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Developing Objective Sensitivity Analysis of Periodic Systems: Case Studies of Biological Oscillators

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Abstract Sensitivity analysis is a powerful tool in investigating the impact of parameter variations on the change of system behaviours quantitatively. For a periodic system, sensitivity analysis is a challenging problem since the standard sensitivity metrics grow unbounded when time tends to infinity. Objective sensitivity analyses using various oscillation features such as period, phase, amplitude, etc. are therefore needed to circumvent this problem. In this work, a new concept of basal state sensitivity is proposed based on which a phase sensitivity calculation is derived. The improved period sensitivity calculation following an existing algorithm using singular value decomposition (SVD) is also presented, which provides a simple calculation for the basal state sensitivity. These new sensitivity calculations are developed with the purpose to analyse biological oscillators since there is an increasing interest in understanding how oscillations occur and what the main controlling factors are following a growing experimental and computational evidence of oscillations in biological systems. The improved calculation of period sensitivity is shown to be consistent with the previous methods through a well studied circadian rhythm model. The calculation of new objective sensitivities are also testified by the same circadian rhythm model as well as an oscillatory signal transduction pathway model, which further illustrates the efficiency of this approach in handling complex biological oscillators in the presence of reaction conservations.

Key words Sensitivity analysis, periodic systems, phase sensitivity, period sensitivity, biological oscillator

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Oscillation is one of the most important nonlinear behaviors which are widely observed in living cells such as circadian rhythm, bacterial cell division cycle, mammalian cell cycle, glycolytic oscillations, calcium signalling pathways[1−3], etc. Cellular oscillations are crucial for biological functions, for example, circadian rhythms are observed at all cellular levels since oscillations in enzymes and hormones affect cell function, cell division, and cell growth[4]. The rhythm is determined by the regulation of some key genes which produce endogenous oscillations of the mRNA and protein levels with a period of nearly 24 hours. Given the importance of oscillatory phenomena in biology, it is imperative to study the functioning of periodic processes comprehensively in a system manner.

Model-based analysis of complex networks using systems methods is a major topic of current systems biology[5−6]. Among the systematic methods, sensitivity analysis is a powerful approach originated from engineering and has been extensively applied in many areas including modeling and analysis of bio-chemical processes[7]. It investigates the effect of parameter variations or changes in initial conditions on system behaviors, including the system output and the derived functions (accordingly called output sensitivity and objective sensitivity, respectively). For a biological network that often involves a large number of parameters and variables, sensitivity analysis can be used to identify the most important interactions in the network, and help to understand the core features as well as assess the robustness of the system.

Due to the fact that the raw state sensitivity coefficients of a periodic system are growing unbounded as time tends to infinity[8−10], the sensitivity calculation for such a system is much more complicated compared with that of general non-periodic systems with stable steady states. In a quantitative study, period, phase and the limit cycles on the state-plane are normally used to characterize the features of oscillatory systems (we discuss limit cycle oscillations in this paper). Objective sensitivities to period, frequency, phase, extrema and amplitude, etc. are accordingly developed to understand the decisive mechanisms of oscillatory biochemical systems[9−17]. Ingalls carried out general sensitivity analysis which addressed period and extrema of oscillating biochemical systems[11]. Bagheri et al. introduced a set of performance sensitivity metrics based on different phase-measures[12]. Wilkins et al. developed methods for sensitivity analysis of oscillatory systems by solving a boundary value problem (BVP)[13]. Sensitivity and control analysis for forced periodically reaction networks was developed using the general Greens function in [14]. For a periodic system, the perturbations in the parameters will generally lead to different limit cycles from the nominal orbit. In phase sensitivity analysis, small variations to nominal parameters are given to obtain perturbed system features measured by different indices such as the parametric impulse phase response curve[15] and the isochron-based phase response[16]. Owing to the complex nature of oscillatory systems, many existing methods for phase sensitivity analysis are computationally complicated in applications especially to biological oscillators with high dimensions. This motivates us to derive easy-to-implement and easy-to-interpret methods on objective sensitivity calculation so as to facilitate systematic investigation of biological oscillators or other systems with limit-cycle oscillations.

