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Activation of thin-filament-regulated muscle by calcium ion: Considerations based on nearest-neighbor lattice statistics

(isometric tension/ATPase/troponin/crossbridge)

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ABSTRACT **We discuss the activation of thin-filament-regulated muscles by calcium ion in terms of a qualitative model based on nearest-neighbor lattice statistics. For the most part, the model takes into account only the essential features of the phenomenon—that there must be an interaction between calcium adsorption to troponin and crossbridge reaction with actin for calcium ion to activate contraction and that the relevant stationary states are nonequilibrium ones. Even so, the model predicts the following features which are seen experimentally but have generally not been considered in previous models: (*i*) the relative activations of stationary-state isometric force and ATPase are not equal; (*ii*) in general, neither activation of force nor that of ATPase is proportional to calcium adsorption to the activating sites; and (*iii*) the slopes of the relations between the activations and the logarithm of the calcium ion concentration generally depend on the necessary interaction between calcium ion adsorption and crossbridge reaction with actin. Thus, these relations show cooperative effects even if there is no interaction between calcium adsorption sites.**

There is significant understanding of the relations between the molecular events and their phenomenological manifestations in the activation of muscle contraction by calcium ion (1–4). Yet this understanding is not complete. Much of it is based on concepts from the theory of equilibrium systems and from other limiting cases, whereas contraction and its activation are distinctly nonequilibrium phenomena, even at the stationary state, and the limiting cases are so particular that they would not seem to obtain in muscle. We have recently begun to develop a model of cooperative systems with nonequilibrium stationary states (5), and in this paper we use this model to offer insights into these facets of the Ca^{2+} activation process. We will attempt to show that some of the previous interpretations of this process have been based on untenable assumptions. We will also offer explanations for some puzzling aspects of the phenomenon, but we will not attempt to develop a complete quantitative model; our goal is qualitative rather then quantitative. We will consider only essential aspects of the phenomenon so that the model reflects its basic features. (Derivations of the approximations and details of other points are available upon request.) The model should thus be considered a paradigm for more accurate models.

THE MODEL

We picture the thin filament as a lattice of two classes of sites: those on troponin that adsorb Ca^{2+} and the actins. Contraction is brought about by a cyclic reaction of projections of myosin from the thick filament, the crossbridges, with the actins and is powered by an ATPase located on the myosins (1–4). It is generally acknowledged that a crossbridge may exist in various states, both when it is reacting with an actin and when it is not reacting. However, because we are concerned with the activation of contraction, not the contraction itself, a two-state crossbridge cycle (Fig. 1*B*) in which an actin is either reacting or not reacting with a crossbridge suffices here. Indeed, two-state cycles have been useful prototypes for models of contraction itself (2, 6). In this simple picture, the ATPase rate is simply the rate of crossbridge cycling. It might also be noted that one of the transition paths in Fig. 1*B* may be taken as effectively one way (7); we neglect k_{-d}. The Ca^{2+} sites on troponin are adequately described as being either occupied by a Ca^{2+} or unoccupied, with transitions as shown in Fig. 1*A*.

As the concentration of Ca^{2+} is raised, it is adsorbed onto troponin (1, 8, 9) and the reaction of crossbridges with actins is stimulated, resulting in increases in the stationary-state isometric force and ATPase in fibers (9–11) and an increase in ATPase in myofibrils (10). To take into account the promotion of crossbridge reaction with actins by Ca^{2+} adsorption to troponin, we assume that when a Ca^{2+} site is occupied and a nearest-neighbor actin is reacting with a crossbridge, there is an attractive (<0) free energy of interaction w_{12}. Because the topology of the interactions is not clear, we must be content at this point to say that each Ca^{2+} site has c_{21} actins as nearest neighbors (in the sense of interactions, not structure), and each actin has c_{12} nearest-neighbor Ca^{2+} sites. ($c_{12}M_1 = c_{21}M_2$, where M_1 is the total number of actins and M_2, the total number of calcium adsorption sites.) For example, if each actin were controlled by one troponin and only two Ca^{2+} sites on troponin were responsible for activation, then c_{12} would be two. With these same conditions, if each troponin controlled seven actins, then c_{21} would be seven. If, on the other hand, four Ca^{2+} sites on troponin were responsible for activation and the other conditions remained the same, then c_{12} would be four, but c_{21} would still be seven.

