Supporting Material

Optimal feedback strength for noise suppression in auto-regulatory gene networks

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auto-regulatory gene networks

Supplementary information

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Appendix A: Extrinsic and intrinsic contributions of noise

We model the time evolution of the number of molecules $\mathbf{x}$ and $\mathbf{z}$ through a Stochastic Hybrid System (SHS) with state $\mathbf{y} = [\mathbf{z}, \mathbf{x}]^T$ characterized by trivial continuous dynamics

$$\dot{\mathbf{y}} = \begin{bmatrix} \dot{\mathbf{z}} \\ \dot{\mathbf{x}} \end{bmatrix} = 0 \tag{A.1}$$

and four reset maps

$$\mathbf{y} \mapsto \phi_1(\mathbf{y}) = \begin{bmatrix} \mathbf{z} + \mathbf{N}_z \\ \mathbf{x} \end{bmatrix}, \quad \mathbf{y} \mapsto \phi_2(\mathbf{y}) = \begin{bmatrix} \mathbf{z} - 1 \\ \mathbf{x} \end{bmatrix} \tag{A.2}$$

$$\mathbf{y} \mapsto \phi_3(\mathbf{y}) = \begin{bmatrix} \mathbf{z} \\ \mathbf{x} + \mathbf{N}_x \end{bmatrix}, \quad \mathbf{y} \mapsto \phi_4(\mathbf{y}) = \begin{bmatrix} \mathbf{z} \\ \mathbf{x} - 1 \end{bmatrix} \tag{A.3}$$

with corresponding transition intensities given by

$$\lambda_1(\mathbf{y}) = K_z, \;\; \lambda_2(\mathbf{y}) = d_z\mathbf{z}, \tag{A.4}$$

$$\lambda_3(\mathbf{y}) = g(\mathbf{x}^*, \mathbf{z}^*) + \frac{dg(\mathbf{x}, \mathbf{z}^*)}{d\mathbf{x}}|_{\mathbf{x}=\mathbf{x}^*}(\mathbf{x} - \mathbf{x}^*) + \frac{dg(\mathbf{x}^*, \mathbf{z})}{d\mathbf{z}}|_{\mathbf{z}=\mathbf{z}^*}(\mathbf{z} - \mathbf{z}^*), \tag{A.5}$$

$$\lambda_4(\mathbf{y}) = d_x\mathbf{x}. \tag{A.6}$$

Using Dynkin's formula (Eq. 6 of the paper) we have that the time evolution of all the first and second order moments of $\mathbf{y}$ is given by

$$
\begin{bmatrix}
\frac{d\mathbf{E}[\mathbf{z}]}{dt} \\[4pt]
\frac{d\mathbf{E}[\mathbf{x}]}{dt} \\[4pt]
\frac{d\mathbf{E}[\mathbf{z}^2]}{dt} \\[4pt]
\frac{d\mathbf{E}[\mathbf{x}^2]}{dt} \\[4pt]
\frac{d\mathbf{E}[\mathbf{zx}]}{dt}
\end{bmatrix}
= \bar{\mathbf{a}} + \bar{\mathbf{A}}
\begin{bmatrix}
\mathbf{E}[\mathbf{z}] \\[4pt]
\mathbf{E}[\mathbf{x}] \\[4pt]
\mathbf{E}[\mathbf{z}^2] \\[4pt]
\mathbf{E}[\mathbf{x}^2] \\[4pt]
\mathbf{E}[\mathbf{zx}]
\end{bmatrix}
\tag{A.7}
$$

for some vector $\bar{\mathbf{a}}$ and matrix $\bar{\mathbf{A}}$. A steady-state analysis of Eq. A.7 shows that the total noise level in the protein population is given by Eq. 24 of the paper.

