ACTIVATION IN A SKELETAL MUSCLE CONTRACTION MODEL WITH A MODIFICATION FOR INSECT FIBRILLAR MUSCLE

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ABSTRACT A sliding filament model for muscle contraction is extended by including an activation mechanism based on the hypothesis that the binding of calcium by a regulating protein in the myofibrils must occur before the rate constant governing the making of interactions between cross-bridges and thin filament sites can take on nonzero values. The magnitude of the rate constant is proportional to the amount of bound calcium. The model's isometric twitch and rise of force in an isometric tetanus are similar to the curves produced by real muscles. It redevelops force after a quick release in an isometric tetanus faster than the initial rise. Quick release experiments on the model during an isometric twitch show that the "active state" curve produced is different from the postulated calcium binding curve. The force developed by the model can be increased by a small quick stretch delivered soon after activation to values near the maximum generated in an isometric tetanus. Following the quick stretch, the force remains near the tetanic maximum for a long time even though the calcium binding curve rises to a peak and subsequently decays by about 50%. The model satisfies the constraint of shortening with a constant velocity under a constant load. Modifications can be made in the model so that it produces the delayed force changes following step length changes characteristic of insect fibrillar muscle.

INTRODUCTION

Recent progress toward understanding the basic features of vertebrate striated muscle contraction has been substantial. In particular, in living muscle fibers the interaction between cross-bridges on the thick filaments and sites on the thin filaments, and not just simple overlap of the filaments, leads to force generation (1). Also, X-ray diffraction diagrams of contracting muscles indicate some longitudinal, unsynchronized movement or tilting of the cross-bridges without any great change in the length of either the thick or thin filaments (2). Finally, considerable evidence indicates that the binding of calcium by the myofibrils regulates the process of contraction and relaxation (3–5, 8, 32, 33).

The first two findings cited above substantiate a model for contraction proposed

by A. F. Huxley (6). Huxley's model is based on a sliding filament mechanism in which force is generated by moving cross-bridges (called side-pieces) interacting with sites on the actin-containing filaments. This paper extends Huxley's model by introducing an activation mechanism based on the last piece of evidence mentioned above. The model is made more realistic by including an elastic connection between the force generator element and the load it drives. Also, some attention is given to the problem of modifying the model so that it responds to sudden length changes in a way similar to insect fibrillar muscle.

DESCRIPTION OF THE MODEL AND ASSUMPTIONS

The parts of the model are shown in Fig. 1. Arrows indicate the way in which events are assumed to flow. The circles with the subscripts "force" and "length, velocity" indicate ideal transducer devices placed in the positions in which they would be found in conventional types of muscle experiments.

Force Generator

Macroscopically, the contractile unit may be thought of as one-half of an A band fixed to a rigid constraint at the level of the M line. Force is generated by the cross-bridges on the thick filaments and transmitted to the thin filaments at the interaction points. The ends of the thin filaments opposite the ends nearest the M line are fixed to the structure of the Z line which is connected to the series elastic element. The initial half-sarcomere length and all subsequent changes are confined to the region of the plateau in the sarcomere length-tension diagram (1).

The microscopic details of the force generator are essentially those proposed by Huxley (6). "Zero" position for the cross-bridges is considered normal to the long axis of the thick filaments. The time rate of change of interacting cross-bridges and thin filament sites is given by an equation similar to Huxley's first equation (reference 6, p. 284)

$$\frac{\partial n'}{\partial t} = f(N - n') - gn' \qquad (1)$$

where f and g are position dependent rate constants and n' and N represent the following quantities in this paper. n' is the number of cross-bridges per centimeter interacting with thin filament sites in a force generating process. N is the "density" of sites in 1/cm at every position when all cross-bridges are interacting.

The force, F, produced by a cross-bridge interacting with a thin filament site x cm away from the zero position is postulated to be kx where the force is in dynes and k is a stiffness coefficient. For positive x, the force tends to make the thin filaments move toward the M line. At any instant, if $n'(x)$ is known, the net force produced by all the interacting cross-bridges in the half-sarcomere is

$$F = \int_{-\infty}^{\infty} kn'x \, dx. \qquad (2)$$

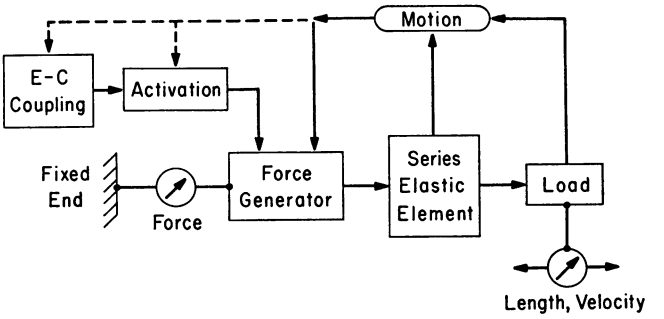

FIGURE 1 A block diagram of the model. *E-C* stands for excitation-contraction. The dashed lines indicate possible motion feedback paths.

The infinite upper and lower limits on the integral can be taken to mean that the integration is extended from the zero position until limits are reached at which the value for the integral no longer changes appreciably.

Following Huxley (6), x is normalized with respect to h, where h represents the positive distance away from the zero position beyond which a cross-bridge may not form a new interaction with a thin filament site; x/h is denoted u. n' is normalized with respect to N; n'/N is denoted n. Solving Equation 1 with the constraint that the contractile unit is held isometric gives

$$n(u) = \frac{f}{f+g} - \frac{f - (f+g)n_0}{(f+g)\exp[(f+g)t]} \tag{3}$$

where n_0 is the initial n value at any u. As t becomes large, $n_{ss} = f/(f+g)$, where n_{ss} is the isometric steady state value for n. Inspection of Huxley's paper (6) shows that a value of 0.8125 is appropriate for n_{ss}. Reducing Equation 2 to a normalized form suitable for the isometric steady state gives

$$\frac{F}{F_0} = 0.8125 \frac{k}{k_0} \int_0^1 u \, du$$

in which F_0 is the isometric force and k_0 is a normalizing factor for the stiffness coefficient. Since F/F_0 must equal 1 in the above equation, k/k_0 is 2.4615. Equation 2 may now be written as

$$P = 2.4615 \int_{-\infty}^{\infty} nu \, du \tag{4}$$

where $P = F/F_0$. Furthermore,

$$k_q = 2.4615 \int_{-\infty}^{\infty} n \, du \tag{5}$$

where k_g is the equivalent, instantaneous stiffness of all the interacting cross-bridges taken to be in parallel. Dividing Equation 4 by Equation 5 gives the equivalent, instantaneous "length" of the force generator. For example, in the isometric steady state, P is 1, k_g is 2, and the "length" is 0.5. This means that if the thin filaments were suddenly shifted along by 0.5 units, the force would drop to zero if the cross-bridges did not change their points of interaction or cease to interact during the sudden motion (7).

