# A PHENOMENOLOGICAL THEORY OF MUSCULAR CONTRACTION

## I. Rate Equations at a Given Length Based on Irreversible Thermodynamics

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ABSTRACT A phenomenological theory for contracting muscle based on irreversible thermodynamics and the sliding filament theory is developed. The individual cross bridges, considered as subunits, are viewed as linear energy converters with constant transport coefficients. With this view of the subunits, phenomenological equations applicable to the whole muscle are obtained. The transport coefficients are shown to be a function of a single parameter which is the number of activated cross bridges at any instant. By requiring Hill's force-velocity relation (1) to be satisfied, the response of the muscle is related to the number of activated cross bridges. The resulting theory differs significantly from the theory developed by Caplan (2) and a comparison of the theories is presented. The theory is shown to correlate well with the heat data of Woledge (3) for a tortoise muscle and gives a value of $Y$ (ratio of chemical affinity to enthalpy of reaction) equal to 0.945. The comparison of the theory with Hill's frog muscle data (1) and (4) is also encouraging. In part II of this series, length variations are considered and the resulting theoretical predictions are shown to be consistent with experimental data.

## INTRODUCTION

In 1966 Caplan (2) demonstrated the value of considering the muscle as a linear energy converter subject to analysis by the methods of irreversible thermodynamics. Caplan considered the muscle to behave as a self-regulated linear energy converter. The regulator, which senses the output of the converter, adjusts the affinity of the driving chemical reaction to achieve a specific output characteristic. Using concepts of cybernetics, Caplan further showed that if the regulator is programmed with minimal information the output follows the classic Hill force-velocity relation. In a subsequent paper Wilkie and Woledge (5) extended Caplan's theory for muscular contraction, compared it with experimental data, and concluded that the chemical rates inferred from heat data do not agree with that predicted by Caplan's theory.

In addition, they concluded that the large variations in the chemical affinity as calculated from Caplan's theory could not occur in living muscle. However, in recent papers, Caplan argues (6, 7) that the basis for the criticism of Wilkie and Woledge involves some questionable assumptions, especially in the calculation of the driving chemical rates from heat data. Furthermore, Caplan (7) points out that the variations in the chemical affinity could occur locally in the muscle while the bulk affinity remains constant. A scheme proposed by Caplan (7) to accomplish this is a dissipative regulator which operates in series with the linear converter. The input to the dissipative regulator is the constant bulk affinity and the output is the reduced affinity seen by the linear converter. In this scheme the over-all machine (regulator plus converter) is a nonlinear energy converter with variable coefficients and is driven by the constant bulk chemical affinity. The efficiency of this over-all machine can be considerably lower than that of the linear converter since free energy is dissipated by the regulator. Although other views may be possible, the following two views of Caplan's theory have emerged: (*a*) a linear energy converter driven by a variable bulk chemical affinity which is adjusted to the required level by a nondissipative regulator, or (*b*) a dissipative regulator in series with a linear converter, where the regulator adjusts the local affinity. The chemical rates inferred from Caplan's theory are identical for either view; however, the over-all efficiency will be lower for view *b* than for view *a*.

In 1969 Bornhorst and Minardi (8), utilizing an integrated form of Caplan's chemical rate equation, found excellent agreement between chemical data and Caplan's theory; however, they also concluded that there is a discrepancy between the heat data and Caplan's theory. If one accepts view *a* of Caplan's theory, the variation of affinity with load as calculated by Bornhorst and Minardi (reference 8, Fig. 5) represents a variation in the bulk chemical affinity. The maximum variation found, 5.44–10.6 kcal/mole, appears to be a rather large variation in the bulk chemical affinity to actually occur in living muscle. One circumvents this problem by accepting view *b*; however, the efficiency shown on Fig. 6 of reference 8 is then not the over-all efficiency (as it is for view *a*), but is the efficiency of the linear converter. The over-all efficiency is reduced because of the dissipative regulation, in fact the over-all peak efficiency is reduced from 38.2 % to 21.9 %. Moreover, at the maximum power output point, 47.2 % of the input free energy is dissipated in the regulator and 33.5 % is dissipated in the converter, leaving only 19.3 % to do useful work. This appears to us to be an excessive price to pay for regulation.

In spite of these objections, we feel that Caplan has demonstrated the usefulness of applying the concepts of irreversible thermodynamics to muscle. Therefore, we have developed a model based on irreversible thermodynamics which operates with a constant bulk chemical affinity and essentially nondissipative regulation. Furthermore, this model gives better agreement with the heat data and preliminary calculations also show that the model is consistent with chemical data.

In this paper we present a theory in which Hill's empirical force-velocity relation is

accepted, the chemical driving force is held constant, and the control of the muscle is achieved through variation in the phenomenological transport coefficients. This variation of the coefficients is related to the sliding filament model of contracting muscle.

In part I of this series, we derive instantaneous rates as a function of load or velocity at a given muscle length, and these results are compared with experimental heat data at the *in situ* length $l_o$. Some of the parameters appearing in the rate equations vary with length; therefore, as the length of the muscle changes during a given contraction, the instantaneous rates are not constant but vary with length. In part II of this series, generalized length variations are determined and then the instantaneous rate equations of part I are expressed as a function of load or velocity and length.

## PHENOMENOLOGICAL EQUATIONS WITH VARIABLE COEFFICIENTS

The theoretical development which follows is based on five major assumptions.

(*a*) The cross bridges are linear energy converters for which linear phenomenological equations with constant coefficients are valid. The cross bridges are considered to be the fundamental subunit of muscle.

