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ON AN OPTIMAL SETTING OF CONSTANT DELAYS FOR THE D-QSSA MODEL REDUCTION METHOD APPLIED TO A CLASS OF CHEMICAL REACTION NETWORKS

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Abstract. We develop and test a relatively simple enhancement of the classical model reduction method applied to a class of chemical networks with mass conservation properties. Both the methods, being (i) the standard quasi-steady-state approximation method, and (ii) the novel so-called delayed quasi-steady-state approximation method, firstly proposed by Vejchodský (2014), are extensively presented. Both theoretical and numerical issues related to the setting of delays are discussed. Namely, for one slightly modified variant 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 the results discussed. Finally, some future prospects related to further applications of the delayed quasi-steady-state approximation method are proposed.

Keywords: reaction network; model reduction; singular perturbation; quasi-steady-state approximation; D-QSSA method; optimization

MSC 2020: 92C45, 34A34, 65K10

1. Introduction

When dealing with many reaction systems, 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, it provides opportunities to reduce the system order, e.g., through singular perturbation methods [8], [9], [20]. Singular perturbation method

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for a controlled system is studied, e.g., in [15]. 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 [3], [17], [18] and references therein. Based on different QSS assumptions, different QSS approximation (QSSA[1]) methods have been proposed, e.g., the standard, reverse, and total QSSA in [5] and zero-derivative principle in [7].

As follows, in Section 2, instead of providing a detailed theoretical description of QSSA methods and their variants, we introduce only two of them: (i) the standard QSSA and (ii) the relatively novel and unexplored delayed QSSA (D-QSSA) recently formulated by Vejchodský [21] for a class of chemical networks. While the time-dependent delay was introduced in [21], here we are looking for a constant delay τ, in some sense optimal. Another study dealing with an observer design for linear systems with time dependent (even discontinuous) delays is presented in [14].

Afterward, in Section 3, an illustrative example (an extension of the 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. Mainly, we present and discuss the results of our numerical experiments, especially those related to the choice of an optimal delay. Finally, in Section 4 we resume our efforts and trace the directions for subsequent investigations. Let us underline that the model reduction methods applied to a class of chemical networks represent a relatively fresh field of study, being therefore worth analyzing.[2]

2. Two model reduction methods: standard QSSA and novel D-QSSA

This section introduces the notations used throughout this study, mainly based on a framework for describing the fast/slow ordinary differential equation (ODE) systems and singular perturbation methods (SPM). Moreover, we keep in mind that one of our aims is to present and promote the relatively novel extension of the QSSA method, i.e., the delayed QSSA (D-QSSA) method introduced by Vejchodský et al. [21], [22] for a class of mass-action models with a wide timescale separation.

[1] The nomenclature for the QSSA abbreviation is not unequivocal. In order to follow the mainstream paved, e.g., by [6], [16] we stick on the term *approximation* within QSSA abbreviation, contrarily to [21], [22].

[2] The authors actually develop one pilot study (concerning a dosing regime optimization for another chemical reaction system) aiming to compare both the precision and the computational cost of respective models solutions. An optimization procedure is expected to run faster on the reduced model than on the full model, while the precision issue is still uncertain.

Thus, we introduce an initial value problem for a system of ODEs that describes the time course of state variables (species concentrations) within a chemical reaction network with the mass conservation property.

First, let us consider the system of differential equations describing the process under study, which is usually written in the form

$$\dot{x}(t) = Ax(t) + b(x(t)) \tag{2.1}$$

for $t \in [0, T]$ with $T > 0$, where $x(t) \in \mathbb{R}^n$, a constant matrix $A \in \mathbb{R}^{n \times n}$ represents a linear part of the system, and $b(x(t)) \in \mathbb{R}^n$ represents non-linear and constant parts of the system. The above system (2.1) is throughout this paper associated with a set of initial conditions, such that $x(0) = x_0$. Suppose the existence of the fast and slow variables $x_F \in \mathbb{R}^{n_F}$ and $x_S \in \mathbb{R}^{n_S}$ and let $x(t) = (\, x_F^\top(t), x_S^\top(t)\,)^\top$ be the partitioning of $x(t)$, where $n_F + n_S = n$. Then for a general fast/slow ODE system it holds

$$\begin{aligned} \varepsilon \dot{x}_F &= f_F(x_S, x_F; \varepsilon), \\ \dot{x}_S &= f_S(x_S, x_F; \varepsilon), \end{aligned} \tag{2.2}$$

when $0 < \varepsilon \ll 1$ and suitable initial conditions are set. Then, the ODE system (2.2) can be approximated by a simpler algebro-differential system (the associated slow subsystem), see, e.g., [8], [9],

$$\begin{aligned} 0 &= f_F(x_S, x_F; 0), \\ \dot{x}_S &= f_S(x_S, x_F; 0). \end{aligned} \tag{2.3}$$

The equations (2.3) 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, 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 [5]. Several mathematical studies were dedicated to quantifying the accuracy of different QSSA methods applied to enzyme kinetics [5], [17], [18]. Common to these efforts is the identification of a presumably small parameter ε, see (2.2), which quantifies the timescale separation. This explicit identification of a suitable ε for every system and operating condition requires non-trivial 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 [6].

Here, for a class of chemical networks with the mass conservation property, we present how the so-called D-QSSA method [21], [22] can be successfully used without the necessity to identify an 'ε-based' condition for its validity. Another parameter of the D-QSSA method is a delay, which should be vigorously treated, e.g., determined through an optimization procedure.

Before stating definitions of QSS and D-QSS approximations, we will make the following assumption.

Assumption 2.1. Assuming a timescale separation for the rates of species evolution in a chemical network (2.1), let the state vector $x(t)$ be partitioned into the fast and slow parts, i.e., $x(t) = (\, x_F^\top(t), x_S^\top(t)\,)^\top$, where $x_F(t)$ is a vector composed of n_F fast variables and $x_S(t)$ is a vector composed from n_S slow variables. Let the non-reduced ODE system (2.1) be rewritten in the form

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

$t \in [0, T]$, with the initial conditions $x_F(0) = x_{F0}$ and $x_S(0) = x_{S0}$. Let $f \in \mathcal{C}^1(\mathbb{R})$, $g \in \mathcal{C}^1([0,T])$, $h \in \mathcal{C}^1(\mathbb{R}, \mathbb{R})$ be continuously differentiable functions (h in both variables) and let $g(t)$ be positive for $t \in [0, T]$.

2.1. Quasi-steady-state approximation for a class of mass-action models. In this subsection, we define a QSS approximation of the general system (2.1).

Definition 2.1. Let Assumption 2.1 be satisfied. Then the quasi-steady-state approximation of the fast variable $x_F(t)$ is defined as

$$x_F^{\mathrm{qss}}(t) = \frac{f(x_S(t))}{g(t)} \tag{2.5}$$

and the reduced ODE system for the slow variable $x_S(t)$ is defined via the *standard QSSA* as

$$\dot{x}_S(t) = h(x_F^{\mathrm{qss}}(t), x_S(t)). \tag{2.6}$$

2.2. Delayed quasi-steady-state approximation (D-QSSA). The standard QSSA method for model reduction is valid only when the timescale of fast species is significantly shorter than the timescale of the other (presumably) slow species. Analyzing the error of the standard QSSA method, Vejchodský et al. [22] 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 a slow invariant manifold. Therefore, if the quasi-steady-state changes (due to the 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 *the delayed quasi-steady-state assumption* (D-QSSA). As follows, we provide a definition of D-QSSA for the general system (2.1).

Definition 2.2. Let Assumption 2.1 be satisfied. Then the delayed quasi-steady-state approximation of the fast variable $x_F(t)$ is defined as

$$x_F^{\mathrm{dqss}}(t) = \frac{f(x_S(t-\tau(t)))}{g(t-\tau(t))}, \tag{2.7}$$

where $\tau(t)$ is generally a function of t, called a delay, and the reduced delayed ODE system for the slow variable $x_S(t)$ is defined via the *delayed QSSA* as

$$\dot{x}_S(t) = h(x_F^{\mathrm{dqss}}(t), x_S(t)). \tag{2.8}$$

R e m a r k 2.1. Note that the term $\tau(t) = 1/g(t)$ is used for the delay in [22] but an arbitrary function can be considered in Definition 2.2. In this paper, we further concentrate on the constant values of delay τ.

R e m a r k 2.2. For times $t < \tau(t)$, the quantity $t-\tau(t)$ is negative. Thus, in order that the D-QSSA approximation be defined, the slow variable x_S and the function g must be defined for negative values. It suffices to make an arbitrary extension, e.g., $x_S(t) = x_S(0)$ and $g(t) = g(0)$ for $t \leqslant 0$. The same is applied if the initial time is generally $t_0 > 0$. In this case $x_S(t) = x_S(t_0)$ and $g(t) = g(t_0)$ whenever $t \leqslant t_0$.

