

Modeling of potential- and noise-induced intracellular dynamics with cell-cell communication

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Abstract: In cellular systems, complicated intracellular reaction circuits implement various types of information processing in response to external stimuli such as decision-making. These processes involve stochastic fluctuations owing to low copy numbers of molecules per cell and uncertainty of environmental signals. Major mechanisms that can cope with such noise, known currently, are potential-induced bistability at the single-cell level, or mutual communication at the population level. Another mechanism, noise-induced bistability, is recently demonstrated to be connected to optimal noise-filtering dynamics from external stimuli. In this work, we focus on the difference of potential-induced and noise-induced dynamics in terms of their information processing ability. Furthermore, we investigate the effect of mutual communication to the noise-induced dynamics. To address these problems, we propose a mathematical model of an intracellular network that combines both bistability. In addition, we also investigate the impact of intercellular communication.

Keywords: Cellular dynamics, Decision making, Stochastic process, Cell-cell communication

1 INTRODUCTION

Information processing in response to external stimuli is a fundamental function of all living systems. In cellular systems, for example, various types of information processing such as decision-making are implemented by complicated intracellular reaction circuits. However, all components of the circuits such as transcriptional control, alternative splicing, translation, diffusion and chemical modification reactions of transcriptional factors, involve stochastic fluctuations owing to low copy numbers of molecules per cell and uncertainty of an external environment. These intrinsic and extrinsic noise in the building components can inevitably disturb the cellular information processing [1].

Two mechanisms are mainly known that can cope with such noise: one is single-cell level, and the other is the population level. At the single-cell level, a cell may have intracellular circuits that can resist to noise. For example, a bistable potential system implemented by mutually inhibitory reactions can sustain its state against noise if the deterministic force exerted by the potential is sufficiently strong. At the population level, cells can also employ mutual communication to realize coordinated behavior out of noisy single-cell level behavior [2, 3, 4]. While these mechanisms are prevalently observed within intracellular circuits, they may be insufficient to explain all the biological phenomena because such strong deterministic potential or communication may reduce not only the noise but also the flexibility and variability of the cells to the external stimuli.

On this issue, one of the authors has recently demonstrated that intracellular networks that can optimally filter out noise in external stimuli have ability to show noise-induced bistability [5, 6], suggesting that noise-induced as well as deterministic potential-induced dynamics can also efficiently cope with noise. Furthermore, it is also suggested that such dynamics can optimally balance the suppression of noise and sensitivity to external stimuli. Nonetheless, the difference between potential-induced and noise-induced dynamics in terms of their information processing ability has not yet been clarified. Furthermore, even though mutual communication of potential-induced dynamics has been intensively investigated [3, 7, 8], almost nothing is known on the effect of mutual communication to the noise-induced dynamics.

In this study, we tackle this problem using a mathematical approach, and propose a model of an intracellular network that combines both potential-induced and noise-induced bistability. First, we analyze deterministic and stochastic properties of this model by calculating null-clines and bifurcation diagram. Next, by numerical simulations, we confirm that this model exhibits bimodal histograms produced by the potential-induced and noise-induced bistability in case of constant external stimuli. We also examine the response of the model to a step-like external stimuli. Finally, we introduce intercellular communication that enables each cell to detect the state of the other cells and react together with them. We investigate the responses to external stimuli for different strength of communication to clarify the impact.

2 COMBINED MODEL OF POTENTIAL- AND NOISE-INDUCED BISTABILITY

2.1 Derivation of equation

In [5], it was demonstrated that the following autophosphorylation and autodephosphorylation reaction as an intracellular network is approximately equivalent to an optimal dynamics to infer the state of environment from noisy receptor signal. Its Gaussian approximation was derived subsequently in [6] to further clarify the noise-induced bistability in that cycle. We extend this model such that a new model can have potential-induced bistability as well as noise-induced bistability that the original model has.

