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Relations between the conditions of admitting cycles in Boolean and ODE network systems

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(Communicated by Richard Rebarber)

This paper is dedicated to our dear friend Professor Kiran Chilakamarri who passed away due to a sudden illness in 2015.

Boolean (BL) systems and coupled ordinary differential equations (ODEs) are popular models for studying biological networks. BL systems can be set up without detailed reaction mechanisms and rate constants and provide qualitatively useful information, but they cannot capture the continuous dynamics of biological systems. On the other hand, ODEs are able to capture the continuous dynamic features of biological networks and provide more information on how the activities of components depend on other components and parameter values. However, a useful coupled ODE model requires details about interactions and parameter values. The introduction of the relationships between the two types of models will enable us to leverage their advantages and better understand the target network systems. In this paper, we investigate the relations between the conditions of the existence of limit cycles in ODE networks and their homologous discrete systems. We prove that for a single feedback loop, as long as the corresponding governing functions of the homologous continuous and discrete systems have the same upper and lower asymptotes, the limit cycle borne via Hopf bifurcation corresponds to the cycle of the discrete system. However, for some coupled feedback loops, besides having the same upper and lower asymptotes, parameters such as the decay rates also play crucial roles.

1. Introduction

Since the end of twentieth century, due to dramatic advances in technology, biological networks such as gene regulatory networks, protein interaction networks, biochemical reaction networks and neuronal networks have attracted attention from

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many different research fields. Mathematical models have shown to be indispensable tools for investigating mechanisms behind biological phenomena. Network systems are often represented by directed graphs, wherein components are represented by nodes and interactions by arrows. Among various modeling frameworks, coupled differential equations (ODEs) and Boolean (BL) networks are popular for modeling regulatory networks.

An n-node BL network is a discrete dynamical system with the form

$$x_i(t+1) = f_i(x_1(t), x_2(t), \ldots, x_n(t)), \tag{1.1}$$

where x_i is the state variable of the i-th node and f_i is a BL function with the value being either 0 or 1. Since the seminal work of Kauffman [1969], BL networks have been widely used to model biological regulatory networks [Campbell et al. 2011; Thakar et al. 2012; Li et al. 2006; Saez-Rodriguez et al. 2007; Sánchez and Thieffry 2001; Albert and Othmer 2003; Espinosa-Soto et al. 2004; Albert and Wang 2009; Abou-Jaoudé et al. 2009; Glass and Kauffman 1973]. They can be set up in situations where the detailed kinetic characterization of interaction is not available and provide valuable insights [Saadatpour et al. 2013; Glass and Kauffman 1973; Snoussi 1989; Thomas and D'Ari 1990; Edwards and Glass 2000; Edwards et al. 2001; Veliz-Cuba et al. 2014]. However, BL systems cannot faithfully represent the dynamics of biological networks that evolve continuously in time [Tyson and Novák 2010].

An n-node ODE network has the form

$$\dot{x}_i = F_i(x_1, x_2 \ldots, x_n), \quad i = 1, 2, \ldots, n,$$

where x_i is the state variable of the i-th node and F_i describes how x_i depends on other variables. Many researchers have used the ODE framework to study biological network systems [Tyson et al. 2001; 2003; Mogilner et al. 2006; Aldridge et al. 2006; Turner et al. 2010]. Compared with BL models, ODE systems are able to capture the continuous dynamic feature of biological networks and provide more information on how the activities of components depend on other components and parameter values. However, it requires detailed information on interactions and parameter values to set up a useful model.

Often, main dynamical features can be captured by both ODE and BL models [Davidich and Bornholdt 2008; Wittmann et al. 2009; Veliz-Cuba et al. 2014; Abou-Jaoudé et al. 2009; Ouattara et al. 2010]. Given a network, the two different types of models are subject to the same set of constraints resulting from the network structure. This leads to the expectation that their dynamics are closely related as shown in many instances [Abou-Jaoudé et al. 2009; Ouattara et al. 2010; Glass and Kauffman 1973; Veliz-Cuba et al. 2012; 2014; Wittmann et al. 2009; Mendoza and Xenarios 2006; Snoussi 1989]. It was proved under certain conditions that if a continuous network model is monotonic, has distinct upper and lower asymptotes and has appropriate parameter values corresponding to its discrete homologue, then they may have the same set of stable steady-states, or at least a stable steady-state in the BL network implies a stable steady-state in the homologous continuous one [Glass and Kauffman 1973; Veliz-Cuba et al. 2012; Wittmann et al. 2009; Mendoza and Xenarios 2006; Snoussi 1989]. Glass and Kauffman [1973] also showed that when each node received only one input from other nodes, then a stable limit cycle gives a stable cycle in the BL system. However, the relations between the cycles of ODEs and BL models are still not clear.

To address this issue, we study the relations between the conditions needed to have a cycle in BL networks and those in their homologous ODE networks. Instead of depending on specific reaction mechanisms and rate constants, the ODE systems we consider here are rather qualitative. In this way, we can focus on the differences of the dynamics due to the contrast between discreteness and continuity. More specifically, the ODE network systems we are interested in are in the form

$$\dot{x}_i = \gamma_i\left(\frac{1}{1+e^{-\sigma_i(a_i+\sum_j v_{ij}x_j)}} - x_i\right), \tag{1.2}$$

where $i \in \{1, \dots, n\}$, γ_i, σ_i and a_i are constants, as well as $v_{ij} = \alpha_{ij} - \beta_{ij}$ ($\alpha_{ij} \geq 0, \beta_{ij} \geq 0$). Here α_{ij} is the activating coupling from node j to node i, and β_{ij} is the inhibitory coupling from node j to node i. *If the coupling from node j to node i is positive then $v_{ij} = \alpha_{ij}$ and if the coupling is negative, then $v_{ij} = -\beta_{ij}$.* Throughout this paper, we assume that there is no self-regulation, i.e., we assume that $v_{ii} = 0$. This type of ODE system was first used by Reinitz et al. [1991] to model gene regulatory networks and then employed by Tyson et al. [2010] to study functional motifs in biochemical reaction networks. So we assume that using the ODE systems in (1.2) to represent biological networks are acceptable. We analytically compare the conditions for supporting a stable limit cycle and find that for a single feedback loop, as long as the corresponding governing functions of the homologous continuous and discrete systems have the same upper and lower asymptotes, a branch of limit cycle borne via Hopf bifurcation corresponds to the cycle of its discrete homologue. However, for coupled feedback loops, besides having the same upper and lower asymptotes, parameters such as the decay rates also play a crucial role.

