Myosin filament polymerization and depolymerization in a model of partial length adaptation in airway smooth muscle

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Ijpma G, Al-Jumaily AM, Cairns SP, Sieck GC. Myosin filament polymerization and depolymerization in a model of partial length adaptation in airway smooth muscle. J Appl Physiol 111: 735–742, 2011. First published June 9, 2011; doi:10.1152/japplphysiol.00114.2011.—Length adaptation in airway smooth muscle (ASM) is attributed to reorganization of the cytoskeleton, and in particular the contractile elements. However, a constantly changing lung volume with tidal breathing (hence changing ASM length) is likely to restrict full adaptation of ASM for force generation. There is likely to be continuous length adaptation of ASM between states of incomplete or partial length adaptation. We propose a new model that assimilates findings on myosin filament polymerization/depolymerization, partial length adaptation, isometric force, and shortening velocity to describe this continuous length adaptation process. In this model, the ASM adapts to an optimal force-generating capacity in a repeating cycle of events. Initially the myosin filament, shortened by prior length changes, associates with two longer actin filaments. The actin filaments are located adjacent to the myosin filaments, such that all myosin heads overlap with actin to permit maximal cross-bridge cycling. Since in this model the actin filaments are usually longer than myosin filaments, the excess length of the actin filament is located randomly with respect to the myosin filament. Once activated, the myosin filament elongates by polymerization along the actin filaments, with the growth limited by the overlap of the actin filaments. During relaxation, the myosin filaments dissociate from the actin filaments, and then the cycle repeats. This process causes a gradual adaptation of force and instantaneous adaptation of shortening velocity. Good agreement is found between model simulations and the experimental data depicting the relationship between force development, myosin filament density, or shortening velocity and length.

shortening velocity; force adaptation; smooth muscle mechanics; asthma

THE SLIDING FILAMENT MECHANISM for contraction is thought to be similar in smooth and skeletal muscle. However, airway smooth muscle (ASM) has an ability to develop an identical maximum force over a wide range of lengths (28), whereas skeletal muscle has one specific optimal length for force generation (8). This difference is attributed to length adaptation (2), which is the ability of smooth muscle to reorganize its internal structure, particularly the actin and myosin filaments, upon length changes. Length adaptation is believed to play a key role in many diseases of ASM, for example, the reduced ability of deep inspiration to relieve airway constriction in asthma (4, 34). Clearly, a greater understanding of length adaptation is required to understand asthma and other respiratory ailments.

Length adaptation is postulated to occur through two mechanisms: the reorganization of the cytoskeleton, and the assembly/disassembly of contractile elements, i.e., one myosin filament with associated actin filaments (2, 10, 23). First, cytoskeletal reorganization may stem from mobility of contractile elements in the relaxed state, which allows for relocation of the contractile elements after a length change to a new organizational state, which is optimal for force generation. Second, changes of myosin and actin filament density indicate that myofilament assembly and disassembly contribute to length adaptation (13, 18, 24, 26). Both mechanisms may occur simultaneously to produce a change in the force and shortening velocity of the cell. The effective number of myosin heads acting in parallel, either by a change in contractile element length or a change in the average number of contractile elements acting in parallel, determines the maximum contractile force (25, 31). The average number of contractile elements acting in series, i.e., head to tail, determines the shortening velocity, assuming that the unloaded shortening velocity of a contractile element is determined solely by the cycling velocity of myosin heads (25, 28, 34).

Length adaptation cannot be seen directly in ASM, because the sarcomeric structure observed in skeletal muscle is absent (19). However, elongation or dissolution of actin and myosin filaments can be estimated from filament density measurements (1, 23, 24, 37). The largest variation in density occurs for myosin filaments, and in fully adapted muscle the myosin filament density is strongly length dependent (18, 23). Polymerization primarily occurs during contractile stimulation, whereas depolymerization seems to occur in the relaxed state facilitated by large length changes (24).

