Smooth muscle contraction: Mechanochemical formulation for homogeneous finite strains

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Abstract

Chemical kinetics of smooth muscle contraction affect mechanical properties of organs that function under finite strains. In an effort to gain further insight into organ physiology, we formulate a mechanochemical finite strain model by considering the interaction between mechanical and biochemical components of cell function during activation. We propose a new constitutive framework and use a mechanochemical device that consists of two parallel elements: (i) spring for the cell stiffness; (ii) contractile element for the sarcomere. We use a multiplicative decomposition of cell elongation into filament contraction and cross-bridge deformation, and suggest that the free energy be a function of stretches, four variables (free unphosphorylated myosin, phosphorylated cross-bridges, phosphorylated and dephosphorylated cross-bridges attached to actin), chemical state variable driven by Ca²⁺-concentration, and temperature. The derived constitutive laws are thermodynamically consistent. Assuming isothermal conditions, we specialize the mechanical phase such that we recover the linear model of Yang et al. [2003a. The myogenic response in isolated rat cerebrovascular arteries: smooth muscle cell. Med. Eng. Phys. 25, 691–709]. The chemical phase is also specialized so that the linearized chemical evolution law leads to the four-state model of Hai and Murphy [1988. Cross-bridge phosphorylation and regulation of latch state in smooth muscle. Am. J. Physiol. 254, C99–C106]. One numerical example shows typical mechanochemical effects and the efficiency of the proposed approach. We discuss related parameter identification, and illustrate the dependence of muscle contraction (Ca²⁺-concentration) on active stress and related stretch. Mechanochemical models of this kind serve the mathematical basis for analyzing coupled processes such as the dependency of tissue properties on the chemical kinetics of smooth muscle.

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1. Introduction

Smooth muscle cells are spindle-shaped contractile elements present in, for example, walls of hollow organs including the vasculature, the gastrointestinal tract, the iris of the eye and many other structures in which contraction is needed. Smooth muscle contraction is caused by the sliding of myosin and actin fibers over each other, for which hydrolysis of ATP is the energy source. Smooth muscle contraction can be initiated by, for example, mechanical, electrical, neural and humoral agents. A common method of achieving contraction of smooth muscle cells in, for example, (excised) arteries is to put them in a solution of KCl or norepinephrine with an appropriate concentration.

Several factors may control smooth muscle contraction/relaxation including local concentrations of O₂, CO₂, NO, PGI₂ etc., and it is the smooth muscle contraction that alters the macroscopic mechanical properties of organs. Subsequently, some examples from arterial wall mechanics are briefly mentioned. For example, opening angles measured in aortas change with smooth muscle contraction and relaxation (Matsumoto and Hayashi, 1996; Zeller and Skalak, 1998), and the local stiffness of vascular smooth muscle (VSM) cells increases significantly under contraction administrated by norepinephrine (see the book chapter by Hayashi, 2003). Furthermore, it is known that arteries can change their radii significantly due to smooth muscle cell contraction/relaxation. For example, the study by Canfield and Dobrin (1987) on dog carotids showed a difference in circumferential strain of about 35% at 100 mm Hg transmural pressure between maximal contraction with norepinephrine and the relaxed state. The seminal works of Rachev and Hayashi (1999), and Humphrey and Wilson (2003) pointed out that a model that considers smooth muscle activation under physiological conditions in addition to residual stress further reduces the computed transmural stress gradient in an arterial wall leading to a near uniform stress distribution.

1.1. Motivation

One essential goal in biophysics, biomechanics and mechanobiology is concerned with the modelling of the inter-relation between physical, mechanical and biochemical processes. One particular aim is to quantify the mechanical environment in which cells and matrix function in health and disease. Coupled constitutive models, when designed within the context of associated comprehensive experimental data for tissue and cellular structures, serve then as an important basis for computational (finite element) models, which offer the potential for realistically predicting physiological structural and functional interactions. An appropriately developed model may provide an ideal tool that enables us to predict the outcome of varying any parameter, and to provide information that would otherwise be difficult to obtain from experiments. Although several experimental studies have pointed to the importance of smooth muscle contraction there have been surprisingly few attempts to provide detailed quantification and related mechanochemical models.

One well-known constitutive model for arteries, which incorporates the active state (smooth muscle contraction) in form of an active stress term, was proposed by Rachev and Hayashi (1999). Therein the active stress depends on an activation function, and, in particular, on the circumferential stretches at which smooth
muscle activation is maximum or zero. Another constitutive model, more recently proposed by Zulliger et al. (2004), is based on a pseudo strain-energy function that extends the model of Holzapfel et al. (2000) by including the effects of the smooth muscle tone. The rather ad hoc additional term in the pseudo strain-energy function depends on the cross-sectional area fraction of VSM, the level of VSM tone, the range of stretch at which the VSM develops maximal force under isometric contraction, the circumferential stretch of the VSM when the artery is in its maximally contracted state, and an elastic modulus. An explicit connection to the $\text{Ca}^{2+}$-concentration was not provided. Although both models mentioned are phenomenologically-based and do not involve the underlying kinetic for cross-bridge interaction with the thin filament in smooth muscles, they have contributed to our current level of understanding of the effects of smooth muscle contraction on mechanical responses in arteries. A different but promising modelling approach was proposed in Yang et al. (2003a, b). Since one part of the present paper is based on their muscle activation model, details of it are included throughout this work. Biochemistry has yet focused little attention to the influence of mechanical quantities on chemical reactions, while continuum mechanics in cell and tissue physiology has likewise focused little attention on reaction kinetics (see the recent volume by Holzapfel and Ogden, 2006). Hence, there is clearly a need to develop a continuum model that incorporates the related chemical kinetics of smooth muscle contraction and which is suitable to use for a whole organ. This is one major aim of the present work. A mechanochemical constitutive model would allow the development of a better theory of the human circulatory system and the autoregulation of the vasculature, for studying the evolution of, for example, tissue properties as functions of the kinetic processes within the cell gaining further insight into the effect of abnormal contractility of smooth muscle cell on diseases such as asthma and hypertension.

1.2. Background

One of the cornerstones in this paper is a chemical state model for smooth muscles proposed by Hai and Murphy (1988). Using fast kinetic data on phosphorylation in smooth muscles, they developed a model for the kinetics of myosin phosphorylation and stress development. The model accounts for the unique ability of smooth muscles to develop and maintain a steady-state stress at low levels of myosin phosphorylation and at low cross-bridge cycling rates. This feature is called a latch state and is physiologically important since it allows for a basal tone at low energy cost.

