A Mechanobiological model for damage-induced growth in arterial tissue with application to in-stent restenosis

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Abstract

In-stent restenosis (ISR) is one of the main drawbacks of stent implementation which limits the long-term success of the procedure. Morphological changes occurring within the arterial wall due to stent-induced mechanical injury are a major cause for activation of vascular smooth muscle cells (VSMCs), and the subsequent development of ISR. Considering the theory of volumetric mass growth and adopting a multiplicative decomposition of the deformation gradient into an elastic part and a growth part, we present a mechanobiological model for ISR. An evolution equation is developed for mass growth of the neointima, in which the activation of VSMCs due to stent-induced damage (injury) and the proliferation rate of the activated cells are considered. By introducing the mass evolution into the balance equation, we obtain the evolution of the growth tensor over time. The model is implemented in a finite element code and the procedure of angioplasty is simulated, whereby the features of the proposed growth model are illustrated.

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1. Introduction

Despite the great developments in medical and surgical treatment of cardiovascular disease (CVD), it has remained the major cause of death worldwide (World Health Organization, 2014). Atherosclerosis is one (major) type of CVD in which fibrous and fatty materials, called plaque, build up inside the artery and cause partial or total occlusion of the artery (see, e.g., Writing Group Members et al., 2016). One way to restore the physiological blood flow of an occluded artery involves the deformation of plaque using intravascular balloon angioplasty with or without stenting. This clinical intervention is accompanied with supra-physiological loading of the arterial wall causing tissue damage (injury) (see Holzapfel and Gasser, 2007, for more details). It may also lead to tissue in-growth and re-blockage, termed in-stent restenosis (ISR) (Boyle et al., 2011), which is one of the major complications associated with stent implementation, often limiting the long-term success of the procedure; usually ISR occurs within six months after stent deployment (see, e.g., Dangas and Kuepper, 2002). The mechanism of restenosis after angioplasty is a combination of elastic recoil, arterial vessel remodeling, and neointimal hyperplasia. Late lumen loss in stented segments of the artery is often the result of neointimal hyperplasia (Hoffmann and Mintz, 2000).

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Despite significant improvements on the stent design, up to 10% of the stenting procedures require a repetition due to ISR, a rate that increases up to 50% in some high-risk lesions (Boyle et al., 2011). Drug-eluting stents (DESs), which are coated with anti-mitogenic or anti-proliferative drugs to prevent smooth muscle cell proliferation and neointimal growth, decrease the rate of ISR in comparison with bare metal stents in coronary arteries (Daemen and Serruys, 2007). However, late in-stent thrombosis and lack of re-endothelialization are the major drawbacks associated with the use of DESs (Tahir et al., 2011).

A successful design of stents requires a mechanobiological model that can predict ISR induced as a function of mechanical changes in the arterial tissue after stent deployment. In order to develop such a predictive model it is important to consider the stent–induced changes on the cellular level, that is excessive migration and proliferation of vascular smooth muscle cells (VSMCs) (Tahir et al., 2015). Given that the degree of vessel injury induced by stent insertion is a stimulus for ISR (Kornowski et al., 1998; Mitra and Agrawal, 2006; Welt and Rogers, 2002; Wieneke et al., 1999) it is a key design aspect for stents. In this context, computational modeling techniques are efficient and powerful to optimize stent design parameters in order to minimize stent–induced arterial stresses and injury. Several computational models of stent deployment procedures have been developed in recent years with the goal of reducing stent-induced arterial stresses (De Beule et al., 2008; Holzapfel et al., 2005; Lally et al., 2005; Migliavacca et al., 2002; Mortier et al., 2010; Wang et al., 2006; Zahedmanesh et al., 2010). The influence of several mechanical parameters such as the stent strut thickness (Holzapfel et al., 2005; Timmins et al., 2007; Zahedmanesh and Lally, 2009) and the plaque composition (Holzapfel et al., 2014; Pericevic et al., 2009) have been studied. Balloon expandable stents have also been compared with self-expanding stents in terms of the level of stresses they induce within the arterial wall, and hence the risk of arterial injury using finite element (FE) models (Migliavacca et al., 2004).

Moreover, computational modeling is a powerful approach to capture the biological response of an implant using mechanobiological models which relate the mechanical environmental changes to the growth and remodeling of vascular cells (Boyle et al., 2011; Zahedmanesh and Lally, 2012). The approaches utilizing discrete methods such as cellular automata (Ilachinski, 2001; Masselot and Chopard, 1998) and agent-based models (Walker et al., 2004; Wooldridge, 2009) have been employed for modeling ISR (Adiguzel et al., 2009; Evans et al., 2008; Tahir et al., 2011). The approach adopted in these studies is mainly based on discrete methods, whereas a continuum method using the FE method may also be considered as valuable. FE methods have shown to be robust for the quantification of arterial stresses, and they have been successfully utilized for patient-specific modeling of the stent–artery interaction (Gissen et al., 2008; Zahedmanesh et al., 2010).

We need to know more about ISR. A constitutive model based on the cellular mechanisms activated after stent deployment, can improve the prediction of ISR. In addition, the numerical implementation of such a mechanobiological model provides a powerful approach to predict late lumen loss due to ISR, and it also optimizes the stenting procedure in terms of devices (such as stent, catheter, etc.) and procedure parameters (such as inner balloon pressure, balloon inflation time, etc.).

The main goal of the present study is to propose a continuum and computational model for ISR that takes into account the cellular changes in the arterial wall caused by stent-induced injury. The underlying idea is the use of a multiplicative decomposition of the deformation gradient into an elastic and a growth part within the framework of volumetric finite growth. In this context, the characterization of the growth tensor evolution is one of the major challenges, where, by most of the available models, a phenomenological evolution for the growth tensor (Göktepe et al., 2010; Himel, 2007). Although the mathematical understanding of these evolution equations seems to be fairly intuitive, their clear biomechanical interpretation is still widely debated and unclear. Thus, it seems natural to seek for a deeper insight into the micromechanical phenomena that are related to tissue growth on the cellular level. Motivated by cellular changes after stent implementation (migration and proliferation of VSMCs), we propose an evolution equation for the mass of the neointima. Considering the effect of the damage intensity on the number of activated VSMCs, and the proliferation rate of the activated VSMCs, the evolution equation has a clear biomechanical interpretation. The evolution for the growth tensor is then obtained by introducing the mass evolution into the balance equation of mass.

The paper is organized as follows: Section 2 explains the mathematical framework and introduces the continuum model for finite growth. The kinematics and mass balance equation are presented, and thermodynamic consistency are investigated. Furthermore, the general constitutive model is specialized for ISR of arterial tissue in terms of an energy function, a density evolution and a growth tensor. In Section 3, the FE implementation and the related verification are presented. The stress and elasticity tensors are determined, and the solution algorithm is explained. A parameter study of the model is conducted in Section 4. The procedure of angioplasty with subsequent restenosis is simulated, and the results are presented in Section 5. In Section 6 we draw some conclusions.

## 2. Modeling of finite growth

In this section we illustrate the governing equations for finite growth which consist of: (i) the kinematic equations, which utilize the concept of an incompatible growth configuration, and the multiplicative decomposition of the deformation gradient; (ii) the mass balance equation, which is an important part of the growth process; (iii) the derivation of the reduced inequality showing thermodynamic consistency; (iv) the constitutive equations, which define the baseline elastic response in the intermediate configuration, supplemented by (v) an appropriate form for the growth tensor and its evolution equation to characterize the ISR phenomenon.
2.1. Kinematics

Within the framework of finite growth, the key kinematic assumption is based on the consideration of an intermediate configuration \( \mathcal{B}_g \), i.e. between the initial configuration \( \mathcal{B}_0 \) and the current configuration \( \mathcal{B}_t \), which naturally leads to the multiplicative decomposition of the deformation gradient \( \mathbf{F} \) into an elastic part \( \mathbf{F}_e \) and a growth part \( \mathbf{F}_g \). (Rodriguez et al., 1994). Thus,

\[
\mathbf{F} = \mathbf{F}_e \mathbf{F}_g.  \tag{1}
\]

We also note that the arterial layers in the initial configuration are characterized by two collagen fiber families, symmetrically distributed by an angle \( \beta \) with respect to the circumferential direction of the artery. Thus, the arterial layers respond orthotropically, and the families of collagen fibers are characterized by the two direction vectors \( \mathbf{a}_0^1 \) and \( \mathbf{a}_0^2 \) with \( |\mathbf{a}_0^1| = 1 \) and \( |\mathbf{a}_0^2| = 1 \), in both the initial and the intermediate configuration (assuming isotropic growth).

