

Mass action realizations of reaction kinetic system models on various time scales

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Abstract. Complex chemical reaction networks often exhibit different dynamic behaviour on different time scales. A combined approach is proposed in this work for determining physically meaningful mass action realizations of complex chemical reaction networks that describe its dynamic behaviour on different time scales. This is achieved by appropriately reducing the detailed overall mass action kinetic scheme using quasi steady state assumptions fit to the particular time scale, and then searching for an optimal realization using mixed integer linear programming.

Furthermore, the relationship between the properties (reversibility, deficiency, stability) of the obtained realizations of the same system on different time scales are also investigated and related to the same properties of the detailed overall model. It is shown that the reduced models obtained by quasi steady state assumptions may show exotic nonlinear behaviour, such as oscillations, when the original detailed is globally asymptotically stable. The proposed methods are illustrated by using a simple Michaelis-Menten type reaction kinetic example. The simplified versions of the well known Brusselator model have also been investigated and presented as a case study.

1. Introduction

Chemical Reaction Networks (CRNs) form an important and wide class of positive (or non-negative) systems attracting significant attention not only among chemists but in numerous other fields such as physics, or even pure and applied mathematics where nonlinear dynamical systems are considered [1]. Beside pure chemical reactions, CRNs are often used to model the dynamics of intracellular processes, metabolic or cell signalling pathways [2]. The increasing interest towards reaction networks as a well defined special class of positive nonlinear systems is clearly shown by recent tutorial and survey papers [3], [4], [5].

Most of the complex CRNs exhibit dynamic behaviour that spans a wide range in the time scale, i.e. they are multi scale by nature. A model that describes the behaviour at a particular time scale is often obtained from a detailed overall model by model reduction. There are various popular engineering model reduction transformations, such as the quasi steady state and quasi equilibrium assumptions or the variable lumping that are widely applied for this purpose [6] but their effect on the dynamic properties of reaction kinetic models is not very well known. Some earlier investigations about biochemical reaction networks indicate that approximate reduced dynamic models can only be applied if certain parametric and/or state-dependent conditions are

met, see e.g. [7], [8]. At the same time, quite different dynamic properties (e.g. special nonlinear effects like oscillatory or chaotic behaviour) have been detected for different simplified versions of the same model. A recent paper [9] even warns against applying "inconsistent assumptions" in mathematical models of protein interaction networks.

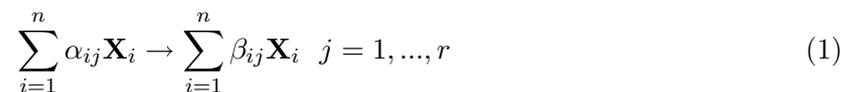
Therefore, the aim of this paper is to identify the reason for the above spurious dynamical properties with a view to later propose ways to overcome them.

2. Chemical reaction networks and their properties

A brief summary of the most important properties of reaction kinetic networks obeying the mass action law is given in this section based largely on [10].

2.1. Mass action law, physical and chemical background

The origin of the reaction kinetic models is found in the molecular collision picture of gas phase chemical reactions, where the reaction rate is proportional to the number of collisions, i.e. to the concentration of the reactants. Here each elementary reaction step is *irreversible* in the form of



where \mathbf{X}_i are the components, and the stoichiometric coefficients α_{ij} and β_{ij} are always non-negative integers, while n is the number of components, and r is the number of reactions.

It is also assumed in classical reaction kinetics that *the system is closed and evolves under isotherm conditions*.

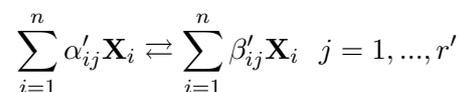
The so called *complexes* $C_k = \sum_{i=1}^n \alpha_{ij} \mathbf{X}_i$ or $C_k = \sum_{i=1}^n \beta_{ij} \mathbf{X}_i$ ($k = 1, \dots, m$) are associated to the left- and right-hand sides of the reaction steps.

When the reaction kinetic system obeys the mass action law, then the *reaction rate* of the j th irreversible reaction step has the following form

$$\rho_j = k_j \prod_{i=1}^n [\mathbf{X}_i]^{\alpha_{ij}} = k_j \prod_{i=1}^n x_i^{\alpha_{ij}} \quad , \quad j = 1, \dots, r \quad (2)$$

where $[\mathbf{X}_i] = x_i$ is the concentration of the i th component, and $k_j > 0$ is the *reaction rate constant* of the j th reaction, that is always positive.

Note that reversible reactions



are regarded as two irreversible steps that share the two complexes but have different reaction rates.

2.2. Algebraic characterization

A set of irreversible reaction steps with MAL kinetics can be characterized by the following model elements. The stoichiometric matrix Y and the reaction monomials $\varphi_j(x)$ are in the form of

$$[Y]_{ij} = y_{ij} \quad , \quad \varphi_j(x) = \prod_{i=1}^n x_i^{y_{ij}} \quad , \quad j = 1, \dots, m; \quad i = 1, \dots, n \quad (3)$$

where the matrix elements are the stoichiometric coefficients of the reactans, i.e. $y_{ij} = \alpha_{ij}$.

Algebraically, the so-called *Kirchhoff matrix of the reaction graph* $A_k \in \mathbb{R}^{m \times m}$ characterizes the reaction structure

$$[A_k]_{ij} = \begin{cases} -\sum_{l=1}^m k_{il} & \text{if } i = j \\ k_{ji} & \text{if } i \neq j \end{cases} \quad (4)$$

that is a column-conservation matrix with non-positive diagonal and non-negative off-diagonal entries.

