The Concept of Active State in Striated Muscle

FRED J. JULIAN AND RICHARD L. MOSS

FOR THE purposes of this review, it will be helpful to consider the simple block diagram of a striated muscle system shown in Figure 1. The system has been generalized, in order to be applicable to heart muscle, by including an isotropic state mechanism. The parallel elastic component is necessary to account for resting tension. However, neither of these elements will be discussed further. According to the classical model for muscle contraction proposed by Hill, a contracting muscle can be represented by a contractile component (CC) in series with a series elastic component (SEC). In the resting state, the CC is freely extensible, whereas in the active state it is supposed to resist strongly any attempt to suddenly change its length. The properties of the active CC are such that its force-velocity behavior can be described by the following equation:

\[(P + a)V = b(P_{at} - P) \tag{1}\]

where \(P\) is the force, \(V\) is the velocity of shortening and \(a\) and \(b\) are constants. The use of \(P_{at}\), where \(t\) is time, can be explained as follows. During a steady state isometric contraction, as in a tetanus, successive stimuli serve to keep the active state at its maximum level, indicated by the tetanic \(P_0\). In this case there is no need for the subscript \(t\) in Equation 1, because \(P_{at}\) is time-invariant. However, in a twitch the peak developed isometric force does not attain the tetanic level. Hill\(^1\) knew from his thermal measurements that heat production starts off at its maximum rate very soon after a stimulus and before any mechanical response is detectable. He therefore reasoned that the transition in the CC from rest to a fully "active state" following a single stimulus was very rapid, so that the active state was completely developed. Relaxation was produced by a slower decline of the active state to its resting level. Hill\(^1\) defined the intensity of the active state at any instant in time to be equal to the magnitude of the developed force when the velocity of shortening of the CC was zero; that is, in Equation 1, \(P_{at} = P\) when \(V = 0\). Using this definition, and expressing the force of the CC, \(P\), relative to the tetanic \(P_{0}\), it can be seen that the active state level varies between 0 and 1.

In view of the fact that Levin and Wyman\(^2\) showed that there was an instantaneous tension change in muscle for suddenly applied length changes, Hill\(^1\) proposed that the SEC was undamped. The SEC force \((F)\) vs. extension \((L)\) characteristic was independent of time and nonlinear (Fig. 2E); the latter of which can be indicated by making the SEC spring constant, \(K\), depend on length. Hill\(^1\) proposed that the explanation for the slow rise of force in an ordinary contraction with total length fixed was that, as internal shortening of the CC occurred, the SEC was stretched out during the phase of rising force. That this was a time-consuming process is borne out in Equation 1, for as the force in the SEC increases, the velocity of shortening of the CC decreases (note that in the absence of a parallel elastic component the SEC and CC forces are always equal, since these elements are in series).

This scheme explains how it is possible for peak twitch force to be well below the tetanic \(P_0\) even though the active state is fully developed in both cases. Since the SEC force, \(F\), is equal to \(K(L)\), then \(F' = K(L')\), where the primes indicate the time derivative. But \(F, P_{at}\), and \(P\) are all equal so that at the peak of the twitch \(F'\) is zero. This makes the CC velocity, \(V\), zero at the peak, because the total velocity is zero in a fixed end contraction and \(L\) therefore is zero. According to Hill's definition, the CC must then instantly produce a force equal to the active state level existing at that time. Hill argued that if, soon after a stimulus, a quick stretch were applied to a muscle in order to extend the SEC to the length which it would be during the plateau of a tetanus, then no internal shortening of the CC would occur; and it would produce a force equal to the tetanic \(P_0\) as long as the active state remained fully developed. Hill\(^1\) showed that this was the case by suddenly stretching a muscle an appropriate amount soon after a stimulus. This caused the force to remain at or near the tetanic \(P_0\) level for a considerable time and thereby presumably revealed the time course of the active state produced by a single stimulus.

