

Analysis Method of Period Sensitivity for Cyclic Expression Pattern Sequences in Gene Regulatory Networks

Yasuaki Kuroe¹ and Yoshihiro Mori²

Abstract—Sensitivity analysis is fundamental and essential in analysis and design of any system. This paper proposes a method of sensitivity analysis for rhythm phenomena in gene regulatory networks (GRNs). In particular, we focus on cyclic expression pattern sequences in GRNs and sensitivity of period which plays one of important roles in periodic phenomena. A piecewise-linear differential-equation model is utilized as a model of GRNs. Rhythm phenomena are expressed by using periodic orbits and corresponding expression pattern sequences. Sensitivity analysis of rhythm phenomena is very difficult because rhythms appear autonomously as periodic phenomena in nonlinear systems, and only a few studies have been done. In general, sensitivities of period are calculated by using numerical methods approximately. In this paper, we analytically derive the mathematical expression of period sensitivity of GRNs. It is shown through numerical examples that the proposed method makes it possible to obtain period sensitivity appropriately.

I. INTRODUCTION

In living organisms, various periodic movements or rhythm phenomena are observed, such as walking, breathing, and heartbeats. There are also rhythm phenomena with a daily cycle, such as sleep, called circadian rhythms. These rhythm phenomena are known to be controlled by specific neural networks or gene regulatory networks (GRNs) in living organisms, and the physiological and mathematical elucidation of these phenomena has been actively studied [1]–[4].

Investigating GRNs is important for understanding functions of living cells and many studies have been done from various viewpoints. Recently there have been increasing research interest in synthesizing GRNs and several studies have been done. Among them, there are studies focusing on the expression patterns of GRNs, examples of which are [5]–[8]. Those studies are motivated by two ways. One is that the synthesis of GRNs is a complementary approach to investigating and understanding functions of real GRNs. That is to say, by synthesizing simple artificial networks and analyzing their behavior and functions, one can get some insights into functions of real GRNs. The other is that synthesis of GRNs could be the first step of controlling and monitoring biochemical processes in living cells.

Meanwhile, investigating how the behavior, characteristics and performance of a system change when its parameters

change slightly, that is, sensitivity analysis, is a very important issue for any system, and is required in various aspects of system analysis and design. Sensitivities of a system's behavior, characteristics and performance with respect to their parameters are usually defined as the derivative with respect to those parameters. Furthermore, consider optimization problems in which a certain performance index in terms of the system's performance or response is given and the parameters that minimize or maximize this are sought. In solving these problems using various optimization algorithms such as gradient based methods, the derivatives of the performance index with respect to the parameters are needed, and in this case, sensitivity analysis is also required. The purpose of this paper is to develop a sensitivity analysis method for cyclic expression pattern sequences in GRNs. In particular, we focus on the period which plays one of important roles in rhythm phenomena and propose an analysis method of period sensitivity.

Sensitivity analysis of systems has quite a history and many studies have been done. However, there are only a few studies on sensitivity analysis of periodic phenomena. The reason is that periodic solutions in systems are generally determined autonomously as the steady state of nonlinear systems independent of the initial state, and it is difficult to obtain a rigorous expression of the dependence of the parameters. There have been done some studies on the sensitivity of periodic phenomena [9]–[11], however, they have problems such as approximate treatment, lack of specific calculation methods, and lack of consideration of computational efficiency. The authors have already proposed sensitivity analysis methods for rhythm phenomena, especially for the period, and proposed a sensitivity analysis algorithm with enough accuracy and computational efficiency [12], [13].

In this paper, we propose an analysis method of period sensitivity for cyclic expression pattern sequences in GRNs. Expression patterns are often used for describing expression levels in analysis and design of GRNs. A piecewise-linear differential-equation model is used as the model for GRNs. This is because this model can easily handle the expression patterns of GRNs. However, in the case of the piecewise-linear differential-equation model, the dynamics of the model switches depending on the expression pattern, and the solution trajectory is not smooth. Therefore, the method in [12], [13] cannot be applied to analyze period sensitivity for the model of GRNs. On the other hand, in this model we can obtain analytical expressions of the coordinates and instants of the solution trajectory when the dynamics switches. In this paper, we propose a method for analytically determining

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¹Yasuaki Kuroe is with Mobility Research Center, Doshisha University, Kyotanabe, Kyoto, Japan kuroe@ieee.org

²Yoshihiro Mori is with Faculty of Information Sciences, The University of Fukuchiyama, Fukuchiyama, Kyoto, Japan mori-yoshihiro@fukuchiyama.ac.jp

period sensitivity by using the expressions. It is confirmed through numerical examples that the proposed method makes it possible to obtain period sensitivity appropriately.

