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# A mechanochemical 3D continuum model for smooth muscle contraction under finite strains

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## Abstract

This paper presents a modelling framework in which the mechanochemical properties of smooth muscle cells may be studied. The activation of smooth muscles is considered in a three-dimensional continuum model which is key to realistically capture the function of hollow organs such as blood vessels. On the basis of a general thermodynamical framework the mechanical and chemical phases are specialized in order to quantify the coupled mechanochemical process. A free-energy function is proposed as the sum of a mechanical energy stored in the passive tissue, a coupling between the mechanical and chemical kinetics and an energy related purely to the chemical kinetics and the calcium ion concentration. For the chemical phase it is shown that the cross-bridge model of Hai and Murphy (Am. J. Physiol. Cell Physiol., 254, C99-C106, 1988) is included in the developed evolution law as a special case. In order to show the specific features and the potential of the proposed continuum model a uniaxial extension test of a tissue strip is analysed in detail and the related kinematics and stress-stretch relations are derived. Parameter studies point to coupling phenomena; in particular the tissue response is analysed in terms of the calcium ion level. The model for smooth muscle contraction may significantly contribute to current modelling efforts of smooth muscle tissue responses.

*Keywords:* active contraction, continuum mechanics, mechanobiology, model, smooth muscle

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## 1. Introduction

Smooth muscles are responsible for the contractility of hollow organs such as blood vessels, the gastrointestinal tract, the urinary bladder, the airway, or the uterus. For example, smooth muscle cells are contained in the middle layer of an artery and are

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responsible for the control of short-term changes in lumen diameter and of the long-term changes in the extracellular matrix turnover (see, for example, Li et al. [15]). Contraction in smooth muscles can be initiated by mechanical, electrical, and chemical stimuli. The contractile mechanism involves several signal transduction pathways, but all of which converge to increase the intracellular calcium concentration resulting in phosphorylation of myosin. The calcium concentration depends upon the balance between the calcium that is removed either back into storage sites or out of the cell, released by intracellular storage sites, and that enters the cell. Smooth muscle undergoes slow, sustained and tonic contractions, which may be due to slow diffusion of calcium from outside the cell or to the slow rate of ATP hydrolysis or both. They develop considerable active tension that varies with muscle length. Smooth muscles are composed of thin (actin) and thick (myosin) filaments that are organized into contractile units that appear in a smooth arrangement. Very little work has been documented on the modelling of smooth muscle activation within the continuum mechanics framework, and the three-dimension modelling of smooth muscle contraction, which is rare in the literature, is the focus of the present study. In particular, the investigation of models that relate to the matrix material (elastin) and to the reinforcement (collagen) of the artery wall has achieved significant attention in the last two decades, however, very little was done in the investigation of smooth muscle models. The activation of vascular smooth muscles is a physiological phenomenon which to consider in a constitutive law is key in order to realistically capture the function of the artery. Naturally, such models combining the effects of elastin, collagen and smooth muscle need then to be implemented into numerical codes in order to solve realistic boundary-value problems such as the control of short-term changes in lumen diameter of arteries due to mechanochemical signals. This turns out to be a very important but also challenging demand for our future activities in biomechanics and mechanobiology.

Most smooth muscle models using continuum modelling aspects pursue purely phenomenological approaches. One of the earliest models for a muscle dates back to the work of Hill [9], which documents the results of a series of carefully performed experiments on the mechanics and heat production in frog skeletal muscle, but also the mechanical Hill model of muscle consisting of contractile and elastic elements in series showing that this model explains many of the key experimental observations. Based on the Hill model several other models have been developed up to these days.

For example, Gestrelus and Borgström [6] extended the classical Hill model by capturing the energy transfer via cross-bridges as a 'friction clutch' mechanism. The authors proposed a one-dimensional dynamic model of smooth muscle contraction and it is shown that the model agrees well with experimental observations on smooth muscle mechanics under isotonic as well as isometric conditions. An extension of the mechanical model to incorporate viscoelasticity was proposed by Yang et al. [22]. The model consists of two major components: electrochemical and mechanochemical subsystem models of the smooth muscle cell, whereby the mechanochemical component couples the model of Hai and Murphy [8] with a mechanical model based on that of Hill.

Rachev and Hayashi [17] developed a simple phenomenological model based on a strain-energy function and an active circumferential wall stress assumed to be controlled by the  $\text{Ca}^{2+}$  concentration of free intracellular calcium ( $\text{Ca}^{2+}$ ) together with

the muscle fiber stretch relative to a reference sarcomere length. In particular, the results of this work show that smooth muscle contraction affects the residual strain state. The authors show that basal muscular tone reduces the strain gradient in the arterial wall and yields a near uniform stress distribution, beyond the reduction due to residual stress; see also the discussion by Humphrey [13]. Zulliger et al. [25] followed the work of Rachev and Hayashi [17]. They suggested a pseudo strain-energy function which quantifies the sum of contributions from elastin, collagen and smooth muscle. The model captures the interaction between mechanical stretch and myogenic contraction and it was used in particular to illustrate the localized reduction of the circumferential stress in an arterial wall due to vascular smooth muscle tone. The same activation as proposed by Rachev and Hayashi [17] was also used by Baek et al. [3]. Within the context of fluid-solid interactions they developed a small deformation theory and showed that the theory is able to predict that the wall stiffness decreases with increasing vasoconstriction. The more recent mechanochemical model of Murtada et al. [16] combines continuum theory with active response controlled by calcium concentration, and it predicts force generation in smooth muscle. It is a simple model incorporating only a few material parameters each of which has a clear physical meaning. The model satisfies the second law of thermodynamics. The results are consistent with isometric and isotonic experiments on smooth muscle tissue.

The model by Stålhand et al. [21] connects the active stress-stretch response with the calcium ion level by using the chemical state law of Hai and Murphy [8]. The model is thermodynamically consistent and it reduces to the constitutive framework of Yang et al. [22, 23] for the linear limit of small deformations. It seems that the model of Stålhand et al. [21] was the first to use a strain-energy function involving the chemical kinetics of smooth muscle contraction and nonlinear kinematics. However, the finite strain model is one dimensional.

The aim of the present work is to extend the mechanochemical model for smooth muscle contraction by Stålhand et al. [21] to three dimensions. The modelling is primarily concerned with the active force generation and chemical or electro-chemical processes are not modelled explicitly, for simplicity. They are instead set to certain values like the intracellular calcium ion concentration or modelled implicitly like the free energy changes associated with myosin transformations. The content of this paper is summarized as follows. In Section 2, we provide in detail a general thermodynamical framework for mechanochemical smooth muscle contraction. In particular, we review the chemical kinetics for smooth muscle contraction and provide balance laws and an overview of the kinematical background, basically finite deformation of a continuum, relevant to the development of constitutive relations and evolution laws. A multiplicative decomposition of the deformation gradient into an active contraction of the smooth muscle cell and an elastic deformation of the sarcomere serves as a basis. The general constitutive relation for the passive tissue and the reduced dissipation inequality is derived and analysed. Section 3 specializes the proposed three-dimensional thermodynamic model, in particular the underlying mechanical and chemical phases are specialized in order to quantify the coupled process. A free energy is proposed as the sum of a purely mechanical energy stored in the passive tissue, a coupling between the mechanical and chemical kinetics and an energy related purely to the chemical kinetics and the calcium ion concentration. For the chemical phase it is shown that the linear

chemical model of Hai and Murphy [8] is included in the developed evolution law as a special case. Section 4 analyses a uniaxial extension test and illustrates the specific features and underlying mechanics of the proposed constitutive framework. Kinematics and related stress-stretch relations are derived under the assumption that the tissue is incompressible. Parameter studies are investigating several coupling phenomena; in particular the influence of the calcium ion level on the biomechanical response is studied in detail. The concluding Section 5 critically discusses the formulation of the proposed three-dimensional mechanochemical model, the obtained numerical results and it also compares the formulation with the one-dimensional model published previously. It points to the need to use approximation techniques such as the finite element method to solve more complex boundary-value problems.

## 2. Thermodynamic model

### 2.1. Chemical kinetics

Contraction of smooth muscle can be triggered by a number of stimuli, e.g., chemical and mechanical. Regardless of the type, the stimulus causes a depolarization of the cell membrane and allows  $\text{Ca}^{2+}$  and other ions to enter the cytosol. The increased cytosolic  $[\text{Ca}^{2+}]$  initiates a change in the chemical state of myosin which leads to phosphorylation of myosin heads and attachment to actin. The attached and activated myosin heads performs a, so called, ‘power stroke’ which translates myosin relative to actin and thereby generate the active force.

