Coupled Positive Feedback Loops Regulate the Biological Behavior

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***Abstract*—Coupled positive feedback loops are frequently-occurring motifs in gene transcription regulatory networks and signaling pathways. So it's very important to investigate the function of coupled positive feedback loops. In this paper we establish mathematical models of coupled positive feedback loops. Through the bifurcation analysis, we prove that two coupled positive feedback loops can generate reversible and irreversible switch. And coupled positive feedback loops can strengthen bistable, enlarge signal and extend the signal reaction time. Coupled positive feedback loops play an important role in regulate biological behaviors.**

I. Introduction

Complex biological behaviors are achieved by the interaction of genes, RNAs, proteins and metabolites within cells. These substances constitute complex biological networks. The biological networks effectively control the interaction between genes, RNA, proteins and metabolites. Coupled positive feedback loops are frequently-occurring motifs in gene transcription regulatory networks and signaling pathways [1]–[4]. The components of a feedback loop are genes, proteins and other molecules which are connected by regulatory interactions. Depending on the components and their interactions, feedback loops have distinct roles in diverse regulatory systems. Many previous studies verified that in biological systems coupled positive feedback loops play an important role in making appropriate biological behaviors. James E. Ferrell $et\ a.l$ demonstrated that coupled positive feedback loops have a very critical role in the process of $Xenopus\ oocyte$ maturation [5]. Andrew Yates $et\ al.$ indicated that differentiation of uncommitted T cells into Th1 and Th2 subpopulations depend on both intracellular events controlling expression of transcription factors T-bet and GATA-3 and interactions between cells mediated by cytokines, particularly IL4 and IFNγ. And coupling positive feedback loops are the body of this regulatory network [4]. Although a single positive feedback loop (X, Y mutual promote or X, Y mutual inhibit) in appropriate circumstances can produce bistable switch [6]–[9]. Interestingly, many biological systems are not just a single positive feedback loop, but is the coupling of multiple positive feedback loops (see Table I).

In this paper we mainly study the function and nature of several different coupled positive feedback loops. And we can extend our results to any topology structure without loss of generality. We can classify the structures of two coupled positive feedback loops into three basic modules: PP1 (X and Y_1 promote each other, X and Y_2 promote each other), PP2 (X and Y_1 mutual inhibit, X and Y_2 mutual promote) and PP3 (X and Y_1 mutual inhibit, X and Y_2 mutual inhibit)(see Fig. 1).

Here we establish mathematical models of three different topological structure of two coupled positive feedback loops. And we investigate the dynamics and the underlying design principle of the two coupled positive feedback loop systems through numerical simulations. Through the bifurcation analysis, we find that the system can exhibit diverse behaviors

TABLE I
COUPLED POSITIVE FEEDBACK LOOPS IN BIOLOGICAL PROCESSES

Muscle cell fate specification [1]	CDO⇌MyoD⇌Akt2
$Ca^{(2+)}$spikes or oscillations [28]	IP3R⇌Ca^{2+}_{cyt}⇌RYR
Th1 and Th2 differentiation [4]	STAT6⇌GATA3⇌STAT4
S. cerevisiae galactose regulation [20]	Gal2→galactose⊣Gal80⊣Gal2 Gal3⊣Gal80⊣Gal3
B cell fate specification [29]	IL-7⇌EBF EBF⊣Notch-1 ⊣E2A→ EBF→Pax-5⊣Notch-1 ⊣E2A→EBF
p53 regulation [30]	p53→PTEN⊣Akt→Mdm-2⊣p53 p53→p21⊣CDK2⊣Rb⊣Mdm2⊣p53
Xenopus oocyte maturation [13]	Cdc2⇌Mos⇌Cdc25 Cdc2⇌Myt1
Start of cell cycle in *budding yeast* [26], [27]	Sic1⊣cdc28⊣Sic1 Cln⇌cdc28
Apoptosis [18]	XIAP⊣caspace-3⊣XIAP caspace-8⊣caspace-3⊣caspace-8

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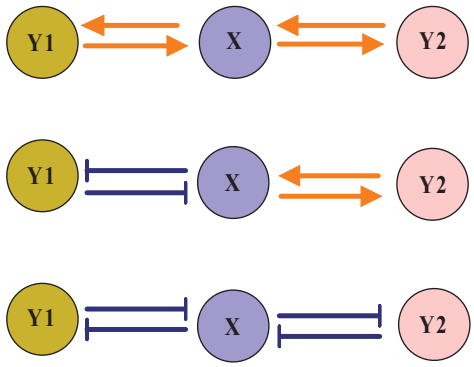

Fig. 1. Three basic modules of two coupled positive feedback loops.

such as monostability and bistability by changing the feedback strength. Firstly, with the increase of the strength of positive feedback the system transfers from monostability to reversible and irreversible bistability. Secondly, the bistability region of system increases with the increasing of the strength of the positive feedback. Thirdly, we investigate the advantages of coupled positive feedback loops which are compared with the following two situations: a single positive feedback loop, coupled with one negative feedback loop.

