Stiffness-distortion sarcomere model for muscle simulation

MARIA V. RAZUMOVA,1,3 ANNA E. BUKATINA,1,4 AND KENNETH B. CAMPBELL1,2
Departments of 1Veterinary and Comparative Anatomy, Pharmacology and Physiology and
2Biological Systems Engineering, Washington State University, Pullman, Washington 99164;
3Department of Physics, Division of Biophysics, Moscow State University, Moscow; and 4Institute
of Theoretical and Experimental Biophysics, Russian Academy of Sciences, Puschino, Russia

Razumova, Maria V., Anna E. Bukatina, and Kenneth B. Campbell. Stiffness-distortion sarcomere model for muscle simulation. J. Appl. Physiol. 87(5): 1861–1876, 1999.—A relatively simple method is presented for incorporating cross-bridge mechanisms into a muscle model. The method is based on representing force in a half sarcomere as the product of the stiffness of all parallel cross bridges and their average distortion. Differential equations for sarcomeric stiffness are derived from a three-state kinetic scheme for the cross-bridge cycle. Differential equations for average distortion are derived from a distortional balance that accounts for distortion entering and leaving due to cross-bridge cycling and for distortion imposed by shearing motion between thick and thin filaments. The distortion equations are unique and enable sarcomere mechanodynamics to be described by only a few ordinary differential equations. Model predictions of small-amplitude step and sinusoidal responses agreed well with previously described experimental results and allowed unique interpretations to be made of various response components. Similarly good results were obtained for model reproductions of force-velocity and large-amplitude step and ramp responses. The model allowed reasonable predictions of contractile behavior by taking into account what is understood to be basic muscle contractile mechanisms.

mathematical model; muscle mechanics; muscle cross bridge; muscle contraction

THOSE WHO HAVE INTEGRATED muscle models into engineering applications have followed various approaches with more or less fidelity in representing contractile processes. As recounted in several reviews (36, 41, 42), serious attempts to capture the essence of muscle behavior have followed one of two options: Hill-based models [based on the experimental work of A. V. Hill (15)] or Huxley-based models [based on the theoretical work of A. F. Huxley (18)]. The pros and cons of Hill-based vs. Huxley-based muscle models have been enumerated repeatedly (30, 37, 41, 42). Briefly, Hill-based models incorporate phenomenological descriptions relating muscle force to shortening velocity and, in addition, often include the relationship between muscle tension and length. In contrast, Huxley-based models attempt to derive overall muscle behavior from basic contractile processes arising from sliding filament and actin-myosin interaction mechanisms. Because of their purported computational simplicity, Hill-based models have been the most popular (30, 37). However, the desirability of incorporating basic contractile mechanisms into a muscle model for application purposes, as with the Huxley-based approach, is well recognized (42), and various authors have given different means for reducing the computational complexity of Huxley-based models (12, 33, 38–40). Despite the elegance of these simplification attempts, a recent comparison between a Hill-based and a simplified Huxley-based model concluded that present theories of cross-bridge dynamics are not a suitable basis for development of mathematical models for force production in human skeletal muscle (8, 35) and that Hill-based models remain the preferred approach. Considering the immensity of our present understanding of contractile processes, it seems that the problem associated with integrating that knowledge into models for application purposes is more related to building a suitable bridge between the molecular and the macroscopic than to a deficiency in the understanding of molecular mechanisms.

Accordingly, the primary objective of this work was to simulate dynamic behavior of muscle with mathematical equations that were inspired by muscle contractile processes. In this sense, the model has its origins in contractile mechanisms but ultimately exists as a descriptor and predictor of general dynamic muscle phenomenology. This method of dynamic physiological modeling is an advance over previous modeling, based solely on limited phenomenological observations. Among the many uses for the resulting model, one will be to reproduce in vivo muscle function in animate movement simulations and to simulate muscle function in actuators in the control of robots or limb prostheses.

MODEL DESCRIPTION

Glossary

| A1, A2, D, R | Cross-bridge states and number of cross bridges in attached (A1, A2), detached (D), and regulatory (R) states, respectively |
| f, f', h, h', g, k_m, k_eq | Rate coefficients |
| f_r, f_o, h_o, h_b, g_0 | Reference values of rate coefficients in isometric condition |
| F(t) | Total force from all cross bridges |
| F | Constant muscle force |
| F_i (t) | Force from cross bridges in i state |
| F_o | Isometric force |
| e | Stiffness of 1 cross bridge |
| E_i = eA_i | Stiffness of all cross bridges in the i state |
| x_i | Average distortion among cross bridges in i state |
| X_i | Total distortion among cross bridges in i state |

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overlapping thick and thin filaments and are bounded by adjacent z lines. Thin filaments project from a z line toward the middle of the sarcomere. Thick filaments are centered between z lines. The two halves of a sarcomere are mirror images of one another such that the force generated in one half just balances the force generated in the other half, and there is no tendency for the thick filaments to move preferentially toward either z line. Force is generated as a result of interactions between thick and thin filaments through myosin cross bridges. Myosin cross bridges extend out of the thick filament and may be attached or not attached to their actin-binding sites on the thin filament. Because cross bridges along a thick filament are arranged in parallel with one another and because thick filaments within a sarcomere also are in parallel with each other, cross bridges within a half sarcomere are all in parallel. Thus the force generated in a half sarcomere equals the sum of forces generated by attached cross bridges in that half sarcomere.

Each cross bridge is considered to be linearly elastic. Force is generated when parallel, linearly elastic cross bridges in attached states are distorted. Cross bridges in detached states (i.e., those not bound to the thin filament) cannot generate force. Attached cross bridges (i.e., those capable of being distorted) may be in n different states. Thus the force generated by all cross bridges within a half sarcomere is given by

\[ F(t) = e \sum_{i=1}^{n} A_i(t) x_i(t) \]  

where \( e \) is the stiffness of a single cross bridge, \( A_i(t) \) is the number of parallel cross bridges in the ith of n attached state, and \( x_i(t) \) is the average distortion among cross bridges in the ith state.

Both \( A_i(t) \) and \( x_i(t) \) are dynamic variables that undergo changes with time to bring about dynamic variation in \( F(t) \). Because \( e \) is a constant and equal for all cross bridges in attached states, it may be brought inside the summation symbol to form \( eA_i(t) \) products, which physically represent the stiffness associated with each of the i populations within the n states, \( eA_i(t) = E_i(t) \). With this, Eq. 1 may be rewritten in a stiffness-distortion format

\[ F(t) = \sum_{i=1}^{n} E_i(t) x_i(t) \]  

Importantly, the population stiffness \( E_i(t) \) (unlike the single cross-bridge stiffness \( e \), which is a fixed value) is a dynamic variable that is subject to both transient and steady-state variations. The dynamic nature of this stiffness is a subject of detailed analysis in this work.

A dynamic sarcomere model consists of mathematical descriptions of processes responsible for time variations in \( E_i(t) \) and \( x_i(t) \). These processes may be divided into several categories: 1) availability of activator
calium; 2) changes in thick- and thin-filament overlap; 3) dynamics of myofilament regulatory proteins; and 4) cross-bridge kinetics. Of these, categories 3 and 4 represent a dynamic core that is modulated by processes in categories 1 and 2. For this reason, this report will focus only on processes within the dynamic core, i.e., myofilament regulation and cross-bridge kinetics during constant calcium activation. It will be shown that a sarcomere stiffness-distortion model based on myofilament regulation and cross-bridge kinetics generates the dynamic behaviors observed in the constantly calcium-activated muscle in response to 1) small-amplitude sinusoidal and step changes in muscle length, 2) perturbations used in protocols to generate the force-velocity relationship, and 3) large-amplitude step and ramp changes in muscle length.