(*b*) The number of operating cross bridges (referred to as activated) varies with velocity or load in a stimulated muscle.

(*c*) The chemical affinity, $A$, of the driving chemical reaction is constant.

(*d*) Internal shear loads due to the stacking of sarcomeres are negligible.

(*e*) Hill's force-velocity relation is valid at the *in situ* length $l_o$. (In part II of this series, Hill's equation is shown to be valid at any length, and therefore the results of this paper are valid at any particular length with the appropriate values of $a$, $b$, and $V_m$ or $P_o$ developed in part II.) These assumptions will be elaborated on in the following development.

As shown by Caplan (2), the dissipation function for a contracting muscle is

$$T\dot{S} = -PV + Av, \tag{1}$$

where $T$ denotes temperature, $\dot{S}$ the rate of entropy generation, $P$ the load, $V$ the velocity of shortening, $A$ the affinity of the chemical reaction driving the contraction, and $v$ the rate of the driving chemical reaction. Assuming the entire muscle to be a linear system, the phenomenological equations relating the fluxes and forces for steady-state operation are

$$V = L_{11}(-P) + L_{12}A \tag{2}$$

$$v = L_{21}(-P) + L_{22}A, \tag{3}$$

where the transport coefficients $L_{11}$, $L_{22}$, $L_{12}$, and $L_{21}$ are unknown coefficients which must be determined from experimental measurements. In Caplan's theory the trans-

port coefficients for the muscle were held constant and the nonlinear response of the muscle is effected by a variation of the chemical affinity (either local or bulk). Here we will assume that the transport coefficients for the subunits are constant and the variation of the $L$'s for the whole muscle appearing in equations 2 and 3 will then be determined.

According to the sliding filament hypothesis, the behavior of the whole muscle is considered to result from the combined effect of the individual cross bridges. Using this premise as a basis, we shall consider the individual cross bridges as fundamental subunits of the muscle and assume that the average performance of a subunit can be described as that of a linear energy converter. For these basic linear converters operating in a steady state, we shall write the following phenomenological equations in which we assume the constancy of the transport coefficients:

$$V_i = L_{11}^i(-P_i) + L_{12}^i A_i \tag{4}$$

$$v_i = L_{21}^i(-P_i) + L_{22}^i A_i, \tag{5}$$

where the subscript and superscript $i$ denote average properties characteristic of the basic subunit (cross bridge). In order to relate equations 4 and 5, which are for the subunit, to equations 2 and 3, which are for the whole muscle, the variables with the subscript $i$ must be expressed in terms of their corresponding variables for the whole muscle. In doing this, we will allow the transport coefficients for the whole muscle to vary while keeping the transport coefficients for the basic subunits constant.

### *Relations between Subunit and Whole Muscle*

In the present discussion we shall consider a half-sarcomere and relate the forces and fluxes of the cross bridge to those of the half-sarcomere. The extension of the theory from a half-sarcomere to a whole muscle, although straightforward, requires some assumptions, and will be discussed later.

Our basic hypothesis is that the operation of a single cross bridge can be described in terms of phenomenological properties which are related by equations 4 and 5. As is true in any thermodynamic treatment, these phenomenological properties are an average of microscopic events. Of course, for a cross bridge this average should be taken only while the cross bridge is operating. These operating cross bridges will be called activated bridges. We define a cross bridge as activated when it is in a condition such that it is capable of utilizing the chemical free energy (chemical affinity) of the driving chemical reaction. It is postulated that only in this condition (activated) is the behavior of the cross bridge described by the linear phenomenological equations. It is assumed that even in a stimulated muscle a cross bridge can exist in either of two states: activated or inactivated. (This is not meant to imply that the inactivated state of the bridges before stimulation is identical to the inactivated state after stimulation.) In order to proceed with the theory, it is not necessary to describe the

activated or inactivated state of a cross bridge in detail, but only that these two different states of a cross bridge exist in a stimulated muscle. However, it is interesting to speculate on reasons why a bridge might be activated or inactivated in a stimulated muscle. It may be that that a bridge must be connected and/or that calcium must be at the cross bridge site in order for the bridge to see the chemical affinity (availability) and therefore be an operating or activated bridge. Also, geometrical effects can cause a bridge to be inactive if the bridge cannot reach any thin filament site.

According to the sliding filament hypothesis, the total load $P$ carried by a half-sarcomere is the sum of the loads carried by the cross bridges. It follows that

$$P = \sum_{i=1}^{n} P_i^{\text{inst}} = nP_i, \tag{6}$$

where $n$ denotes the number of activated bridges, $P_i^{\text{inst}}$ denotes the instantaneous load on a cross bridge, and $P_i$ denotes the average load carried by the activated bridges. It was assumed in writing equation 6 that a bridge which is bearing a load is in the activated state. However, it is not required that all the activated bridges bear a load, since some of the $P_i^{\text{inst}}$ could be zero without affecting the sum in equation 6. Equation 6 would give the correct total load if the summation were taken just over the bridges which were carrying a load, or over all the bridges in the half-sarcomere. However, the resulting average load $P_i$ would not be the appropriate average to use in the phenomenological equations 4 and 5 unless the summation is over the activated bridges, $n$.

Having determined the relation between $P$ and $P_i$ we proceed to determine relations among the remaining three variables of equations 4 and 5. Because of the way the bridges are arranged with respect to the thick and thin filaments, it follows that the relation between the velocities is

$$V = V_i, \tag{7}$$

where $V$ is the shortening velocity of the half-sarcomere and $V_i$ is the average velocity of the cross bridge appearing in equation 4.