In addition to quick stretches, several methods have been used to assess the magnitude and duration of the active state. Perhaps the best known is that introduced by Ritchie\(^4\) to determine the decay of the active state. At various times after a single stimulus, an isometrically contracting muscle is suddenly released (i.e., allowed to shorten) by the amount necessary to drop the force to zero. After the release the muscle length is again held constant. Force redevelops to a peak value, at which point the time derivative of force is
equal to zero and which, as argued above, makes the CC velocity zero. The force magnitude expressed relative to the tetanic \( P_o \) gives the level of the active state at this time. By varying the time of release, the descending limb of the active state curve can be traced out.

Hill\(^5\) himself went on to expand the definition of the active state by including the capacity to shorten, since he thought shortening to be as likely an indicator of the state of muscle activity as exerting tension. The speed of shortening under very light load was taken to be a measure of the ability to shorten. Hill\(^5\) showed that the speed of shortening increased very soon after a stimulus to attain a value near maximum shortening velocity \( V_{\text{max}} \) and that this speed was maintained for some time. By three different criteria [(1) the early appearance of the maximum rate of heat production, (2) the rapid onset of the ability to bear a force equal to \( P_o \) after a quick stretch, and (3) the rapid attainment of a velocity of shortening approaching \( V_{\text{max}} \)] Hill was led to believe that following a stimulus the transition from rest to a fully complete active state was extremely fast. It seems implicit in this view of active state that at any instant in time the capabilities to develop \( V_{\text{max}} \) or \( P_o \) are directly dependent on the level of the active state. In effect, the time course of the variation of \( P_o \) and \( V_{\text{max}} \) could be easily obtained once the time course of variation in the level of active state was known.

Since about 1949 Hill’s active state concept has continued to be widely used, although many have expressed reservations. In 1960 Pringle\(^8\) raised objections to the kind of analog model used by Hill.\(^1,2,8\) He pointed out that all of the methods used to assess the intensity and time course of the active state depend on the assumption that imposed quick length changes, and the consequent force responses, have of themselves no effect on these characteristics. In

**Figure 1**: Block diagram of mechanical components describing striated muscle contraction. Dashed lines indicate possible component interactions in directions of arrows. Encircled letters \( V \) and \( M \), standing for, respectively, Voigt and Maxwell models, indicate the ways a parallel elastic component could be added to the scheme to account for resting tension. (Modified from Julian,\(^2\) Figure 1.)

**Figure 2** A: Schematic diagram of a two-element model including contractile component (CC) detail. The muscle is represented by series elastic component (SEC) and half-sarcomere (CC). Note that load is external to muscle, \( u = \) cross-bridge position coordinate. B: Representation of myofilamentary overlap. Changes in amount of thick and thin filament overlap alters the number of cross-bridges available for attachment. C: Distribution of attached cross-bridges during isometric steady state (left) and during steady shortening (right). \( n(u) \) = fraction of cross-bridges at each position \( u \) which are attached. D: Rate constants for cross-bridge attachment \((t)\) and detachment \((g_1, g_2\) as a function of \( u \). Note that \( g \) has non-zero values only in the interval bounded by 0 and 1, and that \( g_1(+)\) and \( g_2(-)\) apply, respectively, to positive and negative values of \( u \). The notation \((t)\) indicates that it may vary with time, which is also shown graphically by the dashed lines. E: Tension-extension characteristics of the CC and SEC. Note that SEC characteristic is nonlinear and time-invariant, while the CC characteristic is linear and may vary with time (represented by \( K_3 \) and \( K_4 \) as two different times during non-steady state contraction).
fact, according to Pringle,\textsuperscript{4} Hill defined the active state in such a way that it must be assumed that it is unaffected by changes in length and tension.