Myofilament Regulation and Cross-Bridge Kinetics

We look for a blueprint for stiffness dynamics in some elementary aspects of muscle contraction kinetics. Consider the myofilament regulation and cross-bridge cycling scheme in Fig. 2, consisting of an actin thin filament, a regulatory tropomyosin-troponin complex, and a myosin cross bridge. The thin-filament regulatory unit may be in the “off” position ($R_{\text{off}}$) or the “on” position. Switching between off and on positions is governed by the “on” rate coefficient ($k_{\text{on}}$) and the “off” rate coefficient ($k_{\text{off}}$). These regulatory on and off rate coefficients vary depending on the concentration of available activator calcium, as given in Ref. 7. Here, we consider that activator calcium concentration is constant.

Cross bridges can be in attached ($A_1$ and $A_2$) and detached (D) states. Attached cross bridges may be in the pre-power-stroke ($A_1$) and post-power-stroke ($A_2$) states. The power stroke, representing the $A_1$ to $A_2$ transition, is the point in the cycle of chemical-to-mechanical energy transduction. Cross-bridge attachment can occur only when the regulatory unit is in the off configuration. Attachment, power stroke, and detachment occur cyclically. Steps in the cycle are governed by rate coefficients $f$, $f'$, $h$, $h'$, and $g$, where the forward attachment is governed by $f$, the forward power stroke is governed by $h$, and cross-bridge detachment is governed by $g$. Primes designate reverse reactions. Isometric force is generated as cross bridges go through the power stroke.

Ordinary differential equations for the cross-bridge kinetic scheme of Fig. 2 may be written from inspection as

$$\dot{R}(t) = k_{\text{on}} R_{\text{off}}(t) + f' A_1(t) + g A_2(t) - (k_{\text{off}} + f) D(t) \tag{3}$$

$$\dot{A}_1(t) = f D(t) + h' A_2(t) - (f' + h) A_1(t) \tag{4}$$

$$\dot{A}_2(t) = h A_1(t) - (h' + g) A_2(t) \tag{5}$$

where overdots indicate first time derivative, $R_{\text{off}}(t) = R_T - D(t) - A_1(t) - A_2(t)$, and $R_T$ is a constant representing the total number of cross bridges for a given filament overlap. Changes in filament overlap bring about changes in $R_T$ and thus influence cross-bridge recruitment through this mechanism. Such length-dependent changes will not be investigated here but may be easily introduced into the model during future studies.

Changes in $A_1(t)$ and $A_2(t)$ result in direct changes in $E_1(t)$ and $E_2(t)$ according to arguments transforming Eq. 1 to Eq. 2 and, thus, $A_1(t)$ and $A_2(t)$ will be referred to as stiffness variables. Equations 3–5 provide the basis for dynamic changes in stiffness.

Cross-Bridge Distortion

Whereas the preceding cross-bridge kinetic scheme and resulting differential equations are more or less similar to a great many previously published schemes (see Refs. 9, 10, and 16 for equivalent three-state cross-bridge cycle and Refs. 14, 22, 24, and 31 for similar myofilament regulation schemes), there is no satisfactory treatment available for dynamic changes in average cross-bridge distortion. Because our expression for force (Eq. 2) requires an assessment of average distortion, we provide an original treatment for average distortion in the following.
There are two mechanisms for inducing distortion in cross bridges (Fig. 3). During isometric conditions, the power stroke (i.e., the forward step in Fig. 2 regulated by the factor \( h \) and shown schematically in Fig. 3A) induces a distortion in the cross-bridge equivalent to the stretching of a spring that, on the average among \( A_2 \) cross bridges, is \( x_0 \). This \( x_0 \) distortion is lost from a single cross bridge both when it, in the \( A_2 \) state, returns to the \( A_1 \) state by the reverse power stroke (regulated by \( h' \)) and when it detaches during the \( A_2 \) to \( A_1 \) transition (regulated by \( g \)). In addition, changes in sarcomere length (SL) produce sliding movement between thick and thin filaments, causing \( x_2(t) \) to vary from \( x_0 \) (Fig. 3B).

The differential equations for \( x_0(t) \) may be derived by performing a distorsional balance over all parallel cross bridges in the \( A_2 \) state. The collective distortion among the parallel \( A_2 \) cross bridges differs from the force associated with these cross bridges only in not including the stiffness coefficient \( e \). This collective distortion is given by

\[
x_2(t) = A_2(t)x_0(t)
\]

where the \( x_2(t) \) is used to designate the collective distortion and the \( x_2(t) \) designates the average distortion among the \( A_2(t) \) cross bridges. \( x_2(t) \) at some \( t + \Delta t \) can be written as

\[
x_2(t + \Delta t) = x_2(t) + (\text{added distortion due to shear from change in SL over } \Delta t)
\]

\[
+ (\text{added distortion due to formation of new units with baseline distortion over } \Delta t)
\]

\[
- (\text{lost distortion due to detachment of distorted units over } \Delta t)
\]

where

\[
(\text{added distortion due to shear from change in SL over } \Delta t) = [(\text{externally imposed } \Delta S L) \times (\text{no. } A_2 \text{ cross bridges existent at } t)]
\]

\[
= \Delta S L \times A_2(t)
\]

\[
(\text{added distortion due to formation of new } A_2 \text{ cross bridges with } x_0 \text{ distortion over } \Delta t)
\]

\[
= [(\text{no. of newly formed } A_2 \text{ cross bridges}) \times (\text{distortion of newly formed cross bridges})]
\]

\[
= [h \times A_1(t)] \times \Delta t \times x_0(t)
\]

\[
(\text{lost distortion due to detachment of distorted units over } \Delta t)
\]

\[
= [(\text{no. of } A_2 \text{ cross bridges lost}) \times (\text{average distortion of these lost } A_2 \text{ cross bridges})]
\]

\[
= [(g + h') \times A_2(t)] \times \Delta t \times x_2(t)
\]

It is assumed that cross bridges enter the \( A_2 \) state from the \( A_1 \) state via the power stroke with \( x_0 \) distortion, regardless of whatever distortion they may have possessed in the \( A_1 \) state before the transition to \( A_2 \).

From the above, it can be written

\[
x_2(t + \Delta t) = x_2(t) + \Delta S L \times A_2(t) + [h \times A_1(t)] \times \Delta t \times x_0(t)
\]

Rearranging gives

\[
\frac{x_2(t + \Delta t) - x_2(t)}{\Delta t} = A_2(t) \frac{\Delta S L}{\Delta t}
\]

\[
+ [h \times A_1(t)] \times \left( x_0 + \frac{\Delta S L}{2} \right) - ((g + h') \times A_2(t)) \times x_2(t)
\]

Taking the limit as \( \Delta t \to 0 \), yields

\[
\dot{x}_2(t) = A_2(t)S \dot{S}(t) + \left( h \times A_1(t) \right) \dot{x}_0 - (g + h') \times A_2(t) \times x_2(t)
\]

Now, \( \dot{x}_2(t) \) may be eliminated by noting that differentiation of Eq. 6 yields

\[
\dot{x}_2(t) = \dot{A}_2(t)x_0(t) + A_2(t)\dot{x}_2(t)
\]
Equating Eqs. 9 and 10, making appropriate substitutions for \( A_2(t) \) from Eq. 5, and solving for \( x(t) \), gives the desired differential equation

\[
\dot{x}(t) = -h \frac{A_2(t)}{A_1(t)} [x(t) - x_0] + \dot{S}(t)
\]

(11)

In like manner, it can be shown that

\[
\dot{x}(t) = -h \frac{D(t)}{A_1(t)} \left[ \frac{A_2(t)}{A_1(t)} + h' \right] x(t) + \dot{S}(t)
\]

(12)

where cross bridges enter the \( A_1 \) state from \( D \) with no distortion and also return from \( A_2 \) via the reverse power stroke with no distortion.

