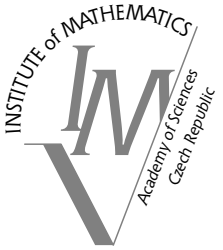

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Reduction of chemical systems by delayed quasi-steady state assumptions

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Abstract

Mathematical analysis of mass action models of large complex chemical systems is typically only possible if the models are reduced. The most common reduction technique is based on quasi-steady state assumptions. To increase the accuracy of this technique we propose *delayed* quasi-steady state assumptions (D-QSSA) which yield systems of delay differential equations. We define the approximation based on D-QSSA and prove the corresponding error estimate showing the accuracy of this approximation. Then we define a class of well mixed chemical systems and formulate assumptions enabling the application of D-QSSA. We also apply the D-QSSA to a model of Hes1 expression to illustrate the improved accuracy of the D-QSSA with respect to the standard quasi-steady state assumptions.

Keywords. Chemical dynamics, mass action, system reduction, ordinary differential equations, delay differential equations, error estimate.

1 Introduction

The dynamic behaviour of complex chemical and biochemical systems can be analysed by the mathematical tools of bifurcation analysis. However, in certain situations the size of the problem can make these tools impractical or even impossible to use. In these cases, we may try to reduce the system to make it amenable to analysis while conserving its dynamic behaviour.

There are already many ideas and methods for model reduction of chemical systems described in the literature. For example, a computational singular perturbation reduction method for chemical kinetics with slow and fast variables is defined and analysed in [25]. The method of invariant manifold is presented

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in [7]. A global approach to model reduction based on the concept of minimal entropy production and its numerical implementation can be found in [10]. A model reduction technique for multiscale biochemical networks is described in [17]. Model reductions based on quasi-steady state assumptions and variable lumping are analysed from the point of view of control theory in [12]. A method for approximation of the slow manifold of a complex system in cases when a direct approximation is not possible is presented in [6]. A collection of methods for analytical derivation and numerical computation of the slow invariant manifolds can be found in [8]. Finally, the paper [15] reviews three general strategies for model reduction of chemical systems: lumping, sensitivity analysis, and time-scale analysis.

Nevertheless, the idea of using time delays for model reduction of chemical systems has, to our knowledge, not been explored. Of course, various models of chemical kinetics with time delays exist. For example, the law of mass action is extended in [18] to allow for delayed effects. Delay differential equations are used in [14] to model transcriptional delay. A stochastic algorithm with delays is presented in [19]. However, a systematic approach for model reduction based on delays does not appear to exist.

In the context of mass action models of chemical systems, the standard tool for model reduction is the quasi-steady state assumption (QSSA). Mathematically, mass action models are systems of coupled ordinary differential equations (ODEs) for a number of variables. Based on practical knowledge of the chemical system, these variables can, in some cases, be split into fast and slow variables, see e.g. [5]. The application of the QSSA then replaces the ODEs for the fast variables by algebraic equations, allowing them to be expressed algebraically in terms of the slow variables, and the original system of ODEs, can thus be reduced to a system for only the slow variables.

The QSSA is used extensively. The first application of the QSSA to chemical kinetic systems dates back to 1913 [2, 22]. The QSSA has been analysed many times, see the review [20] and references therein. Probably the best known example of the application of the QSSA is the Michaelis–Menten kinetics [13]. A suitable change of variables can enhance the quality of the QSSA approximation, see for example the total QSSA approach [3]. The error of the QSSA approximation has been analysed in [21], where ODEs for the error are derived.

Studying the error of the QSSA approximation, we note that in the original system the fast variables always need a certain amount of time to reach their quasi-steady states. Therefore, if the quasi-steady state changes (due to change in the slow variables), the corresponding fast variable will reach the new value of the quasi-steady state with a certain time delay. On the other hand, in the reduced system the QSSA approximation stays in this quasi-steady state and, thus, it changes immediately. This discrepancy between the original and reduced systems can be naturally decreased by introducing time delays to the QSSA. This new approach is called the *delayed quasi-steady state assumption* (D-QSSA).

The idea of D-QSSA has been recently applied to a particular biochemical system modelling circadian rhythms [23] to illustrate the accuracy of the D-QSSA approximation. This has been the first attempt to use the D-QSSA with a specific application and no analysis. However, the D-QSSA can be defined for a general class of problems and its error can be rigorously analysed. Therefore, we present below a general definition of the D-QSSA and its first error estimate.

In Section 2 we define the D-QSSA for a general linear ODE and we formulate and prove the corresponding error estimate. This is an upper bound for instantaneous error of the D-QSSA approximation. It implies that in a special case the error decreases exponentially towards zero as the system evolves in time. Section 3 considers a general chemical system and its corresponding mass action ODE model. We explicitly show how to apply the D-QSSA to such systems and we rigorously state the necessary assumptions. In Section 4 we apply both the QSSA and D-QSSA to a model of expression of Hes1 protein and compare the accuracy of both approximations. Finally, Section 5 discusses the results and draws conclusions.

2 Delayed quasi-steady state assumption and error estimates

The D-QSSA can be applied to an ordinary differential equation of the form

$$\frac{\mathrm{d}}{\mathrm{d}t}x(t) = f(t) - g(t)x(t), \quad \text{for } t \in (0,T), \tag{1}$$

where $T > 0$ and $g(t)$ is positive in $(0,T)$. The D-QSSA approximation is defined as follows.

Definition 2.1. *The delayed quasi-steady state approximation $\tilde{x}(t)$ to the solution $x(t)$ of equation (1) is given by*

$$\tilde{x}(t) = \frac{f(t-\tau(t))}{g(t-\tau(t))}, \quad \textit{where } \tau(t) = \frac{1}{g(t)}. \tag{2}$$

Let us emphasize that $\tilde{x}(t)$ is designed to approximate the long-time behaviour of $x(t)$. If t is close to zero then approximation (2) 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 $\tilde{x}(t)$ depends on arbitrary extensions of f and g to negative values. Thus, we cannot expect good approximation qualities of $\tilde{x}(t)$ for t close to zero. This is in agreement with the properties of the standard QSSA and with the error estimate presented below.

