
SIMULATION OF THE HILL EQUATION FOR FIBER SKELETAL MUSCLE CONTRACTION

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The experimental dependence “velocity – force” for the single fibre skeletal muscle contraction under isometric conditions is well described by the modified Hill equation which was obtained within the framework of a dynamical model of muscle contraction proposed earlier. The mechanism of appearance of the inflection point on this curve is discussed in detail.

1. Introduction

Muscle, as a complex biophysical system, attracts attention of many researchers. This is conditioned mainly by newly obtained experimental data [1–5] on the muscle contraction, in particular, on the dependence between a force which is developed by a skeletal muscle fiber under load and its length, velocity, and other physical parameters under action of the electric stimulation. However, the obtained experimental results did not quite match the postulates of a skeletal muscle contraction model known as the theory of sliding [6]. Therefore, the actual problem is to explain these experimental facts with the use of, first of all, the correct mechanism of contraction and, second, the adequate mathematical description within the well-known theoretical models (for example, by using the classical Hill equation [6]). The solution of this problem is very important for constructing the final theory of muscle contraction on the basis of unified approaches and developed principles.

In the present work, the dependence of the velocity of isotonic contraction of a single fiber skeletal muscle on the force of contraction under isometric conditions

was simulated using the results of previous biophysical experiments [1,3] and theoretical studies on the muscle contraction [7]. The behavior of this curve was analyzed in detail within the framework of the mechanism of muscle contraction [8].

2. Model: Results and Discussion

The dependence between the velocity of muscle contraction v and the isotonic force (stress) P applied to it under the isometric and isothermal conditions is described by the well-known empirical Hill equation [6]

$$v(P) = b \frac{P_0 - P}{P + a}, \quad (1)$$

where P_0 is the maximum value of the isometric muscular force; and b and a are constants which have the dimension of velocity and force, respectively.

If $P = 0$, the velocity of isotonic contraction reaches its maximum value:

$$v(0) = v_{\max} = \frac{bP_0}{a} \Rightarrow b = \frac{a}{P_0} v_{\max}. \quad (2)$$

On the contrary, if $P = P_0$, then $v(P_0) = 0$.

As a result, the classical Hill equation (1) can be rewritten as

$$v(P) = \frac{a}{P_0} v_{\max} \frac{P_0 - P}{P + a}. \quad (3)$$

It is certainly impossible to measure the instantaneous velocity value, and therefore the velocity in formula (1) is the average rate of contraction for some

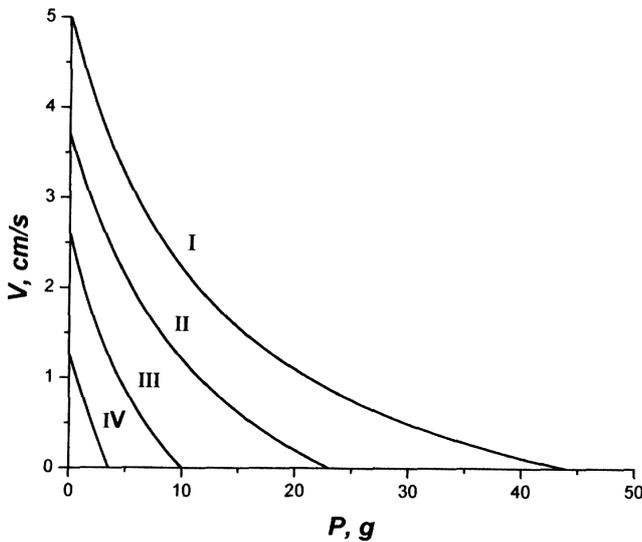


Fig. 1. Dependences of the contraction velocity on the force at different stages of isotonic contraction of a frog skeletal muscle at 0 °C [9]. Curve I is the graph of the excitation phase; curves II, III, and IV are the graphs of relaxation phases at different moments of time: II – in 460 ms, III – in 640 and IV – in 830

period of time t . According to one of the determinations, the mean velocity is determined by a formula

$$v(t) = \langle a(t) \rangle \cdot t, \tag{4}$$

where $\langle a(t) \rangle$ is the mean value of acceleration at the time moment t . The acceleration is determined by the obvious equality

$$a(t) = \ddot{l}(t), \tag{5}$$

where $l(t)$ is the length of a fiber determined by the dynamics of isotonic compression of a skeletal muscle within the framework of the model [7]:

$$l(t) = l_0 \left[1 + 0,4 \sqrt{1 - \frac{Q_0}{f_0} \left(1 - \frac{3}{\text{ch}^2 \alpha (t - t_0)} \right)} \right]. \tag{6}$$

