently computed for all points, and the values for the fifth (central) marker were considered as the mean representative of the specimen under deformation.

It must be noted that the experimental results obtained from the tensile tests provide data in terms of λ and the first Piola-Kirchhoff stress tensor $\mathbf{P}$ (engineering stress). In order to apply the model in equation (33) to the experimental data one needs to convert the engineering stress $\mathbf{P}$ to the Cauchy stress $\boldsymbol{\sigma}$ via $\boldsymbol{\sigma} = J^{-1}\mathbf{F}\mathbf{P}$. Assuming a pure homogenous deformation, and using the notation in equation (33), this conversion can be achieved through $\sigma_{33} = \sigma_{circ.} = \lambda_3 P_{circ.}$ and $\sigma_{22} = \sigma_{rad.} = \lambda_2 P_{rad.}$. The obtained experimental $\sigma - \lambda$ graphs under the equi-biaxial and biaxial (1:3) protocols are shown in Figures 7 and 8, respectively. The curves demonstrate representative samples (Figures 7a and 8a). In order to streamline the fitting process (§3.3) and smoothen the datasets, the representative samples were subjected to a Savitzky-Golay filter (of 3rd order and a frame length equivalent to 25% of the number of the data points in each dataset) using MATLAB[®]. The filtered graphs for the representative samples are shown in Figures 7b and 8b. Using the tracked markers data, the average stretch rates of the representative samples within the gauge area in both directions ($\dot{\lambda}_3$ and $\dot{\lambda}_2$) were also calculated and are presented in Table 1. These values in conjunction with the filtered $\sigma - \lambda$ curves are henceforward used for fitting the experimental data to the model in equation (33).

3.3. Fitting procedure

The starting point for developing the model in equation (33) was indeed equation (1), where the total viscoelastic stress is postulated to be the superposition of the elastic and the viscous contributions. The premise of elasticity requires the elastic response of the continuum to be independent of the stretch rate. The dissipative effects, by contrast, are dependent on the rate. Therefore, when the model is fitted to the stress-stretch curves obtained at various stretch rates, the parameters related to the elastic behaviour are to remain unchanged, while the viscous-related parameters are to alter at each rate. To this end, it is important to experimentally establish the elastic response of the tissue, i.e. the elastic stress-stretch curve, from which the associated elastic parameters of the model may be derived. Those parameters are then set to remain unchanged, while fitting the whole model to the stress-stretch curves obtained at different rates, to characterise the viscous-related parameters.

However, it is perhaps impractical to obtain a pure elastic response from tissue samples that are inherently rate-dependent, where the stress-stretch curve is dependent upon the stretch rate. Pioletti and Rakotomanana (2000) postulate that in these circumstances the choice of the elastic

curve is a matter of definition, and identify the curves obtained at lower rates as the elastic response. In our previous study we qualified this definition further by countenancing the role of the stress-relaxation characteristic time (Anssari-Benam et al., 2017). Stress-relaxation tests enable the quantification of the characteristic times τ , fast and slow, whereby 99% of the relaxation fades within a time $t = 5\tau$ (see, e.g., Anssari-Benam et al., 2011b). Therefore, if the stretch rate of the tensile test of the tissue specimens is chosen sufficiently low to allow enough time for the viscous processes to take effect and fade, the ensuing stress-stretch curve may be deemed intractable to further reductive viscous effects. Such a curve may therefore provide a baseline that, with a degree of tolerance, may be referred to as the elastic curve. In that study we showed that stress-stretch curves obtained at $\dot{\lambda} = 0.001 \text{ s}^{-1}$ or below satisfy this condition and may therefore be considered as the elastic curve. Noting the values of $\dot{\lambda}_2$ and $\dot{\lambda}_3$ in Table 1, we hence treat the curves obtained at the applied rate $\dot{\lambda} = 0.001 \text{ s}^{-1}$ as the elastic response curves.

Now, the required steps to fit the model in equation (33) to the experimental data are as follows. The first phase includes the estimation of the elastic (rate-independent) parameters of the model, namely N , n , κ , k_1 and k_2 . In this phase, therefore, the elastic terms of $\sigma_{circ.}$ and $\sigma_{rad.}$ in equation (33) are fitted to the ‘elastic’ curves (obtained at the applied rate $\dot{\lambda} = 0.001 \text{ s}^{-1}$) in each respective direction, simultaneously for both the equi-biaxial and biaxial (1:3) displacement datasets. The best fit is sought by minimising the residual sum of squares (RSS), defined as:

$$RSS = \sum_i \left(\sigma_{circ.}^{model} - \sigma_{circ.}^{exp.} \right)_i^2 + \left(\sigma_{rad.}^{model} - \sigma_{rad.}^{exp.} \right)_i^2, \text{ using a constrained nonlinear multivariable}$$

function minimisation approach in MATLAB[®]. Here, the superscripts ‘*model*’ and ‘*exp.*’ refer to the values predicted by the model and those of the experimental dataset, respectively, at the i th data point in each loading direction. Note that N , n and κ are structural parameters where, by definition, $\kappa \in [0, 1/3]$, while N and n were characterised in our previous study (Anssari-Benam and Bucci, 2017) with values in the range of $3 < N < 4$ and $10^{23} < n < 10^{24}$. For these three parameters, those designated ranges are considered as the numerical boundaries (constraints) in obtaining the best fits. To ensure the robustness of the fits, the optimisation processes is repeated by invoking different initial points for each circumferential and radial dataset pair.