Activation

The model requires an activation mechanism to regulate the reaction between cross-bridges and thin filament sites if nonsteady-state processes, such as the time course of the rise of tension in an isometric tetanus, are to be calculated. The work of A. Weber and her colleagues (5) indicates that the binding of calcium to the myofibrils triggers ATPase activity and syneresis. S. Ebashi (8) has shown that the presence of a regulating protein complex, called "native tropomyosin", is necessary to make the interaction between actin and myosin calcium-sensitive. Moreover, much evidence points to calcium as the agent triggering contraction in living muscle. (See Sandow [4] for references and discussion.) Following a lead given by Huxley (6) in a discussion concerning activation, I made his forward rate constant f, which governs the rate at which free cross-bridges interact with thin filament sites, depend on the binding of calcium. In the relaxed state when no calcium is available for binding, f is zero and no interactions occur. Upon stimulation, calcium is released from the sarcoplasmic reticulum and subsequently bound by the regulating protein in the myofibrils, allowing interactions between cross-bridges and thin filaments to begin. Huxley's (6) constraints on f are that f is 0 if u is less than 0 or greater than 1. When u varies between 0 and 1, $f = f_1 u$ where f_1 is the value of f at $u = 1$. A variation in f is produced by time modulating f_1 as follows:

$$f = [\gamma(t) f_1] u \tag{6}$$

where $\gamma(t)$ is an activation factor expressing the time course of calcium binding by the myofibrils; it varies between 0 and 1. In the steady state, such as during the force plateau in an isometric tetanus, activation is assumed to be complete, meaning that γ_{ss} equals 1, so that during the maximally activated state in a tetanus, results should be those obtained by Huxley (6), e.g., n as a function of u and the force-velocity relation.

Jewell and Wilkie's (10) experimental results suggest that, in an isometric twitch produced by a single stimulus, the active state must decrease to a very low level by about 1.2 sec after the shock since the force is then about zero. According to Jewell and Wilkie (11), the active state rises with a lag to a peak soon after a single stimulus (about 60 msec later) and then decreases. Since Jewell and Wilkie (11) recorded twitch: tetanus ratios of up to 0.92, I propose that the activation factor reaches a

value of 1 at its peak. In summary, for a single stimulus delivered at $t = 0$ and 0°C: $\gamma = 0$ when t is less than 0 or greater than 1.2 sec and $\gamma = 1$ when $t = t_p$.

Close (12) has carried out the following experiments on real muscles. After plotting rate of force change against force in redevelopment of isometric force and in initial development of force in an isometric twitch, he concluded that activation in a twitch reaches the isometric level about 40 msec after the stimulus and remains there for only a few msec before decreasing. A reasonable figure for t_p would therefore be about 40 msec, the value used in my work. Selecting t_p for the model in this way can be justified as follows: take the time derivative of Equation 4 for the force and in the result replace $\partial n/\partial t$ by Equation 1 and f by Equation 6, giving

$$\frac{\partial P}{\partial t} = 2.4615 \int_{-\infty}^{\infty} \{[\gamma(t)f_1]u(1 - n) - gn\}u \, du. \tag{7}$$

Equation 7 gives the time rate of change of force in the model. In the experiment in which a muscle is rapidly released a short distance during the force plateau of an isometric tetanus (22), the force drops to zero. In the model, force redevelops until it again reaches its maximum value just as a real muscle does. At all times during this experiment γ is equal to 1. Next, consider an isometric twitch during which γ takes on the value 1 only at time t_p. Examination of Equation 7 suggests that if rate of change of force were plotted against force on the same graph for both the force redeveloped during an isometric tetanus and for the inital rise of force in an isometric twitch, points at which the two curves coincided could be used to indicate t_p in a twitch. This would be so because at points of coincidence $\partial P_I/\partial t = \partial P_R/\partial t$ and $P_I = P_R$; also, $n(u)_I \sim n(u)_R$ and $[1 - n(u)]_I \sim [1 - n(u)]_R$ where the subscripts I and R indicate initial and redeveloped rise of force. Therefore, $[\gamma(t_p)f_1]_I \sim (\gamma_{ss}f_1]_R$ but γ_{ss} is equal to 1, which means that $\gamma(t_p)$ must also be 1, and the time t_p can be determined by referring to the plot of rise of force against time in the isometric twitch and reading off the value of time at which P_I appeared. Unfortunately, this line of reasoning is not quite correct. At time zero in a twitch, P is zero because n is everywhere zero. Immediately after a quick release in a tetanus, P also is zero, but in this case because

$$2.4615 \int_{-\infty}^{\infty} nu \, du = 0.$$

This emphasizes the particular feature of the model that equality of forces in two different states does not necessarily imply the same $n(u)$ distributions. Nevertheless, for the case under discussion, it is true that $n = 0$ when u varies between 0.5 and 1, both initially in the twitch and just after release in the tetanus. Equation 7 shows that the rate of change of force is weighted by u, so that in the most influential region of u the initial states of the model are the same, and the argument advanced previously may still be used to obtain an approximation for t_p.

Therefore, in a twitch following a single stimulus, γ is proposed to rise from zero to a maximum 40 msec later, and then to decay back to very near zero 1.2 sec after the stimulus. However, it is necessary that γ be known as a continuous time function. Following Hodgkin and Horowicz (13), the following type of function was selected to represent γ:

$$\frac{b}{b_p} = \frac{a_0}{b_p} \frac{\alpha}{\alpha - \beta} [\exp(-\alpha t) - \exp(-\beta t)] \quad (8)$$

where b is the amount of calcium bound to the myofibrils, b_p is the peak amount bound at t_p, a_0 is the total calcium in 1 gm of muscle, α and β are suitable rate constants and t is in seconds. The variable b/b_p is then equal to γ. The time derivative of Equation 8 can be made equal to zero at time t_p. Rearranging the resulting equation and substituting into Equation 8, setting b/b_p or γ equal to 1 at time t_p and using the value of 0.04 sec for t_p leads to

$$\beta = [\ln (b_p/a_0)]/-0.04.$$

Values are available for b_p, 0.15 μmoles (5), and a_0, 2 μmoles (14). This makes β equal to about 65/sec, and α can be calculated to be about 6/sec. Putting in the appropriate values, Equation 8 can be written as

$$\gamma = 1.41 [\exp(-6t) - \exp(-65t)]. \quad (9)$$

Equation 9 is plotted as the solid line labeled "twitch" in Fig. 2.

A very simple relation is used to calculate γ for a tetanus. It is assumed that γ increases from zero to 1 in a way similar to that given by Equation 9 but remains at 1 thereafter. For a tetanus,

$$\gamma = 1.0 - \exp(-114t) \quad (10)$$

It seems reasonable that the time course of activation should not differ initially for a twitch or a tetanus, but that successive stimuli during a tetanus act to keep the level of activation at a maximum. Equation 10 is plotted in Fig. 2 as the dashed line labeled "tetanus."

Excitation-Contraction Coupling

Excitation-contraction (*E-C*) coupling (4) does not explicitly enter into the calculations. All events leading up to the actual binding of calcium by the myofibrils may be included in *E-C* coupling. In the model, activation, or the time course of calcium binding to the regulating protein in the myofibrils, is separated from *E-C* coupling. Partly, this was done to avoid complications that would lead to unjustifiably long and laborious calculations. Also, it seems worthwhile to keep the two

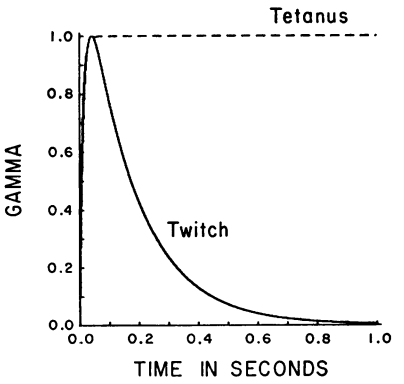

FIGURE 2 Postulated time course of activation for twitch (Equation 9) and tetanus (Equation 10). Gamma refers to the relative amount of calcium bound by a regulating protein in the myofibrils.

processes separate because, as indicated in Fig. 1 by the dashed lines, change in a mechanical variable, e.g., shortening or lengthening of the muscle, might influence one or the other, ultimately affecting force generation by changing f. This kind of effect by which the mechanical output from a muscle may influence activation has already been discussed by Goodall (16) and Pringle (17). Certain characteristics of contraction, such as the latency period between stimulus and development of force, are undoubtedly omitted by not including some E-C coupling processes.

