

Signal Transduction Ability Measurement of Signaling Pathways in Intracellular Communication via Fuzzy Method

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Abstract—Signal transduction plays an important role in biological organisms. Here, we proposed a method to access the information of the signal transduction ability of signal transduction pathway in the cells. Due to the nonlinear signal transduction pathway model, we have to solve the Hamilton-Jacobi inequalities (HJIs) to get the measurement. Instead of directly solving HJIs, fuzzy interpolation method was employed such that we can systematically measure signal transduction ability by solving the linear matrix inequalities (LMIs). The measurement will provide an insight to the characteristics of the signal transduction networks.

Keywords—signal transduction ability, fuzzy interpolation, T-S fuzzy model, MAP kinase cascades, linear matrix inequalities (LMIs)

I. INTRODUCTION

Metabolic processes (homeostasis) [1], the growth and differentiation of tissues (endocrine signaling) [2], the synthesis and secretion of proteins (blood clotting, immune-responses) and the composition of intracellular and extracellular fluids (photoreception, olfaction) are all closely related to signaling pathways. It is apparent that signaling pathways are indispensable for life. In general, a signaling pathway is initiated by protein-protein interaction between ligands and receptors. Conformation changes of a receptor usually occurs when a ligand binds to its specific receptor. This change ultimately induces specific cellular responses. Such converting processes from ligand binding to specific cellular response are termed as signal transductions. On molecular level, signaling pathways involve production or degradation of substances, molecular modification and activation or inhibition of chemical reaction. Thus there are many researches on the signaling pathways have focused on signaling molecules, cell-surface receptors, or the second messengers. Besides mass transferring, signaling pathways can be viewed as the information processing and transferring systems [3]. There are also many researches on the properties of signaling pathways, such as amplification [1], specificity, adaption, ultrasensitivity [4], oscillation [4], or synchronization. In this paper, we investigated the amplification of signaling pathways.

Signaling pathways need an amplification mechanism to reduce expense of signaling molecules and to respond as soon as possible. From the viewpoint of energy expedition, signal amplification can effectively reduce the initial key substances and can cause significant effects. Also, signaling pathways are responsible for the responses to the environmental variation that means the response should be as soon as possible if some deleterious stress was presented to organisms. There are many researches indicated the importance of signal amplification as well as the functional role of signal amplification. In osmo-adaptation in yeast under osmotic stress, Klipp and et al. provided an integrated mathematical model of the signaling pathway which indicated the relationship between rate constants of kinases and phosphatases and signal amplification [5]. In liver glycogenolysis and release of glucose, 10^{-10} M epinephrine in blood can generate an intracellular cAMP concentration of 10^{-6} M, an amplification of 10^4 [6].

In electrical engineering, there are several electrical components having the property of signal amplification, such as transistors. The analysis of amplification property of those gadgets had been done. The same analysis may be performed on the amplification property of a signaling pathway [7]. However, because of nonlinearity of signaling pathways, knowledge about the systematic properties of signaling pathways is still limited and incomplete. The interpretation of experimental data of signaling pathway is still context and knowledge-dependent. In this study, the signaling pathway is studied from the dynamic system perspective for which a signal transduction ability measurement is proposed based on signal and system theory from the systematic point of view. It is according to the ratio of output to input signal energy of the studied signaling pathway. This measurement is only dependent on the system characteristics of the studied signaling pathway.

Nevertheless, the proposed measurement scheme for nonlinear signaling pathways needs to solve the corresponding nonlinear Hamilton-Jacobi inequalities (HJIs). At present, we still have no analytic or numerical solution for HJIs, except some simple cases. Recently, Takagi-Sugeno (T-S) fuzzy systems have efficiently interpolated several local linear systems via fuzzy bases to approximate a nonlinear system [8].

Then the nonlinear signal transduction ability measurement problem can be solved via a set of linear matrix inequalities (LMIs) based on a set of fuzzy local linear signaling systems, which could be easily solved via LMI toolbox in Matlab[®] [9]. Based on fuzzy system theory and signal transmission method, the transduction ability of nonlinear signal transduction pathway could be investigated from these local linear signal transduction pathways. In this situation, more biological transduction insight can be investigated from linear signal system point of view. In near future, the transduction ability measurement may be as the characterization of the signal transmission systems for biotechnological, therapeutic applications and development of drug design.

