Štěpán Papáček; Ctirad Matonoha
A note on the OD-QSSA and Bohl-Marek methods applied to a class of mathematical models

In: Jan Chleboun and Jan Papež and Karel Segeth and Jakub Šístek and Tomáš Vejchodský (eds.): Programs and Algorithms of Numerical Mathematics, Proceedings of Seminar. Hejnice, June 23-28, 2024. , Prague, 2025. pp. 127–136.

Persistent URL: http://dml.cz/dmlcz/703212

Programs and Algorithms of Numerical Mathematics 22
J. Chleboun, J. Papež, K. Segeth, J. Šístek, T. Vejchodský (Eds.)
Institute of Mathematics CAS, Prague 2025

A NOTE ON THE OD-QSSA AND BOHL–MAREK METHODS APPLIED TO A CLASS OF MATHEMATICAL MODELS

Štěpán Papáček[1], Ctirad Matonoha[2]

[1] Institute of Information Theory and Automation of the Czech Academy of Sciences
Pod Vodárenskou věží 4, 182 00 Prague 8, Czech Republic
papacek@utia.cas.cz
[2] Institute of Computer Science of the Czech Academy of Sciences
Pod Vodárenskou věží 2, 182 00 Prague 8, Czech Republic
matonoha@cs.cas.cz

Abstract: The complex (bio)chemical reaction systems, frequently possess fast/slow phenomena, represent both difficulties and challenges for numerical simulation. We develop and test an enhancement of the classical QSSA (quasi-steady-state approximation) model reduction method applied to a system of chemical reactions. The novel model reduction method, the so-called delayed quasi-steady-state approximation method, proposed by Vejchodský (2014) and further developed by Papáček (2021) and Matonoha (2022), is extensively presented on a case study based on Michaelis–Menten enzymatic reaction completed with the substrate transport. Eventually, an innovative approach called the Bohl–Marek method is shown on the same numerical example.

Keywords: mathematical modelling, chemical kinetic systems, model reduction, quasi-steady-state approximation, M-Matrix, quasi-linear formulation

MSC: 92C45, 34A34, 65F60, 65K10

1. Introduction

Since Briggs and Haldane's application of the quasi-steady-state (QSS) assumption, e.g., [11], the idea of reducing complex chemical networks persists in the field of large-scale (bio)chemical systems modeling, see [12] and references therein. On the other side of control theory (cooperative biochemical systems), there are inspiring works of Bohl and Marek [1, 2, 8].

This study presents the development and application of one special model order reduction technique further called the delayed quasi-steady-state approximation method (D-QSSA), first proposed by Vejchodský in 2014 [13, 14] and further developed by our group in [9, 10]. We continue in the direction of papers devoted to the analysis of fast/slow phenomena arising in biology and chemistry, and more

DOI: 10.21136/panm.2024.12

precisely to the problem of parameter estimation for mathematical models describing the drug-induced enzyme production networks [3] aiming to develop biologically meaningful models, which can be used for drug delivery analysis and optimization. Although our ultimate goal is to develop a reliable method for fitting the model parameters of large biochemical networks to given experimental data, here we study certain numerical issues within the framework of efficient computations of inverse problems involving numerical optimization.

The paper is organized as follows. In Section 2, different numerical methods are presented. Then, in Section 3, we employ an illustrative case study to comprehensively account the pros and cons of each of the analyzed techniques. Section 4 concludes the work and outlines the future work. Finally, Appendix A presents a straightforward method for setting up the governing ODE system, while Appendix B provides the reformulation of nonlinear ODEs to the quasi-linear form.

2. Model and methods

This section further introduces the necessary theoretical background and notations used throughout this study, concerning mainly the fast/slow dynamical systems [15] and singular perturbation methods (SPM) with delays [6]. Let us consider the following system of ordinary differential equations (ODE) representing a general class of mathematical models describing (bio)chemical systems

$$\dot{x}(t) = Ax(t) + b(t, x(t)), \tag{1}$$

for $t \in [0, T]$ with $T > 0$, where $x(t) \in \mathcal{R}^n$, constant matrix $A \in \mathcal{R}^{n \times n}$ represents a linear part of the system, and $b(t, x(t)) \in \mathcal{R}^n$ contains nonlinear, time-varying and constant parts of the system. The ODE system (1) is further completed by suitable initial conditions, such that $x(0) = x_0$, defining the initial value problem (IVP). In the following subsections, we introduce the so-called optimal delayed quasi-steady-state approximation method (OD-QSSA) and an innovative approach here called the Bohl–Marek (BM) method.