Series Elastic Element

Connection to the force generator through some element having elastic properties is inevitable. According to Hill (18), this should affect the time course of force development in any "isometric" situation. I obtained a characteristic curve for an undamped elastic element from Jewell and Wilkie (11). Their Fig. 6 *b* shows the resultant nonlinear load-extension curve of all the elastic elements in series with and including the contractile component during isometric recordings. They give evidence for believing that the contribution to this curve from the force generator, i.e. "the bonded region" between the thick and thin filaments, is small. For this work their points are adequately fitted by two straight lines with a breakpoint placed at about a load of 9 g wt and an extension of 0.26 mm. However, it is necessary to express their values of load relative to P_0 and extension relative to h. The value given to h in this paper is 100 A. Using a sarcomere length of about 2 μ, Jewell and Wilkie's 0.26 mm at the breakpoint can be converted to an extension per half-sarcomere (L) of 0.9 in units of h. The isometric tetanic tension, P_0, of their muscle seems to be about 32 g wt, so that 9 g wt is equivalent to a P/P_0 of 0.28. Values for the slopes of the two straight lines just discussed are necessary. Therefore, when

$$0 \leq L \leq 0.9 \quad \text{and} \quad 0 \leq P/P_0 \leq 0.28, \qquad k_1 = 0.31$$

$$0.9 < L \leq 2.17 \quad \text{and} \quad 0.28 < P/P_0 \leq 1.0, \qquad k_2 = 0.56 \qquad (11)$$

where k_1 and k_2 are stiffness coefficients for the series elastic element. Their values may be compared with 2.0, the equivalent stiffness of the force generator in an isometric tetanus during the steady state.

Load

In most cases, the load is a fixed constraint. However, it can be very rapidly moved a given distance in either direction, and then held fixed, making possible quick stretch and quick release experiments. The constraint may also be replaced by a pure force, i.e., the model's response to a constant load of magnitude $P/P_0 < 1.0$ can be calculated.

Motion

Even if the load is fixed, an "isometric" situation, motion feedback is still possible because of the series elastic element. However it occurs, and in whatever direction, motion must affect force generation in the model by shifting the distribution of n as a function of u, so that different values for f and g are encountered. For example, a quick release or a quick stretch will bring the n distribution into regions of u over which g has a large value, causing a rapid decrease in n.

METHODS FOR COMPUTATIONS

The number of computations involved in even a restricted examination of the model's characteristics is very large. Consequently, a digital computer (IBM 1800 operating in an off-line mode) was programmed to do the calculations.

In Huxley's paper (6), the values of the rate constants f and g for positive u are given in proportion to the constants f_1 and g_1, the values for f and g at $u = 1$. For negative u, $g = g_2$ and is independent of u. However, only values for the ratios of rate constants appear in his model. In this work, values are assigned to f_1, g_1, and g_2 such that the ratios in Huxley's paper are satisfied. The values are: $f_1 = 81.25$/sec, $g_1 = 18.75$/sec and $g_2 = 391.9$/sec. This choice can be justified by evaluating Huxley's (6) expression for V_m, the maximum unloaded shortening velocity in muscle lengths per second, which is $V_m = 4(h/s)(f_1 + g_1)$, where s is the sarcomere length. This equation may be rewritten so that the velocity appears in centimeters/second by multiplying both sides by the length of the muscle in cm. Thus, $V_m = 4mh(f_1 + g_1)$ where m is the number of sarcomeres. An approximate value for m in frog sartorius muscle is 10^4, and using the values for h, f_1 and g_1 already given yields a velocity of 4 cm/sec, which is reasonable.

Equations 4 and 5, from which the generator's force and equivalent stiffness can be calculated, require that n be known as a function of distance, u. Equation 1 can be integrated at any given position u only if there is no motion of the thin filament array, i.e., a strictly isometric situation exists. Because f in Equation 1 has been made to depend on t, Equation 3 no longer applies. To gain solutions, the following approximation to the real situation was used: t was allowed to change by only a small increment, Δt, making it possible to neglect the time variation of f in the interval Δt; f could be considered constant over each Δt. Equation 3 could still be used if written as

$$n(u) = \frac{f(\gamma, u)}{f(\gamma, u) + g(u)} - \frac{f(\gamma, u) - [f(\gamma, u) + g(u)]n_0}{[f(\gamma, u) + g(u)] \exp \{[f(\gamma, u) + g(u)]\Delta t\}} \quad (12)$$

where Δt is in seconds. Therefore, given the initial value of n, n_0, at any u and t, a new n value could be calculated Δt later. An appropriate value for γ, depending on whether Equation 9 for a twitch or Equation 10 for a tetanus was selected, was calculated by taking

$$\gamma(\Delta t_j) = \frac{\gamma(t_i + \Delta t_j) + \gamma(t_i)}{2} \quad (13)$$

where $\gamma(\Delta t_j)$ is the constant value for γ in the interval Δt_j. Equation 12 can be written to apply in three distinct regions over which u varies (see Huxley [6], Fig. 6).

$$1) \; -\infty < u < 0: \qquad f = 0, \qquad g = 391.9$$

$$n = n_0/\exp\,(391.9\Delta t_j) \quad (14)$$

$$2) \; 0 \leq u \leq 1: \qquad f = \gamma(\Delta t_j)[81.25u], \qquad g = 18.75u$$

$$n(u) = \frac{\gamma(\Delta t_j)(81.25)}{\gamma(\Delta t_j)(81.25) + 18.75} - \frac{\gamma(\Delta t_j)(81.25) - [\gamma(\Delta t_j)(81.25) + 18.75]n_0}{[\gamma(\Delta t_j)(81.25) + 18.75] \exp \{u[\gamma(\Delta t_j)(81.25) + 18.75]\Delta t_j\}} \quad (15)$$

$$3) \; 1 < u < \infty: \qquad f = 0, \qquad g = 18.75u$$

$$n(u) = n_0/\exp\,[u(18.75)\Delta t_j] \quad (16)$$

Equations 4 and 5 were solved as follows. Equation 4 can be written

$$P = 2.4615\left[\int_A^0 nu\,du + \int_0^1 nu\,du + \int_1^B nu\,du\right] \quad (17)$$

where A and B are as yet undefined limits A Gaussian quadrature approximation was used by the computer to obtain values for each of the above integrals (19). Therefore, given limits on u, $n_0(u)$, Equations 16, 17, and 18 and the factor 2.4615, the computer could calculate the force in the generator after a time step, Δt. The same procedure was used to calculate the generator's equivalent stiffness.

