International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252

A Matrix Factorization Approach to Network Model Reduction

Munyabugingo Valens[1]
[1]*General courses department, Rwanda polytechnic, integrated polytechnic regional college Ngoma, Kibungo, P.O. Box35 KIBUNGO, Country (Rwanda)*

Submitted: 10-06-2021 Revised: 23-06-2021 Accepted: 26-06-2021

ABSTRACT
The purpose of this paper is to understand matrix factorization theory and to be able to apply them to chemical reaction networks for network reduction. After necessary descriptions on chemical reaction networks, in particular, metabolic networks, and brief review on metabolic balancing and flux mode analysis using elementary flux modes (EFMs) we give the motivation for structure and property preserved network model reduction. The paper presents some insights on geometry and numerical computations of matrix factorization such as the traditional SVD and QR method as well as Link matrix factorization in conservation analysis. The paper deals with matrix factorization based reduction technique applied to the problems arising in parameter sensitivity analysis of the dynamical system from chemical reaction networks, metabolic balancing and EFMs in flux mode analysis. In particular, a minimal number reduction of internal reversible reactions is proposed in the last mentioned problem. Numerical examples are given for illustration.

Keywords: Metabolism**,**Stoichiometric matrix, orthogonal factorization, link matrix, elementary flux mode.

I. INTRODUCTION

The term metabolism comes from the Greek word meatball. It means change. A metabolic network is the complete set of metabolic and physical processes that determine the physiological and biochemical properties of a cell. As such, these networks comprise the chemical reactions of metabolism, the metabolic pathways, as well as the regulatory interactions that guide these reactions ([15]). The study of metabolism has changed drastically during the last century, [28]. There is a large variety of research activities within biochemical networks, in particular on computational efficiency. "The activity in a biochemical networks often conserves certain molecular subgroups. Each conserved subgroup contains several molecular species, and the total mass of the species is conserved as the species move around closed loops in the network. The subgroups are called conserved moieties or simply moieties.
Other examples include nicotinamide adenine dinucleotide(NAD)/nicotinamide adenine
dinucleotide hydride(NADH), coenzyme A(CoA)/ Acetyl coenzyme A (Acetyl-CoA), and phosphorylated/ unphosphorylated protein. The total amount of each moiety is determined by the initial conditions" ([13]).
In the complete set of chemical reactions (metabolism) that occur in the smallest unities in biology called cells of an organism, nutrients supplied by the environment are transformed into energy and molecular building blocks. Stoichiometry is a fundamental computation of relative quantities of reactants and products in chemical reactions and is founded on the law of conservation of mass where the total mass of the reactants equals the total mass of the products leading to the insight that the reactions among quantities of reactants and product typically form a ration of positive integers.

Mathematical modeling is a very powerful tool in physics, chemistry, and engineering for interpretation and prediction of natural phenomena and experimental results [9]. It is the method of simulatingreal-life situations with mathematical equations to forecast their future behavior. Mathematical modelof metabolism is used to analyze its properties and capabilities of metabolic networks or to identify suitable targets for that metabolic engineering. A mathematical model is always a simplification of the actual phenomenon and it is therefore possible to establish different mathematical models for the same phenomenon, depending on the objectives of the model and the available measurements [1].

There are two attempts to develop mathematical models for description of metabolism, in contrast to the traditionally followed approach of metabolic modeling using coupled ordinary differential equations and formulation of linear programming problems. Flux balance analysis requires very little

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252

information in terms of the enzyme kinetic parameters and concentration of metabolites in the system.

Its achievement makes two assumptions, steady state and optimality. The first assumption is that the modeled system has entered a steady state, where the metabolite concentrations no longer

change, i.e. in each metabolite node the producing and consuming fluxes cancel each other out.The second assumption is that the organism has been optimized through evolution for some biological goal, such as optimal growth or conservation of resources. The assumption of the steady-state reduces the system to a set of linear equations, which is then solved to find a flux distribution that satisfies the steady-state condition subject to the stoichiometry constraints while maximizing or minimizing the value of the objective function (a pseudo-reaction) representing the conversion of biomass precursors into biomass.

Consider the following dynamical system arising from chemical reaction network described above

$$\frac{dx}{dt} = Sv(x, \kappa)$$

with x being an unknown vector of m-components, S being an $m \times n$ stoichiometric matrix (whose more precise definition is given later) and κ a vector of positive real parameters whose length depends on the specific application.

In general the number of states m will be very large. So it is natural to work on model reduction of such large systems. However, to reduce model is not sufficient. A satisfactory and useful reduction for real world problems should preserve the structure of the original and should capture properties of the original model. This is the objective of the current thesis. Our main focus is on chemical networks, in particular from metabolic networks that mathematically can be characterized by a stoichiometric matrix.

II. MODEL REDUCTION BY MATRIX FACTORIZATION

Now we turn to the stoichiometric analysis and using the network structure to reduce the dimension of networks. We present two methods and their applications in this chapter.

1.1. Orthogonal factorization

TheSVD and QR matrix factorization can be used to remove conservationrelations in the stoichiometric matrix. Theidea is based on [37]. Instead of the link matrix we use the orthogonal matrix Ufrom the SVDor QR factorization of the $m \times n$ stoichiometric matrix S with rank r:

- Using SVD we have the factorization $S = U(\Sigma V^T)$ with $U \in \mathbb{R}^{m\times m}$and $V \in \mathbb{R}^{n\times n}$being orthogonal and $\Sigma \in \mathbb{R}^{m\times n} = (\Sigma_1 \quad 0)$where $\Sigma_1 \in \mathbb{R}^{r\times n}$all components 0 except on the diagonals has. Now partitioning U as follows:

$$U = (L \quad G),$$

Where $L \in \mathbb{R}^{m\times r}$ and $G \in \mathbb{R}^{m\times(m-r)}$.

- Using $QR, SP = QR$ where $Q \in \mathbb{R}^{m\times m}$ is orthogonal, $P \in \mathbb{R}^{n\times n}$ is a permutation matrix and $R \in \mathbb{R}^{m\times n}$ has the form $R = (R_1^T \quad 0)^T$ with $R_1 \in \mathbb{R}^{r\times r}$.This gives the factorization of S inthe form $S = Q(RP^T)$. Partition Q as follows:

$$Q = (L \quad G),$$

Where $L \in \mathbb{R}^{m\times r}$ and $G \in \mathbb{R}^{m\times(m-r)}$.

Apparently the matrices L and G have the following properties due to the orthogonality of $U$and Q

$$L^TL = I_r, G^TG = I_{m-r}, G^TL = 0 \text{ or } L^TG = 0.$$

Let $M = \Sigma V^T$(by SVD) or $M = RP^T$(by QR). Next, we show that we can find a matrix $S_r \in \mathbb{R}^{r\times n}$ such that

$$S = LS_r.$$

In the case of SVD we have

$$S = UM = (L \quad G)\begin{pmatrix}\Sigma_1\\ 0\end{pmatrix}V^T = L(\Sigma_1 V^T).$$

So, we find $S_r = \Sigma_1 V^T$.

In the case of QR we have

$$S = QM = (L \quad G)\begin{pmatrix}R_1\\ 0\end{pmatrix}P^T = L(R_1 P^T).$$

Hence $S_r = R_1 P^T$.

Furthermore we see that the columns of G describes all conservation laws of G since$G^TS = G^TLS_r$.

Applying this factorization to the dynamical system of the network

$$\frac{dx}{dt} = Sv(x, \kappa)$$

where κ is a vector of parameters. Since disturbance of parameters will cause dynamical behavior change, often we want to investigate the sensitivity of steady state and stability properties in terms

of small disturbance of parameter e.g. [21]. It explains why we put another argument in the reaction rate vectors v.

