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A THREE-ELEMENT DESCRIPTION FOR MUSCLE WITH VISCOELASTIC PASSIVE ELEMENTS*†

STANTON A. GLANTZ‡
Cardiology Division and Cardiovascular Research Institute,
University of California, San Francisco, CA 94143, U.S.A.

Abstract—This paper explores the implications of expanding Hill's three-element model by replacing the series and parallel elastic elements with nonlinear viscoelastic elements. The resulting model includes a contractile element whose shortening relates not to a mechanical length, but to the number of active cross-bridges. Given this interpretation, the contractile element behaves in qualitatively agreement with known sarcomere biophysics. It also explains why one cannot vary maximum tetanic force and maximum shortening velocity independently in skeletal muscle, why cardiac muscle fails to exhibit hyperbolic force–velocity curves and why the curve's shape depends on how one obtains the curve. This analysis also shows that the classical formula for contractile element velocity, $V_{CE}(t) = \dot{P}/(KP + C)$, actually gives initial muscle shortening velocity for a twitch that begins shortening at time t, not contractile element velocity. This model suggests a simple hypothesis to relate the inotropic agents action at a subcellular level to the mechanical events and permits indexing inotropic state at constant muscle length with one parameter. These results follow from replacing the two purely elastic elements with viscoelastic ones; they would still follow even if the exact formulation proposed for the viscoelastic element was wrong.

INTRODUCTION

Hill (1949) proposed a model for skeletal muscle which separated the muscle's mechanical properties into three elements: an active contractile element (CE) representing the processes by which the muscle responds to stimulation, and two passive elastic elements, a series elastic element in series with the CE and a parallel elastic element parallel to the other two elements (Fig. 1a). Both elastic elements' instantaneous length determines force. Others applied this model to cardiac muscle (Abbott and Mommaerts, 1959; Sonnenblick, 1962a; Parmley and Sonnenblick, 1967; Edman and Nilsson, 1968; Taylor, 1970; Fung, 1970, 1971; Glantz, 1975). Meanwhile, evidence was accumulating that unstimulated muscle exhibited not simply elastic, but viscoelastic, behavior (Pinto and Fung, 1973a; Glantz, 1974; Loeffler and Sagawa, 1975), and some observers presented data which suggested that the passive element in series with the contractile element also exhibited viscoelasticity (Hoffman *et al.*, 1968; Parmley *et al.*, 1969; Templeton *et al.*, 1974; Loeffler and Sagawa, 1975). McLaughlin and Sonnenblick (1974a,b) specifically addressed the question of whether or not the element in series with the CE exhibits viscoelastic behavior and concluded that it did. In particular, they showed calcium, which affects muscle's active processes, did not affect the velocity-dependence of the series element (McLaughlin and Sonnenblick, 1974a) which indicates a passive viscoelastic element in series with the CE. My paper expands the traditional Hill model by replacing the series and parallel elastic elements with viscoelastic elements (Fig. 1b,c) and systematically examines the implications of this arrangement. The CE, the mechanical element which represents the processes by which muscle responds to stimulation, probably represents the number of active cross-bridges in the muscle, not a physical length, and suggests that there probably is no simple index of inotropic state independent of muscle length that can be based on a single twitch or a few twitches. This analysis shows that, while inotropic agents affect the processes CE shortening represents, most do not affect the process CE extension represents (relaxation). It also shows that, at constant muscle length, inotropic state can, in most cases, be indexed with a single parameter.

The CE represents those biophysical processes by which muscle responds to stimulation. It might, therefore, be appropriate to begin describing CE dynamics with the contraction processes' chemical kinetics. Others have followed this approach (e.g. Huxley and Simmons, 1971; Julian *et al.*, 1974), but the resulting theories focus on microscopic events and are of little direct value in interpreting macroscopic behavior of muscle, such as response to inotropic agents. This situation is not surprising, given the current incomplete understanding of the basic reactions taking place among the contractile proteins and in the various membrane ion pumps. A less ambitious approach to the problem of describing the CE begins with an equation which describes the series and parallel elements' passive viscoelastic behavior and infers the CE behavior necessary to obtain prediction which agree with observed phenomena. Qualitative arguments

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‡ Dr. Glantz is a Fellow of the San Francisco Bay Area Heart Association.

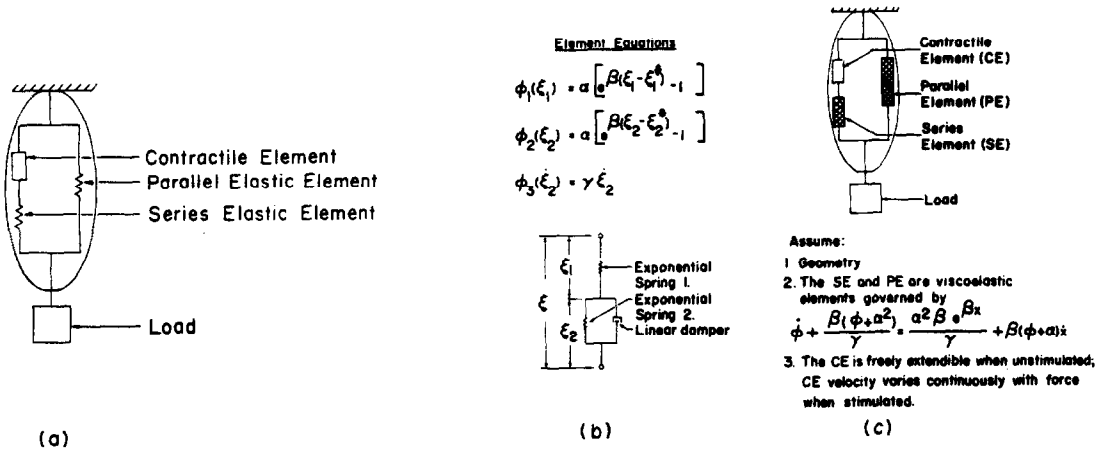

Fig. 1. (a). Classical three-element model consisting of a contractile element and two passive elastic elements. (b). Arrangement of pure elastic and viscous elements used to motivate the constitutive equation, equation (1). The constants α and β are the same for both elements (26). ξ_1^* and ξ_2^* are rest lengths for the two elastic elements; ϕ_j equals force in the element. (c). Three element description of muscle. The CE represents those processes by which muscle responds to stimulation and the SE and PE represent passive viscoelasticity.

based on observed muscle electrophysiology and biochemistry show that this CE does indeed represent the muscle's response to stimulation. While this paper deals with a model beginning with specific starting assumptions, the major qualitative conclusions follow not from the precise mathematical form of the starting assumptions, but rather from the fact that we explicitly replace the elastic elements in the classical Hill model with viscoelastic elements.

DERIVATIONS

The picture in Fig. 1(b) motivated a constitutive equation which relates length, force, and their rates of change for the two passive viscoelastic elements, the series element (SE) and parallel element (PE), shown in Fig. 1(b). Prior analysis of experimental results (Glantz, 1974, 1975), as well as new experiments (Templeton *et al.*, 1974; McLaughlin and Sonnenblick, 1974a; Wise *et al.*, 1973; Bahler *et al.*, 1974) showed that the elastic constants, α and β, and the viscous constant, γ, are unaffected by inotropic agents (which change the active process in cardiac muscle), therefore, these constants truly represent passive properties of muscle. The values of β are the same for both the SE and PE (Glantz, 1975), and it is reasonable to assume that the values of α (Glantz, 1975) and γ (Glantz, 1974) are the same for both elements. Thus, we arrive at the description embodied in three assumptions: (1) The CE, SE and PE are arranged as in Fig. 1(c). (2) The SE and PE are each passive viscoelastic elements like those shown in Fig. 1(b) and described by the constitutive equation (Glantz, 1974):

$$\dot{\phi} + \beta(\phi + \alpha)^2/\gamma = \alpha^2\beta\, e^{\beta x}/\gamma + \beta(\phi + \alpha)\dot{x}, \quad (1)$$

where ϕ = force, x = extension from rest length and the dots denote differentiation with respect to time; the same values of α, β and γ describe both the SE and PE. (3) The CE, which represents the muscle's response to stimulation, extends freely in unstimulated muscle and its shortening velocity is a continuous function of force when the muscle is stimulated.

Basic equations

We first derive equations which relate force development and shortening in terms of CE shortening (Appendix A summarizes all nomenclature). Let x_S equal SE extension from rest length, x_C equal CE shortening measured with respect to CE length at time $t = 0$, x_P equal PE extension from rest length and x equal muscle extension during the isotonic phase. We now derive differential equations which describe an isotonic twitch's three phases (Fig. 2): the isometric phase ($0 < t < t_A$), the isotonic phase ($t_A < t < t_B$) and the post-isotonic phase ($t_B < t$).

