Supporting Text

1. *Deterministic Equations for model described in section 2*

$$\frac{dA_1}{dt} = -k_3 A_1 E - k_5 A_1 S$$

$$\frac{dA_1^{PROT}}{dt} = k_3 A_1 E$$

$$\frac{dE}{dt} = k_1 A_1 + k_4 A_1^{PROT} - k_D E$$

$$\frac{dS}{dt} = k_2 A_2 - k_D S$$

2. *Exploring different ranges of parameters for model described in section 2*

Our computational studies show that any combination of parameters that preserves strong feedbacks leads to a stochastic bimodal response. In addition to the case discussed in the text, bimodal behavior is observed when $k_4, k_5 >> k_1, k_2, k_3$. Biologically, this can correspond to a situation where upon action of the positive regulator E, A_1 gets further activated or it could result from cooperativity (1) with other molecules, resulting in faster rate of production of the positive regulator. Figs. 6 and 7 are drawn in complete analogy to Fig. 2 and 3 of the main text and show stochastic bistability. This "all-or-none" behavior is explained by exactly the same arguments as those described in the text.

3. *Stochastic and mean-field scaling in the model described in section 2*

To illustrate the differences in scaling behavior between the stochastic and deterministic descriptions of the system, we calculated the amount of protected A_1 as a function of the rate constant k_1 for fixed values of k_2 and the amount of A_1. This could be considered to be analogous to computing the cellular response as the nature of agonist is changed. In

Fig. 8, stochastic and deterministic dose-response curves for the system with 10 initial A_1 molecules are plotted. The stochastic behavior (Fig. 8a) is manifested in linear *scaling* of the amount of A_1^{PROT} with k_1 (agonist quality): all curves coincide when the amount of A_1^{PROT} in the steady state is plotted against A_2/k_1, which represents the scaling variable $\frac{k_1 A_1}{k_2 A_2}$ (see main text) with k_2 and A_1 fixed. As can be seen in Fig. 8b, the deterministic solution does not obey this linear scaling. Moreover, the value of k_4 naturally affects the deterministic steady state value of A_1^{PROT}, while it does not have any influence in the stochastic case, since feedback regulation occurs before reaction 4.

4. *Rates of protection and inactivation as functions of time*

On Fig. 9, the time dependence of the rate of production of A_1^{PROT} (red curve) and of A_1^{INACT} (blue curve) are shown for excess of antagonist (Fig. 9a) and equal amounts of agonist and antagonist (Fig. 9b). The parameters of the model are the same as those used in th Figs. 2 and 3 in the main text: $k_1 = 1$, $k_2 = 1$, $k_3 = 100$, $k_4 = 1$, $k_5 = 100$, $k_D = 1$.

5. *Details of the molecular model of antagonism*

As an illustration of the general results described in the main text, we considered a specific molecular system where competition between positive and negative feedback loops has been described in T-cell signaling (2-4). Important features of antagonism are that it is observed for less than optimal amounts of agonist in the presence of relatively large numbers of antagonists. Without considering effects of self-peptides (1), which were explicitly treated by Wylie *et al.* (4), the simplest model accounting for antagonism consists of the following elements (2, 3): a signaling complex is assembled which is composed of MHC-peptide, TCR, coreceptor (CD4 or CD8) and associated kinase. This signaling complex results in activation of negative and positive regulators, Shp-1 and Erk, respectively. Activated Shp-1 can bind to the signaling complex and deactivate it, while activated Erk can phosphorylate the binding complex at a specific position and, by so doing, prevent Shp-1 from binding to the “protected” complex.

Modeling with deterministic kinetic equations (3) has shown the consistency of such a mechanism with experimental data, but could not account for effects of “digital” Erk response: i.e., that an individual cell’s response to stimulus was essentially binary in character – either complete activation or just basal Erk production. Although many effects could contribute to “digital” Erk responses (5, 6), we show here how principles outlined in the previous sections can account for this fact.

The general ideas described in the main text are incorporated in this molecular model by setting the rate of protection of signaling complexes by Erk to be high. Phosphorylated Shp-1 binds and deactivates complexes fast, which provides us with the strong negative feedback like the one in the “*toy*” model.

The reactions that represent the molecular steps that we simulated are detailed in Table 1.