The dynamic model equations The dynamic state equation for the i th component is in the form

$$\frac{dx_i}{dt} = -\sum_{j=1}^r \alpha_{ij} \varphi_j(x) + \sum_{i=1}^n \beta_{ij} \varphi_j(x) \quad (5)$$

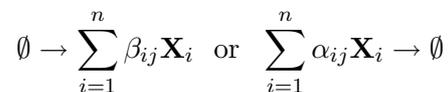
The above equations for all components can be described in vector-matrix form

$$\frac{dx}{dt} = Y \cdot A_k \cdot \varphi(x) = \mathcal{M} \cdot \varphi(x) \quad (6)$$

that forms the dynamic model of the reaction kinetic system with $\mathcal{M} = Y A_k$.

2.3. Open systems and the zero complex

The *zero complex* will play an important role in analyzing the dynamical implications of model reduction. It is a special complex with zero stoichiometric coefficients, i.e. $C_0 = 0$. This appears in the reaction schemes where one considers either an external source or sink of some components, i.e. elementary reaction steps of the form



In both cases *the systems is thermodynamically not closed*, therefore the conservation of the total mass in the system generally does not hold.

2.4. Structural and dynamic properties

Positive (nonnegative) systems The concepts and basic results in this paragraph are mostly taken from [5]. A function $f = [f_1 \dots f_n]^T : [0, \infty)^n \rightarrow \mathbb{R}^n$ is called *essentially nonnegative* if, for all $i = 1, \dots, n$, $f_i(x) \geq 0$ for all $x \in [0, \infty)^n$, whenever $x_i = 0$. In the linear case, when $f(x) = Ax$, the necessary and sufficient condition for essential nonnegativity is that the off-diagonal entries of $A \in \mathbb{R}^{n \times n}$ are nonnegative (such a matrix is often called a *Metzler-matrix*).

Consider an autonomous nonlinear system

$$\dot{x} = f(x), \quad x(0) = x_0 \quad (7)$$

where $f : \mathcal{X} \rightarrow \mathbb{R}^n$ is locally Lipschitz, \mathcal{X} is an open subset of \mathbb{R}^n and $x_0 \in \mathcal{X}$. Suppose that the nonnegative orthant $[0, \infty)^n = \mathbb{R}_+^n \subset \mathcal{X}$. Then the nonnegative orthant is invariant for the dynamics (7) if and only if f is essentially nonnegative.

Kinetic realizability of nonnegative polynomial systems An autonomous polynomial nonlinear system of the form (7) is called *kinetically realizable* or simply *kinetic*, if a mass action reaction mechanism given by equation (6) can be associated to it that exactly realizes its dynamics, i.e. $f(x) = Y \cdot A_k \cdot \varphi(x)$ where φ contains the monomials, matrix Y has nonnegative integer elements and A_k is a valid Kirchhoff matrix. In such a case, the pair (Y, A_k) will be called

a *realization* of the polynomial system (7) (note that Y contains all information about the composition of the monomials in φ in the case of mass-action dynamics). As it is expected from linear algebra, the same polynomial system may have many parametrically and/or structurally different realizations, and this is particularly true for kinetic systems coming from application domains other than chemistry. The problem of kinetic realizability of polynomial vector fields was first examined and solved in [11] where the constructive proof contains a realization algorithm that produces the directed graph of a possible associated mass action mechanism. According to [11], the necessary and sufficient condition for kinetic realizability is that all coordinate functions of the right hand side of (7) must have the form

$$f_i(x) = -x_i g_i(x) + h_i(x), \quad i = 1, \dots, n \quad (8)$$

where g_i and h_i are polynomials with nonnegative coefficients. The very short description of the realization algorithm presented in [11] is the following. Let us write the polynomial coordinate functions of the right hand side of a kinetic system (7) as

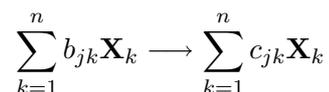
$$f_i(x) = \sum_{j=1}^{r_i} m_{ij} \prod_{k=1}^n x^{b_{jk}} \quad (9)$$

where r_i is the number of monomial terms in f_i . Let us denote the transpose of the i th standard basis vector in \mathbb{R}^n as e_i and let $B_j = [b_{j1} \dots b_{jn}]$.

Algorithm 1 from [11]

For each $i = 1, \dots, n$ and for each $j = 1, \dots, r_i$ do:

- (i) $C_j = B_j + \text{sign}(m_{ij}) \cdot e_i$
- (ii) Add the following reaction to the graph of the realization



with reaction rate coefficient $|m_{ij}|$,
where $C_j = [c_{j1} \dots c_{jn}]$.

Roughly speaking, condition (8) means that *kinetic systems cannot contain negative cross-effects*. From this, it is easy to see that all nonnegative linear systems are kinetic, since a linear system characterized by a Metzler matrix where only the diagonal elements can have negative coefficients is obviously in the form of (8). Moreover, classical Lotka-Volterra (LV) systems are always kinetic. However, there are many essentially nonnegative polynomial systems that are not directly kinetic, since some of the monomials in f_i that do not contain x_i may have negative coefficients. To circumvent this problem, one possible way is the application of a state-dependent time-rescaling [12] with a monomial function (see subsection 3.1).

Deficiency and stability Similarly to [13], we can assign the following directed graph (see, e.g. [14]) to the reaction network (1) in a straightforward way. The directed graph $D = (V_d, E_d)$ of a reaction network consists of a finite nonempty set V_d of vertices and a finite set E_d of ordered pairs of distinct vertices called directed edges. The vertices correspond to the complexes, i.e.