Appendix B: Limit of noise suppression

It is not easy to derive an explicit expression for the minimum protein noise, $CV_{tot-min}$. However, for the biologically meaningful case of

$$
T_z \gg T_{nr},
\tag{A.8}
$$

analytical formulations for both $CV_{tot-min}$ and the optimal level of feedback strength which achieves this minimum noise are possible. Using Eq. A.8 we have from Eq. 24 of the paper that the total protein noise level is given by

$$
CV_{tot}^2 = CV_{int-nr}^2 \frac{\left(1 + (a\mathbf{x}^*)^M\right)^2}{1 + (M+1)(a\mathbf{x}^*)^M} + S^2 CV_z^2 \left(\frac{1 + (a\mathbf{x}^*)^M}{1 + (M+1)(a\mathbf{x}^*)^M}\right)^2.
\tag{A.9}
$$

Straightforward calculus shows that the right-hand-side of Eq. A.9 is minimum when

$$(a\mathbf{x}^*)^M = \frac{M - 2 + \sqrt{M}\sqrt{8S^2CV_z^2 + MCV_{int-nr}^2}/CV_{int-nr}}{2(M+1)}, \qquad \text{(A.10)}$$

which implies from Eq. A.9 that

$$CV_{tot-min}^2 = \frac{2L}{(1+M)^2 \left(\sqrt{M}CV_{int-nr} + \sqrt{8S^2CV_z^2 + MCV_{int-nr}^2}\right)^2}$$

$$L = 4S^4CV_z^4 + 19MS^2CV_z^2CV_{int-nr}^2 + 4M^2CV_{int-nr}^4$$

$$+ 5\sqrt{M}S^2CV_z^2CV_{int-nr}\sqrt{8S^2CV_z^2 + MCV_{int-nr}^2}$$

$$+ 4\sqrt{M^3}CV_{int-nr}^3\sqrt{8S^2CV_z^2 + MCV_{int-nr}^2} \qquad \text{(A.11)}$$

and

$$a_{min} = \frac{d_x\sqrt{M}}{2g_0N_x(M+1)}\left(3\sqrt{M} + \sqrt{8S^2CV_z^2 + MCV_{int-nr}^2}/CV_{int-nr}\right)P$$

$$\text{(A.12a)}$$

$$P = \left(\frac{M - 2 + \sqrt{M}\sqrt{8S^2CV_z^2 + MCV_{int-nr}^2}/CV_{int-nr}}{2(M+1)}\right)^{\frac{1}{M}}. \qquad \text{(A.12b)}$$

From Eq. A.9 we conclude that when $T_z \gg T_{nr}$, the protein noise CV_{tot-nr} when there is no feedback is

$$CV_{tot-nr}^2 = CV_{int-nr}^2 + S^2CV_z^2. \qquad \text{(A.13)}$$

Hence, given experimental measurements of CV_{tot-nr} and the minimal noise $CV_{tot-min}$ in the protein population, one can determine CV_z by simultaneously solving Eq. A.11 and Eq. A.13. In cases where only $CV_{tot-min}$ is obtained experimentally, then given an estimate of CV_{int-nr}, one can compute CV_z from Eq. A.11.

In addition to the above assumption (i.e., $T_z \gg T_{nr}$) if we also have that

$$CV_{int-nr}^2 \ll S^2 CV_z^2, \tag{A.14}$$

then Eq. A.11 reduce to

$$CV_{tot-min}^2 \approx \frac{S^2 CV_z^2}{(1+M)^2} + \frac{5SCV_z CV_{int-nr}\sqrt{M}}{\sqrt{2}(1+M)^2}. \tag{A.15}$$

Appendix C: Estimating the noise in the exogenous signal

Assuming the source of extrinsic noise to be the plasmid population, we have that $g(\mathbf{x}, \mathbf{z}) = \mathbf{z}g(\mathbf{x})$ and therefore

$$S = \frac{\mathbf{z}^*}{g(\mathbf{x}^*, \mathbf{z}^*)} \frac{dg(\mathbf{x}^*, \mathbf{z})}{d\mathbf{z}}|_{\mathbf{z}=\mathbf{z}^*} = 1. \tag{A.16}$$

For this synthetic auto-regulatory gene network we calculate from the reaction rates provided in Table I of reference (24) of the paper,

$$CV_{int-nr}^2 \approx 0.008, \quad T_{nr}/T_z \approx 0.1. \tag{A.17}$$

As Eq. A.8 holds, we use the formulas in Appendix B to quantify the noise CV_z in the exogenous signal. Using $M = 1$, the above estimate of CV_{int-nr}, and the experimentally obtained value of $CV_{tot-min} \approx 0.4$, we obtain from Eq. A.15 that $CV_z = CV_{plasmid}$ is approximately 0.64.

