Investigating the role of smooth muscle cells in large elastic arteries: A finite element analysis

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HIGHLIGHTS

• The influence of intracellular calcium on the biomechanics of arteries is studied.
• FE implementation and model verification are provided using isometric contraction/relaxation.
• Arterial rings are loaded with pressure wave and intracellular calcium functions.

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ABSTRACT

Physiological loading in large elastic arteries is considered to be mainly carried by the passive components of the media but it is not known how much the contraction of the smooth muscle cells is actually involved in the load carrying. Smooth muscle contraction is considered to occur in a relatively slow time domain but the contraction is able to produce significant tension. In the present work the role of smooth muscle contraction in large elastic arteries is investigated by analyzing how changes in the intracellular calcium, and thereby the active tone of smooth muscle cells, influence the deformation and stress behavior; different intracellular calcium functions and medial wall thicknesses with cycling internal pressure are studied. In particular, a recently proposed mechanochemical model (Murtada et al., 2012. J. Theor. Biol. 297, 176–186), which links intracellular calcium with mechanical contraction and an anisotropic model representing the elastin/collagen composite, was implemented into a 3D finite element framework. Details of the implementation procedure are described and a verification of the model implementation is provided by means of the isometric contraction/relaxation analysis of a medial strip at optimal muscle length. In addition, numerically obtained pressure-radius relationships of arterial rings modeled with one and two layers are analyzed with different geometries and at different calcium levels; a comparison with the Laplace equation is provided. Finally, a two-layer arterial ring is loaded with a realistic pressure wave and with various intracellular calcium functions (different amplitudes and mean values) and medial wall thicknesses; residual stresses are considered. The finite element results show that changes in the calcium amplitudes hardly have an influence on the current inner ring radius and the circumferential stress. However, an increase in the mean intracellular calcium value and the medial wall thickness leads to a clear influence on the deformation and the stress behavior.

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1. Introduction

One of the main functions of smooth muscle cells is to regulate size and wall tension of hollow organs through contraction/relaxation. Smooth muscle cells are located in the medial layer of an artery and they play a significant role in maintaining the mechanical strength in the wall and in regulating the blood pressure. During a cardiac cycle, the resulting blood pressure and flow depend on the arterial wall stiffness which may be divided into an active and a passive part. The passive part in the arterial wall is governed by the passive components such as elastin and collagen that are found in the medial and adventitial layers. The active part is related to the contraction/relaxation of smooth muscle cells located in the medial layer. Smooth muscle contraction/relaxation is regulated by phosphorylation of the myosin motors associated to the smooth muscle contractile units. The myosin phosphorylation is mainly regulated by the phosphorylating myosin light-chain kinase (MLCK) and the dephosphorylating...
myosin light-chain phosphatase (MLCP). MLCK activity is regulated by intracellular calcium $[Ca^{2+}]$, through a calcium–calmodulin complex while different calcium sensitizing pathways regulate the activity of MLCP. By varying the MLCK and MLCP activities the active stiffness of the smooth muscle cells can be adjusted. The arterial wall stiffness also depends on the structure and the morphology of the wall.

Smooth muscles can be categorized into two subtypes namely phasic (faster) and tonic (slower) but they are generally considered as a ‘slow muscle type’ (the fastest smooth muscle type has a slower velocity of shortening than the slowest striated muscle type) (Fisher, 2010). The tonic (slow) smooth muscle cells located in the large elastic arteries reach steady-state force during iso-metric contraction in minutes and how this influences the arterial wall during a cardiac cycle, where the load cycle is within a second, is not so well-known. To better understand the role of smooth muscle contraction in larger arteries, it is an important issue to investigate how vascular smooth muscle reacts and affects its surrounding for different levels of active tone.

The pressure–radius relationship of arteries with different levels of activation can be studied by using Laplace’s equation. However, in many cases this is an approximation that is accurate and only valid when the mean radius is much larger than the wall thickness, due to the negligence of any radial stresses. For larger arteries, where the mean radius–wall thickness ratio is smaller, the use of Laplace’s law is not accurate and an alternative approach to analyze the underlying mecha-nochemical process is necessary. The finite element method (FEM) is very useful to study complex boundary-value problems and it can surpass the limitations of Laplace’s law. However, the approach requires a material description of the arterial wall that can be implemented into a finite element (FE) analysis program.

In the present work the mechanochemical model, as proposed by Murtada et al. (2012), is implemented into a three-dimensional framework of the finite element software ABAQUS. The implemented model is then verified by comparing FE results of the isometric contraction/relaxation of a medial strip at optimal muscle length, due to the negligence of any radial stresses. For larger arteries, where the mean radius–wall thickness ratio is smaller, the use of Laplace’s law is not accurate and an alternative approach to analyze the underlying mecha-nochemical process is necessary. The finite element method (FEM) is very useful to study complex boundary-value problems and it can surpass the limitations of Laplace’s law. However, the approach requires a material description of the arterial wall that can be implemented into a finite element (FE) analysis program.

2. Background

In the following section, as a brief review, by starting with a description of the cross-bridge kinetics theoretical models for studying smooth muscle contraction in arteries appropriate for implementations into a finite element analysis program are presented.

2.1. Cross-bridge kinetics

Smooth muscle contraction occurs when myosin filaments interact with actin filaments through load-bearing cross-bridges. The myosin is activated by phosphorylation of the regulatory light chain (RLC), located on the myosin, through the MLCK which is triggered by a calcium–calmodulin complex. Hence, an increase in $[Ca^{2+}]$ is associated to an increased myosin activation. When activated, the myosin interacts with the actin by attaching, pulling (power-stroke) and detaching, more known as the cross-bridge cycle which leads to sliding of the myosin and actin filaments and thereby causing contraction. Deactivation of the myosin is regulated through dephosphorylation of RLC by MLCP in which the cross-bridges slowly detach and the muscle relaxes. A detailed review of the regulatory pathways for MLCP activity can be found in Somlyo and Somlyo (2003). It was observed that smooth muscle is able to maintain tension even though the phosphorylation of myosin RLC is decreased. This phenomenon is referred to as the ‘latch state’ of the cross-bridges in which the myosin is deactivated but is still attached to the actin carrying load (Hai and Murphy, 1988). The latch cross-bridge is described as a slowly cycling cross-bridge or as a weaker cross-bridge (Butler et al., 1986). The equilibrium of the fraction of activated and deactivated cross-bridges in the smooth muscle contractile units defines the level of contraction/relaxation.