In the second phase, the established N , n , κ , k_1 and k_2 values are used to inform the initial guess in fitting the model to the rate-dependent data. The model is fitted to the stress-stretch

curves obtained at each applied $\dot{\lambda}$ (above 0.001 s^{-1}), simultaneously for both the equi-biaxial and biaxial (1:3) datasets at that rate, using the same optimisation process as in the previous phase. We note that the parameters η_1 and η_2 are related to the dissipative properties of the matrix and fibre kinematics, respectively, and shall therefore assume the same numerical value in both directions in each dataset. With this consideration in mind, the best fit is sought by minimising the RSS function and the numerical values of η_1 and η_2 are thus established. The convexity of the strain energy function is verified graphically by plotting W and its contours in (λ_3, λ_2) and (E_{33}, E_{22}) planes (E_{33} and E_{22} represent the principal Green-Lagrange strains). The fitting results and the ensuing analyses are presented in the following section.

4. Fitting results

4.1. Goodness of fit

The curves in Figure 9 graphically compare the fitting outcomes with the experimental data. The continuous curves represent the model and the symbols illustrate the filtered experimental data. The model provides a good fit to the experimental data, with average R^2 value of 0.965. Individual R^2 values for each fit are presented in Table 2.

4.2. Model parameter estimation

As the relationships in equation (33) indicate, the parameters that appear in our model are N , n , κ , k_1 , k_2 , η_1 and η_2 . By fitting the model to the experimental data, these parameters were calculated and summarised in Table 2. Note that N , n and κ are structural parameters associated with the properties of the elastin network (N and n) and the collagen fibre family (κ), and k_1 and k_2 are material parameters related to the (progressive) stiffness of the tissue as the fibres become more recruited with increasing stretch. Therefore, by definition, the values of N , n , κ , k_1 and k_2 are to remain unchanged across the different stretch rates. This is reflected in the reported values in Table 2, wherein one value is reported for each parameter. The reported values

are presented as mean $\pm$ SD. By contrast, η_1 and η_2 are rate-dependent and assume different values at each rate, which is also reflected in Table 2.

5. Discussion

In the present study, a continuum-based transversely isotropic model for application to the AV was introduced, incorporating the rate dependency as an explicit function of the stretch rate and accounting for fibre dispersion. A new fibre orientation density function, motivated by fibre kinematics, was also devised and applied, based on a Lorentzian distribution and in the form of a wrapped Lorentzian distribution function. The pseudo-invariants for $\mathcal{C}$ and $\mathbf{M}$ incorporating fibre dispersion, i.e. $J_j^*, j = 4, 5, 10, 11, 12$, were also presented here. The model was then applied to experimental data obtained from homogenous planar biaxial tensile tests, showing excellent agreement with the data. To the authors' knowledge, this type of model has not been previously introduced for application to heart valves, nor has the rate-dependency of the stress-stretch curves of AV specimens under biaxial loading been previously presented.

The proposed model in this study incorporates the contribution of the elastin network through a specialised strain-energy function (equation (23)), GAGs via a rate-dependent function (equation (26)), and the collagen fibres through a *Holzapfel*-type energy function (equation (24)) with the incorporation of fibre dispersion. These three components are the main structural elements of the AV tissue. This model therefore paves the way for furnishing the development and application of a fully structurally motivated continuum-based model for application to the AV and other such like valves and tissues.

5.1. Remarks on convexity of the strain-energy function

The elastic strain-energy function W_e is the sum of $W_e^{iso} + W_e^{fibres}$ (see equation (22)), and the dissipation function is $W_v = W_v^{matrix} + W_v^{fibres}$ (see equation (26)). The convexity of the W_e^{iso} function was shown in Anssari-Benam and Bucci (2017) with the *a priori* requirement of $N > I_1 / 3$, while the convexity of W_e^{fibres} has too been established in numerous previous studies including Gasser et al. (2006). Mathematically, the sum of two or more convex functions is also convex and therefore the proposed strain energy-function is convex *a priori*. The chosen W_v is

also convex in $\mathcal{E}$ by definition. We therefore refrain to analytically re-demonstrate the convexity of the proposed strain-energy function in the present study.