The D-QSSA approximation can be derived in the case of constant $g(t)$ from the following expression for the solution of (1) with initial condition $x(0) = x^0$:

$$x(t) = x^0 \exp[-tg_c] + \int_0^t f(s) \exp[(s-t)g_c] \, \mathrm{d}s,$$

where $g_c > 0$ stands for the constant value of $g(t)$. The integral in this expression can be approximated by a one-node quadrature rule

$$\int_0^t f(s) \exp[(s-t)g_c] \, \mathrm{d}s \approx w f(t-\tau), \tag{3}$$

where the quadrature node $t-\tau$ and the quadrature weight w are to be determined such that this quadrature rule is exact for all *linear functions* f. This can be seen as a quadrature with weighting function $\omega(s) = \exp[(s-t)g_c]$. Notice that $\omega(t) = 1$ and as s goes from t towards 0, values $\omega(s)$ decrease exponentially fast towards zero. Thus, the value of integral (3) is influenced mainly by values of f close to t. The values of f far from t have little influence on the value of the integral. Therefore, the simple one-node quadrature rule provides reasonable accuracy in many cases. Further, let us note that for $t < \tau$ the approximation $wf(t-\tau)$ depends on values of f outside $(0, t)$. This corresponds to the poor approximation qualities of $\tilde{x}(t)$ for small values of t.

As we mentioned above, quantities τ and w can be explicitly determined such that quadrature rule (3) is exact for all *linear functions* f. The expressions for τ and w are complicated, but if we neglect all terms that decline to zero exponentially with t, we obtain $\tau = 1/g_c$ and $w = 1/g_c$. Consequently, the approximation $x(t) \approx wf(t-\tau)$ coincides with (2). For the explicit formulae for τ and w and for more details about this heuristic derivation, we refer to [23].

Let us note that using a one-node quadrature rule with the node at t,

$$\int_0^t f(s) \exp[(s-t)g_c] \, \mathrm{d}s \approx w_0 f(t),$$

we can determine the weight w_0 such that the rule is exact for all *constant functions* f. Neglecting the exponentially decaying terms, we obtain $w_0 = 1/g_c$ and, thus, the standard QSSA approximation $x(t) \approx f(t)/g_c$.

To analyse the accuracy of the D-QSSA approximation (2), we present the following error estimate. It is an estimate of the difference between the solution $x(t)$ of equation (1) and its D-QSSA approximation $\tilde{x}(t)$ given by (2).

Theorem 2.1. *Let $T > 0$ and $0 < \varepsilon \le M$ be fixed constants, $f \in C^2([-1/\varepsilon, T])$, and $g \in C([-1/\varepsilon, T])$. Let $0 < \varepsilon \le g(t) \le M$ for all $t \in [-1/\varepsilon, T]$. Further, let $x(t) \in C^1([0, T])$ be the solution of the ODE (1) with initial condition $x(0) = x^0$ and let $\tilde{x}(t)$ be given by (2). Then*

$$|x(t) - \tilde{x}(t)| \le 2\left(\frac{1}{\varepsilon} - \frac{1}{M}\right) \max_{[-1/\varepsilon, t]} |f| + \frac{1}{\varepsilon^3} \max_{[-1/\varepsilon, t]} |f''| + Q(t) \tag{4}$$

for all $t \in [0,T]$, where the prime denotes the derivative and

$$Q(t) = \left[|x^0| + \frac{1}{\varepsilon} \max_{[-1/\varepsilon,t]} |f| + \frac{t}{\varepsilon} \max_{[-1/\varepsilon,t]} |f'| + \frac{1}{2\varepsilon} \left(\frac{1}{\varepsilon^2} + t^2 \right) \max_{[-1/\varepsilon,t]} |f''| \right] \exp(-\varepsilon t).$$

Proof. Let $t \in [0,T]$ be fixed. Without loss of generality we set $\varepsilon = \min_{[-1/\varepsilon,t]} g$ and $M = \max_{[-1/\varepsilon,t]} g$.

First, we split the error $x(t) - \tilde{x}(t)$ as follows:

$$|x(t) - \tilde{x}(t)| \leq |x(t) - \hat{x}(t)| + |\hat{x}(t) - \tilde{x}(t)| \tag{5}$$

with

$$\hat{x}(t) = \frac{f(t - \tau(t))}{g(t)}.$$

Note that $\tau(t) \leq 1/\varepsilon$ and, hence, the second term in this splitting can be easily bounded as

$$|\hat{x}(t) - \tilde{x}(t)| \leq \left(\frac{1}{\varepsilon} - \frac{1}{M} \right) \max_{[-1/\varepsilon,t]} |f|. \tag{6}$$

Since the solution of (1) with initial condition $x(0) = x^0$ can be expressed as

$$x(t) = x^0 \exp\left[-G(t)\right] + \int_0^t f(s) \exp\left[G(s) - G(t)\right] \, \mathrm{d}s,$$

where $G(t) = \int_0^t g(r) \, \mathrm{d}r$, we can estimate

$$\begin{aligned} |x(t) - \hat{x}(t)| \leq \left| x^0 \exp\left[-G(t)\right] \right| + \left| \int_0^t f(s) \left(\exp[G(s) - G(t)] - \exp[g(t)(s-t)] \right) \, \mathrm{d}s \right| \\ + \left| \int_0^t f(s) \exp[g(t)(s-t)] \, \mathrm{d}s - \hat{x}(t) \right|. \end{aligned} \tag{7}$$

Clearly, we can bound the first term on the right-hand side of (7) as

$$\left| x^0 \exp\left[-G(t)\right] \right| \leq |x^0| \exp[-\varepsilon t]. \tag{8}$$

To bound the second term, we consider

$$\begin{aligned} Z(s) = \exp[G(s) - G(t)] - \exp[g(t)(s-t)] &= \exp\left[- \int_s^t g(r) \, \mathrm{d}r \right] - \exp[g(t)(s-t)] \\ &\leq \exp[-\varepsilon(t-s)] - \exp[-g(t)(t-s)]. \end{aligned}$$

Hence,

$$\begin{aligned} \int_0^t Z(s) \, \mathrm{d}s &\leq \int_0^t \exp[-\varepsilon(t-s)] - \exp[-g(t)(t-s)] \, \mathrm{d}s \\ &= \frac{1}{\varepsilon} - \frac{1}{g(t)} - \frac{\exp[-\varepsilon t]}{\varepsilon} + \frac{\exp[-g(t)t]}{g(t)} \leq \frac{1}{\varepsilon} - \frac{1}{g(t)} \leq \frac{1}{\varepsilon} - \frac{1}{M}. \end{aligned}$$