II. MODEL OF GRNs AND PROBLEM DESCRIPTION

In this paper, we consider a model of GRNs described by the ordinary differential equations of the form [5]:

$$\dot{x}_i(t) = -d_i x_i(t) + f_i(y_1(t), y_2(t), \dots, y_n(t), w_{i,1}, w_{i,2}, \dots, w_{i,m_i}), \quad x_i(0) = x_{0,i} \quad (1)$$

$$y_i(t) = h(x_i(t)), \quad i = 1, 2, \dots, n \quad (2)$$

where n is the number of genes, $x_i(t)$ is a normalized expression quantity of the i -th gene, $y_i(t) \in \{0, 1\}$ is a binary variable describing on/off information of expression of the i -th gene, that is, $y_i(t) = 1$ if the i -th gene is expressed, $y_i(t) = 0$ if the i -th gene is not expressed, $f_i: \{0, 1\}^n \rightarrow R$ is a nonlinear function describing interactions among genes, $w_{i,j}$ are parameters of f_i , m_i is the number of parameters of f_i , d_i is a positive real number related to the degradation rate of the product of the i th gene and h is a threshold function:

$$h(x) = \begin{cases} 0 & \text{if } x < 0 \\ 1 & \text{if } x \geq 0 \end{cases}.$$

This model is rewritten in the vector form as follows.

$$\dot{\mathbf{x}}(t) = -\mathbf{D}\mathbf{x}(t) + \mathbf{f}(\mathbf{y}(t), \mathbf{w}), \quad \mathbf{x}(0) = \mathbf{x}_0 \quad (3)$$

$$\mathbf{y}(t) = \mathbf{H}(\mathbf{x}(t)) \quad (4)$$

where $\mathbf{x}(t) = [x_1(t) \ x_2(t) \ \dots \ x_n(t)]^T$, $\mathbf{x}_0 = [x_{0,1} \ x_{0,2} \ \dots \ x_{0,n}]^T$, $\mathbf{y}(t) = [y_1(t) \ y_2(t) \ \dots \ y_n(t)]^T$, $\mathbf{f} = [f_1 \ f_2 \ \dots \ f_n]^T$, $\mathbf{w} = [w_1^T \ w_2^T \ \dots \ w_n^T]^T$, $\mathbf{w}_i = [w_{i,1} \ w_{i,2} \ \dots \ w_{i,m_i}]^T$, $\mathbf{D} = \text{diag}\{d_1, d_2, \dots, d_n\}$ and $\mathbf{H}(\mathbf{x}) = [h(x_1) \ h(x_2) \ \dots \ h(x_n)]^T$. \mathbf{x}^T is transpose of a vector \mathbf{x} . $\mathbf{y}(t)$ is the vector that represents the expression or non-expression of each gene at time t , and is called the expression pattern (EP).

As the interaction function f_i , the following function

$$\begin{aligned} f_i(\mathbf{y}, \mathbf{w}_i) &= w_{i,1} + \sum_{j=1}^n w_{i,j+1} y_j \\ &+ \sum_{j=1}^{n-1} \sum_{k=j+1}^n w_{i,j+k+n+2} y_j y_k \\ &+ \dots + w_{i,2n} y_1 \dots y_n, \quad i = 1, 2, \dots, n \end{aligned} \quad (5)$$

or its equivalent is often used [14]. In this paper, we will use this as the interaction function. If there is no need to specify the parameter \mathbf{w} , the interaction function will be abbreviated as $\mathbf{f}(\mathbf{y})$ for simplicity. In the interaction function (5), for example, $w_{i,j+1}$ represents the strength with which the product of the expression of the j -th gene acts on the expression process of the i -th gene, and the coefficients of the quadratic or higher terms, for example, the coefficient of $y_j y_k$, represents that the interaction exists between two proteins produced by the expression of the j -th and k -th genes, and as a result, it acts with the strength of the coefficient on the production of the i -th protein. The state

$\mathbf{x}(t)$ evolves in time according to the differential equations (3) and (4). In the time evolution of $\mathbf{x}(t)$, when the sign of the i -th element $x_i(t)$ of $\mathbf{x}(t)$ changes, the value of the i -th element $y_i(t)$ of $\mathbf{y}(t)$ changes and the expression pattern $\mathbf{y}(t)$ changes from one pattern to another. Therefore, this series of temporal changes in the expression pattern $\mathbf{y}(t)$ represents the order in which the expression and non-expression of the genes in the GRN change.

In this paper, a change in \mathbf{y} is called a transition of EP, and the transition of \mathbf{y} from one EP $\hat{\mathbf{y}}$ to another EP $\bar{\mathbf{y}}$ is denoted as $\hat{\mathbf{y}} \rightarrow \bar{\mathbf{y}}$. Furthermore, suppose that the EP transits as $\mathbf{y}^{(0)} \rightarrow \mathbf{y}^{(1)} \rightarrow \mathbf{y}^{(2)} \rightarrow \dots$ when $\mathbf{x}(t)$ evolves over time from an initial state $\mathbf{x}(0)$ according to the differential equations (3) and (4). The sequence of transitions of this EP is called the expression pattern sequence (EPS), and in this case, the GRN is said to have this EPS.

