

Exact Closed-form Sensitivity Analysis of Phase and Period for Cyclic Expression Pattern Sequences in Gene Regulatory Networks

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Abstract—Sensitivity analysis is important and essential in the 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 sensitivities of phase and period, which play one of the fundamental roles in periodic phenomena. A piecewise-linear differential-equation model is utilized as a model of GRNs. Rhythm phenomena are modeled 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 limited research has been conducted. Generally, phase and period sensitivities are obtained approximately using numerical methods. In this paper, we analytically derive exact closed-form mathematical expressions of the sensitivities of phase and period of GRNs, which is highly advantageous because they bring both the accuracy of the analysis results and computational efficiency.

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 the functions of living cells and many studies have been done from various viewpoints. Recently there has 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].

Meanwhile, investigating how the behavior, characteristic 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, characteristic 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, that is, sensitivity analysis is 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 phase and period which play one of the important roles in rhythm phenomena and propose an analysis method of phase and period sensitivities.

Sensitivity analysis of systems has a long history, and many studies have been conducted. However, research on the sensitivity analysis of periodic phenomena remains limited. 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 on the parameters. Despite these difficulties, several studies on sensitivity analyses of periodic phenomena have been conducted [9]–[12]. However, they have problems such as approximate treatment, lack of specific calculation methods, and lack of consideration of computational efficiency. The authors have already studied sensitivity analysis methods for rhythm phenomena for the period [13] and phase [14], and proposed a sensitivity analysis algorithm with enough accuracy and computational efficiency.

In this paper, we propose a sensitivity analysis method of phase and period for cyclic expression pattern sequences in GRNs. We derive exact close-form expressions of the sensitivities, which is highly advantageous because they bring both the accuracy of the analysis results and computational efficiency. 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 piecewise-linear differential-equation models, the dynamics switch depending on the expression pattern, and the solution trajectory is non-smooth. Therefore, the method in [13], [14] cannot be applied to analyze those sensitivities for the model of GRNs. In contrast, this model allows for the analytical expressions of the coordinates and time instants of the solution trajectory when the dynamics switch. We have already proposed an analysis method of period sensitivity of GRNs [15]. In this paper, we propose a method for simultaneously obtaining phase and period sensitivities of GRNs. The proposed method provides the exact closed-form expressions for both sensitivities.

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II. TARGET SYSTEM AND PROBLEM DESCRIPTION

A. Mathematical Model of Gene Regulatory Networks

In this paper, we discuss sensitivity analysis method for GRNs focusing on their behavior based on expression patterns. There have been several mathematical models developed for GRNs, among which a piecewise-linear differential-equation model is known to be suitable for describing the expression levels of GRNs. Consider a mathematical model of GRNs described by the ordinary differential equations of the form [5]:

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

where n is the number of genes, $x_i(t)$ is the 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:

$$\begin{aligned} \dot{\mathbf{x}}(t) &= -\mathbf{D}\mathbf{x}(t) + \mathbf{f}(\mathbf{y}(t), \mathbf{w}), \quad \mathbf{x}(0) = \mathbf{x}_0, \quad (3) \\ \mathbf{y}(t) &= \mathbf{h}(\mathbf{x}(t)) \quad (4) \end{aligned}$$

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

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

or its equivalent is often used [16]. In this paper, we will use this equation 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 sequence in which the expression and non-expression of genes in the GRN change over time.

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, let the EP transit 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.

B. Problem Formulation for Sensitivity Analysis

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 considered in this paper. Let γ be the orbit in the state space of the periodic solution of the GRN of (3) and (4), and let $\mathbf{x}_\gamma$ 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. Let the EPS of the periodic orbit γ be expressed as the periodic EPS by

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

where p is the number of transitions. The purpose of this paper is to propose an analysis method of parameter sensitivities of phase and period of the periodic solution of the GRN with the periodic EPS given by (7).

Parameter sensitivity is usually defined as the derivative with respect to the parameter, and this paper adopts the definition. The parameter sensitivity of the period T is defined as $\frac{\partial T}{\partial \mathbf{w}}$. In the case of phase, it is first necessary to clarify how the phase is defined. In this paper, we define the phase of the periodic orbit γ as follows. Consider the time when an event of interest occurs within one cycle of γ . This time instance is defined as the difference from an appropriately defined reference time and is denoted by t_{ev} . The time t_{ev} depends on the parameter $\mathbf{w}$ of the GRN and we denote it by $t_{ev}(\mathbf{w})$. Let $\theta(\mathbf{w})$ be the phase at the time t_{ev} and it is defined as follows:

$$\theta(\mathbf{w}) = 2\pi \frac{t_{ev}(\mathbf{w})}{T(\mathbf{w})}. \quad (8)$$

