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Computational Analysis of S-type Biological Systems

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Abstract –

S-systems identify the direct interaction of genes and proteins in biological systems. Therefore, mathematical and computational analysis of the S-type models is important to achieve a true understanding of biological systems. However, theoretical approaches for S-systems are limited, and computational identification of S-systems' parameters is challenging. How to make a trade-off between accuracy and computational cost is in development. In this study, we first propose a memetic differential evolution scheme to identify the parameters of S-systems. The proposed scheme ameliorates the disadvantages in traditional gradient-based optimization methods, and solves the slow-convergence problem of stochastic algorithms. This scheme not only improves the global-search power of differential evolution (DE) but also largely increases the convergence speed. We then discuss and analyze the dynamic behavior of S-type biological systems. Four biological systems are used to demonstrate our approaches.

Index terms: Inverse problem, parameter estimation, memetic computation, evolution algorithm.

I. INTRODUCTION

The inverse problem of nonlinear dynamic pathways of a biological network from their time-course response is a cornerstone challenge in systems biology [1]. S-system structure [2-3] is one of the popular nonlinear dynamic models. This model uniquely maps dynamic interaction onto its parameters, and possesses good generalization characteristics. However, *theoretical analysis to S-systems is rare due to its nonlinearity and high dimension*.

Parameter estimation is the limiting step for biological modeling. Some researchers used gradient-based computation technologies. Marino and Voit [4] wrote an algorithm to gradually increase model complexity. Chou *et al.* [5] adopted an alternating regression (AR) method. Vilela *et al.* [1] proposed an eigenvector optimization method to solve convergence issues in AR approach. Kutalik *et al.* [6] adopted Newton-flow analysis. Many researchers have recently inferred gene-regulatory networks through stochastic-search intelligent technologies such as genetic programming [7-9], evolutionary algorithms [10], evolution strategies [11], differential evolution [12-15], genetic algorithms [16-18], simulated annealing [19], radial basis function networks [20], a neural network with particle-swarm-optimization learning [21-22], memetic algorithms [23-24].

S-systems are composed of highly nonlinear differential equations, which are usually ill-conditioned and multimodal distribution. Traditional gradient-based approaches have the possibility to get trapped at local optima [11]. These kinds of methods depend too much on the degree of system nonlinearity and initial values for learning. [25-26]. Stochastic approaches have the potential to find the global solution. However, they still face some problems. To let the search approaches to the global optimum, various strategies were used to avoid premature convergence. Those largely increased computation cost. How to make a trade off between accuracy and computation time is increasing important.

In this paper, we propose a memetic differential optimization to increase the population diversity and to enhance the searching such that both explorative and exploitative abilities of DE are largely increased. This technology has the advantages in gradient-based methods and solves the problems in evolution algorithms. The proposed technology is tested with a twenty-dimensional biological system. To show the performance of the proposed method, a bad initial start (80 for all parameters) in a wide search apace is used (the range of rate constants is between 0 and 100, and that of kinetic orders is between 100 and 100). Further, we discuss and theoretically analyze the steady-state behavior and systems' response to parameters and environmental changes (sensitivity).

II. PARAMETER IDENTIFICATION

S-system is a well-known canonical nonlinear model for metabolic reaction. Base on biochemical system theory, the net influx (V_i^+) and efflux (V_i^-) of a system is approximated as two

power-law functions. Each individual metabolite, protein or gene is described as

$$\dot{X}_i = V_i^+ - V_i^- = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}},$$

for $i = 1, 2, \ldots, n$, (1)

where n and m are the numbers of dependent and independent variables, respectively; α_i and β_j are rate constants, g_{ij} and h_{ij} are kinetic orders to denote the interaction from X_j to X_i where a positive value denotes excitatory effect and negative for inhibitory effect.

In order to identify parameters of this highly dimensional nonlinear system, we propose a memetic differential optimization (MDO) to achieve global and fast search. The optimization method introduces a migration operation and a dynamic-population strategy to improve the global-search power.

2.1. Memetic Differential Optimization(MDO)

Traditional gradient-based approaches are difficult to get a reliable and accurate global-optimum solution. Stochastic approaches take too much computational cost. Therefore, we propose a memetic approach to improve the accuracy and reliability, and to reduce the computation time at the same time. Different from the most hybrid approaches (using the stochastic approaches to get a good initial start for local search), we use local-search methods as the principle learning and stochastic search just for avoiding premature convergence.

To solve the problem that gradient-based methods depend too much on initial guesses, Kutalik et al. proposed a multi-start method [6]. In this study, we use migrated differential evolution for wider searching and gradient-based methods for fast convergence. MDO introduce a migrated operation to compensate the population diversity of differential evolution (DE). The degree of the population diversity η is defined as

$$\eta = \sum_{i=1}^{NP-1} \sum_{j=1}^{Dim\_I} \frac{temp_{ij}}{Dim\_I * (NP-1)} < \varepsilon_1,$$

$$temp_{ij} = \begin{cases} 0, \ if \left| \frac{x_{ij} - x_{bj}}{x_{bj}} \right| < \varepsilon_2, \\ 1, \ otherwise, \end{cases} \quad (2)$$

where $\varepsilon_2 \in [0,1]$ is the tolerance of real-valued gene diversity, x_{ij} and x_{bj} are, respectively, the jth chromosomes in the ith individual and the best individual, NP is the number of individuals, *Dim_I* is the dimension of individuals, and $\varepsilon_1 \in [0,1]$ is the tolerance threshold of population diversity for migration. If the degree η is small than ε_1, migration starts and a new chromosome is generated as follows.

$$x_{ij} = \begin{cases} x_{bj} + r_2 \times (x_{j,\min} - x_{bj}), \ if \ \frac{x_{bj} - x_{j,\min}}{x_{j,\max} - x_{j,\min}} > r_1 \\ x_{bj} + r_2 \times (x_{j,\max} - x_{bj}), \ otherwise \end{cases}, \quad (3)$$

where $x_{j,max}$ and $x_{j,min}$ are, respectively, the upper and lower bound of the jth chromosome, r_1, $r_2 \in [0, 1]$ are two random numbers. The proposed MDO is described as follow.