Current theories of length adaptation focus on the effective series-parallel reorganization in fully adapted muscle (10, 19, 25, 28, 31, 40), i.e., the state of the muscle after repeated contractions at a certain length have resulted in a stable maximum contractile force. The mathematical model of Silveira et al. (34, 35) was the first to attempt to explain the process of length adaptation in smooth muscle as a function of time. The model shows good agreement with data on the length dependence of force production, shortening velocity, and compliance for fully adapted ASM at different lengths. However, it was not tested for its ability to describe the process of change in the muscle in between fully adapted states, i.e., when the muscle is in a state of partial length adaptation. Recent data from Ali et al. on partial length adaptation (1) shows that the shortening velocity adapts instantaneously, which contradicts the model by Silveira et al. (34, 35). Ali et al. propose that, after a length change, contractile elements quickly reorganize to a new configuration, while polymerization of myosin to establish optimal filament overlap occurs gradually with repeated contractions. However, no further details were given to explain these changes.
Changes of partial length adaptation of ASM may play a key role in asthma (32, 34), given that the volume of the lung changes with tidal breathing, and, therefore, ASM is in a continuous state of partial length adaptation. Many studies also reveal that asthmatic lungs respond differently to breathing and, in particular, deep breathing (5, 11, 22, 41). Consequently, gaining knowledge on the processes that determine the time course of length adaptation is essential to understand the role of ASM behavior in asthma and other respiratory diseases. The aim of the present study was to develop a model that describes length adaptation based on the polymerization and depolymerization of myosin filaments and thereby explain the time course of both force and shortening velocity adaptation after length changes.

**MODEL DEVELOPMENT**

We developed a stochastic model of ASM length adaptation to yield a potential mechanism for the recent findings on partial length adaptation (1). The model describes the behavior of an ASM cell, which consists of a number of homogenously dispersed, axially oriented myosin filaments of different lengths, surrounded by an abundance of actin filaments. These actin filaments are attached to an immobile substrate, which deforms in direct proportion to the total length of the cell. The actin filaments are taken to be all of the same length, independent of the muscle length. This may reflect a physical limitation of the force exerted on either the myofilaments or the associated dense bodies, since actin filament length determines the maximum filament overlap and, therefore, the maximum force a contractile element can generate. Our model applies to the length range over which constant maximal force generation has been reported, which is approximately a threefold length range in ASM (28).

The model describes three main events (Fig. 1) as follows.

- **Contractile activation.** During a contractile stimulation, one myosin filament associates with two actin filaments in a side polar fashion (Fig. 1A), with an activation rate constant $\alpha$. While up to six actin filaments can associate with each myosin filament (12), the simplification to two actin filaments reduces the complexity and minimizes the number of elements for convergence of the model.

  \[
  f(t) = \frac{1}{0.127 \cdot 10^{-3} \gamma + 2.4 \cdot 10^{-4} \gamma + 1}
  \]

  (1)

  If length changes below the adapted length do not affect the subsequent contractile force development (20), this relation results from the amount of time the muscle spends at a length larger than the adapted length. The adapted length, in this case, is the length of the cell at the previous contraction. Consequently, in the current model, the variable

**Myosin polymerization.** After association with actin, the myosin filament elongates through polymerization along the actin filaments (Fig. 1B). Myosin filament polymerization is facilitated considerably by the close proximity of actin (30). It is assumed that myosin filaments polymerize at a constant rate ($\mu$) at both ends, until they have grown to the point of full overlap between both associated actin filaments. There are no direct measurements of myosin filament polymerization in the early phase of contraction, although indirect measurements of filament density have been made using birefringence microscopy (36). It is unclear to what extent the birefringence data correlate with myosin filament content, as polymerization of noncontractile filaments, changes in distribution of filaments, and actin filament growth could all be responsible for the reported birefringence increases. Nonetheless, it may indicate that polymerization occurs quickly from the onset of the contraction, being largely completed 10–20 s after initiation of contraction. Accordingly, we allow polymerization to occur faster than the rate of activation, so that the duration of contractions exceeds the growth phase of the myosin filaments. The $\mu$ value is taken as the minimum value satisfying this condition.