Applying the above factorization of the stoichiometric matrix S we have

$$\frac{dx}{dt} = LS_r v(x, \kappa)$$

which can be reduced to by pre-multiplying $L^T$to this equation and the fact that L is orthogonal:

$$\frac{dz}{dt} = S_r v(x, \kappa)$$

This system has order $r \le min(m, n)$ if we have a system depending only on z. Since L^Thas fewer rows than the columns the variable change $z = L^T x$will not bring back the x by an immediate inversion.

To overcome this difficulty we use the following property from chemical reaction theory [7]: For each concentration vector x_0, the affine space

$$S = x_0 + Im(S)$$

is the stoichiometric compatibility class.

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252

We can prove that $x \in S$ if and only if

$$G^T(x - x_0) = 0 \Leftrightarrow G^T x = G^T x_0.$$

Then for the stoichiometric class determined by $G^T x_0$we have

$$\begin{pmatrix} z \\ G^T x_0 \end{pmatrix} = \begin{pmatrix} L^T x \\ G^T x \end{pmatrix} = \begin{pmatrix} L^T \\ G^T \end{pmatrix} x = U^T x$$

Which yields

$$x = U \begin{pmatrix} z \\ G^T x_0 \end{pmatrix} = Lz + GG^T x_0 \qquad (2.1)$$

Hence we obtained a reduced dynamical system of the network

$$\frac{dz}{dt} = S_r v(Lz + GG^T x_0, \kappa) \qquad (2.2)$$

with the initial condition$z(0) = Lx_0$.

The state vector x obtained by (2.1) is indeed in the stoichiometric class determined by $G^T x_0$ for any r-vector z since

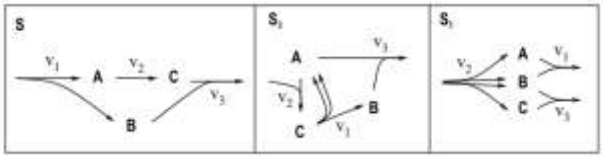
$$G^T x = G^T(Lz + GG^T x_0) = G^T x_0.$$

Above results are taken from [37]. However we can reduce the model further and we show later that such a further reduction benefit some problems in for example calculating steady states, sensitivity analysis and metabolic balancing.

To this end, we take a close look at the equation (2.2). At the steady state we have the equation

$$S_r v(Lz + GG^T x_0, \kappa) = 0$$

Here the matrix



1.2. Link matrix factorizations

We continue exploring the effect of link matrix discussed in the context of model reduction. There is a matrix L_r such that $S = L_r S_r$ where $L_r = (I_r \quad L_0^T)^T$ and L_0 is the link matrix.

Note that subscript r of S stands for the rank of S and subscript r of L stands for row link.

The link matrix $L_r$is also related to the conservation matrix $G = (-L_0 \quad I_{m-r})$. This procedure removes the row redundancy and thus the conservation relations. Therefore the dynamical system and the steady state balance equation are reduced to

$$\frac{dx_{ind}}{dt} = S_r v(Lx_{ind} + C, \kappa),$$

and

$$S_r v(Lx_{ind} + C, \kappa) = 0$$

respectively.

As observed as in the previous section we can reduce the matrix $S_r \in \mathbb{R}^{r \times n}$further if $r < n$. The same principles used for derivation of L_r can be used to represent the dependent columns in S_r. Transpose S_r and partition S_r^T into r independent row S_{rc} and $n - r$ dependent rows which are $L_1^T S_{rc}$ with $L_1 \in \mathbb{R}^{r \times (n-r)}$.

Then

$$S_r^T = \underbrace{\begin{pmatrix} I_r \\ L_1^T \end{pmatrix}}_{L_c^T} S_{rc}^T = L_c^T S_{rc}^T.$$

Hence there are matrices $L_r \in \mathbb{R}^{m \times r}$ and $L_c \in \mathbb{R}^{r \times n}$such that

$$S = L_r S_{rc} L_c,$$

Where$L_r = \begin{pmatrix} I_r \\ L_0 \end{pmatrix}$ and $L_c = (I_r \quad L_1)$.So the dynamical system and the steady state balance equations are reduced to

$$\frac{dx_{ind}}{dt} = S_{rc} L_c v(Lx_{ind} + C, \kappa),$$

And

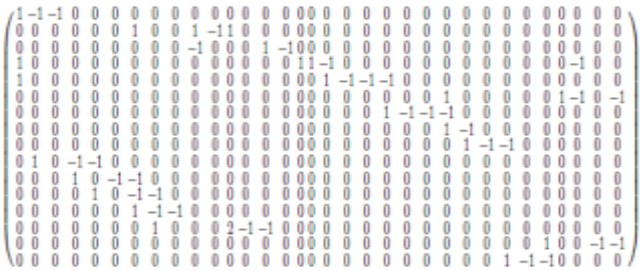
$$L_c v(L_r x_{ind} + C, \kappa) = 0.$$

Since the matrix S_{rc}has full rank. Clearly the steady state balancing depends only on the link matrices, does not depend on S_{rc}.

1.3. Metabolic balancing

We state the problem by an example. Consider the model of Glucose metabolism in bacteria studied in [39].

According to the steady state balancing equation presented in [39] we can write down stoichiometric matrix:



International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252

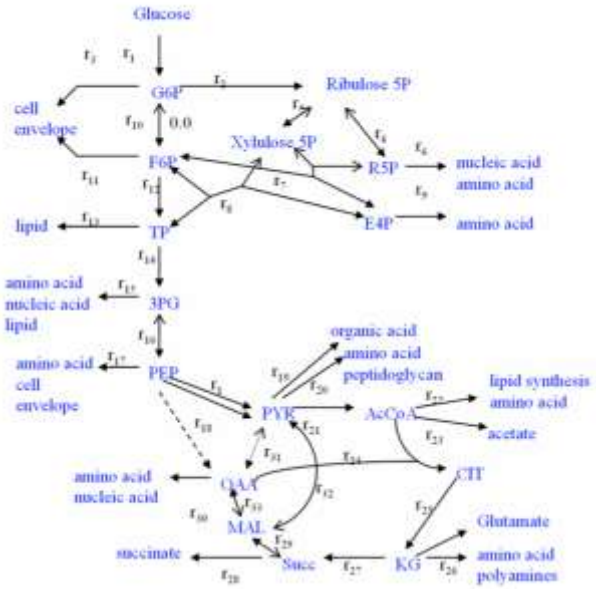


Figure 2.1: Glucose metabolism in bacteria

The rank is 16. So it is a full row rank stoichiometric matrix. A straightforward calculation shows that the columns 1-5, 7-10, 16, 21, 24 to 27 and 29 form a full rank matrix that is the independent part. We only have to find L_c . Moreover $v_3, v_6, v_9, v_{11}, v_{13}, v_{15}, v_{17}, v_{20}, v_{26}$ and v_{30} were derivedfrom cellular mass composition.

In general we split the known and unknown parts in addition to dependent and independent columns so v can be partitioned as

$$v = \begin{pmatrix} v_{ind}^1 \\ v_{ind}^2 \\ v_{dep}^1 \\ v_{dep}^1 \end{pmatrix}$$

wherev^1 and v^2 are known and unknown reaction rates. According to the link matrix factorization

$$(I_r \quad L_1)\begin{pmatrix} v_{ind}^1 \\ v_{ind}^2 \\ v_{dep}^1 \\ v_{dep}^1 \end{pmatrix} = 0 \Leftrightarrow$$

$$\begin{pmatrix} I & 0 & L_{11} & L_{12} \\ 0 & I & L_{21} & L_{22} \end{pmatrix}\begin{pmatrix} v_{ind}^1 \\ v_{ind}^2 \\ v_{dep}^1 \\ v_{dep}^1 \end{pmatrix} = 0$$

Matrix manipulation yields the following

$$\begin{pmatrix} 0 & L_{12} \\ I & L_{22} \end{pmatrix} v^2 = -\begin{pmatrix} I & L_{11} \\ 0 & L_{21} \end{pmatrix} v_1.$$

Next task is to invert the matrix $\begin{pmatrix} 0 & L_{12} \\ I & L_{22} \end{pmatrix}$.

