Transitions in the cell-fate induction induced by colored noise associated with the inductive stimulus

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ABSTRACT

The cell-fate induction based on the saddle-node bifurcation is undoubtedly a very important concept in developmental biology, which provides a possible mechanism to explain the intrinsic irreversibility in the developmental process. In this paper, the effect of a colored noise, which is associated with the inductive stimulus, on the saddle-node landscape of cell-fate induction is investigated, especially, the effect of the change of correlation time of colored noise on cell-fate induction. The main results show clearly that the change of correlation time of colored noise could induce the transitions of the system. This implies that the colored noise associated with inductive stimulus may have a profound effect on the saddle-node bifurcation landscape of cell-fate induction. This will also help us to understand more deeply the role of cell-fate induction in developmental biology.

1. Introduction

Waddington (1957)'s epigenetic landscape is probably the most famous and most powerful metaphor in the developmental biology, which depicts how a cell progress form an undifferentiated state to one of a number of discrete, distinct, differentiated cell fates during development (see also Ferrell, 2012). Recently, unlike Waddington's pattern, Ferrell (2012) proposed the concept of cell-fate induction, which possess an intrinsic irreversibility that is missing from Waddington's picture (Waddington, 1957; Zheng et al., 2018). According to Ferrell (2012), the concept of 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. Ferrell (2012) pointed out that the cell-fate introduction has two key features: (*i*) the inductive stimulus need not be maintained indefinitely; after some commitment point, the stimulus may be withdrawn and the cell will continue with its induced development program; and (*ii*) the induction results in an all-or-none switch between qualitatively distinct cell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. Some studies have shown that the concept of cell-fate induction should be reasonable (Yamamoto, 1994; Smith, 1995; Ferrell and Machleder, 1998; Ferrell et al., 1999; Sternberg, 2005; Shi et al., 2015; Chen et al., 2018). 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 (Xia et al., 2012).

In order to show clearly the concept of cell-fate induction, Ferrell (2012) used a simple single-variable model with positive feedback regulation to characterize the dynamic properties of cell-fate induction. In fact, this simple theoretical model has been investigated by many authors (Smolen et al., 1998; Xiong and Ferrell, 2003; Liu and Jia, 2004; Smits et al., 2006; Bennett et al., 2007; Zheng et al., 2011; Ferrell, 2012), but Ferrell mainly focused on how the inductive stimulus affects the dynamic characteristics of the system. Based on the potential surface of this system, 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 saddlenode landscape resulting in the cell-fate induction should be different from Waddingtons epigenetic landscape (Waddington, 1957). On the other hand, Ferrell (2012) 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. However, he emphasized that the key of pitchfork bifurcation is that the system is symmetrical and any

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Input

α_0 $\alpha_1 \dfrac{x^n}{k^n + x^n}$

$+$

γx

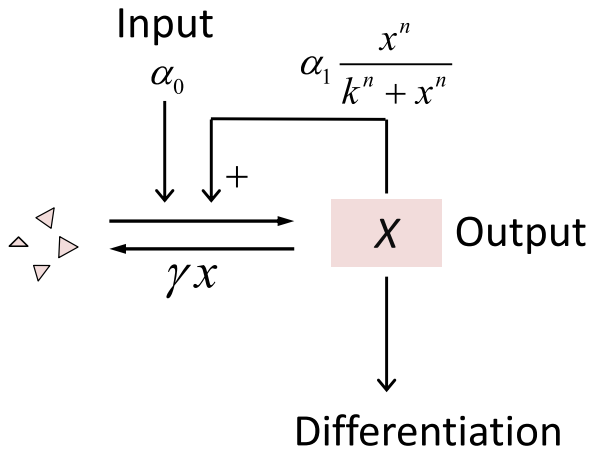X Output

Differentiation

Fig. 1. The scheme of a single gene network associated with the concept of cell-fate induction (Ferrell, 2012).

