# CONSTITUTIVE EQUATIONS OF SKELETAL MUSCLE BASED ON CROSS-BRIDGE MECHANISM

AYDIN TÖZEREN
*Biomedical Engineering and Instrumentation Branch, Division of Research Services, National Institutes of Health, Bethesda, Maryland 20205*

ABSTRACT The statistical mechanics of cross-bridge action is considered in order to develop constitutive equations that express fiber tension as a function of degree of activation and time history of speed of contraction. The kinetic equation of A. F. Huxley (1) is generalized to apply to the partially activated state. The rate parameters of attachment and detachment, and cross-bridge compliance are assumed to be step functions of extension, $x$, with a finite number of discontinuities. This assumption enables integration of the kinetic equation and its moments with respect to $x$ resulting in analytic equations from which $x$ has been eliminated. When the constants in the rate parameters and the force function are chosen so that Hill's force-velocity relation and features of the transient kinetic and tension data can be fitted, the resulting cross-bridge mechanism is quite similar to the one proposed by Podolsky et al. (2). Because the derived constitutive equations simplify mathematical analysis, the influence of various cross-bridge parameters on the mechanical behavior of muscle fibers may be evaluated. For example (*a*) instantaneous elastic response ($T_o - T_1$) and the magnitude of rapid recovery ($T_2 - T_1$) after a step length change can be adequately explained when the rate of attachment is assumed high for positive $x$. In that case $T_2$ corresponds to the force generated by cross-bridges in the region of negative $x$. (*b*) Kinetic transients occur as a result of the jumps that exist in the distribution of attached cross-bridges during the isometric state. Because of the hyperbolic nature of the kinetic equation, these jumps propagate in the $-x$ direction causing rapid changes in the speed of contraction. (*c*) When the number of actin sites available for attachment is assumed to depend on the degree of activation, computational results indicate that the speed of shortening is insensitive to the degree of activation at each relative load. (*d*) It is shown that during sinusoidal oscillation, the mean and second-order harmonics of the experimental force-time curve are strongly dependent on cross-bridge parameters. Therefore, significant information may be lost when the data is expanded into Fourier series and only the first term is considered.

## INTRODUCTION

Here, a set of constitutive equations is developed for skeletal muscle fibers by considering the statistical mechanics of cross-bridge action. As an end result, fiber tension is expressed as a function of the degree of activation and the time history of the speed of shortening. The proposed set of equations may be considered as a more realistic alternative to the two-element muscle model proposed by A. V. Hill (3). Hill's model consists of an elastic spring and a contractile element that are connected in series. The contractile element is characterized by a force-velocity relation known as Hill's equation. This model has been used extensively in the literature to describe the mechanics of muscle contraction. However, the recent experimental data on the time rate of rise of isometric tension during activation (4), isotonic and isometric transients (5, 6) and sinusoidal motion (7, 8) have illustrated the significant shortcomings of Hill's model. More recently, Huxley (1) has proposed a mathematical model of active force generation that is based on cross-bridge kinetics. In this model, cross-bridges are idealized as elastic springs when they form links between thick and thin filaments. Cross-bridge force is assumed to be a function of extension $x$, which is the distance from the stress-free configuration of the cross-bridge to the nearest actin site. The time rate of change of attachment is governed by a first-order hyperbolic partial-differential equation. However, since its introduction, this model has been revised considerably by its author and his co-workers (9) and by others (2, 10). The modifications have been considered in order to account for the recent data on the short-time muscle response to a quick release. As a result, models with distinctly different mechanisms of cross-bridge action have been developed. For example Podolsky and co-workers (2, 11–13) consider a two-state model with a high rate of attachment for $x > 0$, and they characterize cross-bridge force by a nonlinear spring. This model has been shown to describe adequately the isotonic transients as well as steady-state force-velocity relation. However, in order to account for the response to step tension reductions, Podolsky and Nolan (12) had to include a series elastic element of unknown origin in their model. On the other hand, Huxley and Simmons (9) have proposed two states of attachment for a cross-bridge to explain the initial rapid phase of transient tension data. The time rate of attachment is assumed to be slow as in Huxley's original treatment, but the transition between attached states is assumed to occur very fast. The rapid recovery of force observed in transient tension data is associated with the transients between attached states. More recently, Eisenberg and Hill (10, 14) have developed a mathematical model that relates the cross-bridge mechanism to a biochemical kinetic cycle for the actomyosin ATPase activity. This model postulates two cross-bridge states detached from actin and two cross-bridge states attached to actin, and is consistent conceptually with the ideas proposed by Huxley and Simmons (9). The proposed mechanism accounts reasonably well for the rapid phase of the transient tension data as well as the relation between the speed of contraction in vivo and ATPase activity in vitro. The model has several free energy functions and eight rate constants, six of them being functions of $x$. The forms of these functions are chosen by compatibility requirements and curve-fitting experimental data. Isotonic transients have not been considered with this model.

The kinetic models of muscle contraction mentioned above have been introduced mainly to contribute to the present understanding of cross-bridge mechanism; they are not easily reduced to a simpler set of equations that describes the macro-mechanics of muscle contraction. Recently, Huxley's initial model has been generalized in several ways to partial activation and variation of muscle extension (15–17). However, all these models still contain the internal variable $x$ in their equations, which introduces considerable difficulties in numerical computations. For example, analysis of isotonic contraction during a single twitch involves the numerical solution of several thousand simultaneous coupled equations (17). The study by Zahalak (18) recognized the importance of eliminating $x$ from the constitutive equations of muscle fibers and proposed that the number density $n$ of attached cross-bridges at any time be approximated by a Gaussian distribution. However, the solutions of various cross-bridge models mentioned above, for the transient tension and isotonic contraction, indicate that this is not a good assumption. Furthermore, the continuum models mentioned above (15–18) all use cross-bridge parameters suggested in Huxley's original model. These parameters must be modified in order to represent adequately short-time muscle response to quick releases.

The aim here is to derive a set of equations, governing muscle contraction on the continuum level, based on an assumed cross-bridge mechanism. In the section entitled Mathematical Formulation, the kinetic equation governing the time rate of attachment of cross-bridges is generalized to the partially activated state. This equation and its moments are integrated analytically with respect to $x$, resulting in equations free of $x$. The process of integration yields equations governing the time rate of change of averaged quantities such as the tension produced by attached cross-bridges with positive $x$. In the two sections following Mathematical Formulation, entitled Analysis of Isometric Contractions and Analysis of Isotonic Contractions, we discuss mechanical aspects of both types of contraction. The parameters appearing in the kinetic model are determined so that muscle response to quick releases as well as isotonic conditions are adequately represented. The resulting cross-bridge mechanism is similar to the one proposed by Podolsky and Nolan (12). Closed form, analytical solutions obtained in these sections provide further insight into the mechanism of transients. In the section entitled Sinusoidal Analysis, muscle response to sinusoidal motion is considered. An analytical solution is obtained that expresses number density of attached cross-bridges as a function of time. This solution is used in analysis of oscillatory data provided by Kawai and Brandt (8). The derived equations provide useful means of evaluating the influence of cross-bridge parameters on the macromechanical behavior of muscle fibers.

## MATHEMATICAL FORMULATION

The basic contractile unit of skeletal muscle fibers is the sarcomere, which consists of thick and thin elements arranged in parallel. According to the sliding filament hypothesis, the thick filaments have side pieces (cross-bridges) that can slide and attach to an acting site along thin filaments (1, 19). The attachments are assumed to be formed spontaneously but broken by a reaction requiring energy to be supplied from metabolic sources, or when the cross-bridge force reaches a yield value. It is assumed that the cross-bridges exert force only when attached, and that this force is elastic in nature. Let $x$ denote the distance of an actin site on the thin filament from the force-free configuration of the nearest cross-bridge. Let $c = c(t)$ be the fraction density of the actin sites that have been activated and let $n = n(x,t)$ be the fraction density of actin sites at position $x$ with an attached cross-bridge. The time rate of change of attachment of cross-bridges is assumed to be governed by the following equation

$$(\mathrm{D}n/\mathrm{D}t) = \partial n/\partial t - (sV/2)(\partial n/\partial x) = f(c - n) - gn, \quad (1)$$

where $\mathrm{D}/\mathrm{D}t$ is the material time derivative, $s$ is the length of the sarcomere corresponding to the maximum overlap between filaments, $V$ is the speed of contraction per unit length, and $f$ and $g$ are the rate parameters of attachment and detachment, respectively. During contraction, the distance $x$ decreases at a rate, $x$, which is equal to the speed of shortening ($\dot{x} = -sV/2$). Eq. 1 reduces identically to the kinetic equation proposed by Huxley (1) when contractions at full activation are considered. The present formulation is different from the earlier generalization of Julian (20). Julian has assumed that the rate parameter $f$ appearing in Huxley's equation depended on the degree of activation, and therefore was a function of time. In the present study, the number of activated sites, but not the rate parameter $f$ is assumed to vary with the degree of activation.