It is much easier to invert this matrix than directly invert $S^{(1)}$by setting $S^{(1)}v_1 = S^{(2)}v_2$ if the inverse exists. In this case it can be done by standard block matrix manipulation. Note that $\begin{pmatrix} 0 & L_{12} \\ I & L_{22} \end{pmatrix}$is invertible if and only if L_{12} is invertible. Now

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252

$$\begin{pmatrix} 0 & L_{22} \\ I & L_{12} \end{pmatrix}^{-1} = \begin{pmatrix} I & -L_{22}L_{12}^{-1} \\ 0 & L_{12}^{-1} \end{pmatrix}.$$

Then

$$\begin{pmatrix} 0 & L_{12} \\ I & L_{22} \end{pmatrix}^{-1} = \begin{pmatrix} -L_{22}L_{12}^{-1} & I \\ L_{12}^{-1} & 0 \end{pmatrix}.$$

Hence

$$v^2 = -\begin{pmatrix} -L_{22}L_{12}^{-1} & I \\ L_{12}^{-1} & 0 \end{pmatrix}\begin{pmatrix} I & L_{11} \\ 0 & L_{21} \end{pmatrix} v^1$$
$$= -\begin{pmatrix} -L_{22}L_{12}^{-1}v_{ind}^1 + (L_{21} - L_{22}L_{12}^{-1}L_{21})v_{dep}^1 \\ -L_{22}L_{12}^{-1}v_{ind}^1 + L_{12}^{-1}v_{dep}^1 \end{pmatrix}.$$

In general L_{12} is not invertible or not square. Then we can use the pseudoinverse for block matrix. Indeed we made use of the Schur complement in computation of the inverse above. Now we use the generalized Schur complement to determine the inverse for non-square or singular matrix L_{12}.

Let $M = \begin{pmatrix} A & B \\ C & D \end{pmatrix}$ of $(p+r)\times(q+s)$ where $A$is $p\times q$, $B$is $p\times s$, C is $r\times q$ and D is $r\times s$.

First we treat the case where$D \in \mathbb{R}^{r\times s}$ with $r \geq s$ and the rank of D is s then $D^+D = I_s$. It follows that

$$M = \begin{pmatrix} A & B \\ C & D \end{pmatrix}$$
$$= \begin{pmatrix} I_p & BD^+ \\ 0_{r\times p} & I_r \end{pmatrix}\begin{pmatrix} A - BD^+C & 0_{p\times s} \\ C & D \end{pmatrix}$$

So the linear system

$$\begin{pmatrix} A & B \\ C & D \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} u \\ v \end{pmatrix}$$

becomes a block triangular system and if $p \geq q$ and rank of$A - BD^+C$ is q we have

$$x = (A - BD^+C)^+(u - BD^+v)$$
$$y = D^+(v - Cx).$$

Next we deal with the case$D \in \mathbb{R}^{r\times s}$ with $r \leq s$ and the rank of D is r. Then $D^+D = I_r$ and

$$M = \begin{pmatrix} A & B \\ C & D \end{pmatrix}$$
$$= \begin{pmatrix} A - BD^+C & B \\ 0_{r\times q} & D \end{pmatrix}\begin{pmatrix} I_q & 0_{q\times s} \\ D^+C & I_s \end{pmatrix}.$$

The system

$$M^T\begin{pmatrix} x' \\ y' \end{pmatrix} = \begin{pmatrix} u' \\ v' \end{pmatrix}$$

is transformed to a block triangular system and if $p \leq q$ and the rank of $(A - BD^+C)^T$ is p, we have

$$x' = ((A - BD^+C)^T)^+(u' - (D^+C)^T v')$$
$$y' = (D^T)^+(v' - B^T x').$$

Let us return to the example from [39]. Now $L_c$in decomposed form is

$$L_c = \left(\begin{array}{cccccccc|cccccccc}
1 & 2 & 1 & 2 & 0 & -1 & 1 & & -4 & -1 & 1 & -1 & -1 & -1 & 0 & -1 & 0 & -1 \\
0 & -1 & 1 & -1 & 0 & 0 & 0 & & -1 & 2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & -1 \\
\hline
0 & 0 & 0 & 0 & 0 & -1 & 1 & & 0 & 0 & 1 & -1 & -1 & -1 & 0 & -1 & 0 & -1 \\
-1 & -2 & -1 & -2 & 0 & 0 & 0 & & 4 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-1 & -1 & 0 & -1 & 0 & 0 & 0 & & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -1 & -1 & -1 & 0 & 0 & 0 & & 3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -1 & 0 & -1 & 0 & 0 & 0 & & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -1 & 0 & 0 & 0 & 0 & & 2 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 & & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 1 & -1 & & 0 & 0 & -2 & 1 & 1 & 1 & 0 & 0 & 0 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & & 0 & 0 & 0 & 0 & -1 & -1 & 0 & -1 & 0 & -1 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & -1 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & -1 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & -1 & -1
\end{array}\right)$$

$$v_1 = \left(\underbrace{r_3, r_9, r_{26}}_{v_{ind}^1}, \underbrace{r_6, r_{11}, r_{13}, r_{15}, r_{17}, r_{20}, r_{30}}_{v_{dep}^1}\right)^T$$

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252

$$v_{ind}^2 = (r_1, r_2, r_4, r_5, r_7, r_8, r_{10}, r_{16}, r_{21}, r_{24}, r_{25}. r_{27}, r_{29})^T$$
$$v_{dep}^2 = (r_{12}, r_{14}, r_{18}, r_{19}, r_{22}, r_{23}, r_{28}, r_{31}, r_{32}, r_{33})^T$$

Solving the following equation

$$\left(\begin{array}{ccc|ccccccc} 1 & 0 & 0 & 1 & 2 & 1 & 2 & 0 & -1 & 1 \\ 0 & 1 & 0 & 0 & -1 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \hline 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 \\ 0 & 0 & 0 & -1 & -2 & -1 & -2 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & -1 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & -1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{array}\right) v^1$$

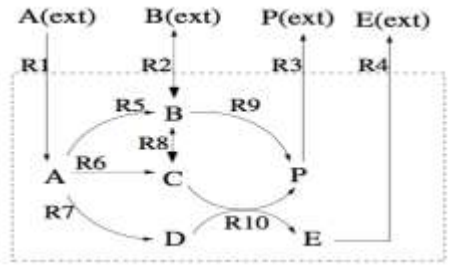
yields the unknown flux distribution

$v_2 = (0.673767, 0.468767, 0.874589, 0.405822,$
$0.022411, 0.383411, 0.606263, 0.0422099,$
$0.60263, 0.209075, 0.209075, 0.498717, 0.289642,$
$0.699574, 0.886737, 0.757197, 0.799407, 0.196777,$
$0.196777, 0.788358, 0.67788, 0.178955, 0.899045)$

1.4. Networks with equivalent steady state

In our reduction procedure we have seen that the full rank matrix S_{rc} does not play any role for analysis of steady state balancing. It depends only on the left and right nullspace of the stoichiometric matrix. In other words the nullspaces of the link matrices L_r and L_c. We demonstrated this by a small network. Now let us study a network from [19]:

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252



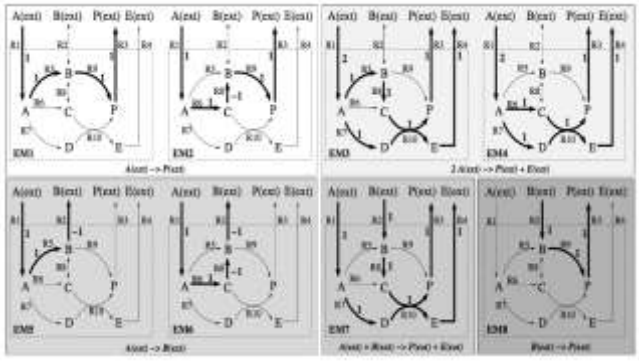
The stoichiometric matrix of this network is

$$\begin{array}{c} \\ A \\ B \\ C \\ D \\ E \\ P \end{array} \begin{array}{c} \begin{array}{cccccccccc} R1 & R2 & R3 & R4 & R5 & R6 & R7 & R8 & R9 & R10 \end{array} \\ \begin{pmatrix} 1 & 0 & 0 & 0 & -1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 1 & 0 & 0 & -1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & -1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & -1 \\ 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 1 & 1 \end{pmatrix} \end{array}$$

efmtool gives 8 EFMs:

$$\begin{array}{c} \\ R1 \\ R2 \\ R3 \\ R4 \\ R5 \\ R6 \\ R7 \\ R8 \\ R9 \\ R10 \end{array} \begin{array}{c} \begin{array}{cccccccc} EM2 & EM7 & EM6 & EM4 & EM3 & EM8 & EM1 & EM5 \end{array} \\ \begin{pmatrix} 1 & 1 & 1 & 2 & 2 & 0 & 1 & 1 \\ 0 & 1 & -1 & 0 & 0 & 1 & 0 & -1 \\ 1 & 1 & 0 & 1 & 1 & 1 & 1 & 0 \\ 0 & 1 & 0 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 1 & 1 \\ 1 & 0 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 1 & 0 & 0 & 0 \\ -1 & 1 & -1 & 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 1 & 1 & 0 \\ 0 & 1 & 0 & 1 & 1 & 0 & 0 & 0 \end{pmatrix} \end{array}.$$

Note that the ordering of the EFMs follows the conversion in [19] that is by the net conversion of external metabolites. In the figure (adapted from [19]) they are grouped by the net conversion of external metabolites (bottom of each box) as indicated by different gray background levels.



The stoichiometric matrix has rank 6. So there is no linearly dependent rows. So we try to findthe link matrix for the columns. Obviously columns 1, 2, 3, 4, 6, and 10 are linearly independent so We re-organized the columns so that

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252

$$S = \begin{pmatrix} 1 & 0 & 0 & 0 & -1 & 0 & -1 & 0 & 0 & -1 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & -1 & -1 & 1 \\ 0 & 0 & 0 & 0 & 1 & -1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 & 1 & 0 & 0 & 1 & 0 \end{pmatrix}$$

where column 5 is R_6, column 6 is R_{10} and column 10 is R_5. The others remain unchanged. Now we choose

$$S_{rc} = \begin{pmatrix} 1 & 0 & 0 & 0 & -1 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & -1 & 0 & 1 \\ 0 & 0 & -1 & 0 & 0 & 1 \end{pmatrix}$$

And

$$L_c = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & -2 & 1 & 0 & -1 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & -1 & -1 & 1 \\ 0 & 0 & 1 & 0 & 0 & 0 & -1 & 0 & -1 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & -1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \end{pmatrix}$$

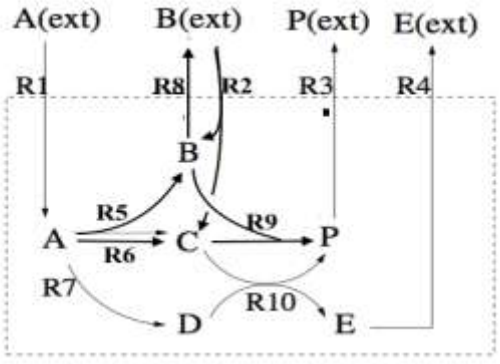
Now any nonsingular matrix S_{rc} with the link matrix L_c will result in a new network which is equivalent to the one we started with.

For example

$$S_{rc} = \begin{pmatrix} 1 & 0 & 0 & 0 & -1 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & -1 & 0 & 1 \\ 0 & 0 & -1 & 0 & 0 & 1 \end{pmatrix}$$

Then the network has stoichiometri matrix

$$S = \begin{pmatrix} 1 & 0 & 0 & 0 & -1 & 0 & -1 & 0 & 0 & -1 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & -1 & -1 & 1 \\ 0 & 0 & 0 & 0 & 1 & -1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 & 1 & 0 & 0 & 1 & 0 \end{pmatrix}$$



1.5. A case study on model reduction in flux mode analysis

The idea comes from model reduction in control theory. Roughly speaking we try to get a minimal model for a given input/output description (external description). It is not necessary that a model we find from the external description should completely agree with the internal model. This gives us more freedom to choose model as far as the input/output description is satisfied. In this section we try to analyze if such an idea can be used in the network problem at hand with aim to reduce computation time.

As proved earlier any stoichiometric matrices having same left and right nullspaces are equivalent

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252

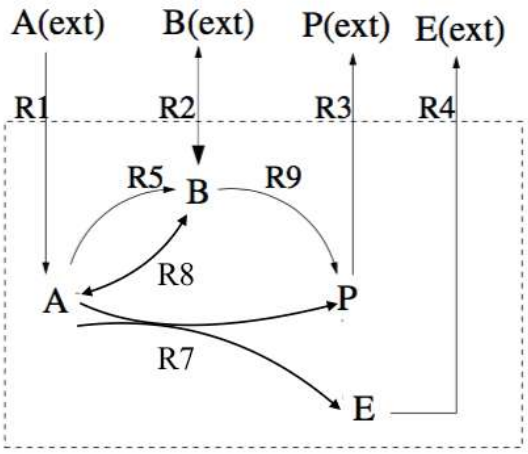
and the full rank matrix S_{rc} plays no roll. Thus we can use any full rank matrix together with the link matrices to generate equivalent networks. However if the rank of this matrix is dropped, thus the original matrix, then the nul spaces are enlarged and the network is reduced to a smaller size. The aim of this section is to examine if this can be applied to flux mode analysis.

We begin with the network studied in the previous section, taken from [19]. There are four exchange reactions R_1, R_2, R_3 and R_4 the others are internal. We have chosen S_{rc} with the tions R_1, R_2, R_3, R_4, R_6 and R_{10} as independent part. Thus it includes two internal reactions R6 and R_{10}. Intuitively if we want to have the network as small as possible. In our case the maximal number of reactions that can be possibly eliminated are two, i.e. R_6 and R_{10} with the particular choice of S_{rc}. In this sense the network we obtain will be minimal since the other reactions in S_{rc} have external connections.

Now setting the columns 5 and 6 in S_{rc} to zero and call the new matrix as $\bar{S}_{rc}$. Define now the stoichiometric matrix S as we have done for generating equivalent networks using the link matrices. In this example it is

$$\bar{S} = \bar{S}_{rc} L_c = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 & -2 & 1 & 0 & -1 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & -1 & -1 & 1 \\ 0 & 0 & 1 & 0 & 0 & 0 & -1 & 0 & -1 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & -1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \end{pmatrix}$$

From this matrix we see two internal spices C and D are eliminated and the other reactions remain unchanged, and R_6 and R_8 in the original model are merged into a single reaction R8 in the reduced one, likewise R_7 and R_{10} are merged to a single tion R_7. In particular the exchange species are consistent with the original network. The network topology is shown in the figure below.Next we analyze flux modes by such reductions. We compute EFMs using efmtool to compare with theoriginal model.



