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Bi-functional biochemical networks

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Abstract

Understanding the relationship between the topology of a network and its function remains an important question in biological physics. However, this is not a one-to-one mapping. Often the behavior of a signaling system varies with the input signal it receives. For example, some biological systems show adaptation when they receive a low input signal while they show oscillation with a high input signal. We therefore set out to find all possible two-node and three-node networks that can perform both adaptation and oscillation with transcriptional regulation and enzymatic reactions. For two-node networks, we identified all bi-functional topologies by analyzing the Jacobean matrix. For three-node networks, they were identified by enumeration. We further investigated how the system can be transformed between these two functions. We found that the switching of functions can be achieved through changing anyone of the several key parameters, including the input signal level.

1. Introduction

Biological systems often show qualitatively different responses to quantitatively different external stimuli. Different responses transfer different signals to the downstream signaling pathways, enabling biological systems make decisions to deal with different circumstances. This raises the important question of whether a simple regulatory network can provide different answers in response to different input signals. Research has shown that the dynamics of the yeast *Saccharomyces cerevisiae* transcription factor Msn2 varies with the degree of glucose limitation [1]. Glucose limitation occurs when the nutrient supplier glucose level in the environment is below a normal level. Msn2 concentration in the nucleus oscillates when the yeast is under minor glucose limitation. When glucose limitation becomes more severe, nuclear Msn2 concentration shows a pulse at first but returns to the prestimulus level. Another example is the single-cell organism amoeba *Dictyostelium discoideum*. During starvation, the amoeba begins to produce cAMP when it is stimulated by extracellular cAMP. The amoeba shows a different response to different levels of extracellular cAMP during the process of starvation [2]. In detail, when an amoeba is stimulated by a high concentration of external cAMP, intracellular cAMP shows oscillation. Conversely, when an amoeba is stimulated by a low concentration of external cAMP, intracellular cAMP shows an initial pulse, but it returns to the prestimulus level, which can be viewed as adaptation.

Motivated by these observations, we considered whether these two different behaviors could occur in a simple regulatory network, i.e. whether a simple network topology can perform two different functions. Previous studies have shown the relationship between a network topology and its function is not a one-to-one mapping [3–8]. On the one hand, some different network topologies perform the same function. For example, both negative feedback loop (NFL) and incoherent feedforward loop can cause a biological system to exhibit adaptation [9]. On the other hand, some network topologies can perform more than one function. The NFL in the cell cycle system induces oscillation (figure 1(a)) while the NFL in bacterial chemotaxis system induces adaptation (figure 1(b)) [6, 10–12].

In this study, we focused on two well-studied functions—adaptation [9, 13] and oscillation [6, 10, 14–16], which are commonly found in signaling systems, such as the p53 [17], Msn2 and cAMP signaling pathways. We systematically searched for two-node and three-node network topologies capable of adaptation and oscillation in the conditions of transcriptional

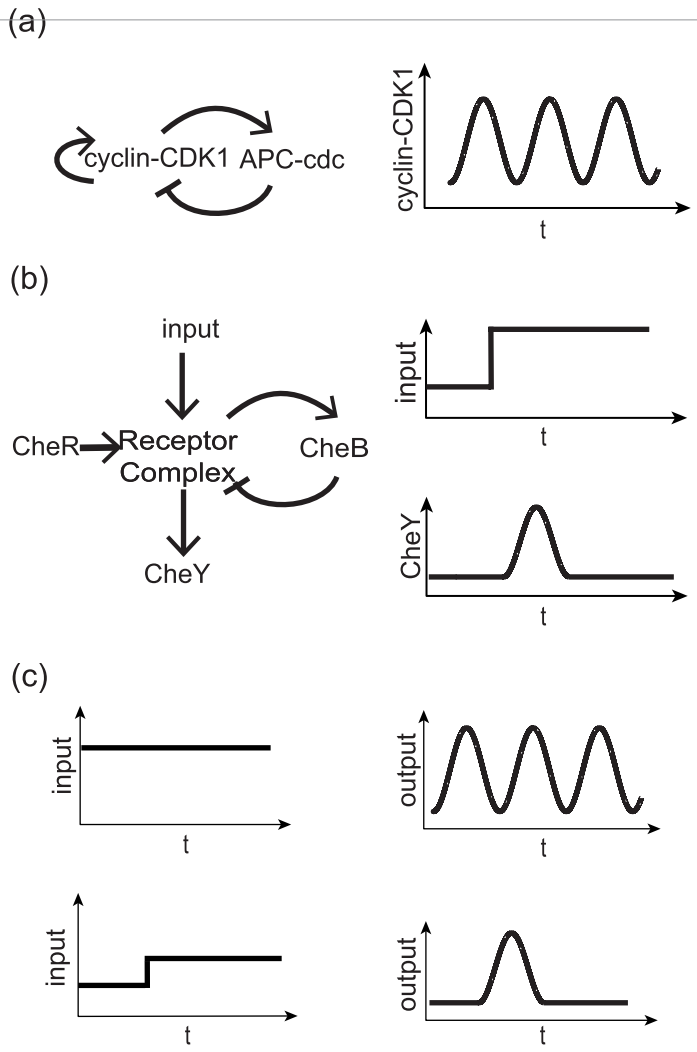

Figure 1. The relationship between network topology and its functions. (a) Negative feedback loop in cell cycle system induces oscillation. (b) Negative feedback loop in chemotaxis system induces adaptation to the input signal. (c) Search for network topologies capable of adaptation and oscillation. The transition between the two functions can be achieved by changing parameters or inputs (shown here).

regulation and enzymatic reactions. Then, we investigated the transition between these two functions (figure 1(c)).