5.2. Remarks on changes in η_1 and η_2 with $\dot{\lambda}$

An interesting feature of the AV tissue that is revealed by modelling the stress-stretch data using the proposed theoretical criterion in this study is the variation of η_1 and η_2 with $\dot{\lambda}$, as listed in Table 2, in effect showing a ‘shear-thinning’ behaviour of the tissue. This data may be used to extrapolate the values of η_1 and η_2 at the physiological strain rates of $440 \pm 80.0\% \text{s}^{-1}$ and $1240 \pm 160.0\% \text{s}^{-1}$ in the circumferential and radial directions (Sacks and Yoganathan, 2007), respectively, which corresponds to mean stretch rates of $\dot{\lambda}_3 \approx 4.4 \text{ s}^{-1}$ and $\dot{\lambda}_2 \approx 12.4 \text{ s}^{-1}$, as shown in Figure 10a. The values of η_1 is plotted versus $\dot{\lambda}_2$, as it is primarily associated with the matrix, excluding the fibre kinematics effects. The values of η_2 , however, is plotted versus $\dot{\lambda}_3$, as it is concomitant with the dissipative effects of the kinematics of fibres, which are principally aligned along the circumferential direction. This feature is overlooked if a hyperelastic modelling criterion is employed. Note that the ‘shear-thinning’ behaviour for the AV tissue in this context is taken to signify the reduction of the tissue dissipative (damping) coefficients with increase in the stretch rate. As the plots in Figure 10a illustrate, the effective damping coefficient of the tissue becomes very low in its physiological domain (stretch). This finding, if coupled with the AV micromechanics, allows a more accurate calculation of the shear stresses exerted on the residing cells *in vivo* that arise from the microstructural reorganisation of the tissue constituents; i.e. the flow-like behaviour of GAGs and the movement of the fibres, during the physiological function of the valve.

Using the extrapolated η_1 and η_2 values, it is possible to have an estimation of the stress-stretch behaviour of the AV under the physiological stretch rate. Since it is experimentally challenging to create stress-stretch datasets that are obtained under physiological rates, the ability to predict $\sigma - \lambda$ curves at those rates may prove useful in the understanding of the deformation behaviour of the AV *in vivo* and in computational modelling of the function of the valve. The predicted curves by the model are shown in Figure 10b for the principal loading directions. The horizontal line in the graph designates the physiological stress level of 240 kPa. At this stress level, we note that the predicted curves indicate stretches of $\lambda_3 = 1.06$ and $\lambda_2 = 1.21$ in the circumferential and radial directions, respectively. These values are below the reported

physiological levels of 1.10 and 1.30, and therefore the predicted $\sigma - \lambda$ curves are somewhat underestimating the reported deformation behaviour of the valve leaflets *in vivo*. However, we also note that the central region of the AV leaflet is likely the stiffest region of the leaflet and therefore basing the behaviour of the entire leaflet on the characteristics of the central region may inevitably result in the underestimation of the whole leaflet deformation. The regional variation in the material properties of the AV leaflets has been well documented in previous studies such as in Billiar and Sacks (2000), reporting marked distinction in the deformation of the central region compared with the regions closer to the commissures. We further note that the reported physiological strain rates too pertain to the whole leaflet and do not necessarily conform to the stretch rates undergone by the central region of the leaflet. This premise was also observed in the present study, as the applied deformation rates did not equate with the measured deformation rates in the centre of the specimens (see Table 1). Both these factors, namely the inhomogeneity of the mechanical properties and the stretch rate of the central region compared to the whole valve leaflet, will therefore contribute to the overestimation of the predicted $\sigma - \lambda$ curves. A more comprehensive investigation of the deformation behaviour of the specimens prepared from various regions across the whole leaflet would provide a better insight to the overall deformation of the leaflet, and would hence allow a more accurate prediction of the AV behaviour under physiological deformation rate *in vivo*.

5.3. Remarks on the structural parameters

We acknowledge that N , n and κ are structurally-based parameters and should ideally be quantified from the structure of the specimens prior to the tests. Instead, however, the value for κ was established prospectively after fitting the stress-stretch data to the model, and N and n values were informed by a previous study. During the fitting procedure it was observed that the convergence of the fits was sensitive to the variation of κ , while it was considerably less sensitive to the values of N and n . To the best of our knowledge, the values of N and n for the AV elastin network have not yet been quantified, and no independent platform for comparison/verification of these values is currently available. For the parameter κ , however, it was possible to numerically recover the (wrapped Lorentzian) distribution of the fibre dispersion from the quantified value of k in Table 2, and by recalling the analytical definition of $R(\theta)$ and κ from §2.3. The reconstructed distribution is shown in Figure 11. Comparing this distribution with those derived experimentally for porcine AV samples using the small angle light scattering

technique (see, e.g., Billiar and Sacks, 1997; Sacks et al., 1998), we note that the obtained distribution from the fitting is closely matched with the reported experimental data. Therefore, while the quantified value of κ in this study was obtained phenomenologically, it may be considered as a reasonable estimation.

5.4. Remarks on inclusion of fibres in tension

The general consensus in the literature is that only fibres which undergo tension should be considered to contribute to the mechanical behaviour of the tissue under deformation, as collagen fibres are not known to support compression. This has motivated the development of analytical criteria to exclude the contribution of the fibres when they are in compression, within fibre dispersion models. Holzapfel and Ogden (2015) have discussed at length that the tension-compression switch is determined based on the invariant I_4 , and not I_4^* , and that the fibres contribute to the load-bearing capacity of the tissue strictly when $I_4 > 1$. Therein they calculate a critical angle, or a maximum angle, up to which the dispersed fibres are extended. This critical angle can then be used to establish the correct boundaries of the dispersion integral in the structure tensor $\mathbf{H}$. In a later study, Holzapfel and Ogden (2016) introduce a deformation dependent dispersion parameter that allows the exclusion of the mechanical influence of compressed fibres within the dispersion. They go on to show that for higher degrees of dispersion, the prediction of the models that do not exclude the contribution of the compressed fibres will be significantly different to those models that do, resulting in quantified model parameters that are commensurate with a softer behaviour. Based on these analyses, a computational method for excluding fibres under compression in modelling soft tissues has also been presented (Li et al., 2016). It is worth noting that Ateshian et al. (2009) have used a Heaviside (step) function to mathematically enforce the tension-only contribution.