The model is described as follows:

$$\frac{dZ_i}{dt} = Z_i \tilde{Z}_i I(t) + r_{on} H(\tilde{Z}_i) \tilde{Z}_i - r_{off} H(Z_i) Z_i, \quad (1)$$

where $Z_i \in [0, 1]$ and $\tilde{Z}_i := 1 - Z_i$ are the state of the system in i -th cell, such as ratios of phosphorylated and un-phosphorylated molecules in a cell. Under this interpretation, $r_{on} H(\tilde{Z}_i)$ and $r_{off} H(Z_i)$ are respectively the rate of input-independent phosphorylation and dephosphorylation reactions that occur spontaneously where $H(Z) := p + 2(1 - p)/(K_0^n + Z^n)$. When $p = 1$, Eq. (1) is equivalent to the model derived in [6]. When $p = 0$, $r_{on} H(\tilde{Z}_i) \tilde{Z}_i - r_{off} H(Z_i) Z_i$ has a bistable potential by the inhibition of state transition between Z_i and \tilde{Z}_i introduced by the Hill's kinetics. Thus, $p \in [0, 1]$ controls the extent to override bistable potential onto the original model. The external input $I(t)$ with extrinsic noise is described as the following:

$$I(t) = \alpha (\int_0^t U dt + \sigma \circ dW_t), \quad (2)$$

where \circ represents Stratonovich interpretation [9]. $\int_0^t U dt$ is the signal that the cell have to detect. σdW_t is the noise that cell receives. α is introduced to control the strength of the signal with respect to noise. The signal noise ratio (SNR) $\int_0^t U dt / \sigma$ determines the ambiguity of the signal. α is the amplification factor of both signal and noise that a cell can control. For notational simplicity, we define the following functions:

$$F(Z, U) = \alpha \int_0^t U Z \tilde{Z} + r_{on} H(\tilde{Z}) - r_{off} Z H(Z),$$

$$G(Z) = \alpha \sigma Z \tilde{Z}.$$

2.2 Deterministic properties of Eq. (1)

Firstly, we analyze deterministic properties of our model. The equilibrium state of Eq. (1) satisfies $F(Z, U) = 0$. By solving this equation with respect to U , we obtain

$$U_{null}^{det}(Z) = \frac{1}{\alpha} \left(\frac{r_{on}}{Z} H(\tilde{Z}) + \frac{r_{off}}{\tilde{Z}} H(Z) \right),$$

which is the analytic expression of the null-cline of Eq. (1). For a given U , the equilibrium state of Z may have more than

one state. In other words, the system can have multi-stable states. While the condition for multi-stable state is not generally expressed analytically, we can derive it for a symmetric condition such that $K_0 = 1/2$, $r_{on} = r_{off} = r_0$. Fig. 1. (a) and (b) show the null-clines of this system with respect to the parameters n and p , respectively. Given these conditions, Eq. (1) becomes symmetric with respect to the exchange of Z and \tilde{Z} . Thus, when $U = 0$, $Z = 1/2$ is always one of the equilibrium state. Therefore, the derivative of $U_{null}^{det}(Z)$ with respect to Z can be used as the condition for the transition from monostable to bistable state. More specifically, $\left. \frac{dU_{null}^{det}(Z)}{dZ} \right|_{Z=1/2} = 0$ is the condition of changing the number of the equilibrium states. By rearranging this equation, we have

$$p = \frac{2^n(n-2)}{2^{1+n} + 2^n n} \quad (n \neq 1),$$

which is depicted by the solid line in Fig. 2.