Let $\phi(t, \mathbf{x}_0, \mathbf{w})$ be the solution of the differential equations at time t with the initial condition $\mathbf{x}(0) = \mathbf{x}_0$. We assume that the GRN of (3) and (4) has a periodic solution, which realizes the rhythm phenomenon. Let γ be the orbit in the state space of the periodic solution of the GRN of (3) and (4), and let \mathbf{x}_γ be a point on this orbit γ . The following equation holds

$$\mathbf{x}_\gamma = \phi(T, \mathbf{x}_\gamma, \mathbf{w}) \quad (6)$$

for any point $\mathbf{x}_\gamma \in \gamma$ where T is the period of the periodic solution and T depends on the parameter \mathbf{w} of the GRN. Let EPS of the periodic orbit γ be expressed as the periodic EPS as

$$\mathbf{y}^{*(0)} \rightarrow \mathbf{y}^{*(1)} \rightarrow \dots \rightarrow \mathbf{y}^{*(p)}, \quad \mathbf{y}^{*(0)} = \mathbf{y}^{*(p)} \quad (7)$$

where p is the number of transitions. The purpose of this paper is to propose an analysis method of parameter sensitivities of the period T of the periodic solution of the GRN with the periodic EPS given by (7). Therefore, we assume that this periodic EPS does not change if the parameter \mathbf{w} changes slightly. In the following, one of the elements of the parameter \mathbf{w} is denoted by w_j and the sensitivity of the period to the parameter w_j is denoted by $\frac{\partial T}{\partial w_j}$. We propose a method to analytically derive the parameter sensitivity of the period, i.e., $\frac{\partial T}{\partial w_j}$.

III. ANALYSIS METHOD OF PARAMETER SENSITIVITY FOR PERIOD

In order to obtain the parameter sensitivity of a periodic orbit γ to the period, it is first necessary to obtain a mathematical expression for the dependence of the period on the parameters. Although it is generally difficult to obtain such an expression, we show that mathematical expressions for the parameter dependence of the period can be derived for the piecewise-linear differential-equation model. In this paper, we propose a method for analytically obtaining period sensitivity using the expressions.

A. Mathematical Preliminary

In the following, some mathematical preliminaries are given in order to derive the period sensitivity. The Poincaré

map is known as an important tool for analyzing the qualitative properties and stability of periodic solutions. The basic concept of the Poincaré map is to replace the analysis of the periodic orbit of a continuous-time system with that of a discrete-time system with the dimension being one lower than it, and it is defined as follows [15].

Let \mathbf{x}_{γ_0} be a point on a periodic orbit γ . We consider a hypersurface $\Sigma \subset \mathbb{R}^n$ of dimension $n-1$ to which the orbit γ is transverse at the point \mathbf{x}_{γ_0} . Σ is called the Poincaré cross section. Let $U \subset \Sigma$ be some neighborhood of the point \mathbf{x}_{γ_0} and U is defined such a way that the solution orbit of the system (3) and (4) starting from the point $\mathbf{x}_0 \in U$ moves and returns to a point in Σ after slight a different time from T . The Poincaré map $P : U \rightarrow \Sigma$ is defined for a point $\mathbf{x}_0 \in U$ by

$$P(\mathbf{x}_0) = \phi(T'(\mathbf{x}_0), \mathbf{x}_0, \mathbf{p}) \quad (8)$$

where $T'(\mathbf{x}_0)$ is the time taken for the orbit $\phi(t, \mathbf{x}_0, \mathbf{p})$ based at \mathbf{x}_0 to first return to Σ , that is $T'(\mathbf{x}_0) = \min \{t \mid \phi(t, \mathbf{x}_0, \mathbf{p}) \in \Sigma\}$. Obviously, the relations $\mathbf{x}_{\gamma_0} = P(\mathbf{x}_{\gamma_0})$ and $T'(\mathbf{x}_{\gamma_0}) = T$ hold, and \mathbf{x}_{γ_0} is a fixed point of the Poincaré map.

B. Mathematical Expression of Parameter Dependence for Period

In this paper, the Poincaré section is set to S_0 defined below, and the initial time $t = 0$ is the time when the target periodic solution γ crosses S_0 . For an EP \mathbf{y} we define a region $\Omega_{\mathbf{y}}$ as

$$\Omega_{\mathbf{y}} := \{\mathbf{x} \mid \mathbf{y} = \mathbf{H}(\mathbf{x})\},$$

that is, $\Omega_{\mathbf{y}}$ is the region of the n -dimensional space in which the GRN takes the EP \mathbf{y} . As can be seen from the definition of the threshold function h , $\Omega_{\mathbf{y}}$ is one of the quadrants of the n -dimensional real space. Here we consider two successive expression patterns $\mathbf{y}^{*(r)}$ and $\mathbf{y}^{*(r+1)}$ in the EPS (7) of the GRN. We assume that there exists the index i_r such that the following relation holds: $y_{i_r}^{*(r)} \neq y_{i_r}^{*(r+1)}$, $y_i^{*(r)} = y_i^{*(r+1)}$, $\forall i \neq i_r$ for $\mathbf{y}^{*(r)}$ and $\mathbf{y}^{*(r+1)}$. Let us define S_r , $r = 0, 1, \dots, p-1$ as

$$S_r := \left\{ \mathbf{x} \mid x_{i_r} = 0, y_i^{*(r)} = h(x_i), \right. \\ \left. i = 1, 2, \dots, i_r - 1, i_r + 1, \dots, n \right\}. \quad (9)$$

Note that S_r is the boundary between the regions $\Omega_{\mathbf{y}^{*(r)}}$ and $\Omega_{\mathbf{y}^{*(r+1)}}$.

