Analysis of Signal Transduction Networks in Michaelis-Menten Equations and S-Systems

Chun-Liang Lin, Yuan-Wei Liu and Chia-Hua Chuang

***Abstract*—**Signal transduction networks of biological systems are highly complicated. How to mathematically describe a signal transduction network by systematic approaches so as to further exploit appropriate control strategies is becoming attractive to engineers. In this paper, a mathematical model of signal transduction networks with a simplified structure is proposed and related analyses are performed.

***Keywords*—**biological system, S-system, sensitivity, signal transduction network

I. Introduction

There are plenty of publication dedicated in construction of the biochemical networks and gene networks, see, for example, [1-4]. Within theses networks, signal transduction networks of biological systems are characterized by their high complexity level, and the networks are composed of many biochemical reactions. The complexity of cellular signal transduction network is incomprehensible. Thus, an effective method to develop a mathematically equivalent model of the biochemical networks is highly desirable.

The synergism and saturation system (S-system) in [1, 5] has been a well-studied approach in modeling biochemical networks which characterizes the signal transduction networks. It was shown that the S-system representation in terms of ordinary differential equations (ODEs) is capable of capturing behaviors of the biochemical dynamics. Applying logarithm on the state variables further linearizes the state equations of the S-system at steady state. Based on the linearlized S-system, it is possible to analyze and predict the system behavior without directly resorting to the original nonlinear model. A linearized S-system was presented and the robust stability analysis was proposed in [6].

Instead of the S-system description, the Michaelis-Menten equation [7, 8] was widely adopted in modeling of biological systems. With the concentration change equations expressed as ODEs, the concentration change of metabolites in each pathway of biochemical networks was investigated. However, it may cost significant computation time to analyze all cellular signal reactions and interactions which are not all important and crucial to the signal transduction networks. Removing the redundant parts is thus an issue worthy of further concerns.

For simplifying the construction of the mathematical model, we propose a method called as the cascaded analysis model. The cascaded analysis model is used to construct a mathematical model of the S-systems form. On the basis of the model, we do not need to solve the complete model, which can be extremely complicated structurally, in a single iteration. Rather, the problem can be broken down into smaller partitions to lessen computational burden.

The purpose of this paper is to model and analyze the signal transduction networks in biological systems and transform the mathematical model described by the S-system and the Michaelis-Menten rate law to a reduced system model. With the simplified model, there will be less computational efforts while performing related analysis and even leading to simpler control designs. A example for is presented for demonstration.

II. Analysis Methods

A signal transduction network includes many scaffolds which can be bound with molecules. The entire pathways which would influence reactions are too large to be conducted, and it requires an effective method for constructing a mathematical model. We demonstrate a new method and construct the mathematical model in the follows.

A. System Modeling

First, consider the scaffold protein with each binding

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domain that can be bound with one molecule. We define all states and pathways of the scaffold protein as follows

$$S=\sum_{i=0}^{n}\binom{n}{i} \tag{1}$$

$$P=\sum_{i=0}^{n-1}\binom{n}{i}\left(\sum_{j=1}^{n-i}2^{j-1}\right) \tag{2}$$

where S means states, P means pathways, n means binding domains, and

$$\binom{n}{i}=\frac{n!}{i!(n-i)!} \tag{3}$$

Second, there are many pathways in the system. Thus, to simplify the system from the complete model to a smaller one is necessary. Consider here the case where the scaffold protein can bind only with one molecule at a time. Under this situation, one can neglect the redundant pathways. To simplify the exceedingly complicated structure, the new pathways are written as follows

$$P=\sum_{i=0}^{n}\binom{n}{i}(n-i) \tag{4}$$

For instance, we consider a scaffold which can be bound with three molecules. There are 8 states and 19 pathways in the original signal transduction network. The original model is shown in Fig. 1. According to (4), we can reduce the number of the reactive pathways (2) in the original system to 12 pathways. The reduced model is shown in Fig. 2.

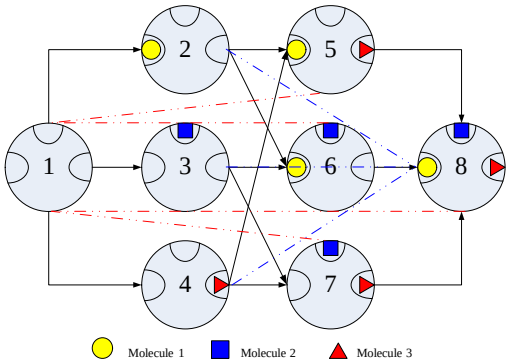

Fig. 1 Original mathematical model of the signal transduction pathway (dashed lines denote all possible connections)

