Biorheology, 1971, Vol. 7, pp. 147-170. Pergamon Press. Printed in Great Britain, London[1].

A KINETIC THEORY OF STRIATED MUSCLE CONTRACTION

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Abstract—Contractile properties of striated muscle are derived from its structural organization under some assumptions about myosin crossbridges cyclic action.

Well-known dynamic properties of striated muscle are given quantitatively by the suggested theory. Hill's equations follow from the theory automatically and precisely. Calculated rates of force development and redevelopment after quick release coincide with experimental data. The theory accounts for auto-oscillations of insect flight muscles.

The theory permits one to predict some new facts, for instance auto-oscillations of force developed by commonly employed frog sartorius muscles under isotonic conditions. These auto-oscillations have been registered under the predicted experimental conditions.

КИНЕТИЧЕСКАЯ ТЕОРИЯ СОКРАЩЕНИЯ ПОПЕРЕЧНОПОЛОСАТЫХ МЫШЦ

Резюме — Сократительные свойства поперечнополосатых мышц получены как следствие их структурной организации и постулатов, конкретизирующих механохимические свойства сократительных белков.

Известные закономерности сокращения скелетных мышц позвоночных в изотоническом и изометрическом режимах и автоколебания летальных мышц насекомых получили исчерпывающее количественное объяснение в терминах замыкания, размыкания и перемещения миозиновых мостиков.

Предсказаны и обнаружены автоколебания силы, развиваемой портняжной мышцей лягушки во время изотонического сокращения. Получено уравнение, описывающее квазистационарное изотоническое сокращение растянутой мышцы.

Проведено обобщение теории на переходные процессы покой-возбуждение и возбуждение-покой.

С позиций предложенной модели каталитическая АТФ-азная активность актомиозинового типа является следствием квазикристаллической структурной организации сократительного аппарата мышц.

Проанализирован механизм синхронизации скорости укорочения саркомеров в мышечном волокне и показана правомерность перенесения свойств простой модели взаимодействия пары протофибрилл на целую мышцу. Определены границы применимости теории.

Предложенная теория может служить удобным инструментом исследования молекулярных процессов в сокращающейся мышце.

INTRODUCTION

A QUANTITATIVE molecular theory of muscle contraction must yield the contractile properties of muscle as a consequence of its macromolecular construction and mechanochemical properties of contractile proteins. The sliding-filament concept [1-3] is presently a single valid basis for such a theory. A number of quantitative models of striated muscle contraction are based on it [4-6]. They differ in the hypotheses about the mechanochemical properties of muscle proteins. All of them are in accordance with Hill's equations. But this agreement itself does not prove the validity of these theories assumptions, concerning the elementary contractile mechanism. The model of PODOLSKY [5] contradicts the experimental length-tension curve [7]. It can be shown that any hypothetic mechanism, based on the shortening

of filaments, let it be local or total, is also inconsistent with this crucial correlation. In the theory of HUXLEY [4] and in its slight modification [6] mathematical treatment of the physical model is not quite correct [8], but the model itself is probably adequate to the experimental principles of the sliding-filament concept.

In the present work a mathematical model of contraction is developed in two steps [9]. At first the experimental principles of sliding-filament concept are formulated mathematically. Analysis of two partial equations system obtained is too complex. Then three assumptions are introduced to visualize the nature of an elementary contractile cycle. This allows us to obtain from the starting mathematical scheme a simple system of ordinary equations, governing the kinetics of making and breaking of cross-links between the myosin cross-bridges and actin filaments. This system allows us to calculate practically any regime of striated muscle contraction. The investigation of this model [8, 10, 11] has shown that it describes quantitatively the contractile properties of vertebrates skeletal and insect flight muscles.

1. THE STATEMENTS OF THE THEORY

Basic experimental facts

(1) As a rule the contractile part of muscle fibre consists of ~10^4 identical sarcomeres connected in series. A sarcomere consists of ~10^6 filaments of two kinds, thick and thin. The change of a sarcomere during contraction is shown schematically in Fig. 1. The left and the right halves of sarcomere are symmetrical in the sense of contractile properties [12].

(2) The complex of two basic muscle proteins, actomyosin, is a mechanochemical transformer [13]. The myosin-actin interaction is a necessary condition for muscle contraction. In a relaxed muscle these proteins do not interact [14].

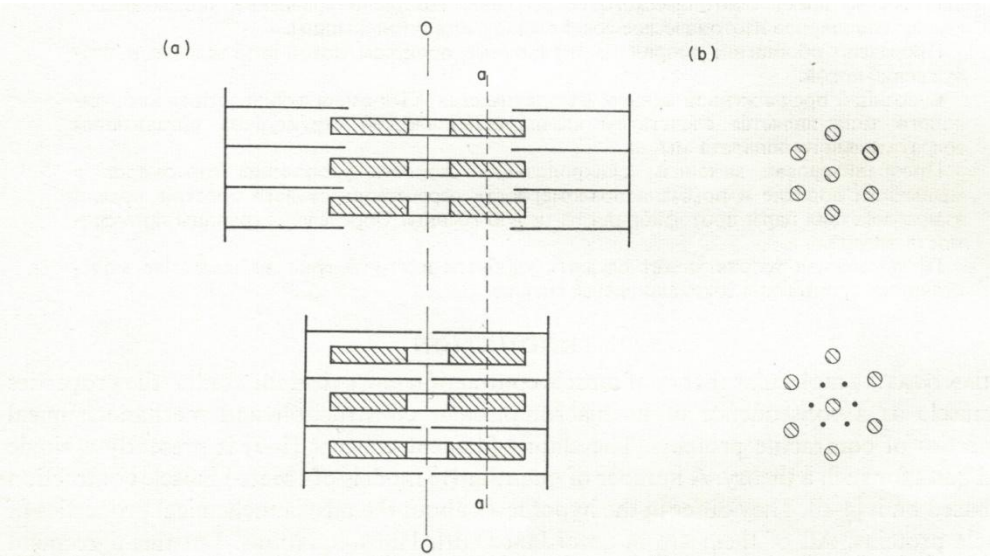

FIG. 1. DIAGRAM OF SARCOMERE CONTRACTION.
A, longitudinal section, the regions of the thick filaments, which contain the cross-bridges, are shown by hatching. B, cross-section along aa.

(3) Myosin and actin are located in the thick and thin filaments respectively. These are able to contact with each other in discrete points only by means of the myosin cross-bridges (*M*) [15].

(4) In a relaxed muscle the *M*'s are placed on the thick filaments in a strict order [16]. There are no *M*'s in the middle part of the thick filament [12].

(5) In the contracting sarcomere the filaments of both kinds slide past one another. The thin filaments do not change in length or in structure. The thick filaments do not change in length, but the order of the *M*'s arrangement is disturbed [16].

(6) Hexagonal packing of the filaments (see Fig. lb) is not disturbed during contraction [17].

(7) Any G-actin monomere (*A*), a thin filament consists of, is able to combine with H-meromyosin, thus being the potential receptor of the *M* [18].

(8) Active isometric tension is proportional to the number of *M*'s in the region of the filament overlap [7].

Experimental fundamentals of muscle contraction

(a) From the items (2), (3), (5) and (8) it follows that the contractile force originates in the *M*'s linked to the *A*'s. Each bridge must act cyclically: make a link with the actin receptor, develop some force and then break the link.

(b) It is evident from (1) and Fig. 1, that the force at the ends of muscle fibre equals to that developed by either of the halves of any sarcomere (the inertial forces inside the muscle are negligible at all the regimes of contraction). The speed of fibre contraction, *V*, equals to $2Nv$, where *N* is the number of sarcomeres and *v* is the speed of sliding of a thick filament relative to a thin one.

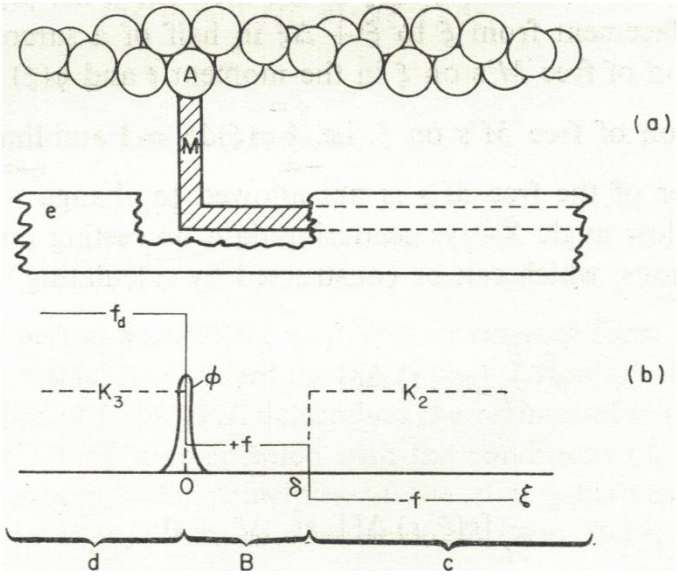

FIG. 2. ILLUSTRATION OF THE MODEL.

