

Analysis of a Model Reduction Method (D-QSSA) applied to a Class of Biochemical Networks^{*}

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Abstract: This paper is aimed to develop and test one novel and unexplored enhancement of the classical model reduction method applied to a class of biochemical networks. Both methods, being (i) the standard quasi-steady-state approximation (QSSA), and (ii) the so-called delayed-QSSA methods are extensively presented. Specially, the numerical issues related to the setting of constant delays are discussed. Finally, for one slightly modified version of an enzyme-substrate reaction network (Michaelis-Menten kinetics), the comparison of the full non-reduced system behavior with respective variants of reduced model is presented and future prospects are proposed.

Keywords: biochemical reaction network, model reduction, D-QSSA method, model parameter estimation

1. INTRODUCTION

Any biochemical reaction network can be described by one of two approaches leading either to: (i) the stoichiometric, or (ii) kinetic models, e.g. Flach and Schnell (2006). While the stoichiometric model is based on the time-invariant properties of the reaction network (reaction kinetic scheme or pathway scheme), known as its connectivity and determined by stoichiometric matrix S (in some sense describing the topology of reaction network, e.g. such drawn in Fig. 1), the time-dependent kinetic model is based on the law of mass action stating that the rate of each elementary reaction (ν_i) is proportional to the product of the concentrations of reactants, where the corresponding proportional constant is a reaction rate (k_i), Ciliberto et al. (2007). The number of reactions constitutes the dimension of the reaction rate vector ν . Consequently, the system of ordinary differential equations (one ODE for every species in the network, including transitory complexes) can be systematically derived using the multiplication of the so-called stoichiometric matrix S by the reaction rate vector ν , Schnell (2014). Moreover, when dealing with many reactions system, some reactions can be classified as fast, some are in between, and some are slow. The existence of slow-fast phenomena in the network represents difficulties for numerical simulation of all species in the network, however, on the other hand, opportunities to reduce the system order through singular perturbation methods, see Snowden et al. (2017); Khalil (2018); Isidori (1995); Reháč et al. (2009).

Hence, due to the timescales separation of respective slow and fast reactions, the simplification of the ODE system by certain order reduction is possible. One of the most famous examples of such reduction is Briggs and Haldane's application of the quasi-steady-state (QSS) assumption for the simplification of an enzyme-substrate reaction network leading to Michaelis-Menten (MM) kinetics, see Briggs and Haldane (1925); Segel (1988); Segel and Slemrod (1989) and references therein. Based on different QSS assumptions different QSS approximation (QSSA)¹ methods have been proposed, e.g. standard, reverse and total QSSA in Eilertsen and Schnell (2020) and zero-derivative principle in Hårdin et al. (2009).

Different other ways of analyzing the system leading to the model reduction have been discussed by Snowden et al. (2017). Eliminating parameters noticed to be the least sensitive in affecting the model comprises the idea of sensitivity analysis Zi (2011). Presented in the 1960s by Kuo and Wei (1969); Wei and Kuo (1969) the lumping method uses the replacement of a group of state variables from the system with a new dynamical variable (lumped), related to the original system by lumping functions Okeke (2013); Pepiot-Desjardins and Pitsch (2008). Another known method of model order reduction - proper orthogonal decomposition, completed with the discrete empirical interpolation method - was applied to kinetic models of biological systems with different initial conditions by Eshtewy and Scholz (2020). This method, based on Galerkin projection, obtains the minimum error

^{*} The work was supported by the Czech Science Foundation through the research grant No. 19-05872S.

¹ The nomenclature for the QSSA abbreviation is not unequivocal. In order to follow the main stream paved by e.g. Flach and Schnell (2006); Schnell (2014), we stick on term *approximation* within QSSA abbreviation, contrarily to Vejchodský (2014).

between the original model and its reduced representation. However, considering as an optimal linear approach, proper orthogonal decomposition may represent a restriction for nonlinear systems, as the complexity of the full order model remains in this case. The approach called the discrete empirical interpolation method can be used to overcome the complexity for nonlinear terms in the dynamical system. A new model reduction method based on a simple stepwise reduction in the number of “complexes”, which are defined as the left and right-hand sides of the reactions in the network is represented by Rao et al. (2014). The error integral, quantifying how much the behaviour of the reduced model deviates from the original, is used to monitor the effect of this stepwise reduction. The model reduction method, analysed in our research, have been applied to a circadian rhythms modelling by Vejchodský (2013) already. It could be used to the modelling of signal transduction and cellular communication mechanisms, like Mitogen-Activated Protein Kinase (MAPK) cascades, as well.