Here, $l_0 = 2.5 \mu\text{m}$ is the initial length of a sarcomere, $Q_0 = Q + q$ is the constant of the total passive force, Q is the force, caused by the strain which varies by depending on a change of the muscle length l , and q is the internal resistance force of a muscle. Thus, the forces Q and q act as resistant forces to a contraction, by neutralizing it, $\alpha^2 = \frac{1.46 f_0}{M l_0} \sqrt{1 - \frac{Q_0}{f_0}}$, where M is the effective mass of the forces of resistance, $f_0 = \frac{kT}{l_0}$ is a parameter which has the dimension of force and can be equal to the maximum force or proportional to it, k is the Boltzmann constant,

T is the temperature, and t_0 is the characteristic time of the dynamics of compression: at the point $t = t_0$, the value of muscle contraction is maximum.

Supposing $Q_0 = Mg$ and by substituting (6) in formula (5) and then in (4), we get

$$v(t) = b(t) \frac{P_0 - P}{P + a}, \tag{7}$$

where

$$b(t) \equiv 3,5gt \left(\frac{3}{\text{ch}^4 \alpha (t - t_0)} - \frac{2}{\text{ch}^2 \alpha (t - t_0)} \right), \tag{8}$$

$$P_0 \equiv f_0 - q, \tag{9}$$

$$P \equiv Q, \tag{10}$$

$$a \equiv q. \tag{11}$$

It is obvious that formula (7) coincides with the classical Hill equation (1) with designations (8)–(11) which give possibility to explain the physical sense of the parameters a and b . According to (11), a equals the proper resistance force of a muscle, q . Knowing [7] that the maximum possible force of a muscle is $P_0 = 0.8f_0 = f_0 - q$, we get $q = 0.2f_0 = 0.25P_0 = a$. The estimated value of a coincides with the experimental result for a frog skeletal muscle obtained by Hill [6].

The only distinction between formula (7) and the classical Hill equation (1) consists in that the theoretically obtained coefficient $b(t)$ depends on time. But if we look at Fig. 1 (the experimental data [9]), we see that the coefficient b for curves II, III, and IV, which correspond to the relaxation phase at different moments of time, is smaller than that for curve I which is related to the phase of excitation. Indeed, according to formula (8), the coefficient $b(t)$ is less at the end of the relaxation phase $(t_0 < t \leq t_0 + \frac{1}{\alpha} \text{arch}(\sqrt{3/2}))$, than it is at the end of the excitation phase $(0 \ll t < t_0)$.

Finally, taking the equality $a = 0.25P_0$ into account, we reduce Eq. (3) to

$$v(P) = 0.25v_{\text{max}} \frac{P_0 - P}{P + 0.25P_0}. \tag{12}$$

On the other hand, when analyzing the dependence “velocity – force” for the skeletal muscle contraction, it’s important to consider the results of previous works [1, 3]: when $v = v_{\text{inf}}$, a certain point P_{inf} divides this curve into two regions with different curvatures (Fig.

2). These regions make about (0–78) and (78–100)%, respectively, of the value P_0 [1]. In general, we can say that the continuous transition between these two regions of the “velocity – force” curve can be considered as the inflection point with $P_{inf} \approx 0.78P_0$.

According to the dynamical model [7], the coefficient $b(t)$ is implicitly dependent on the force P (in particular, this follows from the definition of the parameter α). For some moment (for example, when $b = b_{max}$), formula (7) can be represented as

$$v(P) = b(P) \frac{P_0 - P}{P + 0.25P_0}. \quad (13)$$

The inflection point P_{inf} of function (13) satisfies the condition $v''(P_{inf}) = 0$. However, we cannot analytically solve this equation because the dependence $b(P)$ is unknown in the general case. By applying both analytical and numerical simulations to the experimental data [1], we approximate this dependence by the expression

$$b(P) = 0.25v_{max}\tilde{b}(P), \quad (14)$$

where

$$\tilde{b}(P) = \frac{1 + 9P}{1 + e^{\beta(P - P_{inf})}}. \quad (15)$$

Here, $\beta = 180N^{-1}$ is a fitting parameter which describes the rate of force deceleration in the investigated region.

As a result, we get a modified Hill equation

$$v(P) = 0.25v_{max} \frac{1 + 9P}{1 + e^{\alpha(P - P_{inf})}} \frac{P_0 - P}{P + 0.25P_0}. \quad (16)$$

Thus, to plot dependence (16), one should have only two parameters: the maximum values of isotonic contraction velocity v_{max} and isometric force P_0 which are obtained experimentally.