This paper is constructed as follows. In Section 2, we express the Jacobian matrix as the function of equilibrium, which will facilitate the computation in the later sections. In Section 3, we prove that a negative feedback loop with more than 2 nodes can have stable oscillations borne from Hopf bifurcation. We show in Section 4 that a negative feedback loop of a BL network supports a cycle if and only if each node that has an inhibitor has a background activation (i.e., high basal production rate). Comparing the results from Sections 3 and 4, we conclude that with the same upper and lower asymptotes, a cycle in a BL feedback loop gives a stable limit cycle in the homologous continuous system. In Section 5, we show that the conditions of Hopf bifurcation occurring in an ODE network, which consists of coupled positive and negative feedback loops, include a restriction on the relations between the decay rates which cannot be implied from the BL network.

2. Preliminary: Jacobian matrix at equilibrium

In this section, we give a form of the Jacobian matrix at equilibrium, which will be needed for the computation in the following sections.

Lemma 2.1. *Let* $X_0 = (x_1, x_2, \ldots, x_n)$ (*where* $n \geq 2$) *be an equilibrium to the system* (1.2). *Then the Jacobian matrix at the equilibrium is*

$$\begin{pmatrix} -\gamma_1 & f_{12} & \cdots & f_{1,n-1} & f_{1n} \\ f_{21} & -\gamma_2 & \cdots & f_{2,n-2} & f_{2n} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ f_{n1} & f_{n2} & \cdots & f_{n,n-1} & -\gamma_n \end{pmatrix},$$

where

$$f_{ij} = \gamma_i x_i (1 - x_i) \sigma_i v_{ij}.$$

Proof. Denote the right-hand side of (1.2) by f_i. Then

$$\frac{\mathrm{d} f_i}{\mathrm{d} x_i} = -\gamma_i,$$

and when $j \neq i$,

$$\begin{aligned} \frac{\mathrm{d} f_i}{\mathrm{d} x_j}(X_0) &= \gamma_i \frac{1}{(1 + e^{-\sigma_i (a_i + \sum_j v_{ij} x_j)})^2} e^{-\sigma_i (a_i + \sum_j v_{ij} x_j)} \sigma_i v_{ij} \\ &= \gamma_i x_i^2 \, \frac{1 - x_i}{x_i} \, \sigma_i v_{ij} = \gamma_i x_i (1 - x_i) \sigma_i v_{ij}, \end{aligned}$$

where the second equality is due to the fact that at the equilibrium,

$$\frac{1}{1 + e^{-\sigma_i (a_i + \sum_j v_{ij} x_j)}} = x_i.$$

Hence the Jacobian matrix at the equilibrium X_0 is

$$\begin{pmatrix} -\gamma_1 & f_{12} & \cdots & f_{1,n-1} & f_{1n} \\ f_{21} & -\gamma_2 & \cdots & f_{2,n-2} & f_{2n} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ f_{n1} & f_{n2} & \cdots & f_{n,n-1} & -\gamma_n \end{pmatrix},$$

where

$$f_{ij} = \gamma_i x_i (1 - x_i) \sigma_i v_{ij}. \qquad \square$$

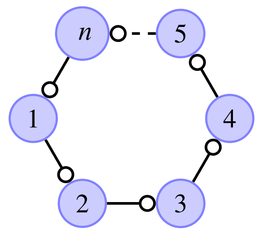


Figure 1. A feedback loop with n nodes.

3. Dynamics of negative feedback loop with ODE equations

In this section, we focus on the dynamics of feedback loops with n nodes, where the arrows can be either inhibiting or activating. If there are an odd number of inhibitory arrows, then the network is a *negative* feedback loop; otherwise, it is a *positive* feedback loop.

The equations associated to the loop in Figure 1 are

$$\begin{cases} \dot{x}_1 = \gamma_1\left(\dfrac{1}{1+e^{-\sigma_1(a_1+v_{1,n}x_n)}} - x_1\right), \\ \dot{x}_i = \gamma_i\left(\dfrac{1}{1+e^{-\sigma_i(a_i+v_{i,i-1}x_{i-1})}} - x_i\right), \end{cases} \tag{3.3}$$

where $i \in \{2, \dots, n\}$ and $v_{i,j} = \alpha_{ij} - \beta_{ij}$ $(\alpha_{ij} > 0, \beta_{ij} > 0)$.

Next we show a result that has been proved in a couple of papers including [Leite and Wang 2010]. Since it is a simple proof, we reproduce it for our system as follows.

Lemma 3.1. *Suppose the network associated to system* (3.3) *is a negative feedback loop. Then the system has a unique equilibrium.*

Proof. An equilibrium $X_0 = (x_1, x_2, \dots, x_n)$ of system (3.3) satisfies

$$\begin{cases} \dfrac{1}{1+e^{-\sigma_1(a_1+v_{1,n}x_n)}} = x_1, \\ \dfrac{1}{1+e^{-\sigma_i(a_i+v_{i,i-1}x_{i-1})}} = x_i, \end{cases} \tag{3.4}$$

where $i \in \{2, \dots, n\}$.

