

The Supporting Material for

Division time-based amplifiers for stochastic gene expression

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A. Influence of time-based division on stochastic trajectories

The following Fig. S1 and Fig. S2 show how time-based division impacts stochastic trajectories governed by the chemical master equation in the main text (1).

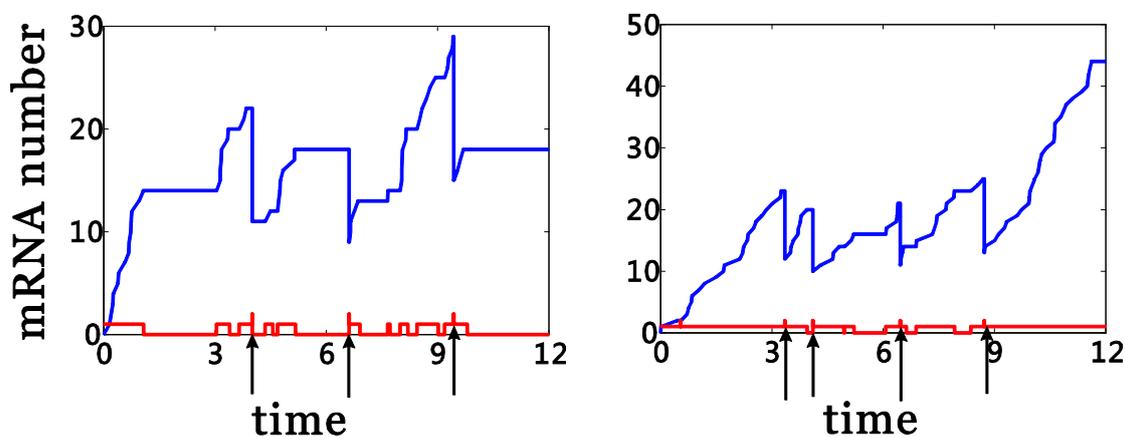


Fig. S1 Influence of time-based division on stochastic trajectories (blue): random division where random division times follow a lognormal distribution. The mean cell cycle is set as $\tau = 3$. The red line describes the activity of gene promoter and arrows represent division time points. The x-axis represents time whereas the y-axis represents the mRNA number. All parameter values are the same as those listed in the main text.

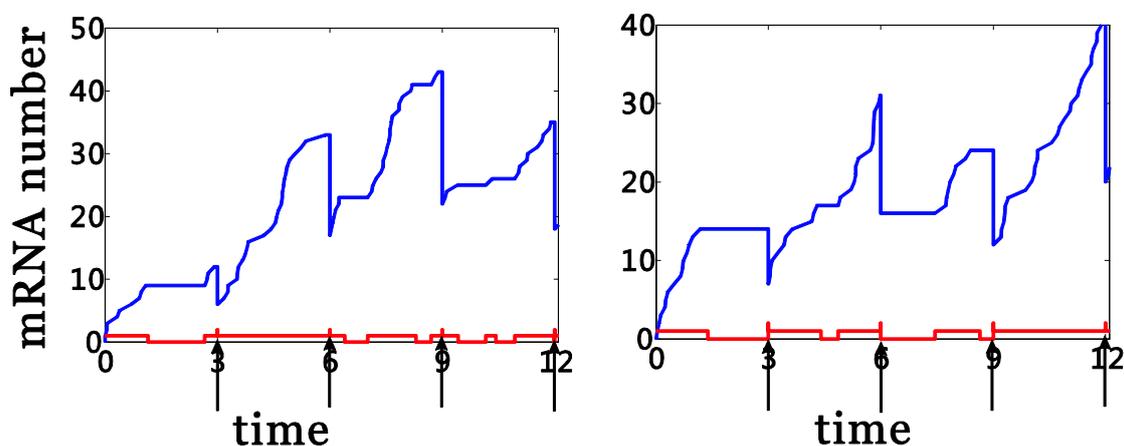


Fig. S2 Influence of time-based division on stochastic trajectories (blue): constant division. The mean cell cycle is set $\tau = 3$. The red line describes the activity of gene promoter and arrows represent division time points. The x-axis represents time whereas the y-axis represents the mRNA number. All parameter values are the same as those listed in the main text.