2.1. Order reduction methods for the fast/slow dynamical systems

Suppose the existence of the fast and slow variables $x_F \in \mathcal{R}^{n_F}$ and $x_S \in \mathcal{R}^{n_S}$ and let $x(t) = \begin{pmatrix} x_F^T(t) & x_S^T(t) \end{pmatrix}^T$ be the partitioning of $x(t)$, where $n_F + n_S = n$. Then for a general fast/slow ODE system it holds

$$\begin{array}{rcl} \varepsilon\, \dot{x}_F & = & f_F(x_S, x_F; \varepsilon), \\ \dot{x}_S & = & f_S(x_S, x_F; \varepsilon), \end{array} \tag{2}$$

when $0 < \varepsilon \ll 1$, and suitable initial conditions are set. Then, the ODE system (2) can be approximated by a simpler algebro-differential system (an associated slow subsystem)

$$\begin{array}{rcl} 0 & = & f_F(x_S, x_F; 0), \\ \dot{x}_S & = & f_S(x_S, x_F; 0). \end{array} \tag{3}$$

Equations (3) are called singularly perturbed in the singular perturbation theory, whereas, in the chemical literature, such a model reduction is called a (standard) quasi-steady-state approximation (QSSA) when the underlying assumption ($0 < \varepsilon \ll 1$) assuring small approximation error, i.e., the validity of the standard QSSA is often referred to as the reactant-stationary assumption [4]. Several mathematical studies are dedicated to quantifying the accuracy of different QSSA methods applied to enzyme kinetics. Identification of a presumably small parameter ε, see (2), is common to these efforts, which quantifies the timescale separation. This explicit identification of a suitable ε for every system and operating condition requires nontrivial mathematical operations. Consequently, when one tries to omit such analysis, the non-justified use of the QSSA method frequently occurs, which in fact represents the QSSA method's abuse [5].

Our solution to the difficulties mentioned above dwells in the relatively novel extension of the D-QSSA method, being the delayed QSSA with the optimal constant delay introduced by Matonoha et al. [9] for a class of chemical networks with the mass conservation property and a wide timescale separation.

For completeness, we provide the main theorem concerning the existence of an optimal constant delay. The proof and detailed description can be found in [9].

Theorem 1. *Let $\bar{x}(t)$ be a solution of the (full) system (2). Choose arbitrary numbers $0 < \underline{\tau} \le \overline{\tau} < T$ and a fixed constant delay $\tau \in [\underline{\tau}, \overline{\tau}]$. Let $x_F^{cdqss}(t,\tau)$ be a constant delay QSS approximation of $x_F(t)$ with this τ. Let $x_S^{cdqss}(t,\tau)$ be a solution of the reduced delayed ODE system, continuous for $t \in [0,T]$. Denote $x^{cdqss}(t,\tau) = \left(\begin{array}{cc} x_F^{cdqss^T}(t,\tau) & x_S^{cdqss^T}(t,\tau) \end{array} \right)^T$. Then there exists at least one value $\tau^* \in [\underline{\tau}, \overline{\tau}]$ minimizing the error between $\bar{x}(t)$ and $x^{cdqss}(t,\tau)$, i.e.,*

$$\tau^* = \arg\min_{\tau} \|\bar{x}(t) - x^{cdqss}(t,\tau)\|^2, \tag{4}$$

subject to $0 < \underline{\tau} \le \tau \le \overline{\tau} < T$, *where* $\|.\|$ *denotes the vector* $L^2[0,T]$*-norm.*