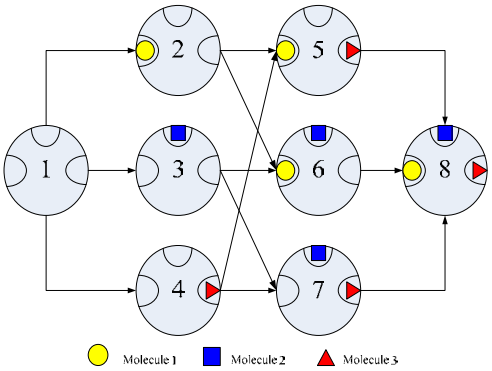

Fig. 2 Simplified mathematical model of the signal transduction pathway

Third, define states and molecules as state variable x and implement the pathways to reactions. By the Michaelis-Menten rate law, each reaction can be represented as an ODE. We implement the S-system by using ODEs and describing the temporary changes in the biochemical system as follows [9]

$$\begin{aligned}\dot{x}_i &= V_i^+ - V_i^-, \quad i=1,2,...,n\\ V_i^+ &= \alpha_i\prod_{j=1}^{n+m}x_j^{g_{ij}},\\ V_i^- &= \beta_i\prod_{j=1}^{n+m}x_j^{h_{ij}}\end{aligned} \tag{5}$$

where $V_i^+ = V_i^+(x_1,x_2,...,x_n,x_{n+1},...,x_{n+m})$ and $V_i^- = V_i^-(x_1,x_2,...,x_n,x_{n+1},...,x_{n+m})$ are the general functions of dependent variables $x_1,x_2,...,x_n$ and independent variables $x_{n+1},x_{n+2},...,x_{n+m}$; α_i and β_i are rate constants; g_{ij} and h_{ij} are kinetic orders.

Further consider the steady state of the system (5). Since all derivatives should be zero at the steady state, therefore

$$\alpha_i\prod_{j=1}^{n+m}x_j^{g_{ij}}=\beta_i\prod_{j=1}^{n+m}x_j^{h_{ij}},\ i=1,2,\ldots,n \tag{6}$$

Given all constants and variable rates in (6) are nonzero, one can take logarithm on it and obtain:

$$\begin{aligned}&\ln\alpha_i+\ln\left(\prod_{j=1}^{n+m}x_j^{g_{ij}}\right)\\ &=\ln\beta_i+\ln\left(\prod_{j=1}^{n+m}x_j^{h_{ij}}\right),\quad i=1,2,...,n\end{aligned} \tag{7}$$

That is

$$\ln \alpha_i + \sum_{j=1}^{n+m} g_{ij} \ln x_j = \ln \beta_i + \sum_{j=1}^{n+m} h_{ij} \ln x_j, \quad i = 1, 2, ..., n \tag{8}$$

Defining $y_j = \ln x_j$ gives

$$\ln\left(\frac{\beta_i}{\alpha_i}\right) = \sum_{j=1}^{n+m} g_{ij} y_j - \sum_{j=1}^{n+m} h_{ij} y_j, \quad i = 1, 2, ..., n \tag{9}$$

Let $b_i = \ln\left(\frac{\beta_i}{\alpha_i}\right)$ and $a_{ij} = g_{ij} - h_{ij}$. A general S-system with n dependent variables and m independent variables can then be characterized by a set of n linear equations:

$$\begin{aligned} &a_{11}y_1 + a_{12}y_2 + ... + a_{1n}y_n + a_{1,n+1}y_{n+1} + ... + a_{1,n+m}y_{n+m} = b_1, \\ &a_{21}y_1 + a_{22}y_2 + ... + a_{2n}y_n + a_{2,n+1}y_{n+1} + ... + a_{2,n+m}y_{n+m} = b_2, \\ &\vdots \\ &a_{n1}y_1 + a_{n2}y_2 + ... + a_{nn}y_n + a_{n,n+1}y_{n+1} + ... + a_{n,n+m}y_{n+m} = b_n \end{aligned} \tag{10}$$

Or equivalently,

$$A_D \vec{y}_D = \vec{b} - A_I \vec{y}_I \tag{11}$$

where

$$A_D = \begin{bmatrix} a_{11} & a_{12} & \cdots & a_{1n} \\ a_{21} & a_{22} & \cdots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \cdots & a_{nn} \end{bmatrix}, \quad \vec{y}_D = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix}, \quad \vec{b} = \begin{bmatrix} b_1 \\ b_2 \\ \vdots \\ b_n \end{bmatrix},$$

$$A_I = \begin{bmatrix} a_{1,n+1} & a_{1,n+2} & \cdots & a_{1,n+m} \\ a_{2,n+1} & a_{2,n+2} & \cdots & a_{2,n+m} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n,n+1} & a_{n,n+2} & \cdots & a_{n,n+m} \end{bmatrix}, \quad \vec{y}_I = \begin{bmatrix} y_{n+1} \\ y_{n+2} \\ \vdots \\ y_{n+m} \end{bmatrix}$$

where the subscripts D and I means, respectively, the dependent and independent variables. It is seen from (11) that all dependent variables have been separated from the independent variables.