The seminal model of Hai and Murphy (1988) consists of four variables, subsequently called ‘species’: free unphosphorylated myosin ($M$), phosphorylated cross-bridges ($M_p$), phosphorylated cross-bridges attached to actin ($AM_p$), and dephosphorylated cross-bridges attached to actin ($AM$). The last state corresponds to the latch state, and its existence is postulated by Hai and Murphy based on experimental data. The four species represent different functional states of a smooth muscle, and the states are connected through seven rates (see Fig. 1). The constants $k_1$ and $k_5$ are the rates for phosphorylation of myosin, $M$ to $M_p$ and $AM$ to $AM_p$, respectively, while $k_2$ and $k_4$ are the rate constants for the dephosphorylation of myosin, $M_p$ to $M$ and $AM_p$ to $AM$, respectively. The constants $k_3$ and $k_4$ are the rates representing attachment and detachment of the fast cycling cross-bridges, respectively. Finally, $k_7$ is the rate constant for latch-bridge detachment. Using these seven constants, the kinetic state model is given by a coupled system of first-order

![Fig. 1. Schematic picture of the four species model proposed by Hai and Murphy (1988). $M$, $M_p$, $AM_p$, and $AM$ are the chemical states, and $k_1$ to $k_7$ are the rate constants, as explained in the text.](image-url)
differential equations:
\[
\begin{align*}
\frac{d}{dt} & \begin{pmatrix} M \\ M_p \\ AM_p \\ AM \end{pmatrix} = \\
& \begin{pmatrix} -k_1 & k_2 & 0 & k_7 \\
 0 & -k_2 - k_3 & k_4 & 0 \\
 0 & k_3 & -k_4 - k_5 & k_6 \\
 0 & 0 & k_5 & -k_6 - k_7 \end{pmatrix} \\
& \begin{pmatrix} M \\ M_p \\ AM_p \\ AM \end{pmatrix}
\end{align*}
\]

with the additional constraint \(M + M_p + AM_p + AM = 1\). This constraint implies that the sum of the fractions \(M, M_p, AM_p,\) and \(AM\) must remain constant. In addition to the constraint, the model also uses two further assumptions. First, the rates \(k_1\) and \(k_6\) are regulated by the calcium ion concentration while all other rates in the matrix are constants. The matrix is henceforth referred to as the (Hai and Murphy) \(K\)-matrix for simplicity. Second, the reaction \(AM \rightarrow A + M\) is irreversible, i.e., cross-bridges cannot attach to actin and form force generating states unless they are first phosphorylated. The recent model of Hai and Kim (2005) extends the four-state law of Hai and Murphy (1988) by the addition of an ultra-slow cross-bridge cycle, which has lower cycling rates. Their results suggest that thin-filament-based regulatory proteins may function as tuners of actomyosin ATPase activity. This would allow a smooth muscle cell to have two discrete cross-bridge cycles.

The other cornerstone for the present paper is a more recent model of Yang and co-workers (see Yang et al., 2003a, b). They proposed an integrated model for smooth muscle activation consisting of two subsystems: one electrochemical and one mechanochemical. The electrochemical subsystem is not considered herein, and the interested reader is referred to the original work of Yang et al. (2003a). The mechanochemical subsystem has much the same structure as in our model, coupling the chemical state model of Hai and Murphy (1988) to a mechanical model. The difference is that the coupling in Yang et al. (2003a, b) is intuitively stated, whereas it is a result of the derivation in our model. A crucial difference is that our approach reveals an additional term in the active stress generation that is not included in the study of Yang et al. (2003a, b). Moreover, the model proposed herein is applicable to finite strains, which is the appropriate kinematics for soft biological tissues such as blood vessels and myocardial tissue.

2. General thermodynamic model

Let the smooth muscle cell consist of two parallel elements: a spring representing the cell stiffness, and a contractile element representing the sarcomere. Consider a soft tissue material in a uniform state and of unit smooth muscle cell length. Let it be the reference configuration of the material and denote it by \(B_0\). The spring is elongated to a length \(\lambda\), defining a new configuration \(B\). The contractile element is first separately activated and changes its length to \(\lambda_a\), defining a new configuration \(B_a\). This initial step represents the active filament motion. The contractile element is then further elongated by a stretch \(\lambda_c\), so as to fit the configuration \(B\). The second step represents a deformation due to cross-bridge elasticity. This geometrical view of the lengthening of the unit cell is shown in Fig. 2 and implies the following multiplicative split of the total elongation:

\[
\lambda = \lambda_c\lambda_a.
\]

2.1. State variables

The elongations \(\lambda\) and \(\lambda_a\) define the geometrical state of the cell. In addition to these geometrical variables, the full thermodynamic state of a smooth muscle also include the chemical state. To that end, we use the model of Hai and Murphy (1988) in Eq. (1), where four fractional species are introduced. These are arranged in a vector \(\mathbf{a}\), and in the notation of Hai and Murphy we have

\[
\mathbf{a} = (M, M_p, AM_p, AM)^T.
\]

Since \(M, M_p, AM_p,\) and \(AM\) are fractions, they satisfy the constraint

\[
\sum_{i=1}^{4} a_i = 1.
\]

\[
(1)
\]
It also clearly holds that $x_i \geq 0$ (and, due to (3), that $x_i \leq 1$). However, the constitutive laws to be introduced subsequently are such that the strict inequalities $x_i > 0$ (and, thus, $x_i < 1$) always hold. This simplifies the presentation and we do not need to deal with the inequality constraints explicitly (see Remark 1 later in this section).

The chemical state is mainly driven by the $Ca^{2+}$-concentration, which we also take as a state variable and denote by

$$\beta = [Ca^{2+}],$$

where the square brackets denote concentration, following standard notation in chemistry.

Clearly there are constraints requiring $\lambda > 0$, $\lambda_a > 0$, $\lambda_c > 0$ and $\beta \geq 0$, but these are also not treated explicitly in what follows. As a final state variable, we also introduce the temperature $T$.

2.2. Derivation of the general model

The unit cell interacts with its surrounding through a thermal power $Q$ and an additional external power. The balance principle of mechanics (principle of virtual power or equations of motion), in its extended form (see, e.g., DiCarlo and Quiligotti (2002)), implies that this external power equals the internal power, denoted $\mathcal{P}$, plus the change of kinetic energy. By disregarding the temperature, the internal power can be written as ‘forces’ times ‘fluxes’, where ‘fluxes’ are the time derivatives of the state variables. The ‘forces’ paring with $\lambda$, $\lambda_a$ and $\beta$ are denoted $P$, $P_a$ and $B$, respectively. On the other hand, the $x$’s are considered internal state variables, so no corresponding force is introduced. In summary we have

$$\mathcal{P} = P\lambda + P_a\lambda_a + B\beta. \tag{4}$$

Comparing to a three-dimensional setting, the elongations are deformation gradients, and $P$ and $P_a$ are to be thought of as first Piola–Kirchhoff stresses.

