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Buckling-induced F-actin fragmentation modulates contraction of active cytoskeletal networks

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Abstract

Actomyosin contractility originating from interactions between F-actin and myosin facilitates various structural reorganization of the actin cytoskeleton. Cross-linked actomyosin networks show tendency to contract to single or multiple foci, which has been investigated extensively in numerous studies. Recently, it was suggested that suppression of F-actin buckling via an increase in bending rigidity significantly reduces network contraction. In this study, we demonstrate that networks may show the largest contraction at intermediate bending rigidity, not at the lowest rigidity, if filaments are severed by buckling arising from myosin activity as demonstrated in recent experiments; if filaments are very flexible, frequent severing events can severely deteriorate network connectivity, leading to formation of multiple small foci and low network contraction. By contrast, if filaments are too stiff, networks exhibit minimal contraction due to inhibition of filament buckling. This study reveals that buckling-induced filament severing can modulate contraction of active cytoskeletal networks, which has been neglected to date.

Graphical abstract

Introduction

Living cells need to generate mechanical forces to perform their physiological functions.¹ The ability of cells to generate forces originates mainly from a non-equilibrium biopolymer network called the actin cytoskeleton.² Myosin motor proteins walk on actin filaments (F-actin) in the actin cytoskeleton by consuming chemical energy stored in ATP, which results in tensile forces.³ The actomyosin contractility facilitates structural reorganization of the

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actin cytoskeleton in cells.⁴ Numerous in vitro experiments have demonstrated that reconstituted actin gels consisting of F-actins, actin cross-linking proteins (ACPs), and myosin motors exhibit active contraction to single or multiple foci. For example, it was shown that contraction of the actin gels emerges above critical motor density with intermediate levels of ACP density⁵ and takes place via multi-stage aggregation⁶ by driving initially well-connected networks to a critical state.⁷ In addition, we and our colleagues recently showed that networks contract at a rate proportional to network size via in vitro and numerical/analytical models, which is reminiscent of telescopic contraction of sarcomeres in muscle cells.⁸ It was also found that buckling induced by compressive forces arising from myosin activity plays a crucial role for contraction of actin gels⁹, consistent with theoretical predictions.^{10,11} A recent computational study showed that suppression of F-actin buckling can significantly slow down contraction.¹² In general, myosin activity can drive actomyosin networks to either of three different states: negligible contraction, contraction to a single focus, or contraction to multiple foci. Known key factors determining the final state of networks are i) network connectivity regulated by cross-linking level and F-actin length and ii) destabilization of ACPs caused by forces exerted from motors.^{7,12-14}

We recently demonstrated that severing of F-actin facilitated by buckling arising from external shear strain can induce distinct stress relaxation in passive cross-linked actin networks.¹⁵ Interestingly, severing was also observed during the active contraction of actomyosin networks.⁹ However, the role of F-actin severing in the myosin-driven network contraction has not been investigated to date. In this study, using an agent-based computational model, we investigated how F-actin severing induced by buckling modulates contraction of cortex-like thin actomyosin networks. We found that the buckling-induced F-actin severing significantly modulates network contraction, which has not demonstrated before.

Method

Model overview

We employed our previous Brownian dynamics model for studying the contraction of actomyosin networks (Fig. 1).^{14,16} Detailed descriptions about the model and parameter values used in this study can be found in the Supplementary Information. In the model, F-actin, ACP, and motor are simplified by interconnected cylindrical segments. F-actin is comprised of serially connected cylindrical segments with polarity (barbed and pointed ends). ACPs consist of two cylindrical segments. Each motor has a backbone connected with 8 arms. A motor arm represents 8 myosin heads. Motions of the segments are governed by the Langevin equation with the Euler integration scheme. Deterministic forces include bending and extensional forces that maintain equilibrium angles and lengths formed by the segments, respectively, and repulsive forces that account for volume-exclusion effects between F-actins. Stochastic forces are applied to induce thermal fluctuation. ACPs bind to F-actin at a constant rate and also unbind from F-actin in a force-dependent manner. A motor arm binds to F-actin and walks toward the barbed end.