The rate parameters and cross-bridge compliance are assumed to be step functions of $x$, with a finite number of discontinuities. The rate functions are chosen as

$$\begin{aligned} f &= f_o\,(H(x) - H(x - h)] \\ g &= f_o\,\{q_o\,[H(x) - H(x - h)] \\ &\quad + q_1\,[H(x - b_1 h) - H(x)] + [q_2\,H(x - h)]\}, \quad (2) \end{aligned}$$

where $h$ is the length of the attachment zone, $b_1$ is a dimensionless constant, $f_o$ is the time constant of attachment, $q_o$, $q_1$, and $q_2$ are the

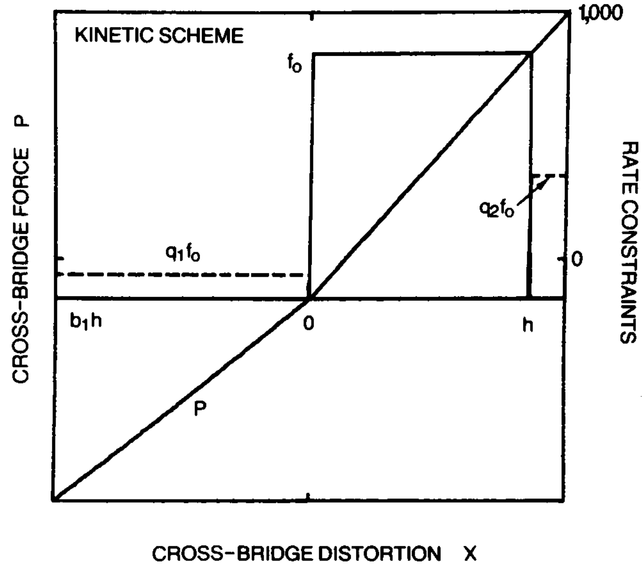

FIGURE 1 Variation of cross-bridge force $P$ (Eq. 3), and rate parameters of attachment $f$ (Eq. 2) and detachment $g$ (Eq. 2) with variable $x$ ($f_o = 2{,}000\ \mathrm{s}^{-1}$, $q_1 f_o = 28\ \mathrm{s}^{-1}$, $G = 0.72$, $h = 100$ Å, $b_1 = 1.14$) are shown.

dimensionless time constants of detachment and the step function $H(x) = 1$ for $x > 0$ and vanishes elsewhere (Fig. 1). The rate parameters $f$ and $g$ are considered to be functions of $x$, because of the varying positions of the enzyme macromolecules along the thick filament (1). These enzymes catalyze the biochemical reactions occurring during contraction. The force, $P$, exerted by a cross-bridge is characterized by the equation

$$\begin{aligned} P &= Kx \text{ for } x > 0 \\ &= GKx \text{ for } x < 0, \end{aligned} \tag{3}$$

where $G$ and $K$ are constants (Fig. 1). It is assumed that cross-bridges detach instantaneously when $x \leq -b_1 h$. This value of $x$ corresponds to the peak negative force that can be exerted by a cross-bridge. Eq. 3 allows for a change in cross-bridge configuration and hence its compliance as the actin site moves from the attachment zone into the detachment zone as a result of shortening. The free energy function corresponding to Eq. 3 is an asymmetric parabola and can be obtained by integrating Eq. 3 with respect to $x$.

Substitution of Eq. 2 into the kinetic Eq. 1 yields the following equations for the region of attachment ($0 < x < h$) and detachment ($x < 0$) respectively

$$\partial n/\partial t = f_o[c - (1 + q_o)n] + (sV/2)(\partial n/\partial x) \tag{4a}$$

$$\partial n/\partial t = (-f_o q_1 n) + (sV/2)(\partial n/\partial x). \tag{4b}$$

Eqs 4a and 4b may be integrated analytically with respect to $x$, for an arbitrary number density function $n$, yielding

$$\begin{aligned} \mathrm{d}M_{(+)}/\mathrm{d}t = \dot{M}_{(+)} = f_o[c - (1 + q_o)M_{(+)} \\ - (V/A)(n_o - n_2)] \end{aligned} \tag{5a}$$

$$\mathrm{d}M_{(-)}/\mathrm{d}t = \dot{M}_{(-)} = f_o[-q_1 M_{(-)} + (V/A)(n_o - n_1)], \tag{5b}$$

where $A = (2f_o h/s)$ and $n_o$, $n_1$ and $n_2$ are the values of the number density distribution at $x = 0$, $-b_1 h$, and $h$, respectively. The quantities, $M_{(+)}$ and $M_{(-)}$, are the measures of the number of attached cross-bridges in the zones of attachment and detachment, respectively. They are defined as

$$M_{(+)} = \left(\int_0^h n(x, t)\mathrm{d}x\right)\Big/ h \tag{6a}$$

$$M_{(-)} = \left(\int_{-b_1 h}^0 n(x, t)\mathrm{d}x\right)\Big/ h \tag{6b}$$

During the fully activated isometric state $M_{(+)} = 1/(1 + q_o)$ and $M_{(-)} = 0$.

When Eq. 4 is multiplied by $x$ and integrated over the range of its definition, it can be shown that the average first moments $Y_{(+)}$ and $Y_{(-)}$ are governed by the following equations

$$\dot{Y}_{(+)} = f_o\{c - (1 + q_o)\, Y_{(+)} - 2(V/A)[M_{(+)} - n_2]\} \tag{7a}$$

$$\dot{Y}_{(-)} = f_o\{-q_1 Y_{(-)} - 2(V/A)[M_{(-)} - b_1 n_1]\}, \tag{7b}$$

where $\dot{Y}_{(+)} = \mathrm{d}\, Y_{(+)}/\mathrm{d}t$. The variables $Y_{(+)}$, and $Y_{(-)}$ are defined as

$$Y_{(+)} = \left[\int_0^h n(x, t)\, x\mathrm{d}x\right]\Big/(h^2/2) \tag{8a}$$

$$Y_{(-)} = \left[\int_{-b_1 h}^0 n(x, t)\, x\mathrm{d}x\right]\Big/(h^2/2). \tag{8b}$$

During the fully activated isometric state $Y_{(+)} = 1/(1 + q_o)$ and $Y_{(-)} = 0$. Eqs. 5 and 7 comprise a set of first-order ordinary differential equations governing the time variation of average cross-bridge quantities $M_{(+)}$, $M_{(-)}$, $Y_{(+)}$ and $Y_{(-)}$. To estimate the force generated by all attached cross-bridges it is assumed that each cross-bridge acts independently. An ergodic principle can then be used to express the average tension generated by cross-bridges

$$\begin{aligned} T &= (T'/T_o) \\ &= \left[\int_{-b_1 h}^{h} P(x)\, n(x, t)\mathrm{d}x\right]\Big/\!\!\Big/\left[\int_0^h P(x)/(1 + q_o)\mathrm{d}x\right], \end{aligned} \tag{9}$$

where $T'$ is the fiber tension, $T_o$ is the isometric tension in the fully activated state, and $P$ is given by Eq. 2. During isometric tension, attached cross-bridges exist only in the region ($0 < x < h$). Using Eqs. 2, 6, and 8, it can be shown that the dimensionless tension $T$ satisfies the following equation

$$T = T_{(+)} + T_{(-)} = [Y_{(+)} + GY_{(-1)}](1 + q_o), \tag{10}$$

where $T_{(+)}$ and $T_{(-)}$ are the dimensionless tensions produced by cross-bridges attached in the regions of attachment and detachment, respectively. If attached cross-bridges exist in the region $x > h$ as a result of stretch, corresponding terms $M_{(R)}$, $Y_{(R)}$ and $T_{(R)}$ must be added to Eq. 10. This case will be considered in the section entitled Sinusoidal Analysis. Eq. 10 expresses fiber tension $T$ as a linear combination of $Y_{(+)}$ and $Y_{(-)}$. The time variation of these quantities are governed by Eqs. 5 and 7. To solve these equations the value of the number density $n$ at locations $x = 0$, and $x = -b_1 h$ must be known. The solution of kinetic Eq. 1 can be obtained analytically by using the method of characteristics. The method of solution is summarized by Zahalak (18) for the case of full activation where $c(t) = 1$. The more general solution that is also applicable to partial activation can be shown to be given by the equation