imperfection in the symmetry will change the pitchfork bifurcation into a saddle-node bifurcation (Momiji and Monk, 2009; Ferrell, 2012). 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 environment cannot be avoided (May, 1973; Becskei and Serrano, 2000; Elowitz and Leibler, 2000; Gardner et al., 2000; Hasty et al., 2000; 2002; Ahmad and Henikoff, 2001; Elowitz et al., 2002; Lande et al., 2003; Kaern et al., 2005; Raj and van Oudenaarden, 2008; Shi et al., 2015; Chen et al., 2018), many studies have investigated the effect of environmental noise on gene expression and regulation (Becskei and Serrano, 2000; Elowitz and Leibler, 2000; Gardner et al., 2000; Hasty et al., 2000; 2002; Ahmad and Henikoff, 2001; Liu and Jia, 2004; Kaern et al., 2005; Xu and Tao, 2006; Raj and van Oudenaarden, 2008; Zheng et al., 2011). For example, some experimental studies based on the single gene networks with positive feedback regulation showed that the basal synthesis rate and degradation rate not only depend on the biochemical reactions, mutations, and concentrations of other proteins but also fluctuate randomly (Becskei and Serrano, 2000; Elowitz and Leibler, 2000; Gardner et al., 2000; Hasty et al., 2000; Ahmad and Henikoff, 2001). More recently, a study investigated the effects of two time-correlated noises on the saddle-node landscape of cell-fate induction (i.e., a single gene network with positive feedback regulation) (Zheng et al., 2018). The main results of this study show that 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. In this study, to reveal more clearly how the correlation time of colored noise affects the stochastic dynamics of cell-fate induction, we still mainly focus on a single gene network with positive feedback regulation, where the basal synthesis rate (or the inductive stimulus) is assumed to be a random variable associated with a colored noise. The results of this study will help us better understand the role of cell-fate induction in developmental biology.

2. Model and analysis

Following Ferrell (2012), we consider also a simple one-variable auto-positive feedback regulation model (the scheme of this model is shown in Fig. 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 pa-

rameter γ 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 α 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 α_0 is the basal synthesis rate and it is also called the inductive stimulus in Ferrell's schematic view of cell-fate induction (Ferrell, 2012; Zheng et al., 2018).

As shown in Introduction, the dynamical properties of Eq. (1) have been investigated by many authors (Smolen et al., 1998; Xiong and Ferrell, 2003; Liu and Jia, 2004; Smits et al., 2006; Bennett et al., 2007; Zheng et al., 2011; Ferrell, 2012), and one of the most important theoretical results of this model is to provide a possible mechanism for the bistable regulation of gene expression (Ferrell, 2012). Especially, Ferrell (2012) used this model to develop the concept of cell-fate induction. Notice that the potential of Eq. (1), denoted by $\Psi(x)$, is $\Psi(x) = -\int \left[\alpha x^n / (k^n + x^n) + \alpha_0 - \gamma x \right] dx$. Then, as shown by Ferrell (2012), we can easily see how the potential surface changes as α_0 changes. Specifically, for given parameters α, k, n (with $n > 1$), and γ, there exist two critical values of α_0, denoted by α_0' and α_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 $\alpha_0 > \alpha''$, and (*ii*) if α_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 (Ferrell, 2012). So, for given α, k, n and γ, (α_0', α_0'') can be called the bistable interval of α_0 for the deterministic dynamics Eq. (1). In mathematics, this is also called the saddle-node bifurcation (Ferrell, 2012).

We now mainly focus our attention on how the stochastic fluctuation of the inductive stimulus influences the process of cell-fate induction. Let α_0 be a positive random variable associated with a colored noise, which is defined as $\alpha_0(t) = \alpha_0 + Q(t) \geq 0$, where α_0 is a positive constant and $Q(t)$ is a colored noise with $\langle Q(t) \rangle = 0$ and

$$\left\langle Q(t)Q(t') \right\rangle = \frac{D}{\tau} \exp \left[-\frac{|t - t'|}{\tau} \right] \tag{2}$$

where τ is the correlation time and D is the noise strength (Castro et al., 1995; Jia and Li, 1997; Gardiner, 2009; Kamenev, 2011; Spanio et al., 2017). Then, the stochastic differential equation (or the Langevin equation) corresponding to Eq. (1) can be given by

$$\frac{dx}{dt} = F(x) + Q(t) \tag{3}$$

where

$$F(x) = \frac{\alpha x^n}{k^n + x^n} + \alpha_0 - \gamma x. \tag{4}$$

Therefore, when we consider only the role of the inductive stimulus, $Q(t)$ is only an additive colored noise of Eq. (3).

