A MODEL FOR THE TRANSIENT AND STEADY-STATE MECHANICAL BEHAVIOR OF CONTRACTING MUSCLE

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ABSTRACT A model was developed which can simulate both the transient and steady-state mechanical behavior of contracting skeletal striated muscle. Thick filament cross-bridges undergo cycles of attachment to and detachment from thin filament sites. Cross-bridges can attach only while in the first of two stable states. Force is then generated by a transition to the second state after which detachment can occur. Cross-bridges are assumed to be connected to the thin filaments by an elastic element whose extension or compression influences the rate constants for attachment, detachment, and changes between states. The model was programmed for a digital computer and attempts made to match both the transient and the steady-state responses of the model to that of real muscle in two basic types of experiment: force response to sudden change in length and length response to sudden reduction of load from P_o. Values for rate constants and other parameters were chosen to try to match the model's output to results from real muscles, while at the same time trying to accommodate structural and biochemical information.

INTRODUCTION

The model for muscle contraction proposed by A. F. Huxley (1957) based on a sliding filament mechanism (A. F. Huxley, 1971; H. E. Huxley, 1971) has been of great value because it provided relatively simple explanations for many of the characteristic features of contraction in skeletal striated muscles (see for examples and discussion: Julian, 1969; Julian and Sollins, 1972; Podolsky et al., 1969; Mommaerts, 1969). Recently, however, Huxley and Simmons (1972) pointed out that the original Huxley (1957) model would not account for the very early transient responses observed when the length or the load is suddenly altered during a contraction. (See also Podolsky and Nolan, 1972, for an attempt to modify the original Huxley model so that it will produce force transients following sudden length changes similar to those observed in real muscles.) Huxley and Simmons (1972) also discuss other aspects of the original 1957 scheme which are now in need of revision.

Huxley and Simmons (1971) have already proposed a mechanism to account for the very early quick phases of tension recovery following sudden length changes, which

they were the first to record from contracting muscles. This paper will show that it is possible to construct a hybrid model based on the original Huxley (1957) model and the new scheme put forth by Huxley and Simmons (1971). It will be shown that this hybrid model can account for much of the transient and steady-state mechanical behavior observed in tetanically contracting skeletal striated muscles. A short description of this hybrid model has already been published (Julian et al., 1972).

DESCRIPTION OF THE MODEL AND COMPUTATIONAL METHODS

Some of the features from the Huxley (1957) model and from the Huxley and Simmons (1971) model that are combined in the present model will be described qualitatively here before dealing with the mathematics.

Although it is possible to imagine many different ways of fitting the model into the microscopic and molecular structure of a skeletal muscle fiber, the following arrangement seems most natural (see also Huxley and Simmons, 1971). An elastic element is assumed to be in the S_2 subfragment of heavy meromyosin. The length-force characteristic of this element is assumed to be linear for both positive and negative (compressive) forces. The importance of this assumption will be seen later. The elastic element connects the cross-bridge head, or S_1 subfragment, to the thick filament. The cross-bridge heads can attach to the actin sites on the thin filaments and undergo changes in configuration (or "flips") between the α and β states (see Fig. 1). When a cross-bridge attaches, the head must be in the α position and there can be no force in the elastic element. After attachment, force can be produced either by a flip of the cross-bridge to the β position or by motion of the filaments relative to each other (or both). It is further assumed that cross-bridges can detach from the thin filament only while in the β state. The rate constant for this process is dependent upon the extension or compression of the cross-bridge elastic element. The rate constants governing the flipping between the α and β states are functions of the work done on or by the elastic element during a flip. The model deals only with the maximally activated state and sarcomere length changes are limited to the plateau region of the length-tension diagram. In accordance with the results of Huxley and Simmons (1971, 1972) and our own experimental findings (manuscript in preparation) there is no series elastic component in the model, i.e. all the elasticity is assumed to be in the cross-bridges themselves.

Referring to Fig. 1 C, the differential equations for the number of attached cross-bridges in each state are derived in the following way. $A_\alpha\ (u, t)$ is the number of attached cross-bridges in the α position having elastic element extension u at time t. $A_\beta(u, t)$ is defined similarly, and $D(t)$ is the number of detached cross-bridges (assumed to have $u = 0$). The u-dependent rate constants refer to the probability of a transition of a cross-bridge with that u-value (before the change) to the state indicated, e.g., $k_\beta(u)$ refers to transitions to the β state by cross-bridges having extension u before the flip.