2.2. Bohl–Marek method (and a quasi-linear M-matrix formulation)

QSSA may increase the nonlinearity of the model, see, e.g., the Michaelis–Menten equation for enzyme kinetics [11]. While the ODEs describing enzyme kinetics are mildly nonlinear (only quadratic through terms containing products of two reactants), the Michaelis–Menten equation represents a rational function in an involved reactant. Conversely, the Bohl–Marek (BM) method, makes the model quasi-linear because the ODE system (1) with conservation properties containing the original mass action kinetics terms can be described using the quasi-linear formulation (5). As far as we know, the first appearance of this approach can be found in the works of Erich Bohl and Ivo Marek, see, e.g., [1, 2, 8], where the principle of total mass conservation was employed to prove the existence of positive solutions and stationary states. The details about the BM method applied to our case study problem are

described in Appendix B, here we state that (under some assumptions) the ODE system (1) for a modified state variable vector $\tilde{x}(t)$ can be formulated as a quasi-linear system

$$\frac{\mathrm{d}\tilde{x}(t)}{\mathrm{d}t} = M(x)\tilde{x}(t), \tag{5}$$

with the block diagonal system matrix $M(x)$ of a special form of a negative M-matrix with some elements containing components of a system variable x. The advantages of this formulation reside in the computational speedup and precision and shall be highlighted in the next Section 3.

3. Case study

As a case study, we take the paradigmatic example consisting of the Michaelis–Menten kinetics with a simple transport process described in Tab. 1.

Description of the related process	**Chem. notation**
Substrate X_{ext} dosing	$\emptyset \to X_{ext}$
R_1: Substrate transport through a membrane, $k_0 = 10^{-1}$	$X_{ext} \rightleftharpoons X_{int}$
R_2: Enzyme E binds to substrate, complex C formation, $k_1 = 10^{6}$	$X_{int} + E \rightleftharpoons C$
R_3: Reverse reaction to R_2, $k_{-1} = 10^{-4}$	
R_4: Complex breaks down into E plus a product P, $k_2 = 10^{-1}$	$C \to E + P$

Table 1: Transport and reaction processes defining the network, parameter values taken from [7].

Introducing a new notation for state variables, i.e., an n-size (here $n = 5$) vector x according to

$$x(t) = \begin{pmatrix} x_1 & x_2 & x_3 & x_4 & x_5 \end{pmatrix}^T \equiv \begin{pmatrix} X_{ext} & X_{in} & E & C & P \end{pmatrix}^T,$$

the ODE system describing the process under study can be written either in the usual form (1), i.e., $\dot{x}(t) = Ax(t) + b(t, x(t))$, see Appendix A or in the quasi-linear Bohl–Marek formulation, see, e.g., [2] and Appendix B, for this special case study.

Equipped by the initial conditions

$$x(0) = \begin{pmatrix} u_0 & 0 & e_0 & 0 & 0 \end{pmatrix}^T = \begin{pmatrix} 5 \cdot 10^{-7} & 0 & 2 \cdot 10^{-7} & 0 & 0 \end{pmatrix}^T, \tag{6}$$

we compare the numerical results obtained from the full (non-reduced) problem (1), (6) with those obtained using different models corresponding to different reduction methods. The state variables x_1 and x_4 can be considered as fast variables x_F, since they satisfy all assumptions for fast variables mentioned in [13]. Thus we use the notations QSSA1, QSSA4, QSSA14, etc. Besides, we compare the results with those obtained from the quasi-linear BM formulation (5), (6).

It is well known that the QSS approximation is derived for larger times (to enable the fast variable to reach its steady state) and hence it may not satisfy the original initial condition. This happens if x_1 is considered as a fast variable yielding $x_1^{qss}(t) = x_2(t)$. This conflicts initial conditions $x_1(0) = u_0 > 0$ and $x_2(0) = 0$ (it cannot hold $x_1^{qss}(0) = x_2(0)$). Therefore, we introduce a parameter t_Q, $0 < t_Q < T$, and derive the QSS approximation for $t > t_Q$, only.