As follows, in Section 2, instead of providing an exhaustive general description of the QSSA methods and its variants, we introduce only two of them: (i) the standard QSSA and (ii) the novel and unexplored delayed-QSSA (D-QSSA) recently formulated in Vejchodský (2014) for a class of biochemical networks. Afterwards, in Section 3, one illustrative example (some extension of classical enzyme catalyzed reaction) is employed to reveal both the problem complexity and the comprehensive account of the numerical issues related to the novel D-QSSA technique. Finally, in Section 4, we resume our efforts and trace the directions for subsequent investigations.

2. STANDARD QSSA AND D-QSSA: TWO MODEL REDUCTION METHODS

Our aim was to present and promote the novel extension of the quasi-steady-state approximation method. The delayed-QSSA (D-QSSA) method was introduced in Vejchodský et al. (2014); Vejchodský (2014) for a class of mass action models with a wide timescale separation. We analysed an initial value problem for a system of ordinary differential equations (ODEs) that describes the time course of state variables (species concentrations) within a biochemical reaction network with the mass conservation property.

First, let us consider a general fast/slow ODE system

$$\begin{aligned}\epsilon \dot{x}_F &= f_F(x_S, x_F; \epsilon), \\ \dot{x}_S &= f_S(x_S, x_F; \epsilon),\end{aligned}\quad (2.1)$$

when $0 < \epsilon \ll 1$. Then, the components of $x_F \in \mathcal{R}^{n_F}$ are called fast variables and $x_S \in \mathcal{R}^{n_S}$ are called slow variables, see Isidori (1995); Khalil (2018). Furthermore, the above ODE system can be approximated with a simpler algebro-differential system (the associated slow subsystem)

$$\begin{aligned}0 &= f_F(x_S, x_F; 0), \\ \dot{x}_s &= f_S(x_S, x_F; 0).\end{aligned}\quad (2.2)$$

While in the singular perturbation theory, the above equations (2.2) are called singularly perturbed, in biochemical

literature, such a model reduction is called as (standard) quasi-steady-state approximation and the underlying assumption ($0 < \epsilon \ll 1$) assuring small approximation error, i.e. the validity of the standard QSSA, is often referred to as the reactant-stationary assumption, see Eilertsen and Schnell (2020). A number of mathematical studies was dedicated to quantify the accuracy of different QSSA methods applied to enzyme kinetics, e.g. Segel (1988); Segel and Slemrod (1989); Eilertsen and Schnell (2020). Common to these efforts is the identification of a presumably small parameter ϵ , cf. (2.1), which quantify the timescale separation. Naturally, this explicit identification of a suitable ϵ for every individual system and operating conditions requires non-trivial mathematical operations. Consequently, when one tries to omit such analysis, the non-justified use of QSSA method represents in fact its abuse, see Flach and Schnell (2006).

Here, for a class of biochemical networks with the mass conservation property, we present how the so-called delayed-QSSA (D-QSSA) method Vejchodský et al. (2014); Vejchodský (2014) can be successfully used without the necessity to identify an “ ϵ -based” condition for its validity. Obviously, there is another parameter of D-QSSA method, i.e. a delay, which should be determined through an optimization procedure.

2.1 Reformulation of governing equations for biochemical networks with the mass conservation property (getting negative M -matrices)

Based on the mass conservation properties, the non-linear ODE (2.1) could be represented as a linear system with the system matrix of special form of a negative M -matrix. To the best of our knowledge, this approach was proposed in Bohl and Marek (2005) and further extended into the framework of control theory in Marek (2009).