Using fast kinetic data on phosphorylation in smooth muscles, Hai and Murphy [8] proposed a model for the chemical state and the force generation of a smooth muscle. The model (in the sequel referred to as the Hai and Murphy model) assumes that the myosin can be in the four chemical states: free unphosphorylated myosin ( $M$ ), free phosphorylated myosin ( $M_p$ ), phosphorylated myosin attached to actin ( $AM_p$ ), and dephosphorylated myosin attached to actin ( $AM$ ). The last state accounts for the unique ability of smooth muscle to develop and maintain steady-state force at low levels of phosphorylation, i.e., low energy consumption, and is often referred to as the ‘latch state’.

The transition between the four states is governed by the first-order differential equation system:

$$\frac{d}{dt} \begin{bmatrix} M \\ M_p \\ AM_p \\ AM \end{bmatrix} = \begin{bmatrix} -k_1 & k_2 & 0 & k_7 \\ k_1 & -k_2 - k_3 & k_4 & 0 \\ 0 & k_3 & -k_4 - k_5 & k_6 \\ 0 & 0 & k_5 & -k_6 - k_7 \end{bmatrix} \begin{bmatrix} M \\ M_p \\ AM_p \\ AM \end{bmatrix}, \quad (1)$$

where  $k_1, k_2, \dots, k_7$  are reaction rates. To have a solvable system, Hai and Murphy [8] introduced the additional constraint

$$M + M_p + AM_p + AM = 1 \quad (2)$$

implying that the sum of the fractions remains constant. Note that equation (2) is a balance law but not in the classical sense since it only applies to the sum of fractions.

The reaction rates  $k_1$  and  $k_6$  control the phosphorylation of myosin in the detached and attached states, respectively, and are often assumed dependent on the  $[\text{Ca}^{2+}]$ , see Stålhand et al. [21] and Yang et al. [22]. The transition between the four states in Eq. (1) is shown schematically in Fig. 1. Note that the reaction  $AM \rightarrow M$  is assumed to be irreversible.

## 2.2. Kinematics

Smooth muscle contraction is modelled from a macroscopic point-of-view in this study to motivate a continuum mechanical approach. This also means that any reference to intracellular microscopic properties is subject to an extrapolation of the homogenised macroscopic behaviour. This is a slightly different approach from the one adopted in Murtada et al. [16] where the actual microscopic filament displacement is modelled.

Let a set of points in the three-dimensional Euclidean space constitute a reference configuration denoted by  $\Omega_0$ . The motion of any point  $X \in \Omega_0$  is given by the bijective time dependent map  $\chi$  according to

$$\chi : \Omega_0 \times \mathbb{R} \rightarrow \Omega$$

where  $X$  maps to  $x = x(X, t) \in \Omega$  and  $t$  is the time. The configuration  $\Omega$  is another subset of the Euclidean space referred to as the current configuration. The velocity of a point  $X$  is given by  $V(X, t) = \dot{\chi}(X, t)$ , where the superscribed dot denotes a time derivative.

Let  $\mathbf{F}$  be the deformation gradient associated with the map  $\chi$  and assume that the smooth muscle activity can be modelled as the following fictitious two-step process: first, an individual filament contraction in which myosin moves relative to actin, and, second, an elastic deformation of the cross-bridges (and possibly other intracellular constituents in series with the cross-bridges, e.g., dense body  $\alpha$ -actinin) to achieve the configuration  $\Omega$ . This leads to a multiplicative decomposition of  $\mathbf{F}$  according to:

$$\mathbf{F} = \mathbf{F}_e \mathbf{F}_a, \quad (3)$$

see Fig. 2. The tensor  $\mathbf{F}_a$  is a map from the tangent space of the reference configuration onto itself and represents the active contraction by filament translation. Since the tensor  $\mathbf{F}_a$  needs not be integrable, infinitesimal parts of  $\Omega_0$  are deformed independently and their union may not form a compatible configuration after the mapping, see Klarbring et al. [14]. The tensor  $\mathbf{F}_e$  is a map between the tangent spaces of  $\Omega_0$  and  $\Omega$ . This tangent map represents the elastic cross-bridge deformation and guarantees a compatible current configuration, see Fig. 2. In one dimension, the process may be thought of as an independent change in the stretch associated with the individual contraction followed by an elastic deformation of the cross-bridges (and other intracellular material in series with the cross-bridges) to fit the deformed cell, see Fig. 2 in Stålhand et al. [21].

Smooth muscle cells are assumed to be aligned along the principle directions for the collagen fibre in this study. Although there are no conclusive evidence for this assumption, studies have indicated a general co-alignment of the principle directions oriented almost circumferentially, see, e.g., [4, 24]. Introduce a set of fibre vectors

$\{\mathbf{\Pi}_1, \mathbf{\Pi}_2, \mathbf{\Pi}_3\}$  in the tangent space to  $\Omega_0$ . The vectors  $\mathbf{\Pi}_1$  and  $\mathbf{\Pi}_2$  are aligned parallel to their respective collagen fibre family direction while  $\mathbf{\Pi}_3$  is not in the plane spanned by  $\mathbf{\Pi}_1$  and  $\mathbf{\Pi}_2$ . Further, assume that smooth muscle cells contract along their fibre vectors such that the directions of the fibre vectors remain unchanged. Under these assumptions, an active contraction tensor may be defined as:

$$\mathbf{F}_a = \lambda_1 \mathbf{\Pi}_1 \otimes \mathbf{\Pi}^1 + \lambda_2 \mathbf{\Pi}_2 \otimes \mathbf{\Pi}^2 + \lambda_3 \mathbf{\Pi}_3 \otimes \mathbf{\Pi}^3, \quad (4)$$

where the vectors  $\mathbf{\Pi}^i$  are the dual base to  $\mathbf{\Pi}_i$  defined by  $\mathbf{\Pi}^i \cdot \mathbf{\Pi}_j = \delta_j^i$ , where  $\delta_j^i$  is the Kronecker delta. Further assume that smooth muscles are mechanically equivalent and undergo the same contraction such that  $\lambda_1 = \lambda_2 = \lambda_a$ . Note that the fibre vectors above are invariant because of their connection to the reference configuration. The convected fibre vectors are, however, associated with the current configuration and strongly depend on the deformation.

It is generally accepted that elastic deformation of soft tissue can be modelled as incompressible, implying  $\det \mathbf{F} = \det \mathbf{F}_e = 1$ . By the multiplicative decomposition in Eq. (3), the active deformation must, therefore, satisfy the constraint

$$\det \mathbf{F}_a = 1, \quad (5)$$

where the determinant can be computed from the definition:

$$\det \mathbf{F}_a = \frac{(\mathbf{F}_a \mathbf{\Pi}_1 \times \mathbf{F}_a \mathbf{\Pi}_2) \cdot \mathbf{F}_a \mathbf{\Pi}_3}{(\mathbf{\Pi}_1 \times \mathbf{\Pi}_2) \cdot \mathbf{\Pi}_3} = \lambda_1 \lambda_2 \lambda_3. \quad (6)$$

Eliminating  $\lambda_3$  by means of Eqs. (5) and (6) allows Eq. (4) to be written in the form

$$\mathbf{F}_a = \lambda_a \mathbf{\Pi}_1 \otimes \mathbf{\Pi}^1 + \lambda_a \mathbf{\Pi}_2 \otimes \mathbf{\Pi}^2 + \lambda_a^{-2} \mathbf{\Pi}_3 \otimes \mathbf{\Pi}^3, \quad (7)$$

which solely depends on the contraction stretch  $\lambda_a$ . Finally, the contraction velocity of the smooth muscle deformation need to be defined. To that end, take the time derivative of  $\mathbf{F}_a$  in Eq. (7) and use the chain rule to obtain

$$\dot{\mathbf{F}}_a = \frac{\partial \mathbf{F}_a}{\partial \lambda_a} \dot{\lambda}_a, \quad (8)$$

where  $\dot{\lambda}_a$  is the contraction speed along the fibre vectors and

$$\frac{\partial \mathbf{F}_a}{\partial \lambda_a} = \mathbf{\Pi}_1 \otimes \mathbf{\Pi}^1 + \mathbf{\Pi}_2 \otimes \mathbf{\Pi}^2 - 2\lambda_a^{-3} \mathbf{\Pi}_3 \otimes \mathbf{\Pi}^3. \quad (9)$$

### 2.3. Balance laws

In this section, balance laws for the contracting smooth muscle are derived by means of the principle of virtual power as given by Germain [5]. To apply the principle of virtual power, we must first define the fluxes associated with a change of state. To that end, let the fluxes be given by  $\{\mathcal{V}, \mathcal{L}, \mathcal{B}\}$ , where  $\mathcal{V}$  belongs to the set of admissible velocities,  $\mathcal{L}$  belongs to the set of admissible contraction rates along the fibre vectors, and  $\mathcal{B}$  belongs to the set of admissible fluxes of  $[\text{Ca}^{2+}]$ . The principle of virtual power for quasi-static conditions then reads,

**Principle of virtual power.** For any part  $\mathcal{P} \in \Omega_0$ , the external and internal power production  $\hat{P}_i$  and  $\hat{P}_e$ , respectively, must satisfy

$$\hat{P}_i(\mathcal{V}, \mathcal{L}, \mathcal{B}) + \hat{P}_e(\mathcal{V}, \mathcal{L}, \mathcal{B}) = 0$$

for all admissible  $\mathcal{V}$ ,  $\mathcal{L}$ , and  $\mathcal{B}$ .

