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Identifiability and identification of switched linear biological models

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ABSTRACT

Pulse is often used to excite biological systems. The inputs such as irrigation, therapy, and treatments to biological systems are also equivalent to pulses. This makes the biological system behave as switched models under the function of the input. To reduce difficulty in model parameter estimation, the system could be represented as a switched linear model under the pulse excitation. In this research, we studied the identification of a class of switched linear biological models with single input and the system matrix dependent on the intensity of excitation. System identifiability and identification were discussed. A recurrent-pulse excitation method was devised to provide necessary constraints for parameter estimation. The recurrent-pulse technique allowed determination of model parameters that would otherwise be difficult to determine uniquely. The usefulness of the method was demonstrated by examples including delayed fluorescence from photosystem II, which was well known as a versatile tool for sensing plant physiological status and environmental changes in the literature.

1. Introduction

Mathematical models are often used for analysis of biological systems (Banik et al., 2007; Baroukh et al., 2013; Fallon and Lauffenburger, 2000; Ropers et al., 2006). In developing a model, it is important to analyze the model identifiability and adequacy of constraints for unique parameter estimates. Although these issues have been extensively discussed (Glonek, 1999; Grewal and Glover, 1976; Harrison et al., 2002; Heijnen and Verheijen, 2013; Orlov et al., 2001, 2002), there are not general identification and experimental design methods to ensure unique parameter solutions. Biological systems are especially difficult to identify. First, biological systems often involve complex biochemical reactions that result in high-order kinetics with many unknown parameters (Guo and Tan, 2009; Lazár and Jablonský, 2009; Zhu et al., 2005). Second, experimental observations are often limited. State variables such as pH, temperature, and some material concentrations may be measurable; but, it is common that not all the state variables are continuously measurable, which can incur non-unique-solution problems (Bystrov et al., 1985). Rich perturbations are very important to parameter identification (Belkoura, 2005), but biological systems often do not allow arbitrary excitation signals, which further increases the difficulty for biological system identification. For example, K^+ ions could be used to perturb cells for bioelectricity generation (Kaufman and Erlij, 1986), but it is very difficult to change K^+ concentration instantaneously and continuously according to a pre-designed pattern. Sometimes, long and strong excitation can damage biological tissues or trigger complex nonlinear adaptation processes, which will dramatically increase the complexity of model structure and the difficulty of model parameter estimation. Electroretinogram (ERG), for example, depends on the degree of dark adaptation (Lei et al., 2006; Lu et al., 2010). The complexity of chlorophyll fluorescence models from plants is also affected by excitation light intensity (Guo and Tan, 2011, 2014).

Although pulse is not believed as a rich perturbation as signals with many variations like white noise or pseudorandom-binary-sequence (Daves, 1970), it is still often used to excite biological systems (Belyaeva et al., 2011; Lei et al., 2006; Lu et al., 2010) due to it is easy to perform and the model structure under its excitation can be simplified. For example, it has been extensively used in medical imaging and laser induced fluorescence generation. The inputs such as irrigation, therapy, and treatments to biological systems are also equivalent to pulses. They are often the only input to the system in given experiments. The biological system behaves as a switched model under the function of the single input. The system matrix may depend on the intensity of the input (Guo et al., 2010; Lu et al., 2010). To make model parameter estimation more realistic, the systems could be simplified as switched linear models (De Jong et al., 2004; Gouzé and Sari, 2002; Guo et al., 2010). In this research, we studied the identifiability and identification techniques of switched

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linear biological models with a single input and system matrix dependent on the intensity of the input. A recurrent-pulse excitation technique was designed to enhance the identifiability of this type of biological models. The usefulness of the method was illustrated by examples including delayed fluorescence from photosystem II, which was well known as a versatile tool for plant physiological status and environmental changes measurement in the literature (Goltsev et al., 2009; Guo and Tan, 2010a, 2013).

2. System responses and identifiability

An input-dependent switched linear biological model with a single input and a pulse excitation may be expressed as:

$$\dot{\boldsymbol{x}} = A(u)x + Bu \quad \boldsymbol{x} \in R^n, \quad A(u) \in R^{n\times n}, \quad B \in R^{n\times 1}, \quad u \in R^1 \tag{1}$$

where

$$u = \begin{cases} u_0 & 0 \le t \le t_d \\ 0 & t > t_d \end{cases} \tag{2}$$

$\boldsymbol{x}$ is a vector of state variables, n is the model order, and t_d is the pulse duration. $A(u)$ contains model parameters that need to be estimated from experimental data. An example of the switched linear biological model could be found in Guo et al. (2010). We will analyze the model identifiablility by assuming one or more the state variables in $\boldsymbol{x}$ are measurable. If an observable system output is a linear combination of states rather than simply a state variable, it can be represented as state by redefining the state variables. For convenience, therefore, we assume that the observations are part of or all the n state variables for discussion of system identifiability. $A(u_0)$ and $A(0)$ are each assumed to have n distinct eigenvalues ($\lambda_1 \in \{\lambda_1^1, \lambda_1^2, \ldots, \lambda_1^n\}$ and $\lambda_2 \in \{\lambda_2^1, \lambda_2^2, \ldots, \lambda_2^n\}$, respectively) and all the states are assumed to be coupled together. If one state variable is measureable, the eigenvalues can be determined by methods such as the eigensystem realization algorithm (ERA) from forced responses or initial condition responses (Juang and Pappa, 1985). It is thus reasonable to assume that all the eigenvalues are available or determinable from experimental data.

