Supporting Online Material for

Reinitiation enhances reliable transcriptional responses in eukaryotes

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Contents

In this supporting material, based on the stationary analysis of the chemical master equations, we derive the theoretical results presented in the main text.

1 Introduction

In this section, we briefly introduce the theory of master equation, which is the main mathematical tool used in this work. Consider a biological system with n molecular species and m elementary reactions

$$x(t) \xrightarrow{W_i(x(t))} x(t) + r_i, \quad i = 1, 2, \cdots, m,$$
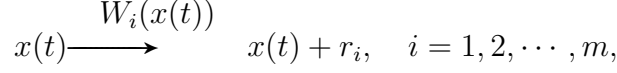
where $x(t) = [x_1(t), \cdots, x_n(t)]^\top$ is the vector of molecular numbers, with $x_j(t)$ being the number of the jth molecular species at time t, $W_i(x(t))$ is the rate of reaction i, $\mathbf{r} = [r_1, \cdots, r_m] \in \mathbb{Z}^{n \times m}$ is the stoichiometric matrix, where $r_i = [r_i^1, \cdots, r_i^n]^\top$ with r_i^j being the change in the number of the jth molecules in reaction i. Let $\mathbb{P}(\cdot, t \mid x_0, t_0)$ be the probability distribution of $x(t)$ for a given initial value $x(t_0) = x_0$, then the master equation for the system is

$$\frac{d\,\mathbb{P}(k, t \mid x_0, t_0)}{dt} = \sum_{i=1}^{m} W_i(k - r_i)\,\mathbb{P}(k - r_i, t \mid x_0, t_0) - \sum_{i=1}^{m} W_i(k)\,\mathbb{P}(k, t \mid x_0, t_0). \tag{1}$$

Letting $\langle x(t) \rangle$ denote the expectation of $x(t)$ and $\Sigma(t) = \langle x(t)x^\top(t) \rangle - \langle x(t) \rangle \langle x^\top(t) \rangle$ be the covariance matrix. When $W_i(x)$ is linear in x such that $\sum_{i=1}^{m} r_i W_i(x) = Ax + f_0$ for some matrix $A \in \mathbb{R}^{n \times n}$ and vector $f_0 \in \mathbb{R}^n$, the authors in [1] showed that the dynamics of $\langle x(t) \rangle$ and $\Sigma(t)$ can be exactly described by the following ordinary dierential equations:

$$\frac{d\langle x(t) \rangle}{dt} = A\langle x(t) \rangle + f_0, \tag{2}$$

$$\frac{d\Sigma(t)}{dt} = A\Sigma(t) + \Sigma(t)A^\top + D(t), \tag{3}$$

where $D(t) = \sum_{i=1}^{m} r_i W_i(\langle x(t) \rangle) r_i^\top$. At the steady state, we have

$$\begin{cases} A\langle x(t) \rangle + f_0 = 0, \\ A\Sigma(t) + \Sigma(t)A^\top + D(t) = 0. \end{cases} \tag{4}$$
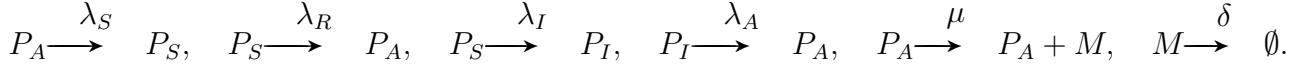
By solving these equations, we can obtain the exact mean and variance of each x_i at the steady state. Furthermore, for the jth molecule species, the noise intensity is defined as its normalized variance, i.e., $\eta_j^2 = \sigma_{jj}^2 / \langle x_j \rangle^2$.

The following sections are devoted to the noise analysis in transcription based on the models presented in the main text.