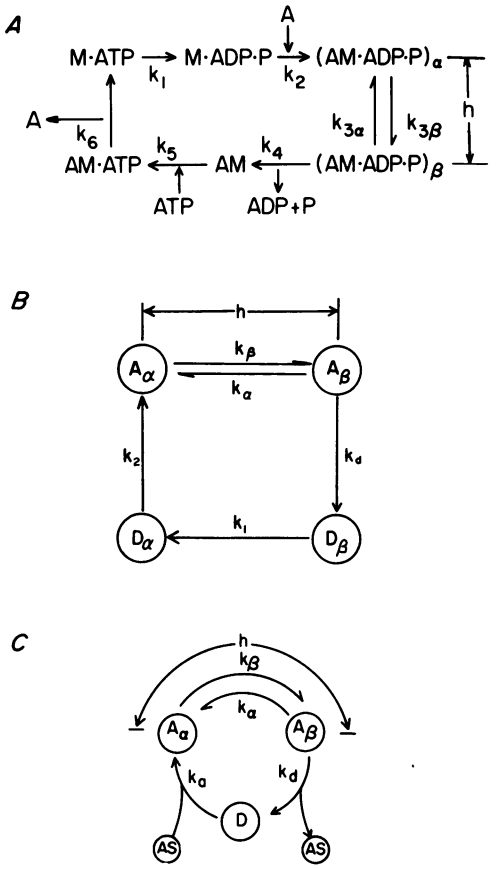

FIGURE 1 (*A*) Possible biochemical scheme for the contraction cycle. In the figure, A represents actin; M, myosin; and the dot, a complex. The k's are rate constants for state transitions. The reversible reaction between states α and β of the complex AM·ADP·P corresponds to the force-generating step. h refers to the change in the cross-bridge spring extension that occurs with changes between states α and β. (*B*) Simplification to a four-state scheme. A_α corresponds to $(AM\cdot ADP\cdot P)_\alpha$; A_β to $(AM\cdot ADP\cdot P)_\beta$; D_β to M·ADP·P. k_4, k_5, and k_6 have been lumped so that k_d is determined by the smallest of them. k_α and k_β are equivalent to $k_{3\alpha}$ and $k_{3\beta}$ in part A. (*C*) Final simplified scheme used in the model. k_1 and k_2 have been lumped to form k_a and D now replaces D_α and D_β. A_α and A_β give number of attached cross-bridges in α and β states, and D the number detached. AS refers to actin sites on the thin filament.

Since a flip of an attached cross-bridge changes its spring extension by the distance h, the equations are written in terms of A_α at u and A_β at $u + h$.

$$\partial A_\alpha(u,t)/\partial t = -k_\beta(u)A_\alpha(u,t) + k_\alpha(u+h)A_\beta(u+h,t) + k_a(u)D(t), \quad (1)$$

$$\partial A_\beta(u+h,t)/\partial t = k_\beta(u)A_\alpha(u,t) - [k_\alpha(u+h) + k_d(u+h)]A_\beta(u+h,t). \quad (2)$$

To make the expressions for the solutions more manageable, the arguments of the

A's, of the k's, and of D will be dropped, i.e., A_α will refer to $A_\alpha(u,t)$; A_β to $A_\beta(u+h,t)$; D to $D(t)$; k_a to $k_a(u)$; k_d to $k_d(u+h)$; k_α to $k_\alpha(u+h)$ and k_β to $k_\beta(u)$. The solutions are:

$$A_\alpha = [(m_1 + k_\alpha + k_d)c_1\exp(m_1 t) + (m_2 + k_\alpha + k_d)c_2\exp(m_2 t) + k_a D(k_\alpha + k_d)/k_d]/k_\beta, \quad (3)$$

$$A_\beta = c_1\exp(m_1 t) + c_2\exp(m_2 t) + k_a D/k_d, \quad (4)$$

where

$$c_1 = A_\beta(u+h,o) - c_2 - k_a D/k_d, \quad (5)$$

$$c_2 = [k_\beta A_\alpha(u,o) - (m_1 + k_\alpha + k_d)A_\beta(u+h,o) + k_a m_1 D/k_d]/(m_2 - m_1), \quad (6)$$

$$m_1 = -[(k_\alpha + k_d + k_\beta) + \sqrt{(k_\alpha^2 + k_d^2 + k_\beta^2 + 2k_\alpha k_d + 2k_\beta k_\alpha - 2k_d k_\beta)}]/2, \quad (7)$$

and

$$m_2 = -[(k_\alpha + k_d + k_\beta) - \sqrt{(k_\alpha^2 + k_d^2 + k_\beta^2 + 2k_\alpha k_d + 2k_\beta k_\alpha - 2k_d k_\beta)}]/2. \quad (8)$$

The equations for A_α and A_β are left in terms of D because in the computer program new values for A_α and A_β are evaluated for discrete time intervals during which it can be assumed that D is constant. These equations hold only if there is no motion between the filaments.

The way in which the u-dependence of k_α and k_β arises will now be described in full. Although the basic reason for the u-dependence of k_α and k_β is the same as that of Huxley and Simmons (1971), the derivation will be somewhat different. Furthermore it will be seen that in this extended version of their model both rate constants must vary with u. First, the energy, W, required to stretch the cross-bridge elastic element the distance h must be found as a function of u, the extension of that spring just before the flip of the cross-bridge head. For flips to states α and β, respectively, the equations are, $W_\alpha(u) = (K/2)(-2hu + h^2)$, and $W_\beta(u) = (K/2)(2hu + h^2)$, where K is the elastic element stiffness (see Fig. 2A). Next, it is assumed, following Huxley and Simmons (1971), that potential energy wells exist for each of the stable states. These can be seen in Fig. 2 B, which shows the activation energies for two possible cases. In each case, the activation energy, B, is made up of the potential energy required to get out of the well plus the mechanical work done on or by the spring. It can be seen in the left-hand case shown, that W is negative for a flip to the β state, and positive for a flip to the α state. The activation energy for a change from α to β, B_β, is just E_β, but for a flip from β to α, $B_\alpha = E_\alpha + W$. The right-hand side illustrates another possible case where W is positive for a flip to the β state (and therefore negative for the flip to α).

Part C shows that the activation energies, B_α or B_β, as functions of u before the

