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Publisher Summary

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KINETIC MODEL OF MUSCLE CONTRACTION

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The myosin-actin interaction is the necessary condition for striated muscle contraction (1). These two basic muscle proteins are located in the two systems of protofibrils, which are able to make contact with each other by means of myosin cross-bridges (2,3) at certain discrete points only. According to the sliding filament concept, it is the interaction of myosin bridges with the active sites of the actin protofibrils that provides the moving force of the contracting muscle (4-6). Each bridge must act cyclically (6) because the filament length does not change considerably during contraction (3).

The mechanical properties of the contracting muscle are probably determined at each moment by the distribution of its myosin bridges among the stages of an elementary working bridge cycle. If so, we may postulate on the series of stages of which the cycle consists, the probabilities of the transition between them and also try to describe muscle contraction by the methods of formal chemical kinetics.

Such an approach is a simplification of the idea given by Huxley (5).

Description of the Model

We shall simulate the behavior of a pair of protofibrils - thick and thin. Then the sarcomere will be considered as a parallel set of such identical pairs, the muscle fiber representing a series of identical sarcomeres. Protofibrils are regarded as rigid pivots with active sites placed periodically along them, i.e. with cross-bridges on myosin fibrils and with sites of their possible binding on

actin fibrils. The following assumptions have been made with regard to the structure of an elementary working bridge cycle.

1. In an excited muscle a cross-bridge has a chance to be bound with a linking site on the actin filament. Binding makes the bridge, or, more probably, the remainder of a myosin molecule associated with the bridge (perhaps the L-meromyosin part), begin to shorten. It is essential that the myosin molecule be allowed to undergo the conformational rearrangement only if the filaments are sliding relative to each other. The speed of shortening of the molecule will be equal to the speed of this sliding. During this "molecular contraction" the cross-bridge will produce an active moving force.

2. Only when the conformational transition is over does the bridge have the chance of splitting. From this moment, up to the point of realizing this chance, the bridge is producing a hindering force due to a continuous sliding of the filaments.

3. Active and hindering forces are constant and do not depend on the velocity of sliding, their absolute values being identical.

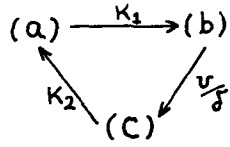
4. The speed of association of the free bridges with the actin filaments is not limited by the frequency of their encountering the receptive sites. This process, as well as the splitting of the associated bridges, follows monomolecular kinetics.

We shall not concentrate on the possible nature of all these processes because it is not important for our model. But the qualitative picture given by Davies (7) may serve as a good illustration for this scheme.

Mathematical Formulation

According to our scheme, the bridge in an excited muscle can be in one of three possible states: a) a free state, b) an associated state, when the bridge produces an active force, i.e. the state of conformational rearrangement, and c) an associated state in which the bridge produces a hindering force, i.e. when the active conformational rearrangement is completed.

An elementary working cycle of the myosin bridge may be depicted as follows:



The symbols near the arrows signify the corresponding transition constants. The constant of transition from (b) to (c) is proportional to the speed of sliding of a thick filament relative to a thin filament, v, and inversely proportional to the mean value of the shortening of the myosin molecule during the active conformational rearrangement, δ.

Suppose that α is the total number of myosin bridges in the muscle layer of a half sarcomere length with the cross-section being 1 cm^2. If n and m represent the number of bridges in states (b) and (c) respectively, the following equations can be written:

$$\frac{dn}{dt} = K_1(\alpha - n - m) - \frac{v}{\delta}n \qquad [1]$$

$$\frac{dm}{dt} = \frac{v}{\delta}n - K_2 m \qquad [2]$$

The force developed by the muscle at any one time will be $f(n-m)$ where f is the absolute value of active and hindering forces of the associated myosin bridges. So, the equation governing the motion of the mechanical system connected to the muscle will be

$$M\frac{d^2L}{dt^2} = f(n-m) - P(L) \qquad [3]$$

where M is the effective mass of the mechanical system, L is the shift of the end of the muscle associated with the mechanical system, and $P(L)$ is the external force dependent on the shift L. The muscle mass and the force of mechanical friction are regarded here as being negligible.