2.2. Theoretical models – a brief review

Cross-bridges are commonly modeled as elastic springs and three major parameters regulate the active stress during muscle contraction/relaxation: the number of attached load-bearing cross-bridges (activation parameter), the average elastic stiffness of the cross-bridges (material parameter) and the average elastic elongation of the attached cross-bridges (deformation parameter). There are several models available with the aim to simulate the behavior of contracting smooth muscle cells. In this section, the basic features of models, specifically designed for describing active vascular smooth muscle cells within a continuum mechanical framework that are appropriate to be implemented into FE codes, are reviewed.

2.2.1. Rachev and Hayashi (1999) and Zulliger et al. (2004)

Rachev and Hayashi (1999) proposed a phenomenological model of uniformly distributed vascular smooth muscle cells in the arterial wall, which accounts for two main characteristics of smooth muscle: (i) the capability to generate stress when activated, (ii) the configuration of the contractile proteins in the muscle which is reflected by the stretch. The model describes the active circumferential stress as a function of a contractile activity parameter specified for a certain stimulus, the stretch in the circumferential direction and a normalized function dependent on the circumferential stretch, which account for the active smooth muscle length–tension relationship.

The model was extended by Zulliger et al. (2004) through a three parallel element model (two passive and one active) where the activity parameter is expressed as a function of the different states of the muscle (fully relaxed, maximally contracted and normal tone), and where the active smooth muscle elasticity is extended to a more sophisticated function of the circumferential stretch.

2.2.2. Schmitz and Böl (2011) and Böl et al. (2012)

Schmitz and Böl (2011) proposed a steady-state model of smooth muscle activation which includes a phenomenological explanation of the active length–tension behavior, similar to the Rachev and Hayashi (1999) model. It also includes a structural description of the smooth muscle layer orientation. The activity parameter in the model was set as constant.

The model was further expanded by Böl et al. (2012) to couple intracellular calcium to the activity parameter in the model through a cross-bridge kinetics model (Hai and Murphy, 1988). The intracellular calcium was described as a field variable and is following Fick’s law of diffusion. The coupled model was then used to study the dependence of chemical activation on the contraction of an arterial muscle strip and the chemo–mechanical contraction performance of a carotid artery. Among the reviewed models, this model was the only one that had been implemented into a FE environment at the point of time when this study was conducted.
2.2.3. Yang et al. (2003) and Stålhand et al. (2008)

Yang et al. (2003) proposed a 1D model based on the modified Hill model (Fung, 1993) of the smooth muscle, which describes the active force generation by the cross-bridge mechanism together with a description of the myofilament mechanical properties. The muscle activity development is simulated through the kinetics model of cross-bridges by Hai and Murphy (1988), and the deformation of the smooth muscle cell is described through three parts: cross-bridge elasticity, an active element and a viscoelastic description of the attachment to the surrounding. The active force generation is described through an evolution law of the active element driven by the attached cycling cross-bridges and the latched cross-bridges.

A new constitutive framework proposed by Stålhand et al. (2008) uses a strain-energy function and is based on similar features. That model describes the smooth muscle as two parallel elements, one passive and the other one active. The total deformation of the active element, representing the sarcomere, is described through a multiplicative split of an active and a passive deformation. The behavior of the smooth muscle contraction is described through an evolution law of the active deformation, as similarly proposed by Yang et al. (2003), but which only depends on the driving stress generated by the attached cycling cross-bridges. The model by Yang et al. (2003) predicts good correlations with smooth muscle active force generation data, induced by electrochemical stimulus, length–force relationships up to optimal muscle length and force–velocity relationships. The model by Stålhand et al. (2008) shows good correlations with experimental data of steady-state active force, generated by different external calcium stimuli at different stretches.

2.2.4. Murtada et al. (2010a, 2010b, 2012)

Based on the ideas of Yang et al. (2003) and Stålhand et al. (2008) a structural description of the smooth muscle contractile unit with a clear description of the elastic elongation of the cross-bridges and the filament sliding was proposed by Murtada et al. (2010a). The model incorporates the Hai and Murphy model (Hai and Murphy, 1988) and describes the deformation in the smooth muscle contractile units through two variables, average elastic elongation cross-bridges and relative filament sliding of myofilaments. The evolution law of the filament sliding is described as an active dashpot, where the rate of the filament sliding is proportional to the resulting stress acting upon it. The driving stress depends on the state of the muscle. During contraction the driving stress depends only on the attached cycling cross-bridges, as in the model of Stålhand et al. (2008), and all attached cross-bridges during muscle extension. The model was extended by Murtada et al. (2012), where a realistic filament overlap is implemented to capture the active length–tension relationship, and the evolution law of the filament sliding is described on the basis of Hill’s equation able to capture the isotonic force–shortening velocity relationship. Another model extension considers the distributions of smooth muscle orientations, see the study of Murtada et al. (2010b).

3. Method

In the following section, the theoretical framework used for analyzing [Ca\textsuperscript{2+}]–regulated muscle contraction/relaxation in a healthy artery, is briefly presented. In particular, we focus on the [Ca\textsuperscript{2+}]–regulated chemical model (kinetics of cross-bridges), the kinematics, the mechanical model of the active and passive components in the media and the passive components in the adventitia, and the implementation of the proposed framework into a user-defined material model using ABAQUS. We focus here on a healthy and young artery which consists of two layers corresponding to the media and the adventitia; these are the main (solid) mechanically relevant components in a healthy artery. We propose here a potential that models each layer of the artery as a fiber-reinforced composite.

3.1. Cross-bridge kinetics model

The kinetics of the cross-bridges is described by the latch state model of Hai and Murphy (1988). It describes the myosin through four different states, and the fractions of each state \( n_{M}, n_{MP}, n_{AM}, n_{AM} \) are described through a system of ODEs according to

\[
\begin{pmatrix}
    n_{M} \\
    n_{MP} \\
    n_{AM} \\
    n_{AM}
\end{pmatrix} = \begin{pmatrix}
    -k_{1} & k_{2} & 0 & k_{7} \\
    k_{1} & -(k_{2}+k_{3}) & k_{4} & 0 \\
    0 & k_{3} & -(k_{4}+k_{5}) & k_{1} \\
    0 & 0 & k_{2} & -(k_{3}+k_{7})
\end{pmatrix} \begin{pmatrix}
    n_{M} \\
    n_{MP} \\
    n_{AM} \\
    n_{AM}
\end{pmatrix}.
\]

Herein \( k_{1}, \ldots, k_{4} \) and \( k_{5} \) are the rate constants between the states, where \( k_{1} \) describes the myosin phosphorylation which can be linked to \([Ca^{2+}]\). Hence,

\[
k_{1} = h \left( \frac{[Ca^{2+}]}{[Ca^{2+}]} + (ED_{50}) \right)^{n}.
\]

where \( n \) and \( h \) are fitting parameters and ED\(_{50}\) is the half-activation constant for \([Ca^{2+}]\) to MLCK (Murtada et al., 2012). For a more detailed description of the cross-bridge kinetics model see Hai and Murphy (1988) and Murtada et al. (2010a).

3.2. Kinematics, free-energy function

We use a multiplicative decomposition of the deformation gradient \( F \) into a volumetric part \( J^{1/3}I \) and a volume preserving (isochoric) part \( F = J^{-1/3}F \), where \( J = \text{det } F > 1 \) denotes the volume ratio and \( I \) is the second-order unit tensor. We introduce a unit vector \( M^{\text{CU}} \), which describes the direction of the smooth muscle contractile unit, subsequently abbreviated as CU, and which is chosen to be aligned in the circumferential direction of the artery. The stretch of a CU oriented in the direction \( M^{\text{CU}} \) is denoted by \( \chi = J^{1/3}\chi \), where \( \chi \) is the modified stretch. Subsequently, \( \chi \) can be described through the modified fourth invariant \( I_{4}^{\text{CU}} \) of the isochoric right Cauchy–Green tensor \( \mathbf{C} = F^{T}F \) and \( M^{\text{CU}} \), i.e.

\[
I_{4}^{\text{CU}} = M^{\text{CU}} \cdot \mathbf{C} M^{\text{CU}} = \chi^{2}.
\]

In order to describe the hyperelastic stress response of the arterial wall, we postulate the existence of a (Helmholtz) free-energy function \( \psi \) per unit reference volume. Subsequently, we assume the decoupled form

\[
\psi = \psi_{\text{vol}} + \psi_{\text{med}},
\]

where \( \psi_{\text{vol}} \) is a given scalar-valued function of \( J \), describing the volumetric (dilatational) elastic response of the material, and \( \psi_{\text{med}} \) is a purely isochoric contribution to the free energy. For numerical purposes \( \psi_{\text{vol}} \) serves only as a penalty function introduced to accommodate incompressibility.

3.3. Constitutive model for the media including smooth muscle cells

The isochoric free-energy function \( \psi_{\text{med}} \) for the medial layer of the artery, here denoted as \( \psi_{\text{med}}^{\text{med}} \), is additively decomposed into an active part \( \psi_{\text{med}}^{\text{med}} \), describing the energy related to the CUs, and
a passive part \( \Psi^\text{med} \), describing the energy related to the passive components of the media. Thus,

\[
\Psi^\text{med} = \Psi^\text{med}_a + \Psi^\text{med}_p.
\]

The mechanical framework for the (active) smooth muscle cells is based on the model proposed by Murtada et al. (2010a). The attached load-bearing cross-bridges in a smooth muscle contractile unit are described as elastic springs, where the normalized average elongation of the attached cross-bridges is \( \tau_a \) and the active stress \( \tau^\text{med} \) in the media of a CU can be expressed as

\[
\tau^\text{med} = \mu_a \lambda_a n_{AM}^a + n_{AM} \tau_e,
\]

where \( \mu_a \) is a physical material parameter, \( \lambda_a \) is the (average) relative actin and myosin filament overlap function and \( \tau_e \) is the average relative filament sliding in a CU. For more details the reader is referred to Murtada et al. (2012). The (average) first Piola–Kirchhoff stress \( \Psi^\text{med} \) is related to the free energy \( \Psi^\text{med} \) of the CUs by (see Holzapfel, 2000 for the relevant continuum mechanics)

\[
\Psi^\text{med} = \int \tau^\text{med} \, d\lambda_a = \frac{\mu_a}{2} \lambda_a^2 n_{AM}^a + n_{AM} \lambda_a \left( \lambda_a - \tau_e \right)^2 - 1,
\]

where, according to (3), \( \lambda_a = (\ell_a^{\text{CU}})^{1/2} \).

In order to describe the energy \( \Psi^\text{med} \) in (5), related to the passive components of the media, we assume that one family of collagen fibers is oriented in the circumferential direction of the artery. Hence, the collagen fibers are aligned with the smooth muscle CUs and they are embedded in the elastin/smooth-muscle matrix. The free-energy function \( \Psi^\text{med} \) for the passive response of the media may be expressed through a free-energy function consisting of an isotropic part and an anisotropic part (Holzapfel and Weizsäcker, 1998; Holzapfel et al., 2000; Holzapfel and Ogden, 2010). Thus,

\[
\Psi^\text{med} = \frac{\mu_p^{\text{med}}}{2} (\lambda_1 - 3) + \frac{C_1^{\text{med}}}{2C_2^{\text{med}}} \exp(C_2^{\text{med}} (\tau^\text{med}_c - \tau_e^2)) - 1,
\]

where \( \lambda_1 = \text{tr}(\mathbf{C}) \) is the first invariant of the isochoric right Cauchy–Green tensor \( \mathbf{C} \), and \( \mu_p^{\text{med}} \), \( C_1^{\text{med}} \) and \( C_2^{\text{med}} \) are three material parameters. The constant \( \mu_p \) is associated with the non-collagenous matrix of the media, which describes the isotropic part of the overall response of the layer. Since the direction of the family of collagen fibers in the media is aligned along the direction of the CUs, \( \tau^\text{med} \) in (9) may be replaced by the modified fourth invariant \( \lambda_4^\text{med} \), as introduced in (3).

The relative filament overlap \( \tau_e \) is described as a parabolic function of the relative filament sliding \( \tau_s \), thus,

\[
\tau_e = \left( \tau_s - \frac{\tau_s^2}{2\tau_e^\text{opt}} + \tau_0 \right),
\]

where \( \tau_s^\text{opt} \) and \( \tau_0 \) are material parameters (Murtada et al., 2012). In the present work the relative filament sliding \( \tau_s \) is described in a slightly modified way as in Murtada et al. (2012). The filament sliding \( \tau_s \) is additively decomposed as

\[
\tau_s = \tau_s^\text{Mech} + \tau_s^\text{Chem},
\]

where \( \tau_s^\text{Chem} \) is the filament sliding which is linked to the active cycling cross-bridges and \( \tau_s^\text{Mech} \) is the filament sliding which rises due to any external mechanical loading or deformation. The evolution law for \( \tau_s^\text{Chem} \) is based on the hyperbolic shortening velocity function, better known as Hill’s equation (cf. Woldedge et al., 1985), i.e.

\[
\tau_s^\text{Chem} = \frac{\tau^\text{med}_a - \tau^\text{med}_c}{\mu_0^\text{med} + \alpha^\text{med}},
\]

where the rate of active cross-bridge filament sliding, \( \tau^\text{Chem} \), is described through the difference between the measurable external active stress \( \tau^\text{med}_a \) and the internal stress \( \tau^\text{med}_c \) related to the active cross-bridges together with the fitting parameters \( \alpha \) and \( \beta \). The internal stress \( \tau^\text{med}_c \) depends on the mechanical state (contraction/relaxation) of the smooth muscle CU. During muscle contraction, \( \tau^\text{med}_c \) is assumed to be driven by the attached phosphorylated cross-bridges causing a negative rate \( \tau_s^\text{Chem} \) of filament sliding, while during muscle relaxation, the internal driving stress \( \tau^\text{med}_c \) decreases below the external stress \( \tau^\text{med}_a \) causing a positive rate \( \tau_s^\text{Chem} \) of filament sliding. Hence, the stress \( \tau^\text{med}_c \) during muscle contraction/relaxation can be summarized as

\[
\begin{cases}
\tau^\text{med}_c = \frac{\tau^\text{med}_a}{2} \left( 1 - \frac{\tau^\text{med}_a}{\tau^\text{med}_c} \right) & \text{for } \tau^\text{med}_a < \tau^\text{med}_c \text{ and } \tau^\text{med}_c < \tau^\text{med}_a, \\
\tau^\text{med}_c = \frac{\tau^\text{med}_a}{2} \left( 1 - \frac{\tau^\text{med}_a}{\tau^\text{med}_c} \right) & \text{for } \tau^\text{med}_a > \tau^\text{med}_c \text{ and } \tau^\text{med}_c > \tau^\text{med}_a, \\
\tau^\text{med}_c = \tau^\text{med}_a & \text{else}.
\end{cases}
\]

where \( \tau^\text{med}_c \) is a parameter related to the force of a power-stroke of a single cross-bridge and \( \tau^\text{med}_c \) is related to the force-bearing capacity of a dephosphorylated cross-bridge during muscle extension.

The relative filament sliding \( \tau^\text{Chem} \) rises due to any external loading or deformation and can be calculated through Eqs. (7) and (11). The active attached cross-bridges are dynamic and detach and re-attach during the cross-brIDGE cycle. Changes in the modified stretch \( \lambda_e \) due to any external force or deformation is taken up by \( \tau^\text{Chem} \) and do not affect \( \tau_s^\text{Chem} \). When there are no attached cross-bridges \( \tau_e = -\tau_s^\text{Chem} = 0 \) and \( \tau_s^\text{Chem} = \lambda_e - 1 \).

### 3.4. Constitutive model for the passive adventitia

Here we focus attention on modeling the (passive) response of the adventitia, where the isochoric free-energy function \( \Psi^\text{Mech} \) is also additively decomposed into an isotropic and an anisotropic part (Holzapfel and Weizsäcker, 1998; Holzapfel et al., 2000). The isotropic part represents the non-collagenous material in the adventitia, modeled through the (classical) neo-Hookean model, while the anisotropic part, representing two families of collagen fibers, is modeled by an exponential function. The fiber families are oriented along two (local) directions \( \mathbf{M}^\text{Adv} \) that are symmetrically disposed with an offset angle with respect to the cylinder axis (cf. Holzapfel et al., 2000). The isotropic free-energy function \( \Psi^\text{Mech} \) for the adventitial layer, here denoted as \( \Psi^\text{Adv} \), may be expressed as

\[
\Psi^\text{Adv} = \frac{\mu^\text{Adv}}{2} (\lambda_4 - 3) + \sum_{i=1}^{4} \frac{C_1^\text{Adv}}{2} \exp(C_2^\text{Adv} (\tau^\text{Adv}_i - 1)^2) - 1,
\]

where \( \mu^\text{Adv} \), \( C_1^\text{Adv} \) and \( C_2^\text{Adv} \) are the material parameters and the invariants, associated with the adventitia, are defined by \( \tau^\text{Adv}_i = \mathbf{M}_i^\text{Adv} . \mathbf{M}_i^\text{Adv} \) and \( \tau^\text{Adv}_i = \mathbf{M}_i^\text{Adv} . \mathbf{M}_i^\text{Adv} \). In a cylindrical polar coordinate system, the components of the direction vectors \( \mathbf{M}_i^\text{Adv} \) and \( \mathbf{M}_i^\text{Adv} \) may have, in matrix notation, the forms

\[
\mathbf{M}_i^\text{Adv} = \begin{bmatrix}
0 \\
\cos \phi \\
\sin \phi
\end{bmatrix}, \quad \mathbf{M}_i^\text{Adv} = \begin{bmatrix}
0 \\
-\sin \phi \\
\cos \phi
\end{bmatrix}.
\]
where $\phi$ is the angle between the collagen fibers (arranged in symmetrical spirals) and the circumferential direction of the adventitia.

3.5. Implementation into the ABAQUS environment

As briefly mentioned in the introduction, one approach to study the role of smooth muscle in arterial walls is to use the law of Laplace. The related equilibrium equations are convenient, straightforward to solve and the law is suitable for some situations. Laplace’s equation is applicable for (cylindrical) membranes where the wall thickness is much smaller than the radius. Thereby the radial stress is much smaller than the stresses in the circumferential and axial directions which is not valid for thick-walled arteries. For many arteries it is more appropriate to consider a thick-walled nonlinearly elastic circular cylindrical tube which is then appropriately analyzed by using the FEM.

The smooth muscle model, as described in the previous sections, was implemented into \textsc{Unisohyper.Inv}, an \textsc{Abaqus} user subroutine designed to describe anisotropic hyperelastic material behavior. The user subroutine requires a free-energy function of the material dependent on a set of scalar invariants, and its derivatives with respect to the scalar invariants. The variables in the smooth muscle model are defined through a set of state variables. For more information about the \textsc{Unisohyper.Inv} subroutine the reader is referred to the \textsc{Abaqus} user’s manual (Abaqus, 2010). The material was modeled as incompressible, and the 8-node brick element C3D8H was used for the mesh. All simulations were solved quasi-statically by using a fixed time step. The fraction of the different chemical states in the Hai and Murphy model and the relative filament sliding $\pi_{\text{Chem}}$ in the CU were solved using a forward Euler algorithm. The adventitia was modeled as two families of collagen fibers oriented in certain directions embedded in an elastin matrix. The free-energy function describing the adventitia was taken by the original (unedited) \textsc{Unisohyper.Inv} subroutine together with the \textsc{Anisotropic Hyperelastic, Holzapfel} option with two local directions, see Holzapfel (2000).

The subroutine was called at each calculation point of the elements containing the user-defined material behavior for each time increment. By discretizing the time interval into $N$ time steps, the following algorithm was used for each time step:

**Algorithm 1.** For each time step and at each element integration point,

1. Update $[\text{Ca}^{2+}]_i$ (INPUT)
2. Calculate new fractions of attached cross-bridges ($\pi^{\text{Amb}}, \pi^{\text{AM}}$) through the model by Hai and Murphy, i.e. Eq. (1), using forward Euler
3. Update $t_e^{\text{CU}}$ and calculate the modified stretch $\tilde{\lambda}$ of a CU, i.e. Eq. (3)
4. Update $\pi_{\text{Mech}}^{\text{CU}}$, i.e. Eqs. (7) and (11)
5. Calculate (total) filament sliding $\pi_{\text{fs}}$, i.e. Eq. (11)
6. Calculate new filament overlap $\Gamma_{\text{fs}}$, i.e. Eq. (10)
7. Calculate $P_{\text{chem}}$, i.e. Eq. (6)
8. Calculate $P_{\text{chem}}^{\text{Cu}}$, i.e. Eq. (13)
9. Calculate $P_{\text{fs}}$, i.e. Eq. (12), by using forward Euler
10. Update total filament sliding $\pi_{\text{fs}}$, i.e. Eq. (11)
11. Update $\pi_{\text{med}}$, i.e. Eq. (7), and $\Gamma_{\text{med}}$, i.e. Eq. (10)
12. Calculate the isochoric free-energy functions, i.e. Eqs. (8), (9), (14), and their derivatives with respect to the scalar invariants.

The implementation of the model was carefully verified by simulating isometric contraction/relaxation of a medial strip and by comparing the FE results with the solution of a 1D problem using the mathematical software-package \textsc{Matlab}. Details of this analysis are provided in Section 5.1.

4. Mechanochemical arterial ring simulations using FEM

Three numerical examples of arterial tubes subjected to internal pressure are studied with the implemented user-material model in \textsc{Abaqus}. In all the examples, the arterial tubes are modeled by a quarter segment of a ring with symmetric boundary conditions and with plane strain boundary conditions in the axial direction.

In the first example, the pressure-radius relationship of a closed tube, representing the medial layer, with different wall thicknesses and $[\text{Ca}^{2+}]_i$, the activation of the smooth muscle cells is studied and compared with the law of Laplace. For an internal pressure $p_i$, the circumferential force equilibrium using the Laplace equation can be expressed as

$$\lambda \frac{\partial \psi^{\text{med}}}{\partial \lambda} - \lambda \frac{\partial R}{H} \theta = 0,$$

where $\lambda$ is the stretch in the circumferential direction, $\psi^{\text{med}}$ is the free-energy function of the medial tube, according to Eqs. (8) and (9), and $R$ and $H$ denote the inner radius and the wall thickness in the undeformed configuration, respectively. It is important to note here that the stretch in the axial direction is fixed with a value of 1. No residual stresses or strains are considered in this first example. Numerical results are provided and discussed in Section 5.2.

