CHAPTER 5

MODELING OF DAMAGE IN SOFT BIOLOGICAL TISSUES

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1 INTRODUCTION

Damage accumulation in materials is a consequence of micro-defect evolution, which may lead to degradation of mechanical properties up to failure. Continuum damage mechanics (CDM) is an inelastic theory which is concerned with the effective continuum representation of a material including distributed micro-defects. The most basic difference between CDM and fracture mechanics (FM) is that the former falls within the standard continuum mechanics framework using continuous displacement fields (hence finite element implementation is rather easy), while in FM the displacement is discontinuous, so that special techniques such as remeshing or the extended finite element should be employed to model the discontinuity in the displacement field.

The emphasis of this chapter is placed on modeling of damage in soft biological tissues. Despite the broad research on the modeling of tissue damage, there is still no clear understanding of what “damage” of a soft biological tissue is from the microstructural point of view. Conventional macroscopic indicators, as known from damage in engineered materials, may not predict damage in biological tissues appropriately and accurately enough. In addition, tissues are living materials, so that damage may trigger a process of health restoration called healing. A better understanding of the damage mechanism in soft biological tissues is critical to the characterization of tissue injury, including its implications on biological (physiological/pathological) responses, and the damage modeling in computational simulations. Such knowledge may help to develop concepts that enable us to accurately predict, for example, the rupture of abdominal aortic aneurysms and vulnerable plaques, as it is crucial for clinical treatment planning, or to optimize the designs of medical devices which are based on a proper understanding of short-term and long-term interactions with biological tissues (Gasser, 2011).

Exposing biological tissues to supra-physiological mechanical loading conditions during interventional procedures, such as balloon angioplasty and arterial clamping, changes the tissue microstructure through irreversible deformations (Peña, 2015). Preconditioned healthy (human) media strips which underwent cyclic uniaxial extension tests showed that the deformation process is associated with inelastic effects (Holzapfel et al., 2000b). Overstretching in the first loading cycle involved dissipation with large hystereses when compared with the elastic domain. A subsequent second loading cycle showed a small hysteresis and (relatively large) nonvanishing strains at the unstressed state (up to 6%), these being responsible for the permanent change of shape of the strip. For more details
the reader is referred to Holzapfel et al. (2000b). Another example is shown in Holzapfel and Gasser (2007), where a typical stress-strain response of a healthy media strip from a human aorta under supra-physiological loading showed inelastic effects (stress softening and nonrecoverable deformation), which leads to significant changes in the mechanical behavior. Furthermore, pressure-diameter responses of balloon-inflated canine carotid arteries also showed nonvanishing (remaining) strains after supra-physiological loading and subsequent unloading (Oktay et al., 1991). In a clinical context those inelastic effects, which occur, for example, during angioplasty, are described as “controlled vessel injury” (Castaneda-Zuniga, 1985). Finally, the experimental study of Castaneda-Zuniga et al. (1980) on balloon-dilated cadaveric arteries also indicated that beyond a certain load, the widening of the artery becomes permanent due to overstretching (Holzapfel and Gasser, 2007).

It is critical that these inelastic phenomena, such as the stress softening and the permanent deformation, are accounted for in constitutive models of biological tissues so that computational models can properly predict the outcome of interventional procedures that involve nonphysiological loading. Damage-related effects (e.g., for tendon and ligament (Parry et al., 1978; Liao and Belkoff, 1999), and vascular tissue (Oktay et al., 1991; Emery et al., 1997a,b; Weisbecker et al., 2012; Fereidoonnezhad et al., 2016)) and plasticity-related effects (e.g., for skin (Ridge and Wright, 1967), tendon and ligament (Abrahams, 1967; Parry et al., 1978; Sverdlik and Lanir, 2002), and vascular tissue (Oktay et al., 1991; Salunke and Topoleski, 1997)) have been documented, whereby experimental data were analyzed using macroscopic engineering metrics such as stress and strain. Mechanically induced damage (injury) may also trigger adaptive processes such as growth in biological tissues. For example, morphological changes that occur in the arterial wall due to stent-induced injury cause a biological response and may lead to the development of in-stent restenosis. For a mechanobiological (growth) model to capture the in-stent restenosis and a related finite element simulation of restenosis after angioplasty, see Fereidoonnezhad et al. (2017). Despite the reported efforts to model the morphology, the internal structure, and the mechanics of biological tissue, a specific multiscale characterization of tissue injury (damage) including its implications on biological responses has not yet been addressed satisfactorily.

This chapter is organized as follows: we provide general aspects of constitutive modeling of damage in biological tissues in Section 2. Physiological and supra-physiological loading conditions on soft tissues are described and consequences discussed, and that is followed by a brief description of damage characterization. Furthermore, we summarize and discuss damage models which are based on CDMs, the theory of pseudo-elasticity, and the softening hyperelasticity approach. Section 3 deals with finite element modeling of damage in soft biological tissues, whereby some more recent accounts on the simulations of interventional procedures, such as arterial clamping and balloon angioplasty, that involve nonphysiological loading are summarized. The chapter concludes with a short summary and identifies open problems and specific needs for improving the damage modeling.

2 CONSTITUTIVE MODELING OF DAMAGE IN SOFT BIOLOGICAL TISSUES

Soft tissues are pretrained in the unloaded configuration; they are highly deformable, (nearly) incompressible, nonhomogeneous, and are preconditioned and may undergo damage-based softening, fracture, and dissection. Several soft tissues are inelastic and display a viscoelastic behavior (relaxation and/or creep), which is related to the shear interaction between the collagen fibers and the glycoproteins in the matrix (the matrix provides a viscous lubrication between collagen fibrils), see Minns et al.
Examples for soft biological tissues are blood vessels, tendons, ligaments, skin, muscles, and articular cartilages just to name a few. The mechanical behavior of each individual soft tissue depends on its composition and structure, with a strong dependence on its properties, the percentage of fibers (collagen/elastin), and its characteristics, directionality, and type of grouping. Another typical feature of soft tissues such as cartilage, skin, cornea, and particularly blood vessels is its layered structure. Soft biological tissues can be viewed as fibrous composites assembled by a matrix material and embedded families of collagen fibers which may be dispersed about a mean direction. The structural arrangement of collagen leads to the characteristic anisotropic behavior of soft tissues.

A major difference between the mechanical responses of hard and soft tissues lies in the magnitudes of the deformations that they can sustain. While infinitesimal deformation theories can reasonably be applied to hard tissues, the deformation of soft tissues requires a nonlinear theory that allows for large deformations, see, for example, the book edited by Holzapfel and Ogden (2006). The tensile response of soft tissues is nonlinear stiffening, and the tensile strength is strain-rate dependent. Fig. 1, modified from Holzapfel (2001), shows a schematic diagram of a typical J-shaped (tensile) stress-strain curve for skin. This form, representative for many soft tissues, differs significantly from stress-strain curves of hard tissues, or from other types of (engineering) materials. In addition, Fig. 1 shows how the collagen fibers straighten with increasing stretch (strain).