2. Model construction

As in many previous studies of biological signaling systems and networks, we used ordinary differential equations to model the dynamics of networks or circuits [18, 19]. For the transcriptional regulatory networks (TRNs), each node stands for a transcriptional gene product which itself is a transcription factor. Transcription factors bind to regulatory sequences of the target genes to modulate their transcriptional activity. A transcriptional factor could up regulate (activation) or down regulate (inhibition) its target gene. The linkages between nodes represent the corresponding regulation and are modeled with the Hill function [18]. We used AND logic to represent the interaction, which means that gene expression is only turned on when all the activators are at high concentrations and the repressors are at low concentrations [13].

For the enzymatic regulatory networks (ERNs), each node stands for an enzyme and the interactions (links) between nodes represent some catalytic reactions, such as phosphorylation, dephosphorylation, methylation, ubiquitination, etc. An enzyme (node) can also be a substrate of other enzymes (including itself) and its activity can be activated or inhibited by other nodes. We modeled the networks of the enzymatic regulation with Michaelis–Menten rate equations [18]. Each node in the model represents an enzyme and it is interconvertable between an active and an inactive state. These states have a fixed total concentration, so variable A represents the active concentration of node A while $(1 - A)$ represents the inactive concentration of node A. We assume that all enzymatic reactions are reversible in the enzymatic network we consider (otherwise, it may evolve to an absorbing 'dead' state). Biologically, for example, when a substrate is phosphorylated by an enzyme, in most cases it could also be dephosphorylated by another enzyme. So, if in a network the reverse reaction is not apparent for a node (manifested as the node only have positive or negative links pointing to it from other nodes), we

assume that there is an additional link from a basal or background enzyme F to do the (constant) reverse reaction [9].

3. Results

3.1. Two-node bi-functional topologies with transcriptional regulation

Adaptation means that the system can respond to changes in external stimulus but return to the previous output level, even when the stimulus change persists. If the output returns to (almost) exactly the same level as before, it is called perfect adaptation. Here we focus on perfect adaptation, as both its definition and theoretic analysis are clear. We started by searching for the simplest two-node networks capable of achieving perfect adaptation and oscillation. Adaptation requires that the system has a stable fixed point (steady state) and that the value of the output node at the steady state is independent of the input level [9]. The simplest way to oscillate, starting from a stable fixed point, is the emergence of a stable limit cycle, resulting from a Hopf bifurcation [6, 15, 20, 21]. Our method was to analyze the Jacobean matrix to find the conditions for perfect adaptation and Hopf bifurcation.

Assume that node A receives the input signal I. Changing the input from I to $I+\Delta I$ and expanding the equations around the fixed point [9],

$$\frac{dA}{dt}=f(A,B,I)=0,\quad \frac{dB}{dt}=g(A,B)=0, \tag{1}$$

$$\begin{pmatrix}\frac{\partial f}{\partial A} & \frac{\partial f}{\partial B}\\ \frac{\partial g}{\partial A} & \frac{\partial g}{\partial B}\end{pmatrix}\begin{pmatrix}\Delta A\\ \Delta B\end{pmatrix}=-\begin{pmatrix}\frac{\partial f}{\partial I}\\ 0\end{pmatrix}\Delta I, \tag{2}$$

or

$$\begin{aligned}\frac{\partial f}{\partial A}\Delta A+\frac{\partial f}{\partial B}\Delta B+\frac{\partial f}{\partial I}\Delta I=0,\\ \frac{\partial g}{\partial A}\Delta A+\frac{\partial g}{\partial B}\Delta B=0.\end{aligned} \tag{3}$$

We have

$$\frac{\Delta A}{\Delta I}=\frac{\frac{\partial f}{\partial I}\frac{\partial g}{\partial B}}{|J|},\ \frac{\Delta B}{\Delta I}=\frac{-\frac{\partial f}{\partial I}\frac{\partial g}{\partial A}}{|J|}, \tag{4}$$

where J is the Jacobean matrix $\begin{pmatrix}\frac{\partial f}{\partial A} & \frac{\partial f}{\partial B}\\ \frac{\partial g}{\partial A} & \frac{\partial g}{\partial B}\end{pmatrix}$ and $|J|=\left(\frac{\partial f}{\partial A}\frac{\partial g}{\partial B}-\frac{\partial f}{\partial B}\frac{\partial g}{\partial A}\right)$ its determinant.