Assume that the muscle has completely relaxed from the prior contraction by $t = 0$. The constitutive equation, equation (1), written for the SE is:

$$\dot{\phi}_S + \beta(\phi_S + \alpha)^2/\gamma = \alpha^2\beta e^{\beta x_S}/\gamma + \beta(\phi_S + \alpha)\dot{x}_S; \quad (2)$$

and, for the PE,

$$\dot{\phi}_P + \beta(\phi_P + \alpha)^2/\gamma = \alpha^2\beta e^{\beta x_P}/\gamma + \beta(\phi_P + \alpha)\dot{x}_P. \quad (3)$$

Note that CE force, ϕ_C, equals ϕ_S. To obtain a differential equation which relates muscle force, $P(t)$, and CE shortening, $x_C(t)$, during the isometric phase, note that during the isometric phase $x_S = x_C$ and $\phi_S = P(t) - P_i$ where P_i = preload, then use these results with (2) to obtain

$$\dot{P}(t) = \alpha^2\beta e^{\beta x_C}/\gamma + \beta(P(t) - P_i + \alpha)\dot{x}_C - \beta(P(t) - P_i + \alpha)^2/\gamma, 0 < t < t_A, \quad (4)$$

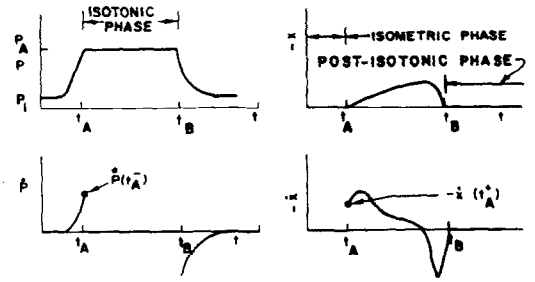

Fig. 2. Isotonic twitch.

with the initial condition

$$P(0) = P_i. \tag{5}$$

The isometric phase ends when the developed force equals the afterload;

$$P(t_A) = P_A, \tag{6}$$

implicitly defines t_A.

During the isotonic phase ($t_A < t < t_B$)

$$x_S(t) = x_C(t) + x(t), \tag{7}$$

$$x_P(t) = x_P(0) + x(t), \tag{8}$$

and

$$P(t) = P_A = \phi_S(t) + \phi_P(t). \tag{9}$$

Differentiate (9) with respect to time:

$$0 = \dot{\phi}_S(t) + \dot{\phi}_P(t), t_A < t < t_B, \tag{10}$$

then substitute from (7), (9), and (10) into (2) to obtain

$$-\dot{\phi}_P + (P_A - \phi_P + \alpha)^2/\gamma = \alpha^2\beta e^{\beta(x_C+x)}/\gamma + \beta(P_A - \phi_P + \alpha)(\dot{x}_C + \dot{x}). \tag{11}$$

Since the PE is in steady state with $\phi_P(t) = P_i$ prior to $t = 0$, $\dot{\phi}_P(0^-) = 0$ so (3) yields

$$x_P(0) = \frac{2}{\beta} \ln \frac{P_i + \alpha}{\alpha}. \tag{12}$$

Substitute from (8) and (12) into (3) to obtain

$$\dot{\phi}_P + \beta(\phi_P + \alpha)^2/\gamma = \beta(P_i + \alpha)^2 e^{\beta x}/\gamma + \beta(\phi_P + \alpha)\dot{x}. \tag{13}$$

Since equations (11) and (13) are linear in $\dot{\phi}_P$ and $\dot{x}$ we can solve them for the differential equations governing the isotonic phase:

$$\dot{x} = \frac{1}{P_A + 2\alpha}\left\{\frac{1}{\gamma}[(P_A - \phi_P + \alpha)^2 + (\phi_P + \alpha)^2 - (\alpha^2 e^{\beta x_C} + (P_i + \alpha)^2)e^{\beta x}] - (P_A - \phi_P + \alpha)\dot{x}_C\right\}, \tag{14}$$

$$\dot{\phi}_P = \frac{\beta(\phi_P + \alpha)}{P_A + 2\alpha}\left\{\frac{1}{\gamma}\left[(P_A - \phi_P + \alpha)^2 + (\phi_P + \alpha)^2 - (P_A + 2\alpha)(\phi_P + \alpha) - \left(\alpha^2 e^{\beta x_C} - \frac{(P_A + \phi_P - \alpha)}{\phi_P + \alpha}(P_i + \alpha)^2\right)e^{\beta x}\right] - (P_A - \phi_P + \alpha)\dot{x}_C\right\}, \tag{15}$$

for $t_A < t < t_B$, with the initial conditions

$$x(t_A) = 0, \tag{16}$$

and

$$\phi_P(t_A) = P_i. \tag{17}$$

The isotonic phase ends when the muscle returns to its original length:

$$x(t_B) = 0,\ t_B > t_A, \tag{18}$$

implicitly defines t_B.

During the post-isotonic phase $x = \dot{x} = 0$. Substitute this result and from $\phi_S = \phi_C$, (7), (8) and (12) into (2) and (3) to obtain

$$\dot{\phi}_C = \beta[\alpha^2 e^{\beta x_C - (\phi_C + \alpha)^2}]/\gamma + (\phi_C + \alpha)\dot{x}_C; \tag{19}$$

$$\dot{\phi}_P = \beta[(P_i + \alpha)^2 - (\phi_P + \alpha)^2]/\gamma, t > t_B; \tag{20}$$

with the initial conditions

$$\phi_C(t_B) = P_A - \phi_P(t_B), \tag{21}$$

and

$$\phi_P(t_B) \text{ given.} \tag{22}$$

Equations (19) and (20) yield $\phi_C(t)$ and $\phi_P(t)$ for $t > t_B$; $P(t) = \phi_C(t) + \phi_P(t)$ for $t > t_B$. Notice that (19) and (20) are independent and that the PE force is changing due to stress relaxation. Table 1 summarizes the equations for a twitch, given $x_C(t)$.

Method to compute CE velocity during an isometric twitch

Define the developed force, $D(t)$:

$$D(t) = P(t) - P_i. \tag{23}$$

Substitute from (23) into (4) to obtain a differential equation for CE shortening, $x_C(t)$, valid during an isometric twitch, in terms of the mechanical parameters α, β and γ and the observed force, $D(t)$:

$$\dot{x}_C(t) = \frac{\dot{D}(t)}{\beta(D(t) + \alpha)} + \frac{D(t) + \alpha}{\gamma} - \frac{\alpha^2}{\gamma(D(t) + \alpha)} e^{\beta x_C(t)}, \tag{24}$$

with

$$x_C(0) = 0. \tag{25}$$

Table 1. Equations for an isotonic twitch

Phase	Dynamic Equations	Initial Conditions	End Time
Isometric	$\dot{P} = \beta[\alpha^2 e^{\beta x_C} - (P - P_i + \alpha)^2]/\gamma + (P - P_i + \alpha)\dot{x}_C$	$P(0) = P_i$	$P(t_A) = P_A$
Isotonic	$\dot{x} = \frac{1}{P_A + 2\alpha}\left\{\frac{1}{\gamma}[(P_A - \phi_P + \alpha)^2 + (\phi_P + \alpha)^2 - (\alpha^2 e^{\beta x_C} + (P_i + \alpha)^2)e^{\beta x}] - (P_A - \phi_P + \alpha)\dot{x}_C\right\}$	$x(t_A) = 0$	$x(t_B) = 0;$ $t_B > t_A$
	$\dot{\phi}_P = \frac{\beta(\phi_P + \alpha)}{P_A + 2\alpha}\left\{\frac{1}{\gamma}\left[(P_A - \phi_P + \alpha)^2 + (\phi_P + \alpha)^2 - (P_A + 2\alpha)(\phi_P + \alpha) - \left(\alpha^2 e^{\beta x_C} - \frac{(P_A + \phi_P - \alpha)}{(\phi_P + \alpha)}(P_i + \alpha)^2\right)e^{\beta x}\right] - (P_A - \phi_P + \alpha)\dot{x}_C\right\}$	$\phi_P(t_A) = P_i$	
Post-isotonic	$\dot{\phi}_C = \beta[\alpha^2 e^{\beta x_C} - (\phi_C + \alpha)^2]/\gamma + (\phi_C + \alpha)\dot{x}_C$	$\phi_C(t_B) = P_A - \phi_P(t_B)$	
	$\dot{\phi}_P = \beta[(P_i + \alpha)^2 - (\phi_P + \alpha)^2]/\gamma$	$\phi_P(t_B)$ given	
	$P = \phi_C + \phi_P$		

We must integrate (24) numerically. (I use fourth-order Runge–Kutta integration with a fixed step size, 1.25 msec, on an IBM 360/67). We must know $\dot{D}$, the derivative of the observations, to integrate (24) as it stands. To remedy this undesirable situation, integrate (24)'s first term from time t_n to $t_{n+1} = t_n + 1.25$ msec:

$$\int_{t_n}^{t_{n+1}} \frac{\dot{D}(t)}{\beta(D(t) + \alpha)}\,dt = \int_{D(t_n)}^{D(t_{n+1})} \frac{dD}{\beta(D + \alpha)} = \frac{1}{\beta}\ln\frac{D(t_{n+1}) + \alpha}{D(t_n) + \alpha}. \quad (26)$$

Now apply the Runge–Kutta method to evaluate the integral in

$$x_C(t_{n+1}) = x_C(t_n) + \frac{1}{\beta}\ln\frac{D(t_{n+1}) + \alpha}{D(t_n) + \alpha} + \frac{1}{\gamma}\int_{t_n}^{t_{n+1}}\left\{(D(t) + \alpha) - \frac{\alpha^2}{(D(t) + \alpha)}e^{\beta x_C(t)}\right\}dt, \quad (27)$$

with the initial condition (25). This equation produces CE shortening as a function of time, $x_C(t)$. I compute $\dot{x}_C$ using central differences.

Figure 3 shows these computations' results based on an isometric twitch of isolated cat papillary muscle which Parmley and Sonnenblick (1969) observed. $\dot{x}_C$ was calculated using the values of α and β reported earlier (Glantz, 1975) ($\alpha = 0.045$ g/mm^2, $\beta = 5.9$ mm^{-1}), and $\gamma = 5$ (g/mm^2)/(mm/sec). Since I could not locate suitable data for computing γ directly using cardiac muscle, I estimated its value based on the value derived for rabbit taenae coli at 22°C, 6.25 (g/mm^2)/(mm/sec) (Glantz, 1974). The twitch presented in Fig. 3(a) occurred at 29°C, so, since muscle viscosity decreases as temperature increases (Templeton *et al.*, 1974), I selected $\gamma = 5$ (g/mm^2)/(mm/sec). These values of α, β, and γ lead to predictions which agree with observations. Changing γ quantitatively, but not qualitatively, changes the value of the derived variable, $x_C(t)$, but, more important, predictions of observable data (Figs. 5–10) are insensitive to the exact value of α, β and γ. For example, varying γ by a factor of two shifts the theoretical curve in Figs. 5 and 7 by less than 10% (in terms of either predicted maximum developed force and the time it occurs). Similar results hold for α and β.

