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# Traveling waves in actin dynamics and cell motility

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Much of current understanding of cell motility arose from studying steady treadmilling of actin arrays. Recently, there have been a growing number of observations of a more complex, non-steady, actin behavior, including self-organized waves. It is becoming clear that these waves result from activation and inhibition feedbacks in actin dynamics acting on different scales, but the exact molecular nature of these feedbacks and the respective roles of biomechanics and biochemistry are still unclear. Here, we review recent advances achieved in experimental and theoretical studies of actin waves and discuss mechanisms and physiological significance of wavy protrusions.

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## Introduction

Actin polymerization endows eukaryotic cells with, among other things, the ability to migrate and modulate cell shape [1]. Usually, cell migration is dissected into discrete steps: first, protrusion based on actin growth and polymerization force, second, adhesion at the front, third, actin–myosin-powered contraction of the cytoplasm, fourth, release of adhesions at the rear, and fifth, forward translocation of the cell body and recycling of the motility machinery [2]. Yet, much of our understanding of cell motility stems from studies of steadily and continuously treadmilling dendritic actin arrays in flat lamellipodia, in which nascent actin filaments are branched by Arp2/3 complex from the sides of existing elongating filaments pushing the leading edge forward until capped, while across the lamellipodium the capped filaments are disassembled by cofilin [3,4••]. However, more often than not, cells in physiological circumstances move unsteadily, and so actin also exhibits a range of non-steady behavior including spatiotemporal patterns [5] for which our understanding is just beginning. A beautiful and paradigmatic example of such behavior comes from recent reports of actin traveling waves (t-waves).

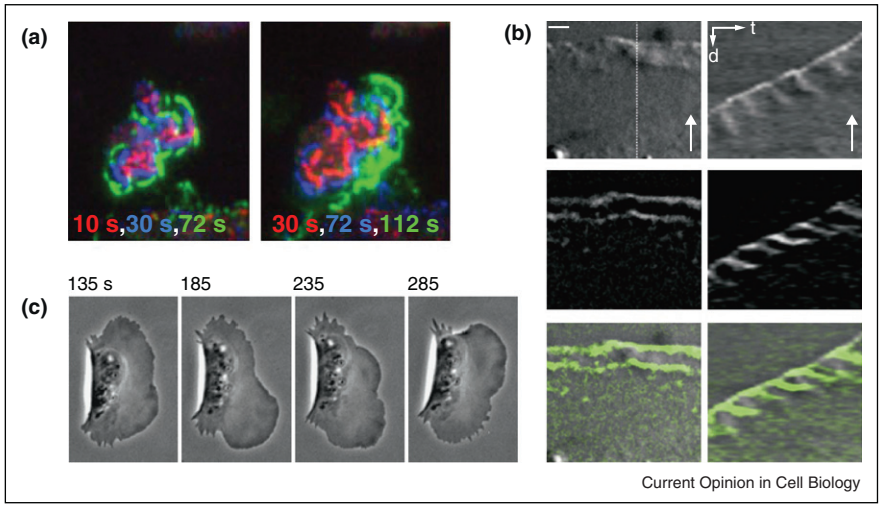
Early reports of actin t-waves traveling around the perimeter of human keratinocytes [6] and other cells types [7] preceded a recent windfall of reported t-waves [8••,9•,10••,11••,12••,13•,14•]. Remarkably, one of the early reports posited that nonlinear mechanics of actin–myosin gels is responsible for the waves [6], while another proposed an underlying biochemical reaction-diffusion system [7]. The recent boom of actin t-waves studies was arguably triggered by reports that the Arp2/3 activator Hem-1 is not distributed uniformly on the ventral surface of neutrophils but rather exhibits irregular, F-actin-dependent t-waves that move toward the cell periphery [9•] (Figure 1a). In fibroblasts, local oscillations of protrusion and retraction at the edge are associated with waves of actin, myosin light chain kinase and alpha-actinin [14•,15] that travel both rearward and laterally along the cell perimeter (Figure 1b). Fish epithelial keratocytes exhibit robust t-waves of F-actin density and protrusion that travel along the leading edge [10••] (Figure 1c). When Dictyostelium cells are held away from a substrate, either electrostatically or by extending off a cliff, they exhibit rearward waves of curvature and protrusion [12••].

