A DISTRIBUTION-MOMENT MODEL OF ENERGETICS IN SKELETAL MUSCLE

SHIPING MA* and GEORGE I. ZAHALAK†

Department of Mechanical Engineering, Washington University, St Louis, MO 63130, U.S.A.

Abstract—In this paper we develop a theory for calculating the chemical energy liberation and heat production of a skeletal muscle subjected to an arbitrary history of stimulation, loading, and length variation. This theory is based on and complements the distribution-moment (DM) model of muscle [Zahalak and Ma, J. Biomech. Engng 112, 52–62 (1990)]. The DM model is a mathematical approximation of the A. F. Huxley cross-bridge theory and represents a muscle in terms of five (normalized) state variables: A, the muscle length; c, the sarcoplasmic free calcium concentration; and Q₀, Q₁, Q₂, the first three moments of the actin-myosin bond distribution function (which, respectively, have macroscopic interpretations as the muscle stiffness, force, and elastic energy stored in the contractile tissue).

From this model are derived two equations which predict the chemical energy liberation and heat production rates in terms of the five DM state variables, and which take account of the following factors: (1) phosphocreatine hydrolysis associated with cross-bridge cycling; (2) phosphocreatine hydrolysis associated with sarcoplasmic-reticulum pumping of calcium; (3) passive calcium flux across the sarcoplasmic-reticulum membrane; (4) calcium–troponin bonding; (5) cross-bridge bonding at zero strain; (6) cross-bridge strain energy; (7) tendon strain energy; and (8) external work. Using estimated parameters appropriate for a frog sartorius at 0°C, the energy rates are calculated for several experiments reported in the literature, and reasonable agreement is found between our model and the measurements. (The selected experiments are confined to the plateau of the isometric length–tension curve, although our theory admits arbitrary length variations.) The two most important contributions to the energy rates are phosphocreatine hydrolysis associated with cross-bridge cycling and with sarcoplasmic-reticulum calcium pumping, and these two contributions are approximately equal under tetanic, isometric, steady-state conditions. The contribution of the calcium flux across the electrochemical potential gradient at the sarcoplasmic-reticulum membrane was found to be small under all conditions examined, and can be neglected.

Long-term fatigue and oxidative recovery effects are not included in this theory. Also not included is the so-called 'unexplained energy' presumably associated with reactions which have not yet been identified. Within these limitations our model defines clear quantitative interrelations between the activation, mechanics, and energetics in muscle, and permits rational estimates of the energy production to be calculated for arbitrary programs of muscular work.

INTRODUCTION

Muscle is a fascinating substance which converts stored chemical energy into mechanical work, but unlike a heat engine it does so at essentially constant temperature. The mechanics and biochemical energetics of muscle are intimately and inseparably linked. As this energy conversion is such a central feature of muscle behavior, it is highly desirable that quantitative models of muscle be able to account for it. One of the great virtues of the mathematical cross-bridge theories first introduced by Huxley (1957), and developed by many workers since then, is that they preserve the close connection between mechanics and energetics. Unfortunately, elegant as they are, the Huxley-type models are too complicated to serve as tractable mathematical representations of the muscle actuators in motor control studies of humans and other animals.

We have developed in a series of previous papers an approach to muscle modeling, called the Distribution-Moment (DM) Approximation, which extracts simplified low order state-variable models of muscle directly from Huxley-type cross-bridge theories. Initially the DM model was confined to contraction dynamics (Zahalak, 1981, 1986; Ma and Zahalak, 1987a) but we have recently extended the theory to include time-varying calcium–activation dynamics (Ma and Zahalak, 1987b, 1988; Zahalak and Ma, 1990), yielding a coupled activation–contraction DM model for a muscle fiber or motor unit. In this paper we take the next logical step in model development and couple the existing DM model (in which much of the energetics is implicit) to a newly developed model which describes the biochemical energetics of muscle—the chemical energy liberation rate and heat production rate. We have published some previous efforts aimed at including energetics within the framework of the DM model (Zahalak, 1986; Ma and Zahalak, 1987a) but these were confined to energy associated with contraction only and did not include energy associated with activation. The present paper can be viewed as an extension and generalization of these prior efforts.

Our new energetics model builds on our previously developed activation–contraction DM model. It is not possible or necessary for us to repeat in this paper the
development of the latter. We must assume in our exposition that the reader has some familiarity with the DM concept; the theory is most fully developed in Zahalak and Ma, 1990.

THE ENERGETICS MODEL

There are several processes that are known to contribute to energy release in contracting muscle; in addition there appear to be contributions from 'unknown' processes, at least in some muscles (Woledge et al., 1985; Kushmerick, 1983). In attempting to build a tractable model of muscle energetics we have focused on those processes which seem most important and are best understood. These are summarized schematically in Fig. 1, and are as follows. The immediate source of chemical energy for contraction is a pool of free ATP in solution in the cytosol (sarcoplasm) bathing the myofilaments. Each cycle of cross-bridge attachment and detachment requires the hydrolysis of one ATP molecule to ADP, and this free energy release drives muscle contraction. In order for a myosin cross-bridge to interact with an actin binding site, however, the latter must be activated by calcium ions (Ebashi and Endo, 1968; Ruegg, 1986) which diffuse passively from the sarcoplasmic reticulum (SR) in response to a concentration gradient. This diffusion is permitted only when the SR membrane is excited electrically by a muscle action potential. The diffusing calcium ions activate the contractile machinery by binding to the protein troponin-C which is attached to the actin filaments (in Fig. 1 actin and troponin-C have been separated for clarity). Calcium ions are pumped back into the SR by ATP-consuming pumping proteins located in the SR membrane; two calcium ions are translocated across the membrane for each molecule of ATP hydrolyzed by the pumping protein (Weber et al., 1966). It should be noted that the calcium ions are driven not only by a concentration gradient but also by an electrical potential difference as, at least in active muscle, the interior of the SR is at a lower electrical potential than the exterior (Somlyo et al., 1981). Once inside the SR the calcium ions bind reversibly to a storage protein, calsequestrin, which maintains the free calcium concentration inside the SR relatively constant (Hasselbach and Oetliker, 1983; Somlyo et al., 1981).

There is one more important reaction to consider. Under normal conditions no depletion of ATP is detectable because the ADP formed in the contraction and pumping processes is immediately re-phosphorylated back to ATP via the Lohmann reaction (Kushmerick, 1983).

\[
\text{ADP} + \text{PCr} \rightleftharpoons \text{ATP} + \text{Cr} \quad (1)
\]

which uses a pool of phosphocreatine (PCr) available in the sarcoplasm outside the SR.

In order to convert this qualitative description into a quantitative model of muscle energetics we begin with some basic thermodynamic considerations. According to the First Law we can write for the contractile tissue under constant pressure

\[
d\mathcal{H} - d\mathcal{U} + d(pV) = -(dQ^+ + dW_e) \quad (2)
\]

where \(\mathcal{U}\) is the internal energy, \(p\) is the pressure, \(V\) is the volume, \(\mathcal{H}\) is the enthalpy, \(Q\) is the heat transferred from the system, and \(W_e\) is the external work done by the contractile tissue (in addition to the \(dpV\) work). As muscular contraction occurs at essentially constant volume (Baskin and Paolini, 1965; Wilkie, 1975) and pressure (Carlson and Wilkie, 1974; Wilkie. 1975; Kushmerick, 1983) we have \(d\mathcal{H} = d\mathcal{U}\). The Gibbs equa-

![Fig. 1. Schematic diagram of the major processes contributing to energy liberation in skeletal muscle. Compartment 1 is the interior of the sarcoplasmic reticulum (SR) and Compartment 2 is the sarcoplasm outside the SR. The electrical potentials are indicated as \(\phi^{(1)}\) and \(\phi^{(2)}\), and the major participating chemical species are indicated (see text for details). Attached and detached cross-bridges are indicated, respectively, as A and D. Troponin C (TNC) is located physically on the thin actin myofilaments, but has been separated in the diagram for clarity.](image-url)
tion for the system (Kestin, 1966) can be written as
\[
d\hat{H} = T \left( \frac{\delta S}{\delta T} \right)_{p,n} dT + \left[ T \frac{\delta S}{\delta P} \right]_{T,n} + \hat{\nu} dP + \sum_i \hat{h}_i d\hat{n}_i
\]
(3)
where \( \hat{S} \) is the system entropy, \( \hat{h}_i \) are the partial molar enthalpies of the chemical constituents, and \( \hat{n}_i \) are the mol numbers of these constituents. Noting again that contraction proceeds at constant pressure, equation (3) reduces to
\[
d\hat{H} = \sum_i \hat{h}_i d\hat{n}_i + C_v dT,
\]
recognizing that \( T(\delta S/\delta T)_{p,n} = C_p = C_v \), the specific heat. (The specific heats at constant pressure and constant volume are equal in this incompressible material.) As we have not written an explicit term for electrostatic energy this is assumed to be included in the \( \hat{h}_i \).