R e m a r k 2.3. The theorems concerning the equivalence of the D-QSSA method to the first-order correction of QSSA (up to terms cubic in the delay τ) as well as the theorems dealing with the D-QSSA error estimates, i.e., differences between the solution of the non-reduced system and its D-QSSA approximations, are presented in [22], e.g., Theorem 3.2 states that the reduced system *via* D-QSSA (2.8) approximates the invariant (slow) manifold of the system (2.4) up to terms quadratic in τ [22]. Furthermore, Vejchodský et al. in [22] claim that *"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 Section 3 on our numerical example.

2.3. Looking for an optimal delay of the D-QSSA technique. In the original works of D-QSSA authors, see [21], [22], the delay $\tau(t) = 1/g(t)$ was used. However, it generally depends on other (slow) system components, which causes some numerical issues when solving delayed differential equations by a computer algebra system.

Thus, the natural question is to consider a constant delay τ (independent of time t). This problem was treated in our publication [13], where the constant delay was used for simulating the states of a compartmental model for the action of pregnane X receptor causing the xenobiotic metabolizing enzyme induction [4], [10].

Consider again the delayed quasi-steady-state approximation of the fast variable $x_F(t)$ and the reduced delayed ODE system for the slow variable $x_S(t)$ but with a constant delay τ as follows (see Definition 2.2),

$$x_F^{\mathrm{dqss}}(t) = \frac{f(x_S(t-\tau))}{g(t-\tau)}, \tag{2.9}$$

$$\dot{x}_S(t) = h(x_F^{\mathrm{dqss}}(t), x_S(t)). \tag{2.10}$$

The solution of (2.10) is denoted as $x_S^{\mathrm{dqss}}(t)$. However, as it depends on the delay τ, we sometimes write $x_S^{\mathrm{dqss}}(t,\tau)$.

Next, we prove that $x_S^{\mathrm{dqss}}(t,\tau)$ depends continuously on the delay τ.

Lemma 2.1. *Let Assumption* 2.1 *be satisfied and let* $\tau \in [0,T]$. *Let* $x_F^{\mathrm{dqss}}(t)$ *(see* (2.9)*) be a D-QSS approximation of* $x_F(t)$ *and let* $x_S^{\mathrm{dqss}}(t,\tau)$ *be a solution of the reduced delayed ODE system* (2.10). *Let* $x_S^{\mathrm{dqss}}(t,\tau)$ *be continuous for* $t \in [0,T]$ *and let Remark* 2.2 *hold. Then* $x_S^{\mathrm{dqss}}(t,\tau)$ *is a continuous function with respect to* $\tau \in [0,T]$.

P r o o f. For the sake of simplification of the notation, let x_S stand for x_S^{dqss}. Let $t \in [0,T]$ and take arbitrary delays $\tau_1, \tau_2 \in [0,T]$, $\tau_1 \neq \tau_2$. Then $x_S(t,\tau_1)$ and $x_S(t,\tau_2)$ satisfy

$$\dot{x}_S(t,\tau_i) = h\Big(\frac{f(x_S(t-\tau_i,\tau_i))}{g(t-\tau_i)}, x_S(t,\tau_i)\Big), \quad i = 1,2,$$

see (2.9)–(2.10). As $t-\tau_2 = t-\tau_1+\tau_1-\tau_2$ and $x_S(\tilde{t},\tau)$, $\dot{x}_S(\tilde{t},\tau)$ are continuous for $\tilde{t} \in [-T,T]$ (continuity of $\dot{x}_S$ follows from Assumption 2.1), then using the Taylor expansion of $x_S(t-\tau_2,\tau_2)$ in $t-\tau_1$, we obtain

$$x_S(t-\tau_2,\tau_2) = x_S(t-\tau_1+\tau_1-\tau_2,\tau_2) = x_S(t-\tau_1,\tau_2) + \dot{x}_S(\hat{\tau}_x,\tau_2)(\tau_1-\tau_2),$$

where $\hat{\tau}_x = t-\tau_1+\vartheta_x(\tau_1-\tau_2)$, $\vartheta_x \in (0,1)$. Substituting into $f(x_S(t-\tau_2,\tau_2))$ and using the Taylor expansion in $x_S(t-\tau_1,\tau_2)$, we obtain

$$\begin{aligned} f(x_S(t-\tau_2,\tau_2)) &= f(x_S(t-\tau_1,\tau_2) + \dot{x}_S(\hat{\tau}_x,\tau_2)(\tau_1-\tau_2)) \\ &= f(x_S(t-\tau_1,\tau_2)) + Df(\hat{x})\dot{x}_S(\hat{\tau}_x,\tau_2)(\tau_1-\tau_2) \equiv \tilde{f}, \end{aligned} \tag{2.11}$$

where $\hat{x} = x_S(t-\tau_1,\tau_2) + \vartheta_f(\dot{x}_S(\hat{\tau}_x,\tau_2)(\tau_1-\tau_2))$, $\vartheta_f \in (0,1)$, and Df denotes the differential of f.

Similarly, using the Taylor expansion of $1/g(t-\tau_2)$ in $t-\tau_1$ we obtain

$$\frac{1}{g(t-\tau_2)} = \frac{1}{g(t-\tau_1+\tau_1-\tau_2)} = \frac{1}{g(t-\tau_1)} - \frac{g'(\hat{\tau}_g)}{g^2(\hat{\tau}_g)}(\tau_1-\tau_2) \equiv \tilde{g}, \tag{2.12}$$

where $\hat{\tau}_g = t-\tau_1+\vartheta_g(\tau_1-\tau_2)$, $\vartheta_g \in (0,1)$.

Substituting (2.11) and (2.12) into $\dot{x}_S(t,\tau_2)$, we obtain

$$\dot{x}_S(t,\tau_2) = h\Big(\frac{f(x_S(t-\tau_2,\tau_2))}{g(t-\tau_2)}, x_S(t,\tau_2)\Big) = h(\tilde{f}\tilde{g}, x_S(t,\tau_2)).$$

Thus, there exist functions $\mathcal{F}(x_S,\hat{\tau}_x,\hat{x},\hat{\tau}_g)$, $\mathcal{H}(x_S,\hat{\tau}_x,\hat{x},\hat{\tau}_g)$ such that

$$\begin{aligned}\dot{x}_S(t,\tau_2) &= h\Big(\frac{f(x_S(t-\tau_1,\tau_2))}{g(t-\tau_1)} + \mathcal{F}(x_S,\hat{\tau}_x,\hat{x},\hat{\tau}_g)(\tau_1-\tau_2), x_S(t,\tau_2)\Big)\\ &= h\Big(\frac{f(x_S(t-\tau_1,\tau_2))}{g(t-\tau_1)}, x_S(t,\tau_2)\Big) + \mathcal{H}(x_S,\hat{\tau}_x,\hat{x},\hat{\tau}_g)(\tau_1-\tau_2),\end{aligned}$$

where $\mathcal{F}$, $\mathcal{H}$ contain remaining terms, i.e.,

$$\begin{aligned}\mathcal{F}(x_S,\hat{\tau}_x,\hat{x},\hat{\tau}_g) = \frac{Df(\hat{x})\dot{x}_S(\hat{\tau}_x,\tau_2)}{g(t-\tau_1)} - f(x_S(t-\tau_1,\tau_2))\frac{g'(\hat{\tau}_g)}{g^2(\hat{\tau}_g)}\\ - Df(\hat{x})\dot{x}_S(\hat{\tau}_x,\tau_2)\frac{g'(\hat{\tau}_g)}{g^2(\hat{\tau}_g)}(\tau_1-\tau_2)\end{aligned}$$

and $\mathcal{H}(x_S,\hat{\tau}_x,\hat{x},\hat{\tau}_g) = h(\mathcal{F}(x_S,\hat{\tau}_x,\hat{x},\hat{\tau}_g))$. Then

$$\begin{aligned}\dot{x}_S(t,\tau_1) - \dot{x}_S(t,\tau_2) = h\Big(\frac{f(x_S(t-\tau_1,\tau_1))}{g(t-\tau_1)}, x_S(t,\tau_1)\Big) - h\Big(\frac{f(x_S(t-\tau_1,\tau_2))}{g(t-\tau_1)}, x_S(t,\tau_2)\Big)\\ - \mathcal{H}(x_S,\hat{\tau}_x,\hat{x},\hat{\tau}_g)(\tau_1-\tau_2).\end{aligned}$$