B. Temporal dynamics of mean mRNA

Suppose that \mathcal{D} is an efficient degradation equivalent to the dilution of cell division. The chemical master equation takes the form

$$\begin{aligned}\frac{\partial P_0(m,t)}{\partial t} &= -k_{on}P_0(m,t) + k_{off}P_1(m,t) + \mathcal{D}(E-I)[mP_0(m,t)] \\ \frac{\partial P_1(m,t)}{\partial t} &= k_{on}P_0(m,t) - k_{off}P_1(m,t) + k_m(E^{-1}-I)[P_1(m,t)] + \mathcal{D}(E-I)[mP_1(m,t)]\end{aligned}\quad (A1)$$

Assume that the gene is initially at OFF state. Then, we have $P_0(0,0)=1$ and $P_1(0,0)=0$, $P_0(m,0)=0$ and $P_1(m,0)=0$ for $m \geq 1$. To solve Eq. (A1), we introduce two factorial

probability-functions defined as $G_i(z,t) = \sum_{m=0}^{\infty} (z+1)^m P_i(m,t)$. For convenience, we denote

$a = k_{off}$, $b = k_{on}$, $c = k_m$. Then, Eq. (A1) can be transformed into the following partial differential equations

$$\begin{aligned}\frac{\partial G_0}{\partial t} &= -bG_0 + aG_1 - \mathcal{D}z \frac{\partial G_0}{\partial z} \\ \frac{\partial G_1}{\partial t} &= bG_0 - aG_1 + czG_1 - \mathcal{D}z \frac{\partial G_1}{\partial z}\end{aligned}\quad (A2)$$

where the initial conditions are $G_0(z,0) \equiv 1$, $G_1(z,0) \equiv 0$, and the boundary conditions are

$$G_0(0,t) = \frac{a}{a+b} + \frac{b}{a+b} e^{-(a+b)t}, \quad G_1(0,t) = \frac{b}{a+b} (1 - e^{-(a+b)t}) \quad (A3)$$

Denote by $P(m,t)$ the total probability, that is, $P(m,t) = P_0(m,t) + P_1(m,t)$. Note that

$$m(t) = \sum_{m=0}^{\infty} mP(m,t) = \left. \frac{\partial G(z,t)}{\partial z} \right|_{z=0} \quad \text{and} \quad m_i(t) = \sum_{m=0}^{\infty} mP_i(m,t) = \left. \frac{\partial G_i(z,t)}{\partial z} \right|_{z=0} \quad \text{with } i = 0, 1.$$

Then, we can derive the following differential equations from Eq. (A2)

$$\begin{aligned}\frac{dm_0}{dt} &= -bm_0 + am_1 - \delta m_0 \\ \frac{dm_1}{dt} &= bm_0 - am_1 + cG_1(0,t) - \delta m_1\end{aligned}\tag{A4}$$

Note that $m_i(0) = \left. \frac{\partial G_i(z,0)}{\partial z} \right|_{z=0} = 0$ with $i=0,1$ because of $G_0(z,0) \equiv 1$ and $G_1(z,0) \equiv 0$,

implying that

$$m'_1(0) = \left. \frac{dm_1}{dt} \right|_{t=0} = \left[bm_0 - am_1 + cG_1(0,t) - \delta m_1 \right] \Big|_{t=0} = 0\tag{A5}$$

In addition, it follows from Eq. (A4) that

$$m_1'' + (a+b+2\delta)m_1' + \delta(a+b+\delta)m_1 = \frac{bc(b+\delta)}{a+b} + \frac{bc(a-\delta)}{a+b} e^{-(a+b)t}\tag{A6}$$

and

$$m_0 = \frac{m_1' + (a+\delta)m_1}{b} - \frac{c}{a+b} (1 - e^{-(a+b)t})\tag{A7}$$