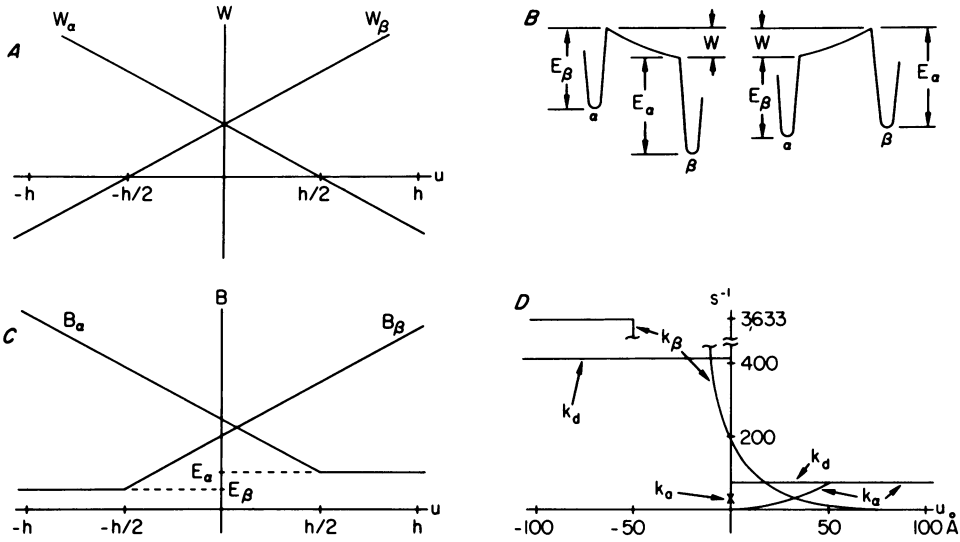

FIGURE 2 Derivation of the rate constants for flipping, k_α and k_β. In all cases the subscript α or β indicates the state to which a cross-bridge is flipping. For example E_β (parts B and C) contributes to the activation energy for a flip to state β even though E_β is the depth of the well associated with the α state. It is important to realize in part B the energies are plotted against some variable measuring the extent to which a flip has progressed (e.g., rotation of the cross-bridge head) as opposed to parts A, C, and D in which the abscissa, u, indicates the initial extension of a cross-bridge spring. (A) W_α and W_β give the work required to stretch the cross-bridge spring in changes of state to α and to β, respectively, as a function of the extension of the spring just prior to the transition. $W < 0$ indicates that energy is released by the spring. (B) Energy considerations for flips between states α and β. The potential energy well associated with each state is labeled. Two examples are shown (corresponding to cross-bridges with different spring extensions before the flip) of the way in which activation energy for a flip depends on well depth and the work required by the spring. (C) B_α and B_β represent the activation energies for flips to the α and β states, respectively, as functions of u, the cross-bridge spring extension just before the flip. (D) Numerical values for k_α and k_β and also k_a and k_d used in the model are:

$$k_\alpha(u) = \begin{cases} 75 & u > h/2 \\ 75 \exp[(-K/2)(-2uh + h^2)/kT] & u \le h/2 \end{cases}$$

$$k_\beta(u) = \begin{cases} 3{,}633 & u < -h/2 \\ 3{,}633 \exp[(-K/2)(2uh + h^2)/kT] & u \ge -h/2 \end{cases}$$

$$k_a = 29 \qquad u = 0$$

$$k_d = \begin{cases} 412.5 & u < 0 \\ 75 & u \ge 0 \end{cases}$$

All rate constants in seconds^{-1}.

flip are linear for u-values where W_α or W_β is positive, but constant where W_α or W_β is negative. The rate constants are assumed to be proportional to the exponential of the negative activation energy, i.e.,

$$k_\alpha(u) = c_\alpha \exp[-B_\alpha(u)/kT], \tag{9}$$

$$k_\alpha(u) = \begin{cases} c'_\alpha & u > h/2 \\ c'_\alpha \exp[-W_\alpha(u)/kT] & u \leq h/2 \end{cases} \tag{10}$$

where $c'_\alpha = c_\alpha \exp(-E_\alpha/kT)$ and

$$k_\beta(u) = c_\beta \exp[-B_\beta(u)/kT], \tag{11}$$

$$k_\beta(u) = \begin{cases} c'_\beta & u < -h/2 \\ c'_\beta \exp - W_\beta(u)/kT & u \geq -h/2 \end{cases} \tag{12}$$

where $c'_\beta = c_\beta \exp(-E_\beta/kT)$.

Part D shows the rate constants $k_\alpha(u)$ and $k_\beta(u)$ for the values chosen for the following parameters: $c'_\alpha = 75\ s^{-1}$, $c'_\beta = 3{,}633\ s^{-1}$, $h = 100$ Å, $K = 2.2 \times 10^{-9}$ dyn/Å. Also shown are the rate constants for attachment and detachment, k_a and k_d. The reasons for the choice of these numbers are discussed later. Using these values for the rate constants and the solutions to the differential equations, the model was programmed for a digital computer. The basic steps in the program are as follows: a small time step, Δt, is chosen. Typically this would be on the order of a millisecond, except during rapid transient phenomena when it might have to be as small as 0.1 ms to achieve the desired resolution. From the current values of $A_\alpha(u,t)$, $A_\beta(u,t)$ and $D(t)$ at time t, $A_\alpha(u, t + \Delta t)$ and $A_\beta(u, t + \Delta t)$ are computed from the equations 3 and 4, derived above. There is no relative sliding motion of the thick and thin filaments at this stage. Next it must be ascertained that D did not change excessively during the Δt since this quantity is assumed to be constant in the equations for A_α and A_β. The distribution functions, $A_\alpha(u)$ and $A_\beta(u)$ are integrated over u to give A, the total number of attached cross-bridges regardless of elastic element extension. (This number, multiplied by K, the stiffness of each individual cross-bridge, gives the total model stiffness.) A is subtracted from the total number of available cross-bridges, which is taken to be 10^{13} in one half-sarcomere, 1 cm^2 in cross section. This gives the new D which is compared with the value before the Δt. Δt is made smaller and the process repeated if the change in D is large enough to cause a significant error in subsequent calculations. To find the total force generated a first moment integral must be computed. Each cross-bridge contributes a force given by the product Ku so the total force is $K\int[A_\alpha(u) + A_\beta(u)]udu$. In the computer, $A_\alpha(u)$ and $A_\beta(u)$ are represented by arrays of values at discrete u-points. As a compromise between accuracy and cost of computer time, a spacing of 5 Å was chosen. Integrals are computed using the trapezoidal rule. This simple approximation was chosen so as to be compatible with a linear interpolation procedure that is applied to the distributions later in the program. For isometric contractions this would complete one time step in the program. For isotonic contractions, however, the model is constrained to maintain a constant force less than the maximum capable, (P_o), by shortening at the proper velocity. In this case the program calculates a distance such that when the filaments are moved with

respect to each other by that amount, the generated force is kept at the desired level. In the program this motion of the filaments is accomplished by shifting the A_α and A_β distributions along the u axis.

