Sensitivity analysis of oscillatory (bio)chemical systems

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Abstract

From the cell cycle to circadian rhythms, oscillatory processes are fundamental to biology. Emerging from nonlinear dynamical interactions, oscillatory mechanisms are best understood through mathematical modeling. Ordinary differential equations (ODEs) are one framework in which the complex interactions giving rise to biological oscillations may be modeled. Key to ODE models are the model parameters that determine whether or not oscillations will occur, and the period and amplitude of the oscillations when they do. Sensitivity analysis is a means to acquire insight about the importance of the model parameters. Sensitivity analysis of oscillatory systems provides unique challenges and must be addressed carefully. In the present study, we describe a method for determining the sensitivity of the period to the model parameters that is straightforward to implement and interpret. We apply this method to a model for circadian rhythms, and obtain results suggesting a link between network structure and parameter sensitivity.

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1. Introduction

Rhythmic processes are fundamental to biology, as is revealed by literature searches on two key oscillatory biological processes, ‘circadian rhythm’ and ‘cell cycle’, that yielded 43,057 and 61,556 articles, respectively (http://www.ncbi.nlm.nih.gov; December 22, 2003). Circadian rhythms are variations in activity (physiological and cellular) with nearly twenty-four hour periods that, for the fly and the mouse, arise from cellular genetic networks containing delayed feedback mechanisms (Hastings, 2000). The cell cycle is the process by which a single cell divides to become two, and is comprised of a complex dynamic nonlinear network of protein interactions (Tyson, Cokus-Nagy, & Novak, 2002). The oscillations in these and other cellular processes arise from biochemical reactions, and thus general principles that have been developed for chemical oscillators apply to biological oscillators. One principle is that computational approaches are necessary to fully understand and explain their behavior (Rabitz & Edelson, 1985; Goldbeter, 1996; Goldbeter, 2002).

The approaches employed for the mathematical analysis of biological oscillators have paralleled those used for chemical oscillators, where both ordinary differential equation (ODE) formulations, derived from mass action kinetics, and discrete stochastic formulations (Gillespie, 1976) have been employed, with the ODE approaches being predominant (Rabitz & Edelson, 1985). Interest in stochastic models of biological oscillators (Barkai & Leibler, 2000; Gonze, Halloy, & Goldbeter, 2002b; Vilar, Kueh, Barkai, & Leibler, 2002; Zak, Doyle, Vlachos, & Schwaber, 2001), and of biological systems in general, is growing, however, and has been strengthened by the publication of several elegant experimental studies that demonstrated the stochastic nature of some biochemical reactions at the single-cell level (Levsky, Shenoy, Pezo, & Singer, 2002; Elowitz, Levine, Siggia, & Swain, 2002), reviewed in (Rao, Wolf, & Arkin, 2002). In spite of this, new models of biological oscillators in the ODE framework continue to be developed (Leloup & Goldbeter, 2003).
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2. Sensitivity analysis of oscillatory systems

In the present section, we first describe basic principles of sensitivity analysis that are applicable to any ODE system. This is followed by a presentation of aspects of sensitivity analysis that are specific to oscillatory systems.

2.1. General principles of sensitivity analysis

Consider the ODE system:

\[ x = f(x, p) \] (1)

where \( x(t) \) is a vector of \( n_x \) states, \( p \) is a vector of \( n_p \) model parameters, and \( f \) is a column vector of the state time derivatives.

Assuming that a solution to Eq. (1) exists, the sensitivity matrix of the system, \( S(t) \), that describes how variations in the parameters near the local point in parameter space, \( p_0 \), influence the state trajectories, may be defined:

\[ S(t) \equiv \left( \frac{\partial f}{\partial p} \right)_{x=x(t), p=p_0} \] (2)

where \( S(t) \) is composed of individual sensitivities of each state to each parameter \( (i,j) \).

The simplest way to calculate \( S(t) \) is by finite differences. For a single parameter \( p_j \):

\[ \left( \frac{\partial f}{\partial p_j} \right)_{x=x(t), p=p_0} \approx \frac{x(t, p_j + \Delta p_j) - x(t, p_j)}{\Delta p_j} \] (3)
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