A DYNAMIC MODEL OF SMOOTH MUSCLE CONTRACTION

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ABSTRACT A dynamic model of smooth muscle contraction is presented and is compared with the mechanical properties of vascular smooth muscle in the rat portal vein. The model is based on the sliding filament theory and the assumption that force is produced by cross-bridges extending from the myosin to the actin filaments. Thus, the fundamental aspects of the model are also potentially applicable to skeletal muscle. The main concept of the model is that the transfer of energy via the cross-bridges can be described as a 'friction clutch' mechanism. It is shown that a mathematical formulation of this concept gives rise to a model that agrees well with experimental observations on smooth muscle mechanics under isotonic as well as isometric conditions. It is noted that the model, without any ad hoc asssumptions, displays a nonhyperbolic force-velocity relationship in its high-force portion and that it is able to maintain isometric force in conditions of reduced maximum contraction velocity. Both these findings are consistent with new experimental observations on smooth muscle mechanics cannot be accounted for by the classical Hill model.

INTRODUCTION

The performance of the peripheral circulatory control system is greatly dependent on the contractile and 'viscoelastic' properties of the blood vessels, which, in turn, are determined by the functional qualities of its smooth muscle layers. Hence, in order to make a detailed analysis of the control mechanisms of the peripheral circulation, it is important to have a quantitative concept of vascular smooth muscle mechanics. Such a concept should preferably take the form of an interpretable mathematical model that is numerically simple enough to be conveniently incorporated in a more complex analysis and yet is able to account for both conventional muscle mechanics and the recent finding of a nonhyperbolic force-velocity relationship in high force regions (Meiss, 1982; Johansson, 1983) and of the maintenance of isometric force in conditions of reduced maximum contraction velocity (Dillon and Murphy, 1982).

Among the already existing muscle models, that presented by A. F. Huxley (1957) has attracted special attention. It is based on the sliding filament theory (H. E. Huxley, 1953; H. E. Huxley and Hanson, 1954; A. F. Huxley and Niedergerke, 1954) and assumes that force is produced by cycling cross-bridges that extend from the myosin to the actin filaments. Mathematically, it involves integration of a spectrum of functional states of the cross-bridges that gives rise to a nonlinear partial differential equation that is not trivially solved. This mathematical complication prevents the original formulation of the concept from being solved by conventional computer programs used in the simulation of dynamic systems and, thus, the applicability of the model has been reduced. Indeed, only a few authors, studying specific and well-defined problems with suitable boundary conditions for which a solution algorithm can be found, have used the equations (Julian, 1969; Huxley and Simmons, 1973; Julian and Sollins, 1973; Julian et al., 1973; Podolsky and Nolan, 1973).

The purpose of this study was to design a model for muscle contraction that accounts for experimental observations on smooth muscle mechanics under isotonic as well as isometric conditions. It was especially hoped that the model should be able to account for recent findings such as a nonhyperbolic force-velocity relationship in the high force portion and the ability to maintain isometric force in conditions of a reduced maximum contraction force, since these cannot be accounted for by the classical Hill model. In order to keep the model as simple as possible the generation of force was averaged so that the individual cross-bridge cannot be discerned. For similar reasons the mechanical properties were stressed at the expense of biochemical and anatomical aspects. (There are already many excellent but for the purpose of whole muscle mechanics far too complicated models on muscle biochemistry e.g. Eisenberg and Hill, 1978). Although the individual cross-bridge interactions and biochemistry cannot be resolved, their effects can be interpreted into some of the model parameters (see below).

The model is based on the following four main assumptions: (*a*) Force is generated by the cross-bridges. (*b*) The action of all cross-bridges can be described as an average cross-bridge function (rather than as the sum of all individual cross-bridge contributions). (*c*) The transfer of energy

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via the cross-bridges extending from the myosin to the actin filaments can be described as a self-regulated 'friction clutch' mechanism (cf. Caplan, 1966). (*d*) Both velocity and friction of the average cross-bridge interaction with the actin filament depend on the average cross-bridge load.

The experimental counterpart of the model is the vascular smooth muscle of the rat portal vein, which has been thoroughly investigated. This muscle type has been frequently used as an experimental in vitro model of small resistance vessels and precapillary sphincters (Mellander and Johansson, 1968; Pegram, 1980). In applying the model to vascular smooth muscle, it was assumed that the basic force-generating mechanism is similar in smooth and skeletal muscle, although it is known that their mode of activation, contraction velocity, and tension economy differ. This assumption, based on ultrastructural evidence and the overall correspondence in the mechanical properties of smooth and skeletal muscle, is generally accepted (for reference and reviews see e.g. Stephens, 1977; Adelstein and Eisenberg, 1980; Bohr et al., 1980; Bulbring et al., 1981). Thus, all fundamental aspects of the model are potentially applicable also to skeletal muscle.

A preliminary report of this study has been published previously (Gestrelius and Borgström, 1984).

THEORY

Arrangement of Muscle Elements

The muscle in the model is assumed to include three muscle elements: (*a*) an active contractile component; (*b*) an external elastic component coupled in series with the contractile component; and (*c*) an elastic component inserted in parallel with the first two components (Fig. 1 *a*). The external series elasticity was included since the compliance of the portal vein is of a magnitude that cannot be attributed solely to the cross-bridges (Johansson et al., 1978), while the parallel elasticity reflects the length-passive force relationship of the muscle. The rather stiff elastic properties of the cross-bridges themselves were included in the contractile component as an additional elasticity in series with the force-producing mechanism.

Active Force Production

Friction Clutch Mechanism. In analogy with the theory of A. F. Huxley (1957), the active force of muscle is assumed to be generated by cycling cross-bridges which constitute part of the myosin filaments but extend over the interfilament gaps and interact with the actin filaments. Due to the large number of active cross-bridges in a muscle, it was assumed that their combined action could be adequately described by an average cross-bridge function rather than a spectrum of functional states of the cross-bridges as was proposed by Huxley. From this basic idea, it was, in the present model, assumed that transfer of energy and force from the active cross-bridges to the actin

