COMPARISON OF CAPLAN'S IRREVERSIBLE THERMODYNAMIC THEORY OF MUSCLE CONTRACTION WITH CHEMICAL DATA

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ABSTRACT Recently Caplan (1) applied the concepts of irreversible thermodynamics and cybernetics to contracting muscle and derived Hill's force-velocity relation. Wilkie and Woledge (2) then compared Caplan's theory to chemical rates inferred from heat data and concluded that the theory was not consistent with the data. Caplan defended his theory in later papers (3, 4) but without any direct experimental verifications. As Wilkie and Woledge (2) point out, the rate of phosphorylcreatine (PC) breakdown during steady states of shortening has not been observed because of technical difficulties. In this paper it is shown that the rate equations may be directly integrated with time to obtain relations among actual quantities instead of rates. The validity of this integration is based on experimental evidence which indicates that certain combinations of the transport coefficients are constant with muscle length. These equations are then directly compared to experimental data of Cain, Infante, and Davies (5) with the following conclusions: (*a*) The measured variations of ΔPC for isotonic contractions are almost exactly as predicted by Caplan's theory. (*b*) The value of the chemical rate ratio, v_m/v_o, obtained from these data was 3.53 which is close to the value of 3 suggested by Caplan (3). (*c*) The maximum value of the chemical affinity for PC splitting was found to be 10.6 k cal/mole which is as expected from in vitro measurements (2). Because of the excellent agreement between theory and experiment, we conclude that Caplan's theory definitely warrants further investigation.

INTRODUCTION

In 1966 Caplan (1) derived the Hill force-velocity relation for muscle by applying irreversible thermodynamics to the muscle which he viewed as a self-regulated linear energy converter. Using Caplan's theory, Wilkie and Woledge (2) derived equations relating the variations in the driving chemical rate and chemical free energy with load. Wilkie and Woledge then compared the theoretically predicted driving chemical rates with chemical rates implied from experimental heat data. Since theory and experiment did not agree on this basis and also because of the large chemical force variations which they calculated, they concluded that the muscle is not an energy converter of the type described by Caplan. However, in

recent papers Caplan points out (3, 4) that the criticisms of Wilkie and Woledge involve some questionable assumptions, especially in the calculation of the driving chemical rates from heat data. Furthermore, Wilkie and Woledge chose a set of parameters which are mathematically inconsistent with Caplan's theory, thus, making the discrepancy between theory and experiment worse than it should have been.

The theory can be tested without the uncertainties surrounding the relation between the driving chemical rates and the heat rates by making a direct comparison of the theory with chemical data. Unfortunately, however, the existing techniques for taking chemical data do not permit sufficient time resolution to determine meaningful chemical rates. One can circumvent this difficulty by integrating the theoretical rate equations and then comparing the results directly with experimental data. This technique is described below and the resulting direct comparison with chemical data is given.

SUMMARY OF CAPLAN'S THEORY

Following the formulations of irreversible thermodynamics, we first write an expression for the rate at which entropy is generated by virtue of the coupled irreversible processes being considered. As shown by Caplan (1) the entropy generation rate 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 at which the load moves, A the affinity of the reaction driving the contraction, and v the driving chemical rate. Assuming a linear system, the phenomenological equations relating the fluxes and forces are

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

and

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

where the transport coefficients L_{11}, L_{22}, L_{12}, and L_{21} are unknown coefficients which must be determined from experimental measurements. Consistent with the assumption of linearity, the transport coefficients may not be functions of the driving forces P and A but may be a function of the state of the system.

Derivation of Chemical Rate Equation

Equations 2 and 3 are the same as those used by Caplan (1, 3, 4), as well as Wilkie and Woledge (2). The procedure here will be to combine Equations 2 and 3 in

order to eliminate the force A and to express the transport coefficients in terms of more physically meaningful quantities (i.e., quantities capable of being determined experimentally).