Severing of F-actin

F-actins can be severed at a rate depending on bending angle as in our previous model.¹⁵ Severing of F-actin is simulated by breaking a chain between two adjacent points on the F-actin, which corresponds to disappearance of one actin segment. The sum of two adjacent bending angles on F-actin, $\theta_{s,A}$, is calculated, and we assume that a severing rate, $k_{s,A}$, exponentially increases as $\theta_{s,A}$ increases:

$$k_{s,A} = k_{s,A}^0 \exp\left(\frac{\theta_{s,A}}{\lambda_{s,A}}\right) \quad (1)$$

where $k_{s,A}^0$ is a zero-angle severing rate constant, and $\lambda_{s,A}$ defines sensitivity to $\theta_{s,A}$. This severing model was verified by comparing with in vitro experiments as described in the supplementary information.¹⁵

Network assembly

A very thin computational domain ($20 \times 20 \times 0.1 \mu\text{m}$) is employed without a periodic boundary condition. F-actin, ACP, and motor are self-assembled to a cross-linked actomyosin network within a circular space whose radius is $8 \mu\text{m}$ (Fig. 1B). During the network assembly, actin monomers are nucleated and polymerized into F-actin. ACPs bind to F-actin to form functional cross-links between pairs of F-actins. Motors are assembled into thick filaments, and motor arms bind to F-actin without walking motion. After the network assembly, motors start walking on F-actin, facilitating network contraction.

Quantification of network contraction

Network contraction is calculated using the x and y coordinates of endpoints of actin segments. Assuming that they are located on a single x-y plane, we create the spatial density map of the endpoints at the final time point of each simulation (Fig. S1A). By decreasing resolution of the map, a three-dimensional histogram is generated to automatically detect the number of foci (Fig. S1B). In the histogram, locations with actin density above a threshold value are considered to be potential centers of foci. If several potential centers are adjacent to each other in the histogram, they are considered to be a single focus. Once the number of foci is identified, we back-trace the endpoints of actin segments that belong to each focus up to the first time point in order to calculate contraction at each time point. For each focus, we first calculate its center by averaging the x and y positions of the actin endpoints. Then, distances between the center and endpoints that belong to the focus are averaged to calculate its mean radius, $R_i(t)$. The extent of network contraction (ξ) is calculated as follows:

$$\xi(t) = 1 - \frac{\sum_i^N \pi R_i(t)^2}{\sum_i^N \pi R_i(0)^2} \quad (2)$$

where N is the number of foci. Note that 0 corresponds to no contraction, whereas 1 means maximal contraction. An instantaneous contraction rate at each time point is determined by calculating the rate of a change in ξ over time ($\dot{\xi}(t) = d\xi/dt$). We define a steady state to be a time point when $\dot{\xi}(t)$ becomes less than ten percent of $\dot{\xi}(0)$. The time required for reaching the steady state is termed τ_{ss} , and the average contraction rate is calculated by dividing ξ at the steady state (ξ_{ss}) by τ_{ss} .

Results

Densities of motors and ACPs regulate contraction of actomyosin networks

First, we evaluate the contraction of actomyosin networks at wide ranges of densities of motor (R_M) and ACP (R_{ACP}) in the absence of F-actin severing. Note that R_{ACP} and R_M are molar ratios defined with respect to actin concentration. In all cases, contraction initially rises at a different rate and eventually reaches a steady-state level (Fig. 2B). At the steady state, motors aggregate to single or multiple aggregates depending on conditions (Fig. 2A). Note that there is not a volume-exclusion effect between motors, so motors may overlap with each other in space, which can lead to very compact motor aggregates. Unlike motors, distribution of F-actins does not show noticeable discontinuity after contraction regardless of the number of motor aggregates. Large contraction greater than 50% occurs only above critical R_M with intermediate values of R_{ACP} (Fig. 2C). A minimum amount of motors are required to obtain cooperativity between local motor activities, resulting in the critical R_M ($R_M^{\min}$).¹⁷ If there are an insufficient number of ACPs, connectivity between F-actins is too poor for motors to generate enough forces to contract networks. However, as R_M is higher, the minimum amount of ACPs required for large contraction ($R_{ACP}^{\min}$) is smaller because motors can also behave as tentative cross-linkers. If average length of F-actins ($\langle L_f \rangle$) is decreased from 2.53 μm to 1.74 μm , more ACPs are needed for large network contraction since a network with shorter F-actins has poorer connectivity compared to that with longer F-actins at the same cross-linking level (Fig. S2A). By contrast, if there are too many ACPs in a network, buckling of F-actins is suppressed either by a decrease in cross-linking distance or formation of F-actin bundles. Therefore, networks show smaller contraction above a certain level of R_{ACP} ($R_{ACP}^{\max}$) because buckling is required for significant network contraction as predicted by theories (Fig. 2C).^{10,11} A 16-fold increase in bending stiffness of F-actin ($\kappa_{b,A}$) reduces $R_{ACP}^{\max}$ because buckling can be suppressed more easily with stiffer F-actins even at larger cross-linking distance or with a less extent of F-actin bundling (Fig. S2B). A decrease in $\langle L_f \rangle$ also reduces $R_{ACP}^{\max}$ since motors generate weaker forces in a network with poorer connectivity although cross-linking distance and F-actin bundling are similar (Fig. S2A). These results showing large contraction only at $R_M \geq R_M^{\min}$ and $R_{ACP}^{\min} \leq R_{ACP} \leq R_{ACP}^{\max}$ are very similar to observations from in vitro experiments using an actin gel consisting of actin, skeletal muscle myosin II, and α -actinin.⁵ A computational study using a highly simplified model predicted that network contraction can be large at high R_{ACP} and intermediate R_M if volume-exclusion effects are negligible.¹⁷ However, we did not observe the secondary regime for large contraction. This might be attributed to indirect consideration of volume-exclusion effects between motors and ACPs due to a limited

