

# Navigating through models of chemotaxis

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Chemotaxis in eukaryotic cells involves the coordination of several related but separable processes: motility, polarization, and gradient sensing. Mathematical models that have been proposed to explain chemotaxis typically focus on only one of these processes. We summarize the strengths and weaknesses of the models and point out the need for an integrated model.

## Addresses

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## Introduction

Chemotaxis, the ability to sense spatial heterogeneities in the concentration of extracellular chemoattractants and to respond by polarizing and migrating toward sources, is crucial for single cell organisms. In mammals, chemotaxis plays a major role during development, and in adults it directs cells of the immune system as well as those in regenerating tissues. Chemotaxis also plays a key role in pathological events such as metastasis and excessive inflammation.

The signaling network regulating chemotaxis is best understood in bacterial cells where it involves just six proteins. These proteins allow the cells to temporally differentiate chemoattractant concentrations, sense gradients as they traverse through their environment, and determine whether the direction of motion is desirable or not—a technique known as temporal sensing. The decision is used to bias a random series of ‘runs’ and ‘tumbles’ to direct cells in the right direction. The deciphering of the bacterial chemotaxis system has been greatly aided by mathematical models that continue to guide experiments [4].

In eukaryotic cells, the signaling networks are more complex, perhaps involving over 100 proteins. Much of

our understanding of the mechanisms of directed migration comes from neutrophils and the model organism *Dictyostelium discoideum*, which share many, though not all, features of the process [1–3]. These cells display motility, polarization, and directional sensing (Figure 1; see Box 1). In gradients, chemoattractant receptors and their associated G proteins remain uniformly distributed along the cell membrane, and the sensing is achieved by the re-distribution or activation of signaling lipids and proteins. Occupancy across the cell is compared and biases the random motility of the polarized cells. Gradient sensing remains even when cells have been immobilized, indicating that cells can use spatial, as well as temporal, gradient sensing mechanisms.

Recent years have seen an impressive series of theoretical studies aimed at explaining the observed phenomena in eukaryotic chemotaxis together with a striking array of biophysical techniques that have greatly enhanced the quantitative study of directed cell migration. Here, we review these advances, emphasizing the role played by coupling models to experiments and suggest schemes for uniting the most useful features of the different models.

## Gradient sensing models

Because different models of chemotaxis deal with different aspects of chemotaxis, it is useful to restrict comparisons to similar types. One class referred to as ‘gradient sensing’ attempts to explain the ability of cells to generate amplified, persistent intracellular responses to static, external gradients of chemoattractant, as well as transient responses to uniform stimuli. Several models are based on a local excitation, global inhibition (LEGI) principle [2,6,7] (see Figure 2; Figure 3a). Receptor occupancy triggers a fast, local excitatory signal as well as a slower, global inhibitory signal. Qualitatively, the LEGI mechanism can account for the observed gradient sensing response of most of the molecules that have been shown in neutrophils and *Dictyostelium* cells to translocate to or be activated transiently on the cell cortex during uniform stimulation and move to or be activated at the front (e.g. Ras, PI3K, PH domains, actin binding proteins) or rear (e.g. PTEN, myosin) in a gradient. A two-LEGI model, where parallel mechanisms act to regulate membrane binding sites for PI3K and PTEN, which together regulate PI(3,4,5)P<sub>3</sub>, the main PH domain binding site was shown to increase the level of amplification, approaching that seen in Latrunculin-treated PH domain responses [8].

Alone, the LEGI model does not fully explain the switch-like behavior observed in the spatial distribution of PH