Similarly, since

$$Z(s) \geq \exp[-M(t-s)] - \exp[-g(t)(t-s)],$$

we bound

$$\int_0^t Z(s)\,\mathrm{d}s \geq \frac{1}{M} - \frac{1}{\varepsilon}.$$

Thus, the second term on the right-hand side of (7) can be estimated as

$$\left| \int_0^t f(s) \left(\exp[G(s) - G(t)] - \exp[g(t)(s-t)] \right) \mathrm{d}s \right| \;\leq\; \left(\frac{1}{\varepsilon} - \frac{1}{M} \right) \max_{[0,t]} |f|. \quad (9)$$

To estimate the final term on the right-hand side of (7), we employ the Taylor expansion for $s \in [0,t]$:

$$f(s) = f(t-\tau) + f'(t-\tau)(s-t+\tau) + R(s)(s-t+\tau)^2/2,$$

where $R \in C([0,t])$ and $\tau = 1/g(t)$ agrees with definition (2). Hence, we can calculate

$$I = \int_0^t f(s) \exp[g(t)(s-t)]\,\mathrm{d}s - \hat{x}(t) = Q_1 + \int_0^t R(s) \frac{(s-t+\tau)^2}{2} \exp[g(t)(s-t)]\,\mathrm{d}s,$$

where $Q_1 = [tf'(t-\tau) - f(t-\tau)]\,\tau \exp[-g(t)t]$. Since R can be bounded as $|R(s)| \leq \max_{[-1/\varepsilon,t]} |f''|$, we can estimate

$$|I| \leq |Q_1| + \frac{\tau^3}{2} \max_{[-1/\varepsilon,t]} |f''| + |Q_2|, \quad (10)$$

where $Q_2 = -\frac{1}{2}\tau(\tau^2 + t^2) \exp[-g(t)t] \max_{[-1/\varepsilon,t]} |f''|$.

Combining (5), (6), (7), (8), (9), (10), and using the fact that $\tau(t) \leq 1/\varepsilon$, we obtain

$$|x(t) - \tilde{x}(t)| \leq 2 \left(\frac{1}{\varepsilon} - \frac{1}{M} \right) \max_{[-1/\varepsilon,t]} |f| + \frac{1}{2\varepsilon^3} \max_{[-1/\varepsilon,t]} |f''| + Q_3,$$

where $Q_3 = |x^0| \exp[-\varepsilon t] + |Q_1| + |Q_2|$. Clearly, $Q_3 \leq Q(t)$. □

Notice that if f, and its first two derivatives, are bounded then the reminder $Q(t)$ tends to zero as t tends to infinity. Hence, for long times the error estimate (4) is dominated by the first two terms on its right-hand side. Further notice that the first term vanishes if $g(t)$ is constant and the second term vanishes if $f(t)$ is a linear function. In this case, the approximation (2) is asymptotically exact. We formulate this statement rigorously:

Corollary 2.1. *Let the assumptions of Theorem 2.1 be satisfied. Further, let $g(t) = g_c$ be constant and $f(t)$ linear in $[-1/\varepsilon, T]$. Then*

$$|x(t) - \tilde{x}(t)| \leq \left[|x^0| + \frac{1}{g_c} \max_{[0,t]} |f| + \frac{|f'|}{g_c} t \right] \exp(-g_c t) \tag{11}$$

for all $t \in [0, T]$.

Proof. This is an immediate consequence of Theorem 2.1, because we can consider $\varepsilon = M = g_c$ and we have $f'' = 0$. □

Notice that error estimate (11) implies that the error tends to zero as t tends to infinity. Moreover, this decrease is exponentially fast.

3 D-QSSA for mass action systems

In this section we show that the mass action ODEs describing kinetics of chemical systems can be, under certain assumptions, expressed in the form (1). We explain how to use the D-QSSA (2) for these systems and provide an explicit formula for the approximation.

We will consider general chemical systems and for their description we will use the notation inspired by [4]. Consider n_x chemical species $X_1, \ldots, X_{n_x}$ and q chemical reactions

$$\sum_{j=1}^{n_x} A_{ij} X_j \xrightarrow{k_i} \sum_{j=1}^{n_x} B_{ij} X_j, \quad i = 1, 2, \ldots, q, \tag{12}$$

where $k_i > 0$ is the reaction rate of the i-th reaction. The stoichiometric coefficients A_{ij} and B_{ij} are assumed to be non-negative integers. Notice that system (12) can be expressed in matrix-vector form as

$$A\boldsymbol{X} \xrightarrow{k} B\boldsymbol{X}, \tag{13}$$

where $\boldsymbol{X} = [X_1, \ldots, X_{n_x}]^\top$ is a column vector of chemical species, $\boldsymbol{k} = [k_1, \ldots, k_q]^\top$ is a column vector of reaction rates, and $A = [A_{ij}]$ and $B = [B_{ij}]$ are $q \times n_x$ matrices of stoichiometric coefficients.

The time evolution of concentrations $\boldsymbol{x}(t) = [x_1(t), \ldots, x_{n_x}(t)]^\top$ of respective chemical species is modelled by a mass action system of ODEs. To express this system in a vector form, we denote by $K \in \mathbb{R}^{q \times q}$ a diagonal matrix with values $k_1, \ldots, k_q$ on the diagonal and by $M = (B - A)^\top \in \mathbb{R}^{n_x \times q}$ the stoichiometric matrix. Further, we introduce the vector-matrix exponentiation [4]. By definition, $\boldsymbol{x}^A(t)$ is a vector in $\mathbb{R}^q$ with entries given by $\prod_{\ell=1}^{n_x} x_\ell^{A_{i\ell}}(t)$ for $i = 1, 2, \ldots, q$. Now, the mass action system can be expressed as

$$\frac{\mathrm{d}}{\mathrm{d}t} \boldsymbol{x}(t) = MK\boldsymbol{x}^A(t), \quad t \geq 0 \tag{14}$$

with an initial condition

$$\boldsymbol{x}(0) = \boldsymbol{x}^0. \tag{15}$$

Equivalently, system (14) can be expressed in component-wise notation as

$$\frac{\mathrm{d}}{\mathrm{d}t}x_j(t) = \sum_{i=1}^{q} M_{ji}k_i \prod_{\ell=1}^{n_\mathrm{x}} x_\ell^{A_{i\ell}}(t), \quad j = 1, 2, \ldots, n_\mathrm{x}. \tag{16}$$

Note that Theorem 2 of [4] guarantees that solution $\boldsymbol{x}(t)$ of (14) has non-negative entries for all $t \geq 0$ provided $\boldsymbol{x}^0$ has non-negative entries. We will use this fact in the rest of the paper.