From (11), the solution of $\vec{y}_D$ is obtained as

$$\vec{y}_D = A_D^{-1}\left(\vec{b} - A_I \vec{y}_I\right) \tag{12}$$

provided that A_D is invertible. By using the pre-described procedure, the originally complicated system could be further transformed into an analyzable form.

B. Cascaded Analysis Model

To simplify the mathematical analysis, we propose here a cascaded analysis model. This is used to construct a simplified mathematical model of an S-system. With it, one does not need to solve the complete model, rather, the problem is broken down into smaller partitions to lessen computational burden.

A molecule bind with a scaffold protein is the basic reactions in the mathematical model. The basic reaction can be described as a signal transduction pathway as shown in Fig. 3. By the Michaelis-Menten rate law, the reactions can be presented as ODEs and built as an S-system.

After estimating all parameters of the S-system, one can compute the output concentration x_1 at the steady state. On the basis of the output concentration, we cascade the output concentration with a new molecule to generate a new signal transduction pathway as shown in Fig. 4. With the same reason, we can cascade molecules to construct a complete mathematical model as shown in Fig. 5. Applying the cascaded analysis model, one can construct the mathematical model step by step that is more easily than construct the model at a time.

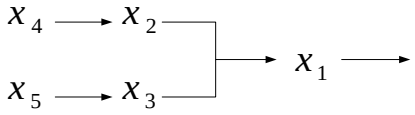

Fig. 3 Basic bimolecular reaction

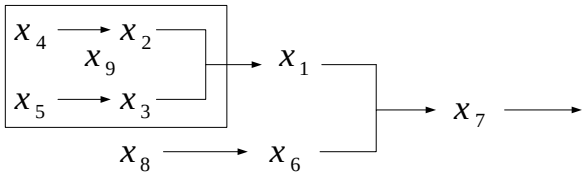

Fig. 4 Two-layer cascaded analysis model. The block constructed by x_2, x_3, x_4 and x_5 is replaced by a new independent variable x_9

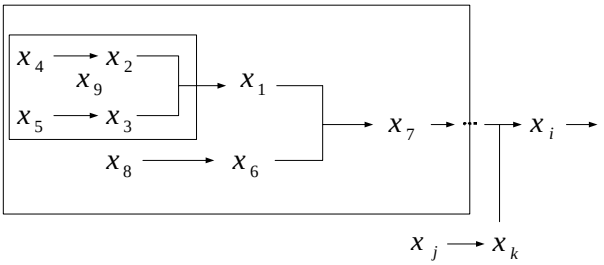

Fig. 5 Complete cascaded analysis model

The proposed method and analyses were demonstrated by a signal transduction network with one scaffold protein and two binding domains, see Fig. 6.

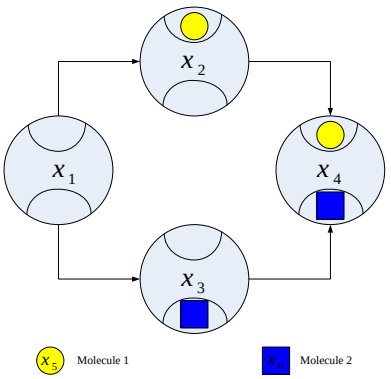

Fig. 6 Reduced model with two binding domains

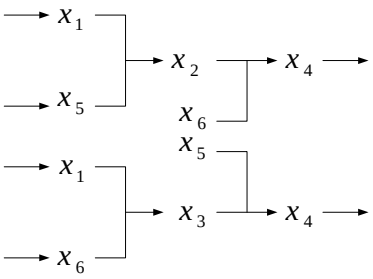

Fig. 7 Signal transduction network with one scaffold protein and two binding domains

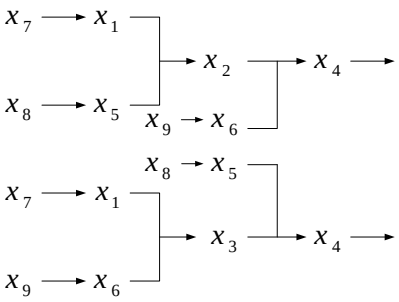

Fig. 8 Adding independent variables to modify the signal transduction network

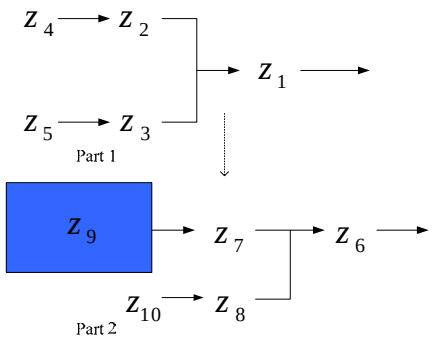

Fig. 9 Example for the cascaded analysis model

We compute the original number of states and pathways of the signal transduction network model. According to (1) and (2), the original number of states and pathways are 4 and 5. Neglecting the redundant pathways described by (4) simplifies the complete model. The number of pathways of the new model becomes 4. Defining states (S) and molecules as state variables x_i and implementing the pathways to reactions, one can then modify the reactions and construct the new signal transduction pathways as shown in Fig. 7.

