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MATHEMATICAL MODELING OF METABOLIC PATHWAYS

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ÖZET

Bir metabolik patway'in kinetik analizini yapmak için, onun kinetik analizini tanımlayan matematiksel modelini inşa etmek en önemli olaydır. Bir metabolik teoride, X_i metabolitinin x_i konsantrasyonundaki değişimin hızı, sistemde bulunan ve her biri X_i metabolitinin stokiyometri katsayısına göre ağırlıklı r tane reaksiyonun hızlarının toplamı olarak kabul edilir. v ve $\mathbf{x}$ sırasıyla hız ve konsantrasyon vektörlerini göstermek üzere, bir sistemin kinetiğinin matematik modeli

$$\frac{d\mathbf{x}}{dt} = Nv$$

olarak yazılır. Burada N metabolitlere ait stokiyometri matrisi, N stokiyometri matrisi genelde bir sisteme ait N , nin ayrışmasına bağlı olan, korunum bağıntılarının çıkarılışında önemli rol oynar. Bu çalışmada, verilen bir metabolik patway için korunum bağıntılarının hepsini çıkarmak amacıyla MAPLE de bir bilgisayar programı geliştirdik. Bu program verilen bir metabolik patway'e ait korunum bağıntılarını hesaplar. Bu metabolik patway de Metabolite ve ara ürünlerde herhangi bir kısıtlama yoktur.

Anahtar Kelimeler: *Metabolik patway, Stokiyometri matrisi, Korunum bağıntıları, Bilgisayar cebiri.*

ABSTRACT

In order to make kinetic analysis of a metabolic pathway, construction of mathematical model describing its kinetics is a major part of the work. In the framework of metabolic kinetic theory, it is assumed that the rate of changes in the concentration x_i of a metabolite X_i is the sum of the r reaction rates, each weighted by corresponding stoichiometric coefficient of X_i. Using v and x to denote the rate vector and concentration vector respectively, mathematical model for kinetics of a system can be written as

$$\frac{d\mathbf{x}}{dt} = Nv$$

where N is stoichiometric matrix which represents how the metabolites involved in the system combine. Derivation of conservation relationship which mainly depends on decomposition of stoichiometric matrix N plays important roles in constructing mathematical model of the system. In present the study, we have developed a computer program in MAPLE in order to derive all of the conservation relationship for a given metabolic pathway automatically that can be applied to any pathway which may include unlimited steps and intermediate metabolites.

Key Words: *Metabolic Pathway, Stoichiometric matrix, Conservation relationship, Computer algebra*

1. INTRODUCTION

Mathematical modelling of metabolic pathway provides us a wide variety of information about behaviour of the system. The kinetic approach to the modelling of the systems is sometimes hampered by the fact that kinetic properties are imperfectly know that makes the structural approach more attractive [8]. The structural property of a metabolic pathway is the characteristics of the system that depends only on the structure of the pathway. Although mathematical description of dynamic of a metabolic system is a system of nonlinear differential equation including a number of parameters that is difficult to solve, the structure of the system imposes linear constrains which can be analyzed independently of the nonlinear kinetics [5].

In a living organism, of course, very few reactants are external, but there are so many reactions to be considered that the entire system is difficult to comprehend. To make metabolism manageable for analysis, therefore, the system must be defined as just part of the whole organism and it must be taken into consideration as a metabolic pathway and then the metabolites at the interfaces with the rest of the organism must be defined as external [2].

In order to analyze a metabolic pathway, Reder (1988) has emphasized on the structural properties of the pathway. The advantages of this approach lies of course in the fact that structure of the metabolic pathway depends neither on the environment nor the internal state of the system.

2. CONSTRUCTION OF MATHEMATICAL MODEL OF METABOLIC PATHWAY

Biochemical systems usually show conservation relationship among some of the intermediates or internal metabolites. From the knowledge of the stoichiometry matrix for a metabolic pathway, considerable information can be derived. One can decide whether the system has conservation relationships or not [7].

Metabolite concentrations are assumed as variables of metabolic systems. Let $X_1, X_2, ..., X_m$ denote these metabolites involved in the system and let $x_1, x_2, ..., x_m$ be their respective concentrations. Concentrations vector $\mathbf{x}$ is defined as:

$$\mathbf{x} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_m \end{bmatrix} \tag{1}$$

In order to construct the model, we at first write stoichiometric reaction scheme that describes how the metabolites x_i combine. In this scheme, we ignore the external metabolites. The stoichiometry matrix N is constructed as follows: The column j of N represents the reaction j and we write $i-th$ member of this column is:

$$N_{ij} = \begin{cases} +\alpha & \text{If the reaction } j \text{ produces } \alpha \text{ molecules of } x_i \\ -\alpha & \text{If the reaction } j \text{ consumes } \alpha \text{ molecules of } x_i \\ 0 & \text{If the reaction } j \text{ neither produces nor consumes } x_i \end{cases}$$