For our numerical experiments, we used parameters given in Tab. 1, $T = 120$, and the time step $\Delta t = 10^{-3}$ for solving the respective ODEs by the backward Euler method. The value $m = \frac{T}{\Delta t}$ denotes the total number of steps. To compare the quality of approximate solutions $x^A(t)$ with a solution $\bar{x}(t)$ of the original non-reduced model (full system) (1),(6), for each of the five state variables we used the error metrics δ_i and the total error δ as follows

$$\delta = \frac{1}{n}\sum_{i=1}^{n}\delta_i, \qquad \delta_i = \sqrt{\frac{4}{m}\sum_{j=0}^{m}\left[\frac{\bar{x}_i(t_j) - x_i^A(t_j)}{\bar{x}_i(t_j) + x_i^A(t_j)}\right]^2}, \quad i = 1, \ldots, n. \tag{7}$$

In (7), the exact solution $\bar{x}_i(t_j)$, $j = 0, 1, \ldots, m$, is supposed to be the solution computed using the non-reduced model (full system) (1),(6). The values $x_i^A(t_j)$, $j = 0, 1, \ldots, m$, $i = 1, \ldots, n$, are approximate solutions computed from the models QSSAk (i.e., $x^{qss}(t_j)$), D-QSSAk (i.e., $x^{dqss}(t_j)$ with the delay $\tau(t) = 1/g(t)$), OD-QSSAk (i.e., $x^{odqss}(t_j)$ with an optimal constant delay τ^* in the sense of optimization problem (4), see Theorem 1), k = 1, 4, 14, and from the BM formulation. The nonconstant delays in models D-QSSAk are $\tau_1(t) = 1/g_1(t) = 1/k_0 = 10$ and $\tau_4(t) = 1/g_4(t) = 1/(k_{-1} + k_2 + k_1 x_1(t))$, respectively. Note that τ_1 is constant because the function $g(t) = k_0$ is constant.

A schematic description of the studied models with obtained optimal values t_Q and optimal constant delays τ_1^*, τ_4^* are given in Tab. 2. Other columns give the total error metric δ, see (7), and the computational time obtained for 1000 simulations with exactly the same parameter values. The last column shows the speedup obtained as the ratio of computational times between individual models and the full non-reduced model.

Fig. 1 shows the behaviour of state variables x_1 and x_4 for different models QSSAk, D-QSSAk, OD-QSSAk, k =1,4, and BM. The left picture shows the value $t_Q = 10.77$, from which the quasi-steady-state solutions are considered. Different approaches $(x^{qss}(t), x^{dqss}(t), x^{odqss}(t))$ give different solutions. The right picture shows the optimal constant delay $\tau_4^* = 4.897$ which gives zero quasi-steady-state solution $x_4(t) = 0$, $t \in [0, \tau_4^*]$. Note that the nonconstant delay $\tau_4(t) = 1/g(t)$ for a D-QSS approximation is for small t nearly the same as the optimal constant value $\tau_4^* = 4.897$. Besides, notice that the BM quasi-linear solution is almost the same as the solution of non-reduced model (1), (6).

Resuming: It can be seen that although it is possible to find optimal values of constant delays τ^* that can significantly speed up the computation when x_1 and x_4 are fast (we are solving small ODE systems), it is more efficient to convert the

model	**description**	t_Q	**delay** τ	**total** δ	**time**	**speedup**
non-reduced	system (1),(6)	-	-	-	21.94	1.00
QSSA1	x_1 fast	opt.	-	1.0408	18.18	0.83
QSSA4	x_4 fast	-	-	0.2736	18.28	0.83
QSSA14	x_1, x_4 fast	opt.	-	1.1524	5.78	0.26
D-QSSA1	x_1 fast	opt.	$\tau_1 = 1/g_1(t)$	0.2960	21.58	0.98
D-QSSA4	x_4 fast	-	$\tau_4 = 1/g_4(t)$	0.1896	20.34	0.93
D-QSSA14	x_1, x_4 fast	opt.	$\tau_i = 1/g_i(t)$	0.3237	9.27	0.42
OD-QSSA1	x_1 fast	10.77	$\tau_1^* = 12.753$	0.1634	21.58	0.98
OD-QSSA4	x_4 fast	-	$\tau_4^* = 4.897$	0.1952	17.44	0.79
OD-QSSA14	x_1, x_4 fast	12.54	$\tau_1^* = 12.417$	0.1563	6.03	0.28
			$\tau_4^* = 11.426$			
BM	system (5),(6)	-	-	0.0006	5.30	0.24

Table 2: Comparison of the studied models: (i) Schematic description, (ii) Computed and used optimal values t_Q and delay τ^*, (iii) Computed total error δ, (iv) Computational times and the speedup.