number of binding sites on each actin segment (40). In addition, large contraction emerging at the intermediate range of R_{ACP} is also consistent with conclusion of a recent computational study that the degree of connectivity determines network contraction.¹² In sum, we found that large network contraction requires a sufficient amount of motors, enough network connectivity, and F-actin buckling. For the following studies, we focused on the narrower range of R_{ACP} between 0.005 and 0.08 since we were interested only in a regime where significant network contraction appears without F-actin severing in Fig. 2C.

Buckling-induced severing may lead to the largest network contraction at intermediate $\kappa_{b,A}$

Recent in vitro experiments have demonstrated that F-actins can be severed spontaneously due to an increase in their bending angle caused by thermal fluctuation, and the probability of severing is significantly enhanced by binding of cofilin.^{18, 19} Since buckling also increases bending angle of F-actins, it can mediate severing of F-actins. We recently showed that external shear strain applied to passive cross-linked actin networks can facilitate severing by making a portion of F-actins buckled, and that the severing induces a very distinct stress relaxation in the passive networks.¹⁵ Considering that buckling also takes place during the active contraction driven by motors, F-actin severing induced by the buckling has potential to play an important role in the network contraction.⁹ By incorporating the severing model implemented in our previous study¹⁵, we evaluated effects of the severing on contractile behaviors. Specifically, we measured contraction at wide ranges of a zero-angle severing rate constant ($k_{s,A}^0$) and $\kappa_{b,A}$ (Fig. 3), with $R_M = 0.08$ and $R_{ACP} = 0.02$ where very large contraction to a single focus occurs in the absence of severing. As expected, networks show smaller contraction with 64-fold higher $\kappa_{b,A}$ since F-actin buckling is suppressed (Fig. 3D). However, motors form aggregation in various fashions, leaving aster-like F-actin structures (Fig. 3A), which is reminiscent of contraction of microtubule networks observed in several experiments.^{20, 21} This contraction is mediated by polarity sorting, meaning that barbed ends of F-actins are brought to the center of the aster-like structures by motors.¹² With higher $k_{s,A}^0$ and lower $\kappa_{b,A}$, F-actins are severed more frequently during contraction (Fig. 3B). Interestingly, under the condition resulting in numerous severing events, a network is transformed to multiple foci with small contraction because F-actins are fragmented into short filaments during contraction, leading to severe deterioration of network connectivity (Figs. 3A, C). Thus, in the presence of F-actin severing, the network contraction can be maximal at intermediate levels of $\kappa_{b,A}$, not the smallest level. Time required for reaching a steady state (τ_{ss}) is proportional to $\kappa_{b,A}$ but is almost independent of $k_{s,A}^0$ (Fig. S3A), indicating that a network comprised of stiffer filaments resists myosin-driven contraction more. An average contraction rate shows dependence on $k_{s,A}^0$ and $\kappa_{b,A}$ similar to dependence of the final contraction (ξ_{ss}) on $k_{s,A}^0$ and $\kappa_{b,A}$ although it shows stronger dependence on $\kappa_{b,A}$ (Fig. S3B).

It is not feasible to change bending rigidity of F-actins in experiments over the range tested in this study although it is known that the bending rigidity is slightly varied by binding of actin-associated proteins, such as phalloidin, calponin, and tropomyosin.²²⁻²⁴ However, cases with 64-fold higher $\kappa_{b,A}$ (corresponding to the persistence length of 0.58 mm) may be compared with networks of microtubules whose persistence length is ~ 5 mm.²⁵ As

mentioned earlier, in those cases, we observed formation of structures similar to microtubule networks contracted by motors. By contrast, it is viable to modulate the F-actin severing rate by including a different amount of cofilin.¹⁹ It will be interesting to test our predictions using reconstituted actomyosin networks with various concentrations of cofilin.

Networks containing more motors and fewer ACPs show optimal $\kappa_{b,A}$ more apparently

We further investigated conditions under which the optimal intermediate $\kappa_{b,A}$ exists. $k_{s,A}^0$ is fixed at 10^{-30} s^{-1} while R_{ACP} is varied significantly from the reference value, 0.02, and $\kappa_{b,A}$ is increased up to a 64-fold higher value as before (Fig. 4). F-actin buckling occurs more frequently at higher R_{ACP} (Fig. 4B), which is consistent with our previous study¹⁵. Buckling of F-actins highly confined by many cross-linking points results in sharp curvature (i.e. large local bending angle), facilitating numerous severing events. Note that the highest R_{ACP} tested here is 0.08 which is much lower than the critical R_{ACP} in Fig. 2C above which buckling is inhibited, ~ 0.32 . By contrast, if F-actins are loosely confined, buckling with mild curvature is not always followed by severing. It was observed the existence of the optimal intermediate $\kappa_{b,A}$ is more conspicuous at lower R_{ACP} (Fig. 4D). Interestingly, at high R_{ACP} , the contraction is very large and leads to a single focus despite numerous severing events since enhancement of network connectivity via more ACPs is superior to deterioration of connectivity induced by F-actin severing during contraction (Figs. 4A, C). Since severing takes place in conjunction with an increase in effective actin concentration during contraction, ACPs can cross-link fragmented short F-actins. This is not identical to a situation where very short F-actins are cross-linked by numerous ACPs before contraction. If initial actin concentration is not very high, ACPs cannot cross-link very short F-actins into a percolated network regardless of their density. We also observe that τ_{ss} is greater with higher R_{ACP} because networks become much stiffer and thus resist contraction to a much higher degree under such conditions. τ_{ss} is still proportional to $\kappa_{b,A}$ as seen in Fig. S3A. As a result, the average contraction rate is greater with higher R_{ACP} and lower $\kappa_{b,A}$ (Fig. S4B).

We also varied R_M from a reference value, 0.08, with R_{ACP} fixed at 0.02 in order to probe the importance of the amount of motors for network contraction (Fig. 5). With higher R_M , frequency of F-actin severing and the number of foci after full contraction tend to be greater because stronger forces exerted by more motors make more filaments buckled and thus severed (Figs. 5B, C). Since R_{ACP} is constant, this leads to significant reduction of network connectivity. As a result, networks show more apparent optimal intermediate $\kappa_{b,A}$ with higher R_M (Fig. 5D). Interestingly, this is opposite to the outcome obtained by an increase in R_{ACP} (Fig. 4D). Since larger forces can contract networks faster, τ_{ss} is smaller with greater R_M (Fig. S5A). As a result, the average contraction rate is greater with higher R_M and lower $\kappa_{b,A}$ (Fig. S5B).

Conclusion

Based on results from this study, we conclude that actomyosin networks consisting of severable filaments can be in three different states after contraction: i) a single focus with large contraction, ii) a single focus with negligible contraction due to inhibition of F-actin buckling, iii) multiple foci with small contraction due to severe F-actin severing (Fig. 6A).

Through further exploration of parametric spaces (Fig. S6), we created a three-dimensional phase diagram involved with four factors: motor density (R_M), ACP density (R_{ACP}), zero-angle severing rate constant ($k_{s,A}^0$), and bending stiffness of F-actin ($\kappa_{b,A}$) (Fig. 6B). Under most conditions, networks exhibit large contraction into a single focus. However, if the ratio of R_{ACP} to R_M is low, two other regimes emerge. With sufficiently high $\kappa_{b,A}$, networks do not show large contraction because most of F-actins are not buckled. The critical $\kappa_{b,A}$ above which contraction becomes substantially small is proportional to R_{ACP}/R_M . Since F-actins are hardly buckled, the critical $\kappa_{b,A}$ is not dependent on $k_{s,A}^0$. By contrast, at small $\kappa_{b,A}$, F-actins are severed frequently if $k_{s,A}^0$ is high. These severing events can be critical for network contraction if R_{ACP}/R_M is low since an insufficient number of ACPs cannot provide enough network connectivity to rescue a network from the deterioration of connectivity induced by severing. Thus, multiple foci appear as a result of contraction. Due to these two regimes with small contractions, an optimal level of $\kappa_{b,A}$ leading to the largest contraction exists above a certain level of $k_{s,A}^0$, which has not been identified in any previous study. Recent theoretical studies predicted that network contraction will always be suppressed with higher $\kappa_{b,A}$ because they did not consider the possibility of F-actin severing induced by buckling. This novel finding provides a more comprehensive, realistic view about the contraction of actomyosin networks. We will extend our study by incorporating actin turnover dynamics, such as polymerization, depolymerization, and capping to capture and study network contraction under more physiologically relevant conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

Contraction of actomyosin networks is investigated using an agent-based computational model. (A) Schematic diagram showing a circular network consisting of actin filaments (F-actin, cyan), actin crosslinking proteins (yellow), and motors (red). The three constituents are simplified via cylindrical segments. (B) Morphology of networks at $t = 0$, 100, and 200 s during contraction. Densities of motors and ACPs are 0.08 and 0.04, respectively.