Based on the assumption that all state variables are involved in the conservation properties, the general form of governing ODE system for modified state variable vector $\tilde{x}(t)$ is

$$\frac{d\tilde{x}(t)}{dt} = M\tilde{x}(t),\quad (2.3)$$

with the block diagonal system matrix of special form (negative M -matrix when the sum of all columns are zero), see Stuart (2013) and references therein.

The reformulation of ODEs according to (2.3) has a little importance for the numerical calculation, however, it assures the fulfillment of all three suppositions demanded in Vejchodský (2014), hence it has rather the theoretical importance for further analysis of D-QSSA method.

Quasi-steady state assumption for a class of mass action models

Definition 1. Assuming a timescale separation for the rates of species evolution in a biochemical network (2.3), the state vector is partitioned, i.e. $\tilde{x}(t) = (x_F(t) \ x_S(t))^T$

and the ODE system has the form

$$\begin{aligned}\dot{x}_F(t) &= f(x_S(t)) - g(t)x_F(t), \\ \dot{x}_S(t) &= h(x_F(t), x_S(t)).\end{aligned}\quad (2.4)$$

The reduced system via **standard QSSA** is

$$\begin{aligned} x_F(t) &= \frac{f(x_S(t))}{g(t)}, \\ \dot{x}_S(t) &= h(x_F(t), x_S(t)). \end{aligned} \quad (2.5)$$

2.2 Delayed quasi-steady state assumption (D-QSSA)

The standard QSSA method for model reduction is valid only where the timescale of fast species is significantly shorter than the timescale of the others (presumably) slow species. Analysing the error of the standard QSSA method, the authors in Vejchodský et al. (2014) noted that in the original system the fast variables always need a certain amount of time to reach their quasi-steady states, i.e. to get the slow invariant manifold (SIM). Therefore, if the quasi-steady state changes (due to change in the slow variables), the corresponding fast variable should reach the new value of the quasi-steady state with a certain time delay, while, if the original system is reduced by the QSSA, the fast variables stay in their quasi-steady states and the time delay is neglected. Thus, Vejchodský et al. propose to solve the discrepancy between the original and reduced systems by introducing time delays to the standard QSSA. This novel approach is called as *the delayed quasi-steady state assumption* (D-QSSA).

Definition 2. Assuming a timescale separation for the rates of species evolution in a biochemical network (2.3), the state vector is partitioned, i.e. $\tilde{x}(t) = (x_F(t) \ x_S(t))^T$, when $x_F(t)$ is vector composed from n_F fast variables and $x_S(t)$ is vector composed from n_S slow variables.

The non-reduced ODE system has the form

$$\begin{aligned} \dot{x}_F(t) &= f(x_S(t)) - g(t)x_F(t), \\ \dot{x}_S(t) &= h(x_F(t), x_S(t)), \end{aligned} \quad (2.6)$$

and its reduction via **delayed QSSA** is

$$\begin{aligned} x_F^{qss}(t) &= \frac{f(x_S(t - \tau))}{g(t - \tau)}, \\ \dot{x}_S(t) &= h(x_F^{qss}(t), x_S(t)), \end{aligned} \quad (2.7)$$

where $\tau = \frac{1}{g(t)}$.

The theorems concerning the equivalence of the D-QSSA method to the first-order correction of QSSA (up to terms cubic in delay τ) and the theorems dealing with the D-QSSA error estimates, i.e. differences between the solution of non-reduced system and its D-QSSA approximations, are presented in Vejchodský et al. (2014).

Further, in this section, we shall study the problem of an optimal setting of constant delays τ for a system of ODEs where two timescales exist. Hence, after two remarks, we propose one Lemma dealing with the optimal choice of constant delays for D-QSSA method.

Remark 1. The reduced system via D-QSSA (2.7) approximates the invariant (slow) manifold of system (2.6) up to terms quadratic in τ Vejchodský et al. (2014), thus, in case of constant and small τ the D-QSSA is equivalent to the standard QSSA (or SPM) and the delay can be avoided. If the delay is not small then there is no theoretical reason for the application of QSSA, however, the D-QSSA still has the potential to yield acceptable accuracy (as it will be shown in the next section).