Let

$$h_i(x) = \frac{1}{1+e^{-\sigma_i(a_i+v_{i,i-1}x)}}$$

for $i \in \{1, \dots, n\}$. Then h_i are obviously strictly monotonic functions.

Since the coordinates of the equilibrium satisfy (3.4), we have

$$\begin{aligned} x_1 &= h_1(x_n) = h_1 \circ h_n(x_{n-1}) \cdots \\ &= h_1 \circ h_n \circ h_{n-1}(x_{n-2}) \cdots = h_1 \circ h_n \circ h_{n-1} \circ \cdots \circ h_2(x_1). \end{aligned} \tag{3.5}$$

Note that the composition of two monotonic functions is monotonic. Since it is a negative feedback loop, $h_1 \circ h_n \circ h_{n-1} \circ \cdots \circ h_2$ is a strictly monotonically decreasing. Hence there is at most one solution to (3.5).

Now consider the existence of the equilibrium. Note that $0 \le x_1 \le 1$. When $x_1 = 0$, we know $h_1 \circ h_n \circ h_{n-1} \circ \cdots \circ h_2(x_1) > 0$ since $h_i(x) > 0$ for any value of x. That is,

$$h_1 \circ h_n \circ h_{n-1} \circ \cdots \circ h_2(0) > 0.$$

On the other hand, $h_i(x) < 1$ for any value of x. It follows that

$$h_1 \circ h_n \circ h_{n-1} \circ \cdots \circ h_2(1) < 1.$$

Now if we let

$$p(x) = h_1 \circ h_n \circ h_{n-1} \circ \cdots \circ h_2(x) - x,$$

then $p(0) > 0$ and $p(1) < 0$. By the intermediate value theorem, there is a value of x, say x^*, such that $p(x^*) = 0$. That is, there exists a x^* such that

$$h_1 \circ h_n \circ h_{n-1} \circ \cdots \circ h_2(x^*) = x^*.$$

So we prove the existence. Therefore, there is a unique equilibrium for any negative feedback loop whose equations have the form of (3.3). □

Theorem 3.2. *Let $X_0 = (x_1, x_2, \ldots, x_n)$ be an equilibrium of an n-node negative feedback loop with associated equations in the form of* (3.3). *Suppose $\gamma_i = \gamma > 0$. Then*:

(1) *The eigenvalues of the Jacobian matrix at the equilibrium are*

$$\lambda_k = -\gamma + \left| \prod_{i=1}^{n} \gamma x_i (1 - x_i) \sigma_i v_{i,i-1} \right|^{1/n} e^{\mathrm{i}(\pi/n + 2k\pi/n)}, \tag{3.6}$$

where $k = 0, 1, \ldots, n-1$.

(2) *When $n = 2$, the unique equilibrium is always stable.*

(3) *When $n \ge 3$ and $a_i = -\frac{1}{2} v_{i,i-1}$, a branch of periodic solutions can bifurcate from equilibrium with $x_i = 0.5$ by varying one of the parameters σ_i and fixing remaining other parameter values.*

Proof. Without loss of generality, we assume $\gamma = 1$ (otherwise, we can always rescale the time so that $\gamma = 1$). By Lemma 2.1, the Jacobian matrix of the system (3.3) has the form

$$\begin{pmatrix} -1 & 0 & \cdots & 0 & f_{1n} \\ f_{21} & -1 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & f_{n,n-1} & -1 \end{pmatrix}.$$

So the characteristic equation of the Jacobian matrix at the equilibrium is

$$0 = (\lambda+1)^n - f_{1n} f_{21} \dots f_{n,n-1} = (\lambda+1)^n - \prod_{i=1}^{n} x_i(1-x_i)\sigma_i v_{i,i-1}.$$

Hence,

$$(\lambda+1)^n = \prod_{i=1}^{n} x_i(1-x_i)\sigma_i v_{i,i-1}. \tag{3.7}$$

Note that when the feedback loop is negative, $\prod_{i=1}^{n} v_{i,i-1}$ is negative. So is the right-hand side of (3.7). Let $\Delta = \prod_{i=1}^{n} x_i(1-x_i)\sigma_i v_{i,i-1}$, then $\Delta = |\Delta| e^{\mathrm{i}\pi}$. It follows that

$$\lambda = -1 + |\Delta|^{1/n} e^{\mathrm{i}(\pi/n + 2k\pi/n)}$$

for $0 \le k \le n-1$.

Note that when $n = 2$,

$$\lambda_1 = -1 + |\Delta|^{1/2} e^{\mathrm{i}(\pi/2)} = -1 + \mathrm{i}|\Delta|^{1/2}$$

and

$$\lambda_2 = -1 + |\Delta|^{1/2} e^{\mathrm{i}(\pi/2+\pi)} = -1 - \mathrm{i}|\Delta|^{1/2}.$$

It follows that $\mathrm{Re}(\lambda_k) = -1$ for $k \in \{1, 2\}$. Hence, a negative feedback loop with only two nodes must only have a stable equilibrium.

