Objective Sensitivity Analysis of Biological Oscillatory Systems

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Abstract: Oscillations are crucial for biological functions regulated by complex networks of interacting components. Model-based analysis will help to understand the oscillation mechanisms and predict system behaviour. Features such as period, amplitude, and phase are normally used to characterise oscillations. The corresponding objective sensitivity analysis is not trivial since the raw state sensitivity of limit cycle oscillators is unbounded as time tends to infinity. By introducing the concept of basal state sensitivity, a new phase sensitivity measure is presented based on the cumulative phase directly derived from the raw state sensitivity. In this context, all the objective sensitivities on amplitude, period, and phase can be related to the raw state sensitivity. The algorithm is developed based on intuitive measures of objective sensitivities that can be efficiently calculated. The results are illustrated by the application to a circadian rhythm model.

Keywords: Sensitivity analysis, oscillatory systems, basal state sensitivity, phase sensitivity, circadian rhythm

1. INTRODUCTION

Biochemical and biophysical rhythms are ubiquitous characteristics of living organisms, from rapid oscillations of membrane potential in nerve cells to slow cycles of ovulation in mammals (Tyson, 2002). These biological oscillations play an important role in dynamic cellular processes. Cellular oscillations can be of direct influence to biological functions such as axonemal beat, hair bundle oscillations and circadian clocks (Kruse and Julicher, 2005). Circadian rhythms are observed at all cellular levels as the daily oscillations in enzymes and hormones affect the timing of cell function, cell division, and cell growth (Edery, 2000). The living cells are complex regulatory networks containing various components and interactions. Systematic study of oscillations will provide valuable insights to cellular dynamics and the mechanisms under the phenomena.

Sensitivity analysis is a useful tool in investigating the effect of the variation in parameters or initial conditions on the system dynamics, including the system output and the derived functions, accordingly called output sensitivity and objective sensitivity, respectively (Varma et al., 1999). Through model-based sensitivity analysis, one can find the most important factors which determine the system feature, and also quantitatively assess the robustness or fragility of the system. In a standard local sensitivity analysis, state sensitivity is normally used as the measure to prioritise the contribution of input factors (mostly model parameters). Three groups of methods are commonly used to compute the state sensitivities: direct differential method (DDM), finite difference method and Green’s function method. Among them DDM is most widely used since it provides complete information on each sensitivity index as a function of the independent variables.

In quantitative studies, period, phase and limit cycles on the state-plane are used to characterize the features of oscillatory systems and the corresponding objective sensitivity measures are developed to understand the decisive mechanisms of oscillatory systems. Since the raw state sensitivity coefficients of a periodic system are growing unbounded as time tends to infinity (Tomovic and Vukobratovic, 1972; Larter, 1983; Larter et al., 1984), the sensitivity calculation of such systems is much more complicated compared with the non-periodic systems with stable steady states. For sensitivity analysis of periodic systems, it is necessary to separate the effective information from the unbounded data to elucidate the impact of changes in parameters on system dynamics.

There are different ways to handle objective sensitivity analysis of oscillatory systems. In an earlier work, the dependence of the period of an oscillating reaction mechanism upon the input parameters of the kinetic model was calculated using the Green’s function method (Edelson and Thomas, 1981). Sensitivity analysis addressing period and extrema of oscillating biochemical systems were carried out in (Ingalls, 2004). The period sensitivity and amplitude sensitivity were calculated to elucidate the relationship between parameters of different control levels and the robustness properties of circadian clock architectures (Stelling et al., 2004). In phase sensitivity analysis, the methods of isochron-based phase response analysis (Gunawan and Doyle III, 2006) and phased-based sensitivity analysis (Bagheri et al., 2007) involve calculation of each component corresponding to each parameter individually. A method employing parametric impulse curve investigates the phase behaviour in various uncertainty and perturbations (Taylor et al., 2008). Objective sensitivities of limit cycle oscillation systems can also be calculated by solving a boundary value problem. Relative phase sensitivities were calculated through decomposing the cleaned-out sensitivity...
into two parts based on Larler’s Green’s function method (Larter et al., 1984; Wilkins et al., 2009). Despite these very useful progresses, objective sensitivity analysis of periodic systems is still a challenging task that would benefit considerably from further systematic investigation. Some calculations are quite complicated and less intuitive in formulation. It is therefore our intention to develop easy-to-implement and hopefully also easy-to-understand methods for sensitivity analysis of oscillatory systems, in particular biological oscillators.

