Text S1 – Rationale for the central values of dimensionless parameters

Dimensional model parameters. Our model involves three types of parameters: those driving protein degradation, those driving gene expression, and those driving bimolecular interactions. For the purpose of converting molar concentrations to number of molecules per cell, we assume a cellular volume of 10^{-12} L.

k_n^- is the rate of constitutive degradation of lateral signaling. Lateral signaling is mediated by complexes of LIN-12-cyto with LAG-1 transcription factor. Silencing of lateral signaling occurs due to proteosomal degradation of LIN-12-cyto [1]. The mean half-life of proteins susceptible to proteolysis has been measured to be approximately 43 minutes [2]. Therefore, the reference value of parameter k_n^- was set to 0.016 min^{-1}.

k_{x_2} is the rate constant of lateral signaling destruction due to MPK-1*-mediated endocytosis of LIN-12 receptors. The reference value of k_{x_2} was set to 2×10^{-6} $(molec/cell)^{-1}$ min^{-1}, obtained from the rate constant for receptor/complex endocytosis [3] adjusted for the fraction of active MPK-1*.

k_n^+ is the constitutive rate of lateral signaling synthesis. This process it thought to be limited by generation of LIN-12 receptors or their ligands. We set the reference value for k_n^+ at 130 molec/cell/min based on the rate of EGF receptor (EGFR) synthesis [3].

k_{x_3} is the rate constant for MPK-1* induced lateral signal generation through transcription of LIN-12 ligands. k_{x_3} reference value is set at 1300 molec/cell/min, which is one order of magnitude larger than the constitutive rates of lateral signal synthesis k_n^+. This latter estimate is based on tenfold change in promoter activity over the basal value [4,5].

k_m^+ and k_m^- are bimolecular rate constants describing the activation and deactivation of MAP kinase MPK-1. Their reference value was estimated from k_{cat}/K_M values for activation and deactivation of MAP kinase by upstream kinases and phosphatases, respectively [6-8]. Hence, the reference value for these parameters is 2×10^{-4} $(molec/cell)^{-1}$ min^{-1}.

The coupling term k_{x_1} combines protein production by lateral signaling induced gene expression and bimolecular reaction between the phosphatase gene products and active MPK-1*. Hence, the reference value is 2 min^{-1}, estimated from the bimolecular reaction rate constant k_m^- and characteristic levels of induced phosphatase gene expression products which we consider to be 10^4 molecules/cell.

We consider that there is a constant number of constitutive phosphatase molecules deactivating MPK-1* during the vulva specification process, and we take this number to be

$Ph_T = 5\times10^3$ molecules/cell. Furthermore, the total amount of MPK-1, active and inactive, does not change during this event; hence, we set $mpk_T = 10^4$ molecules/cell [6]. The characteristic level of lateral signal lat_T is estimated to be on the order of high cellular protein copy numbers; thus, we take $lat_T = 10^5$ molecules/cell. Occupied cell surface receptor levels vary from 100 to 100000 receptors/cell [3] therefore take the following reference value, $Ind_{P6.p} = 10^4$ molecules/cell. Concentration of transcription factors in the nucleus can range from 300 to 10000 molecules/nucleus [9]. Thus, we set the reference values $K_{M_{\mathrm{Ind}}} = 1000$ molecules/cell and $K_{M_{\mathrm{lat}}} = 5000$ molecules/cell.

Centerpoint of dimensionless parameter space. From the reference values for dimensional parameters (Table S2), the following values for dimensionless parameters were computed (using equations (6) of main text):

$$I = 2, \quad \chi = 2, \quad \lambda = 0.08, \quad \phi = 0.8, \quad \theta = 1.25, \quad \kappa_M = 0.1, \quad \kappa_L = 0.05.$$

These values were used as the center point to construct the multidimensional parameter space. To determine a center value for the gradient steepness, we note that a flat gradient would be represented by $\Delta I = 1$. In contrast, the steepest gradient occurs when a maximum number of receptors [3] (10^5 molec/cell) are occupied in the P6.p cell and only a single receptor is occupied in the P3.p cell. Thus, the steepest gradient is represented by $\Delta I = 10^{-5}$. The center value for ΔI (Table S3) was chosen to approximate the geometric mean of these limiting scenarios.

References

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