Appendix D: Keeping the number of protein molecules fixed

When the feedback strength is changed along with the maximum transcription rate g_0 such that $\mathbf{x}^*$ is fixed, we have from Eq. 18, 24, 28, 29, 32 of the paper that the total noise in the protein population is given by

$$
\begin{aligned}
CV_{tot}^2 &= \frac{1 + (a\mathbf{x}^*)^M}{1 + (1 + M)(a\mathbf{x}^*)^M} \frac{N_x^2 + V_x^2 + N_x}{2N_x\mathbf{x}^*} \\
&+ S^2 CV_z^2 \left(\frac{1 + (a\mathbf{x}^*)^M}{1 + (1 + M)(a\mathbf{x}^*)^M} \right)^2 \frac{1}{1 + \frac{T_{nr}}{T_z} \frac{1+(a\mathbf{x}^*)^M}{1+(1+M)(a\mathbf{x}^*)^M}}.
\end{aligned} \tag{A.18}
$$

On the hand, if the feedback strength is varied with the protein degradation rate d_x then we have

$$
\begin{aligned}
CV_{tot}^2 &= \frac{1 + (a\mathbf{x}^*)^M}{1 + (1 + M)(a\mathbf{x}^*)^M} \frac{N_x^2 + V_x^2 + N_x}{2N_x\mathbf{x}^*} \\
&+ S^2 CV_z^2 \left(\frac{1 + (a\mathbf{x}^*)^M}{1 + (1 + M)(a\mathbf{x}^*)^M} \right)^2 \frac{1}{1 + \frac{\mathbf{x}^* ln(2)}{g_0 N_x T_z} \frac{(1+(a\mathbf{x}^*)^M)^2}{1+(1+M)(a\mathbf{x}^*)^M}}.
\end{aligned} \tag{A.19}
$$

A detailed analysis of both Eq. A.18 and Eq. A.19 shows that in these methods of varying the feedback strength, the total noise in the protein population always decreases with increasing feedback strength a.

Finally, we consider the situation where the feedback strength is varied with the average burst size. For simplicity, we assume that the protein burst size $\mathbf{N}_x$ follows a geometric distribution, in which case $V_x^2 = N_x^2 + N_x$. This is a valid approximation when the mRNA half-life is much shorter than the protein half-life. In this case the noise in protein numbers is given by

$$
\begin{aligned}
CV_{tot}^2 &= \frac{1 + (a\mathbf{x}^*)^M}{1 + (1+M)(a\mathbf{x}^*)^M} \frac{\frac{d_x(1+(a\mathbf{x}^*)^M)\mathbf{x}^*}{g_0} + 1}{\mathbf{x}^*} \\
&+ S^2 CV_z^2 \left(\frac{1 + (a\mathbf{x}^*)^M}{1 + (1+M)(a\mathbf{x}^*)^M} \right)^2 \frac{1}{1 + \frac{T_{nr}}{T_z} \frac{1+(a\mathbf{x}^*)^M}{1+(1+M)(a\mathbf{x}^*)^M}}.
\end{aligned}
\tag{A.20}
$$

Analysis on Mathematics of Eq. A.20 shows that

$$
\lim_{a \to 0} \frac{dCV_{tot}^2}{da^M} < 0, \quad \lim_{a \to \infty} \frac{dCV_{tot}^2}{da^M} > 0.
\tag{A.21}
$$

This result shows that in this case the protein noise is a decreasing function of feedback strength (when feedback strength is small) and an increasing function of feedback strength (when feedback strength is large). Thus, if increasing feedback strength is accompanied by an increasing mean burst size so as to keep $\mathbf{x}^*$ fixed, then protein noise is minimized at an optimal level of feedback strength.

Appendix E: Fano factor

We have from Eq. 24 of the paper that the steady-state Fano factor is given by

$$\mathbf{F} = \frac{T_r}{T_{nr}} \frac{N_x^2 + V_x^2 + N_x}{2N_x} + \mathbf{x}^* S^2 CV_z^2 \left(\frac{T_r}{T_{nr}}\right)^2 \frac{T_z}{T_z + T_r}. \qquad (A.22)$$

Recall that both $\mathbf{x}^*$ and response time T_r are decreasing functions of the feedback strength a. This implies from (A.22) that $\mathbf{F}$ is a monotonically decreasing function of a.