

Supplementary Materials for
Toward Single-Cell Control: Noise-Robust Perfect Adaptation in
Biomolecular Systems

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Supplementary Text

Supplementary Figures

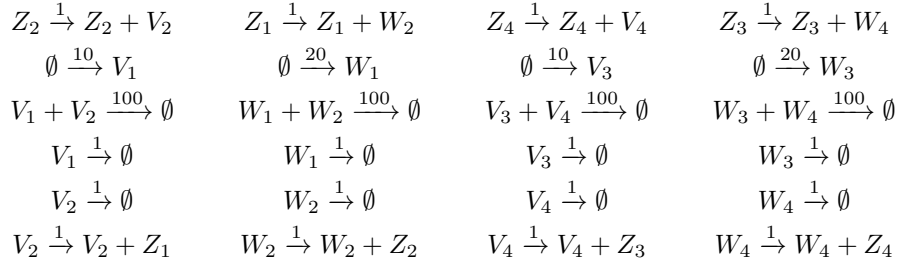
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1 Supplementary Text

S1 Anti-Windup topology prevents the accumulation of controller species

When the target Fano factor is set below 1, certain controller species in MC and NC—specifically Z_1 and Z_4 in Fig. 1—accumulate indefinitely over time (Fig. 2d). This accumulation is detrimental to cellular function and possibly disrupts output control in both MC and NC. To address this issue, we incorporated the anti-windup topology proposed by Filo et al. [1] (Fig. S2). In particular, we constructed the anti-windup topology as shown below and compared the dynamics of Z_1 and Z_4 with and without anti-windup when the target Fano factor temporarily dropped below 1 (Fig. S2):



Without anti-windup, a temporary drop in the target Fano factor below 1 resulted in continuous accumulation of Z_1 and Z_4 (Fig. S2a). Even after the target Fano factor returned above 1, the excess Z_1 and Z_4 decayed slowly (Fig. S2a), delaying the convergence of the Fano factor to its target value (Fig. S2b). In contrast, with anti-windup, when the target Fano factor dropped below 1, Z_1 and Z_4 accumulated only up to a limited level (Fig. S2c). This allowed Z_1 and Z_4 to rapidly reach their stationary values once the target Fano factor returned above 1 (Fig. S2c), enabling the Fano factor to track the desired value more quickly (Fig. S2d). However, the achieved Fano factor deviated slightly from the target (Fig. S2d), as the addition of anti-windup topology changes the moment equations of Z_1 , Z_2 , Z_3 , and Z_4 , as follows:

$$\begin{aligned}
 \mathbb{E}[Z_1] &= \mu_1 - \eta_1 \mathbb{E}[Z_1 Z_2] + \mathbb{E}[V_2], \\
 \mathbb{E}[Z_2] &= \theta_1 \mathbb{E}[X_2] - \eta_1 \mathbb{E}[Z_1 Z_2] + \mathbb{E}[W_2], \\
 \mathbb{E}[Z_3] &= \mu_2 - \eta_2 \mathbb{E}[Z_3 Z_4] + \mathbb{E}[V_4], \\
 \mathbb{E}[Z_4] &= \theta_2 \mathbb{E}[X_2(X_2 - 1)] - \eta_2 \mathbb{E}[Z_3 Z_4] + \mathbb{E}[W_4],
 \end{aligned} \tag{1}$$

where μ_1 , η_1 , θ_1 , μ_2 , η_2 , θ_2 are the MC and NC parameters (see Methods of the main text). This leads to the Fano factor depending on parameters other than those of the controller reactions:

$$\text{Fano factor of } X_2 = 1 - \frac{\mu_1}{\theta_1} + \frac{\theta_1 \mu_2}{\theta_2 \mu_1} + \frac{\theta_1}{\mu_1} \left(\mathbb{E} \left[\frac{V_4 - W_4}{\theta_2} - \frac{V_2 - W_2}{\theta_1} \right] \right). \tag{2}$$

Here, the term $\mathbb{E} \left[\frac{V_4 - W_4}{\theta_2} - \frac{V_2 - W_2}{\theta_1} \right]$ has no closed-form expression that depends solely on the controller parameters, and it may also rely on the parameters of the original networks. This raises uncertainty about whether noise RPA would still hold when anti-windup is incorporated

S2 Z_1 and Z_4 diverges when the target Fano factor is below 1

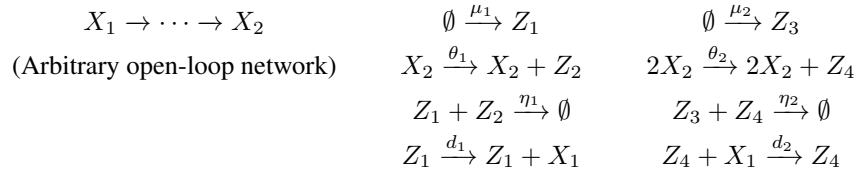
Here, we explain why Z_1 and Z_4 diverge when the target Fano factor is set below 1. Reducing the target Fano factor (i.e., $1 - \frac{\mu_1}{\theta_1} + \frac{\theta_1 \mu_2}{\theta_2 \mu_1}$ to 1 while preserving the target mean (i.e., $\frac{\mu_1}{\theta_1}$) requires $\frac{\mu_2}{\theta_2} < \left(\frac{\mu_1}{\theta_1} \right)^2$, which is equivalent to

$\mu_2 < \theta_2 \left(\frac{\mu_1}{\theta_1} \right)^2$. In this inequality, the left-hand side is the production rate of Z_3 (see (1) in Methods), whereas the right-hand side equals $\theta_2 \left(\frac{\mu_1}{\theta_1} \right)^2 = \theta_2 (\mathbb{E}[X_2])^2 = \theta_2 \mathbb{E}[X_2(X_2 - 1)]$, because the Fano factor of X_2 converges to 1 (i.e., $\mathbb{E}[X_2^2] - (\mathbb{E}[X_2])^2 = \mathbb{E}[X_2]$) when the target Fano factor is set below 1 (Fig. 2b). As $\theta_2 \mathbb{E}[X_2(X_2 - 1)]$ is the average production rate of Z_4 , which is produced from the dimerization of output species (i.e., X_2) (see (1) in Methods), $\mu_2 < \theta_2 \left(\frac{\mu_1}{\theta_1} \right)^2$ indicates that the average production rate of Z_4 becomes bigger than that of Z_3 . As a result, any newly produced Z_3 is rapidly sequestered by the excess Z_4 , making Z_3 converge to 0 (Fig. S3). Once Z_3 disappears, sequestration between Z_3 and Z_4 , the sole degradation pathway of Z_4 , ceases, so Z_4 accumulates without bound. The resulting excess of Z_4 degrades the X_1 and reduces X_2 , hindering the precise output mean control. To preserve the output mean, MC compensates the reduction of X_2 by driving Z_1 upward, leading Z_1 and Z_4 to diverge together.