Furthermore, suppose that the relation

$$\mathbf{e}(\mathbf{y}^{*(j-1)}) \in \text{int}(\Omega_{\mathbf{y}^{*(j)}}), \quad \forall j \in \{1, 2, \dots, p-1\} \quad (10)$$

holds, that is, $\mathbf{e}(\mathbf{y})$ is an interior point of $\Omega_{\mathbf{y}^{*(j)}}$ where $\mathbf{e}(\mathbf{y})$ is defined for an EP \mathbf{y} as follows:

$$\mathbf{e}(\mathbf{y}) := \left[\frac{f_1(\mathbf{y})}{d_1} \quad \frac{f_2(\mathbf{y})}{d_2} \quad \dots \quad \frac{f_n(\mathbf{y})}{d_n} \right]^T. \quad (11)$$

Note that $\mathbf{e}(\mathbf{y})$ corresponds to \mathbf{x} obtained when the left-hand side of (3) is set to zero, $\dot{\mathbf{x}}(t) = 0$. Under this assumption any trajectory passing through $\Omega_{\mathbf{y}^{*(j-1)}}$ evolves to $\Omega_{\mathbf{y}^{*(j)}}$. It

is generally difficult to express a period in terms of system parameters, but by utilizing this piecewise-linear property, the coordinates where the periodic solution intersects with S_r , $r = 1, 2, \dots, p$ and the time at which it passes through that intersection can be expressed in terms of the parameter \mathbf{w} as follows. Under the assumption (10), the intersection point $\Psi^{(r)}(\mathbf{x}_0)$, $r = 1, 2, \dots, p$ where the solution trajectory starting from the point \mathbf{x}_0 on the Poincaré cross section intersects with S_r can be expressed as follows [8]:

$$\Psi_i^{(r+1)}(\mathbf{x}_0) := e_i(\mathbf{y}^{*(r)}) + \left(\Psi_i^{(r)}(\mathbf{x}_0) - e_i(\mathbf{y}^{*(r)}) \right) \\ \times \left(\frac{e_{i_r}(\mathbf{y}^{*(r)})}{e_{i_r}(\mathbf{y}^{*(r)}) - \Psi_{i_r}^{(r)}(\mathbf{x}_0)} \right)^{\frac{d_i}{d_{i_r}}}, \\ i = 1, 2, \dots, n, \quad r = 0, \dots, p-1 \quad (12)$$

where $\Psi^{(0)}(\mathbf{x}) := \mathbf{x}$. Note that $\Psi^{(p)}(\mathbf{x}_0)$ is a point at which the solution trajectory crossing S_{p-1} at the point $\Psi^{(p-1)}(\mathbf{x}_0)$ crosses S_0 . Hence, the Poincaré map is given as follows:

$$P(\mathbf{x}_0) := \Psi^{(p)}(\mathbf{x}_0). \quad (13)$$

Since \mathbf{x}_{γ_0} is the intersection of the the Poincaré cross section and the periodic solution orbit, the following relation holds:

$$\mathbf{x}_{\gamma_0} = P(\mathbf{x}_{\gamma_0}). \quad (14)$$

In addition, the time that it takes for the solution trajectory starting from the point \mathbf{x} on S_r to reach and cross the boundary S_{r+1} , denoted by $T^{(r+1)}(\mathbf{x})$, can be expressed as follows [8]:

$$T^{(r+1)}(\mathbf{x}) \\ = -\frac{1}{d_{i_r}} \left\{ \log \frac{e_{i_r}(\mathbf{y}^{*(r)})}{e_{i_r}(\mathbf{y}^{*(r)}) - x_{i_r}} \right\}. \quad (15)$$

Therefore, the period T of the periodic solution orbit γ can be expressed using the parameters \mathbf{w} and \mathbf{x}_{γ_0} as follows:

$$T = \sum_{r=0}^{p-1} T^{(r+1)}(\Psi^{(r)}(\mathbf{x}_{\gamma_0})). \quad (16)$$

In the following, for simplicity, we will abbreviate $\Psi^{(r)}(\mathbf{x})$ and $T^{(r)}(\mathbf{x})$ as $\Psi^{(r)}$ and $T^{(r)}$, omitting their arguments, unless otherwise necessary.

To aid in understanding the symbols defined so far, an example of the behavior of the GRN using these notations is shown in Fig. 1 for the case $n=3$. Suppose that the solution trajectory starting from \mathbf{x}_0 crosses the boundary S_{r-1} at the intersection point $\Psi^{(r-1)}$ and enters the region $\Omega_{\mathbf{y}^{*(r-1)}}$. The EPS of this region is $\mathbf{y}^{*(r-1)}$, and this solution trajectory evolves in time from the intersection $\Psi^{(r-1)}$ toward the point $\mathbf{e}(\mathbf{y}^{*(r-1)})$. And after $T(\Psi^{(r-1)}(\mathbf{x}_0))$, it crosses the boundary S_r at the intersection $\Psi^{(r)}$ and enters the region $\Omega_{\mathbf{y}^{*(r)}}$, and the EPS changes to $\mathbf{y}^{*(r)}$. Furthermore, the solution trajectory that enters the region $\Omega_{\mathbf{y}^{*(r)}}$ changes direction, evolves in time toward the point $\mathbf{e}(\mathbf{y}^{*(r)})$, and after $T(\Psi^{(r)}(\mathbf{x}_0))$, it intersects with the boundary S_{r+1} at the intersection point $\Psi^{(r+1)}$. In the next section we will

analytically derive the mathematical expression of period sensitivity by taking into account the behavior of the GRN described above.