The D-QSSA will be applied to a portion of system variables x_j. Variables approximated by the D-QSSA will be called fast, and the other variables slow. Identification of the fast and slow variables can be done by the standard quasi-steady state analysis, see e.g. [20]. Without loss of generality, we will assume that variables $x_1, x_2, \ldots, x_{n_\mathrm{f}}$ are fast and will be approximated by the D-QSSA. The dynamics of the slow variables $x_{n_\mathrm{f}+1}, \ldots, x_{n_\mathrm{x}}$ will be determined by the resulting system of delay differential equations. Naturally, we require $0 < n_\mathrm{f} < n_\mathrm{x}$.

In order to transform equations (16) for $j = 1, 2, \ldots, n_\mathrm{f}$ to the form (1), we have to consider the following assumption on the chemical system (12).

A1. If $A_{ij} \neq B_{ij}$ then either $A_{ij} = 0$ or $A_{ij} = 1$, for all $i = 1, 2, \ldots, q$ and $j = 1, 2, \ldots, n_\mathrm{f}$.

Under this assumption equations (16) for the fast variables can be expressed in the form

$$\frac{\mathrm{d}}{\mathrm{d}t}x_j(t) = f_j(t) - g_j(t)x_j(t), \quad j = 1, 2, \ldots, n_\mathrm{f}, \tag{17}$$

where

$$f_j(t) = f_j(x_1(t), \ldots, x_{n_\mathrm{x}}(t)) = \sum_{i \in \mathcal{F}_j} M_{ji}k_i \prod_{\ell=1, \ell\neq j}^{n_\mathrm{x}} x_\ell^{A_{i\ell}}(t),$$

$$g_j(t) = g_j(x_1(t), \ldots, x_{n_\mathrm{x}}(t)) = -\sum_{i \in \mathcal{G}_j} M_{ji}k_i \prod_{\ell=1, \ell\neq j}^{n_\mathrm{x}} x_\ell^{A_{i\ell}}(t)$$

with $\mathcal{F}_j = \{i \in \{1, 2, \ldots, q\} : M_{ji} \neq 0 \text{ and } A_{ij} = 0\}$ and $\mathcal{G}_j = \{i \in \{1, 2, \ldots, q\} : M_{ji} \neq 0 \text{ and } A_{ij} = 1\}$.

Assumption A1 guarantees that there are no quadratic and higher-order terms with respect to x_j in (17). However, it limits the class of systems to which the D-QSSA can be applied. For example, a simple dimerization reaction $2X_1 \to X_2$ violates assumption A1. On the other hand, many chemical systems satisfy this assumption. For examples see Section 4 below or [23].

Note that in general $f_j(t) = f_j(x_1(t), \ldots, x_{n_\mathrm{x}}(t))$ is a function of $x_1(t), \ldots, x_{n_\mathrm{x}}(t)$. However, practically it does not depend on all $x_1(t), \ldots, x_{n_\mathrm{x}}(t)$. In fact, f_j is a

function of $x_\ell(t)$ for $\ell \in \widetilde{\mathcal{F}}_j$, where $\widetilde{\mathcal{F}}_j = \{\ell \neq j : \exists i \in \mathcal{F}_j : A_{i\ell} \neq 0\}$. Namely $f_j(t) = f(\{x_\ell(t) : \ell \in \widetilde{\mathcal{F}}_j\})$. Similarly, $g_j(t) = g(\{x_\ell(t) : \ell \in \widetilde{\mathcal{G}}_j\})$, where $\widetilde{\mathcal{G}}_j = \{\ell \neq j : \exists i \in \mathcal{G}_j : A_{i\ell} \neq 0\}$.

Now, we are ready to apply the D-QSSA (2) to equations (17). As a result we obtain approximations

$$\tilde{x}_j(t) = \frac{f_j(t-\tau_j(t))}{g_j(t-\tau_j(t))}, \quad \text{where } \tau_j(t) = \frac{1}{g_j(t)},\ j = 1, 2, \ldots, n_{\mathrm{f}}. \tag{18}$$

As was recognized already in Definition 2.1, these assumptions are well defined only if all $g_j(t)$ are positive. Therefore we make the following assumption.

A2. Let $g_j(t) > 0$ for all $t > 0$ and $j = 1, 2, \ldots, n_{\mathrm{f}}$.

We use approximations (18) to reduce system (16). In order to do this in a straightforward way, we will assume that the functions $\tilde{x}_j$ are independent of all x_k, $j, k = 1, 2, \ldots, n_{\mathrm{f}}$. This means that functions f_j and g_j for $j = 1, 2, \ldots, n_{\mathrm{f}}$ depend on x_k for $k = n_{\mathrm{f}} + 1, \ldots, n_{\mathrm{x}}$ only. This assumption can be rigorously formulated in terms of sets $\widetilde{\mathcal{F}}_j$ and $\widetilde{\mathcal{G}}_j$ as follows.

A3. Let $\widetilde{\mathcal{F}}_j \cup \widetilde{\mathcal{G}}_j$ be such that it does not contain $1, 2, \ldots, n_{\mathrm{f}}$ for all $j = 1, 2, \ldots, n_{\mathrm{f}}$.