Our model assumes that the following chemical species are important for the energetics of contraction: adenosine triphosphate (ATP), adenosine diphosphate (ADP), inorganic phosphate (P), phosphocreatine (PCr), creatine (Cr), calcium ions (Ca), troponin-C (TNC), calsequestrin (CAS), detached myosin cross-bridges (D), myosin cross-bridges attached to actin (A), calcium bound to troponin-C (TNCCa), and calcium bound to calsequestrin (CASCa); except for calcium, calsequestrin and their combination all these species are found only outside the SR. Thus we write equation (4) explicitly as
\[
(d\hat{H} - C_v dT) = \hat{h}_{\text{Cr}} d\hat{n}_{\text{Cr}} + \hat{h}_{\text{PCr}} d\hat{n}_{\text{PCr}} + \hat{h}_{\text{D}} d\hat{n}_{\text{D}} + \hat{h}_{\text{ATP}} d\hat{n}_{\text{ATP}} + \hat{h}_{\text{Cr}} d\hat{n}_{\text{Cr}} + \hat{h}_{\text{ATP}} d\hat{n}_{\text{ATP}} + \sum_i \hat{h}_i d\hat{n}_i
\]
(5)
The superscripts (1) and (2) refer, respectively, to the interior and exterior of the SR. Actually, the energy of the attached cross-bridges depends on their bond length, so this species should be subdivided into many sub-species, each with a given value of bond length; we will suppress this bond-length dependence for now and return to it presently.

We now reduce equation (5) by making several observations about the variations in the mol numbers. Firstly, in the absence of fatigue, the Lohmann reaction maintains the ATP and ADP levels constant (Woledge et al., 1985), so \( d\hat{n}_{\text{ATP}} = d\hat{n}_{\text{ADP}} = 0 \). Secondly, conservation of mass for calcium ions outside the SR requires that \( d\hat{n}_{\text{Ca}} = d\hat{n}_{\text{CAS}} - d\hat{n}_{\text{CASCa}} \), where \( d\hat{n}_{\text{Ca}} \) is the net increase of calcium transported across the SR membrane into the SR. Next, equation (1) implies that \( d\hat{n}_{\text{PCr}} = -d\hat{n}_{\text{Cr}} \), and as one Cr molecule is produced by this reaction for each inorganic phosphate molecule released by ATP we have \( d\hat{n}_{\text{Cr}} = -d\hat{n}_{\text{P}} \). Further, as the total amounts of troponin and calsequestrin are fixed, we must have \( d\hat{n}_{\text{TNC}} = -d\hat{n}_{\text{TNCCa}} \) and \( d\hat{n}_{\text{CAS}} = -d\hat{n}_{\text{CASCa}} \). Conservation of mass for calcium ions outside the SR requires \( d\hat{n}_{\text{Ca}}^{(1)} + d\hat{n}_{\text{TNCCa}} = -d\hat{n}_{\text{Cr}} \). Finally, as in the current DM model, there are only two possible states, attached and detached, assumed for a cross-bridge; the molar fluxes must balance, so \( d\hat{n}_{\text{D}} = -d\hat{n}_{\text{A}} \) (this must hold true for the entire ensemble of cross-bridges, and also for each sub-ensemble of a partition according to bond-length). Using the preceding results, equation (5) can be simplified to
\[
d\hat{H} = C_v dT = \hat{h}_{\text{Ca}} d\hat{n}_{\text{Ca}} + \hat{h}_{\text{TNC}} d\hat{n}_{\text{TNCCa}} + \hat{h}_{\text{ATP}} d\hat{n}_{\text{ATP}} + \hat{h}_{\text{Cr}} d\hat{n}_{\text{Cr}} + \hat{h}_{\text{ATP}} d\hat{n}_{\text{ATP}} + \sum_i \hat{h}_i d\hat{n}_i
\]
where
\[
\Delta\hat{h}_{\text{Ca}} = \hat{h}_{\text{Ca}}^{(1)} - \hat{h}_{\text{Ca}}^{(2)}
\]
\[
\Delta\hat{h}_{\text{TNC}} = \hat{h}_{\text{TNC}}^{(1)} - \hat{h}_{\text{TNC}}^{(2)}
\]
\[
\Delta\hat{h}_{\text{PCr}} = \hat{h}_{\text{PCr}}^{(1)} - \hat{h}_{\text{PCr}}^{(2)}
\]
\[
\Delta\hat{h}_{\text{CASCa}} = \hat{h}_{\text{CAS}} - \hat{h}_{\text{D}}.
\]
The term \( \hat{h}_{\text{CASCa}} - \hat{h}_{\text{CAS}} - \hat{h}_{\text{CASCa}}^{(1)} - \hat{h}_{\text{CASCa}}^{(2)} \) has been eliminated from equation (6) on the ground that calcium binding to calsequestrin appears to be thermally neutral (Woledge et al., 1985).

These enthalpy differences have obvious interpretations. \( \Delta\hat{h}_{\text{Ca}} \) is the enthalpy change when calcium passes from outside to inside the SR, \( \Delta\hat{h}_{\text{TNC}} \) is the enthalpy of binding of calcium to troponin, \( \Delta\hat{h}_{\text{PCr}} \) is the enthalpy of phosphocreatine hydrolysis, and \( \Delta\hat{h}_{\text{Ca}} \) is the enthalpy of cross-bridge attachment. \( \Delta\hat{h}_{\text{TNC}} \) and \( \Delta\hat{h}_{\text{PCr}} \) have been measured directly in experiments; \( \hat{h}_{\text{Ca}}, \hat{h}_{\text{ATP}} \) and \( \hat{h}_{\text{ATP}} \) require further discussion.

Firstly, we can write the thermodynamic relation
\[
\Delta\hat{h}_{\text{Ca}} = \Delta\hat{\phi}_{\text{Ca}} + T\Delta\hat{S}_{\text{Ca}}
\]
(7)
where \( \Delta\hat{\phi}_{\text{Ca}} \) and \( \hat{S}_{\text{Ca}} \) represent, respectively, the partial molar Gibbs function and entropy, and \( T \) is the absolute temperature. The partial molar Gibbs function is the electrochemical potential which, for a dilute solution of divalent calcium ions takes the form (Stryer, 1981)
\[
\Delta\hat{\phi}_{\text{Ca}} = RT \ln \left( \frac{[\text{Ca}^{(1)}]}{[\text{Ca}^{(2)}]} \right) + 2F(\phi^{(1)} - \phi^{(2)})
\]
(8)
where brackets indicate concentration, \( \phi \) is electrical potential, \( R \) is the gas constant, and \( F \) is Faraday's constant. On the other hand, using the expression for the entropy of a dilute solution (Kestin, 1966) it is easy to show that
\[
\Delta\hat{S}_{\text{Ca}} = -\ln \left( \frac{[\text{Ca}^{(1)}]}{[\text{Ca}^{(2)}]} \right)
\]
(9)
which, when combined with equations (7) and (8) yields
\[
\Delta\hat{h}_{\text{Ca}} = 2F(\phi^{(1)} - \phi^{(2)}).
\]
(10)
Although there appears to be some uncertainty concerning the importance of the contribution which a potential difference across the SR membrane makes to the energy flux in muscle (Hasselbach and Oetliker, 1983), we will include a term for this effect based on the following considerations. It has been estimated that in resting muscle the SR membrane potential is very small (\(<5\,mV\)) but that in tetanized muscle it becomes about 56\,mV, with the SR interior negative (Somlyo et al., 1981). In order to avoid dealing with detailed models of SR membrane dynamics we will assume simply that the transmembrane voltage increases linearly with sarcoplasmic free calcium concentration from a value of zero at zero calcium concentration (relaxed muscle) to a value of 56\,mV at a calcium concentration typical of sustained tetanus (10^-5\,M)—and remains constant for higher concentrations. While this is admittedly by rough empirical assumptions we feel it is adequate at this stage of modelling for an effect which is not expected to be large in the overall energy budget. The mathematical expression of this approximation is: \(\dot{\psi} = \frac{m}{N} \frac{\partial n}{\partial t} + \frac{m}{N} \frac{\partial n}{\partial t} \), where \(\Delta V_0 = 56\,mV\) and