Equations 11–12, describing the dynamic changes for average distortion of the post-power-stroke and pre-power-stroke states, are the key developments that allow a simplified model of sarcomeric dynamics. We know of only one other approach (34) that approximates that given here. However, the results from derivations in Ref. 34 apply only to small-amplitude changes in SL, whereas those given in Eqs. 11 and 12 apply generally to all length perturbations of any amplitude.

**Variable-Dependent Rate Coefficients**

From the differential Eqs. 3–5 and 11–12, it appears that \( S(t) \) drives the system only through its effect on cross-bridge distortion, with no impact at all on stiffness variables, \( A_1(t) \) and \( A_2(t) \). In fact, the stiffness variables may respond to \( S(t) \) through the indirect effect of \( S(t) \) on the rate coefficients. We introduce two of the several potential mechanisms for this into our model, but in so doing we encounter some theoretical difficulties.

Rate coefficient distortion dependence. A central tenet in the cross-bridge theory of muscle contraction is that rate coefficients governing state transitions depend on the mechanical distortions (strains) experienced by the cross bridge (13, 17, 18, 26). Previous treatments of these distortion-dependent effects have taken into account thermal effects causing a distribution of distortions within a population and the impact of strain energy on state transitions (see Appendix). One consequence of these considerations is that the differential equation describing distortion-dependent kinetic events becomes a partial differential equation in the distorsional variable. The resulting mathematical problem takes on a fair measure of difficulty.

There have been various approaches for simplifying the problem of distributed distortion among cross bridges. As outlined by Taylor et al. (33), the simplest and, probably, the most often used approach is simply to ignore the spatial derivative term and solve the resulting ordinary differential equations as if distortion in each cross-bridge state were uniform. More direct have been approaches to formally simplify the problem. Perhaps the first serious attempt was by Deshcherevskii (11), who considered that above one value of distortion, cross bridges were pulling in the direction of shortening, whereas for distortion below this value, cross bridges were hindering shortening. The detachment rate constant was then set to be single valued in each of these regions. This allowed completing a spatial integration over the distortion coordinate such that the partial derivative terms were reduced to variables, and the equations could be written in ordinary differential equation format. A related approach was used by Dijkstra et al. (12) where the distortion coordinate was discretized, and all cross bridges within a discrete distortion range \( x \pm 2 \delta x \) were grouped into a bin. All cross bridges within a bin possessed one value of rate coefficient, but that value varied between bins according to assigned discrete quantities. Ordinary differential equations were written for cross bridges entering and leaving each bin during filament sliding. In accord with the approach of Deschcherevskii (11), the number of bins employed by Dijkstra et al. (12) could be reduced to as few as two, and reasonable results were obtained. A third approach is to consider just small distorsional changes such that spatial average variations in the detachment rate coefficient are not large and can be ignored (34). This changed the role of the distorsional variable in the myofilament system by removing its function as a random variable, which allowed representing the system as a system of ordinary differential equations. Another approach is that of Zahalak (39, 40) where a distribution function for attached cross bridges was assumed, and integration was performed to determine the moments of the bond distribution giving rise to net population stiffness, force, and elastic energy. Ordinary differential equations for these quantities could then be written and integrated to determine their respective dynamic variation. All these approaches to simplification possess considerable merit but suffer in some details when more than one attached-crossbridge state needs to be considered.

Because the basic premise of our model was that muscle force equaled sarcomeric stiffness times average cross-bridge distortion (Eq. 2), our challenge was to find some reasonable relationship between population average rate coefficient and average distortion. We recognized that, starting with such elementary expressions as one may want for the relationship between the rate coefficient and a given \( x \), a strict mathematical derivation for relating the average rate coefficient to the average \( x \) cannot be found (see Appendix). However, as discussed by Thorson and White (34), variation in average distortion from its reference value would be associated with variation in the average rate coefficient from its reference value. To express this, it was convenient to adopt parametrically succinct functional forms that satisfied the experimental fact that the numbers of attached cross bridges decline during constant shortening (20). This meant that, during shortening, rate coefficients leading away from an attached state must increase relative to those leading into that state. Additional considerations resulted from adopting parameter values (Table 1), such that cross bridges in the \( A_1 \) state were short lived relative to cross bridges in the \( A_2 \) state (this is somewhat, but not totally, analogous with
the attachment rate coefficient the model by letting force in one cross bridge enhance bridges. We introduced force-bearing cooperativity into kind, i.e., that which could occur via force-bearing cross mechanism for variable-dependent rate coefficients is consistency, becomes the arbiter of model acceptability. As a result, model behavior, rather than internal arbitrarily formulated to achieve parametric succinctness. Constraints on kinetic relationships cannot reasonably be applied. Thus the distortion-dependent expressions are arbitrarily formulated to achieve parametric succinctness. As a result, model behavior, rather than internal consistency, becomes the arbiter of model acceptability.

Cooperative effects and rate coefficients. A second mechanism for variable-dependent rate coefficients is through cooperative effects (3). These cooperative effects may be of many kinds, but we focus on just one kind, i.e., that which could occur via force-bearing cross bridges. We introduced force-bearing cooperativity into the model by letting force in one cross bridge enhance the attachment rate coefficient \( f \) of a neighboring cross bridge. This enhancement occurs by modification of the activation energy for transition from detached \( D \) to attached \( A_1 \) state (Eq. A1 in Appendix); an attached neighbor reduces the activation energy for that transition. Each cross-bridge attachment site has two adjacent neighbors, and the equation for the attachment rate coefficient must account for the impact of force-bearing cross bridges at both neighboring sites. The neighboring effect may be represented in \( f \) by considering

\[
g = g_0 e^{(\alpha_0 - \alpha_1)^2}
\]  

(13)

In Eq. 13, the zero subscript refers to the value at the isometric condition, and \( \sigma \) is a parameter that grades distorsional dependence, \( \sigma = 0 \) meant no distortional dependence. Accordingly, when \( \sigma > 0 \) increased whether \( x_2 \) was forced below \( x_0 \), as during shortening, or above \( x_0 \), as during stretching. Retrospectively, we found that best results were obtained when \( \sigma \) took on a larger value when \( x_2 > x_0 \) than when \( x_2 < x_0 \). These different values for \( \sigma \) in these two distortion ranges are given in Table 1.

To summarize, the stiffness-distortion approach to muscle modeling leads to development of ordinary differential equation expressions for average distortion of attached cross-bridge states. This average distortion may then be used to introduce distortion dependence into population-average kinetic rate coefficients. Our approach is only an approximation because 1) no account is taken of the role of distortion dependence in the derivation from the macroscopic balances leading to Eqs. 3–5 and 11, 12 and these ordinary differential equations are global approximations of the partial differential equations that properly describe the detailed behavioral features of the system; and 2) lacking a strict mathematical relationship between population-average quantities, the underlying thermodynamic constraints on kinetic relationships cannot reasonably be applied. Thus the distortion-dependent expressions are arbitrarily formulated to achieve parametric succinctness. As a result, model behavior, rather than internal consistency, becomes the arbiter of model acceptability.