### 2.1 LOADING DOMAINS FOR SOFT BIOLOGICAL TISSUES

To capture the mechanical behavior of arterial walls in the physiological loading domain, various experiments have been carried out, see, for example, the reviews of Fung (1981), Abé et al. (1996), Humphrey (2002), and Holzapfel and Ogden (2006, 2010). Typically, the physiological mechanical response of soft biological tissues is anisotropic, nonlinear elastic (or viscoelastic), and within the finite
strain domain. In many cases soft biological tissues are considered (nearly) incompressible. The description of the constitutive behavior of this type of material relies on the identification of an appropriate strain-energy function (SEF) from which the stress-strain relation and its derivative, the elasticity tensor, can be derived (for more information on nonlinear continuum mechanics, see the monograph of, e.g., Holzapfel, 2000). Many SEFs have been proposed to describe the behavior of various soft tissues. It is beyond the scope of this chapter to review all of them.

The experimental study of Castaneda-Zuniga et al. (1980) showed that supra-physiological loading conditions yield remaining deformations as soon as a certain load level is exceeded. This was confirmed by Oktay et al. (1991) for carotid arteries of dogs, and by Holzapfel et al. (2000b) for human iliac arteries. Schulze-Bauer et al. (2002) tested human adventitias under physiological and supra-physiological conditions, and in particular the supra-physiological tests were analyzed in detail by Sommer et al. (2010). By using cyclic tensile tests, the latter study concluded that soft collagenous tissues show a complex stress-softening hysteresis. This has also been investigated in more detail by Weisbecker et al. (2012) where a subsequent irreversible alignment of the collagen fibers turned out to be the reason for the softening (Schmidt et al., 2014). Supra-physiological loading occurs in many clinical treatments, such as arterial clamping and balloon angioplasty; some inelastic phenomena may occur due to damage (injury) induced in the tissue. For such cases hyperelastic models are not appropriate to capture the mechanical response. More sophisticated constitutive models are required to capture the damage-induced inelastic phenomena, such as stress softening (Mullins effect) and permanent deformation, see, for example, Alastrué et al. (2008), Muñoz et al. (2008), and Fereidoonnejad et al. (2016).

Incorporation of damage in constitutive models of soft biological tissues is a prerequisite for a better understanding of clinical treatments involving supra-physiological loading. Many research groups have focused on damage modeling of soft biological tissue in recent years. The developed damage models can be roughly categorized into three groups: (i) models based on CDM, (ii) models based on the theory of pseudo-elasticity to represent damage-induced inelastic phenomena such as stress softening and permanent deformation, and (iii) the softening hyperelasticity approach. In Sections 2.3–2.5 we review the most important damage models in each of the mentioned groups.

The experimental results suggest that, similarly to the elastic properties, the inelastic behavior of soft tissues is also anisotropic, see, for example, Alastrué et al. (2008) and Peña et al. (2009, 2010, 2011). Accordingly, a suitable constitutive model should be adopted for the anisotropic inelastic behavior. An inelastic model should incorporate the Mullins effect, the permanent set, resulted from the residual strains after unloading, and the fiber-matrix disruption under supra-physiological loading conditions or strains (Calvo et al., 2009). Three important softening phenomena associated with soft biological tissue may be distinguished. First, the dependence of the mechanical response on the previously attained maximum load value, very similar to the well-known Mullins effect for rubber-like materials (Ogden and Roxburgh, 1999; Diani et al., 2009). Another typical phenomenon named preconditioning is characterized by the continuous softening at the same load level after the first loading cycle until a certain saturated state is reached (Holzapfel et al., 2005). Finally, the damage behavior resulted from fiber rupture and matrix disruption and should also be considered (Stabile et al., 2004; Calvo et al., 2009). Fiber and matrix rupture means fiber/matrix failure due to tissue fracture which is not related to the Mullins effect. There are several differences between softening as a result of structural rearrangement in the material (Mullins effect) and softening as a result of bond rupture and complete damage (Peña, 2014).
2.2 DAMAGE CHARACTERIZATION IN SOFT BIOLOGICAL TISSUE

In general, damage may be defined as “injury or harm that reduces value or usefulness” (Famaey et al., 2013). Thus, a quantification of damage can be performed by evaluating the reduction in “value” or “usefulness.” Modeling damage in biological tissues requires an objective and quantitative method for evaluation. This can be carried out either directly, through functional assessment, or indirectly, through morphological assessment.

Damage of the mechanical tissue function manifests itself through rupture or degradation of the mechanical constituents of the tissue. One way to quantitatively assess this form of damage is to perform mechanical tests of tissues before and after the initiation of damage. For example, biaxial tensile tests on a patch of cardiovascular tissue can provide information on its stiffness in different directions. Excessive tension will cause a gradual rupture of more and more collagen fibers, which induces a measurable decrease in stiffness in the directions in which the collagen fibers contribute. Another way to assess the mechanical tissue function is to study the morphological integrity of the tissue. Imaging can also provide insight into the composition of a tissue and reveal fractures in the different constituents. Damage of the biological tissue function manifests itself through malfunction, function switch, or apoptosis of involved cells. Quantification of the biological tissue function before and after damaging provides a measure of the degree of damage. Sometimes it is possible to directly measure that damage function. In other situations an indirect approach is taken by measuring the concentration of certain products or the expression of certain genes; the biological tissue function is often the result of a biological cascade of events of cells. Another way to assess the biological tissue function is to study the condition of a tissue through morphological imaging. The spatial resolution of the imaging method determines how the damage can be evaluated at specific locations. Damage to certain constituents or processes can be imaged by applying specific stains and visualizing them through corresponding microscopic techniques. For example, in immunofluorescence microscopy, specific antibodies can be labeled with a fluorophore to visualize endothelial morphology (e.g., with CD31), the smooth muscle cells (e.g., with alpha-smooth muscle actin), elastin (e.g., with antielastin), and collagen (e.g., with anticollagen IV). Cell proliferation and cell death can also be visualized through immunofluorescence microscopy, for example, with a TUNEL assay, or with a combined propidium iodide (PI) and syto 13 staining. PI stains all cell nuclei red, whereas syto 13 stains only intact nuclei green. The combination of these two stains therefore yields a “live-dead”-staining, after which image processing can reveal the percentage of cell death in different regions (Famaey et al., 2013).

