

Minireview

Cortical excitability and cell division

Ani Michaud^{1,2}, Zachary T. Swider^{1,2}, Jennifer Landino³, Marcin Leda⁴, Ann L. Miller³, George von Dassow⁵, Andrew B. Goryachev⁴, and William M. Bement^{1,2,6,*}

¹Cellular and Molecular Biology Graduate Program, University of Wisconsin-Madison, 1525 Linden Drive, Madison, WI 53706, USA

²Center for Quantitative Cell Imaging, University of Wisconsin-Madison, 1525 Linden Drive, Madison, WI 53706, USA

³Department of Molecular, Cellular, and Developmental Biology, University of Michigan-Ann Arbor, 5264 Biological Sciences Building, 1105 North University Avenue, Ann Arbor, MI 48109-1085, USA

⁴Centre for Synthetic and Systems Biology, University of Edinburgh, 2.03 C.H. Waddington Building, King's Buildings, University of Edinburgh, Max Born Crescent, Edinburgh EH9 3BF, UK

⁵Oregon Institute of Marine Biology, University of Oregon, 63466 Boat Basin Road, Charleston, OR 97420, USA

⁶Department of Integrative Biology, University of Wisconsin-Madison, 1117 West Johnson Street, Madison, WI 53706, USA

*Correspondence: wmbement@wisc.edu

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SUMMARY

As the interface between the cell and its environment, the cell cortex must be able to respond to a variety of external stimuli. This is made possible in part by cortical excitability, a behavior driven by coupled positive and negative feedback loops that generate propagating waves of actin assembly in the cell cortex. Cortical excitability is best known for promoting cell protrusion and allowing the interpretation of and response to chemoattractant gradients in migrating cells. It has recently become apparent, however, that cortical excitability is involved in the response of the cortex to internal signals from the cell-cycle regulatory machinery and the spindle during cell division. Two overlapping functions have been ascribed to cortical excitability in cell division: control of cell division plane placement, and amplification of the activity of the small GTPase Rho at the equatorial cortex during cytokinesis. Here, we propose that cortical excitability explains several important yet poorly understood features of signaling during cell division. We also consider the potential advantages that arise from the use of cortical excitability as a signaling mechanism to regulate cortical dynamics in cell division.

Introduction

The cell cortex, classically defined as the plasma membrane and the thin layer of cytoplasm just beneath it, is the responsive interface between the cell and its surroundings¹. Because the information received by the cell assumes many guises — soluble signals, insoluble signals, contacts with neighboring cells, and contacts with the extracellular matrix, to name but a few — the cortex has a correspondingly diverse repertoire of behavioral responses, including extension or retraction of protrusions, formation of endocytic structures such as coated pits or macropinosomes, and construction of cell–cell and cell–substrate adhesions.

Even in the absence of external inputs, the cortex displays complex dynamic behaviors. Among the most intriguing of these is the propensity to generate propagating waves of assembling actin filaments (F-actin) and actin regulators, including small GTPases, phosphoinositides, and their various targets and regulators. This behavior can be loosely termed ‘cortical excitability’ and was originally described 20 years ago in motile cells of the soil amoeba *Dictyostelium discoideum*². Improvements in live-cell imaging and molecular probes have revealed that cortical excitability is a feature of not only motile cells³, but also nonmotile cells^{4,5}, embryos^{6,7}, and tissues⁸.

Cortical waves display several consistent features: the waves can propagate without losing amplitude; waves auto-annihilate, meaning that colliding wavefronts snuff each other out; and

waves can assume complex forms, including spirals and bull’s-eye patterns^{2–5,7,9}. Such behaviors are attributes of excitable media, although they can also be observed in oscillatory systems. Excitable media are continuous excitable systems with the capacity to respond locally to a suprathreshold stimulus by transitioning from a state of low activity (the ground state) to a state of high activity (excitation). Local excitation can then induce the transition to the excited state in neighboring parts of the medium. In this way, excitation spreads across the excitable medium as a traveling wave. After participating in a wave of excitation, the system returns to the ground state, where it remains for a characteristic period of time (the latent or refractory period) before it can be re-excited. At the mechanistic level, excitable systems are underpinned by fast positive feedback coupled to delayed negative feedback (Figure 1). Positive feedback rapidly drives the system into the excited state in an ‘all-or-none’ fashion and, from the standpoint of the waves, operates at their leading edges, advancing them; delayed negative feedback limits the duration of the excited state and, from the standpoint of the waves, operates at their trailing edge, shutting them off.