The general solution of Eq. (A6) can be expressed as

$$m_1(t) = b_1 e^{-\delta t} + b_2 e^{-(a+b+\delta)t} + \varphi(t)\tag{A8}$$

where b_1 and b_2 are any constants, and the special solution is given by

$$\varphi(t) = \frac{bc(b+\delta)}{\delta(a+b)(a+b+\delta)} - \frac{bc(a-\delta)}{\delta(a+b)(a+b-\delta)} e^{-(a+b)t}\tag{A9}$$

Therefore, the general solution to Eq. (A4) takes the form

$$\begin{aligned}m_0 &= \frac{abc}{\delta(a+b)(a+b+\delta)} + \frac{abc}{\delta(a+b)(a+b-\delta)} e^{-(a+b)t} + \frac{ab_1}{b} e^{-\delta t} - b_2 e^{-(a+b+\delta)t} \\ m_1(t) &= \frac{bc(b+\delta)}{\delta(a+b)(a+b+\delta)} - \frac{bc(a-\delta)}{\delta(a+b)(a+b-\delta)} e^{-(a+b)t} + b_1 e^{-\delta t} + b_2 e^{-(a+b+\delta)t}\end{aligned}\tag{A10}$$

where b_1 and b_2 are any constants, determined by initial conditions. In fact, we have

$$b_1 = \frac{-b^2 c}{\delta(a+b)(a+b-\delta)}, \quad b_2 = \frac{abc}{\delta(a+b)(a+b-\delta)}\tag{A11}$$

Thus, we obtain the analytical expression for time-dependent mean mRNA number if the original parameter symbols are recovered

$$\begin{aligned}
m(t) &= m_0(t) + m_1(t) \\
&= \frac{k_m k_{on}}{\delta(k_{on} + k_{off})} + \frac{k_m k_{on}}{(k_{on} + k_{off})(k_{on} + k_{off} - \delta)} e^{-(k_{on} + k_{off})t} - \frac{k_m k_{on}}{\delta(k_{on} + k_{off} - \delta)} e^{-\delta t}
\end{aligned} \tag{A12}$$

where $t \geq 0$. After time t is sufficiently large, the mean mRNA number approaches its limit (i.e., the stable mean mRNA number, denoted by $\langle m \rangle_{ss}$), that is,

$$\langle m \rangle_{ss} = \frac{k_m k_{on}}{\delta(k_{on} + k_{off})} \tag{A13}$$

C. Cell division tends to enhance promoter activity

Here, we examine the effect of cell-cycle variability on promoter activity. Many experimental techniques such as flow cytometry,^{1,2} time-lapse fluorescence microscopy,¹⁻³ pulse labeling with radioactive nucleosides or amino acids⁴ and stable isotope labeling by amino acids in cell culture,^{4,5} have been successfully used to track the single-cell behavior including changes in promoter activity. Note that the level of gene expression including expression noise is closely related to the activity of the gene. This relationship is clear in the case that cell division is not considered⁶⁻⁸ but is not clear in the case of random division. Fig. S3 shows how cell-cycle variability impacts promoter activity, where three mean cell-cycle lengths are considered.

From Fig. S3, we observe that cell division can enhance promoter activity, but this enhancement depends on the speed of promoter switching (i.e., the size of two switching rates between promoter states). Specifically, cell division makes the promoter become more active in the case of slow switching than in the case of fast switching, implying that cell division can increase the efficiency of gene expression. Figure 8 also implies that for a high synthesis rate and two small switching rates, the system is more easily settled in the active steady state where mRNA or protein has a high level but for a low synthesis rate and two large switching rates, it is more easily settled in the inactive steady state where mRNA or protein has a low level. This result is consistent with the random selection rule stated in Ref. (9).