**Relaxation.** This involves dissociation of the myosin filament from the actin filament with rate constant $\gamma$ (Fig. 1C). The relative values of the rate constants for activation and relaxation determine the level of activation and, consequently, the number of active contractile elements. On subsequent contractile activation, the myosin filament will associate again with two random actin filaments (Fig. 1D). The $\gamma$ is estimated from the electrical field stimulation force-time curve (10).

**Full adaptation.** Repeated relaxation and activation of the cell at constant length results in full adaptation to this length.

**Myosin depolymerization.** Strain can induce depolymerization of dephosphorylated myosin filaments, whereas dephosphorylation persists (29). The rate of depolymerization may depend on the absolute cell strain, or be affected by oscillation dynamics. Oscillations in the relaxed state reduce subsequent contractile force development (24, 41, 42), and this may indicate reduced myosin filament density (24). Specifically, myosin filament density is reduced by approximately the same amount as subsequent contractile force after oscillations in relaxed muscle, with similar recovery rates as well (24). Therefore, in the current model, the myosin depolymerization rate is determined from data on force reduction after length oscillations in ASM. An approximately linear relationship was found between oscillation duration and the subsequent contractile force as a fraction of the maximum force (42). However, this linear relation can only exist for a small range of durations, as it would imply negative forces for large durations. Furthermore, an initial 10% drop in force for a single oscillation was found. A more realistic fit of the force ($f_f$), which is the fraction of the maximum force, as a function of duration is found

\[
O_d = \frac{d_1}{d_2}
\]
in Eq. 1 is replaced by \( r \), which is the integral of the length (\( L \)) above the adapted length (\( L_\text{a} \)) over time:

\[
r = \int_0^t I(0,\to)(L - L_\text{a}) \cdot (L - L_\text{a}) \, dt
\]  

(2)

With \( I(0,\to) \) (\( L \) minus \( L_\text{a} \)) as the indicator function,

\[
I(0,\to)(L - L_\text{a}) = \begin{cases} 
1 & \text{if } L - L_\text{a} \geq 0 \\
0 & \text{if } L - L_\text{a} < 0 
\end{cases}
\]

(3)

The above processes, when repeated, result in a gradual elongation of the myosin filament until full overlap of myofilaments occurs, which is maintained in subsequent contractions in the absence of length changes. These processes form the basis of the mathematical model presented here. Apart from the number of myosin filaments, the equations in the following sections do not affect the kinematics of the model.

The shortening velocity of smooth muscle has been shown to change during a contraction, which is likely governed by myosin light chain (MLC) phosphorylation levels. However, for the same MLC phosphorylation levels, the unloaded shortening velocity may also change as a result of reorganization of the contractile element network. As the present model is concerned with length adaptation, the shortening velocity changes in the early phase of contraction are ignored.

Unloaded shortening velocity is linearly related to length and is proportional to the myosin filament density, while the force of fully adapted ASM is independent of its length (Fig. 2A). Therefore, the number of contractile elements in series must be dependent on cell length. However, as the total force generated at full length adaptation is independent of length, the effective number of contractile elements in parallel has to remain constant. Consequently, the total number of contractile elements must be dependent on the cell length. The increase in the number of contractile elements with length may be the result of suboptimal orientation of actin filaments at short lengths. As the length of the cell is increased, the length-to-width ratio increases, and the actin filaments will be oriented more along the cell axis. This results in more parallel-oriented actin filaments, creating more potential sites for contractile element formation. The unloaded shortening velocity \( (V) \) is not directly proportional to the total cell length \( (L) \), but it shows an approximately linear relationship with length according to \( V = 0.63L + 0.33 \) \( (R^2 = 0.94) \), data from Ref. 28 \) for lengths above and including a preestablished reference length (Fig. 2C). Consequently, the number of myosin filaments \( (M) \) also scales with \( L \) according to:

\[
M = 0.63L + 0.33
\]

(4)

This relation may reflect the contribution of the deformation of passive structural components to the deformation of the cell. Hence, the actual deformation of the contractile element network follows the same relation:

\[
L_\text{cen} = 0.63L + 0.33
\]

(5)

where \( L_\text{cen} \) is the effective contractile element network length.