The Jacobian of the deformation gradient \( \mathbf{F} \) and its elastic and growth counterparts are denoted by \( J = \det \mathbf{F} \), \( J_e = \det \mathbf{F}_e \), and \( J_g = \det \mathbf{F}_g \), respectively, such that

\[
J = J_e J_g.  \tag{2}
\]

Next we introduce the right Cauchy–Green tensor \( \mathbf{C} = \mathbf{F}^T \mathbf{F} \) and the elastic right Cauchy–Green tensor, defined by \( \mathbf{C}_e = \mathbf{F}_e^T \mathbf{F}_e \), as

\[
\mathbf{C}_e = \mathbf{F}_g^{-T} \mathbf{C} \mathbf{F}_g^{-1}.  \tag{3}
\]

The velocity gradient \( \mathbf{I} = \dot{\mathbf{F}} \mathbf{F}^{-1} \) then takes on the following form

\[
\mathbf{I} = \dot{\mathbf{F}}_e \mathbf{F}_e^{-1} + \dot{\mathbf{F}}_g (\mathbf{F}_g \mathbf{F}_e^{-1}) \mathbf{F}_e^{-1}.  \tag{4}
\]

The pull-back operation of the spatial velocity gradient (4) to the intermediate configuration \( \mathcal{B}_g \) leads

\[
\mathbf{L} = \mathbf{F}_e^{-1} \dot{\mathbf{F}}_e = \mathbf{L}_e + \mathbf{L}_g, \quad \text{with} \quad \mathbf{L}_e = \mathbf{F}_e^{-1} \dot{\mathbf{F}}_e, \quad \mathbf{L}_g = \dot{\mathbf{F}}_g \mathbf{F}_g^{-1}.  \tag{5}
\]

Moreover, from (4) and the property of the trace of a matrix product, the following additive decomposition is obtained

\[
\text{tr} \mathbf{I} = \text{tr}(\dot{\mathbf{F}}_e \mathbf{F}_e^{-1}) + \text{tr}(\dot{\mathbf{F}}_g \mathbf{F}_g^{-1}).  \tag{6}
\]

Subsequently, we also consider the multiplicative split

\[
\mathbf{C}_e = \mathbf{J}_e^{1/2} \mathbf{C}_g,  \tag{7}
\]

where \( \mathbf{C}_g \) and \( \mathbf{J}_e \) represent the isochoric and volumetric part of the elastic deformation, respectively.

2.2. Mass balance equation

Unlike engineering materials, living biological tissues are known to adapt (grow/atrophy) in response to an environmental change, whereby the mass of the system is changed, and consequently the consideration of the mass balance equation is an important point for such systems. If the infinitesimal mass \( dm_0 \) of an infinitesimal volume element \( dV_0 \) in the initial configuration is \( dm_0 = \rho_0 dV_0 \), where \( \rho_0 \) denotes the related density, the infinitesimal mass \( dm \) of the corresponding element in the intermediate and current configurations is

\[
dm = \rho_g dV_g = \rho dV.  \tag{8}
\]

where \( \rho_g \) and \( dV_g \) denote the density and the infinitesimal volume element in the intermediate configuration, and \( \rho \) and \( dV \) are the corresponding quantities in the current configuration. It is worth noting that the growth, and consequently the mass change of the biological tissue, occurs between the initial and the intermediate configuration, whereby the mass of an element in the current configuration is the same as the mass of the corresponding element in the intermediate configuration.

Subsequently, it is convenient to designate the quantity \( \rho J \) as \( \rho^0_g \), where \( J = dV/dV_0 \). Thus,

\[
\rho^0_g = \frac{dm}{dV_0} = \rho J.  \tag{9}
\]

In addition, with Eq. (8) it follows that

\[
\rho^0_g = \rho_g J_g, \quad \rho_g = \rho J_e,  \tag{10}
\]

where \( J_g = dV_g/dV_0 \), and Eq. (2) was used. Next, if \( r_g \) and \( \rho^0_g \) are time rates of the mass growth per unit current volume \( V \) and initial volume \( V_0 \), respectively, then

\[
\frac{d}{dt} (dm) = r_g dV = \rho^0_g dV_0.  \tag{11}
\]
where \( d/dt(\cdot) \) stands for the material time derivative of \((\cdot)\). In addition, in view of (9)\(_1\) and (11)\(_2\) we can conclude that
\[
\frac{d \rho_g^0}{dt} = \rho_g^0.
\] (12)
By integrating Eq. (11)\(_2\), the following expression is obtained for the mass balance, i.e.
\[
dm = dm_0 + \int_0^t r_g^0 d\tau dv_0.
\] (13)
In view of (9)\(_2\) and (10)\(_1\), the mass balance equation (13) may then be represented as
\[
\rho g_\alpha = \rho_0 + \int_0^t r_g^0 d\tau.
\] (14)
From (14) and (10) we further find that
\[
\frac{d}{dt} (\rho f) = \frac{d}{dt} (\rho g_\alpha) = r_g^0.
\] (15)
This yields the continuity equations for the densities \(\rho\) and \(\rho_g\) according to
\[
\frac{d \rho}{dt} + \rho \text{tr}(\mathbf{F}\mathbf{F}^{-1}) = r_g, \quad \frac{d \rho_g}{dt} + \rho_g \text{tr}(\mathbf{F}_g\mathbf{F}_g^{-1}) = r_g e.
\] (16)
In view of (6), from Eq. (16), it readily follows that
\[
J e \frac{d \rho}{dt} + \rho_g \text{tr}(\mathbf{F}_g\mathbf{F}_g^{-1}) = \frac{d \rho_g}{dt}.
\] (17)
For the growth of soft biological tissues, we assume that the newly born tissue has the same density as the existing tissue (\(\rho_g = \rho_0 = \text{constant}\)), an assumption which is frequently used in the literature, see, e.g., Lubarda and Hoger (2002). With this assumption we have \(\rho f = \rho g_\alpha, \rho_0 = \rho e\), and the continuity equations (16) may be represented as
\[
\frac{d \rho}{dt} + \rho \text{tr}(\mathbf{F}\mathbf{F}^{-1}) = 0, \quad \rho \text{tr}(\mathbf{F}_g\mathbf{F}_g^{-1}) = r_g.
\] (18)
Moreover, due to incompressibility we have
\[
J e = 1, \quad \text{tr}(\mathbf{F}_g\mathbf{F}_g^{-1}) = 0, \quad \text{and} \quad \frac{d \rho}{dt} = 0, \quad \rho = \rho_0 = \text{constant}.
\] (19)
Consequently, the continuity equation for an incompressible tissue, which grows in a density preserving manner, may be represented as
\[
\text{tr}(\mathbf{F}_g\mathbf{F}_g^{-1}) = \frac{r_g}{\rho_g} = \frac{r_g^0}{\rho_g^0}.
\] (20)

2.3. Thermodynamic consistency

For a system with varying mass we now consider the Clausius–Duhem inequality for an isothermal process. Hence,
\[
\frac{1}{2} \mathbf{S} : \mathbf{C} - \rho_g^0 \dot{\Psi} - \rho_g^0 T S_0 \geq 0.
\] (21)
where \(\mathbf{S}\) is the second Piola–Kirchhoff stress tensor, \(T\) is the absolute temperature and the first derivative of \(\Psi\) with respect to time is denoted by \(\dot{\Psi}\). The extra entropy source \(S_0\) in the dissipation inequality, which takes into account the increase of entropy due to non-mechanical components, is necessary to satisfy thermodynamic consistency in the context of growth (Himpel, 2007). Inequality (21) must be fulfilled for arbitrary thermodynamic processes to guarantee the non-negativeness of the internal dissipation (required by the second law of thermodynamics).

Inequality (21) is general and does not include any indication of the variables on which \(\Psi\) depends. At this point, in order to obtain an explicit constitutive law, we need to specify such variables. We assume an elastic response at any stage of the growth and that the stress depends on the growth. Damage-induced inelastic phenomena such as stress softening and permanent deformation, as proposed in Fereidoonnezhad et al. (2016), can be further included in a rather straightforward manner.