Initialize: *Randomly generate initial population. Set the objective function and generation threshold.*
while *the termination condition is not satisfied*
  Calculate the fitness value and update the best by local search.
  for *i < size of population*
    population[i] ← *based on local search*
  end for
  for *i < max_iter*
    DE operation (mutation, crossover, selection)
    Migrate over a wide search space ← *if necessary*
  end for
  if *the best fitness is not improved*
    Increase population number
    Increase max_iter ← *if necessary*
  end if
end while

I. Simulation

In order to examine the effectiveness of the proposed technology we consider a twenty-gene biological system. All computations were performed on an Intel core duo 3.16GHz computer using Microsoft Windows XP. The search range is [0, 100] for the rate constants and [-100, 100] for the kinetic orders, respectively. The proposed optimization technology is to minimize the weighted concentration error,

$$E = \frac{1}{N} \sum_{i=1}^{N} t_a \left(\frac{x^i - x^i_{\exp}}{\max(x^i_{\exp})} \right)^2, \quad (4)$$

where x^i, $i = 1, \ldots, n$ is the ith estimated concentration, $x^i_{\exp}$ is the ith measured concentration, $\max(x^i_{\exp})$ is the maximum of the measured concentrations, t_a is the time-weighting factor, and N is the number of the sampled data.

We consider a medium-scale genetic network with twenty dependent constituents. The artificial network, as shown in Fig. 1, is used by Noman and

Iba [27]. The respective S-system is described in Eq. (5).

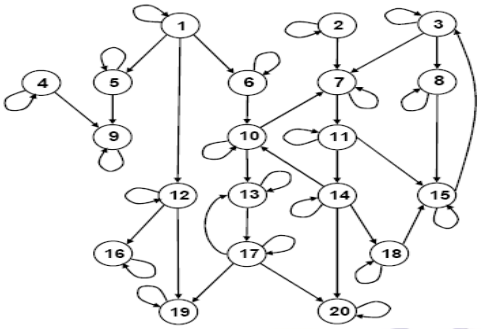


Fig. 1. the medium-scale artificial genetic network [27]

$$
\begin{aligned}
\dot{x}_1 &= \alpha_1 - \beta_1 x_1^{h_{1,1}}, & \dot{x}_{11} &= \alpha_{11} x_7^{g_{11,7}} - \beta_{11} x_{11}^{h_{11,11}},\\
\dot{x}_2 &= \alpha_2 - \beta_2 x_2^{h_{2,2}}, & \dot{x}_{12} &= \alpha_{12} x_1^{g_{12,1}} - \beta_{12} x_{12}^{h_{12,12}},\\
\dot{x}_3 &= \alpha_3 x_{15}^{g_{3,15}} - \beta_3 x_3^{h_{3,3}}, & \dot{x}_{13} &= \alpha_{13} x_{10}^{g_{13,10}} x_{17}^{g_{13,17}} - \beta_{13} x_{13}^{h_{13,13}},\\
\dot{x}_4 &= \alpha_4 - \beta_4 x_4^{h_{4,4}}, & \dot{x}_{14} &= \alpha_{14} x_{11}^{g_{14,11}} - \beta_{14} x_{14}^{h_{14,14}},\\
\dot{x}_5 &= \alpha_5 x_1^{g_{5,1}} - \beta_5 x_5^{h_{5,5}}, & \dot{x}_{15} &= \alpha_{15} x_8^{g_{15,8}} x_{11}^{g_{15,11}} x_{18}^{g_{15,18}} - \beta_{15} x_{15}^{h_{15,15}},\\
\dot{x}_6 &= \alpha_6 x_1^{g_{6,1}} - \beta_6 x_6^{h_{6,6}}, & \dot{x}_{16} &= \alpha_{16} x_{12}^{g_{16,12}} - \beta_{16} x_{16}^{h_{16,16}},\\
\dot{x}_7 &= \alpha_7 x_2^{g_{7,2}} x_3^{g_{7,3}} x_{10}^{g_{7,10}} - \beta_7 x_7^{h_{7,7}}, & \dot{x}_{17} &= \alpha_{17} x_{13}^{g_{17,13}} - \beta_{17} x_{17}^{h_{17,17}},\\
\dot{x}_8 &= \alpha_8 x_3^{g_{8,3}} - \beta_8 x_8^{h_{8,8}}, & \dot{x}_{18} &= \alpha_{18} x_{14}^{g_{18,14}} - \beta_{18} x_{18}^{h_{18,18}},\\
\dot{x}_9 &= \alpha_9 x_4^{g_{9,4}} x_5^{g_{9,5}} - \beta_9 x_9^{h_{9,9}}, & \dot{x}_{19} &= \alpha_{19} x_{12}^{g_{19,12}} x_{17}^{g_{19,17}} - \beta_{19} x_{19}^{h_{19,19}},\\
\dot{x}_{10} &= \alpha_{10} x_6^{g_{10,6}} x_{14}^{g_{10,14}} - \beta_{10} x_{10}^{h_{10,10}}, & \dot{x}_{20} &= \alpha_{20} x_{14}^{g_{20,14}} x_{17}^{g_{20,17}} - \beta_{20} x_{20}^{h_{20,20}},
\end{aligned}
\tag{5}
$$

where x_i, i=1,...,20 are the twenty dependent constitutes. The rate constants and kinetic orders are shown in Row "True" of Table 1, cited from the paper of Noman and Iba [27]. Eight sets of experimental data $x_{\exp}^{i}, i = 1,\ldots,n$ are generated through solving the S-system. The cubic spline technology is used to smooth the eight-set sampled datasets. Each experiment operates during the time period from t=0 to t=1.8 with a sample time 0.01. The estimated values are shown in Column "Simulation" of Table 1. We observe that the estimated values are all close to the true values.

