Supporting Text

Model I: Delayed Protein Degradation

Deterministic Description.

The deterministic dynamics of this system in the rate approximation is described by the following linear delay-differential equation:

$$\frac{dx}{dt} = A - Bx(t) - Cx(t-\tau). \quad [1]$$

It is straightforward to analyze the onset of periodic oscillations in this system. This system has one fixed point $x^* = A/(B+C)$ whose stability determines the transition to oscillations. We look for a solution $x(t)$ in the form $x(t) \sim e^{\lambda t}$, where the eigenvalues are the solutions of

$$(\lambda + B)e^{\lambda\tau} + C = 0. \quad [2]$$

We set $\lambda = \mu + i\omega$. To solve Eq. **2**, we use the Lambert function $W(z)$, which by definition satisfies $W(z)e^{W(z)} = z$

$$\mu = \frac{1}{\tau} Re(W(-\tau C e^{\tau B})) - B, \quad [3]$$

$$\omega = \frac{1}{\tau} Im(W(-\tau C e^{\tau B})). \quad [4]$$

By solving Eqs. **3** and **4** for $\mu = 0$ and $\omega \neq 0$ we find the condition for Hopf bifurcation discussed in the main text.

Stochastic Description

Denote $P(n,t)$ as the probability of having n monomers at time t. Then the master equation for $P(n,t)$ can be written as

$$\begin{aligned}\frac{dP(n,t)}{dt} &= A\left(P(n-1,t)-P(n,t)\right)+B\left((n+1)P(n+1,t)-nP(n.t)\right)\\ &+ C\sum_{m=0}^{\infty} m\left(P(n,t;m,t-\tau)-\Theta_n P(n,t;m,t-\tau)\right), \quad n=0..\infty, \end{aligned} \qquad [5]$$

where $P(n,t;m,t-\tau)$ is the joint probability of having n molecules at time t and m molecules at time $t-\tau$ and the multiplier

$$\Theta_n = \begin{cases} 0, & n=0 \\ 1, & n>0 \end{cases}, \qquad [6]$$

is added to account for the fact that $P(n,t), P(n,t;m,t-\tau)$ should remain zero for negative n.

Assume that the time delay τ is large compared with other characteristic times of the system, so the events at time t and $t-\tau$ are effectively decoupled, then

$$P(n,t;m,t-\tau) = P(n,t)P(m,t-\tau). \qquad [7]$$

Adopting this approximation, we get

$$\begin{aligned}\frac{dP(n,t)}{dt} &= A\left(P(n-1,t)-P(n,t)\right)+B\left((n+1)P(n+1,t)-nP(n,t)\right)\\ &+ C\sum_{m=0}^{\infty} mP(m,t-\tau)\left(P(n+1,t)-\Theta_n P(n,t)\right),\\ &= A\left(P(n-1,t)-P(n,t)\right)+B\left((n+1)P(n+1,t)-nP(n,t)\right)\\ &+ C\langle n(t-\tau)\rangle\left(P(n+1,t)-\Theta_n P(n,t)\right), \quad n=0..\infty. \end{aligned} \qquad [8]$$

By definition, the autocorrelation function for a random process characterized by $n(t)$ is given by

$$K(T) = \langle n(t)n(t+T)\rangle - \langle n(t)\rangle^2 \qquad [9]$$

$$= \sum_{n=0}^{\infty}\sum_{n'=0}^{\infty} nn'P(n,t;n',t+T) - \left[\sum_{n=0}^{\infty} nP_s(n)\right]^2, \qquad [10]$$

For a stationary random process, the joint probability density $P(n,t;n',t+T)$ can be written in the following as

$$P(n,t;n',t+T) = P_s(n)P_c(n',T|n,0), \qquad \textbf{[11]}$$

where $P_s(n)$ is the stationary probability, and P_c is the conditional probability for the sample path to pass through the point n' at time $t=T$, given that it passes through n at time $t=0$. By inserting Eq. **11** into Eq. **10**, we obtain the stationary correlation function

$$K(T) = \sum_{n=0}^{\infty} nP_s(n)\langle n',T|n,0\rangle - \langle n\rangle^2. \qquad \textbf{[12]}$$