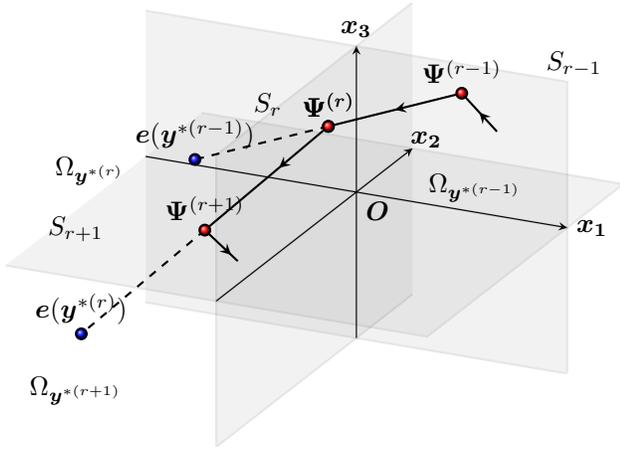


Fig. 1. An example of behavior of the GRN and notations.

C. Deviation of Parameter Sensitivity of Period

The period T can be expressed as in (16). Then, we consider analytically obtaining period sensitivity from this expression. Since the period T is expressed as in (16) and the period T depends on the intersection point x_{γ_0} of the Poincaré cross section and the periodic solution orbit, the problem is how to determine the sensitivity of x_{γ_0} .

First, consider the case of obtaining the sensitivity of the time when the solution trajectory starting from a certain initial state x_0 crosses a certain hyperplane. In this case, since the initial value is given, it does not depend on parameters, that is, the sensitivity is $\frac{\partial x_0}{\partial w_j} = \mathbf{0}$. However, considering the case of calculating the period sensitivity of the periodic solution orbit, the intersection x_{γ_0} between the Poincaré cross section and the periodic solution orbit corresponds to the initial value. In this case, if the parameters vary, the periodic solution orbit varies and so does the intersection x_{γ_0} . In this way, x_{γ_0} depends on the parameter w , and the period T depends on the parameters w and x_{γ_0} . From this fact, when calculating the periodic sensitivity, the problem arises of how to calculate the sensitivity $\frac{\partial x_{\gamma_0}}{\partial w_j}$. The following lemma obtains this sensitivity analytically.

Lemma 1: Suppose that the GRN described by (3) and (4) has a periodic solution orbit and that the EPS of the periodic solution orbit is given by (7). Assume also that (10) holds. Then, the sensitivity of the intersection x_{γ_0} of the Poincaré cross section S_0 and the periodic solution orbit γ is obtained by the following equation.

$$\frac{\partial x_{\gamma_0}}{\partial w_j} = (\mathbf{I} - \mathbf{A}^{(p)})^{-1} \mathbf{B}^{(p)} \quad (17)$$

where

$$\mathbf{A}^{(r+1)} = \prod_{k=0}^r \frac{\partial \Psi^{(k+1)}}{\partial \Psi^{(k)}} \quad (18)$$

$$\begin{aligned} \mathbf{B}^{(r+1)} &= \prod_{k=1}^r \frac{\partial \Psi^{(k+1)}}{\partial \Psi^{(k)}} \frac{\partial \Psi^{(1)}}{\partial e(\mathbf{y}^{*(0)})} \frac{\partial e(\mathbf{y}^{*(0)})}{\partial w_j} \\ &+ \prod_{k=2}^r \frac{\partial \Psi^{(k+1)}}{\partial \Psi^{(k)}} \frac{\partial \Psi^{(2)}}{\partial e(\mathbf{y}^{*(1)})} \frac{\partial e(\mathbf{y}^{*(1)})}{\partial w_j} + \dots \\ &+ \frac{\partial \Psi^{(r+1)}}{\partial \Psi^{(r)}} \frac{\partial \Psi^{(r)}}{\partial e(\mathbf{y}^{*(r-1)})} \frac{\partial e(\mathbf{y}^{*(r-1)})}{\partial w_j} \\ &+ \frac{\partial \Psi^{(r+1)}}{\partial e(\mathbf{y}^{*(r)})} \frac{\partial e(\mathbf{y}^{*(r)})}{\partial w_j}. \end{aligned} \quad (19)$$

Proof: Consider a small change in the parameter w and assume that the GRN of (3) and (4) has a periodic solution orbit even after the change in the parameter. Since the EPS does not change, the values that change due to a small change in w are x_{γ_0} , $e(\mathbf{y}^{*(r)})$, $\Psi^{(r+1)}$, $T^{(r+1)}$, $r = 0, 1, \dots, p-1$, which depend on the parameter w . With this in mind, we derive $\frac{\partial x_{\gamma_0}}{\partial w_j}$.

