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RESEARCH ARTICLE

Study of spatial signal transduction in bistable switches

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Bistable switch modules are among the most important fundamental motifs in signal-transduction pathways. To better understand their spatial signal transduction, we model the diffusion process in the one-dimensional (1–D) domain. We find that when none of the elements diffuse, the response of the system exhibits a spatial switch–like property. However, when one of the elements is highly diffusible, the response of the system does not show any spatial switching behavior. Furthermore, we observe that the spatial responses of the system are more sensitive to the time constant of the switch when none of the elements are diffusible. Further, a slow loop keeps the system in the high steady state more positions than that in the fast loop. Finally, we consolidate our numerical results analytically by performing a mathematical method.

Keywords signal processing, reaction–diffusion model, nonlinear dynamics, spatial switch

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1 Introduction

It is well known that living cells exist in dynamic environments, and they have to respond to a variety of environmental stimuli and make appropriate decisions. Thus, much of the decision making in response to external cues, as well as the regulation and control of intracellular processes, is achieved through complex, nonlinear, and often sophisticated and subtle chemical signal processing [1, 2]. To better understand signal pathways in cellular processes, both experimental and theoretical studies are required in investigating gene regulatory networks and signal transduction underlying a number of important processes.

The notion of feedback is one of the most fundamental concepts in cell signaling [3, 4]. Signaling systems that include positive feedback have the potential to exhibit bistability [5, 6]. A system is considered bistable if it can switch between two distinct stable steady states but cannot rest in intermediate states. A bistable system always displays hysteresis, meaning that the stimulus must exceed a threshold to switch the system to another steady state at which it may remain when the stimulus decreases [7]. Bistable switches module play essential roles in important cellular processes such as cell differentiation [8–10] and cell-cycle progression [11, 12].

Theoretical modeling and dynamics analysis has been a practical and useful tool for better understanding the signaling mechanism of the bistable switch module. However, most of the previous theoretical models are based on rate equations (ordinary differential equations) for homogeneous systems [13–15]. This means that the focus is either on steady states or temporal aspects of the signaling. However, in many cases, spatial aspects cannot be neglected. Examples of these processes include the spatial gradient of phosphoprotein [16–20], the chemotactic migration of eukaryotic cells [21], polarity generation and maintenance in a number of cell types [22–24], and the propagation of intracellular waves of calcium [25, 26]. In all these processes, the spatial aspects combining with the complexity of the underlying networks make them especially difficult to understand. There has been an increasing interest in investigating spatial effects in the signal transduction processes. For instance, Markevich *et al.* [27] established a MAPK model consisting of the spatial distribution of the protein kinase to study long range signaling. They mainly reported that the bistability in a

two–site MAPK cycle generates a phosphoprotein wave that propagates from the surface into the cell interior. van Albada *et al.* [28] explored the consequences of the spatial distribution of the enzymes for the amplification of push–pull networks. However, they only considered the mechanism of zero–order ultrasensitivity.

Inspired by the above studies, we examine spatial signal transduction in a bistable switch module. Our study is similar to the work, where the response of the mutual inhibition bistable switch module was investigated [29]. However, we are interested in the spatial distribution of the mutual-activation bistable module when it is subjected to different spatial signals. We consider two cases, one where all elements are essentially non–diffusible, and the other where one of the network elements may be highly diffusible. We also explore how fast and slow loops influence the response of the bistable module. Then, we consolidate our results using analytical results.

The paper is organized as follows. First, in Section 2, we discuss theoretical models in homogeneous and heterogeneous systems; in particular, depending on the time constant of the switch, we introduced fast and slow loops. Next, in Section 3, using our models, we examine the spatial distribution of the signaling protein in the bistable module when it is subjected to two different spatial signal inputs. We explore the influences of fast and slow loops on the system. Furthermore, in Section 4, we explain our numerical results analytically using a mathematical method. Finally, in Section 5, we discuss and conclude the results.

2 Theoretical models in homogeneous and heterogeneous systems

Figure 1 illustrates the network structure of a bistable switch module, where a mutual activation of X and Y comprises a positive feedback loop. This module is extracted from many realistic biological circuits. A signaling protein X' could be converted into an active form X using a process catalyzed by a stimulus S and another protein Y. For example, the stimulus S could be a kinase, and the conversion from X' to X could be due to phosphorylation. X could be converted back to X' through phosphatase. X could also catalyze inactive form Y' to active form Y.

