

Endocytosis shapes extracellular chemical gradients in autonomous cell-cell attraction

Jeremy Barrios¹, Andrew Goetz², Susan E. Leggett³ and Purushottam D. Dixit^{2,4,5,6,*}

¹Department of Physics, *Yale University*, New Haven, Connecticut 06511, USA

²Department of Biomedical Engineering, *Yale University*, New Haven, Connecticut 06511, USA

³Department of Bioengineering, *University of Illinois Urbana-Champaign*, Urbana, Illinois 61801, USA

⁴Systems Biology Institute, *Yale University*, West Haven, Connecticut 06516, USA

⁵Quantitative Biology Institute, *Yale University*, New Haven, Connecticut 06520, USA

⁶Integrated Graduate Program in Physical and Engineering Biology, *Yale University*, New Haven, Connecticut 06520, USA



(Received 20 April 2026; accepted 27 July 2026; published 29 September 2026)

Receptor-mediated ligand endocytosis underlies essential homeostatic functions and in signaling contexts it is often regarded as a mechanism for signal attenuation. Here, we show that ligand removal can paradoxically enhance directional information in autonomous cell-cell attraction. Many cell systems migrate toward one another in the absence of externally imposed gradients, implying that secretion, diffusion, and uptake must themselves generate usable directional cues. We develop a surface-resolved theory of a finite-sized detector exposed to a nearby source and derive analytical expressions for the steady-state ligand field. The resulting concentration profiles are governed by a single dimensionless Damköhler number that compares receptor-mediated endocytosis to diffusive ligand transport. Increasing ligand removal lowers extracellular ligand concentrations and reduces absolute concentration differences across the detector surface, but preferentially enhances relative surface anisotropy. Thus, destroying the signal can increase the usable information encoded in relative gradients. Incorporating nonlinear downstream processing reveals a trade-off between contrast enhancement and signal depletion, with the directional response greatest within a joint regime of endocytosis and downstream sensing that overlaps the measured range of receptor internalization rates. These results recast receptor-mediated endocytosis as an extracellular information-processing mechanism that reshapes the surrounding ligand gradient to enhance directional information.

DOI: [10.1103/qn2h-7wml](https://doi.org/10.1103/qn2h-7wml)

I. INTRODUCTION

Eukaryotic chemotaxis [1], the directed movement of eukaryotic cells in response to spatial inhomogeneous chemical cues, underlies essential biological processes such as developmental patterning and immune surveillance [2], as well as pathological behaviors including cancer invasion and metastasis [3]. A central problem in quantitative cell biology has therefore been to understand how cells reliably extract directional information from chemical signals, particularly when gradients are shallow and noisy [1].

A dominant theme in chemotaxis research is that cells migrate in stable guidance cues organized at the tissue level. Early theoretical work by Crick [4] showed that localized ligand production combined with distributed degradation can generate persistent concentration profiles over characteristic diffusion lengths, and subsequent extensions established how feedback [5], source-sink organization [6], and tissue geometry [7] shape gradient profiles over long distances. Together, these studies have motivated a vast body of experimental and

theoretical studies focused on how cells sense and respond to fixed, externally imposed chemical fields [8–14].

Notably, an increasing number of experiments over the past two decades show that cells can cluster together and migrate toward one another even without an externally imposed chemical gradient. In developing pancreatic tissue, precursor cell clusters secrete fibroblast growth factor ligands that promote their own aggregation into hormone-expressing clusters [15]. Epithelial cells induced into migratory states extend persistent protrusions toward distant neighbors and assemble into multicellular aggregates, which themselves migrate toward other aggregates over tens to hundreds of microns [16,17]. Similarly, invasive cancer cell lines exhibit robust cluster-cluster attraction in the absence of externally imposed spatial chemical cues [18]. While the molecular mechanisms underlying these behaviors are not always clear, their action-at-a-distance character strongly suggests communication mediated by secreted diffusible ligands. Taken together, these systems pose a basic physical question: How do cells generate surface-resolved directional information at cell-cell length scales when no external guidance cue is provided?

Receptor-mediated endocytosis and subsequent degradation of ligands is known to play an essential role in shaping externally imposed gradients sensed by migrating cells, primarily by acting as a clearance mechanism that sets effective length scales and stabilizes tissue-scale profiles [4–7]. Similarly, endocytosis is also key in interpretation of gradients

*Contact author: purushottam.dixit@yale.edu

Published by the American Physical Society under the terms of the [Creative Commons Attribution 4.0 International](https://creativecommons.org/licenses/by/4.0/) license. Further distribution of this work must maintain attribution to the author(s) and the published article's title, journal citation, and DOI.

[12]; blocking endocytosis disrupts chemotaxis [19–22]. The physical limits with which surface receptors read such fields have themselves been studied, beginning with Berg and Purcell [23] and extended to detailed receptor-ligand kinetics [24] and to gradient sensing by single cells and collectives [25,26]. In these treatments, the cell acts as a passive reader: Ligand uptake perturbs only the fluctuation statistics of receptor occupancy, while the mean-field concentration profile is externally imposed and remains fixed at steady state. In contrast, the role of endocytosis in sculpting the mean-field gradient on the cell surface in autonomous cell-cell communication has not been explored. Most theoretical descriptions of autonomous cell-cell communication adopt phenomenological frameworks in which cells are treated as pointlike sources and detectors, and the ligand concentration is evaluated only in the bulk, without resolving spatial variation along the cell surface [27–29]. Consequently, it remains unclear how biophysical and signaling parameters, such as ligand secretion rates, ligand diffusivity, receptor density and affinity, and receptor-mediated endocytosis kinetics, jointly determine the surface-resolved directional information available to a cell, or under what conditions such information is sufficient to drive robust attraction.

To address this gap, we develop a minimal, surface-resolved theory of autonomous gradient generation based solely on secretion, diffusion, and receptor-mediated endocytosis. Using an idealized geometry, we derive analytical expressions for the ligand concentration in the extracellular medium and along the surface of a finite-sized detector. This analysis reveals that the entire family of concentration profiles is governed by a single dimensionless control parameter, a Damköhler number that integrates ligand transport with kinetics of receptor-mediated endocytosis.

Our analysis reveals a fundamental trade-off in autonomous gradient generation. Increasing receptor-mediated endocytosis reduces overall ligand abundance and therefore weakens absolute concentration differences across the detector. Paradoxically, the same process sharpens relative ligand anisotropy along the cell surface, enhancing directional contrast in relative gradients, the quantity effectively sensed by many chemotactic circuits [1,11,12]. Because relative sensing typically operates only over a finite dynamic range [12,30], endocytosis both amplifies directional information and regulates whether the detector operates within this regime. Incorporating a phenomenological model of downstream signal processing shows that the directional response is greatest within a joint regime of endocytic rate and downstream sensitivity, and that the measured rates of growth-factor and G protein-coupled receptors fall within this regime [31,32].