For a periodic system, Fourier series can be employed to represent the states and the raw state sensitivity can then be decomposed into a combination of shape and period sensitivity measures[8−10]. This group of methods use state-based metrics involving calculation of ordinary differential equations (ODEs) for the raw state sensitivity, based on which period sensitivity can be readily calculated. Zak et al. proposed a method to calculate period sensitivity at

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a large time employing the singular value decomposition (SVD) technique[17]. This algorithm is easy to implement and has a good convergence property. While appreciating the advantages of this method in calculating period sensitivity, we aim to develop simple methods for phase sensitivity calculation employing the similar principle. To this end, a new concept of basal state sensitivity is proposed and the improvement of period sensitivity calculation is made to the existing SVD-based algorithm[17]. The phase sensitivity is formulated based on the basal state sensitivity, which can be computed using the largest SVD term produced from the improved period sensitivity calculation.

The rest of the paper is organized as follows. Development of methods is presented in Section 1. We first outline the state sensitivity for oscillatory systems in Subsection 1.1, and the new concept of basal state sensitivity is introduced. We then present the improved period sensitivity calculation in Subsection 1.2 and construct the basal state sensitivity calculation using the SVD technique. The phase sensitivity analysis algorithm is proposed next in Subsection 1.3. Case studies are undertaken on two important biological oscillators in Section 2. One is the well studied circadian rhythm model on Drosophila period protein, from which existing results on period sensitivities are available for comparison. The other is a simplified NF-κB signal pathway model, for which many previous studies have revealed its importance in cell processes and also its complexity nature in dynamic modeling. We use the second model to show how to handle conservations in a biological network for the purpose of sensitivity calculation. Conclusions are given in Section 3. Differential equation models of the two systems are presented in Appendixes A and B, respectively, with nominal model parameters given.

1 Method development

Consider the general form of an ODE model that can be used for many biological networks under certain conditions:

$$\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x}(t), \boldsymbol{p}), \quad \boldsymbol{x}(t_0) = \boldsymbol{x}_0 \tag{1}$$

where $\boldsymbol{x} \in \mathbf{R}^n$ is the state vector. Each component of $\boldsymbol{x}$ is denoted as x_i, which normally stands for molecule concentration. $\boldsymbol{p} \in \mathbf{R}^m$ is the parameter vector, of which each component is denoted as p_i. $\boldsymbol{f}$ is the column vector function corresponding to the state time derivative with its ith component written as f_i. $\boldsymbol{x}_0$ is the initial condition of $\boldsymbol{x}$ at the initial point t_0. The solutions of system (1), $\boldsymbol{x}(t)$, are state time-series. For limit cycle oscillatory systems, $\boldsymbol{x}(t)$ is periodic in time, i.e., $\boldsymbol{x}(t+\tau) = \boldsymbol{x}(t)$ and τ is the period of the oscillation. Without loss of generality, it can be assumed that $\boldsymbol{f} \neq \boldsymbol{0}$ for a periodic system, i.e., all components of $\boldsymbol{f}$ will never be zero simultaneously.

1.1 State sensitivity and basal state sensitivity

The effect of a parameter change, $\Delta\boldsymbol{p}$, on a state can be approximated by a first-order Taylor series expression:

$$x_i(t, \boldsymbol{p} + \Delta\boldsymbol{p}) = x_i(t, \boldsymbol{p}) + \sum_{j=1}^{m} \frac{\partial x_i}{\partial p_j} \Delta p_j \tag{2}$$

In (2), the partial derivatives $\frac{\partial x_i}{\partial p_j}$ are called the first-order local concentration sensitivity coefficients. All the partial derivatives constitute the $n \times m$ state sensitivity matrix $S = \frac{\partial \boldsymbol{x}}{\partial \boldsymbol{p}}$, which represents a linear approximation of the dependence of the states on parameter changes[18].