As shown, damage can be evaluated quantitatively in multiple ways. This can facilitate a consensus as to how much damage is acceptable for a certain tissue. However, knowing this limit is only meaningful if the amount of load needed to induce damage is identified. Therefore, in the experimental protocol for defining safety limits for tissues, there is a need for controllable force application and subsequent damage evaluation. This way, an unambiguous relation can be defined between mechanical loading and damage (Famaey et al., 2013).

2.3 MODELS BASED ON CONTINUUM DAMAGE MECHANICS

2.3.1 Basic formulation

For computational implementation, a multiplicative decomposition of the deformation gradient $F = J^{1/3}F$ into volume-changing (dilational) and volume-preserving (distortional) parts is usually established, where $J = \det F > 0$ is the volume ratio and $F$ is the modified deformation gradient with...
\[ \text{det} \mathbf{F} = 1. \] Consequently, \( \mathbf{C} = \mathbf{F}^T \mathbf{F} \) denotes the right Cauchy-Green tensor, and \( \overline{\mathbf{C}} = \mathbf{F}^T \mathbf{F} \) is the modified right Cauchy-Green tensor (Holzapfel, 2000).

To characterize isothermal processes, we postulate the existence of a decoupled representation of an SEF, say \( \Psi \). Because of the anisotropy, we require that the function \( \Psi \) explicitly depends on both the right Cauchy-Green tensor \( \mathbf{C} \) and the fiber directions \( \mathbf{m}_0 \) and \( \mathbf{n}_0 \) in the reference configuration. Since the sign of \( \mathbf{m}_0 \) and \( \mathbf{n}_0 \) is not significant, \( \Psi \) must be an even function of \( \mathbf{m}_0 \) and \( \mathbf{n}_0 \), and so it may be expressed as \( \Psi = \Psi(\mathbf{C}, \mathbf{M}_0, \mathbf{N}_0) \) where \( \mathbf{M}_0 = \mathbf{m}_0 \otimes \mathbf{m}_0 \) and \( \mathbf{N}_0 = \mathbf{n}_0 \otimes \mathbf{n}_0 \) are structural tensors.

Based on the kinematic description, the SEF can be rewritten in the decoupled form according to

\[ \Psi(\mathbf{C}, \mathbf{M}_0, \mathbf{N}_0) = \Psi_{\text{vol}}(J) + \overline{\Psi}(\overline{\mathbf{C}}, \mathbf{M}_0, \mathbf{N}_0), \tag{1} \]

where \( \Psi_{\text{vol}} \) is a strictly convex function (with the minimum at \( J = 1 \)), which describes the volumetric elastic response, and \( \overline{\Psi} \) describes the isochoric response of the material, respectively (Holzapfel, 2000).

To incorporate the damage mechanism into a hyperelastic model, we consider the following Helmholtz free-energy function

\[ \Psi(\mathbf{C}, \mathbf{M}_0, \mathbf{N}_0, D_i) = \Psi_{\text{vol}}(J) + \overline{\Psi}(\overline{\mathbf{C}}, \mathbf{M}_0, \mathbf{N}_0, D_i) \]

\[ = \Psi_{\text{vol}}(J) + \sum_{i=m, f_1, f_2} \overline{\Psi}_i, \quad \overline{\Psi}_i = (1 - D_i) \overline{\Psi}^0_i, \tag{2} \]

where \( \overline{\Psi}^0_i \) denote the effective isochoric SEFs of the undamaged materials, in other words, matrix \( m \), first family of fibers \( f_1 \), and second family of fibers \( f_2 \). Note that \( \sum_i \overline{\Psi}^0_i = \text{const} \) in Eq. (1). The damage variables \( D_i \in [0, 1] \) are defined for the matrix \( D_m \), and the two families of fibers, \( D_{f_1} \) and \( D_{f_2} \), and the term \( (1 - D_i) \) is known as the reduction factor first proposed by Kachanov (1958).

Standard arguments based on the Clausius-Duhem inequality \( \mathcal{D}_{\text{int}} = -\dot{\Psi} + \mathbf{S} : \dot{\overline{\mathbf{C}}} / 2 \geq 0 \) lead to the representation (Holzapfel, 2000)

\[ \mathbf{S} = \mathbf{S}_{\text{vol}} + \mathbf{S}, \tag{3} \]

\[ \mathbf{S}_{\text{vol}} = 2 \frac{\partial \Psi_{\text{vol}}}{\partial J} \frac{\partial J}{\partial \mathbf{C}} = J p \mathbf{C}^{-1}, \quad \mathbf{S} = 2 \frac{\partial \overline{\Psi}}{\partial \overline{\mathbf{C}}} : \dot{\overline{\mathbf{C}}} = \sum_{i=m, f_1, f_2} (1 - D_i) \overline{\Psi}_i, \tag{4} \]

where \( p = \partial \Psi_{\text{vol}} / \partial U \) denotes the hydrostatic pressure and \( \overline{\Psi}_i = 2 J^{-\frac{1}{2}} (\mathbf{\mathcal{P}} : \frac{\partial \overline{\Psi}^0_i}{\partial \overline{\mathbf{C}}} / \partial \overline{\mathbf{C}}) \) is a purely isochoric stress contribution of the perfectly elastic material in which the fourth-order projection tensor \( \mathbf{\mathcal{P}} = I - \mathbf{C}^{-1} \otimes \mathbf{C} / 3 \) has been used, while \( \mathbf{I} \) is the fourth-order unit tensor, and

\[ \mathcal{D}_{\text{int}} = \sum_{i=m, f_1, f_2} f_i \dot{D}_i \geq 0, \tag{5} \]

where \( f_i \) denote the thermodynamic forces which govern the damage evolution. They are related (conjugate) to the internal variables \( D_i \) according to

\[ f_m = \overline{\Psi}^0_m(\overline{\mathbf{C}}) = -\frac{\partial \Psi}{\partial D_m}, \quad f_{f_1} = \overline{\Psi}^0_{f_1}(\overline{\mathbf{C}}, \mathbf{M}) = -\frac{\partial \overline{\Psi}_{f_1}}{\partial D_{f_1}}, \quad f_{f_2} = \overline{\Psi}^0_{f_2}(\overline{\mathbf{C}}, \mathbf{N}) = -\frac{\partial \overline{\Psi}_{f_2}}{\partial D_{f_2}}, \tag{6} \]

see relation (2), hence the forces \( f_i \) are identical to the effective isochoric SEFs \( \overline{\Psi}^0_i \) of the undamaged tissue. The damage mechanism is assumed to be associated with the distortional or isochoric energy and is independent of the hydrostatic pressure.
In some cases the damage criterion is defined in strain space according to the condition that, at any time $t$ of the loading process, the following expression is fulfilled (Simo, 1987)

$$\Phi_i(\overline{C}(t), R_{\mu}) = \Xi_i(\overline{C}(t)) - R_{\mu} \leq 0,$$

(7)