The rest of this paper is organised as follows. Method development is presented in Section 2. Firstly, the state sensitivity of periodic systems is presented, based on which the period sensitivity is calculated using an improved SVD-based method. Then the concept of basal state sensitivity is introduced. The phase sensitivity and relative phase sensitivity analysis algorithm is proposed following this new concept. Sensitivity investigation of a circadian rhythm model is performed in Section 3. Conclusions and discussions are given in Section 4.

2. METHOD DEVELOPMENT

Consider a dynamic system in the form of ordinary differential equations (ODEs):

\[ x(t) = f(x(t),p), \quad x(t_0) = x_0 \]

where \( x \in \mathbb{R}^n \) is the state vector. Each component of \( x \) is denoted as \( x_i \), which normally stands for molecule concentrations. \( t \) is time. \( p \in \mathbb{R}^m \) is the parameter vector, of which each component is denoted as \( p_i \). \( f \) is the column vector function corresponding to the state time derivative with its \( i \)th component written as \( f_i \). \( x_0 \) is the initial condition of \( x \) at the initial time \( t_0 \). For limit cycle oscillatory systems, \( x(t) \) is periodic in time, i.e., \( x(t + \tau) = x(t) \) and \( \tau \) is the period of the oscillation. Without loss of generality, it can be assumed that the periodic system is a nonzero system, i.e. \( f \neq 0 \) in all the remaining discussions.

2.1 Raw State Sensitivity, Period Sensitivity and Amplitude Sensitivity

The classical sensitivity analysis employs the first-order derivative of \( x_i \) with respect to parameter \( p_j \), i.e.,

\[ s_{iy} = \frac{\partial x_i}{\partial p_j} \]

which provides information on the effect of a small change in each parameter \( p_j \), around a fixed nominal value, on the change of each independent variable \( x_i \). The sensitivity matrix \( S = \frac{\partial x}{\partial p} \) is composed of elements of \( s_{iy} \).

Differentiation of (1) with respect to \( p \) yields the following sensitivity differential equations (Turanyi, 1990):

\[ \dot{S} = A(t)S + B(t), \quad S(t_0) = S_0 \]

where \( A(t) = \frac{\partial f}{\partial x} \) is the Jacobian matrix, \( B(t) = \frac{\partial f}{\partial p} \) is the parameter Jacobian matrix. Sensitivity matrix \( S \) can be calculated by solving (1) and (2) simultaneously with the parameters taken at the nominal values. In numerical simulations, the initial conditions of \( x(t) \) can be taken from the limit cycle orbit and the initial conditions for \( S \) can be determined by \( s_i(t_0) = \delta(\theta_i - x_i(t_0)) \), where \( \delta \) is the Kronecker delta function. For a periodic system, \( S \) is a full information sensitivity matrix that contains impact of parameter variations on the change in system behaviours including limit cycle shape, amplitude, period, and phase, etc.