As node A receives the input signal, $\frac{\partial f}{\partial I}\neq 0$. $\frac{\partial g}{\partial A}$ represents the interaction between the two nodes (signal transduction from node A to node B), so $\frac{\partial g}{\partial A}\neq 0$ and thus $\Delta B\neq 0$. Therefore, if perfect adaptation could be achieved in a two-node network, it can only happen on node A ($\Delta A=0$), and with the condition $\frac{\partial g}{\partial B}=0$ (equation (4)). For transcriptional regulation, the rate equation of node B is $g(A, B)$ = production term—degradation term = production term—b_2B, where b_2 is the degradation rate. In order to satisfy $\frac{\partial g}{\partial B}=0$, the node B should activate itself (i.e. the production term should have a positive dependence on B) to make up for the degradation. Furthermore, for the fixed point to be stable, the sign of $Tr(J)=\left(\frac{\partial f}{\partial A}+\frac{\partial g}{\partial B}\right)$should be negative and $|J|=\left(\frac{\partial f}{\partial A}\frac{\partial g}{\partial B}-\frac{\partial f}{\partial B}\frac{\partial g}{\partial A}\right)$should be positive. Combined with the condition $\frac{\partial g}{\partial B}=0$, this means that the sign of $\frac{\partial f}{\partial A}$ should be negative and the sign of $\left(\frac{\partial f}{\partial B}\frac{\partial g}{\partial A}\right)$should also be negative. So a NFL is necessary for adaptation. Thus, for a two-node network to achieve perfect adaptation, (1) the node that receives the input signal should also be the output; (2) the other node should have self-activation; and (3) there should be a NFL between the two nodes. The topologies satisfying the three requirements are shown in figure 2(a) [13]. As far as the signs of the Jacobean matrix elements are concerned, it is easy to see that there are two kinds of Jacobean matrix for adaptation:

$$\begin{bmatrix}-&+\\ -&0\end{bmatrix}\quad\text{and}\quad\begin{bmatrix}-&-\\ +&0\end{bmatrix}.$$

Let us take the topology in figure 2(b) as an example and carry out the linear stability analysis. The dynamic equations are:

$$\begin{aligned}\frac{dA}{dt}&=f(A,B,I)=-b_1A+\frac{I{k_1}^{n_1}}{{k_1}^{n_1}+B^{n_1}},\\ \frac{dB}{dt}&=g(A,B)=-b_2B+\frac{a{A}^{n_2}}{{k_2}^{n_2}+A^{n_2}}\frac{B^{n_3}}{{k_3}^{n_3}+B^{n_3}}.\end{aligned} \tag{5}$$

The transcriptional regulation is modeled with Hill functions. Each link has two parameters: the Hill coefficient n and the half activation (inhibition) k. b_1 and b_2 represent the degradation rate of node A and node B respectively. a represents the maximum transcription rate of node B. The input signal acts on node A and takes a linear form for simplicity (the form of the input signal did not affect the results). The output (readout) of the system is the level of A. The Jacobean matrix is

$$\begin{pmatrix}\frac{\partial f}{\partial A}\frac{\partial f}{\partial B}\\ \frac{\partial g}{\partial A}\frac{\partial g}{\partial B}\end{pmatrix}=\begin{bmatrix}-b_1 & \frac{-I{k_1}^{n_1}n_1B^{n_1-1}}{({k_1}^{n_1}+B^{n_1})^2}\\ \frac{a_2n_2A^{n_2-1}{k_2}^{n_2}}{({A}^{n_2}+{k_2}^{n_2})^2}\frac{B^{n_3}}{(B^{n_3}+{k_3}^{n_3})} & -b_2+\frac{a_2A^{n_2}}{A^{n_2}+{k_2}^{n_2}}\frac{n_3B^{n_3-1}}{(B^{n_3}+{k_3}^{n_3})^2}\end{bmatrix},$$

with the signs of its elements

$$\text{Sign}\begin{pmatrix}\frac{\partial f}{\partial A}\frac{\partial f}{\partial B}\\ \frac{\partial g}{\partial A}\frac{\partial g}{\partial B}\end{pmatrix}=\begin{bmatrix}-&-\\ +&\text{uncertain}\end{bmatrix}. \tag{6}$$

The system can achieve perfect adaptation if $\frac{\partial g}{\partial B}=0$ at the fixed point. This condition can be satisfied if the Hill coefficient $n_3=1$ and $k_3\gg B^*$ (* denotes steady state). In this case, equation (5) can be simplified to

$$\begin{aligned}\frac{dA}{dt}&=f(A,B,I)=-b_1A+\frac{I{k_1}^{n_1}}{{k_1}^{n_1}+B^{n_1}},\\ \frac{dB}{dt}&=g(A,B)=-b_2B+\frac{a{A}^{n_2}}{{k_2}^{n_2}+A^{n_2}}\frac{B}{k_3}.\end{aligned} \tag{7}$$

The steady state of A is:

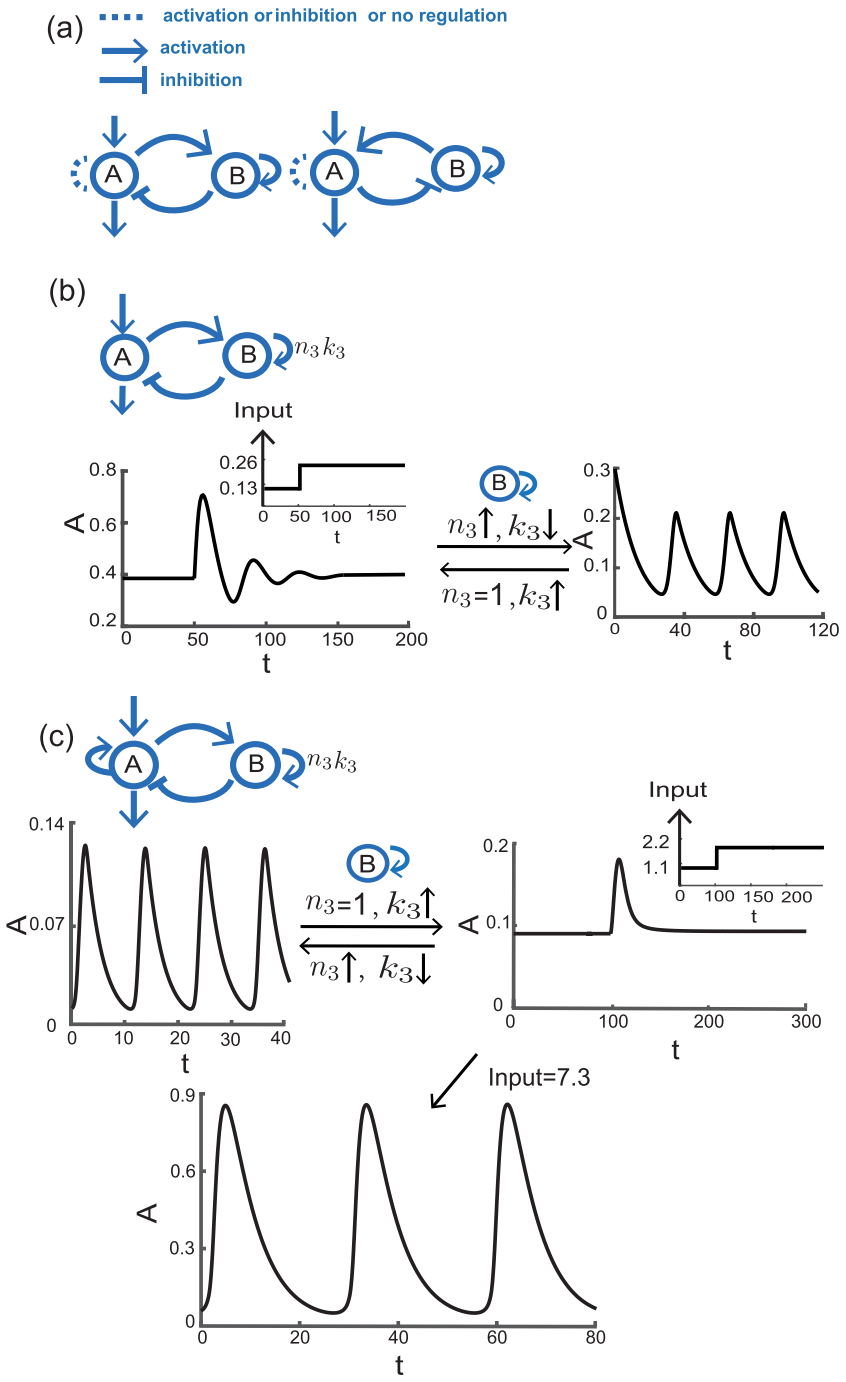

Figure 2. Two-node bi-functional networks with transcriptional regulation. (a) Six two-node network topologies could perform both adaptation and oscillation. Note that the dotted line on node A represents three possible regulations of node A on itself: activation, inhibition or no regulation. All three are allowed in the bi-functional network, so every motif stands for three topologies. (b) An example network. It can switch between the two functions by changing parameters on node B in the direction indicated. (c) An example in which adaptation can be transformed to oscillation in two different ways: parameter changes and input change.

$$A^* = k_2\left(\frac{k_3 b_2}{a - k_3 b_2}\right)^{\frac{1}{n_2}}. \tag{8}$$

This means that the steady state concentration of node A depends only on the parameters and not on the input signal. In other words, when the input signal changes, the output (node A) would return to the same previous value after a transient response (figure 2(b)) [9, 13].

We now proceed to identify the requirements for oscillation. The nonlinear dynamics analysis tells us that a stable limit cycle will emerge if the sign of $Tr(J) = \left(\frac{\partial f}{\partial A} + \frac{\partial g}{\partial B}\right)$ changes from negative to positive and the sign of the $|J| = \left(\frac{\partial f}{\partial A}\frac{\partial g}{\partial B} - \frac{\partial f}{\partial B}\frac{\partial g}{\partial A}\right)$ is positive. According to this rule, there are eight kinds of Jacobean matrixes that Hopf bifurcation could happen [6].

$$\begin{bmatrix} + & + \\ - & - \end{bmatrix}, \begin{bmatrix} - & + \\ - & + \end{bmatrix}, \begin{bmatrix} + & - \\ + & - \end{bmatrix}, \begin{bmatrix} - & - \\ + & + \end{bmatrix},$$
$$\begin{bmatrix} adjustable & + \\ - & 0 \end{bmatrix}, \begin{bmatrix} 0 & + \\ - & adjustable \end{bmatrix}, \begin{bmatrix} adjustable & - \\ + & 0 \end{bmatrix}, \begin{bmatrix} 0 & - \\ + & adjustable \end{bmatrix}.$$

The sign of $\left(\frac{\partial f}{\partial B}\frac{\partial g}{\partial A}\right)$ cannot be zero because $\frac{\partial f}{\partial B}$ and $\frac{\partial g}{\partial A}$ depict the interaction between the two nodes A and B. Thus, for Hopf bifurcation to happen, the sign of $\frac{\partial f}{\partial B}$should be always opposite to the sign of $\frac{\partial g}{\partial A}$, which means that a NFL is necessary for oscillation.