Further objections to the active state concept resulted from the experimental work of Jewell and Wilkie.\textsuperscript{3} They investigated the time course of the active state both by using the Ritchie quick release method\textsuperscript{4} to obtain measures of muscle $P_o$ capability and by allowing shortening under very light load to obtain estimates of the $V_{\text{max}}$ capability. They showed that the time course of the active state depended on the method used to measure it. This suggested that the concept of active state was useful only as a qualitative indicator of muscle activity. In an earlier paper Jewell and Wilkie\textsuperscript{4} called into question other aspects of Hill's classic analog model\textsuperscript{1} for muscle by showing that neither the initial rise of tension in a tetanus nor the redevelopment of tension after a quick release matched the calculated rise of tension in a simple two-component model consisting of a series combination of CC and SEC. The work of Jewell and Wilkie\textsuperscript{4,5} and the review by Pringle\textsuperscript{6} should have made clear the serious shortcomings in the classic analog approach to the study of the mechanical behavior of contracting muscle.

However, there followed further work based on classic methods, measurements, and interpretations, particularly with regard to extending this approach to the study of cardiac muscle.\textsuperscript{7} For example, Brady\textsuperscript{10} discovered that quick stretches applied to rabbit papillary muscles early in a twitch did not produce the same effect as that observed by Hill\textsuperscript{2} for frog skeletal muscle. Instead, stretches applied soon after excitation resulted in nearly the same twitch tension. Presumably, this can be explained by assuming that, in contrast to the very rapid onset of stretch resistance observed in frog skeletal muscle, the active state develops slowly in heart muscle so that the CC cannot resist being lengthened by a stretch applied soon after stimulation. In support of this interpretation Sonnenblick\textsuperscript{11} and Edman and Nilsson\textsuperscript{12} determined the onset of the active state in heart muscle to be slow, as assessed by the capability of muscles to shorten against a small load.

Brady\textsuperscript{10} found, further, that stretches applied later in a papillary muscle twitch, during the phase of tension development, produced a diminished peak isometric tension, or if applied during relaxation they accelerated the relaxation phase of a twitch. In addition, Brady\textsuperscript{10} and Edman and Nilsson\textsuperscript{12} observed that rapid changes in length, or undamped quick releases, could diminish shortening velocity and extent of shortening in papillary muscles. The latter investigators\textsuperscript{13} further showed that the deactivating effect of active shortening on the tension-bearing capability of frog skeletal muscle described by Jewell and Wilkie\textsuperscript{3} and others\textsuperscript{14-15} also was a characteristic of rabbit papillary muscle. Finally, it should be kept in mind that the actual length of a muscle can influence the level of activation throughout its cross section, inasmuch as Taylor and Rüdel\textsuperscript{16} showed for frog skeletal muscle fibers that during tetanic contractions the central core of a fiber becomes inactive at short muscle lengths. These effects produced by motion and shortening seem to indicate that length, as well as changes in length, can influence the intensity and time course of the active state. This violates the implicit assumption\textsuperscript{9} of the active state concept, that the CC is an element in muscle which is unaffected by applied length changes.

In regard to the time of onset of active state, a conclusion different from Brady's has been reached in studies of cat papillary muscle function conducted by Brutsaert and his colleagues.\textsuperscript{17-18} They used simple afterloaded contractions, and observed that cat papillary muscles are capable of shortening with about maximum speed under light load very early during the time course of a twitch contraction; this finding is similar to the result already obtained by Hill\textsuperscript{2} for frog skeletal muscle. Moreover, by use of a load-clamping technique that makes it possible to apply various known load functions of force vs. time to one end of a papillary muscle, Brutsaert observed that if the load were suddenly switched from one level to another during the course of a contraction the resulting shortening velocity depended only on the new load and muscle length and was independent of time over the major portion of shortening. These results seem to indicate that in heart muscle the intensity of the active state develops rapidly to a full value soon after a stimulus. This situation is confusing because it implies that in heart muscle there may be two different active states, one that governs the $P_o$ capability and another, the $V_{\text{max}}$, capability of contracting muscle. An alternate possibility is that there is only one active state of which intensity is a single valued function of time, with the contractile mechanism being of such a kind that its $P_o$ and $V_{\text{max}}$ capabilities manifest themselves at different rates depending on the active state level. The problems that have resulted from active state experiments make understandable Hill's doubts regarding whether the term "active state" has any meaning.\textsuperscript{17}

