Contractile stress generation by actomyosin gels

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The tension generated by randomly distributed myosin minifilaments in an actin gel is evaluated using a rigorous theorem relating the surface forces acting on the gel to the forces exerted by the myosins. The maximum tension generated per myosin depends strongly on the lengths of the myosin minifilaments and the actin filaments. The result is used to place an upper bound on the tension that can be generated during cytokinesis. It is found that actomyosin contraction by itself generates too little force for ring contraction during cytokinesis unless the actin filaments are tightly crosslinked into inextensible units much longer than a single actin filament.

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I. INTRODUCTION

Many key cellular processes in biological cells depend on contraction induced by the combination of the proteins actin and myosin. Actin can polymerize to form filaments, which in turn form a gel that is crucial for the motility and mechanical properties of cells. Actin filaments are asymmetric, having "barbed" and "pointed" ends, with polymerization more rapid at the barbed end. Depending on the concentration of free actin monomers, it is possible for barbed ends to polymerize at the same time as pointed ends depolymerize. Myosin is a two-headed motor protein which, by consuming energy in the form of adenosine triphosphate (ATP), moves toward the barbed ends of actin filaments. This process creates stresses by displacing the actin filaments in the gel relative to each other. The most familiar function of the actin-myosin (actomyosin) system is in the contraction of muscles, but it is crucial for many functions of nonmuscle cells as well. For example, eukaryotic cells undergoing division, or cytokinesis, form actomyosin rings at the cell membrane [1]. The rings contract, typically over a period of minutes or more, and thus "pinch off" the cell into two parts. Actomyosin contraction is also important for wound healing [2], dorsal closure [3], and retraction of the trailing edges of cells during directed motion [4,5].

In order to understand these effects quantitatively, it is necessary to evaluate the contractile stress using established principles of mechanics. Force generation by the ordered myosin arrangements in muscle has been well studied [6]. In addition, several recent continuum-based calculations [7–12] have treated the structure and/or stresses of contractile rings. These calculations have suggested plausible routes to the self-assembly of the ring, and have suggested that the interaction of parallel filaments can lead to contraction. The stress in the contractile ring has also been given in terms of the actin filament length, the filament concentration, the filament velocity, and the filaments' friction coefficient [7]. However, there are no general results available that relate the stress in the disordered structure of observed contractile rings and other cellular contractile structures directly to the myosin concentration, the force per myosin, and the microscopic structure of the actomyosin gel including the distribution of the myosin heads. Such results are useful both for obtaining a physical understanding of the contraction process, and as input for simulation studies of processes such as cytokinesis [13] and cell motility [14].

For the contractile ring in cytokinesis, the problem is conveniently formulated in terms of the tension T (having units of force) in the ring. The ring is attached to the inside of the cell membrane by mechanisms not definitively established. The membrane surface tension opposes ring contraction, and T must be large enough to overcome this effect. The simplest theory relating T for contractile rings to the myosin concentration and force per myosin [15] is that

$$T = NpF, \qquad (1)$$

where N is the total number of myosin heads (twice the number of myosin molecules since myosin is two-headed), p (the duty ratio) is the fraction of myosin heads that are generating force at a given time, and F is the force generated by a myosin head. In this theory, T is independent of the structure of actomyosin gel. In the remainder of the paper, I will show that T depends crucially on both the arrangement of the myosin heads and the structure of the actin gel.

II. ANALYSIS FOR HOMOGENEOUS ACTIN GEL

The approach used here is to treat myosins as external forces acting on the actin gel, which is for now taken to be a homogeneous medium. We will see that the tension generated by the myosins depends strongly on their aggregation. The model can treat nonpolymerized myosin (heavy meromyosin), but I focus on linear myosin aggregates called minifilaments, in which the active myosin heads are concentrated at the ends of the aggregates. Minifilament formation is required for contractile ring formation [16]. The known structure of myosin minifilaments [17] suggests the schematic model shown in Fig. 1. At each end are m myosin heads (circles). These travel toward actin-filament barbed ends and thus tend to pull the filaments in the pointed-end direction. The central region is free of heads. Typical minifilaments are less than 0.5 μm long and contain less than fifty myosin molecules [17]. If the minifilaments are larger than the actin gel mesh size, the assumption of a homogeneous actin gel will hold; corrections to this picture are discussed in the following section.

