Fig. 6. Bimodal stochastic solutions distinct from the monostable deterministic solution. Histogram showing the bimodal distribution of the protected agonists at steady state (red) for a situation when there are 10 agonist (A_1) and 10 antagonists (A_2). The corresponding single steady state solution of the deterministic ODEs (blue) is also shown. The other parameter values are: $k_1 = 3$, $k_2 = 0.7$, $k_3 = 1$, $k_4 = 1000$, $k_5 = 50$, $k_D = 1$, and statistics were collected over 5,000 trajectories obtained using the Gillespie algorithm. The robustness of this result to variations in the parameter values is discussed in the main text and section 1 of the web supplement.

Fig. 7. A purely stochastic instability. Histograms showing the distribution of the protected agonists at steady state (red) and corresponding steady state solution of deterministic ODEs (blue) for different amounts of A_1 and A_2 molecules. All other parameters are identical to that in Fig. 6.

Fig. 8. The variation of the average number of A_1^{PROT} species as a function of the number of A_2 molecules and the parameter k_1 (which could be considered to reflect the quality of the agonist). (*a*) Results of the stochastic simulations collapse to one master curve when scaled with $\frac{A_2}{k_1}$. (*b*) The deterministic results do not follow this scaling. All results are for cases where $k_3, k_5 >> k_1, k_2, k_4$.

Fig. 9. Time dependence of the deterministic rate of production of protected species (red) and inactivated species (blue) as a function of time. (*a*) For 10 molecules A_1 and 100 molecules A_2. (*b*) For 10 molecules A_1 and 10 molecules A_2.

Fig. 10. Simulations of a molecular model of membrane proximal events in T-cell signaling by 100 agonists in the presence of varying numbers of antagonists. The percentage of fully activated trajectories goes down as antagonists are added. As shown on the insets, the distribution of Erk at steady-state is strictly bimodal, i.e., every

trajectory either produces Erk or produces none at all. The bimodal distribution for no antagonists and a 30-fold excess of antagonists are shown.

Fig. 11. Results from the minimal model. (*a*) Exact solution of the Master Equation*:* The exact solution (Eq. 13) shows a bimodal distribution for low values of initial numbers of Y (n = 2) and Z (M = 20) species. The reaction rates are taken to be, k_1 = 0.0012 $s^{-1,}$ k_2 = 0.0010 s^{-1}, and k_3 = 0.0125 s^{-1} (*b*) Minimal model captures the essential characteristics of the larger model: Distribution of the number of X species at steady state is calculated from Gillespie simulations as both N (related to agonist number) and k_3 (related to antagonist number) are increased keeping the ratio N/k_3 fixed. All of the other parameters, as well as the ratio, N/k_3, are the same as in *a*. The distribution is markedly bimodal for a low value (shown in red) of n = 2. The distribution becomes unimodal (shown in blue), peaked at the mean field value (shown with the black bar) as both N and k_3 are increased 1000 fold keeping all other parameters unchanged. We use Gillespie simulations instead of the exact solution (Eq. 13) for the above cases because numerical evaluation of the Gamma functions for large arguments (required to evaluate Eq. 13) is computationally more expensive than carrying out Gillespie simulations. The Gillespie simulations agree with the exact solution (web supplement).

Fig. 12. The steady values of the number (N_x^s) of the x species as the decay rate of the y species (k_3) is varied. Three cases, corresponding to different values of the initial numbers (N) of species Z are shown.

Fig. 13. The distribution of the number of x particles at the steady state. Results obtained from the analytic solutions (given by Eq. 13) are compared with the results from Gillespie simulations. All of the cases have a fixed k_2 = 0.001 s^{-1}, and are started with the same number (M = 20) of particles for the Z species. (*a*) A bimodal distribution is obtained for k_1 = 0.0005 s^{-1}, k_3 = 0.06 s^{-1} and n = 15, where N is the number of Y species at t = 0. (*b*) The bimodal distribution in *a* turns in a unimodal distribution as k_3 is increased to 0.5 keeping other parameters fixed. (*c*) The distribution becomes unimodal

when k_1 is increased to 0.005 s^{-1}. (*d*) The bimodal distribution in *a* becomes sharper as *N* is reduced to 5 with other parameters held fixed.

Fig. 14. The particle number distribution function for the *x* species at the steady state for (*a*) a very strong positive feedback, $k_2 = 2s^{-1}$ and (*b*) for a very weak positive feedback $k_2 = 10^{-7} s^{-1}$. The values of the other parameters are, $k_1 = 0.0005 s^{-1}$, $k_3 = 0.2 s^{-1}$, $M = 20$ and $N = 15$, where, M and N are the numbers of particles at t = 0 for the Z and Y species respectively. The solid line and the red points are obtained from the analytical solution and the Gillespie simulation respectively.

Fig. 15. Particle distribution functions for the X species do not show any bimodality when there is no positive feedback, i.e., $k_2 = 0$. The plots show cases for (*a*) $M = 25$, $n = 5$, $k_1 = 0.005$ s^{-1} and $k_3 = 0.1$ s^{-1}, (*b*) $M = 25$, $n = 100$, $k_1 = 0.005$ s^{-1} and $k_3 = 0.8$ s^{-1}. The Gillespie solution is compared with the exact solution in Eq. B28.