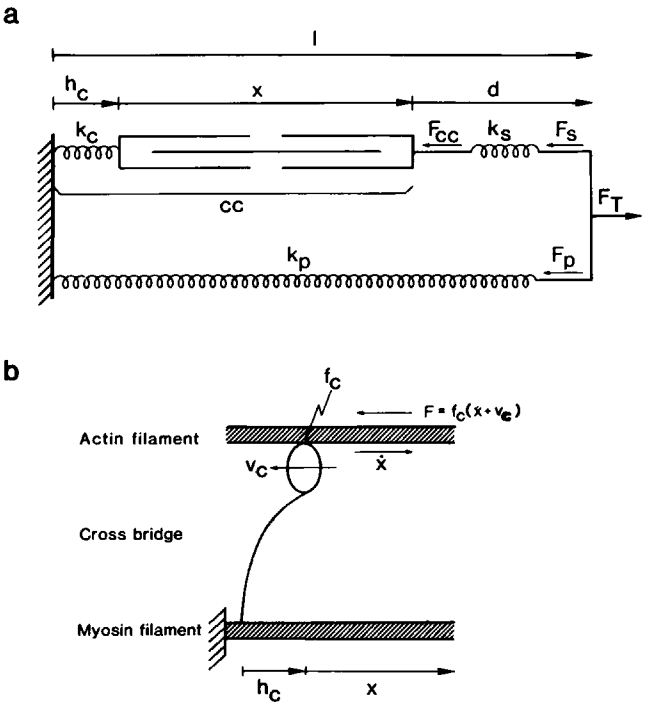

FIGURE 1 (*a*) Schematic diagram of the arrangement of muscle elements. x, h_c, d, and l are lengths, and F_{cc}, F_s, F_p, and F_T denote forces. The model is principally a three-compartment Hill model with the modification that the total series stiffness has been divided into an internal part, k_c, pertaining to the cross-bridges, and an external part, k_s, assumed to reflect a "true" series elasticity. k_p is the passive stiffness of the relaxed muscle. (*b*) Cartoon of the friction clutch assumption used in the model. v_c reflects the average velocity of the cross-bridge displacement, f_c the frictional interaction between the cross-bridges and the actin filaments, $\dot{x}$ the contraction velocity, and F the resulting contraction force.

filaments can be described by a 'friction clutch' mechanism. The great advantage of this view is that the active force of the muscle can be mathematically described by the ordinary differential equation

$$F_{cc} = n_c f_c (v_c + \dot{x}), \quad (1)$$

where F_{cc} is the active force of the contractile component; n_c, a normalized factor, reflecting the maximal number of cross-bridges available for interaction at a certain degree of activation. The factor n_c can vary between zero and unity, the unity value referring to the number of available cross-bridges at optimum muscle length during maximum activation; f_c, a measure of force interaction (friction) between the cross-bridges and the actin filaments; v_c, the average velocity of the cross-bridge displacement; and the time derivative $\dot{x}$, the resulting contraction velocity of the muscle (shortening assumed to have a negative velocity). The product between n_c and f_c, denoting total friction in mechanical physical terms in Eq. 1 will thus reflect the degree of interaction for the average cross-bridge. In turn, the product between 'total friction' and the sum of v_c and $\dot{x}$, denoting the relative velocity at the site of cross-bridge

interaction, will equal the force developed by the average cross-bridge (F_∞). For definitions see Fig. 1 *b*.

Since the average velocity of the cross-bridge displacement can be seen as a function of the stroke length of the cross-bridge multiplied by its cycling rate, it can, from Eq. 1, be deduced that, in order to maintain a constant and finite active force ($F_\infty > 0$) under isometric conditions ($\dot{x} = 0$), a certain number of cycling cross-bridges is needed. All the work produced by the cycling cross-bridges is, however, lost in internal friction heat, since no external work is performed under isometric conditions. It is also seen that a given isometric force can be maintained with a decreasing cross-bridge cycling rate since a decrease in v_c can be compensated for by an increase in total friction, $n_c f_c$. In such a situation, the isometric force can be maintained at a very low cross-bridge cycling rate, corresponding to a state similar to the 'latch-bridge' concept introduced by Dillon et al. (1981). This analysis shows that the friction clutch formulation is capable of accounting for all possible combinations between active force and cross-bridge cycling rate. Furthermore, it indicates that, in order to reproduce the specific force-velocity relationship of a muscle, $n_c f_c$ must be interrelated in a certain way and that this interrelation will express the specific mode of interaction between the cross-bridges and the actin filaments of the muscle.

Self-Regulation of the Active Force Production. It is known from numerous experiments that the behavior of the contractile machinery in a muscle depends on both load and extension of the muscle. In order to account for these findings, any model of muscle contraction must include a mechanism that relates these external quantities to the performance of the contractile machinery. In the model presented by A. F. Huxley, this relationship was obtained by assuming that both the making and breaking of cross-links between the myosin and actin filaments depend upon the degree of extension of the cross-bridges. Since this kind of relationship between force and cross-bridge extension can be assumed to control the interaction of every individual cross-bridge, it was also used as a basis for the formulation of the self-regulation process (i.e. the feedback) in the present model.

Relationship Between Cross-Bridge Extension and Friction. The force interaction between the cross-bridges and the actin filaments implies some kind of chemical bond. In agreement with Eisenberg and T. L. Hill (1978), it was assumed that the chemical energy level of the cross-bridge and the energy contained in its elasticity are intimately connected. Since, in the present model, the stiffness of the cross-bridges is thought to be linear, the energy contained in this elasticity depends on the extension squared. Hence, by assuming that the probability of interaction is a function of the total energy content of the cross-bridges, the strength of interaction, f_c, can be given in the form of the Gaussian expression

$$f_c = f_0 \exp\{b_f[1 - (h_c/h_0)^2]\}. \tag{2}$$

Here b_f is a constant describing the steepness of the relationship between the strength of the interaction and the elastic extension of the crossbridges; h_c, the elastic extension of the cross-bridges; f_0 and h_0 are normalization parameters which, in the adjustment of the model to initial conditions, are given the initial values of f_c and h_c, respectively. This formulation implies that the friction, which reflects the strength of the bonds between the myosin and actin molecules, decreases when an external force opposing the cross-bridge bonds is applied. Hence, the muscle will 'yield' provided the external energy applied is enough to break the cross-bridge bonds.

Relationship Between Cross-Bridge Extension and Velocity. In the model, the velocity of the cross-bridge displacement, v_c, is divided into two components v_S and v_D. v_D is a velocity component of short duration giving rise to the intermediate velocity transient, which is observed during the first 100 ms of a quick release experiment as, a rapid force or length pick-up. In most in vivo circumstances such rapid transients are unimportant and, in applying the model to these conditions, v_D can be ignored. v_S, on the other hand, is an important parameter since it is the main factor determining the steady state contraction velocity of the muscle and, thus, the force-velocity relationship at low forces. From the general shape of the force-velocity curve in its low force portion, it has been suggested that the contraction velocity of the muscle can be described either as a hyperbolic function (Hill, 1938) or as an exponential function (Aubert, 1956) of the force. Since the cross-bridges in the present model are assumed to be elastic with a constant stiffness, the cross-bridge extension, h_c, can be substituted for the force in any of these functions. In the absence of detailed knowledge about the mechanical factors controlling the cross-bridge cycle rate, v_S was chosen to follow the functional formulation of Aubert (1956). A complete description of the velocity of the cross-bridge displacement, v_c, is therefore

$$v_c = v_S + v_D, \tag{3}$$

$$v_S = a_v l_0 \exp[b_v(1 - h_c/h_0)], \tag{4}$$

$$v_D = a_D l_0 (h_D - h_c)/h_0, \tag{5}$$

$$\dot{h}_D = (h_c - h_D)/\tau_D, \tag{6}$$

where a_v reflects the isometric cycling rate of the cross-bridges; b_v, the steepness of the relationship between cross-bridge extension, h_c, and cycling rate; l_0, the optimum muscle length; a_D, a measure of the additional displacement velocity that can be obtained during a quick release transient by the attached cross-bridges; $(h_D - h_c)$ is a measure of the dynamic length changes of the attached

cross-bridges during a quick release transient, while τ_D is the time constant with which h_D relaxes to the average cross-bridge extension, h_c, after the quick release step. The reason for choosing this formulation of v_D, together with a more complete interpretation of the formulation, is given below.