We next assume that the chemical affinity of each activated cross bridge is the same, from which it follows that

$$A = A_i, \tag{8}$$

where $A$ is the bulk chemical affinity in the sarcomere and $A_i$ is the local chemical affinity seen by each activated bridge.

Since each activated cross bridge splits adenosine triphosphate (ATP), the total chemical rate, $v$, for the half-sarcomere is given by

$$v = nv_i, \tag{9}$$

where $v_i$ is the average chemical rate of an activated bridge. Equations 6–9 establish the relations between a property for the subunit and the corresponding property for the half-sarcomere in terms of the one variable $n$. By combining these equations with the phenomenological equations for the subunit, equations 4 and 5, we obtain the phenomenological equations for the half-sarcomere to be

$$V = \frac{L^i_{11}}{n}(-P) + L^i_{12}A \tag{10}$$

and

$$v = L^i_{21}(-P) + nL^i_{22}A. \tag{11}$$

Even though equations 10 and 11 were derived for a half-sarcomere, it can be shown that the same equations hold for a whole muscle made up of many sarcomeres, if the variables appearing in equations 10 and 11 are appropriately scaled: $P$/area, $V$/length, $v$/volume, and $n$/volume. The extension of the theory from individual half-sarcomeres to the whole muscle requires the assumption that each sarcomere experiences the same load and that internal shear loads are negligible as compared to the axial load. From this point on, we shall consider the variables in equations 10 and 11 to be thus scaled and applicable to the whole muscle instead of to a half-sarcomere.

By comparing equations 10 and 11 with equations 2 and 3 we obtain the following equations which describe the variation of the transport coefficients for the whole muscle in terms of the variable $n$ and the transport coefficients for the subunit, which are assumed to be constant.

$$L_{11} = L^i_{11}/n; \quad L_{12} = L^i_{12}; \quad L_{21} = L^i_{21}; \quad L_{22} = nL^i_{22}. \tag{12}$$

## VARIATION OF $n$ WITH LOAD OR VELOCITY

It is clear from the sliding filament model that the number of activated bridges varies with length. In addition, we postulate that, for a given muscle length, the number of activated bridges varies with the velocity or load of the sarcomer. In this paper we will consider only the variations in the number of activated bridges, $n$, due to load or velocity, and in part II of this series we shall include the effects of length variations.

Since it is difficult to see physically how the bulk chemical affinity $A$ can vary with load or velocity, we will assume that $A$ is constant. With the concept that the number of activated cross bridges can vary with load or velocity, it is evident from equation 10 that even with the chemical affinity $A$ held constant, Hill's force-velocity relation can be satisfied with the proper variation in $n$.

Solving for $P$ from equation 10 we obtain

$$P = \frac{n}{L^i_{11}}(L^i_{12}A - V). \tag{13}$$

At the isometric condition equation 13 gives

$$P_o = n_o\left(\frac{L_{12}^i A}{L_{11}^i}\right), \tag{14}$$

where the subscript $o$ denotes the value of the variable at the isometric condition. The chemical affinity $A$ has no subscript since it is assumed to remain constant. Considering the unloaded isotonic condition, we obtain from equation 13

$$V_m = L_{12}^i A, \tag{15}$$

where $V_m$ denotes the velocity at the unloaded isotonic condition. Substituting equations 14 and 15 into equation 13 we find that the relationship between load and velocity is

$$P/P_o = \frac{n}{n_o}[1 - V/V_m]. \tag{16}$$

On the other hand, the relation between $P$ and $V$ is known experimentally to follow Hill's force-velocity relation (1) which is

$$P/P_o = a/P_o \frac{1 - V/V_m}{a/P_o + V/V_m}. \tag{17}$$

In general, $P_o$, $V_m$, and $a$ are functions of length. In part II of this series, we shall relate these length variations to the length variations of $n$ which can be deduced directly from the sliding filament theory. Herein, however, we are considering variations at a given length and, thus, $P_o$, $V_m$, and $a$ will be constant. In order for equation 16 to be the same as equation 17, $n/n_o$ must vary with velocity as described by

$$n/n_o = \frac{a/P_o}{V/V_m + a/P_o}. \tag{18}$$

By replacing $V/V_m$ in equation 18 with $P/P_o$ from equation 17 we obtain

$$n/n_o = \frac{a/P_o + P/P_o}{a/P_o + 1}. \tag{19}$$

Equation 18 or equation 19 gives the required variation in the percentage change of the number of activated bridges as a function of velocity or load, respectively. The reduction in $n$ with increasing velocity as given by equation 18 seems physically plausible since at a high velocity a bridge may be forced to be disconnected and, thus, be inactivated sooner than it would be for a slower velocity. This velocity dependent characteristic of the cross bridges is reminiscent of the velocity dependence described in the theory of contraction by A. F. Huxley (9). In A. F. Huxley's theory two reac-

tion rate constants, $f$ and $g$, are defined for the making and breaking of cross bridges respectively; each is assumed to be a function of the distance that the cross bridge is from the actin filament site. If, in light of the concepts presented herein, the $f$ and $g$ are reinterpreted to be the rate constants for activation and deactivation, then by following the formalism described by A. F. Huxley, one can derive a relationship for $n/n_o$ which is essentially the same as that described by our equation 18. This result is by no means evidence for the validity of equation 18 since the $f$ and $g$ were picked quite arbitrarily; however, it does indicate the variation predicted by equation 18 is plausible in light of the sliding filament theory.