The modified Hill equation (16) describing the experimental dependence “velocity – force” for the muscle contraction has the inflection point close to $P = P_{inf}$ due to the exponential function. Beginning from this point, i.e. in the region of the large loads $P_{inf} < P \leq P_0$, the exponential coefficient in Eq. (16) substantially influences the behavior of the $v(P)$ function, by sharply changing its curvature. The obtained result testifies to the limitedness of the application of the classical Hill equation (12) in the study of the dependence “velocity – force” for the muscle contraction. In particular, it is correct only in the region of the high loads – small

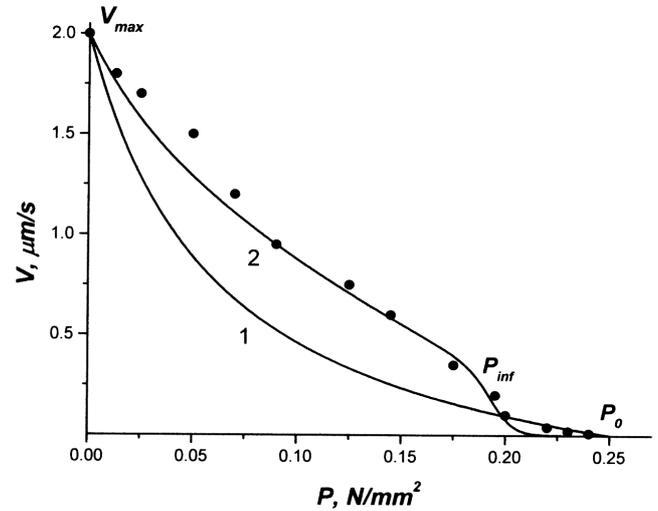


Fig. 2. Dependences “velocity – force” (per unit cross-section area of a muscle) of contraction of a single fibre skeletal muscle of frog under isometric conditions (the length of sarcomere is $L = 2.1 \mu\text{m}$): solid curves 1 and 2 are theoretically calculated by the formulas (12) (the classical Hill equation) and (16) (the modified Hill equation), accordingly; • – experimental data [1]

velocities: $P_{inf} < P \leq P_0$ (Fig. 2). On the contrary, the modified Hill equation (16) allows us to reproduce quite well the behavior of the experimental curve $v(P)$ [1] (dots in Fig. 2) in the whole investigated region (curve 2 in Fig. 2).

One of possible explanations of the presence of the inflection point on the curve “velocity – force” is caused by the fact that the process of contraction consists of two simultaneous processes – the contraction by itself and the resilient twisting of myosin filaments [8]. In other words, the work of heads in a myosin molecule is used for the realization of both these processes. It is understandable that a considerably less energy is spent on the resilient twisting of a filament than that for the contraction itself. At small loadings (to 78% from P_0), the resilient twisting does not influence substantially the dependence of “force – speed” (Fig. 2). At large loadings on a muscular fiber, myosin heads which work asynchronously on the traditional consideration have not enough energies for the realization of compression and resilient twisting. Thus, the heads in a myosin molecule work not independently, but with the specific synchronization. This statement is logical, because the effort of one head is insufficient in order to displace one myosin filament by the specific value equal to a working stroke, and the common effort of some specific number of heads is necessary. This is testified by the experimentally discovered stepped contraction of muscles [2]. Thus, for

large loadings, the offered nature of contraction results in increasing the time necessary for the simultaneous realization of the contraction and the resilient twisting, which leads, consequently, to the appearance of the inflection point on the experimentally obtained curve “velocity – force” (Fig. 2). The partial mechanical strain of a myosin filament as a result of the tension due to both the excitation and the action of a large load can be another possible reason for the inflection point to appear on the curve “velocity – force” under muscle contraction.

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МОДЕЛЮВАННЯ РІВНЯННЯ ХІЛЛА ДЛЯ СКОРОЧЕННЯ ВОЛОКНА СКЕЛЕТНОГО М'ЯЗА

А.Д. Супрун, А.М. Шут, Ю.І. Прилуцький

Резюме

Проведено теоретичне описання експериментальної залежності “сила–швидкість” поодинокого скорочення скелетного м'язового волокна в ізометричних умовах за допомогою модифікованого рівняння Хілла, яке було одержане в рамках динамічної моделі скорочення м'яза, запропонованої раніше. Детально обговорюється механізм появи точки перегину на цій кривій.