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Periodic Oscillation of Piecewise Linear Three-gene Regulatory Network with Negative Feedback Loops

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Abstract In synthetic biology, we need not only to design the basic functional modules, but also to understand the parameters of the designed modules. In this area, the existing theoretical result about periodic oscillation is difficult to achieve. We study the Piecewise Linear three-gene regulatory network with negative feedback loop to show how to control the periodic oscillation.

Keywords Gene regulatory network; negative feedback loops; periodic oscillation; lattice dynamical systems.

1 Introduction

With the rapid advance of genetic engineering, designed gene networks can be implemented in many living organisms. Many important works for designing gene regulatory networks are based on monotone dynamical systems, which are biologically plausible for a large class of biochemical networks or systems.

Up to now, there are a large number of theoretical results (Goodwin, 1965 ; Glass and Kauffman, 1973 ; Hunding, 1974 ; Walther, 1995; Wu and Zou, 1995 ; Belairet *et al.*, 1996 ; Campbell *et al.*, 1999 ; Chen and Aihara, 2002b ; Chen *et al.*, 2004), which provide the sufficient conditions for switching or oscillating dynamics. In particular, Kobayashi *et al.* proved that a general genetic network (GN) with only positive feedback loops has no dynamical attractor except stable equilibria, and is robust to time delay variations. On the other hand, a GN with negative feedback loops has more complex dynamics and may have a periodic oscillation under certain conditions. In the recent years, there are also many results about the effects of time delay on the behavior of periodic oscillation in the GN with negative feedback loops. Some sufficient conditions of the GN with negative feedback loops have been given. But due to complexity of nonlinear monotone functions, all of those studies do not

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explicitly give the qualitative settings of the parameters as well as their ranges for a periodic oscillation, which are strongly demanded from experimentalists.

The construction of the GRN' with the basic function is a focus of synthetic biology and genetic engineering. Synthetic biology needs to characterize the modularity and portability of genetic elements used in genetic constructs. There is therefore a strong need to develop methods to detect and quantify interferences between elements used in genetic constructs so that we can better understand them and use that knowledge in the design of new constructs. The main problem is that the parameters are unknown. Since synthetic biology project eventually completed in the engineering applications, the design parameters of GRN is should to complete. Thus, there is an important problem: how can we find out the specific control parameters.

In this paper, we will discuss a three-gene regulation network with negative feedback loop and find that there is a periodic oscillation in the nolinear system under certain parameter condition. So we think that the above view is reasonable. The general definition of gene regulatory networks and the simplify of GRN are discussed in section II, Our main conclusion and an numerical simulations are given in section III.

2 Simplified Gene Regulatory Networks Model

The dynamics of gene regulatory networks can be modeled by a class of dynamical systems proposed originally by Glass and Kauffman. The model has the general form

$$\dot{x}_i = f_i(x) - \gamma_i x_i, \;\; 1 \leq i \leq n \tag{1}$$

where $x = (x_1, x_2, \ldots, x_n)^T$ is a non-negative vector of protein concentration. the non-negative quantities $f_i(x)$ and $\gamma_i x_i$ represent synthesis and degradation rates for each protein x_i respectively. The function $f_i : \mathbb{R}^n_+ \to \mathbb{R}_+$ represent the dependence of the rate of synthesis a protein encoded by gene i on the concentration x of protein in the cell. They can be written as $f_i(x) = \Sigma_{j=1}^n k_i f_{i,j}(x_j)$, where $f_{i,j}(x_j) = \frac{\theta_i^p}{\theta_i^p + x_j^p}$ (or $f_{i,j}(x_j) = \frac{x_j^p}{\theta_i^p + x_j^p}$) are Hill function, which are donated $f^-_{i,j}(x_j)$(or $f^+_{i,j}(x_j)$). θ_i is the threshold of gene i and $k_i \in [0, +\infty)$. For simplification we assumption the maximum of x_j is 1. Under other situation we can let $\tilde{x}_j = x_j / Max\{x_1, x_2, \ldots, x_n\}$, then $\tilde{x}_j \leq 1$. To describe network structure, we define the type of interactions.