By differentiating both sides of (8) with respect to $\mathbf{w}$, the phase sensitivity is expressed by

$$\frac{\partial}{\partial \mathbf{w}} \theta(\mathbf{w}) = 2\pi \frac{\frac{\partial t_{ev}(\mathbf{w})}{\partial \mathbf{w}} T(\mathbf{w}) - t_{ev}(\mathbf{w}) \frac{\partial T(\mathbf{w})}{\partial \mathbf{w}}}{T^2(\mathbf{w})}. \quad (9)$$

Therefore, the phase sensitivity can be obtained by deriving the sensitivity of the time at which the event occurs, $\partial t_{ev}(\mathbf{w})/\partial \mathbf{w}$, and the sensitivity of the period, $\partial T(\mathbf{w})/\partial \mathbf{w}$. In this paper we propose analysis method of the parameter sensitivities of the period and the phase defined above. We will derive a method for simultaneously obtaining exact closed-form expressions of the sensitivities $\frac{\partial T}{\partial \mathbf{w}}$ and $\frac{\partial \theta}{\partial \mathbf{w}}$.

Here we explain the mathematical model that provides the time t_{ev} . The time t_{ev} when such an event occurs is generally expressed as the time that satisfies the following equation using the function $\mathcal{E}_v : \mathbb{U}_{ev} \times \mathbb{R}^{\sum_{i=1}^n m_i} \rightarrow \mathbb{R}$, which depends on the system state $\mathbf{x}$ and parameter $\mathbf{w}$.

$$\mathcal{E}_v(\mathbf{x}_{ev}, \mathbf{w}) = 0 \quad (10)$$

where $\mathbf{x}_{ev}$ is:

$$\mathbf{x}_{ev} = \mathbf{x}(t_{ev}). \quad (11)$$

Here, $\mathbb{U}_{ev}$ is a region within the state space: $\mathbb{U}_{ev} \subset \mathbb{R}^n$. Examples of the function $\mathcal{E}_v$ is as follows. Consider the event in which the i -th element of state $\mathbf{x}$ becomes zero and all other elements take positive values. Then, (10) can be expressed as $x_i(t_{ev}) = 0$, $\mathbf{x}(t_{ev}) \in \mathbb{U}_{ev}$, $\mathbb{U}_{ev} = \{\mathbf{x} \mid x_j > 0, \forall j \neq i\}$. Therefore, the function $\mathcal{E}_v$ is

$$\mathcal{E}_v(\mathbf{x}_{ev}, \mathbf{w}) = x_i.$$

Similarly, consider the event in which the i -th element of state $\mathbf{x}$ becomes zero and takes an extreme value satisfying $\frac{d}{dt}x_i(t) = 0$, while the other elements take positive values. (10) can be expressed as $\frac{d}{dt}x_i(t_{ev}) = f_i(\mathbf{x}(t_{ev}), \mathbf{w}) = 0$, $\mathbf{x}(t_{ev}) \in \mathbb{U}_{ev}$, $\mathbb{U}_{ev} = \{\mathbf{x} \mid x_j > 0, \forall j \neq i\}$. Thus, the function $\mathcal{E}_v$ is

$$\mathcal{E}_v(\mathbf{x}_{ev}, \mathbf{w}) = \frac{d}{dt}x_i = f_i(\mathbf{x}, \mathbf{w}).$$

III. PROPOSED SENSITIVITY ANALYSIS METHOD FOR PHASE AND PERIOD

A. Mathematical Preliminary

In the following, some mathematical preliminaries are given in order to derive the sensitivities. 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 [17].

Let $\mathbf{x}_{\gamma_0}$ be a point on a periodic orbit γ . We consider a hyper-surface $\Sigma \subset \mathbb{R}^n$ of dimension $n - 1$ to which the orbit γ is transverse at the point $\mathbf{x}_{\gamma_0}$. Σ is called the Poincaré cross section. Let $U \subset \Sigma$ be some neighborhood of the point $\mathbf{x}_{\gamma_0}$ 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

$$P(\mathbf{x}_0) = \phi(T'(\mathbf{x}_0), \mathbf{x}_0, \mathbf{w}) \quad (12)$$

where $T'(\mathbf{x}_0)$ is the time taken for the orbit $\phi(t, \mathbf{x}_0, \mathbf{w})$ based at $\mathbf{x}_0$ to first return to Σ , that is $T'(\mathbf{x}_0) = \min \{t > 0 \mid \phi(t, \mathbf{x}_0, \mathbf{w}) \in \Sigma\}$. Obviously, the relations $\mathbf{x}_{\gamma_0} = P(\mathbf{x}_{\gamma_0})$ and $T'(\mathbf{x}_{\gamma_0}) = T$ hold, and $\mathbf{x}_{\gamma_0}$ is a fixed point of the Poincaré map.