When $n \ge 3$, the pair of conjugate roots $-1 + |\Delta|(\cos\pi/n \pm \mathrm{i}\sin\pi/n)$ have the largest real part: $-1 + |\Delta|\cos\pi/n = -1 + \left|\prod_{i=1}^{n} x_i(1-x_i)\sigma_i v_{i,i-1}\right| \cos\pi/n$. Note that when $a_i = -\frac{1}{2} v_{i,i-1}$, it is straightforward to show that $\{x_i = \frac{1}{2}\}$ is an equilibrium. Since the expression of eigenvalues is independent of a_i, we can vary σ_i so that the real part changes from negative to positive and leaves the other eigenvalues with negative real parts. Therefore, a branch of limit cycles can be borne through Hopf bifurcation. □

Remark 3.3. The theorem states that when $a_i = -\frac{1}{2} v_{i,i-1}$, by varying the parameter of steepness σ_i a limit cycle can be obtained via Hopf bifurcation. Note that $v_{i,i-1}$ is either equal to the activating coupling parameter $\alpha_{i,i-1}$ or equal to the inhibitory coupling parameter $-\beta_{i,i-1}$ in the feedback loop. Note that $1/(1 + e^{-\sigma_i a_i})$ is the basal production rate. That is, when node i has inhibitory input, its basal production rate has to be relatively high since $a_i > 0$.

Also with the parameter setting $a_i = -\frac{1}{2} v_{i,i-1}$, we have

$$\left.\frac{1}{1 + e^{-\sigma_i(a_i + v_{i,i-1} x_{i-1})}}\right|_{x_{i-1}=1} = \frac{1}{1 + e^{-1/2\sigma_i v_{i,i-1}}}$$

and

$$\left.\frac{1}{1 + e^{-\sigma_i(a_i + v_{i,i-1} x_{i-1})}}\right|_{x_{i-1}=0} = \frac{1}{1 + e^{1/2\sigma_i v_{i,i-1}}}.$$

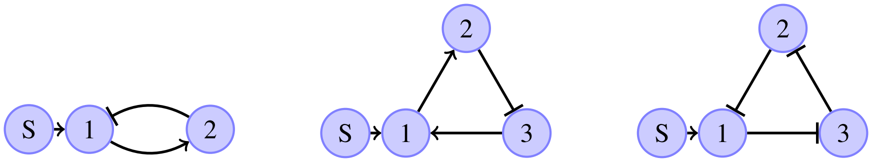


Figure 2. Two- and three-node negative feedback loops with a constant signal to node 1, as in [Tyson and Novák 2010]. The dynamics of the corresponding ODEs are equivalent to those without the signal.

We consider the values of $x_i \in [0, 1]$. So if $v_{i,i-1} = \alpha_{i,i-1} > 0$ (i.e., node i has an activating input from node $i-1$), the sigmoidal has maximum value $(1 + e^{-1/2\,\sigma_i a_{i,i-1}})^{-1}$ at $x_{i,i-1} = 1$ that goes towards 1 as $\sigma_i \to \infty$ and has minimum value $(1 + e^{1/2\,\sigma_i a_{i,i-1}})^{-1}$ at $x_{i,i} = 0$ that goes towards 0 as $\sigma_i \to \infty$. On the other hand, if $v_{i,i-1} = -\beta_{i,i-1} < 0$ (i.e., node i has an inhibitory input from node $i-1$), the sigmoidal has maximum value $(1 + e^{1/2\,\sigma_i \beta_{i,i-1}})^{-1}$ at $x_{i,i-1} = 0$ that goes towards 1 as $\sigma_i \to \infty$ and has minimum value $(1 + e^{-1/2\,\sigma_i \beta_{i,i-1}})^{-1}$ at $x_{i,i-1} = 1$ that goes towards 0 as $\sigma_i \to \infty$.

Remark 3.4. We recall dynamics of some networks studied by Tyson et al. [2010] (reproduced in Figure 2). It was assumed that node 1 has a constant basal production that is indicated by S. The equations to the network in Figure 2 are in the form

$$\begin{cases} \dot{x}_1 = \gamma_1\left(\dfrac{1}{1 + e^{-\sigma_1(S + a_1 + v_{1,n}x_n)}} - x_1\right), \\ \dot{x}_i = \gamma_i\left(\dfrac{1}{1 + e^{-\sigma_i(a_i + v_{i,i-1}x_{i-1})}} - x_i\right), \end{cases} \tag{3.8}$$

where $i = 2$ or $i \in \{2, 3\}$ and $v_{i,j} = \alpha_{i,j} - \beta_{i,j}$.

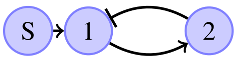
Note that both S and a_1 are constants. We can relabel $S + a_1$ by a_1^*. Then (3.8) is again in the form of the feedback loop without signal as (3.3). So the dynamics are the same as we discussed in Section 3.

4. Dynamics of negative feedback loop with Boolean functions

With a given interaction network, there are many ways to choose BL functions for the nodes. Here we adopt the well-cited assumptions for the associated BL functions proposed by Albert and Othmer [2003]. We make the following assumptions, which we will refer to as *axioms*:

(1) The effects of activators and inhibitors are never additive, but rather, inhibitors are dominant.

(2) The activity of a node will be “on” in the next time step if at least one of its activators is “on” and all inhibitors are “off”.



(x_1, x_2)	$F(x_1, x_2)$
$(0, 0)$	$(1, 0)$
$(1, 0)$	$(1, 1)$
$(1, 1)$	$(0, 1)$
$(0, 1)$	$(0, 0)$

$$\begin{tikzcd}
(0,0) \arrow[r] & (1,0) \arrow[d] \\
(0,1) \arrow[u] & (1,1) \arrow[l]
\end{tikzcd}$$

Figure 3. Left: two-node negative feedback loop that admits a cycle; middle: BL map; right: transition graph.

(3) The activity of a node will be "off" in the next time step if none of its activators are "on".

(4) If a node has a background activation, then we assume that the node has an activator that is permanently "on".