Computer Model of Muscle Behavior

Another way to arrive at conclusions regarding the meaning of "active state" is provided by theoretical and model work.\textsuperscript{20-22} In these studies, a skeletal muscle is conceived of as having three distinct parts: (1) a contractile component that generates force; (2) an activation mechanism that regulates the CC activity; and (3) an external SEC that transmits the CC mechanical output to the ends of the muscle. The design of the CC is based on the sliding filament, cross-bridge interaction cycle model for striated muscle.\textsuperscript{23-26} The essential elements are contained in a half-sarcomere as indicated in Figure 2. The thick and thin filaments and the Z line are taken to be rigid. Cross-bridges project from the thick filament and, if the level of activation is not zero, interact with sites on the thin filament in a force-generating process. The microscopic details of this process are essentially the same as those proposed by Huxley.\textsuperscript{27} Cross-bridges can be thought of as being in a zero position when they project normally from the thick filament; in this case the cross-bridge position coordinate, $u$, is equal to zero. The force generated by a cross-bridge interacting with a thin filament site a distance $u$ away from the zero position is equal to $k_v$, where $k$ is the cross-bridge spring constant. When $u$ is positive, the force produced aids contraction; when it is negative, the force opposes contraction. Cross-bridges can form interactions with thin filament...
sites only when \( u \) has a value between 0 and 1.0, where 1.0 indicates a maximum distance away from the zero position beyond which interactions cannot form. When activation takes place, the time course of cross-bridge attachment is described by a first-order differential equation:

\[
\frac{dn}{dt} = (1 - n)f - ng
\]

(2)

where \( f \) and \( g \) are \( u \)-dependent rate constants for making and breaking cross-bridge attachments, respectively, and \( n \) is the proportion of cross-bridges attached at each \( u \) position. Equation 2 can be easily solved for the case in which there is no relative filament motion:

\[
n(u) = \frac{f}{f + g} - \frac{f - (f + g)n_0}{(f + g)\exp\left[(f + g)t\right]}\]

(3)

where \( n_0 \) is the initial \( n \) value at each \( u \). The time course for force development in an isotonic contraction, which depends on the formation of filamentary interactions, will be influenced by the sum of \( f \) and \( g \) (note the appearance of this quantity in the exponential). The net force generated at any time by all the attached cross-bridges in the contractile component, \( P \), is obtained by summing up all of the individual contributions taking into account the sign of \( u \), so that

\[
P = \int_{-\infty}^{\infty} k n du.
\]

(4)

\( K \), the net equivalent stiffness of the CC, is given simply by finding the total number of attached cross-bridges at any time, regardless of their \( u \) position, since the cross-bridges act in parallel, so that

\[
K = k \int_{-\infty}^{\infty} n du.
\]

(5)

The equivalent tension-extension characteristic of the CC is always linear, although CC stiffness may vary with time as indicated in Figure 2E.

The number of attached cross-bridges can be influenced by length and length changes in two ways. The number of cross-bridges available for interaction varies with the relative positions of the thick and thin filaments as indicated in Figure 2B. However, in this work, the simplifying assumption is made that the initial half-sarcomere length together with subsequent length changes are confined to the plateau region of the sarcomere length-tension diagram, so that the total number of cross-bridges available for interaction is constant. Length changes can also act to change the distribution of attached cross-bridges. An example of this is indicated in Figure 2C, where the change in distribution between the isometric steady state and isotonic steady shortening is shown. Note that in the isometric state all attached cross-bridges aid contraction, whereas in isotonic shortening the total force generated by all cross-bridges aiding contraction is balanced off by the sum of the external load and the “internal” load produced by those interacting cross-bridges opposing contraction. Any externally applied length change, such as a quick stretch or release, will change the distribution of attached cross-bridges. The magnitude of the distribution change will depend on the respective stiffnesses of the series combination of CC and SEC, i.e., the less stiff element will take up more of the applied length change. It is apparent, therefore, in this model that internal length changes in the CC can take place when sudden external stretches or releases are applied. As indicated in Figure 2A, the CC is connected to an external constraint or load through an elastic element of SEC. The SEC is undamped and has a nonlinear tension-extension characteristic similar to that indicated in Figure 2E. The SEC characteristic is independent of time or level of activation. During a steady isometric tetanus, a sudden release in which the SEC length was decreased by about 2% would cause the SEC force to drop to zero.

