A PHENOMENOLOGICAL THEORY OF MUSCULAR CONTRACTION

II. Generalized Length Variations

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ABSTRACT In part I of this series, the theory of irreversible thermodynamics was applied to the sliding filament model to obtain rate equations for a contracting muscle at the *in situ* length l_o. In this paper we extend the theory to include length variations derived from the sliding filament model of contracting muscle using the work of Gordon, Huxley, and Julian (1). Accepting the validity of Hill's force-velocity relation (2) at the *in situ* length, we show that Hill's equation is valid for any length provided that the values of the parameters, a, b, and V_m vary with length as derived herein. The predicted variation with length of the velocity for a lightly loaded isotonic contraction is shown to agree well with that measured by Gordon, Huxley, and Julian (1). Chemical rates are derived as functions of length using parameters that can be obtained experimentally.

INTRODUCTION

Many measurable quantities important in muscle physiology vary significantly as the length of the muscle changes. The variation of most of these quantities can be interpreted in light of the sliding filament model of contracting muscle. However, the variation of the parameters in Hill's force-velocity relation (a, b, and V_m) have not been directly related to the sliding filament theory. In this paper we accept the validity of Hill's force-velocity relation (2) at the *in situ* length and relate the variation of a, b, and V_m to the length-tension curve and the ultrastructure of the sarcomere. This development is based on the sliding filament theory; in particular, it is independent of the theory developed in part I of this series. Thus, it can be applied not only to the theory developed in part I, but also to Caplan's theory (3–5) or other theories of muscular contraction which are consistent with the sliding filament model and Hill's force-velocity relation.

If these theoretical length variations are incorporated with chemical rate equations, then the equations can be integrated with respect to length. In this way the theoretical predictions can be directly compared to experimental chemical data. In a recent paper (6) we integrated Caplan's chemical rate equations and compared the results to chemical data. This integration was based on specific assumptions concerning the length variation of certain combinations of the transport coefficients. In the Appendix these assumptions are shown to be essentially correct but some modifications are required. Also, in reference 6 we fit Hill's force-velocity equation to average data assuming a/P_o to be 0.25 for rectus abdominis muscle. But, this procedure is questionable in light of the length variations presented herein and will be discussed later.

The procedure here will be: first, to develop the generalized length variation; second, to compare these results to the experimental data of Gordon, Huxley, and Julian (1); and third, to apply the length variations to the theory in part I of this series and to Caplan's theory.

GENERALIZED MECHANICAL LENGTH VARIATIONS

It is well known that the length-tension curve has a maximum near its *in situ* length, l_o. This phenomenon is simply explained by the sliding filament theory since the number of cross bridges physically capable of a connection is reduced for lengths longer than or shorter than l_o. This explanation of the length-tension curve requires that the total force developed by the contractile mechanism, P_s, is the sum of the forces developed by the cross bridges. Thus, as in part I of this series, we write

$$P_s = nP_i, \tag{1}$$

where n denotes the number of activated bridges and P_i denotes the average force developed by the activated bridges. The variation of n with length can be approximately determined from the ultrastructure of the muscle.

Gordon, Huxley, and Julian (1) compared equation 1 to their experimental length-tension data and concluded that the external force developed by the muscle, P_e, was less than the intrinsic force produced by the contractile mechanism, P_s, for lengths less than l_o. In order to reconcile their experimental length-tension curve with the sliding filament theory, Gordon, Huxley, and Julian (1) postulated an internal resistance, P_r, at lengths less than l_o. We can express this concept as

$$P_e = P_s - P_r, \tag{2}$$

which simply says that the external force P_e is equal to the force generated by the contractile mechanism P_s minus the internal force P_r.

The theoretical development which follows is based on four major assumptions:

(*a*) The sliding filament theory as expressed by equation 1 is valid.

(*b*) Hill's force-velocity relation is valid at the *in situ* length l_o.

(*c*) The number of activated cross bridges varies with length as described by

Gordon, Huxley, and Julian (1) and *this variation* is independent of velocity or load.

(*d*) As described by Gordon, Huxley, and Julian (1), internal forces P_r which oppose the intrinsic force P_s developed by the contractile mechanism may exist in the muscle for lengths less than l_o and are zero for lengths equal to or greater than l_o. In addition, we assume that P_r is not a function of force or velocity.

These assumptions will be elaborated on in the following development.

We will first derive the characteristics for the basic contractile mechanism and then relate these characteristics to the external force P_e using equation 2.

Force-Velocity Relation for Intrinsic Contractile Mechanism

As stated in assumption (*c*), the variation of n with length is independent of the variation of n with velocity or load. This assumption can be expressed as

$$n = f(l)g(V). \tag{3}$$

The function $f(l)$, which is a function of length only, gives the variation in the number of available bridges with length, whereas $g(V)$, which is a function of velocity only, gives the fraction of these available bridges that are activated. It hould be noted that $g(V)$ could be a constant, indeed it is constant for Caplan's heory.