T-waves extend across subcellular domains (Table 1) that may be the 1D cell edge [8••,16]; 2D ventral [9•,17,18] or dorsal [7] surfaces, or even 3d bulk of the cytoplasm [11••]. Wave-like patterns are reported in a variety of cell types, with some spreading [19], migrating [10••] or stationary [8••], and classifying these patterns and identifying common mechanisms are a daunting task. Major questions about the actin t-wave dynamics include: What combination of positive and negative feedbacks gives rise to t-waves? Do both mechanical and chemical pathways participate in t-waves? Given the diversity of cells exhibiting t-waves, do these patterns play a functional role? We complement a number of recent reviews, (see especially [5]), by outlining conceptual wave-generating mechanisms and the evidence for each in various cell types. We demonstrate that though actin t-waves appear to be highly cell-dependent, recent quantitative modeling, spawned by the need to augment qualitative arguments [20], demonstrates how this diversity is reconciled by the concept of excitability.

## Diversity of mechanisms leading to traveling waves

Waving behavior is ubiquitous from population dynamics [21] to chemical reactions [22] to excitable waves in

**Figure 1**




Experimental observations of actin traveling waves. **(a)** Waves of YFP-Hem1 on the ventral surface of neutrophils (reproduced from [9•] under the CCA License). Time is indicated by color as the wave spreads outward. **(b)** Rearward waves of alpha-actinin in fibroblasts shown in micrograph (left) and kymograph (right) (reproduced from [14•] with permission). Scale bars 2 μm, 30 sec. **(c)** Wave of protrusion across the keratocyte's leading edge (provided by E. Barnhart).

electrophysiology [23]. The concept of excitability (see Box 1) has provided valuable insight into actin t-waves. Evidence that a diversity of actin waves is well-described as excitable systems comes from, among other things, observations that they annihilate upon collision [9•,11••,24], which is a signature of excitation waves. One way of obtaining excitability is by combining fast positive feedback coupled with slow negative feedback.

*Triggering each wave*: Once a system is capable of supporting excitation waves, in general each wave requires a perturbation to 'kick-start' it (Box 1, Figure 2ai), which must be greater than a threshold. A cell may transition into waving by upstream signaling events, such as activation of adhesions and consequent triggering of biochemical pathways. However, the simplest hypothesis for the source of this perturbation is a random fluctuation [8••,25] in F-actin densities or concentrations of factors, possibly arising from inhomogeneities in the environment or thermal fluctuations. There is a narrow window for which random fluctuations are consistent with observed t-waves though: Too little, and fluctuations above the threshold will be rare; too large, and threshold fluctuations will effectively send the system into an oscillatory state in which t-waves are replaced by spatially synchronized oscillations.

An alternative, more robust, kick-starter is a global negative feedback, which may be provided by membrane tension [26] or fast-diffusing inhibitors [27]. Under appropriate circumstances, localized excitations of F-actin occur spontaneously (e.g., if the system is in an oscillatory regime). This could activate global negative feedback, transforming the localized activity into the seed of a t-wave. Recent observations of t-waves in keratocytes [28] demonstrate sequential waves, in which the subsequent wave appears shortly after the previous wave extinguishes. Global negative feedback is necessary for cells to have this apparent ability to limit themselves to one concurrent wave.

*Spatial coupling*: Regardless of the triggering mechanism, a t-wave requires a connection between neighboring subcellular regions. What mediates this spatial coupling? Three possibilities are summarized in Figure 2aii. The most widely hypothesized spatial coupling is the diffusion of an actin regulator molecule (see Table; Figure 2aii b) that either promotes or inhibits F-actin polymerization or branching. Such t-waves fall into the class of reaction-diffusion systems and their propagation velocity is proportional to the square root of the regulator's diffusion coefficient [29], and also depends on the timescale of the regulator's turnover, which could vary spatially and thus give rise to a spatially dependent wave velocity as observed by Weiner *et al.* [9•]. Evidence for the identity of this regulator in various cells includes various actin nucleating factors such as Hem1 [9•].

