

EXPLICIT SOLUTIONS AND EXACT MODEL REDUCTION OF MASS ACTION SYSTEMS

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ABSTRACT. This thesis concerns steady state equations of mass action systems and methods for solving them symbolically in Matlab.

We study two different methods for solving such systems with slightly different applicability. One that is fast but limited, the other one is slower but more general.

We also study the question of parameter dependence of solutions and model reduction. The parameter dependence is done both for all concentrations and for specific outputs.

We apply these methods to a biochemical system arising in neuroscience with the goal of making computations on the system faster and to better understand the behaviour of the system.

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2. INTRODUCTION

Mass action systems are systems that arise in a number of different areas. For example they can be used to describe biochemical systems in neuroscience [1]. Those systems are often solved many times numerically, with different randomized values on parameters and concentrations to draw conclusions about the properties of the system.

This thesis presents a method for solving mass action systems symbolically. The reason why this is useful is that it suffices to solve the system symbolically *once*. This solution can be used multiple times, for example when optimizing unknown parameter values and this can save a lot of time.

The theoretical method is described in detail and it is then applied to a specific mass action system from neuroscience [1].

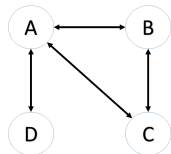
A chemical reaction is a process where chemical substances interact with each other and change into different substances. An elementary chemical reaction has the form



Several chemical reactions that interact with each other is called a chemical reaction network. For example, if we have the system of elementary chemical reactions



the system can be illustrated with the following graph:



where each substance is a node and there is an edge between two nodes if the corresponding substances occur on different sides of a reaction.

Collecting the concentrations of the substances at time t in the network in a column vector $X(t)$, we denote the rate the concentration changes by $\frac{dX}{dt}$. The reaction rates of the reactions v_1, v_2, \dots, v_m are collected in a column vector $\mathbf{v}(X(t), \{k_f, k_r\})$, \mathbf{v} is then a vector valued function of the concentrations $X(t)$ and all the reaction constants $\{k_f, k_r\}$. The structure of the chemical reaction network is represented by the $m \times n$ stoichiometry matrix N (where m is the number of different substances and n is the number of reactions)

$$(3) \quad \frac{dX}{dt} = N \cdot \mathbf{v}(X(t), \{k_f, k_r\}).$$

The scope of this report is, for our specific system, to symbolically analyse steady state solutions of (3). A steady state solutions is when the rate the concentration changes are zero for each substance and is therefore independent of t , which means that we want, for X , to solve the system

$$(4) \quad 0 = N \cdot \mathbf{v}(X, \{k_f, k_r\}).$$

This report will analyse a specific system of chemical reactions that has the form of(4). There are several aspects of this system that we want to investigate from a mathematical standpoint. This report will answer the following questions:

- (a) How can we transform the non-linear system(4) into a linear system in some of the variables?
- (b) How can we solve (4) symbolically for X ?
- (c) How does the solution X to (4) depend on the parameters $\{k_f, k_r\}$?

3. MATHEMATICAL BACKGROUND

3.1. Linear Mappings.

Definition 1. A linear mapping

$$(5) \quad A : \mathbb{R}^n \rightarrow \mathbb{R}^m$$

is a function that satisfies the properties

- (1) $A(u + v) = A(u) + A(v)$ for all $u, v \in \mathbb{R}^n$
- (2) $A(cv) = cA(v)$ for all $c \in \mathbb{R}$ and $v \in \mathbb{R}^n$.

Definition 2. The matrix of a linear mapping $A : \mathbb{R}^n \rightarrow \mathbb{R}^m$ is an $n \times m$ matrix M for which

$$(6) \quad A(u) = Mu \quad \text{for all } u \in \mathbb{R}^n.$$

3.2. Linear subspace.

Definition 3. Assume that $U \subset \mathbb{R}^n$. U is a linear subspace if $au + bv \in U$ for all $u, v \in U$ and $a, b \in \mathbb{R}$.

3.3. Range and Kernel of a matrix.

Definition 4. The kernel of a linear mapping $A : \mathbb{R}^n \rightarrow \mathbb{R}^m$ is the set of all $v \in \mathbb{R}^n$ for which $A(v) = 0$, where 0 denotes the zero vector in \mathbb{R}^m ;

$$(7) \quad \ker(A) = \{v \in \mathbb{R}^n \mid A(v) = 0\}.$$

Proposition 1. Let $A : \mathbb{R}^n \rightarrow \mathbb{R}^m$ be a linear mapping. Then $\ker(A)$ is a linear subspace of \mathbb{R}^n .