(a) diagram of filaments interaction, *A*, actin subunit in the thin filament; *M*, Myosin cross-bridge in the thick filament; *e*, hard backbone of the thick filament. (b) diagram of cross-bridge, *M*, states; ξ—the displacement of the *M* from equilibrium position O; ϕ – the distribution of free *M*'s; *fd* and K_3 are force, developed by *M*, and rate constant of *MA* links breaking resp. in the "superpulling" state *d*; $+f$ – force in the "pulling" state B, $(0, \delta)$ – magnitude of active conformational rearrangement of the *M*, K_2 and $-f$ are rate constant of *MA* links breaking and force, developed by the *M*, in "hindering" state *C* resp.

(c) From (6) it follows that the contractile system should be regarded as essentially one-dimensional one: transversal components of forces must be compensated or be small in comparison with the axial ones. This allows to simulate the behaviour of a pair of filaments, thick and thin and to consider half of a sarcomere as a parallel set of such identical pairs.

These fundamentals (a, b and c) represent the essence of "sliding-filament hypothesis" [3, 4]. They should be supplemented with the fourth principle, which is not so rigorously experimentally substantiated as the preceding ones.

(d) The *M*'s act independently of one another. This follows from the linearity of the length-tension dependence of (8). The lack of synchronization in the *M*'s movements during contraction [16] may be regarded as indirect evidence of this principle.

This means that the breaking of the *M-A* cross links is a first-order reaction. Due to the steric restrictions only a free *A* is allowed to be near a free *M*. So, the *M-A* links formation also obeys first-order kinetics.

The physical model, corresponding to these fundamentals, is given in Fig. 2a. Due to the helical arrangement of *g*-actin monomers in the thin filaments not all the *M*'s are able to be linked with the *A*'s simultaneously. Thus we shall deal only with active bridges, *M*'s, which are "suitably placed" with respect to *A*'s, i. e. which have no steric restrictions on the link formation. For skeletal muscles of vertebrates the fraction of the active *M*'s does not depend on the position of a thick filament relative to a thin one, i. e. on the sarcomere length [7, 12]. It is probably not the case with insect flight muscles (see section 3).

Mathematical formulation and assumptions

From (4) it follows that each free *M* has its own equilibrium position on the backbone of a thick filament, near which it stays most of the time. Let its displacement from this position be ξ. Then for all *M*'s linked with *A*'s the speed of changing ξ equals to v. Let $\rho(\xi,t)$ be a function of distribution of linked *M*'s on ξ in the moment t, i. e. $\rho(\xi, t)\,\Delta\xi$ is a number of linked *M*'s with displacement from ξ to $\xi + \Delta\xi$ in half of a sarcomere. Let $g(\xi, t)$ be a function of distribution of free *M*'s on ξ in the moment t and $\varphi(\xi)$ be a configuration of equilibrium distribution of free *M*'s on ξ, i. e. $\int_{-\infty}^{+\infty} \varphi(\xi)\mathrm{d}\xi = 1$ and $\lim_{t\to\infty} g(\xi,t) = \gamma\cdot\varphi(\xi)$ if γ being a whole number of the free *M*'s is not allowed to change with time. $\varphi(\xi)$ can be determined from the low angle X-rays scattering data on resting muscle. $\rho(\xi,t)$ and $g(\xi,t)$ obey the set of equations, which can be constructed by calculating

$$\frac{\partial}{\partial t}\,[\rho(\xi, t)\,\Delta\xi]$$

and

$$\frac{\partial}{\partial t}\,[g(\xi, t)\,\Delta\xi] \text{ at } \Delta\xi \to 0:$$

$$\frac{\partial\rho}{\partial t} = K_1(\xi)\cdot g - K_2(\xi, v)\cdot\rho - v\cdot\frac{\partial\rho}{\partial\xi} \tag{1}$$

$$\frac{\partial g}{\partial\xi} = -K_1(\xi)\cdot g + K_2(\xi, v)\cdot\rho - K^1(\xi)\cdot\left[g(\xi, t) - \varphi(\xi)\cdot\int_{-\infty}^{+\infty} g(\xi, t)\,\mathrm{d}\xi\right]. \tag{2}$$

Here $K_1(\xi)$ is the rate constant of the *M-A* link formation for the free *M*'s having the displacement ξ, $K_2(\xi,v)$ is the rate constant of the *M-A* links splitting at the velocity of filaments sliding, *v*, and $K^1(\xi)$ is the constant which governs the velocity of free bridge return to its equilibrium position after the cross-link breaking.

$K_1(\xi)$ does not depend on *v*. This may be explained as follows. The link formation of a given *M* with a given *A* is possible during the time interval, which varies as 1/*v*, but the frequency with which *A*-sites are presented to a given *M* is proportional to *v*. So, the mean time of the *M-A* interaction does not depend on *v* and the probability of link formation is allowed to depend only on the state of a free bridge, which is described by one significant variable, ξ. The state of a linked *M* is described by two significant variables, ξ and $v = d\xi/dt$, hence the rate constant of the *M-A* splitting is a function of ξ and *v*.

The variation of $\rho(\xi,t)$ due to the linked *M*'s current with the speed *v* is fitted by the term $-v\cdot d\rho/d\xi$ of equation (1). It is the essential feature of our model. The term of such type necessarily follows from the filaments sliding and should not be excluded *a priori* from any mathematical model, based on sliding-filament mechanism, such as [4, 6].

If $a(l)$ is the whole number of the active *M*'s in the filaments overlap region, then:

$$\int_{-\infty}^{+\infty} (\rho + g)\, d\xi = a(l) \tag{3}$$

and

$$\rho \to 0 \text{ and } g \to 0 \text{ at } \xi \to \pm\infty \tag{4}$$

If an elementary force, developed by linked *M* is $f(\xi,v)$ then the force at the ends of muscle is

$$F(t, v) = \int_{-\infty}^{+\infty} f(\xi, v)\cdot\rho(\xi, t)\, d\xi \tag{5}$$

The equation, governing the motion of a load, is

$$\mathscr{T}\cdot\frac{d^2L}{dt^2} = F(t, v) - P(t, V, L) \tag{6}$$

where $\mathscr{T}$ is the effective inertial mass of the load, *P* is an external force and $L = 2N1$ is the shortening of the whole muscle. It is evident that $d^2L/dt^2 = 2N(dv/dt)$. The value of $\mathscr{T}$ and the form of the dependence of *P* on *t, V, L* determines the regimes of contraction.

The set of equations (1, 2, 6) supplemented with the conditions (3, 4, 5) is the mathematical formulation of experimental principles of the sliding-filament concept. Mathematical treatment of this set is practically impossible in this form. But it can be reduced to a simpler one by introducing some assumptions.

Assumption 1. After the *MA* link splitting *M* comes back instantly to its equilibrium position, i.e. $K^1(\xi) >> K_1(\xi)$ and $K_2(\xi)$ at all ξ. It means also that conformational rearrangements of macromolecules, which take place during the sliding of a linked *M* along the thick filament backbone, are much slower than those occurring during motion of a free *M*. Hence, the sliding of linked *M* is an equilibrium process and K_2 and *f* do not depend on *v*: $K_2 = K_2(\xi)$ and $f = f(\xi)$.

Assumption 2.

$$\left.\begin{aligned} f(\xi) &= +f = \text{const}, \quad \text{at } 0 < \xi < \delta \\ f(\xi) &= -f \qquad\quad \text{at } \delta < \xi < +\infty \end{aligned}\right\} \tag{7}$$

Assumption 3.

$$\left.\begin{aligned} K_2(\xi) &= 0, \qquad \text{if } f(\xi) > 0 \\ K_2(\xi) &= K_2 = \text{const}, \quad \text{if } f(\xi) < 0 \end{aligned}\right\}. \tag{8}$$

Assumptions 2 and 3 are illustrated in Fig. 2b. This figure shows that linked M in the contracting muscle can be in two states: in a "pulling" state with $f(\xi) = +f$ and $K_2(\xi) = 0$ and in a "hindering" one with $f(\xi) = -f$ and $K_2(\xi) = K_2$.

Under assumptions (1, 2, 3) a hypothetical elementary working cycle of myosin bridge in an excited contracting muscle may be described as follows. The MA link formation at $\xi = 0$ causes a conformational rearrangement of the myosin molecule or some part of the thick filament, which results in the sliding of M (more precisely the point of association M and A) along the thick filament backbone towards its new equilibrium position at $\xi = \delta$. So at the distance δ a linked M develops a positive force, i.e. the force oriented to the centre of sarcomere when applied to thin filament. At $\xi = \delta$ an active conformational rearrangement is completed an axial component of the bridge force passes through zero and then becomes negative. The bridge obtains a possibility to split. Probably, some tension is necessary to break the M-A link. It is the cause, which can result in the negative bridge force. After the splitting M returns very fast to its equilibrium position at $\xi = 0$ so that cross-link formation during returning is unprobable.