The classic biological example of an excitable medium is the neuron, wherein an electrochemical wave — the action potential — propagates down the axon. Here, the positive feedback is provided by membrane-depolarization-dependent opening of voltage-gated Na⁺ channels that, upon opening, let more Na⁺ into the neuron, thus further depolarizing the membrane. If the



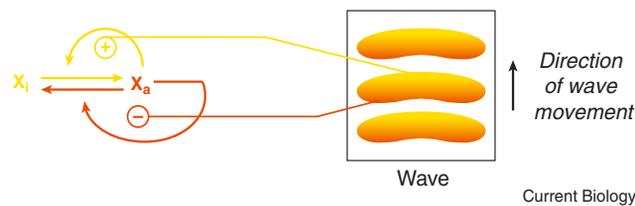


Figure 1. The basics of excitable media.

A schematic diagram of coupled positive feedback and delayed negative feedback. Player X transitions between inactive (X_i) and active (X_a) forms. The active player (X_a) engages in positive feedback, promoting more of its own formation. X_a also engages in delayed negative feedback, promoting its own inactivation. The positive feedback (yellow) dominates at the front of waves, driving the wave forward; the negative feedback (red) dominates at the back of the wave, terminating the wave.

initial stimulus pushes the membrane potential past the threshold, this positive feedback elicits complete, rapid depolarization, initiating an action potential. Negative feedback is provided by the delayed, membrane-depolarization-dependent opening of voltage-gated K^+ channels, which let K^+ out of the neuron, thereby promoting repolarization and inhibiting the propagation of subsequent action potentials until a resting state is reached. The role of excitability in neurons is well established: it is harnessed both to send information (in the form of the action potential) and to decide whether information should be sent. That is, the dendrites and cell body integrate stimulatory and inhibitory input from other cells and, if the membrane potential of the cell body reaches the threshold, an action potential is generated.

Experimental and modeling approaches have revealed that excitable dynamics play an important role in the behavior of the cortical waves of F-actin assembly and the corresponding waves of its regulators^{3,5,7,10}. However, in contrast to neurons, where excitability is carried by ions and ion channels, cortical excitability is carried by the cortical cytoskeleton and its regulators. There are, of course, other differences between neuronal excitability and cortical excitability. First, axons are essentially one-dimensional, meaning that the waves of membrane depolarization within axons are likewise one-dimensional. The waves that characterize cortical excitability, however, are two-dimensional, allowing them to assume the complex forms mentioned above. Second, signal interpretation by the dendrites and cell body of the neuron results in action potentials that arise consistently at the junction between the cell body and the axon, an arrangement that ensures that the action potential moves in one direction only. In contrast, the cortical waves can potentially arise anywhere and move in any direction, a behavior that leads to auto-annihilation as colliding waves move into the cortex in the latent state. Third, cortical excitability waves are distinctly less all-or-none than action potentials, displaying variation in amplitude in different parts of the cell and variation in response to different stimuli^{3,4,7,9}.

The nonlinearity and two-dimensionality of cortical excitability and the presence of multiple feedback loops (Figure 1) collectively defy intuition, rendering computational modeling an essential tool for further understanding of the process. Excitable dynamics are often modeled as reaction–diffusion systems, in which an activator stimulates more of its own

production via positive feedback, while also stimulating the production of an inhibitor that is responsible for negative feedback. The activator and inhibitor vary with respect to their diffusivity, with the inhibitor typically being more diffusible than the activator. Historically, activator–inhibitor systems were first proposed to explain static patterns that arise during development¹¹ and, independently, to describe chemical oscillations¹². More recently, it has become apparent that changes to the reaction mechanism and diffusion parameters in reaction–diffusion systems can produce a broad spectrum of static and moving phenomena, including stable patterns, excitable waves, and a great variety of oscillatory patterns¹³. Below, we first discuss the established role of cortical excitability in driving chemotactic cell migration; then we highlight newly revealed roles for cortical excitability during mitosis and cytokinesis and relate the advantages afforded by cortical excitability in chemotaxis to those in cell division.