Force. Contractile elements generate force only when cross-bridge cycling occurs, with the contribution to the force of noncontractile structures and inertia being ignored. The mechanical response of the contractile elements is governed by the Hill equation relating force and velocity \( (\dot{V}) \), which is a simplification of actual contractile dynamics. The more elaborate model by Hai and Murphy (15, 16) also represents cross-bridge cycling in ASM, but is unsuitable for multielement simulations. Furthermore, any contribution of contractile elements to the dynamic response of ASM \( (7, 27) \) may be dominated by passive viscoelastic dynamics \( (20) \). However, in the present model, initial higher shortening velocities can be modeled adequately by varying Hill constants with contraction time.

The contractile element force \( (f) \) is corrected for the total number of available myosin heads for cross-bridge cycling, which is proportional to the overlap length of myosin and actin filaments \( (O) \). Implementing the velocity as the rate of length change of the contractile element \( (\dot{l}) \), the force can be written as:

\[
f(t) = \begin{cases} 
bf_0 - la & \text{when } f(t) < f_0 \\
bl + b & \text{when } f(t) < f_0
\end{cases}
\]

(6)

with \( a \) and \( b \) as the Hill constants, and \( f_0 \) as the isometric muscle force. The first line of the equation is the typical Hill curve, whereas the second line represents a linear continuation of the Hill curve as found experimentally in Ref. 17 and applied in Ref. 3.

In the model, the filaments are rigid and inextensible, resulting in relative sliding of myofilaments with length changes in contracted muscle. Static balance of forces along the length of the cell requires that the total force in any given cross section of the muscle be constant and equal to the total axial force of the muscle. Hence the total force
F in the cell can be determined by the average cross-sectional force of the elements in the network as given by:

\[ F = \sum_{i=1}^{n} \frac{l_i}{L_{cen}} f_i \]  

(7)

where \( l_i \) is the \( i \)th contractile element length, and \( n \) the number of active contractile elements.

**Shortening velocity.** The shortening velocity is usually measured by suddenly releasing a muscle previously held at a constant length and allowing it to shorten at a constant clamp force (14). This procedure cannot be simulated in our model. However, the potential unloaded shortening velocity can be determined from the organization and length of contractile elements. If each contractile element is governed by the same force-velocity relationship, then the absolute unloaded shortening velocity of each element is identical. The total shortening velocity of the cell is then dependent only on the average number of active contractile elements in series. A pure series configuration of the contractile elements does not exist when there is considerable overlap of elements. However, the effective number of elements in series (CEs), multiplied by the average number of elements in parallel (CEp), must be equal to the total number of elements, i.e.:

\[ n = CE_p CE_s \]  

(8)

CEp is proportional to the total force calculated by Eq. 7. This results in:

\[ CE_p = \sum_{i=1}^{n} \frac{l_i}{L_{cen}} \]  

(9)

This leads to an unloaded shortening velocity \( V \) of

\[ V = \frac{n}{\sum_{i=1}^{n} \frac{l_i}{L_{cen}}} = \frac{v}{L_{cen}} \]  

(10)

where \( v \) is the unloaded shortening velocity of a contractile element. In fully adapted cells, the \( l_i \) is independent of the cell length, and, therefore, the sum of \( l_i \) over all contractile elements is equal to the number of contractile elements multiplied by \( l_i \). Consequently, Eq. 10 reduces to:

\[ V = nL_{cen} vl_i = nli \]  

(11)

From this equation it is apparent that for a constant \( v \) and \( l_i \), there is a linear relationship between \( L_{cen} \) and \( V \).

**Model parameters.** The model uses data from canine ASM for parameter generation to describe the force-velocity relationship (17) and electrical field stimulation force-time curve (10). Partial length adaptation data from Ali et al. (1) are used to establish model parameters for myosin filament depolymerization after length changes. Full-length adaptation simulations are validated using data from Pratusevic et al. (28) and Kuo et al. (23). The parameter values are obtained from the literature (see text).