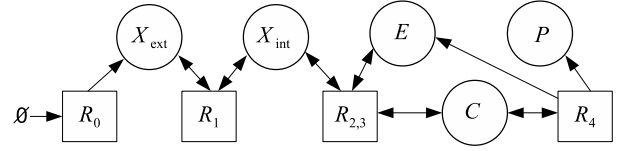


Fig. 1. Graph representation of the action of an enzyme catalyzed reaction with external (periodic) administration of a substrate. Reaction nodes (rectangles) identified by R_i represent reactions between circular species nodes (identified by capital letters).

Remark 2. The delay $\tau(x_S(t))$, introduced for a system in form of (2.7) in Definition 2, depends generally on the other (slow) components of the system. Thus, it evolves in time. This fact may cause some numerical issues when solving delayed differential equations by a computer algebra system. This problem was solved by the following Lemma 1, firstly announced in our work, Papacek and Lynnyk (2021).

Lemma 1. For a system in form (2.7), there exists a constant delay $\tau \equiv \tau^*$ minimizing the error between the non-reduced system (2.6) and the reduced system (2.7). I.e. $\tau^* = \arg \min_{\tau \in \mathcal{R}_+} \|x(t) - \tilde{x}(t, \tau)\|$ subject to $\underline{\tau} \leq \tau(t) \leq \bar{\tau}$. (2.8)

Proof. Based on the specific form of the system under study, the discrepancy between the full and reduced system can be minimized, having τ constant as the argument for the optimization problem. Natural bounds for the delay constant are the minima and maxima of the function $\tau(t)$ defined accordingly to (2.8). \square

Remark 3. Vejchodský et al. emphasize that $x_F^{qss}(t)$ is designed to approximate the long-time behaviour of the fast variable $x_F(t)$. If the independent variable t is close to zero then approximation (2.7) is still defined, but the quantity $(t - \tau(t))$ can be negative. Therefore, technically, the functions f and g have to be defined for negative values of t as well. Consequently, for small values of t , the approximation $x_F^{qss}(t)$ depends on arbitrary extensions of f and g to negative values. Thus, it cannot be expected a good approximation of $x_F^{qss}(t)$ for t close to zero.

3. NUMERICAL EXAMPLE

In this section, two model reduction methods, namely standard QSSA (2.5) as well as its refinement, i.e. D-QSSA (2.7), are applied to one simple biochemical network with mass conservation property, encompassing mass (substrate X) transport and containing enzymatic reactions. The initial value problem for corresponding non-linear system is formulated in (3.5), with initial conditions and parameter values from Tab. 1.

3.1 Enzyme catalyzed reactions with a substrate transport chain: S and Γ matrix

ODE system (3.5), i.e. the system of differential equations describing the process under study, depicted in Fig. 1 and Tab. 1, can be systematically derived using the so-called stoichiometric matrix $S \in \mathcal{R}^{n \times q}$ (q is the number of reactions) in some sense describing the topology of reaction

network. The vector of changes in species concentrations $x \in \mathcal{R}^n$ is then described as linear transformation of the reaction rate vector $\nu \in \mathcal{R}^q$: $\dot{x}(t) = S \nu(x, k)$.

Let us underline, that the first component of the rate vector, $\nu_1 = k_0(x_1 - x_2)$, is set based on the Fick's law.² The other components of the rate vector ν are determined by the law of mass action, i.e. the rate of change of a species (involved in a particular reaction) is proportional to the product of reaction rate constant and concentration of species involved in the reaction:

$$S = \begin{pmatrix} R_1 & R_2 & R_3 & R_4 \\ -1 & 0 & 0 & 0 \\ 1 & -1 & 1 & 0 \\ 0 & -1 & 1 & 1 \\ 0 & 1 & -1 & -1 \\ 0 & 0 & 0 & 1 \end{pmatrix}, \quad (3.1)$$

$$\nu = \begin{pmatrix} k_0 (x_1 - x_2) \\ k_1 x_2 x_3 \\ k_{-1} x_4 \\ k_2 x_4 \end{pmatrix}. \quad (3.2)$$