Note that the sign of a Jacobean matrix element is determined by the specific interaction between the two corresponding nodes or self-loop (see table S1 in supplemental information (stacks.iop.org/Phys-Bio/16/016001/mmedia)). It is easy to see that all six two-node topologies that can perform adaptation have the potential to oscillate through a Hopf bifurcation (figure 2(a)).

3.2. Transition between adaptation and oscillation in two-node TRNs

We next investigated the transition between the two functions. Specifically, starting with a topology that can achieve adaptation, how can one induce a Hopf bifurcation so that the same topology will perform oscillation. From the above analyses of the signs of Jacobean matrix for both adaptation and Hopf bifurcation, we conclude that the possible ways of changing from adaptation to oscillation are

$$\begin{bmatrix} -+ \\ -\ 0 \end{bmatrix} \to \begin{bmatrix} ++ \\ -\ 0 \end{bmatrix}, \begin{bmatrix} -+ \\ -\ 0 \end{bmatrix} \to \begin{bmatrix} -+ \\ -+ \end{bmatrix}, \begin{bmatrix} -+ \\ -\ 0 \end{bmatrix} \to \begin{bmatrix} ++ \\ -+ \end{bmatrix},$$
$$\begin{bmatrix} -- \\ +\ 0 \end{bmatrix} \to \begin{bmatrix} +- \\ +\ 0 \end{bmatrix}, \begin{bmatrix} -- \\ +\ 0 \end{bmatrix} \to \begin{bmatrix} -- \\ ++ \end{bmatrix}, \begin{bmatrix} -- \\ +\ 0 \end{bmatrix} \to \begin{bmatrix} +- \\ ++ \end{bmatrix}. \quad (9)$$

Again, taking the topology depicted in figure 2(b) as an example, we illustrate how the transition from adaptation to oscillation can happen. As discussed above, the signs of the Jacobean matrix elements for adaptation are $\begin{bmatrix} -- \\ +0 \end{bmatrix}$. One way to change the system from adaptation to oscillation is to make the Jacobean matrix changing from $\begin{bmatrix} -- \\ +\ 0 \end{bmatrix}$to $\begin{bmatrix} -- \\ +\ + \end{bmatrix}$ (equation (9)) and to also satisfy the condition $\left|\frac{\partial g}{\partial B}\right| > \left|\frac{\partial f}{\partial A}\right|$. This can be accomplished by changing the parameter of node B, n_3 and k_3, as shown in figure 2(b).

We are particularly interested in the case in which change of the input level can induce the transition, as this is the case often seen biologically. From equation (9) and the relationship between the regulation type and the sign of Jacobean matrix element (table S1), we conclude that the two topologies that have self-activation on node A can switch between the two functions by only changing the input signal level, which correspond to the Jacobean matrix changing from $\begin{bmatrix} -- \\ +0 \end{bmatrix}$ to $\begin{bmatrix} +\ - \\ +\ 0 \end{bmatrix}$ or from $\begin{bmatrix} -\ + \\ -\ 0 \end{bmatrix}$ to $\begin{bmatrix} +\ + \\ -\ 0 \end{bmatrix}$. Figure 2(c) shows an example of one such topology for which the transitions can be induced by changing either from $\begin{bmatrix} -\ - \\ +\ 0 \end{bmatrix}$ to $\begin{bmatrix} -\ - \\ +\ + \end{bmatrix}$ (through parameter changes), or from $\begin{bmatrix} -\ - \\ +\ 0 \end{bmatrix}$to $\begin{bmatrix} +\ - \\ +\ 0 \end{bmatrix}$(through input level change).

3.3. Three-node bi-functional topologies with transcriptional regulation

As it is difficult to exhaustively analyze all three-node networks by analytic means, we numerically studied all possible three-node topologies to identify those capable of oscillation and adaptation with transcriptional regulation. Each topology can be represented by a 3×3 matrix, in which the elements represent the type of links (regulations) between the nodes. Each element can be assigned to a value 0 (no regulation), 1 (positive regulation) or -1 (negative regulation). Taking into account of symmetry considerations and the fact that there should be at least one pathway from input to output, there are a total of 16 038 distinct topologies to be considered [9]. For each topology, we wrote down the differential equations as described in section 2 and simulated its dynamics with 1 000 000 sets of parameters sampled via Latin hypercube sampling method [22]. We found 398 topologies that can perform both functions by certain criteria (details in supplemental information) [9]. We found that the networks perform the two functions in two ways. One is by using the same structure, while the other is to use two different substructures in a network, each satisfying one of the two functions. Based on these two strategies, we divided the 398 topologies into two groups. One is the NFL group, which include 206 topologies that achieved both adaptation and oscillation through a

