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Biased excitable networks: how cells direct motion in response to gradients

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The actin cytoskeleton in motile cells has many of the hallmarks of an excitable medium, including the presence of propagating waves. This excitable behavior can account for the spontaneous migration of cells. A number of reports have suggested that the chemoattractant-mediated signaling can bias excitability, thus providing a means by which cell motility can be directed. In this review, we discuss some of these observations and theories proposed to explain them. We also suggest a mechanism for cell polarity that can be incorporated into the existing framework.

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Introduction

How cells sense and move along chemical gradients, referred to as directed migration or chemotaxis, is one of the fundamental questions in cell biology. This fascinating process plays a crucial role in normal physiological as well as pathological events, from the proper functioning of the immune system to cancer metastasis [1]. Research into chemotaxis is also an area where collaboration between experimental and computational biologists has been fruitful, leading to an increasing number of models that explain many aspects of the response [2,3••]. A consensus has emerged that in order to understand chemotaxis, we must be able to answer several separable but interrelated questions [4]. What drives spontaneous cell motility? How do cells read external chemoattractant gradients? How do the external cues direct the otherwise random motility? How do cells become polarized?

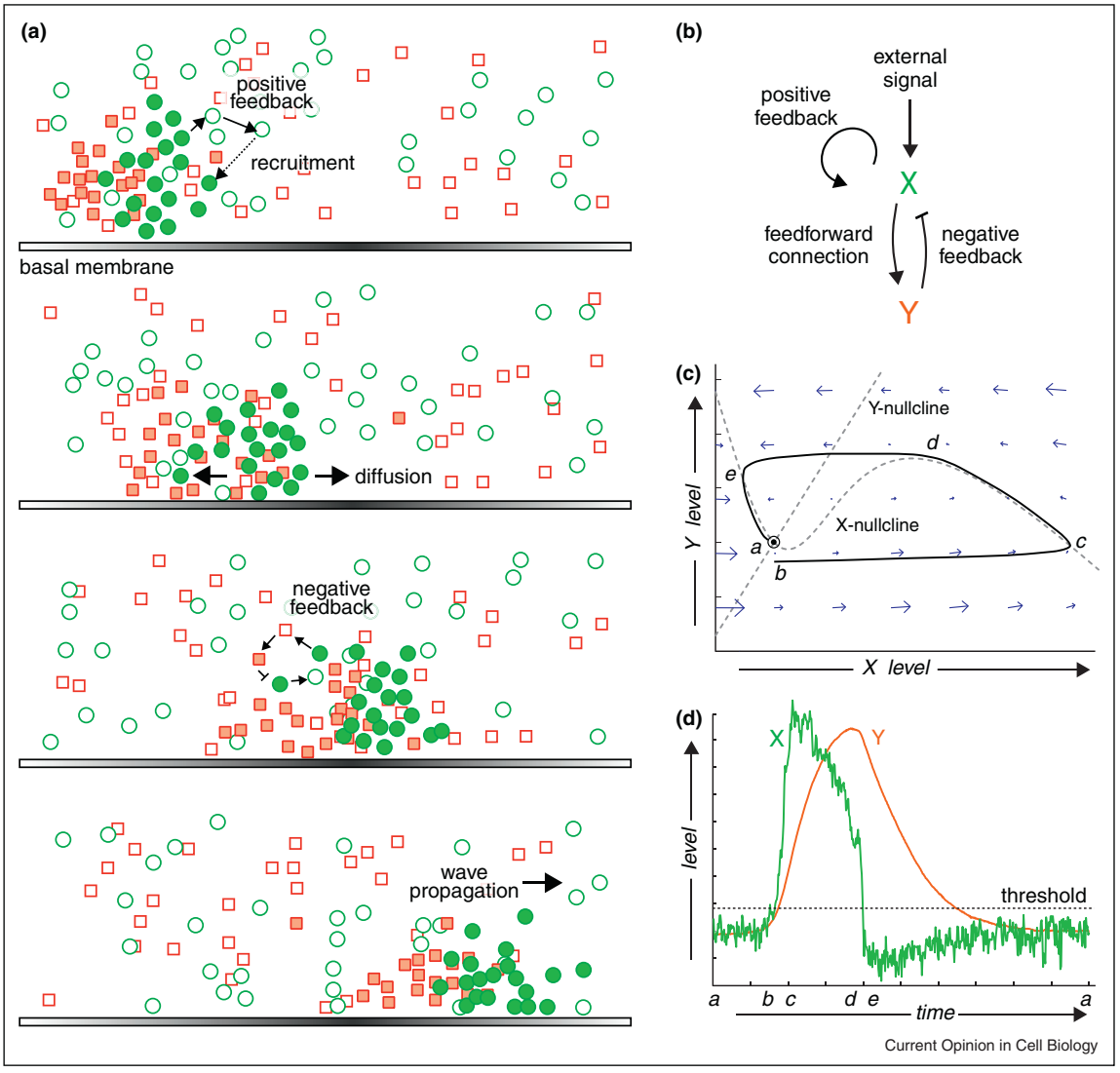
Though chemotaxis is observed in a large number of cells, the mechanisms used to direct eukaryotic cells are best understood in neutrophils and in the social amoebae, *Dictyostelium discoideum* [5]. *Dictyostelium* cells rely on chemotaxis to find nutrients. When starved, they also acquire the ability to chemotax in response to cAMP gradients in a developmental process that enables them to aggregate and survive. The amoeboid motility of neutrophils and *Dictyostelium* cells involves the localized dynamic extension and retraction of pseudopodia. In unstimulated cells, this rhythmic pattern repeats itself without an obvious spatial bias leading to random cell migration. By contrast, the imposition of a chemoattractant gradient provides a guidance cue that biases this stochastic activity and thereby steers cells in the direction of highest chemoattractant concentration.