The activation mechanism used in the model can be explained, at least for skeletal muscle, as follows.26 Excitation of the muscle cell membrane25 causes a membrane potential change that propagates both longitudinally along the surface membrane and inwardly to the interior of the cell via the T tubule system. The membrane potential change of the T tubules in some way causes calcium ions to be released from internal stores, probably the lateral cisternae, into the sarcoplasm. Specific regulating sites on the myofibrillar proteins then bind calcium. This leads to a derepression of the interaction between cross-bridges and thin filament sites29 and produces contraction. However, the sarcoplasmic reticulum has a high affinity for calcium,29 and soon after a single stimulus calcium ions are drawn away from the regulating sites and stored in the sarcoplasmic reticulum, thus causing relaxation. It now appears that there is more than one calcium-binding site and more than one class of calcium-binding sites31,32 on the regulating protein troponin, which is located on the thin filaments.28 There is even the possibility that vertebrate thick filaments have regulating sites that could bind calcium.26 In the model, however, the further simplifying assumption is made that there is only one class of regulating sites and that the proportion of these sites filled with calcium, after a single stimulus, could be approximated by the following second-order equation:

\[
\gamma(t) = \frac{a_p}{b_p} \frac{\alpha}{\beta - \alpha} \left[\exp(-\alpha t) - \exp(-\beta t)\right]
\]

(6)

where \( \gamma \) is the proportion filled at time \( t \); \( a_p \) and \( b_p \) are constants; and \( \alpha \) and \( \beta \) are rate constants governing the filling and emptying of the sites. The rate constants are not considered here to be dependent on length or changes in length, though this possibility is included in Figure 1 by the dashed arrow leading to the block labeled “activation.” In a twitch, \( \gamma(t) \) rises to reach momentarily the value attained during steady tetanic stimulation. It can be seen that the events occurring during the excitation-contraction coupling process, as reviewed by Sandow,33 and the uptake of calcium by the sarcoplasmic reticulum do not explicitly enter into the model, since only the time course of the resultant variation in proportion of filled sites is described. The activation process described by Equation 6 must be coupled to the force-generating process described by Equation 3. There are several ways to do this, as described by Julian47 and Julian and Sollins.39 In the model work presented here, this was done by making \( f \), the rate constant governing the making of
interactions between cross-bridges and thin filament sites, also a function of $\gamma(t)$, so that

$$ F = \gamma(t)f_0 u, $$

where $f_0$ is the value of $f$ at $u = 1.0$ with full activation, i.e., $\gamma(t) = 1.0$. The time variation of $f$ is indicated by the dashed lines in Figure 2D, which also shows that $g$, the rate constant for breaking interactions, depends on $u$ when $u$ is positive, $g_+(u)$, but is constant for negative $u$, $g_-$. Further details concerning the actual values and methods used to obtain the computed output from the model can be found in the original publications.