An alternative possible spatial coupling arises from F-actin polymerization itself (Figure 2aii a). For example, Arp2/3-mediated branching of filaments occurs at ±35 degrees relative to the direction of actin network growth, so the protrusion is accompanied by the lateral propagation of the barbed end along the leading edge, allowing the possibility of propagating a t-wave. Coupling by polymerization predicts a wave propagation velocity that

is not proportional to the square root of the diffusion coefficient of a chemical, but to the protrusion velocity, which has been confirmed in high-adhesion keratocyte waves [28].

A third possibility is that neighboring regions are mechanically coupled, and F-actin affects a regional increase in stress (Figure 2aii c). Several possibilities exist for what mediates the stress. One is the actin gel itself [30,31]. Another possibility involves membrane advancement or retraction, either in combination with membrane proteins that prefer membrane curvature [25] or simply by itself, which exerts additional stresses on nearby filaments by compression or stretching, if they are membrane-anchored [32]. Each of these has been theoretically shown to allow for t-waves. A recent study [33••] reconstituted actin and myosin in an *in vitro* assays with profilin, Arp2/3 and its activator and observed t-waves of contraction and depolymerization in which myosin was an essential player. In stress-mediated t-waves, the wave propagation velocity would be proportional neither to the square root of the diffusion coefficient of a chemical, nor to the actin polymerization rate, but to some function of the mechanical moduli of the cytoskeleton. Using this distinction for experimental testing of the t-wave mechanisms may be complicated, as cell interiors are connected by a combination of all spatial couplings discussed above, each of which may generate a t-wave with a distinct propagation velocity. Theoretically speaking, the coupling that is fastest and capable of supporting excitable t-waves should be the one observed in a given cell. Note also that in contrast to well-studied examples of excitable media, actin polymerization phenomena are coupled to a phase transition, that is, drastic changes in the transport and mechanical properties of the actin network. How this coupling affects the actin wave dynamics is an open question.

*Terminating the excitation behind the wave*: Once the wave has passed a subcellular domain, the region has to return to a steady state in which it can support future excitation. A favored mechanism to explain termination behind the wave is depletion (or accumulation) of an F-actin promoter (inhibitor) on a slower timescale, giving rise to a refractory period after excitation during which the promoter (inhibitor) replenishes (depletes). Without this, t-waves would manifest as t-wave fronts (Box 1) permanently invading the domain and remaining in the excited state. Progress has been made in identifying these 'refractory' factors: In high-adhesion keratocyte t-waves [10••], recent evidence suggests that it is a depletion of VASP and subsequent decrease of an anti-capping activity that extinguishes the actin protrusion [28]. Some models [8••,9•] hypothesize that the accumulation of the F-actin down-regulates a barbed-end nucleation factor, identified as Hem1 [9•]. Machacek *et al.* [13•] suggest the depletion of G-actin or Arp2/3 as the effective inhibitor.

*Traveling waves from non-excitable sources*: One alternative to excitability for inducing t-waves is to use local oscillations as pacemakers [15]. Examples of pacemaker waves in other areas of biology include segmentation clocks in development [34] and rippling in bacterial colonies [35]. In such systems, a region (e.g., the leading edge) undergoes periodic, intrinsic oscillations, and these oscillations are transmitted by advection to neighboring regions (e.g., by retrograde flow) [15]. In this case, the t-wave velocity is the velocity of advection. Evidence for similar pacemaker waves in actin is reported in epithelial cells [15], where these waves originate from cycles of protrusion and retraction at the leading edge and travel rearward at the velocity of retrograde flow. We note that in order for pacemakers to result in robust t-waves, regions away from the pacemaker must not be intrinsically oscillatory,