Together, these results establish a minimal physical framework for autonomous cell-cell attraction at a distance. Our work reframes gradient formation as an extracellular information-processing problem, in which surface-mediated ligand removal tunes the balance between signal amplitude and contrast. This perspective provides a mechanistic foundation for understanding how cells can generate and sense guidance cues without relying on externally imposed gradients.

II. RESULTS

We begin by formulating a minimal physical model for autonomous gradient generation in an idealized geometry

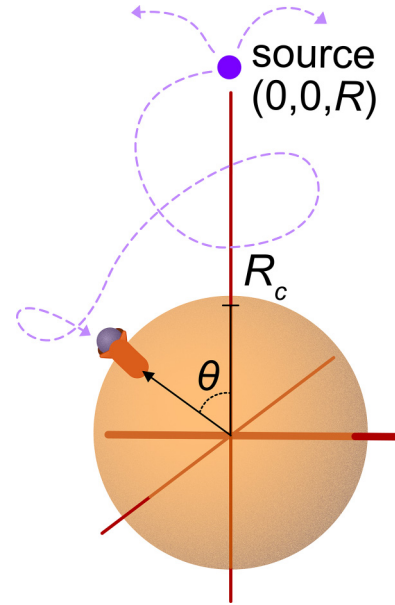


FIG. 1. Schematic of the reaction-diffusion model. A spherical detector of radius R_c is situated at origin. A point source of the chemoattractant is situated at $(0,0,R)$. The ligand diffuses with a diffusion constant D and is taken up and degraded by the detector at a rate k_c . Ligands (pink circles) diffuse from the source and are degraded via receptor-mediated endocytosis on the surfaces of the detector.

(Fig. 1). A finite-sized detector of radius R_c , representing a single cell or a compact cell cluster, is placed at the origin. A second cell or cluster, treated as a point source, is located a distance R away along a fixed axis and secretes a diffusible ligand at a constant rate. The ligand diffuses in the extracellular medium with diffusion constant D and is removed at the detector surface via receptor-mediated endocytosis. The detector may also secrete ligand uniformly from its surface. Owing to the axial symmetry of this configuration, the steady-state ligand concentration depends only on the radial distance from the detector and the polar angle relative to the source. The localized source establishes a nonuniform ligand field, so the detector experiences a front-back concentration difference. The central question we address is how receptor-mediated endocytosis at the detector surface reshapes this field, and thereby the directional information available to the detector.

At steady state, the extracellular ligand concentration satisfies the diffusion equation with a localized source,

$$D\nabla^2 c(\mathbf{r}) + 4\pi R_c^3 Q_0 \delta(\mathbf{r} - \mathbf{R}_0) = 0, \quad (1)$$

where the point source at position $\mathbf{R}_0$ represents a cell or cell cluster that secretes ligand at a constant rate. Q_0 sets the source strength and has units of concentration per unit time. Here, $c(\mathbf{r}) \equiv c(r, \theta, \phi)$ denotes the ligand concentration throughout the three-dimensional extracellular medium, expressed in spherical coordinates (r, θ, ϕ) centered on the detector with the polar axis directed toward the source. By azimuthal symmetry, c is independent of ϕ , so we write $c(r, \theta)$, and its restriction to the detector surface $r = R_c$ is denoted as $c(R_c, \theta)$. Far from the cells, the ligand concentration vanishes, reflecting dilution into the surrounding medium.

At the surface of the detector, ligand dynamics are governed by a Robin boundary condition that balances diffusive flux with receptor-mediated endocytosis and possible surface secretion,

$$-D \frac{\partial c}{\partial r} \Big|_{r=R_c} = -R_c k_c c(R_c, \theta) + R_c \alpha Q_0, \quad (2)$$

where k_c is the effective rate of ligand removal via receptor-mediated endocytosis (a first-order rate constant with units of inverse time) and αQ_0 denotes uniform ligand secretion from the detector surface. Taking the uptake flux proportional to the local surface concentration $c(R_c, \theta)$ is valid in the low-occupancy regime $c \ll K_D$ relevant here, where the density of ligand-bound receptors, and hence the internalization flux, is linear in the local ligand concentration [33] (see the Appendix). This boundary condition captures the essential physics of autonomous gradient generation: Ligand removal occurs locally at the detector boundary, while secretion and diffusion act in the bulk.

Before solving Eqs. (1) and (2), it is useful to rewrite the problem in dimensionless form to identify the minimal set of parameters controlling gradient formation. We measure distances in units of the detector radius, $\lambda = r/R_c$, and define the dimensionless source separation $\rho = R/R_c$. Writing the ligand concentration as $\chi(\lambda, \theta) = c(r, \theta)/\zeta$, with

$$\zeta \equiv \frac{R_c^2 Q_0}{D}, \quad (3)$$

rescales concentrations by the characteristic level set by secretion and diffusion.

In these variables, the governing equations depend on a single dimensionless control parameter,

$$\gamma_0 \equiv \frac{R_c^2 k_c}{D}, \quad (4)$$

a Damköhler number that compares the rate of receptor-mediated endocytosis at the detector surface to diffusive transport in the extracellular medium. The relative secretion rate of the detector is captured by the dimensionless ratio $\alpha = Q_1/Q_0$. Expressed in this form, the steady-state ligand profile is fully specified by ρ , α , and γ_0 , revealing that autonomous gradient generation is governed by a small number of physically transparent parameters.

The full analytical solution to Eqs. (1) and (2) is given in the Appendix. Here, we briefly summarize its structure. Owing to axial symmetry about the source-detector axis, the steady-state ligand concentration depends only on the radial distance from the detector and the polar angle relative to the source direction. The solution naturally separates into two regions: an inner region extending from the detector surface to the source location and an outer region extending from the source to infinity. In each region, the concentration can be expanded in Legendre polynomials,

$$\chi(\lambda, \theta) = \sum_{l=0}^{\infty} f_l(\lambda) P_l(\cos \theta), \quad (5)$$

with radial mode functions $f_l(\lambda)$ determined by continuity of the concentration, the discontinuity in flux at the source, and the Robin boundary condition at the detector surface. This

representation makes explicit how different angular modes contribute to surface anisotropy and provides a direct route to quantifying directional information sensed by the detector.

III. PARAMETER RANGES

Before examining the predictions of the model, we identify biologically relevant ranges for the parameters that control ligand transport and sensing.