Differentiating both sides of (14) with respect to w_j , we have:

$$\frac{\partial x_{\gamma_0}}{\partial w_j} = \frac{\partial \Psi^{(p)}(x_{\gamma_0})}{\partial w_j}. \quad (20)$$

Let express the right side of the above equation by $\frac{\partial x_{\gamma_0}}{\partial w_j}$. From the definition of $\Psi^{(r+1)}$, we obtain the following equation.

$$\begin{aligned} \frac{\partial \Psi^{(r+1)}}{\partial w_j} &= \frac{\partial \Psi^{(r+1)}}{\partial \Psi^{(r)}} \frac{\partial \Psi^{(r)}}{\partial w_j} + \frac{\partial \Psi^{(r+1)}}{\partial e(\mathbf{y}^{*(r)})} \frac{\partial e(\mathbf{y}^{*(r)})}{\partial w_j}, \\ r &= 0, 1, \dots, p-1. \end{aligned} \quad (21)$$

Substituting the expression $\frac{\partial \Psi^{(k)}}{\partial w_j}$ into $\frac{\partial \Psi^{(k+1)}}{\partial w_j}$ in sequence from $k = r-1$ to $k = 0$, and rearranging the results for $\frac{\partial x_{\gamma_0}}{\partial w_j}$ and $\frac{\partial e(\mathbf{y}^{*(r)})}{\partial w_j}$, $r = 0, 1, \dots, p-1$, we obtain the following equation.

$$\begin{aligned} \frac{\partial \Psi^{(r+1)}}{\partial w_j} &= \frac{\partial \Psi^{(r+1)}}{\partial \Psi^{(r)}} \left\{ \frac{\partial \Psi^{(r)}}{\partial \Psi^{(r-1)}} \frac{\partial \Psi^{(r-1)}}{\partial w_j} \right. \\ &+ \left. \frac{\partial \Psi^{(r)}}{\partial e(\mathbf{y}^{*(r-1)})} \frac{\partial e(\mathbf{y}^{*(r-1)})}{\partial w_j} \right\} \\ &+ \frac{\partial \Psi^{(r+1)}}{\partial e(\mathbf{y}^{*(r)})} \frac{\partial e(\mathbf{y}^{*(r)})}{\partial w_j} \\ &= \prod_{k=0}^r \frac{\partial \Psi^{(k+1)}}{\partial \Psi^{(k)}} \frac{\partial \Psi^{(0)}}{\partial w_j} \\ &+ \prod_{k=1}^r \frac{\partial \Psi^{(k+1)}}{\partial \Psi^{(k)}} \frac{\partial \Psi^{(1)}}{\partial e(\mathbf{y}^{*(0)})} \frac{\partial e(\mathbf{y}^{*(0)})}{\partial w_j} \\ &+ \prod_{k=2}^r \frac{\partial \Psi^{(k+1)}}{\partial \Psi^{(k)}} \frac{\partial \Psi^{(2)}}{\partial e(\mathbf{y}^{*(1)})} \frac{\partial e(\mathbf{y}^{*(1)})}{\partial w_j} + \dots \\ &+ \frac{\partial \Psi^{(r+1)}}{\partial \Psi^{(r)}} \frac{\partial \Psi^{(r)}}{\partial e(\mathbf{y}^{*(r-1)})} \frac{\partial e(\mathbf{y}^{*(r-1)})}{\partial w_j} \\ &+ \frac{\partial \Psi^{(r+1)}}{\partial e(\mathbf{y}^{*(r)})} \frac{\partial e(\mathbf{y}^{*(r)})}{\partial w_j} \end{aligned}$$

$$= \mathbf{A}^{(r+1)} \frac{\partial \mathbf{x}_{\gamma_0}}{\partial w_j} + \mathbf{B}^{(r+1)}, \quad r = 0, 1, \dots, p-1. \quad (22)$$

Therefore, (17) is derived from (20) and (22). ■

Once the expression for the sensitivity of \mathbf{x}_{γ_0} is obtained, the expression for the sensitivity of the period can be derived. The result is shown in the following theorem.

Theorem 1: Suppose that the GRN described by (3) and (4) has a periodic solution orbit and that the EPS of the periodic solution orbit is given by (7). Assume also that (10) holds. Then, the sensitivity of the period is obtained by the following equation.

$$\begin{aligned} \frac{\partial T}{\partial w_j} &= \sum_{r=0}^{p-1} \frac{\partial T^{(r+1)}}{\partial \Psi^{(r)}} \mathbf{A}^{(r)} (\mathbf{I} - \mathbf{A}^{(p)})^{-1} \mathbf{B}^{(p)} \\ &+ \sum_{r=0}^{p-1} \left(\frac{\partial T^{(r+1)}}{\partial \Psi^{(r)}} \mathbf{B}^{(r)} + \frac{\partial T^{(r+1)}}{\partial \mathbf{e}(\mathbf{y}^{*(r)})} \frac{\partial \mathbf{e}(\mathbf{y}^{*(r)})}{\partial w_j} \right) \end{aligned} \quad (23)$$

with $\mathbf{A}^{(0)}$ and $\mathbf{B}^{(0)}$ being $\mathbf{A}^{(0)} = \mathbf{I}$, $\mathbf{B}^{(0)} = \mathbf{0}$.