where $\Phi_i$ are damage functions, $\Xi_i$ are damage release rate variables at time $t$, and the parameters $R_{\mu}$ signify the damage threshold at current time $t$ (i.e., the radius of the damage surfaces) for the matrix and the fibers. Then, the equation $\Phi_i(\overline{C}(t), R_{\mu}) = 0$ defines damage surfaces in the (isochoric) strain space. The definitions of $\Xi_i$ and $R_{\mu}$ depend on the damage model; for more details see, for example, Natali et al. (2003), Balzani et al. (2006), and Calvo et al. (2007). Finally, by denoting the normals to the damage surfaces in the (isochoric) strain space as $N_i = \partial \Phi_i / \partial \overline{C}$, the evolutions of the damage parameters $D_i$ are specified by the irreversible rate equations

$$\dot{D}_i = \begin{cases} h_i(\Xi_i, D_i) \Xi_i & \text{if } \Phi_i = 0 \text{ and } N_i : \overline{C} > 0, \\ 0 & \text{otherwise}, \end{cases}$$

(8)

where $h_i$ is a given function characterizing the evolution of damage in the tissue. For more details see, for example, Simo (1987), Holzapfel (2000), and Calvo et al. (2007).

### 2.3.2 Specific models

CDM, as described in the previous section, has been employed by some researchers to model damage-induced inelastic phenomena in, for example, arterial tissues where the basis of the damage models is a hyperelastic model. Various forms of the SEF were proposed in the literature for soft biological tissues. Holzapfel et al. (2000a) proposed an exponential SEF for fibrous soft biological tissues, in particular for arterial walls,

$$\Psi(I_1, I_4, I_6) = \mu \frac{2}{3} (I_1 - 3) + \frac{k_1}{2k_2} \sum_{i=4,6} \{ \exp(\frac{k_2}{2} (I_i - 1)^2) - 1 \},$$

(9)

where $\mu, k_1, k_2$ are material parameters, $i = 4$ corresponds to the first family of fibers and $i = 6$ to the other, while $I_1 = \text{tr}\overline{C}$ is the first invariant of $\overline{C}$ and $I_4 = m_0 : \overline{C}m_0$ and $I_6 = n_0 : \overline{C}n_0$ are the modified pseudo-invariants. It is assumed that the fibers are active only in tension and inactive in compression. Hence, the anisotropic terms in Eq. (9) only contribute when $I_4 > 1$ or $I_6 > 1$. If $I_4$ and $I_6$ are less than or equal to 1, then the response of the tissue is purely isotropic. This model is implemented in commercial software programs such as ABAQUS (Dassault Systèmes Simulia Corp., 2017), ADINA (ADINA, 2017), and ANSYS (ANYS, 2017); it is also implemented in FEAP (Taylor, 2013).

Gasser et al. (2006) proposed a structurally based SEF for fibrous soft tissues by extending Eq. (9) to the case of dispersed fiber distribution. The model may be written as

$$\Psi(I_1, I_4, I_6) = \mu \frac{2}{3} (I_1 - 3) + \frac{k_1}{2k_2} \sum_{i=4,6} \left\{ \exp(\frac{k_2}{2} (I_i - 1)^2) - 1 \right\},$$

where $\kappa \in [0, 1/3]$ is the dispersion parameter. Here it is also required that the fibers contribute only when extended, strictly when either $I_4 > 1$ and/or $I_6 > 1$. For a detailed discussion on the tension-compression switch in soft fibrous solids see Holzapfel and Ogden (2015), and for a related computational method for excluding fibers under compression see Li et al. (2016). The constitutive model (10) is implemented in ABAQUS (Dassault Systèmes Simulia Corp., 2017), in the XML-based language project cellML (cellML, 2017), and in some versions of FEAP (Taylor, 2013). Recently, an extension of
these models was proposed by Holzapfel et al. (2015) to take into account the nonsymmetric collagen fiber dispersion in arterial walls. That model is more general and needed for describing the mechanical behavior of a variety of fibrous tissues.

Balzani et al. (2006) assumed that discontinuous damage occurs in arterial walls, and only along the fiber direction. Other factors may also influence the failure of the vascular wall, as has been reported for the normal bovine aorta by Haslach et al. (2011) or for tendons and ligaments by Knörzer et al. (1986). Balzani et al. (2012) also provided a construction principle for damage models that accounts for remaining strains after unloading, and then applied this principle to collagenous soft tissues such as arterial walls. The basic idea of this model is to incorporate the reduction factor \((1 - D_i)\) directly into the inner function instead of prefixing the term. This makes it possible to obtain remaining strains after unloading. It is considered that damage occurs only in the two families of fibers. Hence, there is no need to modify the SEF of the matrix material, but the two energy functions for the fibers need to be updated as

\[
Ψ(\overline{I}_1, \overline{I}_4, \overline{I}_6, D_4, D_6) = \frac{μ}{2}(I_1 - 3) + \frac{k_1}{2k_2} \sum_{i=4,6} \left\{ \exp\left[k_2\left(1 - D_i\right)\left(κ\overline{I}_1 + (1 - 3κ)\overline{I}_i\right) - 1\right]\right\] - 1, (11)

where \(D_i\) are the damage variables for the fibers, while the Macaulay brackets \(\langle(•)\rangle = [(•) + |(•)|]/2\) filter out negative values. Hence, the exponential function contributes to \(Ψ\) only if \(κ\overline{I}_1 + (1 - 3κ)\overline{I}_i - 1 > 0\) which is not a physically correct tension-compression switch (Holzapfel and Ogden, 2015).

Schmidt et al. (2014) considered a stochastic distribution of microscopic quantities based on a simple fiber unit-cell. The proposed damage model extended a framework in Balzani et al. (2012), and postulates specific damage functions that result from the fibers’ microstructure. Statistical distributions of three different microscopic quantities, such as proteoglycan orientation, fibril length parameter, and ultimate proteoglycan stretch, are considered. Rodríguez et al. (2006) chose to model the collagen fibers using a worm-like chain approach. Discontinuous softening was introduced by defining different failure stresses for bundles of collagen fibers with different lengths. A finite element implementation and numerical examples were presented by Rodríguez et al. (2008). Due to the lack of experimental data, calibration of this structurally motivated model remains a challenge. By employing CDM, Maher et al. (2012) developed a constitutive model for arterial tissues that incorporates stress softening and permanent deformations in both the isotropic ground matrix and the fibers. Marino and Vairo (2014) adopted a bottom-up approach and investigated the influence of intermolecular interactions on the elastodiage mechanics of collagen fibrils. The model has the potential to be integrated in a multi-scale modeling framework to investigate the mechanical response of the tissue at the macroscopic level. Natali et al. (2005) proposed an anisotropic elastodiage constitutive model to address the mechanical behavior of healthy tendons during physiological loading and to address the degeneration phenomena. That was correlated with aging or traumatic events such as chronic or acute overloading during sports activities. It was assumed that the degradation of the mechanical properties is mainly attributed to the fiber response. The following SEF was proposed

\[
Ψ(C, D_f) = Ψ_{\text{vol}}(J) + Ψ_m(\overline{I}_1, \overline{I}_2) + g_f(D_f)Ψ_f(\overline{I}_4), (12)
\]

where \(g_f(D_f)\) denotes an exponential damage function, which is strictly decreasing with the internal damage parameter given as \(∂g_f(D_f)/∂D_f < 0\).
2.3.3 Damage functions of the internal variables