Cortical excitability and cell locomotion

Cortical excitability is best known from studies of *D. discoideum*^{10,14} and neutrophils³. In *D. discoideum*, waves of F-actin and F-actin-binding proteins move throughout the cell cortex, apparently under the control of complementary waves of signals, such as the small GTPase Ras and phosphatidylinositol 3,4,5-trisphosphate (PIP₃)^{14,15}. Similarly, in neutrophils, cortical waves of F-actin and F-actin-regulatory proteins are associated with activation of their upstream regulators, such as the small GTPase Rac³. The feedback interactions among these various players in motile cells are extremely complex¹⁶ and, because they are inherently cyclic, delineating their interactions requires time-resolved manipulations¹⁷. Consequently, many models of cell locomotion subsume the interlocking subsystems (modules) into a single excitable network, to render modeling more tractable^{10,16}.

What is the benefit of cortical excitability in cell movement? Cortical excitability is harnessed by motile cells to generate cell extensions: waves of actin assembly, upon reaching the cell edge, transform into structures such as pseudopodia and lamellipodia that push the cell forward^{3,14}. One of the virtues of using an excitable, wave-based mechanism for cell protrusion is that it allows cells to migrate around obstacles³. That is, because excitable waves are normally extinguished when they are prevented from moving forward (due to the negative feedback catching up with the positive feedback), a wave-based mechanism provides the cell with the ability to ‘sense’ immovable barriers and crawl around them.

Excitability also, in effect, makes the cortex smart. That is, excitability is intimately linked to decision-making in locomoting cells, the key decision being in which direction to crawl¹⁶. In the absence of a chemoattractant, locomoting cells can extend the pseudopodia that arise from excitable dynamics in any direction, a behavior that results in random migration. However, in the presence of a gradient of chemoattractant, excitability becomes polarized, such that the front of the cell (i.e. the side facing the highest concentration of chemoattractant) generates more and higher-amplitude waves than the back of the cell^{3,18}. This results in preferential extension of pseudopods toward the source of chemoattractant and preferential suppression of pseudopod extension at the sides and rear of the cell.

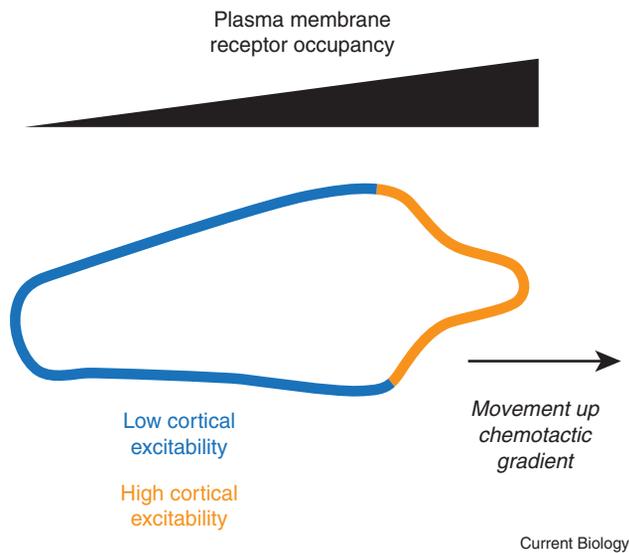


Figure 2. Cortical excitability and chemotaxis.

A schematic diagram of the relationship between the occupancy of plasma membrane chemoattractant receptors, cortical excitability, and cell protrusions. A gradual decline in receptor occupancy (black triangle) is converted into a sharp bias in cortical excitability such that the side of the cell facing the gradient has high excitability (orange), while the sides and back of the cell have low cortical excitability (blue). The high cortical excitability at the front of the cell results in movement of the cell up the chemoattractant gradient.