Combining equations 1 and 3 yields

$$P_s = f(l)g(V)P_i(V), \tag{4}$$

where the notation $P_i(V)$ is used to emphasize the fact that the force developed by a cross bridge is a function of velocity, V. No distinction is made between V and the velocity of a cross bridge, V_i, since they are equal (see equation 7 of part I of this series). The generality of equation 4 will be illustrated by several examples. For the theory developed in part I of this series, the $P_i(V)$ is a linear function of velocity (see equation 4 of part I). For Caplan's theory (4, 5) the $P_i(V)$ is a nonlinear function of velocity since the local value of the chemical affinity is adjusted by a regulator. For A. F. Huxley's theory (7) the $P_i(V)$ is determined from a mechanistic model of the cross bridges. The $g(V)$ for both Caplan's theory and Huxley's theory is constant, whereas, for the theory developed in part I the $g(V)$ gives the velocity variation of the activated cross bridges (see equation 18 of part I). The $f(l)$ for all three theories represents the length variation of the available cross bridges and can be obtained from the ultrastructure of the muscle.

Equation 4 is valid for any length and in particular at l_o is

$$P_s^{l_o} = f(l_o)g(V)P_i(V), \tag{5}$$

where the superscript l_o denotes a quantity evaluated at the *in situ* length. Equation 5 is an implicit relation between force and velocity at l_0. An explicit relation between force and velocity is Hill's force-velocity relation which we assume to be valid at l_o. Thus we write

$$P_s^{l_o} = a^{l_o}\frac{V_m^{l_o} - V}{b^{l_o} + V}. \tag{6}$$

Although Hill's equation relates the external force to the velocity, the symbol $P_s^{l_o}$ may be used since at l_o the intrinsic force, $P_s^{l_o}$, is equal to the external force $P_e^{l_o}$.

Combining equations 5 and 6 yields

$$g(V)P_i(V) = \frac{a^{l_o}}{f(l_o)}\frac{V_m^{l_o} - V}{b^{l_o} + V}. \tag{7}$$

We obtain the desired result by substituting $g(V)P_i(V)$ from equation 7 into equation 4:

$$P_s^l = a^{l_o}\frac{f(l)}{f(l_o)}\frac{V_m^{l_o} - V}{b^{l_o} + V}. \tag{8}$$

Equation 8 is the force-velocity relation for the intrinsic contractile mechanism and is valid for any length. From a comparison of equation 8 with Hill's force-velocity relation it follows that

$$a_s^l = a^{l_o}\frac{f(l)}{f(l_o)}, \tag{9}$$

where the parameter a ordinarily appearing in Hill's equation has been denoted as a_s^l in order to emphasize that it is characteristic of the intrinsic contractile mechanism and that it is a function of length. It is clear from equation 8 that the parameters b and V_m ordinarily appearing in Hill's equation are indepedent of length and are equal to b^{l_o} and $V_m^{l_o}$, respectively. It should be realized that at any given length the maximum velocity of the whole muscle V_{me}^l occurs at zero external force ($P_e^l = 0$) and not when P_s^l is zero. Therefore, in general, V_{me}^l will be less than $V_m^{l_o}$ (the velocity when $P_s^l = 0$) because when P_e^l is zero, the intrinsic force P_s^l is greater than zero. However, at l_o the resistive force P_r is zero and therefore at l_o the observed maximum velocity, $V_{me}^{l_o}$, is equal to the intrinsic maximum velocity $V_m^{l_o}$.

As described by Gordon, Huxley, and Julian (1), the quantity $f(l)/f(l_o)$ can be determined as a function of length from the sliding filament theory. The continuous line on Fig. 1 gives $f(l)/f(l_o)$, which is denoted as F_l, as a function of l/l_o. This curve was determined directly from the dimensions of the ultrastructure given in Fig. 14 of a paper by Gordon, Huxley, and Julian (1), where the length of the bare region on the thick filament (denoted as c in reference 1) was taken to be the average value, 0.175 μ. The *in situ* length l_o was taken as 2.225 μ.

The numbered arrows on our Fig. 1 correspond to the six critical stages of overlap

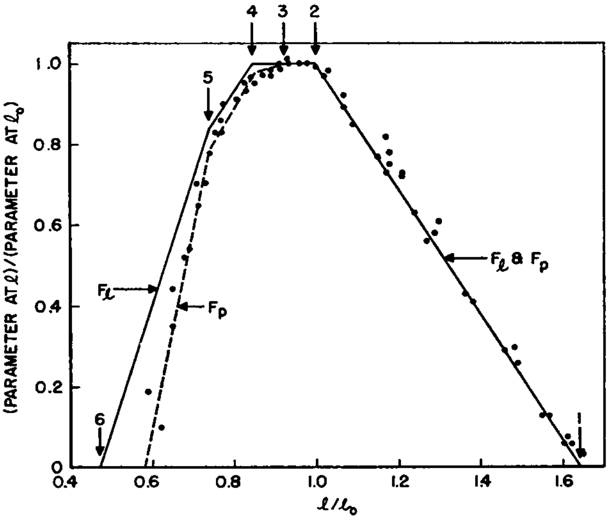


FIGURE 1 Length dependency of available cross bridges, curve labeled F_l, and isometric external load, curve labeled F_p. Force data points and sarcomere dimension for F_l curve taken from Gordon, Huxley, and Julian (1). Coordinates of break points listed as $(l/l_o, F_p, F_l)$: (1.64, 0, 0), (1.0, 1.0, 1.0), (0.921, 1.0, 1.0), (0.843, 0.98, 1.0), (0.741, 0.785, 0.84), (0.580, 0, —), (0.472, —, 0).