It is also interesting that the linear variation of the percentage of activated bridges $n/n_o$ with load as predicted by equation 19 was assumed by Volkenstein (10) in a recent paper describing a molecular theory of muscular contraction. With this assumption Volkenstein (10) derives Hill's force-velocity equation as well as the velocity variation of $n/n_o$ (equation 37 in reference 10) which is identical to our equation 18. Likewise, if we assumed a priori the validity of equation 19, then we could derive (using the phenomenological equations 10 and 11) Hill's force-velocity relation and equation 18.

## VARIATION OF CHEMICAL RATE WITH LOAD

In this section we shall derive the chemical rate equation in terms of load for a given muscle length. We can eliminate $n$ from the chemical rate equation, equation 11, by using equation 19. Thus, we obtain

$$v = L_{21}^{i}\,(-P) + n_o\,L_{22}^{i}\,A\,\frac{(a/P_o + P/P_o)}{(a/P_o + 1)}\,. \tag{20}$$

An equation relating the constants appearing in equation 20 can be obtained by considering the isometric condition, yielding

$$v_o = L_{21}^{i}(-P_o) + n_o L_{22}^{i} A, \tag{21}$$

where $v_o$ is the isometric chemical rate. Assuming the validity of Onsager's reciprocal relation and utilizing equations 15 and 21 to eliminate the transport coefficients in equation 20 in favor of more familiar quantities, we obtain

$$v/v_o = \frac{a/P_o}{1 + a/P_o}\left[\left(1 + \frac{P_o\,V_m}{A v_o}\right) + \left(\frac{P_o}{a} - \frac{P_o\,V_m}{A v_o}\right)\frac{P}{P_o}\right]. \tag{22}$$

Equation 22 gives the normalized chemical rate as a linear function of the normalized load and the two constants $a/P_o$ and $P_oV_m/Av_o$; these two constants can be estimated from existing experimental data. In the discussion section we will compare the chemical rates calculated from equation 22 with chemical rates calculated from Caplan's theory.

## VARIATION OF HEAT RATE WITH LOAD

The heat rate can be obtained from equation 22 through the use of the first law which is customarily written for the muscle as

$$v\overline{\Delta H} = \dot{Q} + PV, \tag{23}$$

where $\overline{\Delta H}$ is the negative of the enthalpy of reaction, and therefore is a positive number for exothermic reactions, and $\dot{Q}$ denotes the rate of heat production. In writing equation 23 we have, of course, considered the muscle to be a closed system and have neglected the effects of any side reactions. Considering equation 23 at the isometric condition, it follows that

$$v_o = \frac{\dot{Q}_o}{\overline{\Delta H}}, \tag{24}$$

where $\dot{Q}_o$ is the heat rate at the isometric condition. If one accepts the assumptions implicit in equation 23, then the parameter $P_oV_m/Av_o$ appearing in equation 22 can be replaced in favor of a heat parameter by utilizing equation 24 to obtain

$$\frac{P_o V_m}{Av_o} = \frac{P_o V_m}{Y\dot{Q}_o}, \tag{25}$$

where $Y$ is defined to be $A/\overline{\Delta H}$ as used by Wilkie (11). Appropriate combinations of equations 22–25 give

$$\frac{v}{v_o} = \frac{a/P_o}{1 + a/P_o}\left[\left(1 + \frac{P_o V_m}{Y\dot{Q}_o}\right) + \left(P_o/a - \frac{P_o V_m}{Y\dot{Q}_o}\right) P/P_o\right] \tag{26}$$

and

$$\frac{\dot{Q}}{P_o V_m} = \frac{a/P_o}{1 + a/P_o}\left[\frac{\dot{Q}_o}{P_o V_m} + \frac{1}{Y}\right] + \frac{1}{1 + a/P_o}\left[\frac{\dot{Q}_o}{P_o V_m} - \frac{a/P_o}{Y}\right]\frac{P}{P_o} - \frac{PV}{P_o V_m}. \tag{27}$$

Equations 26 and 27 describe how the normalized chemical rate and heat rate vary with the normalized load and the three constant parameters which characterize the given muscle: the mechanical parameter $a/P_o$, the maintenance heat parameter $\dot{Q}_o/P_oV_m$, and the chemical parameter $Y$. It is clear from equation 27 that the total normalized energy rate ($\dot{Q}/P_oV_m + PV/P_oV_m$) is a linear function of load. Before we compare these theoretical predictions with experimental data, we shall derive several efficiency relations.

## EFFICIENCY CONSIDERATIONS

It has been shown by Kedem and Caplan (12) that a very meaningful parameter, denoted as $q$, for the measure of the effectiveness of the coupling for two processes is given by

$$q = \frac{L_{12}}{\sqrt{L_{11} L_{22}}}, \tag{28}$$

where $q^2$ is restricted by the second law to be less than or equal to unity. A value of unity represents complete or perfect coupling. Even though $L_{11}$ and $L_{22}$ vary with load according to the theory presented herein, the coupling coefficient $q$ is independent of load and is clearly equal to that of the individual converters (substitute equation 12 into equation 28). It is indeed interesting that the muscle can follow Hill's equation without any change in the coupling coefficient, even though the chemical affinity is constant.