B. Mathematical Expression of Parameter Dependence for Phase and Period

Suppose that the Poincaré cross section Σ is expressed by the following equation:

$$\sigma(\mathbf{x}) = 0$$

where σ is the map $\sigma : \mathbb{R}^n \rightarrow \mathbb{R}$. Suppose that the Poincaré cross section can be set appropriately for the target periodic orbit γ , and that $\sigma(\mathbf{x})$ is known. Let $\mathbf{x}_{\gamma_0}$ be the intersection of the periodic orbit γ with the Poincaré cross section Σ . The following equations hold:

$$\mathbf{x}_{\gamma_0} = \phi(T, \mathbf{x}_{\gamma_0}, \mathbf{w}), \quad (13)$$

$$\sigma(\mathbf{x}_{\gamma_0}) = 0. \quad (14)$$

Note that in (13) we let $\mathbf{x}(0) = \mathbf{x}_{\gamma_0}$ and (11) is rewritten as:

$$\mathbf{x}_{ev} = \phi(t_{ev}, \mathbf{x}_{\gamma_0}, \mathbf{w}). \quad (15)$$

In [13], [14] a method is proposed to obtain the parameter sensitivities of the period and phase of a periodic orbit for nonlinear systems with smooth solution orbits, based on the relations (13), (14) and (15). That is, they derive mathematical expressions for the variations of period and phase when parameters vary slightly, and propose a method for calculating the sensitivities based on these expressions. However, the GRNs targeted in this study do not have smooth solution trajectories, and their dynamics change piecewisely, so their methods cannot be used and a method which can deal with the dynamics of the GRN should be developed.

We first derive expressions corresponding to (13) taking into account the dynamics of the GRNs considered in this paper. For this purpose, we make the following assumptions.

Assumption 1: Suppose that the GRN represented by (3) and (4) has a periodic orbit γ and its EPS is expressed by (7). We assume that only one element differs between two adjacent EPs $\mathbf{y}^{(r)}$ and $\mathbf{y}^{(r+1)}$ for $r = 0, 1, \dots, p - 1$.

This assumption is practically reasonable because it is very rare for the signs of two or more elements of $\mathbf{x}(t) \in \gamma$ to change at exactly the same time. We denote by i_r the indices of the element that differ between $\mathbf{y}^{*(r)}$ and $\mathbf{y}^{*(r+1)}$, that is, 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 some notations necessary for the discussion. 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 $\mathbb{R}^n$ 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. Let us define S_{r+1} , $r = 0, 1, \dots, p-1$ as:

$$S_{r+1} := \left\{ \mathbf{x} \mid x_{i_r} = 0, y_i^{*(r)} = h(x_i), \right. \\ \left. i = 1, 2, \dots, i_r - 1, i_r + 1, \dots, n \right\}, \quad (16)$$

and let $S_0 := S_p$. Note that S_{r+1} is the boundary between the regions $\Omega_{\mathbf{y}^{*(r)}}$ and $\Omega_{\mathbf{y}^{*(r+1)}}$, and S_0 is that between $\Omega_{\mathbf{y}^{*(p-1)}}$ and $\Omega_{\mathbf{y}^{*(0)}}$. Note also that the dynamics of the GRN switch at the boundary of the domain $\Omega_{\mathbf{y}}$. Let the point where the periodic solution and S_0 intersect be $\mathbf{x}_{\gamma_0}$, then the periodic solution starting from $\mathbf{x}_{\gamma_0}$ intersects with S_1 , S_2 , $\dots$, and S_{p-1} in that order, and then intersects with S_0 at $\mathbf{x}_{\gamma_0}$. Let $\Psi^{(r)}$, $r = 1, 2, \dots, p-1$ be the coordinates where this periodic orbit intersects with S_r . Let $T^{(r+1)}$ be the time it takes from the point $\Psi^{(r)}$ on S_r where the periodic orbit intersects with S_r until it next intersects with the boundary S_{r+1} . Let $T^{(p)}$ be the time it takes from the point $\Psi^{(p-1)}$ on S_{p-1} where the periodic orbit intersects with S_{p-1} until it intersects with S_0 . Then, the period T is given by the following equation:

$$T = \sum_{r=1}^p T^{(r)}. \quad (17)$$

Next, we consider each smooth interval of the periodic orbit, that is, each interval of the periodic orbit in the region $\Omega_{\mathbf{y}^{*(r)}}$ for $r = 0, 1, \dots, p-1$, and derive equations corresponding to (13) and (14). Since the dynamics of the GRN are linear in $\Omega_{\mathbf{y}}$, its solution can be obtained analytically as follows. Let $\tilde{\mathbf{x}}_0$ be any point in $\Omega_{\mathbf{y}}$, and let $\phi(t, \tilde{\mathbf{x}}_0, \mathbf{w})$ be the state at time t in $\Omega_{\mathbf{y}}$ of the solution trajectory starting from $\tilde{\mathbf{x}}_0$ at time $t = 0$. Then, we obtain:

$$\phi(t, \tilde{\mathbf{x}}_0, \mathbf{w}) = \mathbf{g}(\tilde{\mathbf{x}}_0, t, \mathbf{e}(\mathbf{y}, \mathbf{w})) \quad (18)$$

