A finite element implementation of a growth and remodeling model for soft biological tissues: Verification and application to abdominal aortic aneurysms

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Highlights
\begin{itemize}
  \item General soft tissue growth and remodeling model implemented in finite element code.
  \item Adaptation of vessel to change in hemodynamics agrees well with clinical observations.
  \item Fiber production in aneurysms is mediated more by wall shear than intramural stress.
  \item Evolution of aneurysmal geometry and stresses agrees well with expectations.
  \item Reestablishment of the endothelium is important for aneurysm stabilization.
\end{itemize}

Abstract

The general framework for growth and remodeling (G\&R) of soft biological tissues shows a great potential for expanding our current understanding of biochemical and biomechanical processes, and to predict disease progression. Yet, its use is held up by the lack of a reliable and verified 3D finite element (FE) implementation capable of describing G\&R processes of soft biological tissues. Thus, in this study we present the implementation of a 3D constrained mixture G\&R model in a FE analysis program. In contrast to traditional finite strain FE formulations, we show that the volumetric–isochoric decomposition not only introduces numerical problems and instabilities, it also provides unphysical results. As a verification of the implementation we present adaptations of realistic aorta models to changes in the hemodynamics, i.e. changes in blood flow and pressure. The obtained results show a correspondence with the membrane theory and with clinical expectations. Application to a fusiform aneurysm model provided realistic growth rates, evolution of thickness and stress, whereas changes in the kinetic parameters show good agreement to animal models. Finally, we present simulated expansions of an asymmetric fusiform aneurysm. Non-axisymmetric elastin degradation increased the curvature of the aorta, which is characteristic for abdominal aortic aneurysms.

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1. Introduction

Models that seek to describe fundamental mechanisms by which changes in the mechanical environment govern biological growth and remodeling (G&R) have been increasingly in use in order to improve our current understanding of biochemical and biomechanical (biochemomechanical) processes and to predict disease progression. For the description of soft biological tissue behavior various constitutive models have been proposed. However, G&R models have shown to capture the behavior the best, as they incorporate anisotropic hyperelastic deformation of structurally important constituents (elastin, collagen, smooth muscle), as well as biochemical influences, which are based on the changes of homeostatic stress and biomechanical dependence of the current stress state of the previous loading.

The general framework for G&R of soft biological tissues, as proposed by Humphrey and Rajagopal [1], can be used for modeling various tissues and diseases, from tendon healing [2] and myocardial hypertrophy [3], to the prediction of arterial adaptations in health (e.g., after a change in flow and blood pressure [4–6] or during aging [7]) and disease (e.g., abdominal aortic aneurysms [8–12]). Yet, its application is limited due to the lack of reliable, verified and validated finite element (FE) implementations capable of describing G&R processes of soft biological tissues. Several attempts to implement G&R models into FE codes have been conducted in the past. Models were first implemented by using membrane FEIs that allowed the modeling of axisymmetric (fusiform) aneurysm enlargement [13]. Using these membrane models, geometrical changes and expansion rates during the aneurysm growth were studied for different kinetic parameters [14], with the importance to study the influence of initial aortic properties and collagen turnover on the evolution of fusiform abdominal aortic aneurysms (AAAs) without a thrombus [8,15]. Furthermore, a computational framework that couples vascular G&R with blood flow by using a 3D patient-specific geometry was presented in [16]. Nevertheless, albeit undoubtedly useful, membrane models are incapable of capturing distributions and parameter changes through the wall. Radial distributions of stresses and masses could be important for the evolution of aneurysms, especially for thrombus-laden aneurysms [17], and thus for modeling the biochemical influence of a thrombus on the aneurysmal wall more accurately, the mean values might not suffice. Additionally, membrane FEIs limit the application to thin-walled soft biological tissue structures.

The first constrained mixture G&R model implementation into a 3D FE code was presented by Valentin et al. [18]. This approach was accompanied by some numerical problems, including instabilities and divergence of solutions with increased G&R time, management of computational requirements for storing histories of kinetics and motions, high CPU time, difficulties with enforcing isochoric responses, but also contra-intuitive responses of the tissue to prescribed changes in the arterial structure. Subsequently, several other groups implemented G&R models using a 3D FE framework. For example, Braeu et al. [19] proposed a homogenized constrained mixture model and compared isotropic growth to anisotropic (in-thickness) one. Their verification of the implementation using a case of the vessel adaptation to a minor increase in blood pressure showed that, while anisotropic growth might lead to expected new homeostatic state depending on model parameters, isotropic growth was mechanobiologically unstable. This opposes 1D studies on vascular adaptations to altered blood flow and pressure presented in [6,20]. In a further study, Grytsyan et al. [11] also investigated differences in isotropic and various anisotropic volume growths (in-plane, in-thickness). Unfortunately, the authors provided no verification of their FE results. Smooth muscle cell contributions, along with respective active stress, were ignored in the model. The authors showed that different types of volume growth can lead to the opposite, sometimes unintuitive and implausible results. The latest paper on G&R implementation within a FE framework was documented by Lin et al. [12]. The authors implemented a simplified G&R theory in the commercial software Abaqus by using the user subroutine UMAT, without active and passive contributions of smooth muscle cells and they used simplified growth expressions with stretch-induced parameters. Furthermore, implemented strain-energy functions for the collagen behavior are based on a volumetric–isochoric split of the deformation gradient, which was shown not to be suitable for 1D constituents [21–24]. Also in the present paper, in Section 2.1., we will show that such a decomposition leads to an unphysical behavior.

To conclude, we consider all these studies dealing with G&R implementation in a FE code to be a guideline for achieving specific goals, e.g., to show the influence of different types of growth on the biomechanical response, or to provide illustrative AAA enlargements. In addition, these various papers were orientated towards simplified axisymmetric geometries without an active contribution of smooth muscle cells. However, we know that cell activation has a great influence on the mechanical response even on the distribution of stresses, and it allows an adaptation to sudden changes in the structure or loading of the aortic wall [25,26].
In the present study, we present the implementation of a comprehensive constrained mixture G&R model into a 3D nonlinear FE code. This implementation can be used for general soft tissue G&R problems. The theory is implemented by using the user subroutine UMAT within the FE analysis program FEAP [27], but it is not restricted to it and can be applied to any open FE code. Although the general theory was presented in previous studies (see, e.g., [5,6,13,18]) in order to provide full insights into all capabilities of the implemented model, we added a short overview of the constrained mixture G&R theory in Appendix A. Nevertheless, in Section 2 the most important expressions necessary for the FE implementation are explained. In addition, we discuss the necessity of avoiding the volumetric–isochoric split for fiber constituents. In Section 3, using realistic non-symmetrical geometries and non-homogeneous material, we tried to verify our implementation by showing results for some known phenomena such as hypertension and the change in blood flow. The full potential of the G&R theory we show through examples of symmetric fusiform growth of a three-layered aortic aneurysm in Section 4.1., and an asymmetric fusiform aneurysm in Section 4.2. For these cases we analyze the capability of the model to describe a realistic behavior of an aneurysm, as reported by clinicians (rupture, linear growth, stabilization, realistic growth rates and stresses in the aortic wall, staccato growth). Moreover, we show the necessity of using a 3D FE model through options of tracking stress changes and wall constituents’ ratios through time and in different directions (radial, circumferential, axial). Finally, in Section 5 we summarize the major capabilities and discuss restrictions of the model.

