Towards kinetic modeling of metabolic networks with incomplete parameters

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Abstract—Modeling is an important direction in systems biology. The target towards kinetic modeling for metabolic network is to develop a practical computational method which can handle incomplete parameters. In principle, we could start with a set of randomly chosen parameters; calculating fluxes and metabolites concentration and comparing with experiments; iterating until the best parameters are found. But the large parametric space may require billions of times of iterations. In order to overcome such a difficulty, we develop a method to obtain the structure of parametric space. We are able to discover the correlation between parameters and variables, which is helpful for us to estimate the possible value of parameters. Differ from previous method, the implicit relationship between parameter and variable are also provided directly by our method, which provides a potential for us to analyze the feature of metabolic network.

Keywords—kinetic model, metabolic network, maximum reaction rate

I. INTRODUCTION

Systems biology requires the essential analytic tools for biological phenomena [1][2]. Accurate representation of metabolic and genetic networks by mathematical models is a central goal of biology. Modeling of a metabolic network is one of the most significant tasks.

The metabolic network usually contains hundreds of substrates which are interconnected through biochemical reactions. There are a large number of variables and parameters such as maximum reaction rates and Michaelis-menten constants involved in metabolic network model [3]. Most enzymatic parameters are not measured under the living conditions [4][5]. These difficulties make the kinetic model construction of metabolic networks through collections of experimental parameters remain impossible [6][7].

In principle, we could choose a set of parameters randomly, calculate fluxes and metabolites concentration, then compare with experiments. Such procedure may be iterated until the best parameters are found. For a kinetic model with ten parameters involved, if each parameter has ten possible values, the maximum time of iteration is 1010. The number of parameters is usually larger than ten. The question naturally arises: is there a better way to address these difficulties?

The similar difficulty was encountered in other areas [8]. In physics, the difficulty is solved by introducing the ubiquitous conception of phase space. "When one wishes to discuss any curve whose equation contains an arbitrary parameter, it is customary to consider simultaneously all the curves obtained by giving this parameter all its possible values."(Boltzmann) [9]. The conception of phase space is describing a single trajectory of the system through its dynamical space. The structure of the phase space is then revealed by methods such as Poincare map [10].

Since the maximum reaction rates are most important in modeling and difficult to be tested in experiments, we regard maximum reaction rates as the key parameters influenced the concentration of metabolites in our work. The key idea is that, for a metabolic network, which the kinetic equation could be expressed as

\[ \frac{dx}{dt} = f(x, \nu(x)) \]  (1)

with metabolite concentrations \( x \) and reaction rates \( \nu \), we rewrite metabolic network as

\[ \frac{dx}{dt} = f(x, V_{\text{max}}) \]

\[ \frac{dV_{\text{max}}}{dt} = g(x, V_{\text{max}}) \]  (2)

with metabolite concentrations \( x \) and maximum reaction rates \( V_{\text{max}} \). Here, \( f \) and \( g \) are both functions of \( x \) and \( V_{\text{max}} \). The metabolic system dynamics is obtained by solving Eq.(2).

The advantage of such rewriting is the following. When the kinetic equation of metabolism is expressed as Eq.(1), trajectory of metabolite concentration variation is determined by value of maximum reaction rate parameter. With the help of computer simulation, we are able to calculate different trajectories by using different values of maximum reaction rates. The collection of trajectories doesn’t provide the correlation between reaction rate and metabolite concentration directly. Then it doesn’t provide knowledge for parametric estimation. If the maximum reaction rate is a variable, the implicit relationship between maximum reaction rate and metabolite concentration are directly shown from their values after calculation. The relationship is helpful for us to estimate the possible value of maximum reaction rate. Such an idea is demonstrated in Fig.1.
This article is organized as following: We demonstrate through a two reactions metabolic network in Method that we can rewrite metabolic kinetics from the form of Eq.(1) into the form of Eq.(2). We demonstrate in Results and Discussion that the kinetic models using both forms are equivalent on dynamics of metabolite. However, the implicit biological relationship are directly shown in the form of Eq.(2). Moreover, the correlation between maximum reaction rate and metabolite concentration, which could help us to estimate possible values of parameters, is provided directly in the form of Eq.(2) in Results and Discussion.

II. METHOD

We consider a metabolic network of \( N \) metabolites with their concentrations represented by a vector \( x^\tau = (x_1, \ldots, x_N) \) where the superscript \( \tau \) indicates transpose of a matrix. A set of kinetic equations can be written down as following:

\[
\begin{align*}
\frac{dx}{dt} &= f(x, V_{max}) = S\nu(x, V_{max}) + b(x) \\
\frac{dV_{max}}{dt} &= g(x, V_{max})
\end{align*}
\]

\( S \) is an \((N \times M)\) stoichiometric matrix containing all relevant chemical reactions involved. \( b(x) \) is a vector representing biomass fluxes in and out of the network. \( \nu(x, V_{max}) \) is an \((M \times 1)\) matrix with \( M \) being the total number of reactions on the network representing reaction rates, \( V_{max} = V_F \) or \( V_B \). We demonstrate the dynamics of metabolism here.