The calculation of the correlation function is done in three steps: *(i)* calculate the conditional mean value of $n(T)$ given $n(0)$, $\langle n',T|n,0\rangle$, (ii) find the stationary probability density $P_s(n)$, and (iii) take the sum. Generating functions are particularly useful here. The generating function $G(s,t)$ is defined as

$$G(s,t) = \sum_{n'=0}^{\infty} s^{n'}P(n',t|n,0). \qquad \textbf{[13]}$$

We convert the infinite set of ordinary differential equations **8** to a single partial differential equation for $G(s,t)$

$$\frac{\partial G}{\partial t} = (s-1)\left(AG(t) - B\frac{\partial G(t)}{\partial s} + C\frac{\langle n(t-\tau)\rangle}{s}(P_0(t) - G(t))\right). \qquad \textbf{[14]}$$

Our numerical simulations show that for a large mean number of molecules, $P_0(t)$ is small and can be neglected in Eq. **14**.

The moments of the probability distribution can be found by expanding the generating function near $s=1$

$$\frac{\partial G}{\partial s}|_{s=1} = \sum_{n'=0}^{\infty} n's^{n'-1}P(n',t|n,0)|_{s=1} = \sum_{n'=0}^{\infty} n'P(n',t|n,0) = \langle n',t|n,0\rangle, \qquad \textbf{[15]}$$

$$\frac{\partial^2 G}{\partial s^2}|_{s=1} = \sum_{n'=0}^{\infty} n'(n'-1)s^{n'-2}P(n',t|n,0)|_{s=1} =$$

$$= \sum_{n'=0}^{\infty} n'(n'-1)P(n',t|n,0) = \langle n'^2,t|n,0\rangle - \langle n',t|n,0\rangle. \qquad \textbf{[16]}$$

(only first and second moments are needed). Substituting the expansion

$$G(s-1,t) = 1 + (s-1)\alpha(t) + \frac{1}{2}(s-1)^2\beta(t) + ... \qquad \textbf{[17]}$$

into Eq. **14** we obtain

$$\frac{d\alpha}{dt} = A - B\alpha(t) - C\alpha(t-\tau), \qquad \textbf{[18]}$$

$$\frac{1}{2}\frac{d\beta}{dt} = A\alpha(t) - C\alpha(t-\tau) - B\beta(t) + C\alpha(t)\alpha(t-\tau), \qquad \textbf{[19]}$$

where the functions $\alpha(t)$ and $\beta(t)$ are Eqs. **15** and **16**, respectively. As expected, the equation for mean **18** coincides with Eq. **1**, which was obtained within that rate equation approximation. Note that since the autocorrelation function has to be symmetric with respect to the transformation $T \to -T$, we have to impose an additional symmetry condition $\alpha(t) = \alpha(-t)$ on the solution of Eq. **18**. Since it is linear, it can be readily solved with initial condition $\alpha(0) = n$

$$\alpha(t) \equiv \langle n', t|n, 0\rangle = (n-1)\frac{\sigma(t)}{1-\zeta e^{-\lambda\tau}} + \left(1 - \frac{A}{B+C}\right)\frac{\sigma(t)}{1-\zeta e^{-\lambda\tau}} + \frac{A}{B+C}, \qquad \textbf{[20]}$$

where

$$\sigma(T) = \begin{cases} e^{-\lambda T} - \zeta e^{\lambda(T-\tau)}, & 0 < T < \tau \\ e^{-B(T-N\tau)}(\sigma(N\tau) - C\int_{N\tau}^{T}\sigma(T'-\tau)e^{B(T'-N\tau)}dT'), & N\tau < T < (N+1)\tau. \end{cases}$$

$$\lambda = \sqrt{B^2 - C^2}, \quad \zeta = \frac{1}{C}(B - \lambda). \qquad \textbf{[21]}$$

The solution of Eqs. **20** and **21** exists if $B > C$, i.e. below the deterministic Hopf bifurcation. The solution for $B < C$ can be derived but it is not as interesting since the amplitude of the oscillations grows without bound.