There is also some evidence of possible interactions between the Ca^{2+} sites (9, 12) and between the actins (13, 14). We assume that each Ca^{2+} site has c_2 other Ca^{2+} sites as nearest neighbors and that each actin has c_1 other actins as nearest neighbors, with interaction energies w_2 when two nearest-neighbor Ca^{2+} sites are occupied and w_1 when two nearest-neighbor actins are reacting with crossbridges. In the actual muscle, all three of the interactions may be mediated wholly or in part by tropomyosin (1, 4). Some possible implications of this are discussed later.

We must now express the effects of these interaction energies on the rate constants of Fig. 1. We follow Hill (15) and assume that the interaction energy, $\tilde{w}$, of the activated complex (Eyring

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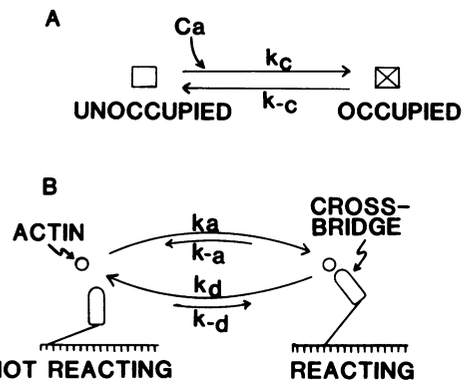

FIG. 1. (*A*) Transitions for an isolated Ca^{2+} adsorption site (the square); (*B*) crossbridge cycle for a single actin. In both *A* and *B*, *k*s denote rate constants.

rate theory) for transitions between some state A with interaction energy w_A and another state B with interaction energy w_B is given by a linear weighted average of w_A and w_B: $\tilde{w} = f_{AB}w_A + (1 - f_{AB})w_B$, where f_{AB} is a real constant (16) which may be chosen independently of all other parameters and variables. Note that in general there will be a distinct f for each of the two transition paths of Fig. 1*B* because detailed balance at equilibrium is required for each path independently of the other. However, if the interactions affect the rate constants for both paths equally, one need consider only one f; a mathematical detailed balance that offers considerable simplification obtains even at nonequilibrium stationary states (15). We treat only this "quasi-equilibrium" case here, but we discuss some implications of the removal of this constraint in the last section.

We must take into account one further complicating aspect of muscle contraction. For the cycle of Fig. 1*B* to be coupled to a net force production, there must be a dependence of its rate constants on some mechanical parameter (7). Relevant macroscopic observable quantities for the muscle fiber are obtained only after averaging over the mechanical parameter. However, a perturbation expansion shows that to first order the number of actins with crossbridges attached and the number of occupied Ca^{2+} sites are given by the unaveraged quantities in the isometric stationary state. Furthermore, to the same approximation, the force under the same conditions is proportional to the number of actins with crossbridges attached, so that the relative force (defined below) is identical to the relative number of actins with crossbridges attached. We will use these results here because we do not want to introduce effects that result from a particular choice for the mechanical dependence of the rate constants of Fig. 1*B*. That this approximation is reasonable is indicated by the qualitative similarity between measurements of the Ca^{2+} activation of ATPase in isometric fibers (10, 11) and those in myofibrils (17).

This model of the Ca^{2+} activation of muscle contraction is formally equivalent to one we have presented earlier (5). Unfortunately, no closed form solution is available for the general model even at equilibrium, much less under the nonequilibrium conditions we consider here. Two approximations have been presented, however (5). The Bragg–Williams approximation does not take into account, for example, that in general $0,1,\ldots c_{12}$ of a given actin's c_{12} nearest-neighbor Ca^{2+} sites may be occupied and $0,1,\ldots c_1$ of the actin's nearest-neighbor actins may be reacting with a crossbridge. Rather, only an "average" actin with an average number of occupied nearest-neighbor Ca^{2+} sites and an average number of nearest-neighbor actins reacting with crossbridges is considered. An "average" Ca^{2+} site is similarly defined. The Bragg–Williams approximation yields qualitatively reasonable results, and we will use it for the most part. However, it does lack topological information; when we ask for such information, we must turn to the more elaborate quasi-chemical approximation, which does retain some topological constraints and happens to be exact for several special cases. This approximation assumes that pairs of nearest neighbors are independent.