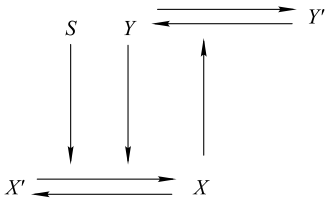

Fig. 1 Schematic illustration of the bistable switch module. A mutual activation of X and Y comprises a positive feedback loop, and the activation of X is catalyzed by the signal S.

For a homogeneous (well–stirred) system, we employed the rate equations to describe this switch module. We consider a similar model to those in Refs. [30, 31], and the dynamic equations for the one–loop switch are

$$\frac{\mathrm{d}X}{\mathrm{d}t} = \tau_A[(k_1 S + k_2 \frac{Y^n}{K_c^n + Y^n})(X_{tot} - X) - k_3 X + k_{minx}], \tag{1}$$

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = k_4 X(Y_{tot} - Y) - k_5 Y + k_{miny}. \tag{2}$$

Here, all parameters and variables are dimensionless. X and Y represent the concentrations of the loop components, and S denotes the stimulus strength. τ_A is the time constant of the switch, which determines its responsiveness. We assume $\tau_A = 1.0$ for the fast loop switch, while $\tau_A = 0.01$ for the slow loop switch. Other parameter values that we used are $k_1 = 0.1$, $k_2 = 0.3$, $k_3 = 1.0$, $k_{minx} = 0.01$, $k_4 = 1.0$, $k_5 = 0.3$, $k_{miny} = 0.003$, $X_{tot} = Y_{tot} = 1.0$, $K_c = 0.35$, and $n = 4$.

Figure 2 shows the bifurcation diagram for the signaling active protein X as a function of S. We can clearly find two saddle-node bifurcation points S_1 (0.2315) and S_2 (0.3706), which enclose a bistable region. For any S within this region, the switch has two stable solutions and one unstable solution, which are represented by solid and dash dotted lines, respectively. The switch therefore exhibits hysteresis, which is the characteristic of bistable systems. Hysteresis is of potential importance in biological switching. First, it reduces the probability that a switch will repeatedly flip back and forth between two states when the stimulus is hovering near its threshold value [5]. Second, it provides a potential mechanism for biochemical memory. For example, during the maturation of Xenopus oocyte, the p42 MAPK/Cdc2 system can keep a long-term memory of a transient differentia-

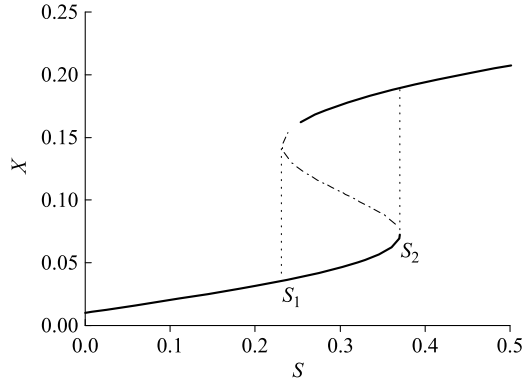

Fig. 2 Steady state dependence of X on S, steady state (–), unstable state (– · – · –).

tion stimulus [9].

Above, we have introduced a theoretical model in the well-stirred case. However, under real biological conditions, the spatial effects cannot be neglected. First, proteins are localized in different spaces so the bistable module is activated spatially. Second, the proteins have to diffuse to the correct location for the appropriate signaling event to occur, and spatial diffusion is crucial for signal propagation. Therefore, these spatial factors should be taken into account. To extend the above theoretical model in the homogeneous case, we developed a reaction–diffusion model in the heterogeneous case.