The shift L is expressed as follows:

$$L = \nu l$$

where $\mathcal{N}$ is the number of sarcomeres along the muscle and ℓ is the shortening of a single sarcomere. Thus the whole system of equations will be:

$$\frac{dn}{dt} = K_1(\alpha(\ell) - n - m) - K_{-1} v n \quad [4]$$

$$\frac{dm}{dt} = K_{-1} v n - K_2 m \quad [5]$$

$$\frac{dv}{dt} = \frac{f}{2\mathcal{N}M}(n - m) - \frac{P(\mathcal{N}\ell)}{2\mathcal{N}M} \quad [6]$$

$$\frac{d\ell}{dt} = 2v \quad [7]$$

where $K_{-1} = \frac{1}{\delta}$ and $\alpha(\ell)$ is the total number of myosin bridges in the filament overlap which depends upon the degree of shortening ℓ.

Stationary Contraction

The stationary contraction, at a constant speed, takes place under isotonic conditions if the muscle length is about the same length in situ. In this case $\alpha(\ell) = \alpha_0$ (8) and $P(\mathcal{N}\ell) = P$ are constant and do not depend on ℓ. Equations [4], [5] and [6] do not contain ℓ, so they form the exclusive system whose steady state ($\frac{dn}{dt} = 0$, $\frac{dm}{dt} = 0$, $\frac{dv}{dt} = 0$) is single:

$$n = \frac{K_1(f\alpha_0 + P) + K_2 P}{f(2K_1 + K_2)}; \quad m = \frac{K_1(f\alpha_0 - P)}{f(2K_1 + K_2)}; \quad v = \frac{K_1 K_2}{(K_1 + K_2)K_{-1}} \cdot \frac{f\alpha_0 - P}{\frac{K_1}{K_1 + K_2} f\alpha_0 + P} \quad [8]$$

The expression for the stationary velocity, v, may be changed in such a way that:

$$(P + a)v = b(P_0 - P) \quad [9]$$

where $P_0 = f\alpha_0$

$$a = \frac{K_1}{K_1 + K_2} f\alpha_0 = \frac{K_1}{K_1 + K_2} P_0 \quad [10]$$

and

$$b = \frac{K_2}{K_{-1}} \frac{K_1}{K_1 + K_2} = \frac{K_2}{K_{-1}} \frac{a}{P_0} = v_{max} \frac{a}{P_0} \quad [11]$$

where v_{max} is the contraction velocity at $P = 0$

Expressions [9], [10] and [11] coincide in detail with the experimental correlations discovered by Hill (9).

The rate of the total energy production will be

$$\frac{dE}{dt} = \varepsilon K_2 m = \frac{\varepsilon K_1 K_2 (f\alpha_0 - P)}{f(2K_1 + K_2)} = Const\,(P_0 - P) \qquad [12]$$

where ε is the energy of the chemical reactions occurring in each elementary cycle. It is probably equal to the energy of hydrolysis of one ATP molecule.

The rate of heat production can be obtained by subtracting mechanical power from equation [12] and by expressing $f\alpha_0 - P$ through the stationary v from equation [8]:

$$\frac{dQ}{dt} = \frac{dE}{dt} - PV = v\left[\frac{\eta K_1}{2K_1 + K_2} P_0 + \frac{\eta(K_1 + K_2) - (2K_1 + K_2)}{2K_1 + K_2} P\right] \qquad [13]$$

where

$$\eta = \frac{\varepsilon K_{-1}}{f} = \frac{\varepsilon}{f\delta} \qquad [14]$$

has the sense of an inverse efficiency of the elementary cycle because $f\delta$ is the mechanical work of the myosin bridge during the elementary cycle.

If $\eta = \frac{K_2 + 2K_1}{K_1 + K_2}$ then $\frac{dQ}{dt} = av$ this being in agreement with the experimental results of Hill (9).

Expression [13] is in conformity with the more recent results of this same author (10), if $\eta = 1.4 \pm 0.3$ and $\frac{K_2}{K_1} = 5.5 \pm 1$

It should be recognized that expression [13] does not contain the activation and maintenance heat, as they are probably due to the action of the muscle activation system rather than the contractile system (11).