Additionally, in order to facilitate the reproduction of the results, we have also included a condensed flowchart of the implemented procedure for obtaining the solution in Appendix C, but also our findings on the reduction of necessary CPU time, memory storage and numerical stabilities in Appendix D.

2. Methods

Similar to previous studies, the G&R model is based on continuum mechanics, and assumptions are used so that the artery follows the constrained mixture of elastin, and four families of collagen fibers and smooth muscle cells. Detailed constitutive model equations can be found in Appendix A. Here we only present the model equations that differ from other studies.

2.1. Finite element description

For our simulations an 8-node hexahedral Q1P0 element was used with three degrees of freedom at each node. Near incompressibility is ensured by a modified quadratic penalty function, i.e.

\[ W_{\text{sph}} = \frac{1}{d_1} \left( J - \frac{M(s)}{M(0)} \right)^2, \tag{1} \]

where \( d_1 \) denotes a penalty parameter. The Jacobian is calculated as \( J = \det\left(\frac{\partial \mathbf{F}}{\partial s}\right) \) (see Appendix A for more details), and \( M(0) \) and \( M(s) \) are initial and targeted current total mass of a certain FE, respectively. Furthermore, we use the augmented Lagrangian method to cope with the quasi-incompressibility condition by changing the parameter \( d_1 \) in each iteration.

2.2. Volumetric-isochoric split vs. full deformation gradient formulation

Several studies (e.g., [21–24]) suggested that, while a volumetric–isochoric split of the deformation gradient can be justified and systematically derived for isotropic materials, in the case of fiber-reinforced material a multiplicative decomposition must be executed with care in order to avoid violation of certain physical requirements [24]. However, some implementations of the G&R theory, documented in [12,18], employed a volumetric–isochoric split of the deformation gradient and the strain-energy function, similar to traditional (finite strain) FE formulations. Thus, we compared results obtained with a volumetric–isochoric decomposition and a full gradient formulation for a fiber-reinforced hyperelastic material (i.e. an aorta).

The formulation using the full deformation gradient is described in Appendix A. The total strain-energy function \( W \) can be written in a decoupled form as

\[ W = W_{\text{sph}} + W_{\text{dis}}, \tag{2} \]
where \( W_{\text{sph}} \) is the spherical (volumetric) part, Eq. (1), and \( W_{\text{dis}} = \sum_k W^k \) is the sum of the elastic constituents contributing to the isochoric deformations. For the fibers \( k \), the isochoric contribution is calculated as

\[
W^k = \frac{k^2}{4k_3^2} \left\{ \exp \left[ k_3^2 (m(\tau)^k \mathbf{C}_{n(\tau)}^k m(\tau)^k - 1)^2 \right] - 1 \right\},
\]

where \( \mathbf{C}_{n(\tau)}^k \) is the so-called modified right Cauchy–Green tensor \( \mathbf{C}_{n(\tau)}^k = \left( \mathbf{F}_{n(\tau)}^k \right)^T \mathbf{F}_{n(\tau)}^k \), and \( \mathbf{F}_{n(\tau)}^k \) is the distortional component of the deformation gradient \( \mathbf{F}_{n(\tau)}^k(s) = (J_{n(\tau)}(s))^{-1/3} \mathbf{F}_{n(\tau)}^k(s) \), while \( k_2^2 \) and \( k_3^2 \) are material parameters. The deformation gradient \( \mathbf{F}_{n(\tau)}^k(s) \) is a mapping from the natural configurations of each constituent produced at time \( \tau \) to a current mixture configuration at time \( s \), and \( J_{n(\tau)}(s) \) is the volume ratio between instance \( s \) and \( \tau \). The orientation of each fibrillar constituent at the time of production of fiber \( \tau \) is defined by the unit vector \( \mathbf{m}^k(\tau) \). For more details see Figure 1 in [18].

On the other hand, the full gradient formulation does not include the decomposition of the strain-energy function. The strain-energy function \( W_{\text{dis}} = \sum_k W^k \) is simply defined as

\[
W^k = \frac{k^2}{4k_3^2} \left\{ \exp \left[ k_3^2 (m(\tau)^k \mathbf{C}_{n(\tau)}^k m(\tau)^k - 1)^2 \right] - 1 \right\},
\]

All variables are defined in Appendix A. These different formulations lead to different forms of the Cauchy stress tensor \( \sigma \) and the elasticity tensor \( \mathbf{C} \).

**Illustrative example — Comparison of the two formulations**

As the first step of a verification of the model implementation in the user material subroutine, a simple test example on a cylindrical geometry was designed. In this test, we have modeled aging (i.e. a gradual loss of elastin, with a half-life of approximately 40 years, without and with G&R of fibers. When a turnover of fibers was not allowed, the masses of collagen and smooth muscle were kept constant by setting the basal production of fiber \( m^k_B \) in Eq. (A.1) to zero, and by setting an infinite half-life of fibers so that there is no removal \( q^k(s-\tau) \), see Eq. (A.3). Thus, the integrals from Eqs. (A.2) and (A.8) are eliminated. All other parameters are according to Table B.1. On the other hand, mass of elastin was degraded, hence the mass ratio is \( J = M(s)/M(0) < 1 \). Results are shown in Fig. 1(a) and compare the change in the inner diameter calculated by using two formulations: the volumetric–isochoric split (dashed curve) and the full deformation gradient formulation (solid curve). Not only the full gradient formulation has shown to be numerically more stable, but also, more importantly, the results indicate a rather opposite behavior. The use of the volumetric–isochoric split leads to a shrinkage of the aorta as elastin is degraded, whereas the full gradient formulation demonstrates a dilation.

Because this example is not physical, we have also modeled aortic aging, i.e. a gradual loss of elastin with turnover of fibers. Clinically, aging causes a monotonous dilation of the diameter, see Fig. 1 in [28]. A full gradient formulation provides results that demonstrate a continuous dilation of the aorta (solid curve in Fig. 1(b)). On the other hand, for the same model parameters, results obtained with the use of the volumetric–isochoric split show a shrinkage of the aorta for the first 6 years (dashed curve in Fig. 1(b)), before a rather steep increase in diameter occurs. This is clearly unphysical. Similarly, the dashed black curve in Fig. 1(a) shows a significant loss in mass, which is also unexpected during aging.

Based on these results and the previously mentioned studies on the volumetric–isochoric split of the deformation gradient [21–24], subsequently we use the full deformation gradient approach for our application.