Let $\phi(x, t)$ denote the probability density distribution that the system state is x at time t. Then, based on the approximation of small τ (Sancho et al., 1982; Hu, 1994; Jia and Li, 1997; Gardiner, 2009), the probability density distribution $\phi(x, t)$ obeys the Fokker-Planck equation

$$\frac{\partial \phi(x, t)}{\partial t} = -\frac{\partial}{\partial x} F(x)\phi(x, t) + D \frac{\partial^2}{\partial x^2} h(x)\phi(x, t) \tag{5}$$

where

$$h(x) = 1 + \tau F'(x) \tag{6}$$

with

$$F'(x) = \alpha n k^n x^{n-1} / (k^n + x^n)^2 - \gamma \tag{7}$$

(Sancho et al., 1982; Hu, 1994; Jia and Li, 1997; Gardiner, 2009). Then we have that $h(x) > 0$ for all possible $x \geq 0$ if $\tau < 1/\gamma$.
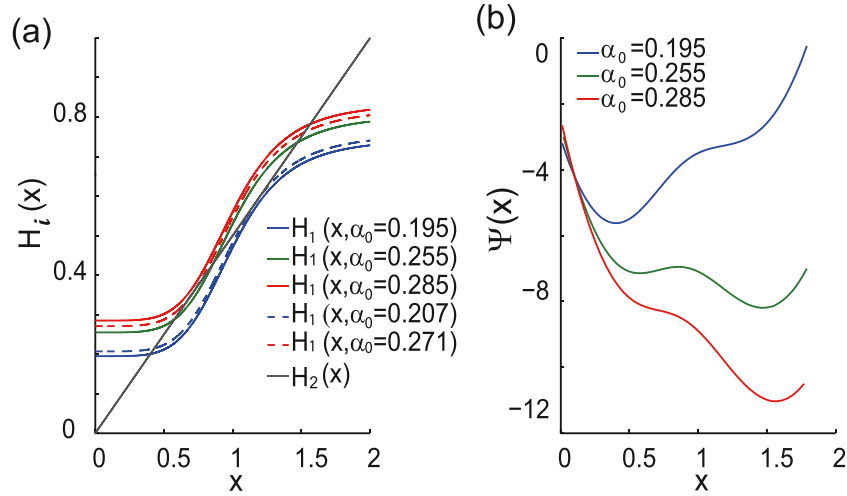
Fig. 2. The phase transitions due to the change of α_0 in the case with $\tau = 0$. For given parameters $\alpha = 0.55$, $k = 1$, $n = 5$ and $\gamma = 0.5$, panel (**a**) shows how the change of α_0 determines the number of intersections of functions $H_1(x)$ and $H_2(x)$; and panel (**b**) shows how the increase of α_0 leads to the change of the number of potential wells in the potential function $\Psi(x)$.
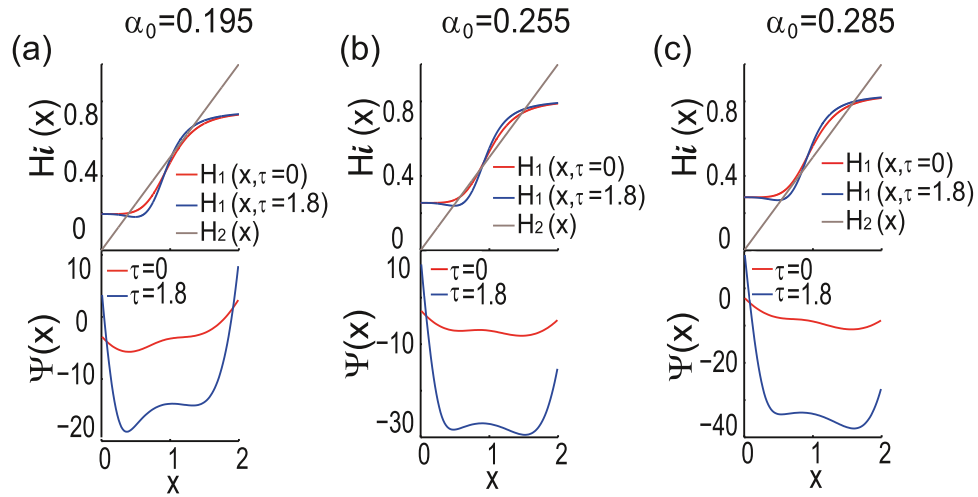

Fig. 3. The phase transitions due to the change of τ. Similarly, for given parameters $\alpha = 0.55$, $k = 1$, $n = 5$ and $\gamma = 0.5$, panel (**a**) shows that when $\alpha_0 < \alpha_0'$, the increase of τ will induce the phase transitions from monostable to bistable; panel (**b**) shows that when α_0 is in the interval $\alpha_0' < \alpha_0 < \alpha_0''$, the change of τ cannot induce the phase transitions, the system is always kept to be bistable; and panel (**c**) shows that when $\alpha_0 > \alpha_0''$, the increase of τ will also induce the phase transitions from monostable to bistable.

The stationary distribution of Eq. (5), denoted by $\phi_{st}(x)$, can be given by $\phi_{st}(x) = \mathcal{N}e^{-\Psi(x)}$, where $\mathcal{N}$ is a normalized constant and the potential function is

$$\Psi(x) = \ln Dh(x) - \int^x \frac{F(s)}{Dh(s)}\, ds \tag{8}$$

(Risken, 1992). Note also that

$$\frac{d\Psi(x)}{dx} = \frac{Dh'(x) - F(x)}{Dh(x)} \tag{9}$$

where $h'(x) = \tau \alpha n k^n x^{n-2}\big((n-1)k^n - (n+1)x^n\big)\big/\big(k^n + x^n\big)^3$. Thus, the solution of $d\Psi(x)/dx = 0$ is also equivalent to the solution of equation

$$Dh'(x) - F(x) = 0$$

$$\Rightarrow D\tau \alpha n k^n x^{n-2} \frac{(n-1)k^n - (n+1)x^n}{(k^n + x^n)^3}$$

$$- \frac{\alpha x^n}{k^n + x^n} - \alpha_0 + \gamma x = 0. \tag{10}$$

For convenience, let

$$H_1(x) = \frac{\alpha x^n}{k^n + x^n} + \alpha_0 - D\tau \alpha n k^n x^{n-2}\frac{(n-1)k^n - (n+1)x^n}{(k^n + x^n)^3},$$

$$H_2(x) = \gamma x. \tag{11}$$

Then, the solutions of Eq. (10) must correspond to the intersections of $H_1(x)$ and $H_2(x)$.

It is easy to see that for the situation with $\tau = 0$, the solutions of Eq. (10) exactly matches the equilibria of the deterministic dynamics Eq. (1), i.e., for given parameters α, k, n and γ (where, as an example, we take $\alpha = 0.55$, $k = 1$, $n = 5$ and $\gamma = 0.5$ Ferrell, 2012), there exist two critical values of α_0, denoted by α_0' and α_0'', respectively, with $\alpha_0' < \alpha_0''$ (where $\alpha_0' = 0.207$ and $\alpha_0'' = 0.271$), such that Eq. (10) has only one solution if $\alpha_0 < \alpha_0'$ or $\alpha_0 > \alpha_0''$, and Eq. (10) has three solutions if α_0 is in the interval $\alpha_0' < \alpha_0 < \alpha_0''$ (Fig. 2a). This also implies that the potential $\Psi(x)$ has only one potential well if $\alpha_0 < \alpha_0'$, or $\alpha_0 > \alpha_0''$, and has two potential wells if α_0 is in the interval $\alpha_0' < \alpha_0 < \alpha_0''$ (Fig. 2b). Therefore, the potential function given by Eq. (8) has the same properties as the potential of deterministic dynamics Eq. (1) if $\tau = 0$ (see also Ferrell, 2012). Obviously, these results also show
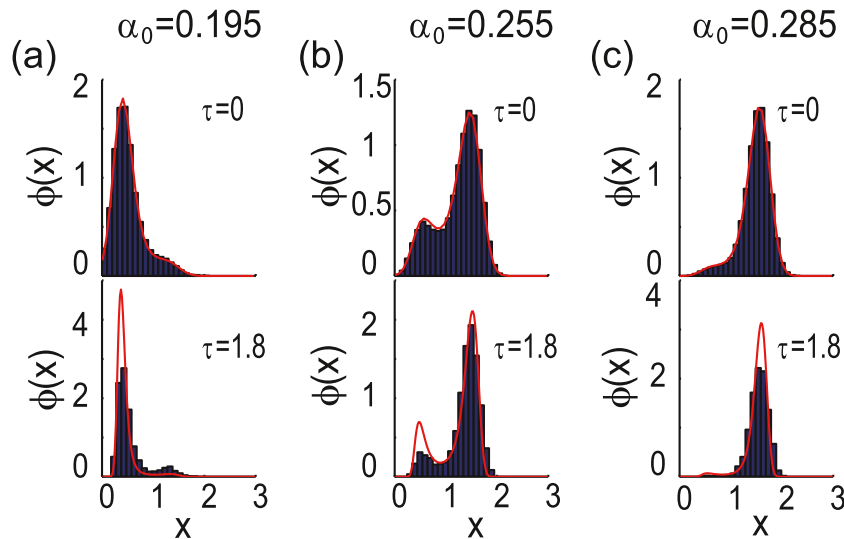
Fig. 4. Stochastic simulation results and stationary distributions corresponding to the theoretical predictions in Figs. 2 and 3. The upper and lower parts of all the panels show the simulation results and stationary distributions corresponding to the theoretical predictions in Fig. 3 for the case $\tau = 0$ and $\tau = 1.8$, respectively.

clearly that if $\tau = 0$, then the solutions of Eq. (10) must be independent of the noise strength D.

On the other hand, for the situation with $\tau > 0$, it is also easy to see that $\lim_{x \to \infty} H_1(x) = \alpha + \alpha_0$ and $\lim_{x \to \infty} H_2(x) = \infty$. Therefore, $H_1(x)$ and $H_2(x)$ have at least one intersection. On the other hand, we can see that for all possible $\tau \in (0, 1/\gamma)$, $H_1(x)$ must pass through a fixed point $\mathbf{P} = (\hat{x}, H_1(\hat{x}))$, where $\hat{x} = \left((n-1)k^n / (n+1)\right)^{1/n}$ and $H_1(\hat{x}) = \alpha(n-1)/2n + \alpha_0$, and that $\partial H_1(x)/\partial \tau < 0$ if $x < \hat{x}$ and, conversely, $\partial H_1(x)/\partial \tau > 0$ if $x > \hat{x}$. These properties imply that the change of τ may induce the transitions. To show this, the numerical analysis of Eq. (10) (where we still take $\alpha = 0.55$, $k = 1$, $n = 5$ and $\gamma = 0.5$, and take $D = 0.015$) shows that (i) when $\alpha_0 < \alpha_0'$ (where $\alpha_0' = 0.207$), with the increase of τ (with $\tau < 1/\gamma$), the system will transmit from monostable state to bistable state, or the system will undergo a succession of two transitions, monostable $\to$ bistable (Fig. 3a); (ii) similarly, when $\alpha_0 > \alpha_0''$ (where $\alpha_0'' = 0.271$), with the increase of correlation time τ, the system will also transmit from monostable state to bistable state, or the system will also undergo a succession of two transitions, monostable $\to$ bistable (Fig. 3c); and (iii) when α_0 is in the interval $\alpha_0' < \alpha_0 < \alpha_0''$, the system is always in bistable sate for all possible τ, that is the change of τ cannot induce the transitions (Fig. 3b). In fact, we can see also that when we assume τ to be a constant with $\tau \in (0, 1/\gamma)$, the change of noise strength D can also result in the similar results.

Furthermore, the stochastic simulations corresponding to the theoretical predictions in Fig. 3 also show clearly that the theoretical predictions are correct, i.e., the stochastic simulation results match the stationary distribution $\phi_{st}(x) = \mathcal{N}e^{-\Psi(x)}$ well (see Fig. 4). Therefore, the theoretical analysis suggests that when the deterministic dynamics of cell-fate induction is monostable, the correlation time of the colored noise associated with the inductive stimulus is also able to lead to the saddle-node bifurcation landscape of cell-fate induction.

3. Conclusion

As we pointed out in Introduction, the cell-fate induction based on the saddle-node bifurcation is undoubtedly a very important concept in developmental biology. It provides a possible mechanism to explain the intrinsic irreversibility in the developmental process that is missing from Waddingtons epigenetic landscape

(Waddington, 1957). In this study, based on Ferrell (2012)'s model of cell-fate induction (i.e., Eq. (1)), the effect of colored noise, which is associated with the inductive stimulus, on the saddle-node landscape of cell-fate induction is investigated. In our analysis, since we mainly focus on the effect of the inductive stimulus on the cell-fate induction, we only assume that the basal synthesis rate (α_0) in Eq. (1) is a positive random variable associated with a colored noise. In spite of this, our analysis still provides a possible mechanism to reveal the role of inductive stimulus associates colored noise in cell-fate induction, especially, how the correlation time of colored noise influences the saddle-node bifurcation landscape of cell-fate induction.

First, it is easy to see that for the deterministic dynamics Eq. (1), there must exist two values of α_0, denoted by α_0' and α_0'', respectively, with $\alpha_0' < \alpha_0''$, such that (i) if $\alpha_0 < \alpha_0'$ (or $\alpha_0 > \alpha_0''$), the system has only one equilibrium, denoted by x^*, and it is globally asymptotically stable (i.e., monostable state); and (ii) if α_0 is in the interval $\alpha_0' < \alpha_0 < \alpha_0''$, then the system has three equilibria, 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 unstable (i.e., bistable state). This is why Ferrell (2012) emphasized that the change of inductive stimulus (α_0) plays a very important role in cell-fate induction. Second, when we assume that the inductive stimulus is a positive random variable associated with a colored noise (i.e., $\alpha_0 = \alpha_0 + Q(t) \geq 0$, where $Q(t)$ is a colored noise with correlation time τ and noise strength D) (see Eq. (2)), we found that (i) if $\alpha_0 < \alpha_0'$ (or $\alpha_0 > \alpha_0''$), then, with the increase of correlation time τ, the system will transmit from monostable state to bistable state, or the system will undergo a succession of two transitions, monostable $\to$ bistable ; and (ii) if α_0 is in the interval $\alpha_0' < \alpha_0 < \alpha_0''$, then the system is always in bistable state for all possible τ, that is the change of τ cannot induce the transitions. All of these results imply that the colored noise associated with inductive stimulus may have a profound effect on the saddle-node bifurcation landscape of cell-fate induction.

Finally, we would like to say that since we here mainly focus on how the random inductive stimulus associated with a colored noise influences the saddle-node bifurcation landscape of cell-fate induction. So, the multiplicative noises related to the Hill-type function and protein degradation rate of protein are not considered in this study. However, this does not imply that the importance of multiplicative noises in cell-fate induction could be

ignored in more general situation. Some studies have shown that when a multiplicative noise source is introduced into a system (Horsthemke and Lefever, 1984; Mikhailov and Loskutov, 2012; etc.), it may give rise to a lot of interesting dynamical phenomena, such as the transition phenomenon (Barbera and Spagnolo, 2002; Fiasconaro et al., 2004; Valenti et al., 2004; Chichigina et al., 2011; Zheng et al., 2011; 2018) and the noise enhanced stability phenomenon (Horsthemke and Lefever, 1984; Mantegna and Spagnolo, 1996; Fiasconaro and Spagnolo, 2009; Spagnolo et al., 2004; Mikhailov and Loskutov, 2012). As an example, we also investigated the effects of two time-correlated noises, which are related to the inductive stimulus and protein degradation rate, respectively, on the saddle-node bifurcation landscape of cell-fate induction (Zheng et al., 2018). Therefore, the unique biological significance of multiplicative noise for cell-fate induction should be considered in the future.

Acknowledgments

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