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Investigation of kinetic-order sensitivities in metabolic reaction networks

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ABSTRACT

Kinetic-order sensitivity (the ratio of relative change in a dependent variable to the relative change in a kinetic order in a power-law–type differential equation) has recently become an important indicator in metabolic pathway analysis using mathematical models with parameter values determined from time-series data on cellular metabolite concentrations. Here, we discuss a potential problem in calculating kinetic-order sensitivities. When the steady-state metabolite concentration is less than unity, a slight increase in the kinetic order changes the metabolite concentration in the incorrect direction, yielding a kinetic-order sensitivity value with an incorrect sign. This is caused by a property of the power-law function ($y=X^n$): when X is less than unity, y decreases for a larger positive n or for a smaller absolute value of negative n. We propose two solutions. The first is to directly calculate the kinetic-order sensitivities and then reverse the sign of the relevant value if a steady-state metabolite concentration less than unity is involved. The second involves calculation of the kinetic-order sensitivities after setting all metabolite concentrations to values greater than unity (e.g., by changing the units from mM to μM). The latter method changes the absolute values of the kinetic-order sensitivities according to the magnitude of a multiplication factor, because kinetic-order sensitivities do not have unique values. Nevertheless, since the normalized absolute values exhibit an almost identical distribution, it should not be difficult to identify which kinetic order has greater effect, although kinetic order rankings may change slightly under different calculation conditions.

1. Introduction

Recent developments in high-performance analytical instruments have enabled comprehensive measurement of the time courses of metabolite concentrations in cells (Fiehn, 2002; Weckwerth, 2003; Schauer and Fernie, 2006; Sawada et al., 2009). Concordant with advancements in metabolomics, methods for constructing a mathematical model for a large-scale metabolic reaction system using time-series data on metabolite concentrations are under development (Chou and Voit, 2012; Heijnen and Verheijen, 2013; Voit, 2013; Sriyudthsak et al., 2014a; 2014b). These methods make it possible to perform computer simulations of metabolic reactions taking place in cells, allowing researchers to comprehensively investigate the characteristics of metabolic reaction systems, elucidate metabolic reaction phenomena, and discover unknown interactions between distant metabolites and enzymes. The analysis could also facilitate practical discussions of metabolic reaction systems, such as the identification of bottleneck enzymes to attain a higher yield of desired product (Sriyudthsak and Shiraishi, 2010; Sriyudthsak et al., 2015).

Biochemical systems theory (BST) (Savageau, 1969; 1976) provides a systematic tool for constructing a mathematical model in a given large-scale metabolic reaction system, where the time course of each metabolite concentration is expressed in terms of differential equations consisting of power law-type flux equations that describe the interaction between a metabolite and an enzyme, *i.e.*, S-system or GMA-system equations (Shiraishi and Savageau, 1992a, 1992b, 1992c, 1992d). Each power-law flux term in the differential equations consists of the product of a rate constant and the relevant dependent and independent variables with an exponential parameter or kinetic order. The sign of each kinetic order and the magnitude of its absolute value provide information on the types and magnitudes of the interactions (Voit, 2000).

BST provides logarithmic gains (independent variable sensitivities) and parameter sensitivities (Savageau and Sorribas, 1989). The kinetic-order sensitivity expresses the ratio of relative change in a dependent variable to the relative change in a kinetic order. A larger absolute value

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of this sensitivity indicates that the system is influenced more strongly by a change in the kinetic order. When plural metabolites interact with a specific enzyme, the kinetic-order sensitivity can be used as an indicator of which metabolite has a stronger effect. Thus, sensitivity is gaining importance as demand for mathematical modeling in large-scale systems increases. As demonstrated here, however, under specific conditions calculation of kinetic-order sensitivities can produce values with opposite signs.

The present study, therefore, pinpoints a difficulty in calculating kinetic-order sensitivities and elucidates the reason for the incorrect results. Moreover, several methods to overcome the difficulty are proposed.