Denoting the internal energy by $U$, the first law of thermodynamics now states

$$\dot{U} = \mathcal{P} + Q. \tag{5}$$
The second law of thermodynamics reads
\[ \dot{\eta}T - Q \geq 0, \]  
where \( \eta \) is the entropy. Combining Eqs. (5) and (6), and introducing a Legendre transformation, resulting in the free energy \( \psi = U - \eta T \), we get the reduced dissipation inequality (see, e.g., Holzapfel, 2000)
\[ \dot{\psi} \leq \mathcal{P} - \eta \dot{T}. \]  
The free energy is taken to be a function of the state variables, including \( \mathbf{a} \), i.e.,
\[ \psi = \psi(\lambda, \lambda_a, \mathbf{a}, \beta, T), \]
which, when introduced into Eq. (7), gives, by means of Eq. (4), the inequality
\[ \left( P - \frac{\partial \psi}{\partial \lambda_a} \right) \dot{\lambda} + \left( P_a - \frac{\partial \psi}{\partial \lambda_a} \right) \dot{\lambda}_a - \sum_{i=1}^{4} \frac{\partial \psi}{\partial \alpha_i} \dot{z}_i + \left( B - \frac{\partial \psi}{\partial \beta} \right) \dot{\beta} - \left( \eta + \frac{\partial \psi}{\partial T} \right) \dot{T} \geq 0. \]  
This inequality should hold for all evolutions of the state variables that satisfy the constitutive equations and the kinematic constraint in Eq. (3). Thus, it serves as a 'guide' to the formulation of constitutive equations. The simplest way of satisfying Eq. (8) is to let the term in front of a 'flux' be zero. We use this strategy for the first, fourth and fifth terms and obtain the state laws
\[ P = \frac{\partial \psi}{\partial \lambda}, \quad B = \frac{\partial \psi}{\partial \beta}, \quad \eta = -\frac{\partial \psi}{\partial T}. \]  
The second term in Eq. (8) is enforced to be non-negative by assuming the constitutive law
\[ P_a - \frac{\partial \psi}{\partial \lambda_a} = C \dot{\lambda}_a, \]  
where \( C = C(\mathbf{a}, \lambda_a) \geq 0 \) is a function which will be made explicit later.

The third term in Eq. (8) has a crucial role in the theory. It is through this term that the coupling between the mechanical and the chemical states is introduced. To treat this term, we define thermodynamic 'forces' as
\[ X_i = -\frac{\partial \psi}{\partial \alpha_i} + r, \]
where \( r \) is an arbitrary multiplier. The multiplier is associated with the constraint placed on the time evolutions of \( z_i \) by Eq. (3), and occurs in much the same way as the 'hydrostatic pressure' for an incompressible material. Noting that Eq. (3) implies that
\[ \sum_{i=1}^{4} \dot{z}_i = 0, \]  
we obtain
\[ -\sum_{i=1}^{4} \frac{\partial \psi}{\partial \alpha_i} \dot{z}_i = \sum_{i=1}^{4} X_i \dot{z}_i \]  
on multiplying Eq. (11) by summing over index \( i \). This equation is valid for all time evolutions of \( \mathbf{a} \) that satisfy the kinematic constraints in Eq. (3).

The thermodynamic 'forces' \( X_i \) are used to obtain an evolution law for the \( z_i \)'s. We take a linear relation between 'fluxes' and 'forces', and, introducing a matrix \( A \) with variables \( a_{ij} \), we assume
\[ \sum_{j=1}^{4} a_{ij} \dot{z}_j = X_i. \]
The elements of the matrix $A$ should satisfy certain conditions in order for Eq. (8) to hold. If
\[
\sum_{i=1}^{4} \sum_{j=1}^{4} \dot{x}_i a_{ij} \dot{x}_j \geq 0
\]  
(15)
for all evolutions that satisfy the kinematic constraints, then the right-hand side of Eq. (13) is greater than zero, and it follows that Eq. (8) is satisfied. Note that the components $a_{ij}$ may depend on any of the state variables. In particular, we will use $a_{ij} = a_{ij}(\lambda_a, \lambda_c, \beta)$ in the following. In summary, constitutive laws introduced here are thermodynamically consistent since (8) is always satisfied.

Eliminating $X_i$ between Eqs. (11) and (14) we obtain
\[
\sum_{i=1}^{4} a_{ij} \dot{x}_j = -\frac{\partial \psi}{\partial x_i} + r,
\]  
(16)
which is a system that together with Eq. (3) defines the evolution of the internal variable $\mathbf{a}$. Moreover, by prescribing $P_a$ and $B$ in terms of the state variables, we obtain an equation defining $\beta$ from Eq. (9)$^2$, and an evolution law for $\dot{\lambda}_a$ from Eq. (10). Similarly, when prescribing also a functional form for $Q$, Eq. (5) gives an evolution equation for $T$. Having thus obtained evolution equations for $\lambda_a, \mathbf{a}, \beta$ and $T$, Eq. (9)$^1$ gives the stress $P$ for a given stretch $\lambda$.

Remark 1. If we are to ensure that the constraints $x_i \geq 0$ are satisfied for all choices of free energies and matrices $A$, the definition of $X_i$ needs to be extended. We need four additional multipliers $r_i$ such that
\[
X_i = -\frac{\partial \psi}{\partial x_i} - r_i + r,
\]  
(17)
\[
r_i x_i = 0, \quad r_i \geq 0, \quad x_i \geq 0, \quad i = 1, 2, 3, 4,
\]  
(18)
where (18) is a so-called complementarity condition, which gives
\[
x_i > 0 \Rightarrow r_i = 0 \quad \text{and} \quad x_i = 0 \Rightarrow \dot{x}_i r_i = 0.
\]

It is easily verified that the Eqs. (12), (17), and (18) together with the conditions above imply Eq. (13). The evolution law for the $x_i$'s now consists of Eq. (16) with the right-hand side substituted for the right-hand side of Eq. (17), and Eqs. (3) and (18).

Note, however, that in this work (see Section 3.2) our particular choices of free energy and matrix $A$ imply that the strict inequalities $x_i > 0$ hold and, therefore, $r_i = 0$.

Remark 2. When $\dot{\mathbf{a}} = 0$, Eq. (14) implies that $X_i = 0$, and then Eq. (11) become necessary conditions for the free energy to take a minimum with respect to $\mathbf{a}$ over the set defined by Eq. (3), keeping other state variables fixed. This is a version of a thermodynamic extremum principle.

Remark 3. With the constitutive laws in Eqs. (9)–(11) and (14), the dissipation in Eq. (6) becomes
\[
\dot{\eta} T - Q = C \dot{\lambda}_a^2 + \sum_{i=1}^{4} \sum_{j=1}^{4} \dot{x}_i a_{ij} \dot{x}_j \geq 0.
\]

Remark 4. The inequality (15) is a condition of positive semi-definiteness of $A$. Note, however, that $A$ need not be symmetric: Eq. (15) implies that the symmetric part of $A$ is positive semi-definite, and the anti-symmetric part is immaterial for the inequality since a quadratic form of an anti-symmetric matrix is zero.