\[
\zeta([Ca]) = \begin{cases} 
0 & \text{for } [Ca] < 0 \\
[Ca]/10^{-5} & \text{for } 0 < [Ca] < 10^{-5} \, M \\
1 & \text{for } 10^{-5} < [Ca]. 
\end{cases}
\]

We turn next to \(\Delta H_{CB}\). For this and subsequent calculations we must draw on results developed in our previous publications on the DM model, particularly Zahalak and Ma (1990). Consider a unit volume of contractile tissue and let \(x\) represent bond length—that is, the distance of the nearest actin binding site to the neutral equilibrium position of a cross-bridge. Then, according to the Huxley two-state cross-bridge model, the number of cross-bridges with bond length lying in the interval \((x, x + dx)\) is \(m(dx/l)\) (a constant independent of time) where \(m\) is the number of cross-bridges per unit volume and \(l\) is the distance between actin binding sites; the number of these cross-bridges which are attached is \(m(dx/l)n(x, t)\), where \(n(x, t)\) is the Huxley bond-distribution function. Thus we may consider the total collection of cross-bridges partitioned into sub-ensembles with respect to bond length, where the fixed limits \(x\) and \(x + dx\) define a typical sub-ensemble.

For any chemical species we may express the partial molar enthalpy as \(\overline{f_{ii}} = \overline{E_{ii}} + \overline{p_{ii}}\), where \(\overline{E_{ii}}\) and \(\overline{p_{ii}}\) are, respectively, the partial molar internal energy and volume, and \(p\) is the pressure. The energy of an attached cross-bridge can be considered as the sum of two parts (Hill, 1977): a purely 'chemical' part, \(\overline{E_{ii}^0}\), associated with attachment at the zero cross-bridge strain, and a strain energy of \(\frac{kx^2}{2}\), where \(k\) is the cross-bridge stiffness. Therefore for the sub-ensemble \((x, x + dx)\) the molar enthalpy change of cross-bridge bonding can be written as

\[
\Delta H_{CB}(x) = (\overline{E_{ii}^0} + \frac{1}{2}kx^2\,N + p\overline{\dot{\psi}}_A) - (\overline{E_{ii}} + p\overline{\dot{\psi}}_D) \tag{12}
\]

where \(N\) is Avogadro's number. We will assume that the partial molar volume of attached cross-bridges, \(\overline{V}_{A}\), is independent of cross-bridge strain. Then if we define \(\Delta H_{CB}^0 = (\overline{E_{ii}^0} - \overline{E_{ii}}) + p(\overline{\dot{\psi}}_A - \overline{\dot{\psi}}_D)\) as the molar enthalpy change of cross-bridge attachment at zero strain, we may write

\[
\Delta H_{CB} = \Delta H_{CB}^0 + \frac{1}{2}kx^2\,N. \tag{13}
\]

The rate of increase in the number of attached cross-bridges of the typical sub-ensemble is

\[
\frac{\partial n}{\partial t} = \frac{m}{N} \left( \frac{\partial n}{\partial t} \right) \tag{14}
\]

so summing over all the sub-ensembles, and multiplying by the volume of contractile tissue \(X_0A_0\), we obtain for the entire ensemble of cross-bridges

\[
\Delta H_{CB} \, d\dot{\psi}_A = X_0A_0 \int_{-\infty}^{\infty} \left\{ \Delta H_{CB}^0 + \frac{1}{2}kx^2\,N \right\} 
\times \frac{m}{N} \left( \frac{\partial n}{\partial t} \right) \, dx.
\]

The current DM model assumes that contractile tissue is an incompressible cylinder. Thus its volume can be written as the product of the contractile tissue length \(X_0\), and cross-sectional area, \(A_0\), in a 'standard state', where this state can conveniently be taken as the one in which maximum isometric tension is developed (see Zahalak and Ma, 1990).
\( \dot{E} \), defined above, is usually referred to in the muscle literature as the 'rate of chemical energy liberation'; it is equal to the sum of the work done and heat evolved by the muscle, including both the heat transferred across the muscle boundary and that absorbed in raising the temperature of the muscle. Although this temperature change is usually small, it is precisely what is measured in myothermic experiments.

To complete our analysis we must express the molar fluxes \( \dot{n}_{Ca} \), \( \dot{n}_{TNCCa} \), and \( \dot{n}_{Cr} \) in terms of the state variables of the DM model: \( \Lambda \) (normalized muscle length), \( \varepsilon \) (normalized sarcomplasmic free calcium concentration), \( Q_0 \) (zero moment, stiffness), \( Q_1 \) (first moment, force), and \( Q_2 \) (second moment, elastic energy). This can be done easily using our previously published results. In Zahalak and Ma (1990), we developed the following expression for the rate of calcium efflux from the SR:

\[
X_0 A_0 \left\{ R_0 \left( 1 - \frac{[Ca]}{[Ca]^*} \right) \chi(t) \right\}
\]

where \( [Ca] \) is the sarcomplasmic calcium concentration, \( \chi(t) \) is a pulse train representing a sequence of action potentials, \( R_0 \) is the calcium concentration injected by a single action potential in a rested muscle, and \( [Ca]^* \) is a constant with dimensions of concentration. On the other hand, the rate of calcium pumping into the SR was assumed to follow the Michaelis–Menten equation

\[
X_0 A_0 \left\{ V_m \frac{[Ca]}{[Ca] + K_m} \right\}
\]

where \( V_m \) and \( K_m \) are the two characteristic constants defining the transport kinetics. The net flux of calcium into the SR is therefore

\[
\dot{n}_{Ca} = X_0 A_0 \left\{ V_m \frac{[Ca]}{[Ca] + K_m} - R_0 \left( 1 - \frac{[Ca]}{[Ca]^*} \right) \chi(t) \right\}
\]

and, as noted previously,

\[
\dot{n}_{TNCCa} = -\dot{n}_{Ca} - X_0 A_0 [\dot{Ca}].
\]

We can divide \( \dot{n}_{Ca} \) into two parts: the flux associated with calcium pumping across the SR membrane, and the flux associated with actin–myosin contractile interactions. It is known that the SR calcium pump consumes one molecule of ATP for every two calcium ions transferred across the SR (Weber et al., 1966). As there is a one-to-one relation between ATP hydrolysis and PCr hydrolysis, expression (18) leads to the following molar PCr flux associated with calcium pumping

\[
\frac{X_0 A_0}{2} V_m \frac{[Ca]}{[Ca] + K_m}.
\]

To calculate the PCr flux associated with actin–myosin interactions we must consider a specific cross-bridge model. All our previous developments of the DM model have been based on two-state cross-bridge models of the type first proposed by Huxely (1957), and the thermodynamically 'self-consistent' version thereof proposed by Hill (Hill et al., 1975); we will continue to restrict ourselves to two-state cross-bridge models in this discussion of muscle energetics. Figure 2 shows a kinetic diagram for such a model, together with the assumed variations of the bonding and unbonding rate functions with bond length. Two distinct reactions paths are postulated between the detached and attached states and we follow Hill et al. (1975) in assuming that one molecule of ATP is hydrolyzed for each cross-bridge detachment via the 'second' path (attachment via this path—assumed to be an unlikely occurrence—would involve ATP synthesis). Thus the net rate of ATP hydrolysis is equal to the net rate of detachment via the second path, which from the kinetic diagram is equal to

\[
\frac{m h}{I} \int_{-\infty}^{\infty} \left\{ g(\xi, n(\xi, t), r) [\xi - n(\xi, t)] \right\} d\xi
\]

molecules per unit volume per unit time. In expression (22) \( \xi = x/h \), \( r \) is a pure function of sarcomplasmic calcium concentration, called the 'activation factor', and \( x \) is the fraction of participating cross-bridges.