$V_d = \{C_1, C_2, \dots, C_m\}$, while the directed edges represent the reactions, i.e. $(C_i, C_j) \in E_d$ if complex C_i is transformed to C_j in the reaction network. The reaction rate coefficients k_j for $j = 1, \dots, r$ in (2) are assigned as positive weights to the corresponding directed edges in the graph. Where it is more convenient, the notation k'_{ij} will be used for denoting the reaction rate coefficient corresponding to the reaction $C_i \rightarrow C_j$. A set of complexes $\{C_1, C_2, \dots, C_k\}$ is a *linkage class* of a reaction network if the complexes of the set are linked to each other in the reaction graph but not to any other complex [15].

We can associate an n -dimensional vector with each reaction in the following way. For the reaction $C_i \rightarrow C_j$, the corresponding *reaction vector* denoted by h_k is given by

$$h_k = [Y]_{\cdot, j} - [Y]_{\cdot, i} \quad (10)$$

where $[Y]_{\cdot, i}$ denotes the i th column of Y . Similarly to reaction rate coefficients, whenever it is more practical, h'_{ij} denotes the reaction vector corresponding to the reaction $C_i \rightarrow C_j$.

The *rank* of a reaction network denoted by s is defined as the rank of the vector set $\{h_1, h_2, \dots, h_r\}$ where r is the number of reactions.

The positive *stoichiometric compatibility class* containing a concentration x_0 is the following set [15]:

$$(x_0 + S) \cap \mathbb{R}_+^n$$

where \mathbb{R}_+^n denotes the positive orthant in \mathbb{R}^n , and $S = \text{span}\{h_1, h_2, \dots, h_r\}$.

The deficiency d of a reaction network is defined as [13], [15]

$$d = m - l - s \quad (11)$$

where m is the number of complexes in the network, l is the number of linkage classes and s is the rank of the reaction network.

A reaction network is called *reversible*, if each of its reactions is a reversible reaction. A reaction network is called *weakly reversible*, if each complex in the reaction graph lies on at least one directed cycle (i.e. if complex C_j is reachable from complex C_i on a directed path in the reaction graph, then C_i is reachable from C_j on a directed path).

The well-known *Deficiency Zero Theorem* [15] says that the ODEs of a weakly reversible deficiency zero CRN are globally stable with a known logarithmic Lyapunov function for all positive values of the reaction rate coefficients. Furthermore, these CRNs have a unique steady-state point in each positive stoichiometric compatibility class. Therefore (among other realization problems) it is of interest whether we can find a weakly reversible deficiency zero kinetic realization of a nonnegative polynomial system.

Computing preferred realizations of CRNs using mixed integer programming Mixed integer linear programming (MILP) is a powerful tool for combining discrete (boolean or integer) and continuous variables within an optimization framework where the objective function, equality and inequality constraints are linear [16]. It was shown that qualitative knowledge about the modeled system that can be expressed in propositional logic form has an equivalent representation as linear equations and inequalities [17]. Using this computational approach, it is possible to rewrite and solve certain CRN synthesis problems as MILP problems [10]. So far, the following problems have been solved: (a) computing the realizations containing the minimal/maximal number of reactions (called sparse and dense realizations, respectively), (b) computing the realization containing the minimal/maximal number of complexes (from within a given set), (c) computing reversible realizations (if they exist) [18]. These tools will be used to compute different realizations of kinetic systems in sections 3 and 4.

Conservation equations Assuming irreversible reaction equations (1) the conservation of component masses associated to the j th reaction is

$$\sum_{i=1}^n \alpha_{ij} M_i = \sum_{i=1}^n \beta_{ij} M_i$$

where M_i is the molecular weight of the i th component. This can be written in the following homogeneous form

$$\sum_{i=1}^n (\alpha_{ij} - \beta_{ij}) M_i = 0 \quad (12)$$

with the matrix $[\mathcal{N}]_{ij} = \alpha_{ij} - \beta_{ij}$ and vector M composed of the molecular weights. In order to have valid component mass conservation it should be required that the homogeneous equation $\mathcal{N}M = 0$ has at least one positive solution.

In order to develop a conservation equation for the component masses, one should take the reaction equation for the i th component in equation (5) and multiply it by its molar weight M_i , because the reaction equations refer to concentrations in molar units, e.g. in mol/m^3 :

$$M_i \frac{dx_i}{dt} = \sum_{j=1}^r (\alpha_{ij} - \beta_{ij}) M_i \varphi_j(x)$$

Summing up the above reaction equations (both of their left and right hand sides), and performing some algebraic manipulations we obtain:

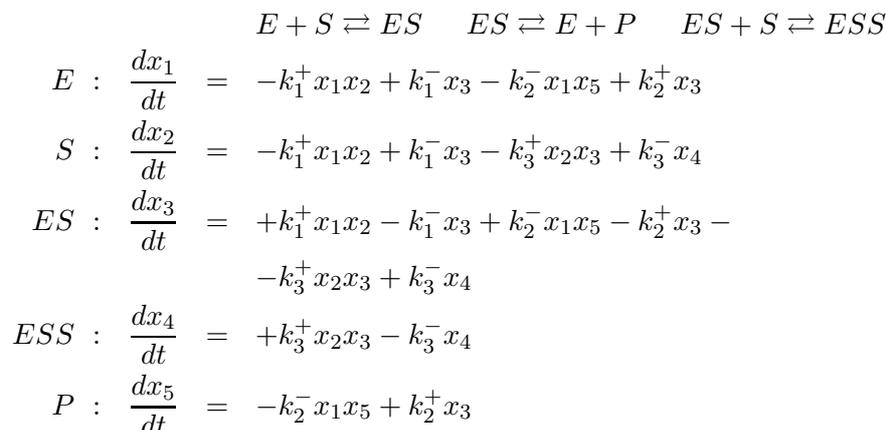
$$\frac{d}{dt} \sum_{i=1}^n (x_i M_i) = \sum_{j=1}^r \left(\sum_{i=1}^n (\alpha_{ij} - \beta_{ij}) M_i \right) \varphi_j(x) \quad (13)$$

Because of the mass conservation of the j th reaction in equation (12), the factor in the bracket on the right hand side in equation (13) is zero, therefore we obtain $\frac{d}{dt} \sum_{i=1}^n (x_i M_i) = 0$. This proves the lemma below.