If $f_{i,j}(x_j) = f^+_{i,j}(x_j)$ (or $f^-_{i,j}(x_j)$), we say the jth gene regulate positively (or negatively)the ith gene and we set $s_{i,j} = 1$ (or $s_{i,j} = -1$).

Definition:In GRN, if there is a path from the ith gene to itself, $p(i,i) = (i = P_1 \to P_2 \to \ldots P_{l-1} \to P_l = i)$ for $l > 2$, then this path is said to be feedback loop. In addition, this feedback loops is said to be positive (or negative) if $\prod_{m=1}^{l} s_{p_{m+1}, p_m} = 1$ (or -1).

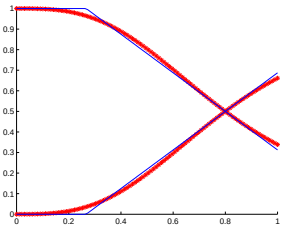

Figure 1: $\theta = 0.8, p = 3$.

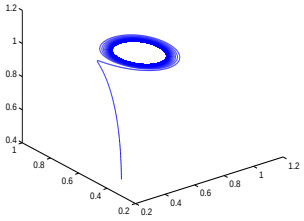

Figure 2: p=3,$\theta_i = 0.8, i = 1,2,3$.

Now, we will consider three-gene GRN with negative feedback loop.

$$\begin{cases} \dfrac{dx_1}{dt} &= k_1 f^-_{3,1}(x_3) - \gamma_1 x_1 + k^0_1, \\ \dfrac{dx_i}{dt} &= k_i f^-_{i-1,i}(x_{i-1}) - \gamma_i x_i + k^0_i. \quad i = 2,3. \end{cases} \tag{2}$$

Due to Hill function is nonlinear and is difficult to analysis in GRN. We plan to replace the Hill function with linear continuous functionand study the model.

Note that Hill function $f^-_{ij}(\theta_j) = \frac{1}{2}$ and $f^-_{ij}(1) = \frac{\theta_i^p}{\theta_i^p+1}$.

When $p \geq 3$ and $\theta_i + 2\frac{\theta_i(1-\theta_i^p)}{p(1+\theta_i^p)} > 1$, we find that the continuous linear function

$$h^-_{ij}(x_j) = \begin{cases} 1, & if \quad x_j \leq \theta_i - \frac{2\theta_i}{p}; \\ -\frac{p(x_j-\theta_i)}{4\theta_i} + \frac{1}{2}, & if \quad x_j > \theta_i - \frac{2\theta_i}{p}. \end{cases} \tag{3}$$

is well coincidence with Hill function $f^-_{ij}(x_j)$.The curve with $*$ symbol represents the Hill function and the real blue line represent the piecewise linear continuous function.

By the approach described above, the model are simplified as follows:

$$\begin{cases} \dfrac{dx_1}{dt} &= k_1 h^-_{3,1}(x_3) - \gamma_1 x_1 + k^0_1, \\ \dfrac{dx_i}{dt} &= k_i h^-_{i-1,i}(x_{i-1}) - \gamma_i x_i + k^0_i. \quad i = 2,3. \end{cases} \tag{4}$$

Thinks to the piecewise linear function nature, we can discuss the parametric condition of periodic oscillation easily.

3 Periodic Oscillation of GRN with Negative Feedback Loop

In this paper,we will only consider the parametric conditions of three-gene negative feedback loops with $p \geq 3$ and $\theta_i + 2\frac{\theta_i(1-\theta_i^p)}{p(1+\theta_i^p)} > 1$.