Combining equations 14, 15, 21, and 24 and the definition of $Y$, we can express $q$ as

$$q = \frac{1}{\sqrt{1 + \frac{Y\dot{Q}_o}{P_o V_m}}} = \frac{1}{\sqrt{1 + \frac{Av_o}{P_o V_m}}}. \tag{29}$$

Since $q$ is a characteristic of the individual converters it follows from equation 29 that the parameter $P_o V_m / Av_o$ is also a characteristic of the individual converters; i.e., it is not dependent on the size of the whole muscle.

The definining equation for the thermodynamic efficiency $\eta$ is

$$\eta = \frac{PV}{Av}, \tag{30}$$

and as shown by Kedem and Caplan (12), the maximum value of the thermodynamic efficiency, $\eta_{max}$, is related to $q$ by the relation

$$\eta_{max} = \frac{q^2}{[1 + \sqrt{1 - q^2}]^2}. \tag{31}$$

In view of equations 29 and 31, it is clear that the maximum efficiency is simply a function of either $Y\dot{Q}_o / P_o V_m$ or $Av_o / P_o V_m$. The latter parameter has the advantage of being independent of any assumptions required to write the first law as expressed by equation 23.

Another measure of efficiency, $PV/(PV + \dot{Q})$, has been shown by Wilkie (11) to be related to the thermodynamic efficiency $\eta$ by the chemical parameter $Y$. The relation is

$$\frac{PV}{PV + \dot{Q}} = Y\eta. \tag{32}$$

In the following section we will compare the predictions of the theory with experimental data.

## COMPARISON OF THEORY WITH EXPERIMENTAL DATA

In order to compare experimental data to the theory as developed herein (that is at a given length), it is required that the experimental data be expressed in terms of instantaneous rates at a given length. Present experimental techniques for obtaining chemical data do not permit a determination of instantaneous chemical rates; therefore, a comparison with chemical data requires an integration of the theoretical rate equations similar to that presented by Bornhorst and Minardi (8) for Caplan's theory. The integration of the rate equations developed herein is more involved than that in reference (8) and requires the length variations of the constants as developed in part II of this series.

Instantaneous rates can be determined, at a given length, from the slopes of experimental heat data or mechanical data plotted versus time. Preferably, all these data should be for an individual muscle, thus eliminating the need to use average values for the constant parameters appearing in the rate equations. Recently, Woledge (3) reported heat and mechanical rate data for an individual tortoise muscle as a function of load extrapolated back to the start of the isotonic phase of contraction (see reference 3, p. 699, Fig. 8). These experimental data are reproduced here on Fig. 1; solid circles are heat rates and open circles are heat plus work rates. The curves on Fig. 1 are the corresponding theoretically derived heat rates and heat plus work rates, both of which can be calculated from equation 27. The constants $P_o$, $V_m$, $a/P_o$ and

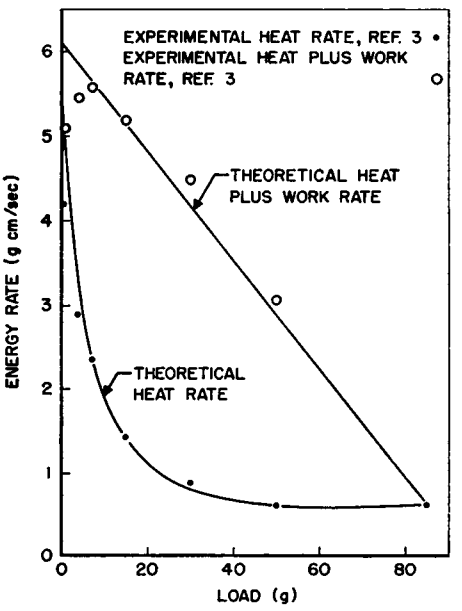


FIGURE 1 Comparison of theoretical and experimental energy rates for a tortoise muscle. Curves calculated from equation 27 with $a/P_o = 0.0612$, $P_o = 85$ g, $V_m = 1.177$ cm/sec, $\dot{Q}_o = 0.62$ g cm/sec, and $Y = 0.945$. Data by Woledge (reference 3, p. 699, Fig. 8).

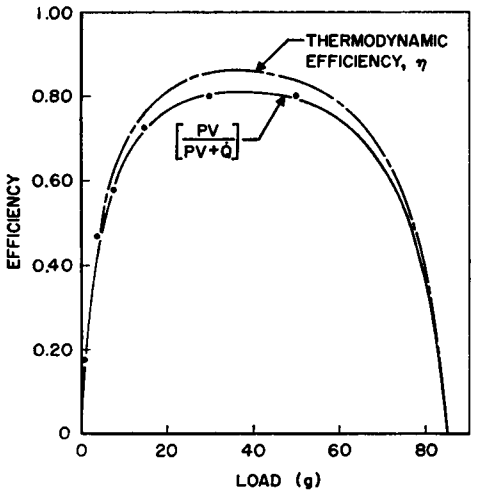


FIGURE 2 Thermodynamic efficiency and comparison of the theoretical and experimental quantity $PV/(PV + \dot{Q})$. Solid circles are data points. Constants and data for tortoise muscle as in Fig. 1.

$\dot{Q}_o$ for this particular muscle were obtained directly from reference 7: $P_o$ = 85 g, $V_m$ = 1.177 cm/sec, $a/P_o$ = 0.0612, and $\dot{Q}_o$ = 0.62 g cm/sec. The one remaining constant, $Y$ in equation 27, was obtained by requiring the theoretical curve to go through the heat data point at 50 g. A value of 0.945 was obtained for $Y$ which is within the range of 0.9–1.2 estimated by Wilkie and Woledge (5).