Fig. 10 shows the dose-response curve for 100 agonists upon addition of antagonists. The ordinate shows the percentage of trajectories in which full activation has occurred (which corresponds to the percentage of activated cells in experiments). One can see that signaling is basically shut down at 10-30 fold excess of antagonists, which is consistent with deterministic calculations (3). The insets show the distribution of activated cells for a given mixture of agonists and antagonists, and one can see from them that the distribution is essentially bimodal: i.e., all-or-none response of individual (cell) trajectories is observed.

5. Mathematical Details of Solutions to the simpler model (eq 12 of the main text)

5a. Solution of the Meanfield Rate Equations

Here we describe the details of the calculations for the meanfield rate equations shown in Eqs. 13-15 in the main text.

The mean field equations are,

$$\frac{dN_x}{dt} = k_2 N_x N_y N_z + k_1 N_z N_y \text{ (A1)}$$

$$\frac{dN_z}{dt} = -k_2 N_x N_y N_z - k_1 N_z N_y \text{ (A2)}$$

$$\frac{dN_y}{dt} = -k_3 N_y \text{ (A3)}$$

and the initial conditions are, $N_x(0) = 0, N_y(0) = N$ and $N_z(0) = M$. Since the total number of *x* and *z* species are conserved at all times, we need to solve only two equations,

$$\frac{dN_x}{dt} = k_2 N_x N_y (M - N_x) + k_1 (M - N_x) N_y \text{ and, } \frac{dN_y}{dt} = -k_3 N_y.$$

The equation for $N_y$can be readily solved to get $N_y(t) = Ne^{-k_3 t}$. Substituting this form of $N_y(t)$ in the equation for N_x we get,

$$\frac{dN_x}{dt} = (k_2 N_x + k_1)(M - N_x) N e^{-k_3 t}$$
$$\Rightarrow \frac{dN_x}{(k_2 N_x + k_1)(M - N_x)} = N e^{-k_3 t} dt$$
$$\Rightarrow \frac{1}{Mk_2 + k_1}\left[\frac{dN_x}{(k_2 N_x + k_1)} + \frac{dN_x}{(M - N_x)}\right] = \frac{N}{k_3}(1 - e^{-k_3 t})$$
$$\Rightarrow N_x(t) = \frac{k_1 M (F(t) - 1)}{Mk_2 + k_1 F(t)}$$

where, $F(t) = \exp\left[(Mk_2 + k_1)\frac{N}{k_3}(1 - e^{-k_3 t})\right]$

Therefore, the solutions to Eq. (A1-A3) are,

$$N_x(t) = \frac{k_1 M (F(t) - 1)}{Mk_2 + k_1 F(t)} \quad \text{(A4)}$$

$$N_y(t) = N e^{-k_3 t} \quad \text{(A5)}$$

$$N_z(t) = M - N_x(t) \quad \text{(A6)}$$

Fig. 12 shows the variation of the steady state value of N_x with k_3 for various initial numbers of the *y* species. The number of *x* species produced at the steady state decreases exponentially as $k_3 > N(Mk_2 + k_1)$.

5b. Large particle number limit ($M \to \infty$ and $N \to \infty$ *) from the mean-field solution*

From Eq. A4, $N_x(t) = \dfrac{M(e^{Nk_1(Mk_2/k_1+1)k_3^{-1}} - 1)}{Mk_2/k_1 + e^{Nk_1(Mk_2/k_1+1)k_3^{-1}}} = \dfrac{M(1 - e^{-Nk_1(Mk_2/k_1+1)k_3^{-1}})}{1 + (Mk_2/k_1)e^{-Nk_1(Mk_2/k_1+1)k_3^{-1}}}$. As, $M \to \infty$ and $N \to \infty$, $Nk_1(Mk_2/k_1 + 1)/k_3 >> 1$, therefore,

$$\underset{\substack{N\to\infty \\ M\to\infty}}{Lt}\ N_x(t) = M(1 - O(e^{-Nk_1(Mk_2/k_1+1)k_3^{-1}}))\ \text{(A7)}$$

In the next section, we will show how the average particle number of species *x*, calculated from the stochastic solution of the Master Equation corresponds to Eq. A7 in large particle number limit.