In the second example, pressure-radius relationships similar to the first example are studied but for a ring with two layers, i.e. media and adventitia, and by considering residual stresses. Different levels of smooth muscle activation $[\text{Ca}^{2+}]_i$ and medial wall thicknesses are analyzed. To account for the residual stresses and strains in the circumferential direction of the arterial ring, a quarter of the ring is modeled in a stress-free configuration with 1/4 of the opening angle $\gamma$, see Fig. 1. As an initial step the opened arterial ring is closed by forcing an angular rotation of the ring segment corresponding to the opening angle, while allowing the ring to move freely in the radial direction, see Fig. 1. Next, the arterial ring is initially loaded with a small internal pressure and then contracted with a certain value of $[\text{Ca}^{2+}]_i$. When equilibrium of the fractions of the myosin states in the chemical model is reached, the internal pressure is successively increased and the resulting radius computed. This is then repeated for different smooth muscle activation $[\text{Ca}^{2+}]_i$ and medial wall thicknesses. Numerical results are provided in Section 5.3.

In the third example, the radial deformation (change in inner radius) and the circumferential stress of an artery during cardiac pressure cycles and different smooth muscle activations are studied. As in the previous example, the arterial ring is modeled with two layers. The smooth muscle cells in the medial layer are simulated to respond with different $[\text{Ca}^{2+}]_i$ functions in response to the cycling internal pressure load. The arterial ring is initially loaded up to a certain level of internal pressure (diastolic pressure level), with no change of smooth muscle activity, and then applied with pressure and corresponding $[\text{Ca}^{2+}]_i$ cycles. After reaching a repeating behavior of the ring deformation during the cardiac pressure cycles, the radial deformations and the circumferential stresses are extracted. The simulations are performed for different wall thicknesses of the media and constant thickness of the adventitia. Residual stresses and strains are considered as in the previous example. Numerical results are provided in Section 5.4.

4.1. Used parameters

The material parameters for the smooth muscle model are according to Murtada et al. (2012); the values relate to isometric
experiments performed on the pig carotid media. The parameters used in the kinetics model (see Eqs. (1) and (2)) are set to $\eta = 0.35917 \text{ s}^{-1}$, $h = 4$, $E_{\text{Dp}} = 0.37 \mu \text{M}$, $k_2 = 0.16267 \text{ s}^{-1}$, $k_3 = 0.06667 \text{ s}^{-1}$, $k_4 = 0.00083 \text{ s}^{-1}$ and $k_5$ was set to 0.00667 $\text{ s}^{-1}$. The material parameters used in the active constitutive model for the media including the filament overlap function (see Eqs. (8), (10), (12), (13)) are set to $\mu_a = 5.3011 \text{ MPa}$, $\eta_{\text{opt}} = 0.48$, $\eta_0 = 0.4255$, $\alpha = 26.68 \text{ kPa}$, $\beta = 0.00833 \text{ s}^{-1}$, $\kappa_{\text{Dp}} = 203.71 \text{ kPa}$ and $\kappa_{\text{med}} = 61.14 \text{ kPa}$. The passive material parameters for the media (see Eq. (9)) are set to $\mu_{\text{med}} = 0.84 \text{ kPa}$, $C_{\text{med}} = 3.15 \text{ kPa}$ and $C_{\text{med}} = 0.035$. The passive material parameters for the adventitia (see Eq. (14)) are set to $\mu_{\text{adv}} = 0.4093 \text{ kPa}$, $C_{\text{adv}} = 23.07 \text{ kPa}$ and $C_{\text{adv}} = 0.2329$. These parameters are obtained by scaling the material parameters for the (carotid) media, as documented by Sommer and Holzapfel (2012), to the material parameters of the (carotid) media estimated by Murtada et al. (2012). The mean orientation of the two families of collagen fibers are set to deviate with an angle $\phi = 49.98^\circ$ from the circumferential direction of the arterial tube.

5. Results

5.1. Verification of the material model implementation: isometric contraction/relaxation of a medial strip

This numerical example deals with the isometric contraction/relaxation of the smooth muscles in a medial strip which are activated through a $[\text{Ca}^{2+}]_i$ transient ranging over 300 s. Mechanical and chemical loading of the medial strip model is performed within three steps:

(i) Medial strip is stretched up to the optimal muscle length ($\lambda = 1.5$) during the first 60 s.
(ii) Isometric contraction for 120 s, which is simulated by an increase in $[\text{Ca}^{2+}]_i$ to a peak value of 400 nM, which then decreased to a steady-state value of 300 nM.
(iii) Relaxation for 120 s with a $[\text{Ca}^{2+}]_i$ decay to a value of 40 nM.

The range of the $[\text{Ca}^{2+}]_i$ transient during isometric contraction was based on $[\text{Ca}^{2+}]_i$ data obtained from swine carotid media (Rembold and Murphy, 1988). For the simulation of the medial strip one-eighth is discretized by using 400 hexahedral elements and symmetric boundary conditions. The geometry of the discretized strip is 5 mm in length, 1.5 mm in width and 0.25 mm in thickness. The collagen fibers are directed along the strip length. The face with the dimensions $1 \times 25 \text{ mm}$ is fixed in all directions. All the results for the isometric contraction/relaxation from the FE simulation are obtained from the node located in the center of the complete medial strip and compared with the 1D solution of Eq. (6) calculated with the mathematical software-package MATLAB. The results of the fractions $n_{\text{Dp}}$ and $n_{\text{AM}}$ of the chemical states triggered by a certain $[\text{Ca}^{2+}]_i$ pulse obtained through the FE implementation and the 1D solution are identical, see Fig. 2(a). The FE results for the Cauchy stress $\sigma$ at the central node of the medial strip agree very well with the 1D solution of Eq. (6), see Fig. 2(b).
Fig. 3. Changes of the Cauchy stress $\sigma$ in a medial strip during isometric contraction and relaxation over a time period of 300 s (displayed is the complete strip). The contour plots refer to four different stages of the simulation: unloaded state at 0 s, stretched up to the optimal muscle length ($\lambda = 1.5$) at 60 s, two minutes isometric contraction at 180 s, two minutes relaxation at 300 s.