between the thick and thin filaments as the sarcomere changes length. These numbers correspond to the numbers on Fig. 14 in reference 1. In the region 2 to 1, the number of available bridges decreases due to the reduction of the overlap of the thick and thin filaments. In the regions 2 to 4, no change in the number of available bridges occurs because the overlap of the thin filaments occurs over the bare region in the center of the thick filament. In going from 4 to 5, the number of available bridges decreases because the thin filaments from the opposite side of the bare region are assumed to cause a complete interference of the bridges. In the region 5 to 6, an additional reduction is caused by the crushing of the thick filaments against the *z*-line.

The various data points shown on Fig. 1 are normalized length-tension data which were obtained by Gordon, Huxley, and Julian (1) from single fibers of frog striated muscle, where they took special precautions to insure uniformity of sarcomere length.

The theoretical intrinsic isometric force variation with length, P_{os}^{l}, can readily be obtained from equation 8 by setting V equal to zero and using the relation

$$b^{l_o}/V_m^{l_o} = a^{l_o}/P_{os}^{l_o}. \qquad (10)$$

The result is

$$\frac{P_{os}^{l}}{P_{os}^{l_o}} = \frac{f(l)}{f(l_o)} \equiv F_l \qquad (11)$$

which indicates that the normalized intrinsic length-tension curve should be identical with the F_l curve. If the external length-tension curve also coincides with the F_l curve, then the internal forces P_r must be negligible. For lengths near l_o and longer than l_o, the data points for the external force shown on Fig. 1 coincide quite well with the F_l curve which implies that the internal forces P_r are negligible in this region. For lengths less than l_o the data lie below the F_l curve, suggesting that the internal forces P_r are significant in this region. These conclusions concerning P_r were previously deduced by Gordon, Huxley, and Julian (1).

Force-Velocity Relation for External Load

With assumption (*d*) that P_r is independent of velocity or load, we can express our results in terms of the external force P_e. From equation 2 and the fact that at l_o

$$P_{oe}^{l_o} = P_{os}^{l_o}, \tag{12}$$

it follows for the isometric case that

$$\frac{P_r^l}{P_{oe}^{l_o}} = \frac{P_{os}^l}{P_{os}^{l_o}} - \frac{P_{oe}^l}{P_{oe}^{l_o}}, \tag{13}$$

where the subscript o is not required on P_r^l since P_r^l is assumed to be independent of velocity or load and again the superscript l denotes the quantity at the length l. For convenience we use the definition of F_l, equation 11, and define the normalized length-tension curve as

$$F_p \equiv \frac{P_{oe}^l}{P_{oe}^{l_o}}. \tag{14}$$

Thus, it follows from equation 13 that

$$\frac{P_r^l}{P_{oe}^{l_o}} = F_l - F_p. \tag{15}$$

Solving equation 2 for P_s, substituting for P_r from equation 15, and normalizing, we obtain

$$\frac{P_s^l}{P_{os}^{l_o}} = \frac{P_e^l}{P_{eo}^{l_o}} + F_l - F_p. \tag{16}$$

Equation 16 relates the intrinsic force P_s^l to the external force P_e^l in terms of F_l and F_p, both of which can be estimated as functions of length from experimental observations. Equation 16 can be used to replace P_s^l in favor of P_e^l in equation 8. The resulting equation is then solved for P_e^l and algebraically arranged to show its similarity to Hill's force-velocity relation. The result is

$$P_e^l = P_{oe}^{l_o}\left[F_l\left(1+\frac{b^{l_o}}{V_m^{l_o}}\right)-F_p\right]\frac{\left\{F_p b^{l_o}\Big/\left[F_l\left(1+\frac{b^{l_o}}{V_m^{l_o}}\right)-F_p\right]\right\}-V}{b^{l_o}+V}. \tag{17}$$

Equation 17 represents the appropriate Hill's force-velocity relation for the external force at any length if the parameters usually appearing in Hill's equation are defined as follows:

$$a_e^l \equiv P_{oe}^{l_o}\left[F_l\left(1+\frac{b^{l_o}}{V_m^{l_o}}\right)-F_p\right] \tag{18}$$

and

$$V_{me}^l \equiv F_p b^{l_o}\Big/\left[F_l\left(1+\frac{b^{l_o}}{V_m^{l_o}}\right)-F_p\right], \tag{19}$$

where the subscript *e* denotes parameters used in a Hill's equation which is in terms of the external force P_e^l. It follows from definitions 18 and 19 and equation 17 that

$$P_e^l = a_e^l\,\frac{V_{me}^l - V}{b^{l_o}+V}. \tag{20}$$

Thus, it is concluded that Hill's force-velocity relation is valid even in terms of the external force at any length if a_e^l and V_{me}^l are taken to be functions of length as described by equations 18 and 19. The parameter b is the only one which, in general, remains constant with length.