Lemma 1 *A closed reaction kinetic system with MAL kinetics and component mass conservation for every reaction has a linear first integral corresponding to the total component mass conservation in the form $\sum_{i=1}^n M_i x_i = \text{const}$ if the equation $\mathcal{N}M = 0$ has at least one positive solution.*

2.5. An example: The Michaelis-Menten reaction scheme

The Michaelis-Menten reaction scheme describes a simple enzyme-kinetic reaction with the following reaction and dynamic model equations



where the concentration state vector x is formed as

$$x_1 = [E], \quad x_2 = [S], \quad x_3 = [ES], \quad x_4 = [ESS], \quad x_5 = [P]$$

from the components E for the enzyme, S for the substrate, P for the product, and ES and ESS being intermediate complexes.

The dynamical behaviour of the concentration variables and the reaction graph that consists of two reversible connected components are seen in figure 1, with the following model parameters used for the simulations:

$$k_1^+ = 1, \quad k_1^- = 0.8, \quad k_2^+ = 1.1, \quad k_2^- = 0.75, \quad k_3^+ = 2, \quad k_3^- = 1.8$$

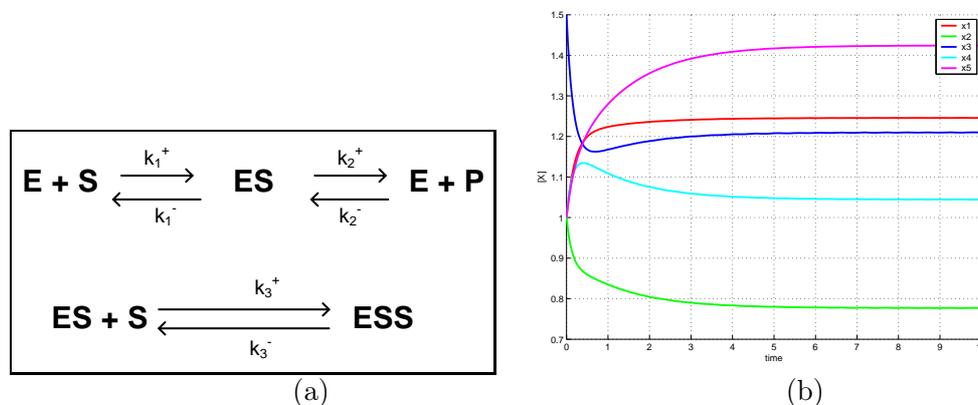


Figure 1. The Michaelis-Menten reaction scheme (a) structure graph (b) system dynamics

The deficiency of this reversible model is zero, therefore its equilibrium points are globally stable because of the deficiency zero theorem.

3. Transformation of reaction kinetic models

The different transformations that are used here are described as formal mathematical transformations applied to the reaction kinetic model equations with MAL.

3.1. Time-reparametrization transformation

The time reparametrization transformation is an equivalence transformation where only the algebraic form but not the structural properties of the model are changed. It is performed by introducing a new time variable $dt = x_1^{\nu_1} \cdot \dots \cdot x_n^{\nu_n} \cdot dt'$ with $\nu_i \in \{0, 1\}$. The transformed model equations are

$$\frac{dx}{dt'} = \mathcal{M}\varphi'(x)$$

where only the reaction monomials change to

$$\varphi'_j(x) = \prod_{i=1}^n x_i^{y_{ij} + \nu_i}$$

It immediately follows from the definition that *the transformed model remains in the MAL reaction kinetic class with the same structural properties.*

The time reparametrization transformation will be used later for the *elimination of negative cross-effects* that may arise during the model reduction.

3.2. Model simplification by steady state assumption transformation

The model reduction using quasi steady state (QSS) assumption(s) is the most popular method of obtaining dynamic models with lower dimension (i.e. with less differential state variables). If the j th component is considered to be in quasi steady state, formally this is written as

$$\frac{dx_j}{dt} = F_j(x) = 0 \quad , \quad x_j = x_j^* = \text{const} \quad (14)$$

The *formal model reduction transformation* is performed in two consecutive formal steps:

SS1 eliminating the component \mathbf{X}_j by setting its concentration x_j to a constant x_j^* whenever it appears,

SS2 substituting the resulting algebraic equation from equation (14), e.g. $F_j(x) = 0$ into the differential ones.

The first step decreases the number of state variables by one, and then step SS2 reduces it further by one.

It is important to note that the algebraic equation from equation (14) is not considered further, i.e. step SS2 is not performed, if the component assumed to be in QSS has formed a complex in itself. In this case this complex is replaced by the zero complex in the reduced model indicating that the reduced system became open. Then the resulting constant terms in the individual reaction kinetic equations may serve as input variables with a help of which the algebraic equation can be enforced.

The steady state assumption transformation is a projection in mathematical sense, therefore the structural properties of the model may change. It is important to note that even the reaction kinetic form may be lost during this transformation. For a more detailed analysis of this transformation we refer to [6].

3.3. Simplified Michaelis-Menten reaction schemes and their realizations

This section shows how the steady state assumption transformation changes the structural properties of a reaction kinetic system model and identifies conditions when the dynamic properties of the reduced model may be different from the original one.

The constant values x_1^* and x_3^* in the following subsections were chosen from the steady state simulation results of the original model described in section 2.5.