The above formulation of v_S implies that the turn-over rate of the cross-bridges will increase with decreasing load, since shortening of the cross-bridge links, due to a decrase in force, will favor rapid cross-bridge cycling. Conversely, the cycle rate will decrease when the muscle is subjected to a force increase that opposes the cross-bridge displacement.

Length-Active Force Relationship. Following a suggestion of Gordon et al. (1966), the length-active force relationship in the model was assumed to mirror the number of active cross-bridges in the muscle (i.e. parameter n_c in Eq. 1). Although this seems to be an accurate interpretation of experimental findings on skeletal muscle, the situation in smooth muscle is somewhat less clear since the muscle length cannot be related to overlap between thin and thick muscle filaments. Expression 7 below is, therefore, only a convenient way of including in the model the length-active force relationship given in Fig. 2.

$$n_c = 1 - a_n|1 - l/l_0|^{b_n}, \quad (7)$$

where a_n and b_n are constants; l, the actual length of the muscle and l_0, the optimum muscle length.

It should be noted that variations in the parameter n_c, reflecting changes in the number of cross-bridges available for interaction, will only alter the total force produced by the muscle, whereas the maximum contraction velocity will remain unchanged. This agrees with the findings in skeletal muscle (Gordon et al., 1966; Edman, 1979). In smooth muscle, the experimental results are more ambiguous, although no explicit dependence between maximum contraction velocity and number of cross-bridges has been found. It seems, however, that the activation process might affect both the number of available cross-bridges and their average cycling rate (Dillon and Murphy, 1982; Aksoy et al., 1982). In the present model, such a dual mode of activation can be accounted for by letting the activation process affect both n_c and a_v. The relative effect of these parameters on the active force is examined in detail in the Discussion.

Passive Elastic Properties

Elastic Properties of the Cross-Bridges. In accordance with the findings in skeletal muscle (Ford et al., 1977), the active cross-bridges were assumed to behave like linear springs. Again, the situation in smooth muscle is unclear but recent experiments on single smooth muscle cells (Warshaw and Fay, 1983) indicate a rather linear stiffness of the cross-bridge elasticity. Hence, the total force sustained by the cross-bridges, which must equal the total active force F_{cc}, was expressed as

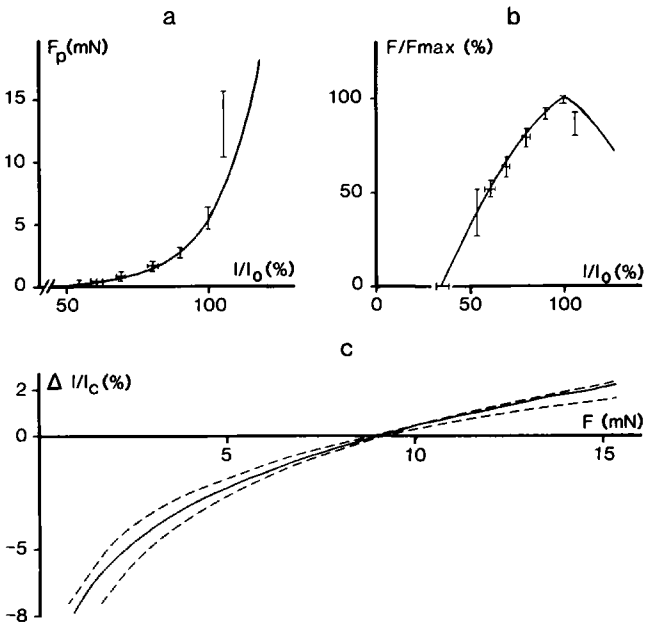

FIGURE 2 (*a*) Length-passive force relationship obtained from 6 different portal veins (from Uvelius et al., 1981). The data was grouped into classes of l/l_0 and are shown as means with 90% confidence limits. The solid line is obtained from Eq. 11 with F_{p0} = 5.6 mN, and b_p = 6.5. (*b*) Length-active force relationship pertaining to the same experiments as in panel *a*. The solid line is drawn in accordance with Eq. 7 using a_n = 1.8, and b_n = 1.4. (*c*) Comparison between the total series elasticity of the model (solid line) and an experimental range (dashed lines). The range was obtained from Johansson et al. (1978) by substituting the extreme values of the standard error for the stiffness k in their formulation of the series elasticity. The parameter l_c denotes the control length of the muscle and was assumed to be 5 mm.

$$F_{cc} = n_c k_c h_c, \quad (8)$$

where n_c is the normalized number of cross-bridges available for interaction; k_c, the stiffness of a cross-bridge and h_c, the average cross-bridge extension.

External Passive Series Elasticity. Most smooth muscle tissues are characterized by a total series elasticity that seems to be exponential (Halpern et al., 1978; Hellstrand and Johansson, 1979; Mulvany, 1979). Since the total stiffness in these preparations is much less than that expected from the cross-bridges alone, a substantial part of it must be attributed to passive elastic responses outside the contractile machinery itself. In the model this external series elasticity is represented by a nonlinear spring in series with the contractile component (cf. Fig. 1 *a*). To simulate releases of the muscle to zero active force within a finite length-range, an exponential stiffness, k_s, was assumed

$$k_s = k_{s0} \exp(b_s d). \quad (9)$$

After integration over the length (d), the force in the

external series elasticity, F_s, was expressed as

$$F_s = k_{s0}/b_s \, [\exp (b_s d) - 1]. \quad (10)$$

In the above expressions, k_{s0} and b_s are constants while d is the extension of the external series elasticity. The lower boundary condition in the integration was chosen such that at $d = 0$, the force was zero.

Length-Passive Force Relationship. The rat portal vein is characterized by an exponential length-passive force relationship (Uvelius et al., 1981). In the model this relationship corresponds to the parallel elasticity and was described in a conventional way by adopting the expression

$$F_p = F_{p0} \exp [b_p (l/l_0 - 1)], \quad (11)$$

where F_{p0} is the passive force at the optimum muscle length l_0; b_p, a constant and l, the actual muscle length. Since there is no muscle length that will give zero passive force in this description, it is evident that the formulation is not valid at very short muscle lengths (cf. Fung, 1967). This short coming can, however, be neglected in the present study, since all experiments to which the model was compared were carried out at muscle lengths within the range of its applicability.

Computational Methods

In order to solve Eq. 1 the following additional relationships were used (see Fig. 1 *a*).

(*a*) Total force equilibrium

$$F_{cc} + F_p + F_T = 0. \quad (12)$$

(*b*) Equality between force of the cross-bridges and force in the external series elasticity

$$F_{cc} = F_s. \quad (13)$$

(*c*) Definition of the different lengths

$$x + h_c + d = l. \quad (14)$$

In the simulations, Eqs. 12 and 13 were taken as algebraic. x, l, h_c, and h_D were chosen as state variables (cf. Fig. 1 *a*) and solved from Eqs. 1, 12, 13, and 6, respectively. d was obtained from Eq. 14. Eq. 12, which was used for solving l, was not necessary when the length of the muscle was controlled during the experiment.