2.3 Stochastic properties of Eq. (1)

Next we clarify the properties of Eq. (1) when noise is introduced. Let consider the situation such that U and σ are constant and that dW_t is the white Gaussian process. Then,

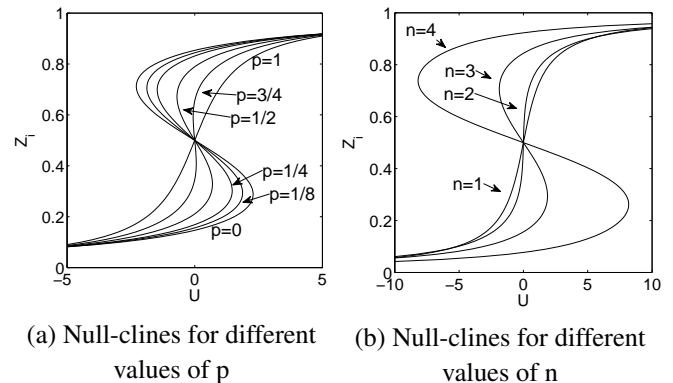


Fig. 1. Null-clines of Eq. (1)

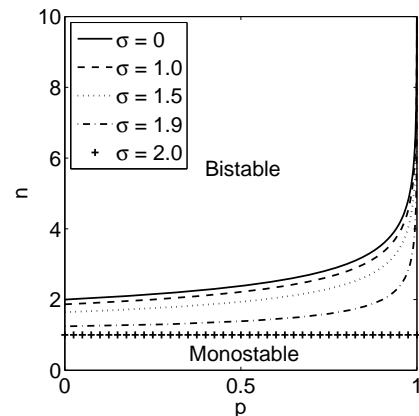


Fig. 2. Bifurcation Diagram. The upper (lower) side area of each curve correspond to bimodal (unimodal) distribution.

Eq. (1) can be described by a stochastic differential equation as

$$dZ_i = F(Z, U)dt + G(Z) \circ dW_t. \quad (3)$$

We here use Stratonovich interpretation as the original work did[6].

The probability distribution $\mathbb{P}(t, Z)$ of Eq. (3) then satisfies the corresponding Fokker-Planck equation [9] as

$$\frac{\partial \mathbb{P}(t, Z)}{\partial t} = \frac{\partial [F_{Ito}(Z, U)\mathbb{P}(t, Z)]}{\partial Z} + \frac{1}{2} \frac{\partial^2 [G(Z)^2 \mathbb{P}(t, Z)]}{\partial Z^2},$$

where $F_{Ito}(Z, U) := F(Z, U) + \alpha\sigma G(Z)(1/2 - Z)$. The stationary state of Eq. (3) can be represented [9] as

$$\mathbb{P}_{st}(Z) = \frac{N}{G(Z)^2} \exp \left[2 \int^Z \frac{F_{Ito}(Z', U)}{G(Z')^2} dZ' \right].$$

This equation can be solved analytically when $p = 1$ as

$$\mathbb{P}_{st}(Z) \propto \frac{1}{Z\bar{Z}} \left(\frac{Z}{\bar{Z}} \right)^{\bar{U}} \exp \left[\frac{2}{(\alpha\sigma)^2 \left(\frac{r_{on}}{Z} + \frac{r_{off}}{\bar{Z}} \right)} \right],$$

where $\bar{U} = \frac{2(\alpha\mu_0 U + r_{on} - r_{off})}{(\alpha\sigma)^2}$.

For $p < 1$, this equation cannot be analytically solved. Nevertheless, some properties, especially stochastic bifurcation, can be analytically derived. Let identify the peak positions of stationary distribution of Eq. (3) with the deterministic equilibrium points considered in the previous section. Then, the change of the number of peaks can be regarded as the bifurcation of the stochastic system, which is known as phenomenological bifurcation [10]. The peak positions of $\mathbb{P}_{st}(Z)$ satisfies $\frac{\partial \mathbb{P}_{st}(Z)}{\partial Z} = 0$. This equation can be solved with respect to U as

$$U_{null}^{st}(Z) = U_{null}^{det}(Z) + \frac{(\alpha\sigma)^2}{\alpha} (1/2 - Z).$$