The free energy per unit current mass of the biological tissue can be expressed in terms of the elastic right Cauchy–Green tensor \(\mathbf{C}_e\), the structural tensors \(\mathbf{A}_b^1 = \mathbf{a}_b^1 \otimes \mathbf{a}_b^1\) and \(\mathbf{A}_b^1 = \mathbf{a}_b^1 \otimes \mathbf{a}_b^1\) and the density \(\rho_g^0\) as
\[
\Psi = \Psi(\mathbf{C}_e, \mathbf{A}_b^1, \mathbf{A}_b^1, \rho_g^0).
\] (22)
By differentiating the free-energy function (22) with respect to time, we have
\[
\dot{\Psi} = \dot{\partial}_\Psi \left[ \partial_{\mathbf{C}_e} : \dot{\mathbf{C}} + \partial_{\mathbf{C}_e} : \dot{\mathbf{C}}_{e} + \partial_{\mathbf{F}_g} : \dot{\mathbf{F}}_{g} + \partial_{\mathbf{F}_g} \partial_{\rho_g} : \dot{\mathbf{F}}_{g} + \frac{\partial_{\rho_g}}{\partial \rho_g} \cdot \dot{\mathbf{F}}_{g} \right] + \dot{\partial}_\rho \partial_{\mathbf{A}_0} : \mathbf{A}_0 + \dot{\partial}_\rho \partial_{\mathbf{A}_3} : \mathbf{A}_3,
\]
(23)
in which \( \mathbf{C}, \mathbf{F}_g, \rho_g, \mathbf{A}_0 \) and \( \mathbf{A}_3 \) are considered to be the independent variables, and \( \mathbf{C}_e \) and \( \rho_g^0 \) are related to the independent variables by Eqs. (3) and (10), respectively. Then, in view of Eqs. (3) and (10), Eq. (23) can be represented as (for a detailed derivation see Appendix A)
\[
\dot{\Psi} = \dot{\mathbf{F}}_{g} : \partial_{\mathbf{C}_e} \dot{\mathbf{F}}_{g} + 2 \partial_{\mathbf{C}_e} \partial_{\mathbf{F}_g} + \partial_{\rho_g} : \dot{\mathbf{F}}_{g}^\text{T} + \frac{\partial_{\rho_g}}{\partial \rho_g} \dot{\mathbf{I}} : \mathbf{F}_g \dot{\mathbf{F}}_{g}^{-1}
\]
\[
+ \frac{\partial_{\rho_g}}{\partial \rho_g} \cdot \mathbf{F}_g \dot{\mathbf{F}}_{g}^{-1}.
\]
(24)
Since we are considering no fiber reorientation, the structural tensors \( \mathbf{A}_0^1 \) and \( \mathbf{A}_3^2 \) change only through \( \mathbf{F} \), and no separate evolution law is required. Thus \( \mathbf{A}_0^1 = \mathbf{A}_3^2 = 0 \). From Eq. (24) and the inequality (21) we then find that
\[
\left( \frac{1}{2} \mathbf{S} - \rho_g \dot{\mathbf{F}}_{g} \cdot \dot{\mathbf{F}}_{g}^\text{T} \right) : \dot{\mathbf{C}} + \rho_g \left( 2 \partial_{\mathbf{C}_e} \partial_{\mathbf{F}_g} + \frac{\partial_{\rho_g}}{\partial \rho_g} \dot{\mathbf{I}} : \mathbf{F}_g \dot{\mathbf{F}}_{g}^{-1}
\]
\[-\rho_g \dot{\rho}_g \dot{\mathbf{F}}_{g} \cdot \dot{\mathbf{F}}_{g}^\text{T} \right) \leq 0.
\]
(25)
Thus, with the standard arguments of continuum thermodynamics we obtain the following expression for the second Piola–Kirchhoff stress tensor, i.e.
\[
\mathbf{S} = \mathbf{F}_g^{-1} \mathbf{S}_e \mathbf{F}_g^{-\text{T}}, \quad \mathbf{S}_e = 2 \rho_g \partial_{\mathbf{C}_e} \dot{\mathbf{C}}_e.
\]
(26)
Moreover, we note that for the density preserving growth, which seems reasonable in the context of arterial growth, the density in the intermediate configuration is constant \( (\rho_g = 0) \), and with the constitutive relation (26) and with (5), the reduced dissipation inequality (25) gives
\[
\left( \mathbf{M}_e - \left( \rho_g^0 \right)^2 \partial_{\rho_g} \dot{\mathbf{F}}_{g} \cdot \dot{\mathbf{F}}_{g}^\text{T} \right) : \dot{\mathbf{L}}_g - \rho_g \dot{\mathbf{T}}_S \geq 0,
\]
(27)
where the Mandel stress tensor \( \mathbf{M}_e = \mathbf{C}_e \mathbf{S}_e \) of the intermediate configuration has been introduced. We will return to this inequality in Section 2.6, after the specification of the free-energy function \( \Psi \), the growth tensor \( \mathbf{F}_g \) and its evolution.

2.4. Specific form of the free-energy function

Various forms of the free-energy function for arterial tissues were proposed in the literature. The model in Gasser et al. (2006) is one which is frequently used and implemented in several commercial software codes such as abaqus (Abaqus, 2013) and feap (FEAP, 2008). Employing this particular model, we consider the following structure of the free energy per unit initial volume, say \( \dot{\Psi} \), i.e.
\[
\rho_g^0 \dot{\Psi} = \dot{\Psi} = \dot{\Psi}_\text{vol}(\dot{\mathbf{C}}_e, \mathbf{A}_0^1, \mathbf{A}_3^2) = \dot{\Psi}_\text{vol}(\dot{\mathbf{J}}_e) + \dot{\Psi}_\text{iso}(\overline{\mathbf{C}}_e, \mathbf{A}_0^1, \mathbf{A}_3^2),
\]
(28)
where \( \dot{\Psi}_\text{vol}(\dot{\mathbf{J}}_e) \) and \( \dot{\Psi}_\text{iso}(\overline{\mathbf{C}}_e, \mathbf{A}_0^1, \mathbf{A}_3^2) \) describe the volumetric and the isochoric elastic response of the biological tissue. It is noted that the additive decomposition of the free-energy function into isochoric and volumetric parts has some limitations when applied to materials which are not incompressible (see, e.g., Ehlers and Eipper, 1998; Helfenstein et al., 2010), which is not the case for arterial tissues.

The isochoric part of the free-energy function (28) may be represented as
\[
\dot{\Psi}_\text{iso} = \dot{\Psi}_\text{iso}^\text{m} + \sum_{i=4,6} \dot{\Psi}_\text{iso}^i,
\]
(29)
\[
\dot{\Psi}_\text{iso}^i = \mu \left( \dot{\mathbf{I}}_e - 3 \right), \quad \dot{\Psi}_\text{iso}^i = \frac{k_1}{2k_2} \left[ \exp \left( k_2 \dot{\mathbf{I}}_e^2 \right) - 1 \right], \quad i = 4, 6.
\]
(30)
where \( i = 4, 6 \) relates to the two fiber families, \( \mu, k_1, \) and \( k_2 \) are material parameters, and \( \dot{\mathbf{I}}_e = \text{tr} \overline{\mathbf{C}}_e \) is the first invariant of \( \overline{\mathbf{C}}_e \). In (30) \( \dot{\mathbf{I}}_e = \kappa \dot{\mathbf{I}}_e + (1 - 3 \kappa) \dot{\mathbf{I}}_e - 1 \), \( i = 4, 6 \). denotes the Green–Lagrange strain–like quantity, where \( \dot{\mathbf{I}}_e = \mathbf{a}_0^1 \cdot \overline{\mathbf{C}}_e \mathbf{a}_0^1 \) and \( \dot{\mathbf{I}}_e = \mathbf{a}_0^2 \cdot \overline{\mathbf{C}}_e \mathbf{a}_0^2 \) are the modified pseudo-invariants, and \( \kappa \in [0, 1/3] \) characterizes the dispersion parameter. Note that the explicit expression in (30) can be replaced by other functions as, e.g., provided in Holzapfel et al. (2015) which considers a
non-symmetric dispersion of the collagen fibers better reflecting structural data (Niestrawska et al., 2016a). In addition, we consider the convex form of $\Psi^{\text{vol}}$ according to

$$\Psi^{\text{vol}}(J_e) = \frac{1}{D_1} \left( \frac{J_e^2 - 1}{2} - \ln J_e \right),$$  \hspace{1cm} (31)$$

which we have numerically used as a penalty function, where $1/D_1$ is a penalty parameter.

2.5. Micromechanically motivated evolution for the mass

In this section we propose a mathematical model for mass growth of the intima triggered on the cellular level after angioplasty with stent deployment. The process of angioplasty with stent deployment denudes the endothelial layer and may stretch, injure or even rupture parts of tissue layers. This arterial injury activates platelet aggregation, triggers the migration of the VSMCs from the medial wall towards the intima where they start to proliferate and form a newly born material, called neointima. Under physiological conditions, VSMCs tend to remain in a contractile quiescent state (G0 of the cell cycle). However, after arterial injury, some of the VSMCs change their phenotypes and enter the G1 growth phase so that the cells become less adhesive to its neighborhood in the later phase of the G1 cell cycle, provoking cell migration (Fukui et al., 2000; Tahir et al., 2015).

