

# Algorithmic Identification of the Fast Processes in Large Multiscale (Stiff) Models

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**Abstract**—The identification of the fast dissipative processes in a complex multi-scale model is an important step towards the construction of a reduced model. These processes produce the fast time scales, which are responsible for the development of the slow invariant manifold (SIM). We address this issue by examining the stoichiometry of the various processes in the original and the reduced (non-stiff) model, produced by the Computational Singular Perturbation (CSP) method.

## I. INTRODUCTION

Large reaction networks in combustion processes, usually involve both fast and slow reactions. The task of simplification and reduction of the resulting complex multi-scale mathematical models, relies heavily on the proper identification of the fast dissipative reactions. In traditional model reduction procedures, the fast reactions are included in the algebraic relations derived on the basis of the *Quasi Steady State approximation* (QSSA) of certain variables and/or the *Partial Equilibrium approximation* (PEA) of certain reactions, and are removed to provide a non-stiff reduced model. Thus, the success of both methods above rely on the accurate (i) identification of the fast reactions responsible for the development of the dissipative fast time scales and (ii) approximation of the SIM by the algebraic relations delivered by the two methods.

Here, we demonstrate how CSP ([1], [2], [3]) can be used to identify the fast reactions, by examining the stoichiometry of the reactions in the original and the reduced model generated by the method.

First, we provide the mathematical setting of the problem. Next, we review the conditions under which the reduced model obtained with CSP simplifies to the reduced model obtained by the QSSA/PEA [4]. This procedure will help us assess the action of CSP on the stoichiometric vectors of the fast and slow reactions, in the case when QSSA/PEA apply, and will suggest a simple algorithm for the identification of the fast ones. The proposed methodology is applied on a biochemical network, modeling the glycolysis cycle in *saccharomyces cerevisiae* [5]. This model has been already analyzed successfully with the CSP method [6].

## II. MATHEMATICAL SETTING

Consider the evolution of the concentration of  $N$  species, governed by a set of  $N$  first order autonomous

ODEs in dimensional vector form:

$$\frac{d\mathbf{y}}{dt} = \mathbf{g}(\mathbf{y}) \quad (1)$$

where  $\mathbf{y} \in \mathbb{R}^N$  is a vector containing the species concentrations, and  $\mathbf{g}(\mathbf{y}) \in \mathbb{R}^N$  is the nonlinear vector field. We assume that  $\mathbf{g}(\mathbf{y})$  can be cast as:

$$\mathbf{g}(\mathbf{y}) = \mathbf{S}\mathbf{R}(\mathbf{y}) \quad (2)$$

where  $\mathbf{S} \in \mathbb{R}^{N \times K}$  is a constant matrix containing the  $N$ -dimensional stoichiometric column vectors of the  $K$  elementary reactions in the kinetic mechanism, and  $\mathbf{R} \in \mathbb{R}^K$  is vector with the corresponding  $K$  reaction rates;  $\mathbf{S} = [\mathbf{S}_1 \ \mathbf{S}_2 \ \dots \ \mathbf{S}_K]$ ,  $\mathbf{R} = [R^1 \ R^2 \ \dots \ R^K]^T$ .

It is assumed that the dynamics of the nonlinear system (1) exhibit  $M$  fast dissipative time scales, so that a  $(N - M)$ -dim. SIM develops. A measure of the gap between the fast dissipative and the slower time scales is provided by the non-dimensional ratio  $\varepsilon = \tau_M/\tau_{M+1}$ , where  $\tau_M$  denotes the slower of the fast time scales and  $\tau_{M+1}$  the fastest of the slower ones, so that  $0 < \varepsilon < 1$ . The  $n$ -th timescale  $\tau_n$  is approximated as the inverse of the modulus of the  $n$ -th eigenvalue of the  $N \times N$ -dimensional Jacobian matrix,  $\mathbf{J} = \mathbf{S}\nabla\mathbf{R}$ ; i.e.,  $\tau_n = |\lambda_n|^{-1}$ . Following the analysis in Ref. [4], it is assumed that the  $M$  reactions, whose rates are collected in  $\mathbf{R}^M$ , are most responsible for the development of the  $M$  fast time scales. Furthermore, it is assumed that the  $M$  variables in  $\mathbf{y}$  affected the most by the fast dynamics are collected in  $\mathbf{y}^M$ . Accordingly, the following block partitions are introduced:

$$\mathbf{y} = \begin{bmatrix} \mathbf{y}^M \\ \mathbf{y}^{N-M} \end{bmatrix} \quad \mathbf{g} = \begin{bmatrix} \mathbf{g}^M \\ \mathbf{g}^{N-M} \end{bmatrix} \quad \mathbf{R} = \begin{bmatrix} \mathbf{R}^M \\ \mathbf{R}^{K-M} \end{bmatrix} \quad (3)$$

$$\mathbf{S} = \begin{bmatrix} \mathbf{S}_M^M & \mathbf{S}_{K-M}^M \\ \mathbf{S}_M^{N-M} & \mathbf{S}_{K-M}^{N-M} \end{bmatrix} \quad \mathbf{J} = \begin{bmatrix} \mathbf{J}_M^M & \mathbf{J}_{N-M}^M \\ \mathbf{J}_M^{N-M} & \mathbf{J}_{N-M}^{N-M} \end{bmatrix} \quad (4)$$

where  $\mathbf{g}$  and  $\mathbf{J}$  can be expressed as:

$$\mathbf{g}^i = \mathbf{S}_M^i \mathbf{R}^M + \mathbf{S}_{K-M}^i \mathbf{R}^{K-M} \quad (5)$$

$$\mathbf{J}_j^i = \mathbf{S}_M^i \frac{\partial \mathbf{R}^M}{\partial \mathbf{y}^j} + \mathbf{S}_{K-M}^i \frac{\partial \mathbf{R}^{K-M}}{\partial \mathbf{y}^j} \quad (6)$$

where  $i, j = M$  or  $N - M$ . According to the partitions introduced here, the original system can be cast as:

$$\frac{d\mathbf{y}}{dt} = \mathbf{S}_M \mathbf{R}^M + \mathbf{S}_{K-M} \mathbf{R}^{K-M} \quad (7)$$

where  $\mathbf{S}_i = [\mathbf{S}_i^M, \mathbf{S}_i^{N-M}]^T$  ( $i = M$  or  $K - M$ ) are the stoichiometric matrices of the fast and slow reactions, respectively.

### III. THE CSP ALGORITHM

Interested in leading order accuracy, CSP provides the following fast and slow basis vectors in the  $\mathbf{A}_M$  and  $\mathbf{A}_{N-M}$  matrices, respectively [7]:

$$\mathbf{A}_M = \begin{bmatrix} \mathbf{I}_M^M - \mathbf{G}_{N-M}^M \\ -\mathbf{R}_M^{N-M} \end{bmatrix} \quad \mathbf{A}_{N-M} = \begin{bmatrix} \mathbf{G}_{N-M}^M \\ \mathbf{I}_{N-M}^{N-M} \end{bmatrix} \quad (8)$$

where:

$$\begin{aligned} \mathbf{G}_{N-M}^M &= -(\mathbf{J}_M^M)^{-1} \mathbf{J}_{N-M}^M \\ \mathbf{R}_M^{N-M} &= -\mathbf{J}_M^{N-M} (\mathbf{J}_M^M - \mathbf{G}_{N-M}^M \mathbf{J}_M^{N-M})^{-1} \end{aligned} \quad (9)$$

The corresponding dual basis vectors are provided by the expressions:

$$\begin{aligned} \mathbf{B}^M &= [\mathbf{I}_M^M, -\mathbf{G}_{N-M}^M] \\ \mathbf{B}^{N-M} &= [-\mathbf{R}_M^{N-M}, \mathbf{I}_{N-M}^{N-M} - \mathbf{R}_M^{N-M} \mathbf{G}_{N-M}^M] \end{aligned} \quad (10)$$