We now define the internal virtual power production as:

$$\hat{P}_i = - \int_{\mathcal{P}} \mathbf{P} : \nabla \mathcal{V} \, dV - \int_{\mathcal{P}} P_a \mathcal{L} \, dV - \int_{\mathcal{P}} P_c \mathcal{B} \, dV, \quad (10)$$

and the external virtual power production as:

$$\hat{P}_e = \int_{\mathcal{P}} \mathbf{T} \cdot \mathcal{V} \, dV - \int_{\mathcal{P}} T_a \mathcal{L} \, dV - \int_{\mathcal{P}} T_c \mathcal{B} \, dV, \quad (11)$$

where  $\cdot$  and  $:$  denote the dot product and the double contraction, respectively,  $\mathbf{T}$  is the material traction vector,  $\mathbf{P}$  is a first Piola-Kirchhoff stress tensor, and  $\nabla$  is the material gradient. The quantities  $P_a$  and  $T_a$  are the internal and external thermodynamic forces, respectively, power-conjugate with  $\mathcal{L}$ , and  $P_c$  and  $T_c$  are the internal and external thermodynamic forces, respectively, power-conjugate with  $\mathcal{B}$ . Substituting Eqs. (10) and (11) in the principle of virtual power and applying the divergence theorem gives the classical equilibrium equations

$$\nabla \cdot \mathbf{P} = \mathbf{0} \quad \text{in } \Omega_0, \quad \mathbf{T} = \mathbf{P}^T \mathbf{N} \quad \text{on } \partial\Omega_0, \quad (12)$$

where  $\mathbf{N}$  is a unit normal to the boundary  $\partial\Omega_0$  of the reference configuration. In addition to the equilibrium equations, the following balance laws are also obtained

$$P_a = T_a \quad \text{in } \Omega_0, \quad P_c = T_c \quad \text{in } \Omega_0. \quad (13)$$

The quantity  $P_a$  is related to the stress generated by the smooth muscle through the power stroke while  $P_c$  may be thought of as a chemical potential driving the cytosolic calcium ion current.

#### 2.4. Constitutive relations

In this section, we will derive constitutive relations linking state and internal variables to stresses using standard techniques from continuum mechanics. The results may be surprising to some readers, unfamiliar to continuum thermodynamics because chemical potentials become primitive quantities contrary to the classical chemical thermodynamics where they are defined quantities, see Gurtin et al. [7].

We assume that some of the power produced internally during smooth muscle contraction is stored while some of the power is dissipated. The dissipation inequality under isothermal conditions can be written

$$\dot{\psi} \leq \mathbf{P} : \dot{\mathbf{F}} + P_a \dot{\lambda}_a + P_c \dot{\beta}, \quad (14)$$

where  $\psi$  is the free energy and  $\beta = [\text{Ca}^{2+}]$ .

The free energy is taken to be a function of the state variables  $\mathbf{F}$ ,  $\lambda_a$ ,  $\beta$ , and the chemical state of myosin. For convenience, let the fraction of myosin in the four chemical states be given by  $\alpha = [M, M_p, AM_p, AM]^T$ . Since the contraction of smooth muscles introduces anisotropy in the material, the free energy becomes dependent on the fibre vectors  $\mathbf{\Pi}_1$  and  $\mathbf{\Pi}_2$ . In addition, the free energy also depends on the elastic deformation of the cross-bridges, and we take

$$\psi = \psi(\mathbf{C}, \mathbf{C}_e, \lambda_a, \mathbf{\Pi}_1, \mathbf{\Pi}_2, \alpha, \beta), \quad (15)$$

where  $\mathbf{C} = \mathbf{F}^T \mathbf{F}$  and  $\mathbf{C}_e = \mathbf{F}_e^T \mathbf{F}_e = \mathbf{F}_a^{-T} \mathbf{C} \mathbf{F}_a^{-1}$  by Eq. (3). The superscribed  $T$  denotes the transpose of a second-order tensor. Note that  $\mathbf{C}_e$  in Eq. (15) is not a state variable since it depends on  $\mathbf{C}$  and  $\lambda_a$ ; it is merely introduced as a convenient measure of the elastic cross-bridge deformation, see Remark 1.

Equations (14) and (15) give

$$\begin{aligned} \left( \mathbf{P} - 2\mathbf{F} \frac{\partial \psi}{\partial \mathbf{C}} \right) : \dot{\mathbf{F}} - 2\mathbf{F}_e \frac{\partial \psi}{\partial \mathbf{C}_e} : \dot{\mathbf{F}}_e + \left( P_a - \frac{\partial \psi}{\partial \lambda_a} \right) \dot{\lambda}_a \\ - \frac{\partial \psi}{\partial \alpha} \cdot \dot{\alpha} + \left( P_c - \frac{\partial \psi}{\partial \beta} \right) \dot{\beta} \geq 0. \end{aligned} \quad (16)$$

The second term in the above inequality can be rewritten by substituting Eq. (3) for  $\mathbf{F}_e$ :

$$\mathbf{F}_e \frac{\partial \psi}{\partial \mathbf{C}_e} : \dot{\mathbf{F}}_e = \mathbf{F} \mathbf{F}_a^{-1} \frac{\partial \psi}{\partial \mathbf{C}_e} \mathbf{F}_a^{-T} : \dot{\mathbf{F}} - (\mathbf{F} \mathbf{F}_a^{-1})^T (\mathbf{F} \mathbf{F}_a^{-1}) \frac{\partial \psi}{\partial \mathbf{C}_e} \mathbf{F}_a^{-T} : \dot{\mathbf{F}}_a,$$

where it is used that  $\dot{\mathbf{F}}_a^{-1} = -\mathbf{F}_a^{-1} \dot{\mathbf{F}}_a \mathbf{F}_a^{-1}$  [10]. Back-substitution into Eq. (16) gives together with Eq. (8)

$$\begin{aligned} \left( \mathbf{P} - 2\mathbf{F} \frac{\partial \psi}{\partial \mathbf{C}} - 2\mathbf{F} \mathbf{F}_a^{-1} \frac{\partial \psi}{\partial \mathbf{C}_e} \mathbf{F}_a^{-T} \right) : \dot{\mathbf{F}} \\ + \left( P_a - \frac{\partial \psi}{\partial \lambda_a} + 2(\mathbf{F} \mathbf{F}_a^{-1})^T (\mathbf{F} \mathbf{F}_a^{-1}) \frac{\partial \psi}{\partial \mathbf{C}_e} \mathbf{F}_a^{-T} : \frac{\partial \mathbf{F}_a}{\partial \lambda_a} \right) \dot{\lambda}_a \\ - \frac{\partial \psi}{\partial \alpha} \cdot \dot{\alpha} + \left( P_c - \frac{\partial \psi}{\partial \beta} \right) \dot{\beta} \geq 0. \end{aligned} \quad (17)$$

Assume that the first term does not depend on  $\lambda_a$ ,  $\dot{\alpha}$ , or  $\dot{\beta}$ , then

$$\left( \mathbf{P} - 2\mathbf{F} \frac{\partial \psi}{\partial \mathbf{C}} - 2\mathbf{F} \mathbf{F}_a^{-1} \frac{\partial \psi}{\partial \mathbf{C}_e} \mathbf{F}_a^{-T} \right) : \dot{\mathbf{F}} = 0, \quad (18)$$

for all  $\mathbf{F}$  satisfying incompressibility. By taking the time derivative of the incompressibility constraint  $\det \mathbf{F} = 1$ , multiplying the result by an arbitrary multiplier  $p$  and adding to Eq. (18), the constraint on  $\mathbf{F}$  is relaxed and the constitutive relation becomes

$$\mathbf{P} = -p\mathbf{F}^{-T} + 2\mathbf{F} \frac{\partial \psi}{\partial \mathbf{C}} + 2\mathbf{F} \mathbf{F}_a^{-1} \frac{\partial \psi}{\partial \mathbf{C}_e} \mathbf{F}_a^{-T}. \quad (19)$$

The sum of the first and second terms on the right-hand side of Eq. (19) is the standard first Piola-Kirchhoff stress tensor associated with the total deformation  $\mathbf{F}$  for an incompressible material, see Holzapfel [10]. The third term, however, is not a standard term. Its physical interpretation is that of an extra stress associated with an elastic deformation of the cross-bridges.