Estimation of the Parameters

There are five parameters in our scheme connected with the intimate mechanism of muscle contraction: α, K_1, K_{-1}, K_2 and f. Comparison with Hill's equation gives three relationships between them:

$$f\alpha_0 = P_0 \ , \quad \frac{K_1}{K_1+K_2} = \frac{a}{P_0} \ , \quad \frac{K_2}{K_{-1}} = V_{max}$$

α_0 may be estimated as 10^{13} from the structural data (6) and formula [14] gives the last relationship we need.

Assuming that $P_0 = 3$ kg (12), $\frac{a}{P_0} = \frac{1}{4}$, $\eta \approx 1$ $V_{max} = \frac{4}{3}$ (a half of the sarcomere length)/sec = 1.5×10^{-4} cm/sec (9) and the energy of hydrolysis of the ATP molecule = 3×10^{-13} g cm^2/sec (13), we shall have $f = 3 \times 10^{-7}$ g cm/sec^2, $K_{-1} = 10^6$ cm^{-1}, $K_2 = 150$ sec^{-1} and $K_1 = 50$ sec^{-1}.

Isotonic Contraction

The dynamics of movement towards the steady state [8] may be obtained by integrating the system of equations [4], [5] and [6] at $\alpha(\ell) = \alpha_0$ and $P(N\ell) = P$. This system, however, has only a slight non-linearity and linear approximation gives quite satisfactory results in this case.

On introducing new variables such as $X = \frac{n}{\alpha_0}$; $\tau = K_1 t$, $y = \frac{m}{\alpha_0}$ and $u = \frac{K_{-1}}{K_1} v$, the system [4], [5] and [6] will be written as:

$$\frac{dx}{d\tau} = 1 - x - y - ux \qquad [15]$$

$$\frac{dy}{d\tau} = ux - 3y \qquad [16]$$

$$\frac{du}{d\tau} = B(x - y - A) \qquad [17]$$

where $A = \frac{P}{f\alpha_0} = \frac{P}{P_0}$ and $B = \frac{P_0}{M} \frac{K_{-1}}{2NK_1^2}$

The steady state [8] in terms of these variables will be

$$x_0 = \frac{4A+1}{5} \ ; \quad y_0 = \frac{1-A}{5} \ ; \quad u_0 = \frac{3(1-A)}{4A+1}$$

The characteristic equation of system [15], [16] and [17] linearized near this steady state is

$$\lambda^3 + (3.25 + 3.75a)\lambda^2 + (15a + 0.4b)\lambda + b = 0 \quad [18]$$

Here $a = \frac{1}{4A+1}$ and $b = B(4A+1)$ have the following limits of change:

$0.2 \leqslant a \leqslant 1$ and $1 < b < 500$ if $\sqrt{} \approx 1.5 \times 10^4$ and $\frac{P_0}{M}$ is allowed to change from 10^2 to 10^4 cm/sec^2 by using various isotonic levels.

The whole picture of the eigenvalues of equation [18] in the plane of the parameters a and b is shown in Figure 1. At almost all values of the parameters, one real negative root λ_1, and a pair of complex roots $\lambda_2 = p + i\omega$ and $\lambda_3 = -p - i\omega$ with the negative real part are present.

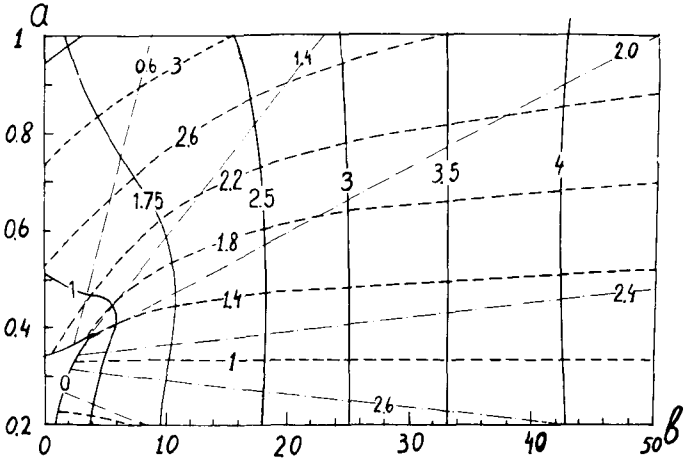


Figure 1. Parametrical plane of equation [8]. The levels of ω, p and λ_1 are given by solid, dashed and dashed-dotted lines, respectively.