Some stages of this cycle are accompanied by adsorption and desorption of Ca^{2+} and by the ATP splitting. We shall not go into the details of these processes because it does not matter for our model, but a qualitative picture given by DAVIES [19] may serve as a good illustration to this scheme.

Under assumption 1 ($K^1 >> K_1, K_2$) equation (2) yields

$$g(\xi, t) = \varphi(\xi) \cdot \int_{-\infty}^{+\infty} g(\xi, t)\, \mathrm{d}\xi = \varphi(\xi) \cdot \gamma(t) \tag{9}$$

where $\gamma(t)$ is the whole number of free M's at the moment t.

By integrating over ξ from $-\infty$ to δ and then from δ to $+\infty$ and by taking into account (8), (9) and (4), equation (1) is reduced to a pair of usual equations:

$$\frac{\mathrm{d}n}{\mathrm{d}t} = K_1 \cdot \gamma(t) - v\rho(\delta, t) \tag{10}$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = -K_2 m + v\rho(\delta, t) \tag{11}$$

Here $n = \int_{-\infty}^{\delta} \rho(\xi,t)\mathrm{d}\xi$ and $m = \int_{\delta}^{+\infty} \rho(\xi,t)\mathrm{d}\xi$ are whole numbers of "pulling" and "hindering" bridges in the moment t, $K_1 = \int_{-\infty}^{\delta} K_1(\xi)\cdot\varphi(\xi)\mathrm{d}\xi$ is an average value of rate constant K_1 (ξ) over the range of equilibrium distribution of free M's. From item (4) it follows that $\varphi(\xi)$ is a very sharp function. So, for quasi-stationary regimes of contraction

$$\rho(\delta, t) = \frac{n(t)}{\delta} = K_{-1}\, n. \tag{12}$$

In virtue of (3) and (5) $\gamma(t) = \alpha(l) - n - m$ and $f(t) = f(n - m)$. So, a complete set of equations is:

$$\frac{\mathrm{d}n}{\mathrm{d}t} = K_1\,[\alpha(l) - n - m] - K_{-1}\, vn \tag{13}$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = K_{-1}\, vn - K_2\, m \tag{14}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = \frac{1}{2N\mathscr{T}}\,[f(n - m) - P] \tag{15}$$

$$\frac{\mathrm{d}l}{\mathrm{d}t} = v. \tag{16}$$

Origination of equation (15) from equation (6) and equation (16) is evident.

It should be noticed that such set of equations may be obtained also if Assumption 2 will not be so strong: it issufficient $f(\xi)$ to be positive and limited at $0 \leq \xi \leq \delta$.

From a formal point of view equations (13)–(14) describe the cycle of three mono-molecular reactions:

$$\begin{array}{ccc} & \overset{K_1}{} & \\ a & \rightarrow & b \\ {\scriptstyle K_2}\nwarrow & & \swarrow{\scriptstyle K_{-1}\, v} \\ & c & \end{array} \tag{17}$$

where a, b and c are the free, pulling and hindering M's respectively. Some stages of this cycle are essentially irreversible due to the coupled process of ATP splitting.

The set of equations (13)–(16) gives a possibility to compute the dynamics of an excited muscle contraction, if parameters are known such as structural function $\alpha(l)$, the number of sarcomeres N, the properties of load, P and t, and the values of the constants K_1, K_2, K_{-1} and f.

It follows from items (2) and (3) that in relaxed muscle all the M's are free. In our model such a state is possible if $K_1 = 0$. As a rule, we shall assume that this rate constant changes instantly from zero to some constant value in the moment of muscle excitation. Such an approach is permissible, unless the initial part of the tetanic contraction is of interest.

2. SKELETAL MUSCLE CONTRACTION

Stationary regime

The stationary contraction with a constant speed takes place under isotonic conditions, if muscle length is about its length *in situ*. In this case $\alpha(l) = \alpha_o$ [12] and the load, P, are constant. Equations (13)–(15) do not contain l, so that they form an exclusive system, whose steady-state $\left(\frac{dn}{dt} = \frac{dm}{dt} = \frac{dv}{dt} = 0\right)$ is single:

$$n' = \frac{K_1(f\alpha_0 + P) + K_2 P}{f(2K_1 + K_2)},\ m' = \frac{K_1(f\alpha_0 - P)}{f(2K_1 + K_2)},\ v' = \frac{K_1 K_2 (f\alpha_0 - P)}{(K_1 + K_2) K_{-1}\left(P + \frac{K_1}{K_1 + K_2} f\alpha_0\right)} \tag{18}$$

The expression for the steady-state velocity, v', may be changed as follows:

$$(P + a)\, v' = b(P_0 - P) \tag{19}$$

so that

$$P_0 = f\alpha_0,\ a = \frac{K_1}{K_1 + K_2} f\alpha_0,\ b = \frac{K_2}{K_{-1}} \frac{K_1}{K\text{'s} + K_2}. \tag{20}$$

It follows from equation (20) that

$$a = \text{const} \cdot P_0 \text{ and } b = v_m \frac{a}{P_0}, \tag{21}$$

where P_o is the force at $v' = 0$ and $v_m = K_2/K_{-1}$ is the contraction velocity at $P = 0$.

Expressions (19) and (21) coincide with the experimental correlations discovered by HILL [20].

The rate of the total energy production will be

$$\frac{dE}{dt} = \epsilon K_2\, m' = \frac{\epsilon K_1 K_2 (f\alpha_0 - P)}{f(2K_1 + K_2)} = \text{const} \cdot (P_0 - P) \tag{22}$$

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

The heat production rate can be obtained by subtracting mechanical power from (22) and by expressing $f\alpha_o - P$ through the V's from (18):

$$\frac{dQ}{dt} = \frac{dE}{dt} - P v' = v' \left[\frac{\eta K_1}{2K_1 + K_2} P_0 + \frac{\eta(K_1 + K_2) - (2K_1 + K_2)}{2K_1 + K_2} P\right] \tag{23}$$

where

$$\eta = \frac{\epsilon K_{-1}}{f} = \frac{\epsilon}{f\delta} \tag{24}$$

so that $1/\eta$ has the sense of maximal efficiency of the elementary cycle, because $f\delta$ is the positive mechanical work of the myosin bridge in cycle.

If $\eta = (K_2 + 2K_1)/(K_1 + K_2)$ then $dQ/dt = av$' this being in agreement with the experimental results by HILL [20].

Expression (23) is in conformity with more recent results of this author [21] if $\eta = 1 \cdot 4 \pm 0 \cdot 3$ and $K_2/K_1 = 5 \cdot 5 \pm 1$.

It should be noticed that expression (23) does not contain the activation and maintenance heat, which probably are due to muscle excitation [22].

Estimation of the parameters

There are five parameters in our scheme connected with the intimate mechanism of muscle contraction: α_o, K_1, K_2, K_{-1} and f. Comparison with Hill's equation gives three relations (20), α_o may be estimated from the structural data and formula (24) gives the last relation we need.

Assuming that $\alpha_o = 10^{13}$, $P_o = 3 \cdot 10^6$ g cm/sec^2 [3], $a/P_o = 1/4$, $v_m = 1 \cdot 5 \times 10^{-4}$ cm/sec at 0ºC [20], the hydrolysis energy of ATP molecule, $\epsilon = 3 \cdot 10^{-13}$ g cm/sec^2 [23] and $\eta = 1$ we obtain:
$f = 3 \cdot 10^{-7}$ g cm/sec^2, $K_{-1} = 10^6$ 1/cm, $K_2 = 150$ 1/sec and $K_1 = 50$ 1/sec.

Isotonic contraction of unstretched muscle

The dynamics of movement towards the steady-state (18) may be obtained by integration of the set of equations (13)–(15) at $\alpha(l) = \alpha_o$ and constant P. This set, however, possess only a slight non-linearity and linear approximation gives quite satisfactory results in this case.

On introducing new variables such as

$$x = \frac{n}{\alpha_0}, \; y = \frac{m}{\alpha_0}, \; u = \frac{K_{-1}}{K_1} v, \; \tau = K_1 t \tag{25}$$

the set of equations (13)–(15) will be written as follows:

$$\begin{aligned} \frac{dx}{d\tau} &= 1 - x - y - ux \\ \frac{dy}{d\tau} &= ux - 3y \\ \frac{du}{d\tau} &= B(x - y - A) \end{aligned} \tag{26}$$

where $A = \dfrac{P}{f\alpha_0} = \dfrac{P}{P_0}$ and $B = \dfrac{P_0}{\mathcal{T}} \dfrac{K_{-1}}{2NK_1^2}$.

