A note on the D-QSSA method with optimal constant delays applied to a class of mathematical models

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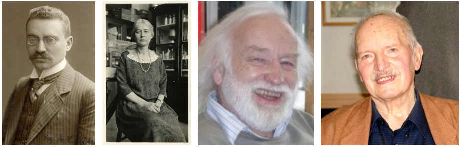
PANM 22, Hejnice, June 26th, 2024

Not so necessary background / 7 Keywords

- (Complex) biochemical **reaction networks**
- (Special) class of mathematical models:
  Dynamic systems with **mass conservation**
- ODEs with **time delay** → delayed ODEs (DDE)
- **Slow-fast** decomposition
- **SPM** (Singular Perturbation Method)
- **QSSA** (quasi-steady-state approximation/assumption)
- Enzyme-substrate reaction system → **Michaelis-Menten** kinetics (with the substrate transport)



Motivation for this study / 2 References

- **Model reduction** techniques for complex **biochemical networks** are wanted.
  - T.J. Snowden, P.H. van der Graaf, M.J. Tindall (2017) *Methods of Model Reduction for Large-Scale Biological Systems: A Survey of Current Methods and Trends.* Bull Math Biol 79, pp. 1449-1486.
- To test and eventually modify (enhance) the **Delayed-QSSA** technique proposed by T. Vejchodský *et al.* (2014).
  - T. Vejchodský, R. Erban, P. K. Maini (2014) *Reduction of chemical systems by delayed quasi-steady state assumptions.* arXiv:1406.4424

Outline

1. **Illustrative example**: Modified Michaelis-Menten chemical reaction
   - Simplification & Order reduction

2. **Quasi-steady-state approximation** (QSSA)
   - (Standard) **Quasi-steady-state approximation** (QSSA)
   - **Delayed**-QSSA (D-QSSA by Vejchodský et al.)

3. Optimal constant delay for QSSA: **OD-QSSA** technique
   - Numerical results
   - Comparison of D-QSSA vs. OD-QSSA models

4. Summary - Future prospects

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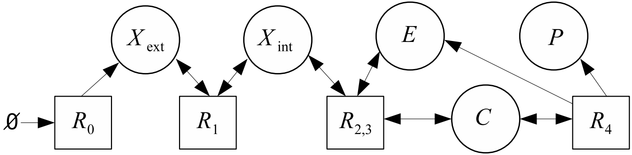
Example – Governing equations (I)

Enzyme kinetics example – Reaction scheme, I.C., ODEs (next slide)

Transport	*& Reactions*		*Rate constants*
$T_1\ (R_1)$:	X_{ext}	$\rightleftharpoons X_{in}$	k_0
$R_{2,3}$:	$X_{in} + E$	$\rightleftharpoons C$	$k_1(k_{assoc}),\ k_{-1}(k_{dis})$
R_4 :	C	$\rightarrow P + E$	k_2

Initial conditions: $x(t_0) = \begin{pmatrix} s_0 & 0 & e_0 & 0 & 0 \end{pmatrix}^T$.



X_{int} means a substrate in the inner compartment, E an enzyme, C a complex (ES), P is a product; $x \in R_+^5$ is the state vector of species concentrations.

Formulation of governing equations (II)

5 ODEs (Fick's law & Law of mass action)

For the state vector

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

it holds

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

Initial value problem (IVP) in (usual) matrix notation

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = Ax(t) + b(t), \quad x(t_0) = x_0, \tag{1}$$

where A is the constant matrix representing the linear part of the system, and the vector $b(t)$ represents the nonlinear (bilinear) parts.