The following sections include description of the generalized nonlinear signal transduction model, proposed measurement of signal transduction ability, fuzzy approximation of the nonlinear signal transduction model, and simulation example of MAP kinase and JAK/STAT signaling pathways, which are widely involved in eukaryotic signal transduction of cellular growth and differentiation and immune-responses respectively.

II. METHODS AND RESULTS

A. Dynamic model of signaling pathways

Mathematical modeling for metabolic networks has been studied extensively and is useful for describing experimental data, deducing regulatory principle and understanding more complex dynamic phenomena such as oscillation. However, in modeling of signaling pathways, there are few examples have been studied since no available experimental data. According to the structure of signaling pathways which is consisted of consecutive activations and deactivations of proteins, we still can model the signaling pathways as series of chemical reactions. That means the signaling pathways can be modeled by a system of rate equations. The choice of the expressions for the rates is a matter of the elaborateness of experimental knowledge and of modeling taste. Linear and bilinear expressions or Michaelis-Menten kinetics have been used to model the signaling pathway [3]. A ubiquitous signaling pathway, mitogen-activated protein (MAP) kinase cascades, which regulate fundamental cellular functions including cell growth and death, differentiation, transformation and motility, is used here to demonstrate the proposed measurement scheme. A general scheme of a MAP kinase cascade (Fig.1) consists of general levels (three or more), where the activated kinase at

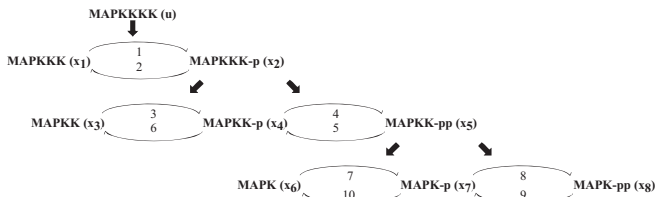


Figure 1. The general scheme of mitogen-activated protein (MAP) kinase cascade.

each level phosphorylates the kinase for the next level. The MAP kinase (MAPK) is at the terminal level of the whole cascade. It is activated by MAPK kinase (MAPKK), which is activated by MAPKK kinase (MAPKKK). Those sequential

phosphorylations can be referred as activation of the signaling pathway. Dephosphorylation of those kinases is thought to inactivate the signaling pathway. At each level, protein phosphatases can inactivate the corresponding kinase. The dynamics of a MAP kinase cascade can be represented by the following ODE system.

$$\begin{aligned}
 \frac{d}{dt} \text{MAPKKK} &= -v_1 + v_2 \\
 \frac{d}{dt} \text{MAPKKKP} &= v_1 - v_2 \\
 \frac{d}{dt} \text{MAPKK} &= -v_3 + v_6 \\
 \frac{d}{dt} \text{MAPKKP} &= v_3 - v_6 - v_4 + v_5 \\
 \frac{d}{dt} \text{MAPKKP}_2 &= v_4 - v_5 \\
 \frac{d}{dt} \text{MAPK} &= -v_7 + v_{10} \\
 \frac{d}{dt} \text{MAPKP} &= v_7 - v_{10} - v_8 + v_9 \\
 \frac{d}{dt} \text{MAPKP}_2 &= v_8 - v_9
 \end{aligned} \tag{1}$$

where $v_i, i = 1, 2, \dots, 10$ are reaction rates. The assumed values for the constants and rate equations are listed in Table 1.

TABLE I. RATE EQUATIONS AND PARAMETERS' VALUES OF THE MAP KINASE CASCADE MODEL.

Reaction number	Rate equation	Constant
v_1	$\frac{k_1 x_1 u}{K_1 + x_1}$	$k_1 = 0.025, K_1 = 15$
v_2	$\frac{k_2 x_2}{K_2 + x_2}$	$k_2 = 0.25, K_2 = 8$
v_3	$\frac{k_3 x_2 x_3}{K_3 + x_3}$	$k_3 = 0.025, K_3 = 15$
v_4	$\frac{k_4 x_2 x_4}{K_4 + x_4}$	$k_4 = 0.025, K_4 = 15$
v_5	$\frac{k_5 x_5}{K_5 + x_5}$	$k_5 = 0.75, K_5 = 15$
v_6	$\frac{k_6 x_4}{K_6 + x_4}$	$k_6 = 0.75, K_6 = 15$
v_7	$\frac{k_7 x_5 x_6}{K_7 + x_6}$	$k_7 = 0.025, K_7 = 15$
v_8	$\frac{k_8 x_5 x_7}{K_8 + x_7}$	$k_8 = 0.025, K_8 = 15$
v_9	$\frac{k_9 x_8}{K_9 + x_8}$	$k_9 = 0.5, K_9 = 15$
v_{10}	$\frac{k_{10} x_7}{K_{10} + x_7}$	$k_{10} = 0.5, K_{10} = 15$