The reaction–diffusion model for the one-dimensional (1D) spatial domain is formulated as follows:

$$\frac{\mathrm{d}X}{\mathrm{d}t} = \tau_A[(k_1 S + k_2 \frac{Y^n}{K_c^n + Y^n})(X_{tot} - X) - k_3 X + k_{minx}] + D_X \frac{\partial^2 X}{\partial \theta^2}, \quad (3)$$

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = k_4 X(Y_{tot} - Y) - k_5 Y + k_{miny} + D_Y \frac{\partial^2 Y}{\partial \theta^2}. \quad (4)$$

Here, D_j is the diffusion coefficient for the species j (X or Y). θ denotes the position of the protein. For the spherical symmetry, we make the analysis of signaling in one dimension nearly equivalent to the analysis in three dimensions. Therefore, the essential results and insight provided in this paper can also apply to 3D domains. The periodic boundary conditions are chosen for protein components in Eqs. (3)–(4), but most results are equally valid for other boundary conditions such as zero-flux, which we also try to use in our paper. The effect of the choice of boundary conditions is minimal. All of the numerical simulations of our model were implemented in Fortran.

3 Spatial distribution of signaling protein for different signal inputs

Here, the active protein in which we are interested is X. Below, we investigated the spatial distributions of X to different signal inputs.

Figures 3(a) and (b) show an example of the signal inputs used in the analysis. In Fig. 3(a), the gradient signal, which is as a function of the domain position, has a cosine variation, and is of the form $S = a_1 + b_1 \cos\theta$. Meanwhile, in Fig. 3(b), the localized signal is of the form $a_2 + b_2 \mathrm{e}^{-\frac{(\theta-\pi)^2}{\alpha}}$. The signal inputs are different from those previously used in Refs. [19, 20], where the time-varying signals were only applied at one domain position.

Next, we will examine the response of the module to the input signals, and Fig. 4 shows the case when none

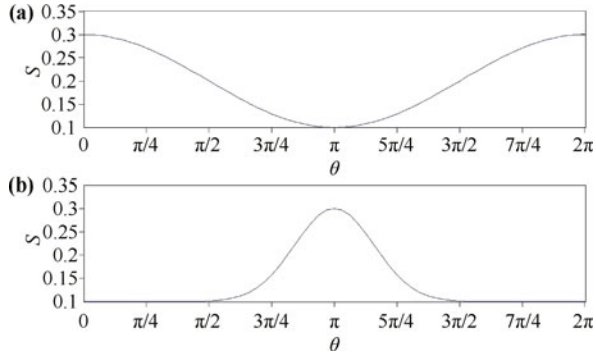

Fig. 3 **(a)** The gradient signal input and **(b)** the localized signal input used in the analysis. The gradient signal has the form $S = a_1 + b_1 \cos\theta$ ($a_1 = 0.2, b_1 = 0.1$), while the localized signal is of the form $a_2 + b_2 \mathrm{e}^{-\frac{(\theta-\pi)^2}{\alpha}}$ ($a_2 = 0.1, b_2 = 0.2, \alpha = 0.5$).

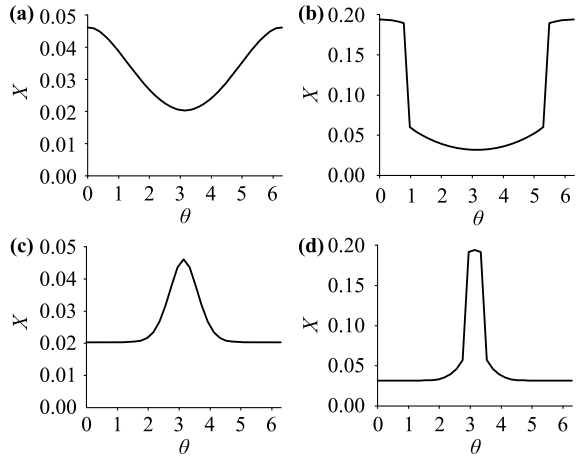

Fig. 4 **(a, b)** The response of the module when it is subjected to gradient signals $S = 0.2 + 0.1\cos\theta$ and $S = 0.3 + 0.1\cos\theta$. **(c, d)** The response of the system when the input localized signals are $S = 0.1 + 0.2\mathrm{e}^{-\frac{(\theta-\pi)^2}{0.5}}$ and $S = 0.2 + 0.2\mathrm{e}^{-\frac{(\theta-\pi)^2}{0.5}}$. We fix $\tau_A = 1.0$.