Recent years have seen a growing number of reports showing that the actin cytoskeleton and the signal transduction events which regulate it behave as an excitable media (Figure 1a, Video S1). More recently, models have been proposed that describe how this random activity can be steered by the chemoattractant gradient. Here we review these findings, and also suggest a means by which polarity can be incorporated into these models.

Excitable behavior in cells

Probably one of the best examples of how biology can motivate a whole new branch of applied mathematics is the study of excitable systems. In biology, the classical model of an excitable system is that proposed by Hodgkin and Huxley to explain the 'all-or-nothing' characteristic of action potentials in neurons [6]. Perturbations of excitable systems can be either subthreshold, simply dying out, or superthreshold, eliciting a full response. When the excitable elements are spatially distributed, as they are along an axon, the system is said to be an excitable medium. In this case, a triggered response gives rise to a propagated wave of activity that travels along the medium and, thus, propagated waves are a signature of excitability. FitzHugh and Nagumo created a simplified mathematical model that recreated the dynamics of the Hodgkin-Huxley model [7,8]. The FitzHugh–Nagumo model belongs to a common class of systems known as activator–inhibitor systems (Figure 1b, Table 1). In these systems one component acts as an activator, as it includes an autocatalytic loop and also turns on the second element, the inhibitor, which provides negative feedback to the activator. Because they only include two components, activator–inhibitor systems can be described by an analytically tractable set of equations facilitating their analysis.

Figure 1



Wave propagation in excitable media. **(a)** This cartoon illustrates one possible way in which excitable systems involving an activator (green) and an inhibitor (red) can give rise to propagating waves. Functional (shaded) molecules of the activator recruit and activate like molecules in an autocatalytic, positive feedback loop as well as inhibitory molecules (red) that act in a negative feedback loop to turn off signaling. Though the activator can diffuse throughout, the presence of the inhibitor in one direction leads to wave propagation in the other direction. **(b)** Schematic of an activator (X)–inhibitor (Y) system. The autocatalytic loop endows the system with a threshold of activation. External signals, which may include stochastic perturbations, can trigger the excitable network (EN) when they are sufficiently large to overcome the threshold. **(c)** Phase-plane analysis of the EN. This plot shows the two *nullclines* (dotted gray lines) – curves for which the levels of X or Y are constant over time. The intersection between the two denotes the equilibrium (circled). Absent a perturbation, the system remains at this point (labeled *a*). However, a disturbance can move the state to another point in the plane (e.g. *b*). The blue arrows show the direction and velocity of the trajectory. In the case shown by the black solid line, a superthreshold increase in the level of X causes a subsequent large change (due to the positive feedback loop) which moves the state to point *c*. At this point the negative feedback loop starts to dominate and begins to lower the level of X. Between points *c* and *d*, the amount of inhibition (level of Y) continues to increase, accelerating the drop in X which is rapid between points *d* and *e*. Thereafter, Y decreases (between *e* and *a*) as the system relaxes to its equilibrium. **(d)** Plots of X and Y as a function of time, labeled to correspond to the phase plane points. Perturbations below the threshold do not trigger large deviations.