II. MODELS AND METHODS

Firstly, we consider a model which has only one positive feedback loop, i.e., X and Y_1 mutually activate.

$$X \rightleftharpoons Y_1$$

The dynamics of system I are as follows:

$$\frac{d[X]}{dt} = V_x \frac{(\frac{[Y_1]}{K_{y_1x}})^n}{1+(\frac{[Y_1]}{K_{y_1x}})^n} - d_x[X] + b_x S, \quad (1)$$

$$\frac{d[Y_1]}{dt} = V_{y_1} \frac{(\frac{[X]}{k_{xy_1}})^n}{1+(\frac{[X]}{k_{xy_1}})^n} - d_{y_1}[Y_1] + b_{y_1}. \quad (2)$$

[X] and [Y_1] denote the concentration of X and Y_1, respectively.

Here, S is a stimulus. V_x denotes the regulatory effectiveness of Y_1 to X, and V_{y_1} represents the strength of the positive feedback. The regulated expression of genes is represented by Hill functions with cooperativity exponent n. The threshold parameter K_{y_1x} and k_{xy_1} denote the threshold of Y_1 inducing a significant response of X and the threshold of X inducing a significant response of Y_1 respectively. Parameters d_x and d_{y1} represent the degradation rate constant of X and Y_1 respectively, and b_x and b_{y1} indicate the basal synthesis rate of X and Y_1 respectively (See table II for the values of these parameters). Next we couple another positive feedback loop, and the model becomes as follows:

$$Y_1 \rightleftharpoons X \rightleftharpoons Y_2$$

TABLE II
THE VALUE OF THE PARAMETERS

I		II	
Parameter	Basal value	Parameter	Basal value
S	0	S	0
V_x	2	V_x	2
k_{xy_1}	1	k_{xy_1}	1
k_{xy_2}	—	k_{xy_2}	1
k_{y_1x}	1	k_{y_1x}	1
k_{y_2x}	—	k_{y_2x}	Variable
b_x	0.01	b_x	0.01
b_{y_1}	0.1	b_{y_1}	0.1
b_{y_2}	—	b_{y_2}	0.1
d_x	2	d_x	2
d_{y1}	2	d_{y1}	2
d_{y2}	—	d_{y2}	0.2
V_{y_1}	3.8	V_{y_1}	3.8
V_{y_2}	—	V_{y_2}	Variable
n	2	n	2

When X is regulated by Y_1 and Y_2 in a competitive way, the dynamics of system II can be described by the following ordinary differential equations:

$$\frac{d[X]}{dt} = V_x \frac{(\frac{[Y_1]}{K_{y_1x}})^n + (\frac{[Y_2]}{K_{y_2x}})^n}{1+(\frac{[Y_1]}{K_{y_1x}})^n + (\frac{[Y_2]}{K_{y_2x}})^n} - d_x[X] + b_x S, \quad (3)$$

$$\frac{d[Y_1]}{dt} = V_{y_1} \frac{(\frac{[X]}{k_{xy_1}})^n}{1+(\frac{[X]}{k_{xy_1}})^n} - d_{y_1}[Y_1] + b_{y_1}, \quad (4)$$

$$\frac{d[Y_2]}{dt} = V_{y_2} \frac{\frac{[X]}{k_{xy_2}}^n}{1+\frac{[X]}{k_{xy_2}}^n} - d_{y_2}[Y_2] + b_{y_2}. \quad (5)$$