5c. Exact Solution of the Master Equation

We describe the details of calculations for the solution of the Master Equation in Eq. 12. The Master Equation is given by,

$$\begin{aligned}\frac{\partial P(n_x,n_y,n_z,t)}{\partial t} &= [k_2(n_x-1)n_y(n_z+1) + k_1 n_y(n_z+1)]P(n_x-1,n_y,n_z+1,t) + k_3(n_y+1)P(n_x,n_y+1,n_z,t) \\ &- (k_2 n_x n_y n_z + k_1 n_y n_z + k_3 n_y)P(n_x,n_y,n_z,t)\end{aligned}$$

(B1)

We define a generating function, $G(s_1,s_2,s_3,t) = \sum_{n_x=0}^{M}\sum_{n_y=0}^{N}\sum_{n_z=0}^{M} s_1^{n_x} s_2^{n_y} s_3^{n_z} P(n_x,n_y,n_z,t)$ (7). The time evolution of the generating function determined by the above Master Equation is given by,

$$\frac{\partial G}{\partial t} = k_2 s_1 s_2(s_1 - s_3)\partial_{s_1}\partial_{s_2}\partial_{s_3}G + k_1(s_1 - s_3)\partial_{s_2}\partial_{s_3}G - k_3(s_2 - 1)\partial_{s_2}G\ \text{(B2)}$$

At $t = 0$, $G(s_1,s_2,s_3,t=0) = s_2^N s_3^M$, in addition to that, it should satisfy $G(1,1,1,t) = 1$ at all times, which is a condition for the conservation of the sum of the probabilities for all possible particle configurations.

If we look for a solution in terms of the reduced variables, s_1, s_2 and $\xi = (s_1 - s_3)/s_1$ then $G(s_1,s_2,\xi,t)$ satisfies the following equation:

$$\frac{\partial G}{\partial t} = -k_2 s_1 s_2 \xi \partial_{s_1} \partial_{s_2} \partial_{\xi} G - k_2 \xi(\xi - 1) s_2 \partial_{s_2} \partial_{\xi}^2 G + (k_2 - k_1) s_2 \xi \partial_{s_2} \partial_{\xi} G - k_3 (s_2 - 1) \partial_{s_2} G \text{ (B3)}$$

We define, $G(s_1, s_2, \xi, t) = s_1^{\alpha_l} G'(s_2, \xi, t)$,

$$\frac{\partial G'}{\partial t} = -k_2 s_2 \xi (1-\xi) \partial_{s_2} \partial_{\xi}^2 G' - (k_2 \alpha_l - k_2 + k_1) s_2 \xi \partial_{s_2} \partial_{\xi} G' - k_3 (s_2 - 1) \partial_{s_2} G' \text{ (B4)}$$

If, $G'(s_2, \xi, t) = e^{E_m t} \phi(s_2, \xi)$, then,

$$E_m = -k_2 s_2 \xi (1-\xi) \partial_{s_2} \partial_{\xi}^2 \phi - (k_2 \alpha_l - k_2 + k_1) s_2 \xi \partial_{s_2} \partial_{\xi} \phi - k_3 (s_2 - 1) \partial_{s_2} \phi \text{ (B5)}$$

Introducing a separation of variables, $\phi(s_2, \xi) = S(s_2) \Xi(\xi)$, Eq. B5 becomes,

$$\frac{k_2 \xi (1-\xi)}{S \Xi} \frac{d^2 \Xi}{d\xi^2} \frac{dS}{ds_2} + \frac{\xi (k_2 \alpha_l - k_2 + k_1)}{S \Xi} \frac{d\Xi}{d\xi} \frac{dS}{ds_2} + \frac{k_3 (s_2 - 1)}{s_2 S} \frac{dS}{ds_2} + \frac{E_m}{s_2} = 0 \text{ (B6)}$$

The above equation will be satisfied if,

$$\frac{k_2 \xi (1-\xi)}{S \Xi} \frac{d^2 \Xi}{d\xi^2} \frac{dS}{ds_2} + \frac{\xi (k_2 \alpha_l - k_2 + k_1)}{S \Xi} \frac{d\Xi}{d\xi} \frac{dS}{ds_2} = A_n f(s_2) \text{ (B7)}$$

and,

$$\frac{k_3 (s_2 - 1)}{s_2 S} \frac{dS}{ds_2} + \frac{E_m}{s_2} = -A_n f(s_2). \text{ (B8)}$$