Solving for A from Equation 2 and substituting into Equation 3 we obtain

$$v = (L_{11} L_{22}/L_{12} - L_{21}) P + (L_{22}/L_{12})V. \tag{4}$$

For an isometric contraction the load is the isometric load, P_o, and the velocity is equal to zero. From equation 4 it follows that

$$\frac{v_o}{P_o} = (L_{11}L_{22}/L_{12} - L_{21}) \tag{5}$$

where v_o denotes the chemical reaction rate for the isometric contraction. Similarly, for zero load isotonic contraction the load is zero and the velocity is the maximum velocity, V_m. Equation 4 then gives

$$\frac{v_m}{V_m} = \frac{L_{22}}{L_{12}} \tag{6}$$

where v_m denotes the zero load isotonic chemical reaction rate. Combining Equations 4, 5, and 6 we obtain an expression for the chemical rate,

$$v = \frac{v_o}{P_o} P + \frac{v_m}{V_m} V. \tag{7}$$

Equation 7 relates the driving chemical rate, v, to the load, P, the velocity V, and the two parameters, v_o/P_o and v_m/V_m. Equation 7 could be checked directly with chemical data if reasonably accurate chemical measurements could be taken for the short periods during which both P and V could be assumed to be constant. By integrating Equation 7 over a longer period of contraction, existing chemical data may be used to check directly the irreversible thermodynamic theory.

INTEGRATION OF CHEMICAL RATE EQUATION AND COMPARISON WITH CHEMICAL DATA

In the following derivation it is assumed that the driving chemical reaction is the phosphorylcreatine (PC) reaction, and the decrease in PC is denoted at $-\Delta$PC. Of course, the results are equally valid for contractions where the resynthesis of adenosine triphosphate (ATP) is inhibited, in which case the ATP reaction becomes the driving reaction.

The decrease in PC associated with a contraction starting at time zero ($t = 0$) and ending at time t_f ($t = t_f$) can be determined from Equation 7.

$$-\Delta\text{PC} = \int_0^{t_f} v\, dt = \int_0^{t_f} \frac{v_o}{P_o} P\, dt + \int_0^{t_f} \frac{v_m}{V_m} V dt. \tag{8}$$

If we assume that the transport coefficients L_{11}, L_{22}, and L_{12} are constant during the contraction, then it is clear from Equations 5 and 6 that v_o/P_o and v_m/V_m are also constant. Clearly P_o changes with time (which is equivalent to saying P_o is a function of the change of muscle length) as is evident from a length-tension curve. In order to keep the ratio v_o/P_o constant, v_o must vary in exactly the same way as P_o varies. The similarity in the variation of P_o and v_o has been clearly demonstrated experimentally, for reasonable length changes, for both frog rectus abdominis muscles (see Fig. 2 in reference 6) and frog sartorius muscles (see Fig. 2 in reference 7). This is consistent with the assumption that the transport coefficients are constant with muscle length. The constancy of v_o/P_o and v_m/V_m permit them to be moved in front of the integral signs and Equation 8 becomes

$$-\Delta PC = \frac{v_o}{V_o}\int_0^{t_f} P\,dt + \frac{v_m}{V_m}\int_0^{t_f} V\,dt. \tag{9}$$

Muscle experiments are customarily done with either an isotonic lever where the load remains approximately constant or with an ergometer in which case the velocities remain approximately constant. The integrations of Equation 9 are handled differently for each of these experiments, thus we shall do each separately.