On the basis of the signal transduction pathways in Fig. 7, we introduce three independent variables (x_7, x_8, x_9) to construct the analyzable model (See Fig. 8). Applying the cascaded analysis model and considering the top part in Fig. 8, we separate the pathways into two parts and define a new variable z_i to substitute x_i as shown in Fig. 9.

Consider part one in Fig. 9, the system includes three dependent variables (z_1, z_2, z_3) and two independent variables (z_4, z_5), and the fluxes contain variables (V^+, V^-). The S-system is built as follows

$$\begin{aligned} \dot{z}_1 &= \alpha_1 z_2^{g_{12}} z_3^{g_{13}} - \beta_1 z_1^{h_{11}}, \\ \dot{z}_2 &= \alpha_2 z_4^{g_{24}} - \beta_2 z_2^{h_{22}} z_3^{h_{23}}, \\ \dot{z}_3 &= \alpha_3 z_5^{g_{35}} - \beta_3 z_2^{h_{32}} z_3^{h_{33}}, \\ z_4, z_5 &= \text{constant} \end{aligned} \tag{13}$$

Consider the system at the steady state and take logarithm on both sides:

$$\begin{aligned} \ln\alpha_1 + g_{12}\ln z_2 + g_{13}\ln z_3 &= \ln\beta_1 + h_{11}\ln z_1 \\ \ln\alpha_2 + g_{24}\ln z_4 &= \ln\beta_2 + h_{22}\ln z_2 + h_{23}\ln z_3 \\ \ln\alpha_3 + g_{35}\ln z_5 &= \ln\beta_3 + h_{32}\ln z_2 + h_{33}\ln z_3 \end{aligned} \tag{14}$$

Define $a_{ij} = g_{ij} - h_{ij}$, $b_i = \ln\left(\frac{\beta_i}{\alpha_i}\right)$ and $y_j = \ln z_j$, separate the dependent and independent variables, and rearrange (14) as follows

$$\begin{bmatrix} a_{11} & a_{12} & a_{13} \\ 0 & a_{22} & a_{23} \\ 0 & a_{32} & a_{33} \end{bmatrix} \begin{bmatrix} y_1 \\ y_2 \\ y_3 \end{bmatrix} = \begin{bmatrix} b_1 \\ b_2 - a_{24} y_4 \\ b_3 - a_{35} y_5 \end{bmatrix} \tag{15}$$

Similarly, one can construct the S-system model for part two in Fig. 9:

$$\begin{aligned}
\dot{z}_6 &= \alpha_6 z_7^{g_{67}} z_8^{g_{68}} - \beta_6 z_6^{h_{66}}, \\
\dot{z}_7 &= \alpha_7 z_9^{g_{79}} - \beta_7 z_7^{h_{77}} z_8^{h_{78}}, \\
\dot{z}_8 &= \alpha_8 z_{10}^{g_{8,10}} - \beta_8 z_7^{h_{87}} z_8^{h_{88}}, \\
z_9, z_{10} &= \text{constant}
\end{aligned} \tag{16}$$

One can proceed to perform steady state analysis for the subsequent layer in the similar way.

Using the cascaded analysis model, the original complete model can be replaced by a simplified one. This is useful for the purpose of numerical analysis of the large biochemical systems.

C. Parameter Thresholds

For S-systems, the local stability analysis can be accomplished with simple linear algebra techniques. One can linearize the nonlinear biochemical system around the steady status to yield a linear one. Then, proceeding to analyze the linear biochemical system would provide a useful insight into the nonlinear system.

Consider the biochemical systems, which have been modeled as an S-system at the steady state. By using the Gershgorin theory, the eigenvalues of the S-system at steady state satisfy the following inequalities:

$$\left|\lambda - a_{ii}\right| \le \sum_{\substack{j=1 \\ j\neq i}}^{n} \left|a_{ij}\right|, \quad i = 1, 2, ..., n \tag{17}$$

and

$$\left|\lambda - a_{ii}\right| \le \sum_{\substack{j=1 \\ j\neq i}}^{n} \left|a_{ji}\right|, \quad i = 1, 2, ..., n \tag{18}$$

where λ denotes the eigenvalue and a_{ij} denotes the element of the system matrix. The inequalities above characterize *n* Gershgorin discs which can be used to estimate distribution of all eigenvalues.

For example, consider an S-system model of three dependent variables as follows

$$\begin{aligned}
\dot{x}_1 &= 2x_3^{-1} - 2x_1^{0.5}, \\
\dot{x}_2 &= 2x_1^{0.5} - 2x_2^{0.5}, \\
\dot{x}_3 &= 2x_2^{0.5} - 2x_3^{0.5}
\end{aligned}$$

The steady-state system matrix A_S can be described as

$$A_S = \begin{bmatrix} -0.5 & 0 & -1 \\ 0.5 & -0.5 & 0 \\ 0 & 0.5 & -0.5 \end{bmatrix}$$

Applying the Gershgorin theory, we can obtain three Gershgorin discs shown as in Fig. 10. The discs one and two are two cycles with the center at -0.5 and the radius 0.5. The disc three has the center at -0.5 and the radius 1.