Unlike the convergent profiles of \( S \) for non-periodic stable systems, the values of \( S \) for limit cycle oscillatory systems are periodic and unbounded when time tends to infinity. Employing Fourier series in states representations, the raw state sensitivity can be decomposed into two vector forms containing period and shape sensitivities (Tomovic and Vukobratovic, 1972; Larler, 1983):

\[ S = \frac{-t}{\tau} f S_r + S_c \]

In (3), \( S_c \) is the period sensitivity which is a constant row vector defined as

\[ S_c = \begin{bmatrix} \frac{\partial \tau}{\partial p_1} & \frac{\partial \tau}{\partial p_2} & \cdots & \frac{\partial \tau}{\partial p_m} \end{bmatrix} \]

When \( f \neq 0 \) and \( S_c \neq 0 \), the first term in (3) will go unbounded with the increase of time. The second term, \( S_r = (\frac{\partial f}{\partial p}) \), is called the cleaned-out sensitivity which is periodic in time and captures how variations in the parameters affect the shape of the trajectory when period \( \tau \) is held constant. Based on this decomposition, a method employing singular value decomposition (SVD) is proposed that can determine all the period sensitivities systematically (Zak et al., 2005). In this algorithm, the SVD of the state sensitivity matrix \( S \) can be written as

\[ S = U \tau = \sum_{i=1}^{r} \sigma_i v_i^\top \]

where \( r = \text{rank}(S) \), the \( n \times n \) matrix \( U \) and \( m \times m \) matrix \( V \) are unitary, and the \( n \times m \) matrix \( \Sigma \) is a diagonal matrix of non-negative singular values, \( \sigma_i (i = 1, \cdots, r) \), that are the square roots of the eigenvalues of \( SS^\top \) or \( S^\top S \) written in a descending order \( \sigma_1 \geq \sigma_2 \geq \cdots \geq \sigma_r > 0 \). At a large time \( t \), the period sensitivity can be approximated by the largest SVD term (Zak et al., 2005)

\[ S_r = \pm \frac{\sigma_i}{\sqrt{\frac{t\tau}{f}}} v_i^\top \]

Using (6) to calculate period sensitivities, the sign of \( S_r \) needs to be calibrated for each parameter, individually, by observing whether a small perturbation to the parameter will increase or decrease the period. To avoid this little trouble, an alternative formulation is given as (Lu and Yue, 2010)

\[ S_r = -\frac{\tau}{f} \tau f \hat{S}_r \]

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where $\tilde{S}_i = \sigma_i u_i v_i^T$ is the largest SVD term of the state sensitivity matrix $S$. Once the period sensitivity is obtained, the cleaned-out sensitivity can be calculated by

$$S_i = \sum_{r=2}^{\infty} S_i$$

(8)

In our sensitivity analysis, amplitude is defined for each state of an oscillator as the difference between the maximum value and the minimum value of the oscillatory trajectory as:

$$A_i = \max(x_i) - \min(x_i)$$

(9)

If $t'_{\text{min}}$ and $t'_{\text{max}}$ are the time points at which the local minimum and maximum occurs (local means within a period), the amplitude sensitivity can be represented as

$$S_{A_i} = \frac{\delta x_i (t'_{\text{max}})}{\delta p} - \frac{\delta x_i (t'_{\text{min}})}{\delta p} = S_i (t'_{\text{max}}) - S_i (t'_{\text{min}})$$

(10)

where $S_i$ is the $i$th row vector of $S$. It is known that $f_i$ is zero at the local extrema of $x_i$, therefore $S_i = (S_i)_{i}$ at $t'_{\text{min}}$ and $t'_{\text{max}}$. Thus the amplitude sensitivity can be described as

$$S_{A_i} = S_i (t'_{\text{max}}) - S_i (t'_{\text{min}})$$

(11)

2.2 Basal State Sensitivity

For a nonzero oscillatory system (\(f \neq 0\)) with $S_i \neq 0$, the state sensitivity $S$ will grow unbounded when $t \rightarrow \infty$. The incremental rate of $S$ in time is determined by the state dynamics and the period sensitivity at nominal value $\tau$. The state sensitivity will increase an amount of $-f S_i$ after each period. With this in mind, we can rewrite (3) and decompose the state sensitivity matrix into two terms:

$$S = S' - l \cdot f S_i$$

(12)

where $S'$ is referred to as the basal state sensitivity corresponding to the state sensitivity in the basal period. $l = \text{fix}(t/\tau)$ represents $l$ periods after the basal period in time. Here the fix function returns the integer part of $t/\tau$. The basal period can be taken as the first period in calculation or any period starting to show a stable oscillation. Without loss of generality, denote the basal period as $[0, \tau)$.