The steady state (18) in terms of these variables will be

$$x_s = \frac{4A+1}{5}, y_s = \frac{1-A}{5}, u_s = \frac{3(1-A)}{4A+1}. \tag{27}$$

The characteristic equation of the set (26), linearized near this steady state, is

$$\lambda^3 + (3{\cdot}25 + 3{\cdot}75a) \times \lambda^2 + (15a + 0{\cdot}4b)\lambda + b = 0 \tag{28}$$

Here $a = 1/(4A + 1)$ and $b = B(4A + 1)$ have the following limits of changing: $0{\cdot}2 \leq a \leq 1$ and $1 \leq b \leq 500$ if $N = 1{\cdot}5{\cdot}10^4$ and P_o/t 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 (28) in the plane of the parameters a and b is shown in Fig. 3. Almost at all values of the parameters, one real negative root – λ and a pair of complex roots $-p \pm i\omega$ with the negative real part are present.

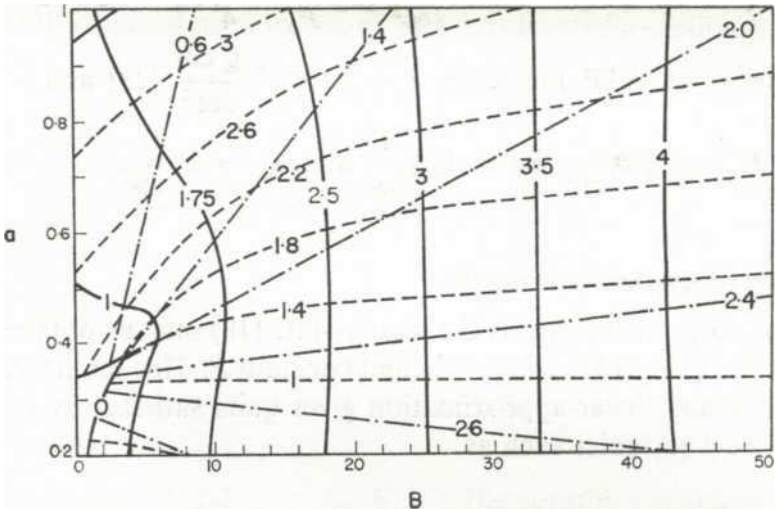

FIG. 3. PARAMETRICAL PLANE OF EQUATION (28): SELF-OSCILLATION OF FROG SARTORIUS MUSCLE UNDER ISOTONIC CONDITIONS.

Parameters a and b represent the value and the effective mass of the load resp. The levels of frequency, ω, and damping constants, p and λ, are given by solid, dashed and dashed and dotted lines respectively.

That means that motion towards the steady state (18) occurs as follows. The mean levels of the variables approach the steady state values with the time constant $1/K_1\lambda$. Around these mean levels the damped sinusoidal oscillations occur with the period $2\pi/K_1\omega$ and the damping constant $1/K_1p$. The amplitude of oscillations is determined by the initial perturbance.

Under ordinary experimental conditions (muscle lifting the weight) $1/K_1\lambda \simeq 10^{-2}$ sec, $2\pi/K_1\omega \simeq 3{\cdot}10^{-2}$ sec and $1/K_1 p \simeq 10^{-2}$ sec. This means that the special conditions (decreasing of t at $P \simeq P_o$) are necessary to observe oscillations.

It should be emphasized that in these calculations we do not take into account the elastic properties of muscle. So system (26) does not contain any resonance elements. The oscillatory mechanism may be explained as follows. The speed of myosin bridges transition from the state (b) to (c) varies directly as the velocity of contraction. If in the first moment the

contraction velocity is low, then the transition from (a) to (b) will prevail. The force developed by the muscle, acceleration and velocity of inertial loading will rise fast, this resulting in the predominance of transition from (b) to (c). Because of loading inertia this will cause the force to fall up to the level, which is insufficient for the steady state speed being maintained, and then the cycle will repeat.

As an illustration, a numerical integration of system (26) is shown in Fig. 4c.

Isotonic contraction of stretched muscle

Stretched muscle behaviour under isotonic conditions is described by the set of equations (13–16) with constant P and with $\alpha(l) = \alpha_o \beta l$. From the structural [12] and physiological data [7] it follows, that $\alpha(l)$ varies linearly from 0 to α_o when the sarcomere length changes from $3{\cdot}65 \times 10^{-4}$ cm, ($l = 0$), to $2{\cdot}25 \times 10^{-4}$ cm, ($l = 0{\cdot}7 \times 10^{-4}$ cm), so that $\beta = 1{\cdot}4 \times 10^4$ cm^{-1}. Upon introducing this modification and substitution of variables (25) we obtain:

$$\frac{dx}{d\tau} = z - x - y - ux \tag{29}$$

$$\frac{dy}{d\tau} = ux - 3y \tag{30}$$

$$\frac{du}{d\tau} = B(x - y - A) \tag{31}$$

$$\frac{dz}{d\tau} = \epsilon u. \tag{32}$$

where $z = \beta l$ and $\epsilon = \beta / K_{-1}$.

Taking into account that $\epsilon = 1/70$ and $B > 1$ we may consider the equation (32) as "slow" in comparison with the group of "fast" equations (29–31). The quasi-stationary solution can be obtained by means of Tikhonov's theorem [24] (z treated as a parameter in the group of "fast" equations). Returning to the initial variables we shall have:

$$\left(P + \frac{K_1}{K_1 + K_2} f\alpha_0 \beta l\right) v_q = \frac{K_2}{K_{-1}} \frac{K_1}{K_1 + K_2} (f\alpha_0 \beta l - P). \tag{33}$$

Taking into account that $f\alpha_o\beta l = f{\cdot}\alpha(l)$ is the isometrical force, developed by the muscle at given shortening l, we may consider the equation (33) as a generalization of Hill's equation for the case of stretched muscle. Parallel elasticity is not included in this equation. This should be taken into consideration by experimental check.

Dependence of quasi-stationary speed from sarcomere length isshown in Fig. 4a. Sarcomere shortening as a function of time is obtained by integration of equation (16) with $v = v_q$ from (33) (Fig. 4b).

The solution of the set of fast equations (29–31) is stable at $0 \leq A \leq Z \leq 1$. So the conditions of Tikhonov's theorem are satisfied and the solutions of the whole system (29–32) will tend to quasi-stationary curves or oscillate around them. In this case oscillations may be undamped in contrast to the case of unstretched muscle (Fig. 4d). Oscillatory approaching

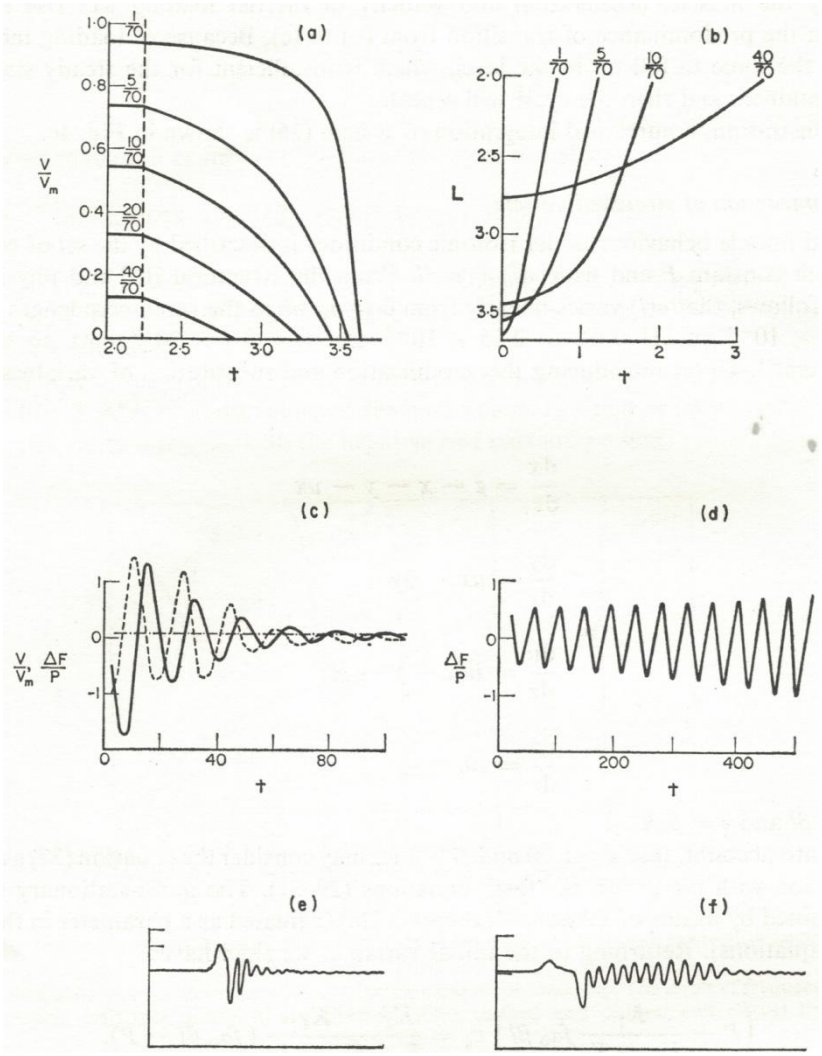

FIG. 4. ISOTONIC TETANI OF FROG SARTORIUS MUSCLE.