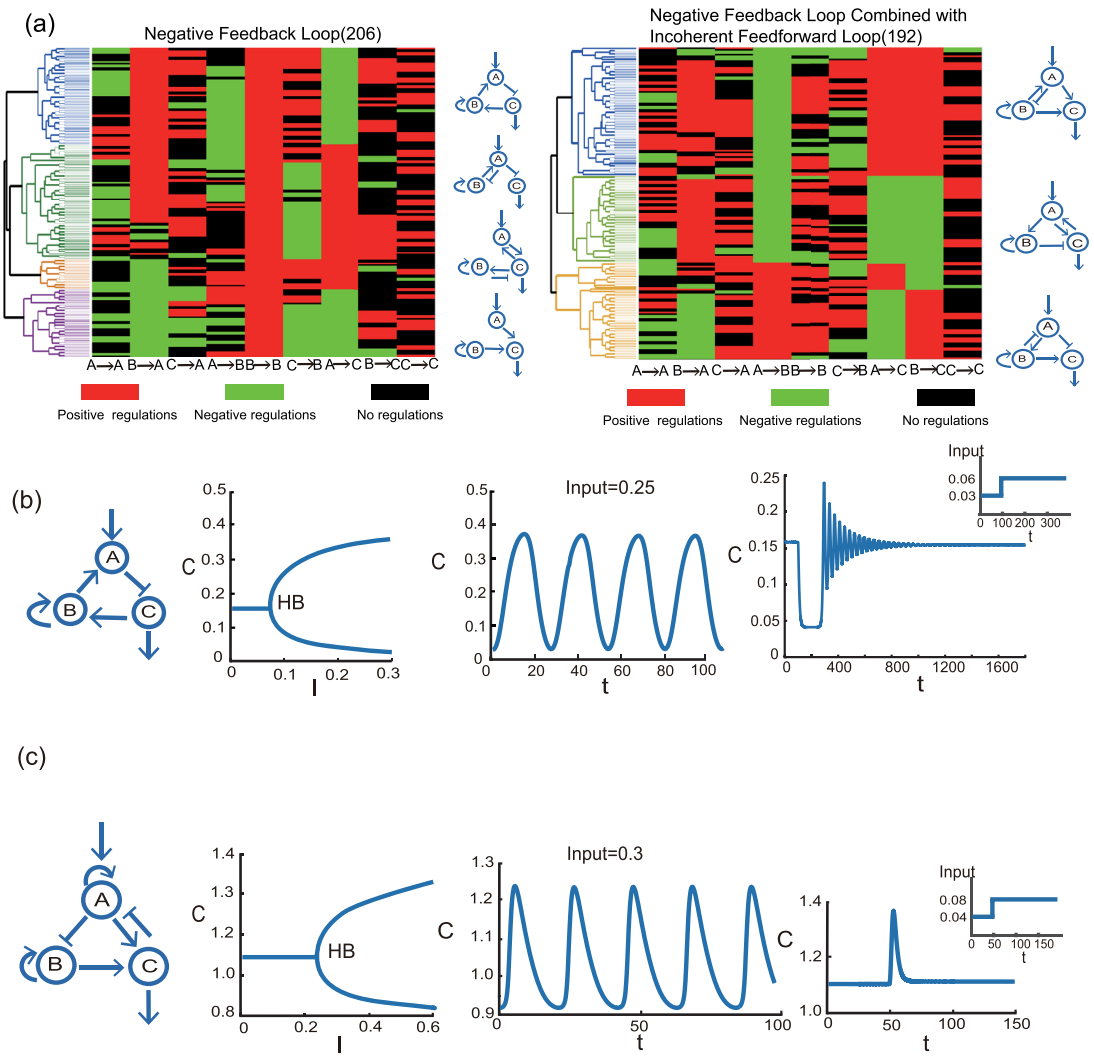

Figure 3. Three-node bi-functional topologies with transcriptional regulation. In our model, input is acting on node A and output is the level of node C. (a) The bi-functional topologies can be divided into two groups, which are separately clustered to identify common features shown on the right of each group. Red lines represent positive regulation, green lines negative regulation and black lines no regulation. (b) An example in the NFL group. The function can be transformed by changing input signal, which induces a Hopf bifurcation. The bifurcation diagram along with the examples of dynamic trajectories of the node C is also shown. (c) The same as (b), but for an example in the NFIFL group.

NFL. The other group has a NFL combined with an incoherent feedforward loop (NFIFL), which include 192 topologies (figure 3(a)). In the NFIFL group, the NFL is for oscillation and the incoherent feedforward loop is for adaptation.

3.4. Transition between adaptation and oscillation in three-node TRNs

We investigated how the networks transform between these two functions by analyzing specific examples belonging to the NFL and NFIFL groups. For the example from the NFL group shown in figure 3(b), the rate equations are

$$\begin{aligned}\frac{dA}{dt} &= -b_1A + \frac{IB^{n_1}}{{k_1}^{n_1}+B^{n_1}},\\ \frac{dB}{dt} &= -b_2B + \frac{a_1C^{n_2}}{C^{n_2}+{k_2}^{n_2}}\frac{B^{n_3}}{B^{n_3}+{k_3}^{n_3}},\\ \frac{dC}{dt} &= -b_3C + \frac{a_2{k_4}^{n_4}}{{k_4}^{n_4}+A^{n_4}}.\end{aligned} \tag{10}$$

Analysis of the rate equation of node B shows that when $n_3 = 1$ and $k_3 \gg B^*$, the steady state of node C can be simplified to:

$$C^* = k_2\left(\frac{b_2k_3}{a_1 - b_2k_3}\right)^{\frac{1}{n_2}}. \tag{11}$$

The concentration of the output node would remain constant independent of the input level I, which is a necessary condition for perfect adaptation. Next, we considered the transition of the system from adaptation to oscillation. We found that many parameters could induce Hopf bifurcation. An example of the transition induced by the input signal level is shown in figure 3(b). When the input signal is low, the system shows adaptation. When the input signal is increased, the system oscillates.