Put $e(t) = x_S(t,\tau_1) - x_S(t,\tau_2)$. Then using the Taylor expansion, we obtain

$$\begin{aligned}\dot{e}(t) =& -\mathcal{H}(x_S,\hat{\tau}_x,\hat{x},\hat{\tau}_g)(\tau_1-\tau_2) + h\Big(\frac{f(x_S(t-\tau_1,\tau_1))}{g(t-\tau_1)}, x_S(t,\tau_1)\Big)\\ &- h\Big(\frac{f(x_S(t-\tau_1,\tau_1)-e(t-\tau_1))}{g(t-\tau_1)}, x_S(t,\tau_1)-e(t)\Big)\\ =& D_1h(\widehat{w}_1,\widehat{w}_2)\frac{1}{g(t-\tau_1)}Df(x_S(t-\tau_1,\tau_1))e(t-\tau_1) + D_2h(\widehat{w}_1,\widehat{w}_2)e(t)\\ &- \mathcal{H}(x_S,\hat{\tau}_x,\hat{x},\hat{\tau}_g)(\tau_1-\tau_2),\end{aligned}$$

where

$$\widehat{w}_1 = \frac{f(x_S(t-\tau_1,\tau_1))}{g(t-\tau_1)} - \vartheta_1\frac{e(t-\tau_1)}{g(t-\tau_1)},\ \widehat{w}_2 = x_S(t,\tau_1) - \vartheta_2 e(t),\ \vartheta_i \in (0,1),\ i=1,2,$$

$D_i h$, $i = 1, 2$, denote the derivatives of h with respect to the first and the second variable, and Df denotes the differential of f. Thus, there exist functions $\mathcal{A}_1(x_S, \widehat{w}_1, \widehat{w}_2), \mathcal{A}_2(x_S, \widehat{w}_1, \widehat{w}_2)$ such that

$$\dot{e}(t) = \mathcal{A}_1(x_S, \widehat{w}_1, \widehat{w}_2)e(t-\tau_1) + \mathcal{A}_2(x_S, \widehat{w}_1, \widehat{w}_2)e(t) - \mathcal{H}(x_S, \hat{\tau}_x, \hat{x}, \hat{\tau}_g)(\tau_1 - \tau_2).$$

We prove that there exists $C > 0$ such that

$$|e(t)| \leqslant C|\tau_1 - \tau_2| \quad \forall\, t \in [0, T].$$

Note that $e(\tilde{t}) = 0$ for $\tilde{t} \in [-\max\{\tau_1, \tau_2\}, 0] \subseteq [-T, 0]$, because (see Remark 2.2)

$$e(\tilde{t}) = x_S(\tilde{t}, \tau_1) - x_S(\tilde{t}, \tau_2) = x_S(0) - x_S(0) = 0. \tag{2.13}$$

It is easy to see that there exists $k_T \in \mathbb{N}$ such that $T \in [k_T\tau_1, (k_T+1)\tau_1]$. Using the method of steps [19], the Gronwall inequality, and the induction for intervals $[(k-1)\tau_1, k\tau_1]$, $k = 1, \ldots, k_T$, we obtain:

$k = 1$: The values $e(t-\tau_1)$ for $t \in [0, \tau_1]$ are fixed, see (2.13), thus by the Gronwall lemma, there exists $C_1 > 0$ such that

$$|e(t)| \leqslant C_1|\tau_1 - \tau_2| \quad \text{for } t \in [0, \tau_1].$$

$k \rightsquigarrow k+1$: Having a solution for $t \in [(k-1)\tau_1, k\tau_1]$, we seek a solution for $t \in [k\tau_1, (k+1)\tau_1]$. The values $e(t)$ for $t \in [(k-1)\tau_1, k\tau_1]$ are known, therefore, the values $e(t-\tau_1)$ for $t \in [k\tau_1, (k+1)\tau_1]$ are also known, and thus $|e(t-\tau_1)| \leqslant C_k|\tau_1 - \tau_2|$. Using the Gronwall lemma, there exists $C_{k+1} > 0$ such that

$$|e(t)| \leqslant C_{k+1}|\tau_1 - \tau_2| \quad \text{for } t \in [k\tau_1, (k+1)\tau_1].$$

This last inequality for $k = k_T$ together with the definition of $e(t)$ imply that

$$|e(t)| = |x_S(t, \tau_1) - x_S(t, \tau_2)| \leqslant C|\tau_1 - \tau_2| \quad \forall\, t \in [0, T]$$

which implies continuity of $x_S(t, \tau)$ with respect to the delay $\tau \in [0, T]$. □

Now we are in a position to state the main theorem concerning the existence of an optimal constant delay.

Theorem 2.1. *Let Assumption* 2.1 *be satisfied. Let* $\bar{x}(t)$ *be a solution of the system* (2.4). *Choose arbitrary numbers* $0 < \underline{\tau} \leqslant \overline{\tau} < T$ *and a fixed constant delay* $\tau \in [\underline{\tau}, \overline{\tau}]$. *Let* $x_F^{\mathrm{dqss}}(t)$ *(see* (2.9)*) be a D-QSS approximation of* $x_F(t)$ *with this* τ.

Let $x_S^{\mathrm{dqss}}(t)$ be a solution of the reduced delayed ODE system (2.10)*, continuous for $t \in [0,T]$. Put $x^{\mathrm{dqss}}(t) = \big({x_F^{\mathrm{dqss}}}^{\top}(t), {x_S^{\mathrm{dqss}}}^{\top}(t) \big)^{\top}$. Then there exists at least one value $\tau^* \in [\underline{\tau}, \overline{\tau}]$ minimizing the error between $\bar{x}(t)$ and $x^{\mathrm{dqss}}(t)$, i.e.,*

$$\tau^* = \arg\min_{\tau} \|\bar{x}(t) - x^{\mathrm{dqss}}(t)\|^2 \quad \textit{subject to} \quad 0 < \underline{\tau} \leqslant \tau \leqslant \overline{\tau} < T, \tag{2.14}$$

where $\|\cdot\|$ denotes the vector $L^2[0,T]$-norm.

P r o o f. The discrepancy between the solution $\bar{x}(t)$ of the non-reduced system (2.4) and the solution $x^{\mathrm{dqss}}(t)$ of the reduced system (2.9)–(2.10) for a constant delay τ can be naturally formulated as a minimization problem in the form (2.14) where τ is a minimization parameter. Natural requirements for optimal τ are positiveness and boundedness from above by a suitable value (here a maximum time value T). Since $f(t)$ and $g(t)$ are continuous and $g(t)$ is positive, $x_F^{\mathrm{dqss}}(t)$ is continuous, and since $x_S^{\mathrm{dqss}}(t)$ is also continuous, the whole $x^{\mathrm{dqss}}(t)$ is continuous for $t \in [0,T]$. Moreover, $x_S^{\mathrm{dqss}}(t)$ is continuous with respect to τ due to Lemma 2.1. These properties ensure that the norm in (2.14) is well defined and thus there exists at least one solution $\tau^* \in [\underline{\tau}, \overline{\tau}]$ satisfying (2.14). □

In case the system (2.4) is solved numerically using, e.g., the Euler method, let $0 = t_0, t_1, \ldots, t_m = T$ be a time discretization with a time step Δt. The optimal delay defined in (2.14) depends on the exact solution $\bar{x}(t)$ of the non-reduced system. As this solution is typically unavailable, it is usually replaced by a numerical approximation or measured data. In the case of measured data, we assume that they may be available only for some points t_k, $k \in K \subset \{0, \ldots, m\}$. Let $x^{\mathrm{dqss}}(t_j)$, $j = 0, \ldots, m$, be a D-QSS approximation at time steps $t_0, \ldots, t_m$. Then the minimization problem analogous to (2.14) can be formulated as

$$\tau^* = \arg\min_{\tau} \sum_{j=0}^{m} [\bar{x}(t_j) - x^{\mathrm{dqss}}(t_j)]^2 \quad \text{subject to} \quad 0 < \underline{\tau} \leqslant \tau \leqslant \overline{\tau} < T, \tag{2.15}$$

where we set $\bar{x}(t_k) = x^{\mathrm{dqss}}(t_k)$ for $k \notin K$ in case the measured data are used.

Definition 2.3. The value τ^* which is a solution of the minimization problems (2.14) or (2.15) is called the *optimal delay* and the corresponding solution

$$x_F^{\mathrm{odqss}}(t) = \frac{f(x_S(t-\tau^*))}{g(t-\tau^*)} \tag{2.16}$$

is called the optimal delayed quasi-steady-state approximation (OD-QSSA) of the fast variable $x_F(t)$. The reduced optimal delayed ODE system for the slow variable $x_S(t)$ is defined via the *optimal delayed QSSA* as

$$\dot{x}_S(t) = h(x_F^{\mathrm{odqss}}(t), x_S(t)). \tag{2.17}$$

3. Numerical example

In this section, two previously defined model reduction methods are examined on a relatively simple example. Namely, the standard QSSA (2.6), as well as its refinement D-QSSA (2.8), are applied to a chemical reaction network with mass conservation property, encompassing mass transport (by a diffusion process) between an outer and inner compartment containing enzymatic reactions, see Table 1.

While the transport process is governed by Fick's law[3], chemical reactions are described as

$$X_{\text{in}} + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C, \quad C \xrightarrow{k_2} E + P.$$

Basically, the resulting ODE system models a two-compartment system that is derived as the combination of one ODE describing the transport of a substrate from outer to the inner compartment with the well-known chemical reaction network leading to the Michaelis-Menten kinetics [3].