**Box 1** Distinct processes during chemotaxis

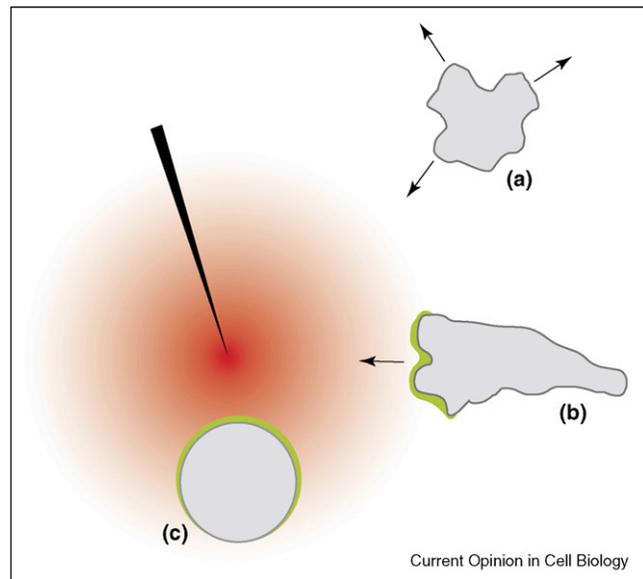
Chemotaxis, the directed movement of cell in response to chemical gradients, involves several independent processes motility, polarization, and gradient sensing [41,42]. Because many self-described models of chemotaxis deal with different aspects, it is useful to delineate clearly between these processes.

**Motility:** Cells move by periodic extension of self-limited pseudopodia at the cell anterior and retraction at the rear; **Figure 1a**. However, no chemotactic gradients are needed to generate pseudopods. For example, *Dictyostelium* cells migrate randomly in the absence of chemotactic cues. Here, we do not consider models of motility but instead point readers to excellent recent reviews on the subject [43,44].

**Polarization:** Cells can rearrange cellular components leading to the development of separate leading and trailing edges with distinct sensitivities for chemoattractant (see **Figure 1b**). Though usually in response to external chemoattractant gradients, in appropriately differentiated cells, polarization occurs even in uniform attractant. For example, when stimulated by a uniform dose of chemoattractant, neutrophils and *Dictyostelium* cells lacking adenyl cyclase (ACA) break symmetry. They acquire distinct leading and trailing edges and begin to migrate randomly [45,46]. Strong polarization is also not required for chemotaxis: *Dictyostelium* early in their developmental cycle chemotax to cAMP gradients despite showing uniform sensitivity throughout the membrane. The degree to which a cell is polarized can be observed in the behavior of cells that experience changes in the direction of the chemoattractant gradient [42]. Whereas unpolarized cells respond immediately to changes by extending new pseudopods in the direction of the newly established gradient, polarized cells turn toward the new gradient while maintaining the same leading edge.

**Gradient sensing:** Finally, eukaryotic cells such as *Dictyostelium discoideum* and neutrophils have the ability to detect and amplify spatial gradients, even while immobile (see **Figure 1c**). This property is best observed by imaging fluorescently tagged proteins in cells that have been immobilized by inhibitors of the actin cytoskeleton, such as Latrunculin. Quantitative measurements of both the stimulus and response reveal three distinct behaviors. First, the chemoattractant-induced response is adaptive: when stimulated by a uniform dose of chemoattractant, proteins are activated or translocate to the inner face of the membrane rapidly but transiently. These responses peak within 5–10 s and mostly disappear within 30 s. In certain cells and under specific situations, a second peak is also observed. Second, static gradients elicit a spatial response: when cells are exposed to a chemoattractant gradient, proteins are preferentially activated or translocate to the side of the cell that is closest to the source and maintain a steady state response there. Responses that occur at the front in a cell lacking an actin cytoskeleton include Ras activation and translocation of PI3K and CRAC (a Pleckstrin Homology containing protein). Other proteins, such as PTEN move toward the back. With the actin cytoskeleton present, many other proteins are known to move to the front (e.g. F-actin, coronin, ABP-120, LimE, MyoB, Dynacortin, and Scar) or rear (Myosin-II, Cortaxillin and PakA) of chemotaxing cells. This translocation is persistent, but removal of the gradient makes the response disappear. It is also amplified, as the localization of the PH domains is more pronounced than that of the external chemoattractant gradient [9].

domains, in which the rear of the cell shows no discernible response [9]. A ‘balanced inactivation’ model has been proposed to explain this observation [10<sup>••</sup>] (see **Figure 3b**). This model shares some of the features of the LEGI mechanism, including the receptor-mediated

**Figure 1**

Distinct processes involved in chemotaxis. As described in **Box 1**, we divide chemotaxis into three separate processes: motility (**a**), polarization (**b**) and static spatial sensing (**c**).