Proof. By Definition 4, $\ker(A) \subset \mathbb{R}^n$. Assume that $u, v \in \ker(A)$ and $a, b \in \mathbb{R}$. Then $A(au + bv) = aA(u) + bA(v)$ by Definition 1, since A is a linear mapping. But we also know that $aA(u) = 0$ and that $bA(v) = 0$, since $u, v \in \ker(A)$. This shows that $A(au + bv) = 0$, which is equivalent to $au + bv \in \ker(A)$. Hence $\ker(A)$ is a linear subspace of \mathbb{R}^n . \square

Definition 5. The range of a linear map $A : \mathbb{R}^n \rightarrow \mathbb{R}^m$ is the set of all elements $w \in \mathbb{R}^m$ for which there exists a vector $v \in \mathbb{R}^n$ such that $A(v) = w$

$$(8) \quad \text{Ran}(A) = \{w \in \mathbb{R}^m \mid \exists v \in \mathbb{R}^n, A(v) = w\}.$$

Proposition 2. Let $A : \mathbb{R}^n \rightarrow \mathbb{R}^m$ be a linear mapping. Then $\text{Ran}(A)$ is a linear subspace of \mathbb{R}^m .

Proof. By Definition 5, $\text{Ran}(A) \subset \mathbb{R}^m$. Assume that $A(u), A(v) \in \text{Ran}(A)$ and $a, b \in \mathbb{R}$. Then $aA(u) + bA(v) = A(au + bv)$ by Definition 1, since A is a linear mapping. This shows that $aA(u) + bA(v) \in \text{Ran}(A)$. Hence $\text{Ran}(A)$ is a linear subspace of \mathbb{R}^m by Definition 3. \square

3.4. Inner product.

Definition 6. The standard inner product between two column vectors a and b in \mathbb{R}^n is denoted by $a \cdot b$ and is defined as

$$(9) \quad a \cdot b = a^T b = a_1 b_1 + a_2 b_2 + \cdots + a_n b_n.$$

Definition 7. Two vectors $a, b \in \mathbb{R}^n$ are orthogonal ($a \perp b$) if their inner product is equal to zero:

$$(10) \quad a \perp b \Leftrightarrow a \cdot b = 0.$$

Definition 8. Let V be a subspace of \mathbb{R}^n . Then the orthogonal complement of V is denoted by V^\perp and is the set of all vectors that are orthogonal to every vector in V

$$(11) \quad V^\perp = \{w \in \mathbb{R}^n \mid \forall v \in V, w \perp v\}.$$

Proposition 3. Let V be a subspace of \mathbb{R}^n . Then V^\perp is a linear subspace of \mathbb{R}^n .

Proof. Assume that $u, w \in V^\perp$ and $a, b \in \mathbb{R}$. Then $(au)^T v = a(u^T v) = 0$ and $(bw)^T v = b(w^T v) = 0$ for all $v \in V$ by Definition 8. This gives us that $0 = (au)^T v + (bw)^T v = (au+bw)^T v$, which is equivalent to $(au+bw) \perp v$ for all $v \in V$. This shows that $(au+bw) \in V^\perp$ if $u, w \in V^\perp$. Hence V^\perp is a linear subspace of \mathbb{R}^n . \square

Theorem 1. If $A : \mathbb{R}^n \rightarrow \mathbb{R}^m$ is a linear mapping, then

$$(12) \quad \ker(A) = (\text{Ran}(A^T))^\perp.$$

Proof. Assume that $x \in \ker(A)$, in other words $Ax = 0$. Then clearly x is orthogonal to every row in A and so it is orthogonal to every column in A^T . Hence $x \in (\text{Ran}(A^T))^\perp$, because the range of a linear map is the linear subspace spanned by the columns of A . Hence $\ker(A) \subseteq (\text{Ran}(A^T))^\perp$.

Now assume that $y \in (\text{Ran}(A^T))^\perp$. Then y is orthogonal to every vector in $\text{Ran}(A^T)$. Hence y is orthogonal to every column in A^T , and so y is orthogonal to every row in A . But then $Ay = 0$, and so $y \in \ker(A)$. Hence $(\text{Ran}(A^T))^\perp \subseteq \ker(A)$.

This proves that $\ker(A) \subseteq (\text{Ran}(A^T))^\perp$ and $(\text{Ran}(A^T))^\perp \subseteq \ker(A)$, and so

$$(13) \quad (\text{Ran}(A^T))^\perp = \ker(A).$$

\square

4. CHEMICAL BACKGROUND

In this section some basic chemical concepts will be defined. The definitions will only be introductory, because the main focus of this thesis is mathematical. For a more thorough definition, see [2] and [3].