In general, the scheme of a signaling cascade can be represented by the following nonlinear dynamic system:

$$\begin{aligned}\dot{x} &= f(x) + g(x) \cdot u \\ y &= C \cdot x\end{aligned}\quad (2)$$

where the vector $x = [x_1 \ \cdots \ x_n]^T$ denote states of protein involved in the signaling pathway. $f(x)$ denotes the interaction among these proteins. $g(x)$ denotes the coupling between m input signals $u = [u_1 \ \cdots \ u_m]^T$ and the signaling pathway. y denotes the outputs of the signaling pathway. For example, if x_n is the output signal to be discussed, then $C = [0 \ \cdots \ 0 \ 1]$.

B. Signal transduction ability measurement

There are many properties of the signaling way to be investigated such as the signaling time, the signal duration or the signal amplitude. As we mentioned previously, our interest is in the signal amplification that is, the signal amplitude. We define the transduction ability from the system gain point of view as follows:

$$T_a = \sup_{u(t) \in L_2[0, t_f]} \frac{\|y(t)\|_2}{\|u(t)\|_2} \quad (3)$$

where $u(t)$ and $y(t)$ are the inputs and outputs of the signaling pathway respectively. The physical meaning of transduction ability is the maximum ratio of signal energy of output to the signal energy of all possible bounded input signals within the time interval $[0, t_f]$. The reason why we consider the maximum energy ratio of output signal to all input signals is that input signals may change under different conditions and the signal energy ratio may change depending on those input signals. However, transduction ability is based on the worst-case effect of all input signals on outputs and is dependent on the characteristics of dynamic systems. Actually, the transduction ability cannot be measured directly by trying each possible bounded input signal which is a measure of system characteristics of the signaling pathway. In general, the maximization problem for measurement of signal transduction ability of a signal transduction pathway cannot be solved directly. It can only be solved indirectly by a systematic analysis method in the following.

Let us denote an upper bound of transduction ability as follows:

$$\frac{\|y(t)\|_2^2}{\|u(t)\|_2^2} \leq \rho^2, \forall u(t) \in L_2[0, t_f] \quad (4)$$

or

$$\|y(t)\|_2^2 \leq \rho^2 \|u(t)\|_2^2, \forall u(t) \in L_2[0, t_f] \quad (5)$$

Therefore, we can find an upper bound them decrease the upper bound as small as possible to approach the transduction ability, i.e., to minimize the upper bound to estimate the signal transduction ability.

Theorem 1

If there exists a positive function $V(x)$ with $V(0) = 0$ satisfying the following Hamilton-Jacobi inequality (HJI):

$$\left(\frac{\partial V(x)}{\partial x} \right)^T f(x) + \frac{1}{4\rho^2} \left(\frac{\partial V(x)}{\partial x} \right)^T g(x) g(x)^T \frac{\partial V(x)}{\partial x} + x^T C^T C x \leq 0 \quad (6)$$

then the signal transduction ability of the signal pathway is less than ρ .

C. Fuzzification

In general, it is still very difficult to solve the nonlinear HJI-constrained optimization problem in proposition 1. Fuzzy interpolation method is employed to overcome this situation and simplify the procedure to solve the transduction ability measurement problem.

