Supporting Text

Parameter Values. Values for the dimensional model parameters shown in Table 1 were chosen based on available experimental data in other systems as outlined below. The associated reference values of dimensionless parameter groups are listed in Table 2.

k_m^+ is a lumped activation constant of MPK-1 based on a more detailed biochemical mechanism of mitogen-activated protein kinase (MAPK) activation by its upstream kinase (MAPKK) (1). Its value was estimated from the rate constant for the formation of activated MAPK from MAPKK*-MAPK complex and the equilibrium constant for MAPKK*-MAPK complex formation. k_m^- is the lumped rate constant with which phosphatases deactivate MPK-1*. Likewise, its value was estimated from data available for MAPK*-Phosphatase complex formation (1). No upregulation or downregulation of constitutive phosphatases was modeled, thus phosphatase levels are constant at $\left(Ph_{\mathrm{T}}\right)$. The maximum number of morphogen:morphogen receptor complexes Ind^{m} and the total number of MPK-1 molecules mpk_{T} are estimated from the total number of epidermal growth factor (EGF) receptor molecules per cell and the total number of MAPK molecules per cell, respectively (1).

k_n^+ is the constitutive rate of lateral signaling generation. This process it thought to be limited by synthesis of ligand LAG-2 or receptor LIN-12. We use a numerical estimate for k_n^+ based on the rate of EGF receptor (EGFR) synthesis (2). k_n^- is the rate of constitutive deactivation of lateral signaling. Deactivation of lateral signaling occurs via two mechanisms: LAG-2:LIN-12 complexes dissociate or the cytoplasmic tail of LIN-12 is cleaved upon association with LAG-1 transcription factor. We assume that cytoplasmic LIN-12–LAG-1 complexes have a finite lifetime after which they are degraded by the proteosomal pathway. Therefore, the kinetic parameter k_n^- is set to a value between the rate of LAG-2–LIN-12 complex dissociation and the rate of proteosomal degradation of the cyto-LIN-12–LAG-1 complex. No experimental data is available about the lifetime of these complexes, thus base parameter estimates on the EGF-EGFR system are used (2).

k_{x_1} is the rate constant of MPK-1* deactivation induced by lateral signaling. Thus it lumps both the lateral signal-mediated upregulation of MPK-1* phosphatases and the action of those phosphatases on MPK-1*. This rate constant is equivalent to that of constitutive phosphatases, except it incorporates the characteristic level of lateral signal-induced phosphatase expression. Therefore, we take $k_{x_1} = k_m^- \left(Ph_{\mathrm{T}}\right)$. k_{x_2} is the rate constant of lateral signaling deactivation due to MPK-1*–mediated endocytosis of LIN-12 receptors. The appropriate value for the kinetic parameter k_{x_2} is then taken to be the rate constant for receptor/complex endocytosis adjusted for the fraction of active MPK-1*. k_{x_3} is the rate constant for MPK-1* induced lateral signal generation. In cells with high inductive signaling, it defines the maximal rate at which lateral signaling is generated in a neighboring cell. k_{x_3} represents an induced process, thus we set its the value to almost one order of magnitude larger than the constitutive rates of gene expression.

$K_{M_{mpk}}$ and $K_{M_{lat}}$ are parameters associated with induced transcriptional events. Their values are unknown, but reasonable choices could be $K_{M_{mpk}} = 0.25\left(mpk_{\mathrm{T}}\right)$ and $K_{M_{lat}} = 0.25\left[k_{x_3} / \left(k_{x_2} mpk_{\mathrm{T}}\right)\right]$, i.e. 25% of the characteristic levels for inductive and lateral signaling, respectively.

Robustness of improved gradient perception in coupled systems. We show here that for any parameter values, $Q^{\mathrm{c}} > Q^{\circ}$ for a two cell system at steady state. At steady state the dimensionless inductive signal is (from Eq. 8 in the text):

$$m_i = \frac{\mu I_i}{\mu I_i + 1 + \chi f\left(l_i\right)}; f\left(l_i\right) = \frac{l_i^2}{\kappa_{\mathrm{L}}^2 + l_i^2}$$

Using the definition for the gradient comparator, showing that $Q^{\mathrm{c}} > Q^{\circ}$ is equivalent to showing that:

$$\frac{\ln\left(m_1^{\mathrm{c}} / m_2^{\mathrm{c}}\right)}{\ln\left(m_1^{\circ} / m_2^{\circ}\right)} > 1, \text{ or } \frac{m_1^{\mathrm{c}}}{m_1^{\circ}} > \frac{m_2^{\mathrm{c}}}{m_2^{\circ}}$$