This means that motion towards the steady state speed given by Hill's equation occurs as follows. The mean level of the contraction speed approaches the steady state value with a time constant of $\frac{1}{K_1\lambda_1}$. Around this mean level there occur damped sinusoidal oscillations with a period of $\frac{2\pi}{\omega} K_1$ and a damping constant of $\frac{1}{K_1 p}$. The amplitude of the oscillations is determined by the initial perturbation.

It should be emphasized that in these calculations we do not take into account the elastic properties of the muscle. Therefore, the system [15]-[17] does not contain any resonance elements. The oscillatory mechanism may be explained as follows. The speed of transition of myosin bridges from state (b) to (c) varies directly with the velocity of contraction. If, at the first moment, the contraction velocity is zero, then the transition from (a) to (b) will prevail. The force developed by the muscle, the acceleration and the velocity of inertial loading will rise rapidly, this resulting in the predominance of the transition from (b) to (c) . Because of the loading inertia this will cause the force to fall to a level insufficient for the steady state speed to be maintained, and the cycle will then repeat.

As an illustration, a numerical integration system for [15]-[17] is shown in Figure 2. The value of the parameter B corresponds to the case of a muscle lifting a weight of $P_0/M \approx 10^3$ cm/sec^2. The oscillation frequency coincides with that calculated using a linear approach.

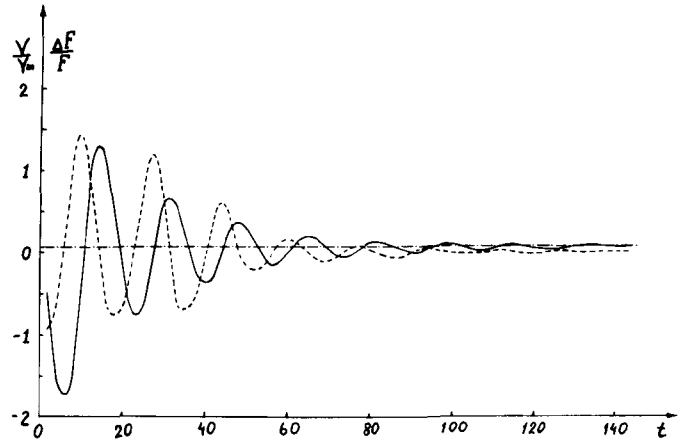


Figure 2. The initial portion of the isotonic contraction curves calculated from system [15]-[17] under the conditions: B=36; A=0.75; X(0)=0; Y(0)=0; U(0)=0. The solid line gives the speed of shortening as a fraction of the value in unloaded tetani. The dashed line gives the difference between muscle tension and load, divided by load. The dashed-dotted line gives the steady state value of contraction speed at A=0.75.

Stretched Muscle Behavior

The behavior of stretched muscle under conditions of isotonic load is described by the system of equations [4]-[7] with $P(\mathcal{N}\ell) = P$ constant and with $\alpha(\ell) = \beta\ell$ being a linear function. From the structural and physiological data it follows that $\alpha(\ell) = \frac{\alpha_0}{1.4 \times 10^{-4}}\ell$ (14), if ℓ is a shortening of the sarcomere in cm from the initial length of 3.65×10^{-4} cm. Upon introducing these modifications, system [4]-[7] can, by substitution of the variables, be reduced to the form:

$$\frac{dx}{d\tau} = z - x - y - ux \qquad [19]$$

$$\frac{dy}{d\tau} = ux - 3y \qquad [20]$$

$$\frac{du}{d\tau} = B(x - y - A) \qquad [21]$$

$$\frac{dz}{d\tau} = \varepsilon u \qquad [22]$$

Here, $x = \frac{n}{\alpha_0}$, $y = \frac{m}{\alpha_0}$, $u = \frac{K_{-1}}{K_1}v$, $z = \frac{1}{7 \times 10^{-5}}\ell$,

$\tau = K_1 t$, $B = \frac{P_0}{M}\frac{K_{-1}}{2\sqrt{K_1^2}}$, $A = \frac{P}{P_0}$, $\varepsilon = \frac{2}{K_{-1} \times 1.4 \times 10^{-4}}$

This system has three natural time scales of order 1 for equations [19] and [20], for [21] and for [22]. Taking into account that $\varepsilon = 1/_{10}$ and $5 < B < 100$ as usual, we may analyse this system in three steps.

