PHASE TRANSITION IN THE SLIDING-FILAMENT MODEL OF MUSCULAR CONTRACTION*

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Communicated January 22, 1968

It was pointed out some time ago¹ that a first-order phase transition would be particularly suitable in the mechanism of muscular contraction at the molecular level because such a transition could provide a very large change in length from a quite small alteration in the force, or in the concentration of a molecule or ion, or in some other condition (e.g., electric field). The primary object of this paper is to call attention to the fact that the sliding-filament model² of muscular contraction, which is now well-established experimentally, is indeed, from the statistical-mechanical point of view, a one-dimensional system that exhibits a first-order transition. Hence, it should be expected to have the required "razor-edge" sensitivity.

Whether the phase transition proves to be a significant feature of the model remains to be seen. But physiologists should at least be aware of the possibility and of some of its implications (see below).

Ordinary one-dimensional systems cannot exhibit a first-order transition,³ but in certain rather artificial cases,^{4, 5} with long-range forces, a transition is found. In contrast, the sliding-filament model is an extremely simple, real (i.e., *not* artificial) one-dimensional system which virtually has a phase transition built into it. In fact it is difficult to see how nature could select a more elementary thermodynamic device to achieve the sensitivity referred to above.

In order to stress the essentials, we shall confine ourselves in this paper to a discussion of the equilibrium properties of a simplified version (Figs. 1 and 2) of the

FIG. 1.—The single-element thermodynamic system (schematic). In this case, $N = 5$, $M = 10$. One myosin filament slides between two actin filaments.

sliding-filament model. In a later paper we hope to treat a somewhat more proper and complicated "hexagonal" model² and consider the kinetics of the problem. Also, some aspects of the model undoubtedly require a steady-state rather than an equilibrium formulation.

Four recent papers^{6, 7} on possible (two-dimensional) phase transitions in biological membranes may also be of interest to the reader.

Single-Element Model.—Figure 1 shows the first system we consider, a single contractile “element.” Following this discussion, we shall turn to a multielement system (Fig. 2). A myofibril is essentially an ensemble of multielement systems arranged in series (one multielement system is equivalent to one half of a sarcomere). A single-element system consists of two actin filaments and one myosin filament. The “dots” on actin (Fig. 1) represent sites for binding to myosin heads (“dashes”). The system contains M units (one unit = two “dots” and a “dash”), each of which can exist in two states: o = overlapping; n = nonoverlapping. (A unit may contain additional myosin heads,² not shown in Fig. 1, which do not bind to actin.) The number of overlapping units is N ($0 \leq N \leq M$); the number of nonoverlapping units is $M - N$. The length of the system is

$$L = (2M - N)a, \quad (1)$$

where a is the length of one unit. Contraction occurs by “telescoping”—i.e., N increases and L decreases. The order of magnitude of M is probably² about 10–50.

Let $j_o(T)$ be the partition function of one overlapping unit (including, of course, the actin-myosin binding free energy) and let $j_n(T)$ be the partition function of one nonoverlapping unit. The relative thermodynamic stability of the two kinds of unit (in the absence of a force, f) depends on the ratio j_o/j_n . If $j_o > j_n$, overlapping units are more stable, etc.

The usual one-dimensional Ising system,³ which does not exhibit a phase transition, also consists of a linear array of two-state units. The essential difference is that, in the present model, all units of a given type necessarily occur in a *single sequence*. This property is responsible for the transition (i.e., the two phases are already separated in the model, from the outset). A very closely related example, with exactly the same kind of transition, is the “unzipper from the ends” model of the helix-coil transition.^{8, 9} However, the sequences in the latter model are artificially imposed for simplicity, whereas the sequences in the present model are an experimental fact. The statistical-mechanical discussion in the next section follows quite closely that given earlier for the helix-coil case.⁸

Statistical Thermodynamics of the Single-Element Model.—The basic thermodynamic equations,^{10, 11} if this small system has environmental variables T , L , M , are

$$dA = -SdT + fdL + \mu_d dM, \quad (2)$$

$$A = \bar{E} - TS. \quad (3)$$

We change independent variables from T , L , M to T , N , M :

$$dA = -SdT - afdN + \mu_d dM, \quad (4)$$

FIG. 2.—The multielement thermodynamic system (schematic), with $C = 4$.

$$\mu = \mu_0 + 2af. \quad (5)$$

Also, for environmental variables T, f, M (N can fluctuate),

$$d(\hat{\mu}M) = -SdT + \bar{N}adf + \mu dM. \quad (6)$$

This is the case of real interest.

The canonical ensemble partition function is simply

$$Q(N, M, T) = j_o(T)^N j_n(T)^{M-N}, \quad (7)$$

$$A = -kT \ln Q. \quad (8)$$

The really appropriate partition function (f independent instead of N), however, is

$$\Delta(f, M, T) = \sum_{N=0}^M Q(N, M, T) e^{-afN/kT} \quad (9)$$

$$\hat{\mu}M = -kT \ln \Delta. \quad (10)$$

From equations (7) and (9), we find

$$\Delta = j_n^M \left(\frac{1 - x^{M+1}}{1 - x} \right), \quad (11)$$

where

$$x = \frac{j_o}{j_n} e^{-af/kT}. \quad (12)$$

The quantity x has a physical significance similar to that of an equilibrium constant for an isomeric chemical reaction.

From equations (6) and (10),

$$\bar{N} = x \left(\frac{\partial \ln \Delta}{\partial x} \right)_{M, T} \quad (13)$$

$$= \frac{x [1 - (M+1)x^M + Mx^{M+1}]}{(1-x)(1-x^{M+1})}. \quad (14)$$

This is, incidentally, a familiar result¹² in B.E.T. (Brunauer-Emmett-Teller) adsorption theory, which is based on a model of linear aggregates. Equation (14) corresponds to c (B.E.T. constant) = 1 and M = maximum number of molecules in an aggregate. Also, in the adsorption problem, $x \leq 1$.

For an infinite system, $M \rightarrow \infty$,

$$\begin{aligned} \ln \Delta &\rightarrow M \ln j_n, \quad \bar{N}/M \rightarrow 0 \quad (x < 1) \\ &\rightarrow M \ln j_o e^{-af/kT}, \quad \bar{N}/M \rightarrow 1 \quad (x > 1). \end{aligned} \quad (15)$$

This shows a first-order transition (see also Fig. 3). For an infinite system, virtually all units are nonoverlapped for $x < 1$, while all are overlapped when $x > 1$. The transition occurs at $x = 1$. If $f = 0$, $x < 1$ means $j_n > j_o$ (the non-overlapped state is more stable), while $x > 1$ implies $j_o > j_n$ (the overlapped state

is more stable). When $f \neq 0$, the force influences the value of x , and hence biases the relative stability of n and o states, through equation (12). A positive force reduces the value of x and tends to increase the length L , as expected.

The reason the infinite system goes to one extreme ($\bar{N}/M = 0$) or the other ($\bar{N}/M = 1$) is that there is no mixing or configurational entropy effect (as in most

FIG. 3.—Equilibrium $\bar{N}/M$ vs. $\ln x$ curves for the model in Fig. 1, as calculated from equation (14). These are also, in effect, length-force curves. The phase transition is “sharp” at $M = \infty$ but is smoothed out for finite M .

systems) to resist the tendency of the more stable type of unit to predominate. Also, *relative* fluctuations about the most probable value of N are negligible when $M \rightarrow \infty$ (see below). A more detailed model should include parallel elastic material which leads to a rest length with $\bar{N}/M > 0$.

The completely “sharp” transition shown in Figure 3 for $M = \infty$ is smoothed out somewhat in a small system.⁸ Figure 3 includes a plot of $\bar{N}/M$ against $\ln x$ for $M = 10$ and $M = 100$, as calculated from equation (14). These curves are symmetrical: it is easy to show that

$$\bar{N}(x) + \bar{N}(x^{-1}) = M, \quad \bar{N}(1) = M/2. \quad (16)$$

The “rounding off” of the curves in Figure 3 for finite M is due to fluctuations.

The probability P_N that a system has a particular value of N at equilibrium is

$$P_N = \frac{Q(N, M, T) e^{-afN/kT}}{\Delta} = \frac{(1-x)x^N}{1-x^{M+1}}. \quad (17)$$

For any M (large or small), if $x < 1$, $N = 0$ is the most probable value of N , while if $x > 1$, $N = M$ is the most probable value of N . But for finite M , fluctuations are important enough to produce the rounded (mean value) $\bar{N}/M$ curves shown in Figure 3. The mathematical relation is

$$\bar{N}^2 - \bar{N}^2 = x \left(\frac{\partial \bar{N}}{\partial x} \right)_{M, T}. \quad (18)$$

When $x = 1$, $P_N = \text{constant} = 1/(M+1)$.

Multielement Model.—Suppose we have a sheet of C independent elements, all with the same value of N or L (Fig. 2), where C is a constant of order of magnitude² about 500. The canonical ensemble partition function for this multielement system is then Q^C , where Q is given by equation (7). Let f be the force per element so that the total force is fC (Fig. 2). Then the appropriate modification of the partition function in equation (9) is

$$\Delta'(f, M, T) = \sum_{N=0}^M Q(N, M, T)^C e^{-afCN/kT}. \quad (19)$$

This is not simply Δ^C (it would be, in effect, if $M \rightarrow \infty$). If we define $y = x^C$, then the probability distribution in N is

$$P_{N'} = \frac{Q^C e^{-afCN/kT}}{\Delta'} = \frac{(1-y)y^N}{1-y^{M+1}}. \quad (20)$$

Also,

$$\begin{aligned} \bar{N} &= y \left(\frac{\partial \ln \Delta'}{\partial y} \right)_{M, T} \\ &= \frac{y [1 - (M+1)y^M + My^{M+1}]}{(1-y)(1-y^{M+1})}, \end{aligned} \quad (21)$$

and

$$\bar{N}^2 - \bar{N}^2 = y \left(\frac{\partial \bar{N}}{\partial y} \right)_{M, T}. \quad (22)$$

These are the same as the results in the preceding section, except that y replaces x .

Because $\ln y = C \ln x$, the curve for $\bar{N}/M$ as a function of $\ln x$, in the case of particular biological interest, $M = O(20)$ and $C = O(500)$, is virtually indistinguishable from the $M = \infty$, $C = 1$ curve in Figure 3. In other words, for given finite M , the phase transition is very much "sharper" for $C \gg 1$ than for $C = 1$. When $C = O(500)$, the "rounding off" in Figure 3 for $M = 10$ or 100 is practically eliminated and the transition is essentially "all-or-none." Fluctuations in N become unimportant except rather precisely at $x = 1$.

Discussion.—As an example, suppose, in the “resting” state, the multielement system is at equilibrium with $x = x_1 = 0.98$ and $M = O(20)$, $C = O(500)$. The value x_1 is determined of course by j_o , j_n , and f in equation (12). Suppose further that excitation changes the value of j_o or j_n , or both, slightly (at, say, constant f), so that x increases from $x = x_1$ to $x = x_2 = 1.02$. Because of the phase transition involved, the system will then contract ($L_1 \cong 2Ma \rightarrow L_2 \cong Ma$) practically completely as a consequence of this very small change in x .

The molecular details of the excitation and of the switch in relative stability ($x_1 \rightarrow x_2$) of the two states are not completely known, but they may involve,² among other things: (1) an initial release of Ca^{++} ; (2) a resulting enzymatic split of adenosine 5'-triphosphate (ATP) at the point of actin-myosin binding; and (3) a decrease in the actin-myosin binding free energy (an increase in binding strength and in j_o). However interesting, these details are not required to understand the basic statistical thermodynamics of the situation, as outlined above.

In particular, if the phase transition is in fact the essential feature, the “cause” of the contraction ($L_1 \rightarrow L_2$) is simply the tendency of the system to proceed spontaneously to its new equilibrium state (in accordance with the second law of thermodynamics), following upon a sudden small change in molecular parameters (i.e., in j_o and j_n). A sufficient mechanism is presumably just an extremely biased “random walk” (see below). Unsymmetrical (directional) features of the myosin heads, the actin sites, or of the ATP splitting may be present; in fact, some have been observed, but they are not needed *in principle* to achieve a workable mechanism. Indeed, some directional “mechanisms” violate the law of microscopic reversibility.

The question of how chemical free energy in ATP is converted into mechanical work is not necessarily a difficult or mysterious one.¹³ It is quite sufficient, for example, as implied above, for Ca^{++} released in excitation to activate the spontaneous, enzymatic splitting of ATP, which in turn increases the strength of actin-myosin binding (e.g., through an electrostatic effect). The second law of thermodynamics then takes over to “produce” the contraction. All the splitting of ATP need do is increase the value of x a little. A *direct* transfer of chemical free energy into mechanical work is quite unnecessary.¹³

Kinetics.—The implied kinetic approach here, which we are pursuing, is a stochastic analysis of a biased but reversible random walk process. In view of the magnitudes of M and C , nucleation and propagation of each step of the walk probably play a key role (in order to assure reasonable activation free energies). We assume that N is not rigidly the same for all C elements but can fluctuate a little—thus providing nucleation. The propagation then probably occurs both transversely and longitudinally (along an actin filament, in the hexagonal model).

Summary.—The sliding-filament model of muscular contraction, considered from the point of view of equilibrium statistical thermodynamics, exhibits a first-order phase transition. A transition of this type causes the length of an elastic system to be extremely sensitive to small changes in environmental conditions, in accordance with the behavior of actual muscle fibers.

The author is indebted to Mr. George M. White for calculating the curves in Figure 3 and to Professor Frank Andrews, Professor Max Delbrück, and Dr. Adi Litan for helpful comments on the manuscript.

* Supported in part by research grants from the General Medical Sciences Institute of the U.S. Public Health Service and from the National Science Foundation.

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