3D FINITE ELEMENT ANALYSIS OF SMOOTH MUSCLE CONTRACTION CONSIDERING CALCIUM DIFFUSION

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Summary. Recently a model of the mechanochemical response of smooth muscle cells has been developed by Murtada et al. [1]. The model is based on a strain-energy function incorporating only a few physical-based material parameters. The main focus of their approach is on the modeling of the response of the cross-bridge interactions and on the related force generation. Based on a one-dimensional analysis the performance of the modeling approach has been shown by comparing to experimental data of smooth muscle cells. The results of the combined coupled model are broadly consistent with isometric and quick-release experiments on smooth muscle tissue. In the present study the aforementioned model has been implemented into a finite element program in order to solve more complex boundary-value problems. In doing so we present here a first three-dimensional simulation of the Fick’s law-driven diffusion of calcium into a cell as well as the related smooth muscle contraction.

1 INTRODUCTION

Since the inception of concept that the intracellular calcium complex controls the contraction of smooth muscle via phosphorylation of myosin head [2, 3] (for a detailed review see, e.g., [4]), many researchers have focused attention on a relationship between the calcium complex and the generated force in the muscle. However, such a relationship can only be established when three fundamental mechanism are known: (i) diffusivity of the calcium concentration into the muscle; (ii) relationship between the calcium complex concentration and the cross-bridge (actin-myosin attachment); (iii) relationship between the cross-bridge and the generated force.

To address the second issue, Hai and Murphy [3] have established a kinetic model that relates the calcium complex to the myosin-actin cross-bridge. The model consists of four differential
equations of first order with seven rate constants. In their box model, however, only one rate constant, namely $k_1$, is regulated by the calcium complex. This particular rate constant is very important because it determines the phosphorylation rate of the myosin head, which plays a major role in force generation. To address the third issue, on the basis of the Hai and Murphy model, recently, Murtada et al. [1] in addition to Stålhand et al. [5] and Yang [6], to mention just a few, have established the relationship between the cross-bridge and the generated forces particularly in a one-dimensional constellation. In the present work, those developments and the Fick’s second law that governs diffusivity of a calcium concentration into a cell are incorporated into a finite element framework such that more complex phenomena in smooth muscle cells can be further investigated.

2 MECHANOCHEMICAL MODEL FOR SMOOTH MUSCLE CONTRACTION

2.1 Chemical Model for smooth muscle contraction by Hai and Murphy [3]

In the Hai and Murphy model [3], two state variables, namely AM and $A_Mp$, are crucial in the force generation. The majority of the force is generated in the $A_Mp$ state where the phosphorylated myosin head attaches to the actin, usually called ‘cross-bridge’. Unlike the $A_Mp$ state, the AM state produces a small amount of force but this state is extremely efficient because it requires only a small amount of energy (i.e. ATP), and the force generation can be maintained for a long duration, which is not the case for the skeletal muscle. For that reason, Marston [4] suggested that this state should be considered as a property of the contractile apparatus in the smooth muscle.

The kinetic model by Hai and Murphy [3], as reproduced in Fig. 1, is governed by a set of ordinary first order differential equations with the form

\[
\begin{align*}
\begin{pmatrix}
\dot{n}_M \\
\dot{n}_{M_p} \\
\dot{n}_{AM_p} \\
\dot{n}_{AM}
\end{pmatrix} &= 
\begin{pmatrix}
-k_1 & k_2 & 0 & k_7 \\
 k_1 & -(k_2 + k_3) & k_4 & 0 \\
 0 & k_3 & -(k_4 + k_5) & k_6 \\
 0 & 0 & k_5 & -(k_6 + k_7)
\end{pmatrix}
\begin{pmatrix}
n_M \\
n_{M_p} \\
n_{AM_p} \\
n_{AM}
\end{pmatrix},
\end{align*}
\]

where the state variables are subjected to the equality constraint $n_M + n_{M_p} + n_{AM_p} + n_{AM} = 1$. Furthermore, we assume that the phosphorylation rate of the myosin head does not depend on the existence of the actin, therefore, $k_1 = k_6$. The same assumption is applied for the de-phosphorylation so that $k_2 = k_5$. Finally, we assume that the myosin cannot bind the actin
without phosphor, but the actin-myosin bond may break; in other words $AM \rightarrow M$ is a one-way reaction. The most important rate constant $k_1$ is assumed to correlate with the external calcium $Ca^{2+}$ concentration through the Michaelis-Menten equation, i.e.

$$k_1 = \frac{[Ca^{2+}]^\alpha}{[Ca^{2+}]^\alpha + (ED_{50})^\alpha},$$

where $ED_{50}$ is the concentration of $Ca^{2+}$ giving half maximal response and $\alpha$ is a parameter determining the shape of the curve.