The additional constraint in the Hai and Murphy model given by Eq. (2) implies that all evolutions of  $\alpha$  must satisfy

$$\mathbf{1} \cdot \alpha = 1, \quad (20)$$

where  $\mathbf{1} = [1, 1, 1, 1]^T$ . By taking the time derivative of Eq. (20) and using an analogous argument as for the incompressibility, it can be concluded that  $\partial\psi/\partial\alpha$  in Eq. (17) can be replaced by  $\partial\psi/\partial\alpha - r\mathbf{1}$ , where  $r$  is an arbitrary multiplier. Finally, assume that the change in  $\beta$  is non-dissipative so the last term in Eq. (17) becomes

$$P_c = \frac{\partial\psi}{\partial\beta}. \quad (21)$$

After back-substitution of Eqs. (19) and (21) into Eq. (17), we arrive at the reduced dissipation inequality

$$\left( P_a - \frac{\partial\psi}{\partial\lambda_a} + 2(\mathbf{F}\mathbf{F}_a^{-1})^T (\mathbf{F}\mathbf{F}_a^{-1}) \frac{\partial\psi}{\partial\mathbf{C}_e} \mathbf{F}_a^{-T} : \frac{\partial\mathbf{F}_a}{\partial\lambda_a} \right) \dot{\lambda}_a - \left( \frac{\partial\psi}{\partial\alpha} - r\mathbf{1} \right) \cdot \dot{\alpha} \geq 0. \quad (22)$$

To satisfy the first term in the inequality for all system changes, we introduce the constitutive relation

$$P_a - \frac{\partial\psi}{\partial\lambda_a} + 2(\mathbf{F}\mathbf{F}_a^{-1})^T (\mathbf{F}\mathbf{F}_a^{-1}) \frac{\partial\psi}{\partial\mathbf{C}_e} \mathbf{F}_a^{-T} : \frac{\partial\mathbf{F}_a}{\partial\lambda_a} = C\dot{\lambda}_a, \quad (23)$$

where  $C \geq 0$  is an arbitrary function. Note that  $P_a$  is equal to the external stress  $T_a$  performing work on the system by Eq. (13)<sup>1</sup>, and hence the energy needed to drive chemical reactions is input to the system through  $P_a$ . For the second term in the inequality, we define the thermodynamic force

$$\mathbf{X} = -\frac{\partial\psi}{\partial\alpha} + r\mathbf{1}. \quad (24)$$

To satisfy Eq. (22) for all evolutions of  $\alpha$ , we assume the constitutive relation

$$\mathbf{X} = \mathbf{A}\dot{\alpha}, \quad (25)$$

where  $\mathbf{A}$  is a square matrix that satisfies

$$\dot{\alpha} \cdot \mathbf{A}\dot{\alpha} \geq 0 \quad (26)$$

for all  $\alpha$ . By equating Eqs. (24) and (25), the evolution law for the chemical state becomes

$$\mathbf{A}\dot{\alpha} = -\frac{\partial\psi}{\partial\alpha} + r\mathbf{1}. \quad (27)$$

This equation describes the change of free energy between the myosin states, where  $\partial\psi/\partial\alpha$  is the driving potential. The matrix  $A$  may depend on any of the state variables but, based on the results in Stålhand et al. [21], we will assume it depends on  $C$  and  $\beta$ .

**Remark 1.** The deformation measure  $C_e$  in Eq. (15) is not an independent variable, as is evident from Eq. (3). Nevertheless, it is sometimes convenient or even necessary to formulate the free energy in a larger space than spanned a minimal set of arguments. For instance, when modelling incompressible materials the strain energy is usually formulated in the right Cauchy-Green stretch tensor  $C$ , which has six components by symmetry. However, the deformation must satisfy  $\det C = 1$  because of incompressibility, which implies that only five of the components are independent. In some cases, e.g., when  $C$  is given by its eigenvalues, it is possible to substitute one component for the others and recover a strain energy given in a minimal set of arguments. In other cases, the strain energy's dependence on the components of  $C$  is too complex to allow for an elimination and then the constraint  $\det C = 1$  is added to the deformation.

### 3. Specialisation of the thermodynamic model

After establishing the general thermodynamical framework of a mechanochemical smooth muscle contraction, the underlying mechanical and chemical phases must be specialised in order to quantify the coupled process.

The free energy is assumed to be additively decomposed in the following way:

$$\psi = \psi_1(C, \mathbf{\Pi}_1, \mathbf{\Pi}_2) + \mathcal{N}(\lambda_a)\psi_2(C_e, \mathbf{\Pi}_1, \mathbf{\Pi}_2, \alpha) + \psi_3(\alpha) + \psi_4(\beta). \quad (28)$$

The first term represents the mechanical energy stored in the passive tissue, mainly comprising of extracellular collagen and elastin, but also intracellular structures in parallel to the cross-bridges are included, e.g. intermediate filaments. Since the principle directions of smooth muscles and collagen fabric are assumed to be co-aligned, their material symmetry will coincide and  $\psi_1$  also becomes dependent on  $\mathbf{\Pi}_1$  and  $\mathbf{\Pi}_2$ .

The second term represents the free energy associated with the actin-myosin interaction.  $\psi_2$  relates to the free energy stored in the cross-bridges (and possibly other intracellular structures in series with the cross-bridges) while  $0 \leq \mathcal{N}(\lambda_a) \leq 1$  is a function that accounts for the filament overlap. The final terms  $\psi_3$  and  $\psi_4$  are purely associated with the energy in the chemical kinetics and the calcium ion concentration, respectively.

By introducing an integrity bases for the arguments  $(C, \mathbf{\Pi}_1, \mathbf{\Pi}_2)$  in  $\psi_1$  and  $(C_e, \mathbf{\Pi}_1, \mathbf{\Pi}_2)$  in  $\psi_2$ , we may replace  $\psi_1$  and  $\psi_2$  in Eq. (28) by  $\psi_1 = \psi_1(I_1, I_4, I_6)$  where

$$I_1 = \text{tr } C, \quad I_4 = \mathbf{\Pi}_1 \cdot C \mathbf{\Pi}_1, \quad \text{and } I_6 = \mathbf{\Pi}_2 \cdot C \mathbf{\Pi}_2, \quad (29)$$

see [11], and  $\psi_2 = \psi_2(J_4, J_6, \alpha)$  where

$$J_4 = \mathbf{\Pi}_1 \cdot C_e \mathbf{\Pi}_1, \quad \text{and } J_6 = \mathbf{\Pi}_2 \cdot C_e \mathbf{\Pi}_2. \quad (30)$$

We assume that collagen and muscle fibres only carry tensile loads [11]. Hence, the invariants  $I_4, I_6, J_4$ , and  $J_6$  contribute to the free energy only when they are greater than

zero. Note that  $I_4$  and  $I_6$  by their definitions may be interpreted as squared stretches for the passive material in the directions of  $\mathbf{\Pi}_1$  and  $\mathbf{\Pi}_2$ , respectively. In analogy,  $J_4$  and  $J_6$  may be interpreted as the squared stretches for the smooth muscle tissue along the same fibre vectors.

### 3.1. Specialisation of the mechanical phase

Take the free energy associated with mechanical deformation of the passive extracellular material to be the strain-energy proposed in Holzapfel et al. [11]

$$\psi_1 = C_p(I_1 - 3) + \frac{c_1}{2c_2} \left( e^{c_2(I_4-1)^2} + e^{c_2(I_6-1)^2} - 2 \right), \quad (31)$$

where  $C_p, c_1, c_2 > 0$  are material constants. The free energy stored in the cross-bridges is taken to be

$$\psi_2 = \frac{2}{3} (E_3\alpha_3 + E_4\alpha_4) \left( J_4^{3/2} + J_6^{3/2} - \frac{3}{2} (J_4 + J_6) + 1 \right), \quad (32)$$

where  $E_3, E_4 \geq 0$  are material constants. The free energy in Eq. (32) is a generalisation of the one-dimensional constitutive relation in Stålhand et al. [21] such that the derivative of  $\psi_2$  with respect to the smooth muscle stretch is linear in the smooth muscle stretch. It is worth noting that the restrictions  $I_4, I_6, J_4, J_6 \geq 0$  render the free energies in Eqs. (31) and (32) polyconvex which implies Legendre-Hadamard ellipticity, see, e.g., Balzani et al. [2].