The Bragg–Williams approximation yields the following stationary state Ca^{2+} adsorption isotherm (5):

$$\ln(q_2 z_2) = ln\left(\frac{\theta_2}{1-\theta_2}\right) + c_2 w_2 \theta_2 + c_{21} w_{12} \theta_1 , \qquad [1]$$

where $q_2 = k_c/k_{-c}$ is the partition function (binding constant) of a single isolated Ca^{2+} site; z_2 is the activity of Ca^{2+}, which we take equal to its concentration; θ_2 is the average fraction of Ca^{2+} sites that are occupied; θ_1 is the average fraction of actins reacting with crossbridges (i.e., $M'_1\theta_1$ is the number of crossbridges reacting with actins, where M'_1 is the total number of actins in the region of overlap of the thin and thick filaments); and the interaction energies have been normalized to temperature through the Boltzmann constant (i.e., wherever a w is written, one should read w/kT). (For those who prefer pCa $\equiv -\log_{10}[Ca^{2+}]$ as a measure of Ca^{2+} concentration, we note that natural logarithms may be converted to logarithms to the base 10 through the factor $\ln 10 \cong 2.303$.) Similarly, we have

$$\ln q_1 = \ln\left(\frac{\theta_1}{1-\theta_1}\right) + c_1 w_1 \theta_1 + c_{12} w_{12} \theta_2 , \qquad [2]$$

where $q_1 = k_a/(k_d + k_{-a})$ is the probability that a single actin subject to no interactions is reacting with a crossbridge. The stationary-state rate of crossbridge cycling or ATPase, which we refer to as a flux, is given by (5):

$$J = k_d e^{f(c_1 w_1 \theta_1 + c_{12} w_{12} \theta_2)} \theta_1 . \qquad [3]$$

RESULTS

The Ca^{2+} activation of stationary-state isometric force and flux calculated from the Bragg–Williams approximation under two sets of appropriate conditions are shown in Figs. 2 and 3. As is customary, we have plotted the relative values of these quantities, ϕ' and J', respectively. The relative activation of force is defined as

$$\phi' = \frac{\phi - \phi_o}{\phi^* - \phi_o},$$

where ϕ is the force, $\phi_o = \lim_{\theta_2 \to 0} \phi$, and $\phi^* = \lim_{\theta_2 \to 1} \phi$. Actually, in our approximation (see above), ϕ is replaced by θ_1. J' is defined analogously to ϕ'. The calculations were carried out by first solving Eq. 2 for θ_2 as a function of θ_1 for the given choice of parameters. $\ln(q_2 z_2)$ was then obtained from Eq. 1. Finally, J was calculated from Eq. 3. Note that k_d cancels out when J' is calculated.

In Fig. 2 we have set $w_1 = w_2 = 0$ and considered only the necessary interaction between Ca^{2+} adsorption and crossbridge reaction with actins. Fig. 2*A* shows the relations of the activations to the concentration of Ca^{2+}, z_2. An elementary calculation shows that both activations generally rise much more steeply with increasing z_2 than does the corresponding analogue of the Langmuir adsorption isotherm, showing what is often referred to as "positive cooperativity." We also note that $J' \neq \phi'$ and the ratio ϕ'/J' generally increases with increasing z_2; i.e., the relative tension cost decreases with increasing activation, as is often but not always observed (10, 11). From Eq. 3 we see that

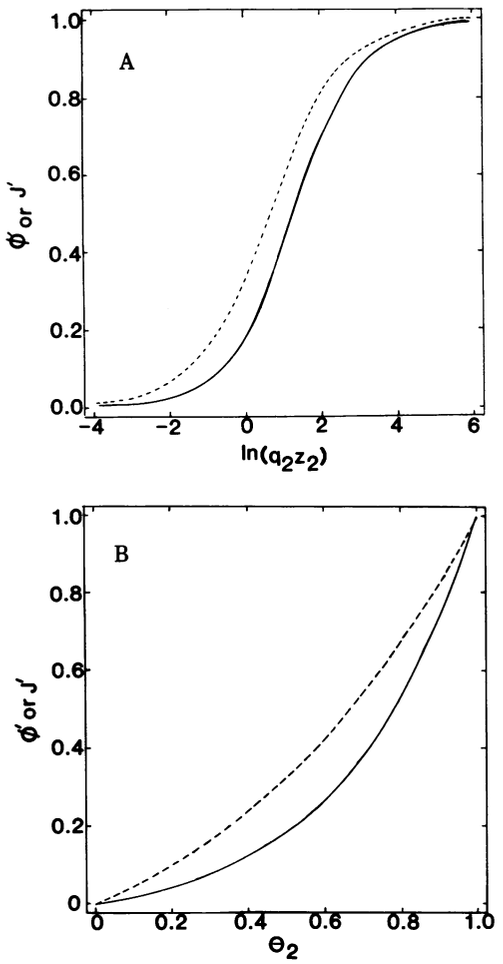

FIG. 2. The dependence of the activations of stationary-state isometric force ϕ' (——) and flux J' (– – –) on Ca^{2+} concentration, z_2 (*A*), and Ca^{2+} adsorption, θ_2 (*B*); calculated from the Bragg–Williams approximation with Eq. 3 for the flux. $q_1 = 0.001$, $c_{12}w_{12} = -3.0$, $c_{21} = 1.75\,c_{12}$, $w_1 = w_2 = 0$, $f = 0.5$.