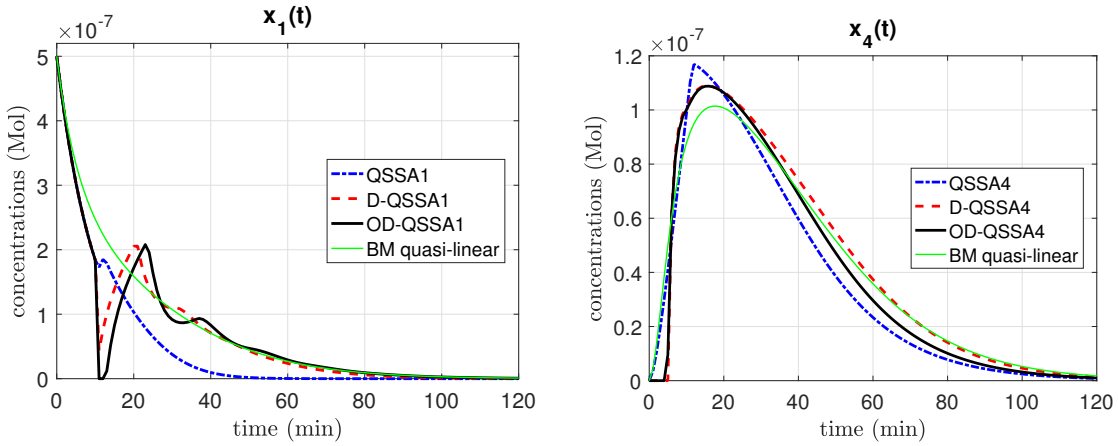

Figure 1: Comparison of $x_1(t)$ and $x_4(t)$ obtained using different models.

problem to the BM quasi-linear form, obviously, if and only if all the corresponding requirements are met (especially the conservation properties).

4. Contribution and Outline

We presented one relatively unknown model reduction technique for a class of (bio)chemical reaction networks proposed first by Vejchodský in [13]. The assumptions for this, the so-called D-QSSA approximation are not too restrictive and D-QSSA applies to the majority of (bio)chemical systems based on the law of mass action. While the standard QSSA ignores the time-fast variables needed to reach

their steady states, the advantage of D-QSSA (and its variant OD-QSSA) is the possibility of a time delay introduction to improve the accuracy. This general conclusion was supported by the example presented in Section 3, where we used the case study of enzyme-catalyzed reactions with a substrate transport chain, see [9] for further details. Moreover, we performed a preliminary comparison of numerical computations for two equivalent formulations of governing (non-reduced) ODEs, i.e., for the classical formulation (1) and the quasi-linear Bohl–Marek formulation (5), showing the considerable speedup for the latter. It is due to eliminating the nonlinear part $b(t, x(t))$ from the system which causes a numerical burden when solving ODEs. Rigorous analysis of numerical issues related to both approaches is the subject of our ongoing work.

Acknowledgments

The work of Ctirad Matonoha was supported by the long-term strategic development financing of the Institute of Computer Science (RVO:67985807).

References

[1] Bohl, E. and Marek, I.: Existence and uniqueness results for nonlinear cooperative systems. In: I. Gohberg and H. Langer (Eds.), *Linear Operators and Matrices*. Birkhäuser Basel, Basel, 2002 pp. 153–170.

[2] Bohl, E. and Marek, I.: Input-output systems in biology and chemistry and a class of mathematical models describing them. Applications of Mathematics **50** (2005), 219–245. `https://doi.org/10.1007/s10492-005-0015-1`.