Following Stålhand et al. [21], take the function  $C$  in Eq. (23) to be

$$C = (f_3\alpha_3 + f_4\alpha_4) \mathcal{N}(\lambda_a), \quad (33)$$

where  $f_3, f_4 \geq 0$  are constants. The thermodynamic force driving smooth muscle contraction must also be specified. To that end, let it be given as in Stålhand et al. [21] and use Eq. (13)<sup>1</sup> to write

$$T_a = P_a = -f_3\alpha_3\nu\mathcal{N}(\lambda_a), \quad (34)$$

where  $\nu$  is a sliding velocity associated with the active force generated by myosin heads sliding over actin, c.f., the friction clutch in Gestrelus and Borgström [6]. Finally, take  $\mathcal{N}(\lambda_a)$  to be the bell-shaped function

$$\mathcal{N}(\lambda_a) = e^{-(\lambda_a - \mu)^2 / (2\xi^2)}, \quad (35)$$

where  $\mu$  is the mean value corresponding to the optimal actin-myosin stretch and  $\xi$  controls the width of the bell-shaped function around  $\mu$ .

### 3.2. Specialisation of the chemical phase

It can be shown that the chemical model proposed by Hai and Murphy [8] is included as a special case in the evolution law (27). By assuming the free energy  $\psi_3$  to

be additively decomposed, Stålhand et al. [21] reformulated Eq. (27) to a system of first-order differential equations,

$$\begin{bmatrix} \dot{\alpha}_1 \\ \dot{\alpha}_2 \\ \dot{\alpha}_3 \\ \dot{\alpha}_4 \end{bmatrix} + \begin{bmatrix} \eta_1 \mathbf{\Gamma}_1 & \eta_2 \mathbf{\Gamma}_2 & \eta_3 \mathbf{\Gamma}_3 & \eta_4 \mathbf{\Gamma}_4 \end{bmatrix} \begin{bmatrix} \alpha_1 \\ \alpha_2 \\ \alpha_3 \\ \alpha_4 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad (36)$$

where  $\mathbf{\Gamma}_i$  ( $i = 1, 2, 3, 4$ ) are column vectors and  $\eta_i$  are functions of the deformation. Take  $\mathbf{\Gamma}_i$  to be equal to the corresponding column vectors in the Hai and Murphy model in Eq. (1), i.e.,

$$\begin{aligned} \mathbf{\Gamma}_1 &= [k_1, -k_1, 0, 0]^T, & \mathbf{\Gamma}_2 &= [-k_2, k_2 + k_3, -k_3, 0]^T, \\ \mathbf{\Gamma}_3 &= [0, -k_4, k_4 + k_5, -k_5]^T, & \mathbf{\Gamma}_4 &= [-k_7, 0, -k_6, k_6 + k_7]^T. \end{aligned} \quad (37)$$

Further, let the functions  $\eta_i$  be bilinear in  $I_4$  and  $I_6$  such that the matrix columns in Eq. (36) become variations around the experimental condition used to derive the Hai and Murphy model, i.e., the matrix is equal to its counterpart in Eq. (1) when  $\eta_i = 1$ . These requirements are satisfied by taking

$$\eta_i = A_i(I_4 - \bar{I}_4) + B_i(I_6 - \bar{I}_6) + 1, \quad (38)$$

where  $\bar{I}_4$  and  $\bar{I}_6$  are the squared experimental stretch in Hai and Murphy [8].

The reaction rates  $k_1$  and  $k_6$  control myosin phosphorylation and are taken to be functions of the total deformation and  $\beta$  while all other reaction rates are assumed constant. The forms of  $k_1$  and  $k_6$  are given by

$$k_1(\beta, I_1) = k_6(\beta, I_1) = \frac{\beta^4}{\beta^4 + \beta_0^4}, \quad (39)$$

where

$$\beta_0 = C_0 + C_1 I_1^{-1}. \quad (40)$$

Equations (39) and (40) are introduced to allow for a three-dimensional dependence on the total deformation. This is motivated by the increased phosphorylation rate observed when the smooth muscle is stretched (c.f., [21] for the one-dimensional case).

Finally, for the calcium-dependent potential  $\psi_4$ , we assume a quadratic dependence on  $\beta$

$$\psi_4 = \frac{1}{2} \beta^2, \quad (41)$$

which is the simplest way to regulate the calcium ion concentration from outside the cell. By substituting  $\psi_4$  in the free-energy function, Eq. (21) gives

$$P_c = \beta. \quad (42)$$

### 3.3. Summary of specialised model

The specialised model comprises of the total stress in Eq. (19), the evolution of the smooth muscle contraction in Eq. (23), and the evolution of the chemical state in Eq. (36). By substitution of Eqs. (31) to (35) and (37) to (42), the following functional relations are obtained:

$$\begin{cases} \mathbf{P} = \mathbf{f}(\mathbf{F}, \lambda_a, \boldsymbol{\alpha}), \\ C\dot{\lambda}_a = g(\mathbf{F}, \lambda_a, \boldsymbol{\alpha}), \\ \dot{\boldsymbol{\alpha}} = \mathbf{K}(\mathbf{F}, \beta)\boldsymbol{\alpha}, \end{cases} \quad (43)$$

where  $\mathbf{f}$  and  $g$  are vector and scalar valued functions, respectively. In the next section, we will choose  $\mathbf{F}$  and  $\beta$  as input and compute  $\mathbf{P}$  as output for a fully coupled uniaxial extension test.

## 4. Uniaxial extension test

In this section we provide an example where the proposed theory is applied to an uniaxial extension test. In particular, this example has the goal to show the specific merits and underlying mechanics of the proposed constitutive framework. Uniaxial extension tests are commonly used in in vitro experiments to determine material properties of various soft tissues, including smooth muscle, see, for example, Arner [1] and Singer et al. [19], and this section can, therefore, also serve as a guide in the planning of such experiments.

### 4.1. Governing equations

Let  $(\mathbf{E}_x, \mathbf{E}_y, \mathbf{E}_z)$  be an orthonormal Cartesian base such that the  $x$ ,  $y$ , and  $z$  directions are parallel to the corresponding circumferential, radial, and axial directions of the artery, respectively, see Fig. 3. Take the collagen fibre families and the smooth muscle cells to be embedded in the  $x-z$  plane and assume that they are symmetrically arranged around the  $x$ -direction with the angle  $\pm\phi$ . The fibre vectors then become

$$\begin{cases} \mathbf{\Pi}_1 = \cos \phi \mathbf{E}_x + \sin \phi \mathbf{E}_z, \\ \mathbf{\Pi}_2 = \cos \phi \mathbf{E}_x - \sin \phi \mathbf{E}_z, \\ \mathbf{\Pi}_3 = \mathbf{E}_y. \end{cases} \quad (44)$$

If the specimen is dissected so that it comprises all three arterial layers, it is necessary to account for the variations in fibre angles and the different material parameters of the individual layers [12]. In the present example, however, we are simulating the experimental protocol presented in Singer et al. [19] where only strips from the media were used. Therefore, we confine ourselves to a one-layer model.

If the artery is assumed to be rotationally symmetric and transmurally homogeneous, there will be no shear when the specimen is stretched in the  $x$ -direction and the deformation gradient can be written

$$\mathbf{F} = \lambda_x \mathbf{E}_x \otimes \mathbf{E}_x + \lambda_y \mathbf{E}_y \otimes \mathbf{E}_y + \lambda_z \mathbf{E}_z \otimes \mathbf{E}_z, \quad (45)$$

where the incompressibility constraint implies that

$$\det \mathbf{F} = \lambda_x \lambda_y \lambda_z = 1.$$

By substituting Eq. (44) in (7) and using that the dual and primal bases are equal in a Cartesian coordinate system, the active contraction tensor becomes

$$\mathbf{F}_a = \lambda_a \mathbf{E}_x \otimes \mathbf{E}_x + \lambda_a^{-2} \mathbf{E}_y \otimes \mathbf{E}_y + \lambda_a \mathbf{E}_z \otimes \mathbf{E}_z \quad (46)$$

and Eq. (9) gives

$$\frac{\partial \mathbf{F}_a}{\partial \lambda_a} = \mathbf{E}_x \otimes \mathbf{E}_x - 2\lambda_a^{-3} \mathbf{E}_y \otimes \mathbf{E}_y + \mathbf{E}_z \otimes \mathbf{E}_z. \quad (47)$$

