Biochemical Reaction Network Analysis

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October 28th, 2002

Introduction

- Developing methods for analyzing large-scale biochemical reaction networks, which avoid the requirment of knowledge about all the detailed reaction kinetics involved in the network, has become a very important problem. One would like to develop a method which only requires knowledge of the stoichiometry of the network.
- Metabolic control analysis (MCA) is one such method used to analyze these large-scale networks.
- Biochemical circuit theory (BCT) is another popular method which includes flux balance analysis (FBA) and energy balance analysis (EBA).

Metabolic Control Analysis (MCA)

– Analyses properties of metabolic networks by studying the effects of small variations of enzyme or metabolite concentrations on the steady-state values of reaction flux J^j and metabolite concentrations x_i.

– The metabolic networks under consideration consist of:

- M enzymes, $E^1, \ldots, E^M$, each of which converts one or more of the N metabolites into products.
- Each metabolite, $X_1, \ldots, X_N$, is converted by one or more of the enzymes.
- Each reaction involves an enzyme.
- Substrates involved in the first reaction and products of the last reaction are held at constant concentrations to act as parameters, $p_1, \ldots, p_k$, within the model.

Assumptions

- The model is assumed to approach a unique steady state if left alone.

- The rates of a given reaction are proportional to the concentration of the enzyme which catalyzes that reaction.

$$\upsilon^j \propto e^j, \quad j = 1, \ldots, M. \tag{1}$$

Local Elasticity Coefficient

Assume the reaction network is at non-equilibrium steady state (NESS) and suppose a perturbation, $x_i^* \to x_i^* + \delta x_i$, occurs. Then

$$\varepsilon_i^j = \frac{x_i^*}{\upsilon_*^j}\frac{\delta \upsilon^j}{\delta x_i} \tag{2}$$

is called the local elasticity coefficient of reaction rate j with respect to metabolite, effector, or enzyme i.

Control Coefficients

Suppose a perturbation, $e_*^j \to e_*^j + \delta e^j$, occurs. Then

$$C_j^{x_i} = \frac{e_*^j}{x_i^*}\frac{\delta x_i}{\delta e^j}, \tag{3}$$

$$C_j^{J^k} = \frac{e_*^j}{J_*^k}\frac{\delta J^k}{\delta e^j} \tag{4}$$

are called the concentration control coefficient of enzyme j acting on metabolite i and the flux control coefficient of enzyme j acting on flux k, respectively.

Homogeneous Functions

A function is homogeneous of degree n in a region R if, and only if, for (x,y) in R and for every positive value t, $f(tx,ty) = t^n f(x,y)$.

Euler provided a theorem about homogeneous functions which states that if a function $f(x,y)$ is continuous, has a continuous derivative, and is homogeneous of degree n in a region R then

$$f_x(x,y)x + f_y(x,y)y = nf(x,y). \tag{5}$$

Homogeneous Functions

A useful modification of Euler's theorem is that if

$$f(tu_1,\ldots,tu_k,u_{k+1},\ldots,u_r) = t\,f(u_1,\ldots,u_r) \tag{6}$$

then

$$f = \sum_{i=1}^{k} u_i \frac{\partial f}{\partial u_i} + \phi \sum_{i=k+1}^{r} u_i \frac{\partial f}{\partial u_i} \tag{7}$$

which means that arguments $k+1$ through r can be ignored when applying Euler's theorem about homogeneous functions.

Summation Theorems

Under the unique steady-state assumption stated earlier,

$$\sum_{j=1}^{M} S_{ij} \upsilon^j(e^j, x'_1, \ldots, x'_N, p_1, \ldots, p_k) = 0, \quad i = 1, \ldots, N \tag{8}$$

has only one solution at NESS. Call the solution $x_i(e^1, \ldots, e^M, p_1, \ldots, p_k)$.

Similarly, $y_i(te^1, \ldots, te^M, p_1, \ldots, p_k)$ is the solution of

$$\sum_{j=1}^{M} S_{ij} \upsilon^j(te^j, y'_1, \ldots, y'_N, p_1, \ldots, p_k) = 0, \quad i = 1, \ldots, N. \tag{9}$$

CCC Summation Theorem

By assumption, υ^j is homogeneous of degree 1 in e^j. Therefore, (9) is equivalent to (8) for all $t \neq 0$. This means that x_i is homogeneous of degree 0 in $e^1, \ldots, e^M$.

$$e^1 \frac{\delta x_i}{\delta e^1} + \cdots + e^M \frac{\delta x_i}{\delta e^M} = 0, \tag{10}$$

$$\sum_{j=1}^{M} C_j^{x_i} = 0, \quad i = 1, \ldots, N \tag{11}$$

Equation (11) is known as the summation theorem for concentration control coefficients.