The distributions in the isometric steady state are easily visualized. Cross-bridges can attach only in state α with $u = 0$. They then flip (reversibly) to the β state stretching the elastic element to $u = h$ and can detach while in the β position. Therefore the A_α distribution is non-zero only at $u = 0$, and A_β has a value only at $u = h$ (see Fig. 4 A). If the model is shortening at some velocity, however, the spring extension of every attached cross-bridge is constantly decreasing. This is equivalent to a continual shift to the left of the distributions (see Fig. 7 H).

In order to assign actual values for the various rate constants and other parameters, their effects on quantities that can be measured in real muscle fibers were considered. Also, values for rate constants were kept compatible with current ideas about the biochemistry of the contraction cycle (see Taylor, 1973). It was not possible to satisfy all the constraints with one set of model parameters, so in some areas the model's behavior had to be compromised to produce reasonable results in others. The steady-state solutions to the differential equations are:

$$A_\alpha(u) = k_a(u)[k_\alpha(u + h) + k_d(u + h)]D/k_d(u + h)k_\beta(u), \tag{13}$$

$$A_\beta(u + h) = k_a(u)D/k_d(u + h). \tag{14}$$

Since $k_a = 0$ for all u except $u = 0$ it can be seen A_α is non-zero only at $u = 0$ and A_β is non-zero only at $u = h$. Dividing Eq. 13 by Eq. 14 we have,

$$A_\alpha(u)/A_\beta(u + h) = [k_\alpha(u + h) + k_d(u + h)]/k_\beta(u). \tag{15}$$

The steady-state isometric tension may be written simply as

$$P_o = A_\beta Kh. \tag{16}$$

Letting y_o equal the amount of instantaneous shortening required to bring the force to zero from P_o,

$$A_\alpha(o)Ky_o = A_\beta(h)K(h - y_o), \tag{17}$$

$$A_\alpha/A_\beta = (h - y_o)/y_o. \tag{18}$$

After a release of y_o it can be assumed that nearly all the cross-bridges in the α state flip to the β state. This is the rapid phase of tension recovery to the level T_2. This occurs because the A_α spike which was at $u = 0$ is now at $u = -y_o$ where k_β is very large. The force developed at this time expressed relative to P_o is

$$T_2(y_o) \approx [A_\alpha(o) + A_\beta(h)](h - y_o)K/P_o. \tag{19}$$

Making use of Eqs. 16 and 18,

$$T_2(y_o) \approx A_\alpha(o)/A_\beta(h). \tag{20}$$

From Huxley and Simmons's (1971) data we would like $T_2(y_o) \approx 0.7$. h was chosen to be 100 Å; so from Eqs. 18 and 20, $y_o = 57$ Å which is an acceptable figure. X-ray studies on skeletal muscle have indicated that only a small fraction of the cross-bridges are attached during the isometric steady state (Huxley and Brown, 1967). Simultaneously meeting this constraint and maintaining a reasonable value for P_o was difficult. The final set of rate constants and parameters used in the model represents a compromise. The P_o was only about 0.5 kg/cm^2 and the fraction of attached cross-bridges was about 40%. The value for P_o is low compared with that observed in living muscles. However, the value depends upon the total number of cross-bridges per half-sarcomere, the number of myosin heads per cross-bridge (it could be that the two heads on a myosin molecule act independently so that each contributes equally to the isometric force), and the fraction of cross-bridges attached during isometric steady contraction. If each cross-bridge contains two myosin molecules (Huxley, 1972) with each head counted separately and the fraction of attached bridges in the isometric steady state is greater, then the above value for P_o could be increased by as much as a factor of five. Huxley and Simmons (1971) have already mentioned that this kind of simple two-state model fails to develop an adequate P_o. The rate constants influenced by these considerations are $k_\alpha, k_d(h), k_\beta(0)$, and $k_\alpha(h)$. In order to obtain the proper rate of tension recovery to $T_2, k_\beta(u)$ for u less than $-h/2$ or c'_β (see Eq. 12) was made 3,633 s^{-1}. Using Eq. 12 and the value for $k_\beta(0)$, K was set at 2.2×10^{-9} dyn/Å. The most powerful influence on shortening speed is the value given $k_d(u)$ for negative u. The value of 412.5 s^{-1} was found to give the best fit to V_{max} and the force-velocity relation. The rate of rise of tension in the slow phase of the recovery was another consideration influencing the choice of values for k_a and k_d.

RESULTS

The first type of model response considered is the force response to sudden changes in muscle length as shown in Fig. 3. It was this type of experiment that led Huxley and Simmons (1971) to their new model so it is important that our extension of that model still accommodate the experimental findings. Taking the case of a release (parts A–D), the force trace first shows a drop in tension in phase with the length step. This is simply the result of the undamped elasticity in the attached cross-bridges. Next the quick recovery to T_2 occurs, fastest for the largest release (part A). A slight dip in the force is seen, followed by the slow recovery back to the steady isometric level, P_o. The stretches also exhibit these phases of the response but in opposite directions.