Thus, the functions $\tilde{x}_j$ can be expressed in terms of $x_{n_{\mathrm{f}}+1}, x_{n_{\mathrm{f}}+2}, \ldots, x_{n_{\mathrm{x}}}$, i.e.,

$$\tilde{x}_j(t) = \tilde{x}_j(x_{n_{\mathrm{f}}+1}(t), \ldots, x_{n_{\mathrm{x}}}(t)) \quad \text{for } j = 1, 2, \ldots, n_{\mathrm{f}}. \tag{19}$$

These relations can be substituted into (16) as approximations for $x_1, x_2, \ldots, x_{n_{\mathrm{f}}}$ and we obtain the reduced system

$$\tilde{x}_j(t) = \frac{f_j(\tilde{x}_{n_{\mathrm{f}}+1}(t-\tau_j(t)), \ldots, \tilde{x}_{n_{\mathrm{x}}}(t-\tau_j(t)))}{g_j(\tilde{x}_{n_{\mathrm{f}}+1}(t-\tau_j(t)), \ldots, \tilde{x}_{n_{\mathrm{x}}}(t-\tau_j(t)))}, \quad j = 1, 2, \ldots, n_{\mathrm{f}}, \tag{20}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\tilde{x}_j(t) = \sum_{i=1}^{q} M_{ji} k_i \prod_{\ell=1}^{n_{\mathrm{f}}} \tilde{x}_\ell^{A_{i\ell}}(t) \cdot \prod_{\ell=n_{\mathrm{f}}+1}^{n_{\mathrm{x}}} \tilde{x}_\ell^{A_{i\ell}}(t), \quad j = n_{\mathrm{f}}+1, n_{\mathrm{f}}+2, \ldots, n_{\mathrm{x}}, \tag{21}$$

where

$$\tau_j(t) = \frac{1}{g_j(\tilde{x}_{n_{\mathrm{f}}+1}(t), \ldots, \tilde{x}_{n_{\mathrm{x}}}(t))}, \quad j = 1, 2, \ldots, n_{\mathrm{f}}. \tag{22}$$

System (20)–(21) is a system of $n_{\mathrm{x}} - n_{\mathrm{f}}$ delay differential equations with delays (22) dependent on the state variables $\tilde{x}_{n_{\mathrm{f}}+1}(t), \ldots, \tilde{x}_{n_{\mathrm{x}}}(t)$. To make this system solvable, we must have values of $x_j(t)$ for t negative. The simplest assumption is the constant extension of the initial condition (15):

$$x_j(t) = x_j^0 \quad \text{for } t \leq 0 \text{ and } j = n_{\mathrm{f}}+1, n_{\mathrm{f}}+2, \ldots, n_{\mathrm{x}},$$

where x_j^0 stand for the entries of $\boldsymbol{x}^0$.

The fact that delays are state dependent might complicate the subsequent analysis, but in practical cases these delays can be approximated by constants. For an illustration of this effect, see Section 4 below.

Assumption A3 is not fundamental. If it is not satisfied, then the reduction method can still be used in a recurrent manner. We can decrease the number of fast variables until assumption A3 is satisfied and construct the reduced system (20)–(21) with a smaller number of fast variables. Then we can attempt to reduce the resulting system again. In many cases this recurrent reduction enables us to reduce the original system substantially.

Let us note that after one step of this reduction, the system need not be in mass action form. However, as soon as the particular equation can be expressed in the form (2) with positive $g(t)$ then the D-QSSA can be applied.

Finally, let us discuss the assumption A2 and sufficient conditions for its validity. Functions $g_j(t) = g_j(x_1(t), \dots, x_{n_\mathrm{x}}(t))$ are in general polynomials in $x_i(t)$, $i = 1, 2, \dots, n_\mathrm{x}$. Since $x_i(t)$ are non-negative, assumption A2 requires positivity of a multivariate polynomial in the non-negative orthant. Characterization of positive polynomials is a difficult question connected to Hilbert's seventeenth problem [16], however, we can provide a simple sufficient condition. A multivariate polynomial is positive in the positive orthant if all its coefficients are non-negative and at least one term is positive. This condition can be used to derive conditions for the chemical system (12) guaranteeing assumption A2.

Lemma 3.1. *Let us consider the sets* $\mathcal{H}(m, j) = \{i \in \mathcal{G}_j : A_{i\ell} = A_{m\ell}$ *for all* $\ell = 1, 2, \dots, n_\mathrm{x},\ \ell \neq j\}$ *for* $m \in \mathcal{G}_j$ *and* $j = 1, 2, \dots, n_\mathrm{f}$, *and the following assumptions.*

A2′. *Let* $\sum_{i \in \mathcal{H}(m,j)} M_{ji} k_i \leq 0$ *for all* $m \in \mathcal{G}_j$ *and all* $j = 1, 2, \dots, n_\mathrm{f}$.

A2″. *Let there exist* $m^* \in \mathcal{G}_j$ *such that* $\sum_{i \in \mathcal{H}(m^*,j)} M_{ji} k_i < 0$ *and* $\prod_{\ell=1, \ell \neq j}^{n_\mathrm{x}} x_\ell^{A_{m^*,\ell}}(t) > 0$ *for all* $t > 0$ *and* $j = 1, 2, \dots, n_\mathrm{f}$.

Then assumption A2 *is satisfied.*

Proof. Let $j \in \{1, 2, \dots, n_\mathrm{f}\}$ be fixed. Clearly, we can split the index set $\mathcal{G}_j$ as $\mathcal{G}_j = \mathcal{H}(m_1, j) \cup \mathcal{H}(m_2, j) \cup \dots \cup \mathcal{H}(m_r, j)$, where $m_1, m_2, \dots, m_r \in \mathcal{G}_j$ are such that the sets $\mathcal{H}(m_1, j), \mathcal{H}(m_2, j), \dots, \mathcal{H}(m_r, j)$ are pairwise disjoint. This enables us to express $g(t)$ as

$$g(t) = -\sum_{s=1}^{r} \left(\sum_{i \in \mathcal{H}(m_s,j)} M_{ji} k_i \right) \prod_{\ell=1, \ell \neq j}^{n_\mathrm{x}} x_\ell^{A_{m_s,\ell}}(t).$$

Thus, the non-negativity of $x_\ell(t)$ and assumption A2′ imply non-negativity of all terms in this expression. Similarly, assumption A2″ implies positivity of at least one of these terms. □

4 Numerical example

4.1 Model reduction

Let us consider the following chemical system which was inspired by the model [14] for expression of the Hes1 protein:

$$D \xrightarrow{\alpha_{\mathrm{m}}} D + M \qquad M \xrightarrow{\alpha_{\mathrm{p}}} M + P \qquad D + nP \underset{\gamma_{-1}}{\overset{\gamma_1}{\rightleftarrows}} D' \qquad M \xrightarrow{\mu_{\mathrm{m}}} \emptyset \qquad P \xrightarrow{\mu_{\mathrm{p}}} \emptyset,$$

where D corresponds to the *hes1* gene, M to *hes1* mRNA, and P to Hes1 protein. In this model, the Hes1 protein can bind to n promoter sites of the gene producing an inactive complex D'. The rate constant α_{m} corresponds to transcription of the gene to the mRNA molecule, α_{p} to translation of the mRNA to the protein, γ_1 and γ_{-1} are binding and unbinding rates of Hes1 to the promoter region, and μ_{m} and μ_{p} are the degradation rates of M and P, respectively.