Imagine the situation at the end of the time step Δt_j, when the generator exerts the force P_g and has an equivalent stiffness k_g. The series elastic element has the force value P_e at length L_e and stiffness k. P_g does not in general equal P_e, and the two forces cannot be in equilibrium. However, consider the instantaneous load line of the generator plotted backward on the graph of the characteristic curve of the series elastic element, where the ordinate for the load line is placed at L_e. The force value at the point of intersection of the two curves is given by $P_g - k_g\Delta L_j = P_e + k\Delta L_j$ or, rearranging,

$$\Delta L_j = \frac{P_g - P_e}{k_g + k} \quad (18)$$

where ΔL_j is both the amount the $n(u)$ distribution must be shifted about the zero position on the cross-bridges and the length change of the series elastic element. Therefore, at the end of Δt_j, the length change ΔL_j is instantly imposed, bringing the forces in generator and spring into equilibrium. Isometric conditions are again imposed, and Δt_{j+1} is allowed to repeat the cycle. Equation 18 is general and can be used to calculate ΔL whether P_g is greater or less than P_e. Over a complete twitch, the sum of all the length steps is zero so that the series elastic element ends up at its initial length. Equation 18 holds when $k = k_1$; that is, for $0 \leq L \leq 0.9$. When $L > 0.9$, the following equation must be used:

$$\Delta L_j = \frac{(P_g - 0.28) - (L_e - 0.9)k_2}{k_g + k_2} \qquad (19)$$

The macroscopic length variable L is related to the cross-bridge distance variable u because, as a result of the small, instantaneous length change, $n(u)$ becomes $n(u + \Delta L)$. An algorithm was written for the computer to calculate $n_0(u)$, without which Equations 16, 17, and 18 for n would be useless. Initially, at each step, it was necessary to provide a value for u and the total number K of shifts, ΔL, which had occurred. The values of all variables required in the calculation were stored in the computer as they were produced, so that they were available for recall. As the program was written, the first value of ΔL was zero. In effect, the given u is transformed to u_0, its value at $t = 0$. At this time, n_0 is known to be zero. At the end of the first Δt, n_0 becomes n, which subsequently becomes n_0 at $u_0 + \Delta L_2$. Eventually, by repeating itself $K - 1$ times, the algorithm produces an n_0 appropriate for the given u and Δt_j.

The limits A and B determine the region of u over which n has appreciable value. A is set by the extent to which n is shifted into regions of negative u. The computer calculates it by summing all the positive ΔL_j that occur. B is set by the extent to which n is shifted into positions where u is greater than 1. It is calculated by summing all the negative ΔL_j.

Obviously, this method of solution would give a better approximation if at each step Δt were very small, in which case ΔL would also be small, and the variation of $\gamma(t)$ between and in successive steps would be very small. However, it quickly became apparent that if Δt was too small, the amount of computer time needed became too large. Preliminary calculations indicated that if Δt were selected to make ΔL fall in the range $0.04 < \Delta L < 0.06$, the results were not appreciably different from those produced by much smaller Δt. The range of ΔL corresponds to a shift of about 5% of h, or 5 A. Using these limits on ΔL as a criterion for selecting Δt led to a maximum variation of about 2% between successive values of $\gamma(t)$ in each step of the calculation.

At all steps, the values for t, Δt, ΔL, L, P and γ were stored in the computer and later recorded on punched cards. A Calcomp plotter was used to produce the graphs using appropriate data from the cards. The data points were closely spaced, so that the plotter pen was left in the down position, and successive points were connected by straight lines.

INTERPRETATION OF RESULTS

Isometric Twitch

To compute the twitch, the load shown in Fig. 1 was fixed so that the force generator pulled against the series elastic element. The $\gamma(t)$ curve labeled "twitch" in Fig. 2 was selected as the activation function (Equation 9). In comparing the model's response (Fig. 3) with Jewell and Wilkie's (10) twitch from a frog sartorius,

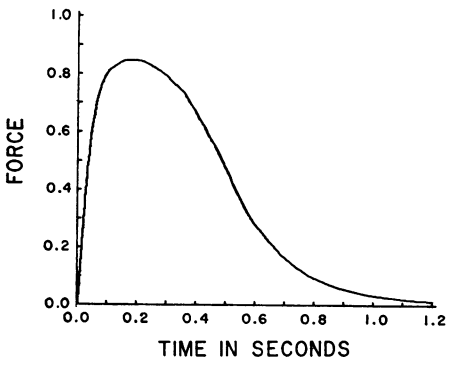

FIGURE 3 The model's isometric force response computed by using the activation curve labeled "Twitch" in Fig. 2 (Equation 9). The time to peak force value is 177 msec, or 137 msec past the maximum of gamma. The value for peak force, 0.85 may be compared to Jewell and Wilkie's (10) figure of 0.92 for their maximum twitch: tetanus ratio. At peak force, the series elastic element was extended 1.91 units or 191 A. From about 260 to 380 msec, the decay of force is almost linear; beyond about 400 msec, the decay seems to be exponential. Similar effects can be seen in real muscles (11).

the initial rise of force in the model seems to be more rapid, and the time to peak value is slightly less than in the real muscle. Overall, however, the model and real muscle show reasonably good agreement in their $P(t)$ curves. By the time of peak force in the model, $\gamma(t)$ has fallen to about half (0.49) its peak value; by 500 msec, $\gamma(t)$ is down to 0.07, whereas $P(t)$ has decreased just under 50%. Clearly, there is a marked difference between the time courses of activation and force generation in an isometric twitch.

Jewell and Wilkie (11) showed that the decay of force in an isometric twitch has a final exponential fall in real muscles. In Fig. 4, the natural logarithm of the force produced in the twitch of Fig. 3 is plotted against time over the range indicated. A reasonably close fit to the $P(t)$ curve from about 0.5 sec to the end of the twitch can be obtained by using a simple exponential equation. No attempt has been made to determine whether the value for the rate constant in this equation, 5.46/sec, is related to the value for the decay rate constant α of 6/sec used to calculate γ. There is no simple reason for the two values being nearly the same.

In Fig. 5, $n(u)$ is plotted at three different times during the twitch shown in Fig. 3. The curve identified by the + symbols is the n distribution 29 msec after activation began, at which point P is 0.42. The force generator has shortened internally against the series elastic element so that n has appreciable value in regions of negative u. The effect is to make the force rise less rapidly than it would if no series elastic element were present. This agrees with Hill's ideas (20) about the effect of elastic parts in series with the contractile element. The curve identified by the × symbols outlines the n distribution 105 msec after time zero, when P is 0.81. At this point, there is very little internal motion, and the distribution is near to that of the isometric steady state (see Fig. 7). The curve identified by triangles shows $n(u)$ 408 msec after time zero, when P is down to 0.64. By this time, $\gamma(t)$ drops to a low value (0.12), and the rate at which new interactions between cross-bridges and thin filament sites occur is low, making n decrease. Therefore, to keep the generator force in

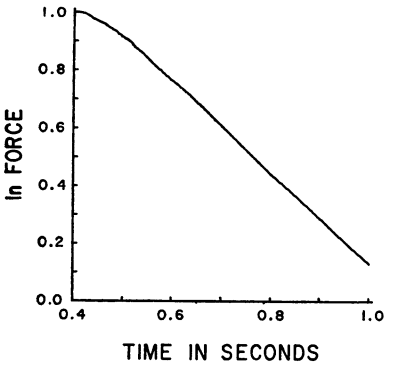

FIGURE 4 A plot of the natural logarithm of the force response shown in Fig. 3 over the indicated time range. Plotting points were computed from the following equation: $y = 1.127 - \{[|\ln P(t)|]/3.4967\}$, where y is the value for the ordinate at time t.