4.1. Elementary Chemical Reaction. An elementary chemical reaction has the form



where A, B and C are different substances. A and B are called reactants and C is called a product.

When both the reaction $A + B \rightarrow C$ and the reaction $A + B \leftarrow C$ occurs, we have a reversible chemical reaction, which we denote by



4.2. Law of Mass Action. Assume that we have a reversible elementary chemical reaction $A + B \rightleftharpoons C$. It is reversible, so it can be seen as two reactions



The law of mass action for the first reaction states that the concentration of A , denoted by $[A]$, decreases with a rate proportional to $[A]$ and $[B]$, with a proportionality constant denoted by k_f . The same is true for $[B]$, with the same proportionality constant. $[C]$ is increased with the same rate $k_f[A][B]$.

The other reaction occurs simultaneously. There $[A]$ and $[B]$ increases (and $[C]$ decrease) with a rate proportional to $[C]$. We denote this proportionality constant by k_r .

If we combine the effect of both reactions, we get that the concentration of the substances changes with rates given by

$$(17) \quad \begin{cases} \frac{d[A]}{dt} = -k_f[A][B] + k_r[C] \\ \frac{d[B]}{dt} = -k_f[A][B] + k_r[C] \\ \frac{d[C]}{dt} = -k_r[C] + k_f[A][B]. \end{cases}$$

The k_f and k_r are rate constants that are different for every reaction. The law of mass action is based on empirical studies [2].

4.3. Reaction Rate. For every chemical reaction, we define the *reaction rate*. For a reversible elementary chemical reaction, it has the form

$$(18) \quad v = k_f[A][B] - k_r[C],$$

and by (17) we see that

$$(19) \quad \begin{cases} \frac{d[A]}{dt} = -v \\ \frac{d[B]}{dt} = -v \\ \frac{d[C]}{dt} = v. \end{cases}$$

4.4. Stoichiometry matrix. When several chemical reactions that interact, we have a chemical reaction network. The rate at which each concentration changes is then the sum of the rate it changes within every reaction. To keep track of this and to be able to write the equations in matrix form, we introduce the stoichiometry matrix N . N is an $m \times n$ matrix, where m is the number of substances and n is the number of reactions in the network. Each stoichiometry coefficient in N is defined by

$$(20) \quad N_{ji} = \begin{cases} -1 & \text{if substance } j \text{ occurs in reaction } i\text{'s reactants} \\ 1 & \text{if substance } j \text{ is reaction } i\text{'s product} \\ 0 & \text{otherwise.} \end{cases}$$

If we let $X(t)$ denote the concentrations at time t and $\mathbf{v}(t)$ denote the reaction rate vector at time t , the rate at which the concentrations change can be described by

$$(21) \quad \frac{dX}{dt} = N\mathbf{v}(t).$$

It is worth noticing that N does not depend on time and does not contain any parameters. It represents the structure of the network. For example, if we have the reversible elementary chemical reaction $A + B \rightleftharpoons C$, then $v(t) = k_f[A][B] - k_r[C]$ and

$$(22) \quad \begin{cases} \frac{d[A]}{dt} = -v(t) \\ \frac{d[B]}{dt} = -v(t) \\ \frac{d[C]}{dt} = v(t). \end{cases}$$

If we denote

$$(23) \quad X = \begin{bmatrix} [A] \\ [B] \\ [C] \end{bmatrix}$$

then the rate of change $\frac{dX}{dt}$ can be described by

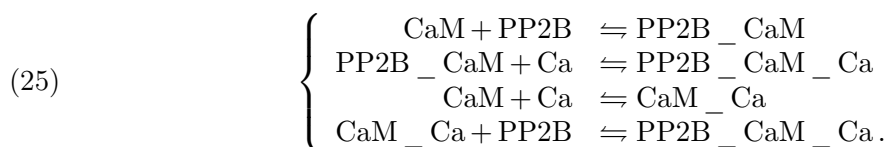
$$(24) \quad \frac{dX}{dt} = Nv(t) = \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix} v(t)$$

and therefore $N = \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix}$. This can also be derived from (20), the definition of N .

4.5. Equilibrium. In a chemical reaction network, equilibrium occurs when all the reaction rates are zero. Hence the system $\mathbf{v} = 0$ can be solved to find the equilibrium solution. To every reversible elementary chemical reaction, we define the equilibrium constant K_d as $K_d = \frac{k_r}{k_f}$.