Variable	α_i		β_j		g_{ij}									h_{ij}		
	True	Simulation	True	Simulation		True	Simulation		True	Simulation		True	Simulation		True	Simulation
X_1	10	9.9998302E+00	10	9.9998319E+00										h1,1	1	1.0000186E+00
X_2	10	9.9998495E+00	10	9.9998128E+00										h2,2	1	1.0000260E+00
X_4	10	9.9933121E+00	10	9.9933614E+00	g3,15	-0.7	-7.0035337E-01							h3,3	1	1.0005253E+00
X_5	10	9.9998294E+00	10	9.9998241E+00										h4,4	1	1.0000170E+00
X_5	10	9.9997346E+00	10	9.9997305E+00	g5,1	1	1.0000293E+00							h5,5	1	1.0000254E+00
X_6	10	1.0000081E+01	10	1.0000072E+01	g6,1	2	2.0000110E+00							h6,6	1	1.0000065E+00
X_7	10	9.9964411E+00	10	9.9964794E+00	g7,2	1.2	1.2002013E+00	g7,3	-0.8	-8.0022296E-01	g7,10	1.6	1.6005491E+00	h7,7	1	1.0005570E+00
X_8	10	1.0010207E+01	10	1.0010224E+01	g8,3	-0.6	-5.9947067E-01							h8,8	1	9.9903390E-01
X_9	10	9.9996121E+00	10	9.9996129E+00	g9,4	0.5	5.0001654E-01	g9,5	0.7	7.0002399E-01				h9,9	1	1.0000323E+00
X_{10}	10	1.0001176E+01	10	1.0001138E+01	g10,6	-0.3	-2.9996611E-01	g10,14	0.9	8.9987462E-01				h10,10	1	9.9979221E-01
X_{11}	10	9.9165818E+00	10	9.9167229E+00	g11,7	0.5	5.0352692E-01							h11,11	1	1.0069385E+00
X_{12}	10	9.9997554E+00	10	9.9997573E+00	g12,1	1	1.0000342E+00							h12,12	1	1.0000236E+00
X_{13}	10	1.0002236E+01	10	1.0002243E+01	g13,10	-0.4	-3.9992872E-01	g13,17	1.3	1.2997268E+00				h13,13	1	9.9977941E-01
X_{14}	10	9.9995521E+00	10	9.9995126E+00	g14,11	-0.4	-4.0008090E-01							h14,14	1	1.0001604E+00
X_{15}	10	1.0019084E+01	10	1.0018921E+01	g15,8	0.5	4.9940498E-01	g15,11	-1	-9.9817948E-01	g15,18	-0.9	-8.9854012E-01	h15,15	1	9.9838021E-01
X_{16}	10	9.9983811E+00	10	9.9983796E+00	g16,12	2	2.0001743E+00							h16,16	1	1.0000957E+00
X_{17}	10	1.0005988E+01	10	1.0005954E+01	g17,13	-0.5	-4.9974225E-01							h17,17	1	9.9946542E-01
X_{18}	10	9.9997202E+00	10	9.9996825E+00	g18,14	1.2	1.2000731E+00							h18,18	1	1.0000349E+00
X_{19}	10	9.9970474E+00	10	9.9970553E+00	g19,12	1.4	1.4002516E+00	g19,17	0.6	6.0005824E-01				h19,19	1	1.0001912E+00
X_{20}	10	1.0002968E+01	10	1.0003010E+01	g20,14	1	9.9989850E-01	g20,17	1.5	1.4997167E+00				h20,20	1	9.9977872E-01

Table 1. Column "True" lists the true parameters in the S-system of the medium-scale genetic network. Column "Simulation" shows the estimated values.

II. DYNAMIC-BEHAVIOR ANALYSIS

To identify the structure and parameters of a dynamic model, the most important and essential job is to find the solution of nonlinear ordinary differential equations efficiently and accurately [28]. In this section, we shall analyze its steady-state behavior and sensitivity phenomenon. Four biological systems shown in Figs. 1 and 2 are used to demonstrate the analysis.

3.1. Steady-State Analysis

Most biochemical and metabolic systems operate at or close to the steady state, even in disease conditions. Therefore, the analysis of the steady-state behavior will reveal many important aspects of the system. The steady-state situation occurs at $\dot{X}_i = 0$, i = 1, 2,…, n:

$$\dot{X}_i = V_i^+ - V_i^- = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}} = 0,$$

$$\alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} = \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}}. \quad (6)$$

By using logarithmic transformation, Eq. (6) is transformed into

$$\ln \alpha_i + \sum_{j=1}^{n+m} g_{ij} \ln X_j = \ln \beta_i + \sum_{j=1}^{n+m} h_{ij} \ln X_j, \; i = 1, 2,\ldots, n. \quad (7)$$

Let $y_j = \ln X_j$. we have

$$\sum_{j=1}^{n+m} g_{ij} y_j - \sum_{j=1}^{n+m} h_{ij} y_j = \ln \beta_i - \ln \alpha_i, \; i = 1, 2,\ldots, n. \quad (8)$$

Then,

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

By defining $a_{ij} = g_{ij} - h_{ij}$ and $b_i = \ln(\beta_i/\alpha_i)$, Eq. (9) is rewritten as

$$\sum_{j=1}^{n+m} a_{ij} y_j = b_i, \; i = 1, 2,\ldots, n. \quad (10)$$

Expand Eq. (10) into a set of linear equations:

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

where n and m are the number of dependent and independent variables, respectively. We further rewrite Eq. (11) into a matrix form:

$$\begin{bmatrix} a_{11}\cdots a_{1n} \\ \vdots \\ a_{n1}\cdots a_{nn} \end{bmatrix} \begin{bmatrix} y_1 \\ \vdots \\ y_n \end{bmatrix} + \begin{bmatrix} a_{1\,n+1}\cdots a_{1\,n+m} \\ \vdots \\ a_{n\,n+1}\cdots a_{n\,n+m} \end{bmatrix} \begin{bmatrix} y_{n+1} \\ \vdots \\ y_{n+m} \end{bmatrix} = \begin{bmatrix} b_1 \\ \vdots \\ b_n \end{bmatrix}. \quad (12)$$

In other words, we have

$$A_D \vec{Y}_D + A_I \vec{Y}_I = \vec{b}, \quad (13)$$

where $A_D = \begin{bmatrix} a_{11}\cdots a_{1n} \\ \vdots \\ a_{n1}\cdots a_{nn} \end{bmatrix}$, $A_I = \begin{bmatrix} a_{1\,n+1}\cdots a_{1\,n+m} \\ \vdots \\ a_{n\,n+1}\cdots a_{n\,n+m} \end{bmatrix}$, $\vec{Y}_D = \begin{bmatrix} y_1 \\ \vdots \\ y_n \end{bmatrix}$, $\vec{Y}_I = \begin{bmatrix} y_{n+1} \\ \vdots \\ y_{n+m} \end{bmatrix}$ and $\vec{b} = \begin{bmatrix} b_1 \\ \vdots \\ b_n \end{bmatrix}$. Therefore, the steady states of the dependent variables are estimated from

$$\vec{Y}_D = A_D^* \vec{b} - A_D^* A_I \vec{Y}_I, \quad (14)$$

where A_D^* is the pseudo inverse of A_D; A_D^* equals to the inverse matrix A_D^{-1} for nonsingular A_D. Eq. (14) indicates that steady states of an S-system are closely related to the rate constants (α_i, β_i), the kinetic orders (g_{ij}, h_{ij}) and the independent variables. There is no relationship between steady-state values and initial values of the dependent variables.