Incorporation of these methods into a mathematical model to fit to the experimental data, or indeed into a computational model, requires complex implementation and calculations, as has also been noted in the cited studies. These developments are relatively new and as per all new concepts are subject to further progress and versatility. In order to avoid additional mathematical/computational complexity, we have not incorporated any inclusion/exclusion criteria into our model yet. We note, however, that our model assumes the mean direction of the family of fibres in the reference configuration to coincide with the Cartesian unit vector $\mathbf{e}_3$,

aligned with one of the principal loading directions of the considered in-plane pure homogenous biaxial deformation (i.e. the circumferential loading direction). Since both λ_3 and λ_2 were observed to increase monotonically within the domain of deformation in our experiments (see, e.g., Figures 7 and 8), it may be the case that I_4 for the fibre family was invariably ≥ 1 , in which case an inclusion/exclusion switch may not have been strictly required. In any case, the incorporation of a suitable switch will be the subject of our future studies and improvements to the introduced model.

5.5. Further improvements

Our experimental results clearly demonstrate that the deformation of the AV tissue is rate-dependent, and our proposed model successfully captures this behaviour. However, we note that the additive split of the stress tensor $\mathbf{S}$ postulated in equation (1) is a mathematical assumption. At this point, we do not stipulate any physical basis for this particular split. Future studies are required to form further consensus on the physical merits of this additive split. In addition, we do not postulate any direct kinematical interpretation for the invariants J_7 and J_{11} used in our model.

From a theoretical (modelling) perspective, two areas of further improvement were noted in §5.3 and §5.4, namely the extraction of structural parameters and incorporation of an inclusion/exclusion switch. From an experimental point of view, we note that our datasets were obtained under equi-biaxial and 1:3 biaxial tensile tests. It may be reasonably argued that more varied experiments and datasets would have resulted in a more comprehensive characterisation of the model parameters. We acknowledge this argument, however, with the following two caveats. First, the primary aim of this study was to propose a continuum-based transversely isotropic model incorporating rate-dependency and fibre dispersion for application to the AV, and to show its capability in describing the biaxial deformation data obtained under various stretch rates (over a range of 1000-fold). From the theoretical point of view, the characterised model parameters ensure the convexity of the strain-energy function, and as such are valid. Of course, for a more ‘complete’ characterisation of the material properties of the AV tissue more datasets would be beneficial, not only obtained at different stretch ratios, but also under other modes of deformation such as shear. Second, since our tests were performed under displacement control, the resulting λ_3 and λ_2 do not bear any specific ratios. Therefore, our experiments have

provided ‘general’ biaxial deformation data, without promoting any specific collinearity or assumptions in the model or the fitting procedure.

We further note that our analyses in this study incorporate two implicit assumptions. First assumption is regarding the arrangement of collagen fibre network in the valve, where no out-of-plane distribution was considered. To the best of our knowledge, the literature to date does not elucidate or suggest the existence of out-of-plane fibre distribution within the AV tissue. As we did not investigate the valve’s microstructure independently in this study, we proceeded under the assumption that no out-of-plane distribution exists. Second assumption is regarding the pure homogenous deformation consideration. The commercially available biaxial loading setups, such as the one used in this study, do not allow for independent control or indeed measurement of shear deformations. To the best of practical possibility, we mounted our samples such that the preferred fibre direction coincided with the circumferential principal loading direction, and the transverse direction along the radial direction, to minimise the occurrence and effect of shear deformations. With this setting, while an approximation, we neglected any shearing effect.

As the graphs in Figures 7 and 8 indicate, the $\sigma - \lambda$ curves highlight a stiffer specimen behaviour with increasing $\dot{\lambda}$. However, the stretch-rate associated stiffening appears to be rate-limited, especially in the circumferential direction, suggesting that the data is approaching a threshold $\dot{\lambda}$ whereby increasing the stretch rate may not significantly alter the related curves. Due to hardware limitations, we were not able to investigate the deformation of the samples under the applied rates of an order of magnitude above our maximum tested rate ($\dot{\lambda}=1 \text{ s}^{-1}$). It would be of interest to experimentally ascertain whether such a threshold exists and if so, what would be the numerical range for this threshold rate.

Finally, while the model presented in this study was primarily developed for application to the AV, the mechanical and mathematical criteria within which the model was derived are general and universal. Therefore, the model and the modelling approach presented here may be applied to other heart valves or indeed collagenous soft tissues with similar structural building blocks and a single preferred direction of the embedded collagen fibres, without loss of generality.