$$\begin{aligned} n = n(x, t) &= n_i\left[x + h\int_0^t (V/A)\mathrm{d}y\right] \\ &\cdot \exp\left\{-\int_0^t L\left[x + h\int_y^t (V/A)\mathrm{d}z\right]\mathrm{d}y\right\} \\ &+ \frac{1}{f_o}\int_0^t f\left[x + h\int_y^t (V/A)\mathrm{d}z\right] \cdot c(y) \\ &\cdot \exp\left\{-\int_y^t L\left[x + h\int_z^t (V/A)\mathrm{d}w\right]\mathrm{d}z\right\}\mathrm{d}y, \end{aligned} \tag{11}$$

where $\bar{t} = f_o t$, $A = 2f_o h/s$, $L = (f + g)/f_o$ and $f[p] = f(x)_{x=p}$. The values of $n_o$, $n_1$ and $n_2$ can be obtained from Eq. 11 at any time by setting $x = 0$, $x = -b_1 h$ and $x = h$, respectively. The first term on the right-hand side of Eq. 11 is a transient representing the influence of initial conditions. The second term on the right-hand side reduces to the steady state solution during isotonic contraction. At full activation it can be shown that

$$n_o = [1 - \exp(-A^*/V)]/(1 + q_o), \tag{12a}$$

$$n_1 = n_o \exp[-b_1 q_1 (A^*/V)], \tag{12b}$$

$$n_2 = 0, \tag{12c}$$

where $V$ is the steady state speed of contraction and $A^* = (1 + q_o)A$. Eqs. 5, 7, 9, and 11 express fiber tension $T$ and other average cross-bridge quantities such as $M_{(+)}$ and $M_{(-)}$, in terms of the time histories of the degree of activation and the speed of the contraction. The analysis given above is valid for sarcomere lengths of 2–2.2 μm, where all cross-bridges are overlapped by thin filaments. Gordon et al. (21) showed that isometric tension decreases linearly with the degree of overlap. The fiber tension Eq. 10 may be used in the descending limb (2.2 μm < $s$ < 3.9 μm) provided that $T_o$ is taken as isometric tension corresponding to the particular sarcomere length. In the ascending limb, thin filaments overlap and there is significant evidence that activation is length dependent in this region (22). Cross-bridge parameters $f_o$, $g_o$, $G$, $h$, and $b_1$ appearing in these equations will be determined next by fitting experimental data on quick releases.

## ANALYSIS OF ISOMETRIC CONTRACTIONS

Here time development of tension after a step length change will be considered first. It is assumed that the fiber is in the activated isometric state before the quick release. For simplicity in analysis, the rate of detachment, $g_o$, in the region of attachment is assumed to be negligibly small compared with $f_o$. Let $z$ be the magnitude of the step length change. When the step size $z$ is smaller than the length of the detachment region ($z < b_1 h$), it can be shown that $n_o = 1$, and $n_1 = 0$ during the duration of contraction. Eqs. 5, 7, and 10 can be used to determine $M_{(+)}$, $M_{(-)}$, $Y_{(+)}$, $Y_{(-)}$, and $T$ immediately after the quick release

$$M_{1(+)} = 1 - Z, \; M_{1(-)} = Z, \tag{13}$$

$$Y_{1(+)} = 1 - 2Z + Z^2, \; Y_{1(-)} = -Z^2, \tag{14}$$

$$T_{1(+)} = 1 - 2Z + Z^2, \tag{15a}$$

$$T_{1(-)} = G(-Z^2), \tag{15b}$$

$$T_1 = T_{1(+)} + T_{1(-)} = 1 - 2Z + Z^2(1 - G), \tag{16}$$

where $Z = z/h$. Subscript 1 is used in Eqs. 13–16 to denote the values of the average cross-bridge quantities just after the release. It is assumed that the number of attached cross-bridges remains the same during quick release. The contraction force given by Eq. 16 corresponds to the experimental $T_1$ curve [$T_1 = T_1(z)$] of Huxley and Simmons (9). Eq. 16 shows that $T_1$ is a linearly decreasing function of $z$ when $G = 1$. Huxley and Simmons (9) have also provided an experimental curve depicting the tension $T = T_2$ as a function of step size $z$ after rapid recovery. To model this curve with the present formulation an assumption must be made about the relative magnitudes of the rate constants $f_o$ and $g_1$. When the ratio $(f_o/g_1) = (1/q_1)$ is assumed to be much larger than one, the rapid recovery $(T_2 - T_1)$ observed in the experiments is explained by the rapid attachment of the cross-bridges in the region ($h - z < x < h$). In this case the experimental $T_2$ curve is equivalent to the curve given by $T_2 = 1 + T_{1(-)}$ (Eq. 15) of the present study. Our computations indicate that, for $q_1 << 1$, the experimental $T_1$ and $T_2$ curves can be fitted well by suitably choosing the cross-bridge parameters $h$ and $G$. The comparison of the experimental data and corresponding curves of the present model are shown in Fig. 2 for $h$ = 110 Å, and $G = 0.72$. Recently, it has been suggested by Ford et al. (23) that the upward curvature observed in experimental $T_1$ curves occurs as a result of the rapid recovery during the application of the length step. Values of parameters $h$ and $G$ can easily be adjusted to fit also the corrected curves of Ford et al. (23).

The time variation of tension after a quick release is governed in the present study by the following equation

$$T = 1 - (T_2 - T_1)\exp(-f_o t) - (1 - T_2)\exp(-q_1 f_o t). \tag{17}$$

This is an exponential curve with two time constants. According to Ford et al. (23), experimental tension response to length step can be divided into four phases. Experiments show that the rapid recovery phase usually lasts between 2–5 ms, however, the rate of recovery increases with the step size.

The present cross-bridge model predicts a single exponential time constant (rate parameter $f_o$) during the rapid recovery phase. This rapid partial recovery is followed by a slowing or reversal of recovery. This step is not well accounted for with Eq. 17. The number of exponential constants appearing in Eq. 17 could be increased if the

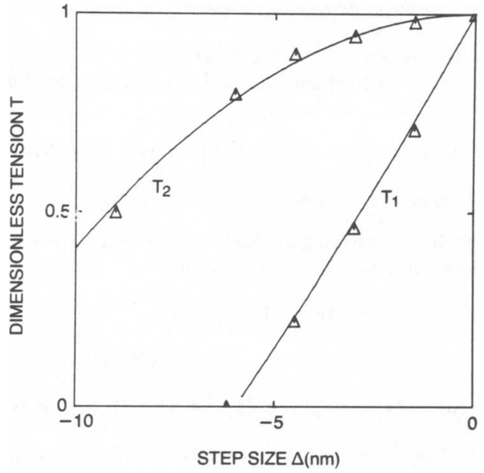

FIGURE 2 Tensions $T_1$ and $T_2$ (response to step length reductions) as a function of step size Δ. Points are taken from the data of Huxley and Simmons (6). Continuous curves are the predictions of the proposed model with parameter values given in Fig. 1. (See Eqs. 15b and 16 with $z$ = Δ).

number of discontinuities in the $f$ and $g$ functions were increased. The third phase of the recovery may be explained to an extent if it is assumed that degree of activation changes with the application of a length step. However, the present mathematical simplification would be lost with these extensions, and as a result the corresponding continuum models would be composed of a considerably larger set of equations. Note also that the rapid recovery occurs so quickly that, on the continuum level it would be observed at most as a spike.

Instantaneous stiffness, $E$, of a muscle fiber is proportional to the number of attached cross-bridges for the kinetic models cited in the Introduction (1, 2, 9, 14). For this reason stiffness measurements have been used in muscle literature to test the validity of these different models of cross-bridge mechanism (2, 24). Here, dimensionless fiber stiffness $E_o$ measured from a fully activated isometric state can be obtained as $E_o = 2$ by taking the derivative of Eq. 16 with respect to $Z$ and setting $Z$ equal to zero.

Stiffness $E$ can also be measured during isotonic contraction and transient tension by applying an infinitesimal step change of length. In all cases $E$ is defined as $E = (\mathrm{d}T/\mathrm{d}Z)$. The dimensionless tension $T$ defined by Eq. 10 is related to the number density function $n$ through Eqs. 5 and 7. The number density $n$ immediately after the quick release can be expressed by the equation

$$n = n(x, t, z) = n(x + z, t). \tag{18}$$

It can then be shown that the instantaneous stiffness $E$ corresponding to the present model can be written as

$$E = 2(M_{(+)} + GM_{(-)} - Gb_1n_1). \tag{19}$$

Eq. 19 shows that the stiffness $E$ is not proportional to the number of attached cross-bridges for the proposed model. This result follows because cross-bridges are assumed to be more compliant in the region of detachment, and it is assumed that cross-bridges break when extended beyond the limit $x < -b_1h$. Ford et al. (24) have measured fiber stiffness at the end of the early recovery of tension by applying a second step change of length after an initial conditioning step. It was observed that 2 ms after the initial step, stiffness decreases slightly. More recently, Julian and co-workers (25; 26) have reported similar results. Using Eq. 19 it can be shown that the stiffness corresponding to the present model increases linearly with increasing size of the initial conditioning step. If it is assumed that the initial step size is $z = h/2$ and that 90% of the rapid recovery has occurred before the second step, then the corresponding increase in stiffness is ~25%. However, this value must be considered as an upper bound because the compliance of the sarcomere structures other than cross-bridges were neglected and it was assumed that the number of attached cross-bridges did not change during the applied length steps. It is expected that some detachment takes place during quick release because of mechanical reasons beyond that predicted by the kinetic equation (Eq. 1). Finite transmission time of mechanical impulses down the length of a muscle fiber sets a natural limit to the speed in which a length step can be applied [Schoenberg et al. (27), Podolsky (28)]. As a result, these factors introduce a velocity dependence in the measurements of stiffness.