Fig. 4. Relationship between the internal pressure $p_i$ and the current inner radius $r$ of a ring – comparison of Laplace equation with finite element results; curves represent the Laplace solution, white circles and squares the finite element results: (a) initial inner radius $R = 2$ mm, wall thickness $H = 2$ mm; not activated (solid curve, filled circles), activated with 200 nM (dashed curve, circles), activated with 220 nM (dash-dotted curve, squares). (b) Solutions for the ring under the same conditions as in (a) except for $H = 0.2$ mm. The difference between the Laplace solution and the finite element solution reduces for smaller $H/R$-ratios for different activations.

The development of the Cauchy stress $\sigma$ in the direction of the muscle strip is presented as a contour plot for four different stages of the simulation: unloaded state at 0 s, stretched up to the optimal muscle length at 60 s, contracted at 180 s, relaxed at 300 s, see Fig. 3.

5.2. Example 1: pressure–radius relationship of a closed tube – comparison of Laplace equation with FE results

A comparison between the pressure–radius relationship of a closed tube on the basis of the Laplace equation (16) and the finite element solution provided by ABAQUS is analyzed. The tube, modeled as a closed tube on the basis of the Laplace equation and the FE solution, has an inner radius of $R = 2$ mm and a wall thickness of $H = 2$ mm and $0.2$ mm. The internal pressure $p_i$ is analyzed as a function of the current inner radius $r$ for three different $[Ca^{2+}]_i$ activations of the smooth muscle cells: 0, 200, 220 nM, see Fig. 4. As expected the FE results for the ring with $2$ mm initial inner radius and $2$ mm wall thickness differ significantly from the Laplace solution for all values of $[Ca^{2+}]_i$, see Fig. 4(a). The Laplace solution and the FE results for the ring with the thinner wall thickness $0.2$ mm have quite a good pressure–radius correlation in the passive state but some deviations can be identified for $[Ca^{2+}]_i > 0$. In general, the Laplace solution shows a stiffer pressure–radius relationship than the FE solution for $[Ca^{2+}]_i > 0$, see Fig. 4(a).

5.3. Example 2: pressure–radius relationship of arterial rings modeled with two layers

Pressure–radius relationships of two-layer arterial rings, activated with different $[Ca^{2+}]_i$ levels and modeled with different medial wall thicknesses are studied. The arterial rings are modeled with an opening angle of $\gamma = 100^\circ$, an inner radius $R = 3$ mm and layer thicknesses $H_{med} = 1$ mm and $H_{adv} = 1$ mm for the media and the adventitia in the stress-free configuration, respectively. To study the problem with a larger medial wall thickness $H_{med}$ is set to $1.5$ mm. The residual stresses and strains in the arterial ring are considered by closing the opening angle before any load is applied.

The closed arterial ring is then loaded with an internal pressure $p_i = 5.25$ kPa and contracted with a certain value of $[Ca^{2+}]_i$. After reaching equilibrium (in the chemical Hai and Murphy model) the arterial ring is then inflated with a linearly increasing pressure from $5.25$ to $25.0$ kPa. The active pressure–radius relationship is simulated for $[Ca^{2+}]_i$ = 180, 200 and 220 nM, see Fig. 5. The dotted lines in the figure indicate the variation of the blood pressure between a maximum (systolic) and a minimum (diastolic) pressure. Note that the mean value of the inner radius decreases with larger medial thickness $H_{med}$.

5.4. Example 3: impact of smooth muscle activation during a cardiac cycle

In the third numerical example, an arterial ring with the same dimensions as in the previous example is loaded with pressure cycles to study the radial ring deformation (change in the inner radius) and the circumferential stress behavior for different $[Ca^{2+}]_i$ functions. The internal pressure $p_i$ increases linearly to the diastolic level, set to be $10.4$ kPa (78 mmHg), and then the pressure varies between the diastolic and the systolic level, set to be $16.5$ kPa (124 mmHg), according to a realistic pressure wave with a period of 1 s. The variation of the internal pressure $p_i$ and two examples of $[Ca^{2+}]_i$ functions used for the simulations are illustrated in Fig. 6(a). An example of the radial ring deformation for the pressure cycles
over 300 s and an activation of \([\text{Ca}^{2+}]_i = 200\) nM is plotted in Fig. 6 (b). Only a representative number of deformation pulses is therein shown and not all the 300 resulting pulses.

The FE analysis is performed for different amplitudes (20, 40 nM) and mean values (180, 200, 220 nM) of the \([\text{Ca}^{2+}]_i\). The current inner radius \(r\), the circumferential Cauchy stress \(\sigma_\phi\) for different \([\text{Ca}^{2+}]_i\) functions and medial wall thicknesses are extracted and compared after 300 s, i.e. 300 pulses, see Figs. 7 and 8. Almost no change can be seen in the distributions of the inner radius \(r\) and the circumferential stress \(\sigma_\phi\) using no amplitude change and different amplitudes (20, 40 nM) but the same mean value (200 nM) of the \([\text{Ca}^{2+}]_i\) functions, see Figs. 7 and 8(a) also representing the circumferential stress distribution obtained with different amplitudes. In the simulation where the mean of the varying \([\text{Ca}^{2+}]_i\) function is increased to 220 nM (decreased to 180 nM), a general decrease (increase) in the inner radius \(r\) between diastolic and systolic pressure is identified, see Fig. 7(b). When the mean value of the \([\text{Ca}^{2+}]_i\) function is increased to 220 nM, then the circumferential stress \(\sigma_\phi\) shows a small decrease during diastolic pressure in the medial layer close to the lumen and a large decrease in the stress of the adventitial layer during systolic pressure, see Fig. 8(b). When the mean value of the
Stress in the adventitial layer increased significantly (Murtada et al., 2012) was implemented into the interactions in the CUs. The implemented model was then verified with the results obtained with the mean value of $[\text{Ca}^{2+}]_i$ and the stress when $[\text{Ca}^{2+}]_i = 220$ nM, see Fig. 8(c). When the medial wall thickness is increased from 1 mm to 1.5 mm, the average inner radius $r$ and the stress $\sigma_{r}$ in both medial and adventitial layers between diastolic and systolic pressure are decreased, see Figs. 7(a) and 8(d).