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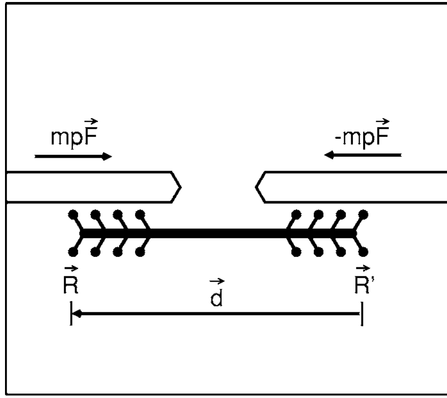

FIG. 1. Schematic of interaction between myosin minifilament (thick line) and pointed ends of action filaments (above myosin). Barbed ends of filaments are out of the picture. The arrows denote forces exerted at points $\vec{R}$ and $\vec{R}'$ by m myosin heads with duty ratio p in contact with the actin filament, each exerting a force of magnitude F; d is the minifilament length.

The net force exerted by a minifilament (or a molecule of heavy meromyosin) on the actin gel is small enough that it can be ignored in our calculations. To see this, note that because a minifilament is very light, the net force exerted on it must effectively vanish to avoid unrealistically large accelerations. This force consists of the forces exerted on it by the actin gel, plus the viscous drag force resulting from its translational motion. For a velocity of 1 μm/s a minifilament length and thickness of 0.3 μm and 50 nm, respectively, and a cytoplasmic viscosity ten times greater than that of water, standard formulas for the viscous drag force on a moving rod [18] yield a viscous drag force of 0.01 pN, much less than the maximum force of several pN generated by even a single myosin head [19]. Since both the viscous torque and the torque exerted by the myosin motor activity are proportional to the minifilament length, the viscous drag torque is also much less than that which could result from the motor activity. Thus we can safely assume that the total force and torque (measured relative to the minifilament's center) exerted on a minifilament by the actin gel vanishes; the corresponding quantitites exerted on the actin gel by a minifilament must then vanish as well, by Newton's third law. The same holds *a fortiori* for heavy meromyosin, since it is smaller than a minifilament.

Therefore it is legitimate to treat a myosin minifilament as a force dipole: a pair of oppositely directed forces $+mp\vec{F}$ and $-mp\vec{F}$ (see Fig. 1). I take the points of action $\vec{R}$ and $\vec{R}'$, respectively, to be at the ends of the minifilament (this approximation strengthens the inequality derived below). F is the magnitude of the force per myosin and, because of the zero-torque condition, $\vec{F}$ is parallel or antiparallel to $\vec{d}=\vec{R}-\vec{R}'$. I take $\vec{F}$ antiparallel to $\vec{d}$ by analogy with the known geometry of muscle. To calculate the tension T induced by the minifilaments, I relate the outward force exerted by the cell membrane on the shrinking contractile ring to the minifilament density and the strength of the force dipole. Figure 2 shows a slice, at a particular time, of the contractile ring, which experiences forces from the myosin minifilaments and the cell membrane. The calculation of T is based on the relation

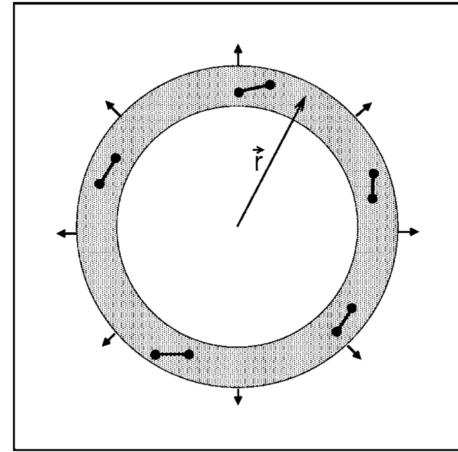

FIG. 2. Contractile ring (stippled) and forces f_{area} opposing contraction (arrows outside the ring). The barbells denote myosin minifilaments.

$$\rho \dot{v}^i = f^i + \sum_j \frac{\partial \sigma^{ij}}{\partial r^j}, \tag{2}$$

where ρ is the mass density of the actin gel, $\vec{v}$ is its local velocity of motion, $\vec{f}$ is the density of force exerted on the gel, and $\hat{\sigma}$ is the gel's stress tensor. This result is simply a statement of Newton's second law for a continuous material and is thus independent of the constitutive relation assumed for the actin gel. The acceleration term in Eq. (2) is exceedingly small. An upper bound of 5×10^{-4} kg/m^2 s^2 for this term is obtained by taking ρ to be the density of water, $v=5$ μm/s, and an extremely short characteristic time of 10 s for cytokinesis. On the other hand, if one assumes a tension of 1 nN (much smaller than experimental estimates discussed below), a cross-sectional area of 1 μm^2, and a characteristic length scale of 1 μm for variations in $\hat{\sigma}$, the second term on the right-hand side is 10^9 kg/m^2 s^2. Thus the left-hand side of Eq. (2) is completely negligible by comparison, and we may safely assume that

$$f^i = -\sum_j \frac{\partial \sigma^{ij}}{\partial r^j}. \tag{3}$$

The validity of Eq. (3) implies that the mean-stress theorem [20] holds. This theorem, obtained from Eq. (3) via an integration by parts, states that

$$\int r^i f^j_{\text{area}} dA = \int \sigma^{ij} dV - \int r^i f^j_{\text{body}} dV, \tag{4}$$

where the total force $\vec{f}$ has been partitioned into components $\vec{f}_{\text{area}}$, the area force due the membrane, and $\vec{f}_{\text{body}}$, the body force due to the myosins. Taking the trace of Eq. (4), one obtains

$$\int (\vec{f}_{\text{area}} \cdot \vec{r}) dA = \int \text{Tr}[\hat{\sigma}] dV - \int (\vec{f}_{\text{body}} \cdot \vec{r}) dV. \tag{5}$$

Since the ring volume decreases due to the forces from the myosins, the hydrostatic part of the stress in the gel, $\text{Tr}[\hat{\sigma}]$, will be negative. Therefore,

$$\int (\vec{f}_{\text{area}} \cdot \vec{r}) dA < -\int (\vec{f}_{\text{body}} \cdot \vec{r}) dV. \tag{6}$$

I emphasize that no specific assumption regarding the constitutive law of the gel has been made to derive this result. It will, for example, hold if the actin gel is treated as a viscous fluid, a viscoelastic medium, or an elastic medium (linear or nonlinear).

Cytokinesis requires a contractile stress, so it may at first seem surprising that the stress $\hat{\sigma}$ in the actin gel is compressive ($\text{Tr}[\hat{\sigma}] < 0$). However, the contraction is driven by the combination of the actin gel and the myosin minifilaments, and the latter contribute a tensile stress, which is sufficient to render the total stress, including both the actin gel and the myosins, contractile. Recalling that the gel is assumed to be homogeneous on the scale of a minifilament, one sees that the gel is compressed in the regions between the ends of a minifilament, leading to a negative stress in this region. If there is an external force opposing contraction, there will be tensile stresses in other regions, but because the overall volume change of the ring is negative, the average stress in the actin portion of the gel is negative. Note that this argument depends on the assumption that the actin gel is homogeneous on the scale of a minifilament; corrections to this picture are discussed in the following section.

I apply Eq. (6) to the geometry of Fig. 2. The ring is most conveniently thought of as a torus, but the result holds for any profile with cylindrical symmetry. The area integral in Eq. (5) is taken over the outer curved surface of the ring. Thus

$$TC = \int (\vec{f}_{\text{area}} \cdot \vec{r}) dA < -\int (\vec{f}_{\text{body}} \cdot \vec{r}) dV$$

$$= -Np(\vec{F} \cdot \vec{d})/2 = NpFd/2, \tag{7}$$

where C is the circumference and N is the total number of myosin heads. The first equality follows from a straightforward calculation of the work done by a virtual contraction of the ring. The second and third inequalities hold because the contribution of each minifilament to the integral is $m\vec{F} \cdot \vec{d}$, the number of minifilaments is $N/2m$, and, since $\vec{F}$ and $\vec{d}$ are oppositely oriented, $\vec{F} \cdot \vec{d} = -Fd$. Therefore

$$T < NpFd/2C. \tag{8}$$

T is thus reduced by a factor of $d/2C$ relative to Eq. (1). This result is clarified by the approximate analogy between mechanics and electrostatics, where force is analogous to electric charge and stress is analogous to electric field. The content of Eq. (8) is that the effect of each force dipole (as in electrostatics) is proportional to both the magnitude of the forces, and the separation between them. If the myosin minifilaments are replaced by heavy meromyosin, d becomes the separation between the two heads.

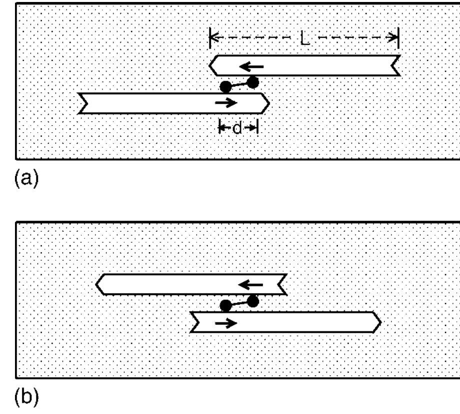

FIG. 3. Interaction between myosin minifilament (barbell) and actin filaments in viscous background (stippled), in contractile (a) and expansive (b) configurations. Both actin filaments have length L, and d is the size of the myosin minifilament. The arrows inside the actin filaments denote the direction of myosin force acting on them.

III. INHOMOGENEOUS ACTIN GEL

The analysis above holds for actin gels in which the mesh size is less than d, which renders them homogeneous on the length scale of a minifilament. However, the mesh size will often be larger than d. The resulting inhomogeneity enhances the contractile stress induced per myosin, because actin filaments are effectively inextensible and thus transfer the myosin force to larger distances. To evaluate this effect, I consider the model shown in Fig. 3(a), in which a minifilament exerts forces on two straight actin filaments of length L embedded in a homogeneous medium comprised of the other filaments. The two actin filaments transfer the force from the minifilament to the medium. The total displacement field is the sum of the fields induced by the two actin filaments. For each filament, the leading-order term in the displacement field at large distances is that of a point force of magnitude mpF exerted at the center of the filament, which decays with distance r as $1/r$. The next-order term, because the filament is symmetric with respect to its center, decays as $1/r^3$. The asymptotic displacement field is then that of the two opposing forces acting at the filament centers, which decays as $1/r^2$; the effect on the medium is the same as if the minifilament had a d value of d_{eff}, where d_{eff} is the distance between the filament centers.

I thus use an analysis parallel to that leading to Eq. (8), but with the forces acting at points a distance d_{eff}, rather than d, apart. I replace the system of minifilaments of size d acting on an inhomogeneous medium, with forces acting at a separation of d_{eff} in a homogeneous medium. Treating the actin gel as homogeneous in the latter case is legitimate because d_{eff} should be on the order of the filament length and thus larger than the mesh size. Therefore our approach will obtain the macroscopic tension in the contractile ring correctly. But it will not accurately describe the spatial variation

of the tension on length scales less than a filament size.

In the most favorable case where the minifilament ends are at the pointed ends of both filaments, $d_{\rm eff}=d+L$, and the maximum possible tension is

$$T_{\rm max}=NpF(d+L)/2C, \tag{9}$$

corresponding to a maximum stress

$$\sigma_{\rm max}=npF(d+L)/2, \tag{10}$$

where n is the number density of myosin heads. Equation (9) is the tension that is obtained in a model of "minisarcomeres" [21] of length $d+L$ placed end-to-end along the ring (a sarcomere is a discrete actin-myosin contractile unit found in muscle). The actual tension is less than $T_{\rm max}$ because not all of the myosins are at actin filament pointed ends.

The contention that Eq. (9) obtains the correct maximum macroscopic tension is confirmed by analysis of a simple one-dimensional model system consisting of two-filament bundles placed end to end. The two filaments in each bundle overlap from end to end, so the bundle length is equal to the filament length L. Each bundle is held together by a number of passive rigid crosslinks. In each bundle, the two filaments are oriented in opposite directions so that one pointed end is exposed at each end of the bundle. At each point where two bundles meet, a minifilament of length d, assumed to be negligible compared to L, pulls on the two available pointed ends. The minifilament has m myosin heads at each end. For simplicity I assume that the opposing force is sufficiently large to prevent contraction. Then the balance of forces on each element of the ring shows that the tension inside each bundle has the constant value mpF. On the other hand, since $N=2mC/L$, and d is assumed small, the right-hand side of Eq. (9) is also mpF. Thus the macroscopic stress is obtained correctly by our analysis even though its variation on length scales below a filament length is not predicted by the theory. Note that a different arrangement of the minifilaments can lead to much smaller tensions. For example, if a minifilament connects two filaments in the same bundle, its action will to expand the ring rather than contracting it. Thus it is appropriate to think of $T_{\rm max}$ as an upper bound for the tension.

The proportionality of the maximum stress to the filament length, displayed by Eq. (10), is consistent with an expression obtained in Ref. [7] from a phenomenological one-dimensional model. For the case of interactions between filaments of like orientation, and an equal number of filaments oriented in both directions around the ring, this expression becomes

$$\sigma_{\rm tot}=\alpha\bar{\eta}L^3n_{\rm fil}^2, \tag{11}$$

where α is a parameter determining the relative velocities of interacting filaments, $\bar{\eta}$ is a friction coefficient per unit length, and $n_{\rm fil}$ is the total density of filaments (pointing in either orientation). In this model, the filament speed is proportional to L because the motion is induced by other filaments, and the number of other filaments it interacts with is proportional to L. The magnitude of the frictional force $F_{\rm fric}$ acting on the filament is thus proportional to L^2, since η is defined per unit length, and thus the drag-speed ratio is proportional to L. Thus $\sigma_{\rm tot}\propto F_{\rm fric}L$, and has the same dependence on force and L as Eq. (9).

IV. BIOPHYSICAL IMPLICATIONS

The model defined above and Eq. (9) have important implications for the biophysics of cytokinesis. First, actin dynamics are required for continuing contraction by the actomyosin ring. The myosin-actin filament configuration in Fig. 3(a) initially induces a contractile stress. But the motion of the myosin heads will eventually place them at the filament barbed ends [Fig. 3(b)]. The separation vector between the filament centers then changes sign, so the force dipole and the stress also change sign, causing expansion rather than contraction [22]. However, actin filaments can undergo "treadmilling," a process in which barbed ends polymerize and pointed ends depolymerize at comparable velocities. If treadmilling occurs rapidly enough, the myosin heads can remain near the pointed ends of the actin filaments despite their motion toward barbed ends. This suggests that the contraction rate is limited by the treadmilling rate. Assuming a net pointed end off rate of 0.7 s^{-1} [23], and a filament length of 0.6 μm [24] or about 200 subunits, the treadmilling rate would lead to a maximum strain rate of 0.003 s^{-1}. This implies that the contraction time must be at least on the order of 300 s, consistent with observed times [15,21]. The rate could, however, be faster if intracellular proteins, such as actin-depolymerizing factor (ADF)/cofilin, accelerate pointed-end depolymerization. Actin dynamics involving processes other than individual filament treadmilling could also enable continuing ring contraction. For example, filament severing by the cellular protein cofilin is enhanced by phosphate release from polymerized subunits [25], and this is more likely to have occurred for the older subunits near the pointed ends. Thus more severing events will occur near pointed ends, and such events will leave the myosin heads nearer the newly created pointed ends. The predicted requirement of actin dynamics for cytokinesis is consistent with observations on the fission yeast *Schizosaccharomyces pombe* [26], which showed that drug treatments inhibiting actin dynamics prevented cytokinesis.

Second, there are two organisms for which accurate counts of the number of myosins in the contractile ring are available, *S. pombe* and the slime mold *Dictyostelium discoideum*. For both of these, $T_{\rm max}$ as given by Eq. (9) is much less than the minimum tension $T_{\rm req}$ required to overcome the membrane tension. For *D. discoideum*, calculations [15] based on the measured membrane tension obtain $T_{\rm req}=7$ nN; extrapolation of these results to *S. pombe*, assuming a membrane tension equal to that in *D. discoideum*, and a proportionality of T to cell size (as suggested by Ref. [27]) gives $T_{\rm req}=4$ nN. In the calculation of $T_{\rm max}$ for *D. discoideum*, I use $N=240{,}000$, $p=0.006$, $C=10$ μm [15], $F=3.5$ pN [19], and $d=0.3$ μm [17], $L=0.6$ μm [24] as representative values. This gives $T_{\rm max}=0.33$ pN, some twenty times smaller than $T_{\rm req}$. For *S. pombe*, the value of p is not known, so I take a value of 0.1, which is in the typical range for myosin. Using the same values of F and d as above, as well as $N=5{,}800$ and $C=7$ μm (30% lower than the uncontracted

value of Ref. [21]), gives $T_{max}=0.14$ pN, again much smaller than T_{req}.

These discrepancies cannot be explained by uncertainties in the parameter values. The main uncertainties are in the membrane tension and p. The membrane tension for *D. discoideum* could be overestimated by the micropipette aspiration measurements used to measure it, and the assumption that *S. pombe* has the same tension as *D. discoideum* could be inaccurate. However, changing either of these estimates by a factor of five would still give $T_{max} \ll T_{req}$. The value of p assumed for *S. pombe* could be inaccurate, but the correct value is not likely to be more than five times larger than the value of 0.1 we assume here; furthermore, an error in p would not explain the discrepancy for *D. discoideum*. In addition, T_{max} is derived using very favorable assumptions, which are unlikely to hold in biological organisms. Two alternative possibilities come to mind:

(1) The crosslinking of the actin gel could create stable clusters of filaments. A cluster of nearly parallel filaments, with sufficiently rigid crosslinks, could form an essentially inextensible "superfilament," which would act elastically as a single filament. If the length of the superfilament were comparable to C, this effect would increase T_{max} by an order of magnitude. Combined with an enhancement of p, this could raise T_{max} above T_{req}. This possibility is supported by the accumulation of cross-linking proteins in contractile rings: α-actinin accumulates in the *S. pombe* contractile ring [21] and cortexillins accumulate in that of *D. discoideum* [28]. Furthermore, myosin II, itself a cross linker, accumulates in the contractile rings of both organisms [15,21]. The possibility of long-range force propagation in actin gels is also supported by the finding that forces in cells can be transmitted over distances much larger than expected from homogeneous elasticity theory [29]. In this study, the force transmission range was reduced by caldesmon, an inhibitor of the actin-myosin interaction, suggesting that some aspect of this interaction can lead to long-range force propagation.

(2) Localized actomyosin contraction is not the main driving force for cytokinesis. Because of the established need for myosin II for cytokinesis of cells in suspension [30], we consider this hypothesis to be less plausible than the preceding one. However, it is consistent with the observation that bacteria, which have no known motor proteins, are able to form a contractile ring and divide [31]. Furthermore, *D. discoideum* on a substrate can undergo cytokinesis in the absence of myosin [32]. If actomyosin contraction is not the main force-generating process, the crucial function of myosin in the contractile ring might be in the acceleration of actin gel dynamics [33] or in the assembly of the contractile ring.

The predictions of this model could be tested by three types of experiments. First, electron-microscopy studies could establish the locations of the myosins in the ring. According to the model, they should be near the pointed ends of the actin filaments, or, if the filaments are linked into clusters with well-defined polarities, the myosins should be near the pointed ends of the clusters. Second, direct measurements could be made of the forces between focal adhesions on elastic substrates, in combination with quantitative fluorescence measurements of the number of myosins. These would not be directly applicable to cytokinesis, but could test Eq. (9) if the duty ratio and filament length were known. Finally, the deformation of microneedles of known mechanical properties placed inside the contractile ring could be measured [34]. This experiment would not measure T directly, because the contractile ring must supply the force to deform both the membrane and the needles. However, it would provide a lower bound, which could be compared with Eq. (9).

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