The presence of wave-like behavior, and hence excitability, in the actin cytoskeleton of *Dictyostelium* was first reported by Vicker *et al.* [9] who imaged fixed cells stained by phalloidin-rhodamine. Subsequent observations in live cells have confirmed the existence of these cytoskeletal waves [10–13]. Actin-binding proteins (e.g. Arp2/3, LimE, coronin) or Scar/WAVE complex components (e.g. Hem-1 in neutrophils and Hspc300 in *Dictyostelium*) are recruited from the cytosol to foci on the basal surface and give rise to waves of recruitment that propagate outwards [14,15]. Myosin-IB is found enriched at the front edge of the wave, coronin at the rear and Arp2/3 throughout [16••]. When

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Table 1

Summary of model types

Model type	Type	Properties explained	References
Excitable network (EN)	Stochastic, reaction-diffusion	Random migration, wave propagation, bursting phenomena	[21–24]
Activator–inhibitor	Reaction system, can also incorporate diffusion and stochastic perturbations	Can be used to represent excitable networks	
FitzHugh–Nagumo	Stochastic, reaction-diffusion	N/A. An early example of an EN based on an activator–inhibitor system that is analytically tractable	[7,8]
Biased excitable network (BEN)	Stochastic, reaction-diffusion	Random and chemotactic migration. Actin wave propagation. Does not explain adaptation or relative sensitivity to varying gradients	[25,28••,36,37]
Local-excitation, global-inhibition (LEGI)	Deterministic, reaction-diffusion	Adaptation, static gradient sensing and relative sensitivity to gradients	[30,31]
LEGI–BEN	Modular, stochastic, reaction-diffusion	A type of BEN that combines properties of LEGI and BEN models. Does not explain polarization or persistence	[18••]

waves reach the cell membrane they probably supply the force, through actin polymerization, needed to push it forward [10,15–17]. As such, wave propagation and extinction is related to extensions and retractions of pseudopods. When any of these waves collide, they annihilate each other, which is consistent with the behavior of activator–inhibitor systems. In *Dictyostelium*, recruitments of Ras binding domains (a measure of activation of multiple Ras proteins) and PH-domains (a measure of PIP_3 accumulation) are propagated in phase with waves of cytoskeletal activity that reach the cell cortex ([18••]; Video S1). Signaling events upstream of the cytoskeleton also display excitable behavior.

These excitable behaviors are seen in cells that are not stimulated by chemoattractant as well as in *Dictyostelium* cells lacking the Gβ-subunit, indicating that the chemoattractant receptor and associated G-proteins are upstream of and not part of the excitable network [16••]. However, chemoattractant signaling can dramatically perturb the system. Application of a spatially uniform stimulus triggers rapid, global recruitment to the membrane of most of the proteins showing excitable behavior. Within 30 s, this response disappears and then is followed by a series of further recruitments at random sites, appearing as flashes of fluorescence, which occur over the next several minutes before the prestimulus spontaneous behavior resumes (Figure 2). These secondary flashes of activity match the second phase of biochemically monitored events and the 'patches' of PIP_3 accumulation seen using fluorescent microscopy [19]. Though waves originate at random on the basal surface, most of the excitable behavior in polarized cells [15] or cells tracking toward a chemoattractant-filled micropipette [18••] is found preferentially near the leading edge.

The overall existence of excitable behavior is quite robust though this may represent the presence of multiple excitable systems. Eliminating the SCAR/WAVE complex or myosin-II does not impair wave formation or extinguish them [16••]. Wave patterns can even be observed in certain cells in which the actin cytoskeleton is disrupted through the addition of polymerization inhibitors, though only in special situations. Synchronous, phase shifted rotation of PIP_3 and actin has been observed in cells lacking amiB (a gene required for aggregation whose absence leads to aberrant cell morphology) that had been treated with a low dose of Latrunculin A [20]. Reciprocal waves of PIP_3 and PTEN are also seen in Latrunculin-treated *Dictyostelium* cells that are treated with caffeine [21]. In both these cases, the period of oscillation of the waves (~3–5 min) is slower than that of cells with intact cytoskeleton, suggesting that these oscillatory behaviors probably differ from the excitable behavior that leads to actin waves.

Models of excitable behavior

Activator–inhibitor models of excitable behavior are now being used to explain the waves seen in chemotactic cells (Table 1). To explain the observed Hem-1 waves in neutrophils, Weiner *et al.* proposed Hem-1 as the activator, actin as the inhibitor and an autocatalytic step which represents the activation (recruitment to the membrane) of Hem-1. Simulations recreate several observed behaviors, including the formation of propagating waves, the annihilation of colliding wave fronts and the way that depolymerization of the actin cytoskeleton freezes waves. Whitelam *et al.* used the FitzHugh–Nagumo equations to explain the presence of stationary spots and their transition to moving waves as observed in *Dictyostelium* cells [22]. The activator is substrate-bound actin, the autocatalytic step involves the recruitment by Arp2/3 to the growing ends of fibers and the inhibitory processes include actin severing and capping proteins. The model assumes that fiber orientation affects the direction of actin growth. Carlsson used a detailed 3D dendritic network model that does not require

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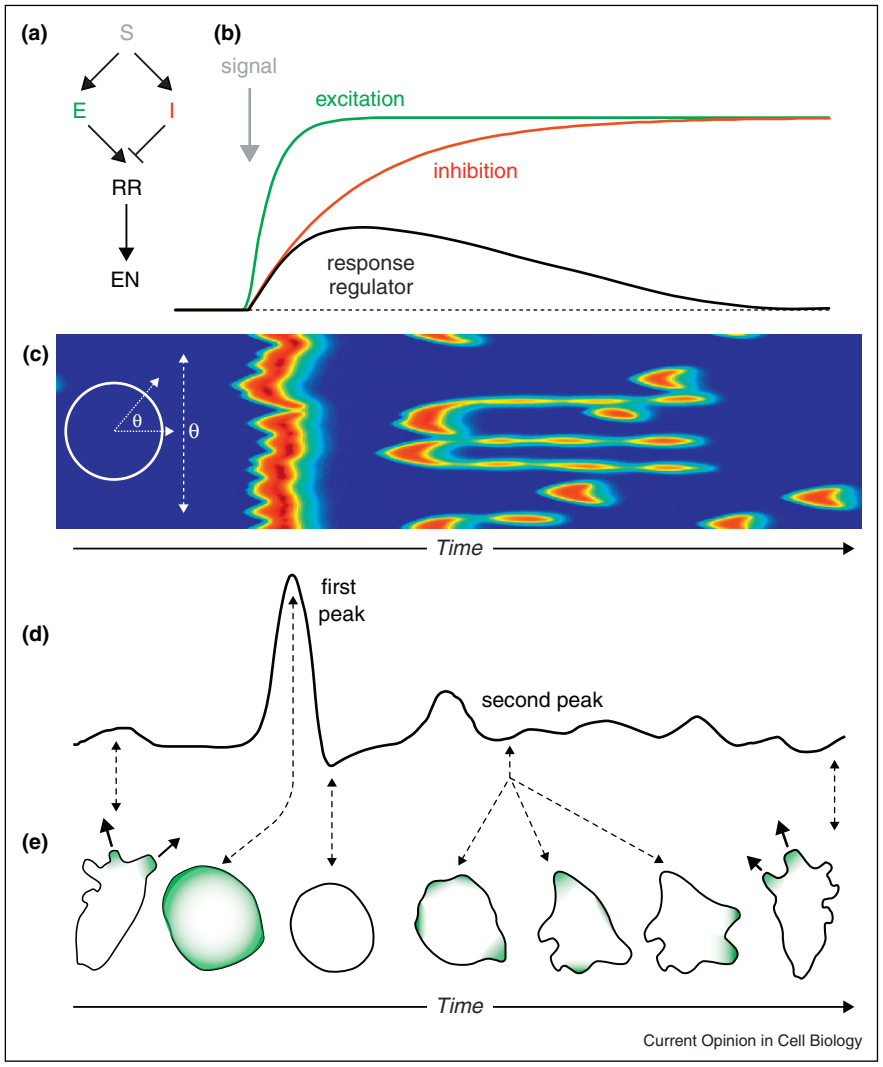
Figure 2



The behavior of a LEGI–BEN when stimulated uniformly. **(a)** In the LEGI system, receptor-mediated signaling turns on excitation and inhibition processes which act in a complementary manner on the response regulator (RR). **(b)** When receptor signaling is spatially uniform, the fast excitation signal leads to a rapid increase in RR before the slower inhibitory signal turns it off, leading to adaptation. In the LEGI–BEN system, RR acts on the excitable network (EN) by lowering the threshold. **(c, d)** Response of the EN shown as a kymograph around the perimeter of a cell **(c)** and showing the total level of activity, integrated over the cell membrane **(d)**. The spatially uniform increase in response regulator causes a large increase in the probability of firing in the EN and this is seen as a first peak of activity. Following a refractory time, during which the RR is decreasing, the probability of firing is higher than before the stimulus. Around the cell, this elicits localized patches of increased activity wherever the local stochastic perturbations are higher than the threshold (arrows in **c**). Other points along the perimeter remain below the threshold. When integrated over the cell perimeter, the total level of activity increases, leading to a second peak, but this is lower than the first as it represents firings over a smaller fraction of the cell perimeter. **(e)** Observed effect in markers of activity (green) around the cell perimeter (e.g. PIP_3) and cell shape at different times.

polarization of filament orientations to connect the observed membrane-bound waves with the dynamics of actin polymerization [23]. The autocatalytic step comes from branching from existing filaments. In a related model, Hecht *et al.* showed that patterns of high activity of finite duration in both space and time arose because of random stimulation of a FitzHugh–Nagumo model [24•], and suggested that these patches of high activity could correspond to the observed patterns of membrane localization of signaling molecules such as PIP_3 [19].

Guidance of the excitable behavior

These models show that excitable systems driven by random fluctuations can give rise to patterns observed in spontaneously migrating cells, but do not address how external chemoattractants can influence this behavior to guide cells. Recently, we suggested a model that shows how to steer this excitable behavior [18••]. The key step is to recall that excitable behavior is triggered by stochastic perturbations that are sufficiently large to move the state of the system across the threshold. Hence, there will be

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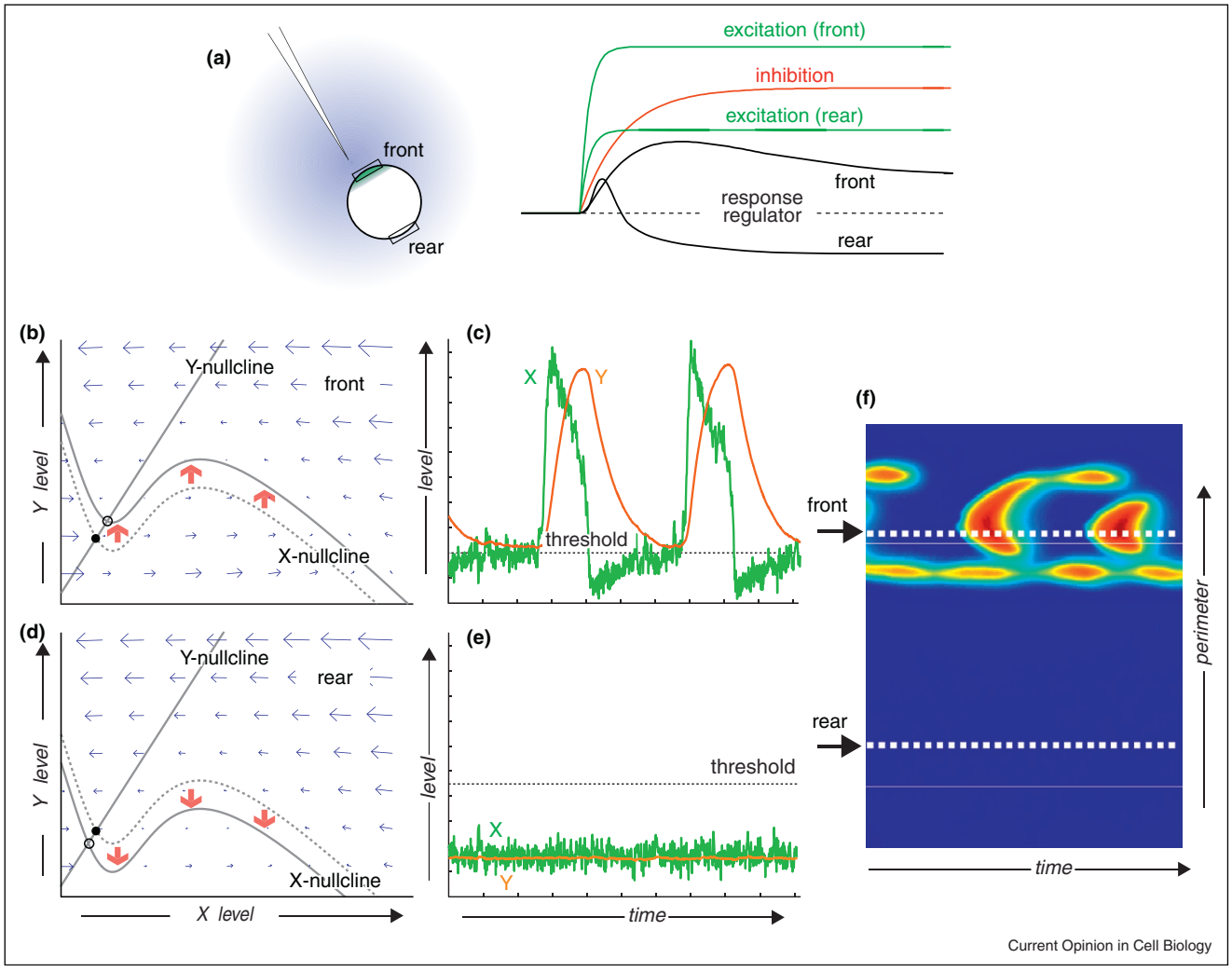
Figure 3



The behavior of a LEGI–BEN when in a chemoattractant gradient. **(a)** Cells in a gradient have increased receptor occupancy at the front of the cell relative to the rear. **(b)** In the LEGI mechanism, the excitation signal rises to a level proportional to the local receptor signal. By contrast, the inhibition signal is global, and so integrates the receptor signal around the cell and plateaus to an intermediate point. Hence, at the front of the cell excitation exceeds inhibition and so the response regulator is above basal levels. **(b, c)** The RR lifts the nullcline which has the effect of lowering the threshold in the EN thus increasing the frequency of firing at the front of the cell. The periodicity in the response comes from the refractory time needed for the system to readjust after each firing. **(d, e)** At the rear, inhibition exceeds excitation and so the RR is below basal level. This lowers the nullcline, thus raising the threshold which extinguishes the firing of the EN. **(f)** This kymograph shows how the patches of activity are localized to the front of the cell, thus steering the motility of the cell toward the regions of high chemoattractant concentration.

more excitable behavior in regions where the threshold is lower. If a chemoattractant lowered the threshold then more excitable behavior would be seen in regions where the cell experiences higher chemoattractant (Figure 3). Such a system can be referred to as a biased excitable network (BEN).

Because the occurrence of the spontaneous activity is tied to the presence and size of a threshold, shallow chemoattractant gradients can give rise to steep differences in the distribution of responses [18••,25]. Chemotactic cells display extraordinary sensitivity, detecting gradients as small as 1%, and amplified biochemical responses have been observed using biosensors [26,27]. Capturing these features has long been a goal of models of chemotaxis [2,3••]. Simulations in which the activity of a BEN trigger pseudopod protrusions give rise to realistic cell morphologies [28••] (Shi *et al.*, in preparation).

Local-excitation, global-inhibition (LEGI) models

As powerful as a BEN is in explaining both the spontaneous activity of cells and the means for directing this activity in response to gradients in receptor occupancy, it

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fails to explain important properties of the chemoattractant-induced response. First, if increased receptor occupancy lowers the threshold for excitable behavior, application of a spatially uniform dose of chemoattractant would give rise to a persistent increase in the frequency of the responses. By contrast, responses to uniform increments in chemoattractant are transient and so a means for eventually reducing the frequency is required. Second, if an external gradient is applied, receptor occupancy increases both at the front *and* the back. Without a means of subtracting the mean level of chemoattractant, a cell relying on a BEN that was merely proportional to the external gradient would increase the excitable behavior everywhere. Gradients with higher midpoints exacerbate this problem.

The original motivation of local-excitation, global-inhibition (LEGI) mechanisms was to account for these important features of the response to chemoattractants [29,30]. In LEGI models, temporal and spatial sensing involves a balance between two opposing processes (Figures 2 and 3). Receptor occupancy controls the steady-state levels of a rapid, local excitation and a slower, global inhibition which together control a response regulator. Upon chemoattractant addition, receptor occupancy increases, eliciting a fast rise in excitation. This induces a response that peaks as excitation plateaus and decreases as the slower rise in inhibition catches up. With a uniform stimulus, the relative change in activity of excitation and inhibition is the same and the level of the response regulator returns to the pre-stimulus level (Figure 2). By allowing the inhibitory molecule to integrate signaling from throughout the cell, and to act globally, while at the same time requiring that excitation be fixed at the membrane, this simple model also accounts for gradient sensing in immobilized cells (Figure 3). However, it fails to capture important aspects of chemotaxis. First, the original implementation of LEGI did not significantly amplify the gradient, although several modifications have remedied this ([31], our unpublished results). Second, it did not capture the dynamic behavior of chemotaxing cells.

We recently suggested a hybrid LEGI–BEN model in which a LEGI mechanism is used to control the size of the threshold level in an excitable network (Figure 2). When a spatially uniform chemoattractant stimulus is applied, the adaptive behavior of the LEGI mechanism transiently lowers the threshold in the excitable network for an extended period before slowly returning to its prestimulus level. During this time, the probability of triggering excitable behavior is higher than before the stimulus and this is seen in the initial response and in the increased presence of localized secondary flashes (Figure 2c,d). Once the LEGI system has adapted, the threshold and, consequently, the frequency of excitable behavior are restored to their prestimulus levels. In a gradient, the persistent elevation of the response regulator lowers the threshold at the front of the cell increasing the local frequency of activity in the direction of highest chemoattractant concentration (Figure 3). Equally important is the fact that, at the rear, the response regulator is lower than the basal level which raises the threshold thereby inhibiting the appearance of excitable behavior.

Persistence and polarization

The LEGI–BEN model accounts for many of the observed properties of chemotactic cells, including the presence of excitable behavior in unstimulated cells, the biphasic response to spatially uniform stimuli, and the focusing of activity in response to gradients. However, simulating cell movement in a gradient shows that two aspects are still missing (Shi *et al.*, in preparation). The first is persistence: Well-differentiated *Dictyostelium* cells migrating in the absence of stimulus move in a persistent random walk [32,33], and this is a consequence of having pseudopodia extend in the same direction [34]. The second is polarization: Cells rearrange intracellular components to form leading and trailing edges with distinct sensitivities to chemoattractants. Whereas unpolarized cells respond immediately to changes in the direction of a gradient by making a new front, strongly polarized cells turn toward the new gradient while maintaining the same leading edge [2,3••,35].

In the context of the LEGI–BEN mechanism, it is easy to envision how persistence and polarity are both consequences of a spatially perturbed threshold. First, because we wish to explain persistence in the absence of receptor occupancy, we assume that the localized firing of the excitable network slowly increases the likelihood of subsequent activity. Thus, we postulate a *localized* positive feedback loop triggered by the excitable behavior ($Y \rightarrow Z \rightarrow X$ in Figure 4). This contribution should be parallel to, or in addition to, that of the LEGI mechanism. The addition of this loop also explains the spontaneous polarization seen in some cells, as well as the maintenance of cell polarity after gradient removal. However, having only a positive feedback loop would eventually lead the whole cell toward an activated state. To circumvent this problem, an inhibitory signal is needed that can help to localize these signals. Thus, the proposed mechanism also entails a secondary global inhibitory signal acting as a feedback loop from the excitable system ($Y \rightarrow W \rightarrow X$ in Figure 4).

The suggestion that a second mechanism is required to explain polarization is reminiscent of an early model of Meinhardt in which a local activator that encompasses an autocatalytic loop is coupled to two antagonistic processes [36]. Recently, Neilson *et al.* incorporated Meinhardt's model into a physical model in which activator level drives membrane protrusions and cell area is conserved, and simulated chemotaxis [37]. These simulations show