[3] Duintjer Tebbens, J., Matonoha, C., Matthios, A., and Papáček, Š.: On parameter estimation in an *in vitro* compartmental model for drug-induced enzyme production in pharmacotherapy. Applications of Mathematics **64** (2019), 253–277.

[4] Eilertsen, J. and Schnell, S.: The quasi-steady-state approximations revisited: Timescales, small parameters, singularities, and normal forms in enzyme kinetics. Mathematical Biosciences **325** (2020). Cited by: 15; All Open Access, Green Open Access.

[5] Flach, E. H. and Schnell, S.: Use and abuse of the quasi-steady-state approximation. Syst. Biol. **4** (2006), 187–91.

[6] Glizer, V. Y.: *Controllability of Singularly Perturbed Linear Time Delay Systems*. Birkhäuser Cham, 2022.

[7] Higham, D. J.: Modeling and simulating chemical reactions. SIAM Review **50** (2008), 347–368.

[8] Marek, I.: On a class of stochastic models of cell biology: Periodicity and controllability. In: *Positive Systems*, pp. 359–367. Springer Berlin Heidelberg, 2009.

[9] Matonoha, C., Papáček, Š., and Lynnyk, V.: On an optimal setting of constant delays for the D-QSSA model reduction method applied to a class of chemical reaction networks. Applications of Mathematics **50** (2022), 831–857. http://eudml.org/doc/298520.

[10] Papáček, Š. and Lynnyk, V.: Quasi-steady state assumption vs. delayed quasi-steady state assumption: Model reduction tools for biochemical processes. In: *2021 23rd International Conference on Process Control (PC)*. 2021 pp. 278–283.

[11] Segel, L. A. and Slemrod, M.: The quasi-steady-state assumption: A case study in perturbation. SIAM Review **31** (1989), 446–477.

[12] Snowden, T. J., van der Graaf, P. H., and Tindall, M. J.: Methods of model reduction for large-scale biological systems: A survey of current methods and trends. Bulletin of Mathematical Biology **79** (2017), 1449–1486.

[13] Vejchodský, T.: Accurate reduction of a model of circadian rhythms by delayed quasi-steady state assumptions. Mathematica Bohemica **139** (2014), 577–585. http://hdl.handle.net/10338.dmlcz/144135.

[14] Vejchodský, T., Erban, R., and Maini, P. K.: Reduction of chemical systems by delayed quasi-steady state assumptions, arXiv:1406.4424, 2014.

[15] Witelski, T. and Bowen, M.: *Fast/slow Dynamical Systems*, pp. 201–213. Springer International Publishing, Cham, 2015.

Appendix A

Matrix A of constant coefficients and vector of nonlinear terms $b(t, x(t))$

The system of differential equations (1) describing the processes under study can be systematically derived using the vector of reaction rates and the so-called stoichiometric matrix $S \in \mathcal{R}^{n\times q}$, where q is the number of reactions (including the transport of species). Generally, for chemical reaction networks, the governing ODE system, i.e., the vector of changes in species concentrations $x \in \mathcal{R}^n$, is described as a linear transformation (imposed by the matrix S) of the reaction rate vector $\nu \in \mathcal{R}^q$ (depending on corresponding states x and a model parameter vector p). For our case study $x \in \mathcal{R}^5$, $q = 4$ (see Tab. 1 in Section 3), and it holds:

$$\dot{x}(t) = S\ \nu(x, p), \qquad \text{where } p = (k_0, k_1, k_{-1}, k_2)^T\,, \tag{8}$$

$$S = \begin{array}{c} \begin{matrix} R_1 & R_2 & R_3 & R_4 \end{matrix} \\ \begin{pmatrix} -1 & 0 & 0 & 0 \\ 1 & -1 & 1 & 0 \\ 0 & -1 & 1 & 1 \\ 0 & 1 & -1 & -1 \\ 0 & 0 & 0 & 1 \end{pmatrix} \end{array}, \qquad \nu = \begin{pmatrix} k_0\ (x_1 - x_2) \\ k_1\ x_2\ x_3 \\ k_{-1}\ x_4 \\ k_2\ x_4 \end{pmatrix}. \tag{9}$$