Excitability polarization in response to a chemoattractant is extraordinarily sensitive, such that the cells can persistently migrate up gradients that are as shallow as 1% (i.e. a 1% difference in exposure to chemoattractant from the front to the back of the cell¹⁶). Strikingly, the degree of excitability polarization is high, regardless of the steepness of the chemoattractant gradient¹⁹. In *D. discoideum*, this and other features of the chemotactic response are explained by the LEGI-BEN (local excitation-global inhibition biased excitable network) model. This model has been covered in several reviews (e.g. Iglesias and Devreotes¹⁰ and Devreotes *et al.*¹⁶) but the basic idea is that the excitable network is throttled by a response regulator that is under the control of chemoattractant-receptor binding. Binding of the chemoattractant to the receptor results in rapid production of a slowly diffusing stimulator of the response regulator and slower production of a rapidly diffusing inhibitor of the response regulator. This results in a higher stimulator:inhibitor ratio where receptor occupancy is high (i.e. at the front of the cell) and a lower stimulator:inhibitor ratio where receptor occupancy is low (i.e. at the sides and back of the cell). The consequence of this is that a shallow gradient of receptor occupancy is converted into sharp differences in local excitability, with high excitability at the front of the cell and low excitability at the sides and back¹⁶ (Figure 2).

Cortical excitability may also endow locomoting cells with the flexibility needed to generate a variety of different dynamic behaviors. For example, modeling studies indicate that excitable dynamics can be converted into bistable dynamics, meaning that the cortical palette of F-actin behavior can be considerably broadened to include coexisting standing F-actin waves and traveling F-actin waves²⁰. Further, manipulation of wave

dynamics via experimental interventions that impact the positive and negative feedback can result in profound alterations in cortical dynamics, such that cells can be driven from amoeboid motility to motile states that more closely resemble those of keratinocytes, involving cell locomotion via continuous extension of stable lamellipodia²¹.

Cortical excitability and mitosis

Thus, cortical excitability is an intrinsic feature of motile cells that can be modulated by external signals in the form of chemoattractants. Because other external signals can also significantly impact cortical excitability^{4,5}, it seems likely that external modulation of cortical excitability will prove to be a commonly utilized mechanism. However, a growing body of evidence indicates that cortical excitability is also responsive to internal signals, particularly during cell division^{7,9,22}. A recent study of mast cells revealed that around 5 minutes after nuclear envelope breakdown, a subset (~27%) of mitotic cells developed striking cortical waves of Cdc42 activity⁹. These ‘metaphase’ Cdc42 activity waves were accompanied by waves of cortical recruitment of the F-BAR protein FBP17 as well as waves of F-actin, and these waves assumed both bull’s-eye and spiral patterns (Figure 3A). The authors noticed that metaphase waves were more common in cells that were more adherent in mitosis. This correlation was strengthened by demonstrating that experimental upregulation of cell–substrate adhesions resulted in a doubling of the fraction of cells that displayed metaphase waves. Moreover, pharmacological inhibition of the metaphase waves with a Cdc42 inhibitor resulted in increased rounding of cells that had displayed waves prior to treatment, but not of cells without waves, implying feedback between the waves and cell–substrate adhesion.

What is the benefit of metaphase excitability? Strikingly, the center of the bull’s-eye or spiral waves consistently predicted the position of the future cleavage plane of the cells (Figure 3A). While this may not seem surprising, in that the wave centers were usually positioned in the center of the cell, which generally corresponds to the future division plane, this correlation also held in very large cells that underwent multipolar divisions: such cells formed multiple wave cores, each of which predicted a future division plane⁹.