Substituting Eq. **20** into Eq. **12** we find that only the first two moments of the stationary distribution are needed. The stationary solution for G is derived from Eq. **14**:

$$G_s(s) = s^{-\frac{C}{B}<n>_s} e^{\frac{A}{B}(s-1)}, \qquad \textbf{[22]}$$

where $\langle n\rangle_s$ denotes the stationary mean: $\langle n\rangle_s = \langle n(t\to\infty)\rangle$ and normalization $G_s(1)=1$ has been taken into account.

From Eq. **22** we obtain the stationary moments of the distribution

$$\frac{dG_s}{ds}|_{s=1} = \frac{d}{ds}s^{-\frac{C}{B}<n>_s}e^{\frac{A}{B}(s-1)}|_{s=1} = \frac{A}{B+C}, \qquad \textbf{[23]}$$

$$\frac{d^2G_s}{ds^2}|_{s=1} = \frac{d^2}{ds^2}s^{-\frac{C}{B}<n>_s}e^{\frac{A}{B}(s-1)}|_{s=1} = \frac{A(AB+BC+C^2)}{B(B+C)^2} \qquad \textbf{[24]}$$

and insert them, along with Eq. **20**, into Eq. **12**. We obtain

$$K(T) = \frac{\sigma(T)}{1-\zeta e^{-\lambda\tau}}\sum_{n=0}^{\infty}n(n-1)P_s(n) + \left(1-\frac{A}{B+C}\right)\frac{\sigma(T)}{1-\zeta e^{-\lambda\tau}}\sum_{n=0}^{\infty}nP_s(n) =$$

$$= \frac{\sigma(T)}{1-\zeta e^{-\lambda\tau}}\frac{d^2G_s(s)}{ds^2}|_{s=1} + \frac{B+C-A}{B+C}\frac{\sigma(T)}{1-\zeta e^{-\lambda\tau}}\frac{dG_s(s)}{ds}|_{s=1} = \frac{A}{B}\frac{\sigma(T)}{(1-\zeta e^{-\lambda\tau})}, \qquad \textbf{[25]}$$

where $T = N\tau + t$.

After calculating the auto-correlation function, we proceed with the power spectrum $S(\omega)$ of the system and obtain

$$S(\omega) = 2\frac{A}{B}\mathrm{Re}\frac{1-Ce^{i\omega\tau}I(\omega)}{B+Ce^{i\omega\tau}-i\omega}, \qquad \textbf{[26]}$$

where

$$I(\omega) = \frac{B}{A}\int_0^{\tau}K(T)e^{i\omega T}dT = \frac{1}{1-\zeta e^{-\lambda\tau}}\left(\frac{1-e^{-(i\omega+\lambda)\tau}}{i\omega+\lambda} + \zeta e^{-\lambda\tau}\frac{1-e^{-(i\omega-\lambda)\tau}}{i\omega-\lambda}\right). \qquad \textbf{[27]}$$

Comparison of Analytical and Numerical Results

In applying the numerical technique described in the main text, it is convenient to calculate the auto-correlation function using

$$K(T) = \lim_{t\to\infty}\frac{1}{t}\int_0^t n(t')n(t'+T)dt' - \left[\lim_{t\to\infty}\frac{1}{t}\int_0^t n(t')dt'\right]^2. \qquad \textbf{[28]}$$

Given the ergodic properties of the system, this method is equivalent to Eq. **10**. The power spectrum $S(\omega)$ of the system has been calculated by numerical integration of Eq. **28**, using $S(\omega) = 2\int_0^{\infty}K(T)\cos(\omega T)dT$.

Model II: Negative Feedback with Delayed Production

Deterministic Description

The deterministic rate equations corresponding to reactions **11** and **12** in the main text read

$$\frac{dx}{dt} = As(t-\tau) - Bx(t), \qquad \textbf{[29]}$$

$$\frac{ds}{dt} = k_{-1} - k_{-1}s(t)(1+\varepsilon x(t)), \qquad \textbf{[30]}$$

where $\varepsilon = k_1/k_{-1}$. This system has only a positive stationary solution:

$$x^* = \frac{1}{2\varepsilon}\left(\sqrt{1+4\varepsilon\frac{A}{B}} - 1\right). \qquad \textbf{[31]}$$

We can show that this solution is always stable, so the system does not possess a Hopf bifurcation.