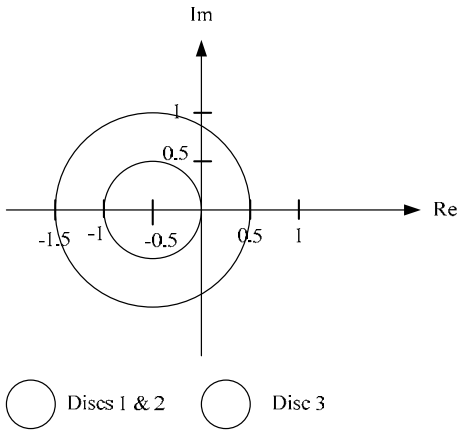

Fig. 10 Gershgorin discs

It is also interested in determining the parameter threshold of the biochemical system under which the system will exhibit stability. To this aim, the F-factors of S-systems are introduced here, which are defined as the relative fluxes at steady state and can be computed from the following equation:

$$F_i = x_{iS}^{-1}\left(\alpha_i \prod_{j=1}^{n+m} x_{jS}^{g_{ij}}\right) = x_{iS}^{-1}\left(\beta_i \prod_{j=1}^{n+m} x_{jS}^{h_{ij}}\right) \tag{19}$$

where x_{iS} and x_{jS} denote, respectively, the steady states of x_i and x_j. By applying the F-factors to the system matrix, the characteristic polynomial $\Delta(\lambda)$ can be determined as

$$\Delta(\lambda) = \begin{bmatrix} F_1 a_{11} - \lambda & F_1 a_{12} & \cdots & F_1 a_{1n} \\ F_2 a_{21} & F_2 a_{22} - \lambda & \cdots & F_2 a_{2n} \\ \vdots & \vdots & & \vdots \\ F_n a_{n1} & F_n a_{n2} & \cdots & F_n a_{nn} - \lambda \end{bmatrix} = 0 \tag{20}$$

It is straightforward to determine the threshold of parameter values, within which the system would be stable, by applying the Routh-Hurwitz criterion.

D. Sensitivity Analysis

When the system remains close to the steady state, sensitivity analysis provides results that relate steady-state concentrations and fluxes. It helps one to predict how the system performance is influenced by changes in related factors of concerns. It can also be used as quantitative measures that show how fast the responses of any system components change with parameter variations. In S-systems, all rate laws for individual steps of the system that tend to increase/decrease a given metabolite are aggregated into a net or aggregate rate law of synthesis/degradation [10].

Logarithmic gain

Consider the logarithmic gain of the steady-state of a metabolite with respect to a change in an independent variable. Our objective now is to predict how strongly changes in independent variables affect the steady state of the system without the need of solving the differential equations.

Special interest is in the relative change in the metabolite x_i caused by the relative change in x_j. We characterize the system response by describing how $y_i = \ln x_i$ responses to changes in $y_j = \ln x_j$. Define the logarithmic gain; the change in y_i per unit change in y_j is given as the derivative of y_i with respect to y_j:

$$L(x_i, x_j) = \frac{\partial y_i}{\partial y_j} \approx \frac{\Delta x_i / x_i}{\Delta x_j / x_j} \tag{21}$$

for small Δx_i. For small changes in the independent variables, the logarithmic gain predicts correspondingly the relative change in the dependent variables.

Sensitivity of rate constants

The analysis of the sensitivities $S\left(x_i, \alpha_j\right)$ and $S\left(x_i, \beta_j\right)$ begin with the steady-state solution of the biochemical system as in the case of logarithmic gains where [9]

$$S\left(x_i, \alpha_j\right) = \frac{\partial \ln x_i}{\partial \ln \alpha_j} \tag{22}$$

and

$$S\left(x_i, \beta_j\right) = \frac{\partial \ln x_i}{\partial \ln \beta_j} \tag{23}$$

with α_j and β_j being rate constants.

If one would like to know the change of the steady-state concentration of x_i with respect to the change of α_j (β_j) then

$$S\left(x_i, \alpha_j\right) = \frac{\partial y_i}{\partial \ln \alpha_j} \tag{24}$$

and

$$S\left(x_i, \beta_j\right) = \frac{\partial y_i}{\partial \ln \beta_j} \tag{25}$$

Sensitivity of kinetic orders

Comparing to the rate constant sensitivity, sensitivity of the kinetic orders can be defined as [9]

$$S\left(x_i, g_{jk}\right) = \frac{\partial \ln x_i}{\partial \ln g_{jk}} = \frac{\partial y_i}{\partial g_{jk}} \cdot g_{jk} \tag{26}$$

and

$$S\left(x_i, h_{jk}\right) = \frac{\partial \ln x_i}{\partial \ln h_{jk}} = \frac{\partial y_i}{\partial h_{jk}} \cdot h_{jk} \tag{27}$$

where g_{jk} and h_{jk} are kinetic orders.