2. Theory

2.1. GMA system-type equations

It is convenient to calculate the kinetic-order sensitivities in such a way that it is possible to investigate how each dependent variable responds to a change in a specific kinetic order in differential equations with more than two flux terms. Hence, we will discuss GMA-system representation. In a metabolic reaction system consisting of n metabolite concentrations (dependent variables) X_i (i=1, ..., n), the metabolic flux, v_k (k=1, ..., z) is generally expressed as:

$$v_k = f(X_1, X_2, ... , X_n) \tag{1}$$

which can be transformed using the steady-state metabolite concentrations and the power-law equation:

$$v_k = \gamma_k \prod_{j=1}^{n} X_j^{f_{kj}} \quad (k = 1, 2, \ldots, z) \tag{2}$$

where γ_k is the rate constant and f_{kj} is the kinetic order associated with X_j in the kth flux equation, z is the number of flux equations, and n is the number of dependent variables. Transformation of Eq. (1) to (2) is performed using the equations:

$$f_{kj} = \left(\frac{\partial v_k}{\partial X_j}\right)^* \frac{X_j^*}{v_k^*} \quad (j = 1, 2, ... , n; \quad k = 1, 2, \ldots, z) \tag{3}$$

$$\gamma_k = \frac{v_k^*}{\prod_{j=1}^{n} X_j^{*f_{kj}}} \quad (k = 1, 2, \ldots, z) \tag{4}$$

where the superscript * indicates that the results are evaluated at the steady state. Consequently, the differential equations in a GMA system, representing the time courses of the metabolite concentrations, X_i (i=1, ..., n), are given as:

$$\dot{X}_i = \frac{dX_i}{dt} = \sum_{k=1}^{z} N_{ik} v_k \quad (i = 1, 2, \ldots, n) \tag{5}$$

where N_{ik} is the stoichiometric coefficient in the flux equation for v_k in the differential equation for X_i.

2.2. Equations for calculating kinetic-order sensitivities

Matrix representation of Eq. (5) is given as (Voit, 2000):

$$\dot{\mathbf{X}}] = [\mathbf{N}] \ \mathbf{v}] \tag{6}$$

where

$$\dot{\mathbf{X}}] = \begin{bmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \vdots \\ \dot{X}_n \end{bmatrix}, \ \mathbf{v}] = \begin{bmatrix} v_1 \\ v_2 \\ \vdots \\ v_z \end{bmatrix}, \ [\mathbf{N}] = \begin{bmatrix} N_{11} & N_{12} & \cdots & N_{1z} \\ N_{21} & N_{22} & \cdots & N_{2z} \\ \vdots & \vdots & \ddots & \vdots \\ N_{n1} & N_{n2} & \cdots & N_{nz} \end{bmatrix}$$

and the symbols] and [] represent vectors and matrixes, respectively. Differentiating Eq. (6) with respect to the kinetic orders f_{pq} (p=1,..., z; q =1,..., n) and arranging the results provides the equations for the kinetic-order sensitivities of metabolite concentrations:

$$\mathbf{S}(\mathbf{X}, f_{pq})\Big] = \begin{bmatrix} \frac{\partial \ln X_1}{\partial \ln f_{pq}} \\ \frac{\partial \ln X_2}{\partial \ln f_{pq}} \\ \vdots \\ \frac{\partial \ln X_n}{\partial \ln f_{pq}} \end{bmatrix} = [\mathbf{S}(\mathbf{X}, \boldsymbol{\gamma})] \ln \mathbf{X}_q] f_{pq} \quad (p = 1, \ldots, z; \ q = 1, \ldots, n) \tag{7}$$

and the kinetic-order sensitivities of fluxes:

$$\mathbf{S}(\mathbf{v}, f_{pq})\Big] = \begin{bmatrix} \frac{\partial \ln v_1}{\partial \ln f_{pq}} \\ \frac{\partial \ln v_2}{\partial \ln f_{pq}} \\ \vdots \\ \frac{\partial \ln v_z}{\partial \ln f_{pq}} \end{bmatrix} = [\mathbf{S}(\mathbf{v}, \boldsymbol{\gamma})] \ln \mathbf{X}_q] f_{pq} \quad (p = 1, \ldots, z; \ q = 1, \ldots, n) \tag{8}$$

where $\ln\mathbf{X}_q]$ is the vector with a value of $\ln X_q$ in the pth line and zero in all other lines, given as:

$$\ln \mathbf{X}_q] = \begin{bmatrix} 0 \\ \vdots \\ \ln X_q \\ \vdots \\ 0 \end{bmatrix} \quad (q = 1, \ldots, n), \tag{9}$$