By linearizing Eqs. **29** and **30** near **31**, and looking for a solution of the form $x \sim e^{\lambda t}$ we obtain

$$\lambda^2 + (B+1+\varepsilon x^*)\lambda + \varepsilon B + \varepsilon\frac{A}{1+\varepsilon x^*}e^{-\lambda\tau} = 0. \qquad \textbf{[32]}$$

This equation has no solution for $\lambda = 0$, and so the transcritical Hopf bifurcation cannot occur. Let us check for a Hopf bifurcation when $\lambda = i\omega$. By inserting this into Eq. **32** we obtain two transcendental equations

$$\begin{aligned} -\omega^2 + (1+\varepsilon x^*)B + \frac{\varepsilon A}{1+\varepsilon x^*}\cos(\omega\tau) = 0, \\ B + 1 + \varepsilon x^* - \frac{\varepsilon A}{1+\varepsilon x^*}\sin(\omega\tau) = 0, \end{aligned} \qquad \textbf{[33]}$$

whose solvability condition yields

$$\omega^2 = \frac{1}{2}\left(-B^2 - (1+\varepsilon x^*)^2 + \sqrt{(B^2+(1+\varepsilon x^*)^2)^2 - 4B^2(1+\varepsilon x^*)^2 + 4\frac{\varepsilon^2 A^2}{(1+\varepsilon x^*)^2}}\right). \qquad \textbf{[34]}$$

The solution exists only if

$$B^2(1+\varepsilon x^*)^2 < \frac{\varepsilon^2 A^2}{(1+\varepsilon x^*)^2}. \qquad \textbf{[35]}$$

By inserting Eq. **31** into Eq. **35** we arrive at the following inequality:

$$A > A + \frac{B}{2\varepsilon}\left(1+\sqrt{1+4\varepsilon\frac{A}{B}}\right), \qquad \textbf{[36]}$$

We see that for $B>0, \varepsilon>0$, this Hopf bifurcation cannot occur either. Thus, the system is linearly stable for any values of the parameters.

Stochastic Description

We introduce two probabilities, $P_n^0(t)$ and $P_n^1(t)$, for the number of proteins to be equal to n at time t and for the state of the operator at time $t-\tau$ to be D_0 or D_1, respectively. Then the master equations for the reactions **11** and **12** in the main text have the form

$$\begin{aligned}
\frac{dP^0(n,t)}{dt} &= A(P^0(n-1,t)-P^0(n,t)) + B((n+1)P^0(n+1,t)-nP^0(n,t)) - \\
&- k_1\sum_{m=0}^{\infty} m[(P^0(m,t-\tau)+P^1(m,t-\tau)]P^0(n,t) + k_{-1}P^1(n,t), \\
\frac{dP^1(n,t)}{dt} &= B((n+1)P^1(n+1,t)-nP^1(n,t)) + \\
&+ k_1\sum_{m=0}^{\infty} m[(P^0(m,t-\tau)+P^1(m,t-\tau)]P^0(n,t) - k_{-1}P^1(n,t). \qquad \textbf{[37]}
\end{aligned}$$

Again, we have made the assumption that the processes at times t and $t-\tau$ are weakly correlated, and to first approximation the two-point probability distribution functions $P(n,t;m,t-\tau) \approx P(n,t)P(m,t-\tau)$. To calculate the correlation function we again utilize generating functions. We introduce two generating functions

$$G_i(s,t) = \sum_{n=0}^{\infty} s^n P_n^i(t), \quad i=1,2, \qquad \textbf{[38]}$$

which correspond to the two operator states. Their sum gives the full generating function $G(s,t) = G_0(s,t) + G_1(s,t)$. Then the equations are given by

$$\frac{\partial G_0}{\partial t} = (s-1)\left(AG_0 - B\frac{\partial G_0}{\partial s}\right) - k_1\langle n(t-\tau)\rangle G_0 + k_{-1}G_1,$$
$$\frac{\partial G_1}{\partial t} = -(s-1)B\frac{\partial G_1}{\partial s} + k_1\langle n(t-\tau)\rangle G_0 - k_{-1}G_1. \quad \textbf{[39]}$$

Let us introduce the hierarchy of marginal moments

$$M_i^0(t) = \sum_{n=0}^{\infty} n^i P_n^0(t), \quad M_i^1(t) = \sum_{n=0}^{\infty} n^i P_n^1(t). \quad \textbf{[40]}$$