Fig. 2.

Network contraction is regulated by densities of motors (R_M) and ACPs (R_{ACP}). Contraction was evaluated under various R_M and R_{ACP} . (A) Network morphology with actins and motors represented by blue and red, respectively. Note that motors can aggregate very tightly due to the absence of a volume-exclusion effect between them. (B) Time evolution of the extent of contraction (ξ) for four different cases. (C) ξ measured at a steady state (ξ_{ss}). A minimum amount of motors are necessary to obtain cooperativity between local myosin activities. If there are an insufficient number of ACPs, motors cannot generate forces due to very poor network connectivity. By contrast, if there are too many ACPs, buckling is suppressed, which leads to small contraction. Thus, large network contraction occurs above critical R_M with intermediate R_{ACP} .

Fig. 3.

If filaments can be severed due to buckling, intermediate bending rigidity can lead to the largest network contraction. We evaluated network contraction with diverse bending stiffness of filaments ($\kappa_{b,A}$) and zero-angle severing rate constant ($k_{s,A}^0$) at $R_M = 0.08$ and $R_{ACP} = 0.02$. (A) Morphology of networks with actins and motors represented by blue and red, respectively. (B) Frequency of filament severing. (C) Number of foci measured at a steady state. (D) ξ_{ss} evaluated at a steady state. If $\kappa_{b,A}$ is very high, buckling is inhibited, leading to small contraction and formation of motor foci and aster-like actin structures. Higher $k_{s,A}^0$ and lower $\kappa_{b,A}$ result in formation of multiple foci with small contraction because filament severing occurs very frequently under such conditions, severely deteriorating network connectivity. Thus, optimal intermediate $\kappa_{b,A}$ exists at high $k_{s,A}^0$.

Fig. 4.

The optimal intermediate bending rigidity is more apparent in loosely cross-linked networks.

We probed network contraction over a wide range of R_{ACP} and $\kappa_{b,A}$ with $k_{s,A}^0 = 10^{-30} \text{ s}^{-1}$ and $R_M = 0.08$. Here, the range of R_{ACP} is narrowed to 0.005-0.08 to consider only a regime where significant network contraction appears without F-actin severing in Fig. 2C. (A) Network morphology showing actins (blue) and motors (red). (B) Frequency of filament severing. (C) Number of foci evaluated at a steady state. (D) ξ_{ss} measured at a steady state. If R_{ACP} is smaller, the range of $\kappa_{b,A}$ leading to large contraction becomes narrower. By contrast, if R_{ACP} is sufficiently high, networks contract to a single focus regardless of $\kappa_{b,A}$ despite much more frequent severing events because enhancement of network connectivity resulting from more ACPs is superior to deterioration of connectivity induced by F-actin severing during contraction.

Fig. 5.

With more motors, the optimal intermediate bending rigidity is more conspicuous. Network contraction was measured over a wide range of R_M and $\kappa_{b,A}$ with $k_{s,A}^0 = 10^{-30} \text{ s}^{-1}$ and $R_{ACP} = 0.02$. (A) Morphology of networks with actins (blue) and motors (red). (B) Frequency of filament severing. (C) Number of foci measured at a steady state. (D) ξ_{ss} at a steady state. If there are a larger number of motors, more filaments are buckled and severed during contraction because larger compressive forces are exerted on filaments. Since R_{ACP} is constant in all cases, networks experiencing more severing events have poorer connectivity. Thus, an increase in R_M leads to formation of multiple foci and small contraction at low $\kappa_{b,A}$ and low contraction at high $\kappa_{b,A}$, making the optimal intermediate $\kappa_{b,A}$ more apparent.

Fig. 6.

Actomyosin networks contract to either of three possible states depending on bending stiffness of F-actin ($\kappa_{b,A}$), zero-angle severing rate constant ($k_{s,A}^0$), ACP density (R_{ACP}), and motor density (R_M). (A) The three possible states are i) small contraction with a single focus (left), ii) large contraction with a single focus (middle), and iii) small contraction with multiple foci (right). (B) Three-dimensional phase diagram showing regimes for the three states.