	Description of the related process	Chem. notation	Param.
T_1:	Substrate transport between compartments	$X_{\text{out}} \rightleftharpoons X_{\text{in}}$	k_0
R_1:	Enzyme E binds to substrate forming	$X_{\text{in}} + E \rightleftharpoons C$	k_1
	a complex C (reversibly)		k_{-1}
R_2:	Complex breaks down into E and	$C \to E + P$	k_2
	product P—altered substrate molecule		

Table 1. Enzyme catalyzed reactions with a substrate transport chain.

Param.	Value	Unit	Description
k_0	10	sec^{-1}	permeability constant
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
u_0	10	μM	initial substrate concentration
e_0	1	μM	initial enzyme concentration

Table 2. The values, units, and descriptions of model parameters, initial conditions, and inputs (mostly from [5]).

[3] The flow of species X from the outer compartment, e.g., dosing device, to the inner compartment (where the enzymatic reaction takes place) depends on the difference of species X concentrations $(x_1 - x_2)$ when 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).

3.1. Enzyme catalyzed reactions with a substrate transport chain: Governing equations. Let us introduce the following notation for the concentrations of the respective chemical species,

$$x(t) = \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \\ x_4(t) \\ x_5(t) \end{pmatrix} \equiv \begin{pmatrix} X_{\text{out}}(t) \\ X_{\text{in}}(t) \\ E(t) \\ C(t) \\ P(t) \end{pmatrix}.$$

Then, based on the law of mass action and Fick's law, the chemical kinetics of this system is described by the five equations

$$\begin{aligned}
\dot{x}_1(t) &= -k_0 x_1(t) + k_0 x_2(t), \\
\dot{x}_2(t) &= k_0 x_1(t) - k_0 x_2(t) - k_1 x_2(t) x_3(t) + k_{-1} x_4(t), \\
\dot{x}_3(t) &= -k_1 x_2(t) x_3(t) + k_{-1} x_4(t) + k_2 x_4(t), \\
\dot{x}_4(t) &= k_1 x_2(t) x_3(t) - k_{-1} x_4(t) - k_2 x_4(t), \\
\dot{x}_5(t) &= k_2 x_4(t).
\end{aligned}$$

The system of differential equations describing the process under study can be expressed in the form (2.1), where the constant matrix (the linear part of the system) reads

$$A = \begin{pmatrix} -k_0 & k_0 & 0 & 0 & 0 \\ k_0 & -k_0 & 0 & k_{-1} & 0 \\ 0 & 0 & 0 & k_{-1} + k_2 & 0 \\ 0 & 0 & 0 & -(k_{-1} + k_2) & 0 \\ 0 & 0 & 0 & k_2 & 0 \end{pmatrix} \tag{3.1}$$

and the vector representing non-linear (quadratic or bilinear) and constant parts

$$b(x(t)) = \begin{pmatrix} 0 \\ -k_1 \cdot x_2(t) \cdot x_3(t) \\ -k_1 \cdot x_2(t) \cdot x_3(t) \\ k_1 \cdot x_2(t) \cdot x_3(t) \\ 0 \end{pmatrix}. \tag{3.2}$$

The initial conditions are

$$x(0) = (\, u_0 \quad 0 \quad e_0 \quad 0 \quad 0 \,)^\top. \tag{3.3}$$

The values of model parameters (initial conditions and parameter values) are summarized in Table 2.

R e m a r k 3.1. Reaction networks frequently possess subsets of reactants that remain constant at all times, i.e., they are referred to as conserved species. For the studied system we observe that $\dot{x}_3(t)+\dot{x}_4(t) = 0$ and $\dot{x}_1(t)+\dot{x}_2(t)+\dot{x}_4(t)+\dot{x}_5(t) = 0$, i.e., the conservation property reads

$$x_3 + x_4 = e_0, \quad x_1 + x_2 + x_4 + x_5 = u_0. \tag{3.4}$$

The existence of relations (3.4) 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 thanks to the fact that all five state variables are involved in relations (3.4). This relatively unknown property was studied in several works of Bohl and Marek, see, e.g., [1], [2], [12].

In what follows, we will study the nine models described in detail in the following subsections and comparing them with the full system.

3.2. Model simplification using the conservation properties. Due to the two relations (3.4), the system (3.1)–(3.3) can be simplified as follows. Since $x_3(t) = e_0 - x_4(t)$, we can (i) replace the state variable $x_3(t)$ by $x_4(t)$ in all equations, and (ii) the corresponding ODE with $\dot{x}_3(t)$ can be omitted. Moreover, we can consider only three equations, because the last variable $x_5(t)$ can be easily computed from the second relation in (3.4). Thus, the full (non-reduced) system can be equivalently reformulated using (only) three variables x_1, x_2, x_4:

$$\begin{aligned}
\dot{x}_1(t) &= -k_0 x_1(t) + k_0 x_2(t),\\
\dot{x}_2(t) &= k_0 x_1(t) - k_0 x_2(t) + k_{-1} x_4(t) - k_1 x_2(t)(e_0 - x_4(t)),\\
\dot{x}_4(t) &= -(k_{-1} + k_2) x_4(t) + k_1 x_2(t)(e_0 - x_4(t)),
\end{aligned}$$

or

$$\dot{x}(t) = \bar{A}x(t) + \bar{b}(x(t)), \tag{3.5}$$

where

$$x(t) = (\, x_1(t) \quad x_2(t) \quad x_4(t) \,)^\top,$$

and

$$\bar{A} = \begin{pmatrix} -k_0 & k_0 & 0 \\ k_0 & -(k_0 + e_0 k_1) & k_{-1} \\ 0 & e_0 k_1 & -(k_{-1} + k_2) \end{pmatrix}, \quad \bar{b}(x(t)) = \begin{pmatrix} 0 \\ k_1 x_2(t) x_4(t) \\ -k_1 x_2(t) x_4(t) \end{pmatrix}.$$

The initial conditions are

$$x(0) = (\, u_0 \quad 0 \quad 0 \,)^\top . \tag{3.6}$$

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 [21]. The functions $f_1(x_S(t))$, $g_1(t)$ for $x_1(t)$ and $f_4(x_S(t))$, $g_4(t)$ for $x_4(t)$, respectively, see (2.4), have the form

$$f_1(x_S(t)) = k_0 x_2(t), \quad g_1(t) = k_0,$$
$$f_4(x_S(t)) = e_0 k_1 x_2(t), \quad g_4(t) = k_{-1} + k_2 + k_1 x_2(t).$$

It is well known that the QSS approximation is derived for larger times (to enable the fast variable to get to its steady-state), and hence it may not satisfy the original initial condition. This happens in system (3.5) if x_1 is considered as a fast variable. Indeed, setting $\dot{x}_1(t) = 0$, i.e.,

$$\dot{x}_1(t) = -k_0 x_1(t) + k_0 x_2(t) \equiv 0,$$

the QSS approximation leads to

$$x_1^{\mathrm{qss}}(t) = \frac{f_1(x_S(t))}{g_1(t)} = x_2(t),$$

conflicting the initial conditions $x_1(0) = u_0 > 0$ and $x_2(0) = 0$ (it cannot hold $x_1^{\mathrm{qss}}(0) = x_2(0)$). Therefore, we introduce a parameter t_Q, $0 < t_Q < T$, and derive the QSS approximation in the sense of Definition 2.1 for $t > t_Q$ only. For $t \in [0, t_Q]$, we use the conservation property (3.4), initial conditions (3.3), and define the "QSS" approximation as

$$x_1^{\mathrm{qss}}(t) = u_0 - x_2(t) - x_4(t),$$

in order that $x_5(t)$ were non-negative for $t \in [0, t_Q]$ and satisfied the initial condition $x_5(0) = 0$. Note that in the case $x_1^{\mathrm{qss}}(t) = x_1(0) = u_0$ for all $t \in [0, t_Q]$, the value $x_5(t) = u_0 - x_1(t) - x_2(t) - x_4(t) = -x_2(t) - x_4(t)$ would be negative, which is not possible for our chemical network system. The discontinuity of $x_1^{\mathrm{qss}}(t)$ for $t = t_Q$ does not mind, because we are primarily interested in the quasi-steady-state solution $x_1^{\mathrm{qss}}(t)$ for $t > t_Q$. Moreover, in the section Numerical results, we optimize the parameter t_Q, which can be in some sense viewed as an optimization of the jump between $x_1^{\mathrm{qss}}(t_Q)$ and $x_2(t_Q)$. Thus,

$$x_1^{\mathrm{qss}}(t) = u_0 - x_2(t) - x_4(t), \quad t \leqslant t_Q, \tag{3.7}$$

$$x_1^{\mathrm{qss}}(t) = x_2(t), \quad t > t_Q. \tag{3.8}$$

The same idea can be applied when x_4 is a fast variable. But in this case

$$\dot{x}_4(t) = e_0 k_1 x_2(t) - (k_{-1} + k_2) x_4(t) - k_1 x_2(t) x_4(t) \equiv 0,$$

the QSS approximation is

$$x_4^{\mathrm{qss}}(t) = \frac{f_4(x_S(t))}{g_4(t)} = \frac{e_0 k_1 x_2(t)}{k_{-1} + k_2 + k_1 x_2(t)}, \tag{3.9}$$

and there is no conflict with the initial conditions $x_4^{\mathrm{qss}}(0) = x_2(0) = x_4(0) = 0$. Thus, we can define the QSS approximation (3.9) for all $t \geqslant 0$ and no t_Q is needed.