Computed output from the model is shown in Figure 3. To begin with, the external load end of the model shown in Figure 2A was held fixed and an isometric twitch response computed. "Isometric" in this case means only that the total length of the series combination of CC and SEC was kept constant; internal shortening of the CC at the expense of the SEC occurs during the rising phase of the twitch, followed by lengthening of the CC during relaxation. In Figure 3A, the dashed line shows the time course of activation given by Equation 6. Activation rises rapidly to reach a peak value equal to that attained during the tetanic steady state; it then decays less rapidly toward zero. The model twitch response is quite similar to that observed in living frog skeletal muscle at $0^\circ$C. The force rises to reach a peak value about 140 msec after the maximum in activation is first achieved; the peak value is about 0.85 of that reached during a steady tetanus. At the twitch peak, activation has fallen to about half its maximum value; and by the time twitch force has fallen to about half its peak value, activation has decreased to less than 10% of its maximum value. In the model, then, there is an obvious difference between the time courses of activation and force generation in a twitch when the total length is held constant. It should be noted that the rise of twitch force in the model would not be much more rapid even if the rise of activation to its maximum value were instantaneous and the CC length were held constant. The reason for this is that the rise of force in the model, given by Equations 3 and 4, is rate-limited by the effective rate constant $(f + g)$, which is never absolutely very large. This shows that, contrary to the classic view of active state, force generated by a fixed length CC, i.e., CC velocity equal zero, need not be simply proportional to level of activation.

**Model Simulation of Classic Experiments**

Hill's experiments, in which he applied quick stretches to living muscles, were repeated on the model and the results are shown in Figure 3B. Initially, the conditions were exactly the same as those used to compute the twitch shown in Figure 3A. About 10 msec after the onset of activation, the load end of the model was suddenly extended by a small amount sufficient to bring the force up to the tetanic steady level. Both the CC and the SEC were extended by the applied stretch. About 60% of the total length increase occurred in the CC and the remainder in the SEC, because early in a contraction the CC is less stiff than the SEC. Total length was again held fixed at the end of the stretch. It can be seen in Figure 3B that, after the stretch, the force remains at or near the tetanic level for a considerable time even though activation varies markedly during this period. This calls into question the classic view of quick stretch experiments in which maintenance of force near the tetanic level after a stretch was thought to indicate a fully developed active state. In the model, the force plateau produced by a quick stretch depends in a complex way on the net effect produced by the slow breaking of cross-bridges already attached and subsequently displaced by the stretch and the

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**Figure 3** Model simulation of muscle mechanics. A: Twitch force (solid line) and activation (dashed line in each part) time courses; the latter is described by Equation 6. B: Determination of active state onset by quick stretch technique; arrow indicates time of stretch onset; note the time scale. C: Determination of active state decay by quick releases to zero force. Arrow indicates time of release (in this case, peak of twitch); filled circles are points on active state curve measured by varying the time of release. (Modified from Julian, Figures 2, 3, 11, and 12.)
addition of new attachments during the course of the contraction. In Hill’s results, the force following a stretch stays at a high level for a considerably longer time than it does in the model. Hill applied large stretches to his muscles and this could have had the effect of making some of the excessively displaced cross-bridges remain attached to thin filament sites for an abnormally long time. Another possibility is that large stretches could affect the calcium-sequestering ability of the sarcoplasmic reticulum, in view of the observation by Jewell and Wilkie that increasing the length of a muscle, even before stimulation, produced an increase in the half-time of force decay in an isotonic twitch. This effect could have been simulated in the model by making the activation function depend in a suitable way on length.

Ritchie’s quick release method for assessing the time course of the decay of active state was also applied to the model, and the results are shown in Figure 3C. As described earlier, one point on the curve describing the decay of active state is given by the peak twitch force, since at this instant CC velocity is zero. Other points were obtained by imposing quick releases on the load end of the model to drop the force to zero at various times after the twitch peak. In Figure 3C we show a release that occurred at the time of the twitch peak. The force instantly drops to zero and then redevelops to reach a maximum, after which it decays toward zero. The response again is very similar to that observed by Jewell and Wilkie in living muscles. For each release, the peak redeveloped force indicates one point on the active state decay curve. The entire time course of the decay of active state is shown by the filled circles in Fig. 3C, and it can be seen that these circles do not fall along the decaying part of the activation function described by Equation 6. These results indicate that, in this model, the curve obtained with quick releases is not an accurate indicator of the proportion of regulating sites filled with calcium. This does not support the contention of Edman and Nilsson that an active state time course thus derived is a measure of activator calcium bound to contractile sites. Actually, in this model, substantial force would redevelop after a quick release even if activation were made zero from the time of the release so that no new attachments were formed. This is because of the large difference in the values of the rate constant \( g \) for negative and positive values of \( u \). This makes the cross-bridges which oppose contraction break much faster than those aiding contraction, and this then leads to a redevelopment of force.