If $A$ is symmetric, Eq. (14) can be expressed by saying that $X_i$ is the derivative of the dissipation potential $\dot{\mathbf{a}}^T A\dot{\mathbf{a}}$ with respect to $\mathbf{a}_i$. However, the particular law to be studied in Section 3.2 contains an unsymmetric $A$ and cannot naturally be represented in this way.
3. Specialization of the thermodynamic model

In this section, we specialize the general thermodynamic model presented above. The particular specialization for the mechanical phase is made in order to recover the model by Yang et al. (2003a, b) in the limit of linear, small deformations. For the chemical phase, the model is specialized so that the evolution law in Eq. (16) includes the state law given by Hai and Murphy (1988).

3.1. Mechanical phase

To begin specializing the general model, we take the free energy to be decomposed as

$$\psi = \psi_1(\lambda) + \mathcal{N}(\lambda_a)\psi_2(\lambda_c, z) + \psi_3(z) + \psi_4(\beta),$$

where, for simplicity, we have assumed isothermal conditions and, the temperature is not, therefore, included. The functions $\psi_1$ and $\psi_2$ are the free energies for the (parallel) spring and the cross-bridges, respectively. The function $\mathcal{N}(\lambda_a)$ in the second term represents the effective area overlap between the filaments in the contractile element, and it takes values between 0 and 1 (see Remark 6). The free energy $\psi_3$ associated with the chemical phase (the four species) will be introduced in the next subsection. Finally, $\psi_4$ is the free energy associated with the calcium ion concentration in the smooth muscle cell.

Specific forms for the functions $\psi_1$, $\psi_2$, $C$ and $P_a$ can be inferred from Yang et al. (2003a). We take

$$\psi_1 = \frac{q_1}{q_2}(e^{q_2(\lambda - 1)} - 1 + q_2(1 - \lambda)), \quad \psi_2 = (x_3 E_1 + x_4 E_2)\frac{1}{2}(\lambda_c - 1)^2,$$

$$C = (f_1 x_3 + f_2 x_4)\mathcal{N}(\lambda_a), \quad P_a = -f_1 x_3 v \mathcal{N}(\lambda_a),$$

where $q_1$, $q_2$, $E_1$, $E_2$, $f_1$, $f_2$ are constants, and $v$ represents the velocity of the cross-bridge motion. The active force generation $P_a$ can be interpreted as a friction clutch with friction coefficient $f_1 x_3$. The phosphorylated cross-bridges slide past the actin surface causing a friction force which, in turn, produces the motion between the filaments (see Gestrelius and Borgström, 1986). Finally, the free energy for the intracellular calcium ion concentration is taken to be

$$\psi_4 = \frac{1}{2}b^2.$$

Eqs. (9), (19), and (22) give

$$B = \beta$$

and the intracellular calcium ion concentration can now be controlled from outside the cell by assigning $B$.

An explicit expression for the total force can be obtained from Eq. (9). Using Eqs. (19) and (2), the state law becomes

$$P = \frac{\partial \psi_1}{\partial \lambda} + \frac{\partial \mathcal{N}(\lambda_a)}{\partial \lambda_a} \frac{\partial \psi_2}{\partial \lambda_c}.$$

The active force can also be given explicitly by rewriting Eq. (10) using the special form in Eq. (19) and the multiplicative decomposition in Eq. (2)

$$P_a = \frac{\partial \mathcal{N}(\lambda_a)}{\partial \lambda_a} \psi_2 - \frac{\lambda_c}{\lambda_a} \frac{\partial \psi_2}{\partial \lambda_c} + C \dot{\lambda}_a.$$

The evolution law for $\dot{\lambda}_a$ is obtained by substituting $\psi_2$, $C$, and $P_a$ into Eq. (25).

Remark 5. Note that the active force in Eq. (21) must not be confused with that in Yang et al. (2003a). The active force, herein, is only the force generated by the attached phosphorylated cross-bridges, c.f., the friction clutch analogy above. The difference is a consequence of the derivation; our active force relates to an input of external power in Eq. (4) whereas Yang and co-workers state their active force more intuitively. Eq. (25), therefore, represents a balance between the external force (left-hand side) and the internal force (right-hand side) for the contractile element, see Remark 7. Despite this difference, it can be shown that the mechanical...
model suggested by Yang et al. (2003a) is recovered in the case of linear, small deformations by using the proposed particular forms in Eqs. (20) and (21) (see Appendix A).

**Remark 6.** The physical significance of \( N(\lambda_a) \) follows by rewriting Eq. (24) using the Cauchy stress

\[
\sigma = \frac{\rho}{\rho_0} \ddot{\lambda} P,
\]

where \( \rho_0 \) and \( \rho \) are densities of configurations \( B_0 \) and \( B \), respectively. Eq. (24) then reads

\[
\sigma = \frac{\rho}{\rho_0} \frac{\partial \psi}{\partial \lambda} \ddot{\lambda} + \frac{\rho}{\rho_0} N(\lambda_a) \frac{\partial \psi}{\partial \lambda_c} \dot{\lambda_c}.
\] (26)

Thus, there are two parallel contributions to the stress: from the cell elasticity and from the cross-bridge elasticity. The former has \( B_0 \) as its reference configuration and the latter has \( B_a \) as its reference configuration.

The area elements \( dA_0 \) and \( dA \) in \( B_0 \) and \( B_a \), respectively, are connected via Nanson’s formula, i.e.,

\[
\lambda^{-1} \frac{dA_0}{dA} = \frac{\rho}{\rho_0}
\] (27)

and substituting Eq. (27) into Eq. (26) gives

\[
\sigma dA = \frac{\partial \psi}{\partial \lambda} dA_0 + \lambda^{-1} \frac{\partial \psi}{\partial \lambda_c} N(\lambda_a) dA_0.
\]

The free energy derivative in the second term on the right-hand side is a first Piola–Kirchhoff stress based on the reference configuration \( B_a \). Multiplying it by \( \lambda^{-1} \frac{\partial}{\partial \lambda_c} \) transforms it to a first Piola–Kirchhoff stress relative to \( B_0 \), and we can interpret \( N(\lambda_a) \) as a change in the effective area \( dA_0 \) that occurs when \( \lambda_a \) changes the configuration \( B_a \), i.e., when the filaments move relative to each other.