To complete the constitutive formulation of anisotropic finite elasticity with damage-based softening effects, we provide equations for the internal damage variables. Several equations for damage variables have been proposed in the context of CDM for soft biological tissues. The damage variables have different forms such as exponential, polynomial, and sigmoidal, and these variables are functions of different mechanical quantities such as stretch and strain energy. Some of these damage variables can be found in the review by Peña (2011b).

One CDM phenomenological approach to model damage in transversely isotropic soft tissues (e.g., in periodontal ligament) was proposed by Natali et al. (2003). Thus, by using an exponential damage (softening) function,

\[
D_i(\lambda_{\text{max}}, N_f) = \frac{1}{C_0} \exp \left\{ -\frac{1}{C_0} \exp \left( \frac{\beta_i}{\lambda_{\text{max}}(a) - \lambda_{\text{max}}(1)} \right) \right\},
\]

where \(a = N_f(\lambda_{\text{max}})/N\), \(N\) is the density of collagen fibers on the surface orthogonal to the fiber direction \(m_0\), \(N_f\) is the density of collagen fibers that have reached failure, \(\lambda_{\text{max}}\) is the maximum stretch that the tissues can reach along \(m_0\), and \(\beta_i\) is a scalar parameter that is chosen on the basis of experimental data. Eq. (13) is proposed in terms of the stretch \(\lambda\), and not in terms of the strain energy \(\Psi^0\) (the thermodynamic force associated to the damage), so it results in a nonsymmetric algorithmic tangent moduli with a high computational cost, see, for example, Simo (1987).

Balzani et al. (2006) and Calvo et al. (2007) proposed continuum damage models for fibrous biological tissues. Balzani et al. (2006) quantified damage in fiber components by using

\[
D_f(\Psi^0_f) = \gamma_1 \left[ 1 - \exp \left( -\frac{-\beta_f(\Psi^0_f)}{\gamma_2} \right) \right],
\]

where \(\gamma_1 \in [0, 1]\) and \(\gamma_2 > 0\) are material parameters, and \(\gamma_1\) describes the maximum possible discontinuous damage. Thereby, the internal variable \(\beta_f(\Psi^0_f)\) is defined as

\[
\beta_f(\Psi^0_f) = \sup_{0 \leq s \leq t} \left\{ \frac{\Psi^0_f(s) - \Psi^0_f(t_{\text{ini}})}{\psi_f(t_{\text{ini}})} \right\},
\]

where \(\Psi^0_f(t_{\text{ini}})\) characterizes the effective transversely isotropic energy at an initial damage state, which differs, in general, from the reference configuration. This is physically reasonable for arterial walls because it can be assumed that there is no damage evolution in the physiological range of deformations. The Macaulay brackets \(\bullet\) imply that no damage evolution occurs on unloading and reloading.

In addition, Calvo et al. (2007) proposed the following damage softening function for the matrix and the fibers

\[
D_i(\Xi_i) = \begin{cases} 
0, & \Xi_i < \Xi_{\text{min}}, \\
1 - \frac{1 - \exp \left[ \mu_i(\Xi_i - \Xi_{\text{max}}) \right]}{1 - \exp \left[ \mu_i(\Xi_{\text{min}} - \Xi_{\text{max}}) \right]}, & \Xi_{\text{min}} < \Xi_i < \Xi_{\text{max}}, \\
1, & \Xi_i > \Xi_{\text{max}},
\end{cases}
\]

where the variables \(\Xi_{\text{min}}\) and \(\Xi_{\text{max}}\) are the strain energies (7) at initial and total damage stages, respectively, for the matrix and the fibers, while \(\mu_i \geq 0\) are material parameters. Similarly, Peña et al. (2008) proposed the following polynomial equation
\[
D_i(\Xi) = \begin{cases} 
0, & \Xi < \Xi_{\text{min}}, \\
\Lambda_i^2 [1 - \eta_i (\Lambda_i^2 - 1)], & \Xi_{\text{min}} < \Xi < \Xi_{\text{max}}, \\
1, & \Xi > \Xi_{\text{max}},
\end{cases}
\]  

(17)

where \(\Lambda_i = (\Xi_i - \Xi_{\text{min}})/(\Xi_{\text{max}} - \Xi_{\text{min}})\) are dimensionless variables, and \(\eta_i\) are model parameters. Another method to define the damage parameter was presented by Rodríguez et al. (2008),

\[
D_i(\Xi) = \frac{1}{2} \left[ 1 + \frac{\xi_i \Xi_i \exp \left\{ 2 \xi_i \left[ (2 \Xi_i / \rho_i) - 1 \right] \right\} - 1}{\xi_i \Xi_i \exp \left\{ 2 \xi_i \left[ (2 \Xi_i / \rho_i) + 1 \right] \right\} + 1} \right],
\]

(18)

where \(\xi_i \geq 0\) and \(\rho_i > 0\) are material parameters. In this model, it is not possible to control damage initiation since no threshold parameters \(\Xi_{\text{min}}\) and \(\Xi_{\text{max}}\) were considered. To include damage initiation in this equation, Peña (2011b) considered a new damage law,

\[
D_i(\Xi) = \begin{cases} 
0, & \Xi < \Xi_{\text{min}}, \\
\frac{1}{2} \left\{ 1 + \frac{2 \xi_i \Lambda_i \exp \left\{ 2 \xi_i \left( 2 \Lambda_i - 1 \right) \right\} - 1}{2 \xi_i \Lambda_i \exp \left\{ 2 \xi_i \left( 2 \Lambda_i / \rho_i \right) + 1 \right\}} \right\}, & \Xi_{\text{min}} \leq \Xi \leq \Xi_{\text{max}}, \\
1, & \Xi > \Xi_{\text{max}},
\end{cases}
\]

(19)

which has been presented in Peña et al. (2009) and Peña (2011b) in slightly different forms, while the damage equation in Peña et al. (2009) seems not to demonstrate the continuity at \(\Xi_i = \Xi_{\text{min}}\).