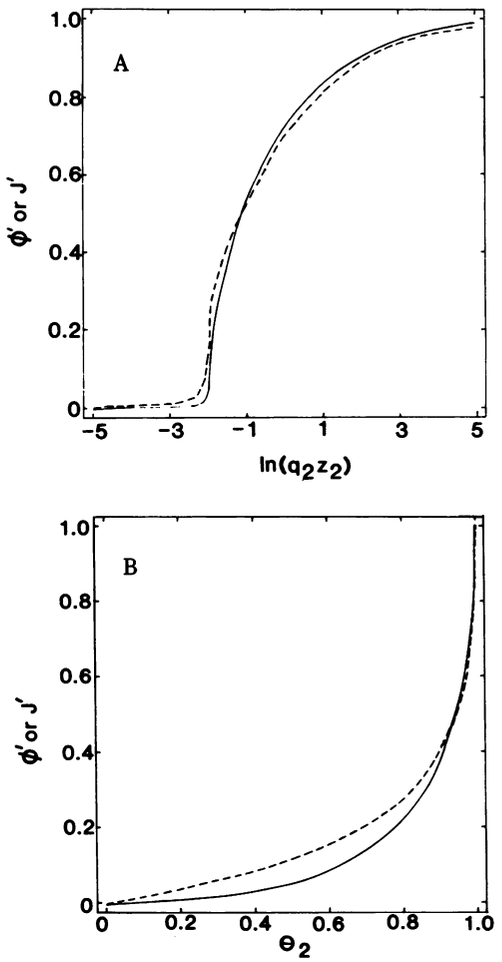

FIG. 3. The dependence of the activations of stationary-state isometric force ϕ' (——) and flux J' (– – –) on Ca^{2+} concentration, z_2 (*A*), and Ca^{2+} adsorption, θ_2 (*B*); calculated from the Bragg–Williams approximation with Eq. 4 for the flux. $\ln q_1 = -\ln(999) - 0.011 \cong -6.918$, $c_{12}w_{12} = -\ln(111) + 1.089 \cong -3.621$, $c_{21} = 1.75\,c_{12}$, $c_1w_1 = -11.0$, $c_2w_2 = -3.88$, $f_{12} = 0.8$, $f_1 = 0.0$.

with $w_1 = 0$ the tension cost J/θ_1 will decrease with increasing activation if $f > 0$, because w_{12} must be negative for Ca^{2+} to activate contraction. Our choice of parameters for this figure is in fact particularly fortuitous in that it reproduces the sort of relationship between the two activations seen by Schädler (18).

Under some experimental conditions (18), it is observed that ϕ' and J' intersect as shown in Fig. 3. An intersection cannot be predicted by Eq. 3; however, this equation assumes that the effects on the rate constants of Fig. 1*B* of the interactions of the actins with other actins (w_1) and with Ca^{2+} sites (w_{12}) may be expressed by the same constant, f. There is no fundamental reason why this should be so; thus, we can generalize Eq. 3 to read

$$J = k_d\,(e^{f_1c_1w_1\theta_1}e^{f_{12}c_{12}w_{12}\theta_2})\theta_1\,, \qquad [4]$$

which was used instead of Eq. 3 for the calculation of Fig. 3.

Also of interest are the relations between the activations and Ca^{2+} adsorption, as shown in Figs. 2*B* and 3*B*. We see that neither ϕ' nor J' equals θ_2 and that the slopes of both these curves increase with increasing activation. If we neglect the possibility of phase transitions (5) for the moment $[1 + c_1w_1\theta_1(1 - \theta_1) > 0]$, this follows for ϕ from Eqs. 1 and 2 with the requirements $w_{12} < 0$ and $\lim_{\theta_2 \to 1} \theta_1 < 0.5$. (In the overlap zone, the ratio of the total number of myosin crossbridges to the total number of actins is approximately 14/72, which implies that if all crossbridges were reacting with an actin, then the fraction of actins reacting with a crossbridge would be 14/72 = 0.19.)

DISCUSSION

These results are in general agreement with data in the literature. However, we (19, 17) and others (10) have not previously analyzed or discussed the data in this way. First of all, we know of no one who has attempted to deal with the difference between the activations of force and ATPase other than to attribute the difference essentially to an artifact rooted in the difference of strain in the myofilament lattice of unloaded myofibrillar preparations as compared to the loaded skinned muscle fiber (18). Yet we (11) and others (10) have found a difference in the activations of stationary-state force and ATPase of loaded skinned fibers prepared from either heart or skeletal muscle. Our results show that this difference between the activations of force and ATPase by Ca^{2+} is to be expected unless $f_1 = f_{12} = f = 0$.

From Eqs. 1–4 we also see that the deviations of the slopes of the activations vs. the logarithm of the Ca^{2+} concentration from that of appropriate analogues of the Langmuir adsorption isotherm in general depend on all three interaction energies w_1, w_2, and w_{12}. The standard approach, however, has been to interpret the slopes as being due only to the interaction between

the Ca^{2+} sites, w_2 (9, 20, 21). However, the slopes are steeper than the corresponding Langmuir analogues even if the only nonzero interaction energy is the necessary one between Ca^{2+} adsorption and crossbridge reaction with the actins (Fig. 2). (This statement is entirely true only for the Bragg–Williams approximation. In the quasi-chemical approximation, whose qualitative topological properties we expect to be correct, the magnitude of the slope of the relative activation of isometric force vs. ln z_2 is independent of w_{12} if $c_{12} = c_{21} = 1$. However, this condition is unlikely to obtain in muscle, and for other lattice topologies the quasi-chemical approximation agrees with the Bragg–Williams approximation about this point.)

Furthermore, the interpretation of the slopes in terms of an interaction between Ca^{2+} sites is often based on a generalization of the Hill equation (22). In this context, the slopes of the activations are taken to be some measure of a lower limit for the number of interacting Ca^{2+} sites per "functional unit". Although the parameters of the Hill equation may be useful in characterizing the dependence of the activation of stationary-state isometric force and that of ATPase on the concentration of Ca^{2+}, its use beyond that is inappropriate for the following reasons: The Hill equation is an equilibrium formulation, whereas muscle contracts actively only under nonequilibrium conditions. The Hill equation has been seen to follow from more general models in the limit that the ratio of an interaction energy to temperature becomes infinitely negative (23). This is unlikely for biological systems in general and muscle in particular, because their effective temperature range is small and in the neighborhood of 300 K. Finally, even supposing an analogue of the Hill equation could be used to describe the interaction between Ca^{2+} sites, one must still reckon with the interaction between Ca^{2+} sites and crossbridge reaction with actin.

We mention another point here. Under some conditions, analysis via the Hill equation yields a lower limit of more than four interacting Ca^{2+} sites per functional unit (24). Some investigators (24) have noted that, because there are only four Ca^{2+} sites per troponin in vertebrate skeletal muscle, factors additional to any interaction between these sites must be considered. In terms of the results presented here, at least part of the explanation lies in the other interactions and the reasons for the inappropriateness of the Hill equation as just discussed. In addition, there are still other factors which are mentioned in the next section.

A second major discrepancy between our present results and previous analyses concerns the relations between the activations of force and flux and adsorption to the Ca^{2+} sites (Figs. 2*B* and 3*B*). In calculating model curves for comparison with data, many investigators (25, 26) have assumed that the activations are proportional, or nearly so (8), to the extent of occupation of appropriate Ca^{2+} sites. This assumption is not born out in Figs. 2*B* and 3*B*, a central feature of which is that very little activation occurs with initial Ca^{2+} adsorption but that activation occurs more and more rapidly with increasing occupation of the Ca^{2+} sites. With the assumption of near proportionality though, the interpretation of this feature has been that there are two classes of Ca^{2+} sites—only one of which is responsible for the activation of contraction—and that most of the initial adsorption when little activation occurs is to the nonactivating class, whereas most of the adsorption when activation is increasing is to the activating class (8, 9, 13). This is an attractive hypothesis, because there is a good deal of evidence now that there are two classes of Ca^{2+} sites on troponin (27). In fact, partially on the basis of this argument, Potter and Gergely (8) have reasoned that Ca^{2+} binding to the Ca^{2+}-specific sites on troponin is responsible for activation. This point of view is strengthened by kinetic measurements showing that Ca^{2+} exchange with the Ca^{2+}-specific sites is rapid enough to occur during a twitch of fast skeletal muscle (28) or a beat of the heart (29), whereas Ca^{2+} exchange with the other sites is slow. Yet, even the titration of the Ca^{2+}-specific sites is not proportional to activation of stationary-state force or ATPase (8, 29). Moreover, conclusions made from comparisons of the activation of myofilament force or ATPase (or both) to Ca^{2+} adsorption to troponin in solution must be viewed with caution because such conclusions ignore the effect of the interaction of Ca^{2+} adsorption and crossbridge reaction with actins on the Ca^{2+} adsorption itself. (This is equivalent to using Eqs. **1–3** or **1**, **2** and **4** to calculate ATPase but setting θ_1 equal to zero in Eq. **1** to calculate Ca^{2+} adsorption.) There must be such an interaction, because otherwise Ca^{2+} adsorption to troponin would not affect the reaction of crossbridges with actins (and therefore contraction).

It is important to emphasize that a feature of the model we have presented here is that it considers only one class of Ca^{2+} sites and predicts an increasing slope in the relation between activation and Ca^{2+} adsorption, although the Ca^{2+} sites in our model are equivalent in all respects. We have argued above on the basis of the Bragg–Williams approximation that this feature is to be expected. However, we would also expect the lattice topology to have some effect that would not be manifest in this approximation. The quasi-chemical approximation though predicts generally that proportionality between the activation of force and Ca^{2+} adsorption requires $w_1 = 0$ and $c_{12} = 1$—i.e., that each actin interacts with only one Ca^{2+} site. Given what is known about the structure of muscle (3), this seems unlikely.

FURTHER CONSIDERATIONS

Up to this point we have neglected several aspects of the Ca^{2+} activation of muscle contraction that we feel will have to be included in a fuller treatment of the problem. The three interactions we have considered here are probably mediated at least in part by tropomyosin. Inclusion in the model of tropomyosin with its attendant states and interactions is straightforward in principle, and the necessary generalization has been outlined previously (5). By assuming the quasi-equilibrium conditions, we have considered only equilibrium-type effects of the interaction energies on population properties (16). However, there are other possible effects—dissipative ones—which would be expected at nonequilibrium stationary states. Such dissipative couplings appear in Shimizu's work (30) and have been discussed in the context of interacting enzyme systems by Hill (31). Relaxation of the quasi-equilibrium conditions is straightforward in the Bragg–Williams approximation to models with two-state crossbridge cycles (5, 31), although such a generalization may not be possible for the quasi-chemical approximation (T. L. Hill, personal communication). A further factor which must eventually be taken into account is the mechanical dependence of the rate constants of Fig. 1*B*, as discussed above.

We would like to mention one final matter: Does muscle display a phase transition? There is some evidence that it may. In measurements of the Ca^{2+} activation of isometric force in contractile threads, Crooks and Cooke (32) first maximally contracted the threads by increasing the Ca^{2+} concentration. The concentration was then lowered to the level where baseline force had been recorded, but the force was reduced to only about one-half of the maximal value. This hysteresis may represent a phase transition, as in ferromagnetism. A further piece of evidence is presented by the equilibrium adsorption of myosin subfragment 1 to regulated F-actin (33). The data in the presence of EGTA are certainly suggestive of a phase transition. The importance of the question of phase transitions may be understood by noting that the quasi-chemical approximation

places topological constraints (minimum numbers of nearest neighbors) on the conditions for such behavior (5). Thus, if hysteresis is conclusively demonstrated in the Ca^{2+} activation of contraction, it could imply certain information about the topology of the relevant interactions. Unfortunately, most experiments to date have been performed so as to minimize the possibility of observing any hysteresis (22). It would seem important to repeat such experiments maximizing any hysteresis that may be present.

Note Added in Proof. The hysteresis predicted above has now been demonstrated. After we submitted this paper, two abstracts (34, 35) were published showing contraction–relaxation hysteresis in single fibers of the barnacle. Unpublished experiments in our own laboratory have shown a similar hysteresis in chemically skinned bundles of heart muscle fibers. The results show that the steady-state force-free Ca^{2+} relations depend on whether a particular free Ca^{2+} is achieved by stepping down to the free Ca^{2+} from a higher level or by stepping up to the free Ca^{2+} from a lower level. Tension is higher in the step down than in the step up, indicating that the sensitivity of tension development to free Ca^{2+} depends on the history of the preparation. The results also suggest that during relaxation a given level of free Ca^{2+} can maintain a higher level of tension than it can produce during contraction.

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