If the dimensionless time constant $q_1$ is taken as $>1$, then it can be shown that the resulting $T_1$ and $T_2$ curves cannot be fit to the experimental data of Huxley and Simmons (6). Therefore, this case is not presented in detail. The proposed mechanism described above is not unique in explaining the $T_1$ and $T_2$ curves of the transient tension experiments. Huxley and Simmons (9) and more recently Eisenberg et al. (14) showed that muscle response during the early phase of rapid recovery may also be accounted for by transients from one attached state to another.

The time development of isometric tension will be considered next. It is assumed that the fraction of activated actin sites $c = c(t)$ is not a function of cross-bridge parameters, but is supplied independently. Using Eq. 11 it can be shown that $n_1 = 0$ and that $n_o$ is given by the following equation

$$n_o = \int_0^t c[t - s] \exp(-f_o s)\mathrm{d}s. \tag{20}$$

Further consideration of Eqs. 5, 7, and 10 yields that the dimensionless tension $T$ is equal to $n_o$ during the time development of isometric tension. When the rate parameter of attachment $f_o$ is sufficiently large, the exponential term appearing in Eq. 20 can be approximated by the Dirac delta function $[\exp(-f_o t) = \sigma(t)/f_o]$ so that $n_o = T = c(t)$ in this case. In Huxley's original model and more recently in Eisenberg et al. (14), it is assumed that the rate of attachment is low, attachment of cross-bridges being the rate-limiting step. In that case, the tension $T$ not only depends on the instantaneous value of $c = c(t)$ but on its time history. It can be shown that there exists a considerable phase lag between $T$ and $c$ when $f_o$ is small. This point is illustrated in Fig. 3. The activation function $c$ is assumed to be given by the relation $c = 1 - \exp(-h_o t)$. Shown in the figure are the two cases where $h_o/f_o = 1/100$ and $h_o/f_o = 1/2$. The figure shows that the rate parameter $f_o$ plays an important role in the time development of isometric tension when the attachment is assumed to be the rate-limiting step.

In this section we have considered muscle contractions in which the sarcomere length has been kept constant. Since the speed of contraction, V, is zero in such cases, the second term on the left-hand side of the kinetic equation (Eq. 1) drops out. Therefore, these experiments yield only partial information on cross-bridge kinetics. To study how the relative sliding motion influences attached cross-bridge distribution $n$, isotonic contractions will be considered in the next section.

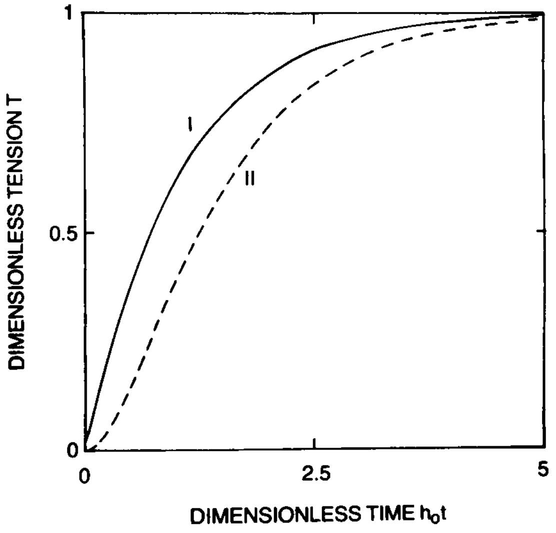

FIGURE 3 Time development of tension in isometric tetanus calculated by using Eq. 20 with $c = 1 - \exp(-h_o t)$ ($I$: $h_o/f_o = 1/100$, II: $h_o/f_o = \frac{1}{2}$).

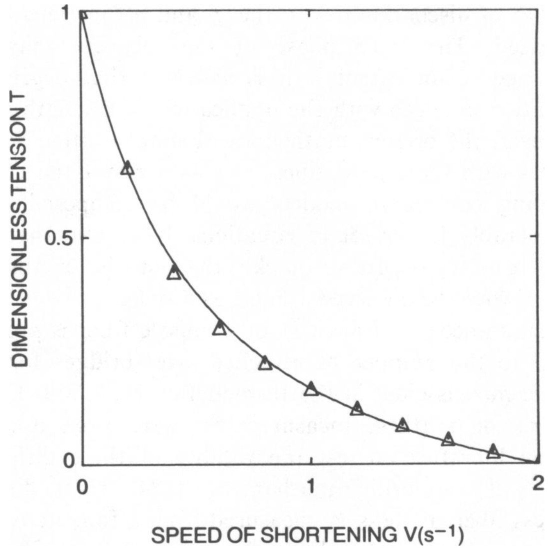

FIGURE 4 Force-velocity relation for isotonic contractions (points obtained from Hill's equation (Eq. 21) with $a = \frac{1}{4}$ and $V_o = 2\ \mathrm{s}^{-1}$ are shown with the symbol +; continuous curve is the prediction of the proposed model with parameter values given in Fig. 1).

## ANALYSIS OF ISOTONIC CONTRACTIONS

Steady state isotonic contractions at full activation will be considered first. Experimental force-velocity relations in this case can be well represented with Hill's equation (3)

$$V = aV_o(1 - T)/(a + T), \tag{21}$$

where $V_o$ is the maximum speed of shortening ($\mathrm{s}^{-1}$) and $a$ is a dimensionless measure of curvature. Here all time derivatives appearing in Eqs. 5 and 7 must be equal to zero during steady state. In this case $n_o$, $n_1$ and $n_2$ are given by Eq. 12. Hence, the variables $M_{(+)}$, $M_{(-)}$, $Y_{(+)}$, and $Y_{(-)}$ can be expressed as functions of the speed of contraction. The corresponding equation for the dimensionless muscle tension $T$ can then be obtained, by using Eq. 10. This equation can be well fitted with Hill's force-velocity relation by adjusting the values of $q_1$ and $b_1$ and using the values of $f_o$, $h$, and $G$ already determined in the best fit of the data for transient tension after a quick release ($f_o = 2{,}000\ \mathrm{s}^{-1}$, $h = 110$ Å, $G = 0.72$). If $V_o = 2\mathrm{s}^{-1}$, and $a = \frac{1}{4}$, as in frog skeletal muscle at 5°C, then the model accurately predicts Hill's force-velocity relation provided that $b_1 = 1.14$ and $q_1 f_o \simeq 28\ \mathrm{s}^{-1}$ (Fig. 4). Our computations indicate that maximum speed of contraction $V_o$ increases in proportion with increasing rate of detachment $q_1 f_o$, but $V_o$ is not sensitive to the rate of attachment $f_o$. Recently Ferenczi et al. (29) have considered the dependence of force and shortening velocity on substrate concentration (MgATP) in skinned muscle fibers. They found that the maximum velocity of shortening, $V_o$, showed a roughly hyperbolic dependence on MgATP concentration. These results indicate that the rate of detachment $q_1 f_o$ must increase with increasing MgATP at low levels of substrate concentration and must attain an asymptotic value with further increases in MgATP.

Using the data on transient tension and steady isotonic contraction, we have determined all six cross-bridge parameters. Fig. 5 shows $M_{(+)}$ and $M_{(-)}$ as functions of the speed of contraction. The figure indicates that the number of attached cross-bridges with $x > 0$, $M_{(+)}$, decreases slightly with increasing speed of contraction, $V$. On the other hand, $M_{(-)}$ increases sharply at first and then levels off with further increases in $V$. Fig. 6 shows dimensionless tensions $T_{(+)}$, $T_{(-)}$, and $T$ as functions of $V$ during steady state isotonic contraction.