However, from Eq. (B7) we get,

$$\frac{1}{S}\frac{dS}{ds_2} = f(s_2) \text{ (B9)}$$

Therefore, to make Eq. B8 consistent with Eq. B9 we have to choose the following form for $f(s_2)$:

$$f(s_2) = -\frac{E_m}{(k_3 + A_n)s_2 - k_3}.$$

Using the above form we get the solution for $S(s_2)$ as,

$$S(s_2) = \left(s_2 - \frac{k_d}{k_3 + A_n}\right)^{-\frac{E_m}{k_3 + A_n}}.$$

$\Xi(\xi)$ satisfies the equation below,

$k_2\xi(1-\xi)\frac{d^2\Xi}{d\xi^2} + \xi(k_2\alpha_l - k_2 + k_1)\frac{d\Xi}{d\xi} - A_n\Xi = 0$, By changing ξ to $\eta = 1 - \xi = s_3 / s_1$, we get,

$$k_1\eta(1-\eta)\frac{d^2\Xi}{d\eta^2} - (1-\eta)\beta_l\frac{d\Xi}{d\eta} - A_n\Xi = 0 \quad \text{(B10)}$$

where, $\beta_l = k_2\alpha_l - k_2 + k_1$

This equation has the form of the ODE which yields hypergeometric functions (8) as its solutions. The following ODE has hypergeometric functions as its solutions.

$$z(1-z)\frac{d^2u}{dz^2} + (c - (a+b+1)z)\frac{du}{dz} - abu = 0 \text{ (B11)}$$

The hypergeometric function is defined as,

$${}_2F_1(a,b,c;z)=\sum_{n=0}^{\infty}\frac{(a)_n(b)_n}{(c)_n}z^n \text{ (B12)}$$

, where, $(a)_n=\frac{\Gamma(a+n)}{\Gamma(a)}$. The series in Eq. B12 is convergent for a positive c and $|z|<1$. If a is a negative integer, i.e., $a = -n$, the series terminates after z^n. Comparing Eq. B10, to Eq. B11 we get,

if, $c=-\frac{\beta_l}{k_2}=-\alpha_l+1-\frac{k_1}{k_2}$, and $a=-n$, then $b=-\alpha_l+n-\frac{k_1}{k_2}$. In that case,

$$A_n=n(-\alpha_l+\frac{k_1}{k_2}-n)k_2.$$

Therefore, the general solution to Eq. B2 is,

$$G(s_1,s_2,s_3,t)=\sum_{m=0}^{\infty}\sum_{l=0}^{\infty}\sum_{n=0}^{\infty}\lambda_{lmn}s_1^{\alpha_l}\left(s_2-\frac{k_3}{A_n+k_3}\right)^{-\frac{E_m}{A_n+k_3}}e^{E_m t}\,{}_2F_1\left(a,b,c;\frac{s_3}{s_1}\right).\text{ (B13)}$$

The constants are chosen in such a way that the solution satisfies the initial condition and also the sum of the probabilities is conserved at all times.

At t = 0, Eq.B13 takes the form,

$$G(s_1,s_2,s_3,t=0)=\sum_{m=0}^{\infty}\sum_{l=0}^{\infty}\sum_{n=0}^{\infty}\lambda_{lmn}s_1^{\alpha_l}\left(s_2-\frac{k_3}{A_n+k_3}\right)^{-\frac{E_m}{A_n+k_3}}{}_2F_1\left(a,b,c;\frac{s_3}{s_1}\right)\text{ (B14)}$$

Now, $s_2^N=\left[\left(\frac{k_3}{A_n+k_3}\right)+\left(s_2-\frac{k_3}{A_n+k_3}\right)\right]^N=\sum_{m=0}^{N}{}^NC_m\left(\frac{k_3}{A_n+k_3}\right)^{N-m}\left(s_2-\frac{k_3}{A_n+k_3}\right)^m$, therefore,

if we choose,

$$E_m = -m(k_3 + A_n) \text{ and } \lambda_{lmn} = {}^N C_m \left(\frac{k_3}{A_n + k_3} \right)^{N-m} \lambda_{ln} \quad \text{for } m \le N$$
$$= 0 \qquad \text{for } m > N$$