3.3.1. Quasi steady state for the component ES (x_3) Here only the first SS1 step of the steady state transformation is performed, because the component ES forms a complex in itself.

$$\begin{aligned} E : \frac{dx_1}{dt} &= -k_1^+ x_1 x_2 + \bar{k}_1^- - k_2^- x_1 x_5 + \bar{k}_2^+ \\ S : \frac{dx_2}{dt} &= -k_1^+ x_1 x_2 + \bar{k}_1^- - \bar{k}_3^+ x_2 + k_3^- x_4 \\ ESS : \frac{dx_4}{dt} &= \bar{k}_3^+ x_2 - k_3^- x_4 \\ P : \frac{dx_5}{dt} &= -k_2^- x_1 x_5 + \bar{k}_2^+ \end{aligned}$$

where the new reaction rate constants are $\bar{k}_i^\pm = k_i^\pm x_3^*$.

The model *remains reaction kinetic (in **generalized** sense)* with the reaction graph seen in figure 2(a).

We can eliminate the resulting zero complex through a time reparametrization transformation by introducing a new time variable $dt = x_1 dt'$ to obtain

$$\begin{aligned}
 E &: \frac{dx_1}{dt'} = -k_1^+ x_1^2 x_2 - k_2^- x_1^2 x_5 + (k_1^- + k_2^+) x_3^* x_1 \\
 S &: \frac{dx_2}{dt'} = -k_1^+ x_1^2 x_2 - k_3^+ x_3^* x_1 x_2 + k_3^- x_1 x_4 + k_1^- x_3^* x_1 \\
 ESS &: \frac{dx_4}{dt'} = k_3^+ x_3^* x_1 x_2 - k_3^- x_1 x_4 \\
 P &: \frac{dx_5}{dt'} = -k_2^- x_1^2 x_5 + k_2^+ x_3^* x_1
 \end{aligned}$$

The resulting model equations are kinetic with the corresponding reaction structure seen in figure 2(b). This structure is fully reversible and of deficiency 0, thus the model is stable.

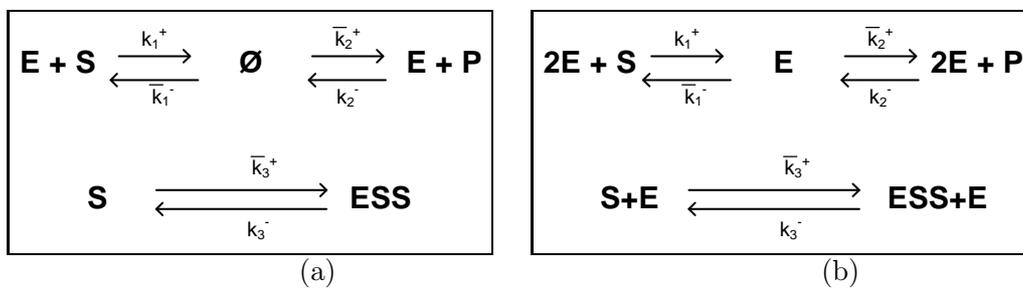


Figure 2. The simplified Michaelis-Menten reaction scheme with ES in QSS (a) reduced reaction graph (b) after time reparametrization

The dynamics of the reduced model is seen in figure 3 with $x_3^* = 1.21$. By comparing figures 1(b) and 3 we can say that even the details of the dynamics are fairly similar.

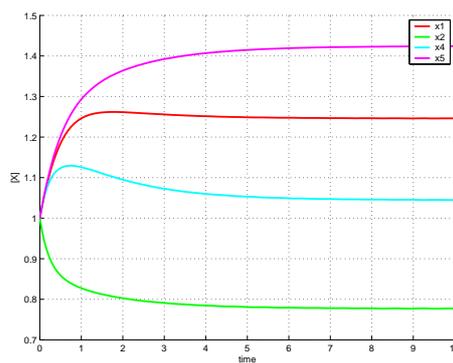


Figure 3. The dynamics of the simplified Michaelis-Menten reaction scheme with ES in QSS

3.3.2. Quasi steady state for the component E

The first step *SS1* of this transformation is to set $x_1 = x_1^*$ without substituting the resulting first integral that results in a model

$$\begin{aligned} S &: \frac{dx_2}{dt} = -k_1^+ x_1^* x_2 + k_1^- x_3 - k_3^+ x_2 x_3 + k_3^- x_4 \\ ES &: \frac{dx_3}{dt} = k_1^+ x_1^* x_2 + (-k_1^- - k_2^+) x_3 + k_2^- x_1^* x_5 - k_3^+ x_2 x_3 + k_3^- x_4 \\ ESS &: \frac{dx_4}{dt} = k_3^+ x_2 x_3 - k_3^- x_4 \\ P &: \frac{dx_5}{dt} = k_2^+ x_3 - k_2^- x_1^* x_5 \end{aligned}$$

The obtained reaction graph is seen in figure 4(a), which is a reversible deficiency 0 structure, and thus structurally stable. The dynamics of the state variables is shown in figure 4(b), that is fairly similar to the original dynamics for the remaining state variables with $x_1^* = 1.246$.