Differentiation of (1) with respect to $\boldsymbol{p}$ yields the following sensitivity differential equations:

$$\dot{S} = AS + B \tag{3}$$

where $A = \frac{\partial \boldsymbol{f}}{\partial \boldsymbol{x}}$ is the Jacobian matrix, $B = \frac{\partial \boldsymbol{f}}{\partial \boldsymbol{p}}$ is the parameter Jacobian matrix. Sensitivity matrix S can be calculated by solving (1) and (3) simultaneously, which involves $n \times (m+1)$ dimension ODEs. The initial conditions of (3), S_0 are typically zeros unless the system initial conditions depend on parameters. This method is called direct differential method[7]. For oscillatory systems, S is a full information sensitivity matrix that contains the change in system behaviours including message on limit cycle shape, amplitude, period, phase, etc. Larter et al. derived a general expression for the state sensitivity of periodic systems using Fourier series expansions[9−10] of states. The periodic $x_i(t)$ can be represented by a Fourier series as

$$x_i(t) = \sum_{n=0}^{\infty} \left(a_n^i \cos \frac{2n\pi t}{\tau} + b_n^i \sin \frac{2n\pi t}{\tau} \right) \tag{4}$$

where a_n^i and b_n^i are Fourier coefficients for the i-th state, and they are functions of the system parameters $\boldsymbol{p}$. Accordingly,

$$\dot{x}_i(t) = \frac{2\pi}{\tau} \sum_{n=0}^{\infty} \left(-n a_n^i \sin \frac{2n\pi t}{\tau} + n b_n^i \cos \frac{2n\pi t}{\tau} \right) = f_i \tag{5}$$

Differentiating x_i with respect to parameter p_j yields an expression for the state sensitivity:

$$s_{ij} = -\frac{t}{\tau} \frac{\partial \tau}{\partial p_j} f_i + \left(\frac{\partial x_i}{\partial p_j} \right)_{\tau} \tag{6}$$

As a result, the state sensitivity for oscillatory systems can be decomposed into two terms[8]:

$$S = -\frac{t}{\tau} \boldsymbol{f} \boldsymbol{s}_{\tau} + S_c \tag{7}$$

where $\boldsymbol{s}_{\tau}$ is the period sensitivity vector defined as

$$\boldsymbol{s}_{\tau} = \frac{\partial \tau}{\partial \boldsymbol{p}} = \left[\begin{array}{cccc} \frac{\partial \tau}{\partial p_1} & \frac{\partial \tau}{\partial p_2} & \cdots & \frac{\partial \tau}{\partial p_m} \end{array} \right] \tag{8}$$

and $S_c = \left(\frac{\partial \boldsymbol{x}}{\partial \boldsymbol{p}} \right)_{\tau}$ is called the cleaned-out sensitivity or shape sensitivity, which is periodic in time[8]. The first term in the right-hand side of (7) contains the information of period change caused by parameter variations, and the second term S_c captures how variation in parameters affects the shape of state trajectory at the constant nominal period.

It is a valid assumption that $\boldsymbol{s}_{\tau} \neq \boldsymbol{0}$ for biophysical oscillatory systems, which means the period will be sensitive to at least one parameter of the system[10]. For a nonzero oscillatory system, the raw state sensitivity obtained by solving (3) will grow unbounded in time when $\boldsymbol{s}_{\tau} \neq \boldsymbol{0}$. It can be observed from (7) that the incremental rate of the state sensitivity in time is determined by the period sensitivity and the system function. The state sensitivity will increase an amount of $-\boldsymbol{f}\boldsymbol{s}_{\tau}$ after each period. With this in mind, we can also decompose the raw state sensitivity matrix into two terms:

$$S = S^* - l \cdot \boldsymbol{f} \boldsymbol{s}_{\tau} \tag{9}$$