Then Eq. B14 satisfies the initial condition for s_2. If we choose,

$\alpha_M = M$ and $\lambda_{ln} = \delta_{lM} \lambda_n$ then Eq.B14 assumes the form below,

$$\begin{aligned}
G(s_1, s_2, s_3, t=0) &= s_2^N s_1^M \sum_{n=0}^{\infty} \lambda_n \, {}_2F_1\left(a,b,c; \frac{s_3}{s_1} \right) \\
&= s_2^N s_1^M \sum_{n=0}^{\infty} \lambda_n \sum_{r=0}^{n} p_{rn} \left(\frac{s_3}{s_1} \right)^r \\
&= s_2^N s_1^M \sum_{n=0}^{M} \sum_{r=n}^{M} \lambda_r p_{nr} \left(\frac{s_3}{s_1} \right)^n \\
&= s_2^N s_1^M \sum_{n=0}^{M} q_n \left(\frac{s_3}{s_1} \right)^n
\end{aligned}$$

where, $p_{rn} = \frac{(a_n)_r (b_n)_r}{(c_n)_r r!}$, $q_n = \sum_{r=n}^{M} \lambda_r p_{nr}$ and $a_n = -n$, $b_n = -M + n - \frac{k_1}{k_2}$ and $c_n = -M + 1 - \frac{k_1}{k_2}$. If $\begin{aligned} q_n &= 0 \text{ for } n < M \\ &= 1 \text{ for } n = M \end{aligned}$ then, Eq.B14 satisfies the initial condition, $G(s_1, s_2, s_3, t=0) = s_2^N s_3^M$.

Therefore, the time dependent generating function is given by,

$$G(s_1, s_2, s_3, t) = \sum_{n=0}^{M} \sum_{r=n}^{M} \lambda_r p_{nr} s_1^{M-n} f(r, s_2, t) s_3^n \text{ (B15)}$$

where,

$$f(s_2,r,t)=\left[\frac{k_3}{A_r+k_3}+\left(s_2-\frac{k_3}{A_r+k_3}\right)e^{-(k_3+A_r)t}\right]^N$$

and $\sum_{r=n}^{M}\lambda_r p_{nr}=0$ for $n<M$

$\lambda_M p_{MM}=1$ for $n=M$

(B16)

It is straightforward to show, $G(s_1=1,s_2=1,s_3=1,t)=1$ for the above choices of the coefficients. The proof follows below. From Eq. B15,

$$G(s_1=1,s_2=1,s_3=1,t)=\sum_{n=0}^{M}\sum_{r=n}^{M}\lambda_r p_{nr}f(r,s_2=1,t)=\sum_{n=0}^{M}\sum_{r=0}^{M}\lambda_n p_{rn}f(n,s_2=1,t).$$

$\because G(1,1,1,t)=1,$ if, $\sum_{r=0}^{n}p_{rn}=0$ for $n>0$ and $\lambda_0=1$. This is because, $f(0,1,t)=1$ and $p_{00}=1$.

Proof: $\sum_{r=0}^{n}p_{rn}=0,$ when, $n>0.$

$$\sum_{r=0}^{n}p_{rn}=\frac{\Gamma(M+k_1/k_2+1-n)}{\Gamma(M+k_1/k_2)}\left[\sum_{r=0}^{n}{}^{n}C_r(-1)^r\frac{\Gamma(M+k_1/k_2-r)}{\Gamma(M+k_1/k_2+1-n-r)}\right]$$

$$=\frac{\Gamma(M+k_1/k_2+1-n)}{\Gamma(M+k_1/k_2)}\left[\sum_{r=0}^{n}{}^{n}C_r(-1)^r\sum_{p=0}^{n-1}S_{n-1}^{(p)}(a-r)^p\right]\text{ where, } a=M+k_1/k_2-1$$

$$=\frac{\Gamma(M+k_1/k_2+1-n)}{\Gamma(M+k_1/k_2)}\left[\sum_{p=0}^{n-1}\sum_{q=0}^{p}S_{n-1}^{(p)}\,{}^{p}C_q a^{p-q}\left(\sum_{r=0}^{n}r^q\ {}^{n}C_r(-1)^r\right)\right]$$

In the above, expressions, $S_n^{(m)}$ denotes the Stirling number of the first kind (9). However, $\left(x\frac{\partial}{\partial x}\right)^q (1-x)^n = \sum_{r=0}^{n} {}^nC_r(-1)^r r^q x^r$, therefore, $\sum_{r=0}^{n} {}^nC_r(-1)^r r^q = \left(x\frac{\partial}{\partial x}\right)^q (1-x)^n \Big|_{x=1}$. For, $0 \le q \le n-1$, $\left(x\frac{\partial}{\partial x}\right)^q (1-x)^n \Big|_{x=1} = 0$, hence,

$$\sum_{r=0}^{n} p_{rn} = 0.$$

Proof: $\lambda_0 = 1$

Using, Eq. B16,

$$\sum_{n=0}^{M}\sum_{r=n}^{M}\lambda_r p_{nr} = 1, \Rightarrow \sum_{n=0}^{M}\sum_{r=0}^{n}\lambda_n p_{rn} = 1, \Rightarrow \lambda_0 p_{00} + \sum_{n=1}^{M}\sum_{r=0}^{n}\lambda_n p_{rn} = 1.$$

Since, $\sum_{r=0}^{n} p_{rn} = 0$ for $n > 0$ and $p_{00} = 1$; $\lambda_0 = 1$.