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\[
f = f_0 \left( 1 + \lambda^{A_1} \left[ e^{x_t/x_0} (n - 1) - 1 \right] + \lambda^{A_2} \left[ e^{x_t/x_0} (n - 1) - 1 \right] \right)
\]  

(15)

The \( \alpha \) subscript on the \( f \) reference value does not refer to the isometric value, as in distortion-dependent \( \alpha \), but to the value when no neighbors are in the force-bearing state.

Using the foregoing considerations, it may be derived that

\[
f = f_0 \left( 1 + \lambda^{A_1} \left[ e^{x_t/x_0} (n - 1) - 1 \right] + \lambda^{A_2} \left[ e^{x_t/x_0} (n - 1) - 1 \right] \right)
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\]  

(15)

The \( \alpha \) subscript on the \( f \) reference value does not refer to the isometric value, as in distortion-dependent \( \alpha \), but to the value when no neighbors are in the force-bearing state.
The model differential equations are nonlinear in that they contain products and ratios of state variables at several locations. In addition, the equations are nonlinear because the rate coefficients, which appear in the equations as multipliers of the state variables, depend on the distortion variables as a consequence of distortion-dependent effects and on variables of the cycle state because of cooperative effects. In its full nonlinear form, the model contains 10 parameters including 7 reference values for the rate coefficients \(k_{r0}, k_{gr}, f_r, f_{r0}, h_r, h_{r0}, g_0\); an index for distortion dependence \((\sigma)\); an index for cooperativity \((\nu)\); and a value for isometric distortion \((x_0)\).

**MODEL PROTOCOLS AND RESULTS**

The purpose of model protocols was to elicit dynamic features of the model that could be compared to experimentally determined dynamic features of constantly activated muscle. The initial focus was on history-dependent dynamic features arising from differential equation relations among variables. This was because such history-dependent dynamics are important features of constantly calcium-activated muscle, and these cannot be reproduced by Hill-based models. Second, the differential-equation-based model was examined for its ability to reproduce hyperbolic force-velocity behavior. Such special-case behavior is the essence of Hill-based models. Third, the model was asked to create large-amplitude behavior in which features of both history-dependent and force-velocity behaviors could be observed. Finally, to demonstrate its versatility, the model was modified to change its dynamic signature from one that is characteristic of skeletal muscle to one that is characteristic of cardiac muscle.

**Linear Dynamic Response**

The standard figures of merit for evaluating dynamic behavior of constantly activated muscle are the frequency-dependent complex stiffness determined by force responses to small-amplitude sinusoidal length changes \((21, 23)\) and the force response to step length changes \((1, 18)\). Accordingly, model-predicted small-amplitude behaviors were obtained by linearization procedures in which small deviations around a steady-state isometric value were considered, and then truncation was performed to eliminate second-order terms. Thus, for small length variation, \(\Delta L(t)\), around some baseline length, \(L_0\), Eq. 16 may be expanded to give

\[
F(t) = F_0 + \Delta F(t) = [E_1^0 + e_1(t)][x_0^t + \delta x_1(t)] + [E_2^0 + e_2(t)][x_0^t + \delta x_2(t)]
\]

\[
= (E_1^0 x_0^t + E_1^0 x_2^t) + [E_2^0 \delta x_1(t) + e_2(t) x_0^t + E_2^0 \delta x_2(t) + e_2(t) x_0^t] + [e_1(t) \delta x_1(t) + e_2(t) \delta x_2(t)]
\]

where \(e_1(t)\) is the variation in \(E_1\) induced by \(\Delta L(t)\), and \(\delta x_1(t)\) and \(\delta x_2(t)\) are corresponding variations induced in the respective variables, \(x_1\), \(E_2\), and \(x_2\). Superscript 0 refers to the value at the reference isometric condition. The three terms in square brackets on the right-hand side represent zero-order, first-order, and second-order effects, respectively. Truncation of Eq. 17 to eliminate second-order effects and substitution of the reference isometric values \(x_0^t = x_0^t = x_0^t = 0\) yield, for the isometric force

\[
F_0 = E_1^0 x_0^t
\]

and, for the linear small-amplitude variation in \(F(t)\) around \(F_0\)

\[
\Delta F(t) = E_1^0 \delta x_1(t) + E_2^0 \delta x_2(t) + x_0^t e_1(t)
\]

Note that \(e_1(t)\) does not enter into \(\Delta F(t)\), because the \(e_1(t)\) contribution is multiplied by \(x_0^t\), which is zero.

**Frequency-dependent complex stiffness.** The concept of stiffness embodied in the time-domain variables \(E_1(t)\) and \(E_2(t)\) is now generalized to the complex quantity \(\Delta F/\Delta L\) in the frequency domain. Taking the Fourier transform of Eq. 19 and dividing through by the Fourier transform of \(\Delta L(t)\) gives the incremental complex stiffness as

\[
\frac{\Delta F(j \omega)}{\Delta L(j \omega)} = E_1^0 \frac{\Delta x_1(j \omega)}{\Delta L(j \omega)} + E_2^0 \frac{\Delta x_2(j \omega)}{\Delta L(j \omega)} + x_0^t \frac{\Delta e_1(j \omega)}{\Delta L(j \omega)}
\]

where

\[
\frac{\Delta x_1(j \omega)}{\Delta L(j \omega)} = \frac{j \omega}{j \omega + f_r + f}
\]

\[
\frac{\Delta x_2(j \omega)}{\Delta L(j \omega)} = \frac{j \omega}{j \omega + g + h}
\]

\[
\frac{\Delta e_2(j \omega)}{\Delta L(j \omega)} = \frac{(k_3 + k_4 j \omega) \Delta x_1(j \omega)}{\Delta L(j \omega) + (k_5 + k_6 j \omega) \Delta x_2(j \omega)}
\]

Equations 21 and 22 were derived from linearized versions of Eqs. 11 and 12, and Eq. 23 was derived from the linearized, single third-order differential equation in \(e_2(t)\), resulting from the combination of the three cross-bridge state Eqs. 3-5. The \(k_i\) in Eq. 23 are combinations of the rate coefficients \(f, f', h, h', g\); these relations are given in the Appendix.

**Distortion-dependent features of \(g\) do not enter into \(k_i\) in this small-amplitude expression, because distortion dependence was formulated as affecting \(g\) only as a result of deviation from isometric (steady-state) values. These deviations fall out in the linearization procedure. Thus, the \(k_i\) depend just on the reference values of \(g\). In contrast, steady-state values depend strongly on the cooperative effects in \(f\). Consequently, the \(k_i\) do depend on the cooperative effects in \(f\) as they appear in the truncated series expansion. Through these effects, the distortional variables \(x_1\) and \(x_2\) appear in the numerator of Eq. 23 as a result of the dependence of \(f\) on \(x_1\) and \(x_2\) in Eq. 15.
Model-predicted complex stiffness consists of three components corresponding to the three terms on the right-hand side of Eq. 20. It is important to note that the physical units for each of the three terms derive from the stiffness variable as it was used in Eq. 2. However, the dynamic features in two of these three complex-stiffness components derive from dimensionless dynamics of distortional variables. We refer to each of these components as the $x_1$, $x_2$, and $e_2$, respectively, because: 1) the frequency dependence of the first component derives from the dynamic response of $x_1$ to changes in length; 2) the frequency dependence of the second component derives from the dynamic response of $x_2$ to changes in length; and 3) the frequency dependence of the third component derives from the dynamic response of $e_2$ to changes in length.