It is assumed that the rate of change of x_i is the sum of the r reaction rates, each weighted by the corresponding stoichiometric coefficient of x_i. According to the biochemical kinetic theory, using v_j to denote the rate of the reaction j we write rate vector as

$$v = \begin{bmatrix} v_1 \\ v_2 \\ \vdots \\ v_r \end{bmatrix} \tag{2}$$

Hence, kinetics of a metabolic system can be written as a system of ordinary differential equations of the form

$$\frac{d\mathbf{x}}{dt} = Nv(x,k,\mu) \tag{3}$$

where $N_{m\times r}$ is a matrix, x s are metabolite concentrations, k s are kinetic parameters and μ s are some external parameters. Here m is the number of metabolites and r is the number of reactions.

Conservation relationships of a metabolic system can be readily deduced from the stoichiometry matrix N. Three new matrices are constructed from N for use in the derivations below. The first consist of the m_0 independent rows of N and arranging these rows at the top of N and named as N_R, then arranging independent columns of N at the right hand side of the matrix which is represented as N_C and the third matrix is denoted by N_{RC} and composed of m_0 independent rows and m_0 independent columns of N. Therefore, we obtained a matrix from N which is N_2 of the form given in eq(4).

$$\boldsymbol{N_2}= \begin{bmatrix} \boldsymbol{N_R} & \boldsymbol{N_{RC}} \\ & \\ & \boldsymbol{N_C} \end{bmatrix} \tag{4}$$

Suppose that N_2 has the rank m_0 where m_0 is less than or equal to m which means that N_2 has m_0 – independent rows and the remaining $(m-m_0)$ dependent rows can be expressed as linear combinations of these independent rows. So,

$$[N_2] = [L_0][N_R]. \tag{5}$$

Since each row in N_2 corresponds to a metabolite, this also means that the pathway has dependent metabolites which can be expressed in terms of the independent metabolites. There may be several combinations of rows in N_2 that can be chosen as independent and the choice is arbitrary [4].

If m_0 is equal to m then there will be no dependent rows in N_2 which means that the system has no conservation relationships. Decomposing N_2 and using Eq(4) and Eq(5), it can be written as

$$\underbrace{\left[\left[A\right]_{m\times(r-m_0)} \vdots \left[N_C\right]_{m\times m_0}\right]}_{N_2} = \left[L_0\right]_{m\times m_0} \underbrace{\left[\left[B\right]_{m_0\times(r-m_0)} \vdots \left[N_{RC}\right]_{m_0\times r}\right]}_{N_R} \tag{6}$$

Which follows that

$$\left[A\right]_{m\times(r-m_0)} = \left[L_0\right]_{m\times m_0}\left[B\right]_{m_0\times(r-m_0)} \tag{7}$$

$$\left[N_C\right]_{m\times m_0} = \left[L_0\right]_{m\times m_0}\left[N_{RC}\right]_{m_0\times r}. \tag{8}$$

Note that since all rows and columns of N_{RC} are independent, it is a square matrix and always invertible. So in order to compute L_0 matrix from Eq(8), it can be written as:

$$\left[L_0\right]_{m\times m_0} = \left[N_C\right]_{m\times m_0}\left[(N_{RC})^{-1}\right]_{m_0\times m_0}. \tag{9}$$

It can easily seen from Eq(5) that L_0 is of form

$$\left[L_0\right]_{m\times m_0} = \begin{bmatrix} \left[I\right]_{m_0\times m_0} \\ \cdots \\ \left[L^*\right]_{(m-m_0)\times m_0} \end{bmatrix} \tag{10}$$

Hence from eq(5), matrix N_2 can be decomposed as

$$\underbrace{\begin{bmatrix} \left[N_R\right]_{m_0\times r} \\ \cdots \\ \left[N^*\right]_{(m-m_0)\times r} \end{bmatrix}}_{N_2} = \underbrace{\begin{bmatrix} \left[I\right]_{m_0\times m_0} \\ \cdots \\ \left[L^*\right]_{(m-m_0)\times m_0} \end{bmatrix}}_{L_0}\left[N_R\right]_{m_0\times r} \tag{11}$$

From eq(11), we can write

$$\left[N^*\right]_{(m-m_0)\times r} = \left[L^*\right]_{(m-m_0)\times m_0}\left[N_R\right]_{m_0\times r} \tag{12}$$

As the rows of N_2 are associated with the components of the concentration vector $\mathbf{x}$, it is also natural to decompose the concentration vector $\mathbf{x}$ into its first m_0-components as $\mathbf{x}_1$ and the remaining $(m-m_0)$ components as $\mathbf{x}_2$. So we have,

$$\begin{bmatrix} \left[\frac{d\mathbf{x_1}}{dt}\right]_{m_0\times 1} \\ \cdots \\ \left[\frac{d\mathbf{x_2}}{dt}\right]_{(m-m_0)\times 1} \end{bmatrix} = \begin{bmatrix} \left[N_R\right] \\ \cdots \\ \left[N^*\right] \end{bmatrix} v \tag{3}$$