FCC Summation Theorem

Similarly, one can show that the steady-state flux J^j is homogeneous of degree 1 in $e^1, \ldots, e^M$ at NESS and derive the summation theorem for flux control coefficients.

$$\sum_{i=1}^{M} C_i^{J^j} = 1, \quad j = 1, \ldots, M. \tag{12}$$

Connectivity Theorems

Taking the total differentials at steady-state of υ^j, J^j, and x_i and dividing through by υ^j, J^j, and x_i, respectively,

$$\frac{d\upsilon^j}{\upsilon^j} = \frac{de^j}{e^j} + \sum_{i=1}^{N} \varepsilon_i^j \frac{dx_i}{x_i}, \tag{13}$$

$$\frac{dJ^j}{J^j} = C_1^{J^j} \frac{de^1}{e^1} + \cdots + C_M^{J^j} \frac{de^M}{e^M}, \tag{14}$$

$$\frac{dx_i}{x_i} = C_1^{x_i} \frac{de^1}{e^1} + \cdots + C_M^{x_i} \frac{de^M}{e^M}. \tag{15}$$

$$\frac{dJ^j}{J^j} = -\sum_{i=1}^{N}[\sum_{k=1}^{M} C_k^{J^j} \varepsilon_i^k] \frac{dx_i}{x_i} = 0, \quad j = 1, \ldots, M \tag{16}$$

$$\frac{dx_i}{x_i} = -\sum_{j=1}^{N}[\sum_{k=1}^{M} C_k^{x_i} \varepsilon_j^k] \frac{dx_j}{x_j}, \quad i = 1, \ldots, N, \tag{17}$$

$$\sum_{k=1}^{M} C_k^{J^j} \varepsilon_i^k = 0, \quad i = 1, \ldots, N, \tag{18}$$

$$\sum_{k=1}^{M} C_k^{x_i} \varepsilon_j^k = -\delta_{ij}. \tag{19}$$

Since $\mathbf{J}^e = \mathbf{0}$ implies $dJ^j = 0$. The last two equations are known as the connectivity theorems for flux control coefficients and concentration control coefficients, respectively.

Relationship Between BCT and MCT

The basic equations of BCT are

$$\sum_{j=1}^{M} S_{ij} J_*^j = -\phi_i^{ext}, \tag{20}$$

$$\sum_{j=1}^{M} (\Delta G^j - \Delta\pi_{ext}^j) K_{ji} = 0 \tag{21}$$

If $e_*^m \longrightarrow e_*^m + \delta e^m$ then

$$\sum_{j=1}^{M} S_{ij} \frac{\delta J_*^j}{\delta e^m} = 0, \tag{22}$$

$$\sum_{m=1}^{M} \sum_{j=1}^{M} S_{ij} J_*^j C_m^{J^j} = \sum_{j=1}^{M} S_{ij} J_*^j (\sum_{m=1}^{M} C_m^{J^j}) = 0, \tag{23}$$

$$C_m^{J^j} = \frac{e_*^m}{J_*^j} \frac{\delta J^j}{\delta e^m} \tag{24}$$

which, if there are no external fluxes, implies

$$\sum_{m=1}^{M} C_m^{J^j} = 1. \tag{25}$$

Research Proposals

MCA provides important insights into large-scale biochemical reaction networks. However, its relation to nonequilibrium thermodynamics has not been made clear. There exists a strong parallel within the linear algebra of BCT and MCT. Developing a unifying representation for these methods would be very interesting and could strengthen both methods.

Further work could be done in the optimization of these networks by using the characteristics of the $\mathbf{S}$ matrix, by including concentration clamping, and by finding ways to determine properties such as rate-limiting steps and internal loops.

It would be interesting to study these networks using topology and graph theory. Attempts have been made, for example, using Petri nets, but the nonlinear aspect of reaction networks were not captured. Creating matroid representations could be beneficial.

References

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