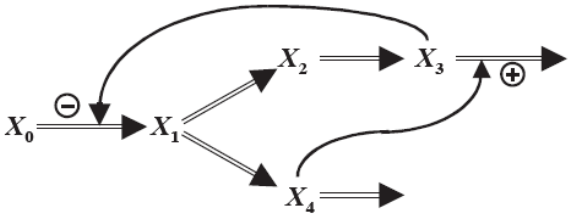
Tables 2, 3 and 4 show the steady-state values for the branch, the cascade and the small-scale genetic network, respectively. Cases 1, 5 and 8 in Table 2 have the same steady-state values since the same independent variable is used; even the initial values of the dependent variables are different. Cases 2, 3 and Cases 4, 6, 7 in Table 2 show the same results. Cases 1, 3 and 4 in Table 2 use the same initial values for the dependent variables but deferent values for the independent variable. Therefore, those cases achieve different steady states. Cases 3, 4, 5 and 8 in Table 3 achieve the same steady states due to the same value for the independent variable is used even those cases start from different initial conditions. Cases 1, 7 and Cases 2, 6 in Table 3 also show the same phenomena. Cases 1, 4 and Cases 2, 3 in Table 3 use the same initial values for the dependent variables but the independent variables are different. Therefore, they approach to different steady states. The steady-state values in Table 4 for a small-scale genetic network are totally different since their independent variables are all different.

For the case with no independent variable (the medium-scale genetic network), the steady-state behavior is

$$\vec{Y}_D = A_D^{-1} \vec{b}; \quad (15)$$

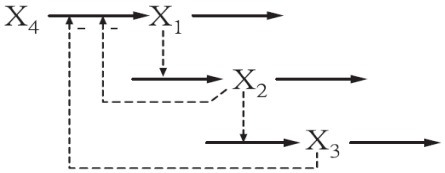
i.e., the steady-state values only relate to α_i, β_i, g_{ij}, h_{ij}.

(a) a branch pathway (4 genes) [17]



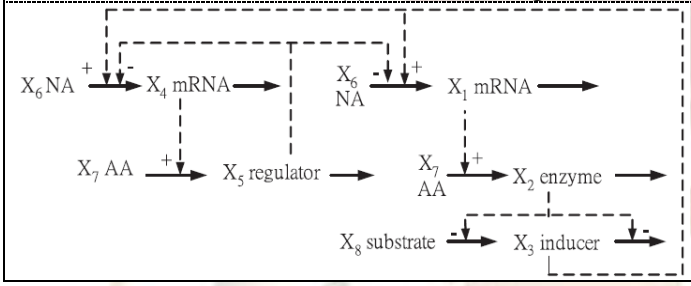
$$\dot{x}_1 = \alpha_1 x_3^{g_{13}} x_0^{g_{10}} - \beta_1 x_1^{h_{11}},$$
$$\dot{x}_2 = \alpha_2 x_1^{g_{21}} - \beta_2 x_2^{h_{22}},$$
$$\dot{x}_3 = \alpha_3 x_2^{g_{32}} - \beta_3 x_3^{h_{33}} x_4^{h_{34}},$$
$$\dot{x}_4 = \alpha_4 x_1^{g_{41}} - \beta_4 x_4^{h_{44}}.$$

(b) a cascade pathway (3 genes) [13]



$$\dot{x}_1 = \alpha_1 x_2^{g_{12}} x_3^{g_{13}} x_4 - \beta_1 x_1^{h_{11}},$$
$$\dot{x}_2 = \alpha_2 x_1^{g_{21}} - \beta_2 x_2^{h_{22}},$$
$$\dot{x}_3 = \alpha_3 x_2^{g_{32}} - \beta_3 x_3^{h_{33}}.$$

(c) a small-scale genetic network (5 genes) [16, 29]



$$\dot{x}_1 = \alpha_1 x_3^{g_{13}} x_5^{g_{15}} x_6 - \beta_1 x_1^{h_{11}},$$
$$\dot{x}_2 = \alpha_2 x_1^{g_{21}} x_7 - \beta_2 x_2^{h_{22}},$$
$$\dot{x}_3 = \alpha_3 x_2^{g_{32}} x_8 - \beta_3 x_2^{h_{32}} x_3^{h_{33}},$$
$$\dot{x}_4 = \alpha_4 x_3^{g_{43}} x_5^{g_{45}} x_6 - \beta_4 x_4^{h_{44}},$$
$$\dot{x}_5 = \alpha_2 x_4^{g_{54}} x_7 - \beta_2 x_5^{h_{55}},$$

Fig. 2. Three biological systems [13, 16, 17, 29].

case (input)		1	2	3	4	5	6	7	8
initial value	x_1 (0)	0.5	1.5	0.5	0.5	1.5	0.5	0.4	1.2
	x_2 (0)	0.5	1.5	0.5	0.5	2.5	1.5	2	2.2
	x_3 (0)	0.5	1.5	0.5	0.5	1.5	1.5	1.6	1.8
	x_4 (0)	1.5	0.5	1.5	1.5	0.5	0.5	0.7	0.4
Independent variable	x_5	0.2	0.4	0.4	0.8	0.2	0.8	0.8	0.2
Steady-state value	x_1	0.1471756	0.2763755	0.2763755	0.518995	0.1471756	0.518995	0.518995	0.147176
	x_2	1.030819	1.569006	1.569006	2.38818	1.030819	2.38818	2.38818	1.030819
	x_3	1.053604	1.69015	1.69015	2.711271	1.053604	2.711271	2.711271	1.053604
	x_4	0.0764708	0.1133798	0.1133798	0.168103	0.07647084	0.168103	0.168103	0.076471

Table 2. Steady states of the branch pathway in Fig. 2(a).

case (input)		1	2	3	4	5	6	7	8
initial value	x_1 (0)	0.1	1	1	0.1	0.8	0.1	0.6	0.6
	x_2 (0)	0.1	1	1	0.1	0.1	0.6	0.1	0.6
	x_3 (0)	1	0.6	0.6	1	0.8	0.6	1	1
Independent variable	x_4	0.7	0.9	0.5	0.5	0.5	0.9	0.7	0.5
Steady-state value	x_1	1.649908	2.428703	0.9832127	0.9832127	0.9832127	2.428703	1.649908	0.9832127
	x_2	3.182694	4.684998	1.89663	1.89663	1.89663	4.684998	3.182694	1.89663
	x_3	0.552551	0.8133678	0.329276	0.329276	0.329276	0.8133678	0.552551	0.329276

Table 3. Steady states of the cascade pathway in Fig. 2(b).

3.2. Sensitivity analysis

We now discuss the response of the S-system to the permanent influence from environment and structure changes inside the organism. Sensitivity analysis plays an important role in the study of dynamic system behavior. Savageau [30, 31] and Voit [3] defined different types of gains and dynamic sensitivities for sensitivity analysis. *Logarithmic gain* (Logarithmic amplification, or log-gain) describes the change of the system to the independent variables (environment). The log-gain indicates the robustness the system.