Thus, the ODE system in the usual form (1), i.e., $\dot{x}(t) = Ax(t) + b(t, x(t))$, has the constant matrix (the linear part of the system)

$$A = \begin{pmatrix} -k_0 & k_0 & 0 & 0 & 0 \\ k_0 & -k_0 & 0 & k_{-1} & 0 \\ 0 & 0 & 0 & k_{-1} + k_2 & 0 \\ 0 & 0 & 0 & -(k_{-1} + k_2) & 0 \\ 0 & 0 & 0 & k_2 & 0 \end{pmatrix} \tag{10}$$

and the vector representing the nonlinear part

$$b(t, x(t)) = \begin{pmatrix} 0 \\ -k_1 \cdot x_2(t) \cdot x_3(t) \\ -k_1 \cdot x_2(t) \cdot x_3(t) \\ k_1 \cdot x_2(t) \cdot x_3(t) \\ 0 \end{pmatrix}. \tag{11}$$

Remark 2. *Reaction networks frequently possess subsets of reactants that remain constant at all times, i.e., they are referred to as conserved species. Generally, there exists a conservation matrix* Γ *(of dimension* $h \times n$*), where the rows represent the linear combination of species (reactants) that are constant in time. It can be solved explicitly for large systems (*$0 = \Gamma\, S$*). For our case of* S *in form* (9)*, the conservation property reads*

$$x_3 + x_4 = e_0, \quad x_1 + x_2 + x_4 + x_5 = u_0. \tag{12}$$

Consequently, here

$$\Gamma = \begin{pmatrix} 0 & 0 & 1 & 1 & 0 \\ 1 & 1 & 0 & 1 & 1 \end{pmatrix}. \tag{13}$$

The existence of two relations (12) signifies not only the possibility to reduce the number of state variables, but also induces the reformulation of the governing equations for species concentration using negative M-matrices, see Appendix B.

Appendix B

Matrix M and Bohl–Marek formulation

Based on the mass conservation properties, the non-linear ODEs (1) can be represented as a linear system with the system matrix of a special form, a negative M-matrix. To the best of our knowledge, this approach was first proposed by Erich Bohl and Ivo Marek [1, 2] and further extended into the framework of control theory in [8].

For the case study defined by Tab. 1, the state variables can be listed in two subsets $\{x_3, x_4\}$, $\{x_1, x_2, x_4, x_5\}$ and the non-linear ODEs (1) can be represented as a linear system with the system matrix of a special form, a negative M-matrix whose

column sums are zero.[1] These two subsets of state variables can be assembled and merged as follows:

$$\tilde{x}(t) = \left({x^{(1)}}^T(t),\ {x^{(2)}}^T(t) \right)^T,$$

where

$$x^{(1)}(t) = \begin{pmatrix} x_3(t) \\ x_4(t) \end{pmatrix}, \quad x^{(2)}(t) = \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_4(t) \\ x_5(t) \end{pmatrix}. \tag{14}$$

Then the ODE system for a modified state variable vector $\tilde{x}(t)$ gets the form which was already announced in (5):

$$\frac{\mathrm{d}\tilde{x}(t)}{\mathrm{d}t} = M\tilde{x}(t). \tag{15}$$

For our case study problem, the block diagonal system matrix $M = M(x(t))$ is of a special form

$$M = \begin{pmatrix} M_1 & 0 \\ 0 & M_2 \end{pmatrix}, \tag{16}$$

where

$$M_1 = \begin{pmatrix} -k_1 \cdot x_2 & k_{-1} + k_2 \\ k_1 \cdot x_2 & -(k_{-1} + k_2) \end{pmatrix}, \tag{17}$$

$$M_2 = \begin{pmatrix} -k_0 & k_0 & 0 & 0 \\ k_0 & -k_0 - k_1 \cdot x_3 & k_{-1} & 0 \\ 0 & k_1 \cdot x_3 & -(k_{-1} + k_2) & 0 \\ 0 & 0 & k_2 & 0 \end{pmatrix}. \tag{18}$$

[1] This property in fact assures the conservation of the sum of all components of the (new) state variable vector $\tilde{x}$.