Utilizing a model parameter set (Table 1) that yielded negative-phase complex stiffness at frequencies within the 1- to 10-Hz range, the polar plot of the model-predicted overall complex stiffness and of each of its component parts was determined as shown in Fig. 4. The model-predicted frequency variation in the overall complex stiffness (Fig. 4, A) is reminiscent of experimentally measured complex stiffness of skeletal muscle (4, 19) in exhibiting a looping locus that may be divided into three regions: a low-frequency positive-phase region (<1 Hz); a midfrequency negative-phase region (for frequencies in a range roughly between 1 and 10 Hz); and a high-frequency positive-phase region (>10 Hz). These various regions reflect changing contributions of the three components, i.e., the $x_1$, $x_2$, and $e_2$ components from Eq. 20. For instance, compare the relative magnitudes of the complex vector for each of the three components at 1 Hz (Fig. 4, A, B, and C). From these relative magnitudes, it can be concluded that the low-frequency positive-phase region of the overall complex stiffness is dominated by the $x_1$ and $x_2$ components (each with large vectors at 1 Hz), with the $x_1$ component (with an extremely small vector at 1 Hz) playing a negligible role. The midfrequency negative-phase region is due to the predominance of the imaginary part of the $e_2$ component; it being the only component with a negative imaginary part and a locus that enters the fourth quadrant. The transition from negative phase to positive phase as frequencies increase above 10 Hz is due to the increasing importance of dynamics associated with the $x_2$ component.

The genesis of complex stiffness in terms of relative contributions of the three above components is unique to the present model and contrasts with previous reproductions of experimentally determined stiffness dynamics using sums of exponentials (1) or sums of first-order filters (43). At least two important interpretative points are to be made from the present model results. The first of these concerns the mechanisms responsible for the negative-phase region of the overall complex stiffness. The negative-phase frequencies are frequencies of positive work (32, 34) in which the subject (muscle or model) is capable of doing work on its (actual or simulated) mechanical environment. At all frequencies of positive-phase complex stiffness, the mechanical environment performs work on the subject. The negative-phase frequencies in the overall model (i.e., the frequencies of positive work) arise because of the dominance of $e_2$ dynamics at these frequencies. Importantly, these $e_2$ dynamics are representative of the entire myofilament-regulation/cross-bridge-cycle system. This may be appreciated by recognizing that the roots of the characteristic equation of Eq. 23 represent the essential dynamic features of the $e_2$ component response and depend on combinations of the $k_i$. In turn, the $k_i$ depend on products and sums of all the rate coefficients (Appendix) in such a way that no single rate coefficient dominates in determining any individual eigenvalue. Thus myofilament regulatory and cross-bridge cycling processes combine in a complicated fashion to determine overall model dynamics at frequencies in the negative-phase, or positive-work, region of the complex stiffness.

This demonstrates that the power stroke has no more obvious influence on the dynamics of positive work than any other step in the cycle. Instead, positive work is the result of a recruitment phenomenon where the relative rates of cross-bridge association exceed those of dissociation, and the $A_2$ state (isometric force-bearing state) is transiently populated to a greater extent than during the initial isometric conditions (which is clearly demonstrated in the delayed tension response to a step shown

---

Fig. 4. Polar plots of model-generated overall complex stiffness (A) and its 3 dynamic components (B, C, and D) over frequency range 0–50 Hz. Distortion dynamics contribute to complex stiffness through the $x_1$ and $x_2$ components. The $e_2$ component expresses dynamics of cross-bridge recruitment. Frequencies of 1 Hz and 10 Hz (●) are marked on polar plots. Magnitudes of complex vector at 1 Hz in each of 3 component polar plots are indicated. Vector in the overall complex stiffness is the sum of vectors in the 3 components. Contributions of each component to overall complex stiffness changes with changes in the respective component vectors at each frequency. $\omega$, Frequency of sinusoidal length changing; Im, imaginary; Re, real.
The kinetics of the recruitment phenomenon responsible for negative-phase frequencies of the complex stiffness should not be confused with the kinetics of the power stroke. Whereas the dynamic features of the recruitment phenomenon are determined by dynamic features of the entire system, the origin and magnitude of the recruitment response are due entirely to the cooperative effect in $f$. This can be appreciated by examining the influence of changes in $v$, the coefficient expressing strength of the cooperative effect, on complex stiffness. In Fig. 5A, the polar plot of the overall complex stiffness has been normalized to the steady-state stiffness, and changes for different values of $v$ are given that correspond to no cooperative effect ($v = 1$), modest cooperative effect ($v = 2.7$), and strong cooperative effect ($v = 3$). The polar plots for the associated $e_2$ component are given in Fig. 5B. Clearly, the magnitude of the $e_2$ component increases with increasing $v$ and, since this is the only component of the overall response that is affected by $v$, these changing magnitudes of the $e_2$ component are entirely responsible for the looping behavior of the overall response that leads to negative-phase (and positive-work) behaviors.

A second important interpretive point arises from the increasing importance and eventual dominance of dynamics associated with the $x_1$ component at frequencies approaching and surpassing 10 Hz. This implicates an important mechanical role for the pre-power-stroke state at frequencies that are within the range of frequencies of physiological importance. Consequently, the pre-power-stroke state is not weakly bound in the usual sense (4, 5) and may not be lumped with detached states as in two-state cycle schemes. As others have

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**Fig. 5.** Changes in model-generated complex-stiffness polar plot (A) plus its $e_2$ component (B) and the step response (C) plus its $e_2$ component (D) with varying degrees of cooperativity. In all panels, thick lines are results with strong cooperative effect ($v = 3$); thin lines are results with moderate cooperative effect ($v = 2.7$); and dashed lines (which reduce to the dot at the origin in B) are results with no cooperative effect ($v = 1$). Complex stiffness at 1 and 10 Hz are indicated by $\circ$ and $\bullet$, respectively. Among the 3 components of the overall dynamic response (A, B, C, in Figs. 5 and 7), cooperativity impacts just dynamic changes in the $e_2$ component. Thus $e_2$ component alone is responsible for changes in the overall response with changes in cooperativity. See Glossary for symbol definitions.

---

**Fig. 6.** Model-generated small-amplitude step response (A) and its dynamic components (B, C, and D). This time-domain step response and its components were calculated directly from frequency-domain complex stiffness and its respective components given in Fig. 4. Overall response is the sum of the 3 components.
found (34), a three-state cross-bridge cycle appears to be a minimum configuration for reproducing the full frequency spectrum of the characteristic frequency-dependent complex stiffness.

Step response. The time domain step response (Fig. 5C and Fig. 6A) and respective component responses (Fig. 6, A–C) corresponding to the polar plots in Fig. 4 were obtained by operations on Eqs. 25–27 to allow solving for the respective time-domain dynamic variables. This was done by rearranging Eqs. 25–27 to solve explicitly for \( F(\omega) \), \( x_1(\omega) \), \( x_2(\omega) \), and \( e_2(\omega) \) assigning \( L(\omega) = 1/\omega \), and then taking the inverse Fourier transform to solve for \( F(t) \), \( x_1(t) \), \( x_2(t) \), and \( e_2(t) \).