The agreement between theory and experiment as shown on Fig. 1 is encouraging. The discrepancy which does exist could be the result of side heat producing reactions not accounted for in the phenomenological equations, i.e. not directly involved in the mechanochemical coupling process. In order to explain the discrepancy shown in Fig. 1, such side reactions must be a nonlinear function of load and could not simply be a constant or linear function of load. In light of the uncertainties concerning side reactions, one might question the validity of comparing *any* theory with heat data that does not explicitly account for side reactions. However, if one accepts the validity of the theory, such comparisons indicate the magnitude of the heat involved in side reactions. It appears encouraging that the magnitude of the heat from side reactions inferred from the theory is relatively small. Ultimately, the theory must be compared directly to chemical data in order to determine its validity.

A comparison between the theoretical and experimental values of the quantity $PV/(PV + \dot{Q})$ for the same data as used in Fig. 1 is plotted on Fig. 2: solid circles are experimental data and the continuous curve is the result of the theory. Using the value of 0.945 as obtained above for $Y$, we can calculate from equation 32 the thermodynamic efficiency as defined by equation 30. This efficiency is shown on Fig. 2 by the interrupted line and has a maximum value of 0.858.

Fig. 3 presents a comparison of theory with averaged experimental heat and mechanical data for frog sartorius muscle using data reported by Hill in 1938 (1) and 1964 (4). The two continuous curves represent both the theory and Hill's 1938

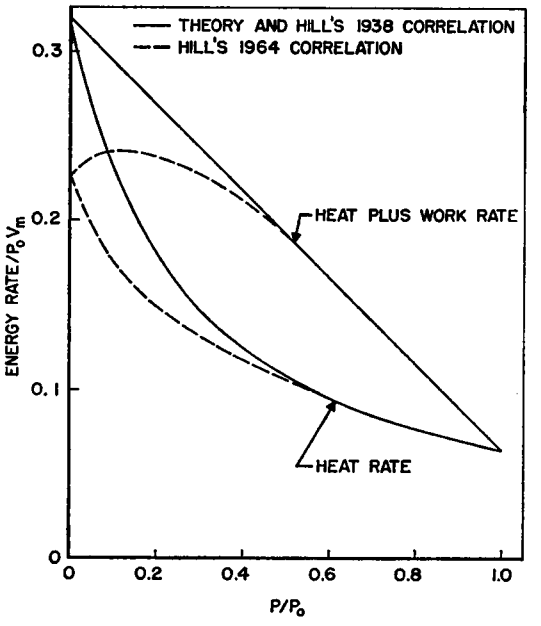


FIGURE 3 Comparison of theoretical and experimental normalized energy rates for frog muscle. Continuous curve calculated from equation 27 with $a/P_o = 0.25$, $\dot{Q}_o/P_oV_m = 0.063$, and $Y = 0.651$. Data: continuous curves reference 1, interrupted curves reference 4.

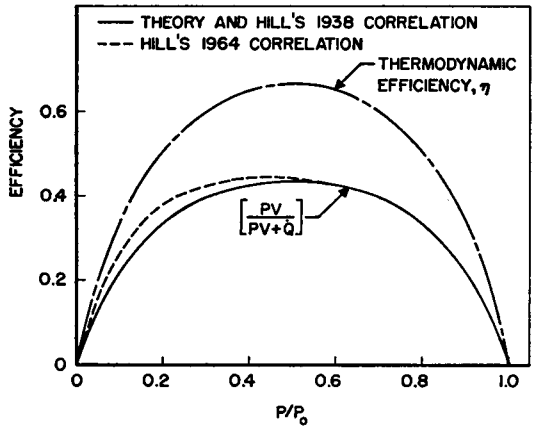


FIGURE 4 Thermodynamic efficiency and comparison of the theoretical and experimental quantity $PV/(PV + \dot{Q})$. Constants and data for frog muscle as in Fig. 3.

(1) correlation of the heat rate and the heat plus work rate data. The fact that the theory is exactly the same as Hill's 1938 correlation is a consequence of the linearity of the heat plus work rate versus load as predicted by Hill in 1938 and predicted here by equation 27. We obtained a value of $Y$ equal to 0.651 from equation 27 using the commonly accepted values of 0.25 for $a/P_o$ and 0.063 for $\dot{Q}_o/P_oV_m$. The value of 0.651 for $Y$ is low when compared to the estimated values of 0.9–1.2 reported by Wilkie and Woledge (5). The interrupted lines on Fig. 3 represent the summary of Hill's 1964 data (4) which were obtained using improved experimental techniques.

For low loads the disagreement between theory and experiment is more pronounced for Hill's 1964 data than for the slower tortoise muscle. Although the reason for this discrepancy is not clear, it may also be due to side reactions as mentioned previously for the tortoise muscle.

The quantity $PV/(PV + \dot{Q})$ for frog sartorius muscle is plotted on Fig. 4 as a function of load. The continuous curve is determined from the theory and the lower dashed line is obtained from the experimental data. Also shown on Fig. 4 is the thermodynamic efficiency (upper dashed line) determined with the value of $Y$ equal to 0.651. The maximum value of the thermodynamic efficiency, 0.669, is significantly lower than 0.858 obtained for the tortoise muscle, which reflects the fact that the coupling coefficient for the tortoise muscle is higher than that for the frog muscle. From equation 29 we obtain a value for $q$ of 0.997 for the tortoise muscle and 0.980 for the frog muscle.