In contrast, if only MC exists without NC, then Z_1 and Z_2 are produced at the same rate; Z_1 is produced at rate μ_1 , and Z_2 is produced at rate $\theta_1 \mathbb{E}[X_2] = \theta_1 \cdot \frac{\mu_1}{\theta_1} = \mu_1$. This enables MC to control the mean over a wide range of target mean values.

S3 Transience of reaction network associated with NC

Through the numerical simulations of various reaction networks and parameter values, we could identify that Z_1 and Z_4 diverges when the target Fano factor is below 1. To mathematically understand this phenomena, we proved that a continuous-time Markov chain associated with the chemical reaction network below is transience for some special choice of parameters whose target Fano factor is although physically feasible.



For the proof, we apply the Foster-Lyapunov criteria. We copied here a theorem for showing transience from [2]:

Lemma 1.1. [2] *Consider an irreducible Markov process on a countable state space with infinitesimal generator $\mathcal{L}$. Then it is transient if and only if there exists a function $V : \mathcal{S} \rightarrow \mathbb{R}_{>0}$ and a non-empty set $A \subset \mathcal{S}$ such that $\mathcal{L}V(x) \leq 0$ for all $x \notin A$ and there exists $x \notin A$ such that $V(x) < \inf_{y \in A} V(y)$*

Theorem 1.2. *For any given open-loop network, if the parameters of MC and NC satisfy $\frac{\mu_1}{\theta_1} > \frac{1}{2}$ and $\frac{\mu_1}{\theta_1} + \frac{\mu_2}{\theta_2} - \left(\frac{\mu_1}{\theta_1} \right)^2 < \min\left(\frac{\mu_1}{\theta_1} - \lfloor \frac{\mu_1}{\theta_1} \rfloor, \lceil \frac{\mu_1}{\theta_1} \rceil - \frac{\mu_1}{\theta_1} \right)^2$, then the continuous-time Markov chain associated with the open-loop network combined with MC and NC is transient.*

Proof. Let $a, b > 0$ be positive constants to be determined, and let d be the number of species in the open-loop network. Define a function $V : \mathbb{Z}_{\geq 0}^{d+4} \rightarrow \mathbb{R}_{>0}$ by

$$V(\mathbf{x}, z_1, z_2, z_3, z_4) = e^{-az_1 + az_2 + bz_3 - bz_4}.$$

If we set $A = \{\mathbf{0}\} \subset \mathbb{Z}_{\geq 0}^{d+4}$, then $V(e_3) = e^{-a} < 1 = V(\mathbf{0})$. Now, it remains to show that we can choose the constant a so that $\mathcal{L}V(x) < 0$ for all $x \in \mathbb{Z}_{\geq 0}^{d+4} \setminus A$.

The infinitesimal generator of V can be written as

$$\mathcal{L}V(x_1, x_2, z_1, z_2, z_3, z_4) = \{\mu_1(e^{-a} - 1) + \mu_2(e^b - 1) + \theta_1 x_2(e^a - 1) + \theta_2 x_2(x_2 - 1)(e^{-b} - 1)\}V.$$

Choosing a, b to be small enough, it follows from the Taylor's expansion that

$$\begin{aligned} & \mu_1(e^{-a} - 1) + \mu_2(e^{-b} - 1) + \theta_1 x_2(e^a - 1) + \theta_2 x_2(x_2 - 1)(e^{-b} - 1) \\ & \approx -\mu_1 a + \mu_2 b + \theta_1 x_2 a - \theta_2 x_2(x_2 - 1)b. \end{aligned} \quad (3)$$

Here, note that $V > 0$ by the definition. Then, it can be shown that finding suitable constants $a, b > 0$ such that (3) is smaller than 0 for all $x_2 \in \mathbb{Z}_{\geq 0}$ completes this proof.

Since (3) is quadratic for x_2 hence attains its maximum at (possibly, real valued)

$$\bar{x} = \frac{a\theta_1}{2b\theta_2} + \frac{1}{2}. \quad (4)$$

Then we can define a function $f : \mathbb{R}_{>0} \rightarrow [0, 1)$ so that $\hat{x} := \frac{a\theta_1}{2b\theta_2} + f(\frac{a}{b}) \in \mathbb{Z}_{\geq 0}$ maximizes (3) over $\mathbb{Z}_{\geq 0}$. In other words, f makes $\hat{x}$ to be the nearest integer from the vertex of the quadratic function (See Fig. S5 for graphical illustration).