a and b: quasi-stationary contraction of stretched muscle V/V_m, relative velocity, L, sarcomere length in microns, t, time in sec; relative load is shown near the curves; calculated from equation (33). c and d: initial portions of contraction of unstretched and stretched muscle respectively; solid lines: difference between muscle tension and load, divided by load; dashed line: relative velocity of contraction; dashed and dotted line: steady-state velocity of contraction at $A = 0{\cdot}75$; t: time in msec; c, calculated from the set of equations (26) under conditions: $B = 36$, $A = 0{\cdot}75$, $x(0) = 0$, $y(0) = 0$, $u(0) = 0$; d, calculated from the set of equations (29–32) under conditions: $B = 20$, $A = 20/70$, $x(0) = 22/70$, $y(0) = 0$, $u(0) = 0$, $z(0) = 24/70$. e and f: experimental records of oscillating component of force, developed by unstretched and stretched muscle resp. under the next conditions: stimulation 30 pulse/sec, temperature 2°C; e: $A = 0{\cdot}75$, $B = 26$, initial muscle length equals the length *in situ*; f: $A = 0{\cdot}9$, $B = 26$, initial muscle length equals 1,3 length *in situ*; frequency of oscillations in both cases equals to 20 cps.

to the steady-state contraction and especially undamping oscillations of stretched muscle under isotonic conditions are unexpected conclusions of the theory.*

A simple estimation shows that muscle force is more suitable for registration than its length or contraction velocity, for investigation of oscillatory types of muscle contraction. In collaboration with V. N. Buravcev the experiment had been performed on frog sartorius muscle and oscillations had been observed under predicted conditions [25]. Alternative component of force had been detected by piezocrystal at one end of muscle, the other being connected with the isotonic lever.

Frequency of sinusoidal oscillations at 2–4°C under tetanic stimulation (35 cps, pulse duration 3 msec) varies from 10 cps up to 70 cps by alteration of t and P/P_o. Oscillatory properties of excited muscle cannot be explained in terms of passive elasticity and viscosity. Oscillations take place only during shortening. Their damping decreases with load increasing. Stretched muscle gives undamping oscillations, amplitude of which can increase up to the value of the load. The experimental frequency is 1·5–2 times lower than calculated one. This discrepancy results from our neglect the series elasticity of muscle in the present calculations [26]. Two records of alternative component of muscle force under isotonic conditions are given in Fig. 4e, f.

It should be noticed that damping oscillations of contraction velocity under isotonic conditions had been observed previously [27], but the authors explained them as a device artifact. Non-monotonous shortening of frog sartorius sarcomeres under slightly non-isotonic conditions, which had been observed by EMELIANOV [28] probably results from the mechanism under consideration.

Isometric contraction

To calculate the speed of force, developing under isometric conditions, it is necessary to know the load – extension curve $P(L)$ for elastic elements connected in series with contractile elements of the muscle. The data we need were taken from work [27].

Isometric contraction is described by the set of equations (13–16) at $\alpha(l) = \alpha_o$ and with equation (15) substituted by the algebraic correlation

$$f(n - m) = P(L) \tag{34}$$

which expresses the equality of elastic and contractile forces. It is evident that lengthening of all elastic elements is equal to shortening of all contractile elements, so that $L = 2Nl$. By differentiation of (34) with respect to time we may exclude v from the set of equations. Upon the substitution of the variables (25) the set of equations takes the form:

$$\frac{dx}{d\tau} = 1 - x - y - x \cdot u(x, y, z) \tag{35}$$

$$\frac{dy}{d\tau} = -3y + x \cdot u(x, y, z) \tag{36}$$

$$\frac{dz}{d\tau} = u(x, y, z) \tag{37}$$

* The last conclusion and Fig. (4d) are based on the wrong calculations conditioned by the unstable performing of our computer. Recent analytical investigations and new calculations [26] had indicated that the set of equations (29–31) cannot give undamping oscillations. So in this point the theory is inconsistent with the experiment. The question is under consideration.

where $$z = 100\,\frac{2l}{s},\quad u(x, y, z) = \frac{K_{-1}\,s}{200}\,\frac{1 - x + 2y}{\dfrac{dA}{dz} + \dfrac{K_{-1}\,s}{200}\,x}$$

$s = 2{\cdot}2 \times 10^{-4}$ cm is the length of a sarcomere and $A(z) = P(z)/P_o$ is the relationship between relative force and relative extension of an elastic component. Recalculation of data [27] gives:

$$A(z) = \begin{cases} 0{\cdot}0897\,z^3 + 0{\cdot}0348\,z^2 + 0{\cdot}2\,z & \text{for } z \leqslant 1{\cdot}15 \\ 0{\cdot}636\,z - 0{\cdot}319 & \text{for } z > 1{\cdot}15 \end{cases}$$

The set of equations (35–37) under initial conditions

$$x(0) = 0{\cdot}5,\ y(0) = 0,\ z(0) = 0$$

describes normal isometric tetani of the muscle. Tension redevelopment after quick release is governed by the same system under initial conditions

$$x(0) = 0{\cdot}5,\ y(0) = 0{\cdot}5,\ z(0) = 0$$

This may be explained as follows. Before the moment of quick release the muscle had developed the maximal isometrical force, all its bridges having been in state (b). During the quick release the force falls, because 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. That the force falls to zero means that a half of bridges is in state (b) and the other half in state (c).

The speed of force development also can be easily calculated from load-extension dependence (38) and stationary force-velocity Hill's relationship (9) [27]. The results of our

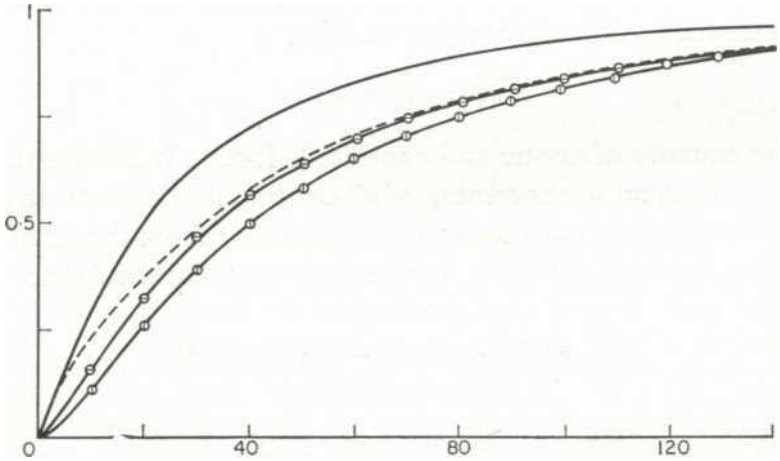

FIG. 5. ISOMETRIC TETANI OF FROG SARTORIUS MUSCLE.

Upper curve calculated from Hill's force-velocity relationship (19) and load-extension dependence for series elasticity (38). Middle curve: tension redevelopment after quick release calculated from the set of equations (35–37) under conditions: $x(0) = 0{\cdot}5$, $y(0) = 0{\cdot}5$, $z(0) = 0$. Dashed curve: "initial rise of tension" calculated from the set of equations (35–37) under conditions: $x(0) = 0$, $y(0) = 0$, $z(0) = 0$ without taking into consideration the time of activation. Lower curve: initial rise of tension, calculated from the set of equations (35–37) modified to take into consideration activation time (see section 4). ⊖ and ⓘ: experimental curves of tension redevelopment and initial rise of tension from [27].

calculations and experimental curves by JEWEL and WILKE [27] are shown in Fig. 5. The initial part of calculated ordinary isometric tetani is more steep than that on experimental curve. This arises from our assumption about instant increasing of rate constant K_1 at the moment of muscle excitation. Taking into account the limited time of its growth (8–10 msec [29]) we obtain the complete coincidence of theoretical and experimental curves. This will be discussed in some detail in section 4.

3. ASYNCHRONOUS MUSCLE OSCILLATORY CONTRACTION

Insect flight muscles are able to produce several rhythmic contractions on the single pulse of excitation [30]. Their glycerinated fibres also yield oscillatory contractions [31]. So, autooscillations are the intimate property of the contractile system of muscles of such type.

Biochemical constitution [32], the properties of contractile proteins [33] and structural organization [34] of insect flight muscles are similar to those of vertebrates skeletal muscles. So, the model of striated muscle contraction must work in this case also.

Specification of the model

Two peculiarities of asynchronous muscles must be taken into account.