**Remark 7.** Rewrite Eq. (25) in a form that identifies the cross-bridge elasticity, i.e., the second term in (26):

\[
\frac{\rho}{\rho_0} N(\lambda_a) \frac{\partial \psi_2}{\partial \lambda_c} \dot{\lambda_c} = \frac{\rho}{\rho_0} \lambda_a \frac{\partial N(\lambda_a)}{\partial \lambda_a} \psi_2 - \left( \frac{P_a}{\lambda_c} \right) \frac{\rho}{\rho_0} + \left( \frac{C \lambda_a}{\lambda_c} \right) \frac{\rho}{\rho_0}.
\] (28)

Thus, the Cauchy stress from the cross-bridge elasticity is balanced by three terms. The first term on the right-hand side comes from the energy gained, or lost, in the cross-bridges when the configuration \( B_a \) is altered by the active contraction \( \lambda_a \), as indicated by the derivative \( \partial N(\lambda_a)/\partial \lambda_a \). This happens, for instance, when stretched cross-bridges at the end of the filament overlap are released when removed from the overlap region and the energy is dissipated. This term is not included in the active force expression given in Yang et al. (2003a, b), because the active force is based on experimental evidence instead of being derived from first principles.

The second term is the Cauchy stress associated with the first Piola–Kirchhoff stress \( P_a \), and the third term can be interpreted as a Cauchy stress associated with the friction stress occurring when passive cross-bridges slide over actin due to filament motion.

### 3.2. Chemical phase

For the chemical phase we take the model of Hai and Murphy (1988), which reads

\[
\dot{x} + Kx = 0
\] (29)

for a certain matrix \( K \). We would like to understand how this model relates to the evolution law given by Eq. (16). To this end, we conclude that Eq. (29) implies the strict inequalities, \( \dot{x}_i > 0 \), and, therefore, we can neglect the multipliers \( r_i \) (see Remark 1).

To obtain an expression for the derivative of the free energy on the right-hand side of Eq. (16), we take the variation of the free energy in Eq. (19) with respect to \( x \):

\[
\delta \psi = \sum_{i=1}^{4} \left[ \frac{\partial \psi_1(x)}{\partial x_i} + N(\lambda_a) \frac{\partial \psi_2(x, \lambda_c)}{\partial x_i} \right] \delta x_i.
\] (30)
The chemical evolution law in Hai and Murphy (1988) is linear and Eq. (30) must therefore be linearized. Let \( \mathbf{z} \) correspond to a minimum point of the free energy, so that \( \delta \psi = 0 \) for \( \mathbf{z} = \mathbf{z}. \) Linearizing Eq. (30) at this point gives

\[
\delta \psi \approx \sum_{i=1}^{4} \sum_{j=1}^{4} \frac{\partial^{2} \psi_{3}(\mathbf{z})}{\partial \mathbf{z}_{i} \partial \mathbf{z}_{j}} (\mathbf{z}_{j} - \mathbf{z}_{j}) \delta \mathbf{z}_{i}.
\]

(31)

When \( \psi_{2} \) is linear in \( \mathbf{z} \), as in our special case (see Eq. (20)), the last term in the square brackets vanishes. From

\[
\delta \psi = \sum_{i=1}^{4} \frac{\partial \psi}{\partial \mathbf{z}_{i}} \delta \mathbf{z}_{i}
\]

for all variations satisfying Eq. (3), i.e.,

\[
\sum_{i=1}^{4} \delta \mathbf{z}_{i} = 0,
\]

it follows that

\[
\frac{\partial \psi}{\partial \mathbf{z}_{i}} \approx \sum_{j=1}^{4} \frac{\partial^{2} \psi_{3}(\mathbf{z})}{\partial \mathbf{z}_{i} \partial \mathbf{z}_{j}} (\mathbf{z}_{j} - \mathbf{z}_{j}) + r' = \sum_{j=1}^{4} \frac{\partial^{2} \psi_{3}(\mathbf{z})}{\partial \mathbf{z}_{i} \partial \mathbf{z}_{j}} \mathbf{z}_{j} + r'',
\]

for some arbitrary multipliers \( r' \) and \( r''. \) Introducing the Hessian-like matrix \( \mathbf{E} \) with the components

\[
E_{ij} = \frac{\partial^{2} \psi_{3}(\mathbf{z})}{\partial \mathbf{z}_{i} \partial \mathbf{z}_{j}},
\]

the evolution law in Eq. (16) can now be written in matrix form as

\[
\mathbf{A} \mathbf{z} + \mathbf{E} \mathbf{z} - r'' \mathbf{1} = 0,
\]

(32)

where \( \mathbf{1} = (1, 1, 1, 1)^{T}. \) This equation together with Eq. (3) result into five equations from which the four elements in the \( \mathbf{z} \)-vector and \( r'' \) can be solved. Elimination of \( r'' \) gives that the elements in \( \mathbf{z} \) can be computed from the evolution law (for details, see Remark 8):

\[
\dot{\mathbf{z}} + \left( \mathbf{A}^{-1} - \frac{(\mathbf{A}^{-1})(\mathbf{1}^{T}\mathbf{A}^{-1})}{\mathbf{1}^{T}\mathbf{A}^{-1}\mathbf{1}} \right) \mathbf{E} \mathbf{z} = 0.
\]

(33)

Note that \( \mathbf{A} = \mathbf{A}(\lambda_{a}, \lambda_{c}, \beta) \) and \( \tilde{\mathbf{z}} = \tilde{\mathbf{z}}(\lambda_{a}, \lambda_{c}). \) Therefore, the chemical evolution depends on the three state variables \( \lambda_{a}, \lambda_{c}, \) and \( \beta. \) This equation is to be compared with the equation in Hai and Murphy (1988), i.e., Eq. (1), where the dependence is only on the calcium ion concentration \( \beta. \) Note that the \( \mathbf{A} \) matrix introduces a coupling between the mechanical and the chemical phase.

If the particular form of \( \psi_{3} \) and the components \( a_{ij} \) are known, the chemical state is completely determined by Eq. (33). This is not the case, however. To the best of the authors’ knowledge, no explicit functions have been published, and they must, therefore, be identified from experimental data. To that end, we first reformulate Eq. (33) by introducing a few further assumptions.