With the above formula for m_i, one needs to show that:

$$\frac{\mu I_1 + 1}{\mu I_1 + 1 + \chi f\left(l_1\right)} > \frac{\mu I_2 + 1}{\mu I_2 + 1 + \chi f\left(l_2\right)}$$

$$\frac{\mu I_2 + 1 + \chi f\left(l_2\right)}{\mu I_2 + 1} > \frac{\mu I_1 + 1 + \chi f\left(l_1\right)}{\mu I_1 + 1}$$

$$1 + \frac{\chi f\left(l_2\right)}{\mu I_2 + 1} > 1 + \frac{\chi f\left(l_1\right)}{\mu I_1 + 1}$$

Since in the coupled case $\chi > 0$, one needs to show that:

$$\frac{f\left(l_2\right)}{f\left(l_1\right)} > \frac{\mu I_2 + 1}{\mu I_1 + 1}.$$

One can show that $f(l)$ is a one-to-one mapping, i.e. if $l_1 < l_2$ then $f\left(l_1\right) < f\left(l_2\right)$.

$$l_1 < l_2 \Leftrightarrow l_1^2 < l_2^2 \Leftrightarrow \frac{1}{l_2^2} < \frac{1}{l_1^2} \Leftrightarrow \frac{\kappa_{\mathrm{L}}^2}{l_2^2} < \frac{\kappa_{\mathrm{L}}^2}{l_1^2} \Leftrightarrow 1 + \frac{\kappa_{\mathrm{L}}^2}{l_2^2} < 1 + \frac{\kappa_{\mathrm{L}}^2}{l_1^2} \Leftrightarrow$$

$$\frac{\kappa_{\mathrm{L}}^2 + l_2^2}{l_2^2} < \frac{\kappa_{\mathrm{L}}^2 + l_1^2}{l_1^2} \Leftrightarrow \frac{l_1^2}{\kappa_{\mathrm{L}}^2 + l_1^2} < \frac{l_2^2}{\kappa_{\mathrm{L}}^2 + l_2^2} \Leftrightarrow f\left(l_1\right) < f\left(l_2\right)$$

If $I_1 > I_2$ then the induced lateral gradient is inverted with respect to the inductive gradient, i.e. $l_1 < l_2$ in either the presence or absence of lateral coupling. For example, in the absence of lateral coupling, if $I_1 > I_2$ then:

$$m_1 = \frac{\mu I_1}{\mu I_1 + 1}; m_2 = \frac{\mu I_2}{\mu I_2 + 1} \Rightarrow m_1 > m_2$$

But, from Eq. 4 in the text:

$$l_1 = \frac{\lambda_s + \psi^{-1} g(m_2)}{\lambda_d + \psi^{-1} m_1}; l_2 = \frac{\lambda_s + \psi^{-1} g(m_1)}{\lambda_d + \psi^{-1} m_2}; g(m_i) = \frac{m_i^2}{\kappa_M^2 + m_i^2}$$

With $m_1 > m_2$ and $g(m)$ being a one-to-one mapping, then $l_1 < l_2$.

For $I_1 > I_2$ then

$$\frac{\mu I_2 + 1}{\mu I_1 + 1} < 1$$

Therefore, for $I_1 > I_2$ and any parameter choices (obviously $\mu \neq 0$ for inductive signaling to exist),

$$\frac{f(l_2)}{f(l_1)} > 1 > \frac{\mu I_2 + 1}{\mu I_1 + 1}$$

Slight asymmetry in VPC array. P6.p is the precursor cell closest to the anchor cell, the source of LIN-3 inductive signal (Fig. 1). The VPC array is not symmetric with respect to this cell. While P4.p receives lateral signals from two neighbors (P3.p and P5.p), the corresponding cell on the other side of the array (P8.p) has only one neighbor (P7.p). Thus, we expect that P8.p will display lower lateral activity than its counterpart P4.p. Fig. 9 shows the position of P6.p, P7.p, and P8.p on the fate plane, analogous to that shown for P6.p, P5.p, P4.p and P3.p in Fig. 7*A*. Comparing the two figures confirms that P8.p displays lower lateral activity than P4.p. Meanwhile, the lateral signal levels in P5.p and P7.p are similar, indicating that these activities are primarily determined by interaction with the P6.p cell. These observations indicate that the response of P3.p – P6.p is similar quantitatively to the response of the other half of the VPC array.

1. Asthagiri, A. R. & Lauffenburger, D. A. (2001) *Biotechnol. Prog.* **17,** 227-239.
2. Lauffenburger, D. A. & Linderman, J. J. (1993) *Receptors: Models for Binding, Trafficking, and Signaling* (Oxford Univ. Press, New York).