The law of mass action yields a system of ODEs for concentrations of $D' = D'(t)$, $D = D(t)$, $M = M(t)$, and $P = P(t)$ of the form (14). We complete this system with a natural initial condition

$$D(0) = 1, \quad D'(0) = 0, \quad M(0) = 0, \quad P(0) = 0. \tag{23}$$

Biologically, binding and unbinding of a transcription factor (Hes1 protein in this case) to the promoter region of a gene is often a frequently occurring reaction in comparison with the relatively slow processes of transcription and translation. Therefore, in analogy with [24], we consider D and D' to be the fast species. With this choice, we can readily verify the validity of assumptions A1 and A2. However, assumption A3 is not satisfied. Fortunately, this assumption is technical only. Moreover, in this case it can be easily overcome by elimination of one of the variables D or D'.

Initial condition (23), together with the fact that $D(t) + D'(t)$ is constant, implies $D'(t) = 1 - D(t)$. Thus, eliminating variable $D'(t)$ from the system yields the following three equations:

$$\frac{\mathrm{d}}{\mathrm{d}t}D = \gamma_{-1} - (\gamma_{-1} + \gamma_1 P^n)D, \tag{24}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}M = \alpha_{\mathrm{m}}D - \mu_{\mathrm{m}}M, \tag{25}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}P = \alpha_{\mathrm{p}}M - \mu_{\mathrm{p}}P + n\left[\gamma_{-1} - (\gamma_{-1} + \gamma_1 P^n)D\right]. \tag{26}$$

Notice that equation (24) now satisfies all assumptions A1–A3.

It is convenient to rescale the unknowns in this system to be of comparable size. We follow the scaling from [14], define $m = M/\alpha_{\mathrm{m}}$, $p = P/(\alpha_{\mathrm{m}}\alpha_{\mathrm{p}})$, and

transform system (24)–(26) to

$$\frac{\mathrm{d}}{\mathrm{d}t}D = \gamma_{-1} - (\gamma_{-1} + \gamma p^n)D, \tag{27}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}m = D - \mu_{\mathrm{m}} m, \tag{28}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}p = m - \mu_{\mathrm{p}} p + \frac{n}{\alpha}\left[\gamma_{-1} - (\gamma_{-1} + \gamma p^n)D\right]. \tag{29}$$

Here, $\alpha = \alpha_{\mathrm{p}}\alpha_{\mathrm{m}}$ and $\gamma = \gamma_1(\alpha_{\mathrm{p}}\alpha_{\mathrm{m}})^n$.

To use the standard QSSA, we approximate $D(t)$ by its quasi-steady state approximation

$$\widehat{D}(t) = \frac{\gamma_{-1}}{\gamma_{-1} + \gamma \hat{p}^n(t)}. \tag{30}$$

Functions $\hat{p}(t)$ and $\widehat{m}(t)$ approximate $p(t)$ and $m(t)$, respectively, and are determined by reducing system (27)–(29) to the following two equations:

$$\frac{\mathrm{d}}{\mathrm{d}t}\widehat{m} = \frac{\gamma_{-1}}{\gamma_{-1} + \gamma \hat{p}^n} - \mu_{\mathrm{m}}\widehat{m}, \tag{31}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\hat{p} = \widehat{m} - \mu_{\mathrm{p}}\hat{p}. \tag{32}$$

Alternatively, we can reduce system (27)–(29) using the D-QSSA. Clearly, equation (27) is in the form (2) with $x(t) = D(t)$, $f(t) = \gamma_{-1}$ and $g(t) = g(p(t)) = \gamma_{-1} + \gamma p^n(t)$. Thus, Definition 2.1 yields the approximation

$$\widetilde{D}(t) = \frac{\gamma_{-1}}{\gamma_{-1} + \gamma \tilde{p}^n(t - \tau(t))}, \quad \text{where } \tau(t) = \frac{1}{\gamma_{-1} + \gamma \tilde{p}^n(t)}. \tag{33}$$

According to (20)–(21), system (27)–(29) reduces to the following system of differential equations with delay:

$$\frac{\mathrm{d}}{\mathrm{d}t}\widetilde{m}(t) = \widetilde{D}(t) - \mu_{\mathrm{m}}\widetilde{m}(t),$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\tilde{p}(t) = \widetilde{m}(t) - \mu_{\mathrm{p}}\tilde{p}(t) + \frac{n}{\alpha}\left[\gamma_{-1} - (\gamma_{-1} + \gamma\tilde{p}^n(t))\widetilde{D}(t)\right].$$

Alternatively, we can use the substitution (33) and rewrite this system as

$$\frac{\mathrm{d}}{\mathrm{d}t}\widetilde{m}(t) = \frac{\gamma_{-1}}{\gamma_{-1} + \gamma \tilde{p}^n(t - \tau(t))} - \mu_{\mathrm{m}}\widetilde{m}(t), \tag{34}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\tilde{p}(t) = \widetilde{m}(t) - \mu_{\mathrm{p}}\tilde{p}(t) + \gamma_{-1}\frac{n}{\alpha}\left[1 - \frac{\gamma_{-1} + \gamma\tilde{p}^n(t)}{\gamma_{-1} + \gamma\tilde{p}^n(t - \tau(t))}\right]. \tag{35}$$

The initial condition (23) extended to negative values of t reads

$$\widetilde{m}(t) = 0, \quad \tilde{p}(t) = 0 \quad \text{for all } t \le 0. \tag{36}$$

At this point, it is interesting to compare the derived systems (31)–(32) and (34)–(35) with the rescaled version of the original delay differential equation system use in [14]:

$$\frac{\mathrm{d}}{\mathrm{d}t}\overline{m}(t) = \frac{1}{1+\left(\overline{p}(t-\tau_{\mathrm{tr}})/p_0\right)^n} - \mu_{\mathrm{m}}\overline{m}(t), \tag{37}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}\overline{p}(t) = \overline{m}(t) - \mu_{\mathrm{p}}\overline{p}(t). \tag{38}$$

Here, $\overline{m}(t)$ and $\overline{p}(t)$ model the rescaled concentrations of M and P, respectively, in the same manner as solutions of systems (31)–(32) and (34)–(35). A distinctive feature of system (37)–(38) is the delay τ_{tr}, which is interpreted as the transcriptional delay. Transcription is a complicated process which moves sequentially along the chain of the mRNA molecule and synthesizes a protein. The time needed to complete the synthesis can be significant and, therefore, system (37)–(38) compensates for it by introducing the delay τ_{tr}.