By plugging $\hat{x}$ into (3), we have

$$\begin{aligned} & -\mu_1 a + \mu_2 b + \theta_1 \left(\frac{a\theta_1}{2b\theta_2} + f\left(\frac{a}{b}\right) \right) a - \theta_2 \left(\frac{a\theta_1}{2b\theta_2} + f\left(\frac{a}{b}\right) \right) \left(\frac{a\theta_1}{2b\theta_2} + f\left(\frac{a}{b}\right) - 1 \right) b \\ & = \frac{\theta_1^2}{4\theta_2} \frac{a^2}{b} + \left\{ -\mu_1 + \frac{\theta_1}{2} \right\} a + \left\{ \mu_2 - \theta_2 f\left(\frac{a}{b}\right) \left(f\left(\frac{a}{b}\right) - 1 \right) \right\} b \\ & = \frac{1}{b} \left[\frac{\theta_1^2}{4\theta_2} a^2 + \left\{ -\mu_1 + \frac{\theta_1}{2} \right\} ab + \left\{ \mu_2 - \theta_2 f\left(\frac{a}{b}\right) \left(f\left(\frac{a}{b}\right) - 1 \right) \right\} b^2 \right] \\ & = \frac{1}{b} \left[\frac{\theta_1^2}{4\theta_2} \left\{ a + \frac{2\theta_2}{\theta_1^2} \left(-\mu_1 + \frac{\theta_1}{2} \right) b \right\}^2 - \left\{ \frac{\theta_2}{\theta_1^2} \left(-\mu_1 + \frac{\theta_1}{2} \right)^2 - \mu_2 + \theta_2 f\left(\frac{a}{b}\right) \left(f\left(\frac{a}{b}\right) - 1 \right) \right\} b^2 \right] \end{aligned} \quad (5)$$

By the assumption $\frac{\mu_1}{\theta_1} > \frac{1}{2}$, we could take a, b such that $\frac{a}{b} = \frac{2\theta_2}{\theta_1^2} (\mu_1 - \frac{\theta_1}{2})$. Then (5) is negative if and only if

$$\left\{ \frac{\theta_2}{\theta_1^2} \left(-\mu_1 + \frac{\theta_1}{2} \right)^2 - \mu_2 + \theta_2 f\left(\frac{a}{b}\right) \left(f\left(\frac{a}{b}\right) - 1 \right) \right\} > 0$$

which is equivalent to

$$\frac{1}{4} - f\left(\frac{a}{b}\right) \left(1 - f\left(\frac{a}{b}\right) \right) > \frac{\mu_1}{\theta_1} + \frac{\mu_2}{\theta_2} - \frac{\mu_1^2}{\theta_1^2}$$

Now, it remains to identify $f(\frac{a}{b})$ in terms of parameters. By the above assumption $\frac{a}{b} = \frac{2\theta_2}{\theta_1^2} (\mu_1 - \frac{\theta_1}{2})$,

$$\bar{x} = \frac{\mu_1}{\theta_1} \quad \text{and} \quad \hat{x} = \frac{\mu_1}{\theta_1} - \frac{1}{2} + f\left(\frac{a}{b}\right).$$

By Definition of f ,

$$f\left(\frac{a}{b}\right) = \begin{cases} \frac{1}{2} + \lfloor \frac{\mu_1}{\theta_1} \rfloor - \frac{\mu_1}{\theta_1} & \text{if } \frac{\mu_1}{\theta_1} - \lfloor \frac{\mu_1}{\theta_1} \rfloor \leq \lceil \frac{\mu_1}{\theta_1} \rceil - \frac{\mu_1}{\theta_1}, \\ \frac{1}{2} + \lceil \frac{\mu_1}{\theta_1} \rceil - \frac{\mu_1}{\theta_1} & \text{otherwise.} \end{cases}$$

Hence,

$$\frac{1}{4} - f\left(\frac{a}{b}\right) \left(1 - f\left(\frac{a}{b}\right) \right) = \min\left(\frac{\mu_1}{\theta_1} - \lfloor \frac{\mu_1}{\theta_1} \rfloor, \lceil \frac{\mu_1}{\theta_1} \rceil - \frac{\mu_1}{\theta_1} \right)^2,$$

which completes this proof. $\square$

Note that $\min(\frac{\mu_1}{\theta_1} - \lfloor \frac{\mu_1}{\theta_1} \rfloor, \lceil \frac{\mu_1}{\theta_1} \rceil - \frac{\mu_1}{\theta_1})^2 < (\frac{1}{2})^2 = \frac{1}{4}$. As an example, if

$$\theta_1 = 2\sqrt{2}, \theta_2 = 1, \mu_1 = 3\sqrt{2} + 3, \mu_2 = \frac{2\sqrt{2} + 3}{\sqrt{2}}, \quad (6)$$

then

$$\begin{aligned} \frac{\mu_1}{\theta_1} &= \frac{3\sqrt{2} + 3}{2\sqrt{2}} > \frac{1}{2}, \\ \frac{\mu_2}{\theta_2} + \frac{\mu_1}{\theta_1} - (\frac{\mu_1}{\theta_1})^2 &= \frac{1}{8} < \min(\frac{\mu_1}{\theta_1} - \lfloor \frac{\mu_1}{\theta_1} \rfloor, \lceil \frac{\mu_1}{\theta_1} \rceil - \frac{\mu_1}{\theta_1})^2 = \frac{1}{8}(11 - 6\sqrt{2}), \end{aligned} \quad (7)$$

therefore, the associated system is transient.

S4 Comparison of NC with other enhanced versions of AIF controller

In previous studies, modified AIF controllers were reported to achieve a Fano factor below 1 [3, 4, 5]. However, the performance of those controllers depend on reaction parameters, and thus they could fail to maintain noise RPA after parameter perturbations.

To compare this point with the performance of NC, we checked the performance of NC with three types of modified AIF controller (Fig. S6a, b, e), which achieved a Fano factor below 1. We perturbed one of the reaction parameters and checked whether the noise level and ergodicity was maintained or not. The results show that two AIF motifs suggested by [5] (Fig. S6a) and [3] (Fig. S6c) could not maintain the low noise level and increased the Fano factor to greater than 1 after perturbation (Fig. S6b, d). On the other hand, our NC maintains the same noise level after perturbation (Fig. S6b, d). When comparing the sensor-actuated controller [4] with NC, since NC does not contain a reaction identical to the actuation reaction in sensor-actuated controller (nu, Fig. S6e), we instead perturbed the reaction parameter of NC's actuation reaction ($X_1 + Z_4 \rightarrow Z_4$), which exerts a similar negative regulation. The results show that the sensor-actuated AIF failed to maintain a Fano factor below 1 after parameter perturbation, whereas NC continued to maintain a Fano factor close to 1 (Fig. S6f).

S5 Effect of saturation effect

One of the obstacles in implementing the NC in an actual biological circuit is the saturation effect. While the propensity of the NC's sensing reaction is represented as a quadratic equation in our theoretical model, in reality there is a maximum allowable reaction rate. To model this, we replace the propensity of sensing reaction with a Hill function of the form :

$$f_{Hill}(X_2) = V_{max} \frac{X_2^2}{K^2 + X_2^2}.$$

Here, K denotes the dissociation constant, where a larger K means weaker binding of the X_2 homodimer to the DNA site. And V_{max} is the maximal allowable reaction rate. To determine θ_2 in this reaction, we require the Hill function to closely approximate mass-action kinetics. Similar to the approach of S1.2 in [6], we do that by assuming that the propensity of sensing reaction, written in mass-action kinetics as $f(X_2) = \theta_2 X_2^2$, passes through the inflection point of the Hill function ($K, \frac{V_{max}}{2}$). Under this assumption, θ_2 is determined by the ratio of V_{max} to K^2 :

$$\theta_2 = \frac{V_{max}}{2K^2}$$

In other words, to achieve the desired value of θ_2 , V_{max} should be proportional to K^2 . By substituting this relationship

into the equation, we get

$$f_{Hill}(X_2) = 2\theta_2 K^2 \frac{X_2^2}{K^2 + X_2^2}.$$

We see that as $K \rightarrow \infty$, the propensity $f_{Hill}(X_2)$ approaches $2\theta_2 X_2^2$. Under this condition, the variance and the set point Fano factor of X_2 changes as follows :

$$\begin{aligned} \text{Var}(X_2) &= \frac{\mu_2}{2\theta_2} - \left(\frac{\mu_1}{\theta_1}\right)^2 \\ \text{FF}(X_2) &= \frac{\frac{\mu_2}{2\theta_2} - \left(\frac{\mu_1}{\theta_1}\right)^2}{\frac{\mu_1}{\theta_1}} \end{aligned}$$

To examine how the saturation effect influences NC functionality, we varied the dissociation constant K and observed the resulting changes in the Fano factor (Fig. S7). As K increased, the Fano factor approached the set-point more closely (Fig. S7b), and the noise level was also maintained after parameter perturbation (Fig. S7b, $t = 300$). To implement such high dissociation constants in an actual biological circuit, one could alter the base sequence of the GH DNA site (Fig. 6d) or engineer the amino acids of the DNA-binding domain in the X_2 homodimer (Fig. 6d) to lower the binding affinity.