2 The influence of reinitiation rate

In this section, we consider the influence of varying the reinitiation rate and scaold stability on the noise intensity in mRNA abundance. We analyze the three-state transcription model (Fig. 1 C) where the mRNA production and the reinitiation scaold formation are assumed independent. As in the main text, let P_A, P_S, and P_I denote the active state, the reinitiation scaold, and the inactive state

respectively, M the mRNA molecules, and $\emptyset$ the outcome of mRNA degradation. Then the elementary reactions involved in the three-state transcription model are given as follows

$$P_A \xrightarrow{\lambda_S} P_S, \quad P_S \xrightarrow{\lambda_R} P_A, \quad P_S \xrightarrow{\lambda_I} P_I, \quad P_I \xrightarrow{\lambda_A} P_A, \quad P_A \xrightarrow{\mu} P_A + M, \quad M \xrightarrow{\delta} \emptyset.$$

Hereafter, as explained in the main text, we assume that all the parameters are normalized by the mRNA degradation rate δ(so that $\delta = 1$).

Then we can solve (4) with

$$A = \begin{bmatrix} -\lambda_S & \lambda_R & \lambda_A & 0 \\ \lambda_S & -(\lambda_I + \lambda_R) & 0 & 0 \\ 0 & \lambda_I & -\lambda_A & 0 \\ \mu & 0 & 0 & -\delta \end{bmatrix},$$

$f_0 = 0$, and

$$D(t) = \begin{bmatrix} \lambda_S\langle x_A \rangle + \lambda_R\langle x_S \rangle + \lambda_A\langle x_I \rangle & -(\lambda_S\langle x_A \rangle + \lambda_R\langle x_S \rangle) & -\lambda_A\langle x_I \rangle & 0 \\ -(\lambda_S\langle x_A \rangle + \lambda_R\langle x_S \rangle) & \lambda_S\langle x_A \rangle + (\lambda_R + \lambda_I)\langle x_S \rangle & -\lambda_I\langle x_S \rangle & 0 \\ -\lambda_A\langle x_I \rangle & -\lambda_I\langle x_S \rangle & \lambda_I\langle x_S \rangle + \lambda_A\langle x_I \rangle & 0 \\ 0 & 0 & 0 & \mu\langle x_A \rangle + \delta\langle m \rangle \end{bmatrix}.$$

Particularly, we obtain the mean and normalized variance at the steady state as

$$\begin{cases} \langle m \rangle = \frac{\mu\lambda_A(\lambda_I + \lambda_R)}{\lambda_A(\lambda_I + \lambda_R) + \lambda_S(\lambda_I + \lambda_A)}, \\ \eta_m^2 = \frac{1}{\langle m \rangle} + \frac{\lambda_S\left[\lambda_I(\lambda_I + \lambda_R) + (1 + \lambda_A)(\lambda_I + \lambda_A)\right]}{\lambda_A(\lambda_I + \lambda_R)[(1 + \lambda_A)(1 + \lambda_S + \lambda_I + \lambda_R) + \lambda_S\lambda_I]}. \end{cases} \tag{5}$$

2.1 The influence of high reinitiation rate

First we analyze how the reinitiation rate influences the noise intensity in mRNA abundance. Substituting $\langle m \rangle$ into η_m^2, we have

$$\begin{aligned} \eta_m^2 &= \frac{\lambda_A(\lambda_I + \lambda_R) + \lambda_S(\lambda_I + \lambda_A)}{\mu\lambda_A(\lambda_I + \lambda_R)} + \frac{\lambda_S\left[\lambda_I(\lambda_I + \lambda_R) + (1 + \lambda_A)(\lambda_I + \lambda_A)\right]}{\lambda_A(\lambda_I + \lambda_R)[(1 + \lambda_A)(1 + \lambda_S + \lambda_I + \lambda_R) + \lambda_S\lambda_I]} \\ &= \frac{1}{\mu} + \frac{\lambda_S(\lambda_I + \lambda_A)}{\mu\lambda_A(\lambda_I + \lambda_R)} + \frac{\lambda_S\left[\lambda_I(\lambda_I + \lambda_R) + (1 + \lambda_A)(\lambda_I + \lambda_A)\right]}{\lambda_A(\lambda_I + \lambda_R)[(1 + \lambda_A)(1 + \lambda_S + \lambda_I + \lambda_R) + \lambda_S\lambda_I]} \\ &= \frac{1}{\mu} + \frac{\lambda_S(\lambda_I + \lambda_A)}{\mu\lambda_A(\lambda_I + \lambda_R)} + \frac{\lambda_S\lambda_I}{\lambda_A[(1 + \lambda_A)(1 + \lambda_S + \lambda_I + \lambda_R) + \lambda_S\lambda_I]} \\ &\quad + \frac{\lambda_S(1 + \lambda_A)(\lambda_I + \lambda_A)}{\lambda_A(\lambda_I + \lambda_R)[(1 + \lambda_A)(1 + \lambda_S + \lambda_I + \lambda_R) + \lambda_S\lambda_I]}. \end{aligned}$$