Remark 8. Starting with Eq. (32), i.e.,

\[
\mathbf{A} \mathbf{z} + \mathbf{E} \mathbf{z} - r'' \mathbf{1} = 0
\]

and multiplying by \( \mathbf{A}^{-1} \) from the left hand side gives

\[
\dot{\mathbf{z}} + \mathbf{A}^{-1} \mathbf{E} \mathbf{z} - r'' \mathbf{A}^{-1} \mathbf{1} = 0.
\]

(34)

The multiplier \( r'' \) can be eliminated by multiplying the equation by \( \mathbf{1}^{T} \) from the left hand side and noting that the time derivative of the constraint in Eq. (3) implies \( \mathbf{1}^{T} \dot{\mathbf{z}} = 0, \) c.f., Eq. (12). Solving for \( r'' \) gives

\[
r'' = \frac{\mathbf{1}^{T} \mathbf{A}^{-1} \mathbf{E} \mathbf{z}}{\mathbf{1}^{T} \mathbf{A}^{-1} \mathbf{1}}.
\]

(34)

Back-substitution of \( r'' \) into Eq. (34) and rearranging the terms gives the desired result in Eq. (33).
3.3. Reformulation of the chemical evolution law

Motivated by Gibbs’ free energy for an ideal process with multiple species, we assume that the free energy has no coupling between the species and can, therefore, be additively decomposed as

$$\psi_3 = \sum_{i=1}^{4} \psi_{3,i}(\lambda_i).$$

As a consequence, the $E$ matrix in Eq. (33) becomes diagonal, and, since $\tilde{x}$ is a function of $\lambda_a$ and $\lambda_c$, we replace the second derivatives in $E$ by four unknown functions $\eta_i = \eta_i(\lambda_a, \lambda_c)$. Let the parenthesis in Eq. (33) be called $\Gamma$ and rewrite Eq. (33) as

$$\begin{pmatrix}
\dot{z}_1 \\
\dot{z}_2 \\
\dot{z}_3 \\
\dot{z}_4
\end{pmatrix} + \begin{bmatrix}
\eta_1 \Gamma_1 & \eta_2 \Gamma_2 & \eta_3 \Gamma_3 & \eta_4 \Gamma_4
\end{bmatrix} \begin{pmatrix}
z_1 \\
z_2 \\
z_3 \\
z_4
\end{pmatrix} = \begin{pmatrix}
0 \\
0 \\
0 \\
0
\end{pmatrix},$$

where $\Gamma_i$ corresponds to the $i$th column vector of the matrix $\Gamma$. Let the column vectors take the same form as the column vectors in the $K$-matrix used by Hai and Murphy (1988), i.e.,

$$\Gamma_1 = \{k_1, -k_1, 0, 0\}^T, \quad \Gamma_2 = \{-k_2, k_2 + k_3, -k_3, 0\}^T,$$

$$\Gamma_3 = \{0, -k_4, k_4 + k_5, -k_5\}^T, \quad \Gamma_4 = \{-k_7, 0, -k_6, k_6 + k_7\}^T$$

for some functions $k_1 = k_1(\beta, \lambda_a, \lambda_c)$ and $k_6 = k_6(\beta, \lambda_a, \lambda_c)$, and some constants $k_2, k_3, k_4, k_5,$ and $k_7$. For the functions $k_1$ and $k_6$, we use variants of those suggested in Yang et al. (2003a), i.e.,

$$k_1(\beta, \lambda_a, \lambda_c) = k_6(\beta, \lambda_a, \lambda_c) = \frac{\beta^4}{\beta^4 + \beta_0^4},$$

where $\beta_0 = \beta_0(\lambda_a, \lambda_c)$ is given by

$$\beta_0(\lambda_a, \lambda_c) = C_0 + C_1(\lambda_a \lambda_c)^{-1} = C_0 + C_1 \lambda^{-1}$$

for some constants $C_0$ and $C_1$. The assumption that $k_1$ equals $k_6$ means that the affinity of myosin to phosphorylate is the same regardless of whether it is attached to actin or not. This assumption follows from the paper by Hai and Murphy (1988). The particular form of $k_1 = k_6$ was chosen for two reasons: first, the fourth-order function is able to reflect the typical saturation behaviour of the dose-tension curves for smooth muscles, second, the exponent is in accordance with the four binding sites for calcium ions on the calmodulin molecule (Bennett et al., 2005).

The forms of the functions $\eta_i = \eta_i(\lambda_a, \lambda_c)$ are unknown and must, therefore, be determined from experiments. To that end, we assume the linear relation

$$\eta_i(\lambda_a, \lambda_c) = A_i \lambda_a \lambda_c + B_k = A_i \lambda + B_i,$$

where $A_k$ and $B_k$ are constants.

The constant $B_k$ can be eliminated by requiring $\eta_k$ to equal 1 when $\lambda$ corresponds to the experimental conditions under which Hai and Murphy (1988) determined $k_1$ to $k_7$, i.e.,

$$B_l = 1 - A_l \lambda,$$

where the experimental value is denoted by $\lambda$. Back-substitution of $B_i$ into Eq. (40) gives

$$\eta(\lambda) = A(\lambda - \lambda) + 1.$$
3.4. Summary of the mechanochemical model

In this section, we summarize the complete mechanochemical model. The following parameters are considered to be known: $E_1$, $E_2$, $f_1$, $f_2$, and $v$ for the mechanical phase, and $k_2$, $k_3$, $k_4$, $k_5$, $k_7$, $C_0$, $C_1$, $A_1$, $A_2$, $A_3$, $A_4$, $Z$, and $\beta$ for the chemical phase. The effective area function $\mathcal{A}(\lambda_a)$ is also assumed to be known.

First, we note that whenever the elastic cross-bridge stretch $\lambda_c$ appears it can be eliminated by Eq. (2). In doing so, the model’s dependence on the geometrical state will only be through $\lambda$ and $\lambda_a$. The total force is obtained from

$$P = \frac{\partial \psi_1}{\partial \lambda} + \frac{\mathcal{A}(\lambda_a) \partial \psi_2}{\lambda_a}$$

(24)

by substituting the free energy functions $\psi_1 = \psi_1(\lambda)$ and $\psi_2 = \psi_2(\mathbf{x}, \lambda_c)$ given in Eq. (20). The total force must be accompanied by evolution laws for the chemical state and the active contraction. The chemical state is governed by the equation

$$\dot{\mathbf{x}} + [\eta_1 \Gamma_1 \eta_2 \Gamma_2 \eta_3 \Gamma_3 \eta_4 \Gamma_4] \mathbf{x} = 0,$$

(35)

where $\eta_i = \eta_i(\lambda)$ are given by Eq. (42) and the column vectors $\Gamma_i = \Gamma_i(\beta, \lambda)$ are given by Eqs. (36)–(39). Finally, the evolution law for the active contraction $\lambda_a$ is computed from

$$C_{\lambda_a} = P_a - \frac{\partial \mathcal{A}(\lambda_a)}{\partial \lambda_a} \psi_2 + \frac{\lambda_c}{\lambda_a} \frac{\partial \mathcal{A}(\lambda_a)}{\partial \lambda_c}.$$

(25)

by substituting the free energy $\psi_2$ from Eq. (20)$^2$, the active force $P_a = P_a(\mathbf{x}, \lambda_a)$ from Eq. (21)$^2$, and the function $C = C(\mathbf{x}, \lambda_a)$ from Eq. (21)$^1$.