2 Supplementary Figures

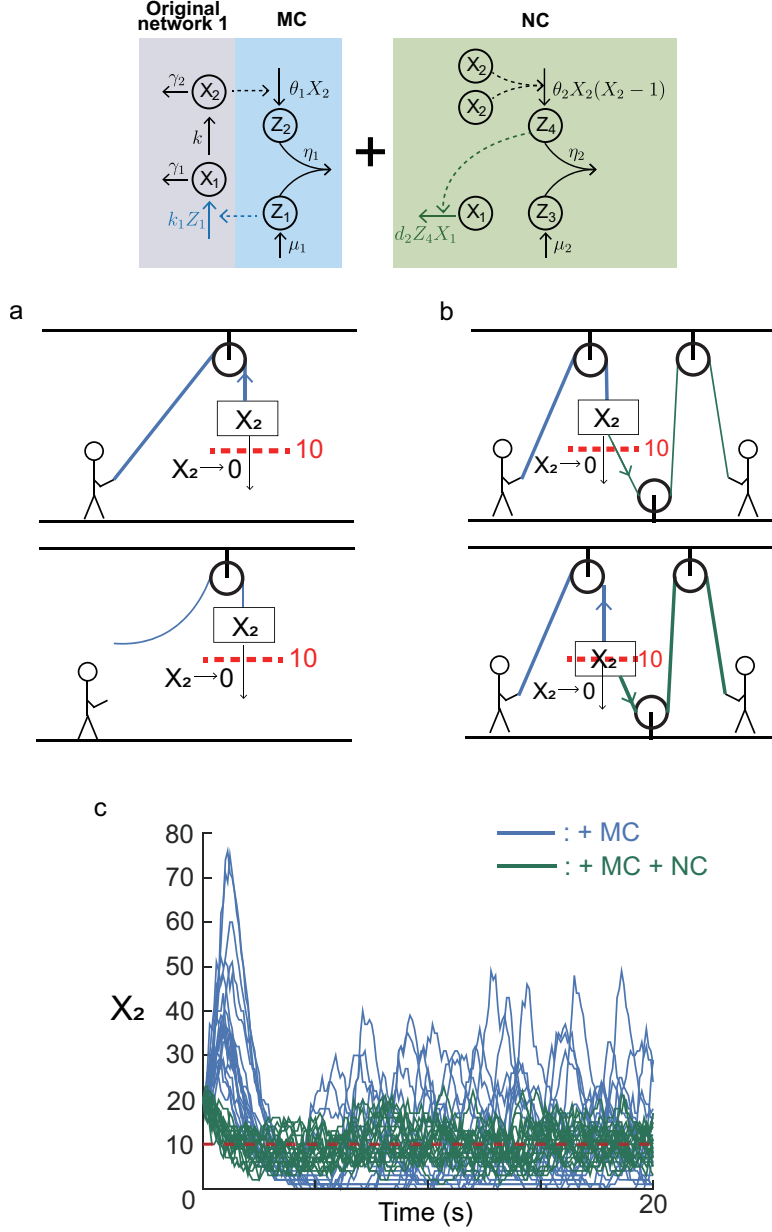


Figure S1: **The structural difference between the NC and the MC enables noise RPA.** (a) Schematic figure illustrating the situation where only the MC is used to recover from stochastic fluctuations. While the MC maintains the mean of the output (X_2) at 10 (red dotted line), stochastic fluctuations may cause the X_2 level to exceed 10 (top image). In such cases, the MC can only halt the production-based actuation reaction (blue line) and rely on the natural degradation of X_2 for recovery. This is analogous to lowering an object (X_2) using a pulley by requiring the object itself to move downwards (bottom). (b) Schematic figure illustrating the situation where both the MC and the NC are used to recover from stochastic fluctuations. Using both MC and NC is analogous to using two pulleys: one pulley pulling the object upward (blue; corresponding to MC) and another pulley pulling the object downward (green; corresponding to NC). The additional pulley (NC) can accelerate the downward movement of the object, analogous to the rapid reduction of excessive protein levels caused by stochastic fluctuations. (c) 20 single-cell trajectories of X_2 from the original network with the MC (blue), and from the original network with the MC and the NC (green) simulated with parameters following those in Fig. 1e-f except for $\mu_1 = 10$, $k_1 = 10$, $\mu_2 = 10$, $\theta_2 = 1/10.5$, $d_2 = 10$, initializing X_2 copy number as 20 and other species as their stationary mean values. Using both the MC and the NC enables the faster convergence to the target value of 10 compared to using the MC alone. Simulations were performed using the Gillespie algorithm.

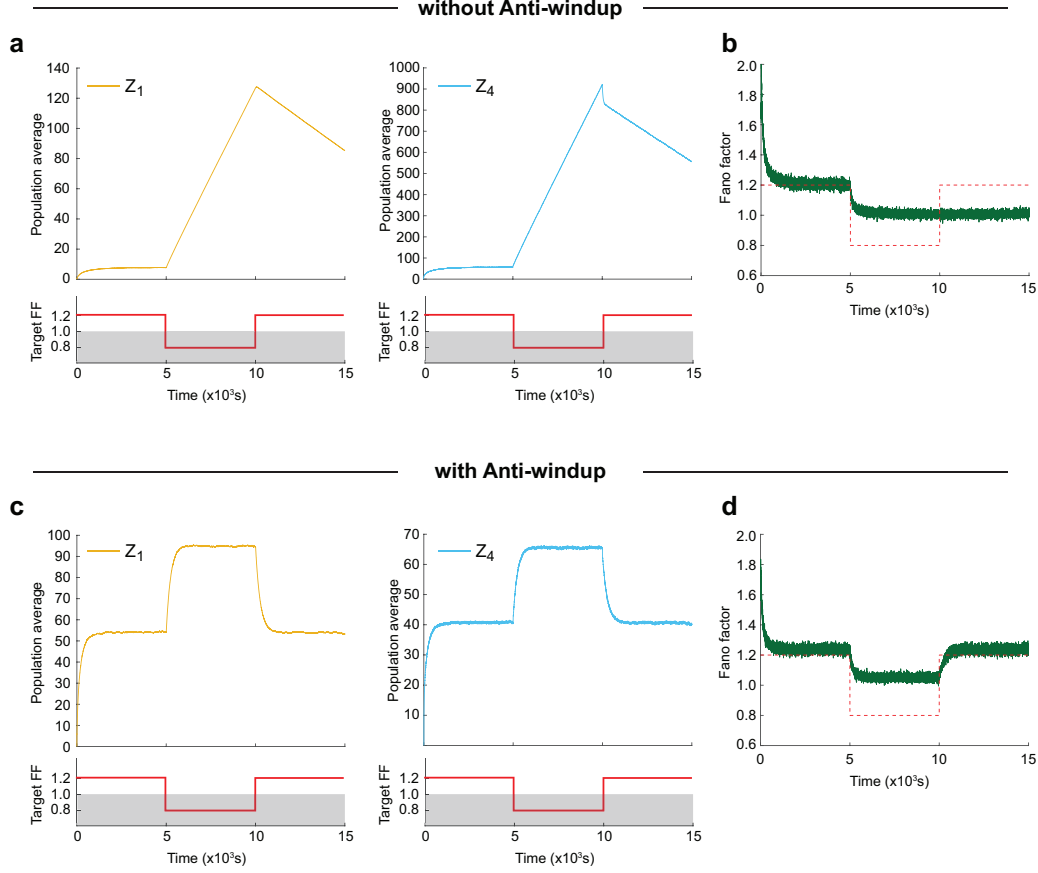


Figure S2: Anti-windup topology suppresses the accumulation of controller species; yet, it disturbs precise noise control. (a) We simulated 10,000 trajectories of Z_1 (left) and Z_4 (right) using the reaction networks and the parameters following those in Fig. 1e-f except for μ_2 . Specifically, μ_2 was set to 9.6 during 0 – 5000s and 10,000s – 15,000s and to 8.4 for 5000 – 10,000s, corresponding to target Fano factor (red lines) of 1.2 and 0.8, respectively. During the period when the target Fano factor falls below 1 (gray shaded regions), Z_1 and Z_4 were accumulated and reduced slowly to the original level after the target Fano factor rose up to 1. (b) The Fano factor of 10,000 trajectories of X_2 simulated under same conditions in (a). The Fano factor of X_2 failed to track the desired value even after the target Fano factor (red dotted line) rose above 1. (c) The mean of 10,000 trajectories of Z_1 (left) and Z_4 (right) from the same system as in (a-c), but combined with anti-windup topology described in Text. S1. Combining the anti-windup topology successfully prevented the accumulation of Z_1 and Z_4 during the period when the target Fano factor (red lines) fell below 1 (gray shaded region) (d) The Fano factor of 10,000 trajectories of X_2 simulated under the same conditions in (c). While the Fano factor failed to track the desired value when the target value (red dotted line) was below 1, it quickly tracked the target once the desired Fano factor exceeded 1. However, the achieved Fano factor deviated slightly from the target, as the addition of anti-windup topology changes the moment equations of Z_1 , Z_2 , Z_3 , and Z_4 (see Text. S1 for more details).