(1) Flight muscle under excitation can change its length cyclically: shorten ($v > 0$) and lengthen ($v < 0$). The sequence of the states the *M*'s come through, depends on the direction of sliding of the thick filaments relative to the thin ones. Previously we have taken into account only the states the *M*'s come through at $v > 0$. So, the diagram of the myosin cross-bridge elementary working cycle (17) should be changed as follows:

$$\begin{array}{ll} K_3\ d\ K_{-3}\ |v| & K_3\ d\ K_{-1}\ |v| \\ \swarrow K_1 \searrow & \swarrow K_1 \searrow \\ a \rightarrow b \quad \text{for } v \geqslant 0 & a \rightarrow b \quad \text{for } v \leqslant 0 \\ \nwarrow \quad \swarrow & \nwarrow \quad \swarrow \\ K_2\ c\ K_{-2}\ |v| & K_2\ c\ K_{-2}\ |v| \end{array} \tag{39}$$

During extension of the excited muscle (at $v < 0$) due to relative sliding of the filaments the linked *M*'s from hindering state (c) turn into pulling state (b) and then into state (d) (see Fig. 2, Section 1). In states (c) and (d) the *M*'s have the probability of splitting, i.e. turning into free state (a). During muscle contraction ($v > 0$) the linked *M*'s pass over the states (d), (b) and (c) in inverted direction. In the case of skeletal muscles the force developed by the *M* in state (d) may be estimated from force-velocity relationship for negative *v* [35]: absolute value d*v*/d*P* at $P > P_o$ about 6 times exceeds such one at $P < P_o$. This may be interpreted in such a way that the elementary force in state (d) 6 times exceeds such one in state (b) and has the same direction. So, state (d) may be designated as "superpulling" one.

(2) Specification of structural function. It is known, that slight extension (2–3 per cent) of glycerinated fibres of flight muscles causes increasing of their Ca^{2+}-activated ATP-ase activity and active force [36]. This may be interpreted as increasing of the number of the active cross-bridges, *M*'s, in a sarcomere with its lengthening. The real dependence is S-shaped but we shall consider only its linear region in which

$$\alpha(l) = \alpha_0 \left(1 - \frac{l}{l_0}\right) \tag{40}$$

Here l is the shortening of the half of the sarcomere, α_o is maximal number of the M's and l_o may be estimated from data [36] as 4×10^{-6} cm.

Such behaviour of flight muscles may be understood in the frame of sliding-filament concept as the dependence of positions of the myosin cross-bridges relative to actin receptor sites upon the displacement of myosin and actin filaments.

The average number of "suitably placed" pairs MA (i.e. active M's) over the whole sarcomere is allowed to depend on the extension, only when two conditions are satisfied:

(a) myosin bridge's helix on the thick filament and actin double helix of the thin one have the same main periods;

(b) myosin helices over all the thick filaments and actin helices over all the thin ones are in register in a half of any of the sarcomeres.

Recent investigation [37] shows, that these conditions have to be satisfied in the case of insect flight muscle in rigor. Myosin and actin main periods are equal to 380 Å, i.e. 3 per cent of a half of a sarcomere length. If such an arrangement were stiff, the number of the active M's would depend on the extension periodically and the range of monotonous increasing could not exceed 1·5 per cent of muscle length. However, muscle elasticity can mask the simple behaviour of the contractile component. The effect of the series elasticity on the hypothetic force–extension steady-state curves is illustrated by Fig. 6. The behaviour of the curves is determined by the relation between the slope of the active force and the stiffness of the series elasticity. It is probably the clue to "high tension" state [31] and rather large amplitudes of self-oscillations of living flight muscles [38].

In our mathematical model the series elasticity is taken into consideration only through the value of the slope of $\alpha(l)$ i.e. through the value of l_o in (40).

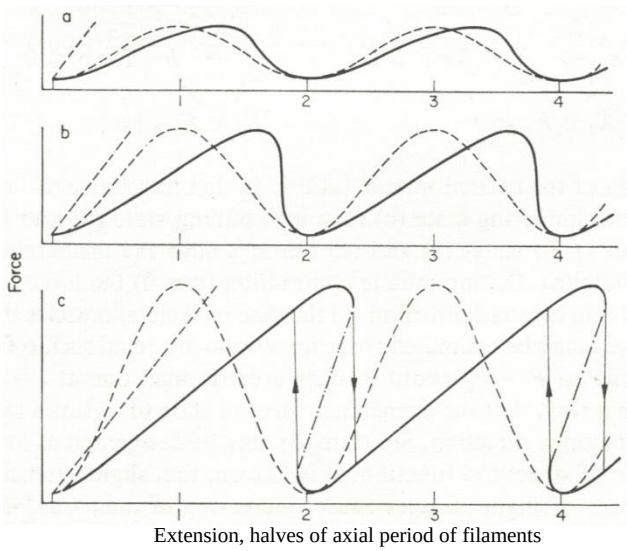

FIG. 6. INFLUENCE OF SERIES ELASTICITY ON IDEALIZED EXTENSION–FORCE STEADY-STATE CURVE OF INSECT FLIGHT MUSCLE.

Dashed curve: idealized extension–force curve of contractile system. Dashed straight line: idealized extension–force characteristic of series elasticity. Solid curves: combined characteristics "real" muscle. Dashed and dotted lines: unstable regions of extension–force curves. Amplitude of active force increases from *a* to *c*, that corresponds to increasing of Ca^{2+} concentration.

Estimation of the parameters and simplification of the elementary working cycle

The transient analysis given by Jewell and Rüegg (see Fig. 10 in [31]) allows the values of the rate constants, K_1, K_2 and K_3 to be obtained. In terms of our model redevelopment of tension after quick release and force falling after quick stretch are conditioned by the splitting of the *M*'s in states (c) and (d) respectively. This gives $K_2 \simeq K_3 \simeq 100$ 1/sec. Delayed rise of tension after stretch is conditioned by the additional *MA* links formation which became available due to extension as follows from (40). This gives $K_1 \simeq 50$ 1/sec. Delayed fall of tension after quick release is conditioned by the splitting of the *M*'s in state (b). As in the case with skeletal muscles we do not take into consideration the splitting of the *M*'s in state (b). This means, that the present model fails to describe quantitatively low frequency contractions of flight muscles at which the number of the *M*'s in state (b) is comparable to that in state (a). This simplification does not change the qualitative behaviour of the final set of equations (42).

The rate constants K_1 and K_2 have the same values in flight muscles as in skeletal ones. So, we shall assume that all the analogous parameters have the same values in the muscles of both kinds, i.e. $K_{-2} \simeq K_{-3} \simeq K'_{-1}{}^* = K_{-1} \simeq 10^6$ 1/cm, $f = 3 \cdot 10^{-7}$ gcm/sec^2 and $\alpha_o = 10^{13}$.

In this case the "superpulling" state, (d), is characterized by the following parameters: $f\mathrm{d} = 6f$, $K_3 = K_2$ and $K_{-3} = K'_{-1}{}^*$. It may be substituted for the state, in which the force equals f as in the state (b) and the rate constant of cross-links dissociation is about (1/6) $K_2 \simeq (1/3)K_1$. This imaginary state is similar to the state (b), if the process of dissociation is neglected. So, instead of the diagram (39) we shall regard:

$$\begin{array}{ccccc} & & a & \longrightarrow & b \\ K_2 & \nwarrow & K_1 & \swarrow & \nearrow K_{-1} \mid v \mid \\ & & c & & \end{array} \qquad (41)$$

The direction of the transition between *b* and *c* is governed by the sign of *v*: at $v > 0$ (shortening) the *M*'s transit from *b* to *c*.

Mathematical treatment of the model

By the diagram (41) the kinetics of the *M*'s transitions is governed by the following set of equations:

$$\begin{array}{ll} \text{at } v \geqslant 0: & \text{at } v \leqslant 0: \\ \dfrac{\mathrm{d}n}{\mathrm{d}t} = K_1[\alpha(l) - n - m] - K_{-1}\, vn & \dfrac{\mathrm{d}n}{\mathrm{d}t} = K_1[\alpha(l) - n - m] - K_{-1}\, vm \\ \dfrac{\mathrm{d}m}{\mathrm{d}t} = K_{-1}\, vn - K_2\, m & \dfrac{\mathrm{d}m}{\mathrm{d}t} = K_{-1}\, vm - K_2\, m \end{array} \qquad (42)$$

where n and m are the number of the *M*'s in states (b) and (c) respectively.

* Possibly the prime mark and/or the abbreviation of this constant (K'_{-1}) is not correct because K'_{-1} does not occur in other places in the paper [note during digitizing the paper.]

We shall regard only driven oscillations which may be preset as follows:

$$\left.\begin{aligned} \frac{dl}{dt} &= v; & l(0) &= \frac{l_0}{2}(1 \pm \gamma) \\ \frac{dv}{dt} &= \omega^2\left(\frac{l_0}{2} - l\right); & v(0) &= 0. \end{aligned}\right\} \tag{43}$$

This pair of equations gives $l = (l_o/2) \pm \gamma(l_o/2) \cos \omega t$ i.e. harmonic oscillations of length around the midpoint of linear region of $\alpha(l)$ with the amplitude $\gamma l_o/2$, ($\gamma \leq 1$), and with the frequency $\omega/2\pi$.

