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Length adaptation of smooth muscle contractile filaments in response to sustained activation

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HIGHLIGHTS

- We model the length adaptation in vascular smooth muscle under sustained contraction.
- The model is derived using fundamental laws and principles in mechanics.
- The effect of length adaptation is elucidated by a parameter study.
- The model is in agreement experimental results.

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ABSTRACT

Airway and bladder smooth muscles are known to undergo length adaptation under sustained contraction. This adaptation process entails a remodelling of the intracellular actin and myosin filaments which shifts the peak of the active force–length curve towards the current length. Smooth muscles are therefore able to generate the maximum force over a wide range of lengths. In contrast, length adaptation of vascular smooth muscle has attracted very little attention and only a handful of studies have been reported. Although their results are conflicting on the existence of a length adaptation process in vascular smooth muscle, it seems that, at least, peripheral arteries and arterioles undergo such adaptation. This is of interest since peripheral vessels are responsible for pressure regulation, and a length adaptation will affect the function of the cardiovascular system. It has, e.g., been suggested that the inward remodelling of resistance vessels associated with hypertension disorders may be related to smooth muscle adaptation. In this study we develop a continuum mechanical model for vascular smooth muscle length adaptation by assuming that the muscle cells remodel the actomyosin network such that the peak of the active stress–stretch curve is shifted towards the operating point. The model is specialised to hamster cheek pouch arterioles and the simulated response to stepwise length changes under contraction. The results show that the model is able to recover the salient features of length adaptation reported in the literature.

1. Introduction

Smooth muscle share many features with striated muscle. For example, the active force originates from a cyclic interaction between actin and myosin filaments and is dependent on the muscle length in a bell-shaped manner. In other aspects smooth muscle differs significantly from striated muscle. One of the most obvious differences is that smooth muscle lacks the highly regular organisation of contractile filaments which give rise to the banded structure in striated muscle. In addition, various types of smooth muscles are able to generate the same maximum isometric force over a wide range of lengths given time to adapt (Pratusevich et al., 1995; Kuo et al., 2003; Herrera et al., 2005; Martinez-Lemus et al., 2008; Tuna et al., 2011). This is in sharp contrast to striated muscle where the maximum isometric force is associated with a particular length (Gordon et al., 1966).

Evidence suggests that smooth muscle length adaptation is connected to a structurally and 'plastic-like' mechanism of contractile and other cytoskeletal filaments (Kuo et al., 2003; Herrera et al., 2005; Seow, 2005; van den Akker et al., 2010). Both actin and myosin polymerise and depolymerise rapidly in response to activation (Mehta and Gunst, 1999; Herrera et al., 2002). This evanescence facilitates reorganisation of the contractile filaments in order to maintain a maximal overlap and, thereby, the maximal

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isometric force. The underlying mechanism for length adaptation is not well understood, but the predominant theory is that sustained activation promotes serial addition or subtraction of contractile filaments. This theory is also supported by experimental observations. First, the maximal isometric force remains invariant of the adapted length (Kuo et al., 2003; Herrera et al., 2005; Bossé et al., 2008). Second, the contraction velocity and power output are proportional to the adapted length (Kuo et al., 2003; Herrera et al., 2005). Third, the adenosine-triphosphate (ATP) consumption is also proportional to the adapted length (Kuo et al., 2003). Fourth, the myosin filament density in the smooth muscle cell increases linearly with the adapted length (Kuo et al., 2003; Bossé et al., 2008). The serial model is also the simplest model which accounts for all these observations and is, therefore, chosen herein.

Compared to the airways or the bladder, surprisingly little is known about length adaptation in vascular smooth muscle (van den Akker et al., 2010; Tuna et al., 2011). The published studies mostly concern small arteries and arterioles (Bakker et al., 2004; Martinez-Lemus et al., 2004; Tuna et al., 2013a, 2013b), but larger arteries have also been reported (Syyong et al., 2008; Murtada et al., 2015). Since small arteries and arterioles are responsible for pressure regulation, it is reasonable to expect that length adaptation in these vessels will play a role for the function of the arterial system. For example, Tuna et al. (2011) suggested that length adaptation can be related to inward remodelling of resistance vessels which is a hallmark of hypertensive disorders. Normal arteries operate at diameters just below the maximum isometric force and the cytoskeleton does not contribute to the passive properties (Tuna et al., 2011, Fig. 1). Under a sustained contraction at low distension, e.g., following an acute pressure increase, the smooth muscle cells undergo length adaptation through a reorganisation of the cytoskeleton. The adaptation shifts the diameter for the maximum isometric force towards the new contracted and smaller diameter. The length adaptation is much faster than the remodelling of the extracellular matrix. As a consequence, the reorganised cytoskeleton will now act as a brake and resist a full dilation of the passive vessel back to the original diameter (Martinez-Lemus et al., 2004). The length adaptation process could, therefore, explain the inward remodelling seen in hypertension, at least partially.