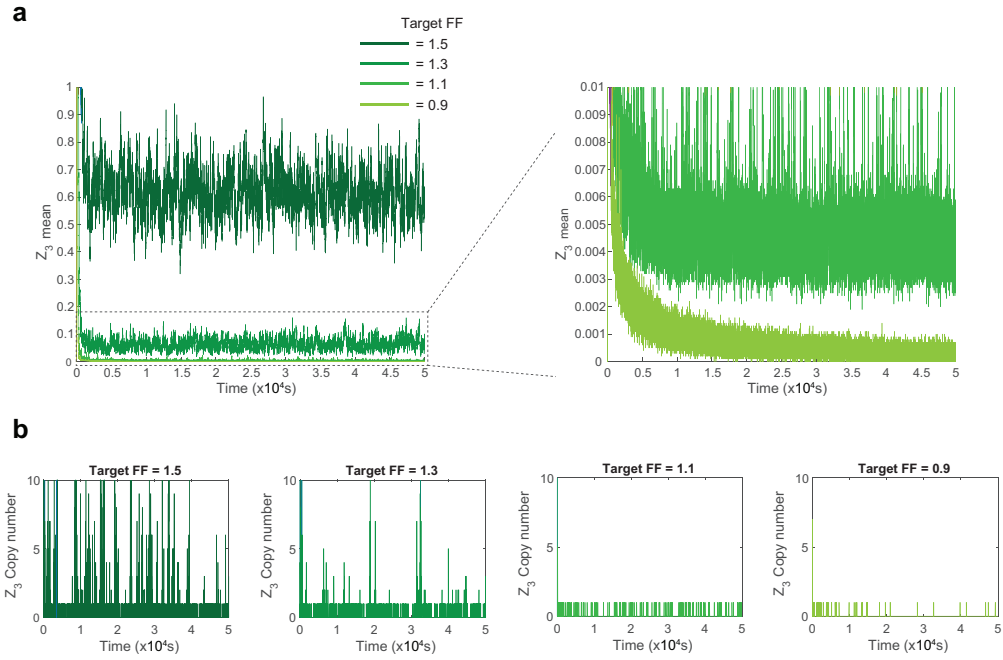


Figure S3: Z_3 converges to zero when the target Fano factor is below 1. (a) The mean of 10,000 trajectories of Z_3 simulated with the reaction networks and the parameters of Fig. 2b (left) and with a magnified version near zero (right). The Z_3 mean converges to 0 when the target Fano factor (Target FF) is set below 1. (b) One representative single-cell trajectory of Z_3 simulated under the same conditions as in (a). The trajectory exhibits prolonged intervals at $Z_3 = 0$, indicating an increased probability mass at zero.

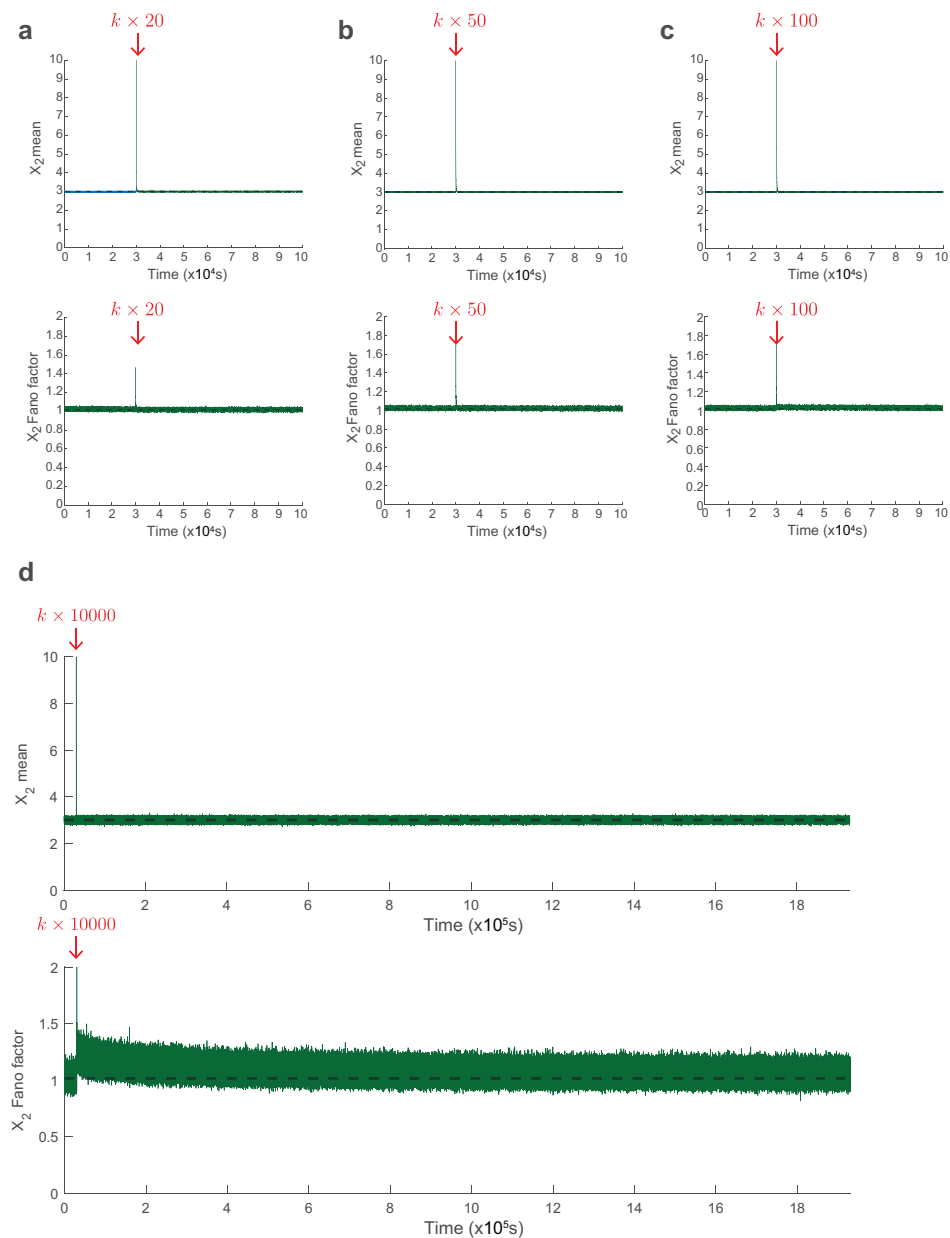


Figure S4: MC and NC preserve the output mean and noise even after large perturbations. (a-d) The mean (top) and Fano factor (bottom) of 20,000 trajectories (1,000 trajectories for (d)) of X_2 simulated with the reaction networks and the parameters of Fig. 1d-f with a perturbation magnitude increased to 20-fold (a), 50-fold (b), 100-fold (c), and 10000-fold (d). Even under higher magnitudes of perturbations, MC and NC preserve the output mean and noise, although larger perturbations result in a longer convergence time to the desired Fano factor level (dotted line).

