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Actomyosin cortex: Inherently oscillatory?

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A new analysis of cytokinetic furrow ingression in the *Caenorhabditis elegans* zygote at high spatiotemporal resolution demonstrates that, rather than being a process of steady, spatially uniform constriction, furrow ingression is modulated by complex contractile oscillations that move around the furrow, possibly in the form of propagating waves.

The actomyosin cortex makes all the difference between complex, dynamically behaving animal cells and the static, spherical bags of chemicals passively floating in the surrounding fluid that cells would be without this cortex. The ability of the actomyosin cortex to actively contract, expand and dynamically remodel itself makes essential contributions to all vital cell functions, most notably to cell migration and cytokinesis[1]. The contractile activity of the cortex is spatially prepatterned on the cell membrane by the activity of small GTPases of the Rho family[2]. During cytokinesis, the furrow is induced by an equatorial belt of active RhoA GTPase, known as the Rho zone, that directly induces both the F-actin polymerization and the activation of myosin II[3]. In turn, myosin contractility feeds back into the regulation of Rho in an important but as yet poorly understood manner, presumably by spatially redistributing the GTPase and its regulators. So far it has been unambiguously established that furrow constriction induces a pronounced furrow-directed flow of the actomyosin cortex (Figure 1A) that both concentrates F-actin and myosin in the furrow and induces nematic ordering of actin filaments, thus further promoting furrow constriction by aligning myosin motors along the furrow[4,5]. Ostensibly, nothing in the biological function of cytokinesis seems to require that furrow ingression should not be an axially symmetric process of radially uniform ingression, starting from the equatorial belt encircling the mother cell all the way to the midbody separating the two nascent sisters, as it is often pictured in the textbooks. However, in many cell types cytokinesis occurs in a highly asymmetrical manner[6]. Thus, in epithelia the furrow ingresses largely in the basal to apical direction, reflecting the highly polarized organization of these cells. Surprisingly, however, highly

asymmetrical furrow ingression is also observed in non-adherent embryonic cells, with the first division of the *Caenorhabditis elegans* zygote being a remarkable example that has been studied genetically at a fine molecular resolution[7]. This well-described phenomenon (Figure 1B) is highly counterintuitive, given the initial axial symmetry of the zygote with the cell-division spindle acting as the axis of symmetry.

In this issue of *Current Biology*, Werner *et al.*[8] revisit the dynamics of the cytokinetic furrow during the first division of the *C. elegans* zygote using a combination of experimental and theoretical approaches. To study this process, these authors developed a live-cell imaging pipeline with unprecedented spatiotemporal resolution. Using an inverted resonant scanning confocal microscope, they were able to acquire z-stacks of 40 optical sections separated by 1 μm every 2.7 seconds. Together with another recent study[9] that put more emphasis on the measurement of the cortical flow surrounding the furrow, Werner *et al.*[8] provide the most complete and detailed quantitative description to date of furrow ingression in the *C. elegans* zygote during its first division. The authors partitioned the furrow circumference into 72 angular sections of 5° each. Their analysis, tracking the dynamics of individual angular segments, not only further confirmed the highly asymmetric nature of furrow ingression but also found stochastic oscillations of individual furrow segments, undetected in the previous studies that analyzed only the spatially averaged dynamics of the furrow diameter. Werner *et al.*[8] also observed similar dynamics of furrow ingression in the consecutive divisions of smaller embryonic cells. The authors further found that the asymmetry of ingression can be decoupled from the oscillations induced by perturbations already reported to abrogate the asymmetry of ingression, such as genetic ablation of the scaffolding proteins anillin and septins[7]. To explain these oscillations, Werner *et al.*[8] turned to the mechano-biochemical model they had previously proposed[10].

These observations by Werner *et al.*[8] are highly consistent with a growing body of publications reporting actomyosin cortex dynamic activity, which is widely observed across many cell types and organisms in the form of contractile pulses[11] and propagating waves[12–16] and is collectively referred to as cortical excitability[2,17]. Summarizing these diverse phenomena in a nutshell, two types of spatially localized temporal peaks, closely following each other in time, are typically observed (Figure 1C). The first peak is heralded by the sharp increase in the activity of a Rho family small GTPase, most notably RhoA, Cdc42 or Rac1, while the second is that of dynamically polymerized F-actin and actin-binding proteins. Mechanistically, this dynamic pattern has been explained via the action of two feedback loops converging on a Rho GTPase. Fast positive feedback induces activation of the Rho GTPase by guanine nucleotide exchange factors (GEFs, the activators) that are recruited by the active, GTP-bound form of the GTPase[18]. The GTPase is then inactivated by time-delayed negative feedback, most commonly traced to the F-actin-bound GTPase-activating proteins (GAPs, the inhibitors). (For details, see a recent review[2] and references therein.) Mechanical stress-generating myosin contraction, preceded by its recruitment and activation, typically follows the actin polymerization peak, sometimes with a pronounced time delay[13]. In static pulses, the peaks of GTPase activity and actin polymerization are co-localized on the cortex, while, in propagating pulses and waves, these peaks are shifted in space, so that the actin-associated inhibitor follows behind the activator (active Rho GTPase). The notion of cortical excitability should be understood broadly in the sense of the underlying molecular mechanism consisting of the activator and the time-delayed inhibitor, rather than in the strict mathematical sense, because both excitable and oscillatory behaviors are always found in the adjacent domains of the system's parameters and can rarely be distinguished in experiments.

In the context of cell division, cortical excitability has been observed during the first mitotic divisions of frog and starfish

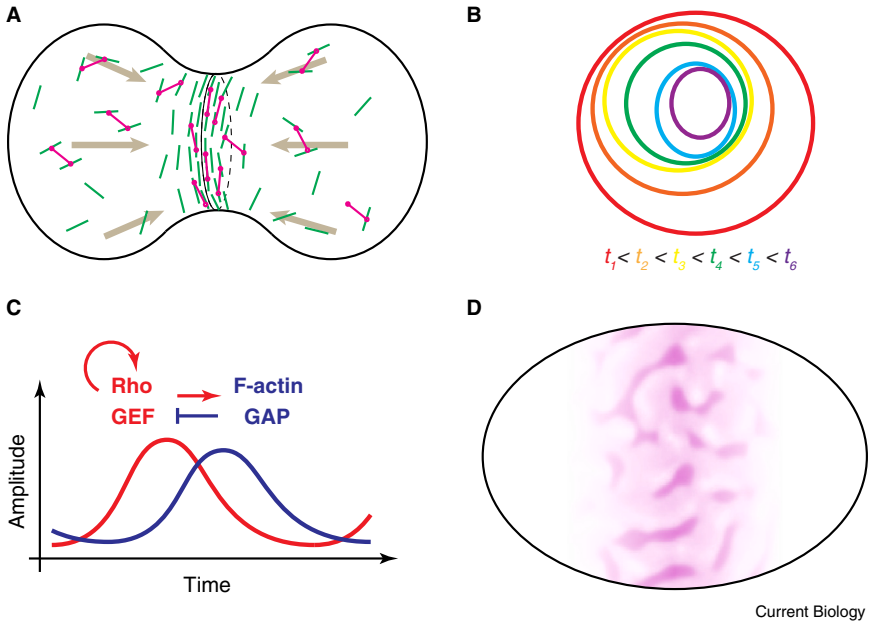

Figure 1. Is the cytokinetic furrow related to waves of actomyosin contractility?
(A) Diagram of cytokinetic furrow ingression. Actomyosin flow (beige arrows) concentrates and aligns actin (green) and myosin-2 (magenta) filaments. (B) Asymmetric ingression of the furrow in the *C. elegans* zygote (adapted from Werner *et al.*[8]). The position of the ingressing furrow in the plane of cytokinesis is schematically shown at the consecutive time points. (C) Biochemical regulation of the pulses and waves by an activator–inhibitor circuit (see text). (D) Cytokinetic furrow in early starfish blastomeres is patterned by the Rho zone, which emerges as a narrowing band of waves (adapted from Bement *et al.*[15]). RhoA activity waves are shown in magenta.

embryonic blastomeres as turbulent wave patterns appearing at the very onset of furrow ingression within the initially broad equatorial cortical band that rapidly shrinks in width as the furrow ingresses[15] (Figure 1D). Theoretical modeling, confirmed by experiment, explained this observation as a result of the progressive spatial concentration of the RhoA GEF Ect2 within the equatorial cortex by the action of the cell-division spindle[15]. This suggested that the Rho zone that initiates furrow formation and, at a low spatiotemporal resolution, appears as a static equatorial belt with a bell-shaped intensity profile may, in fact, be formed via the spatial focusing of an oscillatory wave pattern. The Werner *et al.*[8] data (see video S3 in this paper) presenting the activity of Rho around the ingressing furrow of the *C. elegans* zygote strikingly resemble the earlier observations in starfish[15] and suggest the broad ubiquity of cortical excitability accompanying the onset of furrowing. While the exact nature of the spatiotemporal dynamics in the center of the mature ingressing furrow remains unclear[19] and the narrow, rapidly ingressing furrow is difficult to image, recent data suggest that the Rho-powered actomyosin waves persist well into this advanced phase of cytokinesis[20]. The high-resolution data of Werner *et al.*[8] seem to offer strong support for this observation. Further work will be needed to elucidate the precise mechano-biochemical dynamics in the furrow by using converging experimental and theoretical approaches.

Werner *et al.*[8] conclude: "…contractile oscillations emerge from a system of essential, conserved biochemical and structural elements and may be considered inevitable given the biochemical and mechanical feedback intrinsic to the contractile cytoskeleton." This astute observation summarizes much of the previous work that established various specific mechanisms of actomyosin cortex regulation. From the dynamical systems theory viewpoint, these mechanisms are inherently oscillatory due to the nonlinear molecular circuits of the activator–inhibitor type that are embedded in them. The biological function of these oscillations remains an important and still poorly understood question. Werner *et al.*[8] suggest a functional explanation by proposing that alternating phases of contraction and relaxation promote the cortex remodeling that is needed to counteract cortex compaction, which is associated with prolonged phases of continuous cortex contraction. Future work will address this interesting hypothesis and other potential functional implications of cortical excitability.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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