The simulations were performed on a CAI Alpha LSI 4/90 computer, which has an accuracy of slightly more than seven digits, using a single precision version of a program, developed by Söderlind (1980), for numerical integration of partitioned stiff ordinary differential equations and differential algebraic systems.

TABLE I
NUMERICAL VALUES OF ESTIMATED CONSTANT PARAMETERS

Type of measurement and reference	Estimated parameter values
Elasticity of cross-bridge Ford et al., 1977*	$h_0 = 0.005\ l_0$
Passive length-force Uvelius et al., 1981	$F_{p0} = 5.6$ mN, $b_p = 6.5$
Active length-force Uvelius et al., 1981	$a_n = 1.8$, $b_n = 1.4$
Series elasticity Johansson et al., 1978	$k_{s0} = 1$ mN/mm, $b_s = 6$ mm^{-1}
Force-velocity Uvelius and Hellstrand, 1980	$a_v = 0.025$ s^{-1}, $b_v = 2.3$
Intermediate component in isotonic quick release Uvelius and Hellstrand, 1980	$a_D = 0.4$ s^{-1}, $t_D = 0.025$ s
Imposed stretch and shortening at graded rates Johansson, 1983	$b_f = 3$

*Study on frog muscle fiber.

RESULTS

Parameter Estimation

The model includes a total of 12 constant parameters that must be given values. All these parameters were quite distinguishable in the simulations (see Discussion) and could easily be estimated from the experiments described below. A summary of all estimated parameter values is given in Table I, together with the type of measurement on which the estimation was based.

Adjusting the Model to Different Stationary Control Conditions

The passive length-force relationship of smooth muscle tissue plays an important role as a normalizing factor, since it is often used as a means of obtaining the optimum muscle length, l_0, i.e. the normalization length to which all length changes and contraction velocities are related. In the present paper, this method of normalization was used. Hence, given the passive force, F_p, and length l, in the control situation, the optimum length, l_0, was calculated from Eq. 11. In the calculation, it was assumed that all portal veins follow the length-passive force relationship given in Fig. 2 *a*. (i.e. F_{p0} and b_p were kept at their constant values given in Table I.)

In striated muscle, the extension of the cross-bridges has been estimated to be in the order of 0.5% of the optimum muscle length (Ford et al., 1977). In the portal vein, as well as in all other smooth muscle tissues, estimation of the cross-bridge extension is difficult since the observed length changes are always greater than the length changes of the cross-bridges, due to the existence of an external compliant series elasticity (see above). For this reason, the minimum value obtained in striated muscle was used in the present formulation of the model. Following this estimation, all remaining normalizing factors could be obtained from the active force, F_{cc}, in stationary control conditions.

Length-Passive Force and Length-Active Force Relationships

The length-passive force and length-active force relationships were fitted to the experimental data of Uvelius et al.(1981), where both relationships were measured in the same experiments (see Fig. 2 *a, b*). From Fig. 2 *a*, it can be seen that at muscle lengths below l_0, the length-passive force relationship is well fitted by Eq. 11, whereas at higher degrees of strain, the experimental values tend to increase more than that predicted by the monoexponential function. The situation is similar in Fig. 2 *b*, where Eq. 7 is shown to give a good fit to experimental data on the length-active force relationships at muscle lengths below the optimum length, while the symmetric property of Eq. 7 gives a slight overestimation of the data at higher strains.

Series Elasticity

The series elasticity of the model was fitted to data obtained from isotonic high-time resolution quick release and quick stretch experiments (Johansson et al., 1978). Fig. 2 *c* shows a comparison between the total series elasticity (i.e. external + elasticity of the cross-bridges) of the model and an experimental range pertaining to five experiments, calculated by substituting the maximum and minimum values of the standard error range for the stiffness k into the formulation given by Johansson et al. (1978). From this figure, it can be seen that the total series elasticity of the model falls well within the experimental range. (Model simulation obtained from the control conditions F_p = 0.8 mN, F_{cc} = 9 mN, and l = 5 mm.)

Quick Load Changes and Force-Velocity Relationships

The relationship between load and contraction velocity is usually studied in isotonic quick release and quick stretch experiments. In smooth muscle tissue, the length response to an isotonic quick release can be separated into the following three components (Johansson et al., 1978): (*a*) An instantaneous elastic recoil (see above), (*b*) an intermediate component characterized by a rather rapid velocity transient and (*c*) a slower but more steady contraction velocity that shortens the muscle until it has reached a new stationary state at the lower force. The pattern is also basically the same for quick stretch experiments. Since the higher velocity of the intermediate component is of short duration, it is generally regarded as a special transient (see below) and, as such, is not included in contraction velocity measurements that are therefore obtained as soon as possible after the transient has subsided. In the rat portal vein, contraction velocities have routinely been measured 100 ms after the sudden change in load. Fig. 3 shows a comparison between the force-velocity characteristics of the model (solid line) and the Hill equation (Hill, 1938) for the average force-velocity curve of seven portal veins (Uvelius and Hellstrand, 1980). This figure shows that there is a good correspondence between the traditionally used Hill equation and the model predictions at small loads and high contraction velocities i.e. the range over which the Hill formulation is an adequate description of measured velocities and, thus, that which is routinely used for estimation of the contraction velocity at zero force, by means of extrapolation. At loads above the isometric force, F_0, the model shows an increasing 'yield' or 'give' with increasing force. This is a well known experimental finding (a more detailed account is given below) which is not described by the hyperbolic Hill equation. Another interesting feature of the model is that the inflection point in the force-velocity relationship is found at a load somewhat below F_0. This position of the inflection point and the following decrease in velocity with increasing force has been observed in experiments on smooth muscle (Hellstrand and Johansson, 1979), and has also been studied in detail in skeletal muscle (Edman et al., 1976). It should be noted that the existence of an inflection point in this force region constitutes an intrinsic property of the present model (see Discussion) which is not accounted for by the A. F. Huxley theory of 1957, since his model gives rise to a hyperbolic force-velocity curve equivalent to the Hill equation.

Intermediate Velocity Transient

It has been suggested that the intermediate velocity transient of smooth muscle tissue is a counterpart to the intermediate transient observed in skeletal muscle, although these latter transients are much faster and more complex in their nature (Johansson et al., 1978). In skeletal muscle, the explanation for the transient behavior (Huxley and Simmons, 1971) is that the cross-bridges, followed a sudden change in force, switch from one position to another and, thereby, depending on whether the conditions are isometric or isotonic give rise to a quick recovery in force or length, respectively. In the formulation of the present model, such a shift in position is equivalent to a transient increase in the velocity of the cross-bridge displacement v_c. The most simple formulation of such a transient is the formulation of v_D, as given in Eqs. 5 and 6. It can be seen from Eq. 6 that v_D is entirely dynamic. This formulation implies that only the cross-bridges attached to the sites during the step will react, whereas others that become attached later during the resulting phase of contraction will not be affected by the previous transient. It should be noted that the given formulation for v_D and v_c is the simplest possible and that the inclusion of a relaxation time that depends exponentially on the extension of the cross-bridge, as was suggested by Huxley and Simmons (1971), will give rise to the same type of characteristic 'T2 curve' as they found experimentally. However, since experimental data of the transient in smooth muscle does not show this dependence (Uvelius and Hellstrand, 1980, Fig. 5), the simpler version was preferred.

