# Effect of time-correlated noises on cell-fate induction

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Cell-fate induction is a very important concept in developmental biology, which involves an intrinsic irreversibility in the developmental process. In order to explore how cell-fate induction will be influenced by environmental noise, the effects of the time-correlated noises on the saddle-node landscape of cell-fate induction are investigated in this study. The main results show clearly that if the correlation time is not zero, then the time-correlated noises may not only lead to the change (or disappearance) of saddle-node bifurcation of cell-fate induction but also lead to the occurrence of the reentrance phenomena. All of these results provide a theoretical possibility that the time-correlated noise could lead to the abnormality of a saddle-node landscape of cell-fate induction.

## I. INTRODUCTION

As pointed out by Ferrell [1], Waddington's epigenetic landscape is probably the most famous and most powerful metaphor in developmental biology, which depicts how a cell progresses from an undifferentiated state to one of a number of discrete, distinct, differentiated cell fates during development [1,2]. However, unlike Waddington's pattern, Ferrell proposed the concept of cell-fate induction, which possesses an intrinsic irreversibility that is missing from Waddington's picture [1]. According to Ferrell's definition, cell-fate induction means that a cell or a group of cells produces an inductive stimulus that causes another cell to adopt a new phenotype [1]. Ferrell emphasized two key features of the cell-fate induction: (i) the inductive stimulus need not be maintained indefinitely; after some commitment point, the stimulus may be withdrawn and the cell will continue with its induced development program; and (ii) the induction results in an all-or-none switch between qualitatively distinct cell fates [1]. Obviously, these two features strongly imply that the positive feedback regulation and bistability should be involved in the process of cell-fate induction. Some studies have shown that the concept of cell-fate induction should be reasonable, including mesoderm induction in the early *Xenopus laevis* embryo [3], progesterone-induced maturation in *Xenopus* oocytes [4,5], R7 photoreceptor induction in the *Drosophila melanogaster* eye [6], and vulval induction in *Caenorhabditis elegans* larvae [7]. Recently, a study on the determination of *Drosophila* ovarian germline stem cell fate also provided strong experimental evidence, in which there is a feedback loop with bistable regulation induced by an external BMP signal [8].

For simplicity and without loss of generality, Ferrell uses a simple single-variable model with positive feedback regulation to characterize the dynamic properties of cell-fate induction [1]. Although this simple theoretical model has been investigated by many authors [1,9–14], Ferrell mainly focused on how the inductive stimulus affects the dynamic characteristics of the system. Based on the analysis of the potential surface, he thinks that the cell commits to the induced fate because the valley corresponding to the uninduced fate disappears through a saddle-node bifurcation, so the saddle-node landscape resulting in the cell-fate induction should be different from Waddington's epigenetic landscape [1].

Of course, some other potential factors may also play an important role in cell-fate determination. For example, lateral inhibition based on the double-negative feedback loop underlies the assignment of different fates to cells in many developmental processes [1,15]. A previous study considered the impact of local feedback loops in a model of lateral inhibition based on the Notch signaling pathway and elucidated the roles of intracellular and intercellular delays in controlling the overall system behavior [15]. Ferrell also pointed out that the pitchfork bifurcation based on the lateral inhibition should be one possible important mechanism that can lead to cell-fate determination and used a simple theoretical model to reveal the dynamical properties of pitchfork bifurcation based on the lateral inhibition [1]. However, Ferrell emphasized that the key of pitchfork bifurcation is that the system is symmetrical and any imperfection in the symmetry will change the pitchfork bifurcation into a saddle-node bifurcation [1]. Therefore, in this study, we mainly focus our attention on the concept of cell-fate induction based on the saddle-node bifurcation.