If D_1 and D_2 are the diagonal eigenvalue matrices of $A(u_0)$ and $A(0)$, respectively; P and U are eigenvector matrices of $A(u_0)$ and $A(0)$, respectively; Q and V are the inverse matrices of P and U, respectively; then

$$A(u_0) = PD_1Q = \begin{bmatrix} p_{11} & p_{12} & \cdots & p_{1n} \\ p_{21} & p_{22} & \cdots & p_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ p_{n1} & p_{n2} & \cdots & p_{nn} \end{bmatrix} \begin{bmatrix} \lambda_1^1 & 0 & \cdots & 0 \\ 0 & \lambda_1^2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \lambda_1^n \end{bmatrix} \begin{bmatrix} q_{11} & q_{12} & \cdots & q_{1n} \\ q_{21} & q_{22} & \cdots & q_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ q_{n1} & q_{n2} & \cdots & q_{nn} \end{bmatrix} \tag{3}$$

$$A(0) = UD_2V = \begin{bmatrix} u_{11} & u_{12} & \cdots & u_{1n} \\ u_{21} & u_{22} & \cdots & u_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ u_{n1} & u_{n2} & \cdots & u_{nn} \end{bmatrix} \begin{bmatrix} \lambda_2^1 & 0 & \cdots & 0 \\ 0 & \lambda_2^2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \lambda_2^n \end{bmatrix} \begin{bmatrix} v_{11} & v_{12} & \cdots & v_{1n} \\ v_{21} & v_{22} & \cdots & v_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ v_{n1} & v_{n2} & \cdots & v_{nn} \end{bmatrix} \tag{4}$$

Since D_1 and D_2 are determinable from experimental data, as is obvious from Eqs. (3) and (4), multiple choices for the vector directions of P, Q, U, and V matrices will result in non-unique $A(u_0)$ and $A(0)$.

2.1. System responses

For zero initial condition $\boldsymbol{x} = 0$, the system response during a pulse excitation ($u = u_0$) is:

$$\boldsymbol{x} = \int_0^t e^{A\tau}Bu(t-\tau)d\tau = \Phi \begin{bmatrix} \frac{1}{\lambda_1^1}e^{\lambda_1^1\tau} \\ \frac{1}{\lambda_1^2}e^{\lambda_1^2\tau} \\ \vdots \\ \frac{1}{\lambda_1^n}e^{\lambda_1^n\tau} \end{bmatrix}_0^t \tag{5}$$

where

$$\Phi = \begin{bmatrix} p_{11}\sum_{i=1}^{n} q_{1i}(Bu_0)_i & p_{12}\sum_{i=1}^{n} q_{2i}(Bu_0)_i & \cdots & p_{1n}\sum_{i=1}^{n} q_{ni}(Bu_0)_i \\ p_{21}\sum_{i=1}^{n} q_{1i}(Bu_0)_i & p_{22}\sum_{i=1}^{n} q_{2i}(Bu_0)_i & \cdots & p_{2n}\sum_{i=1}^{n} q_{ni}(Bu)_i \\ \vdots & \vdots & \ddots & \vdots \\ p_{n1}\sum_{i=1}^{n} q_{1i}(Bu_0)_i & p_{n2}\sum_{i=1}^{n} q_{2i}(Bu_0)_i & \cdots & p_{nn}\sum_{i=1}^{n} q_{ni}(Bu_0)_i \end{bmatrix} \tag{6}$$

Following the excitation pulse, the system response will be an initial condition response to the state variable values at the end of the pulse, $\boldsymbol{x}(t_d)$. The response of state variable x_i ($i = 1, 2, \ldots, n$) to initial condition $\boldsymbol{x}(t_d)$ can be expressed as (Guo and Tan, 2010b):

$$\begin{aligned} x_i &= [\varphi_i \boldsymbol{x}(t_d)]^T \begin{bmatrix} e^{\lambda_2^1 t} \\ e^{\lambda_2^2 t} \\ \vdots \\ e^{\lambda_2^n t} \end{bmatrix} \\ &= \left[\Psi_i \begin{bmatrix} \frac{1}{\lambda_1^1}e^{\lambda_1^1 t_d} - \frac{1}{\lambda_1^1} \\ \frac{1}{\lambda_1^2}e^{\lambda_1^2 t_d} - \frac{1}{\lambda_1^2} \\ \vdots \\ \frac{1}{\lambda_1^n}e^{\lambda_1^n t_d} - \frac{1}{\lambda_1^n} \end{bmatrix} \right]^T \begin{bmatrix} e^{\lambda_2^1 t} \\ e^{\lambda_2^2 t} \\ \vdots \\ e^{\lambda_2^n t} \end{bmatrix} \quad (i = 1, \ldots, n) \end{aligned} \tag{7}$$