Examination of the state of the force generator provides insight into how this force response arises. The distribution of attached cross-bridges in the α and β states over the variable u, the extension of the cross-bridge elastic element, completely determines the state of the model at any time. This is shown in Fig. 4 for various times in the re-

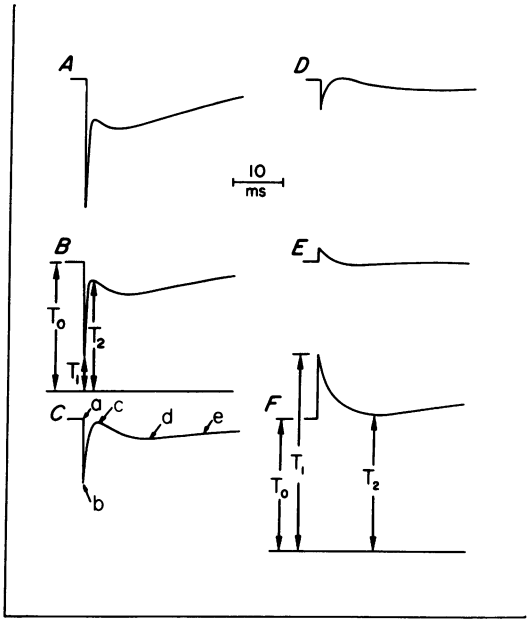

FIGURE 3 Force responses to instantaneous length changes. T_0 is the steady isometric force. T_1, the extreme force attained, is concurrent with the length step, and T_2 is the force at the end of the quick phase of the recovery. In all cases the force returned to T_0 in a time consistent with that observed in real muscle. The sizes of the length changes (stretch taken as positive) are in angstroms: A, −56; B, −43; C, −29; D, −14; E, 6; and F, 29. In part C, the arrows and letters *a–e* indicate the times of the cross-bridge distributions in Fig. 4, e.g., Fig. 4 A is the distribution of cross-bridges at the time indicated by the letter *a* and the arrow. Note the decrease or "dip" in the force record just after the quick recovery to T_2. This feature is characteristic of the responses we have obtained from single frog skeletal muscle fibers at 0°C.

sponse of Fig. 3 C. Fig. 4 A shows the model in the isometric steady state just before application of the length step. As mentioned in the Methods section, cross-bridges in the α state all have $u = 0$, while for those in the β state $u = h = 100$ Å. In part B the instantaneous length step has been applied causing the distributions to be shifted left by the amount of the release, 29 Å. The shift of the spikes of A_α and A_β have caused them to encounter new values of k_α and k_β (see Fig. 2 D). k_α is lower and k_β higher so that the equilibrium is now heavily in favor of the β state as can be seen in part C, where most of the shifted A_α have "flipped" into the β state at $u =$ 71 Å(100 Å − 29Å). This is the mechanism in the model of the quick phase of tension recovery following a release. The dip in the force following T_2 results from detachment of some of the β state cross-bridges at $u = 71$ Å. Eventually the steady-state distribution of part A must be regained, and this can be seen in parts E and F. The two shifted spikes decay, cross-bridges attach in the α state at $u = 0$, and, by flipping, restore the original isometric steady-state distribution. Our model's performance is compared to that of Huxley and Simmons (1971) in Fig. 5. The difference between the length axis intercepts, y_o, of the T_1 curves, is largely due to our assumption that cross-bridges

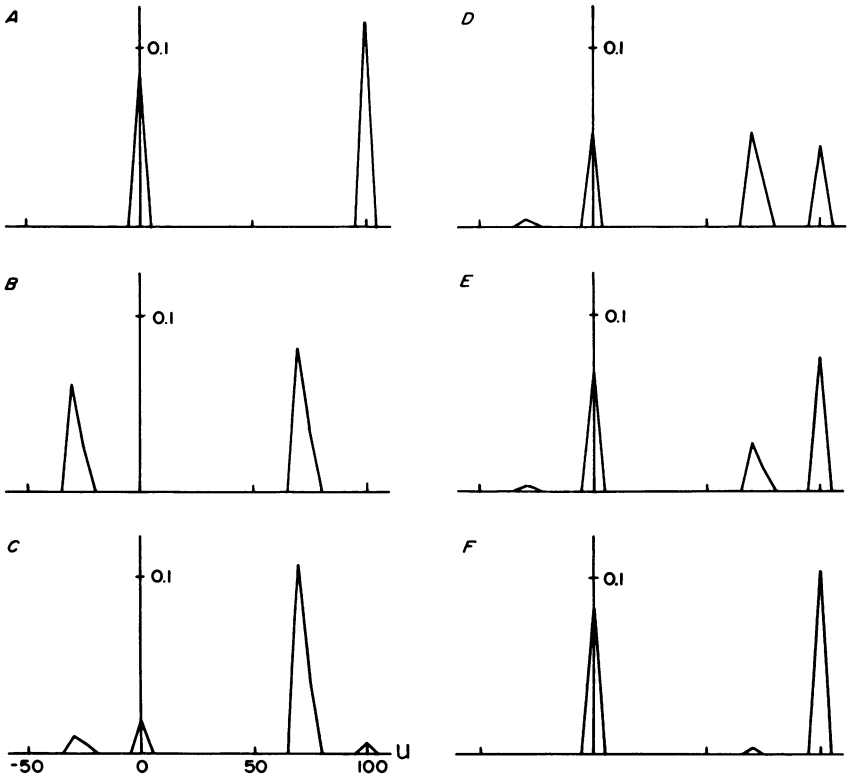

FIGURE 4 Cross-bridge distributions during the model's response to an instantaneous length change (force response shown in Fig. 3 C). The abscissas refer to the extension, in angstroms, of the cross-bridge spring. Positive values indicate tension in the spring, which aids shortening, while negative values indicate a compressive force which opposes shortening. The ordinates give the number of cross-bridges relative to the total number attached in the isometric steady state. The times at which these distributions occur are given in Fig. 3 C by the small letters and arrows. The distribution in part G occurred after the end of the trace in Fig. 3 C.

can have no tension when they attach. Over the range of length steps used in our model, the T_2 curve shows close agreement with that of Huxley and Simmons.