Let $I(i)$ be the set of inhibitors and $A(i)$ be the set of activators of the i-th node. Then we can express the *axioms* by the following logic function:

$$x_i(t+1) = \begin{cases} \left(\neg \bigvee_{j \in I(i)} x_j(t)\right) \wedge \bigvee_{k \in A(i)} x_k(t) & \text{when node } i \text{ has no background activation,} \\ \neg \bigvee_{j \in I(i)} x_j(t) & \text{when node } i \text{ has a background activation.} \end{cases}$$

For example, for the network in Figure 3, node 1 receives two inputs: one inhibitor and another one is a background activator, and node 2 receives one activator from node 1. So if $x_1 = 0$ and $x_2 = 1$, then in the next time step, x_1 remains 0 since its inhibitor node 2 is on and $x_2 = 0$ since its only activator is off. It is straightforward to check that the BL function associated to the network must be the one listed in the table in Figure 3. The dynamics of the two-node network in Figure 2 can be described by the transition graph in Figure 3. Note that this network admits a cycle.

Three-node negative feedback loop. Next we consider a network of three-node negative feedback loops. We assume one of the nodes has a background activation. Then there are three cases as shown in Figure 4.

Case I. Assume node 1 has the background activator shown in Figure 5, left. Then following the *axioms*, the BL functions associated to the network is the one in Figure 5, middle, and the transition diagram is as in Figure 5, right. We can see that $(1, 1, 0)$ is a fixed point and all other points will converge to the fixed point over the time. As a result, no cycle exists.

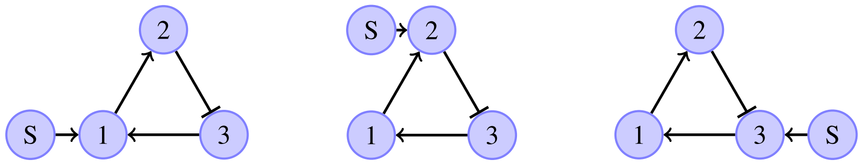
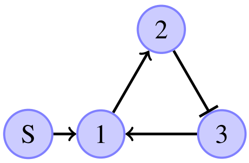


Figure 4. Three different background activation locations.



(x_1, x_2, x_3)	$f(x_1, x_2, x_3)$
$(0, 0, 0)$	$(1, 0, 0)$
$(1, 0, 0)$	$(1, 1, 0)$
$(1, 1, 0)$	$(1, 1, 0)$
$(1, 0, 1)$	$(1, 1, 0)$
$(0, 1, 1)$	$(1, 0, 0)$
$(0, 1, 0)$	$(1, 0, 0)$
$(0, 0, 1)$	$(1, 0, 0)$
$(1, 1, 1)$	$(1, 1, 0)$

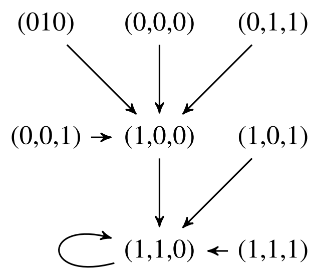
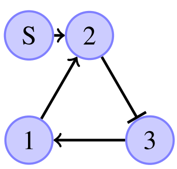


Figure 5. Case I, left: background signal is on node 1; middle: BL map; right: transition graph.



(x_1, x_2, x_3)	$f(x_1, x_2, x_3)$
$(0, 0, 0)$	$(0, 1, 0)$
$(1, 0, 0)$	$(0, 1, 0)$
$(1, 1, 0)$	$(0, 1, 0)$
$(1, 0, 1)$	$(1, 1, 0)$
$(0, 1, 1)$	$(1, 1, 0)$
$(0, 1, 0)$	$(0, 1, 0)$
$(0, 0, 1)$	$(0, 1, 0)$
$(1, 1, 1)$	$(0, 1, 0)$

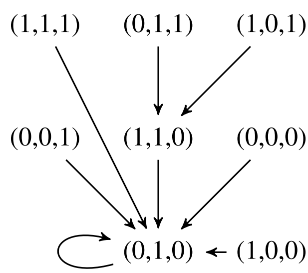
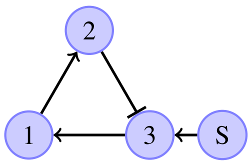


Figure 6. Case II, left: background signal is on node 2; middle: BL map; right: transition graph.

Case II. Assume node 2 has the background activation as Figure 6, left. Then the corresponding BL function and transition graph are Figure 6, middle, and Figure 6, right, respectively. Again, we can see that the system has only a stable fixed point $(1, 1, 0)$. As a result, no cycle exists.

Case III. Assume node 3 has the background activation. Similarly, we can determine its associated BL function and transition graph as in Figure 7. Different from the other two cases, there exists a cycle with length 6.



(x_1, x_2, x_3)	$f(x_1, x_2, x_3)$
$(0, 0, 0)$	$(0, 0, 1)$
$(0, 0, 1)$	$(1, 0, 1)$
$(1, 0, 1)$	$(1, 1, 1)$
$(1, 1, 1)$	$(1, 1, 0)$
$(1, 1, 0)$	$(0, 1, 0)$
$(0, 1, 0)$	$(0, 0, 0)$
$(1, 0, 0)$	$(0, 1, 1)$
$(0, 1, 1)$	$(1, 0, 0)$

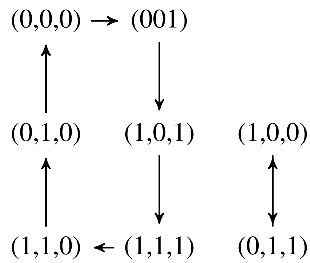


Figure 7. Case III, left: background signal is on node 3; middle: BL map; right: transition graph.