### 2.2 Mechnochemical coupling

Murtada et al. [1] extended the above chemical model to estimate the generated mechanical force. For this purpose it was assumed that the contractile apparatus (or active component) of a smooth muscle cell can be described by a strain-energy function $\Psi_a$, and that the active component is surrounded by a matrix material (or passive component) described by $\Psi_p$. Hence, the total strain-energy function $\Psi$ is composed of two parts $\Psi = \Psi_a + \Psi_p$, where the energy stored in the active component is related to Hai and Murphy’s state variables $n_{AM_p}, n_{AM}$ as

$$\Psi_a = \frac{\mu_a}{2} (n_{AM_p} + n_{AM}) (\lambda_f - 1 + \bar{u}_{rs})^2.$$  

Herein, $\mu_a$ is the shear modulus, $\lambda_f$ is the stretch of the contractile apparatus, and $\bar{u}_{rs}$ is the deformation, i.e. an internal variable describing the normalized relative sliding that occur between the thick and thin filaments. Meanwhile, the passive component stores the energy by an amount of $\Psi_p = \mu_p (I_1 - 3)$, where $\mu_p$ is the shear modulus of the passive material, and $I_1$ is the first principal invariant. The derivative of (3) with respect to $\lambda_f$ gives the stress acting on the active material $P_f = \mu_a (n_{AM_p} + n_{AM}) (\lambda_f - 1 + \bar{u}_{rs})$. Finally, the stress is assumed to depend on the rate of the internal variable $\bar{u}_{rs}$ according to

$$\eta \dot{\bar{u}}_f = \kappa (n_{AM_p} + n_{AM}) - P_f$$

if $P_f < n_{AM_p}$,

$$\eta \dot{\bar{u}}_f = 0$$

if $n_{AM_p} \leq P_f \leq (n_{AM_p} + n_{AM})$,

$$\eta \dot{\bar{u}}_f = \kappa (n_{AM_p} + n_{AM}) - P_f$$

if $P_f > (n_{AM_p} + n_{AM}).$

where $\eta$ and $\kappa$ are material parameters. To include a satisfying representation of calcium distribution inside the smooth muscle, diffusion, the main form of transport in cell biology, has to be taken into account. The diffusion is governed by Fick’s second law $D \nabla^2 Ca^{2+} = \partial Ca^{2+} / \partial t$, where $D$ is the diffusion coefficient, $Ca^{2+}$ denotes the calcium concentration, and $\nabla$ is the gradient operator.

### 3 NUMERICAL EXAMPLES

In order to mimic a stylized artery we analyze a cylindrical-shaped structure subjected to a certain transient loading of the calcium complex, see Fig. 2 (a). On the top side of the cylinder, the calcium concentration is assumed to uniformly diffuse along its longitudinal direction. On the bottom side, the concentration is chosen to be zero regardless of the fact that the latch state of a smooth muscle usually contains a small amount of the calcium concentration. In addition,
the bottom side is constrained from movement in the longitudinal direction. The wave-shaped input calcium concentration is assumed to linearly increase up to 0.06 mM within 10 s, and then it linearly decreases to zero within 20 s. This profile approximates the experimentally measured intracellular calcium transient in response to 1.6 s step depolarization to 0 mV from a holding potential of −60 mV, see [6]. In Fig. 2 (b)–(d) the distribution of calcium on the deformed tube is shown. The maximum value of calcium (0.06 mM) is reached at $t = 10$ s on top of the tube, hence the maximum contraction appeared also here. This is expressed in a shortening of the whole tube as well as in a reduction of the radius at the top of the tube.

Figure 2: Calcium distribution on a deformed tube at various times: (a) structure and boundary conditions at $t = 0$ s; (b) $t = 5$ s; (c) $t = 10$ s; (d) $t = 15$ s.

REFERENCES