Recently, fuzzy dynamic model has been widely employed to interpolate several local linear dynamic systems to approximate a nonlinear dynamic system to simplify nonlinear control problem [10], [11]. Takagi-Sugeno (T-S) fuzzy dynamic model [8] is described by fuzzy If-Then rules and employed here to efficiently deal with the problem of transduction ability measurement of the signaling pathway. The i -th rule of fuzzy model of nonlinear signal transduction pathway is proposed as the following form: [10],[11]

Rule i

If $x_1(t)$ is F_{i1} , $x_2(t)$ is F_{i2} , ..., $x_l(t)$ is F_{il} , then

$$\begin{aligned}\dot{x} &= A_i x(t) + B_i u(t) \\ y &= C x(t)\end{aligned}$$

where $i = 1, 2, \dots, L$, F_{ij} is the fuzzy set, A_i and B_i are known constant matrices, L is the number of fuzzy rules, and l is the number of premise variables. If all state variables are used as premise variables then $l = n$. The physical meaning of fuzzy rule i is that if the state variables $x_1(t), x_2(t), \dots, x_l(t)$ are with fuzzy sets $F_{i1}, F_{i2}, \dots, F_{il}$, then the nonlinear signaling pathway could be represented by the linear systems. The fuzzy system is referred as follows: [10], [11], [8]

$$\begin{aligned}\dot{x} &= \frac{\sum_{i=1}^L \mu_i(x(t)) [A_i x(t) + B_i u(t)]}{\sum_{i=1}^L \mu_i(x(t))} \\ &= \sum_{i=1}^L m_i(x(t)) [A_i x(t) + B_i u(t)] \\ y &= C x(t)\end{aligned} \quad (7)$$

where $\mu_i(x(t)) = \prod_{j=1}^L F_{ij}(x_j(t))$, and

$$m_i(x(t)) = \frac{\mu_i(x(t))}{\sum_{i=1}^L \mu_i(x(t))}. \quad F_{ij}(x_j(t)) \text{ is the grade of}$$

membership of $x_j(t)$ in F_{ij} and $m_i(x(t))$, $i=1,2,\dots,L$ are called the fuzzy bases. The denominator $\sum_{i=1}^L \mu_i(x(t))$ is only for normalization so that the total fuzzy sum of fuzzy bases $\sum_{i=1}^L m_i(x(t)) = 1$. The physical meaning of the fuzzy system is local linear signaling pathways are interpolated through nonlinear bases $m_i(x(t))$ to approximate the nonlinear signaling pathway. Actually, except fuzzy bases, other interpolation bases could be also employed to interpolate linear signaling pathways to approximate a nonlinear signaling pathway.

By fuzzy approximation, the nonlinear signaling pathway can be represented by the following fuzzy interpolated signaling pathway:

$$\begin{aligned} \dot{x} &= f(x) + g(x)u \\ &= \sum_{i=1}^L m_i(x(t)) [A_i x(t) + B_i u(t)] \\ &\quad + \Delta f(x) + \Delta g(x)u(t) \end{aligned} \quad (8)$$

where $\Delta f(x) = f(x) - \sum_{i=1}^L m_i(x(t)) A_i x(t)$ and $\Delta g(x) = g(x) - \sum_{i=1}^L m_i(x(t)) B_i$ denote fuzzy approximation errors. There are many methods to find A_i and B_i for the fuzzy model identification. We would use fuzzy toolbox in Matlab[®] to find A_i and B_i easily. After finding A_i and B_i , we could easily find bounds of fuzzy approximation error as follows:

$$\|\Delta f(x)\|_2^2 \leq a \|x(t)\|_2^2 \quad (9)$$

$$\|\Delta g(x)\|_2^2 \leq b \quad (10)$$

for some positive constants a and b . Then based on fuzzy approximation, we get the following transduction ability measurement for the nonlinear signaling pathway.

Theorem 2:

For the nonlinear signaling pathway, there exists a positive definite symmetric matrix P by solving the following Riccati-like inequalities.

$$\begin{aligned} A_i^T P + P A_i + \frac{2}{\rho^2} P B_i B_i^T P + \frac{2}{\rho^2} P P \\ + \frac{\rho^2 a}{2} I + \frac{2b}{\rho^2} P P + C^T C \leq 0, \end{aligned} \quad (11)$$

$$i = 1, 2, \dots, L$$

In order to solve the above Riccati-like inequalities by the conventional LMI method, we let the positive definite symmetric matrix $W = P^{-1}$. Then above Riccati-like inequalities can be equivalent to

$$\begin{aligned} A_i W + W A_i^T + \frac{2}{\rho^2} [B_i B_i^T + I + bI] \\ + W C^T C W + \frac{\rho^2 a}{2} W W \leq 0, \end{aligned} \quad (12)$$

$$i = 1, 2, \dots, L$$

By the Schur complements, the Riccati-like inequalities is equivalent to the following LMIs:

$$\begin{bmatrix} A_i W + W A_i^T + \frac{2}{\rho^2} (B_i B_i^T + I + bI) & W C^T & W \\ C W & -I & 0 \\ W & 0 & -\frac{2}{\rho^2 a} I \end{bmatrix} \leq 0, \quad (13)$$

$$i = 1, 2, \dots, L$$

Then the signal transduction ability of nonlinear signaling pathway is less than ρ , i.e., is an upper bound of the signal transduction ability.