A. A Two Reaction Metabolic Network

Consider a metabolic network consists of three metabolites, \( A, B \) and \( C \), with reactions as following. These are Uni-Bi and pingpong Bi-Bi enzymatic reactions. The maximum reaction rates are \( V_1 \) and \( V_2 \) for the two reactions, respectively. There is an input flux to metabolite \( A \) and an output flux from metabolite \( C \).

Apply to the metabolic network shown in Fig.2. The input flux to \( A \) and output flux from \( C \) are assumed to be \( 0.2/(1+[A]) \) and \( 0.4[C]/(1+[C]) \). \([A], [B], [C] \) are metabolite concentrations of \( A, B, C \). According to Eq. (3), the kinetic model is:

\[
\begin{align*}
\frac{d[A]}{dt} &= \frac{0.2}{1+[A]} - \nu_1 \\
\frac{d[B]}{dt} &= \nu_1 - \nu_2 \\
\frac{d[C]}{dt} &= 2\nu_2 - \nu_1 - \frac{0.4[C]}{1+[C]}
\end{align*}
\]

One reaction obeys pingpong Bi-Bi mechanism; the other obeys Uni-Bi mechanism. Michaelis-Menten constants for all reactions are set to 1. The steady state rate equations for the pingpong Bi-Bi mechanism and Uni-Bi mechanism [11] are

\[
\begin{align*}
\nu_1 &= \frac{V_1 F[A][C] - V_1 B[B]}{V_1 F[1 + [A]] + V_1 B[1 + [B]]} \\
\nu_2 &= \frac{V_2 F[B] - V_2 B[C]}{V_2 F[1 + [B]] + V_2 B[1 + [C]]}
\end{align*}
\]

B. Rewrite Kinetic Model

Assuming these reactions are both irreversible, use \( V_1 \) and \( V_2 \) to represent the maximum reaction rates \( V_{1F} \) and
V_2$. When $\frac{dV_1}{dt} = \frac{dV_2}{dt} = 0$, the differential equations for metabolites concentration could be written as

$$\frac{d[A]}{dt} = \frac{0.2}{1 + [A]} - \frac{V_1[A][C]}{(1 + [A])(1 + [C])}$$

$$\frac{d[B]}{dt} = \frac{V_1[A][C]}{(1 + [A])(1 + [C])} - \frac{V_2[B]}{1 + [B]}$$

$$\frac{d[C]}{dt} = -\frac{V_1[A][C]}{(1 + [A])(1 + [C])} + \frac{2V_2[B]}{1 + [B]} - \frac{0.4[C]}{1 + [C]}$$

(6)

Based on the conception of reaction rates, we introduce a new dynamics on maximum reaction rate as the following,

$$\frac{dV_1}{dt} = \frac{c_1[A][C]}{(1 + [A])(1 + [C])}(\frac{d[A]}{dt} + \frac{d[C]}{dt} - \frac{d[B]}{dt})$$

$$\frac{dV_2}{dt} = \frac{c_2[B]}{1 + [B]}(\frac{d[B]}{dt} - 2\frac{d[C]}{dt})$$

(7)

c_1 and c_2 are constants. The reason of writing Eq.(7) in such form with V_1 is that, V_1 is the maximum reaction rate of reaction $A + B = C$. The same principle is used on writing differential equation on V_2. Suppose $c_1 = c_2 = 4$, then we obtain the differential equations for V_1 and V_2.

$$\frac{dV_1}{dt} = \frac{4[A][C]}{(1 + [A])(1 + [C])}(\frac{0.2}{1 + [A]} - \frac{3V_1[A][C]}{(1 + [A])(1 + [C])} + \frac{3V_2[B]}{1 + [B]} - \frac{0.4[C]}{1 + [C]})$$

(8)

$$\frac{dV_2}{dt} = \frac{4[B]}{1 + [B]}(\frac{3V_1[A][C]}{(1 + [A])(1 + [C])} - \frac{5V_2[B]}{1 + [B]} + \frac{0.8[C]}{1 + [C]})$$

The kinetics model on metabolites concentration is given by Eq.(6). The dynamics equation for maximum reaction rates V_1 and V_2 is given by Eq.(8).

III. RESULTS AND DISCUSSION

A. Equivalent to Previous Dynamics after Rewriting Kinetic Model

In order to compare the kinetic models which are written in different forms, we use the same values of maximum reaction rates to calculate the variation of metabolite concentrations against time. If the performances of dynamics on metabolites are the same, the kinetic models written in forms of Eq.(1) and Eq.(2) are considered as equivalent.

In Fig.3, different V_1 and V_2 are used to calculate dynamic change of metabolite concentrations using Eq.(6). The dynamics of metabolite concentrations with fixed V_1 and V_2 are shown in Fig.3(a). In Fig.3(b), we solved Eq.(6) and Eq.(8) together using initial V_1 and V_2 values in Fig.3(a). In both ways, the metabolites reach steady states eventually. It is apparent that the metabolite dynamics in Fig.3(a) and Fig.3(b) are almost the same.