Based on these cellular changes, we assume that the time-dependent rate of the mass growth of the neointima is dependent on the extent of injury to the vascular wall induced by the stent, and the current number of proliferating cells in the population. As an evolution equation for the current mass per unit initial volume $\rho^0_\mathbb{g}$ of the neointima we propose the following expression

$$\dot{r}^0_\mathbb{g} = \frac{d\rho^0_\mathbb{g}}{dt} = f^\mathbb{g}(\rho^0_\mathbb{g}, D, t),$$  \hspace{1cm} (32)$$

where $D$ is a measure of damage, $t$ stands for time and $f^\mathbb{g}$ denotes a growth function. Next, we decompose $f^\mathbb{g}$ as

$$f^\mathbb{g}(\rho^0_\mathbb{g}, D, t) = f^\mathbb{g}_1(\rho^0_\mathbb{g}, t) f^\mathbb{g}_2(D),$$  \hspace{1cm} (33)$$

where function $f^\mathbb{g}_1$ represents the time variation of mass due to the change in the cell proliferation rate, and $f^\mathbb{g}_2$ takes into account the effect of damage on the number of activated VSMCs. In other words, the number of VSMCs which migrate to the arterial inner surface are directly related to damage/ Injury induced in the tissue, and the function $f^\mathbb{g}_2$ takes into account such a dependency.

Moreover, the function $f^\mathbb{g}_1(\rho^0_\mathbb{g}, t)$ shows how the migrated VSMCs proliferate or die. The mathematical model of proliferative cell kinetics can be adopted to represent this functionality. Here, in analogy with the cell proliferating model introduced in Schwartz et al. (1996), for $f^\mathbb{g}_1$ we propose the following expression

$$f^\mathbb{g}_1(\rho^0_\mathbb{g}, t) = k \rho^0_\mathbb{g} t \exp(-\alpha t),$$  \hspace{1cm} (34)$$

where $\alpha$ and $k$ are material parameters, and $\rho^0_\mathbb{g}$ is the time−dependent value of mass per unit initial volume of the cells in the population according to (9). This expression contains two parts: (i) the first term $k \rho^0_\mathbb{g} t$, which provides cellular growth within the population proportional to the mass of the cells already present; (ii) the second (exponential) term accounts for the decrease in proliferation within the population over time both due to cell death and daughter cells that cease dividing (Schwartz et al., 1996). We highlight that the first term in (34) is an ascending function, while the second term is a descending function which implies two cellular mechanisms (cell proliferation and death). For small values of $t$ the first term is dominant and the growth rate increases up to a specific time, afterwards the second exponential term becomes dominant and the growth rate decreases and approaches to zero. This is consistent with clinical observations.

Finally, the explicit form of the function $f^\mathbb{g}_2$ must be specified. First, a quantification of damage within the arterial tissue is required. One way to calculate damage is to use experimental data, to establish a relationship between a measurable quantity (e.g., strain) or calculable quantity (e.g., stress) and damage in the arterial wall. In the absence of such experimental data, an alternative way is to choose the maximum isochoric free energy, say $\Psi^{\text{iso}}_{\text{max}}$, attained in the history of deformation as a (phenomenological) measure of damage, as discussed in Weisbecker et al. (2012) and Fereidoonnezhad et al. (2016). Following Fereidoonnezhad et al. (2016) we may define the damage $D$ as

$$D = \frac{1}{r_1} \text{erf} \left( \frac{1}{m_1} \Psi^{\text{iso}}_{\text{max}} \right),$$  \hspace{1cm} (35)$$

where erf(*) is the error function of (*), and $r_1$, $m_1$ are damage parameters. Then for $f^\mathbb{g}_2$ we propose the following expression

$$f^\mathbb{g}_2(D) = (D - D^\text{th}),$$  \hspace{1cm} (36)$$

where $D^\text{th}$ is a threshold value for the growth to be started, and $(\cdot)$ stands for the Macaulay brackets. It indicates that the growth occurs only when the damage in the arterial wall exceeds a certain threshold value.

Finally, in view of (34) and (36), the growth function (33) takes on the form

$$f^\mathbb{g}(\rho^0_\mathbb{g}, D, t) = k \rho^0_\mathbb{g} t \exp(-\alpha t) (D - D^\text{th}).$$  \hspace{1cm} (37)$$

It indicates that the growth occurs only when the damage in the arterial wall exceeds a certain threshold value.
2.6. Specific form for the growth tensor and its evolution

To complete the constitutive formulation, a specific form for the growth tensor \( \mathbf{F}_g \) is presented. The growth of the anisotropic arterial tissue is expected to be anisotropic. However, to the authors’ knowledge to date no experimental data are available to characterize the anisotropic neointimal growth so that for simplicity we start with an isotropic growth tensor of the form

\[
\mathbf{F}_g = \lambda_g \mathbf{I},
\]

where \( \lambda_g \) is the growth stretch and \( \mathbf{I} \) is the second-order identity tensor. It readily follows that the velocity gradient \((5)_3\) in the intermediate configuration is

\[
\mathbf{L}_g = \mathbf{F}_g^{-1} \mathbf{F}_g^{-1} = \frac{\dot{\lambda}_g}{\lambda_g} \mathbf{I}.
\]

In view of \((32)_2\) and \((37)\), the continuity equation \((20)_3\) for an incompressible tissue can then be represented as

\[
3 \frac{\dot{\lambda}_g}{\lambda_g} = \frac{\dot{\alpha}}{\alpha} \left[ \exp(\alpha t) \lambda_g (D - D^{th}) \right],
\]

which gives the evolution of the growth stretch as

\[
\dot{\lambda}_g = \frac{\frac{\dot{\alpha}}{\alpha}}{3} \exp(-\alpha t) \lambda_g (D - D^{th}).
\]

Here we note that the damage parameter \( D \) in \((41)\) is a measure of injury induced in the tissue during angioplasty and stenting, and it acts as a trigger for VSMC migration. It is calculated at the end of the procedure and is not a time-dependent quantity. By integrating Eq. \((41)\) by parts and by using the boundary condition \( \lambda_g = 1 \) at time \( t = 0 \), we obtain after a (lengthy but) straightforward manipulation a closed form solution for \( \lambda_g \), i.e.

\[
\lambda_g = \exp \left( \frac{k}{3 \alpha^2} \left[ 1 - (1 + \alpha t) \exp(-\alpha t) \right] (D - D^{th}) \right),
\]

which provides the growth stretch \( \lambda_g \) over time for a growing restenotic lesion. This is illustrated in Fig. 1(a) for arbitrary values of parameters (summarized in Table 1; we also used \( \Psi_{iso}^{max} = 0.02 \text{ MPa} \)), while the growth stretch rate \( \dot{\lambda}_g \) is shown in Fig. 1(b).

As can be seen from Fig. 1(b) the growth stretch rate \( \dot{\lambda}_g \) increases up to a maximum value, and after that it decays until the growth stretch \( \lambda_g \) approaches its maximum value, i.e.

\[
\dot{\lambda}_g^{max} = \exp \left( \frac{k}{3 \alpha^2} (D - D^{th}) \right).
\]

This non-monotonic rate of growth is consistent with clinical observation, see, e.g., Schwartz et al. (1996). Next let us find the time at which \( \lambda_g \) is a maximum. The time derivative of \((41)\) results to

\[
\frac{d\dot{\lambda}_g}{dt} = \left[ \frac{k}{3} \exp(-\alpha t) (D - D^{th}) \lambda_g \right] \left[ \frac{k t^2}{3} \exp(-\alpha t) (D - D^{th}) + 1 - \alpha t \right].
\]
Hence, we need to find the roots of (44). The first bracket is zero when \( D < D^{\text{th}} \) or \( t \) approaches infinity, where for both cases \( \lambda_g = 0 \). Thus, the time at which the growth velocity is a maximum can be obtained by setting the second bracket in (44) equal to zero, i.e.

\[
1 - \alpha t + \frac{k t^2}{3} \exp(-\alpha t) (D - D^{\text{th}}) = 0.
\]

where the Macaulay brackets are eliminated because (45) has to be solved for \( D > D^{\text{th}} \), as discussed above.

Solving the reduced dissipation inequality (27) for the extra entropy term we use \( L_e = \dot{\lambda}_g I / \lambda_g \), i.e. Eqs. (39)\textsubscript{2}, and (28)\textsubscript{1} which leads to \( \partial \psi / \partial \rho_0^g = -\dot{\psi} / (\rho_0^g)^2 \). Thus we get

\[
S_0 \leq \frac{1}{\rho_0^g T} \frac{\dot{\lambda}_g}{\lambda_g} (\text{tr} M_e + 3 \dot{\psi}).
\]

**Remark.** By using the multiplicative decomposition of the deformation gradient \( \mathbf{F} \) we note that the intermediate configuration is not unique, in general. However, with the symmetry of \( \mathbf{F}_g \) in (38), the rotation is lumped into the elastic part of the deformation gradient, and the intermediate configuration is determined uniquely.