**2.3. Production of collagen and smooth muscle**

Early G&R studies (e.g., [20,29]) suggested that vasoactive molecules, regulated by the endothelium in response to altered wall shear stress, also affect cell and matrix turnover. Furthermore, parametric studies have been conducted to define the range of values that provide physical responses [30]. Despite this, in the former G&R FE studies, the endothelial response was neglected, and only the intramural stress-mediated mass production (i.e., stress or stretch sensed by the fibers), was taken into account.

**Illustrative example — Importance of the biochemically motivated parameter \( K_C \)**

Effects of the parameters describing the influence of intramural (\( K_\sigma \) in Eq. (A.1)) and wall shear stresses (\( K_C \)) were previously investigated for the adaptation of an idealized cylindrical blood vessel to altered hemodynamics in
Fig. 1. Change in arterial inner diameter with change in mass for the case with no turnover of collagen and smooth muscle (gray curves) and during aging (black curves) (a); evolution of aortic inner diameter with aging in time (b). Dashed curves denote results obtained with the volumetric–isochoric split, and solid curves with the full deformation gradient formulation.

Fig. 2. Influence of parameters that model wall stress-mediated mass production ($K_\sigma$) and shear stress-mediated changes ($K_C$). However, in these cases, due to small deformations, the changes in wall shear stress and related mass production are negligible. Thus, the influence of the parameter $K_C$ in a disease such as aneurysm, that significantly deforms the arterial geometry, and consequently considerably alters the wall shear stress, is unknown. For that reason, we studied the differences in a fusiform aneurysm growth (see Section 4.1. for more details) for different mass production parameters, while the other model parameters are according to Table B.1. Fig. 2 shows the evolution of the inner diameter over time, at axial position with highest elastin degradation, of the fusiform aneurysm for different fiber production parameters $K_C$ and $K_\sigma$. It can be seen that for very small values of $K_C$, the stress-mediated growth significantly influences the growth of the aneurysm. On the other hand, for larger values of vasodilation-mediated growth, the change in $K_\sigma$ has a minimal effect. However, it is important to note that the values and changes in $K_C$ remained small when compared to values that were related to health (see, e.g., Figs. 3 and 7, or [6,20]). This could lead to the conclusion that vasoconstriction-mediated growth is more important for aneurysm growth.

The difference in the $K_C$ values for health and disease can be explained by the fact that this parameter describes the response of endothelial cells. Increased wall shear stress upregulates endothelial cell production of nitric oxide, an inhibitor of collagen synthesis and smooth muscle cell proliferation, whereas decreased wall shear stress upregulates endothelial cell production of endothelin-1 (ET-1), a promoter of collagen synthesis and smooth muscle cell proliferation. Yet, functionality of endothelium in aneurysms is not clear. For intact endothelial cell layers, i.e. larger values of $K_C$, irreversible degradation of elastin does not lead to aneurysm formation, e.g., see the solid
3. Verification on the basis of clinically observed phenomena

Before using the model for more complex applications, it is necessary to verify the implementation. This was performed using clinical observations, e.g., adaptation of the blood vessel to changes in blood flow or pressure. An idealized artery was represented by half of a cylinder (180° slice). Axial symmetry and distal-proximal symmetry were assumed. The model was discretized by 7200 finite elements (50 elements in the axial direction, 12 in the circumferential direction, and 12 in the radial direction). Three layers with different structures were defined according to data summarized in Table B.1, see Appendix B. In order to avoid numerical instabilities due to large gradients at the interface, where the layers are connected to each other, we defined a transition zone with a gradual change of the structure from one layer to another. Intensity plots showing collagen fiber orientation and dispersion through the healthy aortic wall thickness, as presented in [32], indicated the existence of “transition layers” in between the layers (intima, media, adventitia) with different fiber orientations (see Fig. 6 in [32]). Thus, the width of the transition zones was chosen to correspond to the width of the transition layers observed by second harmonic generation imaging.

Expectations based on membrane theory. It has been shown that for perturbations of the blood flow and the pressure, given by $Q = \varepsilon Q_h$ and $P = \gamma P_h$, where $\varepsilon$ and $\gamma$ indicate the perturbation parameters, both wall shear stress and circumferential stress tend to return to their homeostatic values, while stress-mediated G&R produces specific changes in the geometry. For example, it is expected that the inner radius in the new equilibrium state changes to $r_i = \varepsilon^{1/3} r_{i,h}$, and $h = \gamma \varepsilon^{1/3} h_h$, where $r_{i,h}$ and $h_h$ are homeostatic values of the inner radius and the thickness before the change in hemodynamics, while $r_i$ and $h$ are inner radius and thickness after adaptation to the perturbation.

3.1. Change in blood flow

Clinical/experimental background. Clinically, widening of arteries with increased blood flow has been observed both in animal models (e.g., using anastomosis to increase blood flow of rabbits [33]) and in humans [34]. Time needed for vascular adaptation after an abrupt blood flow increase by 60% was reported to be approximately 2 months for rabbits. It is interesting to note that the diameters exceeded those of control arteries by 19%, which reasonably matches the membrane theory which predicts a 17% increase in the arterial diameter. On the other hand, a change in blood flow in humans was caused by an exercise, rather than a surgical procedure, making these measurements more difficult to control. However, although the change in arterial geometry varies among arteries (e.g., the difference in diameter of femoral arteries between athletes and sedentary subjects was reported to be 11–17.3%, yet carotid arteries were only slightly dilated [34]), both increase in diameter and wall thickness were shown.

Illustrative example. We performed FE simulations of adaptations to changes in the hemodynamics in three steps. Firstly, for the given idealized cylindrical geometry, the blood pressure and pre-stretches of constituents, as provided in Table B.1 of Appendix B, the material parameters for each constituent were calculated. Secondly, in order for the healthy aorta to be more realistic, we used an inhomogeneous (rather small) degradation of elastin from the idealized cylindrical vessel. After 400 days of the G&R process a new equilibrium, i.e. a healthy artery under normal hemodynamic conditions, was adjusted, which is presented by dashed curves in Fig. 3(c). The end stage of the G&R process can be seen in Fig. 3(a) and (b), for the time 300 to 400 days. Finally, we applied a 20% increase in the blood flow at the instance of 400 days. The increase in flow led to wall shear stress-induced changes in the production of fibers and an active response of smooth muscle cells. This triggered growth and a remodeling process, as shown in Fig. 3(a) (400 to 700 days). The outer contours of the new equilibrium state are shown in Fig. 3(c) (solid curves). From Fig. 3(a) and (b) it can also be seen that the parameter $K_C$ influences the time needed for the vessel to find a new equilibrium, but it does not change the inner radius or the thickness of the new equilibrium state. For larger values of $K_C$, mass was deposited more quickly, and thus the thickness returned faster to a new homeostatic value. Furthermore, it can also be seen that in the middle cross-section ($z = 75$ mm), where a small fraction of elastin was degraded, the diameter of the healthy aorta is slightly greater than the diameter at the part with unchanged structure ($z = 0$ mm).
Fig. 3. Evolution of the inner diameter (a), and the wall thickness (b) at location A (middle cross-section at $z = 75$ mm) and at location B ($z = 0$ mm) for different production rates $K_C$; contours of a healthy artery (dashed curve) and the artery after the (new) homeostatic state is reached (solid curve), after 20% increase in the blood flow for $K_C = 1$ (c).

By using a membrane theory approximation, for the case that the blood flow is 20% above its homeostatic (normal) value ($\varepsilon = 1.2$), both the inner radius and the thickness should change $1.2^{1/3} = 1.06266$ times from the homeostatic value. Thus, an aorta with an inner diameter of 20 mm, the terminal inner diameter would amount to approximately 21.25 mm. Depending on the initial healthy diameter, the new homeostatic diameter, measured from the centerline, gained a value of 21.25–21.4 mm, which shows agreement with the membrane theory and expectations from the clinics.

3.2. Hypertension/hypotension

Clinical/experimental background. Similarly, after abrupt and sustained alterations in the pressure, relevant to a study of hypertension or hypotension, the most empirically observed response of the arterial wall is the change in wall thickness, however no long-term dilatation/shrinkage of the blood vessel was observed \[35,36\]. Again, this matches well the membrane theory.

Illustrative example. Analogous to the increase in flow, FE simulations were performed in three steps. In the first two steps, the geometry of non-cylindrical, healthy and normotensive arteries were found. Then, an abrupt 50% increase in blood pressure ($\gamma = 1.5$), at G&R time $s = 400$ days (Fig. 4(a) and (b)), was applied. The vessel immediately expanded due to the abrupt change in loading, see Fig. 4(a). However, G&R processes, primarily governed by an intramural stress-induced mass production, quickly ensured the return of the inner diameter to a smaller, almost initial value, see Fig. 4(a). It is interesting to note that FE simulations predicted a (hypertension-induced) increased arterial curvature of the artery (Fig. 4(c)). A correlation between hypertension and arterial curvature was also clinically observed \[37,38\].

According to the expectations from the membrane theory, the new thickness should increase approximately 50% with respect to the homeostatic value. Since the homeostatic thickness of the aorta is approximately 1.2 mm, after 50% increase in the blood pressure, the new thickness should be 1.8 mm. Again, the FE results presented in Fig. 4(b) match this expectation with good agreement.
Fig. 4. Evolution of the inner diameter (a), the wall thickness (b) at the location A (middle cross-section at $z = 75$ mm) and at the location B ($z = 0$ mm) for different production rates; contours of a healthy artery (dashed curve) and the artery after the new homeostatic state is reached (solid curve) after 50% increase in the blood pressure for $K_C = 1$ (c).

4. Representative examples — application to an abdominal aneurysm

In order to show the full potential of the implemented constrained mixture G&R theory, we have applied the 3D FE model to cases of fusiform and asymmetric fusiform aneurysm enlargements occurring due to changes in the kinetic parameters. Subsequently, we study whether the calculated growth rates, the thicknesses, and the stresses can be compared with clinical observations.

4.1. Model for fusiform aneurysm

Geometrical changes and stress distributions

In order to exploit the axial symmetry of a fusiform aneurysm, a healthy aorta was modeled as a $2^\circ$ cylindrical segment, with length $L = 150$ mm, and the AAA evolution was predicted. The modeling on one segment reduced significantly the computational cost. The segment is composed of three layers, and the FE mesh consists of 1 200 elements: 100 non-uniform elements in the axial direction (with finer mesh in the middle region, where an aneurysm was developed, and a coarser mesh where no change in the structure was expected), one in the circumferential direction, and 12 throughout the thickness of the wall.

Similar to previous studies, loss of mass in elastin initiates the aneurysm development according to

$$Q^e(z, s) = \phi^e_{rem} + (1 - \phi^e_{rem}) \left[ 1 - \exp\left( -s / \tau^e_{1/2} \right) f_1(z) \right],$$

where $\phi^e_{rem} = 0.2$ is the fraction of elastin not being degraded, $s$ is the current time, and $\tau^e_{1/2}$ is the half-life of elastin.

The remaining functional elastin was set to correspond with data of Tong et al. [17], as these authors showed that even in large aneurysms some functional elastin remained. The function $f_1(z)$, defining the degradation of elastin in the axial direction $z$, is adapted from [15]. This function is defined as

$$f_1(z) = \begin{cases} 
\exp\left[ -0.7 \left( z - z_{down} \right)^2 \right], & z < z_{down}, \\
\exp\left[ -0.7 \left( z - z_{up} \right)^2 \right], & z > z_{up}, \\
1, & z_{down} \leq z \leq z_{up}.
\end{cases}$$
Fig. 5. Outer radius (a), wall thickness (b), circumferential stress $\sigma_\theta$ (c) and axial stress $\sigma_z$ (d) at the inner radius for the model of a fusiform aneurysm along the axial coordinate $z$ at several time instances.

In Eq. (6) $z_{down} = 65\text{ mm}$ and $z_{up} = 85\text{ mm}$. In between these two coordinates, degradation of elastin is maximal and constant, while when $z$ approaches 0 or $L$, $f_1(z)$ gradually tends to zero, leaving elastin intact in the healthy part. In response to a local irreversible elastin loss, a local dilatation forms.

Contours of the outer radius over time are shown in Fig. 5(a). As expected, the circumferential stress $\sigma_\theta$ was the highest in the apex region of this model at all times (Fig. 5(c)). With the expansion of the AAA, the wall thickness at the apex decreased as the production was not sufficient to compensate for the expansion rate. It is interesting to note that the shoulder regions thickened. A similar thickness distribution was predicted by using the membrane model [15], but is also observed clinically using CT scans [39]. It is possible that wall thickening in the shoulder region decreases the wall stress, and thus prevents a rapid growth and consequently a rupture of the aneurysm. It was suggested before that the shoulder stress and the aneurysm expansion are correlated [40]. Thickening in the shoulder region does not seem to happen due to mass production. The inner radius, and thus the wall shear stress, is roughly constant at that location, and also the intramural stress (Fig. 5(b) and (c)). Consequently, mass production is not increased. However, it is interesting to note that the values of the axial stresses are roughly the same as the circumferential stresses (compare Fig. 5(c) with Fig. 5(d)). Axial stresses are the consequence of the blood pressure that is stretching the aneurysm axially, increasing tensile stress in the apex and compression of the shoulder regions. Additionally, this further thins down the apex region and thickens the shoulder region.

Radial distributions of the circumferential stress $\sigma_\theta$ and the axial stress $\sigma_z$ at the aneurysm apex at certain time instances are illustrated in Fig. 6. In this figure, the normalized thickness at the radial position $r(\tau)$ was defined as the distance at that position from the inner radius $r_i(\tau)$ divided by the thickness $h(\tau)$ at the same time instance $\tau$, i.e. $[r(\tau) - r_i(\tau)]/h(\tau)$. The non-continuous stress distributions are the consequence of the layered structure. Note that during AAA evolution, the axial stress component remains slightly smaller when compared with the circumferential stress, until the G&R time of $s = 6130$. However, rupture can probably be assumed when any normal component of the wall stress reaches 460 kPa [41]. High axial stresses are likely the consequence of the fusiform model restriction to out-of-plane deformations of the aortic centerline, i.e. the model does not allow aortic tortuosity or bending commonly seen in AAAs.

The vertical lines denote the interfaces between the wall layers. As can be seen, with loss of elastin, the media becomes thinner, while the intima and the adventitia thicken due to increased production of collagen. Intimal thickening is commonly seen in aneurysmal aortic tissue.

Influence of fiber production rate

The animal model presented by Franck et al. [42] suggested that stabilization of AAA expansion (i.e. decrease in growth rate or complete cessation of growth) can be achieved by an establishment of the endothelial lining that leads to the suspension of proteolysis, and thus an increased collagen production. This reconstitution of a new aortic wall has been associated with the stabilizing effect on rat AAAs. An increase in the endothelial functionality is described in the present model by parameter $K_C$, that captures changes in the mass production in response to altered wall shear stress sensed by endothelial cells. Thus, we simulated AAA expansion and the eventual endothelial layer
Fig. 6. Radial distribution (along normalized thickness) of circumferential stress $\sigma_\theta$ (a) and axial stress $\sigma_z$ (b) at the apex of the fusiform aneurysm model at several time instances. The arterial layers, i.e. intima, media, and adventitia, are marked as “I”, “M” and “A”, respectively.

Fig. 7. Evolution of the inner diameter (a), the wall thickness (b), the growth rate (c), and the circumferential stress $\sigma_\theta$ (d) at the apex for the fusiform aneurysm model for different time-averaged production rates.

healing process by changing the values of $K_C$ in time within the aneurysmal region. The results indicate that an increase in $K_C$ in the AAA sac does indeed lead to a stabilization of the AAA growth, as can be seen in Fig. 7(a). The corresponding growth rates are shown in Fig. 7(c). As expected, high growth rates are related to rupture. For smaller production rates, the thickness decreases rapidly, while in cases with stabilization the thickness remains roughly the same, see Fig. 7(b). The evolution of the circumferential stress $\sigma_\theta$ needed to predict rupture can be seen in Fig. 7(d). In cases where AAA is stabilizing, i.e. where a new equilibrium state can be reached, the stresses tend to be restored towards the homeostatic value, whereas for cases of rupture they grow exponentially.

Again, note that small changes in $K_C$ can change the AAA evolution significantly, and thus the production induced by wall shear stresses should not be neglected.

4.2. Model for asymmetric fusiform aneurysm

Non-axially symmetric AAAs are more common. Similar to the model used above to simulate a fusiform aneurysm, the aneurysm development is initiated by loss of elastin, but in this case, elastin degradation depends also on the circumferential coordinate $\vartheta$, i.e.

$$Q^e (z, s) = \phi^e_{\text{rem}} + \left(1 - \phi^e_{\text{rem}}\right) \left(1 - \exp\left(-s/\tau^e_1/2\right) f_1(\vartheta) f_2(\vartheta)\right),$$

(7)
where the function $f_2$ is defined as

$$f_2(\theta) = \exp \left( - \frac{c_s \theta}{1.005\pi - \theta} \right)^2. \tag{8}$$

In the denominator $1.005\pi$ was chosen in order to avoid a division by zero. For the results shown herein the parameter $c_s = 1$ was used. Note that higher values of $c_s$ lead to a steeper degradation function in the circumferential direction, and thus to a more stable aneurysm growth.

The initial model mesh of the cylindrical artery was used in a similar fashion as for the verification case. The geometry was then discretized by 50 elements in the axial direction, 16 in the circumferential direction, and 12 in the radial direction. The evolution of the asymmetric fusiform aneurysm model, simulated with the set of parameters of Table B.1, is shown in Fig. 8. Similar to ruptured fusiform aneurysm cases, the thickness at the apex decreased rapidly, and the growth rate increased to the value of 6 mm/year.

It is important to note that apart from the mass production other factors play a crucial role in the aneurysm outcome; i.e. rupture, continuous growth without rupture or stabilization (cessation of growth). For example, the above mentioned parameter $c_s$ in the elastin degradation function (i.e., Eq. (8)) changes AAA stability. Additionally, it has been shown that the aneurysmal wall stiffens during the evolution of the aneurysm, not only because of loss of the compliant wall, but also due to stiffening of the collagen fibers [15,43–45]. Collagen stiffening can lead to a stabilization of the growth.

The outer contours of the asymmetric fusiform aneurysm model in the two symmetry planes at different G&R times are illustrated in Fig. 9. It is interesting to note that bending of the AAA occurs typically in plane 1 (i.e. the $xz$ symmetry plane), see Fig. 9(a). This increased arterial curvature of the aorta is the sole consequence of the non-axisymmetric elastin degradation, no additional boundary conditions were imposed (e.g., limitation of growth due to the spine). Arterial curvature could be more prominent if rotations of the upper and lower boundaries were allowed. Note that the asymmetric fusiform aneurysm requires the calculation of the centerline in each time step, because it does not remain vertical, unlike for the fusiform aneurysm.

Growth of the aneurysmal sac can also be seen in the horizontal plane 2 (i.e. the $xy$ plane), see Fig. 9(c). The circular cross-section becomes more elliptical with growth of the sac. Since elastin is degraded only on one side, the aneurysm tends to dilate mostly to that side. Yet, it does not mean that the opposite side remains unchanged. For example, Fig. 10(a) shows changes in the wall thickness along the axial coordinate at several time instances. As expected, thickness changes can mainly be found in the sac, and the wall also thickens on the opposite side of the sac. In the healthy part (where coordinate $z$ is close to zero or $L$) the thickness remains the same. Similar to the fusiform aneurysm, there is a wall thickening in the shoulder region.

Intramural stresses are largest in the aneurysmal sac (Fig. 10(b) and (c)). In the healthy regions the stresses remain at the homeostatic level. However, unlike for the fusiform aneurysm, due to the increase in AAA curvature, the axial stress $\sigma_z$ remains lower than the circumferential stress $\sigma_\theta$ all times, even when the stress exceeds the rupture point.

In addition to the changes in the axial direction, the thickness and the stress also change in the circumferential direction, see Fig. 11. In homeostasis, i.e. for G&R time $s = 0$, the thickness and the stress at the inner diameter do not change in the circumferential direction (see the solid curves in Fig. 11). From Fig. 11(a) it can be seen that the
Fig. 9. Outer contours of an asymmetric fusiform aneurysm model in plane 1 (a) and plane 2 (c) at several time instances; definition of the planes is shown in (b).

Fig. 10. Wall thickness (a), circumferential stress $\sigma_\theta$ (b) and axial stress $\sigma_z$ (c) at the inner radius of an asymmetric fusiform aneurysm model along the axial coordinate $z$ at several time instances.

thickness at the aneurysm apex (i.e., at the circumferential coordinate $0^\circ$) decreases with G&R time much quicker compared to the opposite side (at the circumferential coordinate $180^\circ$, where elastin is intact). Similarly, an increase in the stress is more significant at the aneurysm apex than at the opposite side, see Fig. 11(b) and (c).