The set of equations (42) completed with (43) governs the kinetics of the M's transitions during driven oscillations of insect flight muscles. After linear substitution of the variables $n = \alpha_o x$, $m = \alpha_0 y$, $l = (1/K_{-1})z$, $v = (K_1/K_{-1})u$, $t = (1/K_1)\tau$ this system takes the form:

for contraction $\left(u \geqslant 0,\ 0 \leqslant \tau \leqslant \frac{\pi}{\nu}\right)$

$$\left.\begin{aligned} \frac{dx}{d\tau} &= 1 - x - y - \beta z - ux & x(0) &= x_+{}^0 \\ \frac{dy}{d\tau} &= ux - qy & y(0) &= y_+{}^0 \\ \frac{dz}{d\tau} &= u & z(0) &= z_+{}^0 = \frac{1-\gamma}{2\beta} \\ \frac{du}{d\tau} &= \nu^2\left(\frac{1}{2\beta} - z\right) & u(0) &= u_+{}^0 = 0 \end{aligned}\right\} \tag{44}$$

and for extension $\left(u \leqslant 0,\ 0 \leqslant \tau \leqslant \frac{\pi}{\nu}\right)$

$$\left.\begin{aligned} \frac{dx}{d\tau} &= 1 - x - y - \beta z - uy & x(0) &= x_-{}^0 \\ \frac{dy}{d\tau} &= uy - qy & y(0) &= y_-{}^0 \\ \frac{du}{d\tau} &= \nu^2\left(\frac{1}{2\beta} - z\right) & u(0) &= u_-{}^0 = 0 \\ \frac{dz}{d\tau} &= u & z(0) &= z_-{}^0 = \frac{1+\gamma}{2\beta} \end{aligned}\right\} \tag{45}$$

where $\beta = \dfrac{1}{K_{-1} l_0}, q = \dfrac{K_2}{K_1}, \nu = \dfrac{\omega}{K_{-1}}.$

This system allows to compute the dependence of force, length and velocity of contraction upon time and to obtain the length-tension diagrams under various frequencies and amplitudes of oscillations.

The linear approximation of this system allows us to obtain power output as a function of the parameters for steady-state oscillations [11]. Mathematical treatment includes the cyclic substitution of the solutions of the sets of equations (44) and (45) for the initial conditions of the sets of equations (45) and (44) respectively.

For the dimensionless work in cycle, A', and mean power output, N', such treatment gives:

$$N' = \frac{\nu}{2\pi} A' = \frac{\gamma^2 \nu^2 \left[\nu^2 (4\beta - q) + q^2 (4\beta - 1) - 2q\right]}{32 \beta^2 (1 + \nu^2)(q^2 + \nu^2)}. \tag{46}$$

The usual physical values are expressed through the dimensionless variables as follows:

Relative shortening $$\frac{2l}{s} 100 = \frac{2z}{K_{-1} s} 100 \simeq 0{\cdot}8z\,\%.$$

Linear frequency $$\frac{\omega}{2\pi} = \frac{K_1 v}{2\pi} \simeq 8v \text{ cps}.$$

Tension $$f(n-m) = f\alpha_o\,(x-y) \simeq 3{\cdot}10^6\,(x-y) \text{ dyn} \times \text{cm}^{-2}.$$

Work $$A = \frac{4f\alpha_0}{K_{-1} s} A' \simeq 5{\cdot}10^4\, A' \text{ erg} \times (\text{g muscle})^{-1}.$$

Power output $$N = \frac{4f\alpha_0 K_1}{K_{-1} s} N' \simeq 2{\cdot}5 \times 10^6 {\cdot} N' \text{ erg} \times \text{sec}^{-1} \times (\text{g muscle})^{-1}.$$

Results and discussion

Calculated length–tension diagrams are shown in Fig. 7. Their evolution with frequency of driven oscillations corresponds to the behaviour of the experimental curves (see Fig. in [39]). At sufficiently low frequency the diagram reduces to a straight line, at moderate frequencies it is "ellipse" with positive work in cycle, then it becomes "eight-shaped" and at sufficiently high frequency it is an "ellipse" with negative work in cycle.

Parameters β and q, which represent the slope of structural function and the ratio of rate constants K_2/K_1 respectively, govern the power output and the frequency range, in which work in cycle is positive (see Fig. 8).

A number of experimental results may be explained in the term of our model.

(1) The power output is proportional to the square of the amplitude [31]. This results from formula (46), which holds in the linear region of structural function.

(2) The frequency of self-oscillations may be changed within wide limits [40]. The contractile mechanism under consideration is able to yield positive power output within an infinitely wide frequency band (see Fig. 8).

(3) The frequency, at which power output is maximal, ω_m, is lowered, when the flight muscle is glycerinated. In contrast to this the frequency, at which work in cycle changes the sign, ω_o, after glycerination is higher as a rule [31]. Some possibility exists for such behaviour of the frequency parameters within the range of our scheme (see Fig. 8).

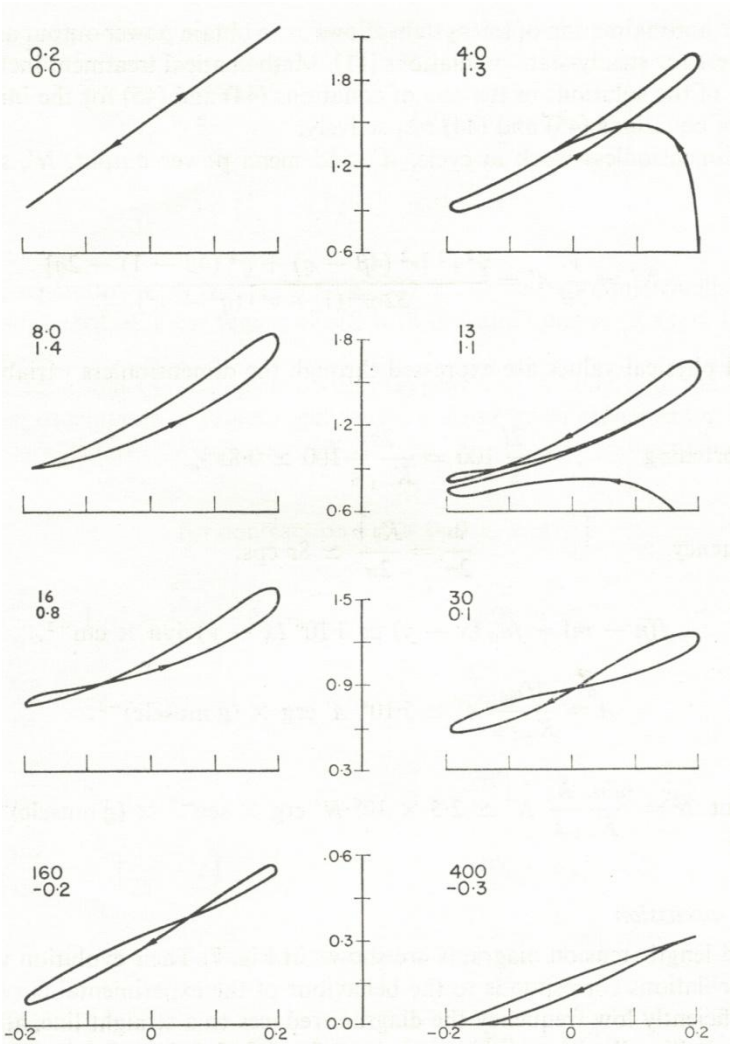

FIG. 7. EVOLUTION OF LENGTH–TENSION DIAGRAMS WITH THE FREQUENCY OF DRIVEN OSCILLATIONS, CALCULATED FROM THE SET OF EQUATIONS (44–45) UNDER CONDITIONS $\gamma = 0{\cdot}4$, $q = 3$, $\beta = 0{\cdot}7$.
Abscissa: relative lengthening in per cent; ordinate: tension in kg/cm^2; the upper number: the frequency in cps; the lower number: work in cycle in 10^3 erg/(g muscle).

(4) The length-tension diagrams become more narrow, their slope and work in cycle fall, when mean length of the muscle is shifted from the optimum [39]. This results from the structural function being S-shaped: the shift of the operating point from the midpoint of linear region of the structural function results in the mean slope falling, i.e. in the decrease of the β in our linear approximation.