where $\mathbf{e}(\mathbf{y}, \mathbf{w})$ is defined by $\mathbf{e}(\mathbf{y}, \mathbf{w}) := [f_1(\mathbf{y}, \mathbf{w})/d_1, f_2(\mathbf{y}, \mathbf{w})/d_2, \dots, f_n(\mathbf{y}, \mathbf{w})/d_n]^T$ and i -th element of $\mathbf{g}(\mathbf{x}, t, \mathbf{e}(\mathbf{y}, \mathbf{w}))$, denoted by $g_i(\mathbf{x}, t, \mathbf{e})$, is given as:

$$g_i(\mathbf{x}, t, \mathbf{e}) = x_i \exp(-d_i t) + e_i (1 - \exp(-d_i t)), \\ i = 1, 2, \dots, n \quad (19)$$

where e_i is the i -th element of $\mathbf{e}(\mathbf{y}, \mathbf{w})$. Furthermore, since $\mathbf{x}_{\gamma_0}$ is a point on the periodic orbit, the following equation holds for $\Psi^{(r)}$, $r = 0, 1, \dots, p-1$.

$$\Psi^{(0)} = \Psi^{(p)} = \mathbf{g}(\Psi^{(p-1)}, T^{(p)}, \mathbf{e}(\mathbf{y}^{*(p-1)}, \mathbf{w})), \quad (20)$$

$$\Psi^{(r+1)} = \mathbf{g}(\Psi^{(r)}, T^{(r+1)}, \mathbf{e}(\mathbf{y}^{*(r)}, \mathbf{w})), \\ r = 0, 1, \dots, p-2 \quad (21)$$

where $\Psi^{(0)} := \mathbf{x}_{\gamma_0}$. Since S_0 is taken as the Poincaré cross section, (20) and (21) provide the Poincaré map, yielding the corresponding expression for (13). Furthermore, besides the Poincaré cross section, there exist points on the hyper-planes

S_r , $r = 1, 2, \dots, p-1$ where periodic solutions intersect. For the intersection point $\Psi^{(r)}$, the following equation holds.

$$\Psi_{i_r}^{(r+1)} = 0, \quad r = 0, 1, \dots, p-1. \quad (22)$$

From (20), (21) and (22) we obtain:

$$T^{(r+1)} = -\frac{1}{d_{i_r}} \log \left(\frac{e_{i_r}(\mathbf{y}^{*(r)}, \mathbf{w})}{e_{i_r}(\mathbf{y}^{*(r)}, \mathbf{w}) - \Psi_{i_r}^{(r)}} \right). \quad (23)$$

Next, we derive an equation corresponding to (15) for the time when the event occurs and the state at that time. Let $\mathbf{x}_{\gamma_0}$ be the reference point in the definition of the phase, and consider the solution trajectory starting from $\mathbf{x}_{\gamma_0}$. For the solution orbit within $\Omega_{\mathbf{y}^{*(r)}}$, $r = 0, 1, \dots, v-1$, (21) holds. Let the time t_{ev} when the event occurs be the time in the time interval which the GRN takes the $(v+1)$ -th expression pattern, that is, $\mathbf{x}(t_{ev}) \in \Omega_{\mathbf{y}^{*(v)}}$. Using T_{ev} that satisfies the following equation

$$\mathbf{x}_{ev} = \mathbf{g}(\Psi^{(v)}, T_{ev}, \mathbf{e}(\mathbf{y}^{*(v)}, \mathbf{w})), \quad (24)$$

the time t_{ev} is expressed as follows:

$$t_{ev} = T_{ev} + \sum_{r=1}^v T^{(r)}. \quad (25)$$

Note that T_{ev} is the elapsed time from when the solution trajectory passes through $\Psi^{(v)}$ until the event occurs.

Supposing that the parameters of the GRN vary from $\mathbf{w}$ by $\Delta \mathbf{w}$ to $\mathbf{w} + \Delta \mathbf{w}$, the equations for the variation of each variable can be derived as follows. From (20) and (21) corresponding to the Poincaré map, and (22) and (17), we obtain:

$$\Delta \Psi^{(0)} = \frac{\partial}{\partial \mathbf{x}} \mathbf{g}^{(p-1)} \Delta \Psi^{(p-1)} + \frac{\partial}{\partial t} \mathbf{g}^{(p-1)} \Delta T^{(p)} \\ + \frac{\partial}{\partial \mathbf{e}} \mathbf{g}^{(p-1)} \frac{\partial}{\partial \mathbf{w}} \mathbf{e}^{(p-1)} \Delta \mathbf{w} + O(\Delta^2), \quad (26)$$

$$\Delta \Psi^{(r+1)} = \frac{\partial}{\partial \mathbf{x}} \mathbf{g}^{(r)} \Delta \Psi^{(r)} + \frac{\partial}{\partial t} \mathbf{g}^{(r)} \Delta T^{(r+1)} \\ + \frac{\partial}{\partial \mathbf{e}} \mathbf{g}^{(r)} \frac{\partial}{\partial \mathbf{w}} \mathbf{e}^{(r)} \Delta \mathbf{w} + O(\Delta^2), \\ r = 0, 1, \dots, p-2, \quad (27)$$

$$\Delta \Psi_{i_r}^{(r+1)} = 0, \quad r = 0, 1, \dots, p-1, \quad (28)$$

$$\Delta T = \sum_{r=1}^p \Delta T^{(r)} \quad (29)$$

where $\mathbf{g}^{(r)} := \mathbf{g}(\Psi^{(r)}, T^{(r+1)}, \mathbf{e}(\mathbf{y}^{*(r)}, \mathbf{w}))$, $\mathbf{e}^{(r)} := \mathbf{e}(\mathbf{y}^{*(r)}, \mathbf{w})$, $r = 0, 1, \dots, p-1$. From (10), (24) and (25) corresponding to the event occurrence time and its condition, we obtain:

$$\frac{\partial}{\partial \mathbf{x}} \mathcal{E}_v \Delta \mathbf{x}_{ev} + \frac{\partial}{\partial \mathbf{w}} \mathcal{E}_v \Delta \mathbf{w} + O(\Delta^2) = 0, \quad (30)$$

$$\Delta \mathbf{x}_{ev} = \frac{\partial}{\partial \mathbf{x}} \mathbf{g}_{ev} \Delta \Psi^{(v)} + \frac{\partial}{\partial t} \mathbf{g}_{ev} \Delta T_{ev} \\ + \frac{\partial}{\partial \mathbf{e}} \mathbf{g}_{ev} \frac{\partial}{\partial \mathbf{w}} \mathbf{e}^{(v)} \Delta \mathbf{w} + O(\Delta^2), \quad (31)$$

$$\Delta t_{ev} = \Delta T_{ev} + \sum_{r=1}^v \Delta T^{(r)} \quad (32)$$

where $\mathbf{g}_{ev} := \mathbf{g}(\Psi^{(v)}, T_{ev}, \mathbf{e}(\mathbf{y}^{*(v)}, \mathbf{w}))$ and $\mathcal{E}_v := \mathcal{E}_v(\mathbf{x}_{ev}, \mathbf{w})$. Note that equations (26) to (32) are simultaneous equations with $\Delta\Psi^{(r)}$, $r = 0, 1, \dots, p-1$, $\Delta T^{(r)}$, $r = 1, 2, \dots, p$, ΔT , $\Delta\mathbf{x}_{ev}$, ΔT_{ev} , and Δt_{ev} as being unknown variables.

C. A Method for Obtaining Exact Closed-form Expressions of Sensitivities

The analytical expression for period sensitivity can be derived as follows. Eliminating $\Delta\Psi^{(r+1)}$ from (27) and (28) and solving the resulting equation for $\Delta T^{(r+1)}$ gives the following equation:

$$\Delta T^{(r+1)} = -\mathcal{A}^{(r)} \Delta\Psi^{(r)} - \mathcal{B}^{(r)} \Delta\mathbf{w} + O(\Delta^2), \quad r = 0, 1, \dots, p-1 \quad (33)$$

where $\mathcal{A}^{(r)} := \frac{\partial}{\partial \mathbf{x}} \mathbf{g}_{i_r}^{(r)} / \frac{\partial}{\partial t} \mathbf{g}_{i_r}^{(r)}$, $\mathcal{B}^{(r)} := \frac{\partial}{\partial \mathbf{e}} \mathbf{g}_{i_r}^{(r)} \frac{\partial}{\partial \mathbf{w}} \mathbf{e}^{(r)} / \frac{\partial}{\partial t} \mathbf{g}_{i_r}^{(r)}$. Substituting these into (26) and (27), we obtain the following equations, respectively.

$$\Delta\Psi^{(0)} = \mathbf{g}_x^{(p-1)} \Delta\Psi^{(p-1)} + \mathbf{g}_w^{(p-1)} \Delta\mathbf{w} + O(\Delta^2), \quad (34)$$

$$\Delta\Psi^{(r+1)} = \mathbf{g}_x^{(r)} \Delta\Psi^{(r)} + \mathbf{g}_w^{(r)} \Delta\mathbf{w} + O(\Delta^2), \quad r = 0, 1, \dots, p-2 \quad (35)$$

where $\mathbf{g}_x^{(r)} := \frac{\partial}{\partial \mathbf{x}} \mathbf{g}^{(r)} - \frac{\partial}{\partial t} \mathbf{g}^{(r)} \mathcal{A}^{(r)}$, $\mathbf{g}_w^{(r)} := \frac{\partial}{\partial \mathbf{e}} \mathbf{g}^{(r)} \frac{\partial}{\partial \mathbf{w}} \mathbf{e}^{(r)} - \frac{\partial}{\partial t} \mathbf{g}^{(r)} \mathcal{B}^{(r)}$. These are difference equations for $\Delta\Psi^{(r)}$ ($r = 0, 1, \dots, p-1$). Therefore, by solving them, we obtain $\Delta\Psi^{(r)}$ ($r = 0, 1, \dots, p-1$) as follows:

$$\Delta\Psi^{(r)} = \mathcal{C}^{(r-1)} \Delta\mathbf{w} + O(\Delta^2), \quad r = 0, 1, \dots, p-1 \quad (36)$$

where $\mathcal{C}^{(r)} := \mathbf{A}^{(r)} \left(\mathbf{I} - \mathbf{A}^{(p-1)} \right)^{-1} \mathbf{B}^{(p-1)} + \mathbf{B}^{(r)}$, $\mathbf{A}^{(r)} := \mathbf{g}_x^{(r)} \mathbf{g}_x^{(r-1)} \dots \mathbf{g}_x^{(0)}$, $\mathbf{B}^{(r)} := \mathbf{g}_x^{(r)} \mathbf{g}_x^{(r-1)} \dots \mathbf{g}_x^{(1)} \mathbf{g}_w^{(0)} + \mathbf{g}_x^{(r)} \mathbf{g}_x^{(r-1)} \dots \mathbf{g}_x^{(2)} \mathbf{g}_w^{(1)} + \dots + \mathbf{g}_x^{(r)} \mathbf{g}_w^{(r-1)} + \mathbf{g}_w^{(r)}$, $\mathbf{A}^{(-1)} = \mathbf{I}$, $\mathbf{B}^{(-1)} = \mathbf{0}$ and $\mathcal{C}^{(-1)} := \mathbf{A}^{(-1)} \left(\mathbf{I} - \mathbf{A}^{(p-1)} \right)^{-1} \mathbf{B}^{(p-1)} + \mathbf{B}^{(-1)}$. From (29), (33) and (36), the following theorem is obtained, which gives the exact closed-form expression for the period sensitivity:

Theorem 1: Suppose that the GRN represented by (3), (4) and (5) has a periodic orbit, and the EPS of this periodic orbit is given by (7). Then the sensitivity of the period is given by the following equation:

$$\frac{\partial T}{\partial \mathbf{w}} = - \sum_{r=1}^{p-1} \left(\mathcal{A}^{(r)} \mathcal{C}^{(r-1)} + \mathcal{B}^{(r)} \right). \quad (37)$$

The analytical expression for the phase sensitivity can be obtained as follows. Eliminating $\Delta\mathbf{x}_{ev}$ from (30) and (31), solving the resulting equations for ΔT_{ev} , and substituting $\Psi^{(v)}$ given by (36) into it, we obtain the analytical expression for ΔT_{ev} . From the analytical expression of ΔT_{ev} thus obtained and equations (32) through (36), the analytical expression for the sensitivity of the time t_{ev} at which the event occurs can be obtained as follows:

Theorem 2: Suppose that the GRN represented by (3), (4) and (5) has a periodic orbit, and the EPS of this periodic orbit

is given by (7). Then the sensitivity of the time t_{ev} is given by the following equation:

$$\frac{\partial t_{ev}}{\partial \mathbf{w}} = -\mathcal{D} \mathcal{C}^{(v-1)} - \mathcal{F} - \sum_{r=0}^v \left(\mathcal{A}^{(r)} \mathcal{C}^{(r-1)} + \mathcal{B}^{(r)} \right) \quad (38)$$

where $\mathcal{D} := \left(\frac{\partial}{\partial \mathbf{x}} \mathcal{E}_v \frac{\partial}{\partial \mathbf{x}} \mathbf{g}_{ev} \right) / \left(\frac{\partial}{\partial \mathbf{x}} \mathcal{E}_v \frac{\partial}{\partial t} \mathbf{g}_{ev} \right)$, $\mathcal{F} := \left(\frac{\partial}{\partial \mathbf{x}} \mathcal{E}_v \frac{\partial}{\partial \mathbf{e}} \mathbf{g}_{ev} \frac{\partial}{\partial \mathbf{w}} \mathbf{e}^{(v)} + \frac{\partial}{\partial \mathbf{w}} \mathcal{E}_v \right) / \left(\frac{\partial}{\partial \mathbf{x}} \mathcal{E}_v \frac{\partial}{\partial t} \mathbf{g}_{ev} \right)$.

The exact closed form expression for the phase sensitivity $\frac{\partial \theta_{ev}}{\partial \mathbf{w}}$ is obtained by substituting (37) in Theorem 1 and (38) in Theorem 2 into (9).

In sensitivity analysis, methods based on sensitivity equations or adjoint equations are commonly used. These methods require solving the sensitivity equations or adjoint equations, which are differential equations, over a certain time interval, or for one period in the case of sensitivity analysis of periodic phenomena. The computational time required to solve these differential equations becomes a problem. The method based on sensitivity equations require solving the same numbers of sensitivity equations as the numbers of parameters, which particularly is the problem. Numerical calculation errors in solving differential equations also become an issue. On the other hand, the method proposed in this paper gives the exact closed-form expressions of the sensitivities, and therefore is computationally highly efficient compared to the methods mentioned above. Furthermore, because it does not require solving differential equations, there is no problem with the numerical errors. Thus, the method proposed is highly useful, especially for gradient-based optimization algorithms, which require repeated sensitivity calculations for the parameters of objective functions.

IV. NUMERICAL EXPERIMENTS

In this section, we present the results of numerical experiments to demonstrate the effectiveness of the proposed method. The GRN used in the experiments is a GRN composed of three genes, i.e., the GRN defined by (3), (4), and (5) with $n = 3$. The parameters in the GRN are chosen as: $d_1 = 1.0$, $d_2 = 2.0$, $d_3 = 3.0$, $\mathbf{w}_1 = [1 \ 1 \ -1 \ -4 \ 2 \ 2 \ 2 \ -4]$, $\mathbf{w}_2 = [-3 \ 4 \ 3 \ -2 \ 1 \ -2 \ -2 \ 4]$, $\mathbf{w}_3 = [-2 \ -1 \ 2 \ 2 \ 1 \ 2 \ 2 \ -4]$. This GRN has a periodic orbit with period $T = 4.209347$, and the periodic EPS of this periodic orbit is:

$$\begin{aligned} [1 \ 1 \ 1]^T &\rightarrow [0 \ 1 \ 1]^T \rightarrow [0 \ 0 \ 1]^T \rightarrow [0 \ 0 \ 0]^T \\ &\rightarrow [1 \ 0 \ 0]^T \rightarrow [1 \ 1 \ 0]^T \rightarrow [1 \ 1 \ 1]^T. \end{aligned} \quad (39)$$

We will obtain the phase and period sensitivities for this periodic orbit by using the proposed method. In the numerical experiment, sensitivity analysis is performed under the condition that the Poincaré cross section is defined as S_0 , and the phase is defined based on the intersection $\mathbf{x}_{\gamma_0}$ of this S_0 and the periodic orbit. The intersection with S_0 is $\mathbf{x}_{\gamma_0} = [1.702971 \ 0.5927983 \ 0.0]^T$. We consider two cases for the time t_{ev} at which an event occurs defining the phase, and obtain the sensitivities for each case using the proposed method. For comparison, the sensitivities are obtained by the difference approximation method.

First, we find the sensitivities when the conditions for the occurrence of the event are as follows: $x_1 < 0$, $x_2 = -1.0$, $x_3 < 0$. In this case, $\mathcal{E}_v$ is defined as:

$$\mathcal{E}_v(\mathbf{x}_{ev}, \mathbf{w}) = x_2 + 1.0.$$

The sensitivities obtained using the proposal method and the difference approximation method are shown in Table I. In the

TABLE I
RESULTS OF NUMERICAL EXAMPLE 1

Sensitivities	Proposed method	$\Delta w_j = 0.0001$	$\Delta w_j = 0.001$
$\frac{\partial \theta}{\partial w_{1,9}}$	1.126735	1.126765	1.127040
$\frac{\partial \theta}{\partial w_{1,10}}$	0.3110589	0.3110409	0.3108799
$\frac{\partial \theta}{\partial w_{1,11}}$	0.1980602	0.1980746	0.1982056
$\frac{\partial T}{\partial w_{1,9}}$	0.0000000	0.00005267000	0.0005264700
$\frac{\partial T}{\partial w_{1,10}}$	-0.3199317	-0.3199071	-0.3196867
$\frac{\partial T}{\partial w_{1,11}}$	0.6542258	0.6542521	0.6544885

difference approximation method, we first obtained the phase and the period, denoted by $\hat{\theta}$ and $\hat{T}$, when the parameter w_j changed slightly by $\Delta w_j = 0.0001$ and 0.001 , and calculated approximated values of the sensitivities by $\Delta \theta / \Delta w_j = (\hat{\theta} - \theta) / \Delta w_j$ and $\Delta T / \Delta w_j = (\hat{T} - T) / \Delta w_j$.

Next, we find the phase sensitivity when the conditions for the occurrence of the event are as follows: $x_1 > 0$, $x_2 < 0$, $x_3 < 0$, and the sum of the velocities dx_1/dt , dx_2/dt and dx_3/dt in each state becomes equal to 2.0. In this case, $\mathcal{E}_v$ is defined as:

$$\mathcal{E}_v(\mathbf{x}, \mathbf{w}) = -\frac{d}{dt}x_1 - \frac{d}{dt}x_2 - \frac{d}{dt}x_3 + 2.0. \quad (40)$$

The sensitivities obtained using the proposal method and the difference approximation method are shown in Table II. Note

TABLE II
RESULTS OF NUMERICAL EXAMPLE 2

Sensitivities	Proposed method	$\Delta w_j = 0.0001$	$\Delta w_j = 0.001$
$\frac{\partial \theta}{\partial w_{1,9}}$	0.7723930	0.7723654	0.7721186
$\frac{\partial \theta}{\partial w_{1,10}}$	0.6711569	0.6711240	0.6708299
$\frac{\partial \theta}{\partial w_{1,11}}$	0.1139321	0.1139366	0.1139780

that 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 I and II show that the values of the sensitivities for $\Delta w_j = 0.0001$ are closest to those of the proposed method which theoretically provides the true values. This shows that the proposed method gives the appropriate values of the sensitivities, which indicates the validity of the proposed method.

V. CONCLUSIONS

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 the 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 a sensitivity analysis method for cyclic expression pattern sequences in GRNs. In the case of the piecewise-linear differential-equation model, its dynamics switch depending on the expression patterns and 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 switch. Using the results, we proposed a method to obtain exact closed-form expressions of sensitivities of phase and period. The proposed method makes it possible to bring both the accuracy of the analysis results and computational efficiency.

REFERENCES

- [1] A. T. Winfree: *The Geometry of Biological Time*, 2nd ed. New York: Springer, 2000.
- [2] E. B. Klerman and M. S. Hilaire, "Review: On Mathematical Modeling of Circadian Rhythms, Performance, and Alertness," *J. Biol. Rhythms*, vol. 22, no. 2, pp. 91-102, Apr. 2007.
- [3] C. H. Johnson, T. Mori, and Y. Xu, "A Cyanobacterial Circadian Clockwork," *Curr. Biol.*, vol. 18, no. 17, pp. 816-825, Sep. 2008.
- [4] J. H. Abel, A. Chakrabarty, E. B. Klerman, and F. J. Doyle, "Pharmaceutical-based entrainment of circadian phase via nonlinear model predictive control," *Automatica*, vol. 100, no. 3, pp. 336-348, Feb. 2019.
- [5] L. Glass, "Combinatorial and topological methods in nonlinear chemical kinetics," *The Journal of chemical physics*, Vol. 63, No. 4, pp. 1325-1335, 1975.
- [6] N. Ichinose and K. Aihara, "A gene network model and its design(In Japanese)," in *Proc. of 15th Workshop on Circuit and Systems*, pp. 589- 593, 2002.
- [7] H. Nakayama, H. Tanaka and T. Ushio, "The formulation of the control of an expression pattern in a gene network by propositional calculus," *J. Theor. Biol.*, Vol. 240, No. 3, pp. 443-450, 2006.
- [8] Y. Mori and Y. Kuroe, "Synthesis Method of Gene Regulatory Networks Having Desired Expression-Pattern Transition Sequences," in *Proc. of 2013 9th Asian Control Conference*, 6 pages, 2013.
- [9] D. Edelson and V. M. Thomas, "Sensitivity Analysis of Oscillating Reactions. 1. The Period of the Oregonator," *J. Phys. Chem.*, Vol.85, No. 11, pp. 1555-1558, 1981.
- [10] M. A. Kramer, H. Rabitz, and J. M. Calo, "Sensitivity Analysis of Oscillatory Systems," *Appl Math Modelling*, Vol. 8, pp. 328-340, 1984.
- [11] D. E. Zak, J. Stelling and F. J. Doyle III, "Sensitivity analysis of oscillatory (bio) chemical systems", *Computers & chemical engineering*, vol. 29, no. 3, pp. 663-673, 2005.
- [12] A. K. Wilkins, B. Tidor, J. White, and P. I. Barton, "Sensitivity Analysis for Oscillating Dynamical Systems," *SIAM Journal on Scientific Computing*, Vol. 31, No. 4, pp. 2706-2732, 2009.
- [13] Y. Kuroe and Y. Mori, "Analysis Method for Parameter Sensitivities of Periods in Rhythm Phenomena - Sensitivity and Adjoint Equations -," in *Proc. of 2023 9th International Conference on Control, Decision and Information Technologies*, pp. 235-240, 2023.
- [14] Y. Kuroe and Y. Mori, "Analysis Method of Phase Sensitivities for Rhythm Phenomena," *Proc. of 2024 10th International Conference on Control, Decision and Information Technologies*, pp. 1873-1878, 2024.
- [15] Y. Kuroe and Y. Mori, "Analysis Method of Period Sensitivity for Cyclic Expression Pattern Sequences in Gene Regulatory Networks," *Proc. of 2025 11th International Conference on Control, Decision and Information Technologies*, pp. 1-6, 2025.
- [16] H. de Jong, "Modeling and simulation of genetic regulatory systems: a literature review," *Journal of Computational Biology*, Vol. 9, No. 1, pp. 67-103, 2002.
- [17] J. Guckenheimer and P. Holmes, *Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Field*, Springer-Verlag, 1983.