The zeroth moments $M_0^s(t)$ characterize the probabilities to find the operator in an unoccupied/occupied state at time $t-\tau$ ($M_0^0(t) + M_0^1(t) = 1$), and the first moments $M_1^s(t)$ characterize the mean number of proteins at time t given the state s of the operator at time $t-\tau$. Hence,

$$M_1^0(t) + M_1^1(t) \equiv \alpha(t) = \langle n(t)\rangle.$$

The equations for the zeroth moment M_0^0 read

$$\frac{dM_0^0}{dt} = k_{-1} - \left(k_1\alpha(t-\tau) + k_{-1}\right) M_0^0. \quad \textbf{[41]}$$

The equations for the first moments read

$$\frac{dM_1^0}{dt} = AM_0^0 - BM_1^0 - k_1\alpha(t-\tau)M_1^0 + k_{-1}M_1^1,$$
$$\frac{dM_1^1}{dt} - BM_1^1 + k_1\alpha(t-\tau)M_1^0 - k_{-1}M_1^1. \quad \textbf{[42]}$$

Summing these, we obtain

$$\frac{d\alpha}{dt} = AM_0^0 - B\alpha(t). \quad \textbf{[43]}$$

As before, the equations for the nonstationary mean number of proteins $\alpha(t)$ and the probability to find the operator in the unoccupied state $s(t)$ coincide with Eqs. **29** and **30**, which were obtained directly within the deterministic description.

To proceed further we simplify the system by assuming that operator fluctuations are much faster than protein transcription and degradation. Then the operator state s reaches equilibrium much faster than the protein concentration, and we write

$$M_0^0 \approx \frac{1}{1+\varepsilon\alpha(t-\tau)}, \qquad \textbf{[44]}$$

and obtain

$$\frac{d\alpha}{dt} = \frac{A}{1+\varepsilon\alpha(t-\tau)} - B\alpha(t). \qquad \textbf{[45]}$$

Unfortunately, Eq. **45** has no general analytical solution. We can solve it approximately for $\varepsilon << 1$. Under this approximation, Eq. **45** reads

$$\frac{d\alpha}{dt} = A - B\alpha(t) - A\varepsilon\alpha(t-\tau). \qquad \textbf{[46]}$$

The solution of Eq. **46** was obtained above (sf. Eqs. **20** and **21**). The fixed point of Eq. **46** gives the stationary mean value $\langle n\rangle_s = A/(B+\varepsilon A)$. Given the linearity of Eq. **46**, only the two first moments of the stationary probability distribution $P_s(n)$ are required to compute the autocorrelation function.

The stationary solution of Eqs. **39** is described by the equations

$$\frac{B}{A}\frac{dG^s}{d\gamma} = G_0^s, \qquad \textbf{[47]}$$

$$B\gamma\frac{d^2G_0^s}{d\gamma^2} + (\delta_1 - A\gamma)\frac{dG_0^s}{d\gamma} - \delta_2 G_0^s = 0, \qquad \textbf{[48]}$$

where $\gamma \equiv s-1$, $\delta_1 \equiv B + k_1\langle n\rangle_s + k_{-1}$, $\delta_2 \equiv A(1+k_{-1}/B)$. In fact, we do not need the complete solution of Eqs. **39**. Rather we need to compute the first and second derivatives of G^s at $\gamma = 0$, as was shown in previous section (see Eqs. **23** and **24**). To find the value of $dG_0^s/d\gamma$ at $\gamma = 0$, we apply the Frobenius method to Eq. **48**. The solution of $G_0^s(\gamma)$ can be written as

$$G_0^s(\omega) = \sum_{m=0}^{\infty} a_m \gamma^{\mu+m}, \qquad \textbf{[49]}$$

where μ and a_m are to be determined. By substituting it in Eq. **48**, we obtain

$$a_0\mu(B(\mu-1)+\delta_1)=0,$$

$$a_{m+1}=a_m\frac{A(\mu+m)+\delta_2}{(\mu+m+1)(B(\mu+m)+\delta_1)}.$$

It is evident that $a_0\neq 0$ and $\mu=0$. In this case

$$\frac{dG_0^s}{d\gamma}|_{\gamma=0}=a_1=a_0\frac{\delta_2}{\delta_1}=\frac{A(B+k_{-1})}{((B+k_{-1})(B+\varepsilon A)+k_1A)}. \quad \textbf{[50]}$$