**Box 1 Excitable dynamics.**

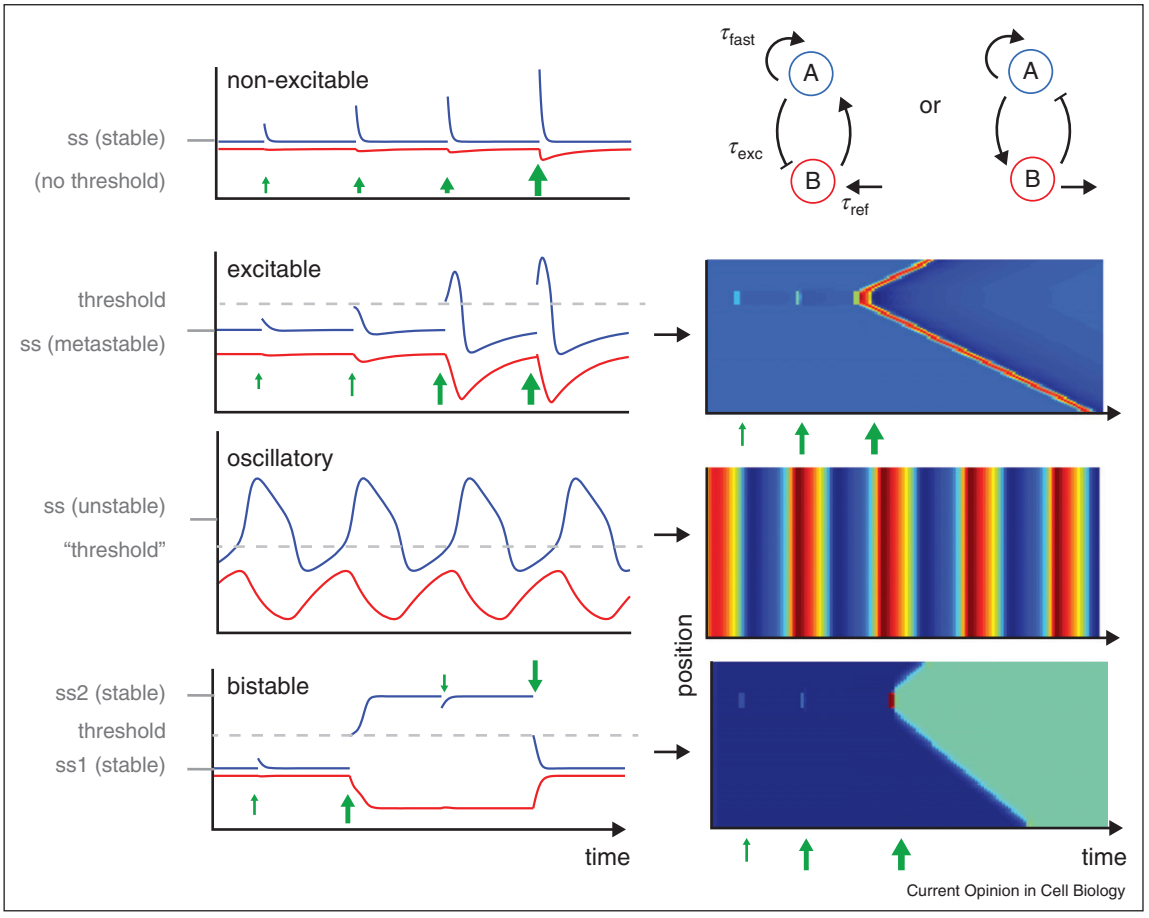
Fast positive feedback combined with slow negative feedback is a motif that recurs in many biological systems. An example is a fast component *A* being local actin *barbed-end* density, and a slow component *B* being local density of an F-actin promoting factor or density of F-actin itself [8••,9•]. For some parameters, such a system has a unique stable steady state in which a stimulus in *A*, regardless of size, decays without significantly affecting *B*. By varying parameters, for example increasing the replenishment rate of *B*, the steady state of *A* is made less trivial and can give rise to a range of dynamics including excitability, oscillation and bistability (Figure B1).

Excitability arises from a steady state in which small perturbations decay, but perturbations larger than a threshold result in a large excursion that eventually, albeit indirectly, returns to the original steady state. The time taken to recover is known as the **refractory period**. Increasing the replenishment rate of *B* further effectively increases the steady state of *A* above the threshold; large excursions occur spontaneously and the system is **intrinsically oscillatory**. **Bistability** is when there are two stable steady states; perturbations larger than a threshold send the system into a different state.

When local dynamics are spatially coupled between neighboring areas, excitability allows for **traveling waves pulses**, while bistability allows for **traveling wave fronts** (Figure B1). In both cases, threshold perturbations are required somewhere in the domain to initiate the excitation, which spreads in all directions if prior conditions are spatially homogenous. Two colliding excitable waves annihilate, since each wave is trailed by a refractory region, making these distinct from, for example, pressure waves. A **wave train** is a sequence of wave pulses; under certain conditions, oscillatory dynamics with spatial coupling give rise to wave trains [36], however these trains are not robust and often transition to synchronized oscillations [54].