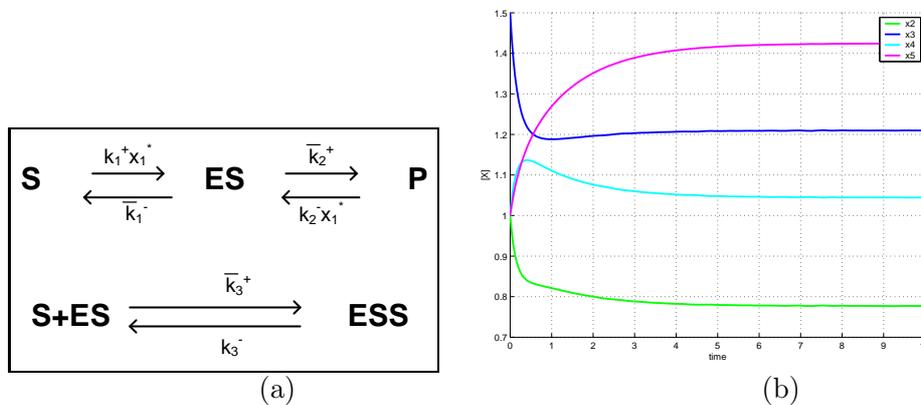


Figure 4. The simplified Michaelis-Menten reaction scheme *E* in QSS without substituting the algebraic equation (a) structure graph (b) system dynamics

The second step *SS2* requires to substitute the resulting algebraic equation from the first differential equation with $x_1 = x_1^*$, i.e.

$$-k_1^+ x_1^* x_2 + (k_1^- + k_2^+) x_3 - k_2^- x_1^* x_5 = 0$$

into the model. This can be performed by expressing x_5 and substituting it to all of the remaining equations to obtain

$$\begin{aligned} S &: \frac{dx_2}{dt} = -k_1^+ x_1^* x_2 + k_1^- x_3 - k_3^+ x_2 x_3 + k_3^- x_4 \\ ES &: \frac{dx_3}{dt} = \underbrace{(k_1^+ x_1^* - k_2^- x_1^* l_2)}_0 x_2 + \underbrace{(k_2^- x_1^* l_3 - k_1^- - k_2^+)}_0 x_3 - k_3^+ x_2 x_3 + k_3^- x_4 \\ ESS &: \frac{dx_4}{dt} = k_3^+ x_2 x_3 - k_3^- x_4 \end{aligned}$$

where $l_2 = \frac{k_1^+}{k_2^-}$ and $l_3 = \frac{k_1^- + k_2^+}{k_2^- x_1^*}$. It is important to note that the polynomial form of the equations remained.

We can now search for a reaction kinetic realization of the above reduced model using MILP. It is obtained that *there exists no reversible realization*, therefore a realization with the minimum number of reactions has been searched for. The resulting irreversible reaction kinetic network is shown in figure 5(a) that does not fulfill the conditions of the deficiency zero theorem. Moreover, the dynamics of the remaining state variables (see figure 5(b)) is rather different from the original ones.

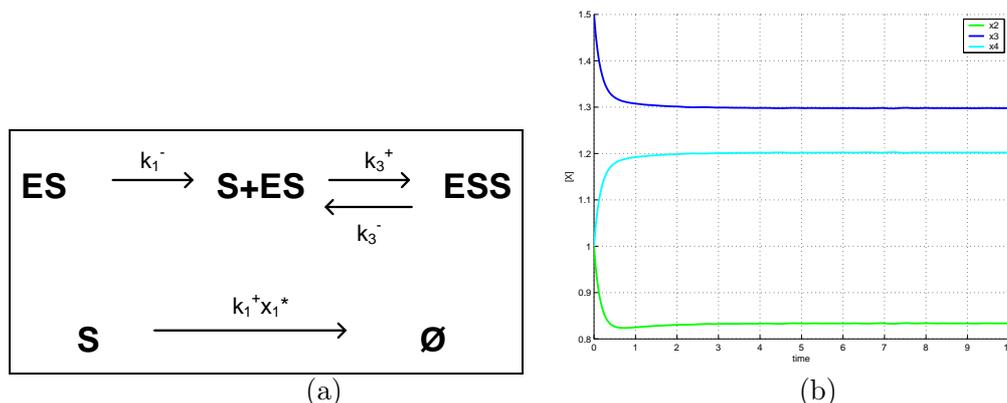


Figure 5. The simplified Michaelis-Menten reaction scheme E in QSS with substituting the algebraic equation (a) structure graph (b) system dynamics

In conclusion one can observe that the second step SS2 is the one that may drastically modify the structure and the dynamics of the system, and this is the one that may bring out the model from the polynomial system class.

Without this step, however, there is no guarantee, that the component assumed to be in QSS is indeed constant, this implies that the pseudo reaction rate coefficients will vary in time. At the same time it is known, that as long as the structure of a deficiency zero CRN remains such that the deficiency zero weakly reversible property is preserved in each time instant, the time-variation of the reaction rate coefficients cannot destroy stability [19].

4. The Brusselator case study

In this section, the effect of QSS assumptions will be shown on the reversible and irreversible versions of the well-known Brusselator example. In order to have polynomial reduced models, only the first step SS1 of the QSS assumption transformation is performed in this case. Thereafter the latest results of optimization based reaction mechanism generation [10, 18] will be used to compute kinetic realizations of the simplified models.

4.1. The irreversible and reversible full models and their properties

The starting point is the most frequently used reaction scheme for the irreversible and reversible Brusselator model that are shown in figure 6 (a) and (b), respectively. The kinetic differential

equations of the irreversible model are the following:

$$\dot{x}_1 = -k_{12}x_1 \quad (15)$$

$$\dot{x}_2 = k_{12}x_1 - k_{23}x_2 + k_{45}x_2^2x_4 - k_{67}x_2x_5 \quad (16)$$

$$\dot{x}_3 = k_{23}x_2 \quad (17)$$

$$\dot{x}_4 = -k_{45}x_2^2x_4 + k_{67}x_2x_5 \quad (18)$$

$$\dot{x}_5 = -k_{67}x_2x_5 \quad (19)$$

$$\dot{x}_6 = k_{67}x_2x_5 \quad (20)$$

The parameter values used for the numerical computations (resulting in oscillatory behaviour in the reduced model) were the following:

$$k_{12} = 1.2, \quad k_{23} = 2.1, \quad k_{45} = 4.2, \quad k_{67} = 6.5 \quad (21)$$