Some chemical reaction networks contain cyclic reactions. Cyclic reactions occur when there exist multiple paths from one substance to another in the network. It is known that for chemical reaction networks at equilibrium, Wegscheider's conditions are satisfied [4]; the product of the K_d parameters for every reaction in each path should be equal.

As an example, let us take the chemical reaction network consisting of the reactions

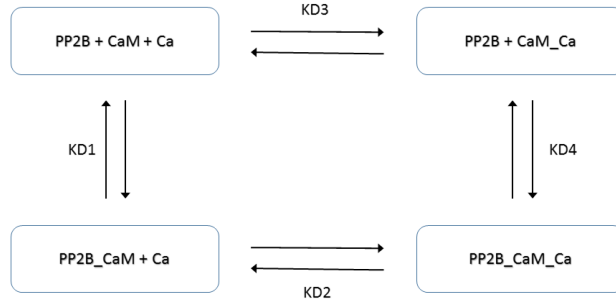


Here the rates of change are

$$(26) \quad \begin{cases} v_1 = & k_{f1}[\text{CaM}][\text{PP2B}] - k_{r1}[\text{PP2B_CaM}] \\ v_2 = & k_{f2}[\text{PP2B_CaM}][\text{Ca}] - k_{r2}[\text{PP2B_CaM_Ca}] \\ v_3 = & k_{f3}[\text{CaM}][\text{Ca}] - k_{r3}[\text{CaM_Ca}] \\ v_4 = & k_{f4}[\text{CaM_Ca}][\text{PP2B}] - k_{r4}[\text{PP2B_CaM_Ca}] \end{cases}$$

and the equilibrium quotients $K_{d1} = \frac{k_{r1}}{k_{f1}}$, $K_{d2} = \frac{k_{r2}}{k_{f2}}$, $K_{d3} = \frac{k_{r3}}{k_{f3}}$ and $K_{d4} = \frac{k_{r4}}{k_{f4}}$.

If we represent the substances in every reaction with a node and there is an edge between two nodes if they appear on different sides of a reaction, we get the following network structure:



This chemical reaction network contains a cycle of reactions, as we can see in the graph of the network, because there are two different paths from CaM to PP2B_CaM_Ca. This means that for the equilibrium solution to exist, Wegscheider's conditions must hold, which gives us that the constants need to fulfil the constraint $K_{d1}K_{d2} = K_{d3}K_{d4}$.

4.6. Steady State. Steady state occurs in a chemical reaction network when all the derivatives of the concentrations is zero. Chemical reaction networks that are in steady state can therefore be described as

$$(27) \quad N\mathbf{v} = 0.$$

In a closed system of chemical reactions (no inflow or outflow) a system at steady state is also at equilibrium [4]. Hence the Wegscheider conditions must be satisfied.

Take for instance the reversible elementary chemical reaction $A + B \rightleftharpoons C$. Then we have $N = \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix}$ and $v = k_f[A][B] - k_r[C]$. The steady state equations for this system $N\mathbf{v} = 0$ is thus

$$(28) \quad \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix} (k_f[A][B] - k_r[C]) = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}.$$

which is equivalent to

$$(29) \quad \begin{cases} -k_f[A][B] + k_r[C] = 0 \\ -k_f[A][B] + k_r[C] = 0 \\ -k_r[C] + k_f[A][B] = 0. \end{cases}$$

This can then be used to retrieve information about the reaction, for example the quotient $\frac{k_r}{k_f}$ (denoted K_d) for each reaction, is in steady state equal to the quotient of the concentrations

$$(30) \quad \frac{k_r}{k_f} = \frac{[A][B]}{[C]}.$$

4.7. Conservation Laws. In a chemical reaction network some substances cannot be decomposed into other substances, since they are not a product in any reaction. We denote these substances by elements. To capture the constraint on the network saying that the total amount of these elements has to be constant (if we have no in- or outflow from the network), we use conservation laws. The conservation laws of a system of chemical reactions is derived from the stoichiometry matrix N in the following way.

Define a row vector \mathbf{a} such that $\mathbf{a}^T \in \ker(N^T)$. Then is $\mathbf{a}N = 0$ by definition. The system $\frac{dX}{dt} = N\mathbf{v}$ can be multiplied with \mathbf{a} , which gives us that $\mathbf{a}\frac{dX}{dt} = \mathbf{a}N\mathbf{v} = 0$. The integral of this equation is $\mathbf{a}X = b$, where b is a constant. We define $\mathbf{a}X = b, \mathbf{a}^T \in \ker(N^T)$ to be a conservation law, where b is a constant.

5. CHEMICAL SYSTEM

In this section we define the chemical reaction network, which is used as an example throughout the thesis. The chemical reaction network is modelled by Nair et al. and described in [1].