Cellular wave-generating systems have more than two participants and multiple spatial couplings, but the above simple cases provide a framework for understanding more complex systems, for example, which include long-range dynamics mediated by fast-diffusing regulators [27] or membrane tension [26] and which display exotic behaviors including 'bipedal' oscillations in which two domains oscillate out of phase evocative of recent observations in cells [55], wave fronts that become 'pinned' inside the domain [56,57], reflecting waves [27], periodic wave trains [28] and t-waves with dead zones [16].

**Figure B1**




Biochemical networks (top right) comprised of fast positive and slow negative feedbacks can exhibit qualitatively different behavior (time series, left) depending on parameters, on several timescales. Blue and red curves show behavior of molecular species A and B respectively. Steady state values of A marked by ss. Green arrows are external stimuli which instantaneously increases A and, if above a threshold (dashed lines), may relax to the only steady state, induce transient excitations in excitable systems, switch to a new steady state in bistable systems, or start fluctuating in oscillatory systems. In a region of space where each location exhibits the local dynamics shown on the left, as well as a spatial coupling to neighboring locations, spatiotemporal patterns of pulse wave, spatially uniform periodic oscillations, or wave of invasion emerge (kymographs, right).

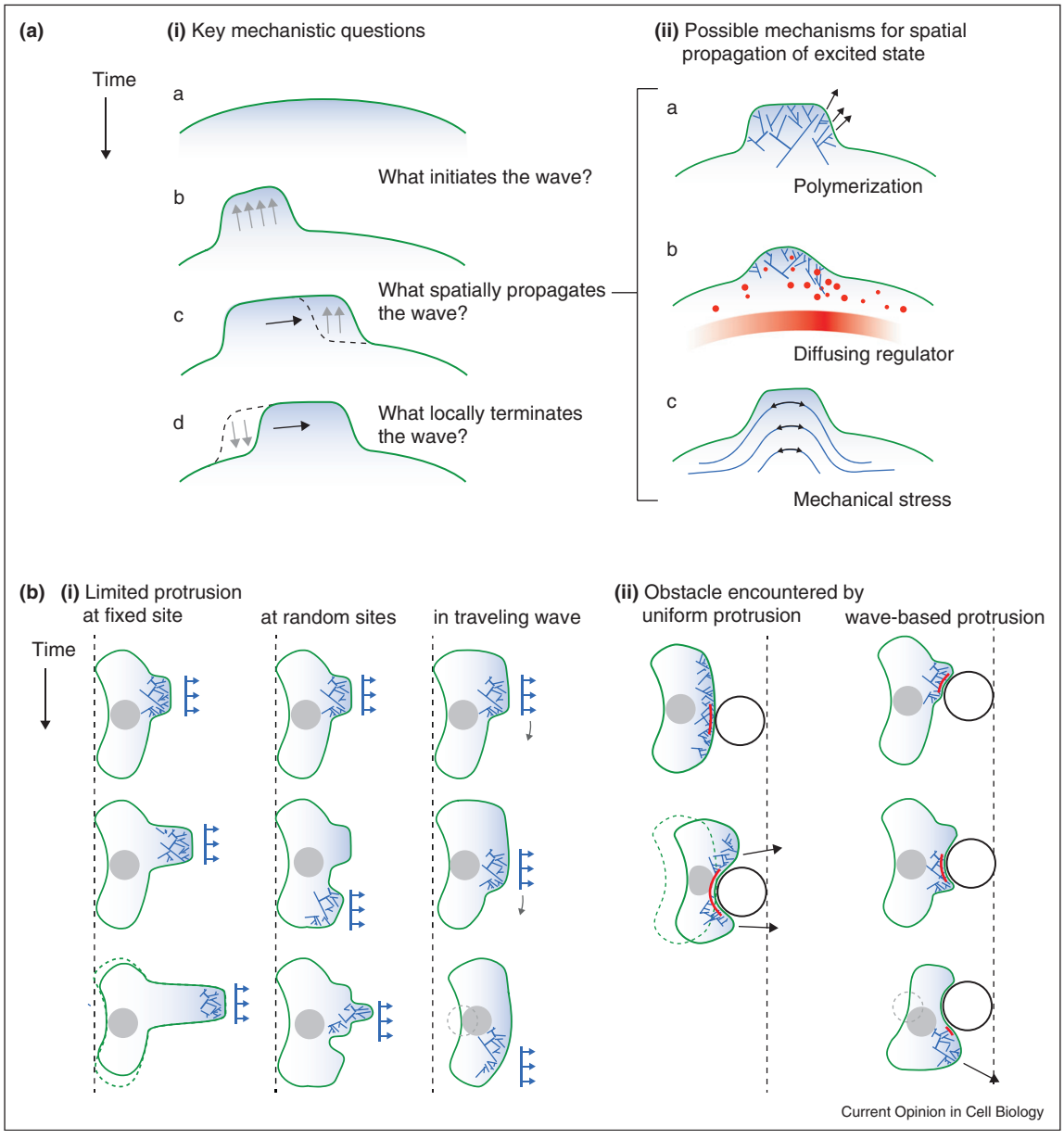
otherwise the domain will gradually settle into a synchronized oscillation (Box 1). (Under narrow circumstances, intrinsic oscillations can avoid synchronization and exhibit t-waves [36].)