Furthermore, one can define the sensitivity of kinetic orders as relative changes in y_i rather than x_i:

$$\hat{S}\left(y_i, g_{jk}\right) = \frac{\partial \ln y_i}{\partial \ln g_{jk}} = \frac{\partial y_i}{\partial g_{jk}} \cdot \frac{g_{jk}}{y_i} \tag{28}$$

and

$$\hat{S}\left(y_i, h_{jk}\right) = \frac{\partial \ln y_i}{\partial \ln h_{jk}} = \frac{\partial y_i}{\partial h_{jk}} \cdot \frac{h_{jk}}{y_i} \tag{29}$$

The advantage of the definitions is that they can be translated as sensitivity of weighted kinetic orders for the linear system at the steady state [11].

Sensitivity of fluxes

The flux can be defined at the steady state as [9]

$$V_i = \alpha_i \prod_{k=1}^{n+m} x_k^{g_{jk}} = \beta_i \prod_{k=1}^{n+m} x_k^{h_{jk}} \tag{30}$$

Consider the sensitivity of flux with respect to the change in the parameter. As the logarithmic gain sensitivity, the rate constant sensitivity, the kinetic order sensitivity and the flux sensitivity are defined as

$$S\left(V_i,\alpha_j\right)=\frac{\partial \ln V_i}{\partial \ln \alpha_j}=\frac{\partial V_i}{\partial \alpha_j}\cdot\frac{\alpha_j}{V_i} \tag{31}$$

$$S\left(V_i,\beta_j\right)=\frac{\partial \ln V_i}{\partial \ln \beta_j}=\frac{\partial V_i}{\partial \beta_j}\cdot\frac{\beta_j}{V_i} \tag{32}$$

$$S\left(V_i,g_{jk}\right)=\frac{\partial \ln V_i}{\partial \ln g_{jk}}=\frac{\partial V_i}{\partial g_{jk}}\cdot\frac{g_{jk}}{V_i} \tag{33}$$

and

$$S\left(V_i,h_{jk}\right)=\frac{\partial \ln V_i}{\partial \ln h_{jk}}=\frac{\partial V_i}{\partial h_{jk}}\cdot\frac{h_{jk}}{V_i} \tag{34}$$

Taking logarithmic in (30) gives

$$\ln V_i=\ln \alpha_i+\sum_{k=1}^{n+m} g_{ik}\ln X_k \tag{35}$$

and

$$\ln V_i=\ln \beta_i+\sum_{k=1}^{n+m} h_{ik}\ln X_k \tag{36}$$

Consider (31), the equation shows that α_j has direct effect with respect to the flux only if $i=j$. When $i\neq j$, the equation shows that α_j has indirect effect with respect to the flux. The flux sensitivity is

$$S\left(V_i,\alpha_j\right)=\begin{cases}1+\sum_{k=1}^{n+m} g_{ik}S\left(x_k,\alpha_j\right), & \text{if } i=j,\\ \sum_{k=1}^{n+m} g_{ik}S\left(x_k,\alpha_j\right), & \text{if } i\neq j\end{cases} \tag{37}$$

Consider (32), the equation shows that β_j has direct effect with respect to the flux only if $i=j$. When $i\neq j$, the equation shows that β_j has indirect effect with respect to the flux. The flux sensitivity is:

$$S\left(V_i,\beta_j\right)=\begin{cases}1+\sum_{k=1}^{n+m} h_{ik}S\left(x_k,\beta_j\right), & \text{if } i=j,\\ \sum_{k=1}^{n+m} h_{ik}S\left(x_k,\beta_j\right), & \text{if } i\neq j\end{cases} \tag{38}$$

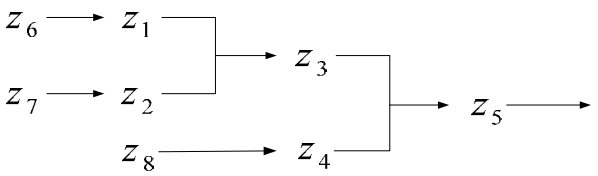

Fig. 11 Complete signal transduction network

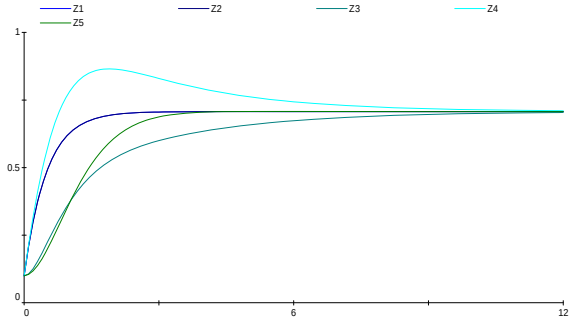

Fig. 12 Dynamic response of (39)