Fig. 3 *b* shows a comparison between isotonic transients

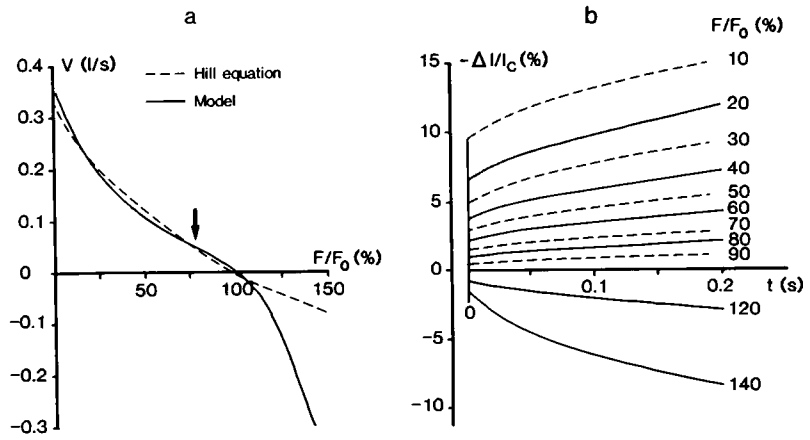

FIGURE 3 (*a*) Comparison between the force velocity curve of the model (solid line) and a Hill equation (dashed line) based on average parameters of seven portal veins (Uvelius and Hellstrand, 1980). Note that the model is nonhyperbolic and has an inflection-point (shown by the arrow) slightly below the isometric force, F_0, whereafter it yields progressively with increasing force. Both curves were obtained by measuring the contraction velocity 100 ms after a sudden step in force, and normalized so as to give contraction velocities relative to the actual muscle length before the force-step. (*b*) High resolution quick release and quick stretch experiments. The intermediate component is shown as a velocity transient within the first 0.1 s. Dashed lines are average curves from Uvelius and Hellstrand (1980), while the solid lines represent the behavior of the model. Contraction velocity is given as relative length change in per cent of the control length, l_c.

of the model and the average quick release traces from seven different portal veins within the first 200 ms (Uvelius and Hellstrand, 1980). The average transients (dashed lines) were obtained from a double exponential expression presented by these authors, which was an excellent fit for the experimental data within the given range. It is interesting to note that the intermediate component in response to a sudden increase in load (quick stretch) and the intermediate component of a quick release, while both experimentally (cf. Hellstrand and Johansson, 1979, Fig. 3) and in the model seem to be similar, have, according to the model, completely different origins. Hence, the quick stretch transient is unaffected after abolition of all quick release transients (by setting a_D in Eq. 5 to zero). The reason for this is that the velocity of the cross-bridges, v_c, is insignificant when the muscle is yielding under the influence of an external force. The time course of the intermediate quick stretch component is, therefore, an expression of a model property that is related to the friction term f_c in Eq. 2 (see Discussion)

Response to Imposed Stretch and Shortening

To obtain more information about the yield of the muscle at forces above the isometric force, the model was compared with experiments in which the force was measured during imposed stretch and shortening at graded rates (Johansson, 1983). Fig. 4 illustrates comparisons between such experiments and the behavior of the mathematical model under similar initial conditions (F_p = 1 mN, F_{cc} = 2 mN, l = 6 mm). It can be seen that, apart from differences in the length-passive force relationship, the model and the experimental results correspond well with regard to the behavior of the active force during both stretch and shortening. During stretch, the model predicts a more abrupt yield then is seen in the portal vein and, in this respect, behaves more like rabbit mesotubarium (Meiss, 1982). The tendency for the force to level out at increasing rates of stretch is, however, similar. The almost complete loss of active force during high rates of shortening has also a counterpart in the experimental situation. However, in conditions of extremely slow stretch and shortening, the model does not produce a hysteresis-loop of the same magnitude as the in vitro recording in Fig. 4. From a theoretical viewpoint, this decrease in hysteresis is understandable since, provided the stretch and shortening is much slower than the average velocity of the cross-bridge displacement, the muscle model will simply follow its length-active force and length-passive force relationships and, thus, not give rise to any hysteresis. Hence, in order for the model also to show a marked hysteresis loop at extremely low rates of stretch, it is necessary to assume a lower velocity of cross-bridge cycling. In the Discussion it will be shown that it is possible to decrease the cross-bridge cycle rate drastically with only small effects on the isometric force (Fig. 7). If this is the correct explanation, it must be assumed that the contraction velocity decreases with time and/or stretch during the K^+ contracture. Experimental findings indicating the possibility of such a decrease in contraction velocity with time have been presented by Dillon and Murphy (1982).

Vibration-Induced Inhibition of Muscle Contraction

To test the ability of the model to predict and interpret mechanical experiments of a completely different nature to those used in the estimation of parameter values described above, the model was compared to experiments of Ljung

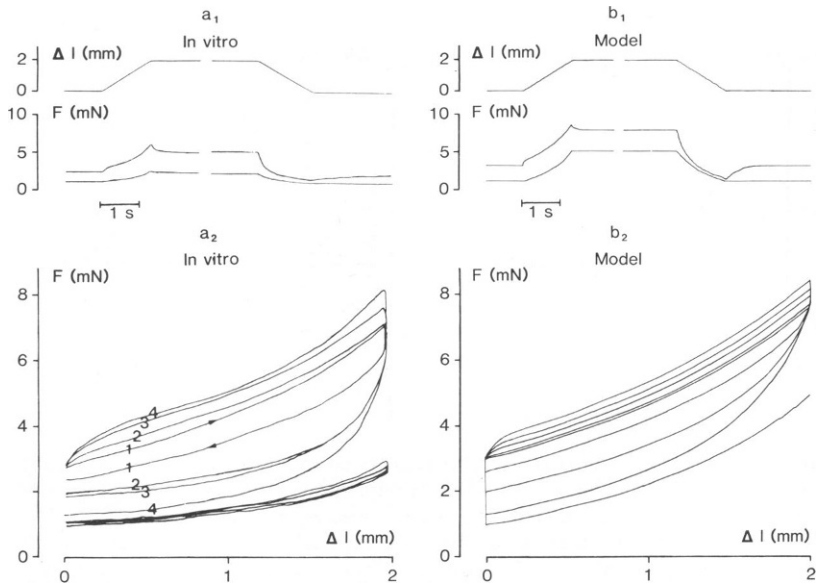

FIGURE 4 Responses to imposed stretch and shortening in a portal vein (*left* panels; Reproduced, by permission, from Johansson, 1983) and in the model (*right* panels). (a_1) Original tracings of changes in length and forces. Lower part shows superimposed recordings from a passive portal vein in Ca^{++} free medium (*below*) and from a K^+ contracture (*above*). (b_1) Model simulations of the same kind of experiments as in a_1. (a_2) Same type of experiment as in a_1 but plotted as force against change in length. The numbered tracings (1 to 4) represent stretching rates of 0.03, 0.28, 0.67, and 1.5 mm/s, respectively. The bottom recordings are from the relaxed muscle at length changes of 0.03 and 1.5 mm/s. (b_2) Model behavior during the same experiments as in a_2. Note that the model shows good agreement with the experiment recording at high rates of stretch, whereas its hysteresis loop at the lowest rate of stretch is smaller (see text). Initial muscle length 6.0 mm.

and Sivertsson (1975), in which longitudinal vibrations were found to inhibit the active muscular contraction in the rat portal vein.