A dramatic example of t-waves occurs in some blebbing cells [37]. Blebs are regions of the plasma membrane that have become transiently detached from the underlying actin cortex and bulge outward under cell pressure. Occasionally, a bleb migrates around the periphery of a cell in what is termed bleb circus movement [37]. These can be thought of as anti-actin t-waves, since the excited state is one in which actin is absent from the plasma membrane. Evidence suggests that spatial propagation is via pressure in the cytosolic fluid and refraction occurs when enough cortical actin and myosin have accumulated to retract the trailing edge of the bleb. These blebs appear to play a role in several instances of cell migration [38].

## Functional role and physiological implications of actin traveling waves

*Motility when protrusive machinery is scarce*: If t-waves arise from such a diversity of mechanisms in a diversity of cell types, do they play a functional role that confers evolutionary fitness? One speculative idea concerns how cells respond when they do not have sufficient material to form a protrusion along their entire leading edge. This limiting material may include total actin, ingredients for focal adhesions, or actin-regulating proteins such as VASP. If an environmental or intracellular perturbation depletes this material, for example by moving to a higher adhesion surface [28], there are two possible cellular responses: If

**Figure 2**




Major questions. **(a)** Mechanisms of waving: (i) T-waves arising from excitability require an initial trigger, typically above a threshold, to initiate a wave (a, b). Once one subcellular region is excited, neighboring regions must be coupled for the wave to propagate (b, c). Many cells exhibit transient wave pulses, after which the region returns to its initial state (c, d). This return is posited to arise because of the depletion of a promoter or replenishment of an inhibitor. (ii) Three possible spatial couplings. (a) Polymerization of actin with a lateral component could transport the excited state. (b) Diffusion of a regulator. (c) Transmission of stress to neighboring regions. The stress could be mediated by the membrane or actin(-myosin) gel. **(b)** Possible functional roles of waving. (i) Migration in the face of limited resources. Unable to protrude uniformly along the entire leading edge, cells may focus their protrusive machinery to a limited region. If this region is stationary (a), protrusion may result in fingering and translocation of the cell body will not occur. (An alternative is narrowing of the migrating cell.) If the protruding region moves randomly (b), cell coherence could be jeopardized. A sequence of traveling waves (c) results in smooth translocation of the cell body, without affecting cell width. (ii) Avoidance of obstacles. A uniformly protruding leading edge could become stuck upon encountering an obstacle (black circle) if the stalled region (red) has no effective means of communicating with nearby regions of the edge. Waves of protrusion may circumvent this problem since the direction of cell migration is defined locally.

slight decreases in material result in a slightly hampered protrusion (i.e., the protrusive material is linear), then the cell can uniformly distribute the limited supply and suffer a slightly hampered migration. If, however, the protrusive machinery is highly nonlinear and there is a threshold below which the protrusion is entirely inhibited, migration requires the cell to concentrate its limited supply, resulting in a small region of protrusion