Hill's equation and force–velocity curves in tetanized skeletal muscle

Hill (1938) extensively studied heat and external work production in tetanized skeletal muscle and showed that

$$(P_A + a)V = b(P_0 - P_A), \quad (28)$$

where a and b are constants, V is the muscle's shortening velocity, and P_0 is the maximum isometric tension obtained during tetanus. We derive an equation relating x_C and ϕ_C in tetanized muscle by formalizing Hill's experiment. (1) Tetanize the muscle isometrically and allow it to reach steady state force, P_0: (2) release the muscle to an afterload P_A at $t = t_R$; (3)

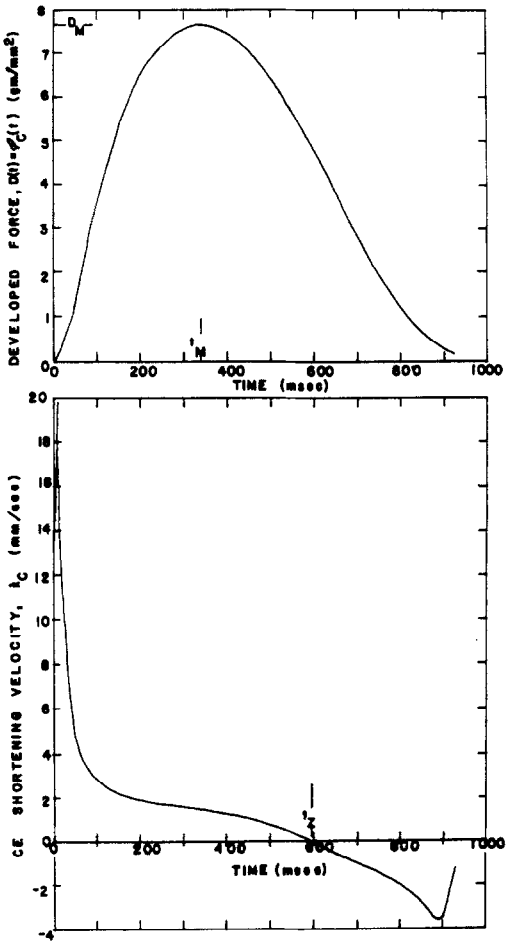

Fig. 3. (a). Developed force during an isometric twitch of isolated cat papillary muscle. Temperature = 29°C; stimulation rate = 12 min^{-1}. (Data from Parmley and Sonnenblick (1969), Fig. 4.) (b). $\dot{x}_C(t)$ computed using $D(t)$ shown in Panel A and equation (24) with $\alpha = 0.045$ g/mm^2, $\beta = 5.9$ mm^{-1}, and $\gamma = 5$ (g/mm^2)/(mm/sec). All times are measured from first detectable tension.

measure the initial shortening velocity (after the initial quick shortening). Thus far we have assumed x_C is a continuous function of force, but only written it as an explicit function of time. Now consider

$$x_C = \dot{x}_C(\phi_C, t). \tag{29}$$

The functional dependence on t expresses the transient effects related to excitation–contraction coupling. With the muscle in steady state tetanus, (29) becomes

$$\dot{x}_C(\phi_C(t_R^-), t_R^-) = 0. \tag{30}$$

Hill carried out his experiment with no preload, i.e. with the PE at rest length. (Skeletal muscle develops maximum force at about the same length it begins to manifest detectable resting tension.) Therefore,

$$x_P(t_R^-) = 0, \tag{31}$$

and the total muscle force equals the developed force;

$$P_0 = \phi_C(t_R^-) = \phi_S(t_R^-). \tag{32}$$

Since the SE is an isometric steady state, we substitute from $x_S = x_C$, $\phi_S(t_R^-) = 0$, and (32) into (12) to obtain

$$x_C(P_0, t_R^-) = \frac{2}{\beta} \ln \frac{P_0 + \alpha}{\alpha}. \tag{33}$$

This experiment resembles the isometric quick release (Glantz, 1974, 1975) in which the muscle forces before and after release are $P = P_0$ and $P_+ = P_A$, respectively. It has been shown (Glantz, 1975) that:

$$\Delta x_P = \frac{1}{\beta} \ln \frac{P_+ + 2\alpha}{P_- + 2\alpha}, \tag{34}$$

relates these forces to the muscle length change and that

$$\Delta x_P = \frac{1}{\beta} \ln \frac{\phi_P(t_R^+) + \alpha}{\phi_P(t_R^-) + \alpha}. \tag{35}$$

Substitute from (31) into (34) to obtain

$$\Delta x_P = x_P(t_R^+) - x_P(t_R^-) = x_P(t_R^+) = \frac{1}{\beta} \ln \frac{P_A + 2\alpha}{P_- + 2\alpha}, \tag{36}$$

for the muscle. Similarly, (35) predicts

$$\Delta x_P = x_P(t_R^+) - x_P(t_R^-) = x_P(t_R^+) = \frac{1}{\beta} \ln \frac{\phi_P(t_R^+) + \alpha}{\alpha}, \tag{37}$$

for the PE. Equate (34) and (35) and solve for $\phi_P(t_R^+)$:

$$\phi_P(t_R^+) = \alpha \left[\frac{P_A + 2_\alpha}{P_0 + 2_\alpha} - 1 \right]. \tag{38}$$

Since $\dot{x}_C$ is assumed to be a continuous function of force,

$$x_C(\phi_C(t_R^-), t_R^-) = x_C(\phi_C(t_R^+), t_R^+). \tag{39}$$

(See Appendix A of Glantz, (1975) for proof.) Appendix B shows that for tetanized muscle in steady state

$$\dot{x}_C(\phi_C, t) = \dot{x}_C(\phi_C). \tag{40}$$

Finally substitute (33), (36), and (38)–(40), into (14) to find the predicted force–velocity equation

$$\dot{x}(t_R^+) = \frac{1}{P_A + 2\alpha} \left\{ \frac{1}{\gamma} \left[\left(P_A - \alpha \frac{P_A + 2\alpha}{P_0 + 2\alpha} + \alpha + \alpha \right)^2 + \left(\alpha \frac{P_A + 2\alpha}{P_0 + 2\alpha} - \alpha + \alpha \right)^2 - \alpha^2 \left(\left(\frac{P_0 + \alpha}{\alpha} \right)^2 + 1 \right) \cdot \frac{P_A + 2\alpha}{P_0 + 2\alpha} \right] - \left[P_A - \alpha \frac{P_A + 2\alpha}{P_0 + 2\alpha} + \alpha + \alpha \right] - \dot{x}_C(\phi_C(t_R^+)) \right\}. \tag{41}$$

$$\dot{x}(t_R^+) = \frac{1}{\gamma} (P_A - P_0) \frac{[1 + (\alpha/P_0)]^2 + (\alpha/P_0)^2}{[1 + 2(\alpha/P_0)]^2} - \frac{1 + \alpha/P_0}{1 + 2\alpha/P_0} \dot{x}_C(\phi_C(t_R^+)). \tag{42}$$

Note that the externally measured velocity, $\dot{x}$, contains a component arising from the muscle's passive viscoelastic properties (the first term) as well as one arising from the muscle's active properties (represented by $\dot{x}_C(\phi_C)$).

Hill's equation accurately describes the measured force–velocity curve. We use this fact to deduce a form for $\dot{x}_C(\phi_C)$ by replacing $\dot{x}$ in (42) with $-V$ from Hill's equation and using the fact that $\alpha/P_0 \ll 1$ to justify neglecting α/P_0 to simplify the algebra. These substitutions yield

$$V = (P_0 - P_A)/\gamma + \dot{x}_C(\phi_C(t_R^+)). \quad (43)$$

Substitute from (28) and solve for $\dot{x}_C$:

$$\dot{x}_C(\phi_C(t_R^+)) = \frac{b}{P_A + \alpha} - \frac{1}{\gamma}(P_0 - P_A). \quad (44)$$

We only need relate $\phi_C(t_R^+)$ to P_A. Substitute from (38) into $\phi_C(t_R^+) = \phi_S(t_R^+) = P_A - \phi_P(t_R^+)$ to obtain

$$\phi_C(t_R^+) = (P_A P_0 + \alpha P_A + \alpha P_0)/(P_0 + 2\alpha); \quad (45)$$

$$P_A = \frac{\phi_C(1 + 2\alpha/P_0) - \alpha}{1 + \alpha/P_0} \quad (46)$$

But $\alpha/P_0 \ll 1$, so (46) is nearly equal to

$$P_A = \phi_C(t_R^+) - \alpha. \quad (47)$$

Substitute from (47) into (44) to obtain

$$\dot{x}_C(\phi_C(t_R^+)) = \frac{1}{\gamma}\frac{(\gamma b + \alpha - a) - \phi_C(t_R^+)}{(a - \alpha) + \phi_C(t_R^+)} \cdot (P_0 - \phi_C(t_R^+)). \quad (48)$$

Finally, replace the constants in (48) with the new constants

$$A = a - \alpha \quad (49)$$

$$B = \gamma b + \alpha - a, \quad (50)$$

and

$$\Gamma = 1/\gamma, \quad (51)$$

and note that (48) holds for all t_R to obtain the equation relating CE shortening velocity to CE force in tetanized skeletal muscle:

$$\dot{x}_C = \Gamma(B - \phi_C)(P_0 - \phi_C)/(A + \phi_C). \quad (52)$$

Notice that we have replaced Hill's two constants, a and b, with the two new constants A and B. Γ follows from the muscle's passive properties and is not a new constant. Appendix C shows that this equation also follows without assuming $\alpha/P_0 \ll 1$.