Reaction networks frequently possess subsets of reactants that remain constant at all times, i.e. they are referred as conserved species. Generally, there exists a conservation matrix Γ (its dimension is $h \times n$), the rows of which represent the linear combination of reactants constant in time. It can be solved explicitly for large systems ($0 = \Gamma S$). For our case of S in form of (3.1), the conservation property reads

$$\begin{aligned} x_3 + x_4 &= e_0, \\ x_1 + x_2 + x_4 + x_5 &= u_0. \end{aligned} \quad (3.3)$$

Consequently, here

$$\Gamma = \begin{pmatrix} 0 & 0 & 1 & 1 & 0 \\ 1 & 1 & 0 & 1 & 1 \end{pmatrix}. \quad (3.4)$$

The existence of two relations (3.3) signifies not only the possibility to reduce the number of state variables, but it also induces the reformulation of the governing equations for species concentration using negative M-matrices.

3.2 Governing equations for enzyme catalyzed reactions with time dependent administration of a substrate

A biochemical reaction kinetic model for the action of an enzyme catalyzed reactions with time dependent (e.g. periodic) administration of a substrate is schematically given in Fig. 1 and further described in Tab. 1 and Tab. 2. Basically, the resulting ODE system models two compartment system and in fact is composed as the combination of one ODE describing the transport of a substrate from exterior to interior compartment with one of perhaps the most well-known biochemical reaction network leading to the Michaelis-Menten kinetics, see Briggs and Haldane (1925).

² The flow of species X from an exterior compartment, e.g. dosing device, to the interior compartment (where the enzymatic reaction takes place) depends on the difference of species X concentrations ($x_1 - x_2$) and the proportionality constant is the first order diffusion coefficient k_0 , the so-called permeability constant encompassing the permeability coefficient and area of the membrane.

Table 1. Description of the transport and reaction process schematically depicted in Fig. 1.

Description of the related process	Chem. notation
R_0 : Substrate X_{ext} dosing ($u(t)$ input)	$\emptyset \rightarrow X_{ext}$
R_1 : Substrate transport (param. k_0)	$X_{ext} \rightleftharpoons X_{int}$
R_2 : Enzyme E binds to substrate, formation of a complex C (param. k_1)	$X_{int} + E \rightleftharpoons C$
R_3 : Reverse reaction to R_2 (param. k_{-1})	
R_4 : Complex breaks into E plus P – altered substrate molecule (param. k_2)	$C \rightarrow E + P$

Table 2. Model parameters values, units and descriptions, initial conditions and inputs; mostly from Eilertsen and Schnell (2020).

Param.	Value	Unit	Description
k_0	10	sec^{-1}	permeation coefficient
k_1	10	$\mu\text{M}^{-1} \text{sec}^{-1}$	association rate (forward rate constant)
k_{-1}	10	sec^{-1}	dissociation rate (reverse rate constant)
k_2	0.01	sec^{-1}	association catalytic rate
K_M	$\frac{k_{-1} + k_2}{k_1}$	μM	Michaelis constant
s_0	10	μM	init. substrate concn.
e_0	1	μM	init. enzyme concn.
u_0	10	μM	dose per period

Introducing the new notation for state variables, i.e. a size five vector x according to

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

the system of differential equations describing the process under study is usually written in the following form

$$\dot{x}(t) = Ax(t) + B(t), \quad (3.5)$$

with the constant matrix (the linear part of the system)

$$A = \begin{pmatrix} -k_0 & k_0 & 0 & 0 & 0 \\ k_0 & -k_0 & 0 & k_{-1} & 0 \\ 0 & 0 & 0 & k_{-1} + k_2 & 0 \\ 0 & 0 & 0 & -(k_{-1} + k_2) & 0 \\ 0 & 0 & 0 & k_2 & 0 \end{pmatrix}, \quad (3.6)$$

and the vector representing nonlinear (quadratic or bilinear) and constant (zero order) parts

$$B(t) = \begin{pmatrix} u(t) \\ -k_1 \cdot x_2(t) \cdot x_3(t) \\ -k_1 \cdot x_2(t) \cdot x_3(t) \\ k_1 \cdot x_2(t) \cdot x_3(t) \\ 0 \end{pmatrix}. \quad (3.7)$$

The initial conditions (at the beginning of the first cycle) are

$$x(0) = (u(t_0) \ 0 \ e_0 \ 0 \ 0)^T. \quad (3.8)$$

Model parameters are summarized in Table 2.