### 3. Finite element implementation

Due to the nonlinear governing equations required for finite growth, it is virtually impossible to find analytical solution for a boundary-value problem such as angioplasty with stenting. To solve the governing equations numerically, the FE method is employed to discretize the equations for finite growth in space. In this section, we first derive the expressions for the stress and elasticity tensors, then we describe the solution algorithm, and finally we provide a verification of the implemented model.

#### 3.1. Stress tensor

Once we have determined the growth stretch \( \lambda_g \) for a given deformation gradient \( \mathbf{F} \), we can successively determine the growth deformation gradient \( \mathbf{F}_g \) from (38), the elastic deformation gradient \( \mathbf{F}_e \), the elastic right Cauchy–Green tensor \( \mathbf{C}_e \) from (3) and the modified right Cauchy–Green tensor \( \mathbf{C}_e \) from (7). Furthermore, it follows from (26)\textsubscript{2} and (28) that

\[
\mathbf{S}_e = \mathbf{S}_e^{\text{vol}} + \mathbf{S}_e^{\text{iso}}, \quad \mathbf{S}_e^{\text{vol}} = 2 \frac{\partial \dot{\psi}_\text{iso}}{\partial J_e} \frac{\partial \mathbf{F}_e}{\partial \mathbf{C}_e}, \quad \mathbf{S}_e^{\text{iso}} = 2 \frac{\partial \dot{\psi}_\text{iso}}{\partial \mathbf{C}_e} : \frac{\partial \mathbf{C}_e}{\partial \mathbf{C}_e},
\]

where \( \mathbf{S}_e^{\text{vol}} \) and \( \mathbf{S}_e^{\text{iso}} \) are the volumetric and isochoric parts of the elastic second Piola–Kirchhoff stress tensor \( \mathbf{S}_e \), respectively. With the specific volumetric free energy (31), the volumetric part is further derived as

\[
\mathbf{S}_e^{\text{vol}} = p J_e \mathbf{C}_e^{-1}, \quad p = \frac{1}{J_e} (J_e - J_e^{-1}),
\]

where the relation \( \partial J_e / \partial \mathbf{C}_e = J_e \mathbf{C}_e^{-1} / 2 \) has been used, and \( p \) denotes the hydrostatic pressure. In addition, with (29), the isochoric part of the elastic second Piola–Kirchhoff stress tensor \( \mathbf{S}_e^{\text{iso}} \) is represented as

\[
\mathbf{S}_e^{\text{iso}} = \sum_{i=4,6} \mathbf{S}_e^{\text{iso}, i}, \quad \mathbf{S}_e^{\text{iso}, i} = 2 \frac{\partial \dot{\psi}_\text{iso}}{\partial \mathbf{C}_e} : \frac{\partial \mathbf{C}_e}{\partial \mathbf{C}_e}, \quad \mathbf{S}_e^{\text{iso}, i} = 2 \frac{\partial \dot{\psi}_\text{iso}}{\partial \mathbf{C}_e} : \frac{\partial \mathbf{C}_e}{\partial \mathbf{C}_e}.
\]
On use of the free-energy function (30), the first and second parts of the second Piola–Kirchhoff stress tensor in (49) are given by

$$S_{e}^{m} = J_{e}^{-2/3} P : \tilde{S}^{m}_{e}, \quad \tilde{S}^{m}_{e} = 2 \frac{\partial \tilde{W}^{\text{iso}}_{m}}{\partial \tilde{E}^{m}_{e}} = 2 \mu \mathbf{I},$$

and

$$S_{e}^{i} = J_{e}^{-2/3} P : \tilde{S}^{i}_{e}, \quad \tilde{S}^{i}_{e} = 2 \frac{\partial \tilde{W}^{\text{iso}}_{i}}{\partial \tilde{E}^{i}_{e}} = 2 \frac{\partial \tilde{W}^{\text{iso}}_{i}}{\partial \tilde{E}^{i}_{e}} \frac{\partial \tilde{E}^{i}_{e}}{\partial \tilde{E}^{i}_{e}},$$

with

$$\frac{\partial \tilde{W}^{\text{iso}}_{i}}{\partial \tilde{E}^{i}_{e}} = k_{1} \tilde{E}_{i} \exp(k_{2} \tilde{E}_{i}^{2}), \quad \frac{\partial \tilde{E}^{i}_{e}}{\partial \tilde{E}^{i}_{e}} = \kappa I + (1 - 3 \kappa) A_{i}^{i},$$

where the fourth–order projection tensor \( P = I - C_{e}^{1} \otimes C_{e}/3 \) has been introduced, while \( I \) is the fourth–order unit tensor (Holzapfel, 2000). Once the elastic second Piola–Kirchhoff stress tensor \( S_{e} \) has been determined from Eqs. (47)–(52), the total stress tensor \( S \) can then be obtained from (26). Moreover, the Kirchhoff stress tensor \( \tau \) is obtained by a push–forward operation of the second Piola–Kirchhoff stress tensor according to \( \tau = FSF^{T} \).

## 3.2 Elasticity tensor

Consistent linearization of the second Piola–Kirchhoff stress tensor \( S \) with respect to the right Cauchy–Green tensor \( C \), which is essential for the application of the proposed (nonlinear) constitutive model within the FE method. Thus, with (26), (3) and the use of the index notation we obtain (for a more detailed derivation see Appendix B)

$$C = 2 \frac{\partial S}{\partial C} = 2 \frac{\partial (F_{g}^{-1} S_{e} F_{g}^{T})}{\partial C} = (F_{g}^{-1} \otimes F_{g}^{-1}) : C_{e} : (F_{g}^{-1} T \otimes F_{g}^{-1} T),$$

with

$$C_{e} = 2 \frac{\partial S_{e}}{\partial C_{e}} = C_{e}^{\text{vol}} + C_{e}^{\text{iso}}, \quad C_{e}^{\text{vol}} = 2 \frac{\partial S_{e}^{\text{vol}}}{\partial C_{e}}, \quad C_{e}^{\text{iso}} = 2 \frac{\partial S_{e}^{\text{iso}}}{\partial C_{e}},$$

where the symbol \( \otimes \) denotes a non–standard tensor product between two second-order tensors according to \((A \otimes B)_{ijkl} = A_{ik} B_{jl}\) (see, e.g., Javili et al., 2015). The volumetric contribution is then calculated as (Holzapfel, 2000)

$$C_{e}^{\text{vol}} = \tilde{\rho} C_{e}^{1} - 2 p C_{e}^{1}, \quad \tilde{\rho} = p + J_{e} \frac{dp}{d\tilde{e}_{e}},$$

where the symbol \( \odot \) has been introduced to denote the tensor product according to the rule \((C_{e}^{1} \odot C_{e}^{1})_{ijkl} = \frac{1}{2} (C_{e}^{1} C_{e}^{1} + C_{e}^{1} C_{e}^{1})\). Moreover, with (49), the isotropic part \( C_{e}^{\text{iso}} \) is obtained in the form of

$$C_{e}^{\text{iso}} = C_{e}^{m} + \sum_{i=1,6} C_{e}^{i},$$

where the two abbreviations

$$C_{e}^{m} = 2 \frac{\partial S_{e}^{m}}{\partial C_{e}}, \quad C_{e}^{i} = 2 \frac{\partial S_{e}^{i}}{\partial C_{e}}$$

have been introduced. It is now required to provide explicit expression for the isotropic part \( C_{e}^{\text{iso}} \) to be used in the FE implementation. Appendix C provides the related details of the derivations.

The related Eulerian elasticity tensor \( C \) is then obtained by a standard push–forward operation of \( C \) according to \((c)_{ijkl} = S_{ij} F_{g}^{-1} F_{g}^{-1} (C)_{ijkl}\). For the isotropic growth tensor (38) and the multiplicative decomposition (1), \((c)_{ijkl}\) can be represented in the following modified form

$$C_{ijkl} = \lambda_{ijkl} F_{e} F_{ijkl} F_{e} F_{ijkl} (C)_{ijkl}.$$

On using the isotropic growth tensor (38) and Eq. (53), we may deduce from (58) after some straightforward recasting in index notation the components of the Eulerian elasticity tensor \( c \) in its final form as

$$c_{ijkl} = F_{ijkl} F_{ijkl} F_{ijkl} (C)_{ijkl}.$$

In other words, for the proposed growth model, the Eulerian elasticity tensor \( c \) is obtained by a push-forward of \( C_{e} \) via the elastic deformation gradient \( F_{e} \). Note, however, that an implementation into the commercial nonlinear FE software ABAQUS/STANDARD (Abaqus, 2013) requires a constitutive relationship in terms of the co–rotational elasticity tensor \( \Lambda \) (Young et al., 2010). The link between the components of \( \Lambda \) and the components of \( c \) is given by

$$J(\Lambda)_{ijkl} = J(c)_{ijkl} + (\tau_{ij} \delta_{jk} + \tau_{jk} \delta_{ij} + \tau_{ik} \delta_{lj} + \tau_{lj} \delta_{ik})/2,$$

where \( \delta_{ij} \) is the Kronecker delta; for more details see, e.g., Fereidoonnezhad et al. (2016).
Table 2
Algorithmic flowchart for damage–induced isotropic growth implemented in abaqus/standard within the user-defined subroutine UMAT, (Abaqus, 2013).