The relative change of the dependent variable X_D (D=1, 2,…, n) to the independent variable X_I (I=n+1, n+2,…, n+m) is defined as

$$L(X_D, X_I) = \begin{bmatrix} L(X_1, X_{n+1}) & L(X_1, X_{n+2}) \cdots L(X_1, X_{n+m}) \\ L(X_2, X_{n+1}) & L(X_2, X_{n+2}) \cdots L(X_2, X_{n+m}) \\ \vdots & \vdots \quad \vdots \\ L(X_n, X_{n+1}) & L(X_n, X_{n+2}) \cdots L(X_n, X_{n+m}) \end{bmatrix}$$

$$= \begin{bmatrix} \frac{\partial y_1}{\partial y_{n+1}} & \frac{\partial y_1}{\partial y_{n+2}} \cdots \frac{\partial y_1}{\partial y_{n+m}} \\ \frac{\partial y_2}{\partial y_{n+1}} & \frac{\partial y_2}{\partial y_{n+2}} \cdots \frac{\partial y_2}{\partial y_{n+m}} \\ \vdots & \vdots \quad \vdots \\ \frac{\partial y_n}{\partial y_{n+1}} & \frac{\partial y_n}{\partial y_{n+2}} \cdots \frac{\partial y_n}{\partial y_{n+m}} \end{bmatrix} = \frac{\partial \vec{Y}_D}{\partial \vec{Y}_I}. \quad (16)$$

By using Eq. (14), we obtain the log-gain,

$$L(X_D, X_I) = -A_D^* A_I . \quad (17)$$

Eq. (17) implies that the log-gain is the function of the kinetic orders g_{ij} and h_{ij}, but is nothing to do with the rate constants α_i and β_i. Figures 3, 4 and 5 show the log-gains for the branch pathway, the cascade pathway and the small-scale genetic network, respectively. There exists no such a log gain in the medium-scale genetic network, the S-system of which has no independent variable.

case (input)		1	2	3	4	5	6	7	8
initial dependent value	x_1 (0)	0.1	0.9	0.9	0.5	0.9	0.9	0.1	0.1
	x_2 (0)	0.9	0.9	0.9	0.5	0.1	0.1	0.5	0.9
	x_3 (0)	0.9	0.9	0.5	0.9	0.1	0.9	0.5	0.9
	x_4 (0)	0.1	0.1	0.1	0.9	0.1	0.9	0.9	0.5
	x_5 (0)	0.5	0.5	0.5	0.1	0.9	0.5	0.1	0.1
Independent value	x_6	1.3	0.7	1.3	1.3	1	1	0.7	0.7
	x_7	1.3	0.7	1.3	0.7	1.3	0.7	1.3	1
	x_8	0.7	1	1	1	1	0.7	1.3	1.3
steady state value	x_1	0.7442498	0.6915438	0.7667031	0.850031	0.7024997	0.7560407	0.63754	0.666036
	x_2	0.8485753	0.578587	0.8741761	0.711187	0.8009728	0.632549	0.7269074	0.666036
	x_3	0.83666	1	1	1	1	0.83666	1.140175	1.140175
	x_4	0.8610993	0.8747414	0.9698113	1.075214	0.8885996	0.8747414	0.8610993	0.899588
	x_5	0.9818043	0.7318611	1.105755	0.8995883	1.013159	0.7318611	0.9818043	0.899588

Table 4. Steady states of the small-scale genetic network in Fig. 2(c).

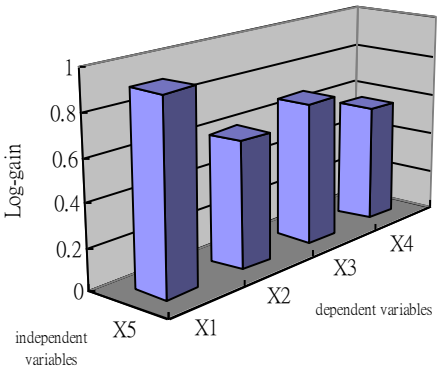


Fig. 3. Log-gains of the branch pathway.

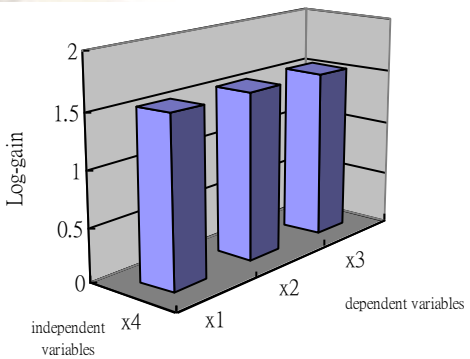


Fig. 4. Log-gains of the cascade pathway.

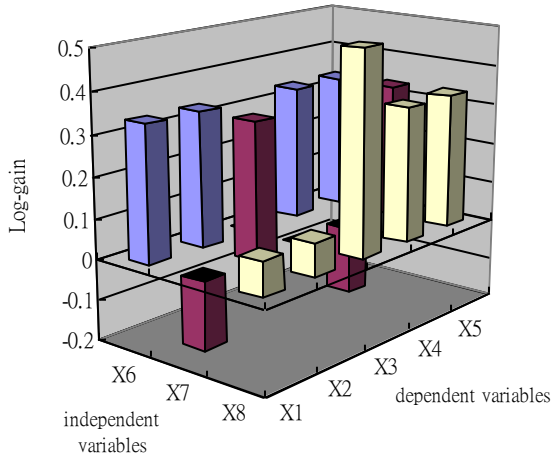


Fig. 5. Log-gains of the small-scale genetic network.