Lemma 3.1. *Let x_1 be a fast variable of the ODE system* (3.5)–(3.6). *Choose $t_Q > 0$ and consider the QSS approximations* (3.7)–(3.8) *of $x_1(t)$. Further, let the system* (3.5) *be solved using the Euler method at time points $t_1, t_2, \ldots$ with a constant time step $\Delta t = t_j - t_{j-1}$. Then:*

(1) *If $t_Q < \Delta t$, then the zero solutions $x_i(t_j) = 0$ for all $i = 1, \ldots, 5$ and for all $j = 1, 2, \ldots$, are obtained.*
(2) *If $t_Q \geqslant \Delta t$, then the non-zero solutions $x_i(t_j)$, $i = 1, \ldots, 5$, $j = 1, 2, \ldots$, are obtained.*

P r o o f. Let no t_Q be considered. As x_1 is a fast variable, then setting $\dot{x}_1(t) = 0$, the first equation in (3.5) implies that $x_1^{\mathrm{qss}}(t) = x_2(t)$ holds for every t. We obtain the reduced system

$$\begin{aligned} \dot{x}_2(t) &= -e_0 k_1 x_2(t) + k_{-1} x_4(t) + k_1 x_2(t) x_4(t), \\ \dot{x}_4(t) &= e_0 k_1 x_2(t) - (k_{-1} + k_2) x_4(t) - k_1 x_2(t) x_4(t). \end{aligned} \tag{3.10}$$

Solving this system for $t = t_1$ using the Euler method leads to a linear system with a regular matrix and a zero right-hand side (due to zero initial conditions for $x_2(0)$ and $x_4(0)$). Thus, a zero solution $x_2(t_1) = x_4(t_1) = 0$ is obtained and a QSSA approximation $x_1^{\mathrm{qss}}(t_1) = x_2(t_1) = 0$ as well. The conservation properties (3.4) lead to zero solutions $x_4(t_1) = x_5(t_1) = 0$. Repeating this process for all t_j, $j = 2, 3, \ldots$, we obtain zero solutions $x_i(t) = 0$, $i = 1, \ldots, 5$ for all t.

On the other hand, let us define the QSS approximation (3.8) for $t > t_Q$ and use (3.7) for $t \leqslant t_Q$ instead. The case $t \leqslant t_Q$ implies that $x_1^{\mathrm{qss}}(t_1) = u_0 - x_2(t_1) - x_4(t_1)$ and we obtain a reduced system

$$\begin{aligned} \dot{x}_2(t) = &-(k_0 + e_0 k_1) x_2(t) + k_{-1} x_4(t) + k_1 x_2(t) x_4(t) \\ &+ k_0 (u_0 - x_2(t) - x_4(t)), \\ \dot{x}_4(t) = &\, e_0 k_1 x_2(t) - (k_{-1} + k_2) x_4(t) - k_1 x_2(t) x_4(t). \end{aligned} \tag{3.11}$$

Solving this system for $t = t_1$ with the use of the Euler method leads to a linear system with a regular matrix and a non-zero right-hand side (due to a non-zero constant term k_0u_0). Thus, a non-zero solution $x_2(t_1)$, $x_4(t_1)$ is obtained.

When $t > t_Q$, we obtain the system (3.10). The use of the Euler method leads to a linear system with a regular matrix and a non-zero right-hand side (due to the non-zero initial conditions for $x_2(t_Q)$ and $x_4(t_Q)$). Thus, a non-zero solution $x_2(t_Q+\Delta t)$, $x_4(t_Q + \Delta t)$ is obtained and a QSSA approximation $x_1^{\mathrm{qss}}(t_Q + \Delta t) = x_2(t_Q + \Delta t)$ as well. The conservation properties (3.4) lead to non-zero solutions $x_4(t_Q + \Delta t)$, $x_5(t_Q + \Delta t)$. Repeating this process for the next time step, we obtain non-zero solutions $x_i(t)$, $i = 1, \dots, 5$, for all $t > t_Q$. □

3.3. Reduced models—3 different ODEs for the standard QSSA. Starting from (3.5), x_1 and x_4 can be considered as fast variables and then using Definition 2.1 and Lemma 3.1 we deal with the three possibilities that are described in detail in the following three subsections.

3.3.1. QSSA1—the fast variable is $x_1(t)$. Letting $\dot{x}_1(t) = 0$ in (3.5) then with an appropriate value t_Q, we obtain the QSS approximation for $x_1(t)$ and reduced ODEs for $x_2(t), x_4(t)$:

▷ For $t \leqslant t_Q$:

$$
\begin{aligned}
x_1^{\mathrm{qss}}(t) &= u_0 - x_2(t) - x_4(t),\\
\dot{x}_2(t) &= -(k_0 + e_0k_1)x_2(t) + k_{-1}x_4(t) + k_1x_2(t)x_4(t)\\
&\quad + k_0(u_0 - x_2(t) - x_4(t)),\\
\dot{x}_4(t) &= e_0k_1x_2(t) - (k_{-1} + k_2)x_4(t) - k_1x_2(t)x_4(t).
\end{aligned}
\tag{3.12}
$$

The initial conditions at $t = 0$ are (see (3.6))

$$x_2(0) = x_4(0) = 0.$$

▷ For $t > t_Q$:

$$
\begin{aligned}
x_1^{\mathrm{qss}}(t) &= x_2(t),\\
\dot{x}_2(t) &= -e_0k_1x_2(t) + k_{-1}x_4(t) + k_1x_2(t)x_4(t),\\
\dot{x}_4(t) &= e_0k_1x_2(t) - (k_{-1} + k_2)x_4(t) - k_1x_2(t)x_4(t).
\end{aligned}
\tag{3.13}
$$

The initial conditions at $t = t_Q$ are the solutions $x_2(t_Q)$, $x_4(t_Q)$ from the system (3.12).

3.3.2. QSSA4—the fast variable is $x_4(t)$. Letting $\dot{x}_4(t) = 0$ in (3.5), we obtain the QSS approximation for $x_4(t)$

$$x_4^{\mathrm{qss}}(t) = \frac{e_0 k_1 x_2(t)}{k_{-1} + k_2 + k_1 x_2(t)} \tag{3.14}$$

and the reduced ODEs for $x_1(t)$, $x_2(t)$

$$\begin{aligned}
\dot{x}_1(t) &= -k_0 x_1(t) + k_0 x_2(t), \\
\dot{x}_2(t) &= k_0 x_1(t) - k_0 x_2(t) - \frac{e_0 k_1 k_2 x_2(t)}{k_{-1} + k_2 + k_1 x_2(t)}.
\end{aligned}$$

The initial conditions are (see (3.6))

$$x_1(0) = u_0, \quad x_2(0) = 0.$$

3.3.3. QSSA14—the fast variables are $x_1(t)$, $x_4(t)$. Both reductions are fulfilled (after some initial transition time), i.e., it holds (3.12) for $t \leqslant t_Q$ and (3.13) for $t > t_Q$ together with (3.14) as well. Thus, after setting $\dot{x}_1(t) = \dot{x}_4(t) = 0$, only one ODE for $x_2(t)$ governs the process. The QSS approximations for $x_1(t), x_4(t)$ and the equation for $x_2(t)$ after substitution are the following:

▷ For $t \leqslant t_Q$:

$$\begin{aligned}
x_1^{\mathrm{qss}}(t) &= u_0 - x_2(t) - x_4^{\mathrm{qss}}(t), \\
x_4^{\mathrm{qss}}(t) &= \frac{e_0 k_1 x_2(t)}{k_{-1} + k_2 + k_1 x_2(t)}, \\
\dot{x}_2(t) &= -\frac{e_0 k_1 k_2 x_2(t)}{k_{-1} + k_2 + k_1 x_2(t)} - k_0 x_2(t) + k_0 (u_0 - x_2(t) - x_4^{\mathrm{qss}}(t)).
\end{aligned} \tag{3.15}$$

The initial condition at $t = 0$ is (see (3.6))

$$x_2(0) = 0.$$

▷ For $t > t_Q$:

$$\begin{aligned}
x_1^{\mathrm{qss}}(t) &= x_2(t), \\
x_4^{\mathrm{qss}}(t) &= \frac{e_0 k_1 x_2(t)}{k_{-1} + k_2 + k_1 x_2(t)}, \\
\dot{x}_2(t) &= -\frac{e_0 k_1 k_2 x_2(t)}{k_{-1} + k_2 + k_1 x_2(t)}.
\end{aligned} \tag{3.16}$$

The initial condition at $t = t_Q$ is the solution $x_2(t_Q)$ from equation (3.15).