Eqs. (24), (25), and (35) is a coupled system of equations that together with initial conditions for $\mathbf{x}$ and $\lambda_a$ constitutes the mechanochemical model. Written in functional form, the model can be summarized as

$$\begin{cases}
P = P(\mathbf{x}, \lambda, \lambda_a), \\
\dot{\mathbf{x}} + K(\beta, \lambda) \mathbf{x} = 0, \\
C(\mathbf{x}, \lambda_a) \lambda_a + f(\mathbf{x}, \lambda, \lambda_a) = 0, \\
\mathbf{x}(t = 0) = \mathbf{x}_0, \quad \lambda_a(t = 0) = \lambda_{a,0},
\end{cases}$$

(43)

where $f$ is the function given in the right-hand side of the repeated Eq. (25).

Eq. (43) has four unknowns ($P, \mathbf{x}, \lambda, \lambda_a$). By specifying one of them as input, the system can be solved for the others. A model of this kind generally applies to one of the following cases: compute $P$ when $\lambda$ is known, or, compute $\lambda$ when $P$ is known. The former case will be exemplified in the next section.

4. Numerical example

To determine the constants in Eqs. (39) and (42), the response curve for the stress is fitted to the isometric tension-length relations for various levels of $[Ca^{2+}]$ (provided in Fig. 8 in Hunter et al., 1998) by a least-squares method. The choice of using data from that study is not obvious since it concerns the mechanics of cardiac muscle instead of smooth muscle. Despite this shortcoming it is used for two reasons: first, relatively few studies have shown the relation between stress, stretch, and calcium ion level. Generally, the stress dependency on other agonists such as norepinephrine or potassium is well documented. Second, the stretch dependence of the dose-response curve has the same behaviour for cardiac and VSMs (compare, for instance, the studies by Kentish et al., 1986 and Price et al., 1981). The use of data from cardiac muscle is not, therefore, critical to the proposed method; the difference will only affect the constants in Eqs. (39) and (42).

The number of unknowns is minimized by adopting values for the parameters that are not part of Eqs. (39) and (42) from other studies (see Table 1). As a consequence, the total stress in Eq. (24) and the stress data from Hunter et al. (1998) need to be normalized to remove possible differences in magnitude. This is achieved by dividing both the data and the model response by their respective minimum stress for the maximally activated case. The parameters left to be identified are: $A_1$, $A_2$, $A_3$, $A_4$, $C_0$, and $C_1$. Let these parameters be the
components of a vector $\mathbf{k}$, and define an objective function

$$
\phi(\mathbf{k}) = \sum_{n=1}^{N} \left[ \hat{P}(\mathbf{k}, \lambda_n, \beta_n) - \tilde{P}_n \right]^2,
$$

(44)

where $\hat{P}_n$ are the stress data, $\lambda_n$ are the from other stretch data, $\beta_n$ are the calcium ion concentration data, and $N$ is the total number of data points. The hat in Eq. (44) denotes a normalized quantity, as described above.

The normalized, isometric, steady-state stress $\hat{P}$ is computed in the following way: first, the chemical evolution given through Eqs. (35)–(42) is solved in order to obtain the fractions of the four species for a given calcium ion level and a given stretch. The different species fractions were initially assumed to be uniform, i.e., $M = M_p = AM_p = AM = 0.25$. The stretch $\lambda$ in Eq. (42) is the stretch at which Hai and Murphy (1988) computed the rate constants. Hai and Murphy (1988) used experimental data from Singer and Murphy (1987), but no explicit value for the stretch is given therein. However, the tests were performed at a length ratio $L/L_{opt} = 0.8$, where $L$ and $L_{opt}$ are the current and the optimal lengths (maximal force production), respectively. By expanding the ratio we get

$$
\frac{L}{L_{opt}} = \frac{L}{L_0} \frac{L_0}{L_{opt}} = \lambda \frac{1}{\lambda_{opt}} = 0.8,
$$

(45)

where $L_0$ is the reference length and $\lambda_{opt}$ is the optimal stretch corresponding to the maximal force production. Rachev and Hayashi (1999) suggest the value $\lambda_{opt} = 1.4$, and by substituting this value into Eq. (45) above, the experimental stretch $\lambda$ can be computed as 1.12. Second, the specific forms of $\psi_2$, $C$, and $P_a$ from Section 3.1 are substituted in Eq. (25) together with the steady-state result of the chemical species. The evolution law is then solved for the active stretch with the initial condition $\lambda_a = 1.0$. Third, the total stress is computed from Eq. (24) by substituting from Eqs. (20), together with the steady-state values for the chemical species and the active stretch. The steady-state is taken to be the stress obtained after 100 seconds.

Finally, the effective area function is taken to be the Gaussian function

$$
\mathcal{N}(\lambda_a) = \exp\left(-\frac{(\lambda_a - \lambda_{opt})^2}{2\xi^2}\right)
$$

(46)

with a band-width $\xi = 1/\sqrt{2}$ to satisfy the function in Yang et al. (2003a, b).

The parameter identification was performed using a classical nonlinear curve fitting algorithm in MATLAB (The MathWorks, Natick, United States), and the result of the identification process is presented in Table 2 and Figs. 3 and 4.
The dependence of the active stress on the stretch in terms of the internal calcium ion concentration is evident in Fig. 3. For maximally activated muscles, the stress is a linear function of the stretch, which is not the case at lower activation levels. A change of variables from stretch to calcium ion concentration for the abscissa is shown in Fig. 4. The plot shows a marked increase in the slope at the inflection point of the curve as the stretch goes from 0.8–1.2. In addition, the onset of the ascending part is shifted to the left as the stretch increases, indicating an increase in the calcium ion sensitivity.

5. Discussion

The problem of modelling the contracting smooth muscles in the arterial wall has been addressed in a few previous studies (see, for example, Rachev and Hayashi, 1999; Yang et al., 2003b; Zulliger et al., 2004). With the exception of the study by Yang and co-workers there is no explicit connection between the calcium ion level and the active stress-stretch response curve. The response is instead obtained by multiplying some ad hoc stretch dependent function by a constant related to the maximal active stress. Using this approach, Zulliger and co-workers introduce a pseudo strain-energy function (Zulliger et al., 2004). The logarithmic strain-energy for the maximally activated smooth muscle is multiplied by two stretch dependent functions, where the first function, \( S_1 \), models the stretch dependence of the active stress at constant calcium ion concentrations, cf. the different curves in Fig. 3, and the second function, \( S_2 \), gives the stretch range for which the smooth muscles
produce active force. Although $S_1$ and $S_2$ are part of the strain-energy function, they are not differentiated with respect to the stretch in the calculation of the stress in Zulliger et al. (2004), and hence the name pseudo strain-energy. There are no such inconsistencies in the model presented in the present work.