Isovelocity Contractions

If the muscle contracts while attached to an ergometer, V is constant and the work done by the muscle, W, becomes

$$W = \int_0^{t_f} PV\,dt = V\int_0^{t_f} P\,dt. \tag{10}$$

Equation 10 is used to replace the force integral in Equation 9 and since V is constant, the velocity integral becomes Vt_f. Equation 10 then gives

$$-\Delta PC = \left(\frac{v_o}{P_o}\right)\frac{W}{V} + \left(\frac{v_m}{V_m}\right)Vt_f. \tag{11}$$

Kushmerick (8) has reported isovelocity chemical data for frog sartorius muscles where all the variable quantities in Equation 11 were directly measured. The muscles contracted from about 130% to 50% of the *in situ* rest length, which is well outside of the range where v_o/P_o was shown experimentally to be approximately constant (see Fig. 2 of reference 7). In any case, Kushmerick's data shows trends which are consistent with Equation 11; however, since the scatter is excessive the results are not presented here.

Isotonic Contractions

If the muscle contracts while attached to an isotonic lever, P is constant and Equation 9 becomes

$$-\Delta PC = \left(\frac{v_o}{P_o}\right) Pt_f + \left(\frac{v_m}{V_m}\right) \Delta l \qquad (12)$$

where Δl, the distance the muscle shortened, replaces the velocity integral. Equation 12 can be directly compared with mechanochemical data reported by Cain, Infante, and Davies (5, 9). Their data as presented in Table III of reference 5 are reproduced in Table I.

TABLE I

EXPERIMENTAL DATA FOR FROG RECTUS ABDOMINIS MUSCLES TAKEN FROM TABLE III OF CAIN, INFANTE, AND DAVIES (5)

Pairs of muscles	$\frac{l_0 - l_s}{l_0} \times 100$	ΔPCr (muscle)	External work (muscle)	Stimulation time (12 pulses/sec)
	Constant shortening—varying external work			
		μmole/g	*g-cm/g*	*sec*
10	19.6±2.24	−0.23±0.15	21.7±1.9	0.6±0.1
10	20.2±2.82	−0.36±0.16	30.8±2.3	1.2±0.1
10	20.5±2.27	−0.47±0.26	46.6±2.3	1.6±0.2
8	21.1±1.28	−0.58±0.18	55.2±0.9	2.0±0.4
5	19.7±3.13	−0.77±0.24	64.2±6.0	2.6±0.5
	Varying shortening—approx. constant external work			
11	10.7±0.81	−0.44±0.22	36.3±4.7	1.9±0.4
11	18.5±0.75	−0.44±0.16	37.3±4.6	1.0±0.2
11	23.4±0.31	−0.48±0.21	39.3±5.1	1.2±0.2
9	29.5±1.08	−0.54±0.11	50.8±4.3	2.0±0.4

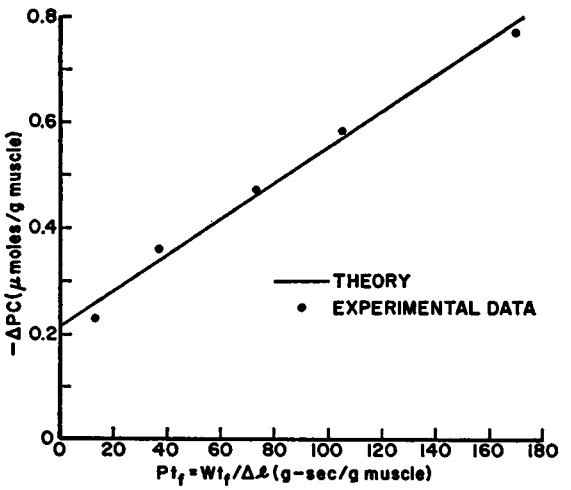

FIGURE 1 Comparison of theoretical and experimental variation of PC splitting as a function of the parameter $Wt_f/\Delta l$ for constant shortening. Straight line variation predicted by theory, Equation 13. Data by Cain, Infante, and Davies (Table III, reference 5) reproduced herein as Table I.