Since the stochastic fluctuations of the environment cannot be avoided [16–22], many studies have investigated the effect of environmental noise on gene expression and regulation [13,14,19–21,23]. For example, some experimental

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studies based on the single gene networks corresponding to Eq. (1) showed that the basal synthesis rate ($\alpha_0$) and degradation rate ($\gamma$) not only depend on the biochemical reactions, mutations, and concentrations of other proteins but also fluctuate randomly [21]. On the other hand, in the gene expression process, many transcription factors are unstable proteins destroyed by ubiquitin-mediated proteolysis [24]. Some experimental evidences showed that a similar overlap of activation domains and destruction elements occurs in some unstable transcription factors and there exists a close correlation between the ability of an acidic activation domain to activate transcription and to signal proteolysis [24,25]. So, a challenging question is whether the time-correlated noises between the basal synthesis rate and the degradation rate will lead to the change in the saddle-node bifurcation of cell-fate induction. The answer to this question should have important biological significance for a better understanding of the role of cell-fate induction in developmental biology.

## II. MODEL AND ANALYSIS

### A. Cell-fate induction model and time-correlated noises

In this paper, we still consider the simple one-variable model studied by Ferrell [1], which is given by

$$\frac{dx}{dt} = \frac{\alpha x^n}{k^n + x^n} + \alpha_0 - \gamma x, \tag{1}$$

where $x$ represents the concentration of protein X, the term $\alpha x^n/(k^n + x^n) + \alpha_0$ denotes the synthesis rate of X, and the parameter $\gamma$ is the degradation rate of X. For the synthesis rate, (i) the function $\alpha x^n/(k^n + x^n)$ is called the Hill-type function, where $\alpha$ represents the maximum rate of feedback-dependent synthesis of X, $k$ is the concentration of X when the feedback synthesis rate is half maximal, and $n$ is called the Hill coefficient; and (ii) the parameter $\alpha_0$ is the basal synthesis rate and it is also called the inductive stimulus in Ferrell's schematic view of cell-fate induction [1].

Notice that the potential of Eq. (1), denoted by $\Psi(x)$, can be easily given by $\Psi(x) = -\int [\alpha x^n/(k^n + x^n) + \alpha_0 - \gamma x]dx$. Then, as shown by Ferrell [1], we can see how the potential surface changes as $\alpha_0$ changes. Specifically, for the dynamic properties of Eq. (1), it is easy to see that for given parameters $\alpha$, $k$, $n$ (with $n > 1$), and $\gamma$, there exist two critical values of $\alpha_0$, denoted by $\alpha_0'$ and $\alpha_0''$, respectively, with $\alpha_0' < \alpha_0''$, such that (i) only one equilibrium exists and it is globally asymptotically stable if $\alpha_0 < \alpha_0'$ or $\alpha_0 > \alpha_0''$, and (ii) if $\alpha_0$ is in the interval $\alpha_0' < \alpha_0 < \alpha_0''$, then three equilibria exist, denoted by $x_1^*$, $x_2^*$, and $x_3^*$, respectively, with $x_1^* < x_2^* < x_3^*$, and both $x_1^*$ and $x_3^*$ are locally asymptotically stable and $x_2^*$ is an unstable saddle point [1,9,14]. So, for convenience, $(\alpha_0', \alpha_0'')$ can be called the bistable interval of $\alpha_0$. The difference between $\alpha_0''$ and $\alpha_0'$ (or the size of the bistable interval), denoted by $\Delta\alpha_0 = \alpha_0'' - \alpha_0'$, characterizes how the change of cell fate depends sensitively on the change of $\alpha_0$. This implies that if $\Delta\alpha_0$ is small (but $\neq 0$), then the cell-fate induction will appear to be a significant critical characteristic with the change of $\alpha_0$. Otherwise, if $\Delta\alpha_0$ is large, then the sensitivity of this process to the change of $\alpha_0$ will be reduced.

We now consider the effect of the time-correlated noises on the cell-fate induction. Let both $\alpha_0$ and $\gamma$ be the random variables, which are defined as $\alpha_0 = \alpha_0 + \xi_{\alpha_0}(t)$ and $\gamma = \gamma + \xi_\gamma(t)$, respectively, where both $\xi_{\alpha_0}(t)$ and $\xi_\gamma(t)$ are white noises with $\langle \xi_{\alpha_0}(t) \rangle = 0$, $\langle \xi_\gamma(t) \rangle = 0$, $\langle \xi_{\alpha_0}(t)\xi_{\alpha_0}(t') \rangle = 2D_{\alpha_0}\delta(t - t')$, $\langle \xi_\gamma(t)\xi_\gamma(t') \rangle = 2D_\gamma\delta(t - t')$, and

$$
\begin{aligned}
\langle \xi_{\alpha_0}(t)\xi_\gamma(t') \rangle &= \langle \xi_{\alpha_0}(t')\xi_\gamma(t) \rangle \\
&= \frac{\lambda\sqrt{D_{\alpha_0}D_\gamma}}{\tau} \exp\left(\frac{-|t - t'|}{\tau}\right) \\
&\to 2\lambda\sqrt{D_{\alpha_0}D_\gamma}\,\delta(t - t'), \quad \text{as } \tau \to 0, \tag{2}
\end{aligned}
$$

where $\tau$ is the correlation time and $\lambda$ is the correlation coefficient between $\xi_{\alpha_0}(t)$ and $\xi_\gamma(t)$ [26,27]. Then, the stochastic differential equation (or the Langevin equation) corresponding to Eq. (1) is

$$\frac{dx}{dt} = \frac{\alpha x^n}{k^n + x^n} + \alpha_0 - \gamma x + \xi_{\alpha_0}(t) - x\xi_\gamma(t). \tag{3}$$

### B. Potential function

Let $\phi(x, t)$ denote the probability density distribution that the system state is $x$ at time $t$. Then, in general, the probability density distribution $\phi(x, t)$ obeys the equation

$$
\begin{aligned}
\frac{\partial\phi(x, t)}{\partial t} &= -\frac{\partial}{\partial x}\left[\frac{\alpha x^n}{k^n + x^n} + \alpha_0 - \gamma x\right]\phi(x, t) \\
&\quad - \frac{\partial}{\partial x}\langle \xi_{\alpha_0}(t)\delta(x(t) - x) \rangle \\
&\quad - \frac{\partial}{\partial x}(-x)\langle \xi_\gamma(t)\delta(x(t) - x) \rangle, \tag{4}
\end{aligned}
$$

where $\phi(x, t) = \langle \delta(x(t) - x) \rangle$ [27,28]. For the situation with small $\tau$, the Fokker-Planck equation of the small-$\tau$ approximation for Eq. (3) is given by

$$
\begin{aligned}
\frac{\partial\phi(x, t)}{\partial t} &= -\frac{\partial}{\partial x}f(x)\phi(x, t) \\
&\quad + D_{\alpha_0}\frac{\partial}{\partial x}g_1(x)\frac{\partial}{\partial x}g_1(x)\phi(x, t) \\
&\quad + \lambda\sqrt{D_{\alpha_0}D_\gamma}\frac{\partial}{\partial x}g_1(x)\frac{\partial}{\partial x}h_2(x)\phi(x, t) \\
&\quad + D_\gamma\frac{\partial}{\partial x}g_2(x)\frac{\partial}{\partial x}g_2(x)\phi(x, t) \\
&\quad + \lambda\sqrt{D_{\alpha_0}D_\gamma}\frac{\partial}{\partial x}g_2(x)\frac{\partial}{\partial x}h_1(x)\phi(x), \tag{5}
\end{aligned}
$$

where $f(x) = \alpha x^n/(k^n + x^n) + \alpha_0 - \gamma x$, $g_1(x) = 1$, $g_2(x) = -x$, and

$$
\begin{aligned}
h_1(x) &= g_1(x)\left[1 + \tau g_1(x)\frac{d}{dx}\left(\frac{f(x)}{g_1(x)}\right)\right], \\
h_2(x) &= g_2(x)\left[1 + \tau g_2(x)\frac{d}{dx}\left(\frac{f(x)}{g_2(x)}\right)\right]
\end{aligned}
$$

[27,28]. Notice also that this equation can be rewritten as

$$\frac{\partial \phi(x,t)}{\partial t} = -\frac{\partial}{\partial x}[f(x) + D_\gamma x - \lambda\sqrt{D_{\alpha_0} D_\gamma}\, h_1(x)]\phi(x,t)$$
$$+ \frac{\partial^2}{\partial x^2}[D_{\alpha_0} + D_\gamma x^2 + \lambda\sqrt{D_{\alpha_0} D_\gamma}$$
$$\times (h_2(x) - xh_1(x))]\phi(x,t), \qquad (6)$$

since $g_1(x) = 1$ and $g_2(x) = -x$. Then, it is easy to see that the stationary solution of this equation, denoted by $\phi_{st}(x)$, can be given by $\phi_{st}(x) = \mathcal{N}e^{-\Psi(x)}$, where the potential function is

$$\Psi(x) = \ln G(x) - \int^x \frac{f(s) + D_\gamma s - \lambda\sqrt{D_{\alpha_0} D_\gamma}\, h_1(s)}{G(s)}\, ds, \qquad (7)$$

where $G(x) = D_{\alpha_0} + D_\gamma x^2 + \lambda\sqrt{D_{\alpha_0} D_\gamma}(h_2(x) - xh_1(x))$. Notice that $h_2(x) - xh_1(x) = -2x - 2\tau x f'(x) + \tau f(x)$ and that $D_{\alpha_0} + D_\gamma x^2 - 2\lambda\sqrt{D_{\alpha_0} D_\gamma}\, x > 0$ holds for all possible $x \geqslant 0$. Then, we take a small $\tau$ such that $D_{\alpha_0} + D_\gamma x^2 - 2\lambda\sqrt{D_{\alpha_0} D_\gamma}\, x - \tau\lambda\sqrt{D_{\alpha_0} D_\gamma}\,(2xf'(x) - f(x)) > 0$ [i.e., $G(x) > 0$] holds for all possible $x \geqslant 0$.

To characterize the property of the potential function $\Psi(x)$ [or the property of the stationary probability density distribution $\phi_{st}(x)$], we need to solve the solution of the equation $d\Psi(x)/dx = 0$. Notice that

$$\frac{d\Psi(x)}{dx} = \frac{-f(x) + D_\gamma x + \lambda\sqrt{D_{\alpha_0} D_\gamma}\,(h_2'(x) - xh_1'(x))}{D_{\alpha_0} + D_\gamma x^2 + \lambda\sqrt{D_{\alpha_0} D_\gamma}\,(h_2(x) - xh_1(x))}, \qquad (8)$$

where $h_2'(x) - xh_1'(x) = -1 - 2\tau xf''(x)$. Then, the solution of $d\Psi(x)/dx = 0$ is also equivalent to the solution of the equation

$$H(x) \equiv -f(x) + D_\gamma x - \lambda\sqrt{D_{\alpha_0} D_\gamma}\,(1 + 2\tau xf''(x)) = 0, \qquad (9)$$

where $f''(x) = \alpha n k^n[(n-1)k^n x^{n-2} - (n+1)x^{2n-2}]/(k^n + x^n)^3$.

For $\tau \geqslant 0$, it is easy to see that (i) if $\alpha_0 + \lambda\sqrt{D_{\alpha_0} D_\gamma} \leqslant 0$, then Eq. (9) has at most two positive real solutions, or has no positive solution, and (ii) if $\alpha_0 + \lambda\sqrt{D_{\alpha_0} D_\gamma} > 0$, then Eq. (9) has at most three positive real solutions and has at least one positive real solution. In this paper, to show the effect of time-correlated noises on the saddle-node landscape of cell-fate induction, we consider only the situation with $\alpha_0 + \lambda\sqrt{D_{\alpha_0} D_\gamma} > 0$.

For $\alpha_0 + \lambda\sqrt{D_{\alpha_0} D_\gamma} > 0$, notice that $\lim_{x \to 0} H(x) = -\alpha_0 - \lambda\sqrt{D_{\alpha_0} D_\gamma} < 0$, $dH(x)/dx|_{x=0} > 0$, and $\lim_{x \to +\infty} H(x) = +\infty$. Then, similar to Eq. (1), the situation for which Eq. (9) has only one positive real solution, denoted by $x^*$, corresponds to the monostable state of Eq. (3) (or $\phi_{st}(x)$ is a monomodal distribution) since $dH(x)/dx|_{x=x^*} > 0$, and, on the other hand, the situation for which Eq. (9) has three positive real solutions, denoted by $x_1^*$, $x_2^*$, and $x_3^*$, respectively, with $x_1^* < x_2^* < x_3^*$, corresponds to the bistable state of Eq. (3) [or $\phi_{st}(x)$ is a bimodal distribution] since $dH(x)/dx|_{x=x_1^*} > 0$, $dH(x)/dx|_{x=x_2^*} < 0$, and $dH(x)/dx|_{x=x_3^*} > 0$.

### C. Effect of noises on cell-fate induction

In the following numerical analysis, we take the parameters $\alpha = 0.55$, $k = 1$, $n = 5$, and $\gamma = 0.5$ [1], and $D_{\alpha_0} = 0.5$ and $D_\gamma = 0.1$. In order to show how the time-correlated noises will act on the saddle-node bifurcation landscape of cell-fate induction, we consider first the situation with $\tau = 0$. For this situation, we can see that (i) there is only one bistable region on the $\lambda$-$\alpha_0$ parameter plane (i.e., the bistable state can only occur in this region) [see Fig. 1(a), where, for $\alpha_0 + \lambda\sqrt{D_{\alpha_0} D_\gamma} > 0$, the gray shaded area denotes the monostable region, and the red shaded area the bistable region; the purple shaded area denotes $\alpha_0 + \lambda\sqrt{D_{\alpha_0} D_\gamma} < 0$), and (ii) for all possible $\lambda \in (0, 1)$, the size of the bistable interval of $\alpha_0$, $\Delta\alpha_0$, is kept as a constant. This result shows clearly that, for $\tau = 0$, although the change of $\lambda$ will lead to a change of the specific position of the bistable interval of $\alpha_0$, the basic characteristics of the saddle-node bifurcation of cell-fate induction, or the size of the bistable interval of $\alpha_0$, $\Delta\alpha_0$, will not change with the change of $\lambda$. Of course, we also noticed that the stationary statistic properties of Eq. (3) with $\tau = 0$ has been preliminarily investigated by a previous study [13].

Second, for the situation with $\tau > 0$ (where we take $\tau = 0.5$), we can see that there are three bistable regions on the $\lambda$-$\alpha_0$ parameter plane, which are marked using red, blue, and green, respectively [see Fig. 1(b)]. Different from the situation with $\tau = 0$, there exist two critical values of $\lambda$, denoted by $\lambda_c'$ and $\lambda_c''$, respectively, with $\lambda_c' < \lambda_c''$, such that the occurrence of a bistable state is impossible for all possible $\alpha_0$ if $\lambda$ is in the interval $\lambda_c' < \lambda < \lambda_c''$ [where $\lambda'$ and $\lambda''$ are denoted by two black vertical dashed lines in Fig. 1(b)]. For each of these three bistable regions, the size of $\Delta\alpha_0$ depends on $\lambda$. For example, the size of $\Delta\alpha_0$ in the red region will decrease with the increase of $\lambda$ in the interval $0 < \lambda < \lambda_c'$ [see Fig. 1(c)]. In particular, we can see also that for some given values of $\alpha_0$, the system will undergo a succession of three phase transitions, bistable phase (red region) $\to$ monostable phase (gray region) $\to$ bistable phase (blue region), with the change of $\lambda$ from $-1$ to $1$. This is the so-called the reentrance phenomenon [26,27]. As an example, for $\alpha_0 = 0.405$ [denoted by the black horizontal line in Fig. 1(b)], a succession of three phase transitions with the change of $\lambda$ is shown in Fig. 1(d). On the other hand, we can see also that for some given values of $\lambda$ [for example, $\lambda = 0.75$, denoted by the black vertical line in Fig. 1(b)], a succession of four phase transitions, bistable phase (green region) $\to$ monostable phase (gray region) $\to$ bistable phase (blue region) $\to$ monostable phase (gray region), occurs with the change of $\alpha_0$ [see Fig. 1(e)]. These results strongly imply that if the correlation time $\tau$ is not zero, then the time-correlated noises could lead to the change in the saddle-node bifurcation landscape of cell-fate induction, or the time-correlated noises could lead to the abnormality of cell-fate induction.