3.4. Reduced model based on D-QSSA. Starting from (3.5), three possibilities for the delayed QSS approximation are again considered. Using Definition 2.2 and Lemma 3.1, we derive the equations with initial conditions in a similar way like in Subsection 3.3. As the delay we use the value $\tau(t) = 1/g(t)$ as in [22].

3.4.1. D-QSSA1—the fast variable is $x_1(t)$. We arrive at the D-QSSA approximation of $x_1(t)$ using the value t_Q and equations for $x_2(t), x_4(t)$ after substitution as follows:

▷ For $t \leqslant t_Q$:

(3.17)
$$\begin{aligned} x_1^{\mathrm{dqss}}(t) &= u_0 - x_2(t) - x_4(t),\\ \dot{x}_2(t) &= -(k_0 + e_0k_1)x_2(t) + k_{-1}x_4(t) + k_1x_2(t)x_4(t) + k_0(u_0 - x_2(t) - x_4(t)),\\ \dot{x}_4(t) &= e_0k_1x_2(t) - (k_{-1} + k_2)x_4(t) - k_1x_2(t)x_4(t). \end{aligned}$$

The initial conditions at $t = 0$ are (see (3.6))

$$x_2(0) = x_4(0) = 0.$$

▷ For $t > t_Q$:

(3.18)
$$\begin{aligned} x_1^{\mathrm{dqss}}(t) &= x_2(t-\tau), \quad \tau = \frac{1}{k_0} = \text{const.},\\ \dot{x}_2(t) &= -(k_0 + e_0k_1)x_2(t) + k_{-1}x_4(t) + k_1x_2(t)x_4(t) + k_0x_2(t-\tau),\\ \dot{x}_4(t) &= e_0k_1x_2(t) - (k_{-1} + k_2)x_4(t) - k_1x_2(t)x_4(t). \end{aligned}$$

The initial conditions at $t = t_Q$ are the solutions $x_2(t_Q)$, $x_4(t_Q)$ from the system (3.17). The value $x_2(t_Q)$ is also taken in case $t - \tau < t_Q$, see Remark 2.2.

3.4.2. D-QSSA4—the fast variable is $x_4(t)$. The D-QSS approximation of $x_4(t)$ is defined as

$$x_4^{\mathrm{dqss}}(t) = \frac{e_0k_1x_2(t-\tau(t))}{k_{-1} + k_2 + k_1x_2(t-\tau(t))}, \quad \tau(t) = \frac{1}{k_{-1} + k_2 + k_1x_2(t)}. \tag{3.19}$$

Substituting into the equations for $x_1(t), x_2(t)$, we obtain

$$\begin{aligned} \dot{x}_1(t) &= -k_0x_1(t) + k_0x_2(t),\\ \dot{x}_2(t) &= k_0x_1(t) - (k_0 + e_0k_1)x_2(t) + (k_{-1} + k_1x_2(t))x_4^{\mathrm{dqss}}(t)\\ &= k_0x_1(t) - (k_0 + e_0k_1 - k_1x_4^{\mathrm{dqss}}(t))x_2(t) + k_{-1}x_4^{\mathrm{dqss}}(t). \end{aligned}$$

The initial conditions at $t = 0$ are (see (3.6))

$$x_1(0) = u_0, \quad x_2(0) = 0.$$

The value $x_2(t - \tau(t)) = 0$ is also taken in case $t - \tau(t) < 0$, see Remark 2.2.

3.4.3. D-QSSA14—the fast variables are $x_1(t), x_4(t)$. This case is again separated using the value t_Q leading to the D-QSS approximations of $x_1(t), x_4(t)$ and one ODE for $x_2(t)$ after substitution as follows:

▷ For $t \leqslant t_Q$:

$$
\begin{aligned}
(3.20)\qquad x_1^{\mathrm{dqss}}(t) &= u_0 - x_2(t) - x_4^{\mathrm{dqss}}(t),\\
x_4^{\mathrm{dqss}}(t) &= \frac{e_0 k_1 x_2(t-\tau_4(t))}{k_{-1}+k_2+k_1 x_2(t-\tau_4(t))}, \quad \tau_4(t) = \frac{1}{k_{-1}+k_2+k_1 x_2(t)},\\
\dot{x}_2(t) &= k_0 x_1^{\mathrm{dqss}}(t) - (k_0 + e_0 k_1) x_2(t) + k_{-1} x_4^{\mathrm{dqss}}(t) + k_1 x_2(t) x_4^{\mathrm{dqss}}(t)\\
&= -(k_0 + e_0 k_1 - k_1 x_4^{\mathrm{dqss}}(t)) x_2(t) + k_{-1} x_4^{\mathrm{dqss}}(t)\\
&\quad + k_0 (u_0 - x_2(t) - x_4^{\mathrm{dqss}}(t)).
\end{aligned}
$$

The initial condition at $t = 0$ is (see (3.6))

$$x_2(0) = 0.$$

▷ For $t > t_Q$:

$$
\begin{aligned}
(3.21)\qquad x_1^{\mathrm{dqss}}(t) &= x_2(t-\tau_1), \quad \tau_1 = \frac{1}{k_0} = \text{const.},\\
x_4^{\mathrm{dqss}}(t) &= \frac{e_0 k_1 x_2(t-\tau_4(t))}{k_{-1}+k_2+k_1 x_2(t-\tau_4(t))}, \quad \tau_4(t) = \frac{1}{k_{-1}+k_2+k_1 x_2(t)},\\
\dot{x}_2(t) &= -(k_0 + e_0 k_1 - k_1 x_4^{\mathrm{dqss}}(t)) x_2(t) + k_{-1} x_4^{\mathrm{dqss}}(t) + k_0 x_2(t-\tau_1).
\end{aligned}
$$

The initial condition at $t = t_Q$ is the solution $x_2(t_Q)$ from equation (3.20). The value $x_2(t_Q)$ is also taken in case $t - \tau_1 < t_Q$ or $t - \tau_4(t) < t_Q$, see Remark 2.2.

R e m a r k 3.2. An algebraic relation (slow manifold) between substrate concentrations is expected in both compartments. Fig. 1 (made in the software Wolfram Mathematica) shows two parametric plots in phase plane $x_1(t)$ vs. $x_2(t)$ and $x_2(t)$ vs. $x_4(t)$, respectively. On the left, the dynamics begins from the initial state $[10, 0]$ in the right down corner and the slow invariant manifold can be detected for the fast variable x_1 ($x_1 = x_2$), which is valid for the interval $x_1 \in (0, 5)$ (i.e., after an initial fast transition ending at the time instant t_Q). Another slow invariant manifold (or x_4-nullcline) can be detected in the right part of Fig. 1 for the fast variable x_4. Here, the dynamics begins from the initial state $[0, 0]$ in the bottom left corner and the slow invariant manifold is described by the Michaelis-Menten relation: $x_4^{\mathrm{qss}}(t) = e_0 k_1 x_2(t)/(k_{-1} + k_2 + k_1 x_2(t))$. Although the difference is hardly visible in certain time intervals, there are the initial and final parts where both trajectories clearly differ.

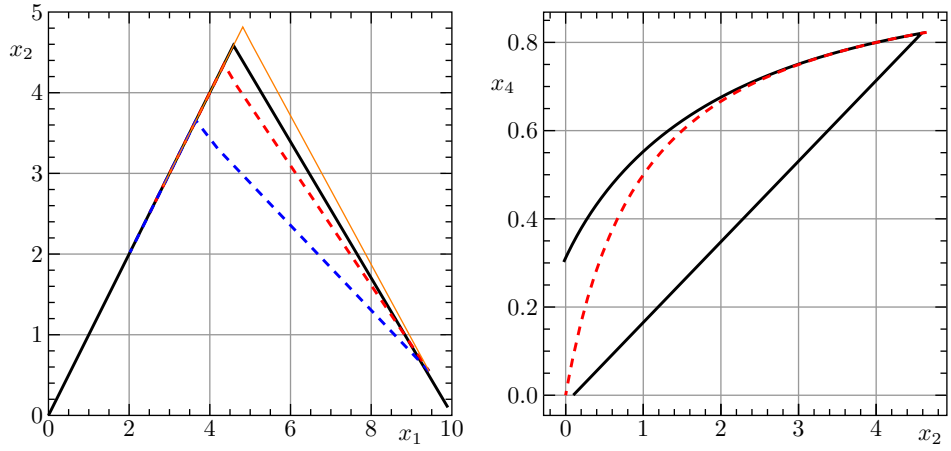

Figure 1. Left: The parametric plot in the phase plane $x_1(t)$ vs. $x_2(t)$ for the full non-reduced system (solid black line) and for three D-QSSA4 approximations where the value of D-QSSA4 delay is growing from up to down: $\tau_1 = 1/(k_{-1} + k_2 + k_1 u_0) \approx 0.02$ (thin orange line), $\tau_2 = 0.05$ (dashed red line), $\tau_2 = 0.1$ (dashed blue line).
Right: The parametric plot in the phase plane $x_2(t)$ vs. $x_4(t)$ for the full non-reduced system (solid black line) and the slow invariant manifold (dashed red line) given by the relation $x_4(t) = e_0 k_1 x_2(t)/(k_{-1} + k_2 + k_1 x_2(t)) = e_0 x_2(t)/(K_M + x_2(t))$ derived from the QSSA4 ($\dot{x_4} = 0$), where $K_M = (k_{-1} + k_2)/k_1$ is the so-called Michaelis constant.