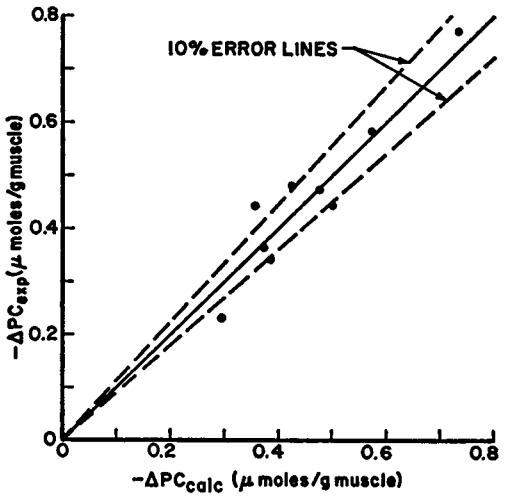

FIGURE 2 Comparison of measured PC splitting, ΔPC_{exp} with calculated PC splitting, ΔPC_{calc}. Calculated values from Equation 13. Measured values from data by Cain, Infante, and Davies (Table III, Reference 5) reproduced herein as Table I.

Since the loads were not reported in Table III of reference 5, the load P in Equation 12 is replaced by its equivalent $W/\Delta l$. Thus, Equation 12 becomes

$$-\Delta PC = \left(\frac{v_o}{P_o}\right)\frac{Wt_f}{\Delta l} + \left(\frac{v_m}{V_m}\right)\Delta l. \tag{13}$$

For constant shortening, a condition which is approximately true for the first block of data in Table I, Equation 13 predicts that ΔPC should be a linear function of the variable $Wt_f/\Delta l$. This first block of data from Table I is plotted in Fig. 1 with ΔPC as the ordinate and $Wt_f/\Delta l$ the abscissa. As predicted by the theory, the data lie on a straight line with very little scatter. The remaining data in Table I can also be compared with Equation 13; however, since three variables are now involved (i.e., ΔPC, $Wt_f/\Delta l$, and Δl) it is more convenient to show the comparison on a ΔPC_{exp} vs. ΔPC_{calc} plot, where ΔPC_{exp} is the measured value and ΔPC_{calc} is the value calculated from Equation 13. The constants, (v_o/P_o) and $v_m/V_m)$ were determined by the best least squares fit using all the data in Table I. The distance shortened, Δl, was calculated from the per cent shortening listed in Table I using 5 cm as the *in situ* rest length as given in reference 9. The results are plotted in Fig. 2; the values of v_o/P_o and v_m/V_m, which give the best fit to the data are 0.00276 μmole/g-sec and 0.268 μmole/cm-g muscle, respectively. These values for the constants are slightly different from those obtained using just the first block of data in Table I. The agreement between theory and experiment, shown in Fig. 2, is within the expected accuracy of the experimental data.

Calculation of the Chemical Rate Ratio v_m/v_o

It is interesting to calculate the ratio v_m/v_o since with this ratio additional information can be extracted from the theory. By dividing the constant v_m/V_m by v_o/P_o

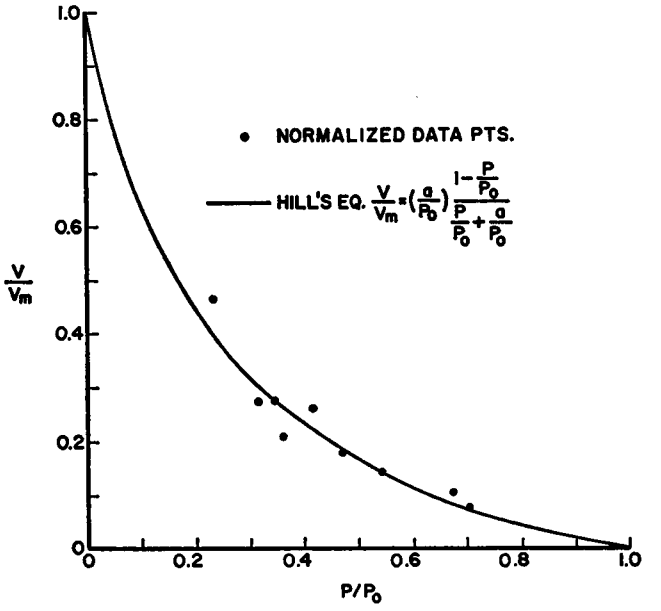

FIGURE 3 Comparison of data from Table I with Hill's force-velocity relation for a/P_o = 0.25, P_o = 97.0 g/g muscle, and V_m = 3.53 cm/sec.

and using the values for these constants which gave the best fit to the experimental data we find that

$$\frac{v_m}{v_o} = \frac{(v_m/V_m)}{(v_o/P_o)} \frac{V_m}{P_o} = 97.1 \frac{V_m}{P_o} \tag{14}$$

where the units for V_m and P_o are cm/sec and g/g muscle, respectively. To obtain values for V_m and P_o which are representative of the muscles used in this comparison we first calculated values for the load P and average velocity V directly from Table I. The load P was calculated by dividing W by Δl, and the average velocity V was calculated by dividing Δl by the time, t_f. The values of P_o and V_m were then determined by the best least squares fit to Hill's force-velocity relation with the commonly accepted value of 0.25 for (a/P_o). The value 3.53 cm/sec was obtained for V_m and 97.0 g/g muscle for P_o. Fig. 3 shows the resulting fit of the data to Hill's force-velocity equation. Relating the average velocity to load by the Hill's force-velocity relation appears to be reasonable in light of the recent work of Matsumoto (10). Matsumoto's experiments indicate that for afterloaded isotonic shortening the Hill's force-velocity relation is valid for lengths less than l_o and that the constants a/P_o and b/l_o remain fixed throughout the length change. The value of P_o using this procedure is an average P_o and thus is expected to be less than the maximum isometric force developed at the *in situ* rest length. Even so, the value 97.0 g/g muscle for P_o is unexpectedly low; however, this value of P_o

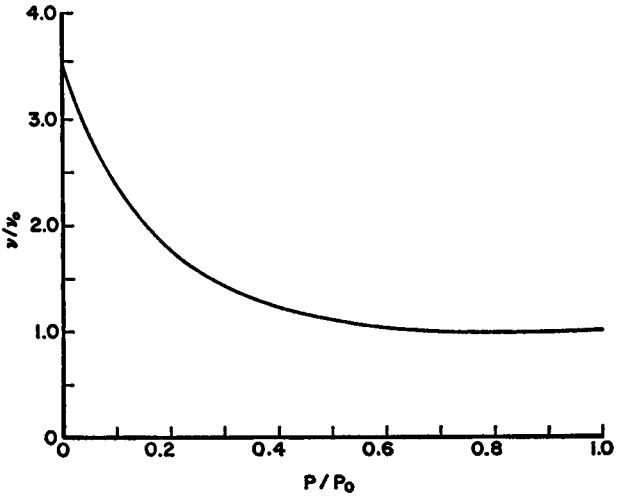

FIGURE 4 The relation between normalized chemical rate and normalized load. Curve calculated from Equation 15 with $v_o/v_m = 3.53$.

will be used herein since it is consistent with Hill's force-velocity relation. With these values for V_m and P_o, Equation 14 gives a value of 3.53 for the ratio v_m/v_o. This value seems to be reasonable and is close to the value of 3 suggested by Caplan (reference 3, p. 1163) on the basis that this would result in optimal regulation.

The normalized chemical rate v/v_o can now be determined as a function of the normalized load P/P_o. Rearranging Equation 7, we obtain

$$\frac{v}{v_o} = \frac{P}{P_o} + \left(\frac{v_m}{v_o}\right)\frac{V}{V_m} \tag{15}$$

where V/V_m is determined from Hill's force-velocity relation assuming 0.25 for a/P_o. Equation 15 is plotted on Fig. 4 using the calculated value of 3.53 for v_m/v_o. As was pointed out by Wilkie and Woledge (2) and is evident from Fig. 4, the shape of the chemical rate curve is inconsistent with the chemical rates calculated from heat data. Caplan (3, 4) discusses this point at length and points out that other energy-producing reactions may be occurring. The reason for the apparent discrepancy between the chemical and heat rates is not at all clear at this time and requires further investigation.

The theory up to this point has not involved any of the Caplan's muscle regulation concepts (1, 3, 4) but only the general concepts of irreversible thermodynamics. Now, however, we shall invoke Caplan's regulation theory in order to calculate the chemical affinity and efficiency.

Evaluation of Chemical Affinity

An expression for the chemical affinity is obtained by relating the constants in Equation 2 to the chemical affinities at the isometric and unloaded isotonic points.

This gives

$$A = A_o \frac{P}{P_o} + A_m \frac{V}{V_m} \tag{16}$$

where A_m and A_o denote the affinity of the driving chemical reaction at the isometric and unloaded isotonic conditions, respectively. Now we proceed to relate the constants A_o and A_m to the experimentally determined constants discussed above.

From Caplan's theory the following relations among the chemical and mechanical constants can be derived (see Equation 28, reference 3; and Equations A1 and A2, reference 4)

$$A_o = P_o \frac{V_m}{v_m} (a/P_o + 1) \tag{17}$$

and

$$A_m = V_m \frac{P_o}{v_o} (a/P_o). \tag{18}$$

Onsager symmetry is implicit in Equations 17 and 18. Prior to Equation 17, Onsager symmetry was not invoked. The chemical affinities A_o and A_m can be calculated from Equations 17 and 18 using, as before, a value of 0.25 for a/P_o and the experimentally determined constants from above; P_o = 97 g/g muscle, V_m = 3.53 cm/sec, v_m/V_m = 0.268 μmoles/cm g muscle, and v_o/P_o = 0.00276 (μmoles/sec)/g. The resulting values are

$$A_o = 452 \text{ g-cm}/\mu\text{mole} = 10.6 \text{ k cal/mole}$$

and

$$A_m = 320 \text{ g-cm}/\mu\text{mole} = 7.5 \text{ k cal/mole}.$$

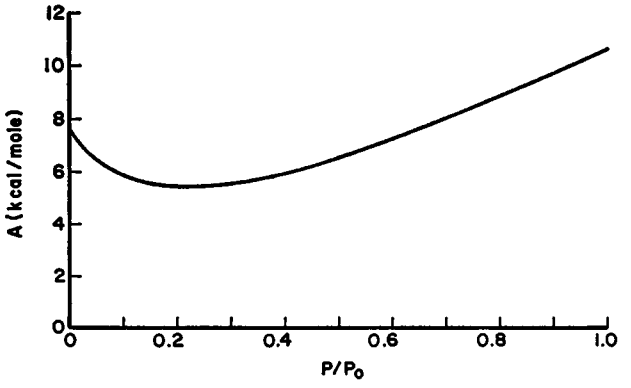

FIGURE 5 The relation between chemical affinity and normalized load. Curve calculated from Equation 16 with A_o = 10.6 k cal/mole and A_m = 7.5 k cal/mole.

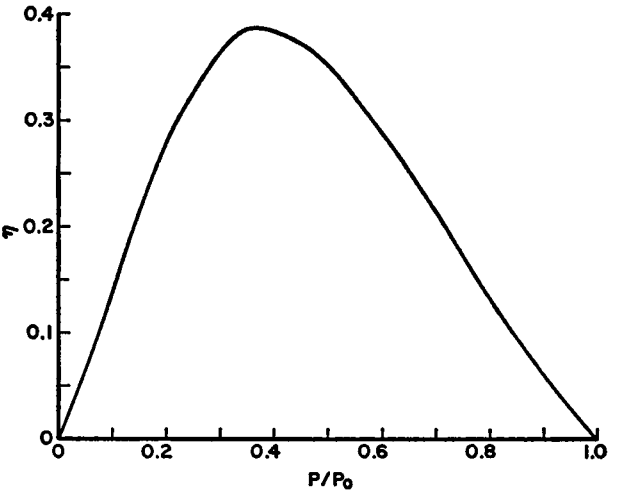

FIGURE 6 The relation between thermodynamic efficiency and normalized load. Curve calculated from Equation 15 as described in text.

The variation of A with P/P_o obtained from Equation 16 is shown in Fig. 5. The chemical affinities are not normalized on Fig. 5 in order to emphasize their absolute values. It is, indeed, interesting that the maximum value predicted here for the chemical affinity is 10.6 k cal/mole. This value is within the range (10.3–12.8 k cal/mole) estimated by Wilkie and Woledge (see reference 2, p. 21) for the bulk in vivo free energy change for PC splitting.

Evaluation of Efficiency

The efficiency, η, is the output power, PV, divided by the input power, vA. It follows that

$$\eta \equiv \frac{PV}{vA} = \left(\frac{P_o V_m}{v_o A_o}\right)\left(\frac{PV}{P_o V_m}\right)\left(\frac{v_o A_o}{vA}\right) = 2.83\left(\frac{P}{P_o}\right)\left(\frac{V}{V_m}\right)\left(\frac{v_o}{v}\right)\left(\frac{A_o}{A}\right). \quad (19)$$

The efficiency η can then be determined as a function of P/P_o by obtaining V/V_m from Hill's force-velocity relation, v/v_o from Equation 15, and A/A_o from Equation 16. The plot of η versus normalized load is given in Fig. 6. The maximum value of the efficiency obtained from Fig. 6 is 38.2%, as it must be for an a/P_o of 0.25 (see Equations 4 and 28, reference 3).

CONCLUSIONS

The linear phenomenological equations of irreversible thermodynamics as applied to the muscle indicate that, for an isometric contraction, the ratio of chemical rate to the load should be constant for any muscle length. This conclusion was

found to be consistent with experimental data (6, 7). This result permitted the linear rate equation to be directly integrated with time to obtain the relationship among actual total quantities, instead of rates, and thus permitted the theory to be compared to chemical data obtained by current experimental techniques.

Using the integrated equation, the theory was compared to existing experimental data in four ways with the following results: (*a*) the variation of ΔPC as measured by Cain, Infante, and Davies (5) for isotonic contractions was shown to be almost exactly as predicted by the theory (see Fig. 1); (*b*) the value of the chemical rate ratio, v_m/v_o, obtained from these data was 3.53 which is close to the value of 3 suggested by Caplan (3) on the basis of optimal regulation; (*c*) using Caplan's regulation theory the maximum value of the chemical affinity for PC splitting was found to be 10.6 k cal/mole which is within the range expected by Wilkie and Woledge (2) (i.e. 10.3–12.8 k cal/mole); (*d*) however, the predicted variation of the driving chemical rate was found to be inconsistent with the chemical rates inferred from heat data (2). This last finding does not invalidate the theory as such, since, as described by Caplan (3, 4) questionable assumptions are involved in the calculation of chemical rates from heat data.

Because of the excellent agreement between theory and experiment, we believe that Caplan's theory definitely warrants further investigation.

APPENDIX

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).
- m Subscript denoting unloaded isotonic contraction.
- o Subscript denoting isometric contraction.
- P Load on the muscle.
- S Entropy ($\dot{S} = dS/dt$).
- T Temperature.
- t Time (t_f denotes time of muscle contraction).
- V Velocity of shortening.
- v Rate of driving reaction.
- W Work done by muscle during contraction.
- Δl Distance muscle shortened.
- ΔPC Change in phosphorylcreatine (ΔPC_{exp} and ΔPC_{calc} denote experimental and calculated values, respectively).
- η Thermodynamic efficiency.

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