of the elements diffuse. In this case, it should be noted that the dynamics and steady states are purely local and completely uncoupled. Here, the initial conditions are chosen to make the system rest in the low steady state when signal inputs are in the bistable region (around 0.23 to 0.37). Therefore, we can use Eqs. (1)–(2) to study the concentration of X at every position in the domain. When the module is subject to a gradient signal $S = 0.2 + 0.1cos\theta$ and a localized signal $S = 0.1 + 0.2\mathrm{e}^{-\frac{(\theta-\pi)^2}{0.5}}$, the responses are found in Figs. 4(a) and (c), respectively. We can see that the steady state of X reflects a heterogeneity broadly mirroring the input signal. On the other hand, when the signals change as $S = 0.3 + 0.1\cos\theta$ and $S = 0.2 + 0.2\mathrm{e}^{-\frac{(\theta-\pi)^2}{0.5}}$, we observe that the system exhibits spatial variation at the steady state of X.

Next, we consider the case when one of the elements

(Y) is highly diffusible. In this case, we use Eqs. (3)–(4) to investigate the steady state of X. The diffusion coefficient D in the cytoplasm was reported to be within the range $1-10\ \mu m^2/s$ [32]. Here, D_Y is set to 5 and $D_X = 0$ unless specified otherwise. As shown in Figs. 5(a) and (c), when $S = 0.2 + 0.1\cos\theta$ and $S = 0.1 + 0.2e^{-\frac{(\theta-\pi)^2}{0.5}}$ are applied to the bistable module, we still find that the response of X mirrors the input signal, but the diffusion makes the profiles of X flatter than those in the case where none of the elements is diffusible. Moreover, in Figs. 5(b) and (d), diffusion induces a much lower response level, and the spatial distribution of X reflects no switch effect for $S = 0.3 + 0.1\cos\theta$ and $S = 0.2 + 0.2e^{-\frac{(\theta-\pi)^2}{0.5}}$. We also study the case when only X is highly diffusible, i.e., $D_X = 5$ and $D_Y = 0$. From the four subplots in Fig. 6, we observe that the spatial distributions of X are flatter than those in the case when Y is diffusible, and they cannot mirror the input signal. The results for the case when both X and Y are highly diffusible are qualitatively similar, so we did not include those data here.

Below, we explain the results obtained. For the case when none of the elements diffuse, the system is in a completely uncoupled bistable switch. If a signal is applied at the position where the local value of the signal never exceeds S_2, then the response of the system ends up at a steady state on the low branch of the bifurcation diagram mirroring the signal. On the other hand, if a signal is chosen such that the local level exceeds S_2, the part of the domain that is subjected to the signal above S_2 evolves to the high stable state, while the other part

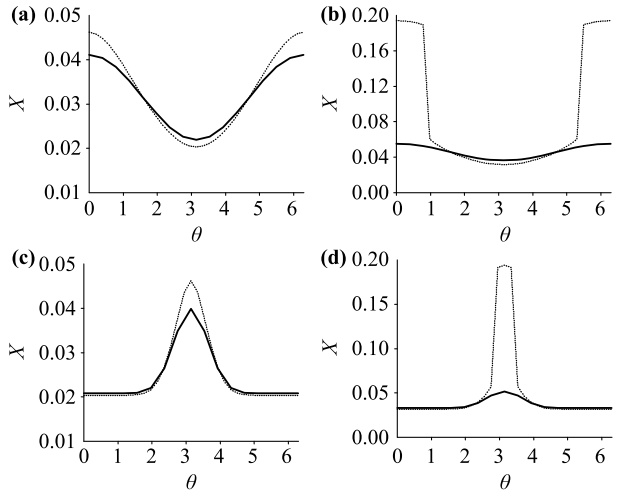

Fig. 5 Concentration profiles of X are shown when only Y is highly diffusible (*solid line*) and non-diffusible (*dot line*) for **(a)** and **(b)** gradient signals $S = 0.2+0.1\cos\theta$ and $S = 0.3+0.1\cos\theta$, while **(c)** and **(d)** localized signals are $S = 0.1+0.2e^{-\frac{(\theta-\pi)^2}{0.5}}$ and $S = 0.2+0.2e^{-\frac{(\theta-\pi)^2}{0.5}}$. We fix $\tau_A = 1.0$.