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Given: $\Psi_{\text{ini}}^{m}$</td>
</tr>
<tr>
<td>2</td>
<td>Check growth criterion: $D - D^h \geq 0$</td>
</tr>
<tr>
<td>3</td>
<td>Calculate growth stretch: ( \lambda_g = \exp\left{ \left( k/3a^2 \right) \left[ 1 - (1 + \alpha t) \exp(-\alpha t) \right] \left[ (D - D^h) \right] \right} )</td>
</tr>
<tr>
<td>4</td>
<td>Calculate elastic deformation gradient: $\mathbf{F}_e = \mathbf{F}/\lambda_g$</td>
</tr>
<tr>
<td>5</td>
<td>Calculate elastic right Cauchy–Green tensor: $\mathbf{C}_e = \mathbf{F}_e^T \mathbf{F}_e$</td>
</tr>
<tr>
<td>6</td>
<td>Calculate elastic second Piola–Kirchhoff stress tensor: $\mathbf{S}_e = 2 \frac{\partial \Psi}{\partial \mathbf{C}_e}$</td>
</tr>
<tr>
<td>7</td>
<td>Calculate second Piola–Kirchhoff stress tensor: $\mathbf{S} = \mathbf{S}_e/\lambda_g^2$</td>
</tr>
<tr>
<td>8</td>
<td>Push–forward to Kirchhoff stress tensor: $\mathbf{\tau} = \mathbf{F}^T \mathbf{S}$</td>
</tr>
<tr>
<td>9</td>
<td>Calculate elastic elasticity tensor: $\mathbf{c}_e = 2 \frac{\partial \mathbf{S}_e}{\partial \mathbf{C}_e} = 4 \frac{\partial \Psi}{\partial \mathbf{C}_e}$</td>
</tr>
<tr>
<td>10</td>
<td>Push–forward to Eulerian elasticity tensor: $(\mathbf{e})_{ijkl} = \mathbf{F}_e^{-1} \mathbf{F}_e^{-1} \mathbf{F}_e^{-1} \mathbf{F}_e^{-1} \mathbf{F}_e^{-1} \mathbf{F}_e^{-1} (\mathbf{C}<em>e)</em>{ijkl}$</td>
</tr>
<tr>
<td>11</td>
<td>Calculate co-rotational elasticity tensor: $J (\mathbf{\lambda})<em>{ijkl} = (\mathbf{e})</em>{ijkl} + \frac{1}{2} (\mathbf{\tau}<em>i \delta</em>{jk} + \mathbf{\tau}<em>j \delta</em>{ik} + \mathbf{\tau}<em>k \delta</em>{ij})/2$</td>
</tr>
</tbody>
</table>

\[
\lambda_g^{\text{max}} = 1.044
\]

Fig. 2. Evolution of the growth stretch $\lambda_g$ comparing finite element results with (semi-analytical) results obtained from MATLAB indicating perfect agreement. The block is first stretched up to 1.4, and afterwards unloaded to 1.0 assuming that damage occurred during that loading path. The material parameters are taken from Table 1.

3.3. Solution algorithm

Table 2 illustrates the algorithmic flowchart for damage-induced isotropic growth. Remarkably, throughout the entire algorithm, we never have to compute or store the coefficients of the growth tensor $\mathbf{F}_g$. Instead, the algorithm manifests itself in a simple scalar scaling with $\lambda_g^{-1}$, and is therefore straightforward and easy to implement. Moreover, we highlight that a closed form solution is presented for the growth stretch $\lambda_g$ in Eq. (42), which eliminates the local Newton iteration from the solution algorithm, and consequently reduces computational time. The algorithm presented in Table 2 was implemented into ABAQUS/STANDARD (Abaqus, 2013) within the user-defined subroutine UMAT. Incompressibility was enforced in the FE simulation through a penalty method, where $1/D_1$ in (31) serves as the analogue of the bulk modulus. To maintain the incompressibility constraint, $D_1$ was set to $10^{-9}$ Pa$^{-1}$ for all simulations.

3.4. Verification

To verify the implemented model, we simulate the growth of a block of biological tissue subject to uniaxial extension, and compare the FE results with the corresponding (semi-analytical) solutions obtained from MATLAB (MATLAB, 2016). For all simulations we use a single 8-node linear brick, hybrid, constant pressure element (C3D8H). This hybrid formulation is used to prevent locking due to incompressibility. The material parameters are taken from Table 1. The block is first extended (loaded) up to a stretch of 1.4, and afterwards the block is unloaded to 1.0, assuming that damage occurred during that loading path. Subsequently, the block grows over time due to induced damage. In Fig. 2 the evolution of the growth stretch $\lambda_g$ is shown indicating perfect agreement between the finite element and the MATLAB results.
4. Parameter study of the growth model

In this section, the sensitivity of the proposed model for damage-induced growth in arterial tissues is investigated. In particular, we investigate the damage parameters $r_1$ and $m_1$, and the growth parameters $\alpha$ and $k$ in more detail. By considering growth of a block of biological tissue subject to uniaxial extension, as described in the previous section, and by employing the parameters from Table 1, each time one of the damage parameters $r_1$, $m_1$ and the growth parameters $\alpha$, $k$ are varied while the other parameters are kept fixed. Fig. 3 shows plots between the growth stretch $\lambda_g$ and the time up to 50 days, where the solid curves are produced with the parameters from Table 1, and the broken curves are obtained by multiplying the individual parameter with a factor ranging between 1.5 and 2.0 for $r_1$, 0.5 and 1.2 for $m_1$, $\alpha$ and $k$. The results indicate that the growth stretch $\lambda_g$ is less sensitive to the variation of the parameter $m_1$ amongst the four investigated parameters. For example, by increasing $r_1$, $m_1$, $\alpha$ and $k$ by a factor of 1.5 (+50%), it results in $-1.72\%$, $-0.48\%$, $-2.39\%$ and $2.20\%$ variation in the maximum growth stretch $\lambda_g$, respectively. Figs. 3(c) and (d) show that a reduction of $\alpha$ entails an increase in the maximum growth stretch $\lambda_g$, while a reduction of $k$ causes a decrease in the maximum $\lambda_g$. In addition, by increasing the parameters $\alpha$ and $k$ the growth stretch $\lambda_g$ reaches its maximum earlier and later, respectively.

5. Finite element simulation of restenosis after angioplasty

This example deals with the simulation of restenosis of an arterial wall occurring after angioplasty triggered by damage. The particular aim of this example is to show the general features of the proposed damage-induced growth model, and that the algorithm, as outlined in Table 2, works within the context of the FE method. This example is of an academic nature, and hence does not reflect a patient-specific geometry and measured material properties.

The 3D FE model was built in ABAQUS/STANDARD where the initial geometry of the artery is considered as a three-layered cylindrical segment with an inner diameter of 4 mm, a wall thickness of 0.75 mm, and a length of 60 mm. The thickness ratios adventitia : media : intima are assumed to be 2 : 3 : 1, and because of the underlying symmetry only one quarter of the arterial segment was discretized. In total 6 elements were used through-the-thickness of the arterial wall (2, 3, and 1
for adventitia, media, and intima, respectively). Eight-node linear brick, hybrid, constant pressure elements (C3D8H) were assigned to the mesh. We applied symmetry boundary conditions on two surfaces. One end of the quarter of the artery was free while at the other end the axial displacements were restricted, see Fig. 4.

To analyze the problem, two steps were considered in ABAQUS/STANDARD: (i) ‘loading/unloading’ during which damage occurred, and (ii) ‘growth’. To simulate balloon inflation/deflation a pressure of 40 kPa was applied at the inner surface of the artery (inflation) and then removed (deflation), i.e. the ‘loading/unloading’ step. The damage which was induced in the wall during that first step is the trigger for growth to build the neointima, i.e., within the second step of the simulation. The used values for the hyperelastic, damage and growth parameters for the individual arterial layers (intima, media, adventitia) are summarized in Table 3.

Fig. 5(a) depicts the FE results immediately after angioplasty, while Fig. 5(b) shows the results after the procedure at 180 days. The results show an increase in the thickness of the intimal layer due to the formation of a neointima. The evolution of the growth stretch \( \lambda_g \) with time (in days), for points on the inner surface of the intimal layer, is presented in Fig. 6. The results indicate that the growth is almost saturated after about 125 days and no significant growth occurs afterwards. Furthermore, from Fig. 6 it can be seen that the rate \( \dot{\lambda}_g \) of growth is increased during the first 40 days after angioplasty, and afterwards it is decreased. These general observations are in a qualitative agreement with clinical observations (see, e.g., Schwartz et al., 1996).