Therefore, $G(1,1,1,t) = 1$. QED.

Expanding the polynomials one can easily get the probability distribution

$$P(n_x, n_y, n_z, t) = \delta_{n_x+n_z, M} \sum_{r=n_z}^{M} \lambda_r p_{n_z r} \; {}^NC_{n_y} \left[\frac{k_3}{A_r + k_3}\left(1 - \exp(-(A_r + k_3)t)\right)\right]^{N-n_y} \exp\left(-n_y(A_r + k_3)t\right)$$

(B17)

where, $A_r = r((M-r)k_2 + k_1)$ and $p_{n_z r} = {}^rC_{n_z}(-1)^{n_z} \dfrac{\Gamma(M + k_1/k_2 + 1 - r)\Gamma(M + k_1/k_2 - n_z)}{\Gamma(M + k_1/k_2 + 1 - n_z - r)\Gamma(M + k_1/k_2)}$.

$\{\lambda_r\}$ are determined from the equations,

$$\sum_{r=n}^{M} \lambda_r p_{nr} = 0 \quad \text{for} \quad n < M$$
$$= 1 \quad \text{for} \quad n = M$$

At large times, $t \to \infty$, $f(s_2, r, t) = \left[\frac{k_3}{A_r + k_3}\right]^N$, because,

$A_r = r((M-r)k_2 + k_1) > 0$ for $r \le M$. Therefore, the generating function at the steady state has the following form,

$$G(s_1, s_2, s_3, t \to \infty) = \sum_{n=0}^{M}\sum_{r=n}^{M} \lambda_r p_{nr} s_1^{M-n} \left(\frac{k_3}{k_3 + A_r}\right)^N s_3^n \quad \text{(B18)}$$

Hence, the probability distribution function at $t \to \infty$ is given by,

$$P(n_x, n_y, n_z, t \to \infty) = \delta_{n_x + n_z, M}\, \delta_{n_y, 0} \sum_{r=n_z}^{M} \lambda_r p_{n_z r} \left[\frac{k_3}{(r(M-r)k_2 + rk_1) + k_3}\right]^N . \quad \text{(B19)}$$

For fixed k_1, k_2, and k_3, the factor $u(r) = \left[\frac{k_3}{(r(M-r)k_1 + rk_2) + k_3}\right]^N$ is peaked at $r = 0$ and $r = M$ which corresponds to the cases at $n_x = M$ and $n_x = 0$ respectively. The values of the peaks are $u(r=0) = 1$ and $u(r=M) = \left(\frac{1}{Mk_1/k_3 + 1}\right)^N$. Therefore, the peak at $r = M$, will have significant contribution when, $k_3 >> Mk_1$, *i.e.*, *the y* particles decay at a much faster rate than it generates particles of the *x* species. Furthermore, if the initial number of the *y* particles increases, the value of the peak at $r = M$ goes down. Therefore, we can expect to see a bimodal behavior in the distribution function for $k_3 >> Mk_1$ and small N. Fig. 13 displays the above characteristics in the distribution function.

5d. Calculation of the average particle number

The average particle number of any species can be easily calculated from the generating function, $G(s_1, s_2, s_3, t)$. For example, the average number of *x* species is given by,

$$\langle x(t) \rangle = \partial_{s_1} G(s_1, s_2, s_3, t)\Big|_{s_1=1, s_2=1, s_3=1} = \sum_{n=0}^{M} \sum_{r=n}^{M} \lambda_r p_{nr} f(r, s_2 = 1, t)(M-n) \text{ (B20)}$$

At, $t \to \infty$, the above average takes the following form,

$$\langle x(t \to \infty) \rangle = \sum_{n=0}^{M} \sum_{r=n}^{M} \lambda_r p_{nr} \left(\frac{k_3}{r((M-r)k_2 + k_1) + k_3} \right)^N (M-n) \text{ (B21)}$$

5e. Limit of large N and large k_1/k_3, keeping the ratio Nk_1/k_3 fixed:

Let us, write,

$$\left(\frac{k_3}{r((M-r)k_2 + k_1) + k_3} \right)^N = \left(\frac{1}{a/N + 1} \right)^N, \text{ where, } a = r((M-r)k_2/k_1 + 1)Nk_1/k_3.$$

Therefore, in the limit, $N \to \infty$ and $Nk_1/\text{k}_3 = const$,

$$Lt_{N\to\infty} \left(\frac{1}{a/N + 1} \right)^N = Lt_{y\to 0} \left(\frac{1}{ay + 1} \right)^{1/y} = g$$

when $y = 1/N$.