We further discuss system response to the perturbation from the systems' parameters (*parameter sensitivity*), which may induced through mutation or disease infection. *Sensitivity with respect to the rate constants* is defined as

$$S(X_D,\alpha)=\begin{bmatrix} S(X_1,\alpha_1) & S(X_1,\alpha_2)\cdots S(X_1,\alpha_n) \\ S(X_2,\alpha_1) & S(X_2,\alpha_2)\cdots S(X_2,\alpha_n) \\ \vdots & \vdots \quad \vdots \\ S(X_n,\alpha_1) & S(X_n,\alpha_2)\cdots S(X_n,\alpha_n) \end{bmatrix}$$

$$=\begin{bmatrix} \frac{\partial y_1}{\partial \ln \alpha_1} & \frac{\partial y_1}{\partial \ln \alpha_2} & \cdots & \frac{\partial y_1}{\partial \ln \alpha_n} \\ \frac{\partial y_2}{\partial \ln \alpha_1} & \frac{\partial y_2}{\partial \ln \alpha_2} & \cdots & \frac{\partial y_2}{\partial \ln \alpha_n} \\ \vdots & \vdots & & \vdots \\ \frac{\partial y_n}{\partial \ln \alpha_1} & \frac{\partial y_n}{\partial \ln \alpha_2} & \cdots & \frac{\partial y_n}{\partial \ln \alpha_n} \end{bmatrix} = \frac{\partial \vec{Y}_D}{\partial \ln \vec{\alpha}} . \quad (18)$$

Through Eq. (14) we know

$$S(X_D,\alpha) = -A_D^* , \quad (19)$$

$$S(X_D,\beta) = A_D^* , \quad (20)$$

and $S(X_D,\alpha) = -S(X_D,\beta)$. In other words, the sensitivity is only related to the kinetic orders g_{ij} and h_{ij}. The parameter sensitivity is shown in Figs. 6, 7, 8 and 9. These figures indicate that $S(X_D,\alpha)$ is the inverse matrix of $S(X_D,\beta)$. We further rewrite the steady states of the S-system in Eq. (14) to Eqs. (21) and (22):

$$\vec{Y}_D = A_D^* \vec{b} - A_D^* A_I \vec{Y}_I$$
$$= S(X_D,\beta)\vec{b} + L(X_D,X_I)\vec{Y}_I$$
$$= -S(X_D,\alpha)\vec{b} + L(X_D,X_I)\vec{Y}_I . \quad (21)$$

$$\vec{Y}_D = A_D^* \vec{b} - A_D^* A_I \vec{Y}_I$$
$$= S(X_D,\beta)\vec{b} + S(X_D,\alpha) A_I \vec{Y}_I$$
$$= S(X_D,\beta)\vec{b} - S(X_D,\beta) A_I \vec{Y}_I . \quad (22)$$

Similarly, the sensitivity with respect to the kinetic orders is defined as

$$S(X_D,g_{ij}) = \frac{\partial \ln X_D}{\partial \ln \vec{g}_{ij}} = \frac{\partial \vec{Y}_D}{\partial \vec{g}_{ij}/\vec{g}_{ij}} = \frac{\partial \vec{Y}_D}{\partial \vec{g}_{ij}}\vec{g}_{ij}, \quad (23)$$

$$S(X_D,h_{ij}) = \frac{\partial \ln X_D}{\partial \ln \vec{h}_{ij}} = \frac{\partial \vec{Y}_D}{\partial \vec{h}_{ij}/\vec{h}_{ij}} = \frac{\partial \vec{Y}_D}{\partial \vec{h}_{ij}}\vec{h}_{ij} \quad (24)$$

for $i, j = 1,2,\ldots,n$. Figures 10, 11 and 12 show the results of the kinetic-order sensitivity for the branch pathway, the cascade branch pathway and the small genetic network, respectively.

III. CONCLUSION

The analysis of complex biological systems with system approach facilitates the research in medicine and molecular biology. S-system model is demonstrated to be a good approximation to continuous biological systems. In this study, we begin with computational approach to identify the S-type biological systems. Simulation results of the twenty-gene system indicate that the proposed memetic DE has reliable performance. This method is different from the traditional memetic DE. Local search is the main search method and migrated DE is to avoid premature convergence. Then, we further analyze the steady-state behavior and various sensitivities of biological systems. Four biological systems are used to discuss the steady-state behavior and to analyze log-gain, rate-constant sensitivity and kinetic-order sensitivity.

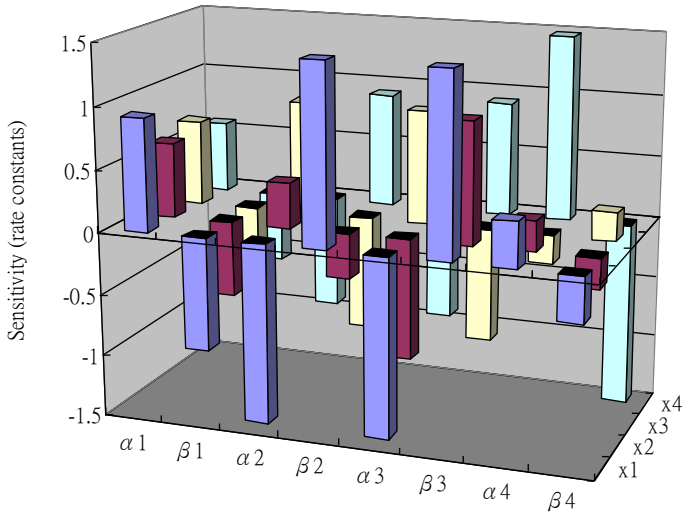


Fig. 6. Rate-constant sensitivity of the branch pathway.

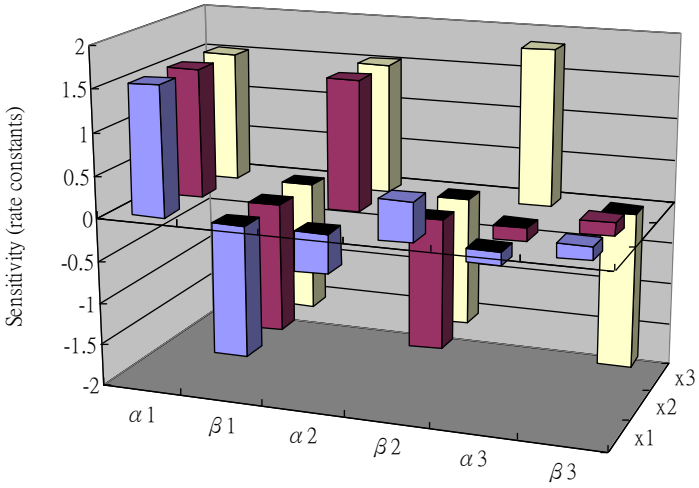


Fig.7. Rate-constant sensitivity of the cascade pathway.