I. All the reactions are reversible. Then efmtoolfinds 44 EFMs and the reduced network 6 EFMs.

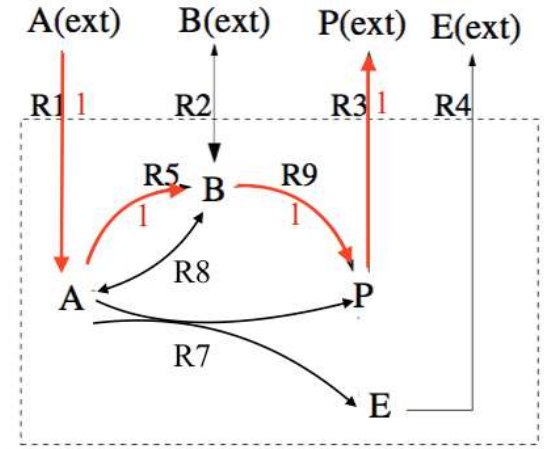
II. If the exchange reactions are irreversible and all others are reversible. efmtool gives 16 and 7 EFMs for the original and the reduced network respectively.

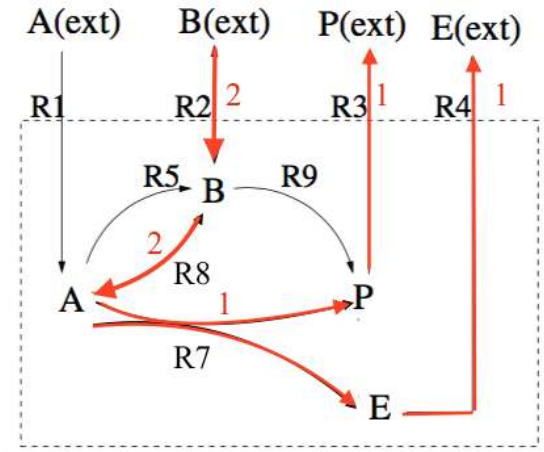
These results indicate that the amount of EFMs are decreased significantly when the internal reversible reactions are eliminated. Now we take a close look in this issue.

III. Assume that R_2 (exchange reaction) and R_8 (internal) are reversible, the others are irreversible. We have already obtained the EFMs for the original model. Now we compute EFMs for the reduced network and obtain 7 EFMs.

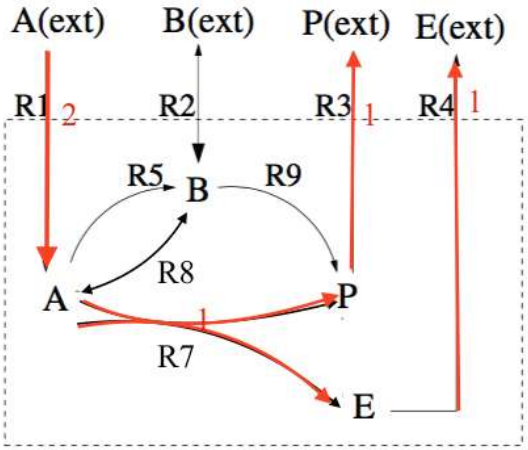
International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252

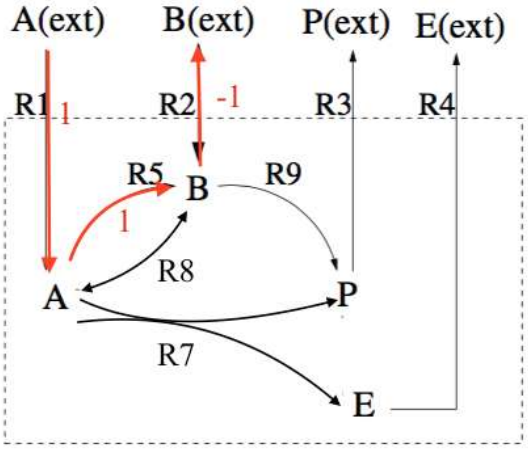
	$EM4$	$EM3$	$EM1$	$EM6$	$EM7$	$EM8$	$EM4$
$R1$	1	0	1	0	0	0	2
$R2$	−1	2	0	0	2	1	0
$R3$	0	1	1	0	1	1	1
$R4$	0	1	0	0	1	0	1
$R7$	0	1	0	0	1	0	1
$R8$	0	2	0	1	0	0	0
$R9$	0	0	1	0	0	1	0
$R5$	1	0	1	1	−2	0	0

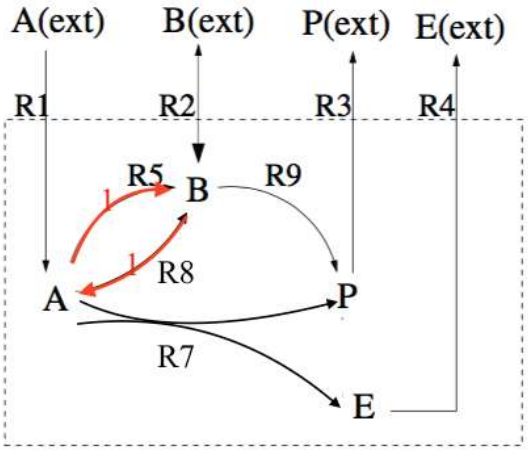




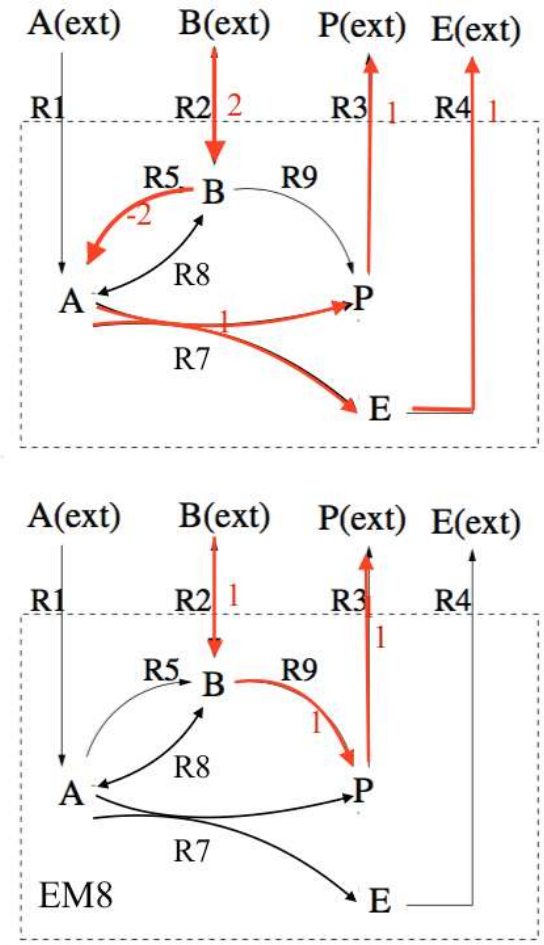
International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252







International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252



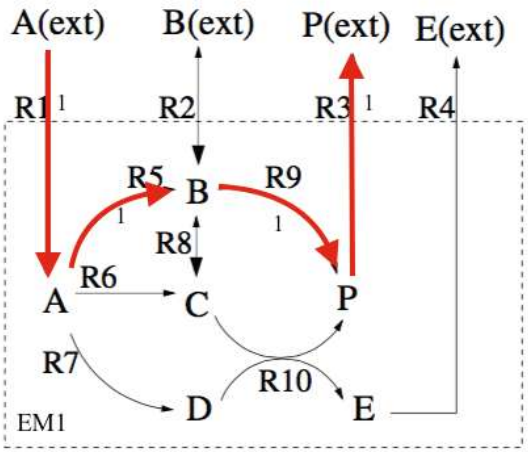
Compare with the EFMs we obtained for the original network we see that the EM1, EM5 and EM8 are identical to the ones in the reduced model. The input/output exchange of EM3 and EM4 in the original model are captured by EM4 in the reduced model. EM3 and EM7 of the reduced network are equivalent and are most likely represent EM7 in the original model. Since there is no R_6 in the reduced model EM2 in the original model should not be found but could be interested by EM1 (from R_1 to R_3). Similar EM6 in the original network would be EM1 in the reduced one. Clearly EM6 in the reduced model is internal and has no counterpart in the original network.