From this result, we can see that the noise intensity η_m^2 is a decreasing function of the reinitiation rate λ_R, which means that increasing the reinitiation rate can reduce the mRNA noise intensity in transcription independent of other parameters.

2.2 Reinitiation vs. non-reinitiation

In this subsection, we compare the transcription noise intensity between the transcription models with and without reinitiation. To show the advantage of reinitiation, the comparison is under the same

transcription level. We construct a non-reinitiation model by setting the reinitiation rate as zero but increase the stability of the active state so that it can have an equal transcription level as the reinitiation model. From (5),

$$\langle m \rangle = \frac{\mu \lambda_A (\lambda_I + \lambda_R)}{\lambda_A(\lambda_I + \lambda_R) + \lambda_S(\lambda_I + \lambda_A)} = \mu \frac{\frac{1}{\lambda_S}\frac{\lambda_I + \lambda_R}{\lambda_I}}{\frac{1}{\lambda_S}\frac{\lambda_I + \lambda_R}{\lambda_I} + \frac{1}{\lambda_A} + \frac{1}{\lambda_I}} = \mu \frac{\frac{1}{\lambda_S \frac{\lambda_I}{\lambda_I + \lambda_R}}}{\lambda_S \frac{\lambda_I + \lambda_R}{\lambda_I} + \frac{1}{\lambda_A} + \frac{1}{\lambda_I}}.$$

This implies that we can get a non-reinitiation model with the same transcription level by setting $\lambda_R = 0$ while λ_S to $\lambda_S \lambda_I / (\lambda_I + \lambda_R)$. Thus we can obtain the stationary noise intensity for the non-reinitiation model, denoted as η_{nr}^2, by substituting these parameters into (5).

$$
\begin{aligned}
\eta_{nr}^2 &= \frac{1}{\langle m \rangle} + \frac{\frac{\lambda_S \lambda_I}{(\lambda_I + \lambda_R)}\big[\lambda_I(\lambda_I + 0) + (1 + \lambda_A)(\lambda_I + \lambda_A)\big]}{\lambda_A(\lambda_I + 0)[(1 + \lambda_A)(1 + \lambda_I + 0) + \frac{\lambda_S \lambda_I}{(\lambda_I + \lambda_R)}(1 + \lambda_A + \lambda_I)]} \\
&= \frac{1}{\langle m \rangle} + \frac{\lambda_S\big[\lambda_I(1 + \lambda_I + \lambda_A) + \lambda_A(1 + \lambda_A)\big]}{\lambda_A[\lambda_S \lambda_I(1 + \lambda_A + \lambda_I) + (1 + \lambda_A)(1 + \lambda_I)(\lambda_I + \lambda_R)]}.
\end{aligned}
$$