Dote $\frac{p\theta_i - 2\theta_i}{p} = T_i, i = 1,2,3$. We make the following assumptions about the GRN:

Assumption I

$$\frac{p^2(p+2)k_1k_2k_3\theta_1 - 4p(p+2)k_1k_3\gamma_2\theta_1\theta_2 + 16(p+2)k_1\gamma_2\gamma_3\prod_{i=1}^{3}\theta_i}{p^3k_1k_2k_3 + 64\prod_{i=1}^{3}\gamma_i\theta_i} + \frac{4p^2k_1k_3k_2^0\theta_1 - 16pk_3^0k_1\gamma_3\theta_1\theta_2 + 64k_1^0\gamma_2\gamma_3\prod_{i=1}^{3}\theta_i}{p^3k_1k_2k_3 + 64\prod_{i=1}^{3}\gamma_i\theta_i} > T_1;$$

$$\frac{p^2(p+2)k_1k_2k_3\theta_2 - 4p(p+2)k_1k_2\gamma_3\theta_2\theta_3 + 16(p+2)k_2\gamma_1\gamma_3\prod_{i=1}^{3}\theta_i}{p^3k_1k_2k_3 + 64\prod_{i=1}^{3}\gamma_i\theta_i} + \frac{4p^2k_1k_2k_3^0\theta_1 - 16pk_1^0k_2\gamma_2\theta_2\theta_3 + 64k_2^0\gamma_1\gamma_3\prod_{i=1}^{3}\theta_i}{p^3k_1k_2k_3 + 64\prod_{i=1}^{3}\gamma_i\theta_i} > T_2;$$

$$\frac{p^2(p+2)k_1k_2k_3\theta_3 - 4p(p+2)k_2k_3\gamma_1\theta_1\theta_3 + 16(p+2)k_3\gamma_1\gamma_2\prod_{i=1}^{3}\theta_i}{p^3k_1k_2k_3 + 64\prod_{i=1}^{3}\gamma_i\theta_i} + \frac{4p^2k_2k_3k_1^0\theta_3 - 16pk_2^0k_3\gamma_1\theta_1\theta_2 + 64k_3^0\gamma_1\gamma_2\prod_{i=1}^{3}\theta_i}{p^3k_1k_2k_3 + 64\prod_{i=1}^{3}\gamma_i\theta_i} > T_3.$$

Let $b = \gamma_1+\gamma_2+\gamma_3$, $c = \gamma_1\gamma_2+\gamma_1\gamma_3+\gamma_2\gamma_3$, $d = \gamma_1\gamma_2\gamma_3 + \frac{k_1k_2k_3p^3}{64\theta_1\theta_2\theta_3}$, $A = b^2-3c$, $B = bc-9d$, $C = c^2-3bd$, $\triangle = B^2-4AC$, $D_1 = Ab + \frac{3(-B+\triangle^{1/2})}{2}$, $D_2 = Ab + \frac{3(-B-\triangle^{1/2})}{2}$, $F(\gamma_i) = -2b + D_1^{1/3} + D_2^{1/3}$.

Now, we give our main results as follows:

Main Theorem If $p \geq 3, \theta_i + 2\frac{\theta_i(1-\theta_i^p)}{p(1+\theta_i^p)} > 1, F(\gamma_i^0) = 0$, $0 < \varepsilon, \tau \ll 1$ and the assumption I is satisfied, there is a periodic oscillation in the (2) when $\gamma_i = \gamma_i^0 + \varepsilon$ and $0 < k_i^0 < \tau (i = 1,2,3.)$.

Proof: See Y. Wang et al.

Now, we use our theorem in a simple case, when $p = 4, \theta_1 = \theta_2 = \theta_3 = 0.85, k_1 = k_2 = k_3 = 0.4, k_1^0 = k_2^0 = k_3^0 = 0.01$ and $\gamma_1 = \gamma_2 = \gamma_3 = 0.23531$, we find there is a periodic oscillation in the the system(2). A simulation is give in the Fig.2. This is accordance with with our theorem.

Since biological systems have many parameters and the interactional function is nonlinear, it is difficult to find parameters conditions for GRN with periodic oscillation in the synthetic biology. In this paper, we considered a gene regulatory network with negative feedback by using lattice dynamical systems firstly and find that there is a periodic oscillation in the linear approximate system under certain condition. This is well coincidence with the real system.

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