The model also provides insight into the problem presented earlier in this review concerning the current conflict over the question of whether active state in heart muscle rises slowly or rapidly. In the model, it has already been mentioned that even if activation rose instantly to its full value in an isometric contraction the formation of new cross-bridge interactions, which causes force generation, would be rate-limited by the effective rate constant \((f + g)\). Because \((f + g)\) is not very large, rate of rise of force, or capacity to bear tension and resist a stretch, would not increase very rapidly. \(V_{\text{max}}\), on the other hand, is very much influenced by the magnitude of \( g_a \), the rate constant for breaking interactions in the region of negative \( u \), which has no influence on the steady state force produced. If the magnitude of \( g_a \) depended on the level of activation, which increases rapidly, then speed of shortening under light load would also increase rapidly. This would lead to the situation observed for heart muscle in which force generation, or resistance to stretch, develops more slowly than does the capacity to shorten at high speed. Finally, the model provides an interpretation with regard to the deactivation by shortening during a twitch in both skeletal and heart muscle. In the model, allowing shortening during a twitch would alter the distribution of attached cross-bridges (Fig. 2C) in such a way as to diminish redeveloped force (due to time constraints) and shorten the duration of activity. Because the model, in its present form, does not have built into it any effects of length or length change to influence activation, the actual experimental results should be interpreted cautiously with regard to the presence of such effects.

### New Methodology

It seems clear that new approaches are needed in the study of the activation of contraction in striated muscle. One new approach is to use techniques that give signals indicating the time course of the change in intracellular free calcium ion concentration which occurs in muscle cells following stimulation. Even though different calcium indicators (murexide and aequorin) and different muscles (whole sartorius of toad, giant fiber of barnacle, single fiber of frog) have been used, the results from each are similar. These indicate that in a contraction occurring with the ends fixed the calcium indicator signal and the external force start to rise almost simultaneously following a stimulus. The calcium indicator signal reaches its peak well before peak force is achieved and then declines to a low level by the time the twitch force reaches a maximum. This seems to indicate that activator calcium is rapidly released and then bound to the myofibrillar regulating sites, and possibly to other sites as well, and that force generation is a slower process. It should be kept in mind, however, that to the extent to which these methods are currently developed, no information is directly available as to the amount of Ca2+ actually bound to activating sites on the contractile proteins.

In recent mechanical experiments on single frog skeletal muscle fibers, special precautions were taken to eliminate any compliance in series with the sarcomere, which constitutes the contractile component. An analysis of the transient force responses observed in these fibers after sudden changes in muscle length applied at both full and reduced overlap and during the rising phase of tetani shows that the rise of tension in an isotonic tetanus corresponds directly to an increasing number of attached cross-bridges. Taken in conjunction with the results obtained with intracellular free calcium ion indicators, it seems reasonable to believe that in these fibers activation, i.e., filling of regulating sites, occurs rapidly, whereas force generation, which depends on the formation of cross-bridge attachments, takes place at a slower pace. This is the situation described for the model as outlined earlier.

Hill’s results and those of Brutsaert which indicate that
Conclusions

The model results provide additional reasons to believe that classic active state concepts are not definitive concerning the time course of the level of activation during a contraction. There can, of course, be no assurance that the model presented here adequately describes the contractile mechanism of a living muscle. On the other hand, the macroscopic responses are very similar to those found for living muscles, and the assumptions made in constructing the model do not appear to be obviously false or implausible. It would seem prudent, therefore, to question the whole concept of the active state. It may well be quite difficult to ascertain the state of activation of a muscle solely by perturbing it in some way and then studying its macroscopic mechanical behavior.

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The concept of active state in striated muscle.
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Circ Res. 1976;38:53-59
doi: 10.1161/01.RES.38.2.53

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

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