Equation (52) shows that $\dot{x}_C$ decreases hyperbolically as force increases, with $\dot{x}_C$ reaching zero when the load reaches a maximum tension. This condition is essential because if $\dot{x}_C(P_0) \neq 0$ the muscle would develop more force than P_0 which is contrary to the definition of P_0. While this situation is qualitatively like Hill's equation (which describes the relationship between muscle shortening velocity, V, and afterload, P_A), equation (52) (which relates $\dot{x}_C$ to ϕ_C) is not identical to Hill's equation. If $\dot{x}_C$ were not a function of ϕ_C the observed force–velocity curve would be a straight line, not a hyperbola. Since the observed force–velocity curve is not a straight line, $\dot{x}_C$ must be a function of ϕ_C. Thus (42) confirms our assumption that $\dot{x}_C$ is a function of ϕ_C.

RESULTS AND DISCUSSION

x_C *is related to the number of active cross-bridges*

$\dot{x}_C$ increases linearly with $\dot{x}$ (equation 42), therefore, Bárány's (1967) observation that myosin ATPase activity is proportional to the externally measured shortening velocity ($\dot{x}$), implies that it is also proportional to $\dot{x}_C$. This conclusion supports the view that the variable x_C reflects those biophysical processes by which the muscle responds to stimulation, i.e. those processes related to control of total sarcomere ATPase activity. Suppose that x_C is a monotonic function of (but not necessarily equal to) the number of cross-bridges. In stark contrast to earlier work (Fung, 1970; Wong, 1971; Sonnenblick and Skelton, 1974) based on Hill's three-element model, I do not propose that x_C, CE shortening, equals sarcomere shortening. If x_C relates to the increase in numbers of active bridges over the resting state and if ATP is split as bridges are activated, we would expect to see more ATP splitting per unit time as $\dot{x}_C$ increases. Thus, at lower afterloads, more ATP is hydrolyzed, not because of higher myosin ATPase activity at a given bridge, but because there are more bridges formed per unit time (each of which is hydrolyzing ATP at a fixed rate). Equation (52) suggests that the rate of bridge formation increases as the number of active bridges (reflected by ϕ_C) decreases. In other words, the bridge formation rate increases with the number of inactive but potential bridges.

The chemical processes related to cross-bridge forming and breaking involve complex kinetics and reactions which take a finite time. These arguments can, therefore, only qualitatively point the way toward more complex quantitative relationships. They do suggest, however, that the variable x_C is related to the number of active cross-bridges. Also, the observed force–velocity curve reflects, at least in part, the fact that the rate at which cross-bridges are formed (and, therefore, ATP split) depends on the pool of inactive potential cross-bridges. In other words, $\dot{x}_C$'s functional dependence on ϕ_C reflects the number of potential cross-bridges which are available to form per unit time. This availability, in turn, depends on the overlap between the sarcomere's thick and thin filaments and the ATPase activity of the enzymes associated with each cross-bridge. In contrast, $\dot{x}_C$'s dependence on t relates to the amount of Ca^{2+} available to activate the potential cross-bridges and the rate at which it becomes available.

Depolarization and CE shortening in cardiac muscle

Figure 3(b) shows the time that $\dot{x}_C = 0, t_Z$, occurs *ca.* 600 msec after the first detectable tension. This means that the CE shortens for about the first two-thirds of the contraction and extends for the remainder. Note that $t_Z > t_M$, where t_M is the time of maximum developed isometric force, D_M. The active process represented by CE shortening continues after the muscle reaches peak developed force. This result permits some interesting speculation on the relationship between depolarization and the CE.

Ca^{2+} is released to the myofilaments during the plateau phase of the action potential. The Ca^{2+} flows quickly into the sarcomere (because of the steep electrochemical gradient) and binds rapidly to troponin. This binding ultimately leads to myofilament activation. Meanwhile, the sarcoplasmic reticulum actively pumps Ca^{2+} out of the sarcomere. Thus, we would expect the amount of actin–myosin interaction to continue increasing about as long as the plateau phase lasts. Therefore, the CE, the element representing these processes, should continue shortening for about the same length of time as the membrane in the actual cell is depolarized. Kavaler (1959) and others (Reuter, 1974) showed that the action potential indeed lasts about two-thirds as long as the twitch.

Since the Ca^{2+} begins quickly entering the sarcomere shortly after depolarization (when actively developed force begins to appear) and since $\phi_C(0)$ equals zero, we would expect $\dot{x}_C$ to jump to its peak value, then decrease as $D(t) = \phi_C(t)$ increases for as long as the process represented by CE shortening continues. Figure 3(b) shows that this three-element description, including a viscoelastic SE, predicts this result.

Yeatman *et al.*, (1971), using a similar experimental preparation, computed CE velocity as a function of time during an isometric twitch from a classical three-element model containing elastic passive elements. They first applied the chain rule for differentiation to $\phi_S(x_S(t))$,

$$\frac{d\phi_S}{dt} = \frac{d\phi_S/dx_S}{dx_S/dt}, \tag{53}$$

then noted that $\dot{x}_s = \dot{x}_c$ and $\dot{P} = \dot{\phi}_s$, defined $V_{CE} = \dot{x}_C$ and used $d\phi/dx_S = KP + C$ to describe their series elastic element. (K and C are empirical constants.) These relationships with (53) produce

$$V_{CE}(t) = \dot{P}(t)/(KP(t) + C) \tag{54}$$

during an isometric twitch. This expression defines $V_{CE}(t)$ in terms of the observed force, $P(t)$ (and its derivative, $\dot{P}(t)$ and the constants $K(=\beta)$ and $C(=2\alpha\beta)$ (Glantz, 1975)), obtained from an isotonic quick release experiment. Yeatman and his colleagues state that CE velocity inferred in this way, that V_{CE} "rises rapidly to a peak". Compared with $\dot{x}_C$ (Fig. 3b), however, V_{CE} increases slowly; V_{CE} takes *ca.* 40 msec (*ca.* $0.12\,t_M$) to reach its maximum value. By this time $\phi_C(t) = D(t) \approx 0.2\,D_M$. Such computations have led to conclusions concerning the "relatively slow onset of active state" (Brady, 1965; Sonnenblick, 1967) and a search for a physiological explanation such as a delay in calcium release into the sarcomere or in calcium binding by troponin. On the other hand, the result depicted in Fig. 3(b), based on a model which accounts for passive viscoelasticity, is consistent with the view that Ca^{2+} enters the sarcomere soon after depolarization and rapidly stimulates cross-bridge formation most rapidly at first (when there are few bridges formed and hence much troponin available for binding), then at a decreasing rate until repolarization.

Mechanical response to inotropic agents: a hypothesis

Most positive inotropic agents increase D_M and decrease t_M in isometric twitches of cardiac muscle. It is common to describe the isolated cardiac muscle's inotropic state using two independent parameters (Henderson *et al.*, 1969; Brutsaert *et al.*, 1970; Buccino *et al.*, 1967a; Siegel and Sonnenblick, 1963; Siegel *et al.*, 1964), which, when taken together, contain information equivalent to the pair (t_M, D_M). These two parameters, commonly selected from among D_M, t_M, $(dP/dt)_{max}$, D_M/t_M, and IIT ($IIT = \int_0^{t_M} D(t)dt$), are taken to reflect independently the duration and magnitude of active state. Electrophysiological and biochemical results seem to support this interpretation. The action potential duration is taken to determine active state duration and the quantity of Ca^{2+} released from the *T*-tubules and surface membrane with each depolarization, active state magnitude (Brady, 1968). Furthermore, a three-element model containing only elastic passive elements requires that both magnitude and duration of CE shortening change to change both D_M and t_M. In contrast, Fig. 1(c) leads to the hypothesis which, at constant muscle length, permits quantifying most inotropic agents with a single parameter.

The SE's viscoelastic properties relate the CE velocity changes necessary to effect changes in t_M with corresponding changes in D_M. A wide variety of positive inotropic agents increase the quantity of Ca^{2+} which enters the sarcomere with each depolarization (Siegel *et al.*, 1964; Entman *et al.*, 1969; Langer, 1968, 1973; Langer and Serena, 1970; Suko *et al.*, 1970; Shinebourne *et al.*, 1969; and Winegrad and Shanes, 1962). Since more Ca^{2+} is available to bind troponin, it activates more myosin ATPase per unit time and speeds chemical to mechanical energy conversion. The higher Ca^{2+} concentration inside the sarcomere also stimulates the sarotubular system's active Ca^{2+} pumps to remove more Ca^{2+} per unit time from the sarcomere. Since the variable x_C reflects the number of active cross-bridges, hypothesize that at constant muscle length inotropic agents modify cardiac muscle's active processes in a way equivalent (in terms of this analytical description) to make the CE shorten faster, but for a shorter time, so that maximum CE shortening remains unchanged.

Since this analysis focuses on isometric twitches of cardiac muscle at constant muscle length, this hypothesis does not consider effects due to Starling's law. This hypothesis proposes that, with respect to a given reference condition at a given muscle length, positive inotropic agents lead to more actin–myosin interaction per unit time for a shorter time, and that these two effects balance to keep the maximum level of actin–myosin interaction independent of inotropic state. Let $x_C\chi(t)$ equal CE shortening when the processes the CE represents are in inotropic state χ; then this CE is related to a CE in the reference state (where $\chi = 1$ by definition) according to

$$x_{C\chi}(t) = x_{C1}(\chi \cdot t), \tag{55}$$

or equivalently,

$$\dot{x}_{C\chi}(t) = \chi \cdot \dot{x}_{C1}(\chi t). \tag{56}$$

Figure 4 illustrates this hypothesis with $\chi = 1.5$.