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Appendix A: Invariants of $\mathbf{C}$, $\mathbf{\mathcal{C}}$ and $\mathbf{M}$

For a transversely isotropic material, the elastic strain energy function $W_e(\mathbf{C}, \mathbf{M})$ may be expressed as a function of five invariants $W_e(I_1, \dots, I_5)$ where:

$$I_1 = \mathbf{C} : \mathbf{I} \quad , \quad I_2 = \frac{1}{2} \left[(\mathbf{C} : \mathbf{I})^2 - (\mathbf{C}^2 : \mathbf{I}) \right] \quad , \quad I_3 = \det \mathbf{C} \quad , \quad I_4 = \mathbf{M} \otimes \mathbf{M} : \mathbf{C} \quad , \quad I_5 = \mathbf{M} \otimes \mathbf{M} : \mathbf{C}^2 . \quad (\text{A.1})$$

Note that $\mathbf{I}$ is the identity tensor, $\otimes$ denotes the dyadic product, the operator $(:)$ is ‘double contraction’, i.e. $\mathbf{A} : \mathbf{B} = \sum_i \sum_j A_{ij} B_{ji}$, and $\mathbf{M}$ is a unit vector representing the preferred direction of the fibres.

The dissipation function $W_v(\mathbf{C}, \mathbf{\mathcal{E}}, \mathbf{M})$ may be expressed as a function of seventeen invariants where:

$$\begin{aligned} J_1 &= \mathbf{\mathcal{E}} : \mathbf{I} , \quad J_2 = \mathbf{\mathcal{E}}^2 : \mathbf{I} , \quad J_3 = \det \mathbf{\mathcal{E}} , \quad J_4 = \mathbf{M} \otimes \mathbf{M} : \mathbf{\mathcal{E}} , \quad J_5 = \mathbf{M} \otimes \mathbf{M} : \mathbf{\mathcal{E}}^2 , \\ J_6 &= \mathbf{C} \mathbf{\mathcal{E}} : \mathbf{I} , \quad J_7 = \mathbf{C} \mathbf{\mathcal{E}}^2 : \mathbf{I} , \quad J_8 = \mathbf{C}^2 \mathbf{\mathcal{E}} : \mathbf{I} , \quad J_9 = \mathbf{C}^2 \mathbf{\mathcal{E}}^2 : \mathbf{I} , \quad J_{10} = \mathbf{M} \otimes \mathbf{M} \mathbf{C} \mathbf{\mathcal{E}} : \mathbf{I} , \\ J_{11} &= \mathbf{M} \otimes \mathbf{M} \mathbf{C} \mathbf{\mathcal{E}}^2 : \mathbf{I} , \quad J_{12} = \mathbf{M} \otimes \mathbf{M} \mathbf{C}^2 \mathbf{\mathcal{E}} : \mathbf{I} . \end{aligned} \quad (\text{A.2})$$

Note that the invariants I_i are given in (A.1).

From matrix calculus, the following expressions can be established:

$$\frac{\partial I_i}{\partial \mathbf{C}} \rightarrow \begin{cases} \frac{\partial I_1}{\partial \mathbf{C}} = \frac{\partial \text{tr} \mathbf{C}}{\partial \mathbf{C}} = \mathbf{I} , \quad \frac{\partial I_2}{\partial \mathbf{C}} = \text{tr}(\mathbf{C}) \mathbf{I} - \mathbf{C} , \quad \frac{\partial I_3}{\partial \mathbf{C}} = \det(\mathbf{C}) \mathbf{C}^{-1} = I_3 \mathbf{C}^{-1} , \\ \frac{\partial I_4}{\partial \mathbf{C}} = \mathbf{M} \otimes \mathbf{M} , \quad \frac{\partial I_5}{\partial \mathbf{C}} = \mathbf{C} \mathbf{M} \otimes \mathbf{M} + \mathbf{M} \otimes \mathbf{M} \mathbf{C} , \end{cases} \quad (\text{A.3})$$

where $\text{tr} \mathbf{C} = \mathbf{C} : \mathbf{I}$.

$$\frac{\partial J_i}{\partial \mathbf{\mathcal{E}}} \rightarrow \begin{cases} \frac{\partial J_1}{\partial \mathbf{\mathcal{E}}} = \frac{\partial \text{tr} \mathbf{\mathcal{E}}}{\partial \mathbf{\mathcal{E}}} = \mathbf{I} , \quad \frac{\partial J_2}{\partial \mathbf{\mathcal{E}}} = \frac{\partial \text{tr} \mathbf{\mathcal{E}}^2}{\partial \mathbf{\mathcal{E}}} = 2 \mathbf{\mathcal{E}} , \quad \frac{\partial J_3}{\partial \mathbf{\mathcal{E}}} = \frac{\partial \det \mathbf{\mathcal{E}}}{\partial \mathbf{\mathcal{E}}} = \det(\mathbf{\mathcal{E}}) \mathbf{\mathcal{E}}^{-1} = J_3 \mathbf{\mathcal{E}}^{-1} , \\ \frac{\partial J_4}{\partial \mathbf{\mathcal{E}}} = \mathbf{M} \otimes \mathbf{M} , \quad \frac{\partial J_5}{\partial \mathbf{\mathcal{E}}} = \mathbf{\mathcal{E}} \mathbf{M} \otimes \mathbf{M} + \mathbf{M} \otimes \mathbf{M} \mathbf{\mathcal{E}} , \quad \frac{\partial J_6}{\partial \mathbf{\mathcal{E}}} = \mathbf{C} , \\ \frac{\partial J_7}{\partial \mathbf{\mathcal{E}}} = (\mathbf{C} \mathbf{\mathcal{E}})^T + (\mathbf{\mathcal{E}} \mathbf{C})^T , \quad \frac{\partial J_8}{\partial \mathbf{\mathcal{E}}} = \mathbf{C}^2 , \quad \frac{\partial J_9}{\partial \mathbf{\mathcal{E}}} = (\mathbf{C}^2 \mathbf{\mathcal{E}})^T + (\mathbf{\mathcal{E}} \mathbf{C}^2)^T , \quad \frac{\partial J_{10}}{\partial \mathbf{\mathcal{E}}} = \mathbf{M} \otimes \mathbf{M} \mathbf{C} , \\ \frac{\partial J_{11}}{\partial \mathbf{\mathcal{E}}} = \mathbf{C} \mathbf{M} \otimes \mathbf{M} \mathbf{\mathcal{E}} + \mathbf{\mathcal{E}} \mathbf{M} \otimes \mathbf{M} \mathbf{C} , \quad \frac{\partial J_{12}}{\partial \mathbf{\mathcal{E}}} = \mathbf{M} \otimes \mathbf{M} \mathbf{C}^2 . \end{cases} \quad (\text{A.4})$$