Proof: Since the period T is expressed as (16), by differentiating both sides with respect to w_j and substituting (22), we obtain the following equation.

$$\begin{aligned} \frac{\partial T}{\partial w_j} &= \sum_{r=0}^{p-1} \frac{\partial T^{(r+1)}}{\partial w_j} \\ &= \sum_{r=0}^{p-1} \left(\frac{\partial T^{(r+1)}}{\partial \Psi^{(r)}} \frac{\partial \Psi^{(r)}}{\partial w_j} + \frac{\partial T^{(r+1)}}{\partial \mathbf{e}(\mathbf{y}^{*(r)})} \frac{\partial \mathbf{e}(\mathbf{y}^{*(r)})}{\partial w_j} \right) \\ &= \sum_{r=0}^{p-1} \left\{ \frac{\partial T^{(r+1)}}{\partial \Psi^{(r)}} \left(\mathbf{A}^{(r)} \frac{\partial \mathbf{x}_{\gamma_0}}{\partial w_j} + \mathbf{B}^{(r)} \right) \right. \\ &\quad \left. + \frac{\partial T^{(r+1)}}{\partial \mathbf{e}(\mathbf{y}^{*(r)})} \frac{\partial \mathbf{e}(\mathbf{y}^{*(r)})}{\partial w_j} \right\} \\ &= \sum_{r=0}^{p-1} \frac{\partial T^{(r+1)}}{\partial \Psi^{(r)}} \mathbf{A}^{(r)} \frac{\partial \mathbf{x}_{\gamma_0}}{\partial w_j} \\ &\quad + \sum_{r=0}^{p-1} \left(\frac{\partial T^{(r+1)}}{\partial \Psi^{(r)}} \mathbf{B}^{(r)} + \frac{\partial T^{(r+1)}}{\partial \mathbf{e}(\mathbf{y}^{*(r)})} \frac{\partial \mathbf{e}(\mathbf{y}^{*(r)})}{\partial w_j} \right) \end{aligned} \quad (24)$$

Substituting (17) into the right-hand side of the above equation, we obtain (23). ■

IV. NUMERICAL EXAMPLE

We calculate the period sensitivity of the periodic phenomenon in the GRN given by the following piecewise linear-differential-equation model.

$$\begin{aligned} \frac{dx_i(t)}{dt} &= -x_i(t) + w_{i,1} + w_{i,2}y_1(t) + w_{i,3}y_2(t) \\ &+ w_{i,4}y_3(t) + w_{i,5}y_1(t)y_2(t) \\ &+ w_{i,6}y_1(t)y_3(t) + w_{i,7}y_2(t)y_3(t) \\ &+ w_{i,8}y_1(t)y_2(t)y_3(t), \quad i = 1, 2, 3 \end{aligned} \quad (25)$$

where the parameters \mathbf{w} are $\mathbf{w}_1 = [1 \ 1 \ -1 \ -4 \ 2 \ 2 \ 2 \ -4]$, $\mathbf{w}_2 = [-3 \ 4 \ 3 \ 1 \ -2 \ -2 \ -2 \ 4]$, $\mathbf{w}_3 = [-2 \ -$

$1 \ 2 \ 1 \ 2 \ 2 \ 2 \ -4]$. This GRN has a periodic orbit as shown in Fig. 2 with a period of $T = 7.62117979882$, and the intersection with the Poincaré cross section S_0 is $\gamma_0 = [2.5615528128 \ 1.4384471872 \ 0.0]^T$. The periodic EPS of this periodic solution orbit is as follows:

$$\begin{aligned} [1 \ 1 \ 1]^T &\rightarrow [0 \ 1 \ 1]^T \rightarrow [0 \ 0 \ 1]^T \rightarrow [0 \ 0 \ 0]^T \\ &\rightarrow [1 \ 0 \ 0]^T \rightarrow [1 \ 1 \ 0]^T \rightarrow [1 \ 1 \ 1]^T. \end{aligned} \quad (26)$$

The period sensitivity of this periodic orbit in the GRN was

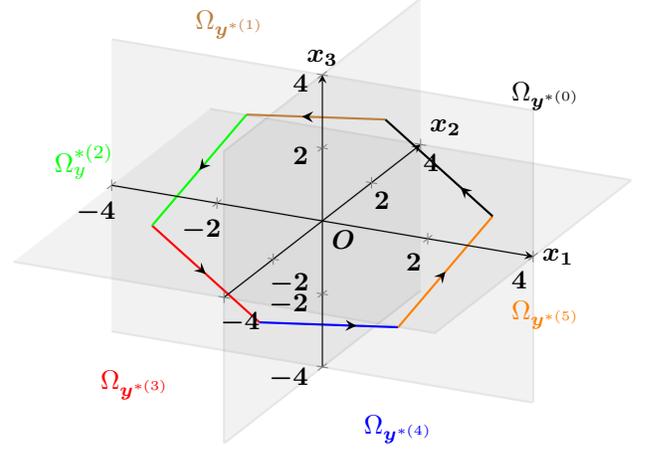


Fig. 2. The periodic solution orbit of the GRN (25).