The other type of experiment done on the model is to study the length response when the load is suddenly decreased and then held at a level less than P_o. Four responses of this kind are shown in Fig. 6. As in the force responses in Fig. 3, there are several separable phases to the response as described in the legend for Fig. 6. Again these features can be explained by considering the cross-bridge distributions at different points in the response as indicated in Fig. 6 C. In Fig. 7, parts A and B are similar to Fig. 4, A and B. In this case, however, the generated force now must be kept at the proper level by letting the filaments slide past each other at the appropriate speed. Just as in the case of the length step, the attached cross-bridges re-equilibrate heavily in favor of the β state, so, in order to maintain the load, the muscle must shorten rapidly (parts C and D). By the time of part E, most of the attached cross-bridges have

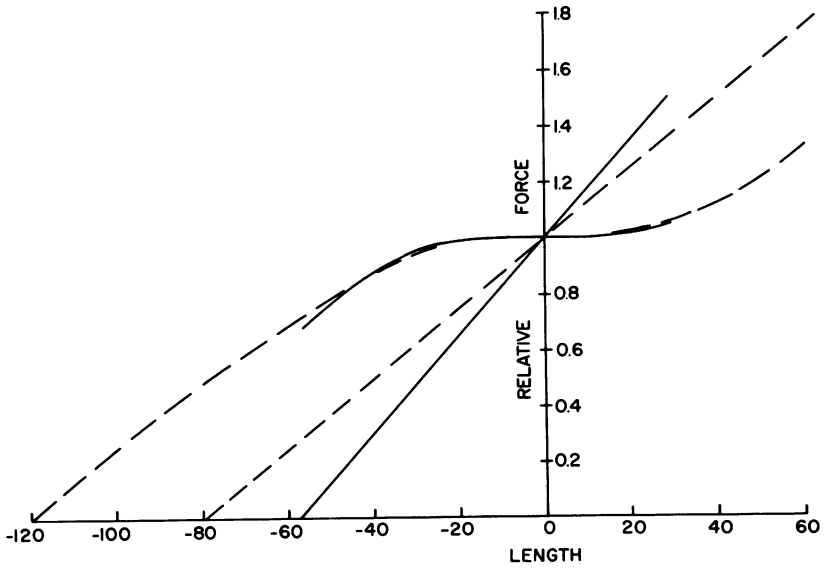

FIGURE 5 T_1 and T_2 responses from models. All forces are plotted relative to the maximum tetanic force, P_o. The length axis refers to the size of the length step expressed in angstroms per half-sarcomere, stretch taken as positive. Solid lines, response of the present model; dashed lines, response of the model of Huxley and Simmons (1971).

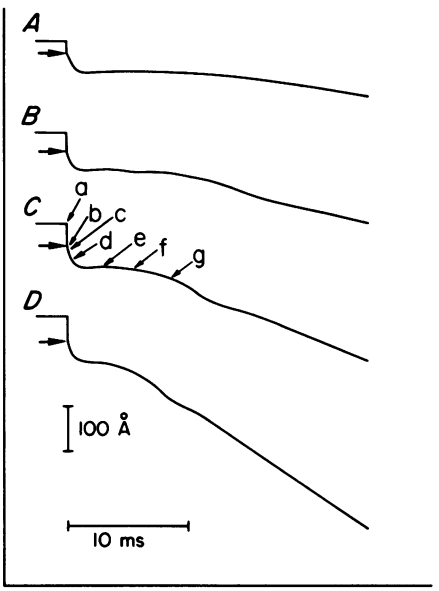

FIGURE 6 Length responses to imposed loads. The unlabeled arrows indicate the size of the initial instantaneous length step required to drop the force to the desired load. Thereafter three features of the length responses are to be noted: first, a short period of very rapid shortening; second, a plateau phase in which practically no shortening occurs; finally, the attainment of a constant velocity of shortening. The loads relative to T_0 and steady-state velocities relative to V_{max}, are, respectively: A, 0.50 and 0.18; B, 0.30 and 0.34; C, 0.15 and 0.57; and D, 0.01 and 0.95. The extrapolated value for V_{max} is 1.93 μm/half-sarcomere per s. The length calibration, 100 Å, applies per half-sarcomere. In part C, the arrows and letters *a–g* indicate the times of the cross-bridge distributions in Fig. 7 (modified from Julian and Sollins, 1972).

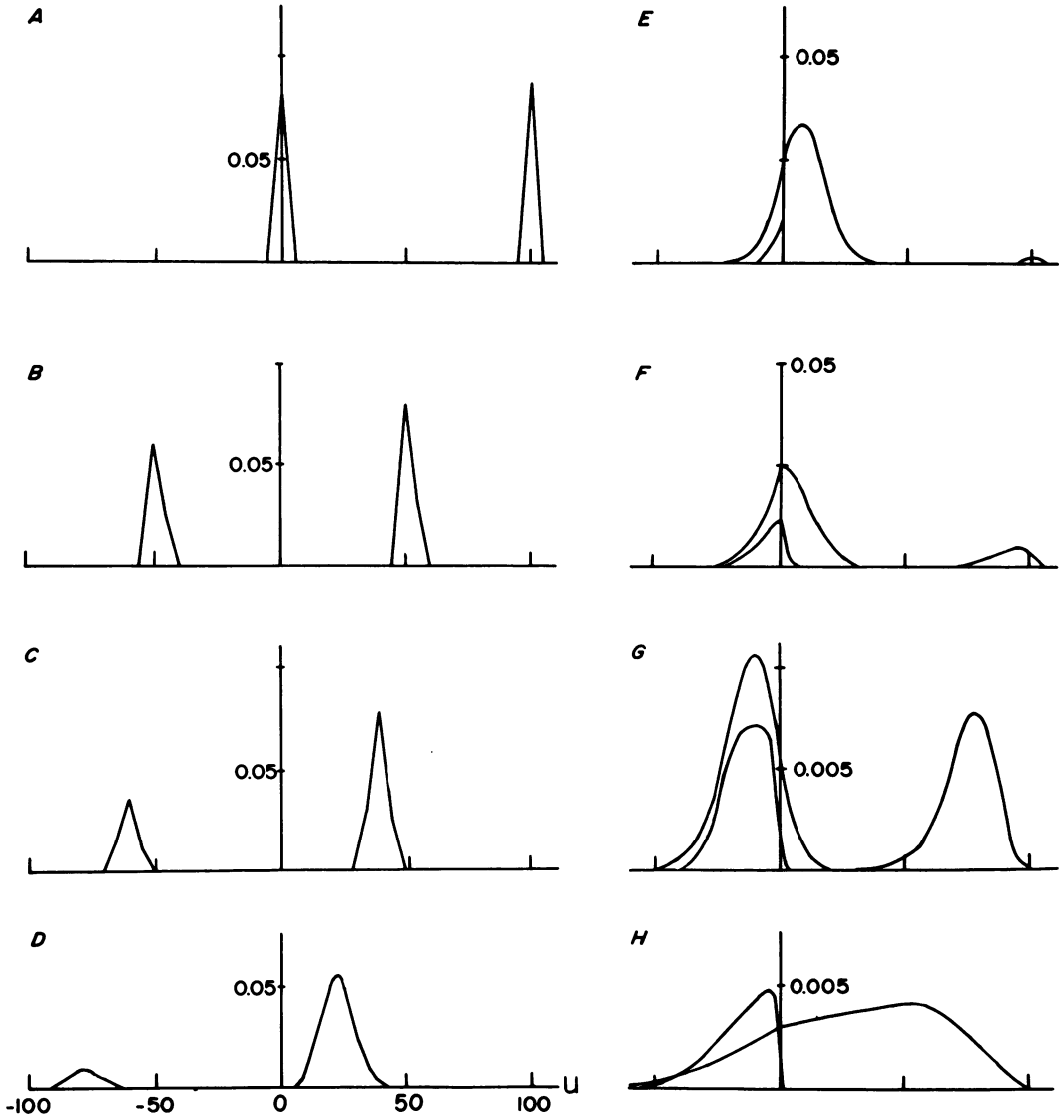

FIGURE 7 Cross-bridge distributions during the model's response to an instantaneously imposed load (length response shown in Fig. 6 C). The abscissas refer to the extension, in angstroms, of the cross-bridge spring. The ordinates give the number of cross-bridges relative to the total number attached in the isometric steady state (note the scale changes). The times at which the distributions occur are given in Fig. 6 C by the small letters and arrows. The distribution in part H occurred after the end of the trace in Fig. 6 C.

flipped and little further motion is necessary until the slower attachment and detachment processes begin to have an affect. At F and G reattachment and subsequent flipping cause shortening to begin again and finally a steady state is attained as shown in part H.

The steady-state shortening velocities are plotted as a function of load in Fig. 8. A hyperbola fits the points well and there is reasonable agreement with our own experimental results (Julian and Sollins, 1972). In Fig. 9 the relation between steady-state stiffness and shortening velocity is shown. The important point here is that as the shortening velocity approaches V_{max}, the force tends to zero, but the stiffness approaches a value of about 0.4 relative to the isometric steady state. A net external force of zero can occur even though a considerable number of cross-bridges are still attached because of the assumption that the cross-bridge elastic element can bear compressive loads.

DISCUSSION

It is now commonly believed that the essential event in the process of contraction is an interaction cycle between a myosin cross-bridge and a site(s) located on actin (see, e.g.,

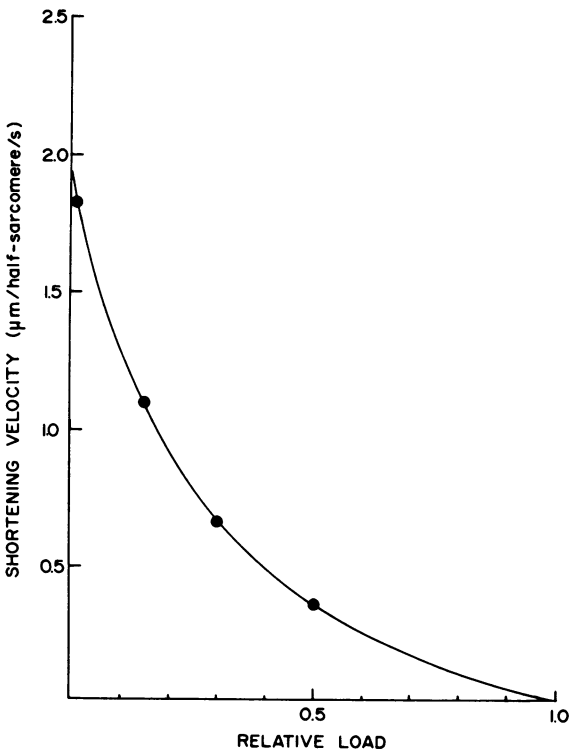

FIGURE 8 Model force-velocity relation. The solid circles show the steady velocities attained in the records of Fig. 6. The solid curve is a hyperbola ($a/P_o = 0.56, b = 0.29$ μm/half-sarcomere per s) fitted by the method of least squares to these points.

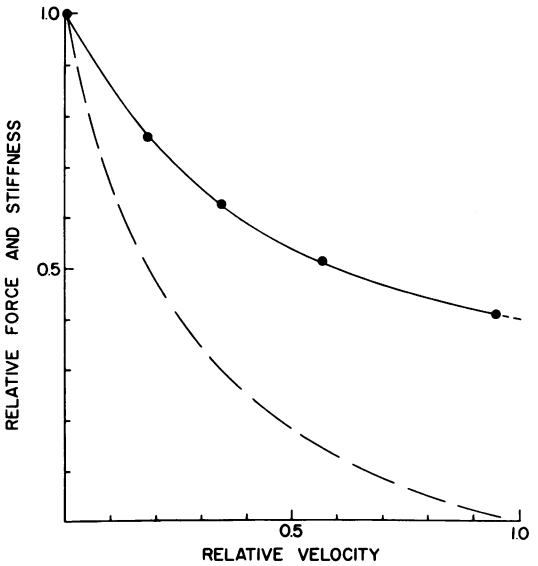

FIGURE 9 Model stiffness as a function of shortening velocity. The points indicate the stiffness (proportional to the number of cross-bridges attached) while in the steady phase of shortening (length records shown in Fig. 5). Stiffness is plotted as a fraction of the stiffness in the isometric steady state and velocity is expressed as a fraction of V_{max}.

Taylor, 1973, for a recent, detailed statement of this view). According to Taylor (1973), a reasonable contraction cycle would consist of at least four steps: (*a*) dissociation of a cross-bridge from actin; (*b*) return of the free cross-bridge to some initial position; (*c*) reattachment of the cross-bridge to an actin site; and (*d*) power stroke tending to translate the thick-thin filament lattices with respect to each other. It can be seen by examining Fig. 1 that this kind of scheme can be very well accommodated by our model, though in the calculations it was assumed that step *b* does not become rate limiting. This means that the model has the potential to use the information obtained from structural, biochemical, and mechanical studies of muscle contraction and thus make it possible to arrive at a deeper understanding of the mechanism of muscle contraction. For example, it is essential in the model that the link between the cross-bridge head and the thick filament be capable of bearing a compressive force. This makes it possible to disprove the model on the basis of structural or physical chemical evidence, if such can be obtained.

It is clear that the model in its present form gives a good qualitative fit to the mechanical responses recorded from contracting muscles after a sudden alteration of either the length or the load. On the other hand, some experimental data (Huxley and Simmons, 1971; Julian and Sollins, unpublished observations) are not accounted for very well. In the case of T_1, the deviation of experimental data from a straight line which becomes more prominent as the magnitude of the length decrease becomes greater can be explained in the way indicated by Huxley and Simmons (1972). That is, in contrast to the model where the length steps are made instantaneously, there is some

flipping of attached cross-bridge heads from the α to the β position during the finite time taken to apply a length step to real muscles. Undoubtedly, if in the model the length decreases were made to take about 1 ms a similar effect would be produced. In the case of T_2, the deviation of experimental data from the model curves at either extreme of size of length step is more difficult to explain. However, in our model, no attempt was made to optimize the fit to the T_2 data, and we did notice that the fit did depend on the values assigned to the various rate constants and parameters. It remains to be seen whether an improved fit to all of the T_2 data can be obtained without sacrificing the good fit obtained to other real muscle responses.

The behavior of the model when the load is suddenly reduced from the isometric level is very similar to that observed in real muscles as shown in Fig. 6. The characteristic features of the real muscle response have been described by Huxley (1971): (*a*) an initial very rapid length change coinciding with the tension change; (*b*) muscle shortening at a speed much greater than the steady-state value; (*c*) speed of shortening then declines to a very low value, or reaches zero and even reverses its direction; (*d*) the steady-state velocity is approached, with or without heavily damped oscillations. It is worth pointing out again (see also Julian and Sollins, 1972) that the existence of phase *b* implies that the steady-state speed of shortening in real muscles is not limited by an internal load, e.g., friction, which is either fixed or varies directly with the level of activation.

As shown in Fig. 8, the model produces a steady-state force-velocity relation very similar to that obtained from real muscles. A very important point to notice is, just as in the original model of Huxley (1957), that the speed of steady shortening at any load is set by the attainment of a force balance in which the sum of the load and force produced by all the attached cross-bridges opposing contraction is equal to the force generated by all the attached cross-bridges aiding contraction. At V_{max}, the external load is zero, and there is a force balance attained by all the attached cross-bridges aiding and opposing contraction. V_{max} in this model is strongly affected by the value of the breaking rate constant k_d for cross-bridges opposing shortening, while the values for the rate constants for flipping, k_α and k_β, have less effect. A consequence of this feature of the model is that the steady-state model stiffness, given simply by the number of cross-bridges attached regardless of their distribution about the equilibrium position, falls as the speed of shortening increases, though less rapidly than does the force. This behavior is shown in Fig. 9. As discussed by Huxley (1971), there is evidence available indicating that the number of attached cross-bridges decreases as the speed of shortening rises.

An objection to this model can be made on the grounds that it does not account for what now seems to be known about the relation between the rate of the energy-producing reaction and the sum of the rates of output work and heat as a function of shortening speed (see Gilbert et al., 1972, for a statement of this criticism). This problem has also recently been discussed by Huxley (1973), Huxley and Simmons (1972), Podolsky and Nolan (1972), and Chaplain and Frommelt (1971). It is true that in the model as it now stands, if one ATP molecule were hydrolyzed each time a cross-bridge turned

over, the rate of ATP splitting would be a monotonic increasing function of shortening speed just as in the original Huxley (1957) model. In addition, the ATP splitting rate is high in the isometric steady state because we chose to keep the fraction of cross-bridges attached small in order to accommodate X-ray evidence (Huxley and Brown, 1967). However, little is known about alternate reaction pathways involving the steps in the cross-bridge interaction cycle postulated in Fig. 1 A (Taylor, 1973). It may be, as suggested by Podolsky and Nolan (1972), that ATP turnover is not tightly coupled to cross-bridge turnover in at least some mechanical states, e.g., while shortening at high speed. Also, Huxley (1973) has shown how the substitution of a two-stage attachment process in his original model (1957) could lead to a fall in ATP splitting rate at high shortening speeds. It seems to us that until still better evidence is available concerning, e.g., the number of cross-bridges attached during the isometric steady state, and the rate of ATP hydrolysis during shortening at high speeds, to reject this model on the basis of current energetic evidence alone is not justified.

One final comment concerning our model is worth making. No account has been taken of the calcium regulating system. In the model, it is assumed that all regulating sites are filled with calcium, so that the contractile system is fully activated. This corresponds to the tetanic state of real muscle. It would, of course, be very interesting to have evidence regarding the behavior of T_1 and T_2 as the level of activation was varied at constant overlap and in the rigor state produced by removing ATP.

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