3.3 Comparison of different model reduction methods

The ODE system (3.5) can be simplified applying the just mentioned conservation properties (3.3). Moreover, it is to be expected an algebraic relation (slow manifold) between substrate concentrations in both compartments. The illustrative figure (made in sw Wolfram Mathematica) Fig. 2

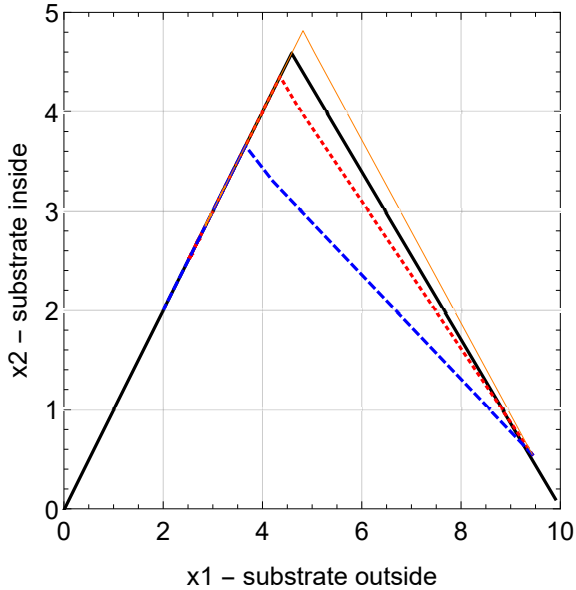


Fig. 2. The parametric plot in phase plane $x_1(t)$ vs. $x_2(t)$ for the full non-reduced system (black full line) and three lines representing three solutions using D-QSSA for 3 different values of delay τ .

confirms this expectation. I.e., slow invariant manifold can be detected for the fast variable x_1 : $x_1 = x_2$, valid for the interval $x_1 \in (0, 5)$. This manifold is reached after an initial transition when the trajectories corresponding to respective methods differ, cf. Fig. 2 – the result for the full non-reduced system (black full line) and three solutions computed based on D-QSSA (represented by three lines with the growing value of delay τ_i (from up to down: $\tau_1 = \frac{1}{k_{-1} + k_2 + k_1 s_0} \approx 0.02$ – thin orange line, $\tau_2 = 0.05$ – dotted red line, resp. $\tau_3 = 0.1$ – dashed blue line). The transitory interval needed to equalize the concentrations x_1 and x_2 ends for $t_{tr} \approx 0.2$, cf. the point $x_1 = x_2 = 5 = s_0/2$, then (for $t > t_{tr}$) all trajectories lie on the slow manifold defined by the relation $x_1 = x_2$.

Thus, using the relation $x_1 = x_2$ (for $t > t_{tr}$), we can further analyze the dynamics of substrate and complex concentrations in the interior compartment only, i.e., $x_2(t)$ vs. $x_4(t)$. The illustrative figure (made in sw Wolfram Mathematica) Fig. 3, shows the parametric plot in phase plane $x_2(t)$ vs. $x_4(t)$. Here, the solution of full non-reduced system is represented by the full black line and the slow invariant manifold resulting from the standard QSSA, while taking the state variable x_4 as the (other) fast variable, is represented by the dashed red line. Although in a certain time interval is the difference hardly visible, there is the initial and final part where both trajectories differ. Here is the room for finding an optimal constant delay using D-QSSA method.

In order to measure the quality of approximate solutions $x^A(t)$ we used the integral error metric comparing the outputs of the non-reduced and the reduced models³

³ In our numerical experiments we consider a time interval $t \in [0, T]$ and suppose an equidistant mesh t_0, t_1, \dots, t_m , with the time step $\Delta t = T/m$.