Figure 1: Time profiles of state variables x_1 and x_2

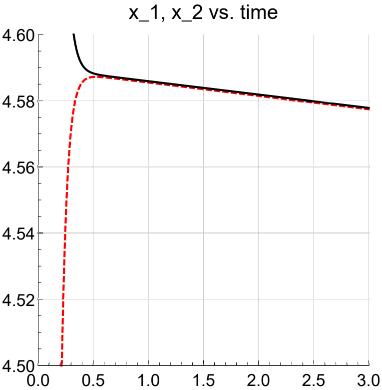


Figure: IVP (1), $x_1(0) = s_0 = 10$, $x_3(0) = e_0 = 1$, $k_2 = 0.01$, $k_i = 10$. The full black (always decreasing) line corresponds to the solution of fast variable x_1, and the red dashed (increasing until $t \approx 0.5$) corresponds to the solution of x_2 for the non-reduced system (1). From $\dot{x}_1 = 0$, the eq. for the slow manifold ($x_1 - x_2 = 0$) is derived.

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Simplification & Order reduction

- **Simplification** is possible due to (two) conservation properties:

$$x_3(t) + x_4(t) = e_0, \quad x_1(t) + x_2(t) + x_4(t) + x_5(t) = s_0.$$

- **Order reduction** using QSSA for the species C (complex ES), i.e., $\dot{x}_4 = 0$ (x_4 reaches (more or less fast) its equilibrium)

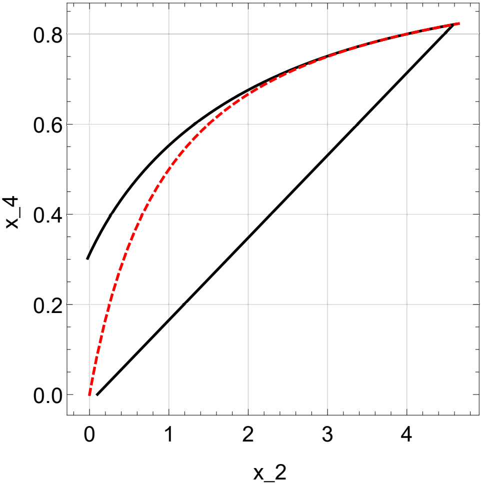
$$x_4^{qss}(t) = \frac{e_0\, k_1\, x_2(t)}{k_{-1} + k_2 + k_1\, x_2(t)}\ . \tag{2}$$

The following reduced ODEs for two variables $x_1(t), x_2(t)$:

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

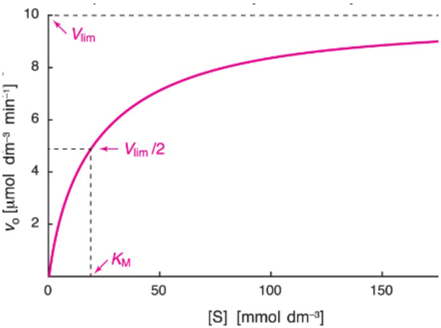
$$\dot{x}_2(t) = k_0\,(x_1(t) - x_2(t)) - \frac{e_0\, k_1\, k_2\, x_2(t)}{k_{-1} + k_2 + k_1\, x_2(t)}.$$

Figure 2: Parametric plot in the space of states x_2, x_4



Full black line: Solution of the non-reduced model.
Dashed red line: QSSA approximations (derived from $\dot{x}_4 = 0$).

Figure 3: Michaelis-Menten kinetics: $\nu_0 = \frac{\nu_{lim}[S]}{K_M+[S]}$



Reaction rate vs. **Substrate concentration** (similar to x_4 *vs.* x_2), cf. subsection 5.2 *Singular perturbation and speed expression* in:

E. Bohl, I. Marek: Input-output systems in biology and chemistry and a class of mathematical models describing them. Appl. Math. 50 (2005), pp. 219–245.

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Quasi-steady-state approximation (QSSA)

Definition

D1: Assuming a timescale separation for the rates of species evolution in a chemical network (1), let the state vector $x(t)$ be partitioned into the fast and slow parts, i.e., $x(t) = \begin{pmatrix} x_F(t)^T & x_S(t)^T \end{pmatrix}^T$, where $x_F(t)$ is a vector composed from n_F fast variables and $x_S(t)$ is a vector composed from n_S slow variables. Let the ODE system have the form

$$\begin{aligned} \dot{x}_F(t) &= f(x_S(t)) - g(t)x_F(t), \\ \dot{x}_S(t) &= h(x_F(t), x_S(t)). \end{aligned} \tag{3}$$