In this example we have focused on a simplified simulation, and several clinically relevant issues were ignored in order to keep the computational effort relatively low. Computational modeling of the angioplasty process with more realistic features including patient-specific geometries and properties (as in, e.g., Holzapfel et al., 2005), inelastic mechanical properties of the arterial wall including residual stresses (as in, e.g., Fereidoonnezhad et al., 2016), and the effect of atherosclerotic plaques on the biomechanical response of the wall (as in, e.g., Kiousis et al., 2009) should be taken into consideration in a more

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**Table 3**

Values for the hyperelastic, damage and growth parameters for the individual arterial layers (intima, media, adventitia) used for the simulation of restenosis after angioplasty.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intima</th>
<th>Media</th>
<th>Adventitia</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu ) [MPa]</td>
<td>0.049</td>
<td>0.020</td>
<td>0.016</td>
</tr>
<tr>
<td>( k_1 ) [MPa]</td>
<td>15.467</td>
<td>0.180</td>
<td>0.845</td>
</tr>
<tr>
<td>( k_3 ) [–]</td>
<td>2.085</td>
<td>100</td>
<td>22.300</td>
</tr>
<tr>
<td>( \beta ) [°]</td>
<td>43.9</td>
<td>5.76</td>
<td>56.3</td>
</tr>
<tr>
<td>( \kappa ) [–]</td>
<td>0.23</td>
<td>0.314</td>
<td>0.32</td>
</tr>
<tr>
<td>( r_i ) [–]</td>
<td>1.37</td>
<td>3.36</td>
<td>3.29</td>
</tr>
<tr>
<td>( m_i ) [MPa]</td>
<td>0.0198</td>
<td>0.0191</td>
<td>0.045</td>
</tr>
<tr>
<td>( D_{th} ) [–]</td>
<td>0.1</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>( \alpha ) [day(^{-1})]</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>( k ) [day(^{-2})]</td>
<td>0.005</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Results show an increase in the thickness of the intimal layer due to the formation of a neointima.

Fig. 6. Evolution of the growth stretch $\lambda_g$ over time (in days) after angioplasty due to damage for points on the inner surface of the intimal layer.

advanced study. However, the results presented here show the model capability to reproduce well-established features of in-stent restenosis.

6. Conclusion

In the present study we proposed a microstructurally–based damage–induced growth model which we used to simulate in-stent restenosis. The finite growth theory was adopted and the multiplicative decomposition of the deformation gradient into an elastic and a growth part employed. The model was developed based on the changes that cells and tissues undergo after stent implementation, including vascular smooth muscle cell migration and proliferation. The mechanobiological growth model provides a link between in-stent restenosis and what happens on the cellular level after stent deployment.

By implementing the growth model into the nonlinear FE software ABAQUS/STANDARD within the user-defined subroutine UMAT, we analyzed growth of a block of biological tissue subject to uniaxial extension, and the implemented model has been verified by comparing the FE results with the corresponding (semi-analytical) solutions obtained from MATLAB. A parameter study of the model has also been conducted, which gives a clear picture of the effect of the involved parameters on the amount of growth.

Finally, the problem of restenosis after angioplasty was analyzed on the basis of a simplified example. It has been shown that the results obtained from the growth model are in qualitative agreement with clinical observations. It should be pointed out that the simulation of restenosis after angioplasty, which was studied here, has a more or less academic character, because the used material parameters, the geometry and the boundary conditions were assumed. However, several features such as nonlinearity, anisotropy and the multi-layered structure of the artery wall were included. Several issues remain, and more complexity need to be considered to obtain more realistic and clinically relevant results. Nevertheless, in the presented FE example, the performance of the model was examined.
Appendix A. Derivation of Eq. (24)

We start by writing Eq. (3) in the index notation as
\[
C_{eij} = F_{g}^{-1} C_{um} F_{g}^{-1} m_{j}. \tag{A.1}
\]

Differentiation of (A.1) with respect to \( C_{ld} \) gives
\[
\left( \frac{\partial C_{e}}{\partial C} \right)_{ijkl} = \frac{\partial C_{eij}}{\partial C_{kl}} = F_{g}^{-1} m_{i} \frac{\partial C_{um}}{\partial C_{kl}} F_{g}^{-1} m_{j} = F_{g}^{-1} m_{i} \delta_{mk} \delta_{ml} F_{g}^{-1} m_{j} = F_{g}^{-1} F_{g}^{-1}. \tag{A.2}
\]

On use of (A.2)_1, the first term of Eq. (23) can be represented as
\[
\frac{\partial \Psi}{\partial C_{e}} : \frac{\partial C_{e}}{\partial C} = \left( \frac{\partial \Psi}{\partial C_{e}} \right)_{ij} \left( \frac{\partial C_{e}}{\partial C} \right)_{ijkl} \hat{C}_{lkl} = \left( \frac{\partial \Psi}{\partial C_{e}} \right)_{ij} F_{g}^{-1} F_{g}^{-1} \hat{C}_{iij} = \left( F_{g}^{-1} \frac{\partial \Psi}{\partial C_{e}} F_{g}^{-1} \right)_{kl} \hat{C}_{lkl} = \left( F_{g}^{-1} \frac{\partial \Psi}{\partial C_{e}} F_{g}^{-1} \right) : \hat{C}. \tag{A.3}
\]

Now, we elaborate on the second term of Eq. (23). Differentiation of (A.1) with respect to \( F_{g}^{kl} \) gives
\[
\left( \frac{\partial C_{e}}{\partial F_{g}} \right)_{ijkl} = \frac{\partial C_{eij}}{\partial F_{g}^{kl}} = F_{g}^{-1} m_{i} \frac{\partial C_{um}}{\partial F_{g}^{kl}} + F_{g}^{-1} F_{g}^{-1} \frac{\partial C_{um}}{\partial F_{g}^{kl}}. \tag{A.4}
\]

It is noted that in Eq. (23), \( C \) and \( F_{g} \) are considered as two independent variables so that \( \frac{\partial C_{um}}{\partial F_{g}^{kl}} = 0 \). Then, the two partial derivatives in (A.4) are obtained by using the following identity (Holzapfel, 2000)
\[
\left( \frac{\partial A^{-1}}{\partial A} \right)_{ijkl} = -\frac{1}{2} \left( A^{-1}_{il} A^{-1}_{kj} + A^{-1}_{il} A^{-1}_{kj} \right). \tag{A.5}
\]

Thus, (A.4)_2 can be represented as
\[
\left( \frac{\partial C_{e}}{\partial F_{g}} \right)_{ijkl} = -\frac{1}{2} C_{eij} \left( F_{g}^{-1} F_{g}^{-1} F_{g} m_{i} F_{g} um F_{g}^{-1} m_{j} + F_{g}^{-1} F_{g}^{-1} F_{g} m_{i} F_{g} jm F_{g}^{-1} m_{j} + F_{g}^{-1} F_{g}^{-1} F_{g} jm F_{g} um + F_{g}^{-1} F_{g}^{-1} F_{g} jm F_{g} jm F_{g} um \right), \tag{A.6}
\]

where \( C_{m} = F_{g} m C_{ez} F_{g} um \) has been used. After simplification of (A.6) we get
\[
\left( \frac{\partial C_{e}}{\partial F_{g}} \right)_{ijkl} = -\frac{1}{2} C_{eij} \left( \delta_{ik} \delta_{ju} F_{g}^{-1} m_{j} + \delta_{ik} \delta_{ju} F_{g}^{-1} m_{j} + \delta_{ik} \delta_{ju} F_{g}^{-1} m_{j} + \delta_{ik} \delta_{ju} F_{g}^{-1} m_{j} \right)
= -\frac{1}{2} \left( C_{ekj} F_{g}^{-1} + C_{ejj} F_{g}^{-1} + C_{ef} F_{g}^{-1} + C_{el} F_{g}^{-1} \right). \tag{A.7}
\]