The typical linear size of a eukaryotic cell lies in the range $R_c \sim 10\text{--}60 \mu\text{m}$ [34]. Diffusible ligands such as growth factors have diffusion constants of order $D \sim 50 \mu\text{m}^2 \text{s}^{-1}$ [34]. Ligand secretion rates are estimated to be in the range $10^3\text{--}10^4$ molecules per cell per minute [35]. The typical separation between communicating cells or compact cell clusters is on the order of a few to ten cell diameters, $R \sim 5\text{--}10 R_c$ [17,18]. The size of such clusters is typically $N_{\text{cell}} \sim 10\text{--}100$ cells [17,18].

When nontransformed epithelial cells acquire motility through epithelial to mesenchymal transition, ligand secretion is often downregulated [36]. We therefore focus on relative detector secretion rates $\alpha \leq 1$. Unless stated otherwise, we set $\alpha = 1$, corresponding to symmetric secretion by the source and detector.

The key dimensionless control parameter in the model is the Damköhler number $\gamma_0 = R_c^2 k_c/D$, which compares the rate of receptor-mediated ligand removal at the detector surface to diffusive transport in the extracellular medium. As shown in the Appendix, γ_0 can be expressed in terms of microscopic signaling parameters as

$$\gamma_0 = \frac{R_c d_0 k_{\text{int}}}{DK_D}, \quad (6)$$

where $d_0 \sim 100 \mu\text{m}^{-2}$ is the surface density of receptors, $K_D \sim 0.1\text{--}1 \text{nM}$ is the equilibrium dissociation constant of the ligand-receptor interaction, and $k_{\text{int}} \sim 10^{-3}$ to 10^{-2}s^{-1} is the internalization rate of ligand-bound receptors [31,32,34,37]. Directly measured first-order internalization rate constants for growth-factor and G protein-coupled receptors span $\sim 0.03\text{--}0.3 \text{min}^{-1}$ (5×10^{-4} to $5 \times 10^{-3} \text{s}^{-1}$) [31], with ligand-activated receptors such as epidermal growth factor receptor (EGFR) internalizing at or above the faster end of this range [32,38]. We emphasize that k_{int} is a per-receptor first-order rate constant rather than a whole-cell uptake flux. Together, these values suggest that γ_0 spans a broad biologically accessible range, $\gamma_0 \sim 10^{-3}$ to 10^1 .

Finally, combining the above estimates yields characteristic concentration scales $\zeta = R_c^2 Q_0/D$ in the range $\zeta \sim 10^{-3}$ to 1nM . In the following, unless stated otherwise, we focus on the representative parameter set $\rho = 4$, $\alpha = 1$, and $\gamma_0 = 1$, which lies well within the experimentally relevant regime.

IV. CONCENTRATION PROFILE IN SPACE

Figure 2(a) shows a representative two-dimensional concentration profile $\chi(\lambda, \theta)$ obtained from the analytical solution. As expected, ligand concentration increases toward the emitting source and decreases far from it. Near the detector, however, the profile exhibits qualitatively different behavior

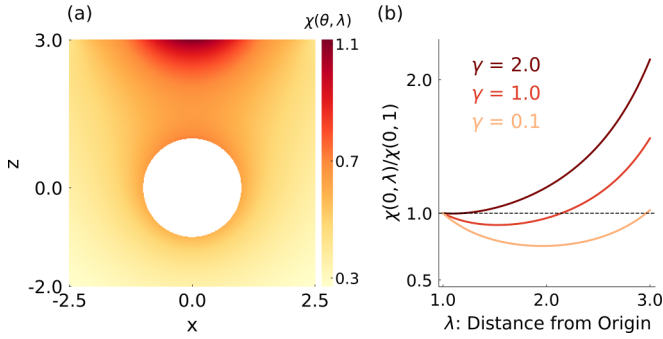


FIG. 2. Concentration profiles in space and on the surface of the detector. (a) A two-dimensional dimensionless concentration profile $[\chi(\lambda, \theta)]$ of the ligand. The detector of unit dimensionless radius is situated at the origin. A point source is situated at $\rho = 4$. We have assumed that $\gamma_0 = 1$ and $\alpha = 1$. (b) Profile of the dimensionless concentration at $\theta = 0$ as a function of λ for different values of γ_0 .

depending on direction. Along the axis pointing away from the source ($\theta = \pi$), the concentration decreases monotonically with distance from the detector. In contrast, along the axis pointing toward the source ($\theta = 0$), the concentration can be nonmonotonic, reflecting the competition between ligand secretion by the detector and endocytotic removal at its surface.

This competition is controlled by the Damköhler number γ_0 . As shown in Fig. 2(b), increasing receptor-mediated endocytosis suppresses the outward flux due to detector secretion, eventually eliminating the nonmonotonicity and producing a concentration profile that increases monotonically away from the detector. These spatial profiles illustrate how surface-localized ligand removal reshapes the extracellular field in a direction-dependent manner, even in the absence of any externally imposed gradient.

Concentration anisotropy on the cell surface. To quantify directional information available to the detector, we focus on the anisotropy of ligand concentration along its surface. Specifically, we define the mean surface concentration on the hemisphere facing the source ($0 \leq \theta \leq \pi/2$),

$$\chi_F = \int_0^{2\pi} d\phi \int_0^{\pi/2} \chi(1, \theta) \sin \theta d\theta, \quad (7)$$

and the corresponding mean concentration on the opposite hemisphere ($\pi/2 \leq \theta \leq \pi$),

$$\chi_B = \int_0^{2\pi} d\phi \int_{\pi/2}^{\pi} \chi(1, \theta) \sin \theta d\theta. \quad (8)$$

These quantities provide coarse-grained measures of the ligand and signal at the front and back of the detector and are natural observables for downstream chemotactic circuits that integrate receptor occupancy over finite regions of the cell surface.

A natural measure of directional signal strength is the absolute difference in ligand concentration across the detector surface,

$$g_{\text{abs}} \equiv \chi_F - \chi_B. \quad (9)$$

Figure 3(a) shows g_{abs} as a function of γ_0 for several source-detector separations. In all cases, the absolute gradient

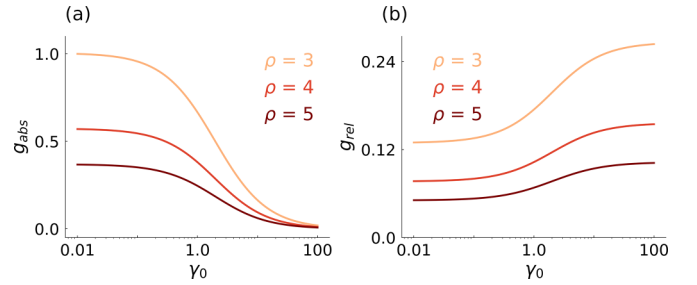


FIG. 3. Absolute and relative ligand gradients as a function of ligand degradation. (a) The absolute gradient g_{abs} as a function of γ_0 for different values of ρ . (b) The relative gradient g_{rel} as a function of γ_0 for different values of ρ .

decreases monotonically with increasing receptor-mediated endocytosis. This behavior is intuitive: Stronger endocytosis lowers ligand abundance throughout the extracellular medium, reducing concentration differences across the detector surface even as it sharpens spatial structure. As a result, when gradients are quantified purely in absolute terms, increased ligand removal appears detrimental to directional sensing.