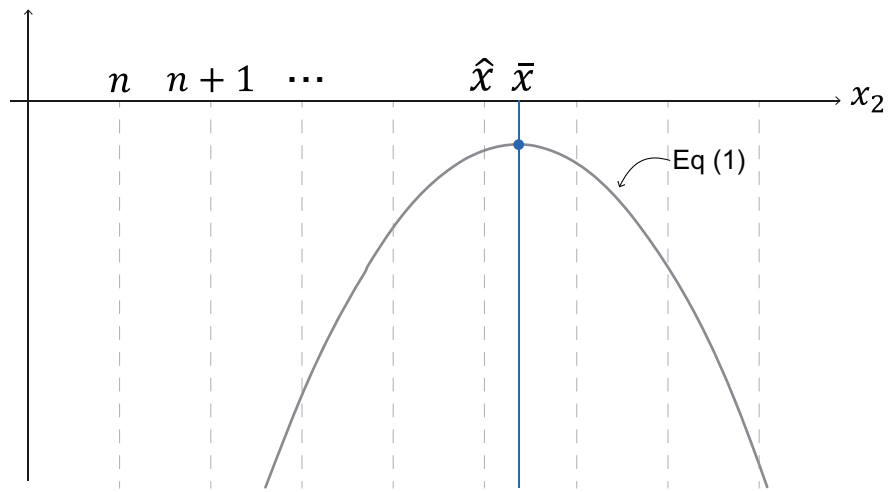


Figure S5: Graphical illustration of eq. (3), $\bar{x}$, and $\hat{x}$

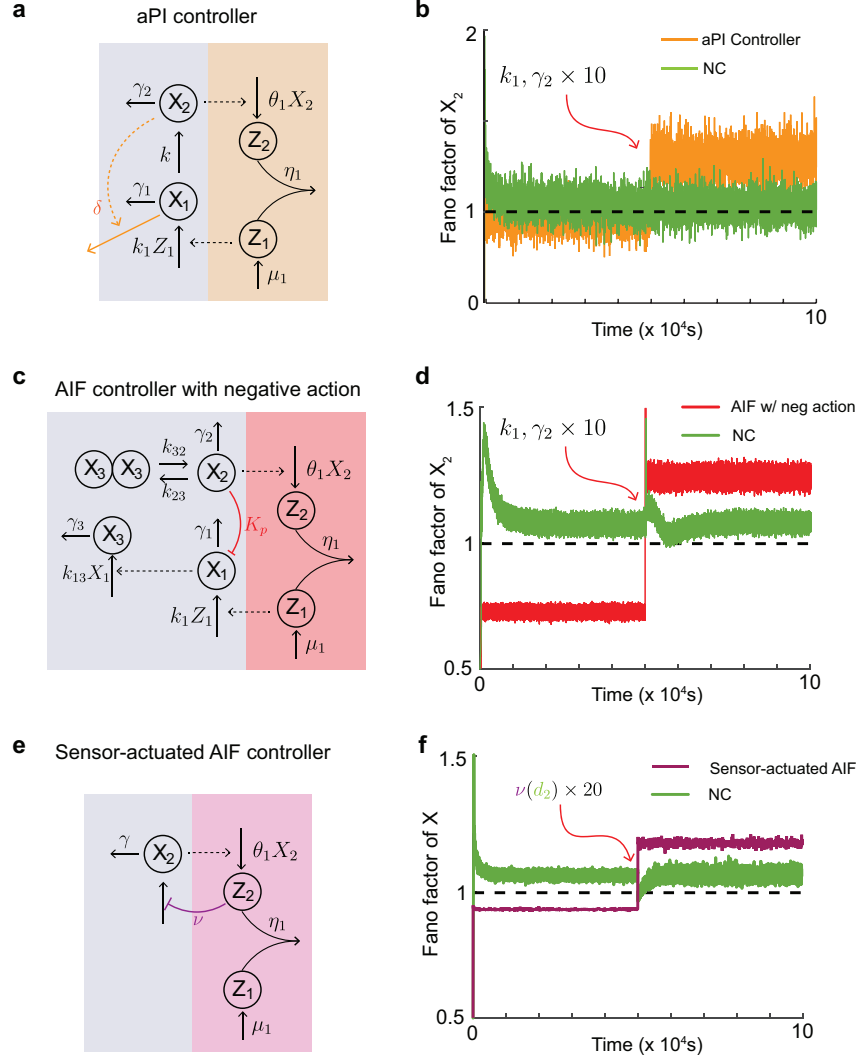


Figure S6: **Modified version of AIF controller does not have a noise RPA.** (a) aPI Class 1 degradation-inhibition controller (aPI controller, orange box, [5]) attached to the sample original network (gray box). The additional negative feedback loop (delta) is also a part of aPI controller. (b) The Fano factor of 500 trajectories of X_2 in (a) and original network of (a) combined with MC and NC simulated with parameters $\mu_1 = 10$, $\theta_1 = 2$, $k = 3$, $\gamma_1 = 2$, $\gamma_2 = 7$, $\delta = 150$, $k_1 = 2$, $\eta_1 = 1000$, and k_1, γ_2 both increased 10-fold at time = 50,000s. The aPI controller (orange) could achieve a Fano factor of X_2 below 1. However, after the perturbation of k_1 ($t = 2,500$), the Fano factor increases rapidly. On the other hand, NC (green) maintains the Fano factor of X_2 close to 1, even after the parameter perturbation ($t = 50,000$). (c) AIF controller with negative action (red box, [3]) attached to the sample original network (gray box). The additional negative feedback loop (K_p) is also a part of the controller. (d) The Fano factor of 10,000 trajectories of X_2 in (c) and original network of (c) combined with MC and NC simulated with parameters $\mu_1 = 10$, $\theta_1 = 2$, $\eta_1 = 100$, $k_1 = 0.25$, $\gamma_1 = 2$, $\gamma_2 = 1$, $\gamma_3 = 1$, $K_p = 5$, $k_{13} = 1$, $k_{32} = 3$, $k_{23} = 1$, and k_1, γ_2 both increased 10-fold at time = 50,000s. Similar to (b), the AIF controller with negative action (red) could not maintain the