**RESULTS**

**Full-length adaptation.** To validate the model’s ability to simulate full-length adaptation, the model simulated 10 repeated cycles of 60 s of maximal activation, followed by 60 s of relaxation over a range of lengths (Fig. 2). Model predictions for full adaptation of isometric force, myosin filament density, shortening velocity, and compliance as a function of cell length during the 10th contraction at each length are closely matched by the experimental data (19, 24). Compliance was calculated through the inverse of the contractile element network stiffness. The stiffness of a contractile element is proportional to the overlap length of the myosin filament with the actin filaments, and the total stiffness \( (K) \) being proportional to the length according to:

\[ K \sim \sum_{i=1}^{n} \frac{l_i}{L} \]  

(12)

The relation between the length and shortening velocity is an imposed model condition, but the myosin filament density and compliance relations are model outcomes. The nonlinear simulation result for compliance can also be derived from Eqs. 4 and 12: assuming that at full-length adaptation \( l_i \) is equal to \( O \) and length independent, \( K \) is proportional to the number of elements \( n \) divided by \( L \). The number of elements is proportional to the contractile element network length, which is governed by Eq. 4. Consequently, the compliance \( (C) \) is proportional to:

\[ C \sim \frac{L}{0.63L + 0.33} \]  

(13)

**Partial-length adaptation.** The simulated force, myosin filament density, and the shortening velocity during repeated length changes in both directions are shown in Fig. 3. The simulation commenced at small myosin filament lengths, and the cell was subjected to repeated cycles of 60-s contraction and 60-s relaxation with any length change applied in the relaxed state. A gradual increase in force and myosin filament density occurs with each length increase, and unloaded shortening velocity instantly adapts to the new length. While the myosin filament content increases in parallel with an increase in force, the shortening velocity remains constant throughout; however, small variations in either direction occur after a length change. Length reductions do not give rise to a gradual adaptation process, but rather show an instant adaptation to the reduced length.

### Table 1. Parameter values. Length adaptation model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha ), s(^{-1} )</td>
<td>0.1</td>
<td>10</td>
</tr>
<tr>
<td>( \gamma ), s(^{-1} )</td>
<td>0.2</td>
<td>10</td>
</tr>
<tr>
<td>( \mu ), s(^{-1} )</td>
<td>0.00135</td>
<td></td>
</tr>
<tr>
<td>( L_A )</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>( a )</td>
<td>0.192</td>
<td>3</td>
</tr>
<tr>
<td>( b ), s(^{-1} )</td>
<td>0.035</td>
<td>3</td>
</tr>
<tr>
<td>( F_0 )</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

\( \alpha, \gamma, \mu: \) Rate constants; \( L_A \), adapted length; \( a \) and \( b \), Hill constants; \( F_0 \), force, in fully adapted muscle; \( L_A \) and \( F_0 \) are designated as 1. Other values are obtained from the literature (see text).
Figure 4 shows the effect of the timing of length changes on the isometric force response. In each simulation, the total cell length was reduced by 50% from the initial length, with the length change applied either 10 s before, or 10 or 80 s after activation. Figure 4 shows that length reductions after activation reduce the peak contractile force, with a progressively diminishing peak force as the time between activation and length reduction is increased. In subsequent activation-relaxation cycles, this force gradually recovers to the peak force achieved without length change.

Cyclic loading. Figure 5 shows the effect of continuous sinusoidal length oscillations with an amplitude of 4% of the initial length and also with a single sinusoidal stretch and release of 30% of the initial length at time \( t = 500 \) s (in line with deep inspiration). The length oscillations caused a reduced contractile force and a lesser force decline with the larger oscillation. While a considerable reduction in myosin filament density was found, the shortening velocity remained unaffected.

DISCUSSION

The main finding of this work is that a simple stochastic model of myosin filament polymerization and depolymerization can adequately describe the main characteristics of both partial and full-length adaptation. An important development with our model is that it accurately describes partial-length adaptation, in particular with regards to gradual-length adaptation of force and instantaneous adaption of shortening velocity (1). Our model also shows good agreement with full-length adaptation data (23, 28) (Fig. 2), as shown with other models (25, 34).