Systems (31)–(32) and (34)–(35) have been derived from mass action kinetics using the QSSA and the D-QSSA, respectively. However, system (37)–(38) was introduced in a phenomenological manner using the heuristic Hill function $[1 + (p/p_0)^n]^{-1}$ combined with the time delay τ_{tr} corresponding to transcription, see [14] and [9]. Interestingly, if $p_0 = (\gamma_{-1}/\gamma)^{1/n}$ and $\tau(t) = \tau_{\mathrm{tr}}$ then equations (34) and (37) are identical. Similarly, equation (32) is the same as (38). Thus, the system (37)–(38) can be rigorously derived from the mass-action kinetics using the QSSA and the D-QSSA. However, the biological meaning of the delay $\tau(t)$ in (34) and the delay τ_{tr} in (37) differs. The delay $\tau(t)$ compensates for the time needed to bind (or unbind) n molecules of P to the promoter region of *hes1* gene, while τ_{tr} corresponds to the transcriptional delay. Therefore, it is not biologically plausible to identify these two delays. From a biological viewpoint, these delays should be summed up. However, the D-QSSA methodology can be used to derive the transcriptional delay rigorously, but this would require a more detailed mass action model of transcription, for example the model [19].

4.2 Numerical results

We will numerically solve and compare system (27)–(29) with its QSSA approximation (31)–(32) and its D-QSSA approximation (34)–(35). We consider parameter values from [14]. However this reference provides values for n, μ_{m}, μ_{p} and not for γ, γ_{-1}, and α, because these are irrelevant for system (37)–(38). Instead, reference [14] provides the value $p_0 = 100$. Since $p_0^n = \gamma_{-1}/\gamma$, we choose values of γ and γ_{-1} to agree with this relation. In particular, we consider

$$n = 5,\ \mu_{\mathrm{m}} = \mu_{\mathrm{p}} = 0.03,\ \gamma = 2 \cdot 10^{-12},\ \gamma_{-1} = 0.02,\ \alpha = 500. \tag{39}$$

The systems of ODEs (27)–(29) and (30)–(32) can be solved by practically any ODE solver. We use the Matlab `ode` solver. Numerical solution of a system

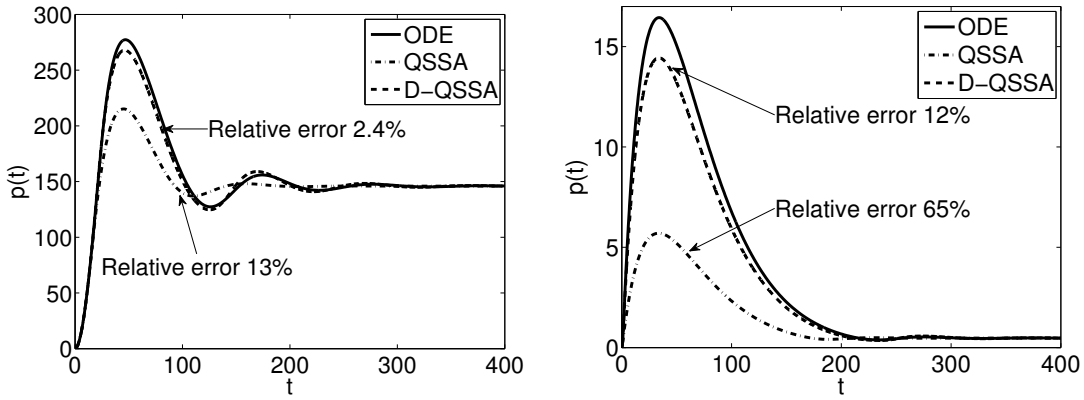

Figure 1: Numerical solutions $p(t)$, $\hat{p}(t)$, and $\tilde{p}(t)$ of ODE system (27)–(29), QSSA system (30)–(32), and D-QSSA system (33)–(35). Left panel corresponds to parameter values (39), the right panel to (40).

with delays is straightforward. For simplicity, we use the explicit Euler method with a sufficiently small time step. In every time step, we compute the delay $\tau(t)$ given by (33) and use the corresponding historical value $\tilde{p}(t-\tau(t))$ to evaluate the right-hand side of (34)–(35). Therefore, values of $\tilde{p}$ have to be stored in every time step.

Figure 1 (left) presents numerically computed values of $p(t)$, $\hat{p}(t)$, and $\tilde{p}(t)$ for $t \in [0,T]$ as given by (27)–(29), (30)–(32), and (33)–(35), respectively. We observe that the approximation provided by the D-QSSA is much more accurate than the standard quasi-steady state approximation. Quantitatively, the L^2 relative error of the quasi-steady state solution $\hat{p}$ is approximately 13 %, while the relative error of the D-QSSA solution is approximately 2.4 %. To be rigorous,

$$\frac{\|p-\hat{p}\|_{L^2(0,T)}}{\|p\|_{L^2(0,T)}} \doteq 0.13, \quad \text{and} \quad \frac{\|p-\tilde{p}\|_{L^2(0,T)}}{\|p\|_{L^2(0,T)}} \doteq 0.024.$$

To show the quality of the QSSA and D-QSSA approximations also in different parameter regimes, we change the values of parameters γ and γ_{-1} to

$$\gamma = 10 \quad \text{and} \quad \gamma_{-1} = 10^{-4} \tag{40}$$

and keep the other parameters the same as in (39). This new choice of γ and γ_{-1} corresponds to $p_0 = (\gamma_{-1}/\gamma)^{1/n} = 10$. Figure 1 (right) shows the numerical solutions for parameter values (40). In this case the relative error of the quasi-steady state solution is approximately 65 % and the error of the D-QSSA is approximately 12 %.