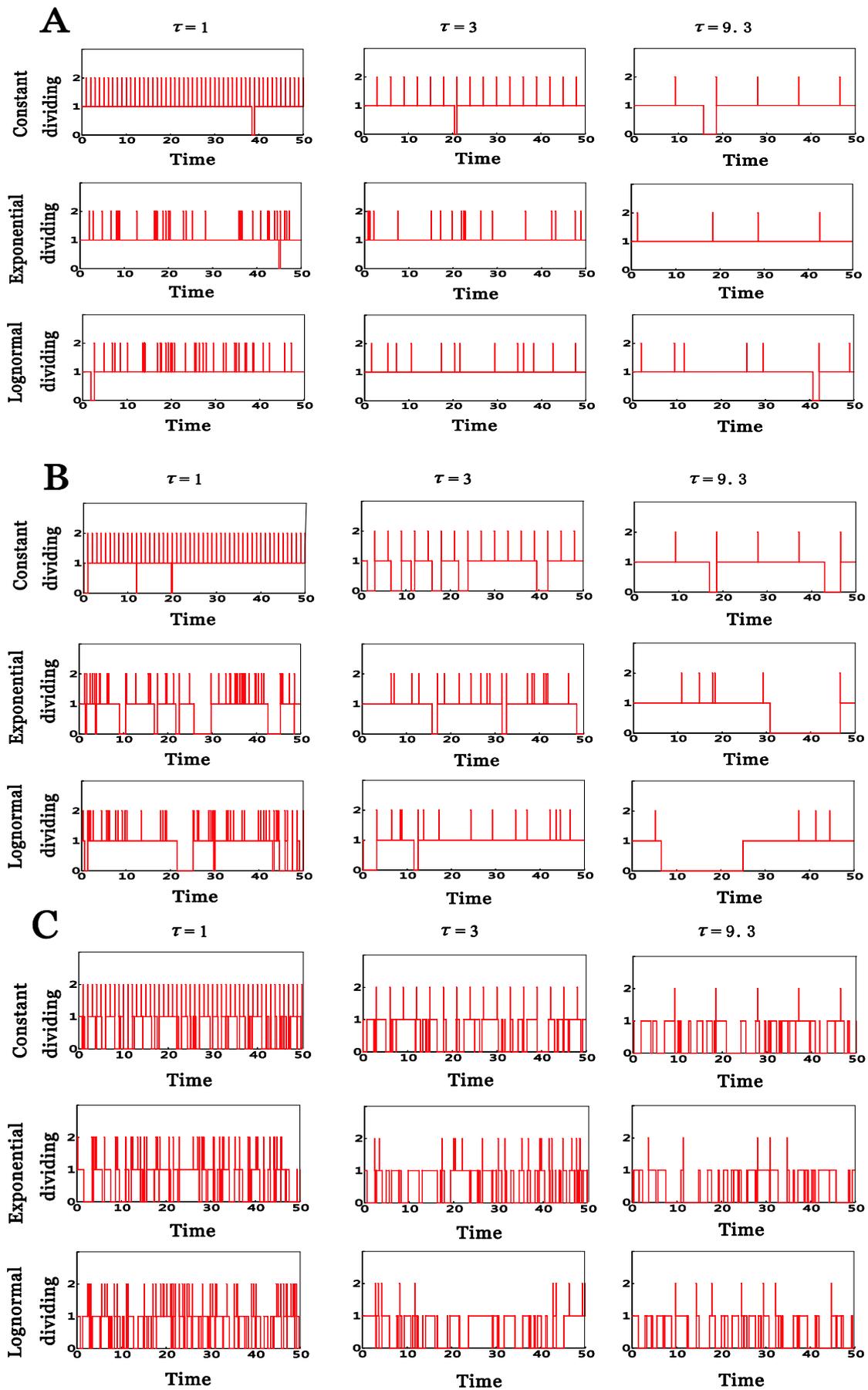


Fig. S3 The influence of mean cell-cycle length on gene activity: (A) slow switching; (B) asymmetric switching; (C) fast switching. The red line represents the promoter state where the zero means that the promoter is at OFF state, the “1” means that the promoter is at ON state, and the “2” means that the cell division happens. The first column corresponds to $\tau = 1$; the second column to $\tau = 3$; and the third column to $\tau = 9.3$. All parameter values are the same as those listed in the main text.

References

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