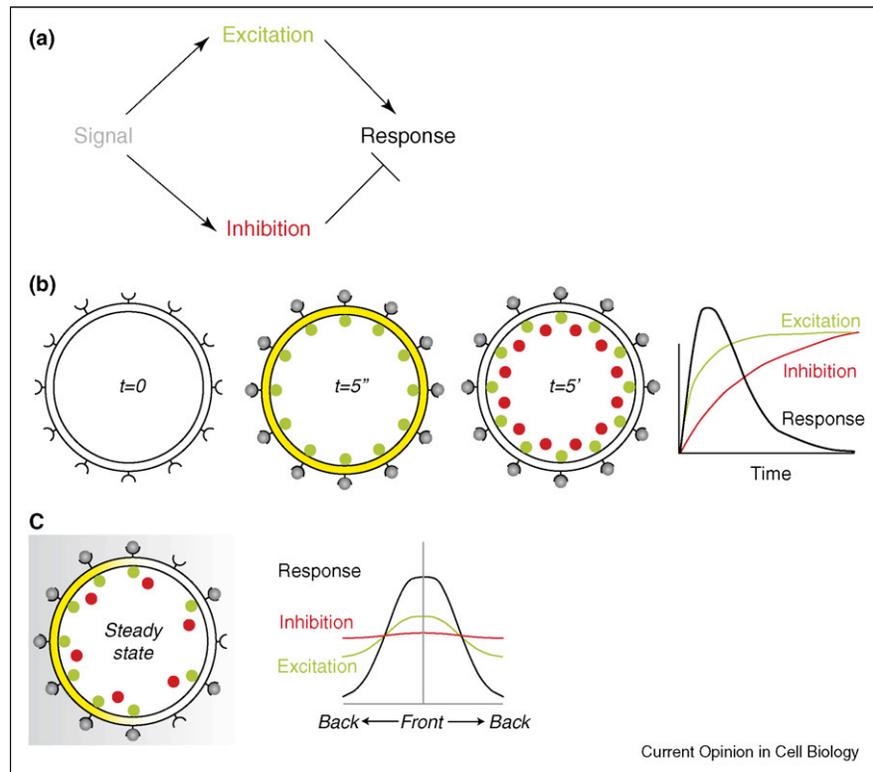
production of two opposing signals, one of which is local, the other global. Its innovative feature is a third component: a membrane bound inactivator that is mutually antagonistic to the response. Inclusion of this extra component induces a switch-like response to external gradients.

**Polarization models**

The observation that cells can chemotax in extremely shallow gradients (1–2% differences in chemoattractant concentration between front and rear) has led to several proposed models in which large amplification is achieved by positive feedback loops [11–13,14<sup>•</sup>,15<sup>•</sup>,16]. If sufficiently strong, the positive feedback also helps to explain aspects of chemoattractant-induced polarization, by which cells acquire and maintain a distinct morphology involving well-defined anterior and posterior regions (see **Box 1**).

Many of these models share some basic features (see **Figure 3c**). As in the LEGI model, the response is locally controlled by receptor occupancy. They also include a locally generated but diffusing inhibitor [11,13,15<sup>•</sup>]. Their most important characteristic, however, is that the local response triggers a positive feedback loop wherein the signaling readout (e.g. the PH domain binding site) enhances its own production either through autocatalytic effects [11,12,13], substrate delivery [14<sup>•</sup>,15<sup>•</sup>], or by inhibiting its degradation [16]. These models all achieve greater amplification than the basic LEGI mechanism. One feature of these models is that the

Figure 2



Local excitation, global inhibition model of gradient sensing. **(a)** The premise of the model is that receptor occupancy (gray dots) triggers both a rapid, excitatory, local excitation (green dots in panels b and c) as well as a slower, inhibitory, global response (red dots), which can represent the action of a diffusive inhibitor. Together, they regulate the cellular response (yellow). **(b)** The transient response observed in cells when stimulated uniformly is the combined effect of first the fast excitation ( $t = 5$  s) followed by its quenching by the slower inhibition ( $t = 5$  min). Because the stimulus is spatially uniform, the distinction between local and global disappears. A typical time course is shown in the right-most panel. **(c)** In a gradient of receptor occupancy, the excitatory signal at the front is stronger than that of the back. Though the inhibitory signal is also triggered more strongly at the front, at steady state it (mostly) equilibrates in space because of diffusion. This leaves a stronger static response at the front (where excitation exceeds inhibition) than at the rear (where inhibition exceeds excitation).

shape of the response becomes nearly independent of the generating stimulus. Quantitative experiments of Latrunculin-treated *Dictyostelium* cells revealed a strong connection between the strength of the stimulus and the response [9] during gradient sensing. Thus, the positive feedback models more accurately describe pathways for chemoattractant-mediated polarization rather than spatial gradient sensing. This shows that the feedback involves the actin cytoskeleton, and its disruption by Latrunculin 'depolarizes' the cells and allows observation of gradient sensing in isolation.

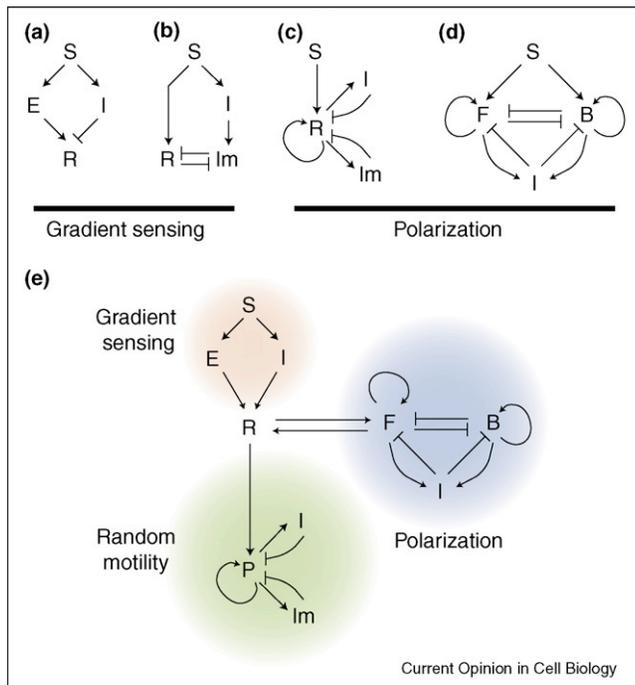
It is well known that a strong positive loop (or double negative feedback), together with nonlinear regulation, can lead to self-sustaining bistable behavior [17] and that, when coupled to diffusion, results in phase separation in systems. Not surprisingly, variations on this principle have been used to account for spontaneous polarization after uniform stimulation, as well as polarized sensitivity to gradients [16,18–21] see (Figure 3d) In these models, the spatially uniform steady-state response is not stable.

Thus, small noise-induced heterogeneities in the system are greatly amplified leading to a separation between antagonistic components. When trying to explain chemotaxis in *Dictyostelium* [16], these components represent PI3K (at the front) and PTEN (at the rear). The double-negative feedback loop comes from PI3K production of PI(3,4,5)P<sub>3</sub> (and hence depletion of PI(4,5)P<sub>2</sub>) at the front that acts to exclude PTEN (which is known to have a PI(4,5)P<sub>2</sub> binding motif) there. This decreases degradation of PI(3,4,5)P<sub>3</sub>. In neutrophils, where the connection between chemoattractant stimulation and GTPases regulating actin (Rho, Rac and CDC42) is better understood, a qualitative model involving the mutual antagonism between 'frontness' (e.g. Gi proteins, PI(3,4,5)P<sub>3</sub>, Rac) and 'backness' (Rho) components has been proposed by Bourne and co-workers [22] and serves as the basis for several mathematical models [19,20,21\*\*].