By fuzzy approximation, the HJI is approximated by a set of algebraic inequalities. Therefore, the signal transduction ability of the nonlinear signaling pathway could be obtained by solving the following constrained optimization.

$$T_a = \min_{\substack{\text{subject to } W > 0 \\ \rho > 0 \text{ and (12)}}} \rho \quad (14)$$

which could be solved by decreasing ρ until no positive definite symmetric matrix exists.

Remark 1. The Riccati-like inequalities are an approximation of HJI at local linear systems. Similarly, the constrained optimization problem for signal transduction ability measurement of nonlinear signaling pathway is also a conventional method based on fuzzy interpolation method to replace the very difficult constrained optimization subject to HJI by the constrained optimization subject to LMIs. In general, the constrained optimization problem for signal transduction ability measurement is called “eigenvalue problem”, which can be efficiently solved by Matlab[®] LMI toolbox.

Remark 2. If ρ is smaller, then the last term in (11) should be larger so that the eigenvalues of A_i would be in the far left hand complex plane (i.e. with more negative real part) and then the total sums would be negative. If ρ is larger, then the eigenvalues of A_i would be near the imaginary axis (i.e. with smaller negative real part). In general, the signaling pathways always amplify the input signals (i.e. $T_a > 1$). In this situation, the eigenvalues of A_i would be near the imaginary axis, in order to amplify the extracellular signals to activate the corresponding genes in the cell.

III. EXPERIMENTAL SIMULATIONS

A. Simulation 1

Here we took into account that enzymes catalyze all steps and therefore consider Michaelis-Menten kinetics for the individual step. In these expressions, the concentrations of the donor and acceptor of the transferred phosphate group, ATP and ADP, are not explicitly expressed but are included in the rate constants. The dynamic of the nonlinear model and the fuzzy model of MAPK kinase cascade were shown in Fig.2 and Fig.3 respectively. The performance of MAPK kinase cascade, i.e., the ability to amplify the signal and to notably enhance the concentration of double-phosphorylated MAPK and the speed of activation, depends on the dynamic system of the signaling pathway and their rate constants. The simulation procedure started from fuzzy interpolation for the nonlinear model and the parameters of the fuzzy model, A_i and B_i , can be identified. Then, the approximation errors, a and b , can be determined. Next, according to *Theorem 2*, the augmented LMIs can be solved via LMI toolbox in Matlab[®]. Finally, signal transduction ability can be obtained by decreasing the prescribed ρ until no positive definite symmetric matrix solutions for the augmented LMIs exist.

First, using method of least-squares estimator, the parameters, A_i and B_i , of the fuzzy model can be identified. Since there are 8 substances or state variables in the ODE

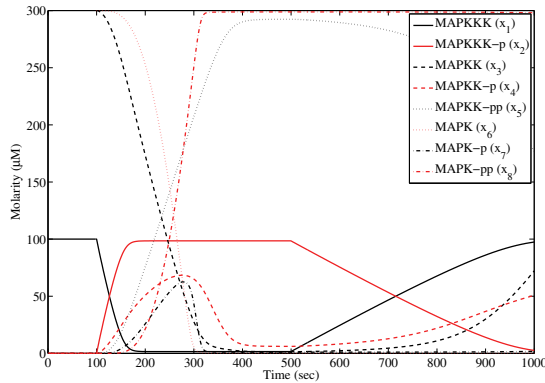


Figure 2. The nonlinear model of mitogen-activated protein (MAP) kinase cascade.