Note that  $\mathbf{F}_a$  does not depend on the angle  $\phi$ . This is a consequence of the assumption that  $\lambda_1 = \lambda_2$ , see Remark 2. From Eq. (29), we obtain the following invariants

$$I_1 = \lambda_x^2 + \frac{1}{\lambda_x^2 \lambda_z^2} + \lambda_z^2, \quad I_4 = I_6 = \lambda_x^2 \cos^2 \phi + \frac{1}{\lambda_x^2 \lambda_z^2} \sin^2 \phi. \quad (48)$$

By Eqs. (3) and (44) to (46), and the definition of  $\mathbf{C}_e$ , Eq. (30) gives

$$J_4 = J_6 = \frac{\lambda_x^2}{\lambda_a^2} \cos^2 \phi + \frac{1}{\lambda_x^2 \lambda_z^2 \lambda_a^2} \sin^2 \phi.$$

Consider a situation with homogeneous stress and strain fields in the centre of the specimen. After substitution of the constitutive relation (19) into the equilibrium equation (12)<sup>1</sup>, we arrive at the following conditions for the Lagrange multiplier  $p$ , expressed in Cartesian coordinates,

$$\frac{\partial p}{\partial x} = \frac{\partial p}{\partial y} = \frac{\partial p}{\partial z} = 0,$$

since the strain field is homogeneous. This constraint implies that  $p = p(x, y, z)$  equals a constant that must be determined from the boundary conditions.

In order to specify the boundary conditions, we assume the height and the thickness of the considered specimen to be  $2b$  and  $2c$ , respectively. Perpendicular to the  $x$ -direction (i.e., the stretch direction) the surfaces are traction free and the boundary conditions read:

$$P_{yx} = P_{yy} = P_{yz} = 0, \quad \text{at } y = \pm c, \quad (49)$$

$$P_{zx} = P_{zy} = P_{zz} = 0, \quad \text{at } z = \pm b. \quad (50)$$

The arbitrary multiplier  $p$  is computed by substituting Eqs. (44) to (46) together with (28) to (32) into the constitutive relation (19) and applying the boundary condition in  $P_{yy} = 0$ . The result is

$$p = 2\lambda_z^2 \frac{\partial \psi}{\partial I_1}. \quad (51)$$

After back-substitution of (51) into (19), the other two non-trivial components of the stress tensor become

$$P_{xx} = 2 \left[ \left( \lambda_x - \frac{\lambda_z^2}{\lambda_x} \right) \frac{\partial \psi}{\partial I_1} + \lambda_x \cos^2 \phi \left( \frac{\partial \psi}{\partial I_4} + \frac{\partial \psi}{\partial I_6} \right) + \mathcal{N}(\lambda_a) \frac{\lambda_x}{\lambda_a^2} \cos^2 \phi \left( \frac{\partial \psi}{\partial J_4} + \frac{\partial \psi}{\partial J_6} \right) \right] \quad (52)$$

and

$$P_{zz} = 2 \left[ \left( \frac{1}{\lambda_x \lambda_z} - \lambda_x \lambda_z^3 \right) \frac{\partial \psi}{\partial I_1} + \frac{1}{\lambda_x \lambda_z} \sin^2 \phi \left( \frac{\partial \psi}{\partial I_4} + \frac{\partial \psi}{\partial I_6} \right) + \frac{\mathcal{N}(\lambda_a)}{\lambda_x \lambda_z \lambda_a^2} \sin^2 \phi \left( \frac{\partial \psi}{\partial J_4} + \frac{\partial \psi}{\partial J_6} \right) \right]. \quad (53)$$

The latter equation must equal zero by Eq. (49)<sup>2</sup> and constitutes a nonlinear equation from which  $\lambda_z$  can be solved given  $\lambda_x$  and  $\lambda_a$ .

The active contraction,  $\lambda_a$ , is computed by substituting Eqs. (44) to (47) together with (28) to (35) in the evolution law (23), i.e.,

$$C\lambda_a = P_a - \frac{\partial \mathcal{N}(\lambda_a)}{\lambda_a} \psi_2 + 2\mathcal{N}(\lambda_a) \left( \frac{\lambda_x^2}{\lambda_a^3} \cos^2 \phi + \frac{1}{\lambda_x^2 \lambda_z^2 \lambda_a^3} \sin^2 \phi \right) \left( \frac{\partial \psi_2}{\partial J_4} + \frac{\partial \psi_2}{\partial J_6} \right). \quad (54)$$

Finally, the chemical evolution law, given by Eqs. (36) to (40), is unchanged but Eq. (38) may be rewritten as

$$\eta_k = D_k(I_4 - \bar{I}_4) + 1, \quad (55)$$

where  $D_k = A_k + B_k$  since  $I_4 = I_6$  by Eq. (48).

The complete set of governing equations for smooth muscle contraction under a uniaxial extension test constitutes a coupled system of differential algebraic equations (DAEs) which can be summarised as:

$$\begin{cases} P_{xx} = \mathcal{F}(\lambda_x, \lambda_z, \lambda_a, \boldsymbol{\alpha}), \\ 0 = \mathcal{G}(\lambda_x, \lambda_z, \lambda_a, \boldsymbol{\alpha}), \\ C\lambda_a = \mathcal{H}(t, \lambda_x, \lambda_z, \lambda_a, \boldsymbol{\alpha}), \\ \dot{\boldsymbol{\alpha}} = \mathbf{K}(t, \lambda_x, \lambda_z, \beta) \boldsymbol{\alpha}, \end{cases} \quad (56)$$

where  $t$  is the time, and  $\mathcal{F}$ ,  $\mathcal{G}$ , and  $\mathcal{H}$  are the nonlinear functions at the right-hand side of Eqs. (52), (53), and (54), respectively.

The DAEs in (56) determines the problem up to a set of unknown model parameters:  $C_p$ ,  $c_1$ , and  $c_2$  for the passive material,  $E_3$ ,  $E_4$ ,  $f_3$ ,  $f_4$ ,  $\nu$ ,  $\mu$ , and  $\xi$  for the active contraction, and  $C_0$ ,  $C_1$ ,  $D_1$ ,  $D_2$ ,  $D_3$ , and  $D_4$  for the chemical evolution. These parameters need to be determined by calibrating the model to experimental data.

**Remark 2.** Substituting the vectors  $\mathbf{\Pi}_1$ ,  $\mathbf{\Pi}_2$ ,  $\mathbf{\Pi}_3$ , and their dual bases into Eq. (4), the active contraction tensor reads:

$$\begin{aligned} \mathbf{F}_a = & (\lambda_1 + \lambda_3)\mathbf{E}_x \otimes \mathbf{E}_x + \frac{(\lambda_1 - \lambda_3)\cos\phi}{2\sin\phi}\mathbf{E}_x \otimes \mathbf{E}_z \\ & + \lambda_2\mathbf{E}_y \otimes \mathbf{E}_y + \frac{(\lambda_1 - \lambda_3)\sin\phi}{2\cos\phi}\mathbf{E}_z \otimes \mathbf{E}_x + (\lambda_1 + \lambda_3)\mathbf{E}_z \otimes \mathbf{E}_z. \end{aligned}$$

The tensor depends on  $\phi$  only through the off-diagonal terms. Taking  $\lambda_1 = \lambda_3 = \lambda_a/2$  the off-diagonal terms cancel and by using Eq. (5), we arrive at Eq. (46).

**Remark 3.** For an incompressible, isotropic and hyperelastic material in simple tension, the stress  $P_{zz}$  in Eq. (53) must equal zero [10]. That this holds true can be realised in the following way: ignore the second and third terms associated with the anisotropy and use the incompressibility to substitute  $\lambda_y$  for  $\lambda_x\lambda_z$ . Equation (53) then becomes  $P_{zz} = (\lambda_y - \lambda_y^{-1}\lambda_z^2)\partial\psi/\partial I_1$ . For the isotropic case,  $\lambda_y = \lambda_z$  and  $P_{zz} \equiv 0$ .

#### 4.2. Parameter study

The unknown parameters listed in the previous subsection are best identified from experiments. Since Eq. (56) is a coupled system of nonlinear time-dependent DAEs, any parameter identification process is potentially problematic and likely to suffer convergence issues. The experiment should, therefore, be tailored to the theory presented to minimise such problems. To the best of the authors' knowledge, no such experiments are yet reported and we, therefore, restrict this example to a parameter study.

Some of the parameters listed in the previous subsection can be estimated from the literature while others are studied for a range of values, see Tables 1 and 2 for a summary.