In order to calculate the length variations of the various quantities it is necessary to know F_l and F_p as functions of length. The values of F_l and F_p which are used in the following calculations are shown in Fig. 1 by the continuous curve and the interrupted curve, respectively. For lengths greater than l_o, the F_p is taken to be equal to F_l. The interrupted line on Fig. 1 was chosen to fit the data and to have break points consistent with the critical stages of overlap indicated by the numbered arrows. The dot-dash line in Fig. 2 shows a plot of the maximum velocity of the muscle V_{me}^l, normalized with the maximum velocity at l_o, as calculated from equation 19. Also shown on Fig. 2 are the F_l and F_p curves which were used for the calculation and are the same as on Fig. 1. The value of the parameter $b^{l_o}/V_m^{l_o}$ (which is equal to $a_e^{l_o}/P_{oe}^{l_o}$) used in the calculation was 0.25. The reduction in the maximum velocity at lengths less than l_o is due to the internal resistance load P_r^l as discussed previously. At lengths greater than l_o the maximum velocity is constant since P_r^l is zero in this region. This result was concluded by Gordon, Huxley, and Julian (1) from their experimental data. A quantitative comparison can be made with their experimental velocity data which was measured at various lengths with a constant load of 0.06 $P_{oe}^{l_o}$. This value of the normalized load was substituted into equation 17 and the normalized velocity was calculated as a function of length using the same values for

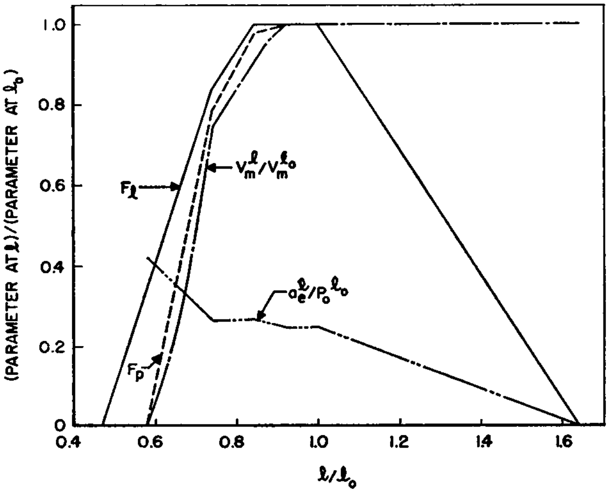


FIGURE 2 Theoretical length dependency of normalized maximum velocity $V_m{}^l/V_m^{ol}$ calculated from equation 19. Also shown is the theoretical length dependency of Hill's force parameter $a_e^l/P_o^{l_o}$ as calculated from equation 18. The F_l and F_p curves repeated from Fig. 1 for orientation.

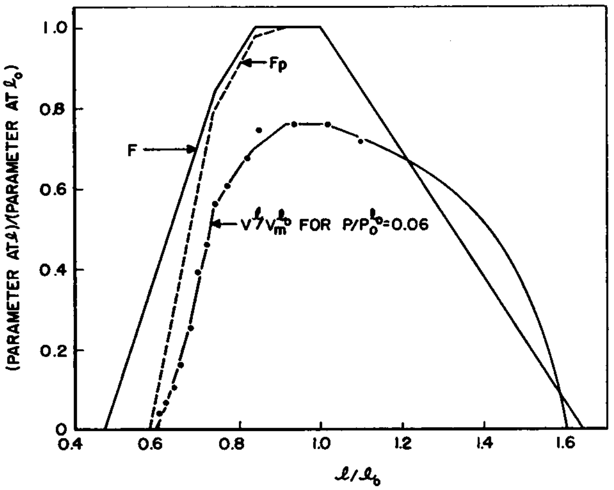


FIGURE 3 Comparison of theoretical normalized lightly loaded isotonic velocity with experimental data for $P/P_o^{l_o} = 0.06$. The curve is calculated from equation 17 with $b^{l_o}/V_m^{l_o} = 0.25$ and the solid circles are data from Gordon, Huxley, and Julian (1). The F_l and F_p curves repeated from Fig. 1 for orientation.

F_l, F_p and $b^{l_o}/V_m^{l_o}$ as in the previous calculation. The result of this calculation is compared to the velocity data of Gordon, Huxley, and Julian (1) on Fig. 3. Since we normalized their velocity data the theoretical curve is forced to fit the data point near l_o. The calculated velocity is quite sensitive to the value of F_p used and therefore the

F_p (the dashed line on Figs. 1–3) was chosen with both the force data and velocity data in mind, while maintaining the break points at the numbered arrows. As can be seen from Figs. 1 and 3, this procedure resulted in satisfactory fits to both the force and velocity data. An almost perfect fit is obtained for both the force and velocity, if the F_l curve is allowed to decrease in the region from 3 to 4. This is not presented since we could not justify such a reduction in F_l from the ultrastructure of the muscle.

The variation in $a_e^l/P_{oe}^{l_o}$ with length can be directly calculated from equation 18 and is shown on Fig. 2. Matsumoto (8) concluded from experimental data that Hill's force-velocity relation is valid for *Rana pipiens* sartorius muscles at lengths less than l_o with both a and b constant with length. The maximum shortening investigated by Matsumoto (8) was only 25% of l_o. In this region ($0.75 \leqq l/l_o \leqq 1$), as indicated by Fig. 2, the theoretically predicted value of a varies less than 8%. The F_l and F_p curves used in our calculations are for striation spacings that are uniform. For a whole muscle this is obviously not true; however, it is interesting that the theoretical results are qualitatively consistent with the experimental data of Matsumoto (8).

CHEMICAL RATES INCLUDING LENGTH VARIATIONS

The chemical rate equations can be derived as a function of length by using the theory developed above in conjunction with the phenomenological equations, equations 10 and 11 of part I:

$$V = \frac{L_{11}^i}{n^l}(-P_s^l) + L_{12}^i A \qquad (21)$$

and

$$v^l = L_{21}^i(-P_s^l) + n^l L_{22}^i A. \qquad (22)$$

Equations 21 and 22 are valid for any length if P_s^l refers to the intrinsic force developed by the contractile mechanism and if the number of activated bridges n^l includes length variations. The transport coefficients which are characteristic of the basic subunit, as well as the chemical affinity A, are independent of length. Again the superscript l is included to emphasize quantities that are functions of length.

Solving equation 21 for A and substituting into equation 22, we obtain, after rearranging,

$$v^l = \left(\frac{L_{11}^i L_{22}^i}{L_{12}^i} - L_{21}^i\right) P_s^l + n^l \frac{L_{22}^i}{L_{12}^i} V. \qquad (23)$$

At the *in situ* length l_o we find from equation 23 for the isometric conditions (subscript o)

$$\frac{v_o^{l_o}}{P_o^{l_o}} = \left(\frac{L_{11}^i L_{22}^i}{L_{12}^i} - L_{21}^i\right). \qquad (24)$$

We omit the subscript e or s on the isometric load at l_o since at l_o $P_{oe}^{l_o} = P_{os}^{l_o}$. Also from equation 23 at l_o for the unloaded isotonic condition (subscript m) we obtain

$$\frac{v_m^{l_o}}{V_m^{l_o}} = n_m^{l_o} \frac{L_{22}^i}{L_{12}^i}, \tag{25}$$

where $n_m^{l_o}$ is the number of activated cross bridges at l_o for the unloaded isotonic condition and, therefore, is a constant. Combining equations 23–25 produces a chemical rate equation which is valid for any length:

$$v^l = \frac{v_o^{l_o}}{P_{os}^{l_o}} P_s + \frac{n^l}{n_m^{l_o}} \frac{v_m^{l_o}}{V_m^{l_o}} V. \tag{26}$$

For convenience, we rewrite equation 26 as

$$\frac{v^l}{v_o^{l_o}} = \frac{P_s^l}{P_{os}^{l_o}} + \frac{n^l}{n_o^l}\left(\frac{n_o^l}{n_o^{l_o}}\right)\frac{n_o^{l_o}}{n_m^{l_o}}\frac{v_m^{l_o}}{v_o^{l_o}}\frac{V}{V_m^{l_o}}. \tag{27}$$

At this point it is worth recalling the meaning of the notation: n^l, v^l, and P_s^l are functions of length and velocity; n_o^l is a function of length only since the velocity is zero; $n_o^{l_o}$, $n_m^{l_o}$, $v_o^{l_o}$, $v_m^{l_o}$, $P_{os}^{l_o}$, and $V_m^{l_o}$ are all constants since both the length and velocity are specified. To determine the chemical ratio in the last term of equation 27, we write equation 22 of part I of this series, which is valid at l_o, for the unloaded isotonic condition

$$\frac{v_m^{l_o}}{v_o^{l_o}} = \frac{a^{l_o}/P_o^{l_o}}{1 + a^{l_o}/P_o^{l_o}}\left(1 + \frac{P_o^{l_o} V_m^{l_o}}{A v_o^{l_o}}\right). \tag{28}$$

The ratios containing the n's in equation 27 can be found from equation 18 of part I of this series, which is valid at l_o

$$n^{l_o}/n_o^{l_o} = \frac{a^{l_o}/P_o^{l_o}}{a^{l_o}/P_o^{l_o} + V/V_m^{l_o}} \tag{29}$$

and from equation 3 which shows that

$$\frac{n^l}{n_o^l} = \frac{n^{l_o}}{n_o^{l_o}}. \tag{30}$$

Combining equations 29 and 30 yields one of the desired ratios

$$\frac{n^l}{n_o^l} = \frac{a^{l_o}/P_o^{l_o}}{a^{l_o}/P_o^{l_o} + V/V_m^{l_o}}. \tag{31}$$

Note that even though n^l and n_o^l are both functions of length, the ratio is not. By setting V equal to $V_m^{l_o}$ (the unloaded isotonic condition at l_o) in equation 29, we acquire another one of the desired ratios

$$n_m^{l_o}/n_o^{l_o} = \frac{a^{l_o}/P_o^{l_o}}{1 + a^{l_o}/P_o^{l_o}}. \qquad (32)$$

In view of equation 3, the remaining ratio in equation 27 is defined as

$$\frac{n_o^l}{n_o^{l_o}} = \frac{f(l)}{f(l_o)} \equiv F_l. \qquad (33)$$

Finally by substituting equations 8, 28, and 31–33 into equation 27, the desired result is obtained for the normalized chemical rate:

$$\frac{v^l}{v_o^{l_o}} = F_l \frac{a^{l_o}}{P_o^{l_o}} \frac{1 + (P_o^{l_o} V_m^{l_o}/A v_o^{l_o})(V/V_m^{l_o})}{a^{l_o}/P_o^{l_o} + V/V_m^{l_o}}. \qquad (34)$$

Equation 34 gives the normalized chemical rate as a function of the normalized velocity and the length (indirectly through F_l) and the two constants $a^{l_o}/P_o^{l_o}$ and $P_o^{l_o} V_m^{l_o}/A v_o^{l_o}$. At the isometric condition equation 34 reduces to

$$\frac{v_o^l}{v_o^{l_o}} = F_l. \qquad (35)$$

The normalized isometric heat rate follows directly from equation 35 since the enthalpy of reaction is not expected to be a function of length. Thus, the result is

$$\frac{\dot{Q}_o^l}{\dot{Q}_o^{l_o}} = F_l. \qquad (36)$$

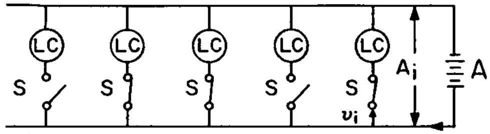
Equation 36 shows that the isometric heat rate follows the isometric intrinsic force rather than the isometric external load, since it was previously shown that the isometric intrinsic force is equal to F_l (see equation 11). This conclusion is not surprising since it can be argued directly from the sliding filament theory without employing any irreversible thermodynamic theory (see references 1 and 9). In fact, in 1956, Aubert (9) inferred from his isometric heat data the existence of an internal resistive force, P_r, at lengths less than l_o because he found that the maintenance heat rate did not decrease as rapidly as the external force. For lengths greater than l_o, Aubert found a direct proportionality between the isometric heat rate and the external load.

The F_l of Fig. 1, as discussed previously, assumes uniform striation spacings; however, to apply equation 34 to a whole muscle, equation 35 can be used to experimentally determine F_l. All the other constant parameters appearing in equation 34 can be estimated from mechanical and chemical or heat data at l_o as discussed in part I of this series. Since chemical rate data are currently not available, a comparison of theory with chemical data requires an integration of equation 34. For experiments in which the velocity is held constant while the muscle changes length, the only length variation appearing in equation 34 is F_l and consequently the integration is straightforward. On the other hand, for experiments in which the load is held constant, the velocity in equation 34 is a function of length (see equation 17) and the integration becomes somewhat involved, although it can be accomplished analytically. Preliminary comparisons of the integrated forms of equation 34 with experimental chemical data reported by Cain, Infante, and Davies (10) (isotonic data) and Kushmerick (11) (isovelocity data) are very encouraging. The results of this study, which are not as yet complete, will be reported in a later paper.

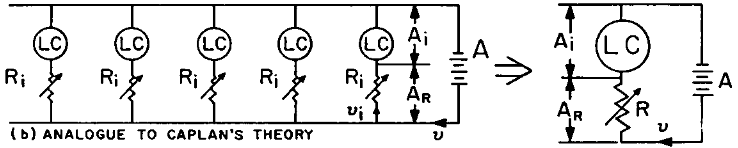
DISCUSSION

In an attempt to further elucidate some of the concepts involved we will consider the electrical analogues shown on Fig. 4: Fig. 4 *a* is an analogue of the theory of part I of this series and Figs. 4 *b* and 4 *c* are analogues of Caplan's theory. The linear converters labeled LC, represent electric motors (analogous to the cross bridges) which are connected to a mechanical load (not shown) so that each motor runs at the same velocity and develops an equal share of the total load e.g., a rack which meshs with a gear on each motor. The source of free energy, the battery with potential A, is connected in parallel with the motors.

The response of the system shown on Fig. 4 *a* (analogy of the theory in part I of this series) is dependent on the number of switches which are closed at any given instant. Closing a switch is equivalent to activating a cross bridge. In the analogy the switches open and close at random in such a way that the same total number of switches are closed for a given steady-state condition. In the muscle the steady-state number of activated cross bridges is assumed to be a function of the velocity. Clearly, the scheme for regulating the output of the system of Fig. 4 *a* is nondissipative.



