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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).

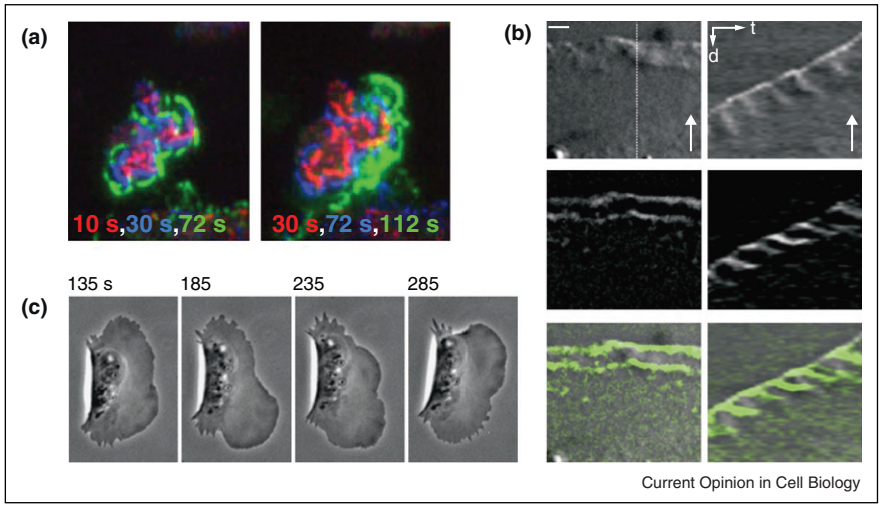
Early reports of actin t-waves traveling around the perimeter of human keratinocytes [6] and other cells types [7] preceded a recent windfall of reported t-waves [8••,9•,10••,11••,12••,13•,14•]. Remarkably, one of the early reports posited that nonlinear mechanics of actin–myosin gels is responsible 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