The parameters  $C_p$ ,  $c_1$ ,  $c_2$ , and  $\phi$  are chosen to obtain reasonable values for the passive stress compared to the values reported in Singer et al. [19]. These parameters are also within the range reported for different arteries, see, e.g., Holzapfel et al. [12].

The chemical evolution parameters  $C_0$ ,  $C_1$ , and  $D_1$  to  $D_4$  are taken from Stålhand et al. [21]. Since these parameters are identified from a one-dimensional experiment, the values must be scaled. To that end, take the chemical evolution to be equal to its counterpart in [21] for the undeformed specimen, i.e.,  $\lambda_x = \lambda_z = 1$ . By incompressibility the first invariant becomes  $I_1 = 3$  for the undeformed specimen. By comparing the two chemical evolutions, it is concluded that  $C_0$  must equal the value in [21] while  $C_1$  must be multiplied by a factor three. For the parameters  $D_k$  ( $k = 1, 2, 3, 4$ ) we use that  $I_4$  ( $= I_6$ ) is the squared fibre stress  $\lambda_f$  and Eq. (55) can be rewritten as  $\eta_k = D_k(I_4 - \bar{I}_4) + 1 = D_k(\lambda_f^2 - \bar{\lambda}^2) + 1 = D_k(\lambda_f + \bar{\lambda})(\lambda_f - \bar{\lambda}) + 1$ , where  $\bar{\lambda} = 1.12$  is the stretch in the experiments by Hai and Murphy [8], see Stålhand et al. [21]. By comparing to the expressions for  $\eta_k$  in [21], it is concluded that the parameters  $D_1$  to  $D_4$  should be divided by the factor  $\lambda_f + 1.12$  where  $\lambda_f$  is computed to be 1 by substituting  $\lambda_x = \lambda_z = 1$  in Eq. (48)<sup>2</sup> and taking the square root.

The parameters associated with the myosin heads,  $E_3$ ,  $E_4$ ,  $f_3$ , and  $f_4$ , must also be specified. Following Rembold and Murphy [18], it is assumed that the latch state is mechanically identical to the phosphorylated cross-bridges, implying that  $E_3 = E_4$  and

$f_3 = f_4$ . Reasonable values for these parameters were obtained manually by a trial-and-error process. In addition, the active stress also depends on the filament overlap, i.e.,  $\xi$  and  $\mu$  controlling the width and location of the optimal stretch, respectively, in Eq. (35). To get a stress response similar to that in Singer et al. [19], the parameters are set to  $\xi = 1/4$  and  $\mu = 1.4$ , the latter suggested by Rachev and Hayashi [17].

To study the behaviour of the model, the uniaxial stretch  $\lambda_x$  and the calcium ion concentration  $\beta$  are taken as input and the axial stress  $P_{xx}$  is considered as response. A protocol similar to the one in Singer et al. [19] was simulated by, first, computing the steady-state solution after 30 minutes at constant stretch  $\lambda_x = \mu$  using the initial conditions  $\lambda_a(0) = 1$  for the active contraction, and  $\alpha_1(0) = 0.6099$ ,  $\alpha_2(0) = 0.0476$ ,  $\alpha_3(0) = 0.0627$ , and  $\alpha_4(0) = 0.2798$  for the chemical evolution (from [8]), and  $\lambda_z(0) = 1.0$ . Since the initial conditions must satisfy Eq. (56), these values are only an initial guess used by the differential algebraic equation solver to compute a consistent initial condition, see Shampine et al. [20]. After the steady-state is reached, the axial stretch  $\lambda_x$  increases linearly from 1.4 to 1.6 in 280 msec and is kept constant for 140 msec. All calculations were made using Matlab (The MathWorks, Natick, Massachusetts, US).

In what follows, we take the passive response to be the situation when only the free energy  $\psi_1$  is considered, and, conversely, the active response to be the situation when  $\psi_1$  is set to zero. The left plot in Fig. 4 shows the stretch protocol (dashed line) and the corresponding passive response (solid line) for the parameters in Tables 1 and 2. The right plot shows the active stress response as a function of time and calcium ion concentration. The active stress increases with  $[\text{Ca}^{2+}]$  in the beginning, but, above approximately 2 mmol, the stress response is saturated. Note that the stress dependence is plotted as a function of time for convenience. For the linearly increasing part of the stretch protocol (0-0.28 s) there is a one-to-one correspondence between time and stretch. This will be used in the sequel when we refer to the model's response to an applied stretch.

Figure 5 shows the effect of altering the cross-bridge stiffness  $E_3$  and the friction-related parameter  $f_3$ . The left plot shows the stress response when  $E_3$  takes the values  $1 \cdot 10^7$ ,  $1 \cdot 10^8$ , and  $1 \cdot 10^9$ , and the right plot shows the response when  $f_3$  takes the values  $1 \cdot 10^5$ ,  $5 \cdot 10^5$ , and  $1 \cdot 10^6$ . The response is also plotted at two different  $[\text{Ca}^{2+}]$ : 0.9 mmol and 2.1 mmol. An increasing  $E_3$  causes the peak stress to raise. In addition, the slope of the active stress at the onset of the stretch protocol is also increased with  $E_3$  and the peak stress position is shifted to the left. This is true for both  $[\text{Ca}^{2+}]$ , but the effect is more pronounced at a higher concentration. An increase in the friction-related parameter  $f_3$  shows a similar behaviour, but the peak stress is higher. Both plots also show the mechanochemical coupling in smooth muscle contraction: at low  $[\text{Ca}^{2+}]$ , the active stress is relatively constant in contrast to higher  $[\text{Ca}^{2+}]$  where it drops off after the peak value.

The left plot in Fig. 6 shows the phosphorylation constant  $k_1$  as a function of the stretch protocol and calcium ion concentration for the parameters in Table 2. Once again, the interaction between the mechanical and chemical phases is evident by the shift of the inflection point towards a lower stretch as the  $[\text{Ca}^{2+}]$  increases. The right plot in Fig. 6 shows the fraction of myosin in the two force generating states  $AM_p$  and  $AM$  at different calcium ion concentrations. At low  $[\text{Ca}^{2+}]$  the  $AM$  state, or latch state, is the predominant force generating state, but as  $[\text{Ca}^{2+}]$  increases, the  $AM_p$  state grad-

ually becomes dominant. Note also the transition line between the  $AM$  and  $AM_p$  states (where the two surfaces intersect) is shifted towards lower  $[Ca^{2+}]$  when the stretch increases.

In Fig. 7 the active stress response with respect to the sliding velocity  $\nu$  is plotted using the values 0.01, 0.5, and 1.0 m/s. The lower and upper curve groups correspond to the calcium ion concentrations 0.9 mmol and 2.1 mmol, respectively. As in Fig. 5, the increase in  $\nu$  leads to an increase in the slope at the onset of the stretch protocol and a higher active stress. In contrast to  $E_3$ , however, the peak stress is shifted to the right when  $\nu$  increases.

Finally, the active contraction  $\lambda_a$  is plotted as a function of the stretch protocol and calcium ion concentration for the velocities  $\nu$  0.01 and 1.0 m/s in Fig. 8. The two cases have a similar response for the unstimulated muscle, i.e.  $[Ca^{2+}]$  close to zero. At  $\nu = 0.01$  the response is almost invariant of the  $[Ca^{2+}]$  which is in contrast to  $\nu = 1$  where the active contraction initially decreases and then a very small decline can be seen.

## 5. Discussion

The aim of this paper was to present a continuum mechanical framework for three-dimensional smooth muscle contraction. The proposed coupled model considers both the mechanical and the chemical phase associated with the contraction, as well as the interaction between them. The model is valid for finite strains and is thermodynamically consistent, meaning that the second law of thermodynamics is satisfied for any thermodynamic process.

First, let us take a look at the parameter study. The parameter study is intended to show the behaviour of the proposed model. Since the primary concern is the response of the model and not the exact values, the parameters listed in Table 2 are chosen by hand such that the models response is reasonable when compared to Singer et al. [19]. It must, therefore, be kept in mind that the results are comparable to [19] only from a qualitative point of view. If the desire is to validate the model, the parameters must be identified from tailored experiments, as discussed above.