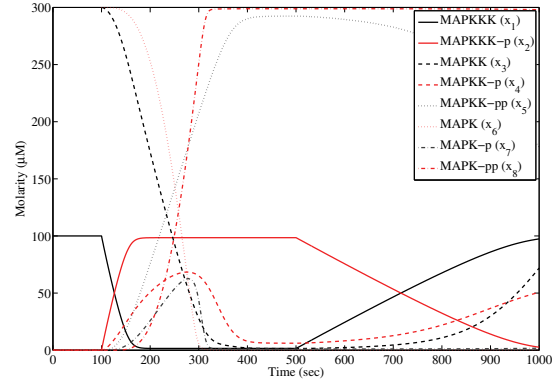


Figure 3. The fuzzy model of mitogen-activated protein (MAP) kinase cascade.

model, and by choosing 2 fuzzy sets for each variable, we have totally 256 fuzzy rules for the fuzzy model. By comparing the fuzzy model with the original ODE model, the approximation errors, $a = 2.35 \times 10^{-16}$ and $b = 1.86 \times 10^{-7}$ were determined. In the end, by solving the eigenvalue problem with LMI toolbox in Matlab[®], the signal transduction ability of the fuzzy signaling pathway is $T_a = 6.39 \times 10^6$ and the corresponding positive definite symmetric matrix is

$$W = \begin{bmatrix} 0.9988 & -0.9988 & -0.0156 & 0.0083 & 0.0073 & + & - & - \\ & 0.9988 & 0.0156 & -0.0083 & -0.0073 & - & + & + \\ & & 0.1165 & -0.0613 & -0.0552 & - & + & + \\ & & & 0.0987 & -0.0374 & + & - & - \\ & & & & 0.0926 & - & + & + \\ & & & & & + & - & - \\ & & & & & & + & - \\ & & & & & & & + \end{bmatrix}$$

where $+$ and $-$ mean the very small positive and negative numbers ($\sim 10^{-12}$), respectively. (The elements in the lower triangular matrix were not shown for symmetry).

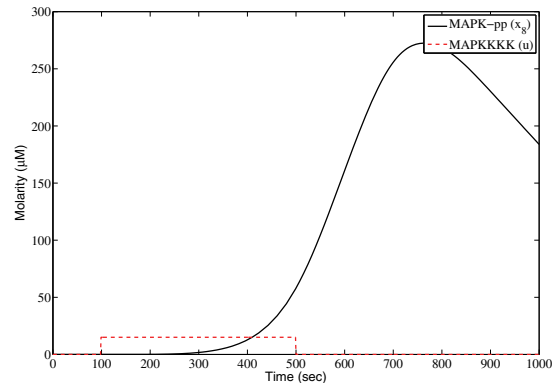


Figure 4. The input (red) and output (blue) of mitogen-activated protein (MAP) kinase cascade.

IV. DISCUSSION

In this work, the proposed measurement provided a new way to access the ability of signal transduction in intracellular communication from a systematic view. The signal transduction ability is not easy to be quantified or determined by a single biological experiment on measuring the concentration of the input and output signals. Hence, a way to quantify the ability which is independent to the measurement of the concentration of the input and output signals is demanded. According to the concept of a system gain, our proposed method can determine the ability of signal transduction and is only dependent on the structure of the signaling pathway and the components involved in. Our result said that the signal transduction ability of MAP kinase cascade is about 10^6 . That matched the description from the textbook [12] which says each level of a signaling pathway can cause about 10^2 times concentration amplification since the cascade is consisted of three-level cascade. It implied the usefulness of our proposed method. However, for a more precise estimation of the signal transduction ability, it needs to be confirmed by biological experiments. Also with the improvement of the knowledge on the structure of the signaling pathway, this method can give a better estimation on the ability of signal transduction.

Moreover, in this study, the nonlinear ODE equations are adopted to describe the signaling pathway, which also have been widely used in quantitative description to metabolism. However, we have to notice the difference between these two modules in the biology. First, signaling pathways serve for information processing and transfer of information, while metabolism provides mainly mass transfer. Second, the metabolic network is determined by the present set of enzymes catalyzing the reactions. Third, the different amounts of components have an effect on the concentration ration of catalysts and substrates.[3] The models for signaling pathway can always be improved according to the improvement on the experimental techniques and the knowledge about signaling pathways. Nevertheless, based on our purposed measurement, the signal transduction ability can always be accessed no matter which model is used to describe the whole signaling pathways.