B. More Dynamical Information Contained

The kinetic models written in Eq.(1) and Eq.(2) are equivalent on dynamics of metabolites. Now, the question is whether or not the mathematical form of Eq.(2) have any advantage. The answer is positive. There are more variables in rewritten kinetic model. The variables connect with each other through Eq.(2) and form a network. The relationship between variables, which is implicit in previous kinetic model, could be obtained directly in rewritten kinetic model.

We linearized Eq.(6) and Eq.(8) using the steady state values in Fig.3(b). The linearized network allows a direct interpretation of the effect of metabolite concentrations [A], [B], [C] on maximum reaction rates V_1, V_2 and the mutual interaction between V_1 and V_2, while such implicit information are usually miss in previous kinetic model after linearization. After linearizing Eq.(6) and Eq.(8) of two reaction model, such interaction relationship are obtained and demonstrates in Fig.4. V_1 is activated by both metabolite A and C, while is inhibited by metabolite B. V_2 is activated by metabolite A and B while inhibited by metabolite C. These substrate activation, allosteric activation, product inhibition are commonly observed
allostERIC MODIFICATION OF ENZYMES. They may also occur at enzyme transcription level.

The substrate activation and product inhibition shown in Fig.4 are commonly observed allosteric modification of enzymes. For example, in glycolysis, the reaction catalyzed by phosphofructokinase 1 (PFK-1) is coupled to the hydrolysis of ATP. When there is too much of the ATP, because of ATP binding to the enzyme, the enzyme is inhibited due to conformational change. In organisms, regulators of transcription factors, for instance AMP kinase and MAP kinase usually form an interacting network, giving rise to an effective interacting network of proteins. It is in this sense that enzyme transcriptions mutually interact \cite{12}\cite{13}. This model suggests that the common interaction among enzymes and the effect of metabolite on enzymes are likely contained in our mathematical form. It is a strong validation for our method.

C. Parametric Space Structure

In this part, varying initial value of maximum reaction rates is used to calculate kinetic model by solving Eq.(6) and Eq.(8). After calculation, we record the calculated values of both maximum reaction rates and metabolite concentrations to find the possible correlation between them. The correlation between maximum reaction rate and metabolite concentration is obtained. Maximum reaction rate $V_2$ is positive correlated with metabolite $C$. The distribution of $V_2$ is $0.2 < V_2 < 2$. Such relationships are shown in Fig.5.

We solved Eq.(6) and Eq.(8) together using initial values $[A] = [B] = [C] = V_1 = V_2 = 0$. Then the trajectory of metabolite concentrations against time is shown in Fig.5(a). If the initial values of maximum reaction rates are varying, the trajectories evolve with variation of maximum reaction rates. Then the distribution map of maximum reaction rates can be obtained by solving Eq.(6) and Eq.(8) with different initial values. The results are shown in Fig.5(b) and Fig.5(c). The relationship between $[C]$ and $V_2$ is shown in Fig.5(b). Every dot in Fig.5(c) represent a pair of possible value of maximum reaction rates $V_1$ and $V_2$. Such information in Fig.5 is helpful for us to estimate the possible values of maximum reaction rates. Furthermore, by introducing the dynamics on maximum reaction rate, a biochemical system could be drawn into the state without the highly stringent constraints of parameters. The kinetic model construction of large scale metabolic network could benefit from such characteristic.

IV. Conclusion

The advances in systems biology require mathematical modeling. To construct a kinetic model of metabolic networks
through experimental data under living condition remains a
difficult task. The target towards kinetic modeling is to de-
velop a practical computational method to handle unavailable
parameters.

In principle, we can start with a set of random parameters;
calculating metabolite concentrations and fluxes; comparing
with experiments. The procedure keep iteration till valid pa-
rameter is found. Generally, the time for trail can be as large
as billion.
For solving the similar problem, some idea has been proposed in other area, such as physic. Inspired by the similar idea, we regard both enzymatic parameters and metabolites concentrations as variables and rewrite the dynamical expression for kinetic model. Then we are able to discover the possible relationship among enzymatic parameters and metabolites concentrations and use it to estimate the possible value of parameters.

Since maximum reaction rate is one of the most important parameters, we regard maximum reaction rates as the key parameters influenced the concentration of metabolites. We developed a new method to rewrite kinetic model. We demonstrated through a two reactions metabolic network that after rewriting the kinetic model, the dynamics on metabolites is consistent with previous method. There are common interactions between enzymes and metabolites, which agrees with biological phenomena, shown in rewritten form. Moreover, we provided the distribution of maximum reaction rates. The correlation between maximum reaction rate and metabolite concentration are obtained. We can utilize the correlation to estimate the possible value of parameter. By designing experiments, we are able to find the adaptive value of parameter, which corresponds to the real metabolic process. It allows us to construct a kinetic model to simulate the dynamical processes of metabolism. We also applied such mathematically method to determine enzymatic reaction rates in the central metabolism of *Methylobacterium extorquens* AM1 and *S.cerevisiae*.

**ACKNOWLEDGMENT**

This work was supported in part by the National 973 Project No. 2010CB529200; and by the Natural Science Foundation of China No. NFSC61073087 and No. NFSC91029738.

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