The small-amplitude model-predicted step response had important features in common with experimentally measured step responses, as described in Refs. 1, 18. Both model-predicted and experimentally measured responses possess a leading edge coincident with the leading edge of the length step, a rapid recovery phase, and a delayed tension transient. In Fig. 5C, the dashed line is the sum of just the \( x_1 \) and \( x_2 \) component responses. From this, it can be seen that the leading edge and rapid recovery phases are due to the \( x_1 \) and \( x_2 \) component responses, i.e., they are due to distortional responses. The individual \( x_1 \) and \( x_2 \) component responses are qualitatively similar but quantitatively different. Their leading edges differ by the multiplying factors \( A_{10}^0 \) and \( A_{20}^0 \) of Eq. 20 and, from Eqs. 25, 26, their time courses of recovery are controlled by rate coefficients regulating transitions away from the respective states. The rate coefficient for \( x_1 \) recovery, \( h + f' = 408 \text{ s}^{-1} \) from Table 1), is much larger than the rate coefficient for \( x_2 \) recovery, \( g + h' = 10 \text{ s}^{-1} \) from Table 1). Thus, in line with the earlier argument about relative disturbances in \( x_1 \) and \( x_2 \) values at different velocities, length-change-induced distortion of the pre-power-stroke state recovers much faster than that for the post-power-stroke state; compare rate of recovery by \( x_1 \) component in Fig. 6A with that by \( x_2 \) component in Fig. 6B. The observability of these individual distortional recovery processes in the overall step response depends on their relative magnitudes and the separation of the time scale of their respective recoveries from one another and from the time scales of the \( e_2 \) response component.

The \( e_2 \) response component is responsible for the slowest part of the response or the delayed tension transient (Figs. 5D and 6C). The delayed tension transient is due to the transient recruitment of more cross bridges into the force-bearing \( A_2 \) state. As shown by Eq. 23, the \( e_2 \) response is being driven by distortion through the effect of the latter on force and the subsequent cooperative effect of force to enhance \( f \). This is not a result of distortion dependence in \( g \). These cooperative effects may be appreciated by results obtained by using different values of the parameter \( \nu \), which grades the magnitude of cooperativity. The delayed transients corresponding to the three polar plots of the \( e_2 \) component in Fig. 5B with strong, modest, and no cooperativity are shown in Fig. 5D.

From these results, it is clear that the step response is usefully decomposed into two distortional and one recruitment components. The distortional components are responsible for the initial and more rapid aspects of the response, and the recruitment component is responsible for the slower aspects, i.e., the delayed transient. The amplitude of the delayed transient depends critically on the magnitude of the cooperative effect. These components of the step response can be mapped one-for-one with their equivalences in the complex-frequency domain.

Force-Velocity Relationship

The force-velocity relationship is the most common figure of merit for muscle models that are used for applied purposes. The challenge was to take the present model, using parameters that produced the realistic small-amplitude responses in Figs. 4, 5, and 6, and generate realistic force-velocity relationships. Model predictions of steady-state velocity for a given constant force \( F \) were obtained by 1) rearranging the differential equations for distortion (Eqs. 11, 12) such that velocity was the dependent variable; 2) setting derivatives in all equations to zero to allow solving at steady state; 3) substituting to replace the distortion variables with their equivalent in terms of force (from Eq. 13); and 4) solving all resulting algebraic equations for velocity at different levels of force by using the Mathcad Levenberg-Marquardt optimization routine for solution of simultaneous, nonlinear, algebraic equations.

Model-predicted force-velocity relationships during shortening and stretch were made by using the same set of parameters (Table 1) as in the small-amplitude analysis. Results are presented in Fig. 7 as normalized for \( V_{\max} \) and \( F_0 \). These results are examined in two regions: force-shortening velocity \( (V/V_{\max} > 0) \), and force-stretching velocity \( (V/V_{\max} < 0) \).

In accord with experimental data obtained from a wide variety of muscles, the force-shortening velocity portion of the model-predicted curve was closely approximated by the hyperbolic curve of the classic Hill
force-velocity equation

\[
V = \frac{V_{\text{max}}}{1 - F/F_0} - \frac{1 - F/F_0}{1 + F/F_0}
\]

with \( \kappa = 0.15 \) for the closely fitting dashed curve in Fig. 7. Typical values of \( \kappa \) for muscle of many types range between 0.15 and 0.25 (25). Thus the value of \( \kappa \) that gave a close approximation to the model-predicted force-velocity relationship was within the accepted range. Given the close fit, similar to the fits obtained with experimental data from muscle and the acceptable \( \kappa \) value, it can be concluded that the model generated satisfactorily realistic force-velocity behavior.

The model-predicted force-stretching velocity region also shares important characteristics in common with muscle, in demonstrating an initial shallow dependence of velocity on force for small clamps above \( F_0 \) and then increasingly larger velocities for larger force clamps. This behavior is unlike that in the force-shortening velocity region and cannot be approximated by the classic Hill force-velocity curve. Similar to actual muscle, "yielding" (19) was observed in the model predictions as force approached an apparent asymptotic value somewhere in the neighborhood of 2 \( F_0 \). A clear asymptote could not be defined by our methods, because the numerical solution procedure became unreliable as the asymptote was approached. Nonetheless, evidence for yielding can clearly be seen in Fig. 7, in those parts of the curve that were obtained at the highest force levels allowed by our numerical procedures.

We examined features of the model responsible for the force-velocity predictions. Whereas distortion-dependent \( g \) played no role in the small-amplitude sinusoidal and step-response model predictions (these small-amplitude behaviors were strongly impacted by the cooperative effects in \( f \), as shown in Fig. 5), distortion-dependent \( g \) played an important role in the force-velocity relationship. We sought to determine the relative contributions of cooperativity in \( f \) and distortion dependence in \( g \) in the force-velocity relationship.

When \( f \) and \( g \) were frozen at their values in the isometric condition, the model predicted a linear force-velocity relationship, as given by the straight line in Fig. 8. In this case, the maximal velocity of shortening was much less (\( \approx 65\% \)) than what was obtained with the full model. When only \( f \) was allowed to vary by expressing cooperative effects, the dotted curve below the straight line in Fig. 8 was obtained. From this it can be seen that these cooperative effects in \( f \), by themselves, tend to reduce the velocity at any given load. This effect is most pronounced at middle loads, and there is no effect on the \( V_{\text{max}} \) at zero load. Furthermore, these cooperative effects in \( f \) did not result in a detectable yielding behavior in the force-stretching velocity region, as velocity retained only a shallow dependence on \( F \) during stretching. In contrast, when \( f \) was frozen at its isometric value and only \( g \) was allowed to change with distortion, the dashed curve in Fig. 8 was obtained. From this, it is seen that the distortion dependence in \( g \) had its greatest effect during shortening at low loads where it brought about a considerable increase in shortening velocity, including a substantial increase in \( V_{\text{max}} \). In addition, distortion dependence in \( g \) caused a pronounced yielding effect with an apparent force asymptote at a load only slightly higher than isometric force.

When both cooperative effects in \( f \) and distortion dependence in \( g \) were taken together, the resultant curve was bounded by the effects of \( f \) alone and of \( g \) alone. At the lowest loads during shortening and the highest loads during stretching, the effects of distortion dependence in \( g \) predominated to elevate \( V_{\text{max}} \) and cause yielding. At intermediate loads (\( 0.5 \text{--} 1.5 F_0 \)), the effects of cooperativity in \( f \) predominated. The transition between dominance by distortion dependence in \( g \) and cooperative effects in \( f \) resulted in a curve that was much more curvilinear than would be obtained by either effect alone.