In these experiments (Fig. 5 *a*), it was shown that on application of vibration, the active force falls almost instantaneously to a lower level, whereas the passive force is not affected appreciably. On cessation of the vibration stimulus, there is a gradual recovery of active force, the rate of which was dependent upon temperature, thus suggesting an active energy-dependent recovery process. With regard to the stimulus amplitude and frequency dependence (cf. Ljung and Sivertsson, 1975, Fig. 3), it was found that the inhibition increased with increasing amplitude, while the frequency dependence was most marked between 1 and 100 Hz, with little extra inhibition at frequencies above 200 Hz. By comparing Figs. 5 *a* and 5 *b*, it is seen that the mathematical model displays the same basic properties as were found experimentally in the portal vein. Thus, the model predicts a loss of active force during the vibrations and a return of force after the vibrations have ceased. The asymmetry between the initial fall and the recover processes are shown in greater detail in Fig. 5 *c*. To facilitate comparison between the model and the in vitro recordings, the force of the model has been filtered with a time constant of 50 ms, thus simulating the properties of the recording devices. In the experiment, the effects of a filtration process are indicated both by the absence of fluctuations in the 100 Hz registration and the seemingly paradoxical increase in passive force during the vibrations (see Fig. 5 *a*). The latter is, however, a natural effect caused by filtering and thereby averaging of the nonlinear passive length-force relationship. The same tendency is shown in the model simulation where, similarly, the 'drop' in active force at the sudden cessation of the vibrations is due to filtration of the nonlinear series elasticity. The amplitude and frequency dependence of the model during vibration induced inhibition are shown in Fig. 5 *d*. It can be seen that the inhibition of active force shows a similar amplitude and frequency dependence as was measured by Ljung and Sivertsson (1975).

Model Interpretation

In the model the cause of vibration induced inhibition can be attributed to the asymmetric response of the friction clutch mechanism to the applied stretches and shortenings. During stretch (cf. Fig. 1 *a*), the x portion of the contractile component is quickly elongated by the yield produced by the increase in force whereas, due to the slow contraction velocity of the contractile component during the following shortening, it is not able to regain its original length before a new pull tears it out again. Since the total muscle length (l) is held constant, the vibration induced elongation of x will shorten both the series elasticity (d) and the elasticity of the cross-bridges (h_c) and, hence, the active force will decrease. The 'stationary' situation during a vibration stimulation is, therefore, very similar to the short instance during an activation process when the cross-bridges are active but not producing much force since

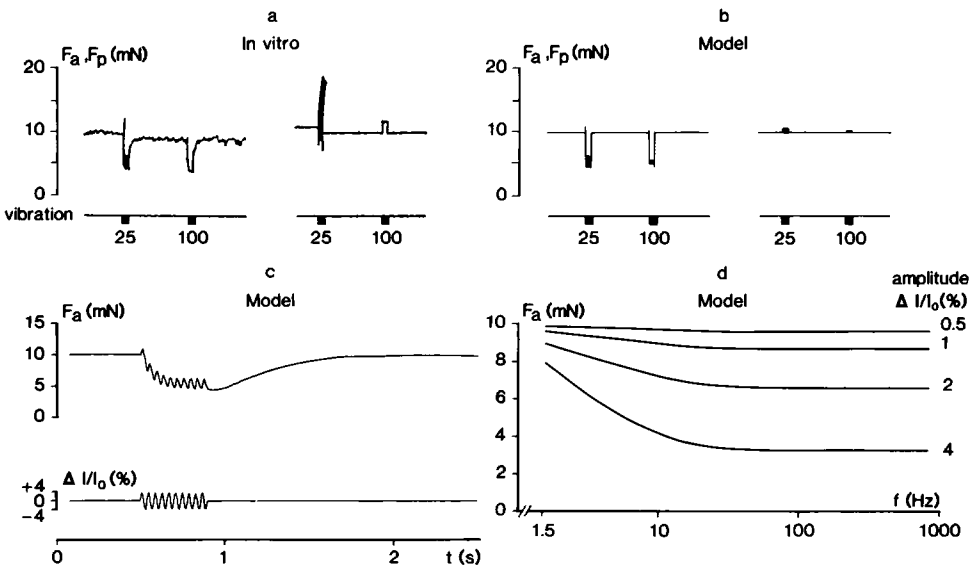

FIGURE 5 Vibration induced inhibition of muscle contraction. (*a*) Experimental recording (Ljung and Sivertsson, 1975) showing the effects of vibration on active force (*left* tracings), and passive force (*right* tracing). (*b*) Model experiment using the same experimental protocol as in panel *a*. Note that the model shows the same type of characteristic inhibition of active force during the vibrations as the in vitro preparation. The active force has been filtered with a time constant of 50 ms, designed to simulate the recording device, in order to facilitate comparison with panel *a*. (*c*) High time resolution of the same type of simulation as shown in *b*, together with the actual length changes of the vibrations (*lower* part). Note the asymmetry between the rapid fall of active force at commencement of the vibrations, and the more gradual recovery of force following its cessation. (*d*) Amplitude and frequency dependence of the vibration induced inhibition in the model. It is seen that there is a marked frequency dependence only between 1 and 100 Hz, and that increasing amplitude gives rise to an increased inhibition. (In vitro data reproduced, by permission, from Ljung and Sivertsson, 1975.)

the external series elasticity has not yet been stretched. This is the reason why active force can be almost instantaneously lost at the onset of a vibration stimulation, while the regained force following its cessation is rather similar to the last phases of a normal activation. An attempt to explain the characteristic frequency dependence of the inhibition is presented in Fig. 6. This figure illustrates variations in length of the contractile element (x) during three different vibration frequencies 1, 10, and 100 Hz, all with the same amplitude. It can be seen from the upper curve that provided the frequency is low (1 Hz), the shortening velocity of the contractile component is sufficient to re-stretch the series elasticity during each repetitive cycle. In this case, the reduction in force will be almost negligible. At higher frequencies, as illustrated by the second curve from the top, the average displacement of x from its initial level will increase since the contraction velocity is too slow to pick up the preceding elongation. This process will continue with increasing frequency until the contraction velocity of the contractile component can be totally neglected in comparison with the velocity of the vibrations, as shown in the third curve from the top. Increasing the frequency beyond this value will, therefore, not give any further reduction in force. This analysis also provides an explanation for the observed amplitude dependence, since larger amplitudes will give rise to larger extensions from which the muscle must recover between the repetitive stretches.