At each time $t \in [0, \tau)$, the basal state sensitivity $S'$ is uniquely determined by the position on the limit cycle orbit without cumulative effect. $S'$ is periodic in time and can also be computed by the SVD-based method. The definition of the basal state sensitivity not only provides an alternative state-based sensitivity metric, but also forms the basis for a phase sensitivity formulation.

2.3 Phase Sensitivity

From (3) and (12), the relationship between $S'$ and the cleaned-out sensitivity can be established as follows:

$$S' = -\frac{\dot{\phi}}{\tau} f S_i + S_i$$

(13)

where $\phi = \text{mod}(t, \tau)$ is defined as phase, which is the modulo operation of the elapsed time going from a reference point to the current position on period $\tau$ (Larter et al., 1984), as illustrated in Fig. 1 using a circadian rhythm model given in (Goldbeter, 1995). For a stable limit cycle, the phase in this definition is bounded and periodic as shown in Fig. 2.

![Fig.1 State position and phase on a limit cycle](image1)

**Fig.1** State position and phase on a limit cycle

![Fig.2 Phase in time: bounded and periodic](image2)

**Fig.2** Phase in time: bounded and periodic

![Fig.3 Phase and relative phase: \(\tau\) is the period, \(\phi_1\) and \(\phi_2\) are phase defined by \(\phi = \text{mod}(t, \tau)\), and \(\psi\) is a relative phase measured by the time difference between the maximum and minimum points.](image3)

**Fig.3** Phase and relative phase: $\tau$ is the period, $\phi_1$ and $\phi_2$ are phase defined by $\phi = \text{mod}(t, \tau)$, and $\psi$ is a relative phase measured by the time difference between the maximum and minimum points. The phase has a one-to-one mapping to the state position on a limit cycle orbit (see Fig.1). An alternative or more general definition of phase, also called relative phase, describes the time difference between two featured positions on a limit cycle orbit. For example, the time difference between two neighbouring peaks of a state or the time difference between the maximum and the minimum of a state. With this definition, period and phase can be regarded as special cases of relative phase. An example of phase and relative phase are illustrated in Fig. 3.

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For a limit cycle oscillator, each elapsed time \( t \) corresponds to a state position along the phase trajectory. Time \( t \) is usually regarded as an implicit variable of \( x \) for oscillatory systems described in (1), which can be written as a function of state position, \( i.e., t = t(x(p)) \). In this context, variation of parameters will affect \( t \) as well. The elapsed time \( t \) is in fact the cumulative phase in a phase-space trajectory. Therefore the parametric sensitivity of the cumulative phase can be derived to obtain the phase sensitivity.

Differentiating (1) with respect to \( t \) yields

\[
\frac{dx}{dt} = \frac{\partial f}{\partial x} = Af
\]

It describes the changing law of the phase trajectory. The differential of \( f \) can be obtained by \( df = Af \, dt \). Remember that \( df \) caused by a small variation in parameters can also be approximated by \( df = A \Delta x + B \Delta p \), therefore

\[
Af \, dt = A \Delta x + B \Delta p
\]

Taking derivative of (15) with respect to \( \Delta p \),

\[
\frac{d}{d\Delta p}Af \, dt = \left( \frac{d}{d\Delta p}A \right) \Delta x + B \Delta p
\]

gives

\[
Af \, \frac{\partial t}{\partial p} = AS + B
\]

For a nonzero oscillatory system, the Jacobian matrix \( A \) is non-singular, the cumulative phase sensitivity can thus be calculated by

\[
\frac{\partial t}{\partial p} = \frac{1}{f^T f} f^T \left( S + A^{-1} B \right)
\]