Properly rescaling these vectors in order to simplify the analysis yields:

$$\mathbf{A}_M = \begin{bmatrix} \mathbf{I}_M^M \\ \mathbf{G}_M^{N-M} \end{bmatrix} \quad \mathbf{A}_{N-M} = \begin{bmatrix} \mathbf{G}_{N-M}^M \\ \mathbf{I}_{N-M}^{N-M} \end{bmatrix} \quad (11)$$

$$\begin{aligned} \mathbf{B}^M &= (\mathbf{I}_M^M - \mathbf{W}_M^M)^{-1} [\mathbf{I}_M^M, -\mathbf{G}_{N-M}^M] \\ \mathbf{B}^{N-M} &= (\mathbf{I}_{N-M}^{N-M} - \mathbf{W}_{N-M}^{N-M})^{-1} [-\mathbf{G}_M^{N-M}, \mathbf{I}_{N-M}^{N-M}] \end{aligned} \quad (12)$$

where

$$\mathbf{G}_M^{N-M} = \mathbf{J}_M^{N-M} (\mathbf{J}_M^M)^{-1} \quad (13)$$

$$\mathbf{R}_M^{N-M} = -\mathbf{G}_M^{N-M} (\mathbf{I}_M^M - \mathbf{G}_{N-M}^M \mathbf{G}_M^{N-M})^{-1} \quad (14)$$

$$\begin{aligned} \mathbf{W}_M^M &= \mathbf{G}_{N-M}^M \mathbf{G}_M^{N-M} \\ \mathbf{W}_{N-M}^{N-M} &= \mathbf{G}_M^{N-M} \mathbf{G}_{N-M}^M \end{aligned} \quad (15)$$

With these basis vectors, CSP yields the following reduced (non-stiff) system:

$$\frac{d\mathbf{y}}{dt} \approx \tilde{\mathbf{S}}_M \mathbf{R}^M + \tilde{\mathbf{S}}_{K-M} \mathbf{R}^{K-M} \quad (16)$$

where

$$\begin{aligned} \tilde{\mathbf{S}}_M &= \mathbf{A}_{N-M} \mathbf{D}_{N-M}^{N-M} [\mathbf{S}_M^{N-M} - \mathbf{G}_M^{N-M} \mathbf{S}_M^M] \\ \tilde{\mathbf{S}}_{K-M} &= \mathbf{A}_{N-M} \mathbf{D}_{N-M}^{N-M} [\mathbf{S}_{K-M}^{N-M} - \mathbf{G}_M^{N-M} \mathbf{S}_{K-M}^M] \end{aligned} \quad (17)$$

and  $\mathbf{D}_{N-M}^{N-M} = (\mathbf{I}_{N-M}^{N-M} - \mathbf{W}_{N-M}^{N-M})^{-1}$ . Equation (16) governs the flow on the SIM, which is defined by the relation:

$$\mathbf{g}^M - \mathbf{G}_{N-M}^M \mathbf{g}^{N-M} \approx \mathbf{0}^M \quad (18)$$

### IV. THE QSSA AND PEA APPROXIMATIONS

In the case where the QSSA or the PEA apply, it was shown in Ref. [4] that a reduced system in the form of Eq. (16) can also be obtained, along with the constraints in the form of Eq. (18).

In the case where  $M$  PEAs apply, the appropriate forms of Eqs. (16,18) are obtained by considering the limits:

$$\begin{aligned} \mathbf{G}_{N-M}^M &= \mathbf{V}_{N-M}^M + O(\varepsilon) \\ \mathbf{G}_M^{N-M} &= \mathbf{a}_M^{N-M} + O(\varepsilon) \end{aligned} \quad (19)$$

where

$$\mathbf{V}_{N-M}^M = -\left(\frac{\partial \mathbf{R}^M}{\partial \mathbf{y}^M}\right)^{-1} \frac{\partial \mathbf{R}^M}{\partial \mathbf{y}^{N-M}} \quad (20)$$

$$\mathbf{a}_M^{N-M} = \mathbf{S}_M^{N-M} (\mathbf{S}_M^M)^{-1} \quad (21)$$

In the case where  $M$  QSSAs apply, the appropriate forms of Eqs. (16,18) are obtained by considering the limit:

$$\mathbf{V}_{N-M}^M = O(\varepsilon) \quad (22)$$

in addition to those in Eq. (19).