For completeness, Table 1 presents relative errors of all three variables in the system for both sets of parameters (39) and (40). This table confirms that the D-QSSA provides a considerably more accurate approximation than the QSSA for all variables in the system.

	Parameters (39)			Parameters (40)		
	D	m	p	D	m	p
rel. err. QSSA	32 %	18 %	13 %	77 %	65 %	65 %
rel. err. D-QSSA	12 %	3.6 %	2.4 %	28 %	12 %	12 %

Table 1: Relative errors of QSSA and D-QSSA for all variables of the system and for both sets of parameters.

The *a priori* error estimate (4) provides a guaranteed bound on the error. It is accurate if the function $g(t)$ is close to constant and bounded well away from zero. However, in general it can overestimate the true error considerably, especially if the function $g(t)$ varies significantly or if it's value is close to zero. The current example has both of these unfavourable properties. The quantities in (4) are $\varepsilon = \gamma_{-1}$, $M = \gamma_{-1} + \gamma \max_{[0,T]} |p|^n$, $f' = f'' = 0$, and $x^0 = D(0) = 1$. Using, for illustration, parameter values (39) and estimate $\tilde{p}(t) \leq 300$, the error bound (4) yields

$$|D(t) - \widetilde{D}(t)| \leq 1.99 + 2\exp(-0.02t),$$

while the true error is at most 0.32 and it does not exceed 0.05 for $t > 50$. Nevertheless, this shows that the D-QSSA can provide accurate results even if the error estimate (4) does not predict so.

Parameter values (39) and (40) have been chosen to show the potential of the D-QSSA technique. In general, if we increase γ_{-1} and correspondingly decrease γ to keep the ratio $\gamma_{-1}/\gamma = p_0^n$ constant, then the delay $\tau(t)$ given in (33) attains smaller values, because $\tau(t) \leq 1/\gamma_{-1}$. Eventually, it is so small that the D-QSSA and QSSA approximations practically coincide. This is the situation when the two time scales in the system are well separated and both approaches provide very accurate approximation. However, in numerical tests we performed in this regime, the D-QSSA was always more accurate than the QSSA. On the other hand, if we decrease γ_{-1} and increase γ to keep the ratio $\gamma_{-1}/\gamma = p_0^n$ constant, then the delay $\tau(t)$ attains high values and the D-QSSA becomes very inaccurate. However, this is the situation when the time scales are not well separated and the standard QSSA is not accurate either. This behaviour of the D-QSSA is well explained by the dependence of the error estimate (4) on ε.

Finally, we note that all these results were achieved with the delay as defined in (33). This delay is state dependent, because it depends on the value $\tilde{p}(t)$. This might be a hindrance and therefore we have tried to replace the state dependent delay by a constant delay. Based on experimental fitting to the system (24)–(26), we have found that even a constant delay can provide very accurate results. Choosing $\tau(t) = 6$ for parameter set (39) and $\tau(t) = 0.89$ for parameters (40), we achieve relative errors in p of approximately 1 %. However, the accuracy of these approximations is quite sensitive to the value of the delay and so far it is not clear how to determine the optimal constant value of the delay.

5 Discussion and conclusions

In this paper, we present the technique of D-QSSA and prove a corresponding error estimate. The technique is well justified for equations of the form (1). We also show explicit application of the D-QSSA to a general mass action model of a general chemical system. However, the D-QSSA can be applied only if assumptions A1–A3 are satisfied. Assumption A1 means that the stoichiometric coefficients of the fast chemical species on the reactant side of the chemical equation cannot be greater than one, unless the species is a catalyst. This is not as severe a restriction as it may first look, because many biochemical reactions are of this type and, moreover, the assumption concerns fast species only.

Assumption A2 requires positivity of functions $g_j(t)$ in the equations for the fast species. This is a technical assumption whose validity can be guaranteed from the stoichiometry and rate constants of the chemical system by sufficient conditions A2′ and A2″.

Assumption A3 means that the fast variables are independent in the sense that reactants of all reactions, where a fast species is either produced or consumed, do not involve any other fast species. This tends to be satisfied in biochemical systems if the fast species correspond to genes, because genes do not directly influence each other. Moreover, this assumption is not fundamental, due to the possibility of recurrent application of D-QSSA (see Section 3).

To summarise, these assumptions are not too restrictive and make the technique of D-QSSA applicable to the majority of mass action models of biochemical systems.

The main idea of the D-QSSA is the introduction of a time delay to improve accuracy. The standard QSSA ignores the time needed by fast variables to reach their steady states. This may result in considerable errors. The D-QSSA compensates for this time delay and improves the accuracy of the approximation. In the example presented in Section 4, the D-QSSA exhibits more than five times smaller error in comparison with the standard QSSA.

In comparison with the standard QSSA, the D-QSSA seems to be especially useful for oscillating systems. The standard QSSA usually causes considerable errors in both the period and amplitude of oscillations [24]. On the other hand, the D-QSSA enables this error to be reduced substantially. In [23] we have successfully applied the technique of D-QSSA to a system for modelling circadian rhythms [24]. This system is described by nine ODEs and it can be reduced to two. The standard QSSA yields roughly 30 % error in the period, while the D-QSSA approach approximates the period with errors of about 1–2 %.

The delay in the D-QSSA systems is in general state dependent. This might be problematic for both numerical solution and subsequent analysis. However, numerical experiments both in this paper and in [23] show that a constant approximation of the state dependent delay seems to provide accurate results as well. Nevertheless, the quality of the approximation is quite sensitive to the

value of the delay and its optimal choice is not clear. To make the constant delay approach practical, subsequent research is necessary.

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. Reference [11] shows how to identify such combinations and how to apply the QSSA to these variables. The technique of the D-QSSA can be applied in these cases as well and we will investigate this possibility in future research.

In chemical systems, the delay in the D-QSSA depends also on the rate constants of the chemical reactions involved. Thus, the technique of D-QSSA can be used in situations where complex chemical processes are modelled by a simple reaction with a time delay [1, 14, 19], to determine and analyse how the delay actually depends on various parameters of the system. This promises new insight and understanding of models with time delays. We plan, in future work, to apply the D-QSSA to a detailed chemical model of transcription [19] to derive and analyse the dependence of the transcriptional delay on the rates of the elementary chemical reactions which comprise the process.

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