Partial-length adaptation. Our model (Fig. 3) accurately simulates the main features of partial-length adaptation: the force adapts gradually with successive contractions, while the...
shortening velocity adapts instantaneously (1). The gradual force adaptation results from gradual shortening of the myosin filaments (i.e., myosin polymerization), combined with greater overlap of the associated actin filaments with each successive contraction. Furthermore, the simulated myosin filament density follows the same curve to full adaptation as for isometric force (1). The shortening velocity is determined by the effective number of contractile elements in series, which is dependent on both the number and length of contractile elements. As the number of myosin filaments adjusts instantaneously to a new length, after which it remains constant if the length is maintained, the average contractile element length, i.e., the length between the dense body attachments, must also be constant. This constant average length is a consequence of the random location of actin filaments relative to the myosin filaments, which ensures that the average length always equals the actin filament length (Fig. 1). While individual contractile elements may change length in successive contractions, the average length remains constant.

Force is reduced immediately after a length increase (Fig. 3), while the myosin filament density of the next contraction is almost unchanged, but increases in subsequent contractions. The reduction in myosin filament length caused by a length change is compensated by the increase in the number of myosin filaments in the first contraction, as may be the case in Ref. 1. However, the newly appeared myosin filaments are short, and the length of the remaining filaments is also slightly reduced, resulting in the simulated decline of force.

The extent of force recovery with each contraction is higher in the simulations than in experimental data, possibly due to the model having fewer actin filaments associated with each myosin filament. The extent of recovery in the model is calculated from the statistically expected overlap of the associated actin filaments (Oa), which predicts the new myosin filament length l_{m2}. The total overlap in a single contractile element consisting of one myosin filament and p actin filaments is given by:

\[
O_a = p[l_m + 2 \min(d_1, l_a - l_m - d_2, \ldots, l_a - l_m - d_p)] = pl_{m2}
\]  

(14)

where \(d_i\) are the distances between the dense bodies associated with each actin filament and the ends of the myosin filament. \(l_a\) and \(l_m\) are the actin and myosin filament lengths, respectively (Fig. 1). \(d_i\) and \(l_a - l_m - d_i\) are uniformly distributed between 0 and \(l_a - l_m\).

The probability distribution (\(Pr\)) for the minimum function is given by:

\[
Pr(\min_{i} x) = \frac{1}{p!} \frac{x^{p-1}}{(l_a - l_m)^p} \quad 0 \leq x \leq l_a - l_m
\]  

(15)

where \(\min_{i} = \min(d_1, l_a - l_m - d_2, \ldots, l_a - l_m - d_p)\).

Consequently, the expected value \(E(\min_{i})\) becomes:

\[
E(\min_{i}) = \int_{0}^{l_a - l_m} x \cdot p \cdot \frac{x^{p-1}}{(l_a - l_m)^p} dx = \frac{1}{p + 1} (l_a - l_m)
\]  

(16)

Evidently, an increase in the number of actin filaments associated with each myosin filament decreases the rate of recovery, with the recovery rate equal to \(2/(p + 1)\) per contraction. Furthermore, the rate of recovery is not affected by the length of the actin filaments, contrary to the model by Silveira et al. (34). The main mechanisms responsible for a change in length adaptation, according to our model, are the number of actin filaments associating with myosin filaments and the depolymerization of myosin filaments upon length changes. Depolymerization of myosin seems to be conditional on the dephosphorylation of the myosin heads (29). In asthma, inflammation of the ASM and surrounding tissues has been shown to prevent full relaxation of the ASM (39), which may prevent dephosphorylation of the myosin heads, and thus inhibit depolymerization. Furthermore, the length adaptive ability of asthmatic ASM may be further inhibited by the lack of mobility of the myosin and actin filaments in a persisting (partially) contracted state.

For length increases, the force reduction due to breaking of passive cross-links between cytoskeletal elements may cause the irreversible (without successive contractions) force reduction after length increases in contracted muscles. Consequently, permanent force reductions resulting from oscillations by contracted ASM are likely to occur when the maximum length during oscillation exceeds the adapted length. This is suggested by the finding of conservation of maximum contractile force after oscillations that do not exceed the adapted length (33). However, the model predicts instantaneous adaptation of all parameters after length reductions, contrary to the more gradual adaptation found in experimental data. We speculate that this is attributed to the effect of length changes on the cytoskeletal network, when slack in the cytoskeleton (38) reduces stiffness and, consequently, the force transmission from the contractile apparatus.