DISCUSSION

The proposed model is the least complicated model that is able to account for the many different muscle behaviors described in the present paper. These include: (*a*) Steady shortening and lengthening during isotonic release and

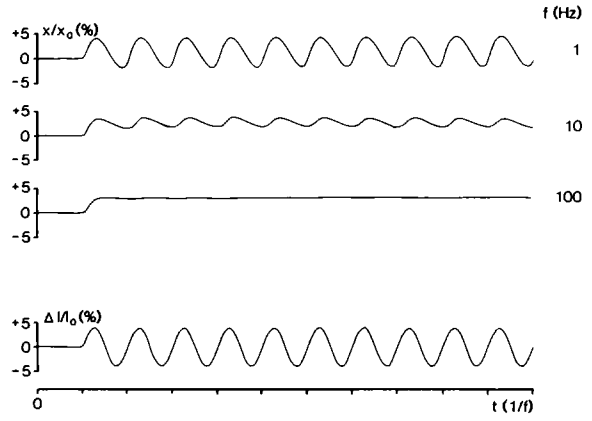

FIGURE 6 *Upper* tracings: Changes in length of the contractile element, x/x_0, during length vibrations with frequencies, f, of 1, 10, and 100 Hz. The time scale has been changed between the simulations in order to facilitate comparison. Note that the average elongation increases with increasing frequency until the contraction velocity of the muscle can be totally neglected in comparison with the velocity of the imposed length change. When this occurs both the elongation and, thus, the vibration induced force-inhibition level out at maximum values. *Lower* tracings: Relative length changes, $\Delta l/l_0$, of the imposed vibrations.

stretch; (*b*) isotonic high-time resolution quick stretch and quick release behaviors; and (*c*) yield in active force during imposed graded stretch, and pick-up during the subsequent shortening. The model has also shown explanatory power in the study of (*d*) amplitude and frequency dependence of vibration induced force-inhibition; and (*e*) existence and position of the inflection point in the force-velocity relationship. Furthermore, the model predicts certain relationships, e.g. between (*f*) isometric force and maximum contraction velocity, which have not yet been fully studied quantitatively (see below). In view of the above observations, it seems justified to conclude that the present model is a reasonably adequate description of the contraction process of (smooth) muscle. It will, therefore, be used in a further analysis of muscle function in which the principle of self-regulation plays a crucial role.

Force-Velocity Relationship

The initial steady contraction velocity (i.e. the contraction velocity obtained directly after the initial transient in an isotonic experiment has subsided) can be obtained as a function of the ratio between the active force, F, and the isometric force, F_0, by solving $\dot{x}$ from Eq. 1, and substituting Eq. 2 for f_c, and Eq. 4 for v_c, respectively. In this analysis, the parameter n_c can be set to unity, since this parameter does not directly affect the contraction velocity (see above). Hence,

$$\dot{x} = F/f_0 \exp\{b_f[(h_c/h_0)^2 - 1]\} - a_v l_0 \exp\{b_v(1 - h_c/h_0)\}. \quad (15)$$

Since the cross-bridges are assumed to behave like linear springs, the extension, h_c, is proportional to the active force, F. Thus, by substituting F/F_0 for h_c/h_0, and inserting the initial condition $f_0 = F_0/(a_v l_0)$, Eq. 15 can be written as

$$\dot{x} = a_v l_0 [F/F_0 \exp\{b_f[(F/F_0)^2 - 1]\} - \exp\{b_v(1 - F/F_0)\}]. \quad (16)$$

From this expression, which corresponds to the force-velocity relationship of Fig. 3 *a*, it is evident that all three constant parameters of the friction clutch formulation (a_v, b_f, and b_v), can be estimated by fitting Eq. 16 to experimental force-velocity measurements. This procedure is markedly facilitated by the observation that the term of the active contraction on the right hand side of the parenthesis of Eq. 16 refers to the low force part of the curve, whereas the friction term on the left hand side refers to the high force part of the curve. This partitioning of the curve into distinct components is the main reason why all parameters of the model are so easily estimated. It also explains the previously described simulation result that the intermediate component of the isotonic quick release experiments is not related to the intermediate component of isotonic quick stretch experiments (cf. Fig. 3 *b*). Hence, the quick release component is caused by a transient increase in the cross-bridge cycling rate, whereas the quick stretch component is brought about by an initial lower friction. This reduced friction results from a larger load on the cross-bridges before any sliding has occurred and gives rise to a higher rate of cross-bridge breaking than occurs during the subsequent stationary yield.

Inflection-Point in The Force-Velocity Relationship

The inflection-point of the force-velocity relationship is obtained by finding the zero solution to the second derivative of Eq. 16. Inserting the numerical values of b_f and b_v given in Table I in the resulting equation gives an inflection-point at a force of 0.77 F_0. This finding is in good agreement with measurements of the inflection point in single muscle fibers from the frog, in which it has an estimated value of 0.78 ± 0.01 F_0 (16 fibers, S.E.M.) (Edman et al., 1976). To appreciate this similarity, it should be noted that the location of the inflection-point is rather insensitive to variations in the parameters b_v and b_f. Hence, b_v must be increased by 39%, or b_f decreased by 57%, in order to shift the inflection point towards F_0 by 10%. The good agreement between the location of the inflection points does, however, reflect a certain similarity in shape between the force-velocity relationships. In this comparison, account must be taken of the fact that the magnitude of the cross-bridge cycling rate, given by the parameter a_v, is distinctly separable from the shape of the curve, which is determined by the parameters b_f and b_v. This can be deduced from Eq. 16, where a_v enters as a scaling factor.

The Dependence of Active Force on the Number of Cross-Bridges and Contraction Velocity

As was explained in the 'Theory' section, the force-generating interaction between the cross-bridges and the actin filaments implies a specific interrelation between friction and average velocity of the cross-bridge dislocation. Since, for a given adjustment of the model, friction and cross-bridge velocity are dependent only on the average cross-bridge load, there exists a certain relationship between active force, friction, and cross-bridge cycling rate. In order to study this relationship, the friction and cross-bridge cycling rate were selectively altered by letting f_0 and a_v vary under isometric conditions. Since variations in f_0 are equivalent to varying the number of active cross-bridges (cf. Eqs. 1 and 2), the latter procedure, i.e. varying n_c, was preferred. The result of this analysis is presented in Fig. 7, panels *a* and *b*. It is seen that the active force is absolutely linearly correlated to the number of active cross-bridges. Changes in the cross-bridge cycling rate within a range from 10 to 200%, i.e. varying a_v, gives, however, only very moderate changes in the force. This is quite a remarkable result which, however, is in full agree-