5. Discussion and conclusions

In our preceding studies, we have used the semi-analytical method to model cylindrical thrombus-laden AAAs [9,45]. Yet, AAA is a large local dilatation of the infrarenal aorta, and therefore its geometry cannot be
approximated by a cylinder. The semi-analytical solution of the biochemomechanical G&R model of thrombus-laden AAAs gave us important insights into the disease and empowered us to formulate certain hypotheses. However, these hypotheses should be tested on more realistic geometries, which can only be pursued by using the FE method. As an initial step, we implemented a constrained mixture G&R model of soft biological tissues in a FE code. It was suggested by several studies [21,22,24,46] that the use of a volumetric–isochoric split of the deformation gradient for fiber-reinforced materials provides non-physical results. In this paper we show that in case of G&R it may predict a completely opposite behavior. Thus, we use the (complete) deformation gradient for the calculation of the strain-energy.

We have validated the implementation of the model by analyzing cases of aortic adaptations to changes in the hemodynamics, i.e. changes in blood flow and pressure of a non-idealized aorta. The results show good agreement with the membrane theory, with animal models and clinical observations.

Furthermore, we have investigated the importance of intramural and wall shear stress-mediated mass productions on the outcome of aneurysm growth. Our results show that for an axisymmetric fusiform aneurysm the reestablishment of endothelial cells or the increase in their functionality (i.e. increased wall shear stress-induced production of fibers) leads to a stabilization of the aneurysm, as was also suggested by the animal model documented in [42]. Yet, it is important to keep in mind the functionality of endothelial cells in human aneurysms is not well understood. In the stabilization cases, the stress tends to return to the homeostatic level, whereas in the case of rupture, the stress increases rapidly in time, while the wall becomes significantly thinner at the model aneurysm apex. Note that homeostasis was maintained in the healthy regions, far from the aneurysm sac.

Fig. 11. Wall thickness (a), circumferential stress $\sigma_\theta$ (b) and axial stress $\sigma_z$ (c) at the inner radius of an asymmetric fusiform aneurysm model at $z = 75$ mm along the circumferential coordinate (given by the angle) at several time instances.
Application of a non-axisymmetric elastin degradation provided realistic deformation and wall stress distributions. Computed evolutions of wall thicknesses and stress components agreed well with clinical observations. The most important feature of the used non-axisymmetric aneurysm model was the increase in the arterial curvature, which is likely caused by the high axial stresses in the aneurysmal sac and the local weakening of the aortic wall.

Nevertheless, there are several limitations in the presented formulation. For example, wall shear stress is calculated by the simple and standard Hagen–Poiseuille formula that is valid for laminar flow through a cylindrical pipe. Such an assumption should not be used for more complex geometries, as shown in Figs. 5 and 9, where turbulent flow and development of vortices are expected. Yet, this can be partially compensated by changing the parameter $K_C$. Furthermore, elastin loss is defined by time- and space-depended functions. This is likely not realistic. As an additional simplification the surrounding tissues were neglected. We considered the aorta as an isolated organ, which is not realistic.

In conclusion, the presented results indicate a great potential. Hence, we suggest that this is an important step towards patient-specific modeling of soft tissue G&R.

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Appendix A

A.1. Kinematics of AAA

We use here a similar notation as described in [6]. Briefly, although we assume that each constituent deforms with the artery as a whole, each constituent can otherwise possess an individual stress-free configuration. Constituent $k$ deposited at certain instant $\tau$ was incorporated within the extracellular matrix with a pre-stretch $G^k(\tau)$ (mapping between natural configurations of the constituent at an instant $\tau$, and the in vivo configuration of the mixture at the same instant). On the other hand, a mapping from the natural configurations of each constituent produced at time $\tau$ to a current mixture configuration at time $s$ is defined by the deformation gradient $F^k_{n(\tau)}(s)$ (see Figure 1 in [6] for clarification). The corresponding right Cauchy–Green tensor $C^k_{n(\tau)}(s)$ can be calculated as $C^k_{n(\tau)}(s) = (F^k_{n(\tau)}(s))^T F^k_{n(\tau)}(s)$. The deformation gradient $\mathbf{F}$ from the initial in vivo mixture configuration to the current configuration was calculated using the FE program. Subsequently, we denote this deformation gradient by $\mathbf{F}$, with the associated right Cauchy–Green tensor $\mathbf{C} = \mathbf{F}^T \mathbf{F}$.

A.2. Kinetics of AAA

In accordance with previous G&R models, we let collagen and smooth muscle cells turnover continuously, whereas elastin is produced in the prenatal period and cannot be produced in maturity. In health, its mass is assumed either constant (for a short G&R time) or to decrease with a natural half-life of 40 years during aging. Turnover implicates that the constituent can be degraded and deposited with production rate $\dot{m}^k(\tau)$. Deposition in the arterial wall during homeostasis is constant, and has a basal production rate value $m^k_B$, whereas during adaptations after injury or during disease it is assumedly driven by deviations from the homeostatic intramural stress, measured as the Cauchy stress $\sigma^k_h$, and deviations from the wall shear stress $\tau^w_h$ that regulates vasoactive molecules so that

$$\dot{m}^k = m^k_B \left[ 1 + K^K_{\sigma}(m(s) \sigma^k(s) - m(0) \sigma^k_h(s)) + K^K_{\tau}(\tau^w - \tau^w_h) \right], \quad (A.1)$$

where $\sigma^k$ and $\tau^w$ are the current Cauchy stress tensor and the wall shear stress, respectively, $m(s)$ and $m(0)$ denote the current and initial orientations, while $K^K_{\sigma}$ and $K^K_{\tau}$ are (gain-type) rate parameters that model wall stress- and
shear stress-mediated changes. The current mass of each constituent $k$ was computed as

$$
M^k(s) = M^k(0)Q^k(s) + \int_0^s \dot{m}^k(\tau) q^k(s - \tau) \, d\tau \quad \text{for } s \leq 7\tau_{1/2}^k,
$$

$$
M^k(s) = M^k(0)Q^k(s) + \int_{s-7\tau_{1/2}^k}^s \dot{m}^k(\tau) q^k(s - \tau) \, d\tau \quad \text{for } s > 7\tau_{1/2}^k,
$$

(A.2)

where the survival function $q^k(s - \tau)$ defines a fraction of the constituent produced at the past time $\tau$ that remained at the current time $s$, with a special case $Q^k(s) = q^k(s - 0)$, and $M^k(0)$ is the initial mass of the constituent; the half-life of the fibers is denoted by $\tau_{1/2}^k$. As there is no production of elastin, for elastin Eq. (A.2) reduces to $M^\text{el}(s) = M^\text{el}(0)Q^\text{el}(s)$.