Now, $\ln(g) = -1/y \ln(ay+1) \to -a + O(y)$ as $y \to 0$.

$$\because\ Lt_{N\to\infty} \left(\frac{1}{a/N + 1} \right) = \exp(-a)$$

Thus,

$$\underset{\substack{N\to\infty \\ k_3\to\infty \\ k_3/N \text{ fixed}}}{Lt} \langle x\rangle = \sum_{n=0}^{M}\sum_{r=n}^{M}\lambda_r p_{nr}(M-n)\exp(-r((M-r)k_2/k_1+1)Nk_1/k_3). \text{ (B22)}$$

5f. Large M limit:

Rewriting, Eq. B22 as,

$$\begin{aligned}\underset{\substack{N\to\infty \\ k_3\to\infty \\ k_3/N \text{ fixed}}}{Lt} \langle x\rangle &= \sum_{n=0}^{M}\sum_{r=0}^{n}\lambda_n p_{rn}(M-r)\exp(-n((M-n)k_2/k_1+1)Nk_1/k_3) \\ &= M-\sum_{n=1}^{M}\lambda_n \exp(-n((M-n)k_2/k_1+1)Nk_1/k_3)\sum_{r=0}^{n} rp_{rn}\end{aligned} \quad \text{(B23)}$$

In the limit, $M\to\infty$, each term in the sums of Eq. B23 decay exponentially with M, thus, we can write, $\underset{\substack{N\to\infty \\ k_3\to\infty \\ k_3/N \text{ fixed} \\ M\to\infty}}{Lt} \langle x\rangle = M(1-O(e^{-Nk_1/k_3(Mk_2/k_1+1)}))$.

This form is consistent with the large particle limit of the solutions of the meanfield rate equations in Eq. A7.

5g. Strong feedback limit ($k_2\to\infty$ and $k_1/k_2=\varepsilon\to 0$ *)*

In this limit, $k_2\to\infty$ and $k_1/k_2=\varepsilon\to 0$.

Particle distribution function

The probability of having no *x* species in the steady state is given by,

$P(n_x = 0, n_y = 0, n_z = M) = \lambda_M\, p_{MM} \left(\frac{k_3}{Mk_1 + k_3}\right)^N = \left(\frac{k_3}{Mk_1 + k_3}\right)^N$, because, $\lambda_M\, p_{MM} = 1$ from Eq.B16. Note, the distribution does not depend on k_2 and this form of the distribution function holds good for any value of k_2.

Now, in the limit, $k_1/k_2 = \varepsilon \to 0$,

$$p_{MM} = {}^M C_M (-1)^M \frac{\Gamma(1)\Gamma(\varepsilon)}{\Gamma(-M+1+\varepsilon)\Gamma(M)} = -1, \text{ using (10),}$$

$$\Gamma(-n+\varepsilon) = \frac{(-1)^n}{n!}\left(\frac{1}{\varepsilon} - \gamma\right) \text{ as } \varepsilon \to 0. \text{ (B22)}$$

where, $\gamma \approx 0.5772$ is the Euler Mascheroni constant.

We need to evaluate, other p_{nr} for $r = n....M$ $(0 \le n \le M)$ and $\lambda_1.....\lambda_M$ to compute the probability distribution function for all particle numbers. Now,