III. Demonstrative Results

A. Cascaded Analysis Model

Consider the complete S-system as follows and the signal transduction pathways shown as in Fig. 11.

$$\begin{aligned}
\dot{z}_1&=2z_6^{0.5}-2z_1^{0.6}z_2^{0.4}\\
\dot{z}_2&=2z_7^{0.5}-2z_1^{0.4}z_2^{0.6}\\
\dot{z}_3&=2z_1^{0.5}\hat{z}_2^{0.5}-2z_3^{0.6}z_4^{0.4}\\
\dot{z}_4&=2z_8^{0.5}-2z_3^{0.4}z_4^{0.6}\\
\dot{z}_5&=2z_3^{0.5}z_4^{0.5}-2z_5^{1}\\
z_6&=z_7=z_8=1
\end{aligned} \tag{39}$$

The simulation result of (39) is shown in Fig. 12. The final output concentration of the S-systems is $z_5(t_\infty)=0.707$.

Next, consider the basic bimolecular reaction describing the signal transduction pathway shown in Fig. 3. By the Michaelis-Menten rate law, the reaction is presented as an S-system as

$$\begin{aligned}
\dot{x}_1&=2x_2^{0.5}x_3^{0.5}-2x_1^{1},\\
\dot{x}_2&=2x_4^{0.5}-2x_2^{0.6}x_3^{0.4},\\
\dot{x}_3&=2x_5^{0.5}-2x_2^{0.4}x_3^{0.6},\\
x_4&=0.5,\\
x_5&=0.5
\end{aligned} \tag{40}$$

On the basis of the output concentration and (16), we can determine the parameters α_7 and β_7 to construct the next stage as follows

$$\begin{aligned}
\dot{x}_6 &= 2x_7^{0.5}x_8^{0.5} - 2x_6^1, \\
\dot{x}_7 &= 1.68x_9^{0.5} - 1.68x_7^{0.6}x_8^{0.4}, \\
\dot{x}_8 &= 2x_{10}^{0.5} - 2x_7^{0.4}x_8^{0.6}, \\
x_9 &= 0.701, \\
x_{10} &= 0.5
\end{aligned} \tag{41}$$

Simulation of (41) is shown in Fig. 13 and the final output concentration is $x_6(t_\infty) = 0.769$.

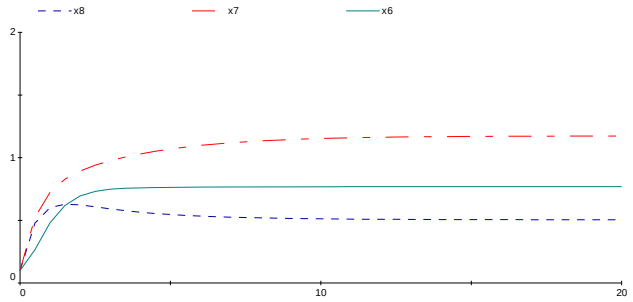

Fig. 13 Response of the second layer in the cascaded analysis model

Results of comparison of Figs. 12 and 13 are listed in Table 1. Compared the cascade analysis model (41) with the complete model (39), we see that the change of output concentration and the system eigenvalues didn't change significantly.

Table 1 Comparison of cascaded analysis model and complete S-system

	Final output concentration	Eigenvalues	Convergent time (s)
First layer	0.707	-2, -2, -0.4	4.2
Second layer	0.769	-2, -2.088, -0.322	4.8
Complete S-system	0.707	-2, -2, -2, -0.4, -0.4	7.5

B. *Sensitivity Analysis*

Logarithmic gain

We know that changes in one of the independent variables can cause the system converging to different steady states. The logarithmic gains can correctly predict changes in steady-state values for changes in independent variables. The advantage of logarithmic gains sensitivity is to predict how changes in independent variables affect the steady state of the system. We use the PLAS to predict the logarithmic gains sensitivity of the simplified system model and the resulting sensitivities are listed in Table 2. The gains reflect the approximate percentage change in dependent variables x_6, x_7 and x_8 caused by 1% changes in independent variables x_9 and x_{10}.

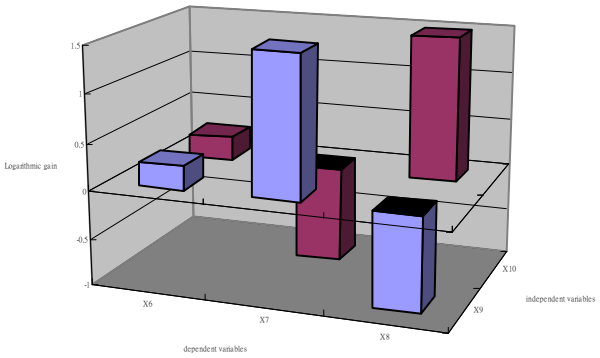

Fig. 14 Logarithmic gain of the simplified model

Sensitivity of rate constants

Rate constants sensitivity quantifies how a system responds to changes in rate constants. These changes only affect the dependent variables. It can be used to predict how a relative change in a rate constant affects the steady-state concentration of the metabolite. The results are listed in Table 2.