This study prompts a number of fascinating questions. Firstly, how are the metaphase waves positioned? One possibility is that positioning is mediated by a gradient of Ran-GTP, which has been linked to furrow positioning in cultured cells²³. Secondly, how is it possible that the metaphase waves, which disappear at anaphase onset, specify furrow positioning, which occurs well after the start of anaphase? The authors suggested that the cortex retains a memory of the metaphase waves that somehow impacts events in anaphase. Although this point has not been directly tested, the possibility of a cortical memory is intriguing and mirrors ideas developed for crawling cells¹⁶. Thirdly, how exactly are the metaphase waves linked to cleavage-plane specification? Because the division plane is dictated by the orientation of the spindle, one possibility is that the Cdc42 waves somehow control spindle rotation. This notion is consistent with the observation that cells displaying metaphase waves showed more extensive rotations in anaphase than cells without metaphase waves⁹. A second, nonexclusive possibility is that the metaphase waves act more directly on the

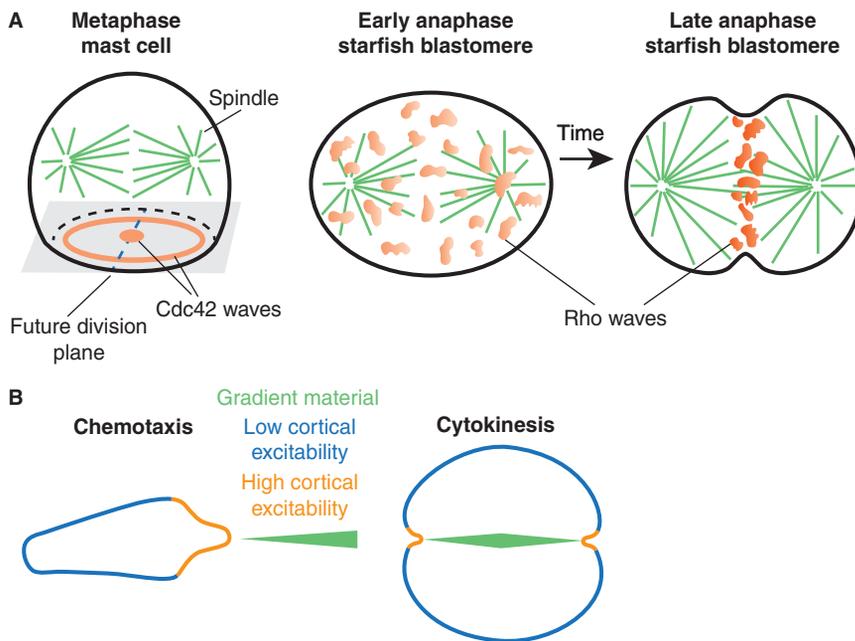


Figure 3. Cortical excitability in cell division.

(A) Wave organization in mitotic cells. Left: Schematic diagram of a metaphase mast cell showing the spatial relationships of the Cdc42 waves (orange), the mitotic spindle (green), and the future division plane (dashed blue line). Right: diagram of starfish blastomere showing changes in Rho waves (orange) between early and late anaphase. Over time, the waves are lost from polar cortical regions, while becoming concentrated and amplified (darker orange) at the equatorial cortex. (B) Cytokinesis as inverted chemotaxis. Left: Chemotaxing cell migrating up an external chemotactic gradient (green). As in Figure 2, excitability is high (orange) where the cortex faces the gradient and low (blue) elsewhere. Right: Cell undergoing cytokinesis with equatorial cortex ingressing up an internal chemotactic gradient (green). Excitability is high (orange) where the cortex faces the gradient and low (blue) elsewhere.

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specification of the cytokinetic apparatus. That is, direct comparison of metaphase waves to anillin, a marker of the cytokinetic apparatus, revealed that, while low-level, peripheral anillin waves were present in metaphase, these were largely excluded from cortical regions where Cdc42 waves dominated. Upon the transition to anaphase, however, anillin accumulated in these regions, coincident with the disappearance of the Cdc42 waves, suggesting that the two wave systems may antagonize each other.

Another fascinating finding is that metaphase excitability scales with cell size. Specifically, the authors demonstrated that the period and wavelength of the metaphase waves of Cdc42 and FBP17 are positively correlated with the basal surface area of the cell⁹. This finding not only explains why waves might be particularly useful — scaling allows the cell to ensure that furrow specification is normally singular — but also potentially explains the formation of multiple furrows in extremely large cells: once the cells exceed a certain size limit, multiple wave cores develop, resulting in the loss of furrow singularity. Alternatively, it may be that, beyond a certain size, multipolar spindles develop, resulting in multiple Ran-GTP gradients, which give rise to multiple wave cores.

While this study was limited to mast cells, there are hints that other cell types also have metaphase waves: in HeLa cells metaphase waves of cortical and subcortical F-actin have been reported²⁴, and cortical F-actin waves are present throughout the cell cycle in frog embryos⁷. There is also ample evidence that Cdc42 is important for control of cleavage-plane positioning in epithelial cells^{25,26}, although this has been proposed to reflect a role for Cdc42 in spindle positioning. Finally, from a technical standpoint, it would not be surprising if metaphase waves had been overlooked in previous studies, given that mitotic cells typically round up, making it more difficult to image the cortex at high spatiotemporal resolution.

Cortical excitability and cytokinesis

Cytokinesis in animal cells has long been conceptualized as an essentially linear process, in which the mitotic spindle elicits furrowing activity in the cortical annulus surrounding the spindle midplane. In cellular and molecular terms this means a set of spindle-derived cues activate the small GTPase Rho via the Rho guanine nucleotide exchange factor (GEF) Ect2, which is concentrated and activated near the equatorial cortex via a collaboration between microtubule geometry and the central-spindlin complex^{27,28}. Upon patterned activation of Rho at the equator, active Rho promotes actin polymerization and myosin-2 activation and recruits other components of the cytokinetic apparatus, such as anillin²⁹. After the apparatus has completed constriction, it is believed that Rho is inactivated by a GTPase-activating protein (GAP), and the apparatus disassembles. However, studies of the activated eggs and early embryos of the frog *Xenopus laevis* and the starfish *Patiria miniata* revealed a distinctly non-linear behavior of active Rho and F-actin during cytokinesis⁷. In *Patiria*, low-amplitude cortical waves of Rho activity and F-actin appear shortly after anaphase onset and become progressively concentrated and amplified at the cell equator (Figure 3A). Both concentration and amplification likely result from spindle-mediated redistribution of Ect2, given that depolymerization of microtubules after the concentration of Rho activity at the equator results in the dispersion of the waves and a reduction in their amplitude, and that overexpression of Ect2, which presumably saturates the spindle mechanisms involved in Ect2 redistribution, amplifies the nonequatorial Rho waves as well as those at the equator⁷. In *Xenopus*, while the spindle also concentrates and amplifies Rho waves at the equator in anaphase, nonequatorial F-actin waves persist throughout the cell cycle. Nonetheless, as in *Patiria*, Ect2 overexpression in *Xenopus* amplifies the nonfurrow Rho waves and drives them into overtly spiral forms. In both species, furrowing commences

even while Rho activity and F-actin remain wave-like within the cleavage furrow, although as the starfish blastomeres decrease in size equatorial Rho activity eventually appears as a continuous stripe rather than discrete wavefronts.

Cortical excitability in these cells is negatively regulated by cyclin-dependent kinase 1 (Cdk1) but to different degrees: high Cdk1 activity in prometaphase through metaphase terminates cortical excitability in *Patiria*, and Cdk1 inactivation at anaphase results in the reappearance of cortical excitability. Artificially arresting cells with high Cdk1 activity via expression of a nondegradable form of cyclin B results in suppression of excitability; this suppression is immediately lifted upon pharmacological inhibition of Cdk1. In *Xenopus*, cortical excitability is present throughout the cell cycle, but it can nonetheless be terminated by the expression of nondegradable cyclin B⁷.

In situations where Rho waves have high amplitude, as occurs naturally at the equator or throughout the cortex when Ect2 is overexpressed, Rho waves are ‘chased’ by waves of F-actin, such that where F-actin concentration is highest, Rho activity is waning. Moreover, local reduction of F-actin increases the amplitude of the Rho waves⁷. In light of these and other findings, a reaction–diffusion model based on Ect2- and Rho-dependent Rho positive feedback and delayed, F-actin-mediated negative feedback was developed. This model captured basic features of anaphase cortical excitability as well as microtubule-dependent concentration and amplification of Rho activity at the equator. The same model also explains the transition of Rho and F-actin waves at the equator to a uniform stripe of overlapping Rho and F-actin³⁰.

What is the benefit of cortical excitability for cytokinesis? Besides inducing furrowing, excitability provides a relatively straightforward way for the cell to ensure Rho flux. That is, there is good reason to think that Rho is not simply activated and left ‘on’ in Rho zones, but instead undergoes constant flux through the GTPase cycle^{31–34}. Cortical excitability accounts for this flux because the time the GTPase remains active is limited by negative feedback. From this standpoint, cortical excitability has the potential to explain two important but poorly understood features of cytokinetic signaling — its sensitivity, and its capacity for error correction. With respect to sensitivity, the induction of a Rho zone and a furrow normally depends on complementary signaling contributions from both the central spindle and the astral microtubules, but cells can nonetheless divide when one or other of these populations is experimentally compromised³⁵. Positive feedback arising from excitability could account for this sensitivity, by amplifying otherwise faint signals at the equatorial cortex, analogous to one of the roles of excitability in chemotaxis¹⁶. With respect to error correction, the experimental displacement of the spindle after furrowing onset results in disappearance of the original Rho zone (and furrow regression) and formation of a new Rho zone and furrow over the midplane of the repositioned spindle³⁶. This result can be explained by excitability in that the positive feedback between Rho and spindle-provided Ect2 would be lost upon spindle repositioning. Consequently, the negative feedback would rapidly efface the original Rho zone. Meanwhile, a new zone of cortical excitability would form in the newly defined cleavage plane due to the concentration of Ect2 by the spindle.

Another fruitful line of thought arises via the comparison of excitability in cytokinesis to excitability in chemotaxis. It was previously noted that some of the same players that adopt polarized distributions in migrating amoeba — phosphoinositide 3-kinase (PI3K), PIP₃ and the PIP₃ 3'-phosphatase PTEN — also adopt polarized distributions during cytokinesis, and this polarization is important for both cytokinesis and directed migration³⁷. If one grants that in both cases excitability drives cortical dynamics, a new idea emerges: furrow ingression as a form of inward-directed chemotaxis, with the cortex tracking a gradient of diffusible signal toward the center of the cell (Figure 3B). In this model, the microtubules are primarily responsible for shaping the gradient, while the cortex is responsible for interpreting the gradient. This may seem at odds with the manner in which cytokinesis is usually conceptualized, i.e. as the closure of a circumferential contractile ring. The standard conceptualization of cytokinesis can differ significantly from reality, however; for example, highly asymmetric furrow ingression is the rule in many cell types³⁸.

If cortical excitability allows the cortex to track a gradient of diffusible material to the spindle midzone, what is the diffusible signal? One reasonable candidate is Ect2 itself, which normally forms an internal gradient with its maximum at the spindle midzone as a result of its interaction with the centralspindlin component MgcRacGAP (e.g. Su *et al.*³⁹). If so, Ect2 would serve both as a critical participant in cortical excitability and as a soluble signal. One objection to this idea is that elimination of the spindle midzone by a variety of approaches eliminates the normal ladder of centralspindlin and Ect2 localization in the cell midplane, but fails to prevent cytokinesis³⁹. However, this objection is less potent than it seems: in the absence of a central spindle, centralspindlin and Ect2 can nonetheless accumulate on cortical, equatorial microtubules, forming a simulacrum of the central spindle just beneath the equatorial cortex and ahead of the ingressing furrow³⁹. Assuming that the furrow keeps pushing the simulacrum inward, the source of Ect2 remains in front of the furrow, analogous to a chemotaxing leukocyte hunting a bacterium and, occasionally, pushing it forward before it finally manages to engulf it. One of the virtues of such an inverted chemotaxis model is that it explains the results of experiments in which furrows that initially form away from the axis defined by the spindle midplane can nonetheless track toward the center of the cell⁴⁰, as well as experiments in which displacement of the spindle to one side of the cell produces a highly asymmetric furrow and Rho zone that somehow manage to split the cell in half³⁶.