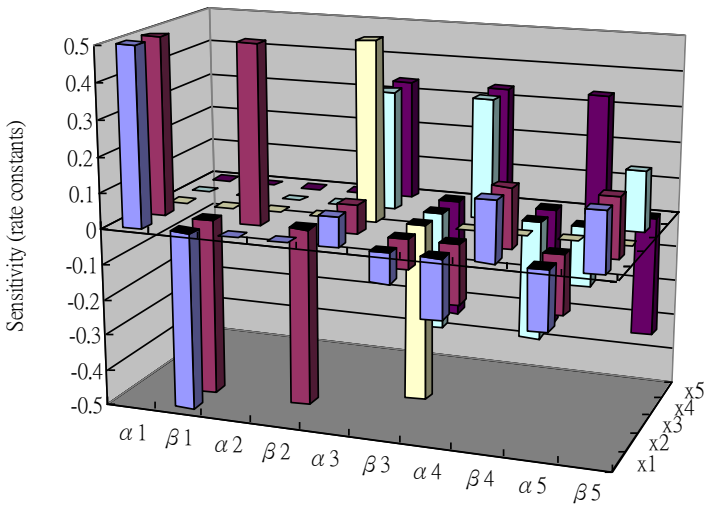


Fig 8. Rate-constant sensitivity of the small-scale genetic network.

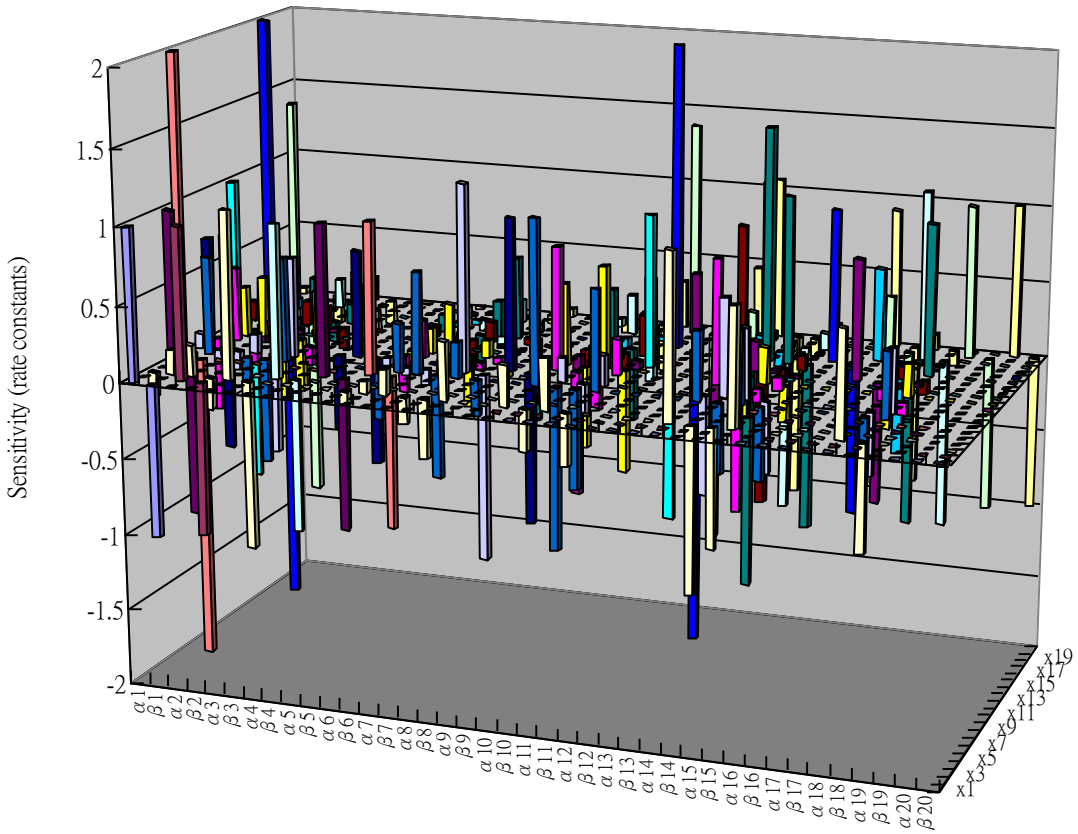


Fig. 9. Rate-constant sensitivity of the medium-scale genetic network.

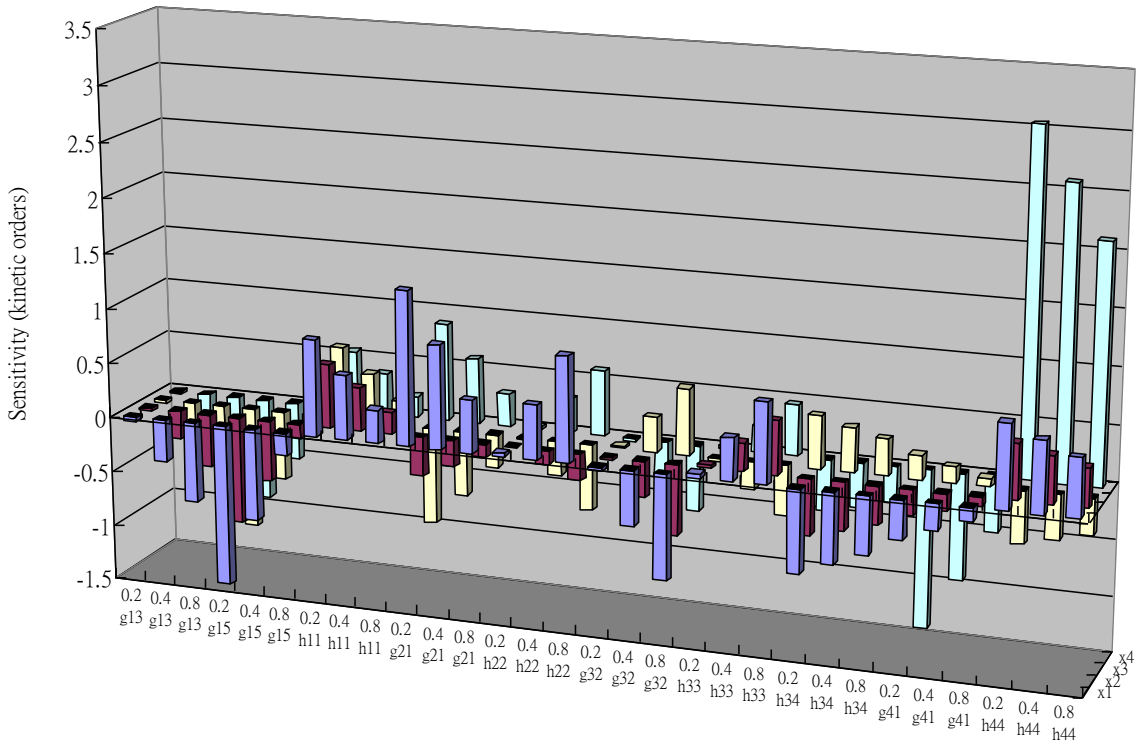


Fig. 10. Kinetic-order sensitivity of the branch pathway. The used independent variable x_5 is 0.2, 0.4 and 0.8, as shown in Table 7.