For the NFIFL group, an example is shown in figure 3(c) with the following rate equations

$$\begin{aligned}\frac{dA}{dt} &= -b_1A + \frac{IA^{n_1}{k_{13}}^{n_2}}{({k_{11}}^{n_1}+A^{n_1})(C^{n_2}+{k_{13}}^{n_2})},\\ \frac{dB}{dt} &= -b_2B + \frac{a_1{k_{21}}^{n_4}B^{n_3}}{(A^{n_4}+{k_{21}}^{n_4})(B^{n_3}+{k_{22}}^{n_3})},\\ \frac{dC}{dt} &= -b_3C + \frac{a_2A^{n_5}B^{n_6}}{({k_{31}}^{n_5}+A^{n_5})({k_{32}}^{n_6}+B^{n_6})}.\end{aligned} \tag{12}$$

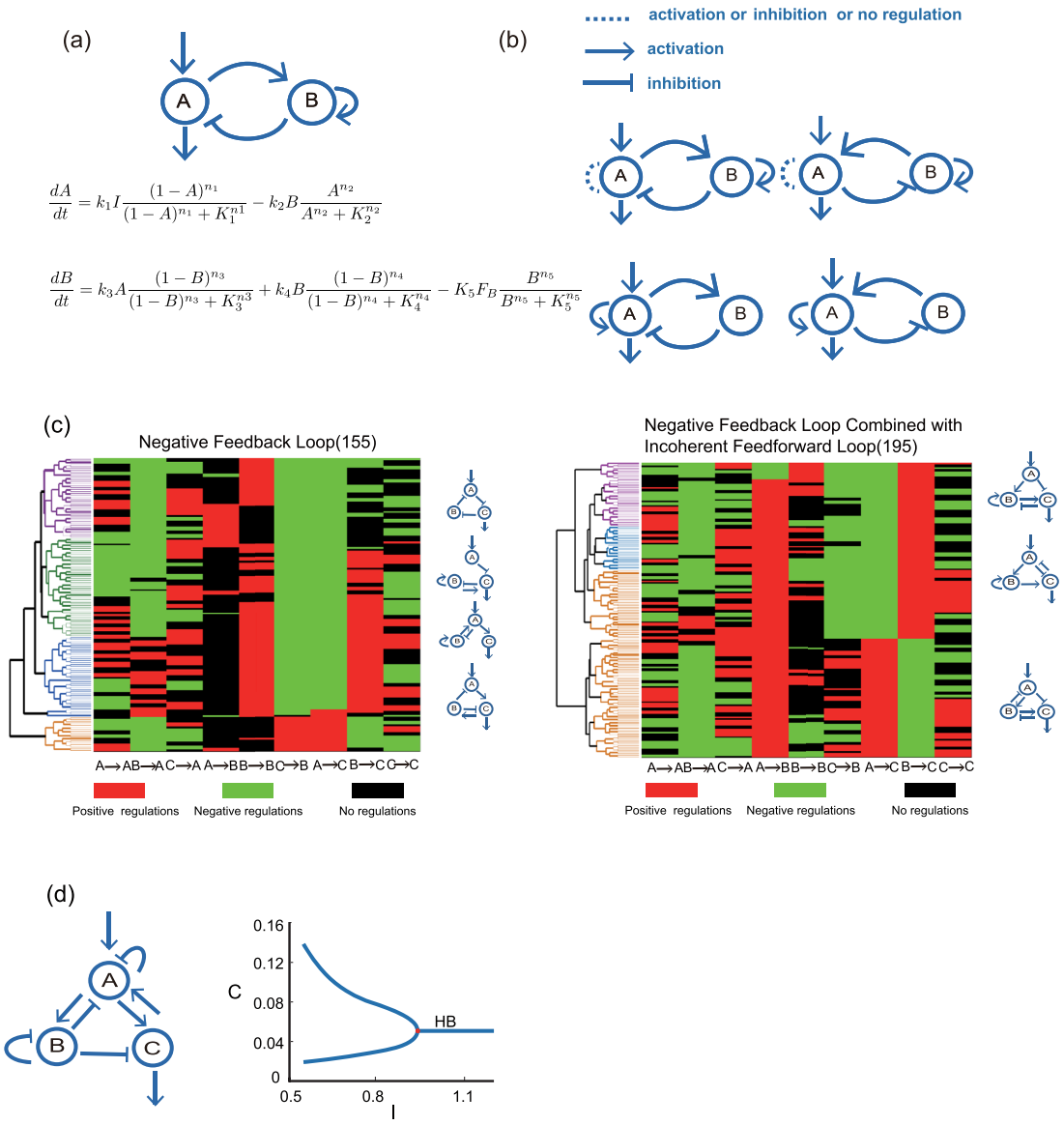

Figure 4. Bi-functional topologies with enzymatic regulation. (a) An example network. The enzymatic regulation is modeled with Michaelis–Menten rate equation. (b) Eight two-node enzymatic bi-functional topologies. Note that the dotted line on node A represents three possible regulations of node A on itself: activation, inhibition or no regulation. All three are allowed in the bi-functional network. (c) Three-node bi-functional topologies can be divided into two groups, which are clustered separately. (d) An example in the NFIFL group. The function can be transformed by changing input signal, which induces a Hopf bifurcation. The bifurcation diagram is also shown.