Similarly to the deterministic case, $U_{null}^{st}(z)$ becomes symmetric around $Z = 1/2$ when $r_{on} = r_{off} = r_0$. In addition, $Z = 1/2$ and $U = 0$ is always the equilibrium state under the symmetric condition. Thus, the bifurcation points from unimodal to bimodal distribution satisfy

$$\left. \frac{dU_{null}^{st}(Z)}{dZ} \right|_{Z=1/2} = \left. \frac{dU_{null}^{det}(Z)}{dZ} \right|_{Z=1/2} - \frac{(\alpha\sigma)^2}{\alpha} = 0,$$

which is also the condition for the change of the number of peaks when $\left. \frac{d^2 U_{null}^{st}(Z)}{dZ^2} \right|_{Z=1/2} \neq 0$. Then we have

$$\begin{cases} p = \frac{2^n(n-2)}{2^{1+n}+2^{2n}} + \frac{(\alpha\sigma)^2/(4r_0)}{2^{1+n}+2^{2n}} & (n \neq 1) \\ \sigma = 2 & (n = 1), \end{cases}$$

which is depicted in Fig.2.

2.4 Simulation results

We compare monostable and bistable potential cases for external input signal $U = 0$. We choose $p = 1$ for monostable potential case and $p = 1/8$ for bistable potential case. We set parameter of Hill function $n = 3$ to have bistable potential for $p = 1/8$, and noise intensity $\sigma = 7$ to realize noise-induced bistability for $p = 1$. We simulate Eq. (1) for $t = 0.001$ and $N = 2000$ by using Milstein scheme [9]. Fig. 3. (a) and (b) show the results of monostable potential case whereas Fig. 3. (c) and (d) show those of bistable potential case.

Then we simulate the response of cells to step-wise change of external signal U from $-$ to $+$. Now $n = 21$, and time of step-wise change is at $t = 0.1$. Fig. 4. (a) and (b) show responses of populations to the inputs. Both figures show similar Z_i trajectories and mean trajectory of Z_i .

3 CELL-CELL COMMUNICATION MODEL

We modify Eq. (3) to have cell-cell communication by adding the term for diffusive cell-cell communication. The equation is described as follows:

$$dZ_i = F(Z_i, U)dt + G(Z_i) \circ dW_t + \frac{D}{N} \sum_{j \neq i} (Z_j - Z_i)dt, \quad (4)$$

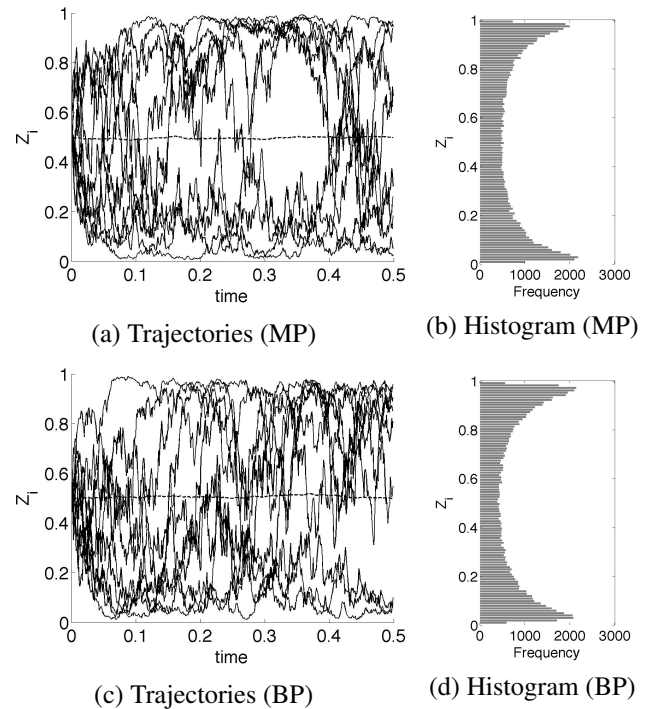


Fig. 3. Response to constant input. MP and BP represent monostable and bistable potentials, respectively. (a) and (c) show the trajectories of Z_i . Solid curves are the trajectories of Z_i (We plot trajectories of only 10 cells). Dashed curve is the trajectory of mean of Z_i . (b) and (d) are the histogram.

where D is the diffusion constant controlling the strength of communication, and N is the total number of cells.