To test the validity of our assumption that distortion dependence in \( g \) was the most important distortion-dependent effect among the rate coefficients, the remaining rate coefficients were assigned distortion dependence according to

\[
h = h_0 e^{x_2}
\]

\[
f' = f_0 e^{x_2}
\]

\[
h' = h_0 e^{x_2 - x_1}
\]

When these, all with the same distortion-dependent coefficient \( \sigma \), were incorporated into the model, and force-velocity was predicted, it was found that, relative to distortion dependence only in \( g \), distortion dependence in all rate coefficients caused an increase in \( V_{\text{max}} \), a slightly greater tendency for yielding during shortening, and a slightly greater tendency for yielding during stretching. These effects, due to distortion dependence in all coefficients, were a matter of degree only, and it was concluded that,
for all intents and purposes, the effects of distortion
dependence in g alone sufficed to enable the model to
predict the important behaviors due to distortion-
dependent rate coefficient effects.

In addition to the influence on the force-velocity
relationship of varying rate coefficients with coopera-
tive effects and distortion dependence, we investigated
the sensitivity of this relationship to fixed quantities of
selected rate coefficients. In Fig. 9, we compared
the sensitivity to the forward rate coefficient governing the
power stroke, h, to that governing detachment, g. The
reference curve of Fig. 7 (calculated with the param-
eters of Table 1: h = 8 s^{-1}, g = 4 s^{-1}) is reproduced in
Fig. 9, A and B, as the solid curve. In Fig. 9A, results
from variation in h were obtained by setting h to be
variously 12 and 4 s^{-1} and by calculating new force-
velocity curves. These were then graphed by using V_{max}
and F_{0} of the reference curve as normalizing factors.
Changes in h had a large effect on curve orientation and
isometric force but very little effect on V_{max}. A decrease
in h shifted the curve down so as to decrease F_{0}; an
increase in h shifted the curve up so as to increase F_{0}.
Even though changes in h did not change V_{max} appreci-
able, these brought about marked changes in shortening
velocity for all F > 0. This is not unexpected as one
would anticipate shortening velocity to be influenced by
the speed of the power stroke (likened to the cross-
bridge rowing motion that propels filaments past one
another).

In Fig. 9B, results from variation in isometric g were
obtained according to the following: g = 4 s^{-1} was made to be
variously 6 and 2 s^{-1}, distortion-dependent g was
calculated according to Eq. 13, and the resulting force-
velocity curves were normalized as was done in Fig. 9A.
An increase in isometric g caused a decrease in isometric
force and an increase in V_{max}, whereas a decrease in
isometric g had opposite effects. Thus isometric force is
enhanced by changes in kinetic coefficients that pro-
vote the formation of the A_{2} state (increased h and/or
decreased g) while V_{max} is enhanced strongly by in-
creased A_{2} breakage due to increased g but only weakly
by increased h. The sensitivity of model-predicted
force-velocity relations to model parameters suggests
that the model may be used to describe and interpret
force-velocity data obtained from muscles of very differ-
ent characteristics.

Large-Amplitude Steps and Ramps

To predict responses to large-amplitude step and
ramp length change, 1) changes in SL(t) were imposed
analytically as a step and 2) Eqs. 3–5 and 11–12, which
included distortion-dependent and cooperative-depend-
ent rate coefficients, were integrated numerically by
using fourth-order Runge-Kutta integration; integra-
tion step size equaled 0.5 ms.

Large-amplitude step responses differ from small-
amplitude step responses in the rate of recovery from
the distortional response, in the relative amplitude and
time course of the delayed transient, and in asymmetry
of responses to stretch relative to those of release (Fig.
10). For release responses, the classic four phases of the
response may be identified as in Ref. 17. Force response
to large-amplitude ramp stretches differs from force
responses to ramp shortening (Fig. 11) in exhibiting
yielding during ramp stretches, which limits the magni-
dude of force (see especially curve a in Fig. 11). Yielding
in the response to positive ramps is as would be
expected from the yielding observed in the force-
stretching velocity relationship in Figs. 7 and 8. Thus
large-amplitude behaviors, obtained from the model by
numerical integration, exhibit features different from,
but consistent with, those derived analytically for
small-amplitude steps and with those derived from
steady-state solutions for force-velocity relationships.

These realistic large-amplitude step and ramp re-
sponses, in conjunction with realistic model-predicted
force-velocity relationships, lead us to conclude that the
model may, in general, be used with confidence in the
prediction of muscle behavior in response to large-
amplitude perturbations of all kinds.

Changes in Dynamic Profile to Represent Muscles
of Different Types

Large changes in the model’s dynamic profile may be
achieved with changes in model parameters. It was
shown in Fig. 5 that increases in the cooperative
weighting parameter v affected the polar plot of the

complex stiffness by increasing the size of the loop and increasing the frequency range of the negative-phase region. Also, it was shown in Fig. 9 that variations in the rate coefficients regulating the power stroke \( h \) and detachment \( g \) changed the curvature, \( V_{\text{max}} \), isometric force, and \( F_{\text{yield}} \) in the force-velocity curves in characteristically different ways. A systematic study of model sensitivity to all parameters is not warranted here, but suffice it to say that all parameters can be used to sculpt the shape of the complex-stiffness and force-velocity dynamic profiles to accommodate differences in contractile behavior of muscles of different types and speeds.

A particularly dramatic change in the model’s complex-stiffness profile is achieved by adding a length-sensing feature to the attachment rate constant \( f_r \), as shown in Fig. 12. Length sensing in \( f_r \) was introduced according to

\[
f_r = f_m \left(1 + \varepsilon \frac{S_L - S_{L0}}{S_{L0}}\right)
\]

where \( f_r \) is the \( f_r \) of Eq. 15, \( f_m \) is a constant, \( S_{L0} \) is a reference sarcomere length, and \( \varepsilon \) is the parameter that scales the influence of length sensing in \( f_r \). Similar to the findings of Thorson and White (34), increased length sensing in \( f_r \) moves the zero-frequency stiffness from the origin to increasingly rightward locations on the positive real axis (Fig. 12). Additionally, the rightward movement along the positive real axis reduces the phase angle and frequency range of the positive-phase low-frequency region of the polar plot while increasing the phase angle and frequency range of the negative-phase region (Fig. 12, locus b). With sufficient length sensing in \( f_r \), the low-frequency positive-phase region disappears, and the polar plot begins with a negative-phase leftward sweep through the fourth quadrant before eventually passing into the first quadrant at higher frequencies (Fig. 12, locus c). Polar plots like locus c are characteristic of cardiac muscle and asynchronous insect flight muscle (2, 7, 23, 27–29, 34).

Changes in the overall complex stiffness due to length sensing are entirely the result of corresponding changes induced in the \( e_2 \) component, and there is no effect on the \( x_1 \) and \( x_2 \) components. These effects on the \( e_2 \) component exhibit in the time domain as slowed,
enhanced, and sustained delayed tension; an effect known as "stretch activation."

Thus the model contains features that allow flexibility in reproducing dynamic behavior of constantly activated muscles with very different types of contractile behavior, from skeletal muscle of different speeds to muscles such as cardiac muscle and asynchronous insect flight muscle, which exhibit pronounced stretch activation (27).