Because the eggs, zygotes, and blastomeres of *Xenopus* and *Patiria* are large, and because frogs and starfish develop externally, it might naturally be wondered whether cytokinetic excitability reflects an evolutionary specialization. This point remains to be settled, but the following observations suggest that cortical excitability during cytokinesis may be broadly conserved. Firstly, 8-cell mouse embryos display traveling waves of cortical F-actin that have roughly the same spatiotemporal characteristics as those seen in early *Xenopus* embryos⁶. Secondly, in a study of cytokinesis in Ptk1 (rat kangaroo kidney epithelial) cells, depolymerization of microtubules just after the onset of anaphase results in the formation of traveling, Rho-dependent waves of cortical F-actin⁴¹. Thirdly, in mast cells treated with nocodazole and then driven into anaphase via Cdk1 inhibition, waves of

cortical Rho activity and anillin recruitment develop⁹. We interpret these results to indicate that, as in *Xenopus* and *Patiria*, the spindle confines cortical Rho activity waves, but in these smaller cells the microtubules more rapidly reach the cortex, making the initial development of anaphase cortical waves difficult to detect. Depolymerization of microtubules in anaphase thus unmask the excitability of the cortex.

Future perspectives

Excitable dynamics are fun — indeed, exciting — to observe, and they tempt one to ascribe functional and interesting roles wherever such behaviors emerge: from cortical or electrical excitability in cells, to migrating swarms of soil amoebae, bees on their hives, or soccer fans. Yet as every heart patient or migraine sufferer can likely attest, excitability is not universally welcome; in many contexts, excitability is a potentially disastrous liability of systems that entangle positive and negative feedback for the sake of coordination, sensitivity, or homeostasis. In other cases, excitability may be only an epiphenomenon with no functional role, good or bad. But even core traits of living organisms, like the citric acid cycle or microtubule dynamic instability, were once epiphenomena too; emergent traits of complex systems for which evolution found an adaptive value. In the case of cortical excitability, it may be that in some cells or in some contexts this behavior is irrelevant or even pathological, but in others it has clear functional roles. Direct tests of adaptive significance are thus a high priority.

Regarding the role of cortical excitability in cell division, many critical pieces of mechanistic detail are missing. Currently, we have almost no information on the feedback mechanisms that result in metaphase excitability. Further, for the working model of the cytokinetic excitability circuit, the basis of the proposed positive feedback between Ect2 and Rho is unknown. It could be direct: it was recently shown that Ect2 has a binding site for active Rho independent of its GEF domain⁴². Upon binding to active Rho, Ect2 autoinhibition is relieved, increasing GEF activity. Similarly, the basis of negative feedback between F-actin and Rho is unknown. A promising candidate is ARHGAP11a (also known as RGA3/4 and MPGAP), which negatively regulates Rho during *Caenorhabditis elegans* and HeLa cytokinesis^{34,43}, and which is associated with delayed, F-actin-dependent negative feedback during pulsed contractions in *C. elegans*⁴⁴.

Based on comparisons to chemotaxis, it also seems certain that the core cytokinetic excitability circuit sketched above is excessively simplistic. Indeed, other feedback loops are thought to exist in cytokinetic signaling^{45,46}; it will be important to determine how they connect to the core circuit. Additionally, it will be useful to consider other well-known cytokinetic proteins such as MgcRacGAP (also known as Cyk-4) through the lens of cortical excitability. That is, the role played by this protein in cytokinesis has proven controversial^{32,47–50}; perhaps this reflects the inherent difficulty in assigning an epistatic role to a participant in what is apparently a cyclical network rather than a linear pathway.

Finally, recent studies of motile cells indicate that excitable circuits enable a diversity of motile behaviors that may be selectively expressed depending on the constraints imposed by the cell's environment^{20,21}. Cell division is also subject to various constraints based on cell size, cell–cell adhesions, tissue

mechanics, and spindle orientation, all of which vary dramatically between organisms and over the course of development and disease. It will be of great interest to determine whether specific features of excitability, such as wavelength and period, show consistent variation in different cellular contexts.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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