Fano factor of X_2 after parameter perturbation ($t = 50,000$), while NC (green) maintains the Fano factor of X_2 after the perturbation. (e) Sensor-actuated AIF controller (purple box, [4]) attached to the sample original network (gray box). The negative feedback reaction (ν) is also a part of the controller. (f) The Fano factor of 50,000 trajectories of X_2 in (e) and original network of (e) combined with MC and NC simulated with parameters $\mu_1 = 1.574$, $\theta_1 = 13.967$, $\eta_1 = 0.132$, $\gamma = 1$, $\nu = 0.125$, and ν increased 20-fold at time = 50,000s. Since the reaction corresponding to ν does not exist in MC and NC, we instead increased the parameter of NC's actuation reaction (d2), which exerts a similar negative regulation. The sensor-actuated controller (purple) could not maintain the Fano factor of X_2 after parameter perturbation ($t = 50,000$), while NC (green) maintains the Fano factor of X_2 after the perturbation.

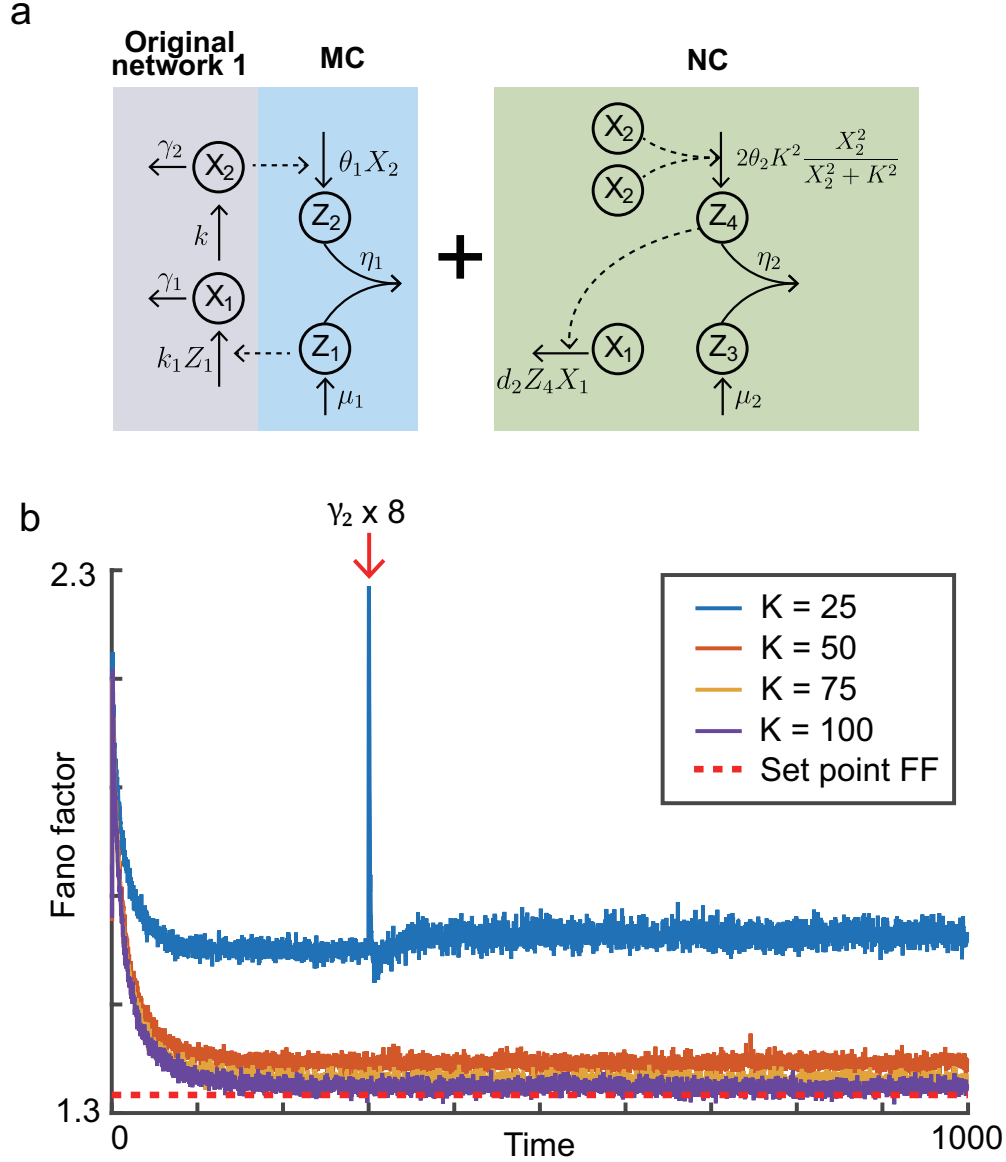


Figure S7: **Even in the presence of the saturation effect, the NC operates properly when the dissociation constant is sufficiently large.** (a) NC with the saturation effect. Considering the saturation effect, the sensing reaction of NC is represented in Hill-function form. (b) The Fano factor of 50,000 trajectories of X_2 from the original network with MC and NC with the saturation effect. As the dissociation constant (K) increases, the Fano factor closely follows the set point (red dotted line) and maintains a stable noise level even after parameter perturbation ($t = 300$).

Supplementary References

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