### Noise and the limits of detection

As discussed above, noise-driven fluctuations in the numbers of interacting molecules have been suggested as a

Figure 3



Models of gradient sensing and polarization. We distinguish models that describe gradient sensing (**a and b**) or polarization (**c and d**). (a) Local excitation (E), global inhibition (I) model described in detail in Figure 2. S and R refer to the stimulus and response, respectively. (b) Balanced inactivation model [10<sup>\*\*</sup>]. This model is similar to the LEGI model but incorporates an additional membrane bound inhibitor (Im) that is mutually antagonistic to the response. (c) A number of models rely on autocatalytic activation of the response [11–14,15<sup>\*</sup>]. This leads to a large amplified response. Both local (Im) and global (I) inhibitors are used to quench this signal. (d) Spontaneous polarization has been modeled as the product of mutually antagonistic signals, which regulated frontness (F) and backness (B) signals [16,18–20]. (e) Complete models of chemotaxis will need to explain different aspects of chemotaxis. Here we illustrate what such a model could look like. Models that generate strong highly localized transient signals (e.g. c) can be used to account for noise-driven random protrusions (green). This process can be guided by gradient sensing mechanisms (red) such as those in panels (a or b). On a slower time scale, and mediated by gradient sensing, cells can polarize using a mechanism such as that in panel (d) (blue).

means of breaking symmetry and driving cells to polarize spontaneously. Recently, the role that stochastic fluctuations have on chemotaxis has received renewed interest. Single molecule imaging of the receptor-ligand binding for *Dictyostelium* cells exposed to a chemoattractant gradient have demonstrated fluctuations in the order of 11% of the difference in bound receptors between front and rear [23]. These findings have led to several theoretical investigations that address how a cell can chemotax effectively when it cannot accurately determine the concentration of chemoattractant in its environment [24–27]. The basic idea, borrowed from engineering, is that cells reduce the effect stochastic fluctuations through temporal and spatial filtering of receptor occupancy [28]. Low pass

filtering of stochastic noise is used by chemotaxing bacteria, where it has been demonstrated that nearly optimal filtering is present [29]. On the basis of theoretical derivation of the ability to discern between a front and back in the presence of stochastic variations, it has been suggested that chemotaxis in shallow gradients is achieved by temporal and not spatial mechanisms [27].

### Coupling gradient sensing and polarization to chemotaxis

To elucidate chemotaxis mechanisms fully will require that gradient sensing and polarization mechanisms be coupled to cellular morphology and motility (see Figure 3e). Despite these connections, no models have successfully combined these key features. Furthermore, while gradient sensing biases motility during chemotaxis, motility and associated cellular deformations also have an impact on the signaling, either because of temporal changes in the chemoattractant concentration or because of changes in the membrane topology [30]. Those that have attempted to bring together various aspects of chemotaxis have taken a simple mechanistic interpretation of one or both of these processes [31,32]. More realistic cellular shapes have been obtained in the simulation of polarization and movement of keratocytes in response to extracellular cues [33]. An interesting model, though based on a simplified one-dimensional model of protrusion, demonstrated stable amplified internal profiles of regulatory components, and persistent motility [34<sup>\*</sup>]. These models assume that phosphoinositide signaling drives protrusion by regulating F-actin polymerization. Recent experimental observations, however, suggest more subtle schemes, where phosphoinositide signaling may bias the lifetime of random protrusions [35], at least in shallow gradients, thus reviving an old mechanistic model in which protruding pseudopodia serve as temporal sensors of chemoattractant concentration [27,36].

### Conclusions

Research into eukaryotic chemotaxis is at an exciting time as some of the basic theories are being tested. For nearly 10 years, the PI3K pathway has been seen as the primary mediator of chemotaxis in *Dictyostelium* and neutrophils as well as fibroblasts. It was through the localization of downstream effectors of this pathway that it was clearly demonstrated that cells employ a spatial sensing mechanism. As such, nearly all modeling efforts have concentrated on accounting for the spatial response of this pathway to various chemoattractant stimuli. Recent experiments, however, are showing that cells can chemotax nearly as efficiently when lacking PI(3,4,5)P<sub>3</sub> regulation [37], and that there are other pathways that act in parallel to mediate chemotaxis [38–40]. Future models will need to incorporate these new experimental discoveries. These models will also need to clearly delineate between different processes involved in chemotaxis,

showing how gradient sensing interacts with polarization and random motility.

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