3.5. Reduced model based on OD-QSSA with the optimal constant delay τ^*. This case is the same as the case described in Subsection 3.4. The only difference is that the optimal constant delay τ^* computed from (2.15) is used instead of the delay $\tau(t) = 1/g(t)$. Here the exact solution $\bar{x}(t_j)$ in (2.15)—the values $\bar{x}_i(t_j)$, $j = 0, 1, \ldots, m$, $i = 1, 4$, are supposed to be the values computed using the non-reduced model (full system) (3.1)–(3.3). The meaning of t_Q is the same as in the previous subsections.

R e m a r k 3.3. Suppose that all the above ODE systems are solved using the Euler method and the solutions at times $t_1, \ldots, t_j$, $j \geqslant 1$, are computed. Then, before computing the solution at time t_{j+1}, in case of the D-QSSA model and a time dependent delay $\tau(t)$, e.g., $\tau(t) = 1/g(t)$, all the old values $x_2(t_k - \tau(t_k))$, $k = 1, \ldots, j$, must be stored because $g(t_k)$ can attain arbitrary values. On the other hand, in the case of the OD-QSSA model, the delay is constant and thus it suffices to store only the last $\lfloor(\tau/\Delta t)\rfloor$ values of $x_2(t_k - \tau)$.

3.6. Numerical results (comparison of different model reduction methods) and some issues related to the setting of an optimal delay. In this subsection, we compare the models described in detail above and introduced in Table 3.

Model	Description
Non-reduced	full system (3.1)–(3.3)
QSSA1	x_1 is a fast variable
QSSA4	x_4 is a fast variable
QSSA14	both x_1 & x_4 are fast
D-QSSA1	x_1 is a fast variable, delay $\tau = 1/g(t)$, see Definition 2.2
D-QSSA4	x_4 is a fast variable, delay $\tau = 1/g(t)$, see Definition 2.2
D-QSSA14	both x_1 & x_4 are fast, delay $\tau = 1/g(t)$, see Definition 2.2
OD-QSSA1	x_1 is a fast variable, delay $\tau =$ const. optimal, see Sec. 2.3
OD-QSSA4	x_4 is a fast variable, delay $\tau =$ const. optimal, see Sec. 2.3
OD-QSSA14	both x_1 & x_4 are fast, delay $\tau_i =$ const.$_i$ optimal, $i = 1, 4$

Table 3. Schematic description of the ten models studied.

The models introduced in Table 3 were used to obtain approximate solutions $x^A(t)$. In our numerical experiments we consider a time interval $t \in [0, T]$ and suppose an equidistant mesh $0 = t_0, t_1, \ldots, t_m = T$ with the time step $\Delta t = T/m$.

To compare the quality of approximate solutions $x^A(t)$ with a solution $\bar{x}(t)$ of the original non-reduced model (full system) (3.1)–(3.3), for each of the five state variables we used the error metric

$$\delta_i = \sqrt{\sum_{j=0}^{m} \frac{(\bar{x}_i(t_j) - x_i^A(t_j))^2}{(\bar{x}_i(t_j))^2}}, \quad i = 1, \ldots, 5. \tag{3.22}$$

Then, in order to quantify the integral error for different models (different reduction methods), the total error value

$$\delta = \sum_{i=1}^{5} \delta_i \tag{3.23}$$

is defined.

In (3.22), the exact solution $\bar{x}_i(t_j)$, $j = 0, 1, \ldots, m$, is assumed to be the values computed using the non-reduced model (full system) (3.1)–(3.3). The values $x_i^A(t_j)$, $j = 0, 1, \ldots, m$, $i = 1, \ldots, 5$, are approximate solutions computed from the models QSSAk (i.e., $x^{\mathrm{qss}}(t_j)$), D-QSSAk (i.e., $x^{\mathrm{dqss}}(t_j)$), and OD-QSSAk (i.e., $x^{\mathrm{odqss}}(t_j)$), $k = 1, 4, 14$.

Moreover, we also optimize the value t_Q when needed. This leads to a small-scale optimization process for (i) two variables τ and t_Q in the case of OD-QSSA1, (ii) one variable τ in the case of OD-QSSA4, and (iii) three variables τ_1, τ_4, and t_Q in the case of OD-QSSA14. The optimization system UFO [11] was used for minimization purposes.

We used the values of parameters given in Table 2, $T = 0.5$, and the time step $\Delta t = 10^{-4}$. The ODEs were solved using the backward Euler method (outer iteration). The resulting non-linear equation for a solution at time t_j was solved using the Newton method (inner iteration).

In Fig. 2 we plot the solutions for the fast variable $x_1(t)$, computed using four strategies (models): the full system, QSSA, D-QSSA, and OD-QSSA. Both the D-QSSA1 (on the top) and D-QSSA14 (bottom part of the figure) provide unsatisfactory results. Note that on the first graph (solution $x_1(t)$ for the fast variable x_1), the QSSA1 curve (dashed blue) nearly coincides with the OD-QSSA1 curve (solid green).

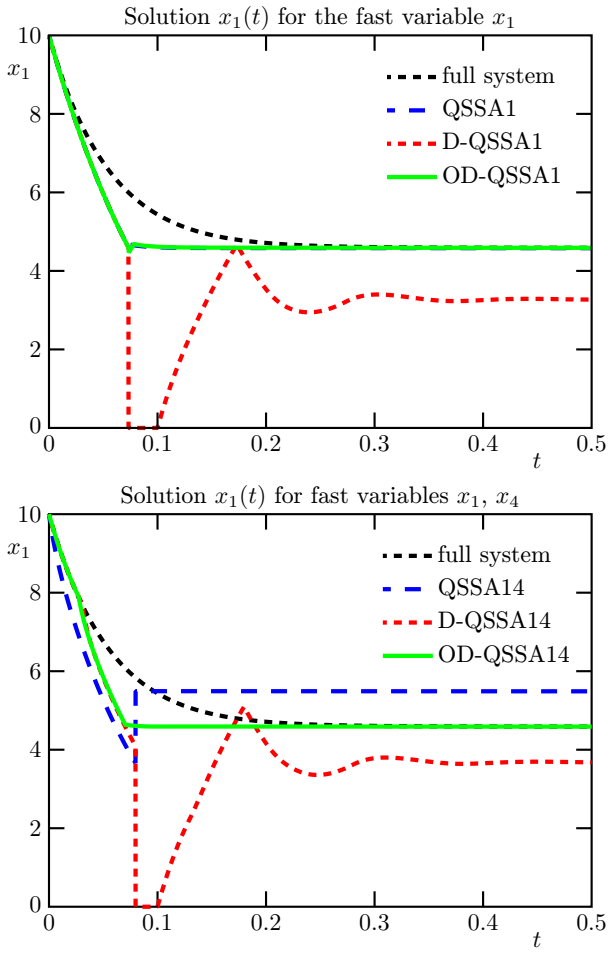

Figure 2. Solution x_1 obtained by using five different strategies: the full system, QSSA approach, delayed QSSA approach with $\tau = 1/g(t)$, and delayed QSSA approach with the optimal constant delay τ. Upper: QSSA1 nearly coincides with OD-QSSA1.