![Fig. 2. (a) Kinetic diagram for a two-state cross-bridge model, showing two distinct reaction paths between the attached and detached states; (b) the corresponding rate functions vs dimensionless bond length \( \xi = x/h \). The analytic expressions for these rate functions are given in the Appendix. The dashed 'exponential tails' of \( f \) and \( f' \) are required in principle for self-consistency by the detailed balance relations (see Hill et al., 1975); but they have a very small effect on the DM model's behavior, and have been omitted in all calculations.](image-url)
(sometimes called the ‘overlap function’) (see Zahalak and Ma (1990) for details). The term \( r g'(\xi) \) represents the effective bonding rate function in the second path, and it depends on calcium concentration because this determines how many actin sites are available for bonding. If now the distribution-moment approximation is applied to expression (22), we obtain the following molar flux of ATP, and therefore PCr also, associated with actin–myosin interactions, for the entire volume of contractile tissue

\[
\frac{(m h X_0 A_0)}{N l} \Psi(Q_0, Q_1, Q_2, \nu, \Lambda) \tag{23}
\]

where

\[
\Psi = \int_{-\infty}^{\infty} \left( g(\xi) + r(\xi) g'(\xi) \right) \frac{Q_0}{\sqrt{2\pi q}} e^{-\frac{1}{2} \left( \frac{g(\xi) - r(\xi) g'(\xi)}{2q} \right)^2} d\xi \tag{24}
\]

and

\[
p = Q_1/Q_0 \quad \text{and} \quad q = \sqrt{[(Q_2/Q_0) - (Q_1/Q_0)^2]}. \tag{25}
\]

Equation (24) indicates explicitly that the activation factor \( r \) is a function of the normalized sarcoplasmic calcium concentration \( c = N [Ca]/m \), and the fraction of participating cross-bridges, \( \alpha \), is a function of normalized muscle length \( \Lambda = L/L_0 \), where \( L \) is the muscle length and \( L_0 \) is the length in an arbitrary but fixed standard state. Note that \( \Psi \) is a function of the five state variables of the DM model; it is calculated explicitly in the Appendix [equation (A11)]. The net molar flux of phosphocreatine hydrolysis, \( \dot{h}_{cr} \), is the sum of (21) and (23).

We can now assemble our results and insert them into equation (15) to get the following expression for the rate of chemical energy liberation

\[
\dot{E} = -2 F A \phi X_0 A_0 \left\{ \frac{V_m [Ca]}{[Ca] + K_m} - R_0 \left( 1 - \frac{[Ca]}{[Ca]^*} \right) \chi(t) \right\}
\]

\[-\Delta \dot{h}_{rec} X_0 A_0 \left\{ \frac{[Ca]}{[Ca] + K_m} - \left[ \frac{C k_m}{C k_m} \right] \right\}
\]

\[-\dot{h}_{PCR} X_0 A_0 \left( \frac{V_m [Ca]}{[Ca] + K_m} - \beta \right)
\]

\[-\frac{\Delta \dot{h}_{PCR} m h X_0 A_0}{N l} \Psi
\]

\[-\frac{\Delta \dot{h}_{PCR} m h X_0 A_0}{N l} Q_0 - \frac{\dot{k} m h^3 X_0 A_0}{2 l} Q_2. \tag{26}
\]

To compute the rate of heat production we return to equations (2) and (16), writing

\[
\dot{E} = C v \dot{T} - H = (\dot{Q} + \dot{H}) + C v \dot{T}. \tag{27}
\]

If the contractile tissue is connected to an external load through a passive elastic (possibly nonlinear) tendon then \( W_e = U_i + \dot{W} \), where \( U_i \) is the rate of increase of elastic strain energy stored in the tendon and \( \dot{W} \) is the rate at which the muscle does work on the external load. We define the ‘rate of heat production’ \( \dot{H} \), as

\[
\dot{H} = \dot{Q} + C v \dot{T}, \tag{28}
\]

the sum of heat transferred across the muscle boundary to the surroundings and the heat absorbed by the muscle, from chemical reactions, in raising its own temperature. We have previously calculated \( U_i \) (Zahalak, 1986) in terms of the first moment

\[
U_i = \Gamma L_0 \kappa (Q_1) Q_1 \dot{Q}_1 \tag{29}
\]

where \( Q_1 \) is the first moment, \( \kappa (Q_1) \) is the normalized tendon compliance (expressed as a function of \( Q_1 \), which is proportional to the muscle force), and \( \Gamma \) is a constant with dimensions of force equal to \( (m k^2 s_0 A_0/2 l) \), where \( s_0 \) is the sarcomere length in the standard state. As the muscle force is equal to \( \Gamma Q_1 \), then the rate at which the muscle does work on the external load can be expressed as

\[
\dot{W} = -\Gamma L_0 Q_1 \dot{A}. \tag{30}
\]

Thus we may express the rate of heat liberation as

\[
\dot{H} = \dot{E} + \Gamma L_0 \dot{Q}_1 \dot{A} - \Gamma L_0 \kappa (Q_1) Q_1 \dot{Q}_1 \tag{31}
\]

where \( \dot{E} \) is given by equation (26). Finally, we can cast equations (26) and (31) into dimensionless form by introducing the following parameters

\[
C = [Ca]/(m/N), \quad C^* = [Ca]^*/(m/N), \quad \rho = R_0/(m/N),
\]

\[
k_m = K_m/(m/N), \quad \tau_0 = (m/N)/V_m, \quad b = h/l.
\]

Let \( P_0 = \Gamma Q_1^{(0)} \) be the force generated by the muscle in its standard reference state (this state can be taken as that of the maximally stimulated muscle held at its optimal length, and therefore producing maximum force). Let \( L_m - L_0 \Lambda_m \) be the maximum speed of shortening of the unloaded muscle. Then

\[
\left( \frac{\dot{E}}{P_0 L_m} \right) = (Q_1(0) \Lambda_m)^{-1} \left[ \hat{v}_x \tau_0^{-1} \frac{c}{c + k_m}
\right.
\]

\[
+ \hat{v}_1 \Psi(Q_0, Q_1, Q_2, \nu, \Lambda)
\]

\[
+ \hat{v}_2 \zeta(c) \left\{ \tau_0^{-1} \frac{c}{c + k_m} \rho \left( 1 - \frac{c}{c^*} \right) \chi(t) \right\}
\]

\[
+ \hat{v}_3 \left\{ \rho \left( 1 - \frac{c}{c^*} \right) \chi(t) - \tau_0^{-1} \frac{c}{c + k_m} \right\}
\]

\[
+ \hat{v}_4 \zeta_0 - \frac{1}{2} \hat{v}_2 \zeta. \tag{32}
\]
and
\[
\left( \frac{\dot{H}}{P_0 L_m} \right) = \left( \frac{E}{P_0 L_m} \right) + (Q_{\text{g}}) (Q_{\text{f}}) \left( Q_{\text{r}} - \kappa Q_1 Q_2 \right).
\] (33)

The parameters appearing in the above equations may be expressed as follows:
\[
\begin{align*}
\dot{v}_o &= \gamma \left( -\frac{\Delta_{\text{PCR}}}{RT} \right) \quad \dot{v}_1 = 2b\dot{v}_o \quad \dot{v}_3 = \frac{\gamma}{bk} \left( \frac{F \Delta V_o}{RT} \right) \\
\dot{v}_4 &= \frac{\gamma}{b} \left( \frac{-\Delta_{\text{TRC}}}{RT} \right)
\end{align*}
\]
where \( \gamma \) and \( k \) have been defined in our previous publications (Zahalak and Ma, 1990) as
\[
\gamma = \frac{2X_k h}{L_o s_0} \quad \text{and} \quad k = \frac{\tilde{k} N h^2}{RT}.
\]

The function \( \zeta(c) \) appearing in equation (32) is the SR membrane potential function of equation (11), rendered dimensionless; if we take \( (m/N) \) to be \( 10^{-4} \text{ M} \) (Huxley, 1957; Tregear and Squire, 1973) we may write this function as
\[
\zeta(c) = \begin{cases} 
0 & \text{for } c < 0 \\
10c & \text{for } 0 < c < 0.1 \\
1 & \text{for } 0.1 < c
\end{cases}
\] (34)

The derivation of equations (32) and (33) was the main objective of this paper. These equations express the chemical energy liberation rate and the heat production rate in terms of the five-state variables of the DM model: \( \Lambda \) (length), \( c \) (calcium concentration), \( Q_0 \) (stiffness), \( Q_1 \) (force), and \( Q_2 \) (elastic energy). As written, each term of these equations has a clear physical interpretation. The terms containing the parameters \( \dot{v}_o \) through \( \dot{v}_4 \) represent energy releases associated, respectively, with: PCR splitting in calcium pumping (\( \dot{v}_o \)), PCR splitting in actin–myosin interactions (\( \dot{v}_1 \)), calcium ion current through the SR membrane (\( \dot{v}_3 \)), calcium binding to troponin (\( \dot{v}_4 \)), and myosin binding to actin at zero cross-bridge strain (\( \dot{v}_4 \)). The term involving \( Q_3 \) accounts for the additional elastic energy of cross-bridge strain. In equation (33) \( Q_1 \) \( \dot{A} \) represents the external work of the muscle, and \( \kappa Q_1 Q_2 \) represents the strain energy stored in the elastic tendon. Thus, if the DM equations (Zahalak and Ma, 1990; see equations (35)–(39) below) can be solved to yield the state variables at any instant, equations (32) and (33) permit the calculation of the energy rates at that instant.

**PARAMETER ESTIMATION**

Because it is based on detailed biophysical mechanisms the activation–contraction DM model contains a large number of parameters. There exist, however, a large number of experiments—mechanical, thermodynamic, biochemical, and morphological—to aid in the estimation of these parameters. Parameter identification for a given muscle requires a substantial amount of data and involves rather complex iterative procedures. Using data from purely mechanical experiments we have identified appropriate parameters for a few vertebrate muscles which are well documented in the literature (Ma, 1988), and we list the results of our investigation in Tables 1 and 2; the first gives the parameters of the bonding and unbonding rate functions shown in Fig. 2, and the second lists the remaining dimensionless parameters of the model. These parameters determine completely the solutions to the normalized equations of the DM model, which are reproduced below for reference
\[
\begin{align*}
\dot{C} &= \rho (1 - c/c^*) \chi(t) - \tau_0^{-1} \left[ c/(c + k_m) \right] \\
\dot{Q}_2 &= -r(c) \kappa(\Lambda) \beta_2 \quad r(c) \phi_{12}(Q_0, Q_1, Q_2) \\
&- \phi_{21}(Q_0, Q_1, Q_2) - \alpha \mu(t) Q_2 - 1, \quad \lambda = 0, 1, 2 \quad (36) \\
\Lambda &= \kappa(Q_1) Q_1 - N \mu(t) \quad (37)
\end{align*}
\]
with
\[
C(c, Q_0) = c + 2bQ_0 + r(c)(2 + \mu/c)(1 - bQ_0) \quad (38)
\]
and
\[
r(c) = \frac{c^2}{(c^2 + \mu c + \mu^2)} \quad (39)
\]

\begin{table}[h]
\centering
\caption{Identified parameters of the actin–myosin bonding and unbonding rate functions}
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Parameter} & \textbf{Frog sartorius} & \textbf{Rat soleus} & \textbf{Cat soleus} \\
\hline
\textbf{\( f_1 \)} & 30 & 26 & 50 \\
\textbf{\( q_1 \)} & 8 & 15 & 14 \\
\textbf{\( q_2 \)} & 170 & 300 & 600 \\
\textbf{\( f \_0 = f_1 \)} & 20 & 30 & 50 \\
\hline
\end{tabular}
\end{table}

All rate parameters are in inverse seconds.

To reduce the number of free parameters in the model \( f_0 \) has been constrained to be equal to \( f_1 \); that is, the unbonding rate function \( f'(\xi) \) is assumed to be simply proportional to \( \xi \) for \( \xi > 1 \).

Table 1. Identified parameters of the actin–myosin bonding and unbonding rate functions

<table>
<thead>
<tr>
<th>Muscle/temperature (°C)</th>
<th>Frog sartorius</th>
<th>Rat soleus</th>
<th>Cat soleus</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f_1 )</td>
<td>30</td>
<td>26</td>
<td>50</td>
</tr>
<tr>
<td>( q_1 )</td>
<td>8</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>( q_2 )</td>
<td>170</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>( f_0 = f_1 )</td>
<td>20</td>
<td>30</td>
<td>50</td>
</tr>
</tbody>
</table>
### Table 2. Activation-contraction DM model parameters

<table>
<thead>
<tr>
<th>Description</th>
<th>Parameter</th>
<th>Definition</th>
<th>Muscle (temperature)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Frog sartorius (0°C)</td>
</tr>
<tr>
<td>Calcium injection pulse magnitude</td>
<td>$\rho$</td>
<td>$\frac{[Ca]}{(N/m)}$</td>
<td>2.0</td>
</tr>
<tr>
<td>Inverse maximum Ca uptake rate by SR</td>
<td>$\tau_0$</td>
<td>$\frac{K_m}{(m/N)}$</td>
<td>0.25 s</td>
</tr>
<tr>
<td>Ca concentration at half-maximum uptake rate by SR</td>
<td>$k_m$</td>
<td>$\frac{[Ca]}{(m/N)}$</td>
<td>0.006</td>
</tr>
<tr>
<td>Calcium–troponin equilibrium constant</td>
<td>$\mu$</td>
<td>$\frac{(k_+ - k_)}{(m/N)}$</td>
<td>0.01</td>
</tr>
<tr>
<td>Free energy of ATP hydrolysis</td>
<td>$\varepsilon$</td>
<td>$\frac{\Delta A}{(N/R)T}$</td>
<td>23.0</td>
</tr>
<tr>
<td>Free energy of cross-bridge attachment</td>
<td>$\Delta A$</td>
<td>$\frac{\Delta A}{(R/N)T}$</td>
<td>14.0</td>
</tr>
<tr>
<td>Cross-bridge stiffness</td>
<td>$k$</td>
<td>$\frac{k_s}{(R/N)T}$</td>
<td>28.0</td>
</tr>
<tr>
<td>Limiting Ca concentration</td>
<td>$c^*$</td>
<td>$\frac{[Ca]^*}{(m/N)}$</td>
<td>1.0</td>
</tr>
<tr>
<td>Sarcomere structural parameter</td>
<td>$\gamma$</td>
<td>$\frac{2X_a h}{L_0 S_0}$</td>
<td>0.02</td>
</tr>
<tr>
<td>Cross-bridge structural parameter</td>
<td>$b$</td>
<td>$\frac{h}{l}$</td>
<td>0.5</td>
</tr>
<tr>
<td>Tendon compliance</td>
<td>$\kappa$</td>
<td>$\frac{\Gamma}{L_0} C(P)$</td>
<td>0.08</td>
</tr>
<tr>
<td>Fraction of participating cross-bridges</td>
<td>$\alpha$</td>
<td></td>
<td>1.0</td>
</tr>
</tbody>
</table>

All parameters are dimensionless except $\tau_0$, which is in seconds.

The tendon compliance $\kappa$ is assumed constant.

See Zahalak and Ma (1990) for an explanation of the significance of these parameters. (In this reference $\kappa$ and $\varepsilon$ are denoted by $k$ and $\varepsilon$.)

In general $\rho$ and $\alpha$ may vary with muscle length, $A$, but they are assumed to be constants for the simulations in this paper. This implies that muscle motions are confined near the plateau of the isometric length-tension curve.