By comparing exponential, polynomial and sigmoidal damage functions, Peña (2011b) furthermore proposed a simple sigmoidal function, with a classical “S” shape,

\[
D_i(\Xi) = \frac{1}{1 + \exp \left\{ -\alpha_i (\Xi_i - \gamma_i) \right\}},
\]

(20)

where the damaged release rate is \(\Xi_i = [2 W^0(\bar{C})]^{1/2}\). The parameter \(\alpha_i\) controls the slope, and \(\gamma_i\) defines the value \(\Xi_i\) such that \(D_i(\Xi_i) = 0.5\).

As presented in Peña (2011b), damage models can be compared from different points of view: (i) the first derivatives of some damage functions are zero at the initial damage state. This represents a potential advantage over numerical calculations since smooth derivatives are obtained. This property is not verified by Eqs. (14), (16); (ii) unlike Eqs. (16), (17), (19), some damage functions have a pair of horizontal asymptotes in \([0, 1]\), so that it is possible to obtain a damage function without consideration of additional parameters; (iii) the damage function must be a monotonically increasing function for all values of the energy and parameters. This important characteristic does not hold for Eq. (17); (iv) the damage functions in Eqs. (14), (16), (20) follow the Eyring theory of thermally activated processes (Eyring, 1936), which has a physical meaning, namely the theory can be used to define the rates of breakage of the active regions of matrix and collagen fibrils (Ciarletta and Ben Amar, 2009). However, it is important to note that the term “physical meaning” should be used with care because the CDM theory represents only a constitutive assumption, which is mainly based on phenomenological considerations. That holds particularly for complex composite materials such as fibrous tissues.

To assess the applicability of the different damage functions, the prediction of each type of function (exponential, see Eq. (16); polynomial, see Eq. (17); and sigmoidal, see Eq. (20)) was compared by Peña (2011b) with experimental data of muscular vaginal tissue and presented in Fig. 2. As shown, the best fit was obtained using the sigmoidal function (20). However, the fit of the
exponential and polynomial functions (compare with Eqs. (16) and (17)) is better in the beginning and then becomes worse in the final loading stage.

2.4 MODELS BASED ON THE THEORY OF PSEUDO-ELASTICITY

An alternative phenomenological approach for modeling damage in soft biological tissues is based on pseudo-elasticity, in which the material is treated as one elastic material in loading and another one in unloading. This concept was used by, for example, Fung et al. (1979) within the context of modeling arterial walls, and extended by Ogden and Roxburgh (1999) and Dorfmann and Ogden (2004) to model the Mullins effect in rubber. The advantages of this modeling approach are that it is convenient and simple to describe the stress-strain relationships in cyclic loading, and the numerical (finite element) implementation is straightforward. Gracia et al. (2009) compared the model of Ogden and Roxburgh (1999) with a CDM model according to Simo (1987) in terms of its capability to describe the Mullins effect in industrial rubber components. The inherent simplicity of the pseudo-elasticity approach makes it especially suitable for practical applications.

2.4.1 Basic formulation in pseudo-elasticity

We briefly review the main formulas within the theory of pseudo-elasticity. For the sake of simplicity, the formulation for isotropic damage is presented; an extension to anisotropic damage is straightforward. To consider isotropic damage in the sense of a decoupled volumetric-isochoric response,
according to the multiplicative split of the deformation gradient $F$, we have a decoupled representation of the SEF $\Psi(C, \eta)$, where $\eta \in [0, 1]$ is a damage variable. Thus, by considering the pseudo-elastic damage model, as introduced by Ogden and Roxburgh (1999), we write

$$\Psi(J, C, \eta) = \Psi_{\text{vol}}(J) + \eta \Psi^0(C) + \phi(\eta),$$

(21)

where the second function $\Psi^0$ denotes the isochoric strain energy of the undamaged material similarly to $\Psi^0$ in Eq. (2), which captures the isochoric elastic response so that the damage phenomenon affects only the isochoric part of the deformation (Simo, 1987), while $\phi$ is a damage function.

By definition the damage variable $\eta$ is set to 1 on the primary loading curve. The material behavior on this curve is then described by the SEF such that $\phi'(1) = 0$, and $\Psi(C, 1) = \Psi_{\text{vol}}(J) + \Psi^0(C)$. In the case of subsequent unloading and reloading, in other words, when $\eta < 1$, the damage evolves with the deformation so that

$$\frac{\partial \Psi}{\partial \eta} = \Psi^0(C) + \phi'(\eta) = 0,$$

(22)

where $\phi'(\eta) = d\phi(\eta)/d\eta$. Ogden and Roxburgh (1999) defined the damage function as

$$\eta = 1 - \frac{1}{r} \text{erf} \left[ \frac{1}{m} \left( \Psi^\text{max} - \Psi^0 \right) \right],$$

(23)

where $\text{erf}(\bullet)$ is the error function of $(\bullet)$ and $\Psi^\text{max}$ denotes the maximum strain energy obtained by the deformation history. The maximum material damage that can occur under loading is characterized by $r > 1$, and $m > 0$ determines the dependence of the damage on the deformation. Small values of $m$ indicate that significant damage occurs at small strains, whereas for larger values of $m$ damage progresses more slowly, see Weisbecker et al. (2012). The degree of damage in the fiber family can be characterized by the minimum value $\eta^\text{min}$ of the damage variable according to

$$\eta^\text{min} = 1 - \frac{1}{r} \text{erf} \left( \frac{1}{m} \Psi^\text{max} \right).$$

(24)

Other constitutive equations for the softening function have been proposed by Beattie et al. (1998) and Elías-Zúñiga (2005), for example.

Given the SEF (21), the second Piola-Kirchhoff stress tensor can be obtained by Eq. (3). Hence, the volumetric part is according to Eq. (4), while the isochoric part $\bar{S}$ of the second Piola-Kirchhoff stress tensor is now determined by

$$\bar{S} = \eta \bar{S}^0 + 2 \left( \Psi^0(C) \frac{\partial \eta}{\partial C} + \phi \frac{\partial \eta}{\partial C} \right), \quad \bar{S}^0 = 2 \frac{\partial \Psi^0(C)}{\partial C},$$

(25)

where $\bar{S}^0$ is the isochoric second Piola-Kirchhoff stress tensor related to the primary loading path.