The second limit in Eq. (19), which applies to both the QSSA and PEA, denotes the fact that the  $M$  vectors in  $\mathbf{A}_M$  are - to leading order - approximated by a linear combination of the stoichiometric vectors of the fast reactions:

$$\mathbf{A}_M = \mathbf{S}_M (\mathbf{S}_M^M)^{-1} + O(\varepsilon) \quad (23)$$

### V. THE EFFECT ON THE FAST PROCESSES

Let us consider the case where the fast subspace is approximated by the stoichiometric vectors of the fast reactions; i.e., the case where Eq. (23) holds. In this case, the expression for  $\tilde{\mathbf{S}}_M$  simplifies to:

$$\begin{aligned} \tilde{\mathbf{S}}_M &= \begin{bmatrix} \mathbf{V}_{N-M}^M \\ \mathbf{I}_{N-M}^{N-M} \end{bmatrix} \mathbf{D}_{N-M}^{N-M} [\mathbf{S}_M^{N-M} - \mathbf{a}_M^{N-M} \mathbf{S}_M^M] \\ &\quad + O(\varepsilon) \end{aligned} \quad (24)$$

where

$$\mathbf{D}_{N-M}^{N-M} = \mathbf{I}_{N-M}^{N-M} - \mathbf{a}_M^{N-M} \mathbf{V}_{N-M}^M \quad (25)$$

Clearly, Eq. (24) suggests that  $\tilde{\mathbf{S}}_M = O(\varepsilon)$ .

Similarly, the expression for  $\tilde{\mathbf{S}}_{N-M}$  simplifies to:

$$\begin{aligned} \tilde{\mathbf{S}}_{N-M} &= \begin{bmatrix} \mathbf{V}_{N-M}^M \\ \mathbf{I}_{N-M}^{N-M} \end{bmatrix} \mathbf{D}_{N-M}^{N-M} [\mathbf{S}_{K-M}^{N-M} - \mathbf{a}_M^{N-M} \mathbf{S}_{K-M}^M] \\ &\quad + O(\varepsilon) \end{aligned} \quad (26)$$

Let us consider the case where the first  $L$  stoichiometric vectors in  $\mathbf{S}_{K-M}$  are linear combinations to those in  $\mathbf{S}_M$ , i.e.:

$$\mathbf{S}_L = \mathbf{S}_M (\mathbf{Q}_M^M)^{-1} \quad (27)$$

where

$$\mathbf{S} = [\mathbf{S}_M, \mathbf{S}_{K-M}] = [\mathbf{S}_M, \mathbf{S}_L, \mathbf{S}_{K-M-L}] \quad (28)$$

or

$$\mathbf{S} = \begin{bmatrix} \mathbf{S}_M^M & \mathbf{S}_L^M & \mathbf{S}_{K-M-L}^M \\ \mathbf{S}_M^{N-M} & \mathbf{S}_L^{N-M} & \mathbf{S}_{K-M-L}^{N-M} \end{bmatrix} \quad (29)$$

It is straightforward to show that the terms inside the brackets in Eq. (26) yields:

$$\begin{aligned} & [\mathbf{S}_{K-M}^{N-M} - \mathbf{a}_M^{N-M} \mathbf{S}_{K-M}^M] = \\ & [\mathbf{0}_L^{N-M}, \mathbf{S}_{K-M-L}^{N-M} - \mathbf{a}_M^{N-M} \mathbf{S}_{K-M-L}^M] \end{aligned} \quad (30)$$

so that Eq. (26) simplifies to:

$$\begin{aligned} \tilde{\mathbf{S}}_{N-M} = & \begin{bmatrix} \mathbf{V}_{N-M}^M \\ \mathbf{I}_{N-M}^{N-M} \end{bmatrix} \mathbf{D}_{N-M}^{N-M} [\mathbf{0}_L^{N-M}, \mathbf{X}_{K-M-L}^{N-M}] \\ & + O(\varepsilon) \end{aligned} \quad (31)$$

where

$$\mathbf{X}_{K-M-L}^{N-M} = \mathbf{S}_{K-M-L}^{N-M} - \mathbf{a}_M^{N-M} \mathbf{S}_{K-M-L}^M \quad (32)$$

Clearly, Eq. (31) suggests for the first  $L$  vectors in  $\tilde{\mathbf{S}}_{K-M}$ , say  $\tilde{\mathbf{S}}_L$ , holds  $\tilde{\mathbf{S}}_L = O(\varepsilon)$ .