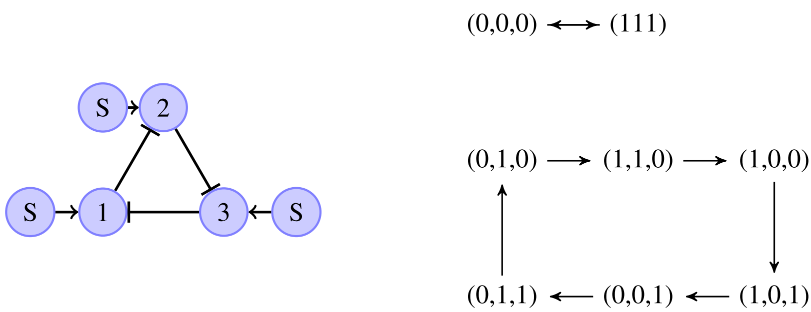


Figure 8. BL network that admits cycles.

Similarly, we can show for the three-node network in Figure 8, the network admits cycle only if each node receives a background activation.

Dynamics of n-node negative feedback loop in Figure 2, right. The analysis of BL three-node negative feedback networks discussed in the previous section shows that a network admits cycles only if each node that receives inhibitory input has background activation. This observation can be generalized to any n-node negative feedback loop.

Let x_i^m be the value of the state variable of node i at the m-th time step. Then the BL system of the feedback loop in Figure 1 has the form

$$\begin{cases} x_1^{m+1} = f_1(x_n^m), \\ x_i^{m+1} = f_i(x_{i-1}^m). \end{cases} \tag{4.9}$$

Lemma 4.1. *Let $\mathcal{G}$ be an n-node feedback loop with associated BL system having the form of* (4.9). *Then for any $m > n$,*

$$x_1^{m+1} = f_1 \circ f_n \circ f_{n-1} \circ \cdots \circ f_2(x_1^{m+1-n}).$$

Proof. It follows straightforwardly from (4.9). $\square$

Lemma 4.2. *Let $\mathcal{G}$ be a feedback loop with the associated BL system satisfying the* axioms. *Suppose each node with an inhibitory input from some other node has a background activation. Then*

(1) *if node i receives a negative input, then the associated BL function is $f_i(0) = 1$ and $f_i(1) = 0$;*

(2) *if node i receives a positive input, then the associated BL function is $f_i(0) = 0$ and $f_i(1) = 1$;*

and the compositions of f_i are bijections.

Proof. Items (1) and (2) follow straightforwardly from the *axioms*. So all f_i are bijections. It then follows that the compositions of f_i are bijections. □

Lemma 4.3. *Let $\mathcal{C}$ be a node of an n-node feedback loop $\mathcal{G}$. Suppose the value of the state variable of $\mathcal{C}$ stays constant after a finite number of time steps. Then the associated BL system does not have nontrivial cycles.*

Proof. Without loss of generality, we relabel the nodes of $\mathcal{G}$ so that $\mathcal{C}$ is node 1 and the rest of the nodes are relabeled as in Figure 1. Let x_i^m be the value of the state variable of node i at the m-th time step. Then the BL system has the form of (4.9).

Since this is a deterministic system, when the value x_1 is fixed after a finite series of steps, say M, then by Lemma 4.1, the values of all other x_i will be fixed after $M + n$ time steps. So the system only has fixed points and does not admit nontrivial cycles. □

Theorem 4.4. *Let $\mathcal{G}$ be a negative feedback loop with the associated BL system satisfying the* axioms. *Then $\mathcal{G}$ admits cycles if and only if each node with a negative input from some other node has a background activation.*

Proof. We first prove by contradiction that if one of the nodes with negative inputs from other nodes has no background activation, then the system does not admit cycle. Suppose node $\mathcal{C}$ of the negative feedback loop $\mathcal{G}$ has a negative input from the other node and has no background excitation. Note that if the initial state value of $\mathcal{C}$ is zero, then the value of $\mathcal{C}$ stays zero forever; if the initial state value of $\mathcal{C}$ is 1, then because $\mathcal{C}$ has no excitation input, the value of $\mathcal{C}$ becomes zero in the next time step and remains zero forever. By Lemma 4.3, the negative feedback does not have a cycle.

Next we prove that if all suppressed nodes have background activation, then a cycle exists. It is sufficient to show that the value of each state variable changes over time. By Lemma 4.1, for any $m > n$,

$$x_1^{m+1} = f_1 \circ f_n \circ f_{n-1} \circ \cdots \circ f_2(x_1^{m+1-n}).$$

Since $\mathcal{G}$ is a negative feedback loop,

$$f_1 \circ f_n \circ f_{n-1} \circ \cdots \circ f_2(0) = 1 \quad \text{and} \quad f_1 \circ f_n \circ f_{n-1} \circ \cdots \circ f_2(1) = 0.$$

So the value of the state variable of node 1 changes every n steps. Because f_i are bijections, the values of other node states also change over time. □

Comparison. Theorem 4.4 states that a BL feedback loop admits a cycle only if every node with an inhibitory input has a background activation. In the other words, the governing BL function of a node i with an inhibitory (negative) input must be $f_i(x) = 1 - x$.

Compared with the results for the discrete homologue, the conditions for the continuous system are essentially the same. As discussed in Remark 3.3, each node with an inhibitory input must have a relatively high basal production rate, and as the steepness parameter σ_i goes to ∞, the governing function is the same as the BL system.

5. Networks with two or more feedback loops

Dynamics of the network in Figure 9. The first network we examine is the one in Figure 9, which was studied by Tyson et al. [2010]. The authors showed that without the positive input from node 3 to node 2 (i.e., $\alpha_{23} = 0$), the network of ODEs demonstrates oscillations in a certain range of the parameter value S (with other parameter values fixed). The oscillating range of S shrinks as the coupling parameter α_{23} increases and it disappears when α_{23} increases to a certain value. We show next that the effect of the parameter α_{23} can be captured by two BL systems:

(1) Besides functions based on the *axioms*, the governing function of node 2 which has two inputs, $f_2(x_1, x_3)$, satisfies

$$f_2(1, *) = 1 \quad \text{and} \quad f_2(0, *) = 0,$$

i.e., the activity of node 2 is dominated by the activity of node 1 and the effect of node 3 is negligible. For this setting, the dynamics of the network is the same as the three-node network feedback loop in Figure 7 and it has a stable cycle. This BL system can capture the dynamics of the corresponding ODE system with $\alpha_{23} = 0$ or relatively small.