### 2.4.2 Pseudo-elastic models for soft biological tissues

Franceschini et al. (2006) proposed an isotropic pseudo-elastic model (the same pseudo-elastic parameters for matrix and fibers) for brain tissue. Peña et al. (2009) presented a pseudo-elastic anisotropic model to reproduce the softening behavior exhibited in soft biological tissues without permanent set. However, the pseudo-elastic model is not able to reproduce the failure region as a result of bond rupture and complete damage, while CDM and other models are able to do so (Peña, 2011a). Weisbecker et al. (2012)
proposed an anisotropic model for the stress softening in aortic layers when loaded beyond the physiological range. However, the permanent deformation observed in the supra-physiological loading was not considered. Recently, Fereidoonnezhad et al. (2016) proposed an anisotropic pseudo-elastic model to describe the discontinuous softening and permanent deformation in arterial tissues. The model can capture specific features of arterial tissues including anisotropy, nonlinearity, stress softening and the permanent deformation when loaded beyond the physiological range. The damage model was implemented in ABAQUS (Dassault Systèmes Simulia Corp., 2017) as a user-defined subroutine UMAT. The authors compared the numerical results with experimental data, cyclic uniaxial tension in circumferential and longitudinal directions, and showed the capability and efficacy of the damage model.

### 2.5 SOFTENING HYPERELASTICITY APPROACH

As an alternative to the sophisticated CDM approach and to the theory of pseudo-elasticity, Volokh (2008) proposed the so-called “softening hyperelasticity approach” to predict the failure of soft biological tissues. Thereby, the constitutive description of tissue is enhanced with strain softening, which is controlled by material constants. In that approach, the energy limiters are introduced in the strain energy as (Volokh, 2007)

\[
\Psi(\phi, W) = \phi \left[ 1 - \exp \left( -\frac{W}{\phi} \right) \right],
\]

where \( W \) is the strain energy of the intact tissue and \( \phi \) is the failure energy, in other words, the energy limiter (note that the symbol \( \phi \) should not be confused with the function introduced in Eq. 21). We highlight that, if the failure energy is infinite (\( \phi \to \infty \)), this model reduces to the classical hyperelastic model.

Fig. 3, taken from Volokh and Vorp (2008), shows a representative set of experimental data (Cauchy stress \( \sigma_{11} \) vs. stretch \( \lambda \)) obtained from an uniaxial extension test of a strip excised from an abdominal aortic aneurysm sample. The data, used for validation of the failure model (26), illustrated by the dotted curve in Fig. 3, are taken from Raghavan et al. (1996). In Fig. 3 the solid curve shows the theoretical result which is based on model (26) where \( W = \alpha(I_1 - 3) + \beta(I_1 - 3)^2 \) was used as the strain energy, see Raghavan and Vorp (2000) (\( \alpha \) and \( \beta \) are material parameters). As can be seen from Fig. 3, model (26) is useful for a description of smooth failure with a flat limit point on the stress-strain curve, which corresponds to a gradual process of bond rupture. In the case of more abrupt bond ruptures, however, a much sharper transition to the material instability occurs. To describe such a sharp transition to failure, Eq. (26) was generalized as (Volokh, 2010)

\[
\Psi(\phi, W) = \frac{\phi}{m} \left[ \Gamma \left( \frac{1}{m}, 0 \right) - \Gamma \left( \frac{1}{m}, \frac{W^m}{\phi^m} \right) \right],
\]

where the upper incomplete gamma function

\[
\Gamma(s, x) = \int_x^\infty t^{s-1} \exp(-t) \, dt
\]

has been used, and the material parameter \( m \) controls the sharpness of the transition to material instability on the stress-strain curve. Volokh (2011) employed the approach in Eq. (27) to modify the strain energy (9) as
for the matrix, with energy $\Psi_m$, and

$$\Psi_m(I_1, \phi) = \frac{\phi}{m} \left\{ \Gamma\left(\frac{1}{m}, 0\right) - \Gamma\left[\frac{1}{m}, \left(\frac{\mu}{2\phi}(I_1 - 3)\right)^m\right] \right\}$$

(29)

for the two families of fibers, with energy $\Psi_f$, where the parameters $\phi, \phi_4, \phi_6$ are the strain energy limiters for the matrix and the two families of fibers, $m, m_4, m_6$ are the sharpness factors for the matrix and the two families of fibers.

This approach is simpler than the CDM approach, because it involves neither internal variables nor their critical threshold condition and evolution equations. However, this method has not yet been adopted by other research groups, and more investigations are needed to verify the capabilities and limitations of the softening hyperelasticity approach.

3 COMPUTATIONAL MODELING OF DAMAGE IN SOFT BIOLOGICAL TISSUE

Because of the nonlinear nature of the damage laws and the involved finite strains which are typical for basically all soft biological tissues, it is usually not possible to find an analytical solution for clinical applications. Robust and efficient numerical simulations are required for the evaluation of the stress...
and damage evolutions throughout the deformation history. Accurate constitutive models of soft biological tissue combined with appropriate numerical approaches such as the finite element method can potentially aid the study of pathologies such as atherosclerosis and heart dysfunction, and the simulation of surgical interventions and accident trauma.

Even though different SEFs have convincingly proven to be successful for particular applications, and for describing many of the material properties, their use is limited. In many cases the SEFs are used within the range of physiological loading, hence within the toe and linear regions as, for example, Farquhar et al. (1990) for cartilage, Weiss et al. (1996) for a cylindrical annulus fibrosus bonded between two perfectly rigid plates, Weiss et al. (1996) and Peña et al. (2006) for ligaments, Alastruí et al. (2006) for the cornea, and Alastruí et al. (2007) for deterministic and stochastically based 3D finite strain damage models for fibrous soft biological tissues. Moreover, several researchers implemented the developed constitutive (damage) models in a finite element framework and showed the efficacies of the models for some simplified problems, where several issues were ignored for the sake of simplicity.

The constitutive model of Balzani et al. (2012), as described in Section 2.3.2, was implemented in the finite element analysis program FEAP (Taylor, 2013) with the goal to show the applicability of the damage model. The authors applied a cyclic pressure beyond the physiological blood pressure to a simplified 2D cross-section of an artery with an atherosclerotic plaque, see Fig. 4; a damage distribution in the arterial cross-sections was analyzed. This computational example has a limited validity with respect to quantitative results. For more realistic simulations, in particular of diseased arteries, more sophisticated models with a 3D geometry are required. As mentioned in Section 2.3.2, an extension of the model presented in Balzani et al. (2012) was developed by Schmidt et al. (2014), and also implemented

FIG. 4

(A) Finite element model of a highly sclerotic arterial segment (Taken from Holzapfel, G.A., Schulze-Bauer, C.A.J., Stadler, M., 2000. Mechanics of angioplasty: wall, balloon and stent. In: Casey, J., Bao, G. (Eds.), Mechanics in Biology. The American Society of Mechanical Engineers (ASME), New York, NY.) discretized with 6048 quadratic triangular finite elements; the considered components are adventitia, (nondiseased) media, fibrotic (diseased) media, fibrous cap, lipid pool and calcification; (B) variation of the applied internal pressure \( p \) (in mmHg) as a function of time.

in FEAP (Taylor, 2013). The authors analyzed numerically the consequences of overexpansion of simplified atherosclerotic arteries that occur during angioplasty, and pursued the goal to assess the applicability and robustness of the approach within the finite element program. A thin 3D section of an atherosclerotic artery (model 1) and a longer section (model 2) was adopted with five different tissue components, and axial residual stretches were also incorporated. Fig. 5 depicts the resultant damage distribution for both investigated models at an internal pressure of 80 kPa. In both models, rather high values of damage $D_{(1)}$ are observed in the fibrous cap and the healthy media. The model approach described in Balzani et al. (2012) can serve the basis for more realistic clinical applications, for example, to simulate balloon angioplasty with (and without) stent deployment or arterial clamping.