Our model (Fig. 4) shows that shortening of ASM during contraction reduces the force after stabilization. Also, a larger reduction occurs when shortening is applied later in the contractile process, as seen elsewhere (9). In our model, this involved a differential response of active and inactive contractile elements to a length change. An inactive myosin filament is thought to be free to move within the cell, so that, when activated after a length change, it associates with actin, leading to maximal overlap of the myosin heads with actin. However, when a length change is applied to an activated contractile element, the actin filaments slide along the myosin filament, and myosin heads may not align with actin. Consequently, the later during a contraction that a length change is applied, the greater will be the force decline.

\[E(l_{m2}) = l_m + 2E(\min_{i}) = l_m + \frac{2}{p + 1}(l_a - l_m)
\]  

(17)

Length oscillations. The simulations of tidal breathing (4% sinusoidal length oscillations, and a single sinusoidal stretch and release by 30% of initial length) showed that contractile force fell during oscillations, but the effect of a deep inspiration is slightly reduced (Fig. 5). We have demonstrated that passive mechanisms in ASM can play an important role in the dynamic force response (20). Hence the present model may underestimate the actual forces during oscillation, but this should not influence myosin filament density and unloaded
shortening velocity. The model shows that the rate of length adaptation does not affect unloaded shortening velocity, so that any change in shortening velocity in asthmatic ASM (6) may not be the result of a difference in length adaptive response. However, reduced length changes of ASM from increased airway wall stiffness (7) may result in much less myosin depolymerization and, consequently, less force reduction in asthma in response to deep inspiration.

Validity of simplifications in the model. MLC phosphorylation is not incorporated as a model parameter, despite its presumed role in regulating shortening velocity (15, 16) and (de)polymerization. However, as the shortening velocity has been found to change only during the initial phase of contraction in parallel with MLC phosphorylation, its effects are not expected to contribute to length adaptation. Similarly, if MLC phosphorylation regulates polymerization and depolymerization, then this could occur in the initial phase of contraction. This is not expected to considerably affect the model outcomes, as the total amount of polymerization is governed by the number of associated actin filaments, rather than the polymerization rate.

The assumed dependency of the number of myosin filaments on the cell length may stem from a change in relative orientation of actin filaments as the length-to-width ratio changes. While the myosin filament density is not modeled in Refs. 34 and 35, the length-to-width ratio has a similar effect on the series to parallel transition. As myosin filaments have been shown to polymerize along actin filaments, it is likely that a more parallel orientation of actin filaments increases the formation and growth of myosin filaments.

Actin filament length has been assumed constant so that contractile elements have an optimal length that is independent of the cell length. As force generation in fully adapted muscle is constant over a large length range, it is likely that either the force generated by contractile elements, or the force in the cytoskeleton has a maximum value. Consequently, the contractile element length has an optimal, length-independent, value. This optimal value may be self-regulating, as the contractile element or its connections with the dense bodies in the cell are incapable of withstanding forces greater than those at optimal length. This may also explain the long-term decrease in force after a temporary stretch of ASM during contraction as contractile elements disintegrate or detach. The good agreement between model simulations and experimental data (Figs. 2–4) implies a considerable role for myosin polymerization and depolymerization in length adaptation of ASM, without a need for actin (de)polymerization. The reduced-length adaptive potential of ASM with stabilized actin filaments indicates a role for actin filaments in the length adaptation process (21, 30). However, inhibition of actin filament polymerization does not influence myosin phosphorylation (26), indicating that it does not affect the length of the myosin filaments. Perhaps the actin density increase observed in ASM during contractile activation (18) is due to formation of passive links within the cytoskeletal network. Alternatively actin polymerization may occur during contraction to connect the contractile elements to the cytoskeletal network, and actin depolymerization occurs during relaxation (21).

In summary, this new model utilizes the processes of myosin filament elongation and mobility to simulate experimental data on mechanical responses and myofilament densities of ASM.

The model shows good agreement with data on both partial- and full-length adaptation.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

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