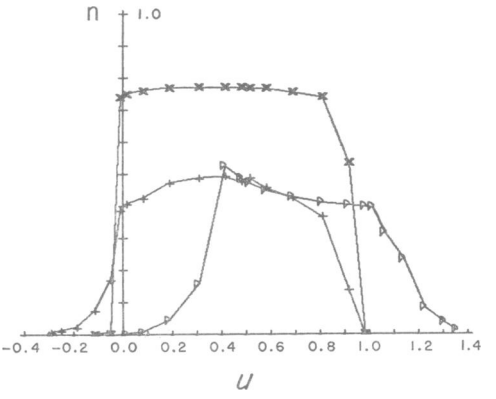

FIGURE 5 The distribution of n plotted before reaching the peak force value (+), near the peak (×), and after the peak (△) for the twitch shown in Fig. 3.

equilibrium with the force in the series elastic element, the n distribution is shifted in the direction of more positive u, and n now has appreciable value beyond $u = 1$. Fig. 5 indicates that the motion allowed internally by a series elastic element certainly influences the course of $P(t)$ in the model's "isometric" twitch.

Rise of Force in an Isometric Tetanus

Jewell and Wilkie (11) reduced the amount of series elastic material in their study of isometric contractions. In testing the theory (20) that the course of $P(t)$ in an isometric myogram is determined by the isotonic force-velocity curve and the stress-strain curve of the series elastic element, they found a clear discrepancy between theory and experiment. Since the characteristic for the series elastic element was based on their measurements, the model was subjected to the same test.

The load shown in Fig. 1 was fixed. However, in this experiment the curve of $\gamma(t)$ labeled "tetanus" in Fig. 2 was selected as the activating function (Equation 10). The results show that $P(t)$ rises to at least 0.99 by about 360 msec after time zero. This compares well with the results of Jewell and Wilkie (11) shown in their

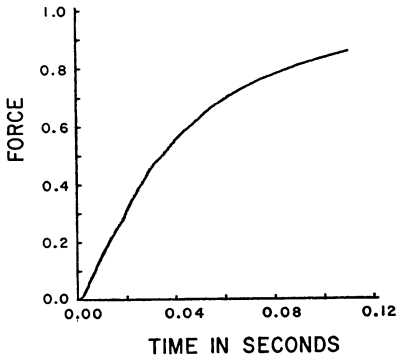

FIGURE 6 The model's early rise of force in an isometric tetanus computed by using the activation curve labeled "Tetanus" in Fig. 2 (Equation 10).

Fig. 4. Only the early part of the model's $P(t)$ is shown in Fig. 6 on a time scale similar to that used by Jewell and Wilkie in their Fig. 7. Comparison of the two curves for the initial rise of force shows that they are remarkably similar. To about 20 msec, Jewell and Wilkie's plot curves slightly under the more nearly straight line produced by the model operating in the range of P where the series elastic element has stiffness k_1. Beyond about 20 msec, where k_1 switches to k_2, $P(t)$ from the model seems to run slightly below the curve from the real muscle. An even better fit may have been obtained by using a more realistic nonlinear function to represent the characteristic of the elastic element in the model, but the computer would have taken more time to find an approximation to the load line intersection point.

Fig. 7 shows the n distribution at various times during the isometric tetanus. The distribution marked by the + symbols occurred 27 msec after activation began, and the appropriate P value is 0.42. Internal shortening against the series elastic element has again led to the appearance of appreciable n in regions of negative u. Late, 365 msec after time zero ($\times$ symbols), internal shortening is virtually complete. The series elastic element is extended 2.17 units or 217 A, and P is equal to 0.99. Notice the straight line drawn according to the relation $n = 0.8125$ for $0 \leq u \leq 1$. This is the steady-state value for $n(u)$ according to Huxley's equations (6). By 365 msec the n distribution is approaching this line. Finally, the triangles show that after 725 msec $n(u)$ is the same as n in Huxley's steady-state curve when the velocity of shortening is zero. The computer calculated P as 0.9998 for this $n(u)$.

Why did Jewell and Wilkie's (11) calculations based on the concepts of Hill (20) produce a curve for the time course of the rise of force in an isometric tetanus that was so much quicker than the real muscle's? The answer may be found in Fig. 8 in which force is plotted against velocity of shortening. The curves connecting the value 1.0 on the ordinate and abscissa apply only in the steady state. The equation for the solid curve is taken from Huxley (6). The dashed curve is given by Hill's hyperbolic equation (20). Another curve beginning at zero and ending at $P = 1$ is plotted in Fig. 8. The data for this curve were taken from the force generator's velocity of internal shortening as it pulled against the series elastic element in the

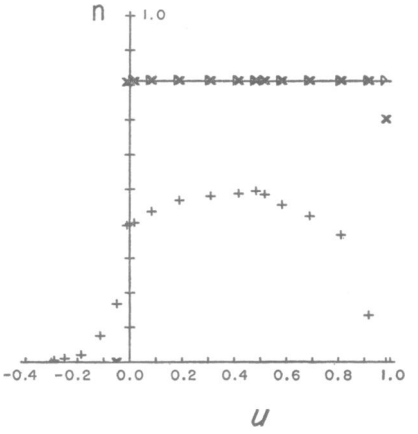

FIGURE 7 The distribution of n plotted well before reaching P_0(+), approaching P_0(×), and late in the plateau (△) for the isometric tetanus shown partly in Fig. 6. The solid line is computed from Huxley's Equation 7 as the velocity tends to zero.

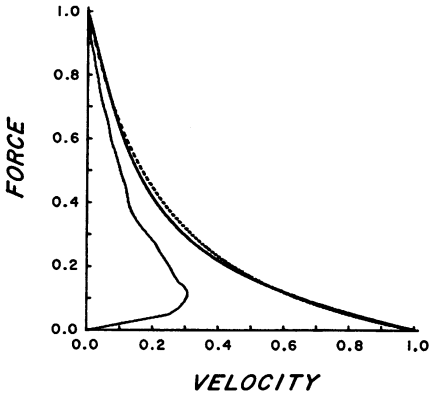

FIGURE 8 The model's velocity of internal shortening during the rise of force in an isometric tetanus approaches the values given by the steady-state equations of Hill (20) and Huxley (6) only at force values near P_0. The equations used to plot the curves connecting the value 1.0 on the ordinate and abscissa are as follows. The equation for the solid curve is based on Huxley's Equation 11: $P = 1 - \{4V[1 - \exp\cdot(-0.25/V)][1 + 0.1302V]\}$, where P is P/P_0, V is V/V_m and ϕ/V_m is equal to 0.25. The dashed curve is given by a form of Hill's hyperbolic equation which can be written as: $P = [0.3125/(V + 0.25)] - 0.25$, where P is P/P_0, V is V/V_m and both a/P_0 and b/V_m have the value 0.25.

isometric tetanus shown in Fig. 6. That is, at the end of each Δt_j in the calculation a length change ΔL_j was allowed to bring the generator and elastic element forces into equilibrium. An approximation for the velocity, V_j, is given by $\Delta L_j/\Delta t_j$. Jewell and Wilkie (11) show in their Fig. 5 that V_m must have been about 48 mm/sec, or, in a muscle 30 mm long with sarcomere length about 2 μ, about 2 μ per half-sarcomere/sec. In the model, V_m can be calculated from Huxley's expression given on page 554. Both sides of that relation can be divided by $2m$, the number of half-sarcomeres. This gives $V_m = 2h(f_1 + g_1)$, where V_m is given in cm per half-sarcomere/sec. The result is that V_m is 2×10^{-4} cm or 2 μ per half-sarcomere/sec, which is the same value as that given for real muscle. The approximation for V_j is therefore modified so that unit velocity corresponds to 2 μ/sec, i.e.

$$V_j = (\Delta L_j/\Delta t_j)/(200/\text{sec}) \qquad (20)$$

when $P = P_j$. For their numerical integration, Jewell and Wilkie (11) had to read off values for V at a given P by using the steady-state force-velocity curve. According to Fig. 8 this would be erroneous. Only as P tends to 1 do the curves tend to converge on the same velocity. This may explain why Jewell and Wilkie's theoretical curve rose too fast: the velocity used for a given force was too large, leading to a too rapid extension of their series elastic element. This view agrees with that of Podolsky (23).