In an attempt to develop more advanced nonlinear, anisotropic constitutive descriptors accompanied with realistic computational modeling, Fereidoonnezhad et al. (2016) simulated an arterial clamping procedure in which specific features, such as nonlinearity, anisotropy, multilayered structure, residual stresses, stress softening, permanent deformation, and the contact, were considered within the computational analysis. Fig. 6 depicts the distribution of the maximum principal nominal strain, which is calculated with respect to the physiological loading configuration. The results indicate the damage-induced permanent strain in the artery wall after unclamping. In spite of the capabilities of this constitutive and computational approach, this model has some limitations. It only captures the mechanical behavior of aortic tissues without the active contraction of the smooth muscle cells. Hence, an adequate extension would also incorporate the active state; for a calcium-driven mechanochemical model to predict force generation in the smooth muscle, and related finite element analysis see, for example, Murtada and Holzapfel (2014). Moreover, a simplified geometry of the arterial wall and the clamp were considered in Fereidoonnezhad et al. (2016), whereby more realistic geometries are necessary for more clinically relevant results.

![FIG. 5](image)

Distribution of the damage variable $D_{(1)}$ of atherosclerotic arteries with five different tissue components and axial residual axial stretches at an internal pressure of 80 kPa: (A) model 1 (thin 3D section), with 21,835 quadratic tetrahedral elements; (B) model 2 (longer section), with 61,858 elements.

Li et al. (2012) made use of a structural multimechanism anisotropic damage model to analyze the cerebral angioplasty procedure performed to open cerebral vessels and partially blocked vertebral and carotid arteries in the neck. The authors modeled cerebral arteries as multilayer heterogeneous walls composed of the internal elastic lamina, media and adventitia, and they considered mechanically induced vessel injury. The inelastic constitutive model has been developed to characterize the load-bearing, damage, and failure behavior of the arterial components. The model was implemented in the general purpose finite element code ANSYS (ANSYS, 2017) through user subroutines, and was validated by analytical solutions. To study arterial injury due to percutaneous transluminal angioplasty, first the authors used an axisymmetric arterial model and a simplified balloon model. A more realistic 3D model of an artery, plaque, balloon, and stent were also created to simulate the contact between the heterogeneous artery and the balloon that occurs during cerebral angioplasty. The constitutive and computational approaches were demonstrated to be robust. Some approximations in this model could be refined in future studies such as the consideration of residual stresses, which may change the state of wall stress. Arterial residual stresses could be considered by opening angles in the load-free configuration, as, for example, performed in Fereidoonnezhad et al. (2016). Moreover, because of the large number of material parameters utilized in the model, a sensitivity analysis should be carried out in subsequent studies. In addition, the model considered only the passive response of arterial tissues. The contribution of smooth muscle cells should also be considered to study the related active tissue response.

**FIG. 6**

Distribution of the maximum principal nominal strain in regard to the physiological configuration of the wall after unclamping of a cylindrical clamp with 6 mm in diameter. The values represent the damage-induced permanent strain in the artery wall after unclamping.

4 CONCLUDING REMARKS AND FUTURE DIRECTION

In soft biological tissues damage occurs, for example, under supra-physiological (therapeutical) loading conditions. Constitutive modeling of damage and related computer simulation is important to gain more insights into the complex biomechanical processes during therapeutical interventions, such as balloon angioplasty, and for the optimization of treatment methods. This review aims to provide a state-of-the-art overview on the modeling of damage in biological tissues (mainly arterial tissues). Moreover, we note here that there are several similarities between soft biological tissues and rubber-like materials in terms of the underlying mechanics. However, many differences between these two materials can be identified in particular in terms of their microstructure so that, in general, damage models which were originally developed for rubber-like materials are not suitable to capture damage and stress softening of soft tissues.

It is highlighted that three important softening phenomena are associated with soft biological tissues, including the Mullins effect, hysteresis, and the softening behavior resulting from fiber rupture and matrix disruption. Pseudo-elasticity is a favorable approach in modeling the first two softening phenomena (Mullins effect and hysteresis) due to its simplicity, which makes it also suitable for computational implementation, and for realistic clinical applications. However, the pseudo-elastic models are not able to reproduce softening as a result of bond rupture and complete damage. On the other hand, models which are based on CDMs are able to capture all mentioned softening phenomena but with increased computational costs when compared with pseudo-elastic models. We have also reviewed the “softening hyperelasticity approach,” although this method has not yet been adopted by other research groups, so that more investigations are needed to better assess this method.

Future research in this challenging area should aim to develop a mathematical framework to model the most important features of damage-based softening. That should incorporate external variables which can be observed and controlled, and which can be linked to the microstructure of the considered tissue. Hence, related damage functions will then have a clearer physical interpretation. In such a way the proposed models will be more predictive. Another important problem in the modeling of soft biological tissues is the determination of the initial reference (zero stress) state. Soft tissues are under pretension/precompression which arise from certain growth mechanisms of the different layers. For example, the residual stresses in arterial walls are reducing the circumferential stress gradient along the wall thickness. The consideration of residual stresses is essential for the prediction of the physiological stress state, and for the better understanding of tissue homeostasis. In several available documentations, damage parameters were identified so that they correspond to data obtained from in vitro uniaxial extension tests. In the future, further data need to be collected not only from uniaxial extension tests but also from clinical situations, for example, after arterial clamping, under different clamping forces, or after implantations of stents in patients to calibrate the model for a wider loading range. Hence, an effective computational model should also consider patient-specific geometries and multi-layered tissue structures.

Moreover, to better verify and refine current constitutive damage models, in vivo studies are also needed. For the long-term impact of tissue injury induced by clinical interventions, tissue mechanobiology including growth, remodeling, adaptation, and repair is an important area to be focused on in future. In the future, simulations of realistic clinical problems should also be given more attention, for example, the modeling of morphology, internal structure, and mechanics of biological tissue in a
multiscale context, which increase the computational costs significantly. Future research should therefore also be directed toward a speed-up of the underlying algorithms through, for example, a GPU (Graphics Processing Unit) parallel implementation with CUDA (Compute Unified Device Architecture) as developed by NVIDIA.

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