**Table 1**

**Traveling waves in observation and theory. We attempt to classify experimentally observed actin and protrusion t-waves by the wave propagation mechanism. Theoretical models are classified by the dominant spatial coupling that gives rise to spatial propagation. Note that we classify papers containing both theoretical models and experimental results under 'experimental'.**

| Spatial propagation | 1D domain | 2D or 3D domain |
|---|---|---|
| Diffusion | | |
| exp | Leading edge waves in XTC cells [8••]<br>Membrane bound regulator waves in [24]<br>Circular dorsal ruffles in fibroblasts [58]<br>Rac waves in fibroblasts [50]<br>Rho waves upstream of actin in PtK1 [59••] | Hem-1 in neutrophils [9•]<br>Reaction-diffusion waves in Dicty [60–62], fibroblasts and melanoma [7]<br>Circular dorsal ruffles in fibroblasts [58] |
| theory | Circumferential reaction-diffusion [16]<br>Fast-diffusing inhibitor [27]<br>Rac diffusion [63] | Cellular Potts [64]<br>FitzHugh-Nagumo based [65] |
| Polymerization | | |
| exp | Leading edge waves in keratocytes [10••,28] | Dicty recovery after latrunculin [11••,17,45,66,67] |
| theory | | Dendritic nucleation [4••]<br>Hem-1 [68] |
| Experimental, Yet to be classified | Rearward curvature in Dictyostelium [12••]<br>Contraction in fibroblasts [19]<br>Keratinocytes [6] | |
| Stress (all 1D so far) | | |
| exp | Fibroblast and PtK1 cells [13•]<br>*In vitro* actin [33••]<br>Bleb circus movement [37] | |
| theory | Membrane curvature [25,69,70]<br>Stress mediated by membrane [32,71,72]<br>Stress in F-actin gel [30] | |
| Pacemaker (all 2D so far) | | |
| exp | | Lamellipodial contractions in fibroblasts [14•,15] |
| theory | | Focal adhesion formation [51] |

(Figure 2bi). Assuming that overall cell geometry is preserved, moving the protrusion by employing a t-wave would result in successful, albeit slow, translocation of the cell body. In comparison, protrusion at a fixed site would result in a finger-like protrusion without cell body translocation, and protrusion at random sites may jeopardize cell coherence. The question of how cells respond to a shortage of protrusive machinery is intimately linked to the mechanism determining cell width [39]. Indeed, in some circumstances cells may respond to limited protrusive machinery by becoming skinny (Figure 2bi left row), obfuscating this hypothesized need for protrusive t-waves.

*Obstacle avoidance*: An attractive hypothesis put forward by Weiner *et al.* [9•] is that, in the presence of obstacles, cell migration is favored by a wave-based form of protrusion rather than a uniform protrusion (Figure 2bii). The in situ environment of many cells is indeed crowded. The conceptual idea is that, in the case of uniform protrusion, a barrier that stalls a region of the cell's leading edge may stall the entire cell or threaten cell coherence. Alternatively, if protrusions arise from waves with some degree of randomness, the leading edge will explore alternative routes around the obstacle. Indeed Bretschneider *et al.* [11••] describe ventral waves as a 'free-running actin assembly in search of a leading edge'. Cell strategies for avoidance were addressed in a recent theoretical study [40], where the authors simulated a cell that secretes a repellant to accelerate obstacle-avoidance. Similar simulations with wave-based protrusion will help to resolve whether t-waves play a role in obstacle avoidance, which for now remains a thought experiment.

*'Chimneying' through 3D ECM*: Another possibility is that protrusion waves at the cell sides act as paddles allowing cells to swim through viscous media [12••]. This could be especially important for cells crawling through the 3D extracellular matrix (ECM): even though the ECM is not viscous, but rather elastic or viscoelastic, the t-waves at the cell sides could press on the ECM fibers and help the cell to 'chimney' through ECM pores, for example if adhesion to ECM is insufficient [41]. Actin t-waves could also aid in the search for larger ECM pores for protrusion.

Other oscillatory mechanical strategies in 3d motility have recently been considered [42].