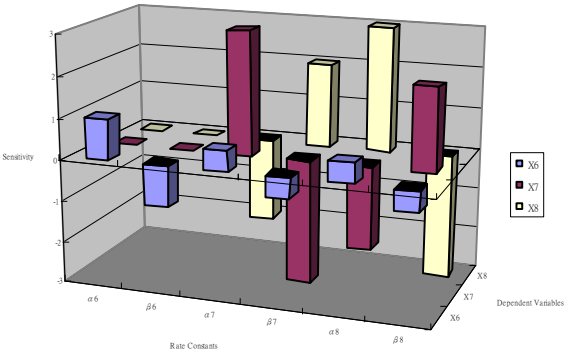

Fig. 15 Sensitivity of rate constants of the simplified model

Sensitivity of kinetic orders

Similar to the rate constant sensitivity, the kinetic order sensitivity is used to predict how a relative change in a

kinetic order affects the steady-state concentration of the metabolite. The results are listed in Table 2.

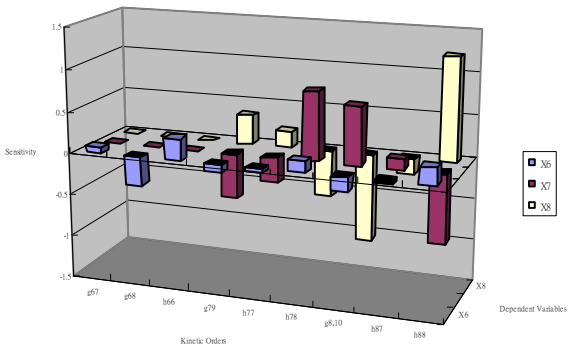

Fig. 16 Sensitivity of kinetic orders of the simplified model

Sensitivity of fluxes

Flux sensitivity can be used to predict how a relative change in a parameter value affects the flux of a metabolite. The results are summarized in Table 3. The sensitivities of $V_6(x), V_7(x)$ and $V_8(x)$ reflect the approximate percentage changes in fluxes caused by 1% changes in the parameters x_9, x_{10}, α_i, β_i, g_{ij} and h_{ij}.

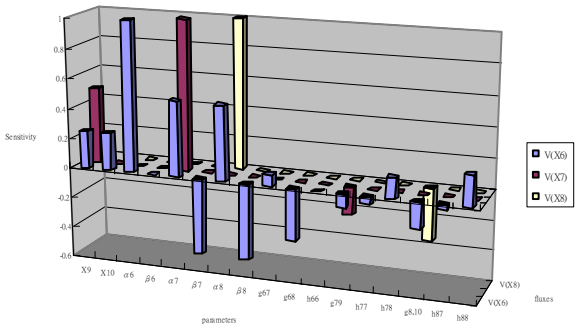

Fig. 17 Sensitivity of fluxes of the simplified model

Table 2 Parameter sensitivity

	x_6	x_7	x_8
x_9	0.25	1.5	-1
x_{10}	0.25	-1	1.5
α_6	1	0	0
β_6	-1	0	0
α_7	0.5	3	-2
β_7	-0.5	-3	2
α_8	0.5	-2	3
β_8	-0.5	2	-3
g_{67}	0.08014	0	0
g_{68}	-0.34224	0	0
h_{66}	0.2621	0	0
g_{79}	-0.08881	-0.53287	0.35525
h_{77}	-0.04808	-0.2885	0.19233
h_{78}	0.13689	0.82137	-0.54758
$g_{8,10}$	-0.17329	0.69315	-1.03972
h_{87}	-0.03206	0.12822	-0.19233
h_{88}	0.20534	-0.82137	1.23205

IV. Conclusion

This paper presents a method for constructing the dynamic model of signal transduction networks. A cascaded analysis method is proposed for constructing simplified mathematical models of signal transduction networks and related analyses are performed. A numerical example of the biochemical system of one scaffold protein with two binding domains is presented for demonstration. On the basis of the ODEs obtained, it is expected that the traditional control theory can be applied to prompt biochemical reactions of the signal transduction networks on the theoretical basis.

Table 3 Flux Sensitivity

	$V(x_6)$	$V(x_7)$	$V(x_8)$
x_9	0.25	0.5	0
x_{10}	0.25	0	0.5
α_6	1	0	0
β_6	0	0	0
α_7	0.5	1	0
β_7	-0.5	0	0
α_8	0.5	0	1
β_8	-0.5	0	0
g_{67}	0.08014	0	0
g_{68}	-0.34224	0	0
h_{66}	0	0	0
g_{79}	-0.08881	-0.17762	0

h_{77}	-0.04808	0	0
h_{78}	0.13689	0	0
$g_{8,10}$	-0.17329	0	-0.34657
h_{87}	-0.03206	0	0
h_{88}	0.20534	0	0

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