(a) ANALOGUE TO THEORY IN PART I



(b) ANALOGUE TO CAPLAN'S THEORY

(c) LUMPED EQUIVALENT TO (b)

Figure 4 Electrical analogues.

The response of the system shown on Fig. 4 *b* (analogy of Caplan's theory) is dependent on the setting of the variable resistors at any given instant. All the resistors are assumed to have the same setting. Adjusting a resistor is equivalent to regulating the local chemical affinity seen by a cross bridge. In the muscle the regulation of the local chemical affinity is a function of the velocity or load. Clearly the scheme for regulating the output of the system of Fig. 4 *b* is dissipative.

The lumped system shown in Fig. 4 *c* is equivalent to the system shown in Fig. 4 *b*; however, the effect of length variations is clearer for Fig. 4 *b*. Length variations for either Fig. 4 *a* or 4 *b* are accounted for by simply changing the total number of elements.

Plausibility Arguments for the Velocity Variation of n

A plausibility argument for the velocity variation of n can be developed by considering the time history of an individual cross bridge. It is not necessary that an activated cross bridge be connected, but for purposes of this discussion we will assume that a bridge is activated if and only if it is connected. The following quantities could be observed, at least in principle, for an individual cross bridge or a sarcomere:

t = the total observation time.

Σt_c = the total time that the bridge is connected (activated) during the period of observation t. This is an accumulated time which must be less than t, since during part of the observation time the bridge will be disconnected.

N = the total number of bridges in the half-sarcomere that are capable of a make-break. The value of N is independent of load and velocity but is dependent on changes of the sarcomere length ($N = 5$ in Fig. 4 *a*).

n = the number of cross bridges connected at any instant of time ($n = 3$ in Fig. 4 *a*).

For steady-state conditions the average number of cross bridges connected per half-sarcomere at any time is equal to the total number of cross bridges capable of a connection multiplied by the percentage of time that a cross bridge is connected. That is

$$n = N(\Sigma t_c/t) \equiv N\tau, \qquad (37)$$

where to simplify the notation we replaced the symbol $\Sigma t_c/t$ with τ. An implicit assumption in equation 37 is that the steady-state, time-average behavior of any cross bridge capable of a make-break is the same.

It is clear from equation 37 that a variation in the number of cross bridges connected is the result of either a variation in the number of cross bridges capable of a connection, namely N, or a variation in the percentage of time that a cross bridge spends connected, namely τ. In light of the sliding filament theory, it appears reasonable to assume that N is a function of length only and that τ is independent of length. However, it certainly seems plausible for τ (the percentage of time that a cross bridge is connected) to be affected directly by the velocity since as the velocity increases the bridge is forced to disconnect sooner than it would for a slower velocity. This reduction in τ with increasing velocity is consistent with that predicted from equation 18 of part I of this series. The function $f(l)$ and $g(V)$ used previously in equation 3 are equivalent to N and τ, respectively.

Previous Comparison of Caplan's Theory to Experimental Data

We compared Caplan's theory with experimental chemical data in a previous paper (6). In the Appendix we incorporate length variations into Caplan's theory and conclude that the previous comparison with chemical data as given in Fig. 1 of reference 6 is essentially correct. However, we can show an equally good fit to these data by using approximate methods for integrating the equations developed herein. The reason that both theories can fit the same experimental data is that different values for the constants are used. The ability to decide which, if either, set of constants is reasonable requires a knowledge of the mechanical constants: $a^{l_o}/P_o^{l_o}$, $P_o^{l_o}$, and $V_m^{l_o}$. Since these data were not available for the set of muscles used for the comparison in reference 6, we fit Hill's force-velocity equation to the averaged mechanical data which was available. To do this we assumed, for the frog rectus abdominis muscles, a value of 0.25 for $a^{l_o}/P_o^{l_o}$. Preliminary calculations using the equations developed in part II of this series for length variations have convinced us that our treatment of the mechanical data in reference 6 was invalid. This explains the unexpectedly low value of P_o obtained in reference 6.

A detailed study of length variations, which includes a comparison of both theories with the experimental data of references 10 and 11, is currently being performed and will be reported in a later paper.

CONCLUSIONS

We have shown that by combining irreversible thermodynamic theory with the sliding filament theory that the steady-state behavior of muscle can be adequately described. Basic to our approach is the concept that the individual cross bridges are identical linear energy converters; their combined effects then produce the observed performance of the whole muscle which behaves as a nonlinear energy converter. We further assume that in a stimulated muscle only a portion of the converters (cross bridges) are operating or activated at any instant of time. The performance of the whole muscle is thus the result of two somewhat independent phenomenon: (*a*) the operating characteristics of the individual cross bridges while activated, and (*b*) the number of cross bridges that are activated for a given condition of the whole muscle.