(5) Some properties of "high tension" state [31] may be understood by analysis of hypothetical steady-state force-extension curves, which are shown in Fig. 6. The amplitude and hence the slope of the active force depend on the Ca^{2+} concentration. If this slope is more steep, than the stiffness of the series elasticity (at high Ca^{2+} concentration), some regions of the force-extension curve become unstable. This can occasionally result in the

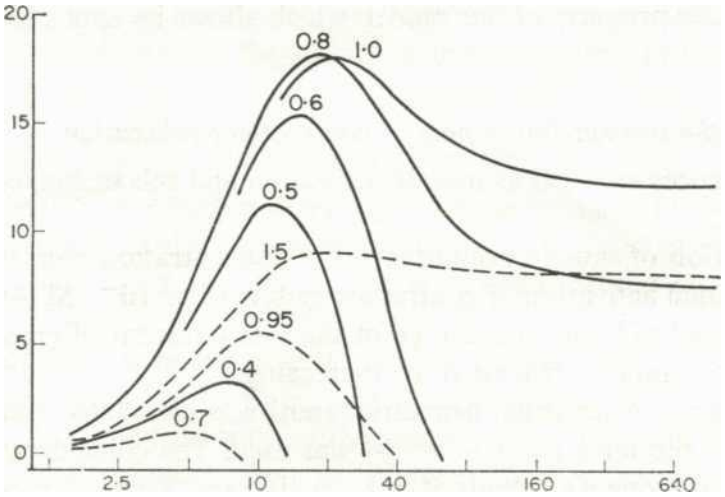

FIG. 8. DEPENDENCE OF POWER OUTPUT OF INSECT FLIGHT MUSCLE UPON THE FREQUENCY OF DRIVEN OSCILLATIONS, CALCULATED FROM EQUATION (46) AT $\gamma = 1$.
Solid curves: $q = 4$; dashed curves: $q = 2$; the magnitudes of β are shown near the curves.

jump-like shortening some of the sarcomeres at the expense of the lengthening of the series elasticity: the mean tension will rise and the operating point shift in the nonlinear region of $\alpha(l)$. The probability of such a process increases when the muscle is pre-stretched, as at the rest length *A*-filaments are against *Z*-lines. Large amplitudes and high frequencies of oscillations also must facilitate asynchronous jump-like redistributions of the sarcomeres lengths, i.e. cause "high tension" state.

It should be noted that rigorous treatment of this state is probably not possible in terms of the stiff-filaments model.

(6) The model gives reasonable values power output, ω_m and ω_o, even though it is oversimplified.

4. GENERAL POINTS OF THE THEORY

Mechanochemical feedback

It appears not so strange that the simplest two-filament's model gives all the essential contractile properties of whole striated muscle, because filaments and sarcomeres all behave identically at contraction. But the source of such behaviour is not itself evident. Moreover, the state in which all sarcomeres are equal in length seems to be unstable, when prestretched muscle is contracting isometrically, because the force of a sarcomere increases with its shortening [7]. But this instability does not usually show itself.

Some properties of the model under consideration allow us to explain this fact. If a sarcomere develops the force, exceeding the mean level, the speed of its shortening and hence the transition of the *M*'s from pulling state (b) to hindering one (c) increases. This latter results in the force and the velocity of contraction falling up to the mean level. If some sarcomere is stretched its force increases due to the transition of the *M*'s in the superpulling state (d). This mechanism may be regarded as a negative feedback on the tension.

If the sarcomeres were all equal in length before contraction, then this mechanism is able to synchronize their length changes during usual contraction time.

It is evident that this feedback originates from the interaction of thick and thin filaments and makes possible the stabilization of thick filament in the middle part of sarcomere during

contraction. It is this property of our model which allows its application to the contraction of whole muscle.

Generalization of the theory: Initial part of contraction; relaxation

The transient processes such as muscle activation and relaxation, can be included in the presented scheme.

After the initiation of muscle excitation Ca^{2+} concentration rises up to a level which is sufficient for maximal activation of contractile system (5×10^{-7} M [41]), in 5–10 msec [29]. It means that instead of jump-like change of the rate constant of cross-links formation we should consider the smooth process of its increasing.

This had been done when usual isometric tetani was calculated (see Fig. 5). In equation (13) instead of K_1 the term $K_1(1 - e^{-t/t_0})$ was used. The coincidence of calculated curve with the experimental one was obtained at t_0 = 10 msec. This value being close to the time of Ca-ions emergence means that activation of contractile system by Ca^{2+} is a fast process as compared with the contraction. It is this circumstance, which allows us to ignore the specific nature of this process in our consideration.

Stimulation being over, Ca^{2+} concentration and, hence, the rate constant of cross-links formation fall to zero. This does not result in the muscle relaxation in our scheme, as far as we assume, that the pulling *M*'s in state (b) have no opportunity to split. But rather small value of rate constant of transition from (b) to (a), $K' = 7$ 1/sec, is sufficient to obtain reasonable time of muscle relaxation at 0°C (150 msec [4]). The term $K'n$, included for this purpose in equation (13), plays an important role only when other rate constants in this equation (K_1 and $K_{-1}\nu$) get small. This means that for activated muscle the splitting of the pulling *M*'s in state (b) may be neglected as slow process. It should be noted that the transition of the *M*'s from state (b) into (a) may not be so slow in flight muscles.

The foregoing generalization may give clearer insight into time limits of the theory. In general form this may be explained as follows. Let all processes, bearing on the muscle contraction, be described by the next set of equations:

$$\epsilon \frac{d\tau}{d\tau} = \mathbf{f}(\tau, \mathbf{u}, \mathbf{s}) \qquad \text{(x)}$$

$$\frac{d\mathbf{u}}{d\tau} = \mathbf{s}(\tau, \mathbf{u}, \mathbf{s}) \qquad \text{(xx)}$$

$$\frac{d\mathbf{s}}{d\tau} = \epsilon \Psi(\tau, \mathbf{u}, \mathbf{s}) \qquad \text{(xxx)}$$

where $\epsilon << 1$ and mechanochemical variables are denoted as **u.** For the times of order 1 the approximation $\epsilon = 0$ is true. In this case the "slow" variables, $\mathbf{s} = \mathbf{s}_0$, are constant and the "fast" ones τ, can be determined from the quasi-stationary equations $\mathbf{f}(\tau_q, \mathbf{u}, \mathbf{s}_0) = 0$, so that the mechanochemical equations (xx) can be treated as the exclusive system, in which "fast" and "slow" processes are included only as some effective parameters.

If muscle behaviour on the small or large times is of interest the additional equations should be taken into consideration. For example, the simulation of muscle excitation must involve the equations for Ca^{2+} release from sarcoplasmic reticulum, its diffusion to

contractile system, reaction with the receptor sites and maybe some other processes. Our method of the generalization of the theory is less valid, but probably more effective at present.

Muscle as the mechanochemical quasi-crystalloid system

The whole elementary working cycle of myosin cross-bridge is probably not reversible, as it is coupled with the hydrolysis of ATP molecule. One stage of this cycle, namely, the transition from pulling to hindering state is not possible without mechanical movement of the filaments.

The first stage of this movement is active: the bridge, being in the state of conformational rearrangement, develops positive force, which results in the filament sliding. The second stage of the movement, the transition of the bridge in the hindering state and the cross-link splitting is passive and originates from the filament's sliding, i.e. this state is performed at the expense of positive work of the other cross-bridges, which are in the pulling state. So, the mechanical connection between active sites, i.e. "crystalloid" organization of contractile system, makes possible to use the energy of ATP hydrolysis for the lowering of the activation barrier of this reaction.

This mechanism is probably responsible for high ATP-ase activity of actomyosin and may be applicable to some other enzyme's complexes. Protein oligomeres can be able to use the energy, which is liberated at one of the active sites during the exothermic stage of the reaction, in the endothermic stage of this reaction at the adjacent active site. We assume, that regulation of fermental activity is based on this physical mechanism. The kinetical aspects of the mechanism of such type are regarded in general form in [42].

In our model "chemical" equations for the cross-links formation and splitting are dependent on the "mechanical" variables. Probably such property must be inherent to any mechanochemical system.

The field and the limits of application of the theory

Within the range of our model contractile properties of striated muscles are derived from its structural organization under some assumptions about myosin cross-bridges cyclic action.

Well known properties of striated muscle are given quantitatively: Hill's equations follow irom the theory automatically and precisely, calculated rates of force development and redevelopment after quick release coincide with experimental data, the theory accounts for selfoscillations of insect flight muscles.

The theory permits one to predict some new facts, for instance, self-oscillations of force, developed by commonly employed frog sartorius under isotonic conditions, the generalization of Hill's equation to stretched muscle isotonic contraction.

Two circumstances should be remembered in an experimental check. Firstly, the theory is applicable to the muscle portion, in which all sarcomeres have approximately the same length, secondly, in the present calculations of skeletal muscle self-oscillations we did not take into consideration its passive elasticities. Neglect of series elasticity must result in the overestimation of calculated frequency of oscillations. Parallel elasticity can disturb isotonic conditions for a contractile system at high extension of muscle.

Experimental check of the consequences of the theory probably results in the refinement of the parameters of the model. The foregoing estimation of the parameters (section 2) gives accurately only three combinations of the five parameters, which enter into Hill's equation.

Absolute values of the parameters are determined with a small accuracy (about 300 per cent). There exist sharply unstationary regimes of contraction, which give the opportunity to determine the absolute values of the parameters more accurately. The constant K_{-1} is of particular interest, as the value of conformational rearrangement of myosin molecule is determined through it and probably cannot be measured directly at the present.

The assumptions, on which the theory is based, do not concretize the nature of the processes, which result in muscle contraction. Integral action of these processes is regarded as cross-bridges formation, movement and disruption. The investigation of the parameter's dependence upon external conditions (such as temperature and chemical constitution of environment) can give an additional information on the nature of these processes.

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