## DISCUSSION

In a muscle there must be a direct connection between the mechanical output and the chemical driving source. Since the muscle is not a heat engine, the heat involved results as an incidental consequence of this coupling. Thus, it should be possible to relate directly the mechanical events to the chemical happenings, irrespective of the thermal effects. It is the second law of thermodynamics which dictates the mechanochemical coupling; and with the development of irreversible thermodynamics it is now possible to express this connection in analytical terms.

A number of advantages will be realized from the development of a valid phenomenological theory. An established phenomenological theory for muscle contraction certainly will be very useful in interpreting and interrelating the wealth of existing information on muscle contraction. A theoretical representation, corroborated by a large number of experimental results, would enable one to extend more confidently the range of application of the conclusions obtained from much muscle research. This approach, if successful, is clearly superior to that of extrapolating isolated experimental results or empirical relations. Also, the implications resulting from theory often suggest critical experiments which otherwise may remain undone.

In 1966 Caplan presented a theory based on irreversible thermodynamics which directly related the mechanical and chemical quantities involved in muscular contraction. The theory presented herein is based on the same general concepts as first applied by Caplan to the muscle; however, the specific model is different. The essential difference between the two models lies in the mechanism responsible for the nonlinear force-velocity response of the muscle: in Caplan's model the nonlinearity is the result of the variation in the local chemical affinity seen by the linear converter; in our model the nonlinearity is caused by the variation in the number of operating linear converters. These differences are manifested in the chemical rates predicted by each theory. For convenience in comparing the two theories, we have, in the Ap-

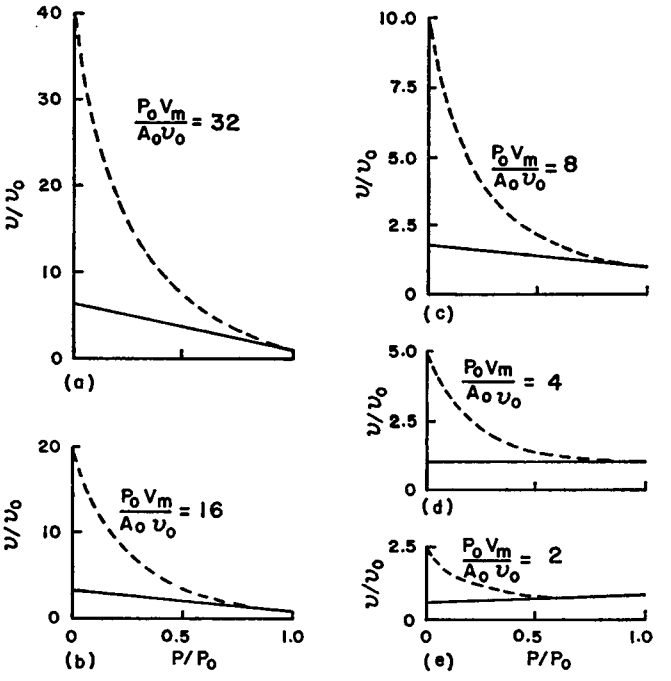


FIGURE 5 Comparison of normalized chemical rates predicted from Caplan's theory (interrupted curves) and the theory presented herein (continuous line) for $a/P_o = 0.25$ and the five values of $P_oV_m/A_ov_o$ shown. As explained in the text, the expected value of $P_oV_m/A_ov_o$ for frog sartorius muscle at 0°C is about 16.

pendix, expressed Caplan's equations in terms of the same parameters ($a/P_o$ and $P_oV_m/A_ov_o$) as used herein. The parameter $P_oV_m/Av_o$ is used instead of $P_oV_m/YQ_o$ to avoid the uncertainties concerning heat data. An estimate for $P_oV_m/Av_o$ of 16.4 is obtained for frog sartorius muscle at 0°C using the following values: $P_ol_o$/weight = 1800 g cm/g muscle, $V_m$ = 1.3 muscle length/sec, $v_o$ = 0.335 ($\mu$mole/sec)/$g$ muscle, and $A$ = 10 kcal/mole (426 g cm/$\mu$mole). The values for $P_ol_o$/weight and $v_o$ are from Carlson, Hardy, and Wilkie (13) and are for the same set of muscles. Since no $V_m$ values were reported for this specific set of muscles, a typical value of 1.3 muscle length/sec is used (see reference 3). The remaining parameter $A$ cannot be directly measured in vivo; however, as discussed by Wilkie and Woledge (5), one would expect $A$ to be like 10 kcal/mole. In Fig. 5 a comparison between the two theories is given for $a/P_o$ equal to 0.25 and for five values of $P_oV_m/Av_o$ : 2, 4, 8, 16, and 32. The expected value for frog sartorius, as mentioned above, is about 16; the curves for the other values are shown in order to cover a reasonable range of the parameter. It is clear from Fig. 5 that there is a significant difference between the chemical rates predicted from the two theories. (Note the change in scale between Figs. 5 *b* and 5 *c*.)

In Caplan's theory the coupling coefficient $q$ for the linear converter (i.e. not including the regulator) is a function of $a/P_o$ only and, therefore, is the same for each of the diagrams of Fig. 5. In the theory presented herein, the coupling coefficient is a function of the parameter $P_oV_m/Av_o$ only. The coupling coefficients are the same for both theories only in Fig. 5 *d*, since $a/P_o$ is 0.25 and $P_oV_m/Av_0$ is 4 (see last paragraph in the Appendix). Thus, the higher chemical rate predicted by Caplan's theory as shown on Fig. 5 *d* represents the price paid for dissipative regulation. For values of $P_oV_m/Av_o$ greater than 4, the coupling coefficient for the theory presented herein increases. This accounts for the increase in the difference between the two theories for the larger values of $P_oV_m/Av_o$. Conversely, the difference between the two theories decreases for values of $P_oV_m/Av_o$ less than 4.