Instantaneous stiffness may be measured during isotonic contraction by the application of a second force step or by imposing a small sinusoidal length change of high frequency (25, 26). Experimental measurements using sinusoidal oscillations (25, 26, 30) indicate that stiffness decreases with tension during steady shortening. Some

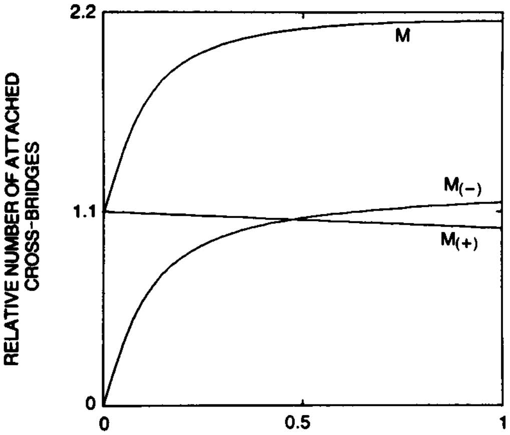

FIGURE 5 The number of attached cross-bridges given by Eq. 6 during steady state isotonic contraction as a function of the speed of shortening [$M = M_{(+)} + M_{(-)}$].

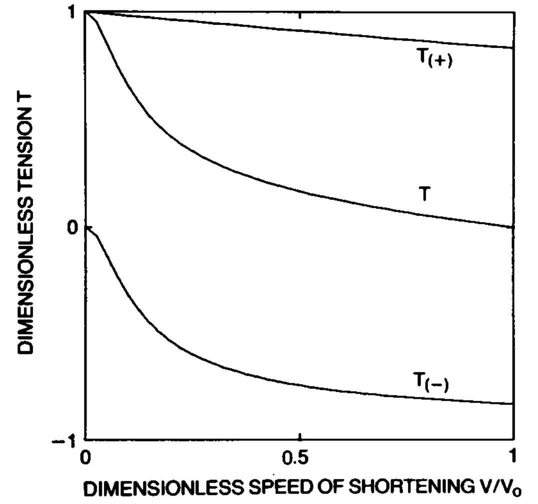

FIGURE 6 The relation between the steady speed of shortening and the average forces $T_{(+)}$ and $T_{(-)}$ produced by cross-bridges in the regions of attachments and detachment, respectively.

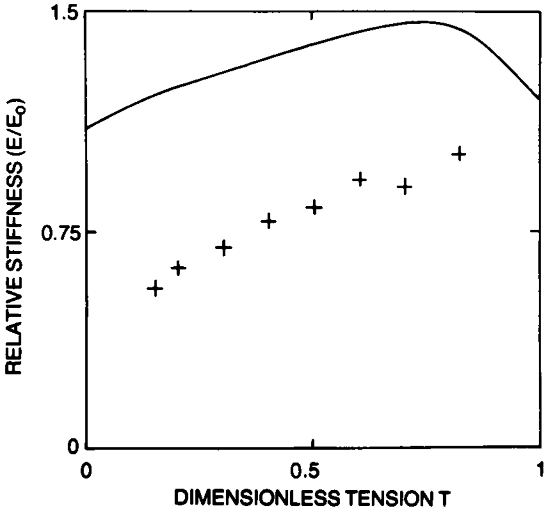

FIGURE 7 Fiber stiffness $E = \mathrm{d}T/\mathrm{d}Z$ ($Z = z/h$ is the dimensionless step size) during isotonic contractions as a function of the relative tension $T$. Continuous curve corresponds to the present model, data points from Julian and Morgan (26) are shown with the symbol +; $E_o = 2$ denotes the fiber stiffness during isometric tension.

significant problems that exist in stiffness measurements have been discussed in the previous section. The accuracy of the stiffness measurements involving sinusoidal oscillations may be improved to an extent by direct computer control of the input and output signals. Sinusoidal oscillations will be considered in the next section. Stiffness would increase with the speed of contraction in the model proposed by Podolsky and Nolan (11) because the total number of attached cross-bridges would increase with decreasing isotonic load. On the other hand, stiffness $E$ would decrease with decreasing load for Huxley's original model and its extensions (1, 9, 14).

It is also of interest to see how the stiffness $E$ corresponding to the present analysis depends on the isotonic load. This is illustrated in Fig. 7. It is shown that the stiffness $E$ increases when the fiber load is reduced from $T = 1$, to $T = 0.90$, and then decreases with further reduction in isotonic tension. The peak stiffness $E$ that occurs at $T = 0.9$ is ~30% larger than the corresponding stiffness during steady state isometric state. At zero-load stiffness is slightly lower than its isometric value. Present analysis illustrates that stiffness $E$ need not be proportional to the number of attached cross-bridges during contraction. Also shown in Fig. 7 are some representative data points from Julian and Morgan (26). The figure shows that the stiffness of the present model is significantly higher than the corresponding data. However, the slopes of the experimental and theoretical stiffness-tension curves are nearly the same.

It is generally assumed that the contraction is activated by the binding of calcium to the thin filament regulatory proteins (31). Podolsky and Teicholz (32) have provided experimental evidence that shortening velocity is insensitive to the degree of activation, $c$, at each relative load. Because the experiments mentioned above were performed on skinned fibers, activation level, $c$, is not a function of time. Our computations show that the force-velocity relation in the case of partial activation ($c < 1$) can be obtained from the corresponding relation for full activation ($c = 1$) provided that the dimensionless tension $T$ in the equation be replaced by $T/c$. Hence, the proposed generalization to partial activation assumes implicitly that calcium acts as a simple twitch, removing the inhibition from actin sites so that cross-bridges can attach. Experimental data of Podolsky and Teicholz (32) have not been uniformly supported by the results obtained in other laboratories. For example, Julian (32) has found evidence of an additional calcium-dependent effect. These experiments have recently been reviewed (33). However, the controversy about the influence of the activation level on cross-bridge kinetics has not yet been resolved.

Isotonic transients will be considered next, with the proposed model. First experimental results were presented by Civan and Podolsky (5). In these experiments fiber length is measured as a function of time after the application of a force step. It was observed that shortening speed is at first greater than, and then less than, the steady state value, resulting in an unsteady oscillatory motion. Podolsky and co-workers (2, 11, 12) have presented a numerical iterative procedure to compute isotonic transients, and chose cross-bridge parameters in order to fit data on isotonic transients. In the present study, cross-bridge parameters have already been determined. These values will be used in the analysis of isotonic transients. Eqs. 3 and 11 are combined to obtain simplified expressions for $n_o$ and $n_1$. The number density at $x = 0$, $n_o$, can be expressed as

$$n_o = 1, \text{ for } I(\bar{t}) < 1$$

$$n_o = 1 - \exp[-(\bar{t} - tp)], \text{ for } I(\bar{t}) > 1, \qquad (22)$$

where $\bar{t} = f_o t$, and $I(tp) = I(\bar{t}) - 1$. The function $I$ is defined by the relation

$$I(\bar{t}) = \int_0^{\bar{t}} (V/A)\,\mathrm{d}t. \tag{23}$$

Similarly $n_1$ is found to be

$$\begin{aligned} n_1 &= 0, \text{ for } I(\bar{t}) < b_1 \\ &= \exp\left[-q_1(\bar{t} - t_x)\right], \text{ for } b_1 < I(\bar{t}) < (1 + b_1) \\ &= \exp\left[-q_1(\bar{t} - t_x)\right]\{1 - \exp\left[-(t_x - t_y)\right]\}, \\ &\quad \text{for } I(\bar{t}) > (1 + b_1), \end{aligned} \tag{24}$$

where $I(t_x) = I(\bar{t}) - b_1$ and $I(t_y) = I(\bar{t}) - (1 + b_1)$. These equations must be combined with Eqs. 5, 7, and 10 to estimate the speed of contraction as a function of time. In the computations, the tension $T$ is taken constant. Fig. 8 shows modelled fiber sarcomere length as a function of time $t$ for $T = 0.38$. The nonlinear oscillatory behavior observed in the figure is the result of propagation of the discontinuities that exist in the distribution with respect to $x$ of attached cross-bridges during the isometric state. This point is more clearly illustrated in Fig. 9. During the initial isometric state the function $n$ is discontinuous at locations $x = 0$, and $x = h$. These discontinuities propagate in the negative $x$ direction after the reduction of muscle force to a constant value ($T = 0.38$). Propagation occurs because of the hyperbolic nature of the kinetic equation (Eq. 1). The magnitudes of the jumps decrease with time because of the detachment of cross-bridges in the region $(-b_1 h < x < 0)$. When these jumps reach the location $x = -b_1 h$, a rapid change in the speed of contraction is observed as shown in Fig. 9. The time derivatives of the variables $M_{(+)}$, $M_{(-)}$, $Y_{(+)}$, $Y_{(-)}$ are not necessarily equal to zero during the transient phase. Our computations indicate that the duration of the transient phase decreases with increasing force step. This is consistent with the experimental results of Civan and Podolsky (5). Recently, Sugi and Tsuchiya (35) have studied isotonic velocity transients on tetanized frog skeletal muscle fibers. Quick increases in load as well as quick releases were considered. Velocity transients following quick decreases in load were found to be very similar to those reported by Civan and Podolsky (5). These authors have extended the Podolsky and Nolan model (11, 12) to simulate isotonic motions after step increases in load by choosing appropriate $f$ and $g$ functions in the region $x > h$. They have also assumed that $g$ increases with load and then returns to the initial value exponentially with time. Transients after a quick increase in load have not been considered in the present study. However, the method of solution described above can easily be adopted to this case. Analysis of isotonic transients provide evidence that the Eq. 1 represents actual cross-bridge kinetics.

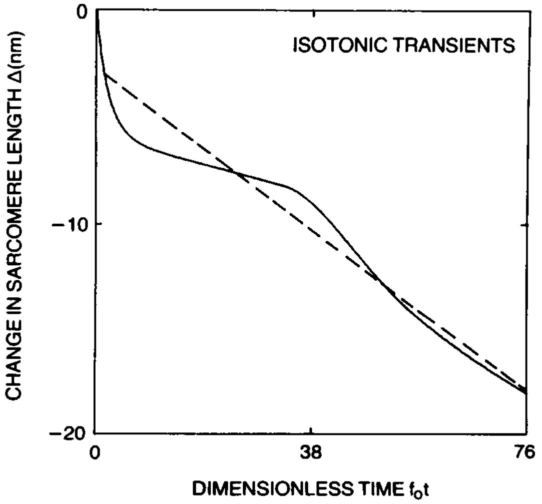

FIGURE 8 Change in sarcomere length as a function of dimensionless time $f_o t$ after a step tension reduction of $\Delta T = 0.62$. Parameters used in the computations are shown in Fig. 1.

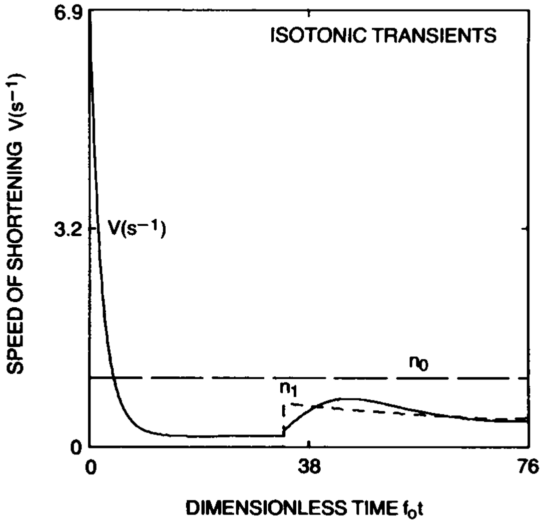

FIGURE 9 The dimensionless speed of shortening $V$ and fraction of attached cross-bridges $n_o$ and $n_1$ computed by using Eqs. 21 and 23, respectively, as functions of the dimensionless time $f_o t$ for the case shown in Fig. 8.

## SINUSOIDAL ANALYSIS

In this section, oscillatory experiments on muscle fibers will be considered. In these experiments the length of a muscle fiber is oscillated sinusoidally and the resulting force amplitude and phase shift are observed. This technique has been used in insect muscle (7, 35) and other muscle types (8). The experimental scheme has been improved by introducing direct computer control of the length driver (8). As a result the time required for measurement is greatly reduced and a wider frequency range can be considered. Kawai and Brandt (8) have observed three time constants in their data and have correlated these time constants with the different rate processes observed in transient tension experiments. However, the assumed correspondence between sinusoidal and step analyses would hold if the fiber length and tension were related by a linear differential equation of the form (36)

$$a_oT + a_1DT + a_2D^2T + \ldots + a_nD^nT = b_o\ell + b_1D\ell + b_2D^2\ell + \ldots b_mD^m\ell \quad (25)$$

where $\ell$ is the fiber length, $T$ is the tension, and $D$ denotes the time derivative ($D = \mathrm{d}/\mathrm{d}t$). It is known that Eq. 25 is too restrictive even to represent linear viscoelastic materials (38). In a recent study, Thorson and White (39) considered the sinusoidal data presented by Kawai and Brandt (8) by using a lumped-bridge model. They have concluded that the data can be interpreted in terms of the Huxley and Simmons (9) mechanism of multiple configurational states of myosin heads during attachment. However, the model used by these authors in interpreting the data does not follow directly from the cross-bridge kinetic model put forward by Huxley (1) or its more recent extensions (9, 14). Because the model of Thorson and White is based on the concept of interfilament shear force produced by attached cross-bridges, their equations do not contain the variable $x$. The fraction $n = n(t)$ of attached cross-bridges in Thorson and White's (39) notation is proportional to the variable $M = M_{(+)} + M_{(-)} + M_{(R)}$ in the present study. Furthermore, attachment and detachment parameters $f(t)$ and $g(t)$ used by these authors can be shown to be not equivalent to the position-dependent rate constants $f(x)$ and $g(x)$ defined in Huxley (1). In general $f(t)$ is expected to be smaller than $\max[f(x)]$ and $g(t)$ is expected to increase with increasing speed of shortening. Thorson and White (39) have concluded that if the sinusoidal data are fitted with sums of first-order signals as in Kawai and Brandt (8), the rate constants obtained in these fits may have no discernible relationship to those events at the cross-bridge level. Sinusoidal experiments will now be considered by using the two-state kinetic model described in the section Mathematical Formulation. It is assumed that the fully activated muscle is oscillated sinusoidally according to the relation

$$1 = 1_o[1 - (2ha^*/s)\sin 2\pi m f_o t], \quad (26)$$

where $1_o$ is the fiber length before oscillation, $a^*$ is the dimensionless amplitude, and $m$ is the dimensionless frequency of oscillation. The parameter $h$ was defined previously as the length of the attachment zone of a cross-bridge ($h = 110$ Å). The dimensionless speed of contraction corresponding to deformation (Eq. 26) is given by the equation

$$(V/A) = 2\pi\ m\ a\cos(2\pi m f_o t). \quad (27)$$

Using Eq. 11, it can be shown that parameters $n_o$ and $n_2$ representing the values of the number density distribution at locations $x = o$, and $x = h$, respectively, are given by the following equations

$$\begin{aligned} n_o &= [1 - D(d_1)]/[1 - B(q_1, d_1)D(d_1)] \text{ for } f_o t \in R_1 \\ &= B(q_1, d_1)[1 - D(d_1)]/[1 - B(q_1, d_1)D(d_1)] \\ &\quad \text{for } f_0 \mathrm{t} \in R_2 \\ n_2 &= [1 - D(d_2)][B(q_2, d_2)]/[1 - B(q_2, d_2)D(d_2)] \\ &\quad \text{for } f_o t \in R_1 \\ &= [1 - D(d_2)]/[1 - B(q_2, d_2)D(d_2] \\ &\quad /[1 - B(q_2, d_2)D(d_2)] \text{ for } f_o t \in R_2 \\ D(x) &= \exp(-x), B(y, x) = \exp(-y^*x) \\ d_1 &= d_1(t) = (1/2m) + 2f_o t \text{ for } f_o t \in R_1 \\ &= (3/2m) - 2f_o t \text{ for } f_o t \in R_2 \\ d_2 &= d_2(t) = (1/m) - d_1(t), \end{aligned} \quad (28)$$

where $q_1f$ and $q_2f$ are the rates of detachment in the zones $x < o$, and $x > h$, respectively, and the time domains $R_1$ and $R_2$ are defined as $R_1 = (-\frac{1}{4}m, \frac{1}{4}m)$ and $R_2 = (\frac{1}{4}m, \frac{3}{4}m)$. Eq. (28) is valid for steady state oscillations and therefore consideration of a single period of oscillation is sufficient for analysis. Once the parameters $n_o$ and $n_2$ are expressed as functions of time, muscle tension $T$ can be determined as a function of time by solving the ordinary differential Eqs. 5 and 7. The closed form analytical solutions are available for these equations in the case of sinusoidal oscillations. Initial conditions are chosen such that the dimensionless tension $T$ assumes the same value after a period of oscillation.

Numerical computations in this section have been carried out for two different sets of the values of cross-bridge parameters appearing in the equations. The first set corresponds to the parameter values used in the previous sections; in addition, time constant $q_2$, which was not assigned a value previously, is taken as $q_2 = 0.1\ q_2 = 1.0$. In the second set a slower rate of attachment is assumed ($f_o = 100\ \mathrm{s}^{-1}$), and the detachment is considered to occur considerably faster in the regions $x < 0$ and $x > h$ ($q_1 = 10$, $q_2 = 5$). The second set of parameters yields qualitatively similar results to Huxley's initial model (1). Our numerical computations indicate that perturbation in muscle tension as a result of sinusoidal oscillations is not sinusoidal even for very small amplitudes ($ah < 10$ Å). This nonlinearity is most pronounced for frequencies at ~10 Hz, and decreases with increasing frequency. Fig. 10 shows fiber tension $T$ as a function of time for $mf_o = 10$ Hz. Note that the tension response is quite different for the two sets of parameter values defined above. The cross-bridge model with a high rate of attachment predicts an increase in fiber tension with increasing frequency of oscillation. The variation of the number density of attached cross-bridges with the frequency of oscillation is illustrated in Fig. 11. The detachment is significant even for the model corresponding

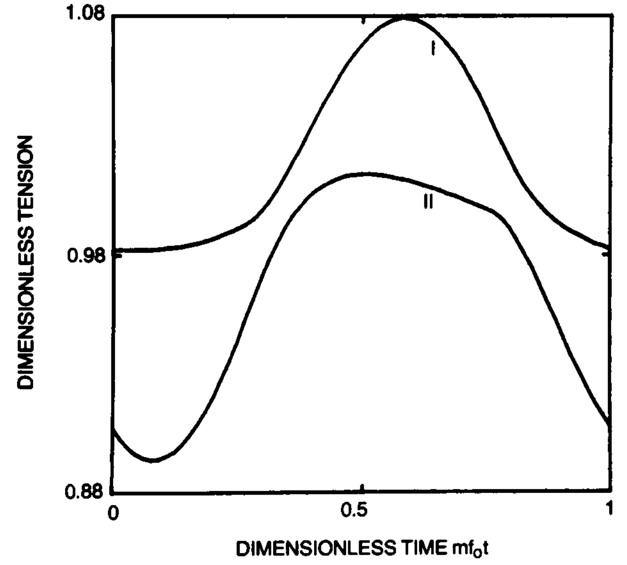

FIGURE 10 Fiber tension $T$ as a function of dimensionless time $mf_o t$ during a single period of oscillation is shown: (a) present model with $f_o = 1{,}000\ s^{-1}$, $q_1 = 0.014$, $b_1 = 1.14$, $q_2 = 1/10$; (b) model with low rate of attachment and high rate of detachment with $f_o = 100\ s^{-1}$, $q_1 = 10$, $q_2 = 5$, $b_1 = 1.14$.

to the first set of cross-bridge parameters when the frequency of oscillation is small. We have also expanded the computed tension-time curves into Fourier series to be able to compare them with the data presented by Kawai and Brandt (8). Present computations indicate that the amplitude ratio increases and the phase lag decreases with increasing frequency of oscillation. If the computational data are represented as a Nyquist plot as in Kawai and Brandt (8), the two models would predict semicircles in the upper right quadrant. Our computations show that for all frequencies, the first harmonic of the tension-time curve is most sensitive to cross-bridge parameters $q_2 f_o$ defining the rate of detachment after a step stretch. This is illustrated in Fig. 12 for the present model with $q_2 = 0.1$ and $q_2 = 1$. In this figure, viscous modulus, $A_v$, is plotted as a function of the elastic modulus, $A_E$. The figure shows that the radius of the semicircle in Nyquist plot increases with increasing $q_2$. The zeroth harmonic (mean tension) is larger for cross-bridge models with high rates of attachment and the second and third harmonics also depend strongly on the values of the rate parameters assumed in the computations. Note also that at least three rate constants ($f$, $q_1$, $q_2$) are used in the analysis of sinusoidal oscillation; however, the Nyquist plot corresponding to the first harmonic of the computed tension-time curve yields only a single time constant. Our computations indicate that significant information about cross-bridge kinetics may be lost when the data are expanded in Fourier series and only the first term is considered. As a result, correspondence between oscillatory experiments and step change experiments can not be modeled with that of a simple linear, isotropic response. However, these observations do not deny the usefulness of the sinusoidal method. This treatment may be considered as a first step in analysis of such data by using a cross-bridge model.

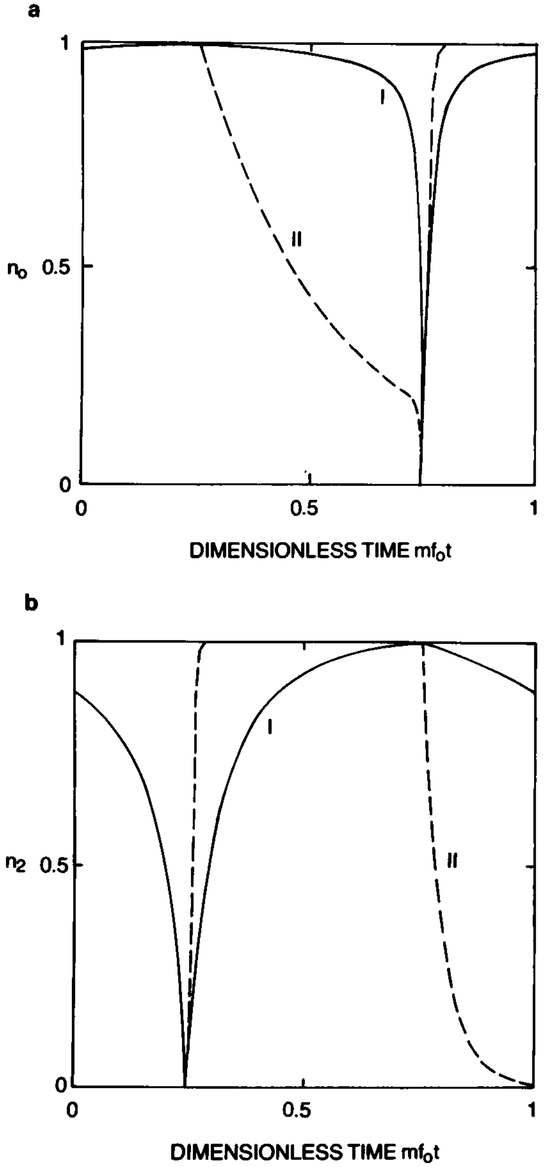

FIGURE 11 The variables $n_o$ (a) and $n_2$ (b) given by Eq. 28 as a function of time during a period of oscillation for the present model with parameter values given in Fig. 1 (I: $mf_o = 10$, II: $mf_o = 1$, $q_2 = 0.1$).

## CONCLUSION

Constitutive equations of skeletal muscle fibers are derived on the basis of an assumed cross-bridge mechanism. As an end result, fiber tension is expressed in terms of peak isometric tension, time history of speed of contraction and the level of activation. The internal variable $x$, denoting cross-bridge extension, has been eliminated in the final equations by the method of integration described in the section entitled Mathematical Formulation. Parameters of the proposed cross-bridge mechanism have been deter-

TABLE I

| Experiments | Model predictions | | | | |
|---|---|---|---|---|---|
| | Huxley (1)* | Podolsky and Nolan (12) | Huxley and Simmons (9) | Eisenberg et al. (14) | Present study |
| Steady isotonic force-velocity relation; Hill (3) | + | + | ? | + | + |
| Isometric transients $T_1$, $T_2$; Ford et al. (23) | − | − | + | + | + |
| Isotonic transients; Civan and Podolsky (5) | − | + | ? | ? | + |
| Sinusoidal oscillations; Kawai and Brandt (18) | ? | ? | ? | ? | (+)<br>(−) |

*The numbers in parentheses refer to the corresponding reference.

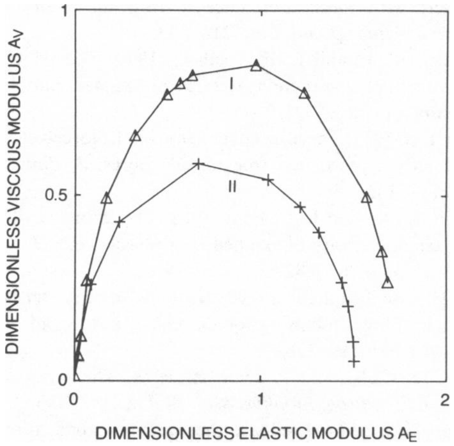

FIGURE 12 The variation of complex dynamic viscosity $A_V$ as a function of the elastic modulus, $A_E$, for the present model with parameter values given in Fig. 1 (I: $q_2 = 1$, II: $q_2 = 0.1$).

mined by fitting experimental data on the transient tension and isotonic-force velocity relation. The resulting cross-bridge model is quite similar to the one proposed by Podolsky and Nolan (12). However, in the present study cross-bridge compliance and the rate functions are allowed to change values at only three $x$ locations. Cross-bridges are assumed to be more compliant in the region of detachment ($-b_1h < x < o$) than in the region of attachment ($o < x < h$). Furthermore, all cross-bridges extended beyond $x < -b_1h$ are assumed to break instantaneously as a result of a mechanical process. During isotonic contraction, estimated fiber stiffness for the proposed model is less than the prediction of Podolsky and Nolan model, but greater than corresponding experimental data. However, the recent electron microscopy data (39) indicate that thin filaments may be quite compliant during contraction. Filament compliance was neglected in the present analysis. The proposed constitutive equations satisfactorily predict the mechanical behavior of skeletal muscle fibers during steady isometric and isotonic contraction. The transient mechanical response to quick releases (step shortening, step decrease in load) is also described accurately with the present model. The relationship between the present study and previous models is summarized in Table I, which compares the results of this work with that of other theoretical studies and with experimental data. The present study provides considerable mathematical simplification in the mechanical analysis of contraction with arbitrarily prescribed external conditions, such as oscillatory motion and isotonic transients. This type of analysis may provide additional insight on the influence of cross-bridge parameters to the mechanical behavior of muscle fibers.

The author would like to thank Doctors Murray Eden, Richard J. Podolsky, and Mark Schoenberg for useful discussions.

*Received for publication 5 January 1984 and in final form 3 August 1984.*

## REFERENCES

1. Huxley, A. F. 1957. Muscle structure and theories of contraction. *Prog. Biophys. Biophys. Chem.* 7:255–318.
2. Podolsky, R. J., A. C. Nolan, and S. A. Zavelier. 1969. Cross-bridge properties derived from muscle isotonic velocity transient. *Proc. Natl. Acad. Sci. USA.* 64:504–511.
3. Hill, A. V. 1938. The heat of shortening and the dynamic constants of muscle. *Proc. R. Soc. Lond. B. Biol. Sci.* B216:136–195.
4. Jewell, B. R., and D. R. Wilkie. 1958. An analysis of the mechanical components in frog's striated muscle. *J. Physiol.* (*Lond.*). 143:515–540.
5. Civan, M. M., and R. J. Podolsky. 1966. Contraction kinetics of striated muscle fibres following quick changes in load. *J. Physiol.* (*Lond.*). 184:511–534.
6. Huxley, A. F., and R. M. Simmons. 1971*a*. Mechanical properties of the cross bridges of frog and striated muscle. *J. Physiol.* (*Lond.*). 218:59–60P.
7. Abbot, R. H. 1973. The effects of fiber length and calcium ion concentration on the dynamic response of glycerol extracted insect fibrillar muscle. *J. Physiol.* (*Lond.*). 231:195–208
8. Kawai, M., and P. W. Brandt. 1980. Sinusoidal analysis: a high resolution method for correlating biochemical reactions with physiological processes in activated skeletal muscles of rabbit, frog and crayfish. *J. Muscle Res. Cell Motil.* 1:279–303.
9. Huxley, A. F., and R. M. Simmons. 1971*b*. Proposed mechanism of force generation in striated muscle. *Nature* (*Lond.*). 233:533–538.
10. Eisenberg, E., and T. L. Hill. 1978. A cross-bridge model of muscle contraction. *Prog. Biophys. Mol. Biol.* 33:55–82.

11. Podolsky, R. J., and A. C. Nolan. 1972. Cross-bridge properties derived from physiological studies of from muscle fibres. *In* Contractility of Muscle Cells and Related Processes. R. J. Podolsky, editor. 247–260.

12. Podolsky, R. J., and A. C. Nolan. 1973. Muscle contraction transients, cross-bridge kinetics and the Fenn Effect. *37th Cold Spring Harbor Symp. Quant. Biol.* 661–668.

13. Hill, T. L., E. Eisenberg, Y. Chen, and R. J. Podolsky. 1975. Some self-consistent two-state sliding filament models of muscle contraction. *Biophys. J.* 15:335–372.

14. Eisenberg, E., Y. Chen, and T. L. Hill. 1980. A cross-bridge model of muscle contraction, quantitative analysis. *Biophys. J.* 29:195–227.

15. Julian, F. J., K. R. Sollins, and M. R. Sollins. 1973. A model for muscle contraction in which cross-bridge attachment and force generation are distinct. *37th Cold Spring Harbor Symp. Quant. Biol.* 685–688.

16. Wong, A. Y. K. 1972. Mechanics of cardiac muscle, based on Huxley's model: Simulation of active state and force-velocity relation. *J. Biomech.* 5:107–117.

17. Panerai, R. B. 1980. A model of cardiac muscle mechanics and energetics. *J. Biomech.* 13:929–940.

18. Zahalak, G. I. 1981. A distribution-moment approximation for kinetic theories of muscular contraction. *Math. Biosci.* 55:89–116.

19. Huxley, H. E. 1957. The double array of filaments in cross-striated muscle. *J. Biophys. Biochem. Cytol.* 3:631–647.

20. Julian, F. J. 1969. Activation in a skeletal muscle contraction model with a modification of insect fibrillar muscle. *Biophys. J.* 9:547–570.

21. Gordon, A. M., A. F. Huxley, and F. J. Julian. 1966. The variation in isometric tension with sarcomere length in vertebrate muscle fibers. *J. Physiol.* (*Lond.*). 184:170–192.

22. Jewell, B. R. 1977. A re-examination of the influence of muscle length on myocardial performance. *Circ. Res.* 40:221–230.

23. Ford, L. E., A. F. Huxley, and R. M. Simmons. 1977. Tension responses to sudden length change in stimulated frog muscle fibers near slack length. *J. Physiol.* (*Lond.*). 269:441–515.

24. Ford, L. E., A. F. Huxley, and R. M. Simmons. 1976. The instantaneous elasticity of frog skeletal muscle fibres. *J. Physiol.* (*Lond.*). 260:28–29P.

25. Julian, F. J., and M. R. Sollins. 1975. Variation of muscle stiffness with force at increasing speeds of shortening. *J. Gen. Physiol.* 66:287–302.

26. Julian, F. J., and D. L. Morgan. 1981. Variation of muscle stiffness with tension during tension transients and constant velocity shortening in the frog. *J. Physiol.* (*Lond.*). 319:193–203.

27. Schoenberg, M., J. B. Wells, and R. J. Podolsky. 1974. Muscle compliance and the longitudional transmission of mechanical impulses. *J. Gen. Physiol.* 64:623–642.

28. Podolsky, R. J. 1976. The kinetics of cross-bridge turnover. *In* 26. Colloquium-Mosbach 1975 Molecular Basis of Motility. Heilmeyer, G., J. C. Rüegg, and T. Wieland, editors. Springer-Verlag, Berlin, 55–67.

29. Ferenczi, M. A., Y. E. Goldman, and R. M. Simmons. 1984. The dependence of force and shortening velocity on substrate concentration in skinned muscle fibres from *Rana temporaria*. *J. Physiol.* (*Lond.*). 350:519–543

30. Sugi, H., and T. Tsuchiya. 1981. Enhancement of mechanical performance in frog muscle fibres after quick increases in load. *J. Physiol.* (*Lond.*). 319:239–252.

31. Ebashi, S., I. Ohtsuki, and K. Mihashi. 1973. Regulatory proteins of muscle with special reference to troponin. *37th Cold Spring Harbor Symp. Quant. Biol.* 215–223.

32. Podolsky, R. J., and L. E. Teicholz. 1970. The relation between calcium and contraction kinetics in skinned muscle fibres. *J. Physiol.* (*Lond.*). 211:19–35.

33. Julian, F. J. 1971. The effect of calcium on the force-velocity relation of briefly glycerinated frog muscle fibres. *J. Physiol.* (*Lond.*). 218:117–145.

34. Podolin, R. A., and L. E. Ford. 1983. The influence of calcium on shortening velocity of skinned frog muscle cells. *J. Muscle Res. Cell Motil.* 4:263–282.

35. Sugi, H., and T. Tsuchiya. 1981. Isotonic velocity transients in frog muscle fibres following quick changes in load. *J. Physiol.* (*Lond.*). 319:219–238.

36. White, D. C. S., and J. Thorson. 1973. The kinetics of muscle contraction. *Prog. Biophys. Mol. Biol.* 27:173–255.

37. Machin, K. E. 1964. Feedback theory and its application to biological systems. *Symp. Soc. Exp. Biol.* 18:421–445.

38. Christiensen, R. M. 1971. Theory of Visoelasticity: An Introduction. Academic Press, Inc., New York/London.

39. Thorson, J., and D. C. S. White. 1983. Role of cross-bridge distortion in the small-signal mechanical dynamics of insect and rabbit striated muscle. *J. Physiol.* (*Lond.*). 343:55–84.

40. Heuser, J. E., and R. Cooke. 1983. Actin-myosin interactions visualized by the quick-freeze, deep-etch replica technique. *J. Mol. Biol.* 169:97–122.