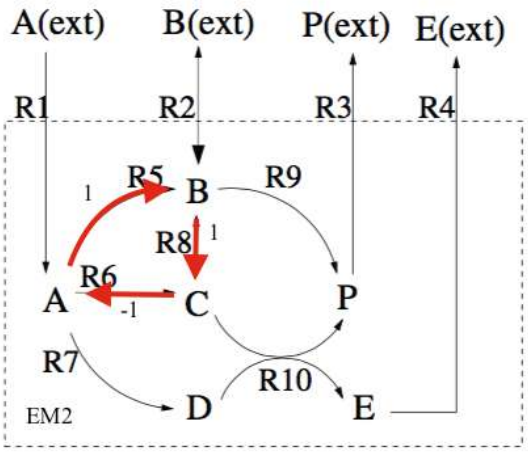
IV. Assume that R_6 and R_{10} (both are internal) are reversible and the others are irreversible then the original model has 7 EFMs:

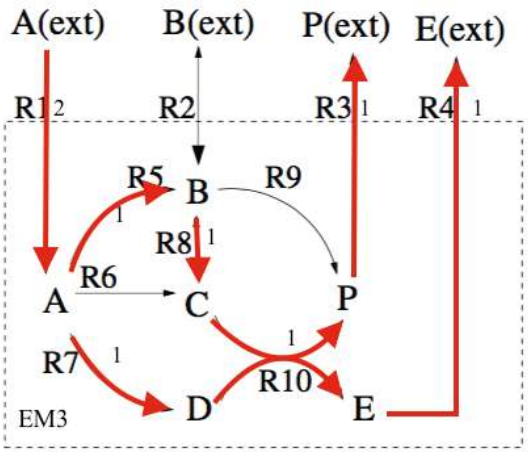
	EM4	*EM5*	*EM6*	*EM3*	*EM7*	*EM1*	*EM2*
R1	2	0	1	2	0	1	0
R2	0	2	1	0	1	0	0
R3	1	1	1	1	1	1	0
R4	1	1	1	1	0	0	0
R6	1	−1	0	0	0	0	−1
R10	1	1	1	1	0	0	0
R7	1	1	1	1	0	0	0
R8	0	2	1	1	0	0	1
R9	0	0	0	0	1	1	0
R5	0	0	0	1	0	1	1

They are shown below.

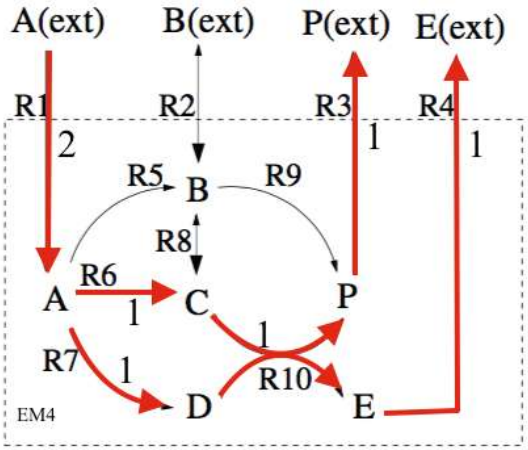
International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252

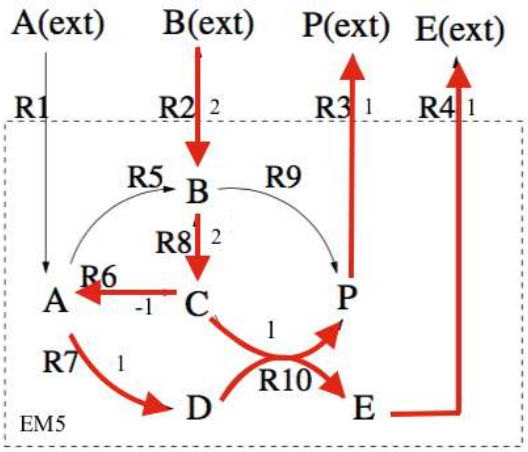


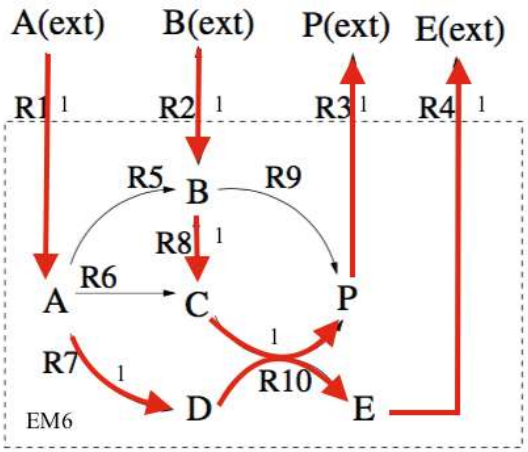




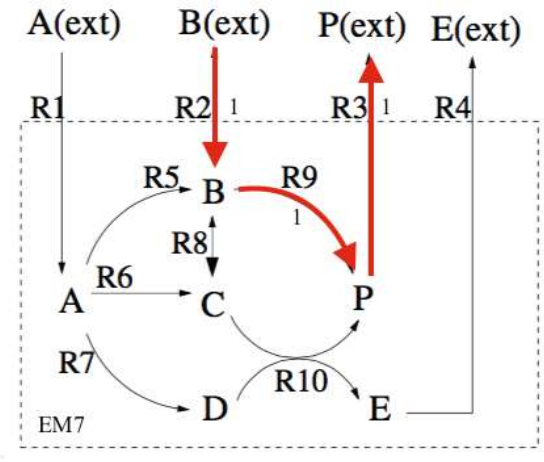
International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252





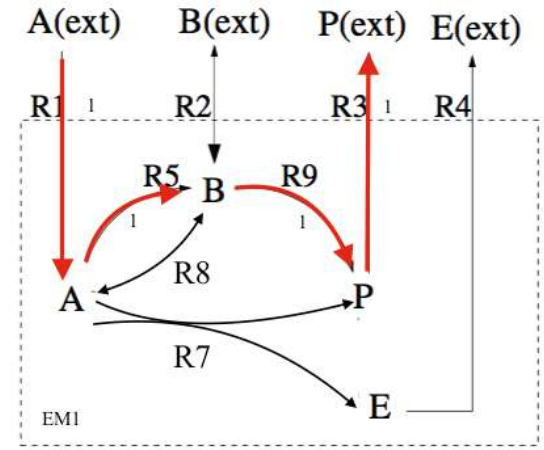


International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252

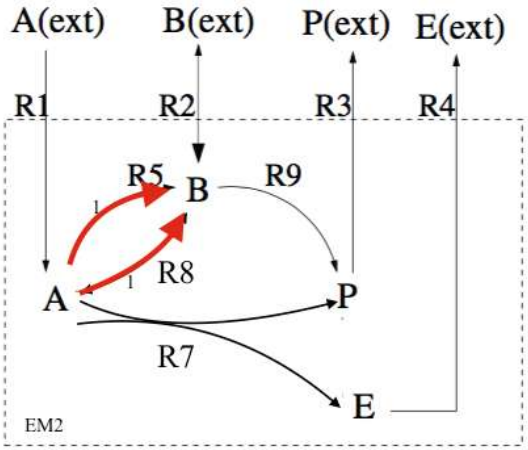


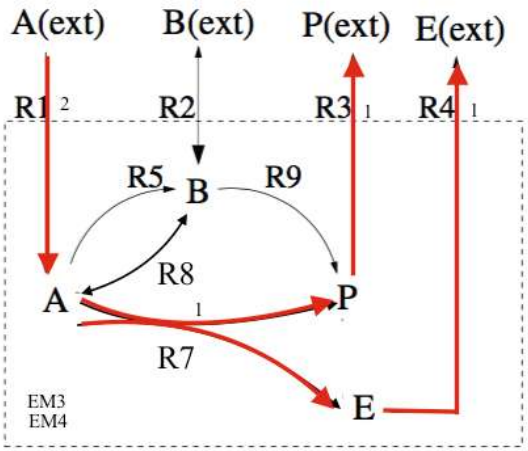
The reduced model with all reactions irreversible has 5 EFMs