Thus, the second term of Eq. (23) can be written as
\[
\frac{\partial \Psi}{\partial C_{e}} : \frac{\partial C_{e}}{\partial F_{g}} : \hat{F}_{g} = \left( \frac{\partial \Psi}{\partial C_{e}} \right)_{ij} \left( \frac{\partial C_{e}}{\partial F_{g}} \right)_{ijkl} \left( \hat{F}_{g} \right)_{kl} = -\frac{1}{2} \left[ \left( \frac{\partial \Psi}{\partial C_{e}} \right)_{ij} C_{ekj} F_{g}^{-1} F_{g} F_{g}^{-1} + \left( \frac{\partial \Psi}{\partial C_{e}} \right)_{ij} C_{ejj} F_{g}^{-1} F_{g} F_{g}^{-1} \right]
+ \left( \frac{\partial \Psi}{\partial C_{e}} \right)_{ij} C_{ekj} F_{g}^{-1} F_{g} F_{g}^{-1} + \left( \frac{\partial \Psi}{\partial C_{e}} \right)_{ij} C_{ejj} F_{g}^{-1} F_{g} F_{g}^{-1}
= -\frac{1}{2} \left[ \left( C_{e} \frac{\partial \Psi}{\partial C_{e}} \right)_{kl} \left( \hat{F}_{g} F_{g}^{-1} \right)_{kl} + \left( C_{e} \frac{\partial \Psi}{\partial C_{e}} \right)_{li} \left( \hat{F}_{g} F_{g}^{-1} \right)_{li} \right]. \tag{A.8}
\]
where we have used the fact that $\partial \Psi / \partial C_e$ and $C_e$ are symmetric tensors. We note that the rotation is lumped into the elastic part of the deformation gradient and $F_g$ is symmetric (see the Remark after Eq. (46)). With this in mind, (A.8) can finally be represented as

$$
\frac{\partial \rho}{\partial C} : \tilde{F}_g : \dot{F}_g = -2C_e \frac{\partial \Psi}{\partial C} : \dot{F}_g F_g^{-1}.
$$

(A.9)

With (10) and the property $\partial I / \partial F_g = F_g F_g^{-T}$ the third term in Eq. (23) is obtained as

$$
\frac{\partial \Psi}{\partial \rho} \frac{\partial \rho}{\partial F_g} : \dot{F}_g = \frac{\partial \Psi}{\partial \rho} \frac{\partial (\rho J_2)}{\partial F_g} : \dot{F}_g = \frac{\partial \Psi}{\partial \rho} \rho \frac{\partial \rho}{\partial \rho} : \dot{F}_g F_g^{-1}.
$$

(A.10)

**Appendix B. Derivation of the elasticity tensor (53)**

We start by writing (53) in the index notation as

$$
(C)_{ijkl} = 2 \left( \frac{\partial (I_{ijkl} S_{mn} F_{g}^{-1})}{\partial C_{mn}} \right) = 2 L_{ijkl} \left( \frac{\partial S_{mn}}{\partial C_{ml}} \right) F_{g}^{-1}.
$$

(B.1)

In view of (A.2), Eq. (B.1) can be reformulated as

$$
(C)_{ijkl} = F_{g}^{-1} L_{ijkl} \left( C_e \right)_{mn} r_{kl} F_{g}^{-1}.
$$

(B.2)

Finally, (B.2) can be represented in the tensor notation as displayed in (53).

**Appendix C. Derivation of the explicit expressions of the elasticity tensor**

This appendix deals with the calculation of the explicit expression for the isochoric part $C_e^{\text{iso}}$ of the elasticity tensor $C_e$. We start from (56) and consider first $\tilde{C}_e^{\text{iso}}$ which results from the matrix material. With the definition (57) and with (50), we obtain after some straightforward manipulations (see also Holzapfel, 2000)

$$
\tilde{C}_e^{\text{iso}} = 2 \frac{\partial (I_{e}^{2/3} P : \tilde{S}_e^{\text{m}})}{\partial C_e} = \mathbb{P} : \tilde{C}_e^{\text{iso}} + \mathbb{P}^T + \frac{2}{3} \text{Tr}(I_{e}^{2/3} \tilde{S}_e^{\text{m}}) \mathbb{P} - \frac{2}{3} (C_e^{-1} \otimes \tilde{S}_e^{\text{m}} + \tilde{S}_e^{\text{m}} \otimes C_e^{-1}),
$$

(C.1)

where $\text{Tr}(\mathbb{C}) = \mathbf{C}$ is the trace of $\mathbb{C}$ and $P = C_e^{-1} \otimes C_e^{-1} - C_e^{-1} \otimes C_e^{-1}$ is the fourth-order projection tensor in the material description, while $\tilde{C}_e^{\text{iso}} = 2 I_{e}^{4/3} \partial \tilde{S}_e^{\text{m}} / \partial C_e$ is the (fictitious) elasticity tensor in the material description. Next, we note that according to (50), $\tilde{C}_e^{\text{iso}}$ is a zero tensor, and (C.1) can be simplified as

$$
\tilde{C}_e^{\text{iso}} = \frac{4}{3} I_{e}^{2/3} \mu I_{e} \mathbb{P} - \frac{2}{3} (C_e^{-1} \otimes \tilde{S}_e^{\text{m}} + \tilde{S}_e^{\text{m}} \otimes C_e^{-1}),
$$

(C.2)

where $I_{e} = \text{tr} C_e$. In view of (50), $\tilde{S}_e^{\text{m}}$ is obtained as

$$
\tilde{S}_e^{\text{m}} = 2 \mu I_{e}^{2/3} \left( I - \frac{1}{3} C_e^{-1} \otimes C_e \right) : I = 2 \mu I_{e}^{2/3} \left( I - \frac{1}{3} I_{e} C_e^{-1} \right).
$$

(C.3)

Second we calculate $\tilde{C}_e^{\text{fi}}$, i.e. (57), which relates to the two families of collagen fibers. We note that, in view of (51) and (52), the explicit expression for $\tilde{S}_e^{\text{fi}}$ and $\tilde{S}_e^{\text{fi}}$ can be obtained as

$$
\tilde{S}_e^{\text{fi}} = 2 \tilde{k}_1 E \exp(k_2 E^2) \left[ \kappa I + (1 - 3\kappa) A_0 \right],
$$

(C.4)

and

$$
\tilde{S}_e^{\text{fi}} = 2 \tilde{k}_1 \tilde{E} \exp(k_2 \tilde{E}^2) \left( \tilde{k}_1 I + (1 - 3\kappa) A_0 - \frac{1}{3} \left( \tilde{k}_1 I_{e} + (1 - 3\kappa) I_{e} \right) C_e^{-1} \right).
$$

(C.5)

in which $I_{e} = a_0^i \cdot C_e a_0^i$, $i = 4, 6$, has been utilized.
Then, by employing the same procedure which let to (C.1) 2, from (57) 2 we may deduce \( \mathbf{C}^{(i)}_{e} \) by using (C.4) and (C.5) 2. Thus,

\[
\mathbf{C}^{(i)}_{e} = \mathbf{P} : \mathbf{C}^{(i)}_{e} : \mathbf{P}^T + 2 \frac{2}{3} \mathbf{Tr}(\mathbf{e}^{2/3} \mathbf{S}^{(i)}_{e}) \mathbf{P} - \frac{2}{3} \{ \mathbf{C}^{-1}_{e} \otimes \mathbf{S}^{(i)}_{e} + \mathbf{S}^{(i)}_{e} \otimes \mathbf{C}^{-1}_{e} \}
\]

\[
\mathbf{P} : \mathbf{C}^{(i)}_{e} : \mathbf{P}^T + 4 \mathbf{e}^{2/3} k_1 \mathbf{E}^{(i)} \exp(k_2 \mathbf{E}^{(i)}_e) \{ 1 + (1 - 3 \kappa) I_{le} \} \mathbf{P}
\]

\[
- \frac{4}{3} \mathbf{e}^{2/3} k_1 \mathbf{E}^{(i)} \exp(k_2 \mathbf{E}^{(i)}_e) \{ \kappa \{ \mathbf{C}^{-1}_{e} \otimes \mathbf{I} + \mathbf{I} \otimes \mathbf{C}^{-1}_{e} \} - \frac{2}{3} \{ \mathbf{I} + (1 - 3 \kappa) I_{le} \} \mathbf{C}^{-1}_{e} \otimes \mathbf{C}^{-1}_{e} \}
\]

where, in view of (C.4), \( \mathbf{C}^{(i)}_{e} \) can be calculated using (52) 2, i.e.

\[
\mathbf{C}^{(i)}_{e} = 2 \mathbf{e}^{4/3} \frac{\partial \mathbf{S}^{(i)}_{e}}{\partial \mathbf{C}^{-1}_{e}} = 2 \mathbf{e}^{4/3} \frac{\partial \mathbf{S}^{(i)}_{e}}{\partial \mathbf{E}^{(i)}_e} \frac{\partial \mathbf{E}^{(i)}_e}{\partial \mathbf{C}^{-1}_{e}}
\]

\[
= 4 \mathbf{e}^{4/3} k_1 \exp(k_2 \mathbf{E}^{(i)}_e) \{ 1 + 2k_2 \mathbf{E}^{(i)}_e \}
\]

\[
\times \{ \kappa^2 \mathbf{I} + (1 - 3 \kappa) \mathbf{A}_0 \otimes \mathbf{A}_0 + \kappa^2 \mathbf{I} \} \}
\]

(C.7)

an expression which is needed in (C.6) 2.

References