Thus, the derivatives are

$$\frac{dG^s}{ds}|_{s=1}=\frac{A}{B}G_{s0}|_{s=1}=\langle n\rangle_s, \quad \textbf{[51]}$$

$$\frac{d^2G^s}{ds^2}|_{s=1}=\frac{A}{B}\frac{dG_{s0}}{ds}|_{s=1}=\frac{A^2(B+k_{-1})}{B((B+k_{-1})(B+\varepsilon A)+k_1A)}. \quad \textbf{[52]}$$

We next proceed to the calculation of the auto-correlation function. Substituting the solution of Eq. **46** and Eqs. **51** and **52** into Eq. **12**, we obtain

$$K(T)=\frac{\sigma(T)}{1-\zeta e^{-\lambda\tau}}\frac{d^2G_s}{ds^2}|_{s=1}+\left(1-\frac{A}{B+\varepsilon A}\right)\frac{\sigma(T)}{1-\zeta e^{-\lambda\tau}}\frac{dG_s}{ds}|_{s=1}=$$

$$=\left(\frac{A^2(B+k_{-1})}{B((B+k_{-1})(B+\varepsilon A)+k_1A)}+\frac{A(B+\varepsilon A-A)}{(B+\varepsilon A)^2}\right)\frac{\sigma(T)}{1-\zeta e^{-\lambda\tau}},$$

with the same $\sigma(T)$ as in Eq. **21**.

Transient Behavior

The delayed feedback does not change the stationary state of the system, but it affects strongly its transient behavior. As an example, we show here the response of the negative feedback model with dimerization to a sudden change of one of the system parameters (degradation rate B). A comparison of the stochastic dynamics of the system without (Fig. 1A) and with (Fig. 1B) time delay demonstrates that the transition to a new fixed point in the delayed system is accompanied by significant stochastic oscillations, whereas the nondelayed system exhibit a more rapid nonoscillatory transion.

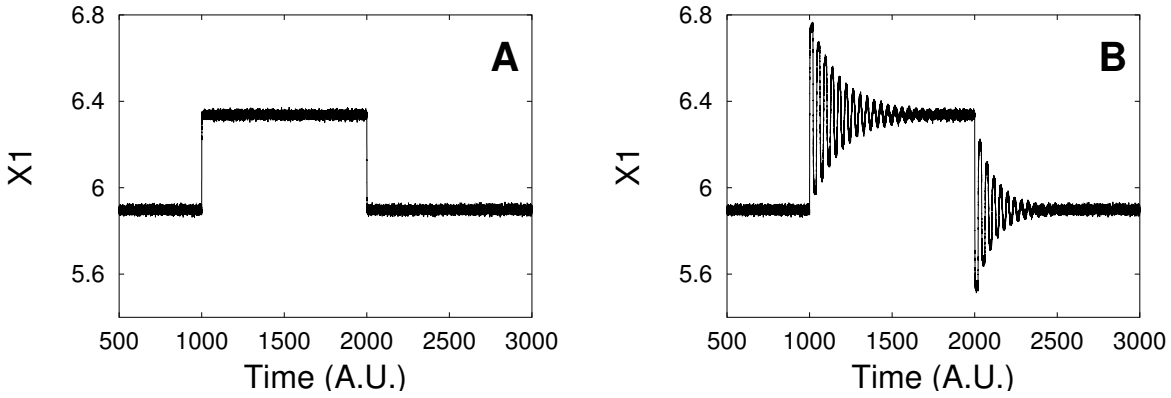

Figure 1: Time series obtained in stochastic simulations without (A) and with (B) delay. In both cases the suddent decrease of the degradation rate from $B = 4$ to $B = 3.5$ was applied in the range $1000 < t < 2000$. The trajectories are averaged over 100 samples. The fixed parameters are $A = 40$, $\tau = 20$, $k_1 = 100$, $k_{-1} = 1000$, $k_2 = 200$, $k_{-2} = 1000$.