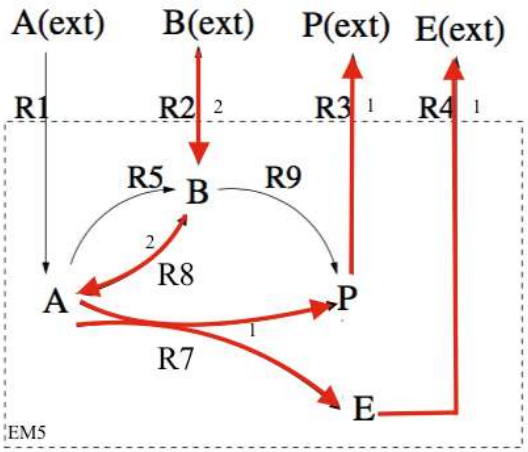
	EM5	*EM1*	*EM7*	*EM3&4*	*EM2*
R1	0	1	0	2	0
R2	2	0	1	0	0
R3	1	1	1	1	0
R4	1	0	0	1	0
R7	1	0	0	1	0
R8	2	0	0	0	1
R9	0	1	1	0	0
R5	0	1	0	0	1



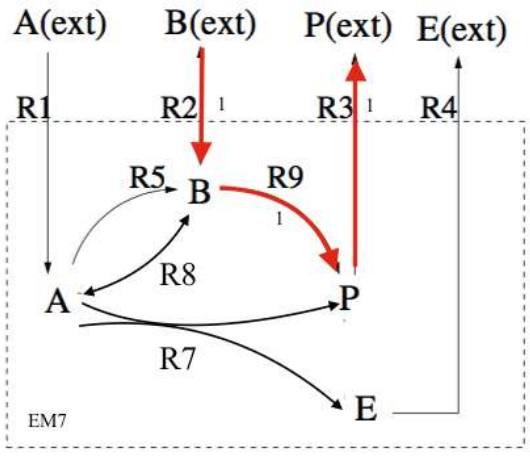
International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252







International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252



Evidently the EFMs agree to each other very well, Means that the method can recover EFMs in a system in which they are already known. EM6 in the original network does not have an elementary mode because this can be obtained by (ME3+ME5)/2 (reduced) which is not elementary. Exploiting the fact that any combination of infeasible EFMs with other infeasible or feasible EFMs is again infeasible[40], and can be removed from the analysis without impacting biologically relevant EFMs.

Overall we saved memory by removing infeasible EFMs and this reduces the time to perform in computation of the EFMs, since only EFMs that are thermodynamically consistent with a given metabolic network are computed. The time saved depends of the number of reactions removed in the network.

1.6. Further discussions and conclusions

The purpose of model reduction investigation is, as described in the Introduction section, the concern of memory usage and computation time. This is the motivation behind this thesis. Our approach to these issues is matrix factorization since the network systems are very often big but sparse. In particular, we investigated the use of the concept Link matrix in study of conservation laws in the following problems, reduction of number of states and thus differential equations when analyzing steady state behavior, parametric sensitivity analysis, metabolic balancing equivalence of steady states and flux mode analysis to reduce the number of elementary flux modes (EFMs) through the network.

In the last mentioned problem we proposed to eliminate the internal reversible reactions using the factorized structure. Note that this technique is inspired by the realization theory in control theory where we are only interested in the input-output model description so to reach a minimal realization and hence to get a smaller model. We worked out some examples taken from the existing research papers in each of these problems to illustrate the idea and our results. Due to the limit of time and computing facilities we only worked on small examples. However the meaning of such an approach can be made clear as argued below. In [22] the core metabolic network in E. coli is discussed in the context of finding functional states. On the webpage http://systemsbiology.ucsd.edu/InSilicoOrganisms/Ecoli/Ecol-Reactions a condensed version of the genome-scale E. coli reconstruction is presented. It contains central metabolic reactions. There are 62 internal reactions, 14 exchange reactions and a biomass objective function. Thus there are 77 reactions. The network has 63 reactants. The rank of the resulting stoichiometric matrix is 57. This means, according to the theory of the conservation laws, we can reduce 6 equations since there are $6(= 63 - 57)$ conservation laws. In other words in this example about 10% of the differential equations are redundant and so they can be safely eliminated from the model by using conservation laws. This has been done in many research papers. However, we carried the reduction procedure further in this thesis by doing sort of column reduction. Let us call this a complete reduction. Now we argue that this further reduction is on the line of the idea for save storage and computational costs. To this end we consider three of the issues we have worked on. Let us first turn to the model reduction discussed earlier where the steady state behavior is reduced to

$v_1^T v(Lz + GG^T x_0, \kappa) = 0$ where

$v = (v_1, v_2), v_1 \in \mathbb{R}^{n\times r}, U = (L, G), L \in \mathbb{R}^{m\times r}$

by SVD.

Consequently we can see, since V_1 is nonsigular that the matrix storage cost can be reducedby storing only L and $GG^T x_0 \in \mathbb{R}^m$, which is $m \times r + m$ instead of the whole S which needs mn. In the

International Journal of Advances in Engineering and Management (IJAEM)
Volume 3, Issue 7 July 2021, pp: 138-157 www.ijaem.net ISSN: 2395-5252

E. coli case $m = 63, n = 77$, it will be 4851 without reduction and 3668 with reduction, respectively.

Hence it results in a reduction of more than 75 percent. Of course we can still argue that the storage cost will be insignificant if the technique for the sparsity is used since the matrix S is sparse. So we next discuss the situation where we compute the sensitivity matrix with reduction, without reduction$\frac{\partial x}{\partial \kappa} =$ tion$\frac{\partial x}{\partial \kappa} = -\left(\frac{\partial v}{\partial x}\right)^{-1}\frac{\partial v}{\partial \kappa}$. It is apparent that the latter needs to compute m^2 partial derivatives while the former r2. In the E. coli case they are 3249 and 3969 respectively. So we save about 81% of computation time for derivations. Now we turn to the study of model reduction to reduce the number of EFMs through the network. The number of EFMs supported by a network increases fast with the size of a network. This leads to the difficulty of using EFM-based analysis for large networks. In this thesis we proposed a reduction technique that preserves all exchange fluxes in order that the interaction between the network and environment is not changed. This was inspired by realization theory in mathematical control theory. If we are not interested in exactly how the interactions in the "blockbox" work but how the input and output behavior is described then we just have to describe this behavior, using as less internal reactions as possible. As a first attempt we tried to eliminate reversible internal reactions since these reactions will be through the whole network in some way. We illustrated the technique by a small example taken from the paper [19] which contains 4 exchange reactions and 6 internal reactions with 6 reactants. It showed that the number of EFMs is reduced from 44 to 6 if all reactions are reversible, indicating that the fast growth of the number of

EFMs with the number of reversible interactions; and the number of EFMs are reduced from 16 to 7

if all internal reaction are reversible and exchange reactions are irreversible; and the number of EFMs are reduced from 7 to 5 if two of the internal reactions reversible and all others are irreversible. For this small example it is not so significant by looking at the absolute numbers. However the first mentioned reduction tells us that, the reduced network has EFMs less than 44% of the original network has, and the second reduction is less than 71% of EFMs of the original network. Hence the reduction is significant even in small problem cases. If a network size is large then the situation will be different apparently. Let us take a close look at the E. coli core model mentioned above. Among the 77 reactions 14 are reversible exchange reactions and the biomass production can be considered as an irreversible exchange reaction. Among the 62 internal reactions, 27 are irreversible and 35 are reversible. The program efmtool yields 2295967 EFMs. So reducing the number of EFMs will be desirable and more significant reduction is expected. By our approach we can eliminate 35 reversible internal reactions and 9 reactants. This will give us a network model with 52 reactants involved in 42 reactions among which 15 are exchange reactions and $27 (= 62 - 35)$ are irreversible internal reactions. Unfortunately we did not have enough time to carry out and verify all the computations and computation results need for this model. It remains as a further research topic. The second drawback in the discussion is that we have no theoretic statements to guarantee a good reduction, say "under what conditions a minimal number reactions is sufficient". This becomes a topic for further investigation. Finally, note that the networks studied in this thesis are basically dynamical systems with polynomials of the state riables $x_1, \ldots, x_n$. So the steady state analysis, for example, determination of number of real steady states can be expected to use Groebner basis, which, we expect, can provide us more insight of the problems we studied here and much more in general for example how parameters will influence the number of steady states. We would like to point out that there are several difficulties in such a study of Groebner basis application, despite its advantage of possibility of qualitativedescription for the parameters. First, the underlying field in our study is the set of the reals which is not closed. This increases difficult level significantly. Next, the computation complexity is very high. This requires a better understanding of the problem structure so to possibly make the computation efficient.