Then, we two equations of the form

$$\left[\frac{d\mathbf{x_1}}{dt}\right]_{m_0\times 1} = \left[N_R\right]v \tag{14}$$

$$\left[\frac{d\mathbf{x}_2}{dt}\right]_{(m-m_0)\times 1} = \left[N^*\right] v \tag{15}$$

Substituting eq(12) into eq(15) and then using eq(14), it can be written as,

$$\left[\frac{d\mathbf{x}_2}{dt}\right]_{(m-m_0)\times 1} = \left[L^*\right]_{(m-m_0)\times m_0} \underbrace{\left[N_R\right]_{m_0\times r} v}_{\left[\frac{d\mathbf{x}_1}{dt}\right]} \tag{16}$$

As a result we get all conservation relationships for a metabolic pathway of which stoichiometry matrix is N as follows,

$$\frac{d}{dt}\left\{\left[\mathbf{x}_2\right] - \left[L^*\right]\left[\mathbf{x}_1\right]\right\} = 0 \tag{17}$$

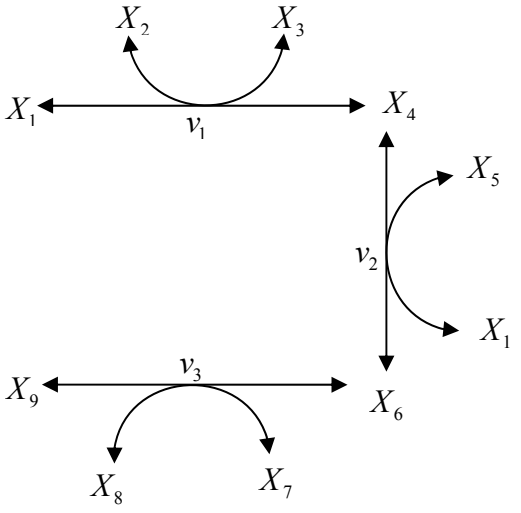
which means that the values of these combinations remain constant at their initial values during the time course of the reactions. Each structural conservation relationship is a linear combination of these $(m-m_0)$ independent conservation relationships described in eq(17) [6,9]. A program was written in algebraic and symbolic REDUCE form [1].

3. MAPLE AS A COMPUTER ALGEBRA SYSTEM

Computers are usually used to manipulate numbers. However, they can just as work with other symbols such as algebraic variables. Computer algebra systems such as MAPLE can perform numerical computations, manipulate symbolic expressions and plot graphs. They use exact algebraic techniques rather than using the approximation methods of numerical analysis. Computer algebra systems accept their input in a quasi-mathematical notation that is simple to use and remember. To construct conservation relationships of the system, we have used linear algebra package of MAPLE to perform matrix operations. MAPLE V Release 5 on WindowsXP operating system has been employed in our computations.

4. EXAMPLE

We have chosen following metabolic pathway as an example in order to derive all conservation relationship to illustrate results the program we have developed.



Schema 1. A Hypothetical reaction topology including nine metabolites and three distinct fluxes
Since $m = 9$ and $m_0 = 3$ for above system there are six conservation relationships for the metabolic pathway, these are:

$$\frac{d}{dt}\left[X_3(t) + X_2(t)\right] = 0$$
$$\frac{d}{dt}\left[X_4(t) + X_2(t)\right] = 0$$
$$\frac{d}{dt}\left[X_5(t) + X_1(t) - X_2(t)\right] = 0$$
$$\frac{d}{dt}\left[X_6(t) - X_1(t) + X_2(t) - X_7(t)\right] = 0$$
$$\frac{d}{dt}\left[X_8(t) + X_7(t)\right] = 0$$
$$\frac{d}{dt}\left[X_9(t) + X_7(t)\right] = 0$$

5.CONCLUSION

The method based on decomposition of a stoichiometric matrix of metabolic pathways provides us a wide variety of information for comprehending the complex topology of metabolic pathways in a systematic way. One of the main advantage of using conservation relationships is to reduce computation loads in kinetic analyzes of a metabolic pathway. For instance, if $m_0 < m$ then, instead of solving a system of ordinary differential equations including *m*-differential equations, it is enough to solve a system composed of m_0 −differential equations and then using $\left(m - m_0\right)$ conservation equations, we obtained all solutions of the system.

The MAPLE program we have developed is easy to use and can be employed to derive all of the conservation relationships for a given metabolic pathway automatically. Furthermore it is able to compute conservation relationships of any metabolic pathways which may include unlimited steps and intermediate metabolites.

There is certainly scope for the application of modern computer algebra techniques to analyze a complex metabolic system but at present it is a largely unexploited field [8]. MAPLE as a computer algebra system provides a powerful tool for analyzing such systems. We hope that this program may make a partial contribution in this field.

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