[X] , [Y_1] and [Y_2] denote the concentration of X , Y_1 and Y_2, respectively. Here, S is a stimulus. V_{y_1} and V_{y_2} can be taken as the strength of the two positive feedback, respectively (The values of these parameters are shown in Table II). When X is regulated by Y_1 and Y_2 in a noncompetitive way, the dynamics of this system can be described by the following ordinary differential equations:

$$\frac{d[X]}{dt} = V_x \frac{(\frac{[Y_1]}{K_{y_1x}})^n + (\frac{[Y_2]}{K_{y_2x}})^n}{(1+(\frac{[Y_1]}{K_{y_1x}})^n)(1+(\frac{[Y_2]}{K_{y_2x}})^n)} - d_x[X] + b_x S, \quad (6)$$

$$\frac{d[Y_1]}{dt} = V_{y_1} \frac{(\frac{[X]}{k_{xy_1}})^n}{1+(\frac{[X]}{k_{xy_1}})^n} - d_{y_1}[Y_1] + b_{y_1}, \quad (7)$$

$$\frac{d[Y_2]}{dt} = V_{y_2} \frac{\frac{[X]}{k_{xy_2}}^n}{1+\frac{[X]}{k_{xy_2}}^n} - d_{y_2}[Y_2] + b_{y_2}. \quad (8)$$

[X] , [Y_1] and [Y_2] denote the concentration of X , Y_1 and Y_2, respectively. All parameters in Eqs. (6)-(8) have the same meanings with Eqs. (3)-(5) which are shown in table II.

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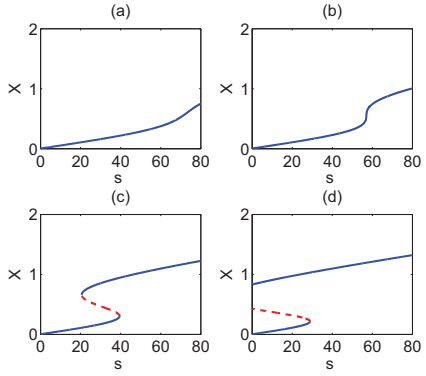

Fig. 2. The signal-response curves of the system. (a) Only one positive feedback loop. (b) Coupled another positive feedback loop with $V_{y2} = 7$. (c) Coupled another positive feedback loop with $V_{y2} = 15$. (d) Coupled another positive feedback loop with $V_{y2} = 25$. V_{y2} is the coupled strength of X and Y_2. The solid line denotes stable steady state and the dotted line denotes unstable steady state. In all situations the values of other parameters are same as in table II.

We can similarly give the dynamics of the other two different topology of coupled positive feedback loops.

III. RESULTS

A. Coupling-induced bistable switches

Positive feedback is known to be an essential ingredient for bistability in biochemical systems [10]. And coupled positive feedback loops often act as biological motifs [3], [4]. Here, we show that coupled positive feedback loops can induce bistability. We achieve this by increasing V_{y2} while V_{y1} is fixed at 3.8. The signal-response relationship is shown in Fig. 2.

When there is only one positive feedback loop, the system exhibits monostability (Fig. 2(a)). If we couple a positive feedback loop to this system with $V_{y2} = 7$, the coupled system is still monostability but it shows ultrasensitivity (Fig. 2(b)). When V_{y2} is increased to 15, the coupled system can exhibits bistability (Fig. 2(c)). In this case the coupled system acts as a toggle-switch. Clearly, [X] converges to a low or high state depending on the initial condition. This calls hysteresis. It makes the system able to remember the stimulus long after it has been removed and this system can act as a memory module. Continue to increase V_{y2} until it's value is large enough the coupled system can act as a one-way switch (Fig. 2(d)). The one-way switch is an extreme case of hysteresis since it can permanently remember the stimulus. And we have similar results for the noncompetitive model.

For a system to be bistable, the underlying molecular circuit must incorporate positive feedback, together with step(s) that can transfer signal in an ultrasensitive fashion with effective Hill coefficient larger than one. [5], [11]–[13]. What makes bistable behavior possible in this case is the fact that when two positive feedback loops are coupled together, each loop in effect serves as an ultrasensitive motif for the other loop. Therefor, coupled positive feedback loops can induce bistable switch. And it can both induce toggle switch and one-way

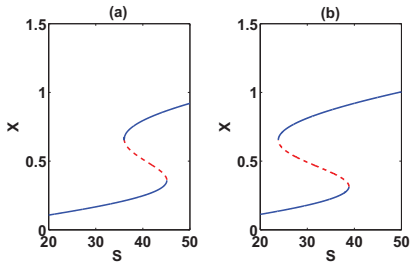

Fig. 3. The strength of the positive feedback loops affect the robustness of a bistable switch. (a) Only one positive feedback loop with $V_{y1} = 6$. (b) Coupled another positive feedback loop with $V_{y1} = 6$, $V_{y2} = 3$ and $K_{y_2x} = 100$. In all situations the values of other parameters are same as in table II.