In reality, the modules operated in a living system always have inherent noise due to random events. The amount of noise is a property of the system itself, and it may or may not cause significant deviation from the deterministic model. Some stochastic models [13] have been developed due to the consideration of the nature of the signaling pathways, that is, signaling pathways execute their functions under external disturbances and internal noises. One way to improve the estimation is to modify our proposed measurement with noise term $v(t)$, i.e.,

$$T_a = \sup_{u(t) \in L_2[0, t_f]} \frac{\|y(t)\|_2}{\|u(t)\|_2 + \|v(t)\|_2} \quad (15)$$

Then, the signal transduction ability can also be investigated under such noisy environments, which is more

real. Hence we can also investigate the robustness of signaling pathways with this proposed measurement [14]. The more robust the signaling pathway is the smaller variation the signal transduction ability is.

This methodology characterize the output-to-input energy ratio of the signal transduction systems and can apply on the biological modular device, such as amplifiers, logic elements, and actuators, or biochemical circuit designs to estimate signal transduction ability. Through the measurement, the signaling pathways can be analyzed and the importance of each component in the pathway can also be estimated. In the end, through the analysis of the signal transduction ability, each step in the signaling pathway can be analyzed and calculated its signal transduction ability which may be determined by the properties of reactants (for example: kinases or phosphatases) and the state of the interested cell. According to the conception of the BioBrick, we can also build the library of the building bricks of signaling pathways, and then the signaling pathway with desired signal transduction ability can be designed.

V. ACKNOWLEDGMENT

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VI. REFERENCES

- [1] S. Hohmann, "Osmotic stress signaling and osmoadaptation in Yeasts," *Microbiology and Molecular Biology Reviews*, vol. 66, pp. 300-+, Jun 2002.
- [2] J. Herrington and C. Carter-Su, "Signaling pathways activated by the growth hormone receptor," *Trends in Endocrinology and Metabolism*, vol. 12, pp. 252-257, Aug 2001.
- [3] E. Klipp, *Systems biology in practice : concepts, implementation and application* : Wiley-VCH, Weinheim., 2005.
- [4] B. N. Kholodenko, "Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades," *European Journal of Biochemistry*, vol. 267, pp. 1583-1588, Mar 2000.
- [5] E. Klipp, *et al.*, "Integrative model of the response of yeast to osmotic shock," *Nature Biotechnology*, vol. 23, pp. 975-982, Aug 2005.
- [6] A. B. Harvey Lodish, S Lawrence Zipursky, Paul Matsudaira, David Baltimore, and James Darnell., *Molecular Cell Biology*, 4th edition: New York: W. H. Freeman, 2000.
- [7] P. B. Detwiler, *et al.*, "Engineering aspects of enzymatic signal transduction: Photoreceptors in the retina," *Biophysical Journal*, vol. 79, pp. 2801-2817, Dec 2000.
- [8] T. Takagi and M. Sugeno, "Fuzzy Identification of Systems and Its Applications to Modeling and Control," *Ieee Transactions on Systems Man and Cybernetics*, vol. 15, pp. 116-132, 1985.
- [9] G. Balas, Chiang, R., Packard, A. and Safonov, M., *Robust Control Toolbox User's Guide*, 2008.
- [10] B. S. Chen, *et al.*, "Robustness design of nonlinear dynamic systems via fuzzy linear control," *Ieee Transactions on Fuzzy Systems*, vol. 7, pp. 571-585, Oct 1999.
- [11] B. S. Chen, *et al.*, "Mixed H-2/H-infinity fuzzy output feedback control design for nonlinear dynamic systems: An LMI approach," *Ieee Transactions on Fuzzy Systems*, vol. 8, pp. 249-265, Jun 2000.
- [12] A. B. Harvey Lodish, Paul Matsudaira, Chris A. Kaiser, Monty Krieger, Matthew P. Scott, Lawrence Zipursky, and James Darnell., *Molecular Cell Biology*, 5 ed., 2003.
- [13] A. Hoffmann, *et al.*, "The IkappaB-NF-kappaB signaling module: temporal control and selective gene activation," *Science*, vol. 298, pp. 1241-5, Nov 8 2002.
- [14] B. S. Chen, *et al.*, "A new measure of the robustness of biochemical networks," *Bioinformatics*, vol. 21, pp. 2698-705, Jun 1 2005.