---

* The rate parameters employed in the calculations of this paper are those listed in the second column of Table 1. Although these parameter values differ somewhat from those in Huxley’s (1957) paper ($f_1 = 43.3 \text{ s}^{-1}$, $g_1 = 10 \text{ s}^{-1}$, $g_2 = 209 \text{ s}^{-1}$), when used in conjunction with the DM model they produce excellent fits of the predicted force in an isometric twitch or in steady isotonic shortening to experimental measurements on frog sartorius at 0°C, and in addition provide a good prediction of the force in steady isotonic stretch. (See Zahalak and Ma, 1990, Fig. 7.)

---

Early experiments (on frog sartorius at 0°C) suggested that $\Delta H_{\text{PCr}}$ was in the range $-42$ to $-46$ KJ mol$^{-1}$, and suggested further that all the measured energy release could be accounted for by measured PCr splitting (Carlson et al., 1963; Wilkie, 1968). This is now known to be incorrect; $\Delta H_{\text{PCr}}$ is approximately $-34$ KJ mol$^{-1}$, which has led to the discovery of some ‘unexplained energy’ in certain muscles (Woledge et al., 1985). If we use the more correct value with $T = 273 \text{ K}$ and $R = 8.314 \text{ J mol}^{-1} \text{ K}^{-1}$ then $\Delta f_{\text{PCR}}/(RT) = 15$, which gives $v_f = 0.0107$. As $2b = 1$, $v_f$ has the same value as $v_0$.

The SR membrane potential of tetanized muscle has been estimated as $\Delta f = -0.056 \text{ V}$, so with $F = 9.656 \times 10^4 \text{ J V}^{-1} \text{ mol}^{-1}$ we obtain $\frac{\Delta f}{RT} = 2.38$, and $v_2 = 0.0068$. 

---

sets as given, and focus on estimating the new parameters introduced by the energetics model.* Where possible we will assume conditions applicable to frog sartorius at 0°C, as most energetics experiments have been done under these conditions.
The enthalpy of calcium–troponin binding for the low affinity sites has been measured in the range between $-25 \text{ KJ mol}^{-1}$ at 10°C (Yamada, 1978) and $-32 \text{ KJ mol}^{-1}$ to $-74 \text{ KJ mol}^{-1}$ at 25°C (Potter et al., 1977; Homsher and Kean, 1978). For the simulations presented in this paper we will adopt a value of $-10 \text{ KJ mol}^{-1}$ as characteristic of frog sartorius at 0°C, which gives $(-\Delta H_{\text{NC}}/RT) = 4.4$ and $\tilde{\varphi}_1 = 0.0063$.

Finally we obtain an estimate of $\Delta H_{\text{CB}}^{(0)}$ from calorimetric experiments on binding of purified myosin heads to actin in solution. If we represent the cross-bridge cycle in terms of a simplified Lymn–Taylor kinetic scheme (Squire, 1981)

\[ (A + M \cdot ATP) \rightarrow (A + M \cdot ADP \cdot P) \rightarrow (AM) \rightarrow (A + M \cdot ATP) \rightarrow \ldots \]

then estimates for the enthalpies of steps 1–4 can be based on the measurements of Kodama and Woledge (1979). These, in KJ mol$^{-1}$, are as follows: step 1 (+83), step 2 (+23), step 3 (−88 + 72 = −16), step 4 (−90); where a negative enthalpy change indicates an exothermic process. (All enthalpies are measured except that of step 2, which is calculated from the requirement that the enthalpy changes around the complete cycle sum to zero.) To adapt these properties of a four-state cycle to our two-state model, we identify the transition from 'detached' to 'attached' with the rate-limiting step of the cycle, which is step 3 (Squire, 1981), and take $\Delta H_{\text{CB}}^{(0)} = -16 \text{ KJ mol}^{-1}$. This gives $(-\Delta H_{\text{CB}}^{(0)}/RT) = -7$ and $\tilde{\varphi}_4 = 0.005$. Table 3 summarises the estimates of the energetics parameters.

Steady-state solutions of the DM equations [equations (35)–(39)] at maximal activation ($r(c) = 1$) using parameters listed in Tables 1 and 2 yield values of $Q_1^{(0)}$ and $\Lambda_m$, which appear in the energetics equation [equations (32) and (33)]. $Q_1^{(0)}$ is simply the value of $Q_1$ when the isometric constraint is imposed ($\Lambda = 0$), and $\Lambda_m$ is the value of $\Lambda$ when the muscle is unloaded ($Q_1 = 0$). For the three muscles listed in Tables 1 and 2 the following values can be calculated for $Q_1^{(0)}$, $\Lambda_m$: frog sartorius at 0°C (0.4, −2.0 s$^{-1}$), rat soleus at 20°C (0.314, −2.5 s$^{-1}$), cat soleus at 37°C (0.384, −5.5 s$^{-1}$). This provides all the necessary information needed to determine the dimensionless response of the model. In order to interpret this response in dimensional terms for a specific muscle, three more scaling parameters (appropriate for that muscle) are needed.

The first of these parameters is $L_0$, the length of the muscle in its standard state, which is usually taken to be the muscle length at the peak of the isometric length tension curve. Appropriate values for adult animals are: frog sartorius (30 mm), rat soleus (20 mm), and cat soleus (50 mm), although these numbers will obviously vary with species. The second scaling parameter is the force parameter $\Gamma = (m_0 A_g \bar{k} k^2/2l_1)$ (Zahalak and Ma, 1990). This parameter can be estimated from the maximum isometric force generated by the muscle $P_0$, via the relation $\Gamma = P_0/Q_1^{(0)}$ using the values of $Q_1^{(0)}$ listed above. As the values of $P_0$ listed in the literature are approximately 1 N, 2 N, and 20 N, respectively, for frog sartorius at 0°C, rat soleus at 20°C, and cat soleus at 37°C, the corresponding values of $\Gamma$ for these three muscles can be taken as 2.5 N, 6.4 N, and 52 N. The third scaling parameter is the molar concentration of cross-bridges, $(m/N)$, which we take to be $10^{-4} \text{ M}$ in all cases. With $L_0$, $\Gamma$, and $(m/N)$ available, all physical quantities of interest can be calculated from solutions of the normalized DM equations, equations (35)–(39). In particular (see Zahalak and Ma, 1990)

\[ [Ca] = c(m/N) \quad \dot{L} = L_0 \Lambda \quad K_c = (\Gamma/\gamma L_0) Q_0 \]

\[ P = \Gamma Q_1 \quad U_c = (\gamma L_0/2) Q_2 \]

where $[Ca]$, $L$, $K_c$, $P$, and $U_c$ are, respectively (i) the sarcoplasmic free calcium concentration; (ii) the length; (iii) the instantaneous ('series elastic') stiffness; (iv) the force; and (v) the elastic energy stored in the (cross-bridges of) the contractile tissue.

**SIMULATIONS**

In this section we present the results of energy calculations employing equations (32) and (33) for several experiments reported in the muscle energetics literature. It must be emphasised that the model parameters used in these simulations were estimated a priori from biochemical and mechanical experiments, and not chosen expressly to fit our model to the energetics data. In a single isometric twitch of frog semitendinosus at 0°C, Rall (1982) measured the time courses of the evolution of both the total heat and the activation heat (Fig. 3, right-hand side) and found that the activation heat was about 40 % of the total heat liberated. The activation heat was measured at muscle lengths so large that there was negligible myofilament overlap. A DM simulation of this experiment, employing parameters appropriate for a frog sartorius at 0°C (Fig. 3, left-hand side) shows time courses of activation and total heat similar to those measured, and gives a (activation heat/total heat) ratio of about 55 %. In this case all the terms in equations (32) and (33) contribute to the predicted heat production, except the $Q_1 \Lambda$ term which represents the external work. The most important contributions are due to PCR splitting associated with cross-bridge interactions and Ca$^{2+}$ pumping across the SR membrane, which are of comparable...
Fig. 3. Predicted responses of frog sartorius at 0°C in an isometric twitch. The parameters employed in this calculation are those listed for frog sartorius in Tables 1 and 2, together with the energetic parameters listed in Table 3. Lower left panel: force (as a fraction of maximum isometric force) as a function of time; upper left panel: total heat \( (H) \) and activation heat \( (H_a) \) as a function of time; \( H_a \) is the sum of the terms associated with \( \dot{v}_r, \dot{v}_s, \) and \( \dot{v}_t \) in equations (32) and (33). The lower and upper right panels show corresponding experimental results for frog semitendinosus at 0°C (after Rail, 1982).