### III. CONCLUSION

In this paper, based on Ferrell's simple theoretical model [Eq. (1)], we investigated the possible effects of the time-correlated noises between the basal synthesis rate and the degradation rate on the saddle-node landscape of cell-fate
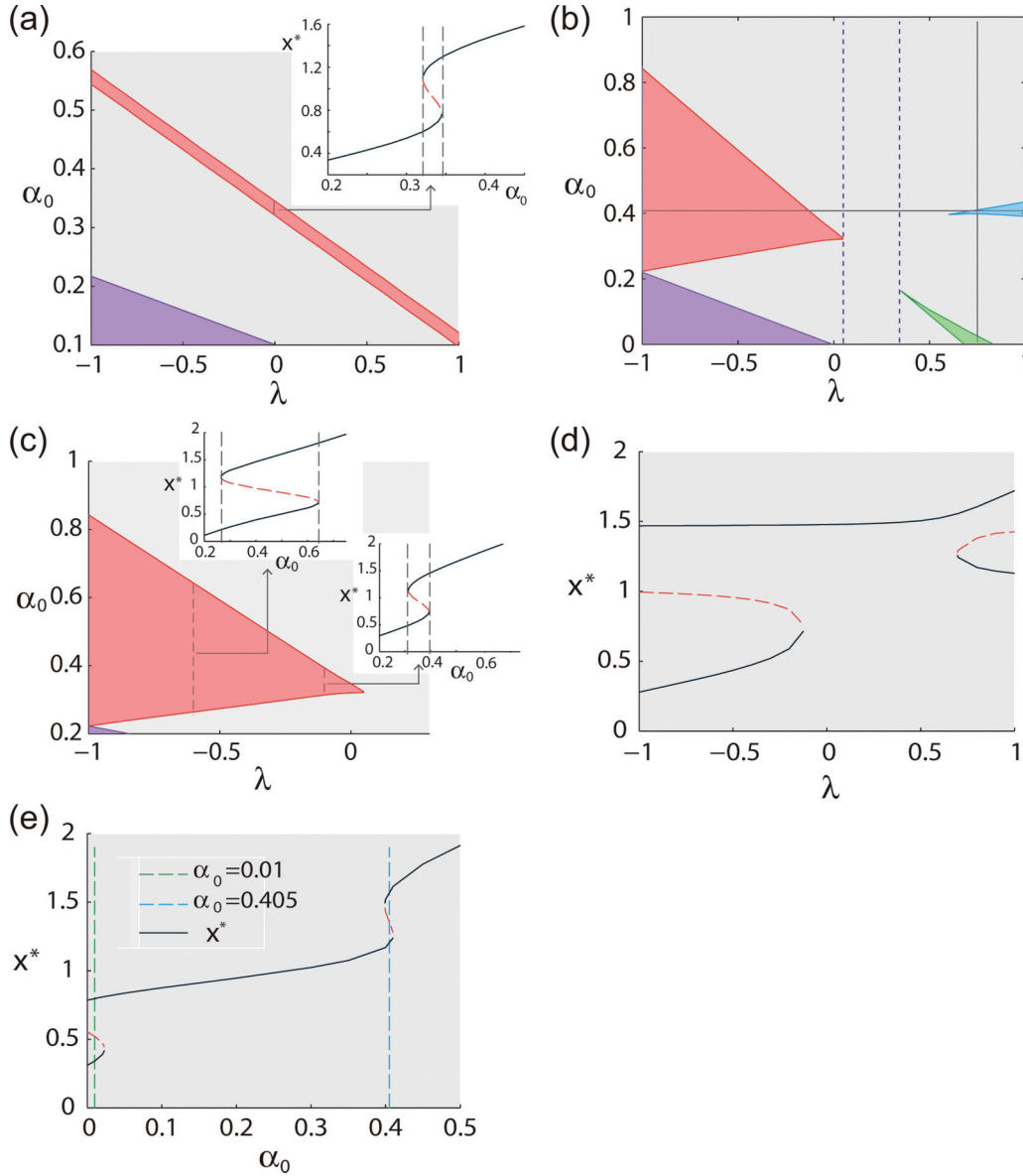
FIG. 1. The effects of the inductive stimulus $\alpha_0$ and correlation coefficient $\lambda$ on the saddle-node bifurcation of cell-fate induction. (a) For the situation with $\tau = 0$, the red shaded area on the $\lambda$-$\alpha_0$ parameter plane denotes the bistable region, and the purple shaded area corresponds to $\alpha_0 + \lambda\sqrt{D_{\alpha_0}D_\gamma} \leqslant 0$ [this is the same also in (b)]. In this situation, the size of the bistable interval of $\alpha_0$ is kept as a fixed constant for all possible $\lambda$. (b) For the situation with $\tau > 0$ (where we take $\tau = 0.5$), there are three bistable regions on the $\lambda$-$\alpha_0$ parameter plane, which are red, blue, and green areas, respectively. The two black vertical dashed lines correspond to the two critical values of $\lambda$, denoted by $\lambda'$ and $\lambda''$ with $\lambda' < \lambda''$, such that the bistability is impossible for all possible $\alpha_0$ if $\lambda' < \lambda < \lambda''$. (c) As an example, the size of the bistable interval of $\alpha_0$ depends on the change of $\lambda$ in the red bistable region. (d) Corresponding to the black horizontal line in (b) (i.e., $\alpha_0 = 0.405$), a succession of three phase transitions occurs with the change of $\lambda$. (e) Similarly, corresponding to the black vertical line in (b) (i.e., $\lambda = 0.75$), a succession of four phase transitions occurs with the change of $\alpha_0$.