In part II of this series, a generalized theory for length variations has been developed with the following conclusions:

(*a*) Accepting the validity of Hill's equation at the *in situ* length l_o, it has been shown that Hill's equation for the *intrinsic contractile mechanism* is valid at any length with the parameters b and V_m constant and the parameter a varying with length as F_l (see equation 9).

(b) It has also been shown that Hill's force-velocity relation is valid at any length for the *external* load with the parameter b constant and the parameters V_m and a varying with length (see equation 18 and 19).

(c) The theoretically predicted variation of velocity with length for a lightly loaded contraction agrees well with that measured by Gordon, Huxley, and Julian (see Fig. 3).

(d) It is shown that chemical rates can be derived in terms of length, velocity, and parameters which can be determined experimentally.

APPENDIX

Length Variation for Caplan's Theory

In view of Fig. 4 b, equations 21 and 22 are valid for Caplan's theory for any length if n^l is taken to be a function of length only and if the chemical affinity A is replaced by the local chemical affinity A_i. Therefore the development through equation 26 is also valid if the subscript m is omitted on $n_m^{l_o}$, in which case the ratio n^l/n^{l_o} is F_l. Thus we get

$$v^l = \frac{v_o^{l_o}}{P_{os}^{l_o}} P_s + F_l \frac{v_m^{l_o}}{V_m^{l_o}} V. \tag{A 1}$$

From equation A3 of part I of this series, it follows that

$$\frac{v_m^{l_o}}{v_o^{l_o}} = \left(1 + \frac{a^{l_o}}{P_o^{l_o}}\right) \frac{P_o^{l_o} V_m^{l_o}}{A_o^{l_o} v_o^{l_o}}. \tag{A 2}$$

Combining equations 8, A1, and A2 yields

$$\frac{v^l}{v_o^{l_o}} = F_l \left[\frac{a^{l_o}}{P_o^{l_o}} \frac{1 - V/V_m^{l_o}}{a^{l_o}/P_o^{l_o} + V/V_m^{l_o}} + (1 + a^{l_o}/P_o^{l_o}) \frac{P_o^{l_o} V_m^{l_o}}{A_o^{l_o} v_o^{l_o}} \frac{V}{V_m^{l_o}}\right]. \tag{A 3}$$

Equation A3, valid for Caplan's theory at any length, is comparable to our equation 34. Note that equations 35 and 36 also follow from equation A3.

In reference 6 we applied length variations to Caplan's theory based on the assumptions that the transport coefficients for the whole muscle were constant with length. In light of the development herein, equation 7 of reference 6 should be replaced by equation A1 above. The essential difference between these two equations is the F_l and the subscript s on P appearing in equation A1. Since the variation of v_o^l and P_{oe}^l is about the same for frog rectus abdominis muscle (see Fig. 2 in reference 11) it follows from equations 14 and 35 that F_l equals F_P, and thus P_e^l is equal to P_s^l (see equation 16). Thus for an isotonic experiment, we can integrate equation A1 as we did for equation 7 of reference 6 and obtain

$$-\Delta PC = \left(\frac{v_o^{l_o}}{P_o^{l_o}}\right) Pt_f + \left(\frac{v_m^{l_o}}{V_m^{l_o}}\right) \int_{l_i}^{l_f} F_l \, dl \tag{A 4}$$

where $-\Delta PC$ is the decrease in phosphorylcreatine; t_f denotes the contraction time; and l_i and l_f denote the initial and final muscle length, respectively. For contractions with the same shortening the integral appearing in equation A4 is surely a fixed number. Therefore, the comparison of Caplan's theory with experimental data as shown on Fig. 1 of reference 6 is valid with a reinterpretation of the constants.

LIST OF SYMBOLS

A	Affinity of driving chemical reaction.
a	Force parameter in Hill's force-velocity equation.
b	Velocity parameter in Hill's force-velocity equation.
$f(l)$	The number of available cross bridges as a function of length.
F_l	The ratio of the number of available cross bridges at the length l to the number at l_o; $F_l \equiv f(l)/f(l_o)$.
F_p	The ratio of the external isometric force at the length l to the value at l_o; $F_p \equiv P^{l}_{oe}/P^{l_o}_{oe}$.
$g(V)$	Percentage of available cross bridges that are activated as a function of velocity.
L	Phenomenological transport coefficient (L_{11}, L_{22}, L_{12}, and L_{21}) defined by equations 2 and 3 in part I of this series.
l	Muscle length.
l_o	*In situ* length.
n	Number of activated cross bridges at any instant.
P	Force.
$\dot{Q}$	Heat rate.
V	Velocity of shortening.
v	Chemical rate of driving reaction.

Subscripts or Superscripts

e	Subscript denoting an external parameter.
i	Superscript or subscript denoting individual converter.
l	Superscript denoting the value of the parameter at the length l.
l_o	Superscript denoting the value of the parameter at the *in situ* length l_o.
m	Subscript denoting unloaded isotonic contraction.
o	Subscript denoting isometric contraction.
s	Subscript denoting a parameter for the intrinsic contractile mechanism.

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