The active stress in Fig. 5 is qualitatively comparable to the results reported in Singer et al. [19]. The stress dependence on the  $[Ca^{2+}]$  may be explained by the chemical evolution. At low  $[Ca^{2+}]$ , the phosphorylation rates  $k_1$  and  $k_6$  become significant only at the end of the stretch protocol (see left plot in Fig. 6) and the chemical evolution is, therefore, governed by the other constants in the Hai and Murphy model. These constants favour a motion towards the attached states initially, and, in particular, the  $AM$  state. As the  $[Ca^{2+}]$  increases, the phosphorylation rates  $k_1$  and  $k_6$  become significant earlier and drives the evolution towards the  $AM_p$  state at the expense of the  $AM$  state. The active stress is dependent on the sum of the cross-bridges in the  $AM_p$  and  $AM$  states, as given in Eq. (32). The fraction sum is obtained by summing the two surfaces in Fig. 6, and it turns out that the sum is not constant but decreases with the external stretch, particularly at higher  $[Ca^{2+}]$ . This is likely to be the causes for the drop in the active stress seen after the peak value.

When the sliding velocity  $\nu$  is increased at the higher  $[Ca^{2+}]$  in Fig. 7, the peak stress is shifted to the right as opposed to the case when  $E_3$  is increased. Note that

this tendency only occurs at the higher concentration, at the lower concentration the peak value remains almost constant. The explanation of this behaviour is related to the response of the active contraction parameter  $\lambda_a$ . When  $\nu$  is at the lower value 0.01,  $\lambda_a$  is close to invariant with respect to the  $[\text{Ca}^{2+}]$ . As  $\nu$  increases to 1.0, the higher  $[\text{Ca}^{2+}]$  gives a reduction in  $\lambda_a$ , c.f., the two plots in Fig. 8. The major effect on the active generation, i.e., the third term in Eq. (52), is that the strain energy derivative term becomes a linear function of the applied stretch after initial increase. The linear part then causes the rightward shift of the peak stress.

In a previous study by the authors Stålhand et al. [21], the one-dimensional smooth muscle contraction is studied. Therein, the evolution for  $\alpha$ , i.e., the counterpart to Eq. (43)<sup>3</sup>, only depends on the external stretch. This makes it possible to solve  $\alpha$  independently of the stress and the active contraction  $\lambda_a$ . In contrast to that case, this is not possible for the example analysed in this work, even though the loading protocol is one-dimensional in a uniaxial test. The boundary condition  $P_{zz} = 0$  at  $y = \pm b$  is a constraint which must be satisfied for all  $\lambda_x$ . Since the problem is three-dimensional and the constraint depends on  $\lambda_a$ , the model becomes a fully coupled system and the differential algebraic system must be solved simultaneously.

An appealing feature of the presented framework is the way the filament overlap is included in the free-energy function in Eq. (28). By introducing the filament overlap as a function  $\mathcal{N}(\lambda_a)$  in the free energy, the active stress becomes a natural result of the derivation. This in contrast to other studies where this dependence is introduced in an *ad hoc* manner by multiplying the stress with a function similar to  $\mathcal{N}$ , see, e.g., Rachev and Hayashi [17] and Zulliger et al. [25]. For further discussion, see Stålhand et al. [21].

It is generally accepted that the active stress generation in smooth muscles is dependent on the applied stretch and that the maximum stress occurs when the filaments completely overlap. From the third term in Eq. (52) it is clear that the effect of filament overlap relates to  $\lambda_a$  rather than to the applied stretch  $\lambda_x$ . This is in contrast to the studies by Rachev and Hayashi [17] and Zulliger et al. [25] where it is assumed that the overlap is given directly as a function of the applied stretch  $\lambda_x$ . This implies that the location of the maximum stress is invariant of the  $[\text{Ca}^{2+}]$ . In the left plot of Fig. 5 the location of the maximum stress for the solid curve moves from about 0.085 s to 0.102 s when the  $[\text{Ca}^{2+}]$  increases from 0.9 mmol to 2.1 mmol.

## 6. Conclusion

A three-dimensional mechanochemical model was developed to capture the active stress generation due to smooth muscle contraction. A general thermodynamic model was specialized by proposing an appropriate form of the free energy, the mechanical phase, and by using a well-established model for the chemical kinetics for smooth muscle contraction, the chemical phase. In summary, the thermodynamic model is described by the total stress, the evolution of the smooth muscle contraction and the evolution of the chemical state. A uniaxial extension test was finally worked through in detail arriving at a set of coupled and time-dependent differential equations; finally parameter studies were performed using Matlab. This example has shown that the model inevitably requires a computational mechanics approach, and computational methods

such as finite element methods are important to provide more realistic simulations with more complex boundary conditions. The proposed three-dimensional constitutive law used in combination with an appropriate finite element approach has the potential, for example, to realistically predict the physiological function of arteries including the muscular tone. Naturally, computational models need to prove both their effectiveness and accuracy, in particular numerical results need to agree well with the experimental data from which we require more.

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Figure 1: Schematic picture for the evolution model proposed by Hai and Murphy [8].  $M$ ,  $M_p$ ,  $AM_p$ , and  $AM$  represent the four states for the myosin in smooth muscle and  $k_1$  to  $k_7$  are reaction rates.

Figure 2: Schematic picture of the deformation. The tangent vectors  $\mathbf{\Pi}_i$  ( $i = 1, 2, 3$ ) at point  $X$  in the unstressed reference configuration  $\Omega_0$  are mapped onto their own directions by the active contraction  $\mathbf{F}_a$ , and the new vectors become  $\lambda_i \mathbf{\Pi}_i$  ( $i = 1, 2, 3$ ). Since  $\mathbf{F}_a$  is not generally related to any global deformation, the active contraction may deform adjacent parts of  $\Omega_0$  such that their union does not form a compatible region, as indicated by the mapping of the small squares to the left in the  $\Omega_0$  configuration. The elastic deformation  $\mathbf{F}_e$  then restores the compatibility such that  $\Omega$  becomes a compatible configuration. The lower picture describes the orientation of the smooth muscle cell (SMC) families in the reference configuration.

Figure 3: Orientation of the Cartesian base in the numerical example.  $r$ ,  $\theta$  and  $z$  correspond to the radial, circumferential and axial directions, respectively.

Figure 4: Stretch protocol (dashed line) and corresponding passive stress response (solid line), left figure; active stress response as a function of time and calcium ion concentration, right figure.

Figure 5: Active stress for different cross-bridge stiffness  $E_3$  and calcium ion concentrations (left figure). The curves represent  $E_3$  equal to  $1 \cdot 10^7$  (dashed),  $1 \cdot 10^8$  (solid) and  $1 \cdot 10^9$  (dashed-dotted). The lower group is for a calcium ion concentration  $\beta = 0.9$  mmol and the upper group is for  $\beta = 2.1$  mmol. Active stress for different friction-related parameters  $f_3$  parameters and calcium ion concentrations (right figure). Curves represent  $f_3$  equal to  $1 \cdot 10^5$  (dashed),  $5 \cdot 10^5$  (solid) and  $1 \cdot 10^6$  (dashed-dotted). The lower curves are for a calcium ion concentration  $\beta = 0.9$  mmol and the upper curves are for  $\beta = 2.1$  mmol.

Figure 6: Phosphorylation rate constant  $k_1$  as a function of time and calcium ion concentration (left figure). Fractions of  $AM_p$  and  $AM$  as a function of time and calcium ion level (right figure).  $AM_p$  is the upper surface up until approximately 0.28 s and thereafter becomes the lower surface, and conversely for  $AM$ .

Figure 7: Active stress at  $\nu$  equal to 0.01 (solid), 0.5 (dashed-dotted), and 1.0 m/s (dotted). The upper group corresponds to a calcium ion concentration 2.1 mmol and the lower group to 0.9 mmol.

Figure 8: The active contraction  $\lambda_a$  as a function of time and calcium ion concentration for  $\nu = 0.01$  (left) and  $\nu = 1$  (right).

	<i>parameter</i>	<i>value</i>	<i>(unit)</i>
<i>passive response</i>	$C_p$	5000	(Pa)
	$c_1$	3000	(Pa)
	$c_2$	1.5	(-)
	$\phi$	20.0	(deg)
<i>active response</i>	$\xi$	0.25	(-)
	$\mu$	1.40	(-)
	$C_0$	-13.723	(mmol)
	$C_1$	59.421	(mmol)
	$\bar{I}_4 = \bar{I}_6$	1.2544	(-)
	$D_1$	0.976	(-)
	$D_2$	-1.551	(-)
	$D_3$	-0.823	(-)
	$D_4$	0.467	(-)

Table 1: Parameters fixated in the numerical example.

<i>parameter</i>	<i>values</i>	<i>(unit)</i>
$E_3, E_4$	$1 \cdot 10^7, 1 \cdot 10^8, 1 \cdot 10^9$	(Pa)
$f_3, f_4$	$1 \cdot 10^5, 5 \cdot 10^5, 1 \cdot 10^6$	(Pa)
$\nu$	0.01, 0.5, 1.0	(m/s)

Table 2: Parameters varied in the numerical example.