obtained by the proposed method. For comparison, the period sensitivity was obtained by the difference approximation method. The results are shown in Table I. In the difference approximation method, we first obtained the period, denoted by \hat{T} , when the parameter w_j changed slightly by $\Delta w_j = 0.0001, 0.001, \text{ and } 0.01$. and calculated approximated values of the period sensitivity by $\Delta T / \Delta w_j = (\hat{T} - T) / \Delta w_j$. The difference approximation method is expected to give a good approximation of the sensitivities with good accuracy if the value of the difference Δw_j is chosen appropriately. Table 1 shows that the values of the sensitivities for $\Delta w_j = 0.001$ are closest to those of the proposed method which theoretically provides the true values, and give approximations with good accuracy. This shows that the proposed method gives the appropriate values of the sensitivities, which indicates the validity of the proposed method.

V. CONCLUSION

Rhythm phenomena are interesting nonlinear phenomena found in any kind of systems, and there is a growing research effort to elucidate the mechanisms of their occurrence and to use the results to solve various problems in the analysis and design of systems. One of the important tools in these studies is the sensitivity analysis method. In this paper, we consider a piecewise-linear differential-equation model as a model of GRNs and proposed an analysis method for period sensitivity of periodic phenomena in GRNs. In the case of the piecewise-linear differential-equation model, its dynamics switches depending on the expression patterns,

TABLE I

AN EXAMPLE OF THE RESULTS OF PERIOD SENSITIVITY OBTAINED BY THE PROPOSED METHOD AND DIFFERENCE APPROXIMATION METHOD

Sensitivities	Proposed method	$\Delta w_j = 0.0001$	$\Delta w_j = 0.001$	$\Delta w_j = 0.01$
$\frac{\partial T}{\partial w_{1,1}}$	-0.03563	0.00009730	0.0009726	0.009726
$\frac{\partial T}{\partial w_{1,2}}$	1.137	1.174	1.175	1.179
$\frac{\partial T}{\partial w_{1,3}}$	1.009	1.038	1.039	1.043
$\frac{\partial T}{\partial w_{1,4}}$	1.077	1.106	1.107	1.111
$\frac{\partial T}{\partial w_{1,5}}$	0.5536	0.5532	0.5536	0.5576
$\frac{\partial T}{\partial w_{1,6}}$	0.8638	0.8639	0.8643	0.8687
$\frac{\partial T}{\partial w_{1,7}}$	0.7958	0.7958	0.7962	0.8006
$\frac{\partial T}{\partial w_{1,8}}$	0.8638	0.8639	0.8643	0.8687
$\frac{\partial T}{\partial w_{2,1}}$	0.008250	-0.06021	0.0009726	0.01591
$\frac{\partial T}{\partial w_{2,2}}$	-0.5470	-0.4418	-0.5527	-0.5598
$\frac{\partial T}{\partial w_{2,3}}$	1.174	1.800	1.175	1.117
$\frac{\partial T}{\partial w_{2,4}}$	0.3106	0.9262	0.3106	0.2488
$\frac{\partial T}{\partial w_{2,5}}$	1.039	1.725	1.110	1.046
$\frac{\partial T}{\partial w_{2,6}}$	0.2425	0.2453	0.2425	0.2420
$\frac{\partial T}{\partial w_{2,7}}$	1.106	1.119	1.107	1.110
$\frac{\partial T}{\partial w_{2,8}}$	0.2425	0.2453	0.2425	0.2420
$\frac{\partial T}{\partial w_{3,1}}$	0.01682	-1.719	0.0009726	0.1817
$\frac{\partial T}{\partial w_{3,2}}$	-1.022	-2.702	-1.038	-0.8670
$\frac{\partial T}{\partial w_{3,3}}$	-0.5405	-1.841	-0.5527	-0.4203
$\frac{\partial T}{\partial w_{3,4}}$	-0.7829	-2.094	-0.7952	-0.6613
$\frac{\partial T}{\partial w_{3,5}}$	1.174	1.225	1.175	1.174
$\frac{\partial T}{\partial w_{3,6}}$	0.06806	0.07102	0.06810	0.06778
$\frac{\partial T}{\partial w_{3,7}}$	0.3105	0.3240	0.3106	0.3088
$\frac{\partial T}{\partial w_{3,8}}$	0.06806	0.07102	0.06810	0.06778

the sensitivity analysis method previously proposed cannot be utilized. However, it is possible for the piecewise-linear differential-equation model to analytically derive the coordinates and the time instants of the solution trajectory when the dynamics switches. Using the results, we proposed a method to analytically obtain period sensitivity. It is confirmed from numerical examples that period sensitivity can be obtained appropriately by the proposed method. In general, the difference approximation method is often used to obtain sensitivities. However, this method cannot obtain a good approximation of sensitivities unless the difference width is appropriately chosen. In contrast, the method proposed in this paper theoretically gives the true values of sensitivities, so the above problem of the difference approximation method does not occur.

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