Fig. 4. (c) and (d) show the simulation results of the response of cells to step-wise change of external signal U from 0 to 1. Now $N = 21$, $D = 10$, rising time of step input is $t = 0.1$.

Comparison of Fig. 4. (a) (b) and Fig. 4. (c) (d) show that fluctuation of Z_i by noise is moderated by communication, which means that intercellular communication made the transitions of cellular populations more adequate.

To confirm the effect of diffusion constant D , we conduct simulation for various D . Fig. 5. (a) and (b) are the results of monostable and bistable potential cases, respectively. We plot the trajectories of mean of Z_i for various D . The larger

D becomes, the faster the reaction of cellular population is in both monostable and bistable potential cases.

4 DISCUSSION

In this study, we have examined the difference of potential-induced and noise-induced bistability with respect to their response to external stimuli with and without intercellular communication. However, their difference is not clearly observed. The reason of this small difference may be attributed to the property of our model; bistable potential is overridden onto the noise-induced bistability, indicating that two mechanisms are not clearly separated. In order to reach firm conclusion, we need further investigation and/or modification of our models.

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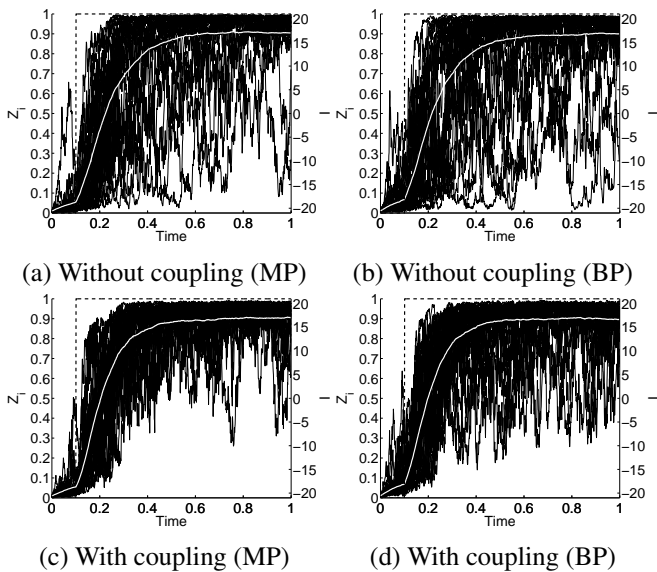


Fig. 4. (a) and (b) are the response to step-wise input without coupling. Solid curves are trajectories of Z_i (We plot trajectories of only 30 cells) and correspond to left axis. White curve is trajectory of mean of Z_i , correspond to left axis. Dashed curve is external signal U and correspond to right axis. (c) and (d) are the response to step-wise input with coupling. The meaning of curves are the same as (a) and (b).

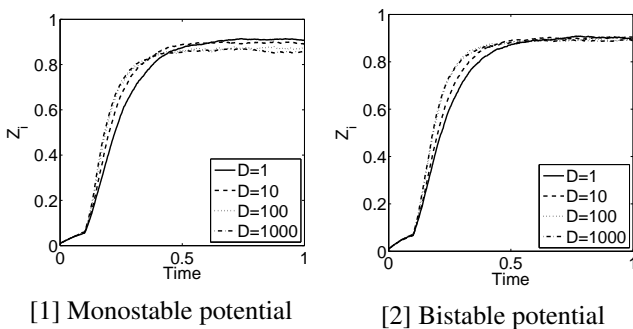


Fig. 5. Average Z_i in switching at various diffusion constant