$p_{nr} = {}^r C_n (-1)^n \dfrac{\Gamma(M+\varepsilon+1-r)\Gamma(M+\varepsilon-n)}{\Gamma(M+\varepsilon+1-n-r)\Gamma(M+\varepsilon)} \to 0$ for $n + r \ge M+1$ and $n \ne r$. For $n + r \ge M+1$ and $n = r$; $p_{nn} = -1$. Therefore, $\lambda_r = 0$ for $M/2 \le r < M$ which can be easily shown from Eq. B16. For, $n + r < M+1$ $p_{nr} \to {}^r C_n (-1)^n \dfrac{\Gamma(M+1-r)\Gamma(M-n)}{\Gamma(M+1-n-r)\Gamma(M)}$, however, from Eq. B16 it can be shown that, $\lambda_r = 0$ for $0 < r < M/2$ and $\lambda_0 = 1$. Therefore, the probability distribution is,

$$P(n_x, n_y = 0, n_z) = \left(\frac{k_3}{Mk_1 + k_3}\right)^N \delta_{n_x,0}\delta_{n_z,M} + \left[1 - \left(\frac{k_3}{Mk_1 + k_3}\right)^N\right]\delta_{n_x,M}\,\delta_{n_z,0} \text{ (B23)}$$

Note, that the distribution is strictly bimodal with peaks at $n_x = 0$ and $n_x = M$. The magnitudes of the peaks depend on Mk_1, N and k_3. The probability of having no particles of x species is easy to guess from following observation: Starting with N particles of y species at $t = 0$, the probability of having N successive y annihilation events is $\left(\frac{1}{Mk_1/k_3+1}\right)^N$, which is also the probability of having no particles of x species in the steady state. Now intuitively on can think that when a single reaction for the creation of the x species occurs, the strong positive feedback will convert all of the z species into the x species. Fig. 14 shows the comparison of Eq. B23 with the Gillespie simulation with a very large positive feedback.

5h. Calculation of the average particle number

Using the same properties of the coefficients, $\{\lambda_r\}$ and $\{p_{nr}\}$ it can be shown that,

$$\langle x(t\to\infty)\rangle = \lambda_0 M + \lambda_M M\left(\frac{k_3}{k_3+Mk_1}\right)^N = M\left(1-\left(\frac{k_3}{k_3+Mk_1}\right)^N\right) \quad \text{(B24)}$$

5i. No Feedback Limit ($k_2 \to 0$)

The limit, $k_2 \to 0$, is tricky to take directly from Eq. 13 because k_2 multiplies the highest derivative in Eq. B3, therefore, analyzing the limit $k_2 \to 0$ becomes a case of singular perturbation theory. A simpler approach would be to analyze the case with $k_2 = 0$ from the Master Equation and solve it directly. In that case, the Master Equation will be given by,

$$\begin{aligned}\frac{\partial P(n_x,n_y,n_z,t)}{\partial t} &= k_1 n_y(n_z+1)P(n_x-1,n_y,n_z+1,t) + k_3(n_y+1)P(n_x,n_y+1,n_z,t) \\ &-(k_1 n_y n_z + k_3 n_y)P(n_x,n_y,n_z,t)\end{aligned} \quad \text{(B25)}$$

The equation followed by the generating function,

$G(s_1,s_2,s_3,t) = \sum_{n_x=0}^{M}\sum_{n_y=0}^{N}\sum_{n_z=0}^{M} s_1^{n_x} s_2^{n_y} s_3^{n_z} P(n_x,n_y,n_z,t)$ is,

$$\frac{\partial G}{\partial t} = k_1 s_2 (s_1 - s_3)\partial_{s_2}\partial_{s_3} G - k_3 (s_2 - 1)\partial_{s_2} G \text{ (B26)}$$

This equation can be solved in a similar way by changing to variables, s_1, s_2 and $\xi = (s_1 - s_3)/s_1$ and performing separation of variable on the ensuing equation. The general solution of Eq. B26 is

$$G(s_1, s_2, s_3, t) = s_1^M \sum_{m=0}^{N}\sum_{n=0}^{M} (-1)^n \, {}^M C_n \, {}^N C_m \left(1 - \frac{s_3}{s_1}\right)^n \left(s_2 - \frac{k_3}{k_3 + nk_1}\right)^m \left(\frac{k_3}{k_3 + nk_1}\right)^{N-m} \exp(-m(k_3 + nk_1)t)$$

(B27)

In the steady state ($t \to \infty$), the probability distribution can be easily obtained from Eq. B27, which is given by,

$$P(n_x, n_y, n_z, t \to \infty) = \delta_{n_x + n, M} \delta_{n_y, 0} \sum_{r=n_z}^{M} {}^M C_r \, {}^r C_{n_z} (-1)^{r+n_z} \left(\frac{k_3}{rk_1 + k_3}\right)^N . \text{ (B28)}$$

This form always gives a unimodal distribution (Fig. 15, also see Fig. 14(b)). Therefore, the nonlinear feedback is essential to realize a bimodal distribution.

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