Redevelopment of Force in an Isometric Tetanus after a Quick Release

Jewell and Wilkie (11) in their Fig. 7 have plotted the initial rise of force in an isometric tetanus together with the quicker redevelopment of force after a quick release timed to occur at a point well after the beginning of stimulation. Hill (21) also showed that the force rises more rapidly after a quick release, presumably because activation is complete during the redevelopment.

A similar experiment was done on the model using the starting conditions given in the previous section describing an isometric tetanus. The resulting curve for $P(t)$ labeled I for initial, is shown in Fig. 9. Then, 165 msec after the onset of activation, and a long time (~125 msec) after γ had reached its constant value of 1, the computer calculated ΔL to have a value such that the integral for force (Equation 4) became very nearly zero. In effect, the load end of the model was shifted along the distance ΔL plus an additional distance required to discharge the force in the series elastic element. Force redeveloped as shown in Fig. 9 by the curve R. Clearly, the curves diverge from the origin with the redeveloped force rising more rapidly; however, after about 120 msec, the difference between the two disappears and they run together. Comparing this to Jewell and Wilkie's curves shows close similarity including the time (~120 msec) at which the curves come together. The results from the model indicate that complete activation leads to a quicker rise of redeveloped force.

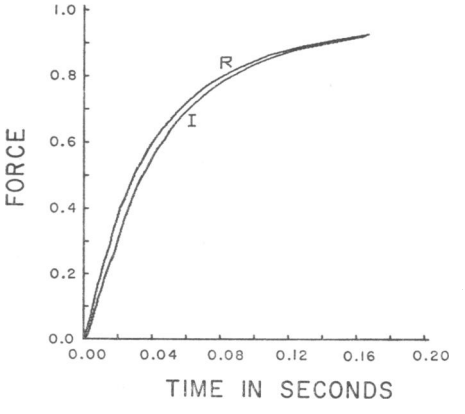

FIGURE 9 The model's initial rise of force (I) and redeveloped rise of force (R) after a quick release in an isometric tetanus computed by using the activation curve labeled "Tetanus" in Fig. 2 (Equation 10). The quick release was accomplished by suddenly moving the load end along by 2.445 units. Of this total, ΔL was 0.46, and the distance required to reduce the force to zero in the series elastic element was 1.985. Distance is expressed in units of Huxley's h (6), which is 100 A.

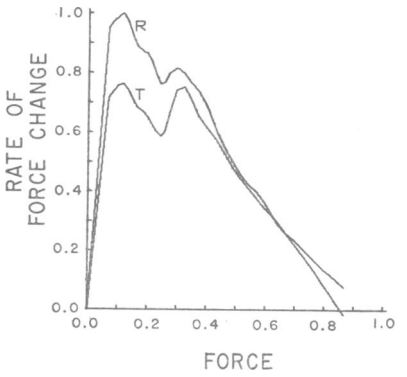

FIGURE 10 Phase-plane plots computed for the rise of force after a quick release in an isometric tetanus (R) and for the rise of force in an isometric twitch (T). Values for $\Delta P/\Delta t$ are normalized with respect to the maximum that occurred during the rise of redeveloped force. The R curve tends towards zero; the T curve crosses zero and becomes negative corresponding to decay of force following the twitch peak.

It was necessary to try Close's experiment (12) on the model to see if $\gamma(t_p)$ could be obtained from such plots. As has already been discussed in the Activation section, the model's characteristics make it unlikely that an exact value for t_p could be determined. Also, the available data make it necessary to approximate the continuous time derivatives of the forces by $dP/dt \approx \Delta P_j/\Delta t_j$. Finally, the two straight lines approximation for the stiffness characteristic of the series elastic element introduces a jump into $\Delta P/\Delta t$ plots when k_1 switches to k_2.

In Fig. 10, time rate of change of force is plotted against force for redeveloped force in curve R using data from curve R in Fig. 9, and for initial rise of force in a twitch in curve T using the data from the twitch shown Fig. 3. The curves diverge from the origin to reach separate maxima after which they decrease up to the point at which the stiffness k_1 switches to k_2. This leads to a sudden increase, most apparent in the T curve, in their values. There is a region in the plot past the peaks where the curves run closely together similarly to Close's Fig. 1 (12). In fact, in the interval $0.45 \leq P \leq 0.67$, the two curves differ by at most about 2%. Reference to the twitch $P(t)$ curve in Fig. 3 shows that the P value 0.45 occurred about 30 msec after activation began, while $P = 0.67$ occurred 57 msec afterwards. In a twitch at $t = 0.03$ sec, γ has the value 0.97, and at $t = 0.057$ sec, it has passed through the peak to reach 0.96. Taking the average of 30 and 57 msec, produces a value of 43.5 msec, which is just a few milliseconds beyond the actual t_p.

ACTIVE STATE

Pringle (17) pointed out that active state (20) must be some property of the contractile component which is not changed by quick releases or quick stretches. If the activation processes described by Equations 9 and 10 are assumed to remain unchanged after small, quick length changes have been imposed, the model's active state curve during an isometric twitch can be measured by Ritchie's method (22). The starting conditions were those described in the Isometric Twitch section. The solid curve in Fig. 11 shows, however, that near the maximum of $P(t)$, 150 msec after activation began, the force suddenly drops to zero as the result of a quick

release; then it rapidly rises to a peak and decays along a course similar to the twitch shown in Fig. 3. The entire process is similar to the response of a real muscle shown by Jewell and Wilkie (10). Additional experiments were done in which the quick releases occurred at various times after the beginning of activation. The results are rather similar to Jewell and Wilkie's (10) shown in their Fig. 12 *b*. Clearly, the × symbols plotted in Fig 11 do not follow the time course for activation in a twitch given by Equation 9. The peak force values are, in order, 0.85, 0.61, 0.37, 0.19, and 0.07, whereas the γ values at the same times are 0.57, 0.21, 0.09, 0.04, and 0.01. After a quick release, considerable force would be redeveloped even if at the time of release γ, and f, became zero. The explanation for this effect rests on the very large difference between g for negative and positive values of u.

Hill (18) applied quick stretches to muscles at various moments after a single stimulus had been given at time zero. Hill argued that since the muscles could bear forces of about the same magnitude as P_0 in an isometric tetanus soon after the stretches, the active state was also set up suddenly and completely. Although the concept of active state does not seem to apply,to any definite process in the model, its force response to a quick stretch was compared with the time course of the activation process given by Equation 9. The stretch response is shown in Fig. 12, where the starting conditions were those just described for quick releases. Fig. 12 shows that the stretch brings the force up to just beyond P_0, and that subsequently there is only a slow fall in 200 msec. The γ curve labeled "twitch" in Fig. 2 has only reached the value 0.63 by 11 msec after time zero. It then reaches a peak at about 40 msec, and by 200 msec it has fallen to 0.45. The fact that the force level remains at or near the tetanic value in a muscle after a quick stretch may not necessarily mean that activation is complete over the time range considered.