The equations corresponding to the reversible Brusselator model version can be written as

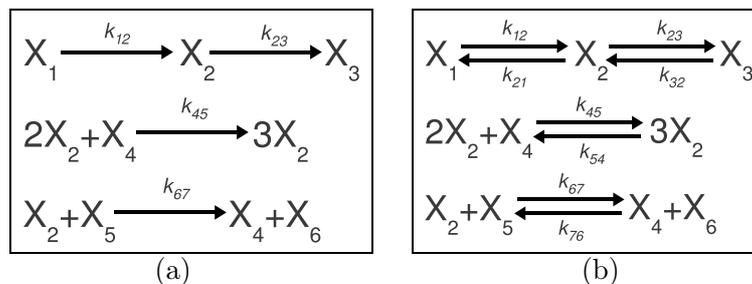


Figure 6. Brusselator reaction schemes: (a) irreversible case, (b) reversible version

$$\dot{x}_1 = -k_{12}x_1 + k_{21}x_2 \quad (22)$$

$$\dot{x}_2 = k_{12}x_1 - (k_{21} + k_{23})x_2 + k_{32}x_3 + k_{45}x_2^2x_4 - k_{54}x_2^3 - k_{67}x_2x_5 + k_{76}x_4x_6 \quad (23)$$

$$\dot{x}_3 = k_{23}x_2 - k_{32}x_3 \quad (24)$$

$$\dot{x}_4 = -k_{45}x_2^2x_4 + k_{54}x_2^3 + k_{67}x_2x_5 - k_{76}x_4x_6 \quad (25)$$

$$\dot{x}_5 = -k_{67}x_2x_5 + k_{76}x_4x_6 \quad (26)$$

$$\dot{x}_6 = k_{67}x_2x_5 - k_{76}x_4x_6 \quad (27)$$

The parameter values (also causing oscillatory behaviour in the reduced model) were the following:

$$k_{ij} = 1, \quad \forall i, j \quad (28)$$

It can be easily computed that the deficiency is zero for both of the above models. This means that there is no equilibrium point in the interior of the positive orthant in the case of the irreversible Brusselator, and there is exactly one equilibrium point in each stoichiometric compatibility class of the reversible model. Moreover, the dynamics of the reversible model is globally stable with a known Lyapunov function, and it cannot produce complex behaviour such as oscillations in its original closed form.

4.2. Simplified versions of the irreversible variant

To produce oscillations, two concentrations, namely x_1 and x_5 , must be kept constant. This practically means opening the originally closed network and feeding in the necessary amount of these species. From the modeling point of view, this is a QSS assumption where $x_1 = x_1^*$ and $x_5 = x_5^*$ is assumed. The resulting dynamical equations are then the following:

$$\dot{x}_2 = k_{12}x_1^* - (k_{23} + k_{67}x_5^*)x_2 + k_{45}x_2^2x_4 \quad (29)$$

$$\dot{x}_3 = k_{23}x_2 \quad (30)$$

$$\dot{x}_4 = -k_{45}x_2^2x_4 + k_{67}x_5^*x_2 \quad (31)$$

$$\dot{x}_6 = k_{67}x_5^*x_2 \quad (32)$$

The numerical values of the chosen steady states were $x_1^* = x_5^* = 1$. It is easy to check that the polynomial system (29) - (32) is kinetic. Using the methodology described in [10], the sparse realization of the model can be determined which is shown in figure 7. Equations (30) and (32)

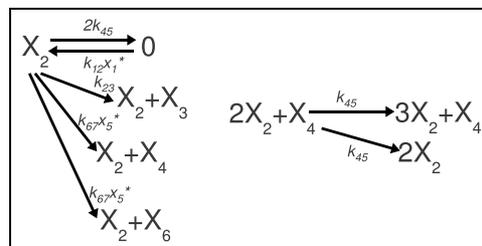


Figure 7. Sparse reaction scheme corresponding to the kinetic system (29) - (32)

can be omitted from the model if we are not interested in the dynamics of product composition. In this case, the remaining equations are

$$\dot{x}_2 = k_{12}x_1^* - (k_{23} + k_{67}x_5^*)x_2 + k_{45}x_2^2x_4 \quad (33)$$

$$\dot{x}_4 = -k_{45}x_2^2x_4 + k_{67}x_5^*x_2 \quad (34)$$

Naturally, the above equations are still kinetic, and the corresponding sparse reaction network can also be determined. This structure can be seen in figure 8. It is immediately visible that the network in figure 8 is a proper subgraph of the one shown in figure 7. The deficiency of both CRNs are 2, and with proper parametrization (for example the one in equation (21)), both are able to produce stable limit cycles. Moreover, it can also be shown through optimization, that no reversible CRN realization exists either for equations (29)-(32) or for (33)-(34) which is not very surprising, since the original closed CRN shown in figure 6 (a) was completely irreversible (although one reversible reaction pair appears between the zero complex and X_2).

In summary, we can observe that the deficiency and even the minimal number of reactions in a kinetic system may increase as a result of a QSS assumption. This might be contrary to our expectations, since the dynamics is seemingly simplified by the elimination of certain differential equations. Additionally, the physical opening of the system (needed to keep the appropriate concentrations constant) appears in the violation of component mass conservation (zero complex and autocatalytic reactions). Then, these factors can result in complex dynamical behaviour such as a limit cycle that is not observable in the original closed system.