6. Summary

In the present work a finite element approach to study the role of smooth muscle contraction in larger elastic arteries is presented. The computational approach is three-dimensional and based on the recently proposed mechanochemical model of Murtada et al. (2012). In particular, the influence of different smooth muscle activations and medial wall thicknesses on the mechanochemical response of the wall with different loading conditions is studied. The active tone in the smooth muscle cells is regulated through changes in $[\text{Ca}^{2+}]_i$ during the cardiac (pressure) cycle which trigger the activation of the actin–myosin interactions in the CUs.

The mechanochemical model of smooth muscle contraction (Murtada et al., 2012) was implemented into the finite element software ABAQUS. The implemented model was then verified by comparing FE results of the (elastic) isotropic contraction/relaxation of a medial (circumferential) strip at optimal muscle length with the results obtained from a 1D problem using MATLAB. The 1D results for the changes of chemical and mechanical quantities (fractions $n_{\text{Mnp}}, n_{\text{AM}}$ and Cauchy stress $\sigma$) over a time period of 300 s are almost identical to the FE results at the node located in the center of the modeled medial strip (see Fig. 2). In this example, the FE solution of the average relative filament sliding $n_{\text{M}}$ in a CU deviates slightly from the 1D solution which can be explained by the differently stretched elements in the circumferential direction compared to the 1D solution which has a uniform circumferential stretch.

The relationship between the internal pressure $p_{\text{i}}$ and the inner radius $r$ of an artery is frequently studied by using the Laplace equation. However, an analysis based on Laplace gives only accurate pressure–radius relationships when the wall thickness is much smaller than the mean radius of the artery. In larger arteries, the wall thickness is of significant dimension compared to the mean radius so that the Laplace equation may produce misleading results. For geometries where the mean radii and the wall thicknesses are in the same range, significant differences in the pressure–radius relationships can be found when comparing the Laplace equation with the FE solution (see Fig. 4(a), comparing the passive response approaches shows more similar results (Fig. 4(b)). Thereby, the two solutions for the passive behavior are very close but the two solutions for the active behaviors differ. The reason for the difference in the active behaviors is the significant increase in radial stresses through the wall thickness due to contraction which is considered within the FE solution but not by the Laplace equation.

In a second example, the influence of $[\text{Ca}^{2+}]_i$–regulated contraction on the pressure–radius relationship is investigated on the basis of two-layer arterial rings with different medial wall thicknesses, see Fig. 5. In the simulation with a medial wall thickness increased by 50%, it is found that the mean value of the inner radius decreases for higher activation of $[\text{Ca}^{2+}]_i$. In this example, the medial thickening assumes that the content of the smooth muscle increases with the increasing volume, i.e. the density of smooth muscle CU is constant.
In the final numerical example an arteriolar ring is loaded with a realistic pressure wave with a period of 1 s (Fig. 6(a)). In this example it is studied how smooth muscle contraction, regulated through different $[Ca^{2+}]$, functions, can influence the mechanical behavior of the ring, i.e. the change in the (current) inner radius $r$ and the circumferential Cauchy stress $\sigma_{rr}$: different medial wall thicknesses are also considered (see Figs. 7 and 8). Very little difference in the radial ring deformation and the transmural stress during a single pressure cycle is found for simulations with no amplitude change and different amplitudes of the $[Ca^{2+}]$, but the same mean value ($200$ nM) of $[Ca^{2+}]$ (see Figs. 7 and 8(a)). This suggests that tension development in arterial smooth muscle media (Fig. 8(b)). This suggests that the adventitia does not carry diastolic and systolic pressure due to the higher activity in the media (Fig. 8(b)). This suggests that the adventitia does not carry diastolic and systolic pressure due to the higher activity in the adventitia (Fig. 8(d)). The gradients of the circumferential stress in the adventitia decreases during both diastolic and systolic pressure due to the higher activity in the adventitia (Fig. 8(b)). This suggests that the adventitia does not carry that much load during this condition. For a lower activation (lower mean $[Ca^{2+}]$), the circumferential stress in the adventitia increases significantly (Fig. 8(c)) which suggests that the adventitia carries more load during this condition. It has been demonstrated that the medial layer is the main load carrying layer during normal pressure in the arterial wall, while for higher pressure the main load is carried more by the adventitial layer for a constant value of smooth muscle tone (Holzapfel and Gasser, 2007; Bellini et al., 2014). For higher pressure the load could be transferred back to the media by increasing the $[Ca^{2+}]$ concentration in the smooth muscle cells. These results indicate that the active tone of smooth muscle in large elastic arteries would have a more prominent role in the long-term changes of the vascular wall than regulating the wall stability during a pressure cycle.

One possibility with the proposed implementation is that it also allows to easily study the effects of morphological changes in the vascular wall such as medial wall thickening. The simulations with the increased medial wall thickness result in a general decrease in the circumferential stress $\sigma_{rr}$ in both the media and the adventitia (Fig. 8(d)). The gradients of the circumferential stresses along the radial wall position through both layers decrease when comparing to the simulation when $[Ca^{2+}]$ is set constant. With the increased medial wall thickness it was assumed that the smooth muscle content increased correspondingly.

In all examples, the internal pressure is set as a constant function which means that the pressure is not affected by changes in the lumen diameter. A decrease in diameter would normally lead to an increase in the internal pressure and vice versa, which in turn affect the wall stress. However this coupling effect was not considered in the present examples.

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References


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