Then, at the same transcription level, the dierence in noise intensity between these two models is

$$
\begin{aligned}
\eta_{nr}^2 - \eta_m^2 &= \frac{\lambda_S \lambda_R(1 + \lambda_A)(1 + \lambda_A + \lambda_I)[\lambda_A(\lambda_I + \lambda_R) + \lambda_S(\lambda_I + \lambda_A)]}{\lambda_A(\lambda_I + \lambda_R)F(\lambda_S, \lambda_I, \lambda_R, \lambda_A)G(\lambda_S, \lambda_I, \lambda_R, \lambda_A)} \\
&> 0,
\end{aligned}
$$

where

$$
\begin{aligned}
F(\lambda_S, \lambda_I, \lambda_R, \lambda_A) &= (1 + \lambda_A)(1 + \lambda_S + \lambda_I + \lambda_R) + \lambda_S \lambda_I > 0, \\
G(\lambda_S, \lambda_I, \lambda_R, \lambda_A) &= \lambda_S \lambda_I(1 + \lambda_A + \lambda_I) + (1 + \lambda_A)(1 + \lambda_I)(\lambda_I + \lambda_R) > 0.
\end{aligned}
$$

2.3 The influence of reinitiation rate at a constant transcription level

In this subsection, we investigate the influence of reinitiation rate when the transcription level is kept constant. For this purpose, we decrease the stability of the active state while increasing the reinitiation rate. Specifically, we set λ_S to $\lambda_S(\lambda_I + \lambda_R)/\lambda_I$, so that the transcription level

$$\langle m \rangle = \frac{\mu \lambda_A(\lambda_I + \lambda_R)}{\lambda_A(\lambda_I + \lambda_R) + \frac{\lambda_S(\lambda_I + \lambda_R)}{\lambda_I}(\lambda_I + \lambda_A)} = \frac{\mu \lambda_A}{\lambda_A + \frac{\lambda_S}{\lambda_I}(\lambda_I + \lambda_A)} = \frac{\mu \lambda_A \lambda_I}{\lambda_A \lambda_I + \lambda_S(\lambda_I + \lambda_A)}$$

is independent of the reinitiation rate. By substituting $\lambda_S(\lambda_I + \lambda_R)/\lambda_I$ into (5), we get the noise intensity at a constant transcription level

$$
\begin{aligned}
\eta_m^2 &= \frac{1}{\langle m \rangle} + \frac{\frac{\lambda_S(\lambda_I + \lambda_R)}{\lambda_I}\big[\lambda_I(\lambda_I + \lambda_R) + (1 + \lambda_A)(\lambda_I + \lambda_A)\big]}{\lambda_A(\lambda_I + \lambda_R)[(1 + \lambda_A)(1 + \lambda_I + \lambda_R) + \frac{\lambda_S(\lambda_I + \lambda_R)}{\lambda_I}(1 + \lambda_A + \lambda_I)]} \\
&= \frac{1}{\langle m \rangle} + \frac{\frac{\lambda_S}{\lambda_I}\big[\lambda_I(\lambda_I + \lambda_R) + (1 + \lambda_A)(\lambda_I + \lambda_A)\big]}{\lambda_A[(1 + \lambda_A)(1 + \lambda_I + \lambda_R) + \frac{\lambda_S(\lambda_I + \lambda_R)}{\lambda_I}(1 + \lambda_A + \lambda_I)]} \\
&= \frac{1}{\langle m \rangle} + \frac{\lambda_S\big[\lambda_I(\lambda_I + \lambda_R) + (1 + \lambda_A)(\lambda_I + \lambda_A)\big]}{\lambda_A[\lambda_I(1 + \lambda_A)(1 + \lambda_I + \lambda_R) + \lambda_S(\lambda_I + \lambda_R)(1 + \lambda_A + \lambda_I)]} \\
&= \frac{1}{\langle m \rangle} + \frac{\lambda_S \lambda_I}{\lambda_A[\lambda_S(1 + \lambda_I + \lambda_A) + \lambda_I(1 + \lambda_A)]} \\
&\quad + \frac{\lambda_S(1 + \lambda_A)[\lambda_S(\lambda_I + \lambda_A)^2 + (\lambda_S + \lambda_I)(\lambda_I + \lambda_A) + \lambda_I \lambda_A^2]}{\lambda_A[(\lambda_S + \lambda_I)(1 + \lambda_A) + \lambda_S \lambda_I][\lambda_S(1 + \lambda_I + \lambda_A)(\lambda_I + \lambda_R) + \lambda_I(1 + \lambda_A)(1 + \lambda_I + \lambda_R)]}.
\end{aligned}
$$

It is obvious that η_m^2 is a decreasing function of the reinitiation rate λ_R.

4

3 The influence of scaold stability

Next, we find the influence of the scaold stability on the transcription noise intensity. By a proper rearrangement, we have

$$
\begin{aligned}
\eta_m^2 &= \frac{1}{\mu} + \frac{\lambda_S}{\mu\lambda_A} + \frac{1}{1+\lambda_S+\lambda_A} + \frac{\lambda_S(\lambda_A-\lambda_R)}{\mu\lambda_A(\lambda_I+\lambda_R)} \\
&\quad + \frac{\lambda_S(1+\lambda_A)(\lambda_A-\lambda_R)}{\lambda_A(1+\lambda_S+\lambda_A)[(1+\lambda_S+\lambda_A)\lambda_I+(1+\lambda_A)(1+\lambda_S+\lambda_R)]} \\
&\quad + \frac{\lambda_S(1+\lambda_A)(\lambda_A-\lambda_R)}{\lambda_A(\lambda_I+\lambda_R)[(1+\lambda_S+\lambda_A)\lambda_I+(1+\lambda_A)(1+\lambda_S+\lambda_R)]} \\
&= \frac{1}{\mu} + \frac{\lambda_S}{\mu\lambda_A} + \frac{1}{1+\lambda_S+\lambda_A} + \frac{\lambda_S(\lambda_A-\lambda_R)}{\lambda_A}S_I(\lambda_I),
\end{aligned}
$$

where
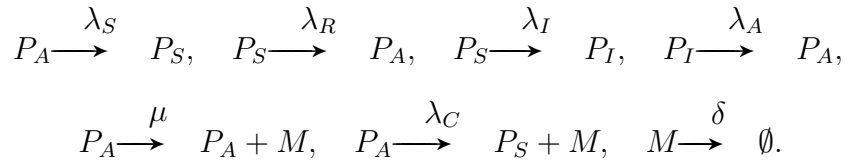
$$
S_I(\lambda_I) = \frac{1}{\mu(\lambda_I+\lambda_R)} + \frac{1+\lambda_A}{(1+\lambda_S+\lambda_A)\lambda_I+(1+\lambda_A)(1+\lambda_S+\lambda_R)}\left(\frac{1}{1+\lambda_S+\lambda_A}+\frac{1}{\lambda_I+\lambda_R}\right).
$$

Since $S_I(\lambda_I)$ is a decreasing function of λ_I, we can see that the monotonicity of η_m^2 with respect to λ_I is determined by $\lambda_A - \lambda_R$. If $\lambda_A - \lambda_R > $ (or $<$)0, then increasing λ_I, which means that the scaold becomes more unstable, can reduce (or increase) the transcription noise intensity. In the critical case $\lambda_A - \lambda_R = 0$, varying the scaold stability does not influence the transcription noise intensity. Intuitively, this can be understood as the competition between two possible paths for mRNA synthesis, namely, initiation and reinitiation.

4 The influence of transcription coupling

In this subsection, we consider the coupling model shown in Fig. 1D of the main text. In this model, a new elementary reaction that incorporate the mRNA production and the scaold formation is introduced. This reaction introduces direct coupling between the promoter activation and mRNA synthesis process, and its reaction rate, λ_C, is a measure of the coupling stength. Using the same notations as in the preceding section, the elementary reactions involved in the coupling model now become

$$
P_A \xrightarrow{\lambda_S} P_S, \quad P_S \xrightarrow{\lambda_R} P_A, \quad P_S \xrightarrow{\lambda_I} P_I, \quad P_I \xrightarrow{\lambda_A} P_A,
$$

$$
P_A \xrightarrow{\mu} P_A + M, \quad P_A \xrightarrow{\lambda_C} P_S + M, \quad M \xrightarrow{\delta} \emptyset.
$$

By a similar process we can solve the mRNA average and transcription noise intensity at the steady state as

$$
\begin{aligned}
\langle m \rangle &= (\mu+\lambda_C)\lambda_A(\lambda_I+\lambda_R)/[\lambda_A(\lambda_I+\lambda_R)+(\lambda_S+\lambda_C)(\lambda_I+\lambda_A)], \\
\eta_m^2 &= \frac{1}{\langle m \rangle}\left[1 - \frac{\lambda_C(1+\lambda_I+\lambda_A)}{(\lambda_S+\lambda_C)(1+\lambda_I+\lambda_A)+(1+\lambda_A)(1+\lambda_I+\lambda_R)}\right] \\
&\quad + \frac{(\lambda_S+\lambda_C)[\lambda_A(1+\lambda_I+\lambda_A)+\lambda_I(1+\lambda_I+\lambda_R)]}{\lambda_A(\lambda_I+\lambda_R)[(\lambda_S+\lambda_C)(1+\lambda_I+\lambda_A)+(1+\lambda_A)(1+\lambda_I+\lambda_R)]}.
\end{aligned}
$$

Compared with the independent model under the same transcription level(i.e., letting $\mu+\lambda_C$, $\lambda_S+\lambda_C$ in the coupling model equal to μ, λ_S in the independent model, respectively), we can find that the
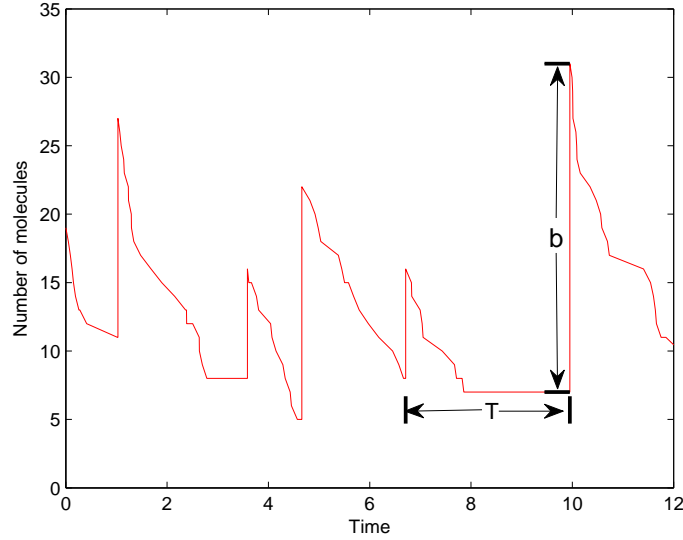
Figure S1: **Illustration of a burst model**

noise intensity in the coupling model is reduced by the quantity

$$\frac{1}{\langle m \rangle} \frac{\lambda_C(1 + \lambda_I + \lambda_A)}{\lambda_{SC}(1 + \lambda_I + \lambda_A) + (1 + \lambda_I + \lambda_R)(1 + \lambda_A)}.$$

At last, we show that the coupling does not change the qualitative influence of the reinitiation rate on the transcription noise intensity. For simplicity, we only consider the extreme case where $\lambda_C = \lambda_S = \mu$. In this case, by the following rearrangement of the expression of the noise intensity

$$\eta_m^2 = \frac{1}{\mu} + \frac{\lambda_I(1 + \mu)}{\lambda_A[(1 + \lambda_A)(1 + \mu + \lambda_I + \lambda_R) + \mu\lambda_I]} + \frac{(1 + \mu)(1 + \lambda_A)(\lambda_I + \lambda_A)}{\lambda_A(\lambda_I + \lambda_R)[(1 + \lambda_A)(1 + \mu + \lambda_I + \lambda_R) + \mu\lambda_I]}.$$

we can see that the noise intensity still is a decreasing function of the reinitiation rate λ_R independent of other parameters in the coupling model.