$[\mathbf{S}(\mathbf{X}, \boldsymbol{\gamma})]$ represents the rate constant sensitivities of the metabolite concentrations, expressed as:

$$[\mathbf{S}(\mathbf{X}, \boldsymbol{\gamma})] = \begin{bmatrix} \left(\frac{\partial X_1}{\partial \gamma_1}\right)^* \frac{\gamma_1}{X_1^*} & \left(\frac{\partial X_1}{\partial \gamma_2}\right)^* \frac{\gamma_2}{X_1^*} & \cdots & \left(\frac{\partial X_1}{\partial \gamma_z}\right)^* \frac{\gamma_z}{X_1^*} \\ \left(\frac{\partial X_2}{\partial \gamma_1}\right)^* \frac{\gamma_1}{X_2^*} & \left(\frac{\partial X_2}{\partial \gamma_2}\right)^* \frac{\gamma_2}{X_2^*} & \cdots & \left(\frac{\partial X_2}{\partial \gamma_z}\right)^* \frac{\gamma_z}{X_2^*} \\ \vdots & \vdots & \ddots & \vdots \\ \left(\frac{\partial X_n}{\partial \gamma_1}\right)^* \frac{\gamma_1}{X_n^*} & \left(\frac{\partial X_n}{\partial \gamma_2}\right)^* \frac{\gamma_2}{X_n^*} & \cdots & \left(\frac{\partial X_n}{\partial \gamma_z}\right)^* \frac{\gamma_z}{X_n^*} \end{bmatrix} = -([\mathbf{N}][\mathbf{v}][\mathbf{f}]_{\mathrm{d}})^{-1}[\mathbf{N}][\mathbf{v}] \tag{10}$$

and $[\mathbf{S}(\mathbf{v}, \boldsymbol{\gamma})]$ represents the rate constant sensitivities of the fluxes, expressed as:

$$[\mathbf{S}(\mathbf{v}, \boldsymbol{\gamma})] = \begin{bmatrix} \left(\frac{\partial v_1}{\partial \gamma_1}\right)^* \frac{\gamma_1}{v_1^*} & \left(\frac{\partial v_1}{\partial \gamma_2}\right)^* \frac{\gamma_2}{v_1^*} & \cdots & \left(\frac{\partial v_1}{\partial \gamma_z}\right)^* \frac{\gamma_z}{v_1^*} \\ \left(\frac{\partial X_2}{\partial \gamma_1}\right)^* \frac{\gamma_1}{X_2^*} & \left(\frac{\partial X_2}{\partial \gamma_2}\right)^* \frac{\gamma_2}{X_2^*} & \cdots & \left(\frac{\partial v_2}{\partial \gamma_z}\right)^* \frac{\gamma_z}{v_2^*} \\ \vdots & \vdots & \ddots & \vdots \\ \left(\frac{\partial v_z}{\partial \gamma_1}\right)^* \frac{\gamma_1}{v_z^*} & \left(\frac{\partial v_z}{\partial \gamma_2}\right)^* \frac{\gamma_2}{v_z^*} & \cdots & \left(\frac{\partial v_z}{\partial \gamma_z}\right)^* \frac{\gamma_z}{v_z^*} \end{bmatrix} = [\mathbf{f}]_{\mathrm{d}} \ [\mathbf{S}(\mathbf{X}, \boldsymbol{\gamma})] + [\mathbf{I}] \tag{11}$$

where the subscripts $_{\mathrm{d}}$ and $_{\mathrm{i}}$ indicate that the results are evaluated using the dependent and independent variables, respectively. The matrix $[\mathbf{v}]$ is given as:

$$[\mathbf{v}] = \begin{bmatrix} v_1 & 0 & \cdots & 0 \\ 0 & v_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & v_z \end{bmatrix}$$

and $[\mathbf{I}]$ is the unit matrix. Moreover, $[\mathbf{f}]_{\mathrm{d}}$ is the matrix for the kinetic orders associated with the dependent variables, given as: