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ScienceDirect
Computers and Chemical Engineering 32 (2008) 1956–1962
Computers & Chemical Engineering
www.elsevier.com/locate/compchemeng

Uniform design-based sensitivity analysis of circadian rhythm model in *Neurospora*

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Received 8 July 2005; received in revised form 18 October 2007; accepted 18 October 2007
Available online 30 October 2007

Abstract

The period of circadian rhythms often fluctuates around 24 h due to the changes of environmental factors. Actually, the period varies directly with the ambient stimuli which could be expressed as different values of the kinetic parameters included in the circadian models. Therefore, to study the relationships between kinetic parameters and period, which is also known as sensitivity analysis, is a more convenient and direct way than experimental observation. The reduced circadian rhythm model for *Neurospora*, including nine kinetic parameters and three species, is selected to study the above-mentioned relationships. In order to provide an efficient and accurate sensitivity analysis method, the uniform design is adopted for the sampling strategy in which the values of these kinetic parameters could vary within a relative large region. Regression analysis is then implemented according to the recorded periods of *frq* mRNA with respect to different parameter sets. We obtain a quadratic model which could quantitatively explain the influences of kinetic parameters and external factors on the period and educe the conclusions accordant with other studies. Compared with another sensitivity analysis method, the Morris method, the sequence of the importance of parameters is consistent. Besides, the regression model could provide the prediction of period for a given ambient stimuli or different values of parameters. Uniform design-based sensitivity analysis can be successfully applied in the complicated circadian models.

Keywords: Uniform design; Circadian rhythms; Regression analysis; *Neurospora*; Nonlinear model

1. Introduction

Circadian rhythm, involved in almost all organisms, is an oscillation in a biochemical, physiological, or behavioral function which under conditions in nature has a period of exactly 24 h, in phase with the environmental light and darkness, but which continues to oscillate with a period of approximately but usually not exactly 24 h (Loros & Dunlap, 2001). Meanwhile, with the variation of external conditions (such as the light, temperature, etc.), the period of a circadian rhythm would change correspondingly (Jay & Jennifer, 2006).

Theoretically, the effects of exoteric stimuli are carried out by altering some kinetic parameters in circadian networks which leads to different periods finally. So, to observe the influences of outside factors to period, we could instead examine the relationships between kinetic parameters and period, which will be more convenient and direct. Usually, these relationships are obtained through parameter sensitivity analysis (Goldbeter, 1995; Ihekwaba et al., 2004; Zak, Stelling, & Francis, 2005).

Sensitivity analysis is a good way to compare the different contribution(s) of parameters to the system output(s). It is the study of how variation in the output of a statistical model can be apportioned, qualitatively or quantitatively, to different sources of variation. Sensitivity analysis has been applied in many areas, but most focus has been on local sensitivity analysis. Local sensitivity analysis is problematic when a most likely value cannot be reliably determined (Tomlin, 2005), and it cannot provide the real variation of the model output with respect to each parameter within its boundary. For a rather nonlinear model, global sensitivity analysis should be

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doi:10.1016/j.compchemeng.2007.10.013

performed. There is a vast literature on numerical methods and applications of global sensitivity analysis (for a review see Saltelli, 2004a; Saltelli, Ratto, Tarantola, & Campolongo, 2005; Saltelli, Tarantola, Campolongo, & Ratto, 2004b). However, because of high computational cost of most of the global sensitivity analysis methods, they are seldom applied in the complicated biosystems. Among them a screening method, the Morris method (Morris, 1991), is computationally cheap compared to other Monte Carlo type methods. It deals efficiently with models with a large number of input factors and can rank them in order of their importance, but does not quantify by how much a given factor is more important than another. Although this approach can reflect the sensitivity of each kinetic parameter to some extent, it could not provide the coeffects between parameters that actually play important roles.

In order to understand the connections between kinetic parameters and rhythmic period more comprehensively, we have developed a new sensitivity analysis method with its sampling strategy being based on the uniform design (Fang, 1980; Wang & Fang, 1981), which is one type of design of experiments. On the basis of number theory, uniform design aims to generate representative data in terms of uniform distribution of experimental samples. Moreover, the experimenter could decide the number of variable levels and experiments based on the available knowledge. On the other hand, the nonlinearity between responses and factors (namely, dependent and independent variables) including the coeffects between different factors can be described with the combination of regression analysis. Due to its practicability, uniform design becomes widely used not only for physical experiments but also for computer experiments (Fang, 1994).

In this paper, we focus on a circadian model in *Neurospora* (Leloup, Gonze, & Goldbeter, 1999) which is introduced in the second section. In the third section we give a detailed description of the so-called uniform design-based sensitivity analysis and the subsequent regression analysis on the circadian model. The application of Morris method on the same model is in the fourth section. The analysis results are compared and discussed in the last section.

2. Circadian model for *Neurospora*

With advances in molecular biology, understanding of the circadian clock in *Neurospora* has improved (Dunlap, 1999; Dunlap & Loros, 2004; Loros & Dunlap, 2001; Merrow, Brunner, & Roenneberg, 1999; Young & Kay, 2001), leading to more models being proposed (Gonze, Leloup, & Goldbeter, 2000; Leloup et al., 1999; Paul, 2005; Smolen, Baxter, & Byrne, 2001). Molecular analysis begins with the cloning of the clock gene *frequency* (*frq*). In *Neurospora*, as schematized in Fig. 1, a protein known as FRQ (main clock protein in *Neurospora*) enters the nucleus where it represses the transcription of its gene *frq* (Crosthwaite, Dunlap, & Loros, 1997). In contrast, light controls the circadian system by inducing the transcription of *frq* (Crosthwaite, Loros, & Dunlap, 1995). Among different circadian models, a minimal model composed of the core feedback loop is able to produce sustained oscillations. For the sake of convenience, we consider the reduced model as a qualified example in the study. In the minimal model, there are three variables M (*frequency* Messenger Ribonucleic Acid, *frq* mRNA), F_c (cytoplasmic forms of FRQ protein) and F_N (nuclear forms of FRQ protein) and their concentrations are governed by the following three ordinary differential equations (ODEs), respectively (Leloup et al., 1999):

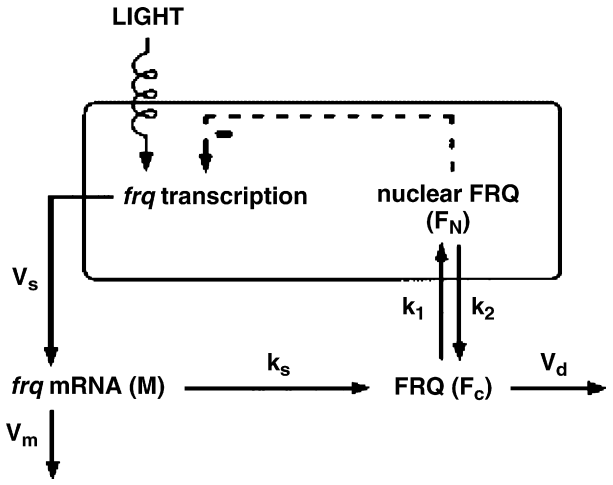

Fig. 1. Scheme of the model for circadian oscillations in *Neurospora*. The model is based on the negative feedback exerted by the protein FRQ on the transcription of the *frq* gene; the rate of gene expression is enhanced by light. The model includes gene transcription in the nucleus, accumulation of the corresponding mRNA in the cytosol with the associated protein synthesis, protein transport into and out of the nucleus, and regulation of gene expression by the nuclear form of the FRQ protein in *Neurospora* (Leloup et al., 1999).

$$\frac{dM}{dt} = \frac{V_s K_I^n}{K_I^n + F_N^n} - \frac{V_m M}{K_m + M} \tag{1a}$$

$$\frac{dF_c}{dt} = k_s M - \frac{V_d F_c}{K_d + F_c} - k_1 F_c + k_2 F_N \tag{1b}$$

$$\frac{dF_N}{dt} = k_1 F_c - k_2 F_N \tag{1c}$$

V_s: the rate of *frq* transcription; K_I: constant related to the threshold deciding when nuclear FRQ represses *frq* transcription; V_m: the maximum rate of *frq* mRNA degradation; K_m: Michaelis constant; k_s: rate constant measuring the rate of FRQ synthesis; V_d: the maximum rate of FRQ degradation; K_d: Michaelis constant; k_1 and k_2: rate constants for the transport of FRQ into and out of the nucleus; n: the Hill coefficient (set to 4).

In the ODEs, the concentrations of *frq* mRNA (M), cytoplasmic FRQ proteins (F_c), and nuclear FRQ proteins (F_N) are defined with respect to the total cell volume. The first term in Eq. (1a) is a Hill function describing negative feedback by F_N on gene transcription, while the other terms are of a linear type for translation of *frq* mRNA and for transport of FRQ into and out of the nucleus, and of Michaelis–Menten type for mRNA and protein degradation. Autonomous oscillations of FRQ proteins and *frq* mRNA can be obtained by numerical integration of Eqs.