Similarly, by another rearrangement of the expression of the noise intensity

$$\begin{aligned}
\eta_m^2 &= \frac{1}{\mu} + \frac{(1 + \mu)}{\lambda_A(1 + \mu + \lambda_A)} + \frac{(\lambda_A - \lambda_R)(1 + \mu)(1 + \lambda_A)}{\lambda_A(1 + \mu + \lambda_A)[(1 + \mu + \lambda_A)\lambda_I + (1 + \lambda_A)(1 + \mu + \lambda_R)]} \\
&+ \frac{(\lambda_A - \lambda_R)(1 + \mu)(1 + \lambda_A)}{\lambda_A(\lambda_I + \lambda_R)[(1 + \mu + \lambda_A)\lambda_I + (1 + \lambda_A)(1 + \mu + \lambda_R)]} \\
&= \frac{1}{\mu} + \frac{1}{\lambda_A} - \frac{1}{(1 + \mu + \lambda_A)} + \frac{(\lambda_A - \lambda_R)(1 + \mu)(1 + \lambda_A)}{\lambda_A} S_C(\lambda_I),
\end{aligned}$$

where

$$S_C(\lambda_I) = \frac{1}{[(1 + \mu + \lambda_A)\lambda_I + (1 + \lambda_A)(1 + \mu + \lambda_R)]} \left(\frac{1}{\lambda_I + \lambda_R} + \frac{1}{1 + \mu + \lambda_A} \right)$$

is also a decreasing function in λ_I, we can that in the coupling model, the qualitative influence of the scaold stability on the transcription noise intensity still depends on $\lambda_A - \lambda_R$ in the same manner as that in the independent model.

By using a burst model approximation (Fig. S1), we provide an intuitive explanation for the noise reduction eect of the transcription coupling. To be more intuitive, we also consider the extreme case
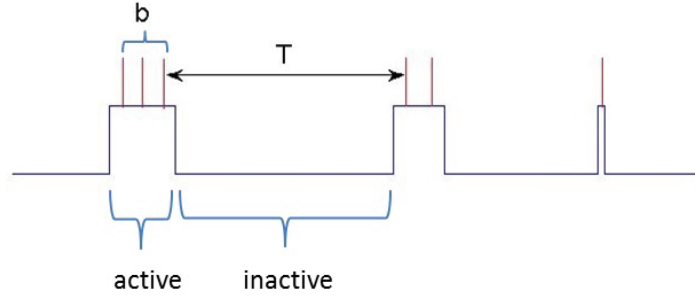
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Figure S2: **Illustration of approximating the mRNA production as a burst model.** The promoter activity is indicated by the blue line, while the production of one mRNA molecule is depicted by one vertical red line. This figure illustrates how to extract the parameter T and b for a burst model approximation from a two state transcription model.

where $\lambda_C = \lambda_S = \mu$. In a burst model, the molecules are released in random quantal bursts of b molecules during random time intervals T. When using a burst model to approximate the mRNA synthesis, we define b as the number of mRNA molecules produced during one transcription cycle and T as the time between the release of the last mRNA molecule in one burst and that of the first mRNA molecule in its successive burst (Fig. S2). In the approximation, it can be seen that under the same parameter sets, the independent model and the coupling model have the same distribution of the time interval T, and the dierence lies only in the burst size b. In the independent model, the burst size $b_I = \sum_{i=1}^{n_r}(a_i - 1)$, where $a_i - 1$ is the number of mRNA molecules released during one transcription cycle without reinitiation (see [2]), with a_i's being independent and identically distributed geometric random variables with parameter $1/2$, and $n_r - 1$ is the times that reinitiation occurs during one transcription cycle, with n_r being a geometric random variable with parameter $\lambda_I/(\lambda_I + \lambda_R)$. Yet in the coupling model, the burst size $b_C = n_r$. The average in mRNA molecules $\langle b_I \rangle = \langle b_C \rangle = \langle n_r \rangle = 1 + \lambda_R/\lambda_I$, indicating that the coupling does not change the transcription level. On the other hand, the variances of b_I and b_C are
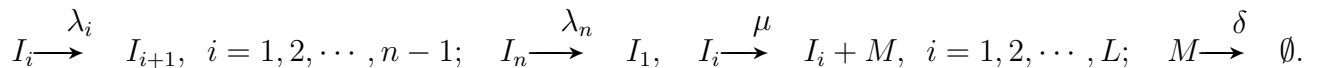
$$
\begin{aligned}
\sigma_{b_I}^2 &= \left(1 + \frac{\lambda_R}{\lambda_I}\right)\left(2 + \frac{\lambda_R}{\lambda_I}\right), \\
\sigma_{b_C}^2 &= \frac{\lambda_R}{\lambda_I}\left(1 + \frac{\lambda_R}{\lambda_I}\right).
\end{aligned}
$$