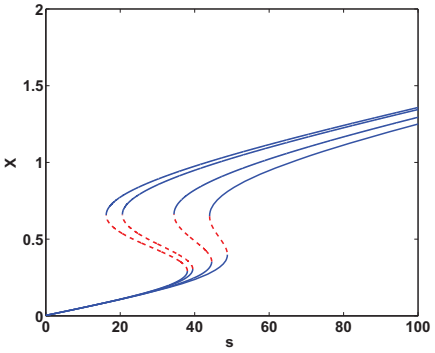

Fig. 4. The strength of the positive feedback loops affect the robustness and flexibility of a bistable switch. The strength of one positive feedback loop V_{y2} is separately 10, 12, 15, 18(from right to left), while the strength of another positive feedback loop V_{y1} is fixed at 3.8. The solid line denotes stable steady state and the dotted line denotes unstable steady state. In all situations the values of other parameters are same as in table II.

switch(reversible switch and irreversible switch). The bistable switch can be reversible or irreversible under different feedback intensity. It is irreversible switch When the strength of positive feedback V_{y2} exceeds a critical value. In many biological progress coupled positive feedback loops act as a bistable switch. For instance, in the progress of B-cell differentiation coupled positive feedback loops act as a bistable switch [14]. And coupled positive feedback loops also act as a bistable switch in *Xenopus oocyte* maturation [5], [15].

B. Coupling-induced robustness and flexibility of bistable switches

In Fig.3 we change the parameter V_{y1} from 3.8 to 6, i.e., the strength of the positive feedback is increasing. In this case, system I also can exhibit bistability. Fig. 3(a) and 3(b) shows the bistable region of system I (only one positive feedback loop) and system II (two coupled positive feedback loops) respectively. It shows that the bistable region increases since we couple a positive feedback loop to system I. This means that coupled positive feedback loops enhance the bistability, i.e., coupled positive feedback loops increase the robustness of the bistable system.

We can also indicate that with the increasing of the strength

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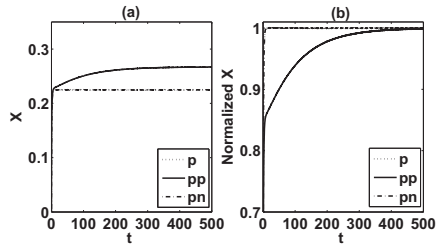

Fig. 5. (a)Response curves of P (one positive feedback loop), PP(two positive feedback loops) and PN (one positive feedback loop and one negative feedback loop). (b)Normalized response curves of P (one positive feedback ,blue line), PP (two positive feedback , red line) and PN (one positive feedback loop and one negative feedback loop).

of the positive feedback the bistability region is expanded (Fig. 4). We change the strength of one positive feedback to explore its effect on bistability while the strength of another positive feedback is fixed at $V_{y1} = 3.8$. With increasing V_{y2}, the bistability regime becomes larger while the upper threshold changes moderately. And When V_{y2} is large enough the coupled system can act as a one-way switch (Fig. 2(d)). It indicates that larger positive feedback intensity makes better robustness of the bistable switch. And we can also flexibly and effectively regulates the switch by changing the strength of the positive feedback. For example in the process of T cell differentiation, T helper cell differentiation is controlled by a complex set of signals including the cytokines made by the T cells themselves. High expression of GATA-3 induce the bifurcation of T cell to Th2. STAT6 activates the expression of GATA-3 and then GATA-3 promotes STAT6. This form a positive feedback loop. And GATA-3 have a direct positive feedback onto themselves [4]. When there is no external signal promote Th2, GATA-3 low expression, only a few cells bifurcate to Th2. when the external promotion of Th2 signal reaches a certain threshold value, causing high GATA-3 expression. So a lot cells bifurcate to Th2. If now we reduce the external signal that promote Th2, GATA-3 expression can still be in the high state until the external signal down to a certain threshold. Here we can control the two threshold by regulating the strength of the positive feedback loops. Once the high GATA-3 expression levels can be sustained entirely by the self-promotion of GATA-3, this process may be irreversible, and we can also say that the coupled strength of the self-promotion of GATA-3 is large enough to induce a irreversible switch.