Appendix B: second Piola-Kirschhoff ($\mathbf{S}$) and Cauchy ($\boldsymbol{\sigma}$) stress tensors

From equation (21), the second Piola-Kirschhoff tensor $\mathbf{S}$ incorporating rate-dependency is obtained as:

$$\begin{aligned}
 \mathbf{S} = & -p\mathbf{C}^{-1} + 2(W_e)_1 \mathbf{I} + 2(W_e)_2 [\text{tr}(\mathbf{C})\mathbf{I} - \mathbf{C}] + 2(W_e)_3 I_3 \mathbf{C}^{-1} + 2(W_e)_4 \mathbf{M} \otimes \mathbf{M} \\
 & + 2(W_e)_5 (\mathbf{C}\mathbf{M} \otimes \mathbf{M} + \mathbf{M} \otimes \mathbf{M}\mathbf{C}) + 2(W_v)_1 \mathbf{I} + 2(W_v)_2 2\dot{\mathbf{C}} \\
 & + 2(W_v)_3 J_3 \dot{\mathbf{C}}^1 + 2(W_v)_4 \mathbf{M} \otimes \mathbf{M} + 2(W_v)_5 (\dot{\mathbf{C}}\mathbf{M} \otimes \mathbf{M} + \mathbf{M} \otimes \mathbf{M}\dot{\mathbf{C}}) \\
 & + 2(W_v)_6 \mathbf{C} + 2(W_v)_7 [(\mathbf{C}\dot{\mathbf{C}})^T + (\dot{\mathbf{C}}\mathbf{C})^T] + 2(W_v)_8 \mathbf{C}^2 \\
 & + 2(W_v)_9 [(\mathbf{C}^2 \dot{\mathbf{C}})^T + (\dot{\mathbf{C}} \mathbf{C}^2)^T] + 2(W_v)_{10} (\mathbf{M} \otimes \mathbf{M}\mathbf{C}) \\
 & + 2(W_v)_{11} (\mathbf{C}\mathbf{M} \otimes \mathbf{M}\dot{\mathbf{C}} + \dot{\mathbf{C}}\mathbf{M} \otimes \mathbf{M}\mathbf{C}) + 2(W_v)_{12} (\mathbf{M} \otimes \mathbf{M}\mathbf{C}^2), \tag{B.1}
 \end{aligned}$$

where, for simplicity, the notations $(W_e)_i$ and $(W_v)_j$ have been adopted to represent $\frac{\partial W_e}{\partial I_i}$ and $\frac{\partial W_v}{\partial J_j}$, respectively.

The condition of incompressibility requires $I_3 = \det \mathbf{C} = 1$. In addition, in view of equations (22) and (26), it may be observed that W_e is $W_e(I_1, I_4)$, and W_v is $W_v(I_1, J_7, J_{11})$. Therefore,

$$\left(\frac{\partial W_e}{\partial I_i} \right)_{i=2,3,5} = 0, \text{ and } \left(\frac{\partial W_v}{\partial J_j} \right)_{j=1 \text{ to } 6, 8 \text{ to } 10, 12} = 0. \text{ It follows that:}$$

$$\begin{aligned} \mathbf{S} = & -p\mathbf{C}^{-1} + 2(W_e)_1 \mathbf{I} + 2(W_e)_4 \mathbf{M} \otimes \mathbf{M} + 2(W_v)_7 [(\mathbf{C}\mathbf{E})^T + (\mathbf{E}\mathbf{C})^T] \\ & + 2(W_v)_{11} (\mathbf{C}\mathbf{M} \otimes \mathbf{M}\mathbf{E} + \mathbf{E}\mathbf{M} \otimes \mathbf{M}\mathbf{C}). \end{aligned} \quad (\text{B.2})$$

