Available online at www.sciencedirect.com
ScienceDirect
Physica A 378 (2007) 573–582
PHYSICA A
www.elsevier.com/locate/physa

New network architecture for stoichiometrically, thermodynamically and kinetically balanced metabolic reaction systems

Ilie Fishtik*, Ravindra Datta

Department of Chemical Engineering, Worcester Polytechnic Institute, Worcester, MA 01609-2280, USA

Received 16 July 2006
Available online 27 December 2006

Abstract

The conventional way of assembling the metabolic reactions into networks by placing the metabolites on the nodes and associating the edges with reactions is shown to violate the mass balance, thermodynamics and kinetics. A new type of metabolic networks referred to as reaction route (RR) networks is discussed. The distinct feature of the RR networks is that both the nodes and edges are subject to mass balance, thermodynamic and kinetic constraints. To satisfy these constraints, it is necessary to introduce two different types of nodes. One of these, referred to as terminal nodes, satisfy the mass balance conditions for external metabolites. The other type of nodes, referred to as intermediate nodes, satisfy the quasi steady-state conditions for internal metabolites. It is further required that every cycle in the network be thermodynamically consistent in that the sum of affinities (Gibbs free energy changes) of the reactions comprising the cycle should add up to zero. A balanced RR metabolic network possesses a remarkable property, namely, every conceivable walk between two terminal nodes involves a sequence of metabolic reaction steps that produce an overall reaction (OR), i.e., a reaction comprising only external metabolites. A key result is that many metabolic reaction networks may be balanced if and only if the network is allowed to be infinite and periodic.

Keywords: Reaction routes; Reaction route networks; Metabolic networks

1. Introduction

The term ''reaction network'' is used in a variety of contexts in the study of complex chemical and biochemical systems. The most common usage, of course, is in graphical depiction of the underlying chemistry [1]. In depicting the metabolic reaction networks, invariably, the metabolites are individually located at the nodes that are interconnected via arrows representing reactions [2,3]. Such schematics of metabolic reaction networks are no doubt invaluable tools in visualizing and comprehending various structural and topological aspects of complex biochemical systems. However, due to a lack of accepted guidelines or organizing principles for such graphical representations, the topology of the network is usually left largely to the artistic

*Corresponding author. Tel.: +1 508 8315445; fax: +1 508 8315853.
E-mail address: ifishtik@wpi.edu (I. Fishtik).

0378-4371/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.physa.2006.12.031

flair of the investigators. For instance, a monomolecular reaction, i.e., a reaction of the type $A \rightarrow B$, is typically depicted as two nodes representing the species A and B connected via an edge depicting the reaction. For reactions involving three or more species, however, such graphical representation becomes jumbled and, usually, requires bipartite or, even, tripartite graphs [4]. In practical applications, metabolic reaction networks are used as weighted networks, that is, the edges (reactions) are associated with various physicochemical characteristics of the reactions, e.g., fluxes (rates) or affinities (Gibbs free energy changes). If so, weighted metabolic reaction networks should satisfy certain fundamental physicochemical principles, namely, mass balance for external metabolites, path independence of the reaction affinities and quasi-steady state (QSS) conditions for internal metabolites. This aspect of the metabolic reaction networks is especially important in connection with the metabolic flux analysis (MFA) [3]. Apart from the trivial case of metabolic reaction networks involving only monomolecular reactions, the conventional metabolic reaction networks, as shown below, are not balanced in that the weighted networks violate these mass balance and thermodynamic constraints.

In this communication, we show how the reaction route (RR) network approach recently developed by us [5–7] may be extended to construct balanced and, consequently, thermodynamically and kinetically consistent metabolic reaction networks.

2. Notation and general theoretical considerations

We consider the general case of a metabolic reaction system comprising p reaction steps s_ρ $(\rho = 1, 2, \ldots, p)$. The species involved in the reaction steps are divided into l internal metabolites $\mathrm{I}_1, \mathrm{I}_2, \ldots, \mathrm{I}_l$ (alternatively, intermediate species) of which q are independent, and n external metabolites (reactants and products) T_1, $\mathrm{T}_2, \ldots, \mathrm{T}_n$. Thus, the reaction steps may be presented as

$$s_\rho\colon \sum_{k=1}^{l} \alpha_{\rho k} \mathrm{I}_k + \sum_{i=1}^{n} \beta_{\rho i} \mathrm{T}_i = 0 \quad (\rho = 1, 2, \ldots, p). \tag{1}$$

By convention, the stoichiometric coefficients of the internal metabolites $\alpha_{\rho k}$ $(\rho = 1, 2, \ldots, p; k = 1, 2, \ldots, l)$ and external metabolites $\beta_{\rho k}$ $(\rho = 1, 2, \ldots, p; i = 1, 2, \ldots, n)$, are assumed to be positive for products and negative for reactants. Each of the reaction is characterized by its rate r_ρ $(\rho = 1, 2, \ldots, p)$ and affinity A_ρ $(\rho = 1, 2, \ldots, p)$ that are given by

$$r_\rho = \vec{r}_\rho - \overleftarrow{r}_\rho, \tag{2}$$

$$A_\rho / RT = \ln \frac{\vec{r}_\rho}{\overleftarrow{r}_\rho}, \tag{3}$$

where $\vec{r}_\rho$ and $\overleftarrow{r}_\rho$ are the rates of the forward and backward reactions.

The theory of RRs is rooted in the mathematical description of the QSS assumption for internal metabolites, i.e.,

$$\boldsymbol{\alpha}^{\mathrm{T}} \mathbf{r} = \mathbf{0}, \tag{4}$$

where $\boldsymbol{\alpha} = [\alpha_{\rho k}]$ $(\rho = 1, 2, \ldots, p; k = 1, 2, \ldots, l)$ is the stoichiometric submatrix of the internal metabolites and $\mathbf{r}$ is the reaction rate vector $\mathbf{r} = (r_1, r_2, \ldots, r_p)^{\mathrm{T}}$. It was Horiuti [8] who first observed that Eq. (4) may be elegantly reformulated in terms of the concept of stoichiometric number σ and RR. He defined a RR as a linear combination of the reaction steps $\sum_{\rho=1}^{p} \sigma_\rho s_\rho$ such that all internal metabolites are cancelled thus producing an overall reaction (OR), i.e., a reaction involving only external metabolites. Depending upon the type of the produced OR one may further distinguish between full RRs, or, shortly, full routes (FRs) and empty RRs, or, shortly, empty routes (ERs). More specifically, a FR produces a stoichiometrically distinct OR while an ER produces a so-called "zero" OR, i.e., an OR in which the stoichiometric coefficients of the external metabolites are equal to zero. The number m of linearly independent RRs is determined by the Horiuti–Temkin theorem, according to which $m = p - \operatorname{rank} \boldsymbol{\alpha} = p - q$ (9). A set of linearly independent RRs, that is, a set of m vectors of stoichiometric numbers may be determined by solving the following system of