Comparing the curve in Fig. 12 with Hill's (18) experimental curves is useful. In the first place, most of Hill's records show a long interval of about 30 msec following the stimulus, and before the stretch is delivered, in which the force remains at zero. Certainly, the curve in Fig. 12 shows no appreciable latency effect. It would be surprising if it did, since *E-C* coupling has been neglected, and the series elastic

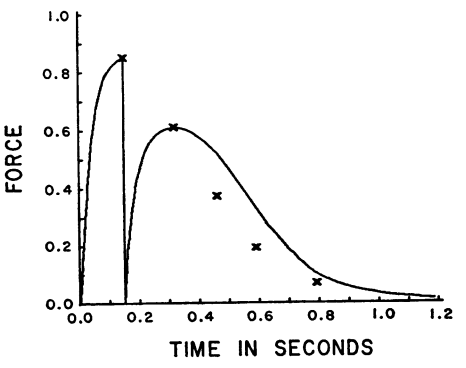

FIGURE 11 The model's response to a quick release timed to occur at the peak of a twitch computed by using the activation curve labeled "Twitch" in Fig. 2 (Equation 9). For this and other quick releases, the points at which peak force redeveloped are marked by × symbols. The first × marks peak force in the twitch. Subsequent × symbols mark peak force values attained following quick releases occurring 150, 289, 442, and 682 msec after time zero.

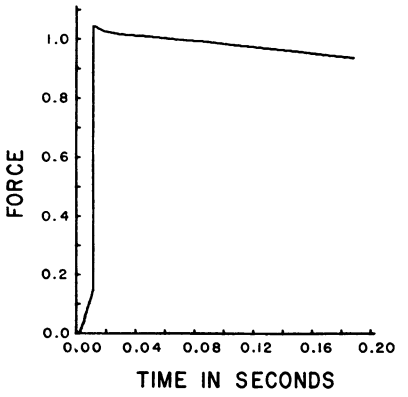

FIGURE 12 The model's response to a quick stretch timed to occur soon after the beginning of activation computed by using the activation curve labeled "Twitch" in Fig. 2 (Equation 9). 11 msec after activation began, the load end was suddenly extended 4.27 units. Of the total 4.27, ΔL was 2.5 units and the series elastic element was extended by 1.77 units. One unit equals 100 A.

element has the stiffness characteristic given by Jewell and Wilkie (11). The rise of force could be slowed in the model by considerably decreasing the stiffness of the series elastic element. This might be justified since Hill delivered stretches of as much as 18% of the initial length, or about four times that used in the model, in order to raise the force to tetanic level.

In Fig. 12, there is an initial rapid phase in the decline of force following the stretch similar to that in Hill's curves (18). In the model it probably results from a rapid decrease in n for u values greater than 1, where g is large.

Another interesting effect in Hill's results (18) is that following a quick stretch the force stays at a high level for a very long time. No such effect is seen in the model, where, by about 360 msec, the decay of force is already much like that of the twitch in Fig. 3. An explanation for Hill's effect may be found in some results given by Jewell and Wilkie (10). In their Fig. 7, they show that there is a considerable increase in the half-time of force decay in an isometric twitch as the muscle length is increased before stimulation. This raises the interesting possibility that length changes may somehow influence the force generator in ways besides those mentioned in the Motion section. Two possibilities are shown in Fig. 1 by the dashed arrows connecting motion to *E-C* coupling and activation. In vertebrate skeletal muscle, the more likely possibility seems to be through some effect on *E-C* coupling, perhaps by some physical effect on the calcium pumping ability of the sarcoplasmic reticulum, because Jewell and Wilkie's length increases were applied to resting muscle before stimulation and activation took place. Another explanation, similar to one made by H. E. Huxley (15), is that after a stretch, some of the excessively displaced cross-bridges may remain attached to thin filament sites for an abnormally long time.

Velocity of Shortening under a Constant Force

The model must satisfy the condition of shortening with a constant velocity under a constant force. This is a vital test not only of the model, but also of the methods of

solution used in the computations. The program was modified so that the force in the series elastic element could be made constant, which means

$$\Delta L_j = (P_j - P_c)/k_j \tag{21}$$

where P_c is the clamp force, and P_j and k_j are the force and equivalent stiffness in the generator after Δt_j. Dividing Equation 21 by Δt_j yields the velocity. This scheme is similar to one proposed by Podolsky (26).

One result is shown in Fig. 13. The initial conditions were those described for an isometric tetanus, which means that Equation 10 was used for activation. The curve labeled F in Fig. 13 shows that the force was held clamped at 0.66. The curve labeled L in Fig. 13 is the length shortened up to time t or

$$L(t) = \left(\sum_{j=1}^{k} \Delta L_j \right) / L_m$$

where k is the number of ΔL up to t and L_m is the total length shortened (363 A). It is clear from Fig 13 that beyond 54 msec the model shortens with a constant velocity. In its linear portion, $L(t)$ has a slope of about 15/sec. This velocity can be divided by the factor 200/sec used to make unit shortening velocity in the model correspond to 2 μ per half-sarcomere/sec or V_m. (See the section describing isometric tetanus.) The result is that the normalized steady shortening velocity is 0.08. Using Huxley's equation with $V = 0.08$ gives $P = 0.69$. (See the legend in Fig. 8 for the Huxley equation).

The $n(u)$ distribution for Fig. 13 is shown in Fig. 14. The + symbols refer to 41 msec after the beginning of activation, the × symbols to 122 msec, and the triangles to 190 msec. Obviously the distributions are identical for the last two cases because $n(u, t)$ must become $n(u)$ in the steady state since the force is constant. The solid curves in Fig. 14 were drawn using the steady-state $n(u)$ Equations 7 and 8 of Huxley (6) in which the velocity parameter was given the value 0.08. The close correspondence between the curves and the points calculated by the computer for

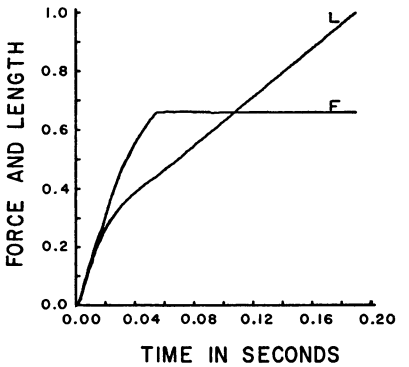

FIGURE 13 The length (L) change of the model under a particular force (F) constraint computed by using the activation curve labeled "Tetanus" in Fig. 2 (Equation 10). The clamp was applied 54 msec after activation began, when gamma was equal to 1.

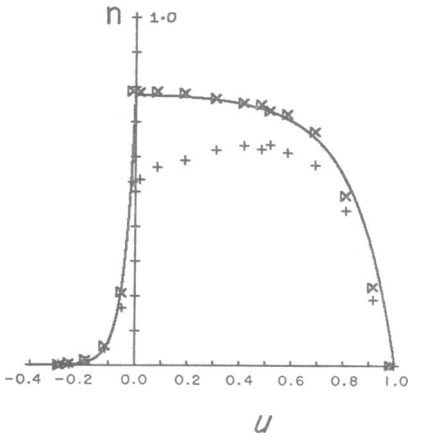

FIGURE 14 The n distribution for the result shown in Fig. 13 plotted before the force clamp was applied (+) and after at two different times in the steady state (×, △). The solid lines are computed from Huxley's (6) Equations 7 and 8 with $V/V_m = 0.08$ and $\phi/V_m = 0.25$.

$n(u)$ during the steady state can be taken as a measure of the accuracy of the methods used in the computations. The fact that the numerical methods are not exact is reflected in the value for P of 0.66 generated by the computer for $V = 0.08$, which is about 4% less than the exact value of $P = 0.69$ calculated from Huxley's steady-state equation using the same velocity.

Modification for Insect Fibrillar Muscle

Recently, much attention has been given to studying the contraction mechanism of insect fibrillar muscle, which can oscillate a suitable load at a frequency higher than the nerve impulse rate. (Pringle [27], who also proposes the idea of activation by calcium binding, may be consulted for details). The model would not demonstrate this property. The impetus for pursuing the problem of suitable modification came from Jewell and Rüegg (28), who showed that the oscillatory behavior was an intrinsic property of insect myofibrils. They suggest that stretch might produce a delayed increase in the amount of calcium bound to the myofibrils. Although this led to the idea of making motion in the model produce delayed changes in activation (Fig. 1), the problem of how to show that the proposed modifications would produce oscillatory behavior arose. Jewell and Rüegg's method (28) of recording the force responses to small, suddenly applied length changes was chosen because it demonstrates the essential delayed force changes a model must produce in order to oscillate a load. The following modifications were selected because they led to a force response similar to Jewell and Rüegg's.

(*a*) k_1 and k_2 were made very large, making the series elastic element virtually inextensible. High stiffness, even in the resting state, is a characteristic of insect fibrillar muscle (27).

(*b*) Beyond 1, g was made no longer to depend on u, but was given the constant value of 1.8750. In the regions $0 \leq u \leq 1$ and $-\infty < u < 0$, g varied as already described.

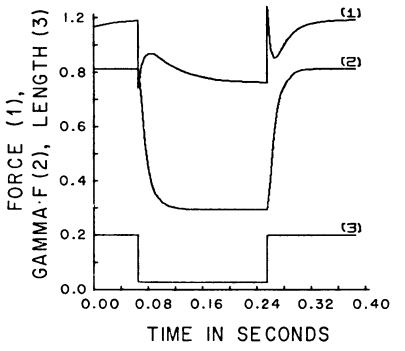

FIGURE 15 A plot of the modified model's force responses (*1*) and variations of the product of gamma and f (*2*) after sudden small length changes (*3*). Time zero refers to the time 77 msec after the onset of complete activation, when P is equal to 0.97. The initial value 0.2 for the length (curve *3*) has no significance. However, the change from 0.2 to 0.025 does indicate the magnitude of the length step, 0.175 units or 17.5 A. The equation used to calculate the fall in gamma is: $\gamma = (0.64) \exp\cdot[(-100/\text{sec})(t - t_s)] + 0.36$. The rise of gamma is calculated from: $\gamma = 0.64\{1 - \exp[(-100/\text{sec})(t - t_s)]\} + 0.36$. In both equations, $t = t' + (\Delta t/2)$, where t' is the time in seconds up to Δt, and t_s refers to the time at which the step occurred.

(*a*) The activation function γ was made to change so that it decreased exponentially from 1 with a rate constant of 100/sec following a sudden shortening. It subsequently returned exponentially to 1 with the same rate constant after a sudden return to the initial length.

The results are shown in Fig. 15, where the initial conditions were those used in the isometric tetanus except that γ did not vary according to Equation 10 but was given the value 1. Curve *3* in Fig. 15, the length trace, shows that 65 msec after zero time a step shortening was imposed on the load end of the model. After 190 msec, a step return to the original length occurred, and the load end was held fixed for the remaining 130 msec. The exponential response of the factor γf is shown in curve *2*. Curve *1* shows that there is an initial partial redevelopment of force after the length decrease, but this is not sustained. There is an initial fall in force after the return to initial length, but this also is not maintained. The results in Fig. 15 should be compared to Fig. 10 of Jewell and Rüegg (28). If their tension change is normalized with respect to steady tension, the two graphs are generally similar with respect to force and length curves.

DISCUSSION

This paper attempts to add to Huxley's (6) model an activation mechanism based on the hypothesis that the binding of calcium by a regulating myofibrillar protein must occur before Huxley's forward rate constant f can take on nonzero values. The time course for activation in a twitch given by Equation 9 seems reasonable. Recent studies (29, 30) on the time course of the free calcium ion concentration

change in the myoplasm following a single stimulus show a process that rises quickly to a peak, which occurs well before the peak in the force record, and subsequently decays less rapidly than it rose. The time course for $\gamma(t)$ in a twitch also shows a close resemblance to Brown's alpha process curve (31), raising the question of how pressure applied at various times early in a twitch might affect calcium movement. Recent papers (32, 33) indicate that activating calcium seems to bind to the troponin component found in "native tropomyosin" (8). Troponin is not obligatory in the superprecipitation reaction (5). This fits with the hypothesis that calcium binding increases the interaction rate between cross-bridges and thin filament sites without acting as a bridge as Davies proposed (9). The hypothesis could be tested if the time course of calcium binding in a twitch can be measured.

Preliminary calculations have shown that after a force clamp has been applied, the model can produce a constant velocity of shortening with a value near to that given by the steady state force-velocity relations of Hill and Huxley. A detailed study of the nature of the velocity transient produced under such conditions has not yet been made. There is very little in the way of a transient seen in Fig. 13 for $P = 0.66$, and this agrees with the calculated response shown by Civan and Podolsky (24) in their Fig. 10 for $P = 0.65$. However, their results were obtained from Huxley's model (6) by suddenly changing the load from P_0 to P by allowing a very quick release of appropriate size. Available evidence (25) indicates that the transient length responses of frog fibers to step changes of force to levels not far below P_0 can be quite complex. The sudden length changes involved in making a step force change may affect the state of activation in muscle. Such an effect would have to be introduced into model calculations.

The modified model demonstrates a characteristic feature of insect fibrillar muscle by its response to step length changes. The step decrease in length shifts some n into regions of negative u where g is very large. Consequently, n decays rapidly leading to an initial force rise. However, γf falls with a delay, which means that eventually the force must decrease. After the step increase in length, some n is shifted to regions where u is greater than 1, where again g is large, and this leads to rapid decay of n and an initial fall in force. But γf rises with a delay to its initial value, and this, in turn, brings the force up to its original level. The reason for writing γf is that this product is what the computer actually calculates for use in the equations for n. Initially, it was assumed that γ was sensitive to length changes. However, it is only necessary that γf follow the time course in Fig. 15. For example, γ could be constant and f a variable which depended on length. Equation 1 could be written in its form by assuming that the number of thin filament sites do not vary appreciably, permitting this factor to be lumped in with the forward rate constant f. The length changes in insect fibrillar muscle may produce in some way a delayed variation in the number of thin filament sites available for interaction. Finally, some of the results of Armstrong, Huxley, and Julian (25) obtained from vertebrate striated muscle fibers subjected to sudden small length changes could probably be reproduced

by the modified model if the delayed fall of γf after the step length decrease were not maintained, and γf were allowed to return to its initial value. A similar transient characteristic would have to be given to the delayed rise of γf after the step length increase.

The results presented in this paper show that A. F. Huxley's model can be extended to provide an explanation for many different phenomena of muscle contraction. The effects of parameter variation, the length responses following step force changes, and a more complete examination of the consequences of the modification for insect fibrillar muscle are areas in which further work is now underway in the extended model.

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