induction. Although this model may be not enough to be true, it reflects some essential dynamical characteristics of cell-fate induction. In our analysis, for simplicity, we assume only the inductive stimulus ($\alpha_0$) and degradation rate ($\gamma$) to be two time-correlated random variables. In spite of this, our results still clearly indicate that the time-correlated noises may have a profound impact on the process of cell-fate induction. First, if the correlation time, $\tau$, is zero ($\tau = 0$), then the size of the bistable interval of $\alpha_0$, $\Delta\alpha_0$, should be a fixed constant for all possible $\lambda$, or the basic characteristics of cell-fate induction

will not be changed for all possible $\lambda$. Second, if $\tau > 0$, then there may be some values of $\lambda$ such that the occurrence of the saddle-node bifurcation is impossible for all possible $\alpha_0$. Third, for the situation with $\tau > 0$, in the bistable regions on the $\lambda$-$\alpha_0$ parameter plane, the size of $\Delta\alpha_0$ may strongly depend on the change of $\lambda$. Finally, if $\tau > 0$, then, (i) for some given $\alpha_0$, the existence of reentrance phenomena could be possible with the change of $\lambda$, and (ii) similarly, for some given $\lambda$, the reentrance phenomena could be also possible with the change of $\alpha_0$.

Cell-fate induction based on the saddle-node bifurcation is an important theoretical concept in developmental biology. It provides a possible mechanism to explain the intrinsic irreversibility in the developmental process that is missing from Waddington's epigenetic landscape [1,2]. However, our results provide a theoretical possibility that the time-correlated noises could lead to the abnormality of the saddle-node landscape of cell-fate induction. Therefore, a further challenging question that should be considered in the future is how cell-fate induction in a real-life system resists environmental stochastic fluctuations.

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