Fig. 4. Individual contributions to the heat production shown in Fig. 3. (a) PCr hydrolysis in SR calcium pumping; (b) movement of calcium across SR electrochemical potential; (c) calcium–troponin bonding; (d) external work; (e) PCr hydrolysis in cross-bridge cycling; (f) cross-bridge bonding at zero strain; (g) cross-bridge strain energy; (h) tendon strain energy.

The relative magnitudes of the activation and total heats (Fig. 5, left-hand side). Again, the model permits the decomposition of the predicted total heat evolved into contributions from several discrete sources (Fig. 6), and shows that in a three-second tetanus the dominant mechanisms are PCr splitting in cross-bridge interactions and SR calcium pumping. In this case all other contributions, including calcium–troponin binding, are relatively small.

A DM simulation of A. V. Hill’s classic quick-release experiment (Hill, 1938) reproduces qualitatively the well-known result that the additional heat of magnitude (Fig. 4). In this twitch experiment the heat associated with calcium–troponin binding is also significant, but the remaining contributions are relatively minor.

Similar data were measured by Homsher and Kean (1978) for a frog sartorius at 0°C, but in a ten-second isometric tetanus rather than a single isometric twitch (Fig. 5, right-hand side). After a brief initial transient both the activation and total heat rates were found to be constant; the total heat evolved was roughly twice the activation heat. DM model simulations exhibit the salient features of these experimental results, including
Distribution-moment model in skeletal muscle

Fig. 5. Predicted responses of frog sartorius at 0 °C in a three-second isometric tetanus (the stimulation rate is 100 Hz). The conditions of this calculation are the same as those listed in the caption of Fig. 3. Lower left panel: force (as a fraction of maximum isometric force) as a function of time, upper left panel: total heat (H) and activation heat (Hₐ) as a function of time. The lower and upper right panels show corresponding experimental results for frog sartorius at 0 °C (after Homsher and Kean, 1978).

Fig. 6. Individual contributions to the heat production shown in Fig. 5. Panels (a)–(h) have the same significance as in Fig. 4.

shortening is approximately proportional to the distance shortened (Fig. 7). An examination of the various discrete contributions to the energy balance (Fig. 8) reveals that the major items in the energy budget which affect the transient heat perturbation from the steady maintenance heat are the PCr splitting in cross-bridge interactions and the external work done by the muscle; in contrast to the previous experiments considered, the tendon strain energy is an important contribution in this case.

The model does reasonably well in reproducing the relation between steady-state energy liberation and muscle velocity which has been reported for frog sartorius at 0 °C (Fig. 9), except that it does not predict the large drop in energy liberation rate for slow stretches. Further, predicted and measured values of the 'mechanical' efficiency in shortening, η, agree quite well, and have a maximum value of about 35% achieved at a low speed of about 10% of the maximum shortening speed (Fig. 9, inset). A decomposition of the chemical energy liberation rate into a contribution associated with activation and one associated with actin–myosin interactions shows that the two are approximately equal under isometric conditions, but the activation contribution becomes relatively less important as the speed of shortening increases (Fig. 10). The external work rate in stretch can be seen to be much greater than the chemical
**DISCUSSION**

We have shown in this paper how to couple rationally the known processes of muscle energetics to those of mechanics and activation via the DM model. This opens the possibility of detailed theoretical studies of the relations between these important aspects of muscle behavior, both under steady and unsteady conditions. No new state variables need be introduced to account for energetics; the five-state variables required for activation and contraction suffice. Further, the additional physical parameters of the energetics model (enthalpies of reaction, SR membrane potential) were all estimated from the published biochemical literature and were not treated as adjustable free parameters to be determined by curve fitting. In view of this we find the comparison of the model with the available experimental data reasonably satisfying. Most of the major features of muscle energetics seem to be predicted, at least qualitatively. We have, of course, restricted ourselves to a DM model based on a two-state cross-bridge model, and consequently one cannot demand great numerical accuracy in the results. At a minimum, however, the present work illustrates clearly what is required to proceed from a cross-bridge model to a consistent model for whole muscle. We believe that even with limited accuracy a tractable model which is based directly on cross-bridge theory and encompasses the essential processes of calcium activation, actin–myosin bonding, and biochemical energetics, will be useful in understanding the complex dynamics of muscle as it functions in the living animal.

Under presumably steady state conditions the DM energetics model reasonably predicts experimental measurements (Fig. 9). In shortening, the model's energy liberation rate agrees well with A. V. Hill's improved 1963 measurements, except under isometric conditions where the measured rate is about 70% of the predicted rate. It would undoubtedly be possible to decrease this error, without degrading the accuracy of the prediction at high shortening velocities, by changing the values of several model parameters. But this would probably decrease the accuracy of the model's predictions of mechanical responses such as the isometric twitch force and the isotonic force–velocity relation. In view of the natural biological variability present in isolated muscle preparations, and the limited quantity of data available, further refinement of the model parameters does not seem to be warranted at this point. Figure 9 also illustrates what is probably the model's major shortcoming: it fails to predict the very sharp decrease in chemical energy liberation in slow muscle stretches. With the two-state kinetic model we are using, it does not appear possible to choose parameters which produce both a reasonable mechanical behavior and a large decrease of energy liberation in slow stretch. The agreement between model and experiment improves at higher stretch velocities. Figure 10 indicates, however, that this error in predicted energy liberation rates does not substantially affect the predicted heat production rates, except at very low stretch velocities; this is because the heat generated by muscle in stretch is dominated by the external work done on the muscle.

Careful measurements of heat, work, and PCr hydrolysis (Woledge et al., 1985; Kushmerick, 1983) have suggested that a minor but significant contribution to the measured enthalpy changes comes from reactions which have not yet been identified; this (relative) contribution, dubbed the 'unexplained energy', may reach 20–30% of the total in the first few seconds of an isometric tetanus, and decreases thereafter. Clearly, as the sources of this additional energy are unknown at present, it is not possible to include them rationally in our model of muscle energetics, and we have made no attempt to do so empirically. The error due to this omission is probably comparable to others inherent in the model.

Another phenomenon which we have not modelled is the so-called 'labile heat' which appears at the beginning of a tetanus in frog muscles. This is an exponential contribution to the heat production which decays with a time constant of 1–3 s. Labile heat has been associated with the binding of calcium to
Fig. 8. Individual contributions to the heat production shown in Fig. 7 for the largest step, $\Delta A = 0.15$. The left panel shows the total heat production. The contributions shown in the right panel are as follows: (a) PCr hydrolysis in SR calcium pumping; (b) PCr hydrolysis in cross-bridge cycling; (c) movement of calcium across SR electrochemical potential; (d) calcium–troponin bonding; (e) cross-bridge bounding at zero strain; (f) cross-bridge strain energy; (g) external work; (h) tendon strain energy.

Fig. 9. Comparison of the steady-state rate of chemical energy liberation predicted by the DM energetics model with experimental measurements, for frog sartorius at 0 °C. The parameters employed in this calculation are the same as those listed in the caption of Fig. 3. Solid curve: model prediction. Data for shortening is based on heat and work measurements of A. V. Hill: open triangles (Hill, 1938) and open circles (Hill, 1964). Data for stretch based on ATP hydrolysis measurements from several sources (collected in Woledge et al., 1985). The inset shows the 'mechanical' efficiency, defined as the ratio of work rate to chemical energy liberation rate (i.e. heat plus work), as a function of shortening velocity.