Then the reduced system *via* **standard QSSA** is

$$\begin{aligned} x_F(t) &= \frac{f(x_S(t))}{g(t)}, \\ \dot{x}_S(t) &= h(x_F(t), x_S(t)). \end{aligned} \tag{4}$$

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Introducing the delay $\tau(t)$: **Delayed-QSSA technique**

Definition

D2: Let the state vector $x(t)$ be partitioned into the fast and slow parts, i.e., $x(t) = \begin{pmatrix} x_F(t)^T & x_S(t)^T \end{pmatrix}^T$. Let the non-reduced ODE system have the form

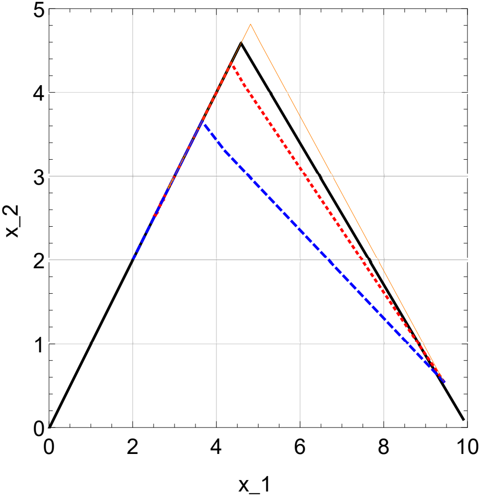
$$\begin{aligned} \dot{x}_F(t) &= f(x_S(t)) - g(t)x_F(t), \\ \dot{x}_S(t) &= h(x_F(t), x_S(t)). \end{aligned} \tag{5}$$

Then its reduction *via* **delayed QSSA** is

$$\begin{aligned} x_F^{dqss}(t) &= \frac{f(x_S(t-\tau))}{g(t-\tau)}, \\ \dot{x}_S(t) &= h(x_F^{dqss}(t), x_S(t)), \end{aligned} \tag{6}$$

where $\tau(t) = \frac{1}{g(t)}$ (time variable delay proposed in Vejchodský et al. (2014) to make the QSSA more precise . . .).

Figure 4: Parametric plot in the space of states x_1, x_2



Motivation example, IC: $x_1(0) = 10$, $x_2(0) = 0$, i.e., it starts at RHS lower corner. **Full black line**: non-reduced model ('exact solution'). Dashed/dotted lines: Approximations via D-QSSA for 3 (constant) delays: 0.02, 0.05, 0.1 (from up to down). After a short time, the slow manifold ($x_1 = x_2$) is reached.

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Looking for an optimal constant delay of D-QSSA technique

Theorem

Consider ordinary differential equation $\dot{x}(t) = f(t) - g(t)x(t)$ *with* $g(t) > 0$ *and its D-QSSA approximation* $x^{dqss}(t) = \frac{f(t-\tau)}{g(t-\tau)}$ *with a delay* $\tau(t)$. *Then there exists an optimal constant* τ^* *giving the best possible approximation* $x^{dqss}(t) = \frac{f(t-\tau^*)}{g(t-\tau^*)}$ *of the exact solution.*

For the proof, see

C. Matonoha, S. Papacek, V. Lynnyk:
On an optimal setting of constant delays for the D-QSSA model reduction method applied to a class of chemical reaction networks.
Applications of Mathematics, Vol. 67, No. 6, p. 831-857, 2022.

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Model parameters (more realistic than previous ...)

The values and descriptions of 4 model parameters and 2 initial conditions are:

Parameter	**Value**	**Description**
k_0	1.0E-01	permeability constant
k_1	1.0E+06	association rate (forward rate constant)
k_{-1}	1.0E-04	dissociation rate (reverse rate constant)
k_2	1.0E-01	association catalytic rate
s_0	5.0E-07	initial substrate concentration
e_0	2.0E-07	initial enzyme concentration

This choice of parameters represents the situation where cell membrane transport and complex formation are near immediate, whereas enzyme reactions are several orders of magnitude slower.

Further defined ODE systems are solved for $t \in [0, 120]$, using the backward Euler method with the time step $\Delta t = 10^{-3}$.

The models and fast variables

Three models are considered:

- QSSA – quasi steady-state approximation
- D-QSSA – delayed quasi steady-state approximation with the time dependent delay $\tau(t) = 1/g(t)$
- OD-QSSA – delayed quasi stead-state approximation with the optimal constant delay τ computed by minimization of the error metric δ (see below)

Fast variables: x_1 and x_4 can be considered as fast variables. Thus, for each model three possibilities are considered:

- x_1 is fast
- x_4 is fast
- both x_1, x_4 are fast

Schematic description of studied models end error metric

model	**description**
non-reduced	full system (1)
QSSA1	x_1 is fast variable
QSSA4	x_4 is fast variable
QSSA14	both x_1 & x_4 are fast
D-QSSA1	x_1 is fast variable, $\tau = 1/g(t)$
D-QSSA4	x_4 is fast variable, $\tau = 1/g(t)$
D-QSSA14	both x_1 & x_4 are fast, $\tau = 1/g(t)$
OD-QSSA1	x_1 is fast variable, $\tau = const.$
OD-QSSA4	x_4 is fast variable, $\tau = const.$
OD-QSSA14	both x_1 & x_4 are fast, $\tau = const.$

For each of the five state variables, we use the error metric

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

Parameter t_Q (time shift for the error metric evaluation)

We introduce a parameter t_Q to avoid e.g. the conflict between different initial conditions.

For example, when x_1 is fast, then $x_1^{\text{qss}}(t) = x_2(t)$ which cannot hold for $t = 0$ since

$$0 < s_0 = x_1(0) \neq x_2(0) = 0.$$

Then, the QSSA, D-QSSA and OD-QSSA will be considered only for $t > t_Q$.

Computed and used optimal values t_Q and delays τ

Model	t_Q	**delay** τ
QSSA1	used optimal	-
QSSA4	-	-
QSSA14	used optimal	-
D-QSSA1	used optimal	$1/k_0 = 10$
D-QSSA4	-	$1/(k_{-1} + k_2 + k_1 x_1(t))$
D-QSSA14	used optimal	$\tau_1 = 1/k_0 = 10,$ $\tau_4(t) = 1/(k_{-1} + k_2 + k_1 x_1(t))$
OD-QSSA1	10.770	12.753
OD-QSSA4	-	4.897
OD-QSSA14	12.541	$\tau_1 = 12.417,\ \tau_4 = 11.426$

These values compute time profiles of concentrations $x_1(t), \ldots, x_5(t)$.

Comparison of approximate solutions $x^A(t)$ with a solution of the original non-reduced model

Computed total errors δ for each model, computational times (1000x), and the speedup as the ratio of the individual model to the non-reduced model:

model	**total δ**	**time**	**speedup**
non-reduced	-	21.94	1.00
QSSA1	0.1041E+01	18.18	0.83
QSSA4	0.2736E+00	18.28	0.83
QSSA14	0.1152E+01	5.78	0.26
D-QSSA1	0.2960E+00	21.58	0.98
D-QSSA4	0.1896E+00	20.34	0.93
D-QSSA14	0.3237E+00	9.27	0.42
OD-QSSA1	0.1634E+00	21.58	0.98
OD-QSSA4	0.1952E+00	17.44	0.79
OD-QSSA14	0.1563E+00	6.03	0.28

Figure 5: Comparison of different models

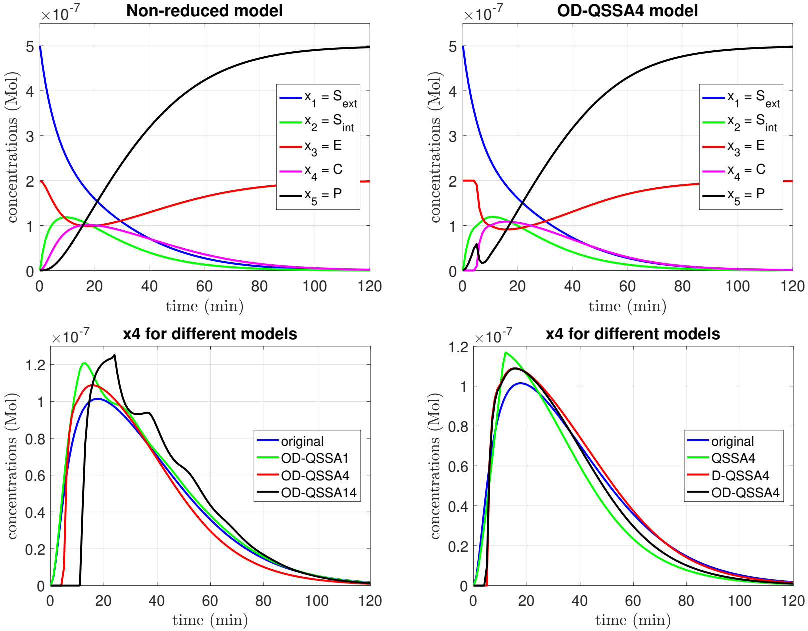

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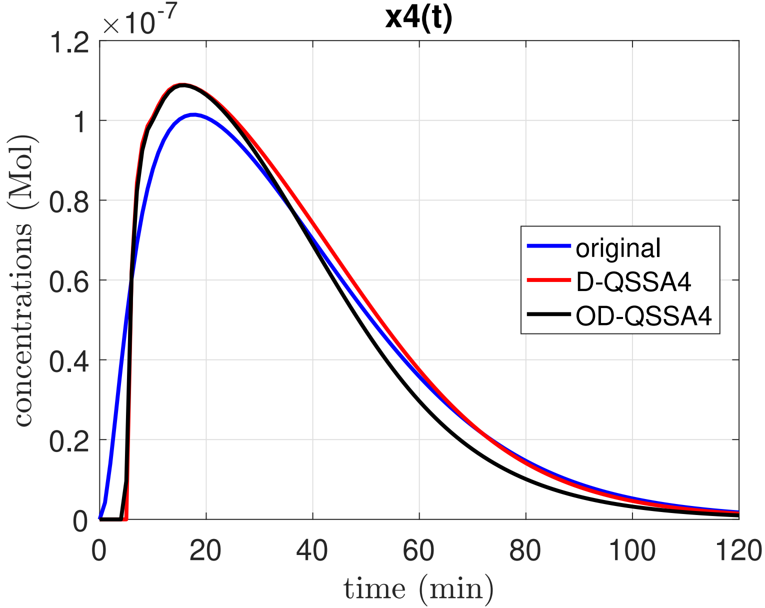
Figure 6: Comparison of D-QSSA vs. OD-QSSA models



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- The modification of D-QSSA has been introduced, and the existence of an **optimal constant delay** for a general slow/fast dynamic system has been proven.

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- On a simple chemical reaction network (3 or 2 or 1 ODE) the comparison of *QSSA, delayed-QSSA, and OD-QSSA* has been performed (cf. Figs. 5–6).

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- On a simple chemical reaction network (3 or 2 or 1 ODE) the comparison of *QSSA, delayed-QSSA, and OD-QSSA* has been performed (cf. Figs. 5–6).
- While the accuracy of both methods is comparable, the issue of an **computational speedup** w.r.t. both non-reduced and D-QSSA systems due to the model order reduction **is being tested** for an inverse problem of parameter estimation . . .

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- On a simple chemical reaction network (3 or 2 or 1 ODE) the comparison of *QSSA, delayed-QSSA, and OD-QSSA* has been performed (cf. Figs. 5–6).
- While the accuracy of both methods is comparable, the issue of an **computational speedup** w.r.t. both non-reduced and D-QSSA systems due to the model order reduction **is being tested** for an inverse problem of parameter estimation . . .
- Simultaneously, we work on an application of the optimal constant delay (OD-QSSA) technique for more general systems of nonlinear ODEs arising in **pharmacology** (Matonoha et al., in preparation).

THANK YOU FOR YOUR ATTENTION !