As the first approach we may consider the group of equations [19]-[21] as "fast", while equation [22] is "slow". Then we may obtain the solution by means of Tikhonov's theorem (15). System [19]-[22] is stable at all values of the "slow" variable, z; therefore, the conditions of this theorem are satisfied. The solution can be obtained by substitution into the "slow" equation of the steady state value of the fast variable u, which can be derived from system [19]-[21] with z treated as a parameter. Coming back to the initial variables, we have:

$$\frac{1}{2}\frac{d\ell}{dt} = v = \frac{K_2}{K_{-1}}\frac{K_1}{K_1 + K_2}\frac{f\frac{\alpha_0}{1.4}\ell - P}{\frac{K_1}{K_1 + K_2}f\frac{\alpha_0}{1.4}\ell + P} \qquad [23]$$

where ℓ is measured in microns.

Taking into consideration that $(f\alpha_0/1.4)\ell$ is the isometrical force $P_0'(\ell)$ developed by the sarcomere at a given shortening ℓ, and assuming, as usual, $K_1/(K_1 + K_2) = 1/4$ and $K_2/K_{-1} = v_{max}$ we obtain:

$$\left[P + \frac{P_0'(\ell)}{4}\right]v = \frac{v_{max}}{4}\left[P_0'(\ell) - P\right] \qquad [24]$$

This is analogous to the Hill equation. It describes the quasi-stationary isotonical contraction of stretched muscles (the sarcomere length ranges from 3.65 to 2μ).

The second approach to the solution of system [19]-[22] may be obtained by substitution of the algebraic expression x-y = A for equation [21].

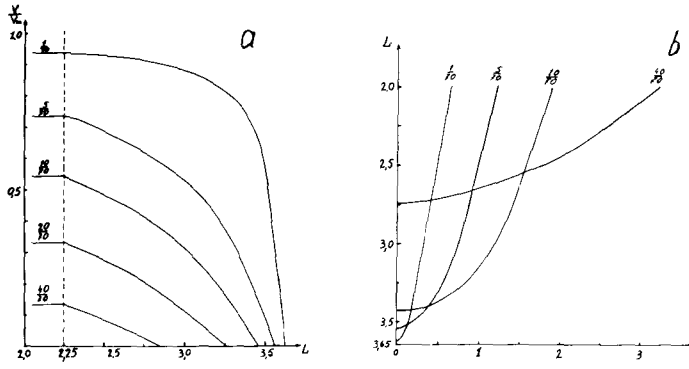


Figure 3. Isotonic contraction of stretched muscle. a) Mean of contraction speed as a function of sarcomere length, at various loads. Ordinate - speed of shortening as a function of the value in unloaded tetani. Abscissa - sarcomere length in microns. b) Shortening as a function of time at various loads. Ordinate - sarcomere length in microns. Abscissa - time in seconds. The load, as a fraction of isotonic tetani tension, is indicated above each curve.

Numerical integration of such a system of equations at several values of the parameter A is shown in Figure 3. It differs slightly from the calculations from formula [23] only at a very low load.

The whole system [19]-[22] has a single unstable steady state

$$u_s = 0 \ , \quad y_s = 0 \ , \quad x_s = \Gamma \ , \quad z_s = \Gamma \qquad [25]$$

corresponding to the load being balanced precisely by the muscle force at a given lengthening. Investigation of this system as a linear approximation in the neighborhood of this steady state shows that its approach to the quasi-stationary speed of contraction [24] is approximately the same as in the case of unstretched muscle. But there is a region in the plane of the parameters where oscillations of the contraction speed are undamped. As an illustration, the integration of system [19]-[22] for such a case is shown in Figure 4.

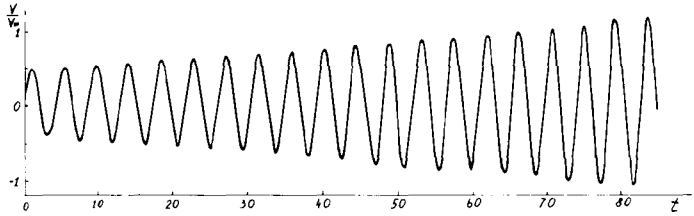


Figure 4. The initial region of stretched muscle isotonic contraction calculated from system [19]-[22] under the conditions: B=20, A=20/70, X(0)=22/70, Y(0)=0, U(0)=0, Z(0)=24/70. Ordinate - speed of shortening as a fraction of the value in unloaded tetani. Abscissa - time in milliseconds.