Previously, mathematical models have been used to study length adaptation in airway smooth muscles, see, e.g., Silveira et al. (2005), Ijpma et al. (2011) and Donovan (2013). Models for length adaptation in the vascular system are very rare, however, particularly models based on continuum mechanics. A notable exception is the recent study of Murtada et al. (2015). The continuum mechanical modelling is equipped with several challenges. First, the limited number of studies for length adaptation in vascular smooth muscles makes it difficult to find relevant data. Second, the available experimental data are often obtained or manipulated in a way that makes them inappropriate for continuum mechanical modelling. For example, in uniaxial extension tests of muscles it is customary to measure the optimal length for which the generated force is maximised. The muscle length is then normalised with respect to this value rather than the undeformed length which is customary in solid mechanics. Furthermore, if the study fails to give the specimen's undeformed geometry, it is virtually impossible to compute the stress and deformation quantities needed in the modelling. Given these limitations, any study involving the length adaptation in vascular smooth muscle will be subject to indirect evidence and qualitative comparisons to existing studies for other smooth muscles. This does not diminish the importance of studies, however. Given a solid model based on fundamental physical principles, parameter studies can tell us much about the behaviour of the underlying process. Parameter studies can also act as test guide for future experiments.

In this paper, we develop a novel micro-mechanically motivated continuum model for contractile filament length adaptation in smooth muscle. The model is an extension of previously published smooth muscle contraction models (Stålhand et al., 2008; Murtada et al., 2012; Sharifimajd and Stålhand, 2014) and is derived from fundamental principles to assert a mechanically and thermodynamically consistent behaviour. The number of parameters are also kept to a minimum to facilitate their identification from standard experiments. The model is presented in Section 2 and it is then specialised to hamster cheek pouch arterioles in Section 3. Finally, it is used to simulate length adaptation in Section 4.

2. Continuum model

In this section, we present a continuum model for smooth muscle length adaptation under sustained contraction. The model is nonlinear and assumes a homogeneous deformation field.

The force in the smooth muscle cell is generated by the contractile units, like in all other muscle cells. Even though there is no immediate equivalence to the contractile unit in a striated muscle, it is commonly defined to comprise two adjacent dense bodies including the actin and myosin filaments spanning between them. The contractile unit is modelled by a spring in series with a friction clutch. The spring accounts for the elasticity in the actomyosin network while the clutch symbolises the contractile effect generated by an ensemble of cycling cross-bridges.

2.1. Kinematics

Let the reference length of the contractile unit be L_0 and assume that the whole cell in its reference state comprises N_0 contractile units in series, see Fig. 1. Assume that a contraction, or an extension, can be described by a relative sliding of the filaments u_{fs}, followed by an elastic displacement of the actomyosin network u_{e}. Note that deformations are taken to be positive in extension throughout the text. Furthermore, assume that the filament length is uniform and remains invariant in the adaptation process. Then, any adaptation of the cell length is necessarily associated with a change in the number of contractile units in series. Let N be the number of contractile units in series in the cell after adaptation such that its length l in a contracted state becomes

$$l = N(L_0 + u_{\mathrm{fs}} + u_{\mathrm{e}}). \tag{1}$$

Since the deformation is assumed to be homogeneous, the stretch λ can be computed by dividing Eq. (1) with the referential cell length $N_0 L_0$, resulting to

$$\lambda = n(1 + \varepsilon_{\mathrm{fs}} + \varepsilon_{\mathrm{e}}), \tag{2}$$

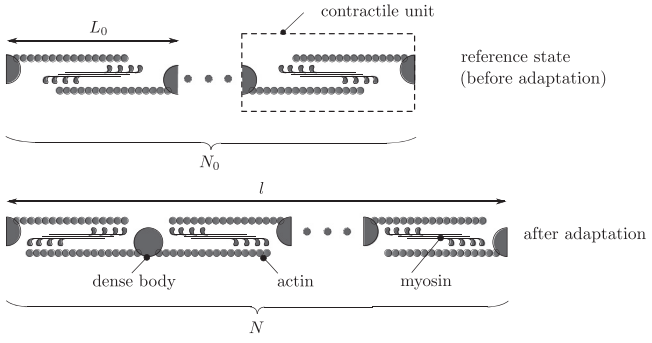

Fig. 1. Schematic representation of the smooth muscle length adaptation. The reference state comprises N_0 contractile units in series which changes to N contractile units after length adaptation.