We can see the variance in the burst size is reduced by $2(1 + \lambda_R/\lambda_I)$ in the coupling model. To obtain a more intuitive understanding, we may consider the extreme case where the reinitiation rate is 0. In this case, the average number of mRNA molecules released by each transcription cycle is $\langle b_I \rangle = \langle b_C \rangle = 1$. In the coupling model, each transcription cycle can produce 1 and only 1 mRNA, with $b_C = 1$ and $\sigma_{b_C}^2 = 0$. While in the independent model, the number of mRNA molecules produced in each transcription cycle is $a_1 - 1$, with a_1 being a geometrically distributed random variable with parameter $1/2$, and $\sigma_{b_I}^2 = 2$.

5   Comparison with the multistep mechanism

At last, we briefly introduce the so-called multistep mechanism [3, 4] and compare it with the transcription coupling. Here we still use a transcription model to illustrate this mechanism. For simplicity, we consider an irreversible transcription cycle in which the gene sequentially experiences n states, some

of which are active ones and the others inactive ones. Let I_i, $i = 1, 2, \cdots, n$ denote the n promoter states, respectively, and M and $\emptyset$ be defined as before. If we assume I_i, $i = 1, \cdots, L$ to be active states and the others to be inactive ones, the elementary reactions involved in this model are given as follows:

$$I_i \xrightarrow{\lambda_i} I_{i+1}, \quad i = 1, 2, \cdots, n-1; \quad I_n \xrightarrow{\lambda_n} I_1, \quad I_i \xrightarrow{\mu} I_i + M, \quad i = 1, 2, \cdots, L; \quad M \xrightarrow{\delta} \emptyset.$$

The above model generalizes the one in [4] by considering both multiple active and multiple inactive steps of the promoter. By solving (4), we can obtain the noise intensity at the steady state

$$\langle m \rangle = \frac{\mu \tau_{on}}{\langle T \rangle},$$

$$\eta_m^2 = \frac{\langle T \rangle}{\mu \tau_{on}} + \frac{\langle T \rangle}{\tau_{on}^2} \left[\frac{1}{1 + x_{on} x_{off}/(x_{on} + x_{off})} + \frac{\tau_{on} \tau_{off}}{\tau_{on} + \tau_{off}} - 1 \right],$$

where $\tau_i = 1/\lambda_i$ is the average lifetime of state i, $\tau_{on} = \sum_{i=1}^{L} \tau_i$ is the average lifetime of the active state, $\tau_{off} = \sum_{i=L+1}^{n} \tau_i$ is the average lifetime of the inactive state, $\langle T \rangle = \tau_{on} + \tau_{off}$ is the average time of a transcription cycle, $x_{on} = \prod_{k=1}^{L}(1 + \tau_k) - 1 > 0$, and $x_{off} = \prod_{k=L+1}^{n}(1 + \tau_k) - 1 > 0$. From this result, when the average transcription cycle period $\langle T \rangle$ is fixed, adding one more state, either active or inactive, can reduce the transcription noise intensity independent of other parameters. Clearly, this result also extends that in [4].

Although both the transcription coupling and the multi-step mechanism can reduce noise independent of transcription level, from the viewpoint of a burst model approximation, the multi-step mechanism reduces the fluctuations in the time intervals T, which can be attributed to the extrinsic noise from the upstream dynamics, while the transcription coupling reduces the fluctuations in the burst size b, which can not be simply attributed to either intrinsic or extrinsic noise. Thus they are both similar and complementary.

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