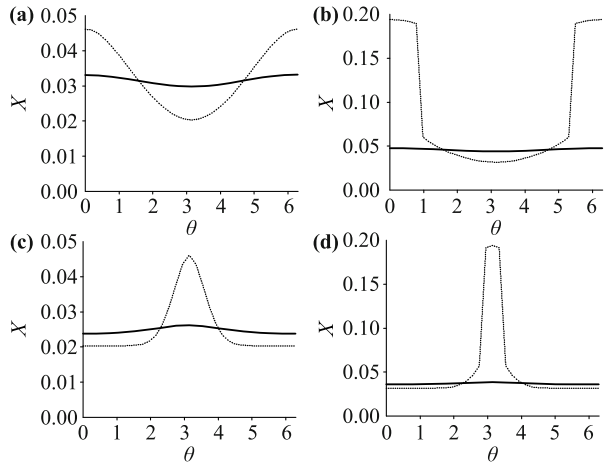

Fig. 6 Concentration profiles of X are shown when only X is highly diffusible (*solid line*) and non-diffusible (*dot line*) for **(a)** and **(b)** gradient signals $S = 0.2+0.1\cos\theta$ and $S = 0.3+0.1\cos\theta$, while **(c)** and **(d)** localized signals are $S = 0.1+0.2e^{-\frac{(\theta-\pi)^2}{0.5}}$ and $S = 0.2+0.2e^{-\frac{(\theta-\pi)^2}{0.5}}$. We fix $\tau_A = 1.0$.

of the domain is in the low stable state, so the spatial switch is observed. When one of the elements is highly diffusible, the situation can be understood easily in terms of the Maxwell condition for uniform bistable system [33]. A large diffusion coefficient means that more proteins arrive at the same position in the system, generically one of the two steady states will engulf the other through traveling fronts that sweep across the domain.

In addition to the spatial characteristics, we observe that the feedback strength can also be regarded as a controllable parameter in some conditions, e.g., lowering (or increasing) the motility of kinase increases the strength of the positive (or negative) feedback of receptor–kinase interaction [34, 35].

We investigate the impact of the feedback strength on the spatial distributions of X for input signals $S = 0.3 + 0.1\cos\theta$ and $S = 0.2 + 0.2e^{-\frac{(\theta-\pi)^2}{0.5}}$. For fast and slow loops when none of the elements diffuse, as shown in Figs. 7(a) and (b), we find that the slow loop keeps the systems in the high steady state more positions than that in fast one. However, when one of the elements is highly diffusible, we observe that changing the strength of the switch τ_A does not influence the shape of the response, and the two curves overlap with each other. This is easy to understand as the spatial distributions of X are more sensitive to the strength of the switch in our model when the system is spatially uncoupled, and the slow loop is responsible for the switching speed. However, when the system is spatially coupled, the dynamics of X at one position can communicate with adjacent positions because of the diffusion, so the system is insensitive to the time constant of the switch.