Summary

Virtually all interesting dynamic behavior of constantly activated muscle that is important to practical applications can be generated by a model of the muscle sarcomere that treats force as the product of two dynamic variables: stiffness and distortion. The dynamics of sarcomeric stiffness originate from the kinetics of cross-bridge cycling and arise, following a change in sarcomere length, as a result of cooperativity and distortion dependence in the rate coefficients. The dynamics of distortion originate from shearing motions between thick and thin filaments, and may be described by an ordinary differential equation. For small-amplitude behavior, the stiffness and distortion components can be separated and identified as to their individual contributions to overall dynamics, allowing interpretations to be made of contractile processes in large-amplitude and other kinds of behaviors. Thus a broad range of muscle phenomenology can be reproduced by a simple model built on concepts from underlying contractile processes.

Furthermore, the model is structured so that it may easily be extended to applications where time-varying calcium activation and changes in myofilament overlap are important. The former can be achieved by considering \( k_\text{on} \) and \( k_\text{off} \) as function of calcium concentration as in Ref. 7. Supplying the appropriate time-varying myoplasmic free calcium to appropriate expressions for \( k_\text{on} \) and \( k_\text{off} \) will result in a simulated twitch contraction or brief tetanus, as desired. Myofilament overlap effects are achieved by supplying appropriate length-dependent \( R_F \) as required for Eqs. 3–5. Also, complications concerning thin-filament regulatory processes, such as cooperative feedback effects as treated in Ref. 6, may be accommodated through an appropriate functional dependence of the rate coefficients \( k_\text{on} \) and \( k_\text{off} \) on any of the several model variables. Whereas these complications involving contractile processes may be easily introduced through the present structure of the model, complications such as noncontractile series elastance and spatial inhomogeneity will require more elaborate model structures in which the proposed sarcomere model would be one component.

In conclusion, we present a model of the muscle sarcomere that is sufficiently simple that it may be used in application settings where simulation of natural muscle behavior is desired for purposes of control, engineering design, and greater understanding.

APPENDIX

Distortion-Dependent Rate Coefficients

Thermodynamics requires that the transition between any state \( \alpha \) to another state \( \beta \) be governed by Boltzmann statistics according to

\[
\frac{k_{\beta}}{k_{\alpha}} = e^{\frac{-\Delta E - \Delta T}{kT}} \tag{A1}
\]

where \( k_\beta \) is an attempt frequency, \( k \) is Boltzmann’s constant, \( T \) is absolute temperature, and \( \Delta E \) is the activation energy that must be overcome to make an \( \alpha \rightarrow \beta \) transition. \( \Delta E \) is given by \( \Delta E = E^\beta - E^\alpha \), where \( E^\beta \) is a barrier energy and \( E^\alpha \) is the energy of the \( \alpha \) state. Not knowing details of changes in the reaction profile during linearly elastic distortion, we at least know how linearly elastic distortion changes the energy of state: \( E_\alpha = E_\alpha + \epsilon \), where the second term on the right-hand side is the change in energy due to mechanical distortion. From this, the ratio of the forward and reverse rate coefficients may be written as

\[
\frac{k_{\beta}}{k_{\alpha}} = Be^{(\zeta - \zeta_0)} \tag{A2}
\]

where

\[
B = \frac{k_\beta}{k_\alpha} e^{(E_\alpha - E_\beta)/kT}
\]

and

\[
\zeta = \frac{\epsilon}{2kT}
\]

is a form of cross-bridge stiffness in units of nm⁻².

Traditionally, these thermodynamic constraints are imposed as follows. Because it is impossible to know how distortion affects \( \Delta E \) in Eq. A1, one is free to choose a dependence of \( k_{\beta} \) on \( x \), that is reasonable. For instance, the arbitrary but reasonable dependence of \( g \) on \( x \) in the 1957 Huxley model (18) is well known. However, once \( k_{\beta} \) is specified, thermodynamic consistency requires that the reverse rate coefficient, \( k_{\alpha} \), obey Eq A.2 (13, 17, 26).

Further theoretical concerns arise from mathematical issues when considering a population of cross bridges that, because of thermal effects, exhibits variation in cross-bridge distortion (17). That is to say that, within the population, there is a statistical distribution of \( x \). As long as the rate coefficient changes with \( x \) as it must, the number of cross bridges within a state will also be distributed over \( x \). One consequence is that the differential equations describing changes must include derivative terms in \( x \) as well as in time; i.e., they are properly partial differential equations rather than ordinary differential equations as given in Eqs. 3–5. Another consequence is that these distributions complicate writing simple expressions for rate coefficients, as we wish to do in the construction of a simple model. This complication arises because of the following. Let \( \eta(x) \) be the distribution function for numbers of cross bridges over \( x \). The distribution function is subject to change during filament sliding such that \( \eta(x) = \eta(x, v) \), where \( v \) is the velocity of filament sliding (18, 25). Under these conditions, average \( k_{\beta} \) and average \( x \) are given by

\[
\bar{k}_{\beta} = \int_{-\infty}^{\infty} \eta(x, v)/k_{\beta}(x) \, dx \tag{A3}
\]

\[
x = \int_{-\infty}^{\infty} \eta(x, v) \, dx \tag{A4}
\]

where the overbar indicates the population average value of the variable. Equations A3 and A4 suggest that caution must be exercised in assuming that \( \bar{k}_{\beta} \) is uniquely related to \( x \). Furthermore, even if a unique relationship could be assumed,
such a relationship would most certainly obey a different functional form than one that may have been chosen for the relationship between $k_{db}$ and $x$ at every $x$ in the distributed population. Because the whole premise for our model was that muscle force equaled sarcomeric stiffness times average cross-bridge distortion (Eq. 2), our challenge was, in lieu of a strict mathematical derivation, to find some reasonable relationship between population average rate coefficient and average distortion.

Coefficients in Linearized Model

Relationships of $k_i$ in Eq. 23 to rate coefficients are

$$k_0 = f_{ss}k_{on}(h_0 + h'_0 + g_0) + (k_{on} + k_{off})$$

$$k_1 = \frac{\partial f}{\partial A_{ss}} D_{ss} h_0 + h_0 g_0 + f_0(h_0 + g_0) + (k_{on} + k_{off})$$

$$k_2 = f_0 + h'_0 + g_0 + f_{ss} h_0 + h'_0 + g_0 + k_{on}$$

$$k_3 = (k_{on} + k_{off} + f)^2 h_0$$

$$k_4 = h_0$$

$$k_5 = (k_{on} + k_{off})$$

$$k_6 = \frac{\partial f}{\partial x_{ss} D_{ss}}$$

where the indicated steady-state values (subscript $ss$) were calculated as

$$f_{ss} = f_0 \left(1 + \frac{A_{2ss}}{R_T} (e^{x_{ss} - 1} - 1)\right)^2$$

$$\frac{\partial f}{\partial A_{2ss}} = 2f_0 \left(1 + \frac{A_{2ss}}{R_T} (e^{x_{ss} - 1} - 1)\right) \frac{(e^{x_{ss} - 1} - 1)}{R_T}$$

$$\frac{\partial f}{\partial x_{ss} D_{ss}} = 2f_0 \left(1 + \frac{A_{2ss}}{R_T} (e^{x_{ss} - 1} - 1)\right) (v - 1)A_f(R_X)$$

Because of the complexity of the system of differential Eqs. 3–5, the steady-state condition cannot be found analytically. It was found by numerical integrating of the system using the Runge-Kutta method.

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Address for reprint requests and other correspondence: K. B. Campbell, Dept. of VCAPP, Washington State University, Pullman, WA 99164 (E-mail: cvskbc@etmed.wsu.edu).

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