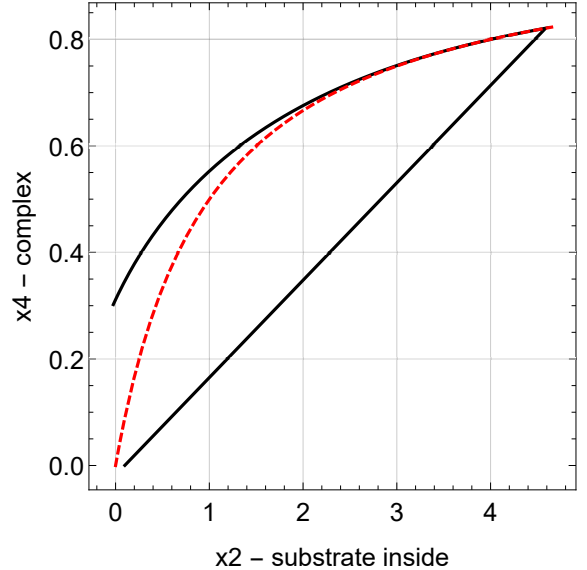


Fig. 3. The parametric plot in phase plane $x_2(t)$ vs. $x_4(t)$ for the full non-reduced system (full black line) and the slow invariant manifold (dashed red line) given by the condition $\dot{x}_4 = 0$.

$$\delta_i = \sum_{j=0}^m \frac{\|x_i(t_j) - x_i^A(t_j)\|}{\|x_i(t_j)\|}, \quad i = 1, \dots, 5. \quad (3.9)$$

In (3.9), the “exact” data $x_i(t_j)$, $j = 0, 1, \dots, m$, are computed values using the non-reduced model (full system) (3.5) and $x_i^A(t_j)$, $j = 0, 1, \dots, m$, $i = 1, \dots, 5$, are approximate solutions computed from models QSSA4, and D-QSSA4 (for the reduced fast variable x_4 using standard QSSA and delayed D-QSSA).

The following Tab. 3 gives the values δ_i computed for state variables $x_i(t)$, $i = 1, \dots, 5$, and two considered models. Indeed, using the D-QSSA method we obtain smaller error than using standard QSSA.

Table 3. Computed errors δ_i for state variables $x_i(t)$ corresponding to different models.

model	$i = 1$	$i = 2$	$i = 3$	$i = 4$	$i = 5$
QSSA4	0.0771	0.0943	0.3664	0.1214	187.2839
D-QSSA4	0.0136	0.0172	0.1423	0.0471	34.2719

4. CONCLUSION

We presented and further developed one novel technique of model reduction for a class of biochemical reaction networks. This technique has the potential to fill the gap between merely heuristic QSSA methods (in all their variants) and more theoretical methods, like singular perturbation methods. The assumptions for D-QSSA are not too restrictive and D-QSSA is applicable to the majority of biochemical systems based on the law of mass action. While the standard QSSA (or SPM) ignores the time needed by fast variables to reach their steady states, the advantage of D-QSSA is the possibility of a time delay introduction in order to improve the accuracy of approximation. This general conclusion has been supported by our example presented in Section 3.

Because the time varying delays may cause some difficulties in both numerical solution and subsequent theoretical analysis, we have treated the case of an approximation of the varying delay by a constant one. The essential first step for both the standard QSSA and the D-QSSA is the identification of the fast variables. However, in some systems none of the variables can be considered as fast, while a suitable combination can. Here, for the Michaelis-Menten enzyme kinetic network, the slow-fast variables separation and the condition for the validity of standard QSSA is well known. The expected advantage of the technique of the D-QSSA is the extension of D-QSSA to the model parameter domain prohibited for the standard QSSA.

Finally, an appealing feature of the D-QSSA (in comparison with the standard QSSA) is its suitability for oscillating systems. While the standard QSSA usually causes considerable errors in both the period and amplitude of oscillations the D-QSSA enables this error to be reduced substantially, cf. Vejchodský et al. (2014). It copes with our ongoing research devoted to the optimization of dosing regimes.

ACKNOWLEDGEMENT

We thank Prof. Ivo Marek, R.I.P., for his inspiring and original work in the field of Cell Biology. He put not only the basis of a novel approach (making linear ODEs from nonlinear cooperative systems) but he also traced new directions in the spirit of Control Engineering. Moreover, we thank to Dr. Ctirad Matonoha (ICS of CAS, Prague) for consulting some numerical issues related to the performance measures.

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