While absolute concentration differences decrease with increasing receptor-mediated endocytosis, many chemotactic systems respond not to absolute signals but to relative differences across the cell surface [10,12,39,40]. We therefore define the relative gradient as

$$g_{\text{rel}} \equiv \frac{\chi_F - \chi_B}{\chi_B}. \quad (10)$$

Figure 3(b) shows g_{rel} as a function of γ_0 for several source-detector separations. In contrast to the absolute gradient, the relative gradient increases monotonically with increasing endocytosis over a broad parameter range. Compared to the limit of vanishing endocytosis, strong receptor-mediated ligand removal can enhance the relative surface anisotropy by up to a factor of 2. Notably, the benefit of endocytosis becomes relevant around $\gamma_0 = 1$, well within the ranges predicted by typical signaling parameters (dashed black box).

This behavior highlights a central and counterintuitive feature of autonomous gradient generation: Degrading the very signal being detected sharpens the directional contrast available to the detector. Physically, surface-localized ligand removal suppresses the isotropic background concentration more strongly than the anisotropic component induced by the distant source, thereby enhancing relative differences across the detector surface.

Endocytosis rates may be aligned with downstream processing. If receptor-mediated endocytosis sharpens relative gradients, a natural question is why cells do not simply maximize ligand removal. One reason is that increasing endocytosis, while enhancing relative anisotropy, simultaneously reduces the absolute ligand concentration at the detector surface. Because downstream chemotactic circuits typically respond nonlinearly to ligand exposure, relative sensing is effective only over a finite dynamic range of background signal levels [12,30]. At very low concentrations, the response is negligible, while at high concentrations it saturates.

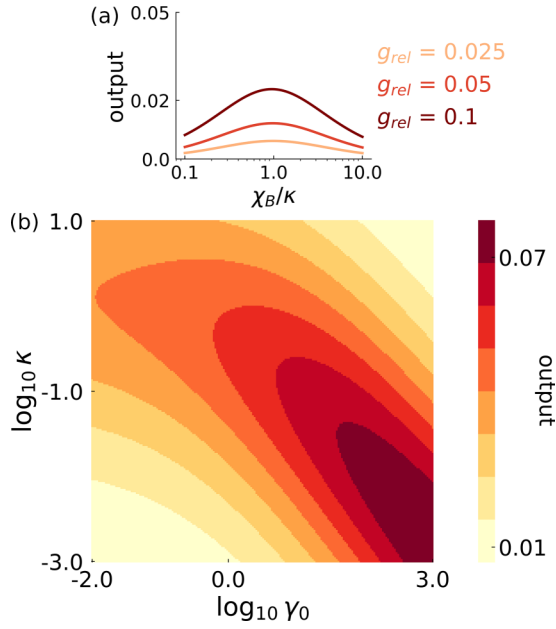


FIG. 4. Downstream processing of relative gradients defines a joint optimal regime in the (γ_0, κ) plane. (Top) A schematic of the output as a function of background ligand levels χ_B for increasing values of the relative gradient g_{rel} . (Bottom) Heatmap of the output of the downstream circuit as a function of midpoint of activation κ and γ_0 .

To capture this constraint on downstream processing in a minimal way, we introduce a phenomenological output that maps surface ligand levels onto a directional response,

$$o = \frac{\chi_F}{\chi_F + \kappa} - \frac{\chi_B}{\chi_B + \kappa}, \quad (11)$$

where κ sets the midpoint of the downstream activation curve. This form captures the qualitative behavior of many adaptive chemotactic circuits that respond to relative differences only within a limited concentration window (top schematic in Fig. 4). Typically, the sensitive ligand concentration range c_{FCD} for fold change detection, centered around κ , is a couple of orders of magnitude lower than the equilibrium dissociation constant of the ligand ($c_{FCD} \sim 0.01K_D$) [12,30]. Since $K_D \sim 0.1$ – 1 nM and $\zeta = 10^{-3}$ to 1 nM, this suggests that the typical values of the dimensionless concentration $\kappa = c_{FCD}/\zeta \sim 10^{-3}$ to 10^1 . Because the directional signal is interpreted by downstream components with a finite dynamic range, the output o depends jointly on the endocytic rate γ_0 and the downstream activation midpoint κ . As shown in Fig. 4, o is maximized over a joint regime in the (γ_0, κ) plane, reflecting a balance between contrast enhancement and signal depletion. The independently measured ranges of the receptor internalization rate and of the downstream fold-change-detection window both fall within this joint optimal regime, so the coupled system of surface ligand removal and downstream processing appears to operate near its optimum.

Together, these results establish a minimal and physically transparent mechanism by which cells can generate and sense directional cues in the absence of any externally imposed gradient. By resolving ligand concentrations along the surface of a finite-sized detector, we show that receptor-mediated

endocytosis plays a dual role: It suppresses absolute signal levels while simultaneously enhancing relative surface anisotropy. This trade-off leads naturally to a joint optimal regime of endocytosis and downstream processing once downstream nonlinearities are taken into account. Importantly, all of these behaviors are controlled by a small number of dimensionless parameters, with the Damköhler number γ_0 acting as the primary control knob. These findings demonstrate that secretion, diffusion, and receptor-mediated endocytosis alone are sufficient to generate robust, surface-resolved directional information at cell-cell length scales.

V. DISCUSSION

Receptor-mediated endocytosis underlies essential homeostatic functions such as nutrient uptake and receptor turnover [41], and in the context of signaling it is thought to be crucial for attenuating cellular responses to extracellular signals. In the context of chemotaxis, it is well known to shape tissue-scale gradients by acting as a sink that stabilizes long-range concentration profiles [4–7]. Here, by resolving ligand concentrations along the surface of a finite-sized detector, we show that endocytosis plays a fundamentally different and previously underappreciated role in autonomous cell-cell communication. Rather than merely suppressing signals, surface-localized ligand removal actively reshapes the spatial structure of the extracellular gradient, suppressing absolute concentrations while sharpening relative surface anisotropy, the quantity most directly relevant for directional sensing [10,12,39,40].

A central implication of our results is that secretion, diffusion, and receptor-mediated endocytosis alone are sufficient to generate usable directional information at cell-cell length scales, even in the absence of any externally imposed guidance cue. Our work shows that the detector surface can sharpen the anisotropy in ligand fields set by nearby sources via endocytosis of ligands without invoking any additional signal processing or patterning.

The paradoxical enhancement of relative gradients by endocytosis highlights an important distinction between signal amplitude and information content. While increased ligand removal lowers absolute concentrations throughout the extracellular medium, it preferentially suppresses the background relative to the directional component induced by a distant source. In this sense, receptor-mediated endocytosis functions as an information-processing element that tunes the statistics of the signal before it is decoded by downstream pathways. Importantly, relative gradient enhancement does not imply that endocytosis should be maximized. Once downstream nonlinearities are taken into account, the directional output depends jointly on the rate of ligand removal and on the dynamic range of the downstream readout, and is greatest within a joint optimal regime of this combined system rather than at any single endocytic rate. The experimentally measured ranges of receptor internalization rates [31,32] and of the downstream fold-change-detection window [30] both fall within this joint regime. Therefore, while endocytosis serves many functions beyond chemotaxis and is bounded by its own physical and molecular constraints, the coupled system of surface ligand removal and downstream processing appears to operate near its optimum.

Recent theoretical work has shown that signal degradation can similarly enhance directional sensing in three-dimensional settings where the receiver cell secretes enzymes to degrade the ligand in space [42]. These findings highlight a broader principle whereby ligand removal can enhance usable information in diffusive fields. It will be interesting to systematically compare such three-dimensional sensing strategies with the surface-resolved mechanism studied here, where boundary-localized uptake reshapes extracellular gradients. Such a comparison may clarify how dimensionality and geometry jointly constrain optimal strategies for gradient formation and sensing in biological systems. We leave this exploration for future studies.

Our framework makes several experimentally testable predictions. Pharmacological inhibition or genetic perturbation of endocytosis [43] should increase overall ligand abundance while reducing relative surface anisotropy, leading to weaker directional bias at long intercellular distances despite higher ligand levels. Conversely, moderate enhancement of endocytosis should improve directional sensing over a finite range of separations before signal depletion dominates. Such effects could be tested by measuring migration speed, directional persistence, or clustering dynamics as a function of distance between communicating cells or clusters [17,18].

Several simplifications underlie our minimal description. The single effective rate k_c is the net rate of ligand-coupled removal at the surface, aggregated over whatever molecular pathway (clathrin mediated, fast endophilin mediated, or other) carries it out. Endocytosis is constitutive and operates continuously in all eukaryotic cells, not only motile ones, and internalizes receptors regardless of ligand occupancy, including adhesion molecules and receptors that have already released their ligand as part of the exocytic cycle [41]. Such ligand-independent internalization does not remove free extracellular ligand and therefore does not enter the equation governing the gradient; it bears on our description only through the receptor density that sets the value of k_c .

Several extensions follow naturally. First, we treat k_c as uniform and constant, whereas endocytic initiation is sensitive to the local density of membrane receptors, both experimentally [41] and in recent theoretical models of membrane-associated assembly [44]. Second, we do not model ligand-triggered degradation of receptors, which would render k_c dependent on the local ligand concentration and therefore on position, $k_c(\theta)$. Because the source-facing surface is exposed to more ligand, such coupling would generate a feedback that could further sharpen the front-back asymmetry or, through receptor depletion, eventually saturate it. Third, the anisotropic, locally regulated uptake assumed here has a concrete biological counterpart in fast endophilin-mediated endocytosis, which is triggered by extracellular cues, selectively internalizes G protein coupled receptors (GPCRs) and other receptors, and is spatially biased toward the leading edge of motile cells [45]. Incorporating receptor-density dependence, ligand-dependent internalization, and spatially polarized uptake would couple extracellular gradient shaping to the intracellular signaling and trafficking machinery, and is a natural direction for future work.

More broadly, our results suggest a shift in how autonomous chemotaxis is conceptualized. Rather than viewing

gradient sensing solely as an intracellular decoding problem [8,11], our work emphasizes the role of the sensing machinery in shaping the signal itself. This study provides a minimal physical foundation for understanding how cells communicate directionally in the absence of externally imposed cues. Such mechanisms are likely to be relevant for collective migration, tissue organization, and pattern formation in complex multicellular environments.

ACKNOWLEDGMENTS

S.E.L. acknowledges the National Science Foundation under Award No. 2428662. P.D.D. acknowledges the National Institutes of Health under Award No. R35GM142547.

DATA AVAILABILITY

There are no publicly available research data or software supporting this manuscript. Requests for further information or data should be sent to the authors.

APPENDIX

1. Analytical solution

We start with the dimensionless equations

$$\nabla_\lambda^2 \chi + 4\pi \delta(\lambda - \rho_0) = 0, \quad (\text{A1})$$

where $\rho_0 = (0, 0, \rho)$ is the dimensionless location of the source. The boundary conditions read

$$(1) \chi(\lambda, \theta) \rightarrow 0 \quad \text{as } \lambda \rightarrow \infty \quad \text{and} \quad (\text{A2})$$

$$(2) \left. \frac{\partial \chi}{\partial \lambda} \right|_{\lambda=1} = \gamma_0 \chi(1, \theta) - \alpha. \quad (\text{A3})$$

Due to the azimuthal symmetry, the general solution for the problem is given by

$$\chi(\lambda, \theta) = \sum_{l=0}^{\infty} f_l(\lambda) P_l(\cos \theta), \quad (\text{A4})$$

where $P_l(\cos \theta)$ are Legendre polynomials and radial functions $f_l(\lambda)$ satisfy

$$\frac{d}{d\lambda} (\lambda^2 f_l'(\lambda)) - l(l+1)f_l(\lambda) = 0. \quad (\text{A5})$$

The solutions to Eq. (A5) are given by

$$f_l^<(\lambda) = X_l \lambda^l + Y_l \lambda^{-(l+1)}, \quad 1 \leq \lambda < \rho, \quad (\text{A6})$$

$$f_l^>(\lambda) = Z_l \lambda^{-(l+1)}, \quad \lambda > \rho. \quad (\text{A7})$$

The far field solutions ($\lambda > \rho$) do not contain λ^l terms to ensure finite concentration as $\lambda \rightarrow \infty$. To ensure continuity of the solution at $\lambda = \rho$, we require

$$f_l^<(\rho) = f_l^>(\rho) \Rightarrow \boxed{Z_l = X_l \rho^{2l+1} + Y_l}. \quad (\text{A8})$$

To determine X_l and Y_l , we use (1) the jump discontinuity in the radial derivative arising from the point source and (2) the Robin type boundary condition on the surface of the sink. First, we focus on the discontinuity. To evaluate the discontinuity, we start with the governing equation Eq. (A1):

$$\nabla_\lambda^2 \chi + 4\pi \delta(\lambda - \rho_0) = 0 \quad (\text{A9})$$

and recognize $\chi(\lambda, \theta) = \sum_{m=0}^{\infty} f_m(\lambda) P_m(\cos \theta)$ [Eq. (A4)]. Multiplying both sides by $P_l(\cos \theta)$ and integrating over the full solid angle $d\Omega = \sin \theta d\theta d\phi$:

$$I_1 + I_2 = 0, \quad (\text{A10})$$

where

$$I_1 = \iint_{S^2} P_l(\cos \theta) \nabla_{\lambda}^2 \chi d\Omega \quad (\text{A11})$$

and

$$I_2 = 4\pi \iint_{S^2} P_l(\cos \theta) \delta(\lambda - \rho_0) d\Omega. \quad (\text{A12})$$

Using

$$\nabla_{\lambda}^2 \chi = \sum_{m=0}^{\infty} \left[\frac{1}{\lambda^2} \frac{d}{d\lambda} (\lambda^2 f'_m(\lambda)) - \frac{m(m+1)}{\lambda^2} f_m(\lambda) \right] P_m(\cos \theta) \quad (\text{A13})$$

and

$$\iint_{S^2} P_l P_m d\Omega = \frac{4\pi}{2l+1} \delta_{lm}, \quad (\text{A14})$$

we obtain

$$I_1 = \frac{4\pi}{2l+1} \left[\frac{1}{\lambda^2} \frac{d}{d\lambda} (\lambda^2 f'_l(\lambda)) - \frac{l(l+1)}{\lambda^2} f_l(\lambda) \right]. \quad (\text{A15})$$

To evaluate I_2 , we recognize $\delta(\lambda - \rho_0) = \frac{1}{\lambda^2} \delta(\lambda - \rho) \delta(\Omega - \Omega_0)$, where Ω_0 is the source direction ($\theta_0 = 0, \phi_0 = 0$). Then,

$$\begin{aligned} I_2 &= \frac{1}{\lambda^2} \delta(\lambda - \rho) \iint_{S^2} P_l(\cos \theta) \delta(\Omega - \Omega_0) d\Omega \\ &= \frac{1}{\lambda^2} \delta(\lambda - \rho) P_l(1) = \frac{1}{\lambda^2} \delta(\lambda - \rho). \end{aligned} \quad (\text{A16})$$

Therefore,

$$\begin{aligned} &\frac{4\pi}{2l+1} \left[\frac{1}{\lambda^2} \frac{d}{d\lambda} (\lambda^2 f'_l(\lambda)) - \frac{l(l+1)}{\lambda^2} f_l(\lambda) \right] \\ &+ 4\pi \frac{1}{\lambda^2} \delta(\lambda - \rho) = 0. \end{aligned} \quad (\text{A17})$$

Multiplying by λ^2 and integrating over $\lambda \in (\rho - \varepsilon, \rho + \varepsilon)$:

$$\begin{aligned} &\frac{4\pi}{2l+1} \int_{\rho-\varepsilon}^{\rho+\varepsilon} \frac{d}{d\lambda} (\lambda^2 f'_l(\lambda)) d\lambda \\ &- \frac{4\pi}{2l+1} \int_{\lambda-\varepsilon}^{\lambda+\varepsilon} l(l+1) f_l(\lambda) d\lambda \\ &+ 4\pi \int_{\lambda-\varepsilon}^{\lambda+\varepsilon} \delta(\lambda - \rho) d\lambda = 0. \end{aligned} \quad (\text{A18})$$

The second term evaluates to zero as $\varepsilon \rightarrow 0$. We have

$$\frac{4\pi}{2l+1} [\lambda^2 f'_l(\lambda)]_{\rho^-}^+ = -4\pi. \quad (\text{A19})$$

Using Eq. (A19), we determine X_l . We have

$$\text{region I } (1 \leq \lambda < \rho) : f_l^<(\lambda) = X_l \lambda^l + Y_l \lambda^{-(l+1)}, \quad (\text{A20})$$

$$\text{region II } (\lambda > \rho) : f_l^>(\lambda) = Z_l \lambda^{-(l+1)}. \quad (\text{A21})$$

Therefore,

$$\lambda^2 f_l^<'(\lambda) = X_l l \lambda^{l+1} - Y_l (l+1) \lambda^{-l} \quad (\text{A22})$$

and

$$\lambda^2 f_l^>'(\lambda) = -(l+1) Z_l \lambda^{-l}. \quad (\text{A23})$$

Continuity at $\lambda = \rho$ gives $Z_l = X_l \rho^{2l+1} + Y_l$. Therefore,

$$\begin{aligned} [\lambda^2 f'_l(\lambda)]_{\rho^-}^+ &= (\lambda^2 f_l^>'(\lambda))|_{\lambda=\rho} - (\lambda^2 f_l^<'(\lambda))|_{\lambda=\rho} \\ &= -(l+1) Z_l \rho^{-l} - (X_l l \rho^{l+1} - Y_l (l+1) \rho^{-l}) \\ &= -X_l (2l+1) \rho^{l+1}, \end{aligned} \quad (\text{A24})$$

where the Y_l terms cancel using $Z_l = X_l \rho^{2l+1} + Y_l$. Therefore, we have

$$X_l = \rho^{-(l+1)}. \quad (\text{A25})$$

Next, we determine Y_l using the Robin boundary conditions. At $r = R_c$, we impose

$$\frac{\partial \chi}{\partial \lambda} \Big|_{\lambda=1} = \chi(1, \theta) - \alpha. \quad (\text{A26})$$

We evaluate the derivatives in region 1,

$$f_l^<(1) = X_l + Y_l \quad (\text{A27})$$

and

$$f_l^<'(1) = X_l l - Y_l (l+1). \quad (\text{A28})$$

Next, we project the boundary condition onto $P_l(\cos \theta)$. Since $-\alpha \gamma_0$ does not depend on θ , it contributes only to the $l = 0$ mode. Therefore, for $l > 0$,

$$[X_l l - Y_l (l+1)] = \gamma_0 [X_l + Y_l]. \quad (\text{A29})$$

Solving for Y_l yields

$$Y_l = X_l \frac{l - \gamma_0}{l + \gamma_0 + 1} \quad \forall l > 0. \quad (\text{A30})$$

For $l = 0$,

$$Y_0 = \frac{\alpha \rho - \gamma_0}{(1 + \gamma_0) \rho}. \quad (\text{A31})$$

Z_l can be obtained from X_l and Y_l using Eq. (A8).

2. Expressing γ_0 using signaling parameters

Let us consider the boundary condition:

$$\frac{D}{R_c} \frac{\partial c}{\partial r} = k_c c \quad (\text{A32})$$

$$\Rightarrow \frac{D}{R_c k_c} \frac{\partial c}{\partial r} = c. \quad (\text{A33})$$

The total flux of ligands at the surface is (from the environment to the cell)

$$\int D \sin^2 \theta \frac{\partial c}{\partial r} d\theta d\phi = k_c R_c^3 \int \sin^2 \theta c(\theta) d\theta d\phi \quad (\text{A34})$$

$$= k_c R_c^3 C_0, \quad (\text{A35})$$

where

$$C_0 = \int \sin^2 \theta c(\theta) d\theta d\phi. \quad (\text{A36})$$

Let us assume that the receptor density is d_0 . When the ligand concentration is small, the total number of bound receptors in a small region of the surface is given by $\frac{c}{K_D} d_0 R_c^2 \sin^2 \theta d\theta d\phi$, where K_D is the equilibrium dissociation constant of the ligand. Therefore, we have an expression for the net number of receptors degraded along the cell surface:

$$\int k_{\text{int}} \frac{c}{K_D} d_0 R_c^2 \sin^2 \theta d\theta d\phi = \frac{k_{\text{int}} d_0 R_c^2}{K_D} C_0, \quad (\text{A37})$$

where k_{int} is the internalization rate of receptors. Equating the two fluxes, we have

$$\frac{k_{\text{int}} d_0 R_c^2}{K_D} C_0 = k_c R_c^3 C_0 \quad (\text{A38})$$

$$\Rightarrow k_c = \frac{k_{\text{int}} d_0}{R_c K_D}. \quad (\text{A39})$$

The relevant dimensionless constant is $\gamma_0 = R_c^2 k_c / D$, given by

$$\gamma_0 = \frac{R_c d_0 k_{\text{int}}}{D K_D}. \quad (\text{A40})$$

This derivation also clarifies the sense in which the diverse endocytic activity of a cell is reduced to a single effective rate. The flux that enters the boundary condition is the removal of free extracellular ligand, which occurs only through internalization of ligand-bound receptors and is proportional to the local ligand concentration in the low-occupancy regime ($c \ll K_D$). Endocytosis that carries no ligand, such as constitutive internalization of receptors or uptake of adhesion molecules and ligand-free receptors, removes no free ligand and therefore does not appear in the mass balance for c . Such pathways influence the extracellular field only indirectly, by setting the steady-state surface receptor density d_0 that enters k_c through Eq. (A39). The single effective rate k_c thus captures the net ligand-coupled removal at the surface, independent of which molecular pathway (clathrin mediated, fast endophilin mediated, or other) executes it.

-
- [1] H. Levine and W.-J. Rappel, The physics of eukaryotic chemotaxis, *Phys. Today* **66**(2), 24 (2013).
 - [2] B. Moser and K. Willmann, Chemokines: Role in inflammation and immune surveillance, *Ann. Rheum. Dis.* **63**, ii84 (2004).
 - [3] E. T. Roussos, J. S. Condeelis, and A. Patsialou, Chemotaxis in cancer, *Nat. Rev. Cancer* **11**, 573 (2011).
 - [4] F. Crick, Diffusion in embryogenesis, *Nature (London)* **225**, 420 (1970).
 - [5] A. Eldar, D. Rosin, B.-Z. Shilo, and N. Barkai, Self-enhanced ligand degradation underlies robustness of morphogen gradients, *Dev. Cell* **5**, 635 (2003).
 - [6] S. R. Yu, M. Burkhardt, M. Nowak, J. Ries, Z. Petrášek, S. Scholpp, P. Schwill, and M. Brand, Fgf8 morphogen gradient forms by a source-sink mechanism with freely diffusing molecules, *Nature (London)* **461**, 533 (2009).
 - [7] C. M. Nelson, Geometric control of tissue morphogenesis, *Biochim. Biophys. Acta, Mol. Cell Res.* **1793**, 903 (2009).
 - [8] H. Levine, D. A. Kessler, and W.-J. Rappel, Directional sensing in eukaryotic chemotaxis: A balanced inactivation model, *Proc. Natl. Acad. Sci. USA* **103**, 9761 (2006).
 - [9] D. Ellison, A. Mugler, M. D. Brennan, S. H. Lee, R. J. Huebner, E. R. Shamir, L. A. Woo, J. Kim, P. Amar, I. Nemenman, *et al.*, Cell-cell communication enhances the capacity of cell ensembles to sense shallow gradients during morphogenesis, *Proc. Natl. Acad. Sci. USA* **113**, E679 (2016).
 - [10] K. Takeda, D. Shao, M. Adler, P. G. Charest, W. F. Loomis, H. Levine, A. Groisman, W.-J. Rappel, and R. A. Firtel, Incoherent feedforward control governs adaptation of activated Ras in a eukaryotic chemotaxis pathway, *Sci. Signaling* **5**, ra2 (2012).
 - [11] A. Levchenko and P. A. Iglesias, Models of eukaryotic gradient sensing: Application to chemotaxis of amoebae and neutrophils, *Biophys. J.* **82**, 50 (2002).
 - [12] A. Goetz and P. Dixit, Emergent eukaryotic directional sensing via receptor degradation and diffusion, *Proc. Natl. Acad. Sci. USA* **122**, e2516077122 (2025).
 - [13] C. Janetopoulos, L. Ma, P. N. Devreotes, and P. A. Iglesias, Chemoattractant-induced phosphatidylinositol 3, 4, 5-trisphosphate accumulation is spatially amplified and adapts, independent of the actin cytoskeleton, *Proc. Natl. Acad. Sci. USA* **101**, 8951 (2004).
 - [14] J. M. Haugh, F. Codazzi, M. Teruel, and T. Meyer, Spatial sensing in fibroblasts mediated by 3 phosphoinositides, *J. Cell Biol.* **151**, 1269 (2000).
 - [15] A. A. Hardikar, B. Marcus-Samuels, E. Geras-Raaka, B. M. Raaka, and M. C. Gershengorn, Human pancreatic precursor cells secrete FGF2 to stimulate clustering into hormone-expressing islet-like cell aggregates, *Proc. Natl. Acad. Sci. USA* **100**, 7117 (2003).
 - [16] M. G. Castro, S. E. Leggett, and I. Y. Wong, Clustering and jamming in epithelial-mesenchymal co-cultures, *Soft Matter* **12**, 8327 (2016).
 - [17] S. E. Leggett, Z. J. Neronha, D. Bhaskar, J. Y. Sim, T. M. Perdikari, and I. Y. Wong, Motility-limited aggregation of mammary epithelial cells into fractal-like clusters, *Proc. Natl. Acad. Sci. USA* **116**, 17298 (2019).
 - [18] A. Puliafito, A. De Simone, G. Seano, P. A. Gagliardi, L. Di Blasio, F. Chianale, A. Gamba, L. Primo, and A. Celani, Three-dimensional chemotaxis-driven aggregation of tumor cells, *Sci. Rep.* **5**, 15205 (2015).
 - [19] I. Pinilla-Macua and A. Sorkin, Cbl and Cbl-b independently regulate EGFR through distinct receptor interaction modes, *Mol. Biol. Cell* **34**, ar134 (2023).
 - [20] L. J. Mutch, J. D. Howden, E. P. L. Jenner, N. S. Poulter, and J. Z. Rappoport, Polarised clathrin-mediated endocytosis of EGFR during chemotactic invasion, *Traffic* **15**, 648 (2014).
 - [21] G. Assaker, D. Ramel, S. K. Wculek, M. González-Gaitán, and G. Emery, Spatial restriction of receptor tyrosine kinase activity through a polarized endocytic cycle controls border cell migration, *Proc. Natl. Acad. Sci. USA* **107**, 22558 (2010).

- [22] M. Nowak, A. Machate, S. R. Yu, M. Gupta, and M. Brand, Interpretation of the FGF8 morphogen gradient is regulated by endocytic trafficking, *Nat. Cell Biol.* **13**, 153 (2011).
- [23] H. C. Berg and E. M. Purcell, Physics of chemoreception, *Biophys. J.* **20**, 193 (1977).
- [24] W. Bialek and S. Setayeshgar, Physical limits to biochemical signaling, *Proc. Natl. Acad. Sci. USA* **102**, 10040 (2005).
- [25] R. G. Endres and N. S. Wingreen, Accuracy of direct gradient sensing by single cells, *Proc. Natl. Acad. Sci. USA* **105**, 15749 (2008).
- [26] A. Mugler, A. Levchenko, and I. Nemenman, Limits to the precision of gradient sensing with spatial communication and temporal integration, *Proc. Natl. Acad. Sci. USA* **113**, E689 (2016).
- [27] C. Carmona-Fontaine, E. Theveneau, A. Tzekou, M. Tada, M. Woods, K. M. Page, M. Parsons, J. D. Lambris, and R. Mayor, Complement fragment C3a controls mutual cell attraction during collective cell migration, *Dev. Cell* **21**, 1026 (2011).
- [28] B. A. Camley, J. Zimmermann, H. Levine, and W.-J. Rappel, Collective signal processing in cluster chemotaxis: Roles of adaptation, amplification, and co-attraction in collective guidance, *PLoS Comput. Biol.* **12**, e1005008 (2016).
- [29] H. Knútsdóttir, E. Pálsson, and L. Edelstein-Keshet, Mathematical model of macrophage-facilitated breast cancer cells invasion, *J. Theor. Biol.* **357**, 184 (2014).
- [30] E. Lyashenko, M. Niepel, P. D. Dixit, S. K. Lim, P. K. Sorger, and D. Vitkup, Receptor-based mechanism of relative sensing and cell memory in mammalian signaling networks, *eLife* **9**, e50342 (2020).
- [31] J. A. Koenig and J. M. Edwardson, Endocytosis and recycling of G protein-coupled receptors, *Trends Pharmacol. Sci.* **18**, 276 (1997).
- [32] H. S. Wiley, Trafficking of the ErbB receptors and its influence on signaling, in *The EGF Receptor Family*, edited by G. Carpenter (Academic Press, Cambridge, 2003), pp. 81–91.
- [33] D. A. Lauffenburger and J. J. Linderman, *Receptors: Models for Binding, Trafficking, and Signaling* (Oxford University Press, Oxford, 1996).
- [34] R. Milo, P. Jorgensen, U. Moran, G. Weber, and M. Springer, Bionumbers—The database of key numbers in molecular and cell biology, *Nucl. Acids Res.* **38**, D750 (2010).
- [35] E. Deguchi, S. Lin, D. Hirayama, K. Matsuda, A. Tanave, K. Sumiyama, S. Tsukiji, T. Otani, M. Furuse, A. Sorkin, *et al.*, Low-affinity ligands of the epidermal growth factor receptor are long-range signal transmitters in collective cell migration of epithelial cells, *Cell Rep.* **43**, 114986 (2024).
- [36] C. Scheel, E. N. Eaton, S. H.-J. Li, C. L. Chaffer, F. Reinhardt, K.-J. Kah, G. Bell, W. Guo, J. Rubin, A. L. Richardson, *et al.*, Paracrine and autocrine signals induce and maintain mesenchymal and stem cell states in the breast, *Cell* **145**, 926 (2011).
- [37] T. Shi, M. Niepel, J. E. McDermott, Y. Gao, C. D. Nicora, W. B. Chrisler, L. M. Markillie, V. A. Petyuk, R. D. Smith, K. D. Rodland, *et al.*, Conservation of protein abundance patterns reveals the regulatory architecture of the EGFR-MAPK pathway, *Sci. Signaling* **9**, rs6 (2016).
- [38] A. Sorkin and L. K. Goh, Endocytosis and intracellular trafficking of ErbBs, *Exp. Cell Res.* **315**, 683 (2009).
- [39] H. Youk and W. A. Lim, Secreting and sensing the same molecule allows cells to achieve versatile social behaviors, *Science* **343**, 1242782 (2014).
- [40] K. Kamino, Y. Kondo, A. Nakajima, M. Honda-Kitahara, K. Kaneko, and S. Sawai, Fold-change detection and scale invariance of cell–cell signaling in social amoeba, *Proc. Natl. Acad. Sci. USA* **114**, E4149 (2017).
- [41] M. Mettlen, P.-H. Chen, S. Srinivasan, G. Danuser, and S. L. Schmid, Regulation of clathrin-mediated endocytosis, *Annu. Rev. Biochem.* **87**, 871 (2018).
- [42] R. LeFebvre, J. A. Landsittel, D. E. Stone, and A. Mugler, Role of signal degradation in directional chemosensing, *Phys. Rev. Lett.* **133**, 138402 (2024).
- [43] T. Kirchhausen, E. Macia, and H. E. Pelish, Use of dynasore, the small molecule inhibitor of dynamin, in the regulation of endocytosis, *Methods Enzymol.* **438**, 77 (2008).
- [44] S. L. Foley and M. E. Johnson, Membrane-associated self-assembly for cellular decision-making, *Phys. Rev. Res.* **8**, 023280 (2026).
- [45] A. Casamento and E. Boucrot, Molecular mechanism of fast endophilin-mediated endocytosis, *Biochem. J.* **477**, 2327 (2020).