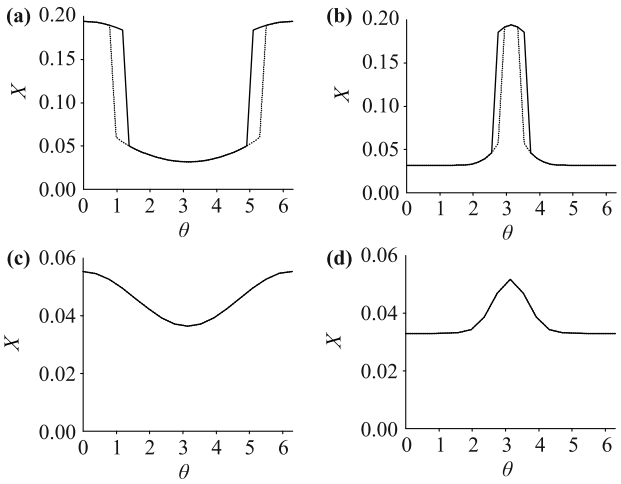

Fig. 7 Concentration profiles of X are shown when the module is one slow loop (*solid line*, $\tau_A = 0.01$) or one fast loop (*dot line*, $\tau_A = 1.0$). **(a, b)** The input signals are $S = 0.3+0.1\cos\theta$ and $S = 0.2+0.2\mathrm{e}^{-\frac{(\theta-\pi)^2}{0.5}}$ when the elements are non–diffusible. **(c, d)** The input signals are $S = 0.3+0.1\cos\theta$ and $S = 0.2+0.2\mathrm{e}^{-\frac{(\theta-\pi)^2}{0.5}}$ when Y is highly diffusible.

4 Analytical results for bistable switch module

Above, we present numerical results for the bistable switch. These results can be explained analytically as follows.

First, in the non-diffusible case, the system reaches a steady state governed by

$$[k_1 S(\theta) + k_2 \frac{Y^n}{K_c^n + Y^n}](1 - X) - k_3 X + k_{minx} = 0, \quad (5)$$

$$k_4 X(1 - Y) - k_5 Y + k_{miny} = 0. \quad (6)$$

The behavior of this system simply reflects the local bistability. Now, in the case where Y are highly diffusible, we see that Y will attain a spatially homogeneous profile. The steady states for this system are controlled by

$$[k_1 S(\theta) + k_2 \frac{Y^n}{K_c^n + Y^n}](1 - X) - k_3 X + k_{minx} = 0, \quad (7)$$

and $$k_4\langle X\rangle(1 - Y) - k_5 Y + k_{miny} = 0. \quad (8)$$

where $\langle X\rangle$ represents the spatial average of X.

Eq. (7) can be written as

$$X = 1 + \frac{k_{minx} - k_3}{k_3 + k_1 S(\theta) + k_2 \frac{Y^n}{K_c^n + Y^n}}. \quad (9)$$

Eq. (9) reveals that the spatial heterogeneity of X directly arises from the signal rather than through any spatial switching effect. Note that in this equation, Y is homogeneous, but is an implicit function of X. Averaging both sides of this equation spatially, we obtain

$$\langle X\rangle = 1 + \langle \frac{k_{minx} - k_3}{k_3 + k_1 S(\theta) + k_2 \frac{Y^n}{K_c^n + Y^n}} \rangle, \quad (10)$$

where

$$\langle \frac{k_{minx} - k_3}{k_3 + k_1 S(\theta) + k_2 \frac{Y^n}{K_c^n + Y^n}} \rangle = \frac{1}{2\pi} \int_0^{2\pi} \frac{k_{minx} - k_3}{k_3 + k_1 S(\theta) + k_2 \frac{Y^n}{K_c^n + Y^n}} \mathrm{d}\theta.$$

If we know the details of the input signal $S(\theta)$, we can calculate $\langle X\rangle$. Using Eqs. (8) and (10) to eliminate $\langle X\rangle$, we obtain Y numerically. Then, at each position in the domain, we know that X is a function of $\frac{1}{S(\theta)}$ when Y is diffusible. Then, we can get X from Eq. (9). Therefore, the response of the module results in heterogeneity without any spatial switching.

5 Discussion and conclusions

In summary, we investigated the spatial signal transduction of the signaling protein in a mutual-activation bistable module by performing numerical simulations and theoretical analysis. We constructed a reaction–diffusion model for this module, in which we considered the spatial effects. Then, we introduced two input signals, the gradient signal and the localized signal. We explored the spatial distributions of X for different signals in two cases by performing computational simulations. Furthermore, we considered the influence of fast and slow loops on the response of the system. We first determined that when none of the elements diffuse, the response of the system exhibits a spatial switch–like property if the signal value crosses the high threshold in some parts of the domain. However, when one of the elements is highly diffusible, the system mirrors only the input signal, and does not show any spatial switching behavior. Moreover, we found that the system is more sensitive to the time constant of the switch when none of the elements are diffusible. Meanwhile, varying the strength of the switch does not affect the shape of the response when one of the element diffuses. Finally, we consolidated our results using the analytical results obtained. We expect that the analysis performed here can provide valuable insights into our understanding of the spatial aspects of signal processing and other relevant issues.

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