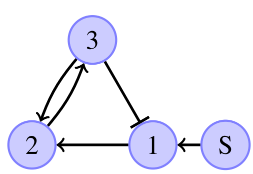


Figure 9. A network consists of two feedback loops.

$$\begin{tikzcd}
(001) \arrow[d] & & (101) \arrow[r] & (010) \arrow[d] & \\
(000) \arrow[r] & (100) \arrow[r] & (110) \arrow[r] & (111) \arrow[r] & (011) \arrow[loop above]
\end{tikzcd}$$

Figure 10. Transitions of the network in Figure 9 with the governing function for node 2 is node 2 is on if either node 1 or node 2 is on.

(2) Besides functions based on *axioms*, the governing function of node 2, $f_2(x_1, x_3)$, satisfies

$$f_2(1, *) = 1, \quad f_2(*, 1) = 1, \quad \text{and} \quad f_2(0, 0) = 0,$$

i.e., node 2 is on if either node 1 or node 3 is on.

This transition diagram of the system is shown in Figure 10. It is clear that the system only has a fixed point which captures the case when α_{23} is sufficiently large.

Remark 5.1. From this example, we can observe that ODE systems can be viewed as "organizing centers" of BL systems.

Boolean system of the network in Figure 11. Suppose the network in Figure 11 receives a signal through one of the nodes. The possible networks are as in Figure 12.

It is rather straightforward to check that when the signal goes to node 1 or 2, the corresponding BL network can only have a stable steady-state, and when the signal goes through node 3, then it has a stable cycle: $(000) \to (001) \to (111) \to (110) \to (000)$.

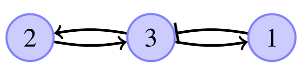


Figure 11. Another network consisting of two feedback loops.

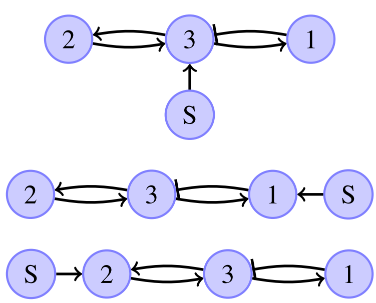


Figure 12. Three possible signal input places.

Dynamics of the ODE systems of the network in Figure 11. By Lemma 2.1, the Jacobian matrix of an ODE system associated to the network in Figure 11 at an equilibrium has the form

$$\begin{pmatrix} -\gamma_1 & 0 & f_{13} \\ 0 & -\gamma_2 & f_{23} \\ f_{31} & f_{32} & -\gamma_3 \end{pmatrix},$$

where $f_{ij} = \gamma_i x_i(1-x_i)\sigma_i v_{ij}$.

Therefore, the characteristic polynomial equation of the matrix is

$$\begin{aligned} |\lambda I - J| &= (\lambda+\gamma_1)(\lambda+\gamma_2)(\lambda+\gamma_3) - (\lambda+\gamma_2) f_{31} f_{13} - (\lambda+\gamma_1) f_{32} f_{23} \\ &= \lambda^3 + (\gamma_1+\gamma_2+\gamma_3)\lambda^2 + (\gamma_1\gamma_2+\gamma_2\gamma_3+\gamma_1\gamma_3 - f_{13}f_{31} - f_{23}f_{32})\lambda \\ &\qquad + \gamma_1\gamma_2\gamma_3 - \gamma_2 f_{13} f_{31} - \gamma_1 f_{23} f_{32}. \end{aligned} \tag{5.10}$$

Theorem 5.2. *The condition $\gamma_2 > \gamma_1$ is necessary for Hopf bifurcation to occur.*

Proof. Let us label the coefficient of λ^2 as c_1, the coefficient of λ as c_2 and the constant term as c_3. Then the conditions for having a pair of pure imaginary eigenvalues are:

- $$c_1 = \gamma_1 + \gamma_2 + \gamma_3 > 0. \tag{5.11}$$
- $c_2 = \gamma_1\gamma_2 + \gamma_2\gamma_3 + \gamma_1\gamma_3 - f_{13}f_{31} - f_{23}f_{32} > 0$. It follows that
$$\gamma_1\gamma_2 + \gamma_2\gamma_3 + \gamma_1\gamma_3 - f_{13}f_{31} > f_{23}f_{32}. \tag{5.12}$$
- $c_3 - c_1c_2 = 0$, i.e.,

$$\begin{aligned} &\gamma_1\gamma_2\gamma_3 - \gamma_2 f_{13}f_{31} - \gamma_1 f_{23}f_{32} \\ &\qquad - (\gamma_1+\gamma_2+\gamma_3)(\gamma_1\gamma_2+\gamma_2\gamma_3+\gamma_1\gamma_3 - f_{13}f_{31} - f_{23}f_{32}) = 0. \end{aligned} \tag{5.13}$$

It follows that

$$\begin{aligned} &(\gamma_2+\gamma_3) f_{23}f_{32} - \gamma_1^2(\gamma_2+\gamma_3) - \gamma_2^2(\gamma_1+\gamma_3) \\ &\qquad - \gamma_3^2(\gamma_1+\gamma_2) - 2\gamma_1\gamma_2\gamma_3 + (\gamma_1+\gamma_3) f_{13}f_{31} = 0. \end{aligned} \tag{5.14}$$