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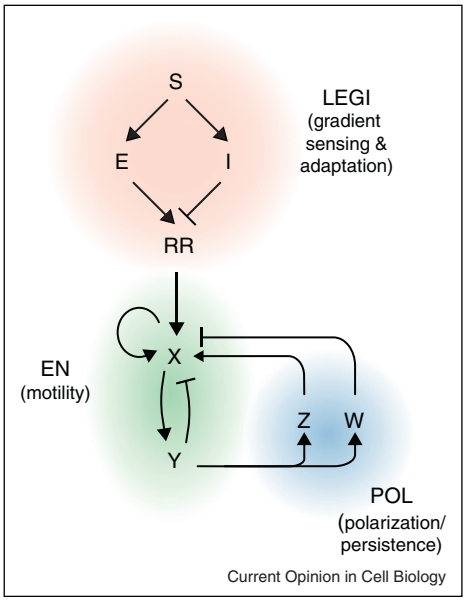
Figure 4



Modular view of chemotaxis consisting of a LEGI–BEN and incorporating a putative polarization component. The system consists of three interconnected components. The LEGI mechanism connects the system to receptor occupancy. It adapts to spatially uniform stimuli and senses chemoattractant gradients. The excitable network provides amplification and regulates motility. In the absence of receptor signals, it results in random motility, but can be steered by the external gradient through a LEGI-mediated bias. The polarization (POL) component further biases its activity based on the history of the EN firing. When these firings represent random motility, this component provides persistence. When the firings are the result of a gradient, this component leads to polarization.

migrating cells whose tracks display persistence when unstimulated, and turns in response to changes in external gradient. However, when stimulated by a uniform stimulus, the response of these systems does not subside and hence still requires a LEGI-type mechanism for explaining adaptation. Moreover, by omitting the slow positive feedback loop ($Y \rightarrow Z \rightarrow X$ in Figure 4) these models cannot explain the slow build up of polarity observed in cells.

Molecular mechanisms

To date, our understanding of the molecular mechanisms giving rise to excitability is rather limited. Thus, models proposed either eschew the assignment of molecular identities to the components of the excitable network [18••,24•], provide exceedingly simple models of the network [15], or focus on a small portion of the network [22,23,25]. In fact, models cannot even agree on whether actin forms part of the activator [22,23] or inhibitor [15]!

Because of the complexity of the signaling mechanisms, involving a number of parallel pathways in which many components display excitability, it is difficult to assign components to the simple networks. A key component in all models is the autocatalytic loop and there is wide consensus that this involves actin polymerization in one form or another. There is evidence such a positive feedback path exists which involves Ras, PI3K, and actin [38]. The strength of this loop could be amplified by the presence of further feedbacks involving just the actin cytoskeleton components. Another interesting possibility entails the coupling of curved membrane proteins, like BAR-domain proteins, with actin polymerization [39•].

A possibly more fruitful approach at this time is to focus on the loops of the excitable networks, to perturb these computationally and to compare the predicted behavior with the observed phenotypes of genetically and pharmacologically altered cells. For example, disrupting the negative feedback loop in the BEN enhances the excitable behavior and interferes with the response to a gradient [18••]. This mimics the observed behavior of cells lacking the PIP_3 phosphatase, PTEN, which display many lateral pseudopods [40,41]. Similar behavior is seen in cells lacking NF1, a GTPase activating protein for RasG, as well as cells expressing the constitutively active RasCQ62L [42–45]. Thus, the negative feedback loop may act to curtail the activation of the Ras proteins. The mechanical properties of the cell may also contribute to the inhibitory loop. When simulating cell shape changes elicited by the LEGI–BEN, we have noted that addition of a uniform stimulus gives rise to a large spatially homogeneous increase in activity. Rather than causing the cell to spread out everywhere as force is applied throughout the cell perimeter, we instead see a damping of protrusions because of the mechanical model implemented ([46], Shi *et al.*, in preparation). Thus, global mechanical constraints can serve as an inhibitory process.

Conclusion

The last couple of years have begun to shed light on a connection between observed excitability of cytoskeletal events and directed cell migration and this is providing fresh new insights into our understanding of chemotaxis. We wish to highlight here how a hierarchical approach into this complex system has aided this progress. A key early step was the conceptual decoupling of the different processes that make up chemotaxis: gradient sensing, random motility and polarization. Rapid excitability can be associated with motility. Gradient sensing and polarity can be treated as systems that temporally and spatially alter the threshold of the rapidly excitable system in different ways for specific purposes. We have now reached the point where these models can be integrated to understand the chemotactic behavior. Clearly, many questions remain, including the identification of molecular components

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and feedback loops. Nevertheless, these are truly exciting times in chemotaxis research.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ceb.2011.11.009.

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