If a dissipative regulator is used to regulate the local chemical affinity in Caplan's theory, the bulk chemical affinity must be at least as large as the largest value of the local chemical affinity. As given by equation A4 in the Appendix, the value of the chemical affinity for Caplan's theory at the unloaded isotonic condition, $A_m$, is

$$A_m = a/P_o \frac{P_o V_m}{v_o}. \tag{33}$$

Using the values for frog sartorius at 0°C as given above, the value of $A_m$ is 41 kcal/mole. Thus the bulk chemical affinity would have to be at least 41 kcal/mole. This appears to us to be a rather large value.

In this section we have pointed out several significant differences which exist between the two models. Nevertheless, to convincingly establish the validity of either theory will require a direct comparison of the theories with chemical data for a wide range of conditions. To accomplish this requires a knowledge of the length variations of the parameters appearing in the chemical rate equations. In part II of this series, these length variations of the parameters are determined and shown to be consistent with experimental data.

## CONCLUSIONS

A phenomenological theory involving the application of irreversible thermodynamics to the sliding filament model of contracting muscle has been developed. In this theory individual cross bridges are viewed as individual energy converters which operate with a constant chemical affinity and constant transport coefficients. With this view phenomenological equations with a constant affinity, but variable coefficients, are obtained for the whole muscle. Then, in order to satisfy Hill's force-velocity equation, it is shown that the variation of the transport coefficients is directly related to the number of activated cross bridges, $n$. The number of activated bridges decreases as the velocity increases, a result which appears to be compatible with molecular models of muscular contraction.

The theory correlates well with the heat data for a tortoise muscle, except for very

low loads, and predicts a value of the chemical parameter $Y$ which is consistent with previously estimated values. The theory agrees exactly with Hill's 1938 correlation (1) of his heat data, but the theory agrees well with Hill's improved 1964 correlation (4) only for loads greater than 50% of $P_o$. These discrepancies may be due to side reactions which are heat producing.

## APPENDIX

In this appendix we will express several of Caplan's equations in terms of $a/P_o$ and $P_oV_m/Av_o$ for convenience in comparing his results with those presented in this paper.

The chemical rate equation for Caplan's theory (equation 15 of reference 8) is

$$\frac{v}{v_o} = \frac{P}{P_o} + \left(\frac{v_m}{v_o}\right)\frac{V}{V_m} \qquad (A\,1)$$

and the local chemical affinity at the isometric condition, $A_o$, is (see equation 28, reference 6, and equation A2, reference 7)

$$A_o = (1 + a/P_o)P_o\,V_m/v_m\,. \qquad (A\,2)$$

Solving equation A2 for $v_m$ and substituting into equation A1, we obtain Caplan's chemical rate equation in terms of the desired parameters

$$\frac{v}{v_o} = \frac{P}{P_o} + (1 + a/P_o)\left(\frac{P_o\,V_m}{A_o\,v_o}\right)\frac{V}{V_m}\,. \qquad (A\,3)$$

Equation A3 was used to calculate the chemical rates for Caplan's theory which appear on Fig. 5.

The ratio of the local chemical affinities at the unloaded isotonic condition, $A_m$, to that at the isometric condition, $A_o$, is (see equation 28, reference 6, and equation A1, reference 7)

$$\frac{A_m}{A_o} = \frac{a}{P_o}\left(\frac{P_o\,V_m}{A_o\,v_o}\right). \qquad (A\,4)$$

Caplan also shows (equation 28, reference 6) that

$$q^2 = \frac{1}{1 + a/P_o}\,. \qquad (A\,5)$$

Combining equations A4 and A5 we obtain

$$q^2 = \frac{1}{1 + \left(\frac{A_o\,v_o}{P_o\,V_m}\right)\frac{A_m}{A_o}}\,. \qquad (A\,6)$$

From equation A4 it follows that if $P_o/a$ is equal to $P_oV_m/Av_o$, then $A_m/A_o$ equals unity. For this special case the expression for $q^2$ for Caplan's theory is indentical to the $q^2$ for the theory presented in this paper (see equation 29).

## LIST OF SYMBOLS

$A$ Affinity of driving chemical reaction.
$a/P_o$ Dimensionless parameter in Hill's force-velocity equation.
$L$ Phenomenological transport coefficient ($L_{11}$, $L_{22}$, $L_{12}$, and $L_{21}$ defined by equations 2 and 3).
$n$ Number of activated cross bridges at any instant of time.
$P$ Load on the muscle.
$\dot{Q}$ Heat rate.
$q$ Coupling coefficient.
$\dot{S}$ Entropy rate.
$T$ Temperature.
$t$ Time.
$V$ Velocity of shortening.
$v$ Rate of driving reaction.
$Y$ Chemical parameter $A/\overline{\Delta H}$.
$\overline{\Delta H}$ Negative of the enthalpy of reaction (positive for exothermic reactions).
$\eta$ Thermodynamic efficiency.

### *Subscripts or Superscripts*

$i$ Subscript or superscript denoting individual converter.
$m$ Subscript denoting unloaded isotonic contraction.
$o$ Subscript denoting isometric contraction.

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