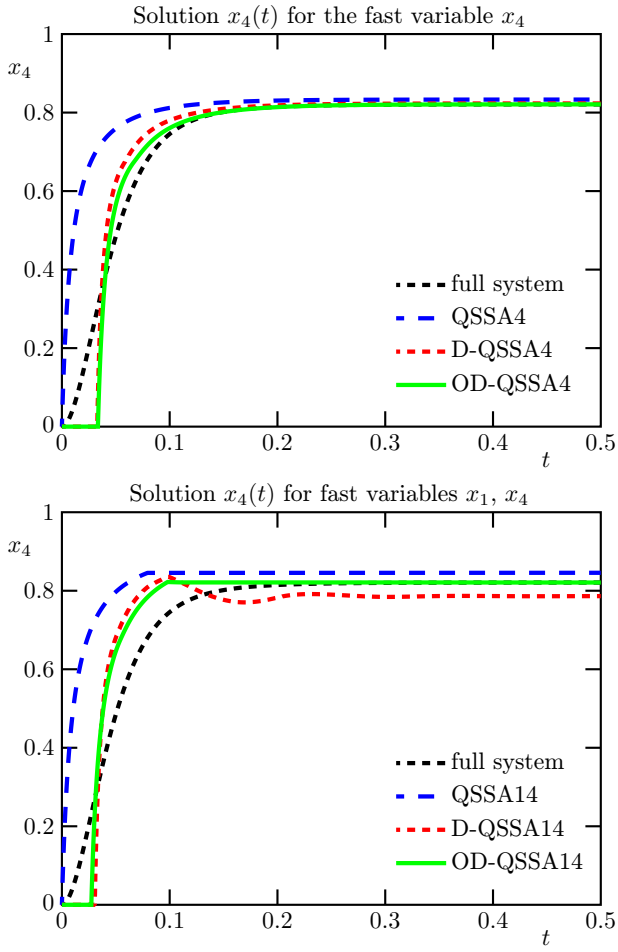

Figure 3. Solution x_4 obtained by using five different strategies: the full system, QSSA approach, delayed QSSA approach with $\tau = 1/g(t)$, and delayed QSSA approach with the optimal constant delay τ.

In Fig. 3 we plot the solutions for $x_4(t)$, computed using the same strategies (models). Again here, the OD-QSSA variant of the D-QSSA technique outperforms other model reductions, although they provide more satisfactory results than similar models in Fig. 2.

The QSSA and D-QSSA models give a poor approximation of the solution. It is clearly visible especially for D-QSSA when x_1 (as well as both x_1 and x_4) is considered as fast. The equality $x_1^{\mathrm{dqss}}(t) = x_2(t-\tau)$ does not approximate well the exact solution. The constant value of delay $\tau = 1/k_0$ is bad in this case, and another value should be found. Better results are obtained for the fast variable x_4, where the delay τ depends on time t.

Finally, using an optimal constant delay τ, the OD-QSSA model leads to rather good results. As mentioned in [21], it cannot be expected that this approximation is good for small t. This phenomenon is clearly seen for t smaller than 0.2. After that, for $t \geqslant 0.2$, the OD-QSSA approximation is nearly identical to the exact solution. Moreover, as we have a more suitable value of the constant delay τ, the approximation $x_1^{\mathrm{odqss}}(t)$ is now much more accurate than $x_1^{\mathrm{dqss}}(t)$ for $\tau = 1/k_0$. An important question is how to determine this optimal constant value without knowing the exact solution and no subsequent comparison with the computed ones. This will be a subject of our future research.

Model	δ_1	δ_2	δ_3	δ_4	δ_5	total δ	time1	time2
Non-reduced	-	-	-	-	-	-	1.00	1.00
QSSA1	0.0586	0.0636	0.0696	0.0231	2.3492	2.5641	0.79	0.79
QSSA4	0.0771	0.0943	0.3664	0.1214	187.2839	187.9431	0.69	0.69
QSSA14	0.1117	0.1427	0.3987	0.1321	214.4269	215.2122	0.19	0.19
D-QSSA1	0.3449	0.2792	0.1997	0.0662	626.6338	627.5239	0.92	0.92
D-QSSA4	0.0136	0.0172	0.1423	0.0471	34.2719	34.4921	1.02	1.02
D-QSSA14	0.3557	0.2867	0.2642	0.0875	644.3346	645.3288	0.39	0.39
OD-QSSA1	0.0589	0.0634	0.0696	0.0231	2.3079	2.5229	0.89	1.24
OD-QSSA4	0.0013	0.0039	0.1272	0.0421	9.5216	9.6960	0.89	1.02
OD-QSSA14	0.0618	0.0628	0.1497	0.0496	0.5187	0.8425	0.13	0.31

Table 4. Computed errors δ_i for each component $x_i(t)$ and each model, the total value δ, and times as the ratio of the individual model to the non-reduced model (time2 are the values with minimization).

Table 4 gives the values δ_i computed for each component $x_i(t)$, $i = 1, \ldots, 5$, and each considered model. We see that using the optimal τ we obtain the smallest errors. Also, we can see that the component $x_5(t)$ contributes the most to the total error metric δ which means that x_5 is far from the exact solution. Using a suitable constant delay τ, this can be significantly reduced up to the accepted value.

Moreover, in Table 4, we give time comparison of each model as the ratio of the individual model to the non-reduced full system model. Values time1 are the times of computation of the solution $x(t)$ for given values t_Q and delay(s), while values time2 are the times that include the minimization process, i.e., seeking for optimal t_Q and/or optimal delay(s).

From the column time1 we can make some simple and clear conclusions. (i) The QSSA models do not work with the vector $x_2(t - \tau(t))$ and thus they are faster than other models. (ii) Both D-QSSA1 and OD-QSSA1 models work with a constant delay and thus they are almost equally fast. (iii) Similarly, both OD-QSSA1 and OD-QSSA4 models work with a constant delay and thus they are almost

equally fast. (iv) This is not the case of D-QSSA1 (constant delay) and D-QSSA4 (delay depends on t) models and thus the former is faster. (v) The D-QSSA4 model, in contrast to the OD-QSSA4 model, computes the delay $\tau(t_j)$ at each iteration and thus it is slower. (vi) The same can be said for D-QSSA14 and OD-QSSA14 models. (vii) The D-QSSA14 model is much faster than D-QSSA1 and D-QSSA4 models as it works only with one differential equation. (viii) The same can be said for the OD-QSSA14 model compared to OD-QSSA1 and OD-QSSA4 models. (ix) The OD-QSSA14 model is the fastest as it works only with one differential equation and constant delays. (x) Seeking the optimal values t_Q, τ_1, τ_4 is very cheap as it is a small-scale optimization problem (1–3 dimensions) and thus the models using optimal delay(s) do not consume too much extra time compared to models using standard delay(s) $1/g(t)$ (see a small increase of time in the column time2).

In Table 5 we present the optimal values of t_Q and τ, computed using the UFO system [11], that minimize δ. To compare the results correctly, we first computed the optimal value t_Q and then used the same value in the models QSSA1, QSSA14, D-QSSA1, and D-QSSA14.

Method	t_Q	Delay τ
QSSA1	used optimal	-
QSSA4	-	-
QSSA14	used optimal	-
D-QSSA1	used optimal	$1/k_0 = 0.1$
D-QSSA4	-	$1/(k_{-1} + k_2 + k_1 x_1(t))$
D-QSSA14	used optimal	$\tau_1 = 1/k_0 = 0.1,\ \tau_4(t) = 1/(k_{-1} + k_2 + k_1 x_1(t))$
OD-QSSA1	0.07344	0.004697
OD-QSSA4	-	0.03343
OD-QSSA14	0.07086	$\tau_1 = 0.0006762,\ \tau_4 = 0.02732$

Table 5. Optimal values of t_Q and delay τ used.

4. Discussion and conclusion

We presented and further developed one relatively novel model reduction technique for a class of chemical reaction networks. This technique can 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 most chemical 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 improving the approximation accuracy. This general conclusion has been supported by our numerical example presented in Section 3.

Special attention was paid to searching for a constant delay in some sense optimal. We announce Theorem 2.1 claiming the existence of an optimal delay introduced when each approximation based on respective QSSA is applied. Numerical results show that there exists some optimal constant value giving better results than the original value of delay proposed by Vejchodský et al. [21], [22]. Although the existence of an optimal constant delay for the D-QSSA technique was already stated in our recent conference paper [13], in this work, we present a more detailed study of the same phenomenon. Finding optimal delay(s) is not computationally expensive as the optimization problem is small-scale; on the other hand, in order to compute an optimal delay, we need an approximate solution or at least some measured data.

Our ongoing research concerns the dosing regime optimization for different biochemical reaction systems. Namely, we work on the application of the D-QSSA technique to the previously studied compartmental model for the action of pregnane X receptor causing the xenobiotic metabolizing enzyme induction [4], [10] with periodic dosing, i.e., the governing ODE system is defined either as (i) a non-autonomous initial value problem, or (ii) a boundary value problem. Here we aim to compare both the precision and the computational cost of the respective model solution. We expect that the times of computation of a suitable optimization procedure are more favorable for reduced models than for the full model, while the precision issue should be thoroughly checked. There is one more issue to be examined: the slow-fast variables separation and the setting of QSSA. While for the Michaelis-Menten enzyme kinetic network (with one simple diffusion transport between two compartments) the separation between slow and fast variables is relatively straightforward, for a more complex biochemical system the possibility of such separation and the application of order reduction techniques is definitely not so clear. The expected advantage of the application of the D-QSSA technique is the extension of D-QSSA to the model parameter domain prohibited for the standard QSSA, as it was stated in [22]: *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.*

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