Physica A 419 (2015) 498–505

Contents lists available at ScienceDirect

Physica A

journal homepage: www.elsevier.com/locate/physa

Motif for controllable toggle switch in gene regulatory networks

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HIGHLIGHTS

- The motif of a toggle switch with double negative feedback loops is suggested.
- The controllability of the switch could be adjusted to fit different situations.
- The motif could regulate self-oscillating gene regulatory networks as a toggle.

ARTICLE INFO

Article history:
Received 13 June 2014
Received in revised form 18 August 2014
Available online 16 October 2014

Keywords:
Network
Gene regulation
Motif
Toggle switch

ABSTRACT

Toggle switch as a common phenomenon in gene regulatory networks has been recognized important for biological functions. Despite much effort dedicated to understanding the toggle switch and designing synthetic biology circuit to achieve the biological function, we still lack a comprehensive understanding of the intrinsic dynamics behind such phenomenon and the minimum structure that is imperative for producing toggle switch. In this paper, we discover a minimum structure, a motif that enables a controllable toggle switch. In particular, the motif consists of a transformative double negative feedback loop (DNFL) that is regulated by an additional driver node. By enumerating all possible regulatory configurations from the driver node, we identify two types of motifs associated with the toggle switch that is captured by the existence of bistable states. The toggle switch is controllable in the sense that the gap between the bistable states is adjustable as determined by the regulatory strength from the driver nodes. We test the effect of the motifs in self-oscillating gene regulatory network (SON) with respect to the interplay between the motifs and the other genes, and find that the switching dynamics of the whole network can be successfully controlled insofar as the network contains a single motif. Our findings are important to uncover the underlying nonlinear dynamics of controllable toggle switch and can have implications in devising biology circuit in the field of synthetic biology.

1. Introduction

The use of mathematical modeling to gain insight into gene regulatory network behavior across different organisms has increased dramatically in recent years. Systems-level biological modeling is a necessary and powerful tool for understanding how the regulatory network achieves a switch between the two stable states of a bistable behavior. Bistability is discussed with respect to all-or-none cellular processes such as differentiation, proliferation, survival and apoptosis [1–6]. However, much evidence about reversible switches has been observed in the regulatory network in biological experiments [7–11].

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http://dx.doi.org/10.1016/j.physa.2014.10.028

Network structures that are composed of double negative feedback loop (DNFL) have been proposed to explain the switch [12–15]. In these studies, it is found that a switch between the two stable states can be achieved by building a layer DNFL model or a cascade DNFL model [16–22] or by applying stimulation to the DNFL [23–26,8,27]. In some cases, an unresponsive switch could be necessary, and an unusually sensitive method could also be necessary to describe the ultra-sensitization of the cellular signaling in other cases. Thus a controllable toggle switch is very important for controlling gene regulatory networks. In a recent study about genetic switch [11], the authors find a stochastic model that can generate a predictable toggle switch. Further more, a library of genetic toggle switch experiments was built to tested the function of this model exactly. Based on the previous studies, our research focuses on the controllable toggle-switch motif with simplified dynamics [28] and its function in regulating self-oscillating gene regulatory networks (SONs). We addressed the minimum module as a motif, which can generate a controllable toggle switch to fit different situations, and its toggle-switch function for SONs. So it is designed to implement the function as a controllable toggle switch by a transformative DNFL (Driven-DNFL), which is composed of a DNFL that is driven by an external driving node. As this motif is quite simple, we can analyze the dynamical property and the influence of parameters in detail. Then a network that includes a Driven-DNFL and a three-node SON is designed to test the toggle-switch function that can turn or the oscillation of the SON. Finally, a simulated confirmatory test is built in a more general situation to confirm the function of this motif in several ten-node gene regulatory networks.

2. The bistability with a controllable gap

For designing a toggle switch, one should first consider it as a dynamics of bistability. Bistability has been shown in many studies to be caused by a positive feedback loop composed of two genes (nodes) with a double negative feedback loop (DNFL) [29–33]. A set of ordinary differential equations has been widely used for describing genomic regulation [28,34,35], this approach adopts an 'OR' gate between all repressive and active regulations. A generic mathematical description of GRNs with size N is given as follows:

$$\frac{dx_i}{dt} = \gamma_i(1 - x_i) + \sum_{j=1}^{N} f_{ij} \quad i = 1, 2, \dots, N, \tag{1}$$

where

$$\begin{cases} f_{ij} = (1 - x_i)\dfrac{(x_j)^{h_{ij}}}{(K_{ij})^{h_{ij}} - (x_j)^{h_{ij}}}, & \text{positively regulate;} \\ f_{ij} = 0, & \text{null;} \\ f_{ij} = -x_i\dfrac{(x_j)^{h_{ij}}}{(K_{ij})^{h_{ij}} - (x_j)^{h_{ij}}}, & \text{negatively regulate;} \end{cases} \tag{2}$$

where x_i $(i = 1, 2 \dots N)$ represents the concentration of the ith protein. There are three parameters in Eq. (2). The parameter K is the half-maximal concentration of the activator (repressor). Parameter h stands for the Hill coefficient, and parameter γ represents the decay rate. For mathematical simplicity, we take identical parameters in Eq. (2) for all of the nodes, such as $K_{ij} = K$, $h_{ij} = h$, $\gamma_i = \gamma$, $i, j = 1, 2 \dots, N$.

The kinetic equations of DNFL have three fixed points. According to the linear stability analysis, two of the three fixed points are stable, and the remaining point is unstable. Two steady-state fixed points are the detached states of the bistability of DNFL. Considering a controllable switch, the gap of the detached states should be changed as required for different situations. As discussed in former studies [36,37], changing some parameters of the kinetic equations can make the gap changing. How to obtain a switch without all of the parameters changing is still a question; as a result, we use another strategy to design a three-node motif to solve this problem.

A controllable gap can be achieved by adding a node as a driving node to regulate the two nodes of the DNFL (Driven-DNFL). Three probable topologies are discussed: one negative regulation and one positive regulation; two positive regulations; and two negative regulations, as shown in Fig. 1. The gap could be adjusted by controlling the driving node. A bistability can be generated in the structure with a couple of opposite regulatory feedbacks (Fig. 1B). However, because of the opposite regulations, the node that is regulated by the positive regulation always stays in the higher state, and the other node stays in the lower state. When a very strong stimulation is applied to the DNFL, the switch between the two states cannot yet be achieved. A bistability can not only be generated in the other two structures with a couple of negative regulations or a couple of positive regulations (Fig. 1A or Fig. 1C); it can also be adjusted by an appropriate stimulation from the driving node. It is obvious that the smaller the gap is, the more easily the switches are achieved. The switch is more effective. Only the two structures can both achieve a controllable bistability. For the double positively regulating in Fig. 1A, the driving node of the Driven-DNFL can be regarded as a signal emitter with a stable strength called ω. The coupled ordinary differential equations of the Driven-DNFL should be written as follows (where K, h, and γ are all constants):

$$\begin{cases} \dfrac{dx_1}{dt} = \gamma(1 - x_1) - x_1\dfrac{(x_2)^h}{(K)^h - (x_2)^h} + (1 - x_1)\dfrac{(w)^h}{(K)^h - (w)^h} \\ \dfrac{dx_2}{dt} = \gamma(1 - x_2) - x_2\dfrac{(x_1)^h}{(K)^h - (x_1)^h} + (1 - x_2)\dfrac{(w)^h}{(K)^h - (w)^h}. \end{cases} \tag{3}$$