Inequality (5.12) and equation (5.14) imply that

$$\begin{aligned} &(\gamma_2+\gamma_3)(\gamma_1\gamma_2+\gamma_2\gamma_3+\gamma_1\gamma_3 - f_{13}f_{31}) \\ &\qquad > \gamma_1^2(\gamma_2+\gamma_3) + \gamma_2^2(\gamma_1+\gamma_3) + \gamma_3^2(\gamma_1+\gamma_2) \\ &\qquad\qquad + 2\gamma_1\gamma_2\gamma_3 - (\gamma_1+\gamma_3) f_{13}f_{31}. \end{aligned} \tag{5.15}$$

Simplifying (5.15), we have

$$-(\gamma_2 - \gamma_1) f_{13}f_{31} > \gamma_1^2(\gamma_2+\gamma_3). \tag{5.16}$$

By the condition of the network, $f_{13}f_{31} < 0$, so inequality (5.16) implies $\gamma_2 > \gamma_1$. □

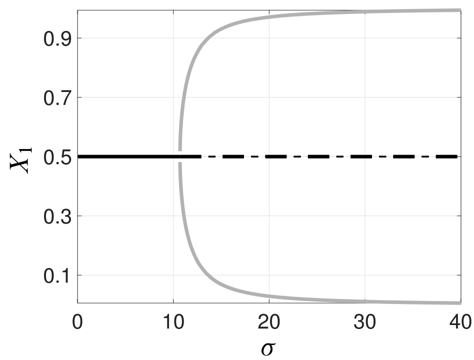


Figure 13. Bifurcation diagram at the parameter values $\sigma_1 = \sigma_3 = \sigma_2 = \sigma$, $\gamma_1 = \gamma_3 = 1$ and $\gamma_2 = 1.5$, $\alpha_{13} = \beta_{31} = \alpha_{23} = \alpha_{32} = 1$, $a_1 = a_2 = -0.5$ and $a_3 = 0$, and with the rest of the parameters being zero. Here the gray curve represents a branch of stable limit cycle, the solid black line represents a branch of stable equilibria and the black dashed line a branch of unstable equilibria.

How can we choose parameter values so that we will observe sustained oscillations that close to the Hopf bifurcation point? Suppose the bifurcation is supercritical; then near the bifurcation point, $c_3 - c_1c_2 \geq 0$ while c_1 and c_2 remain positive. Now by substituting f_{ij} by $\gamma_i x_i(1-x_i)\sigma_i v_{ij}$ in inequalities (5.16), (5.12) and $c_3 - c_1c_2 \geq 0$, we obtain

$$(\gamma_2-\gamma_1)\gamma_1\gamma_3x_1x_3(1-x_1)(1-x_3)\sigma_1\sigma_3\beta_{31}\alpha_{13} > \gamma_1^2(\gamma_2+\gamma_3), \tag{5.17}$$

$$\begin{aligned}\gamma_1\gamma_2+\gamma_2\gamma_3+\gamma_1\gamma_3+\gamma_1\gamma_3x_1x_3(1-x_1)(1-x_3)\sigma_1\sigma_3\beta_{31}\alpha_{13}\\ > \gamma_2\gamma_3x_2x_3(1-x_2)(1-x_3)\sigma_2\sigma_3\alpha_{32}\alpha_{23}\end{aligned} \tag{5.18}$$

and

$$\begin{aligned}\gamma_1^2(\gamma_2+\gamma_3)+\gamma_2^2(\gamma_1+\gamma_3)+\gamma_3^2(\gamma_1+\gamma_2)+2\gamma_1\gamma_2\gamma_3\\ +(\gamma_1+\gamma_3)\gamma_1\gamma_3x_1x_3(1-x_1)(1-x_3)\sigma_1\sigma_3\beta_{31}\alpha_{13}\\ \leq (\gamma_2+\gamma_3)\gamma_2\gamma_3x_2x_3(1-x_2)(1-x_3)\sigma_2\sigma_3\alpha_{32}\alpha_{23}.\end{aligned} \tag{5.19}$$

Focusing on the equilibria with $x_i = 0.5$, we can find a range of parameter values that satisfy conditions (5.16), (5.18) and (5.19). For example, $\sigma_1 = \sigma_3 = \sigma_2 = \sigma$, $\gamma_1 = \gamma_3 = 1$ and $\gamma_2 = 1.5$, $\alpha_{13} = \beta_{31} = \alpha_{23} = \alpha_{32} = 1$, $a_1 = a_2 = -0.5$ and $a_3 = 0$. By setting the rest of the parameters to zero and varying the value σ, we can find a branch of limit cycle occuring through Hopf bifurcation; see Figure 13.

Comparison of discrete and continuous homologues. Now we compare the conditions for the homologous systems of the network in Figure 11. The BL system requires that node 3 has a background activation, which is reflected in the choices of parameter values associated to basal production rates in the ODE system: $a_1 = a_2 = -0.5$ and $a_3 = 0$, where a_3 is actually the summation of the two parameters a_3 and signal S with $a_3 = -0.5$ and $S = 0.5$. In order to realize oscillations in the continuous system, we need to find suitable values for other parameters as well. For example, we need to impose a restriction on the relation of decay rates $\gamma_2 > \gamma_1$ in order to observe stable oscillations. Such requirements in the parameter values of ODE systems do not have correspondence in the BL systems.

6. Discussion

Glass and Kauffman [1973] showed that a stable limit cycle of a continuous network gives a cycle in its discrete homologue under the condition that each node has only one input from other nodes. In this work, we compared the conditions for each type possessing a stable cycle for the case where each node has one input and also examined two cases when some nodes have two inputs. Our strategy of focusing on the type of ODE systems in a rather abstract form enables us to perform analytical examinations and to possibly extract essential dynamical differences between the two types of network models. The strategy has the potential to be used for more extensive study of the relations as to provide more efficient algorithms for converting between continuous and discrete network systems.

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