Fig. 10. Individual contributions to the steady state chemical energy liberation rate shown in Fig. 9 (- - -) cross-bridge cycling [term associated with $\delta_2$ in equations (32) and (33)], and (- - - -) SR calcium pumping [term associated with $\delta_0$ in equations (32) and (33)], and (-----) total. Also shown (- - -) is the rate of work done on the muscle. The parameters employed in this calculation are the same as those listed in the caption of Fig. 3.

Serious deficiency as many muscles, such as rat and tortoise muscles (Woledge et al., 1985) do not produce this heat.

Finally, we note that our model does not include oxidative recovery effects. It assumes that the PCr concentration does not decrease drastically during contraction. This is an acceptable assumption providing that stimulation is not too intense and prolonged, for otherwise ATP and PCr depletion will affect the operation of the contractile machinery. Of course, the PCr hydrolysed during contraction must be re-phosphorylated oxidatively via the Krebs cycle and the cytochrome chain. But this is a long process with a time scale of an hour, which can be clearly separated

Parvalbumin (Homsher and Kean, 1978) a protein prevalent in the muscles of aquatic and amphibious animals. In the interest of simplicity we have not included parvalbumin kinetics in our model, although there should be no difficulty in doing so. The failure of the model to predict the labile heat is probably not a...
from the processes occurring during brief contractions with time scales of a few seconds. The addition of a representation for oxidative recovery will be one of the next steps in the evolution of the DM model.

The several simulations we have exhibited enable us to rank the various known contributions to chemical energy liberation and heat production according to order of importance (at least for frog sartorius at 0°C). Clearly the most prominent contributions in all cases are the PCR splitting associated with cross-bridge cycling and the PCR splitting associated SR-calcium pumping. These two contributions are of approximately equal magnitude under isometric steady state conditions; under isotonic steady state conditions the latter becomes relatively less important as the shortening speed increases and relatively more important as the shortening speed increases. The reversible heat of calcium–troponin binding is quite significant in a single twitch, but becomes less so with sustained stimulation. With the parameters used in our simulations the energies associated respectively with cross-bridge bonding at zero strain and with cross-bridge strain turned out to be relatively small; further in all cases the contributions of these factors to the heat production tended to cancel each other. The cross-bridge strain energy was smaller than, but comparable to, the elastic strain energy stored in the tendon. Finally the energy changes due to the electrochemical potential gradient of calcium ions across the SR membrane were uniformly small. As this last factor is difficult to model with precision and confidence, and as we have included it in a semi-empirical manner, we believe that it should be dropped from the energy equation (this is equivalent to setting \( f_2 \) equal to zero).

Acknowledgement—This work was supported by NSF Grants MSM-8407567 and BCS-891641.

REFERENCES


APPENDIX

We list first the parameters \( f_2 \) and the functions \( f_{11} \) and \( f_{12} \) which appear in the normalized DM equations [equation (36)] for the rate functions illustrated in Fig. 2. The analytical expressions for these rate functions are

\[
\begin{align*}
|f(\xi)| & = f_{11}(\xi) g(\xi) = \left\{ \begin{array}{ll}
g_{0} & \xi \geq 0 \\
g_{1} & \xi < 0
\end{array} \right. \\
0 & \text{otherwise}
\end{align*}
\]
Distribution-moment model in skeletal muscle

\[ f'(t) = \begin{cases} f_1 \exp(k t^2 / 2 - \Lambda \Delta t) & \text{for } t \leq 0 \\ f_0 + f_1^*(t) \text{ (1)} & \text{for } 0 < t < 1 \\ 0 & \text{for } t \geq 1 \end{cases} \]

where the top line in each of the above expressions refers to the argument range \( t \leq 0 \), the middle line to \( 0 < t < 1 \), and the bottom line to \( t \geq 1 \). Note that these rate functions satisfy the detailed balance conditions

\[ g'(t) = g(t) \exp(\Lambda \Delta t - k t^2 / 2) \]

and

\[ f'(t) = g(t) \exp(\Lambda \Delta t - k t^2 / 2) \]

of the self consistent cross-bridge formalism of T. L. Hill (Hill, 1977), which can be considered to give rise to the exponential tails shown in dashed lines in Fig. 2. The values of the parameters \( \Lambda, \Delta, \text{ and } k \), listed in Table 2 as characteristic of normal conditions in unfatigued muscles, suggest some simplifications. Firstly, the exponential tails are small and calculations have shown that they have a negligible influence on the behavior of the model. Therefore we will neglect these tails and set \( f(t) = 0 \) for \( t > 1 \) and \( g(t) = 0 \) for \( t < 1 \). Secondly, the rate function \( g'(t) \) is small everywhere compared to the other rate functions, so we will neglect it entirely. With these simplifying approximations the rate functions \( f, g, \) and \( f' \) become piecewise linear. Detailed calculation procedures to determine \( f_1, f_2, \) and \( f_3 \) for such functions have been provided in Zahalak (1981, 1986) and may be summarised as follows. Let

\[ G_0(z; p, q) = \sum_{m=n}^{k} \left( \begin{array}{c} k \\ m \end{array} \right) p^m q^{k-m} F_m(z) \]

where

\[ F_m(z) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{+\infty} e^{-z^2/2} F_1(z) = -\frac{1}{\sqrt{2\pi}} e^{-z^2/2} \]

and

\[ F_{k+1}(z) = k F_k(z) - \frac{z^k}{\sqrt{2\pi}} e^{-z^2/2} \text{ for } k \geq 1. \]

In equation (A3), \( p \) and \( q \) represent, respectively, the mean and standard deviation of the distribution function, \( n \), as defined by equation (25). Then it can be shown that

\[ \beta_2 = f_1(k + 2)^{-1} \]

and

\[ \phi_{1\lambda} = f_1 \left[ G_{\lambda+1} \left( \frac{1-p}{q}; p, q \right) - G_{\lambda+1} \left( \frac{p}{q}; p, q \right) \right] \]

Further,

\[ \phi_{2\lambda} = g_2 G_0 \left( \frac{1-p}{q} ; p, q \right) + g_1 \left[ G_1 \left( \frac{1-p}{q} ; p, q \right) \right. \]

\[ - G_1 \left( \frac{p}{q} ; p, q \right) \]

\[ + \left( f_0 - f_1 \right) \left[ 1 - G_0 \left( \frac{1-p}{q} ; p, q \right) \right] \]

\[ + f_1^* \left[ \frac{p - G_1 \left( \frac{1-p}{q} ; p, q \right)}{q} \right] \]

\[ = g_1 G_0 \left( \frac{1-p}{q}; p, q \right) + g_1 \left[ G_1 \left( \frac{1-p}{q}; p, q \right) \right. \]

\[ - G_2 \left( \frac{p}{q} ; p, q \right) \]

\[ + \left( f_0 - f_1 \right) \left[ \frac{p - G_1 \left( \frac{1-p}{q} ; p, q \right)}{q} \right] \]

\[ + f_1^* \left[ \frac{p^2 + q^2 - G_2 \left( \frac{1-p}{q} ; p, q \right)}{q} \right] \]

\[ = g_1 G_0 \left( \frac{1-p}{q}; p, q \right) + g_1 \left[ G_1 \left( \frac{1-p}{q}; p, q \right) \right. \]

\[ - G_3 \left( \frac{p}{q} ; p, q \right) \]

\[ + \left( f_0 - f_1 \right) \left[ p^2 + q^2 - G_3 \left( \frac{1-p}{q} ; p, q \right) \right] \]

\[ + f_1^* \left[ \frac{p^3 + 3pq^2 - G_3 \left( \frac{1-p}{q} ; p, q \right)}{q} \right]. \]

The function \( \Psi \) defined in equation (24), which determines the ATP and PCR fluxes associated with actin-myosin interactions, assumes a particularly simple form under the approximation we have made that \( g'(t) = 0 \). In this case

\[ \Psi(Q_0, Q_1, Q_2)/Q_0 = g_2 G_0 \left( \frac{1-p}{q}; p, q \right) \]

\[ + g_1 \left[ G_1 \left( \frac{1-p}{q}; p, q \right) \right. \]

\[ - G_1 \left( \frac{p}{q}; p, q \right) \]

for \( \lambda = 0, 1, 2. \) is independent of \( c \) and \( \Lambda. \)