It can be seen from (18) that the cumulative phase sensitivity is also unbounded in time. After each period, the cumulative phase sensitivity is increased by a fixed term determined by the period sensitivity. Since phase \( \phi \) is bounded in \([0, \tau]\), the phase sensitivity can be defined as

\[
S_p = \frac{\partial \phi}{\partial p} = \frac{1}{f^T f} f^T \left( S' + A^{-1} B \right)
\]

The phase sensitivity in (19) eliminates the cumulative effect and provides a bounded and periodic solution. It describes the variation tendency of phase caused by small perturbations in parameters. It should be pointed out that both the phase sensitivity and the cumulative phase sensitivity are evaluated at the nominal model parameters.

For the relative phase defined by the time difference between two featured positions on a limit cycle orbit, the sensitivity can be computed similarly. Denoting \( \phi_a \) and \( \phi_b \) as the phase at positions a and b, the relative phase between these two positions is \( \psi = \phi_a - \phi_b \). The sign of the relative phase indicates phase lag or phase ahead. Accordingly, the relative phase sensitivity can be calculated by

\[
\frac{\partial \psi}{\partial p} = \frac{\partial \phi_a}{\partial p} - \frac{\partial \phi_b}{\partial p} = \frac{1}{f^T f} f^T \left( S' + A^{-1} B \right)
\]

where

\[
h(t) = h(t_0) - h(t_1)
\]

Equation (19) shows that the phase sensitivity can be easily calculated based on the basal state sensitivity \( S' \), where the latter is represented by (13) through the period sensitivity \( S_p \).

As discussed in Section 2.1, the period sensitivity can be approximated by the largest SVD term of \( S \) as in (7). This makes the phase sensitivity calculation very simple in applications.

We compare our method with an earlier work, where the phase sensitivity is given as (Wilkins et al., 2009):

\[
\tilde{\delta}(t) = \frac{1}{f^T f} f^T S_p
\]

and the relative phase sensitivity is computed by

\[
\frac{\partial \psi}{\partial p} = -\frac{\psi}{\tau} S_p + \tilde{\delta}(t)
\]

Comparing (19) with (22) for phase sensitivity, or (20) with (23) for relative phase sensitivity, it can be seen that both algorithms contain the information on period and the Jacobian matrices for state and parameters. However, there is a fixed-term difference between these two algorithms. In the work of (Wilkins et al., 2009), the state sensitivity is decomposed into path-dependant and path-independent parts, while in our work, the phase sensitivity is represented by the basal state sensitivity. This causes the difference in objective sensitivity calculations between the two methods. Nevertheless, the analysis results from the two algorithms should be consistent in terms of ranking model parameters by their sensitivities.

3. APPLICATION STUDY

The proposed algorithm is applied to a model of Drosophila circadian rhythm gene network which contains 5 states and 18 parameters (Goldbeter, 1995) (See Appendix A). The sustained oscillation phenomenon is believed to be induced by the negative feedback of the transcriptional inhibition and the delay of the feedback by multiple phosphorylation. The circadian rhythm model presents a limit cycle oscillation and has a period of 23.7h with nominal parameters. In the simulation, the state sensitivity is firstly obtained by solving the joint ODEs in (1) and (2). Then the period sensitivity is calculated by the modified method in (7). Next, the cleaned-out sensitivity, the basal state sensitivity and the phase sensitivity are computed by (8), (13) and (19), respectively. Based on these results, the amplitude sensitivity, the relative phase sensitivity, and the extrema sensitivity can also be calculated. Figures 4-6 give selected results on these objective sensitivities. The period sensitivity analysis results are the same as those given in (Zak et al., 2005).
Objective sensitivities using different features of an oscillator may provide inconsistent results. Here we investigate the correlation between the amplitude sensitivity and the period sensitivity, also the correlation between the relative phase sensitivity and the period sensitivity, all of which are given in normalised values (i.e., $\bar{S}_A = \ln A/\ln p$, $\bar{S}_r = \ln r/\ln p$, $\bar{S}_\varphi = \ln \varphi/\ln p$). The results are illustrated in Fig. 7 and Fig. 8. The correlation analyses show that some parameters have similar effects on the selected features (those distributed alongside the diagonal in Fig. 7-8), some have distinctive effects. The sensitivities of the relative phase $\varphi$ and period $\tau$ are mostly consistent except for $v_m$ (Fig. 8). The amplitude sensitivities are generally low except for $v_r$ and $v_m$. Parameters close to the centre of the plane have less impact on the objective features than those far away from the centre of the plane.