*A side-effect of local excitability*: It is possible that t-waves do not directly confer evolutionary advantage, but rather are a side effect of local excitable dynamics which, when combined with the unavoidable spatial coupling, naturally give rise to t-waves (Box 1). The concept is similar to oscillations during the polarization of budding yeast [43], in which negative feedback confers robustness to the polarity cue, and the observed oscillations are a natural side effect of negative feedback. What could be the role of excitability? If F-actin's effects are highly nonlinear, then rapid, localized spikes in local F-actin density may be favored over a lower uniform density. Recent work [44] demonstrates that mechanisms for directional sensing leading to polarity in migration, such as local-excitation global-inhibition, can be made more responsive when coupled with local excitable dynamics, and that explains observed alternating 'zig-zag' protrusion patterns.

*Other possible functional roles* include: first the possibility that actin waves scan a surface for particles that might be engulfed during phagocytosis [45], based on the observation that the phosphoinositide content of actin waves resembles the interior of phagocytic cups; second, effective closure of cell wounds by a centripetal wave of F-actin, Cdc42 and Rho recently shown to occur in the absence of contractility [46].

## Open questions and future directions

Actin t-waves are observed *in vitro* [33••,47], and one of the open questions is about the connection between these *in vitro* waves and those in the motile cells. If there is a such connection, *in vitro* reconstitution will help understanding the minimal ingredients required for generating t-wave behavior. More generally, the molecular pathways underlying non-steady actin dynamics will have to be elucidated. These include the recently discovered 'rocket launcher' mechanism which involves a delicate balance of interactions between actin filaments, formins on growing barbed ends and the tumor suppressor adenomatous polyposis coli that jump-starts actin growth [48], as well as the complex interactions of actin dynamics, contractility and adhesion, which generate oscillatory behavior on many scales, from filopodia [49], to leading edges of flat protrusions [14•,50–52], to whole-cell traction forces [53]. Of particular importance will be to analyze actin t-wave in 3d and to test their functional roles. Last but not least, quantitative understanding will require continuing collaboration between experimentalists and modelers, which proved to be crucial in the initial surge of the actin t-wave studies of the past decade.

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After observing waves of protrusion at the lamellipodial leading edge and finding that they are driven by fluctuations of the actin polymerization rate, rather than by the retrograde flow, the authors propose a model of these actin dynamics as an excitable system in which a diffusive, autocatalytic activator causes actin polymerization. As Arp2/3-complex concentrations spiked several seconds before rise of F-actin concentration, the authors suggest that the Arp2/3 complex participates in an activation mechanism that includes additional diffuse components, while F-actin accumulation inhibits further activator accumulation.

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In this seminal paper that started the current actin waves' boom, advanced light microscopy was used to follow the distribution of Hem-1, which is WAVE complex that activates Arp2/3 in neutrophils. The authors found that Hem-1 does not moves laterally, but exhibits complex cycles of activation and inhibition to generate waves of propagating Hem-1 and actin assembly. F-actin dynamics was essential for the waves, which annihilated upon collisions and showed zones of inhibition between consequitive waves. On the basis of analogy with previously studied waves in excitable systems, the authors suggested that mechanisms similar to those generating the action potentials in neuronal signaling are responsible for the actin waves that potentially explain the ability of cells to flow around barriers.

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Fish keratocytes that for decades were renown for their fast and steady protrusions exhibited traveling waves of protrusions when crawling on highly adhesive surfaces. The waves usually started at one side of the cell, propagated in 100–400 sec to another side and extinguished, after which another wave started. Interestingly, the wave lateral propagation speed was similar to the actin polymerization speed hinting that it is skewed growth of actin filaments rather than a biochemical oscillator coupled with diffusion that underlies the waves. The authors propose that a competition of the actin protrusion machinery with mature adhesion complexes for an unidentified molecular regulator is necessary for these protrusion waves.

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The authors find that myosin pulls the rear of the lamellipodial actin network (which appears to sit above the lamellum), causing upward bending and edge retraction. The network then separates from the edge and condenses. Protrusion resumes as lamellipodial actin regenerates from the front and extends rearward until it reaches newly assembled myosin, initiating the next cycle. Thus, actin polymerization periodically builds the lamellipodium, connecting myosin motors with the initiation of adhesion sites, suggesting that the actin oscillator and retrograde waves are mechanical in nature.

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