The Cauchy stress $\boldsymbol{\sigma}$ is obtained from $\mathbf{S}$ via $\boldsymbol{\sigma} = \mathbf{F}\mathbf{S}\mathbf{F}^T$, and by using (B.2) may be expressed as:

$$\begin{aligned} \boldsymbol{\sigma} = & \mathbf{F} \left\{ 2(W_e)_1 \mathbf{I} + 2(W_e)_4 \mathbf{M} \otimes \mathbf{M} + 2(W_v)_7 [(\mathbf{C}\mathbf{E})^T + (\mathbf{E}\mathbf{C})^T] \right. \\ & \left. + 2(W_v)_{11} (\mathbf{C}\mathbf{M} \otimes \mathbf{M}\mathbf{E} + \mathbf{E}\mathbf{M} \otimes \mathbf{M}\mathbf{C}) \right\} \mathbf{F}^T - p\mathbf{I}. \end{aligned} \quad (\text{B.3})$$

where $\mathbf{F}$ is the deformation gradient and $\mathbf{I}$ is the identity tensor.

Appendix C: Partial derivatives of $(W_e)_i$ and $(W_v)_j$

The following partial derivatives appear in equation (B.3), and therefore need to be derived in order to establish the components of $\boldsymbol{\sigma}$: $(W_e)_1$, $(W_e)_4$, $(W_v)_7$ and $(W_v)_{11}$. Given the definitions of W_e^{iso} and W_e^{fibres} in equations (23) and (25) we may write:

$$W_e = n B T N \left[\frac{1}{6N} (I_1 - 3) - \ln \left(\frac{I_1 - 3N}{3 - 3N} \right) \right] + \frac{k_1}{2k_2} \left\{ \exp \left\{ k_2 [\kappa I_1 + (1 - 3\kappa)I_4 - 1]^2 \right\} - 1 \right\}. \quad (\text{C.1})$$

We note that:

$$\frac{\partial W_e^{iso}}{\partial I_1} = \frac{1}{6} n B T \frac{9N - I_1}{3N - I_1},$$

$$\frac{\partial W_e^{iso}}{\partial I_4} = 0 ,$$

(C.2)

$$\begin{aligned} \frac{\partial W_e^{fibres}}{\partial I_1} &= \kappa k_1 [\kappa I_1 + (1-3\kappa)I_4 - 1] \exp \left\{ k_2 [\kappa I_1 + (1-3\kappa)I_4 - 1]^2 \right\} , \\ \frac{\partial W_e^{fibres}}{\partial I_4} &= k_1 (1-3\kappa) [\kappa I_1 + (1-3\kappa)I_4 - 1] \exp \left\{ k_2 [\kappa I_1 + (1-3\kappa)I_4 - 1]^2 \right\} \end{aligned}$$

Therefore:

$$\frac{\partial W_e}{\partial I_1} = \frac{1}{6} n B T \frac{9N-I_1}{3N-I_1} + \kappa k_1 [\kappa I_1 + (1-3\kappa)I_4 - 1] \exp \left\{ k_2 [\kappa I_1 + (1-3\kappa)I_4 - 1]^2 \right\} , \quad (C.3)$$

and

$$\frac{\partial W_e}{\partial I_4} = k_1 (1-3\kappa) [\kappa I_1 + (1-3\kappa)I_4 - 1] \exp \left\{ k_2 [\kappa I_1 + (1-3\kappa)I_4 - 1]^2 \right\} . \quad (C.4)$$

Following the definitions of W_v^{matrix} and W_v^{fibres} given in equations (27) and (28) we obtain:

$$W_v = \frac{1}{4} (I_1 - 3) [(\eta_1 + \kappa \eta_2) J_7 + \eta_2 (1-3\kappa) J_{11}] . \quad (C.5)$$

We note that:

$$\frac{\partial W_v}{\partial J_7} = \frac{1}{4} (I_1 - 3) (\eta_1 + \kappa \eta_2) . \quad (C.6)$$

and

$$\frac{\partial W_v}{\partial J_{11}} = \frac{1}{4} \eta_2 (1-3\kappa) (I_1 - 3) . \quad (C.7)$$

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Table legends

Table 1 - Corresponding stretch rates in the central region of the specimens in both loading directions ($\dot{\lambda}_3$ and $\dot{\lambda}_2$) at each applied stretch rate. Note that the given applied $\dot{\lambda}$ is that of the circumferential direction.

Table 2 - Model parameters at different applied stretch rates. The values are presented as mean ($\pm$ SD). Note that $B = 1.38 \times 10^{-23}$ (JK⁻¹), $T = 300$ K and the given applied rate $\dot{\epsilon}$ is that of the circumferential direction.