C. Comparison between different coupling scenarios: P, PN, PP

We know that a single positive feedback loop with ultrasensitivity is sufficient to create bistability [16]. It is intriguing that many biological systems not only have a single positive feedback loop but several coupled positive feedback loops. This raise a question that what advantages of the system with coupled positive feedback loops have.

First, strong positive feedback tends to enhance bistability (Fig. 4). With the increasing of the strength of the positive feedback loops the bistable region is increasing.

Next, in order to investigate the effect of coupled positive feedback loops, we compared the response curves of P (one positive feedback loop), PP (two positive feedback loops) and PN (one positive feedback loop and one negative feedback loop). The system first in a steady state with S = 0. Then we change the stimulus S to 38 and investigate the change of concentration of X when the system reaches a new steady state and it's response time (the time taken for X to reach the 90 percent between its initial and steady-state values). Coupled positive feedback loops can amplify the signal(Fig. 5(a)). Most signaling molecules are find such low concentrations that their effects in the cytoplasm would be minimal unless the signal were amplified. So we can improve the sensitivity of cell to signals through coupling a positive feedback loop. Fig. 5(b) shows the normalized response curves of P, PP and PN. We find that coupled positive feedback loops effectively slow down the system's response speed. Actually, using Matlab we can calculate the response time of P, PP and PN and they are $\tau = 2.10, 49.92, 2.08$, respectively. we can see that PP elongates the time a system needed to arrive at a new steady state. So coupling a positive feedback loop can reduce response speed and induce hysteresis. Such a slow response might be disadvantageous in making an instantaneous decision for critical or lethal stimuli, but it helps to avoid a careless decision, such as those involving cell development and apoptosis [17], [18]. And the irreversible hysteretic switch realized by coupled positive feedback loops play an important role in cell cycle or developmental control [4], [19]–[23].

Another study on the noise robustness of PP shows that coupled positive feedback loops with different feedback reaction speeds can effectively reduce the signal noise [10], [24], [25]. In summary, we found that coupled positive feedback loops can enhance bistability. And coupled positive feedback loops switch is sensitive to stimuli. It also can slow response which can help to avoid a careless decision. Actually, such a PP module is found in networks requiring those characteristics. For instance, PP is found in the muscle-cell-fate specification networks [1], T-cell differentiation (Th1 cell or Th2 cell) network [4], and the cell-cycle start system [26], [27]. Since the cell-fate decision, cell differentiation, and cell-cycle start should be irreversible, their switching mechanisms require strong bistability. Therefore, these systems might have evolutionarily acquired PP [10]. In cell fate decisions positive feedback based memory module is widely exploited [5], [20], [24].

IV. Conclusion

Coupled positive feedback loops have been observed in various biology progress. It is well known that single feedback loop have particular roles. Positive feedback loop can amplify signals, cause bistability or hysteresis, and elongate response time. Such single positive feedback loop might not be sufficient to cope with various environmental changes, and coupled positive feedback structures might thus have emerged as a result of evolution. In this case we investigated the advantage

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of the coupled feedback loops. We have demonstrated that the system with coupled positive feedback loops can act as a tunable switch, which manifests diverse behaviors when the feedback strength is varied. The system undergoes the transition from monostability to bistability through increasing the strength of positive feedback, and the bistability regime can be modulated by the strength of positive feedback. In summary, the system with coupled positive feedback loops is a tunable motif such that the desirable dynamic behavior can be realized by tuning the feedback strength. For instance, coupled positive feedback loops can complete the expected role that a single positive feedback with a mutated node cannot properly carry. We also revealed that coupled positive feedback loops often achieve some properties that can not be found in a signal positive feedback loop. For instance, it can eliminate signal noise effectively. And on the other hand, coupled positive feedback loops strengthen individual feedback loops and enhance the amplification of signal response and bistability.

In this paper, we mainly study the first module of two coupled positive feedback loops. In addition, the other two modules can be similarly discussed. And it's possible to extend our results to a general model with more coupled positive feedback loops.

Biological network is a complex system and in many cases we can not isolate the role of particular coupled positive feedback loops since they are embedded in a large complex circuit. This paper provides us with a hint that we can investigate their hidden role in making up the integrated stimulus-response characteristics. Conversely, we can also infer the global properties of a given biological network by investigating the coupled feedback loops inside. If a network contains many positive feedback loops coupled with each other, we can infer that the system might exhibit strong signal amplification or bistable characteristics.

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