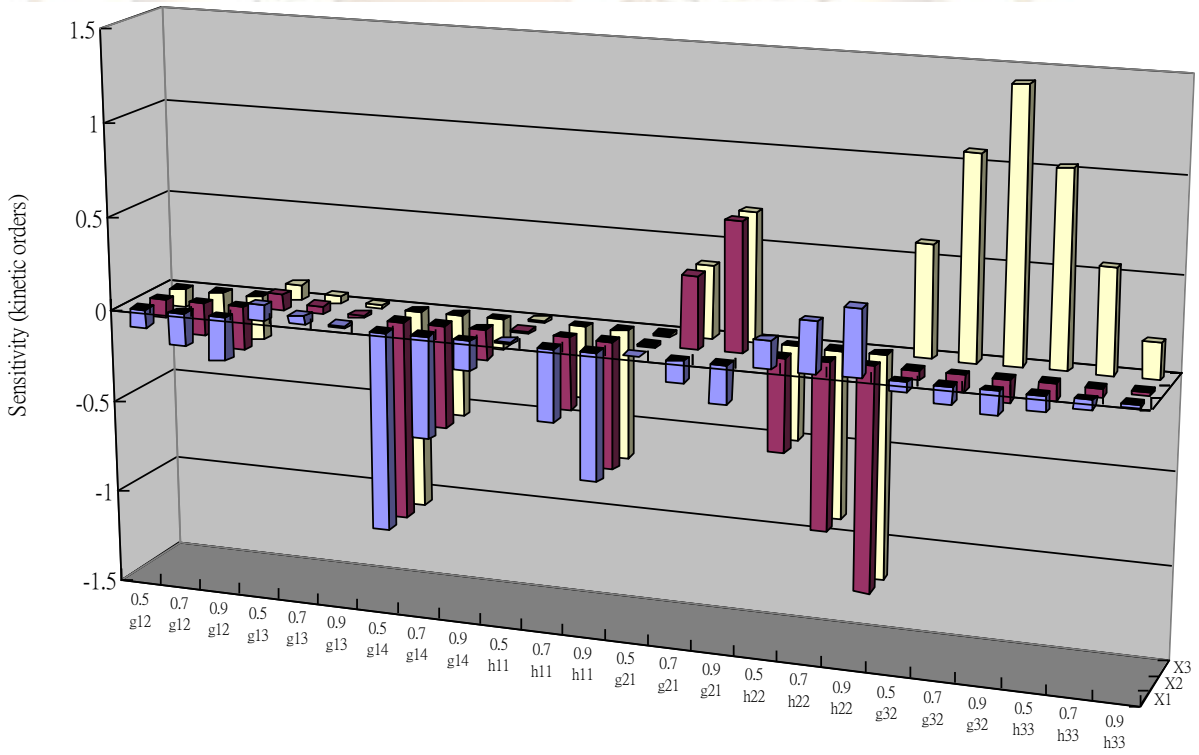


Fig. 11. Kinetic-order sensitivity of the cascade branch pathway. The used independent variable x_4 is 0.5, 0.7 and 0.9, as shown in Table 8.

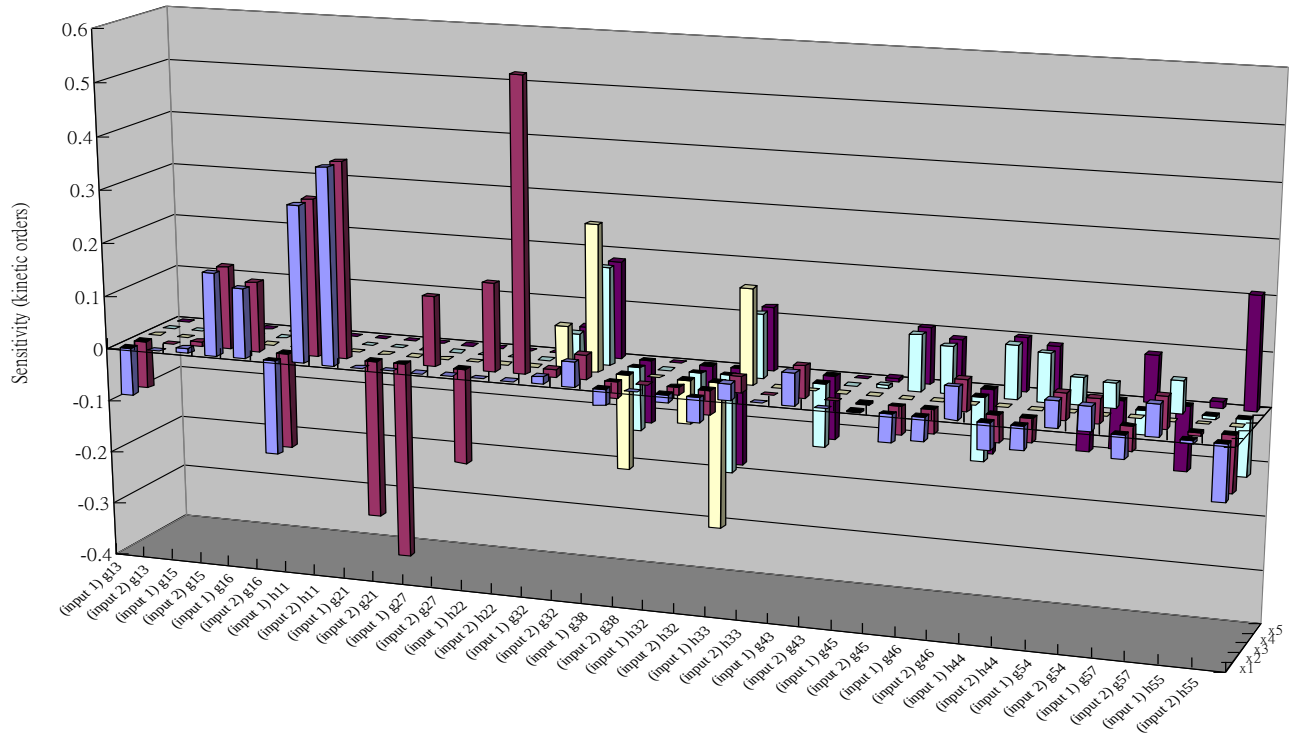


Fig 12. Kinetic-order sensitivity of the small-genetic network. The used independent variables (x_6, x_7, x_8) are (1.3, 1.3, 0.7) and (0.7, 0.7, 1.0), as shown in Table 9.

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