For an oscillatory biological network, it is argued that those global parameters have more impacts on the oscillatory behaviour (Stelling et al., 2004). This is true in our study for parameters $k_i$, $v_r$, $v_m$. Another important parameter identified from our sensitivity analysis is $K_f$, which is responsible for the negative feedback exerted by nuclear PER on the production of per mRNA. This result concurs with the main biophysical mechanism of oscillations in this circadian rhythm system (Goldbeter, 1995).

While the objective sensitivity analyses describe the effect of small parameter changes on features of oscillations, a global analysis can be easily carried out through bifurcation analysis.
Fig. 9 shows the range of parameter $K_i$ over which the oscillatory behaviour persists.

4. CONCLUSIONS AND DISCUSSIONS

We discussed several objective sensitivity measures for limit cycle oscillators including period sensitivity, basin state sensitivity, cumulative phase sensitivity, phase sensitivity, and relative phase sensitivity, etc. All these measures can be categorized as state-based sensitivity metrics. The raw state sensitivity contains all the information on the limit cycle such as shape, amplitude, period, and phase, etc., and shows cumulative effect in time. The cumulative phase sensitivity derived from the raw state sensitivity has the same unbounded nature. In order to extract effective, measurable information from the cumulative measures, a concept of basin state sensitivity is introduced, based on which a new phase sensitivity measure is derived. Period sensitivity is naturally presented in the proposed method, which can be calculated by employing a SVD-based algorithm at large time $t$.

Compared with some earlier works on phase sensitivity analysis that need to calculate the Green’s function or involve a boundary value problem, the key advantage of this algorithm is that it has intuitive formulation and is also simple to implement. This is mainly benefited from the introduction of the basin state sensitivity.

In this algorithm, the linear concept is used in defining the sensitivities that may not be suitable for the analysis of nonlinear systems within a large range. The results of analysis are inherently local while those oscillatory features may depend on initial conditions for nonlinear systems. Nonetheless, the objective sensitivity analysis should prove useful in investigating the way various parameters control the period, phase and amplitude of biological oscillators. For most biological models reported so far, the local sensitivity analysis results are largely consistent with the global sensitivity analysis results. This may partly due to the strong robustness inherent in biological networks.

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APPENDIX A

The circadian rhythm model (Goldbeter, 1995) is as follows:

$$\frac{dM_p}{dt} = \frac{v_i}{K_i + P_i} - \frac{V_i}{M_p}, \quad M_p = M_0$$

$$\frac{dP_i}{dt} = k_i M_p - V_i K_i + P_i + V_i P_i$$

$$\frac{dP_i}{dt} = V_i K_i + P_i - V_i K_i + P_i + V_i P_i$$

$$\frac{dP_i}{dt} = V_i K_i + P_i + V_i K_i + P_i + V_i P_i$$

$$\frac{dP_i}{dt} = k_i P_i - k_i P_i$$

The nominal values of parameters are $k_i = 1.9$, $K_i = 1.3$, $V_i = 3.2$, $V_i = 1.58$, $V_i = 5$, $V_i = 2.5$, $v_i = 0.76$, $v_i = 0.65$, $K_i = 0.5$, $k_i = 0.38$, $v_i = 0.95$, $K_i = 0.2$, $n = 4$, $K_i = 2$, $K_i = 2$, $K_i = 2$, $K_i = 1$.

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