The survival function $q^k(s - \tau)$ was defined as

$$
q^k(s - \tau) = \exp \left(-\int_{\tau}^{s} K_q^k(\tilde{\tau}) \, d\tilde{\tau} \right) Q^{k,e}(s),
$$

(A.3)

where $K_q^k$ is the mass removal rate-type parameter, and $Q^{k,e}(s)$ equals 1 for all constituents but smooth muscle cells. To model apoptosis of smooth muscle cells caused by loss of attachment to the surrounding matrix (i.e., elastin), degradation of the smooth muscle was linked to degradation of the elastin such that $Q^\text{SMC,e}(s) = Q^e(s)$. The removal rate $K_q^k(\tilde{\tau})$ was let to depend on the stress of the fiber compared to the homeostatic value as

$$
K_q^k(\tilde{\tau}) = \frac{1}{\tau_{1/2}^k} \frac{\exp \left(0.5 \left( I_4(\tilde{\tau}) - 1 \right)^2 \right) (I_4(\tilde{\tau}) - 1) I_4(\tilde{\tau})}{\exp \left(0.5 \left( I_4(0) - 1 \right)^2 \right) (I_4(0) - 1) I_4(0)}.
$$

(A.4)

The half-life of collagen and smooth muscle cells is denoted again by $\tau_{1/2}^k$, while

$$
I_4(\tilde{\tau}) = m(\tilde{\tau})^k \mathbf{C}^{k}_{m(\tilde{\tau})} m(\tilde{\tau})^k.
$$

A.3. Stress analysis

The Cauchy stress tensor related to the aortic wall was calculated as

$$
\sigma = \frac{2}{\det F} F \frac{\partial W}{\partial C} F^T + \sigma_{\text{act}} m_{\text{SMC}}^k \otimes m_{\text{SMC}}^k.
$$

(A.5)

Under the assumption of constrained mixture, the overall strain-energy function $W$ was defined as $W = \sum_k W^k + W_{\text{adh}}$. Finally, $\sigma_{\text{act}}$ was the active stress contribution from the smooth muscle contractility oriented in the direction $m_{\text{SMC}}^k$ of the cells. The active stress was considered to be

$$
\sigma_{\text{act}}(s) = T_m \phi_{\text{SMC}}^k(s) \left(1 - e^{-C(s)^2}\right) \lambda_{\text{act}}^k(s) \left[1 - \left(\frac{\lambda_m - \lambda_{\text{act}}^m(s)}{\lambda_m - \lambda_0}\right)^2\right].
$$

(A.6)

In (A.6) $T_m$ is the maximum actively generated stress, $\lambda_m$ is the circumferential stretch at which the active stress is a maximum, $\lambda_0$ is the circumferential stretch at which the active stress goes to zero, $\phi_{\text{SMC}}^k$ is the mass fraction of the muscle cells, $C(s)$ is the net ratio of vasoconstrictors/vasodilators, and $\lambda_{\text{act}}^m(\tau) = \frac{\lambda_{\text{SMC}}^m(\tau)}{r^2(\tau)}$. This is slightly modified from the original model [47], where $\lambda_{\text{act}}^m(\tau)$ was defined as $\lambda_{\text{act}}^m(\tau) = \frac{\lambda_{\text{SMC}}^m(\tau)}{r^2(\tau)}$, where $r$ is the arterial radius. In general, the geometry does not need to stay axially symmetric, and thus the radius is not necessarily defined. Therefore, we have extended the model for more general geometries by replacing the ratio of radii with the ratio of stretches. Note that for a cylindrical geometry the value of the active stress is not changed by this modification. The stretch $\lambda^A$ evolves via a first-order rate equation, similar to the original model. Thus,

$$
\frac{d\lambda^A(\tau)}{ds} = K_{\text{act}} \left[\lambda_{\text{SMC}}^A(\tau) - \lambda^A(\tau)\right],
$$

(A.7)

where $\lambda^A(0) = \lambda_{\text{SMC}}^A(0)$ in a normal artery, and $K_{\text{act}}$ is a rate parameter.
Since fibers deposited into the matrix at different times possess different deformation gradients, they also possess different energies. The strain-energy function is accordingly defined as

\[
W^k(s) = \sum_k \frac{M^k(0)}{M^k(s)} \hat{W}^k \left( C^k_{n(0)}(s) \right) Q^k(s) + \int_0^s \frac{\hat{m}^k(\tau)}{M^k(s)} \hat{W}^k \left( C^k_{n(\tau)}(s) \right) q^k(s - \tau) \, d\tau \quad \text{for } s \leq \tau_{1/2}^c
\]

\[
W^k(s) = \sum_k \frac{M^k(0)}{M^k(s)} \hat{W}^k \left( C^k_{n(0)}(s) \right) Q^k(s) + \int_{s - \tau_{1/2}^c}^s \frac{\hat{m}^k(\tau)}{M^k(s)} \hat{W}^k \left( C^k_{n(\tau)}(s) \right) q^k(s - \tau) \, d\tau \quad \text{for } s > \tau_{1/2}^c
\]

(A.8)

The isotropic elastin is modeled as a neo-Hookean material, while collagen and smooth muscle were modeled as fiber-like structures without compressive stiffness and with a specific exponential strain-energy function \(\hat{W}\) in tension [48]. Collagen fibers in aneurysms may disperse in plane, but also re-orient out of the cylindrical plane [32], yet due to lack of adequate experimental data this was not modeled here. Trapezoidal integration scheme and Simpson rule were used for time integration.

**Appendix B**

As can be seen from Table B.1, some parameters are fixed (e.g., initial mass fractions, homeostatic values of stretch and stress, and some mechanical properties), and others are calculated to ensure equilibrium. This inverse problem is difficult to solve in finite elements, and thus the remaining parameters are calculated, meaning that they can only be obtained for a cylindrical geometry. For that reason, we model the expansion of the aneurysms with an initially healthy aorta. Furthermore, by starting from the healthy aorta we avoid to make assumptions on the initial mass fractions, orientations and the mechanical properties of a diseased aorta.

In Table B.1, \(\rho\) refers to a mass density, which is assumed to be constant, \(\mu\) is the viscosity, \(P_h\) is the homeostatic mean pressure, \(\tau_{h}^v\) is the homeostatic shear stress on the endothelial layer, \(r_i\) is the inner radius, and \(\sigma_0\) is the assumed stress in the wall. Furthermore, the index “int” refers to the intima, “med” stands for media while “adv” for adventitia, “h” refers to the homeostatic state. The upper indices “c”, “SMC” and “e” refer to collagen, smooth muscle cell and elastin, respectively. The mass fraction of the constituent \(k\) is defined as \(\phi^k = M^k / M\). The initial collagen fraction was subdivided among the four collagen fiber families with the ratio 1:1:4:4 for axial, circumferential, and two helical directions, respectively. Furthermore, \(\tau_{1/2}\) denotes the half-life of each constituent, \(G\) are prostrates, and \(c\) are stiffness parameters. The maximal actively generated stress is \(T_m\), \(\lambda_M\) is the circumferential stretch at which the active stress is a maximum, while \(\lambda_0\) is the circumferential stretch at which the active stress goes to zero.