4.3. Simplified versions of the reversible model

Let us consider now the reversible Brusselator variant given by equations (22)-(27). The following QSS assumptions have to be made for oscillating behaviour:

$$x_i = x_i^*, \quad i = 1, 3, 5, 6 \quad (35)$$

The remaining dynamics is then given by

$$\dot{x}_2 = (k_{12}x_1^* + k_{32}x_3^*) + (-k_{21} - k_{23} - k_{67}x_5^*)x_2 - k_{54}x_2^3 + k_{45}x_2^2x_4 + (k_{76}x_6^*)x_4 \quad (36)$$

$$\dot{x}_4 = -k_{45}x_2^2x_4 + k_{54}x_2^3 + k_{67}x_5^*x_2 - k_{76}x_6^*x_4 \quad (37)$$

The values of the steady states were chosen as follows: $x_1^* = 1$, $x_3^* = 1$, $x_5^* = 16$, $x_6^* = 0.5$. It is immediately visible that equations (36) - (36) are kinetic, therefore we can run **Algorithm 1** to compute a CRN realization which is shown in figure 9. It can be seen from the figure that this realization of deficiency 4 contains 8 reactions and none of the two linkage classes is (at least weakly) reversible.

However, an attempt to compute a fully reversible realization is successful in this case and gives the CRN that is depicted in figure 10. We remark that this CRN is also a sparse realization of the dynamics (36) - (37), since the MILP optimization method tells us that the minimal number of reactions needed to realize that dynamics is 6. The deficiency of the obtained reversible network is 1, therefore we can apply the *Deficiency one theorem* [15] which says that the differential equations of the CRN admit precisely one steady-state in each positive stoichiometric compatibility class. This fact, however, does not exclude the possibility of oscillating behaviour, that is to have a stable limit cycle around this steady-state. The stable limit cycle produced by the CRN with parameters in equation (28) started from the initial state $x(0) = [2 \ 2.5]^T$ can be seen in figure 11.

5. Conclusion and future work

The models relevant on a given time scale of a CNR are constructed by using QSS assumption(s) in this paper, that are defined as formal model transformations consisting of two steps. A MILP

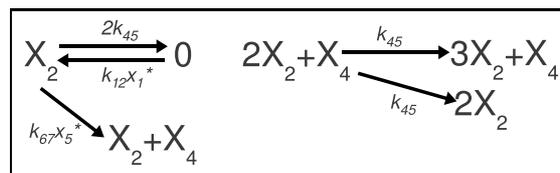


Figure 8. Sparse reaction scheme corresponding to the kinetic system (33) - (34)

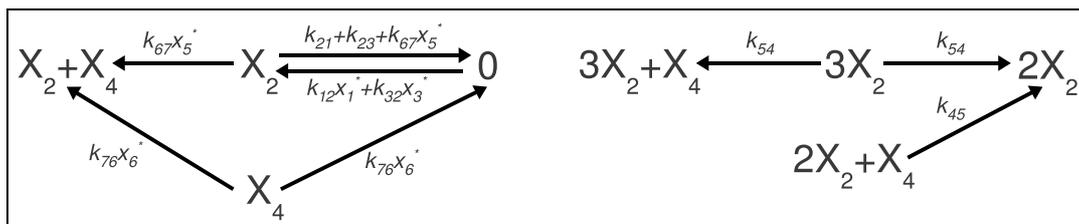


Figure 9. Reaction network produced by **Algorithm 1** corresponding to the kinetic system (36) - (37)

approach is proposed further for determining physically meaningful mass action realizations of these reduced models.

The relationship between the properties (reversibility, deficiency, stability) of the obtained realizations of the same system on different time scales were also investigated and related to the same properties of the detailed overall model. It has been shown that the QSS assumption can cause the increase of the deficiency and that of the minimal number of reaction in the realization, as well as the appearance of the zero complex. This implies that spurious exotic nonlinear behaviour, such as multiple steady-states and oscillations can appear in the reduced models that were not present in the original detailed ones.

The proposed methods are illustrated by using a simple Michaelis-Menten type reaction kinetic example. The simplified versions of the well known Brusselator model have also been investigated and presented as a case study.

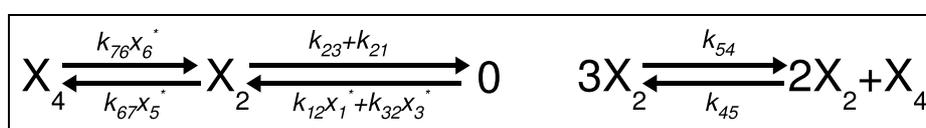


Figure 10. Sparse reversible realization corresponding to the kinetic system (36) - (37)

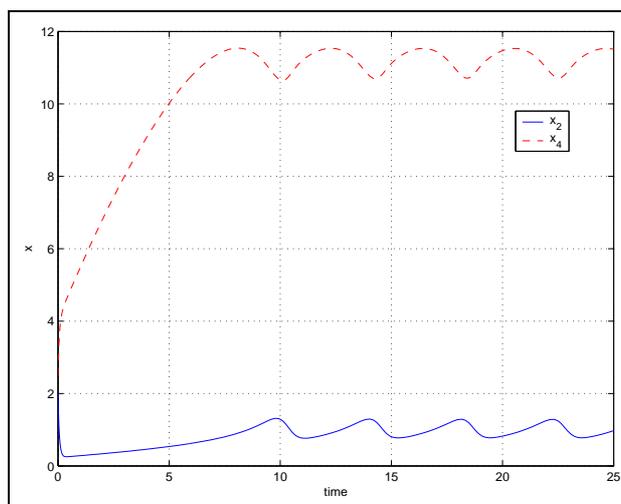


Figure 11. Time-domain behaviour of the CRN shown in Fig 10

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