Isometric Contraction

To calculate the speed of the muscle-force developed under isometric conditions, it is necessary to know the load-extension curve $P(\ell)$ for elastic elements connected in series with contractile elements of the muscle. The data we need were taken from the work of Jewel and Wilkie (16).

The isometric contraction is described by system [4]-[7] at $\alpha(\ell) = \alpha_0$ and with equation [6] substituted by the algebraic correlation

$$f(n-m) = P(\ell) \qquad [26]$$

which expresses the equality of elastic and contractile forces. It allows υ to be excluded from this system. After a linear substitution of the variables, it takes the form:

$$\frac{dx}{d\tau} = 1 - x - y - \beta \frac{1 - x + 2y}{\frac{dA}{dz} + 2\beta x} x \qquad [27]$$

$$\frac{dy}{d\tau} = -3y + \beta \frac{1 - x - 2y}{\frac{dA}{dz} + 2\beta x} x \qquad [28]$$

$$\frac{dz}{d\tau} = \frac{1 - x + 2y}{\frac{dA}{dz} + 2\beta x} \qquad [29]$$

Here $x = \frac{n}{\alpha_0}$, $y = \frac{m}{\alpha_0}$, $z = 100\frac{l}{\delta}$, $\beta = \frac{K_{-1}\delta}{200}$; $\delta = 2.2 \times 10^{-4}$ cm is the length of a sarcomere, $A(z) = \frac{P(z)}{P_0}$ is the relationship between relative force and relative extension of an elastic component, which has the following analytical form:

$$A(z) \begin{cases} 0.0897z^3 + 0.0348z^2 + 0.2z & \text{for } z \leq 1.15 \\ 0.636z - 0.319 & \text{for } z \geq 1.15 \end{cases} \qquad [30]$$

System [27]-[29], under initial conditions of X(0)=0, Y(0)=0, Z(0)=0 describes normal isometric tetani of the muscle. Tension redevelopment, after quick release is governed by the same system under initial conditions of X(0)=0.5, Y(0)=0.5, Z(0)=0. This may be explained as follows. Before the quick release the muscle develops the maximum isometrical force, all its bridges being in state (b). During the quick release the force falls and the bridges shift at the speed $K_{-1}v$ to state (c), but not to state (a), due to the limited value of the constant K_2. The fact that the force falls to zero means that half of the bridges are in state (b) and the other half are in state (c).

The speed of the force development can also be calculated easily from the load-extension dependence [30] and the stationary force-velocity relationship [9] (see ref.16). The results of our calculations are shown in Figure 5. For a comparison, the experimental and calculated curves from (16) are shown in Figure 6.

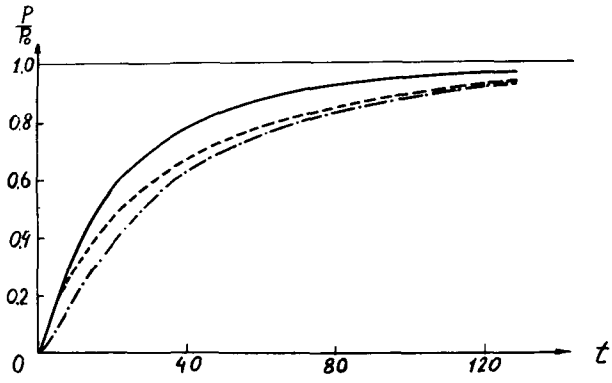


Figure 5. Isometric contraction. Ordinate - tension as a fraction of the maximum value. Abscissa - time in milliseconds. Solid line: calculation from the force-velocity [9] and load-extension [30] correlations. Dashed line: initial rise of tension calculated from system [27]-[29] under the conditions: X(0)=0, Y(0)=0, Z(0)=0. Dashed-dotted line: tension redevelopment after quick release, calculated from system [27]-[29], under the conditions: X(0)=0.5, Y(0)=0.5, Z(0)=0.