## VI. POINTER OF FAST PROCESSES

These developments suggest that the reduced (non-stiff) system can be cast in the form:

$$\frac{dy}{dt} \approx \tilde{\mathbf{S}}_M \mathbf{R}^M + \tilde{\mathbf{S}}_L \mathbf{R}^L + \tilde{\mathbf{S}}_{K-M-L} \mathbf{R}^{K-M-L} \quad (33)$$

where  $\mathbf{R}^M$  contains the rates of the  $M$  fast reactions,  $\mathbf{R}^L$  contains the rates of the  $L$  the stoichiometric vectors of which are linearly dependent to those of the fast reactions and  $\mathbf{R}^{K-M-L}$  contains the rates of the remaining  $K - L - M$  reactions.

Since Eqs. (24) and (31) show that  $\tilde{\mathbf{S}}_M = O(\varepsilon)$  and  $\tilde{\mathbf{S}}_L = O(\varepsilon)$ , it is reasonable to introduce the following stoichiometric index (SI) for the  $K$  elementary reactions:

$$S_i = \frac{\|\tilde{\mathbf{S}}_i\|_\infty}{\|\mathbf{S}_i\|_\infty}, \quad (i = 1, \dots, k) \quad (34)$$

where  $\|\bullet\|_\infty$  denotes the maximum norm of a vector. It will be shown, that the SI is a convenient tool to identify the fast reactions in a reduced model provided by CSP.

## VII. FAST PROCESSES IN THE GLYCOLYSIS MODEL

The glycolysis model developed in Ref. [5] involves 24 reactions among 22 metabolites. CSP analysis of the mathematical model in the oscillatory regime revealed that there exist 10 real dissipative (i.e. negative) eigenvalues, producing a fast/slow time scale ratio  $\epsilon \approx 0.5$  [6]. When the corresponding 10 fast time scales become exhausted, 10 equilibria are established and the solution evolves on a SIM.

In order to have a precise measure of the influence of the 24 reactions to the formation of the 10 fast dissipative eigenvalues, the Eigenvalue Participation Index (EPI) was employed in Ref. [8]. The results of the EPI are summarized in Table I. It is seen that the 10 fastest reactions of the biochemical network are: 9, 6, 24, 10, 4, 8, 7, 18, 2, 13. The outcome from the use of the SI on the reduced model produce by CSP are presented in Fig. (1). The ten colored lines at the bottom of Fig. (1), correspond to the 10 reactions with the 10 smallest SI. Rightfully the SI identifies the same reactions as the EPI does, being the 10 fastest ones in the glycolysis model.

TABLE I  
THE REACTIONS IN THE GLYCOLYSIS MODEL CONTRIBUTING TO THE DEVELOPMENT OF THE 10 FAST DISSIPATIVE EIGENVALUES

Fast eigenvalue	Reactions
$\lambda_1$	-9f, -8b
$\lambda_2$	-6b, -8f, -7b, -6f
$\lambda_3$	-24f, -24b
$\lambda_4$	-10, -9b, -8b, +9f
$\lambda_5$	-4b, -4f, -5
$\lambda_6$	-8f, -12, -10, -9f, -6f, -15, +9b
$\lambda_7$	-7b, -6f, -7f, +6b
$\lambda_8$	-18f, -12
$\lambda_9$	-2b, +2f
$\lambda_{10}$	-13f

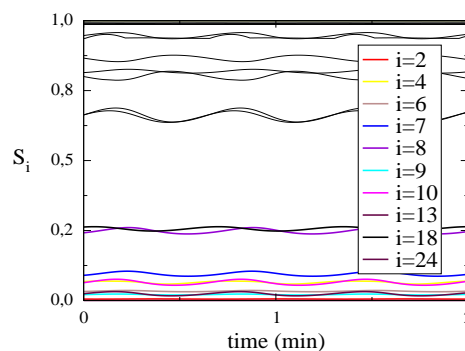


Fig. 1. Stoichiometric Indices for the 24 reactions in the glycolysis model

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