Figure 5 displays the theoretical relationship between t_M and D_M obtained by varying χ from 0.80 to 2.00 with the muscle in Fig. 3 as the reference state, $\chi = 1.00$, and using the values of α, β, and γ reported earlier (Glantz, 1974, 1975). This reference twitch is slightly stronger than average ($t_M = 337$ msec and $D_M = 7.65\,g/mm^2$ compared with 379 ± 59 ($M \pm SD$) msec and $6.60 \pm 2.16\,g/mm^2$ for the 32 muscles stimulated at $12\,min^{-1}$ in Table 2, but well within one standard deviation of average). The parameters used to compute the theoretical curve in Fig. 5 (and subsequent figures) were not adjusted to fit the observed data. In all cases, I first computed and plotted the theoretical curves, then added the experimental observations to the graph. This approach permitted zero degrees

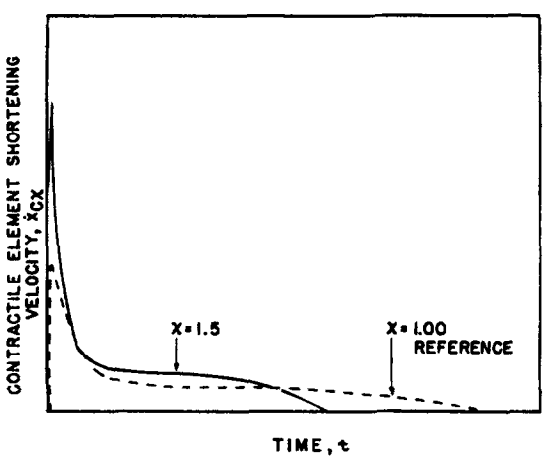

Fig. 4. CE in inotropic state $\chi = 1.5$ (see equation (55) or (56)). If the reference state, $\chi = 1.0$, corresponds to a stimulation rate of 12/min, $\chi = 1.5$ corresponds to a stimulation rate of *ca.* 50/min. Note that while x_C increases, the maximum value of x_C remains unchanged. This corresponds to forming more cross-bridges per unit time for a shorter time than the reference state, so that there is no increase in the maximum number of activated cross-bridges.

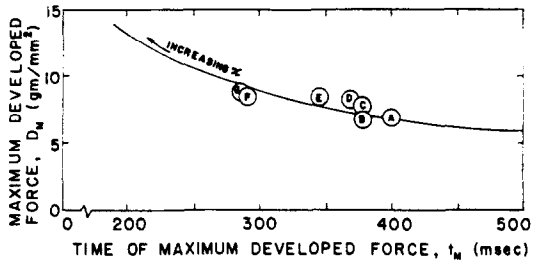

Fig. 5. $D_M(t_M)$ obtained by varying χ in (55) and using the resulting $x_{C\chi}(t)$ in (24) to find D_M and t_M. $x_{C1}(t)$ comes from Fig. 3(b). As χ increases, D_M increases and t_M decreases, as is the case with most inotropic agents. The data points show D_M and t_M for cat papillary muscle stimulated at $6\,min^{-1}$ (A), $12\,min^{-1}$ (B), $18\,min^{-1}$ (C), $24\,min^{-1}$ (D), $30\,min^{-1}$ (E), $36\,min^{-1}$ (F), and $48\,min^{-1}$ (G). Notice that these points fall along the theoretical $D_M(t_M)$ curve. (Data from a variety of sources. See Table 2.)

of freedom in fitting the data. This fact makes the agreement reported here all the more significant.

There is especially strong evidence that changing the stimulation rate alters the quantity of Ca^{2+} made available to the myofilaments upon depolarization (Langer, 1968). The data points on Fig. 5 show measured (t_M, D_M) for isometric twitches at increasing stimulation rates move up along the theoretical $D_M(t_M)$ curve. Furthermore, (55) or (56) implicitly defines $t_{Z\chi}$, the time at which CE (in inotropic state χ) shortening ends; $t_{Z\chi}$ is proportional to $1/\chi$. I argued above that this point approximately coincides with the end of the plateau phase of the action potential. Hoffman and Suckling (1954) used isolated dog papillary muscle to show that the action potential duration linearly as the stimulation rate increases. Thus we would expect $1/\chi$ to be a linear, decreasing function of stimulation rate. Figure 6 shows that it is.

Figure 7(a) shows that other inotropic agents known to change the amounts of Ca^{2+} bound to the sarcolemma and *T*-tubule basement membrane also fall along the theoretical $D_M(t_M)$ curve. These agents are: stimulation rate, paired stimulation, increased extracellular Ca^{2+}, strophanthidin, glucagon, and norepinephrine. The first four agents have been shown to decrease action potential plateau phase duration (Reuter, 1974; Hoffman and Suckling, 1954; Brooks *et al.*, 1955; Stutz *et al.*, 1954). Although there is no direct evidence that other agents alter Ca^{2+} inflow, many fall along the theoretical $D_M(t_M)$ curve: isoproterenol, acetylcholine, tramine, serotonin, hypothyroidism, and hyperthyrodism (Fig. 7b). All these agents' inotropic effects can be indexed using the single parameter χ. This agreement between theory and experiment provides indirect evidence that the hypothesis is reasonable.

Four agents, strontium, pentobarbital, propranolol and theophylline, do not conform to this theory (Fig. 7c). Strontium (Buccino *et al.*, 1967a), pentobarbital (Nayler and Szeto, 1972), propranolol (Nayler, 1973)

Table 2. Response of isolated cat papillary muscle to various inotropic agents*

Point†	Experiment	State‡	t_M (msec)	D_M (gm/mm^2)	N	Data source§
		Agents known to alter Ca^{2+} bound to *T*-tubule basement membrane				
A	Stimulation rate	6 min^{-1}	400 ± 45	6.90 ± 2.14	44	6,7,12,13,14
B		12 min^{-1}	379 ± 59	6.60 ± 2.16	32	1–9, 11–15
C		18 min^{-1}	379 ± 37	7.77 ± 1.89	24	6,13,14
D		24 min^{-1}	370 ± 39	8.15 ± 1.80	24	6,13,14
E		30 min^{-1}	346 ± 36	8.23 ± 1.74	30	6, 13–15
F		36 min^{-1}	290 ± 24	8.42 ± 2.01	20	7,12
G		48 min^{-1}	287 ± 36	8.72 ± 1.59	45	1,6,13–15
H	Paired stimulation		290 ± 41	10.56 ± 2.84	44	4,8,12,15
I	Increased [Ca^{2+}]	6.5 mM	357 ± 41	9.00 ± 2.24	14	1
J		7.5 mM	315 ± 39	10.4 ± 2.29	21	4,12,15
K	Glucagon	10^{-5}M	342 ± 30	8.10 ± 0.54	4	15
L	Norepinephrine	10^{-6}M	330 ± 53	8.51 ± 2.30	33	1,4,10
M	Strophanthidin	10^{-6}M	363 ± 71	8.50 ± 3.00	6	1
		Other agents which fall along the predicted D_M vs t_M line				
N	Isoproterenol	10^{-6}M	259 ± 31	9.85 ± 1.31	8	15
O		10^{-5}M	260 ± 47	11.0 ± 1.69	14	8,12
P	Acetylcholine	10^{-3}M	345 ± 42	6.20 ± 1.70	8	1
Q	Tryamine	10^{-3}M	308 ± 58	11.0 ± 2.40	4	1
R	Serotonin	2×10^{-4}M	410 ± 54	8.70 ± 2.90	5	1
S	Thyroid‖	Hyper-	308 ± 86	7.70 ± 1.62	22	1,5
T		Hypo-	440 ± 58	5.40 ± 2.40	26	1,5
		Agents which do not fit this theory				
U	Strontium	8.8×10^{-3}M	492 ± 85	12.3 ± 7.70	7	1
V	Pentobarbital	5×10^{-4}M	300 ± 49	1.8 ± 1.72	6	2
W	Propranolol	10^{-5}M	365 ± 51	3.9 ± 2.00	5	2
X	Theophylline	2.5×10^{-3}M	441 ± 60	8.9 ± 2.40	9	9

* Temperature for all experiments = 29-30 C°. Results are presented in M ± SD.

† These letters correspond to points on Figs. 5 and 7.

‡ With the exception of stimulation rate experiments, all experiments were performed while the muscle was stimulated at 12 min^{-1}. The method for measuring force and shortening were similar in all cases, but there are minor differences in bathing medium from source to source.

§ Key to sources: 1. Buccino *et al.* (1967a) Table 1. 2. Buccino *et al.* (1967a) Table 2. 3. Buccino *et al.* (1967a) Table 3. 4. Buccino *et al.* (1967a) Table 5. 5. Buccino *et al.* (1967b) Text. 6. Buccino *et al.* (1967b) Fig. 5. 7. Henderson *et al.* (1969) Fig. 6(b). 8. Henderson *et al.* (1969) Text. 9. Marcus *et al.* (1972) Table 1. 10. Marcus *et al.* (1972) Fig. 2. 11. Parmley and Sonnenblick (1969) Fig. 4. 12. Parmley and Sonnenblick (1969) Table 2. 13. Spann *et al.* (1967) Fig. 6. 14. Spann *et al.* (1966) Fig. 4. 15. Yeatman *et al.* (1971) Table 1.

‖ The sample muscles came from cats with experimentally induced chronic thyroid malfunction. See Henderson *et al.* (1969) for the experimental procedure.

and theophylline (Blinks *et al.*, 1972; Nayler, 1963; Nayler and Hasker, 1966), all act not only at the *T*-tubule, but probably also depress the activity of the calcium pumps in the sarcoplasmic reticulum and therefore prolong the time that Ca^{2+} remains in the sarcomere. These agents, and others like them, should be considered a distinct class because they do not act through the same mechanisms as the majority of agents which fall along the theoretical $D_M(t_M)$ curve. Table 2 summarizes the experimental data presented in Figs. 5 and 7. This theory rests on the hypothesis that inotropic agents modify the active process in cardiac muscle in such a way that this change can be described in terms of a CE and equation (55) or (56).

None of these agents affect the passive properties α, β and γ (Glantz, 1974, 1975), their action is confined to the CE. Lowering temperature, which is often considered a negative inotropic agent, acts both to change α, β and γ, and to slow down the active processes in the muscle (which, after all, are chemical reactions). Since lowering temperature makes the passive muscle stiffer and slows down the active processes, we would expect both t_M and D_M to increase as has been observed (Buccino *et al.*, 1967; Yeatman *et al.*, 1971). Since temperature alters both the active and passive properties of muscle, however, it should not be considered merely an inotropic agent.

CE extension

Thus far we have related the CE shortening phase to known sarcomere biophysics. The derived mechanical characteristic, x_C, is consistent with observed biophysical results. In sum, I have proposed that CE shortening represents those biophysical processes involving Ca^{2+} released from *T*-tubules and sarcolemma during the action potential plateau phase. This process ends at $t = t_Z$. What process does CE extension represent? Perhaps it represents cross-bridge deactivation which occurs as the sarcoplasmic reticulum removes Ca^{2+} from the sarcomere. On the

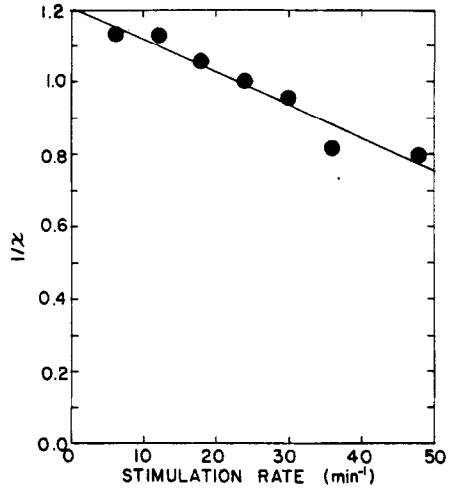

Fig. 6. $1/\chi$, which is proportional to $t_{Z\chi}$, decreases linearly with stimulation rate as one would expect from the observation that action potential duration decreases linearly as stimulation rate increases. The data points on this figure were obtained from Fig. 5 as follows: (1) Find the values of $D_M(t_M)$ at a given stimulation rate; (2) note the value of χ which defines nearest point on the theoretical curve; (3) plot $1/\chi$ vs stimulation rate in this figure. ($r = 0.98$, $p < 0.001$.)

other hand, Ca^{2+} is quickly turned over at the troponin sites as the cross-bridges break and re-form during activation; a given calcium ion is not held at a single troponin site until the whole muscle relaxes. Thus, if the period t t_Z represents the sarcoplasmic reticulum drawing off the Ca^{2+}, there would still be some free Ca^{2+} in the sarcomere to bind to troponin. Parsons and Porter (1966) proposed that extension corresponds to release of elastic energy stored in cross-bridges. Others (Spencer and Worthington, 1960; Ingles and Thompson, 1966; Iwazumi, 1970) proposed that muscle develops tension through electrical forces between the thin and thick filaments. While most biochemical and biophysical evidence now supports the theory of mechanical linkage between the filaments (cross-bridges). Iwazumi (1970) raises some good objections to this theory and presents an interesting alternative. Electrostatic forces may dominate the process CE extension represents.

Figure 8 shows $D(t)$ for twitches obtained with stimulation rates of $6\,min^{-1}$ along with the theoretically predicted $D(t)$ using χ equal to 0.93 and 1.27, respectively. The predicted $D(t)$ drops off too quickly when $\chi = 0.93$ ($6\,min^{-1}$) and too slowly when $\chi = 1.27$ ($36\,min^{-1}$). To correct this discrepancy, replace the original hypothesis of inotropic agent action with the new hypothesis:

$$x_{c_\chi} = \begin{cases} x_{c1}(\chi t), & t < t_{Z\chi} \\ x_{c1}(t + t_{Z1} - t_{Z\chi}) & t > t_{Z\chi}. \end{cases} \quad (57)$$

In other words, changing the stimulation rate speeds up processes represented by CE shortening, but leaves the processes represented by CE extension unaffected. In terms of cross-bridges we are saying that inotropic agents do not affect cross-bridge dynamics during the period that the number of active bridges is decreasing.

The dashed lines on Fig. 8 were computed using this new hypothesis; they come closer to predicting the observed data than prediction based on the original hypothesis. This new hypothesis contrasts with the view (Yeatman *et al.*, 1971; Parmley and Sonnenblick, 1969; Parmley and Chuck, 1973) that inotropic agents speed up both the processes represented by the CE shortening and extension. Since inotropic agents do not affect the processes CE extension represents, these processes differ from those corresponding to CE shortening.

Force–velocity curves in cardiac muscle

Hill's original work (1938) dealt with muscle in terms of a two-element model containing only con-

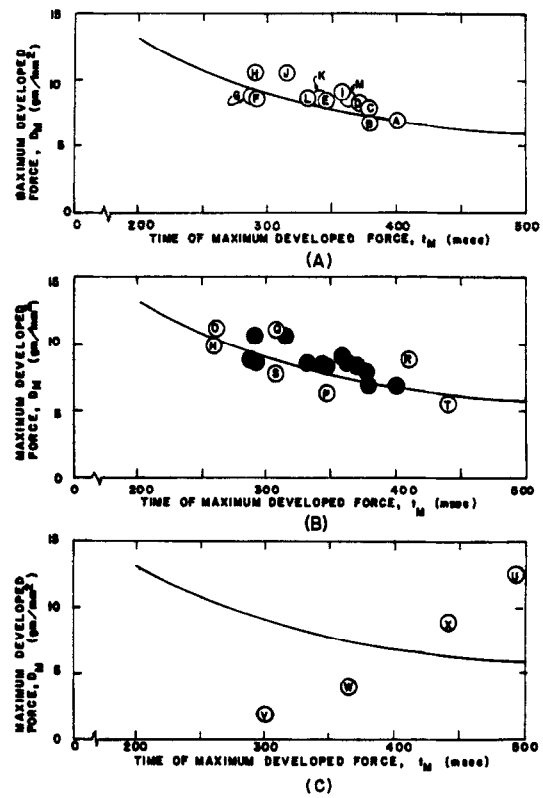

Fig. 7. Comparison of theoretical $D_M(t_M)$ with actual values obtained in isolated cat papillary muscle under the influence of inotropic agents. (Data from a variety of sources. See Table 2.) *Panel A*: Agents known to change quantity of Ca^{2+} bound to basement membrane: $6\,min^{-1}$ (A), $12\,min^{-1}$ (B), $18\,min^{-1}$ (C), $24\,min^{-1}$ (D), $30\,min^{-1}$ (E), $36\,min^{-1}$ (F), $48\,min^{-1}$ (G), paired stimulation (H), 6.5 $mM[Ca^{2+}]_0$ (I), 7.5 $mM[Ca^{2+}]_0$ (J), 10^{-5} glucagon (K), 10^{-6} M norepinephrine (L), 10^{-6} M strophanthidin (M). *Panel B*: Agents which fall along the theoretical $D_M(t_M)$ curve but about which there is no evidence that they change Ca^{2+} bound to basement membrane (dark points carried over from Panel A): 10^{-6} M isoproterenol (N), 10^{-5} M isoproterenol (O), 10^{-3} M acetylcholine (P), 10^{3} M tryamine (Q), 2×10^{-4} M serotonin (R), hyperthyroid (S), hypothyroid (T). *Panel C*: Agents which do not fit this theory: 8.8×10^{-3} M strontium (U), 5×10^{-4} M pentobarbital (V), 10^{-5} M propranolol (W), 2.5×10^{-3} M theophylline (X).

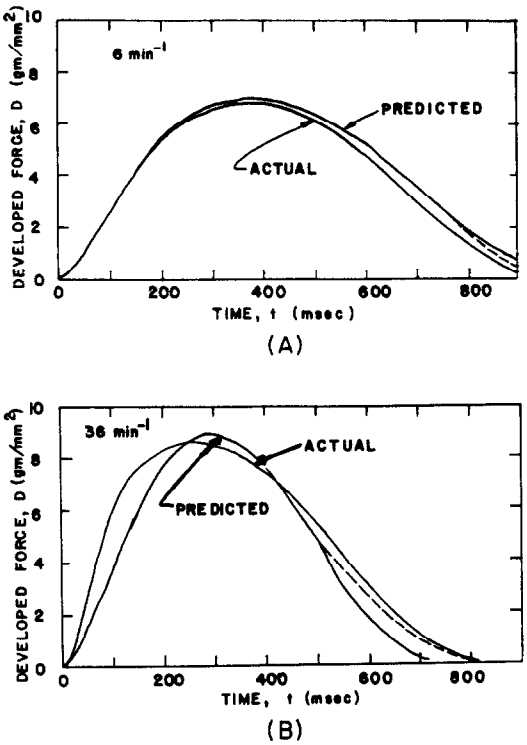

Fig. 8. $D(t)$ predicted using equation (55) (solid lines) and equation (57) (dashed lines) compared with observed $D(t)$ ($x_{CI}(t)$ taken from Fig. 3(b); data from Parmley and Sonnenblick (1969), Fig. 4).

tractile and series elastic elements. In this model, muscle shortening velocity equals CE shortening velocity while the muscle is shortening. Thus, Hill concluded that the force–velocity relationship was the fundamental governing relationship for the CE. This conclusion has been widely accepted and many authors have attempted to apply a similar analysis to cardiac muscle. These attempts have met with some difficulty, primarily because cardiac muscle cannot be tetanized, and because the preload in cardiac muscle must be relatively large compared to that required in experiments with skeletal muscle. To obtain force–velocity curves in cardiac muscle, most experimenters either perform a series of isotonic contractions at different afterloads in which they observe the maximum shortening velocity (Sonnenblick, 1962b, 1965; Parmley *et al.*, 1970) or a series of isotonic quick releases to different afterloads during an isometric twitch (e.g. Brady, 1965; Noble *et al.*, 1969). While these two methods give the same force–velocity curve when they are performed on tetanized skeletal muscle (Jewell and Wilkie, 1958; Parmley *et al.*, 1970), they produce markedly different results when carried out during a cardiac muscle twitch.

We can predict the cardiac muscle force–velocity curve obtained by plotting the initial shortening velocity vs afterload in a series of isotonic twitches, because $P(t_A^-) = P(t_A^+) = P_A$, and $x(t_A^-) = x(t_A^+) = 0$ in an isotonic twitch. These facts mean that $\phi_P(t_A^+) = \phi_P(t_A^+) = P_i$ and, since $\dot{x}_C$ is a continuous function of force by assumption, $\dot{x}_C(t_A^-) = \dot{x}_C(t_A^+) = \dot{x}_C(t_A)$ and $x_C(t_A^-) = x_C(t_A^+)$. (See Appendix A of Glantz (1975) for proof). Substitute from these equalities into (4) and (14) to obtain

$$\dot{P}(t_A^-) = -\beta\left\{\frac{1}{\gamma}[(P_A - P_i + \alpha)^2 - \alpha^2 e^{\beta x_C(t_A)}] - (P_A - P_i + \alpha)\dot{x}_C(t_A)\right\}, \quad (58)$$

and

$$\dot{x}(t_A^+) = \frac{1}{P_A + 2\alpha}\left\{\frac{1}{\gamma}[(P_A - P_i + \alpha)^2 - \alpha^2 e^{\beta x_C(t_A)}] - (P_A - P_i + \alpha)\dot{x}_C(t_A)\right\}. \quad (59)$$

But the terms in braces in the two equations are equal, so substitute from (58) into (59) to obtain

$$-\dot{x}(t_A^+) = \dot{P}(t_A^-)/(\beta P_A + 2\alpha\beta). \quad (60)$$

This equation relates the initial shortening velocity in an isotonic contraction, $-\dot{x}(t_A^+)$, to the observed isometric force $P(t)$, and the muscle's elastic properties (α and β). Equation (60) is identical to equation (54) used to infer CE velocity V_{CE} in a classical three-element model; equation (54) yields initial shortening velocity of the entire muscle, $-\dot{x}(t_A^+)$, not the CE velocity, $\dot{x}_C(t_A)$. Furthermore, (60) shows that $V_{CE}(t)$ contains no more information about $\dot{x}_C(t)$ than does $P(t)$ obtained during an isometric twitch. Parmley *et al.* (1972) remarked that the $V_{CE}(t)$ they computed using (54) or (60) was nearly identical to the observed initial shortening velocity of the muscle. This observation actually shows that, rather than describing $\dot{x}_C(t)$ as Yeatman, Parmley, and others believed (60) provides an excellent description of the observed force–velocity curves obtained by plotting initial shortening velocity vs afterload (Fig. 9).

Noble *et al.* (1969), Brady (1965), and Pinto and Fung (1973b) obtained force–velocity curves by quick

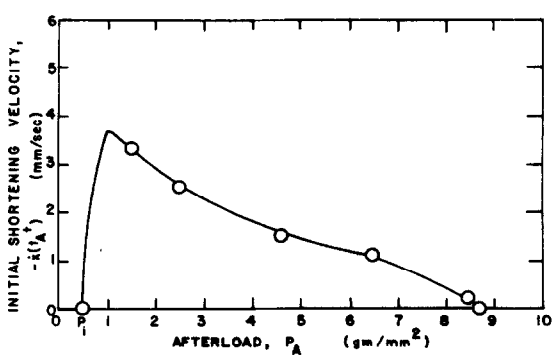

Fig. 9. Force–velocity curve obtained by plotting initial shortening velocity vs afterload in a series of isotonic contractions of cardiac muscle. Solid line computed using (60). Muscle length = 8.5 mm, preload = 0.5 gm, stimulation rate = 12 min^{-1}, temperature = 29°C. (Data from Parmley *et al.* (1970), Figs. 2 and 3.)

releases to different afterloads at a fixed time during the twitch. Their curves were neither hyperbolic nor constant over time (Fig. 10). This theory agrees with their qualitative reasoning. We derive an expression for the muscle's shortening velocity immediately following a release at time $t = t_R$ by noting that $\phi_P(t_R^-) = P_i$ and substituting from (36) and (34) into (14):

$$\dot{x}(t_R^+) = \frac{1}{P(t_R^-) + 2\alpha}\left\{\frac{1}{\gamma}\left[(P_A + 2\alpha) \times \frac{(P(t_R^-) - P_i + \alpha)^2 + (P_i + \alpha)^2}{P(t_R^-) + 2\alpha} - \alpha^2 e^{\beta x_C(t_R)} - (P_i + \alpha)^2\right] - (P(t_R^-) - P_i + \alpha)\dot{x}_C(t_R^+)\right\}. \quad (61)$$

The observed initial shortening velocity following release is a complex function of not only afterload, P_A, but also of the state of the muscle prior to release $P(t_R^-)$ and $x_C(t_R^-)$ as well as $\dot{x}_C$ following release, $\dot{x}_C(t_R^+)$. Furthermore, $\dot{x}_C = \dot{x}_C(\phi_C, t, \chi, \ldots)$ and $\phi_C(t_R^+) \neq \phi_C(t_R^-)$. Thus, we expect the observed curves to display a complex time-varying nature.

Is it possible to separate inotropic changes from Starling changes?

Cardiac muscle alters its performance in two ways which act through different means: Starling changes and inotropic state changes. Changing muscle length prior to stimulation changes the overlap between the thick and thin filaments and so the number of potential cross-bridges (the Starling mechanism). Inotropic agents modulate the amount of Ca^{2+} released into the sarcomere with each depolarization. Thus far, we have confined our discussion to experiments concerning inotropic interventions made at constant muscle length. At constant muscle length we proposed the single parameter χ and showed it to be a good index of inotropic state. If we simultaneously change muscle length and inotropic state, is it possible to define such a simple parameter which separates the effects of these two changes? Probably not.

Just as the variable x_C does not equal a mechanical length (i.e. sarcomere length), its derivative, $\dot{x}_C$, does not correspond to a mechanical velocity. $\dot{x}_C$ corresponds to the net rate at which cross-bridges are formed. There are two ways to form more cross-bridges per unit time: one could increase the amount of Ca^{2+} available to bind to troponin (until the sarcomere is saturated), thus activating more cross-bridges per unit time, or; one could increase $\dot{x}_C$ by increasing the myosin ATPase activity of the individual bridges so that a given amount of Ca^{2+} will be cycled through more bridges per unit time (Bárány, 1967). Over the short term, a given species myosin ATPase activity is constant and the former mechanism controls $\dot{x}_C$. On the other hand, Goodkind *et al.* (1974) have presented evidence that suggests that, while thyroxine exerts short term inotropic effects in cardiac muscle through controlling the amount of Ca^{2+} released into the sarcomere with depolarization, it also has a long-term effect on myosin ATPase activity. Heller and Whitehorn (1972) demonstrated similar long-term parallel changes in myosin ATPase and active mechanical properties associated with aging. In any event, both myosin ATPase activity changes and changes in available Ca^{2+} control $\dot{x}_C$.

With a fixed muscle length, more calcium will lead to more bridges being formed per unit time and hence higher isometric force. Similarly, with a given amount of calcium more available bridges also gives rise to more bridges being formed per unit time because there are more inactive potential bridges. Simultaneous inotropic and length changes act through both these effects and they probably are not additive. At a greater initial muscle length (below the Starling curve peak) there are more potential cross-bridges. Increasing quantity of calcium would activate more cross-bridges per unit time than at the original length because of more unactivated bridges and more calcium available to activate them. Thus, the net bridge formation rate (which $\dot{x}_C$ reflects) should be higher than if either of the effects acted alone. Anderson *et al.* (1973) and Parmley and Chuck (1973) documented this interaction between muscle length and inotropic state. This complex interaction probably precludes any simple index of inotropic state which is independent of muscle length.

The anatomical location of the SE, PE *and* CE

The equations for a twitch (Table 1) involve the state variables related to muscle's active properties (x_C and ϕ_P or P) and variables and constants related to muscle's passive viscoelasticity (variables, x_P or x and ϕ_P and constants α, β, and γ). The SE state variables, x_S and ϕ_S, do not appear. Thus, even though we used a picture (Fig. 1b) which contained a distinct SE to motivate the equations in Table 1, these equations show that the SE and CE merged mathemati-

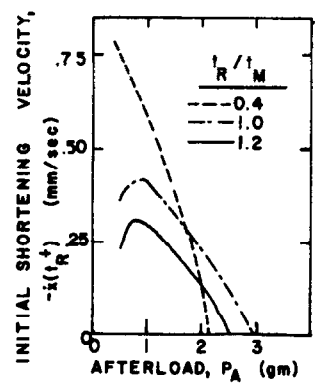

Fig. 10. Typical force–velocity curves for cat papillary muscle obtained using the inotonic quick-release method. Note that the curves change with time. Temperature = 24°C. (After Noble *et al.* (1969), Fig. 6(b).)

cally. In other words, one may equivalently consider the SE and CE as two distinct elements (Bahler *et al.*, 1974; Sonnenblick and Skelton, 1974; Meiss and Sonnenblick, 1974), or as a single element (Huxley and Simmons, 1971; Pollack *et al.*, 1972; Noble and Else, 1972) with properties of both.

It is tempting to identify the three elements with specific muscular structures. For example, one might identify the PE with the sarcolemma and the SE with the tendons near the specimen's ends. Grimm and Whitehorn (1966) studied this question by selectively digesting different cellular components and concluded that the resting tension in cardiac muscle arises from within the sarcomere. Many others (Huxley and Simmons, 1970; Alexander, 1959; Hill, 1968; Takauji and Honig, 1972), have used skeletal, cardiac, or smooth muscle to argue that resting tension and stress relaxation follow from a residual interaction between the actin and myosin. The CE also represents processes involving actin and myosin, but these processes differ from those represented by the SE and PE. All three elements probably describe processes at least partially within the sarcomere. One should not, therefore, identify the variable x_C with sarcomere length. In fact, the variable x_C is related to the number of active bridges. In light of these considerations, it is more instructive to think of this description of muscle as depicted in Fig. 11; an active process embedded in passive viscoelastic medium.

Fig. 11. Another way to picture the three-element model. Light squares represent the active process (CE), dark squares represent passive viscoelastic material (SE and PE) governed by equation (1).

What if the constitutive equation is wrong?

This three-element description analytically separates muscle's mechanical properties based on whether or not they change when the muscle is stimulated. Unlike classical three-element models, in which passive elements represent elasticity, this model includes viscoelastic passive elements. It includes a contractile element which represents the mechanical manifestations of the response to stimulation of muscle's biochemical processes. The CE, while not an anatomical entity, behaves in accordance with known cardiac muscle electrophysiology and biochemistry. CE shortening velocity peaks rapidly within a few milliseconds of first detectable force (about when the plateau phase of the action potential begins), drops sharply, then more slowly, finally reaching zero (well after maximum force) about when the plateau phase of the action potential ends. The viscoelastic series element suggests the hypothesis that, at constant muscle length, inotropic agents speed CE shortening by a constant factor which depends on the agent and its concentration (or magnitude) without affecting total CE shortening. This hypothesis leads, with no adujstment of parameters for the purpose of curve-fitting, to an accurate theoretical relationship between time of maximum tension and maximum tension in cardiac muscle length, inotropic state may be indexed with a single parameter.

The results follow from the fact that we explicitly considered passive muscle's viscoelastic nature. The specific mathematical results, of course, depend on the exact form of the constitutive equation, equation (1), so, should that equation be in error so would the specific quantitative results. (For example, Pinto and Fung (1973a) present data showing that muscle exhibits creep and stress relaxation for much longer than (1) predicts. However, they applied stretches that were so large as to probably be beyond (1)'s useful range. In addition, the muscle they tested failed to respond to stimulation following their experiments.) On the other hand, the important results presented here follow from qualitative differences between a model containing elastic versus viscoelastic passive elements.

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APPENDIX A

NOTATION*

a	constant in Hill's equation
b	constant in Hill's equation
C	elasticity constant
D	developed elasticity isometric force
K	elasticity constant
N	number of samples
p	signifiance level
P, P_j	muscle force
r	correlation coefficient
s	muscle shortening
t, t_j	time
V	muscle shortening velocity
V_{CE}	inferred CE velocity using a classical three-element model
V_{max}	muscle shortening velocity when afterload equals zero in tetanized skeletal muscle
x, x_j	length, measured with respect to rest length
Δx, Δx_j	change in length
α	elasticity constant
A	constant in (52)
β	elasticity constant
B	constant in (52)
γ	viscosity constant
Γ	constant in (52)
ζ	α/P_0
ξ, ξ_j	length
ξ^*, ξ^*_j	rest length
ϕ, ϕ_j	force
χ	inotropic state
Subscripts	
0	maximum isometric tetanic tension
1	exponential spring No. 1
2	exponential spring No. 2
3	linear damper
A	afterload, beginning of isotonic phase
B	end of isotonic phase
C	contractile element
$C\chi$	contractile element in inotropic state χ
i	preload
M	maximum isometric twitch force
P	parallel element
R	release
S	series element
Z	end of contractile element shortening
$Z\chi$	end of contractile element shortening when in inotropic state χ
$-$	before
$+$	after
Superscripts	
$-$	before
$+$	after.

* This notation differs from that used in Glantz (1975). There x_S and x_C refer to absolute SE and CE length; here x_S refers to SE extension from rest lengths and $x_C(t)$ refers to CE shortening with $x_C(0) = 0$, regardless of the absolute length of CE at $t = 0$.

APPENDIX B

JUSTIFICATION OF EQUATION (40)

Do a Maclauren series expansion of (29).

$$\dot{x}_C(\phi_C + \Delta\phi_C, t + \Delta t) = \dot{x}_C(\phi_C, t) + \left(\frac{\partial \dot{x}_C}{\partial \phi_C}\Delta\phi + \frac{\partial \dot{x}_C}{\partial t}\right) + \frac{1}{2!}\left(\frac{\partial^2 \dot{x}_C}{\partial \phi_C^2}(\Delta\phi_C)^2 + \frac{\partial^2 \dot{x}_C}{\partial t \partial \phi_C}(\Delta\phi)(\Delta t) + \frac{\partial^2 \dot{x}_C}{\partial t^2}(\Delta t)^2\right) + \frac{1}{3!}\left(\frac{\partial^3 \dot{x}_C}{\partial \phi_C^3}(\Delta\phi_C)^3 + 3\frac{\partial^3 \dot{x}_C}{\partial t \partial \phi_C^2}(\Delta\phi)^2(\Delta t) + 3\frac{\partial^3 \dot{x}_C}{\partial t^2 \partial \phi_C}(\Delta\phi)(\Delta t)^2 + \frac{\partial^3 \dot{x}_C}{\partial t^3}(\Delta t)^3\right) + \frac{1}{4!}\left(\frac{\partial^4 \dot{x}_C}{\partial \phi_C^4}(\Delta\phi)^4 + \ldots\right). \quad \text{(B1)}$$

Since the muscle is in steady state tetanus at time t, $\dot{x}_C(\phi_C, t) = 0$. By definition of steady state, all partial derivatives with respect to time equal zero. Therefore (B1) becomes

$$\dot{x}_C(\phi_C + \Delta\phi_C, t + \Delta t) = \sum_{n=1}^{\infty} \frac{1}{n!}\frac{\partial^{(n)} \dot{x}_C}{\partial \phi_C^{(n)}}(\Delta\phi)^n \quad \text{(B2)}$$

which is the Maclauren series expansion for $\dot{x}_C(\phi_C)$.

APPENDIX C

DERIVATION OF EQUATION (52) WITHOUT ASSUMING $\alpha/P_0 \ll 1$

Let $\zeta = \alpha/P_0$, then (52) becomes

$$\dot{x}(t_R^+) = \frac{1}{\gamma}(P_A - P_0)\frac{(1+\zeta)^2 + \zeta^2}{(1+2\zeta)^2} - \frac{1+\zeta}{1+2\zeta}\dot{x}_C(\phi_C(t_R^+)). \quad \text{(C1)}$$

Replace $\dot{x}(t_R^+)$ with $-V$ from Hill's equation (28) and solve (C1) for $x_C(\phi_C(t_R^+))$:

$$\dot{x}_C = \frac{1+2\zeta}{1+\zeta}\left[\frac{b}{P_A + a} - \frac{1}{\gamma}\frac{(1+\zeta)^2 + \zeta^2}{(1+2\zeta)^2}\right](P_0 - P_A). \quad \text{(C2)}$$

From (46)

$$P_A = \frac{\phi_C(1+2\zeta) - \alpha}{1+\zeta}. \quad \text{(C3)}$$

Substitute from (C3) into (C1) to obtain

$$\dot{x}_C(\phi_C(t_R^+)) = \frac{\dfrac{\gamma b(1+\zeta)(1+2\zeta)^2 - a(1+\zeta)(1+2\zeta) + [(1+\zeta)^2 + \zeta^2]\alpha}{[(1+\zeta)^2 + \zeta^2](1+2\zeta)} - \phi_C(t_R^+)}{\dfrac{(1+\zeta)a - \alpha}{1+2\zeta} + \phi_C(t_R^+)} \cdot \frac{P_0 - \phi_C}{(1+\zeta)^2(1+2\zeta)\gamma}. \quad \text{(C4)}$$

Let

$$A = \frac{(1+\zeta)a - \alpha}{1+2\zeta} \quad \text{(C5)}$$

$$B = \frac{\gamma b(1+\zeta)(1+2\zeta)^2 - a(1+\zeta)(1+2\zeta) + [(1+\zeta)^2 + \zeta^2]\alpha}{[(1+\zeta)^2 + \zeta^2](1+2\zeta)} \quad \text{(C6)}$$

$$\Gamma = \frac{1}{(1+\zeta)^2(1+2\zeta)\gamma}. \quad \text{(C7)}$$

So (C4) becomes

$$\dot{x}_C = \Gamma(B - \phi_C)(P_0 - \phi_C)/(A + \phi_C). \quad \text{(C8)}$$

which is identical to (52). As before the constants A and B replace Hill's constants, a and b; Γ represents an aggregate of the other constants, not a new constant.