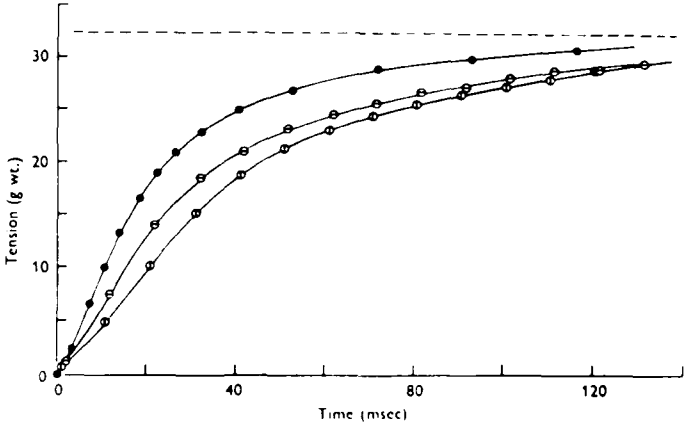


Figure 6. Isometric myograms from reference (16). Solid circles: curve of rise of tension calculated from the force-velocity and load-extension curves. Open circles: observed isometric myograms; ⊕ , initial rise of tension; ⊖ , redevelopment of tension after quick release.

Discussion

The sliding filament concept is at present the most valid scheme of muscle contraction. The first qualitative theory of muscle contraction based on it was advanced by Huxley (5).

The most essential feature of the work presented here is that it postulates a discrete spectrum of states in which the bridges are allowed to exist. This makes possible the simplification of mathematical formalism by using ordinary differential equations instead of partial ones.

The formalism of partial differential equations employed by Huxley(5) permits the analysis of only the simplest case of the stationary isotonic contraction. In this work, the partial equation has been derived for the fraction $n(X,t)$ of myosin bridges combined with actin acceptors, where X is the deviation of the myosin bridge equilibrium position from the nearest actin binding site. The equation has the form:

$$\frac{\partial n}{\partial t} = (1-n)f(x) - n\,g(x)$$

where $f(x)$ and $g(x)$ are the rate constants of bridge binding and splitting, respectively. This equation should contain the term $\frac{\partial n}{\partial x}\frac{dx}{dt}$ governing the variation of $n(x,t)$ conditioned by the bridge current due to filament sliding. It is probably the lack of this term that leads to some of the discrepancies mentioned by the author, himself (5).

The constant parameters of our model K_1, K_{-1}, K_2 and f can be treated as the average values of some arbitrary limited functions of the variables characterizing the myosin bridge state. We suppose, however, that good physical grounds exist for some of them to be truly constant.

The independence of these parameters from the speed of muscle contraction arises from the following fact. The rates of free macromolecular transitions exceed by several orders the maximum rates of conformational transitions permissible for myosin molecules when the bridges are combined with the actin filaments. So, in this case, any change of its state may be regarded as an equilibrium process. This leads to independence of K_{-1}, K_2 and f from v. Independence of K_1 from v results directly from assumption 4 made at the

beginning of this paper. The validity of this assumption is increased by the fact that all g-actin monomers consist of a thin filament capable of combining with H-meromyosin, thus being the potential binding sites for myosin bridges (17).

Some of these actin monomers, however, due to a periodic organization of the thin filament, may occupy a more suitable position relative to the given thick filament. This is not important for the case of skeletal muscles of vertebrates in view of the lack of synchronization of periodicity of thin filaments across the sarcomere (3). But it does become essential in the case with insect flight muscles, due to their crystalloid organization (18). A slight modification of our model is sufficient to describe an oscillatory contraction of these muscles.

The independence of f from the degree of myosin molecule conformation rearrangement, ξ, may be explained as follows. Evidently, $f = d\varepsilon/d\xi$, where $\varepsilon(\xi)$ is an energy change of the myosin molecule during its conformational rearrangement. If a large number of weak hydrogen or van der Waals bonds are formed, or broken, in this process, then $d\varepsilon/d\xi$ may be a constant. This would be so, for example, if the conformational rearrangement were similar to the wave propagation along the uniform molecular backbone.