REFERENCES

[1]. Bailey JE: Mathematical modelling and analysis in biochemical engineering: past accomplishments and future opportunities. Biotechnol Prog.1998

[2]. Bj□orck, _A., Numerical Methods for Least Squares Problems. Philadelphia, PA: SIAM, 1966

[3]. Chan T., Rank revealing QR factorizations, Linear Algebra and its Application, 88{89 (1987), pp.67-82.

[4]. Clarke B.L., Stability of Complex Reaction Networks, Vol. 42, Wiley, New York, 1980.

[5]. Davis, T. A. (2011) Algorithm 915, SuiteSparseQR: Multifrontal multithreaded rank- revealing sparse QR factorization. ACM Trans. Math. Softw., 38(1), 8:1?8:22.

[6]. "efmtool" package, Computational systems biology, http://www.csb.ethz.ch/tools/efmtool

[7]. Feinberg M., Chemical reaction network structure and the stability of complex isothermal

reactors{I. The de_ciency zero and de_ciency one theorems. Chem. Eng. Sci., Vol. 42 pp. 2229?68,1987.

[8]. Gagneur J., and Klamt S., Computation of elementary modes: a unifying framework and the new binary approach, BMC Bioinformatics, (2004) 5:175

[9]. Gershenfeld NA: The Nature of Mathematical Modelling. Cambridge: Cambridge University-Press; 1999.

[10]. Golub, G.H. and van Loan, C.F. (2013) Matrix Compuations, John Hopkins University Press,4th ed.

[11]. Groetsch CW, King JT. Matrix methods and applications 1988. Prentice Hall.

[12]. Heinrich R. and Schuster S., The Regulation of Cellular Systems, Chapman and Hall, 1996.

[13]. Henderson N.W. et al, (2016) Conservation analysis of genome-scale biochemical networks,https://pdfs.sema ticscholar.org/f779/d06b9edb4345fd8ecd51e70765243b5aafed.pdf

[14]. Hong Y.P. and Pan C.-T., Rank-Revealing QR Factorizations and the Singular Value Decomposition, Mathematics of computation, 58 (1992) pp. 213-232.

[15]. https://en.wikipedia.org/wiki/Metabolic_network, April 15, 2018

[16]. http://slideplayer.com/slide/9967240/, april 15, 2018

[17]. Kelk S.M., Olivier B.G., Stougie L. and Bruggeman F.J., (2012) Optimal ux spaces of genomescale stoichiometric models are determined by a few subnetworks, Nature, Scienti_c Reports 2 :580 DOI: 10.1038/srep00580

[18]. Klamt S, et al Regensburger G, Gerstl MP, Jungreuthmayer C, Schuster S, Mahadevan R, etal. (2017) From elementary ux modes to elementary flux vectors: Metabolic pathway analysiswith arbitrary linear ux constraints. PLoS Comput Biol 13(4): e1005409. https://doi.org/10.1371/journal.pcbi.1005409

[19]. Stoichiometric and Constraint-based Modeling, in: Systems Modeling in Cellular Biology, Z.Szallasi, J. Stelling and V. Periwal, ed., MIT Press, Cambridge Massachusetts, 2006.

[20]. Poolman M.G., Venakatesh K.V., Pidcock M.K. and Fell D.A., A method for the determination of flux in elementary modes, and its application to Lactobacillus rhamnosus, Biotechnology and Bioengineering, 88 (2004), pp.601{612.

[21]. Reder, C., (1988) Metabolic control theory: a structural approach, J. Theor., 135, 175{201.

[22]. Palsson B. _., Systems Biology: Properties of Reconstructed Networks volume 1, 2006 Cambridge University press.

[23]. Palsson, B.(2006) Systems biology: Properties of reconstructed networks published by Cambridge University press.

[24]. Quek L.-E. and Nielsen L.K. A depth-_rst search algorithm to compute elementary ux modes by linear programming, MC Systems Biology, 2014, 8:94

[25]. Rockafellar R.T., Convex analysis, Princeton University Press, 1970.

[26]. R□ohl A. and Bockmayr A, A mixed-integer linear programming approach to the reduction of genome-scale metabolic networks, Bioinformatics, vol 30, No. 15, 2014, 9197{2203.

[27]. Ruckerbauer DE, Jungreuthmayer C, Zanghellini J. (2015). Predicting genetic engineering targets with Elementary ux mode analysis: a review of four current methods. New Biotechnnol. 1-13.

[28]. Ruppin E, et al., Metabolic reconstruction, constraint-based analysis and game theory to probe genome-scale metabolic networks, Curr Opin Biotechnol (2010), doi: 10.1016/j.copbio.2010.07.002

[29]. Sauro H.M. and B. Ingalls B., Conservation analysis in biochemical networks: computational issues for software writers. Biophys. Chem., 109(1):1{15, April 2004.

[30]. Schuster S., Dandekar T., and Fell D., Description of the algorithm for computing elementary flux modes,Comp. Appl. Biosci. 9 (1993)

[31]. Schuster S., Hilgetag, C., Woods J., and Fell D., Reaction routes in biochemical reaction systems: algebraic properties, validated calculation procedure and example from nucleotide metabolism, J. Math. Biol. 45 (2002) 153{181.

[32]. Stephanopoulos G, Aristidou A. and Nielsen J., Metabolic Engineering, Academic Press, 1998.

[33]. http://mathworld.wolfram.com/FundamentalTheoremofLinearAlgebra.html

[34]. Strang g., introduction to linear algebra, fifth edition, wellesley-cambridge press (2016).

[35]. Tamil E.R. and Thenmozhi M., Computation of elementary ux mode using right null space approach, Volume 11, Number 3 (2016)

[36]. Wagner C., Nullspace approach to determine the elementary modes of chemical reaction systems. J Phys Chem B 2004, 108(7):2425?2431.

[37]. Waldherr, S, A guideline to model reduction by stoichiometric decomposition for biochemical network analysis, 21st International Symposium on Mathematical Theory of Networks and

Systems July 7-11, 2014. Groningen, The Netherlands

[38]. Zanghellini, J, Ruckerbauer D., Hanscho M. and Jungreuthmayer C., Elementary ux modes in a nutshell: Properties, calculation and applications, Biotechnol. J. 2013, 8, 1009{1016

[39]. Zhu, T. , Convex analysis of metabolic network for optimal cell design and ux validation by GC-MS or NMR PhD thesis, University of Pittsburgh, 2003.

[40]. Jol, S. J., Kummel, A., Terzer, M., Stelling, J. Heinemann, M. System-Level Insights into Yeast Metabolism by Thermodynamic Analysis of Elementary Flux Modes. PLoS Comput. Biol. 8,e1002415; DOI:10.1371/journal.pcbi.1002415 (2012).