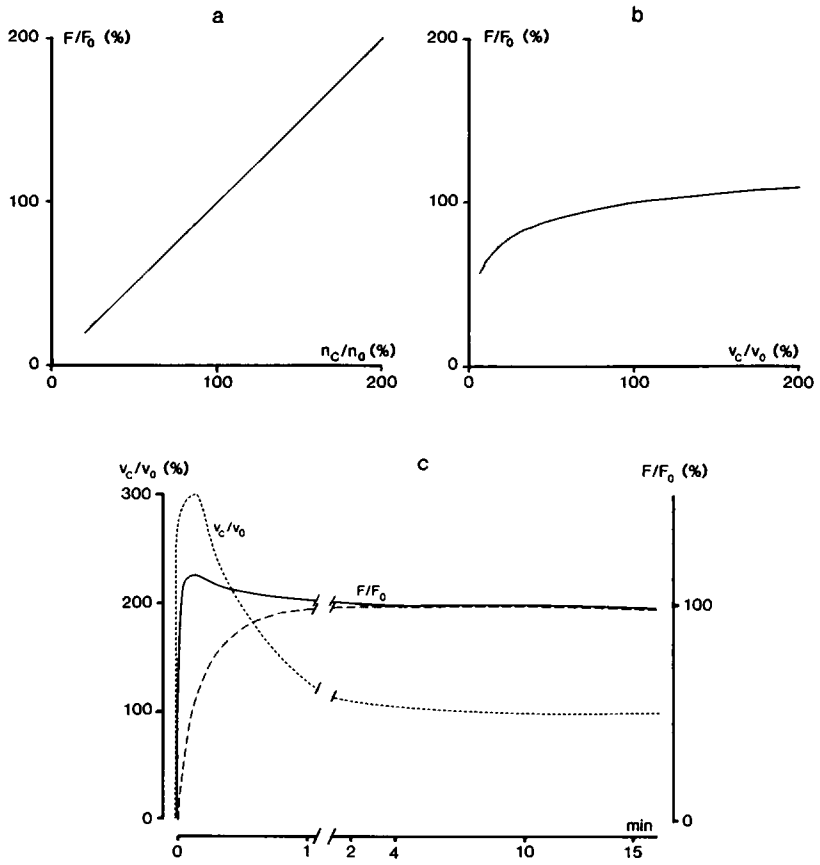

FIGURE 7 (*a*) Relationship between number of active cross-bridges, n_c/n_0, and active isometric force, F/F_0, in the model. Note the absolute correlation of these two parameters as can be predicted from Eq. 1. (*b*) Relationship between average velocity of the cross-bridge displacement, v_c/v_0, and active isometric force, F/F_0. A decrease in cross-bridge cycling rate is compensated for by an increase of the degree of cross-bridge interaction, making the isometric force almost independent of the contraction velocity. (*c*) Comparison of active force-time relationships between model prediction (solid line) and AC stimulated hog carotid smooth muscle (dashed line), assuming the same velocity-force curve (dotted line) in the model simulation as in the in vitro experiment (Dillon and Murphy, 1982). The difference in early force development is due to the fact that the model reacts instantaneously since it does not include any activation kinetics, whereas full activation in the experimental situation requires more than 30 s of stimulation. However, it can be seen that the model is fully able to mimic the experimentally observed maintenance of isometric force also in conditions of a reduced maximum contraction velocity.

ment with what intuitively has been thought to be the case in muscle tissue (cf. Ruegg, 1971). Furthermore, it indicates that the assumed interrelation between average velocity of cross-bridge displacement and friction is able to account for situations in which the cross-bridge cycle is altered. Hence, by including regulatory effects on the average cross-bridge cycle (by altering a_v), the model is able to account for conditions in which force is maintained although the contraction velocity is lowered. This is illustrated more clearly in panel 7*c* where the model behavior is compared with data obtained by Dillon and Murphy (1982). The dashed line shows active-force and the dotted line contraction velocity (expressed in relative terms) in response to AC stimulation on swine carotid media tissue. The solid line shows a computer simulation of the force development, obtained by a step increase in the number of active cross-bridges (n_c), and then changing the average cross-bridge cycling rate (a_v) in order to follow the same velocity-time curve as the in vitro experiment. The difference in early force development is due to the fact that the model reacts instantaneously since it does not include any activation kinetics, whereas full activation in the experimental situation requires more than 30 s of stimulation. These results indicate that the model seems able to reproduce conditions in which regulatory mechanisms might affect both the number of cross-bridges (n_c), and the average isometric cross-bridge cycling rate (a_v). Multiple regulatory mechanisms of this kind have been proposed by many authors and there is at present much research being done on the biochemical kinetics controlling the smooth muscle mechanics. In view of this it is possible that the model might serve as a link connecting biochemical and mechanical results.

The relationship, shown in Fig. 7 *b* and implicit in 7 *c*, between average velocity of the cross-bridge displacement, v_c, and active isometric force, F, can be obtained analytically from Eq. 1 by making the same substitutions as were used in the derivation of Eq. 16 (see above) for the case of

stationary conditions ($\dot{x} = 0$). Hence,

$$F = F_0 v_c / v_0 \exp\{b_f[1 - (F/F_0)^2]\}, \quad (17)$$

which after rearrangement gives

$$F/F_0 \exp\{b_f[(F/F_0)^2 - 1]\} = v_c/v_0, \quad (18)$$

where v_0 denotes the initial value of v_c.

A similar relationship, but pertaining to the maximum contraction velocity, which is an experimentally obtainable quantity, can be derived along similar lines. This gives

$$F/F_0 \exp\{b_f (F/F_0)^2 + b_v (F/F_0) - (b_v + b_f)\} = v_{max}/v_{max0}, \quad (19)$$

where v_{max} is defined as the contraction velocity at zero active force ($h_c = 0$ in Eq. 4); and v_{max0} the initial value of v_{max}. By comparing this expression with Eq. 18, it can be seen that the isometric force is, actually, less dependent on the maximum contraction velocity than on the average velocity of the cross-bridge displacement. Note that the friction term, b_f, is the only factor related to the shape of Eq. 18, and it is also the most important factor in the relationship between the isometric force and v_{max} as given in Eq. 19.

Remark on Energetics

The present model was designed exclusively for the purpose of accounting for observed smooth muscle mechanics. However, in view of the apparent similarity between the behavior of the model and experimental observations regarding the mechanics, it would be interesting to extend the study to see if data on muscle energetics also can be accounted for. Such a study should be possible since all mechanical components in the model are well defined and friction heat etc. can easily be calculated. An extended study of this kind was, however, beyond the scope of the present project.

Application of the Model to Other Studies

In the study of biological systems in vivo, the fast initial velocity transients with time constants of ~25 ms, observed in high-resolution quick stretch experiments, can be neglected. Under such conditions, the proposed model reduces to one differential and two algebraic equations. This somewhat simplified form can easily be incorporated in the analysis of more complex systems where the mechanical properties of smooth muscle play an important part. In a project in progress, we have, thus, included the vascular smooth muscle model in an investigation of the local circulatory control of vascular resistance in cat skeletal muscle. Preliminary results from this study (Borgström and Gestrelius, 1984) indicate that the interpretability at the cellular (smooth muscle) level of the contractile machinery of vascular smooth muscle is an important feature for the understanding of the adjustments observed in vivo during autoregulation of blood flow. Hence, the model may serve as an explanatory link connecting in vivo measurements, which are difficult to interpret directly, to important regulatory functions on the cellular level.

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