In our model we suggest that the rate constant for splitting of the bridge in state (b) should be zero. A good reason for this assumption is given by the independence of the isometric muscle force, P_o, from temperature (19). In our model P_o does not depend on temperature since α_o, the structural characteristics of the muscle, does not depend on it. If the rate constant, K_1', of splitting for the bridge in state (b) were comparable to K_1, then P_o would be:

$$P_o = \frac{f\alpha_o K_1}{K_1 + K_1'}$$

In this case P_o would be independent of temperature only if very special assumptions concerning the K_1 and K_1' temperature dependence were made.

The present form of our model fails to describe the process of muscle relaxation. For this purpose it is necessary to postulate a fourth possible state of the myosin bridge. The bridge is allowed to change to this state from states (a) and (b) when the muscle is being stretched ($v<0$). The force produced by the bridge in this state may be equal to f and the rate constant of its splitting may be about $K_2/6$. Such values of the parameters are in accordance with the findings of Katz (20):

$$\left|\frac{dv}{dP}\right|_{P<P_0} \approx 6\left|\frac{dv}{dP}\right|_{P>P_0}$$

According to this modification of our model, relaxation is possible only if the muscle is subjected to an external force. It should be noted that under some conditions the process of relaxation is a very slow one. The high frequency Young's modulus of frog sartorius muscle maintains an increased value for 1 sec after the muscle stimulation has ended (21).

When describing muscle relaxation it is necessary also to take into account the rate of Ca^{++} removal from the contractile system of the muscle. This should also be done if the twitch and the first moments of tetani are of interest. For this purpose it is sufficient to assume that the constant K_1 is dependent of time.

The parameters of our model were estimated by checking with the Hill equations. Thus, the model is able to predict the dynamics of muscle contraction under various conditions if the stationary characteristics of muscle contraction are known.

This model satisfies the Hill equations exactly, with all parameters having reasonable values. It is in good conformity with the data on the isometric tetani force development and explains the distinctions between the normal isometric contraction and the force redevelopment after quick release.

A wide range of behavior patterns of the model under various conditions gives the probability of good experimental varification.

Some experimental data indicate that the oscillatory modes of ordinary skeletal muscle contraction are possible (22,23). In reference (16) the authors explain oscillations of the speed of isotonic contraction, following controlled release, as an artifact arising from oscillations of the release relay, - though this is not always the case.

It should be noted that oscillatory modes of contraction are more efficient than monotonous ones.

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References

1. Сент-Джиордъи, А., О мышечной деятелъности, Москва (1947).
2. Hanson, J. and Huxley, H.E. Nature, 172, 530 (1953).
3. Huxley, H.E. and Brown, W. J. Mol. Biol., 30, 383 (1967).
4. Huxley, A.F. and Niedergerke, R. Nature, 173, 971 (1954).
5. Huxley, A.F. Progr. Biophys. and Biophys. Chem., 7, 255, (1957).
6. Хаксли, Х., сб. Молекулярная биология, Москва (1963).
7. Davies, R.E. Nature, 199, 1068 (1963).
8. Page, S. and Huxley, H.E. J. Cell Biol., 19, 369 (1963).
9. Hill, A.V. Proc. Roy. Soc., B126, 136 (1938).
10. Hill, A.V. Proc. Roy. Soc., B159, 297 (1964).
11. Хилл, А., сб. Молекулярная биология, Москва (1963).
12. Ramsey, R.W. and Street, S.F. J. Cel. Comp. Physiol., 15, 11 (1940).
13. Benzinger, T.H. and Hens, R. Proc. Natl. Acad. Sci., 42, 896 (1956).
14. Gordon, A.M., Huxley, A.F. and Julian, F.I. J. Physiol., 184, 170 (1966).

15. Тихонов, А.Н., Математический сборник, 22, 193 (1948).

16. Jewel, B.R. and Wilkie, D.R. J. Physiol., 143, 515 (1958).

17. Huxley, H.E. Proc. Roy. Soc., B160, 442 (1964).

18. Reedy, M.K. J. Mol. Biol., 31, 155 (1968).

19. Ernst, E., Biophysics of the Striated Muscle, Budapest (1963).

20. Katz, B. J. Physiol., 96, 45 (1939).

21. Сарвазян, А.П., Пасечник, В.И., Труды Тбилисского симпозиума (1969).

22. Frank, G.M. Proc. Roy. Soc., B160, 473 (1964).

23. Armstrong, C.F., Huxley, A.F. and Julian, F.I. J. Physiol., 186, 26P (1966).