The linearization of the free energy variation in Eq. (30) is not necessary for the proposed model, it is only introduced to recover the evolution law proposed by Hai and Murphy (1988). If the free energy function $\psi_3$ and the components $a_{ij}$ are known, Eq. (30) can be used directly to calculate the chemical evolution law. This approach probably requires new, tailored experiments to find the functions $\psi_3$ and $a_{ij}$ involved since no such data are yet available in the literature to the best of the authors’ knowledge.

The inflection point $b_0$ in Eqs. (38) and (39) is a function of the stretches $\lambda_a$ and $\lambda_c$. This functional form is introduced to make the dose-tension curve stretch dependent (see Fig. 4). This coupling originates from a deformation induced depolarization of the (smooth muscle) cell membrane (Davis and Hill, 1999). The depolarization activates voltage-gated channels through which calcium ions enter the cell. In a more accurate analysis, this stretch-dependency should be accounted for by a separate model of the smooth muscle cell membrane, such as the electrochemical subsystem in Yang et al. (2003a, b). The intracellular calcium ion level $b$ is then controlled by assigning the output from the membrane model to the input ‘force’ $B$.

In the numerical example, we have assumed that the chemical state for the smooth muscle has reached its steady-state condition when solving for the active stretch $\lambda_a$. This assumption requires that the time chemical evolution is much faster than the evolution of the active stretch. It is difficult to assess the validity of this assumption, but on comparing Figs. 2 and 3 in Hai and Murphy (1988), and assuming the active force to be proportional to $\lambda_a$, it can be concluded that the time constants for the first order systems are of the same order of magnitude (the time constant for the chemical state is 2–4 s faster than the time constant for the force). The assumption is, therefore, likely to be incorrect and the evolutions should be solved simultaneously. As a first approximation, however, we assume the difference to be sufficient to neglect any error introduced by not solving the evolution laws simultaneously.

In conclusion, we have presented a mechanochemical model for smooth muscle contraction at homogeneous finite strains herein. The model is thermodynamically consistent and includes a chemical state
law due to Hai and Murphy (1988) and a recent model for smooth muscle contraction due to Yang et al. (2003a, b) in the limit of linear, small deformations. The model has been applied to experimental data from Hunter et al. (1998) and is able to capture the salient increase in sensitivity with the stretch observed in stress–strain curves. We believe that models of this kind are invaluable for understanding the effect that smooth muscles have in the cardiovascular system.

Appendix A. Linearization of the proposed mechanochemical model

In this appendix we show that the mechanochemical model suggested of Yang et al. (2003a, b) is a special case of our model obtained under linear, small strain conditions. To show this, we first note that the model by Yang and co-workers does not account for the derivative of the effective area function with respect to \( \lambda^e \). We, therefore, set

\[
\frac{\partial N(\lambda^e)}{\partial \lambda^e} = 0
\]

(A.1)

whenever present in the derivation below.

By substituting Eqs. (20) in Eq. (24), the total stress reads

\[
P = q_1(e^{\eta_2(\lambda^e-1)} - 1) + \frac{N(\lambda^e)}{\lambda^e}(E_1\dot{z}_3 + E_2\dot{z}_4)(\dot{\lambda}_c - 1),
\]

where the first and second terms on the right–hand side are the contributions to the passive response originating from the parallel element and the contractile element, respectively. Substituting the approximation \( e = \lambda - 1 \), valid for linear elastic materials within the small strain domain, it is seen that the first term already equals its counterpart, i.e., Eq. (26) in Yang et al. (2003a) (or, Eq. (7) in Yang et al., 2003b), so we focus on the second part. Let \( P_{cb} \) denote the passive stress obtained from the cross-bridge elasticity. We linearize it by taking a Taylor expansion in the vicinity of \( \lambda^e = \lambda_c = 1 \), and substitute Eq. (A.1). The result reads

\[
P_{cb} = (E_1\dot{z}_3 + E_2\dot{z}_4)N(\lambda^e)(\dot{\lambda}_c - 1).
\]

In analogy with above, substitute \( \lambda^e \) and \( \dot{\lambda}^e \) with their linear elastic, small strain approximations which gives

\[
P_{cb} = (E_1\dot{z}_3 + E_2\dot{z}_4)N(\dot{\lambda}^e)\dot{\lambda}_c.
\]

(A.2)

This expression for the stress from the cross-bridge elasticity is in agreement with its counterpart Eq. (24) in Yang et al. (2003a) (or, Eq. (7) in Yang et al., 2003b).

What remains to be shown is the equivalence of the linearized evolution laws to those given in Yang et al. (2003a, b). To do so, we first rewrite Eq. (25) using Eq. (A.1), which gives

\[
P_a = -\frac{\dot{\lambda}_c}{\dot{\lambda}_a}N(\lambda^e)\frac{\partial \psi_2}{\partial \lambda_c} + C\dot{\lambda}_a.
\]

Substituting Eqs. (20)\(^2\) and (21), and dividing both sides by \( N \), we get

\[
(f_1\dot{z}_3(\dot{\lambda}^e) + f_2\dot{z}_4\dot{\lambda}_a) - (E_1\dot{z}_3 + E_2\dot{z}_4)\frac{\dot{\lambda}_c(\dot{\lambda}_c - 1)}{\dot{\lambda}_a} = 0.
\]

To allow this operation, we require the effective area function to satisfy \( N(\lambda^e) \neq 0 \) for all admissible \( \lambda^e \). Linearizing this equation by taking the Taylor expansion in the vicinity of \( \lambda^e = \lambda_c = 1 \), we arrive at

\[
(f_1\dot{z}_3(\dot{\lambda}^e) + f_2\dot{z}_4\dot{\lambda}_a) - (E_1\dot{z}_3 + E_2\dot{z}_4)(\dot{\lambda}_c - 1) = 0.
\]

(A.3)

Substituting the linear elastic, small strain approximation for \( \lambda^e \) and \( \dot{\lambda}_c \) in Eq. (A.3) gives the linear evolution law for \( \dot{\lambda}^e_1 \), i.e.,

\[
(f_1\dot{z}_3(\dot{\lambda}^e_1) + f_2\dot{z}_4\dot{\lambda}_a) - (E_1\dot{z}_3 + E_2\dot{z}_4)\dot{\lambda}_c = 0
\]

or

\[
\dot{\lambda}_1 = \frac{(E_1\dot{z}_3 + E_2\dot{z}_4)\dot{\lambda}_c - f_1\dot{z}_3\dot{\lambda}}{f_1\dot{z}_3 + f_2\dot{z}_4}.
\]

(A.4)
This result is the same as in Yang et al. (2003b) and we conclude that the proposed mechanochemical model includes the linear, small deformation model presented in Yang et al. (2003a, b) as a special case.

References