Table 1

Applied $\dot{\epsilon}$ [s ⁻¹]	Equi-biaxial displacement protocol		Biaxial (1:3) displacement protocol	
	$\dot{\epsilon}_3$ [s ⁻¹]	$\dot{\epsilon}_2$ [s ⁻¹]	$\dot{\epsilon}_3$ [s ⁻¹]	$\dot{\epsilon}_2$ [s ⁻¹]
0.001	0.00065	0.001	0.00023	0.002

0.01	0.0035	0.0065	0.001	0.01
0.1	0.035	0.075	0.016	0.20
1	0.2	0.5	0.1	1.58

Table 2

$\mathcal{L}$ [s ⁻¹] (Applied)	Model parameters			
	0.001	0.01	0.1	1
N [-]	3.65 ± 0.50			

n [m ⁻³]		$4.12 \times 10^{23} \pm 2.89 \times 10^{23}$					
κ [-]		0.20 ± 0.09					
k_1 [MPa]		2.05 ± 1.90					
k_2 [-]		49.61 ± 33.10					
η_1 [MPa s]	---	1:1	1:3	1:1	1:3	1:1	1:3
		5.03	4.01	3.80	0.90	0.080	0.001
η_2 [MPa s]	---	1:1	1:3	1:1	1:3	1:1	1:3
		20	600	1.02	1.80	0.05	0.06
R^2 (Circ.- Rad.)	0.98-0.96	0.95-0.99		0.92-0.99		0.95-0.99	

Figure legends

Figure 1 – Typical intact porcine AV leaflet used in this study. The principal loading directions of the leaflet, i.e. the circumferential and radial loading directions, are shown in reference to the

leaflet. Square specimens ($12\text{mm} \times 12\text{mm}$) were prepared from the central region of the AV leaflet for in-plane biaxial tensile tests.

Figure 2 - Unit vectors $\mathbf{M}$ and $\mathbf{N}$ define the mean direction of, and the direction of an arbitrary fibre from, the fibre family, respectively. Note that the angles Θ and Φ are defined similar to θ and φ .

Figure 3 – (a) Schematic of a transversely isotropic fibre dispersion around a mean direction $\mathbf{M}$. The right panel depicts a case where the preferred direction $\mathbf{M}$ coincides with the Cartesian unit vector $\mathbf{e}_3$; (b) In-plane (2D) distribution of fibre dispersion by the projection of the conical 3D transversely isotropic distribution into a plane that coincides with the centre plane of the cone (note that for simplicity, only the top half of the conical distribution is presented).

Figure 4 - The family of fibres are assumed to only rotate along the same end, such that the unit vector $\mathbf{N}$ of the mean direction of the fibre family in the reference configuration rotates to a new position characterised by the unit vector $\mathbf{N}'$.

Figure 5 - Graphical representation of the wrapped Lorentzian angular distribution of the collagen fibres with varying ρ and corresponding dispersion parameter κ .

Figure 6 – (a) Square specimens were secured in the testing device using BioRake (CellScale[®]) tines; (b) Prior to the start of the tests, five ink-markers were printed on the central region of the specimens to facilitate the measurement of the stretches λ_3 and λ_2 . The scale bar represents 1 cm.

Figure 7 – Cauchy stress-stretch curves ($\sigma - \lambda$) obtained using the equi-biaxial displacement protocol under various applied stretch rates: (a) experimental data for the representative samples; (b) filtered curves for the representative samples using a Savitzky-Golay filter. The letters ‘C’ and ‘R’ next to the curves indicate the direction of deformation, i.e. circumferential and radial, respectively.

Figure 8 - Cauchy stress-stretch curves ($\sigma - \lambda$) obtained using the biaxial displacement protocol (1:3) under various applied stretch rates: (a) experimental data for the representative samples; (b)

filtered curves for the representative samples using a Savitzky-Golay filter. The letters ‘C’ and ‘R’ next to the curves indicate the direction of deformation, i.e. circumferential and radial, respectively.

Figure 9 - Fitting results for (a) equi-biaxial and; (b) biaxial (1:3) displacement protocols. Markers represent the experimental data and the continuous curves represent the best fit provided by the model. The letters ‘C’ and ‘R’ next to the curves indicate the direction of deformation, i.e. circumferential and radial, respectively.

Figure 10 - (a) Variation of η_1 and η_2 with the stretch rate $\dot{\lambda}$, and extrapolation to the physiological loading rates of $\dot{\lambda}_3 \approx 4.4 \text{ s}^{-1}$ and $\dot{\lambda}_2 \approx 12.4 \text{ s}^{-1}$, plotted in logarithmic scale. The equations of the lines of best fit are $\eta_1 = 0.024 \dot{\lambda}_2^{1.287}$ and $\eta_2 = 0.0946 \dot{\lambda}_3^{0.921}$; (b) Predicted $\sigma - \lambda$ curves at the physiological loading rate generated by using the model in equation (33) and the extrapolated values of $\eta_1 = 0.0093 \text{ MPa s}$ and $\eta_2 = 0.0035 \text{ MPa s}$. The elastic parameters are listed in Table 2.

Figure 11 - Representative fibre orientation density distribution ($\rho = 0.386$) in the tested specimens reconstructed from the average dispersion value $\kappa (= 0.2)$ given in Table 2. The inset compares the normalised distribution with the experimental data as reported by Billiar and Sacks (1997), shown in the graph with hollow circles. The distribution in the inset was obtained by normalising the true fibre orientation density distribution with respect to its peak value and then correcting for the offset. Note that the shift between the centres of the two distributions is a result of the different reference positions used in the two studies for the initial preferred direction of the fibres.

Figure 1

Figure 2

Figure 3

Figure 5

Figure 6

(a)

(b)

Figure 7

(a)

R

(b)

(a)

Figure 10

Figure 11