**Table B.1**

<table>
<thead>
<tr>
<th>Class</th>
<th>Role</th>
<th>Parameter value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>Physical constants</td>
<td>(\rho = 1050 \text{ kg m}^{-3}), (\mu = 0.0037 \text{ Pa s}), (r_i = 10 \text{ mm})</td>
</tr>
<tr>
<td>Initial loading</td>
<td></td>
<td>(P_h = 90 \text{ mmHg}), (\tau_{h}^v = 0.506 \text{ Pa}), (\sigma_0 = 100 \text{ kPa})</td>
</tr>
<tr>
<td>Composition by layer</td>
<td></td>
<td>(\phi_{\text{int}} = 0.16), (\phi_{\text{med}} = 0.52), (\phi_{\text{adv}} = 0.32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\phi_{\text{int}}^c = 0.1), (\phi_{\text{med}}^c = 0.55), (\phi_{\text{adv}}^c = 0.25), (\phi_{\text{SMC}}^c = 0.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(\phi_{\text{int}}^e = 0.9), (\phi_{\text{med}}^e = 0.25), (\phi_{\text{adv}}^e = 0.75)</td>
</tr>
<tr>
<td>Homeostatic kinetics</td>
<td></td>
<td>(\tau_{1/2}^c = \tau_{1/2}^{\text{SMC}} = 80 \text{ days}), (\tau_{1/2}^e = 2 \text{ years})</td>
</tr>
<tr>
<td>Passive elasticity</td>
<td></td>
<td>(c_1^c = 22), (c_3^\text{SMC} = 3.5)</td>
</tr>
<tr>
<td>Bounded</td>
<td>Pre-stretches</td>
<td>(G_{\text{c}0}^c = G_{\text{c}z}^c = 1.4), (G_{\text{SMC}}^c = 1.2), (G_{\text{h}}^c = 1.08)</td>
</tr>
<tr>
<td></td>
<td>SMC activation</td>
<td>(T_m = 100 \text{ kPa}), (\lambda_m = 2), (\lambda_0 = 0.4), (K_{\text{act}} = 0.05)</td>
</tr>
<tr>
<td></td>
<td>Production</td>
<td>(K_{\text{o}}^c = 5), (K_{\text{SMC}}^c = 5), (K_{\text{SMC}}^e = 0.1), (K_{\text{SMC}}^e = 0.1)</td>
</tr>
</tbody>
</table>

\(\rho\) is the homeostatic shear stress on the endothelial layer, \(w\) is the homeostatic wall shear stress, \(\tau_{1/2}\) is the wall shear stress at which the active stress is a maximum, \(\lambda_0\) is the wall shear stress at which the active stress goes to zero.
Appendix C

1. Zeroth time step — homeostasis

READ input file with data for homeostasis
LOOP until convergence of the augmented Lagrange scheme
  UPDATE geometry
  GET deformation gradient $\delta F$
  LOOP over integration points until convergence of the Newton-Raphson scheme
    CALL user material (UMAT) subroutine
    INPUT deformation gradient $\delta F$
    READ history variables
    CALCULATE constituents’ masses and orientations, stresses
    WRITE to history fields the masses, orientations, deformation gradient, stresses
    OUTPUT: components of the stress tensor $\sigma$, elasticity tensor $C$
  END LOOP (equilibrium)
END LOOP (augmented Lagrange)
WRITE data

2. Growth and remodeling

LOOP for time
  UPDATE geometry
  GET deformation gradient $\delta F$
  LOOP over integration points until convergence of the augmented Lagrange scheme
    LOOP until convergence of the Newton-Raphson scheme
      CALL user material (UMAT) subroutine
      INPUT deformation gradient $\delta F$
      READ history variables
      CALCULATE mass production, fiber orientations
      LOOP for time
        CALCULATE survival functions, strain-energy function
      END LOOP (time)
      CALCULATE masses, stresses
      WRITE to history fields the masses, orientations, deformation gradient, stresses
      OUTPUT components of the stress tensor $\sigma$, elasticity tensor $C$
    END LOOP (equilibrium)
  END LOOP (time)
END LOOP (augmented Lagrange)
WRITE data
END LOOP (time)

Appendix D

Solid mechanics elements in FEAP are available based on displacement, mixed, and enhanced-strain formulations. A FE formulation, which is free from locking at the incompressible or nearly incompressible limit, may be developed from a mixed variational approach using, e.g., the Hu–Washizu variational principle. In that principle, the
displacements appear up to first derivatives, while the stresses and strains appear without derivatives. Accordingly, the continuity conditions that may be used in FE approximations are $C^0$ for the displacements and $C^{-1}$ for the stresses and strains (a $C^{-1}$ function is one whose first integral is continuous). Thus, we use Q1P0 elements in FEAP. Note that the formulation is not restricted for the use of first-order 3D FEAs but according to FEAP, a follower pressure can only be analyzed with this type of element.

The G&R theory requires an explicit tracking of the kinetics and the motion, see Appendix C. The integral-based formulation requires a storage of the history of the intervals in order to perform the related numerical integration. Thus, in every integration point we store 70 variables for every time step within the observed life-span (54 variables relate to elastin and fiber kinematics, nine to the deformation gradient $\delta F$, five are related to mass production, one to the simulation time of the current time step, and one to the active stretch computation of smooth muscle cells). Additionally, six stress components are stored only for the previous time step. Here it is noted that the minimum necessary number of stored variables is actually lower; it is 17 (nine components for the deformation gradient $\delta F$, six for the Cauchy stresses, one variable for the simulation time, and another one for the active stretch computation), while the remaining variables can be computed afresh at every time increment. Yet, our simulations showed that a decrease in the storage of history variables led to a significant increase in the process time. Therefore, we decided to optimize the process time at the expense of memory requirements. Due to that, the memory requirements were five times higher; however the process time was roughly two times shorter.

In order to additionally reduce the process time, the maximal life-span of fibers was set to seven half-lives. By using time steps of ten days, this means that only approximately 50 increments (with 70 variables per integration point) were stored in the history, and integrated at every increment. This did not influence the result, as in homeostasis less than 0.1% of the fiber mass remains after that time. Moreover, in the case of aneurysms, fibers produced more than seven half-lives days ago are likely overstressed to the point they would rupture, and could not bear load anymore. By not considering those fibers that also led to more stable simulations.

Both decision to store more variables and definition of maximal life-span reduced the computational requirements significantly. On average, it takes about 30 h to complete the simulation of fusiform aneurysm growth on one core of an Intel Xeon E5-2630 processor for a mesh with 1200 elements. This can be further decreased by shortening the maximal life-span to 300 days (like Wilson et al. [15] suggested) or by increasing the time step to, say 15 days. Unfortunately, parallel computation, which usually drastically reduces the process time, is difficult to apply to this type of problem, because both spatial and temporal discretizations are needed to find a solution. On the other hand we can run multiple simulations at the same time (up to the number of processor cores), and thus compensate for a longer process time of a single simulation.

References