When the parameters meet the requirements: $k_{22} \ll B^*, k_{21} \ll A^*, k_{31} \gg A^*, k_{32} \gg B^*$, equation (12) can be simplified to

$$\begin{aligned} \frac{dA}{dt} &= -b_1 A + \frac{I A^{n_1} {k_{13}}^{n_2}}{({k_{11}}^{n_1} + A^{n_1})(C^{n_2} + {k_{13}}^{n_2})}, \\ \frac{dB}{dt} &= -b_2 B + \frac{a_1 {k_{21}}^{n_4}}{A^{n_4}}, \\ \frac{dC}{dt} &= -b_3 C + \frac{a_2 A^{n_5} B^{n_6}}{{k_{31}}^{n_5} {k_{32}}^{n_6}}. \end{aligned} \tag{13}$$

The steady state of node C is:

$$C^* = \frac{a_2}{b_3 k_{31}^{n_5} k_{32}^{n_6}} \left(\frac{a_1 k_{21}^{n_4}}{b_2} \right)^{n_6}. \tag{14}$$

C^* is independent of the input level I. Therefore, the system is capable of adaptation to the input. With these requirements for the parameters, changing any one of multiple parameters can induce Hopf bifurcation. Switching between the two functions via changing the input signal level is shown in figure 3(c).

3.5. Bi-functional topologies with enzymatic regulation

We used the same methods to identify the bi-functional topologies in ERNs (figure 4(a)). We found eight two-node topologies that can perform the two functions (figure 4(b)) (details in Supplemental Information). Two more bi-functional network topologies appeared for enzymatic networks (figure 4(b)) compared with transcriptional networks (figure 2(a)). This is due to the different interaction forms of the two types of regulation, which result in different kinds of Jacobean matrix elements. The correspondence tables between

regulation links and the signs of the matrix elements can be found in table S2 in supplemental information. For three-node enzymatic networks, we enumerated all topologies and numerally studied them using the same method as for the transcriptional networks. We found that 350 of them can exhibit oscillation and adaptation. All three-node bi-functional topologies (155 topologies in the NFL group and 195 topologies in the NFIFL group) are shown in figure 4(c).

3.6. Transition between adaptation and oscillation in ERNs

Similar to the transcriptional networks, the mechanism to induce transition between the two functions in enzymatic networks is Hopf bifurcation. For the two-node topologies, the transition between the two functions depends on the sign of Jacobean matrix elements. Perfect adaptation requires $\frac{\partial g}{\partial B} = 0$, and transition to oscillation can be induced by Hopf bifurcation. Eight two-node topologies shown in figure 4(b) can all switch between oscillation and adaptation by changing the sign of $\frac{\partial g}{\partial B}$ and/or the input level (details in Supplemental Information). For the three-node topologies, an example from the NFIFL group is shown in figure 4(d), in which the input signal induces the Hopf bifurcation.

3.7. Different features of the bi-functional topologies between transcriptional and enzymatic networks

In agreement with previous works [9, 13], we found two significant differences in topologies of TRNs and ERNs.

(1) An auto-activation on the node B is necessary for the NFL group in TRNs but it is not necessary for the NFL group in ERNs (figures 3(a) and 4(c)).
(2) The direct regulation that node C received should have opposite sign for the NFIFL group in ERNs, while this rule is not compulsory for the NFIFL group in TRNs (figures 3(a)] and 4(c)).

These differences are due to the different regulatory forms of transcriptional and enzymatic regulations.

4. Summary

In this study, we focused on two well-studied functions, adaptation and oscillation, and investigated simple networks that can perform both functions. We identified all two-node and three-node bi-functional topologies with transcriptional and enzymatic regulations. We found that the transformation between the two functions is achieved by Hopf bifurcation. The bifurcation can be induced by changing network parameters. Importantly, for certain topologies the switch of the functional behavior can also be accomplished by changing the input level, which is the hallmark of some biological signaling systems. Interestingly, the three-node networks can be divided into two groups according to their strategy to be bi-functional. One is similar to the two-node networks, in that they achieve both functions using the same NFL. The other achieves the two functions using two motifs: a NFL for oscillation and an incoherent feedforward loop for adaptation.

There are plenty of biological examples in which the system demonstrates bi- or multi-functionality. The two examples mentioned in the INTRODUCTION, that of the yeast [1] and amoeba [2], are examples of changing input leading to changes in network dynamics. On the other hand, in the tumor suppressor p53 network of mammalian cells it was shown that suppression of a negative feedback between Wip1 and ATR in the UV pathway is sufficient to change the p53 dynamics from oscillation to adaptation [23], suggesting that switching of function can be achieved by changing network parameters. Note that the different network dynamics not only code for different environmental information but often lead to different fates of the cell, highlighting its biological importance [1, 17, 24].

The bi-functional networks we identified have rather simple topologies with clear parameter requirements. It should not be very difficult to synthesize them. In a broader context, it would be desirable to further investigate other bi- or multi-functional networks in terms of mechanism, biological significance, and issues such as evolvability, compatibility and trade-offs [25, 26].

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