This system of chemical reactions describes calcium-dependent activation of the protein calmodulin (denoted CaM), protein phosphatase 2B (denoted PP2B) and the calcium/calmodulin-dependent protein kinase II (denoted CaMKII). These four elements react with each other in elementary chemical reactions of the form



The system has 31 reactions of this type and one exceptional reaction of a more complicated type. This system involves 24 different substances and 63 parameters. The parameters, k_f , k_r and K_d are related by the equation $\frac{k_r}{k_f} = K_d$. A table of the substances can be found in Table 1 and a table of the chemical reactions can be found in Table 2.

Number	Name	Element (Yes/No)
1	Ca	Yes
2	CaM	Yes
3	PP2B	Yes
4	CaMKII	Yes
5	pCaMKIIaut	No
6	CaM_Ca1	No
7	CaM_Ca2	No
8	CaM_Ca3	No
9	CaM_Ca4	No
10	PP2B_CaM	No
11	PP2B_CaM_Ca1	No
12	PP2B_CaM_Ca2	No
13	PP2B_CaM_Ca3	No
14	PP2Bc	No
15	CaMKII_CaM	No
16	CaMKII_CaM_Ca1	No
17	CaMKII_CaM_Ca2	No
18	CaMKII_CaM_Ca3	No
19	CaMKIIc	No
20	pCaMKII_Ca0	No
21	pCaMKII_Ca1	No
22	pCaMKII_Ca2	No
23	pCaMKII_Ca3	No
24	pCaMKII	No

TABLE 1. The different substances in Nair et al.'s system [1].

One consequence of the fact that the chemical reactions has the form (31) is that the \mathbf{v} functions will be of the form (18) (except for chemical reaction 32 in Table 2). This will be important in later sections.

1	$\text{Ca} + \text{CaM} \rightleftharpoons \text{CaM_Ca1}$	$k_f = k_{f1}$	$k_r = k_{r1}$	$K_d = K_{d1}$
2	$\text{Ca} + \text{CaM_Ca1} \rightleftharpoons \text{CaM_Ca2}$	$k_f = k_{f2}$	$k_r = k_{r2}$	$K_d = K_{d2}$
3	$\text{Ca} + \text{CaM_Ca2} \rightleftharpoons \text{CaM_Ca3}$	$k_f = k_{f3}$	$k_r = k_{r3}$	$K_d = K_{d3}$
4	$\text{CaM_Ca3} + \text{Ca} \rightleftharpoons \text{CaM_Ca4}$	$k_f = k_{f4}$	$k_r = k_{r4}$	$K_d = K_{d4}$
5	$\text{CaM} + \text{PP2B} \rightleftharpoons \text{PP2B_CaM}$	$k_f = k_{f5}$	$k_r = k_{r5}$	$K_d = K_{d5}$
6	$\text{CaM_Ca1} + \text{PP2B} \rightleftharpoons \text{PP2B_CaM_Ca1}$	$k_f = k_{f6}$	$k_r = k_{r6}$	$K_d = K_{d6}$
7	$\text{CaM_Ca2} + \text{PP2B} \rightleftharpoons \text{PP2B_CaM_Ca2}$	$k_f = k_{f7}$	$k_r = k_{r7}$	$K_d = K_{d7}$
8	$\text{CaM_Ca3} + \text{PP2B} \rightleftharpoons \text{PP2B_CaM_Ca3}$	$k_f = k_{f8}$	$k_r = k_{r8}$	$K_d = K_{d8}$
9	$\text{CaM_Ca4} + \text{PP2B} \rightleftharpoons \text{PP2Bc}$	$k_f = k_{f9}$	$k_r = k_{r9}$	$K_d = K_{d9}$
10	$\text{PP2B_CaM} + \text{Ca} \rightleftharpoons \text{PP2B_CaM_Ca1}$	$k_f = k_{f10}$	$k_r = k_{r10}$	$K_d = K_{d10}$
11	$\text{PP2B_CaM_Ca1} + \text{Ca} \rightleftharpoons \text{PP2B_CaM_Ca2}$	$k_f = k_{f11}$	$k_r = k_{r11}$	$K_d = K_{d11}$
12	$\text{PP2B_CaM_Ca2} + \text{Ca} \rightleftharpoons \text{PP2B_CaM_Ca3}$	$k_f = k_{f12}$	$k_r = k_{r12}$	$K_d = K_{d12}$
13	$\text{PP2B_CaM_Ca3} + \text{Ca} \rightleftharpoons \text{PP2Bc}$	$k_f = k_{f13}$	$k_r = k_{r13}$	$K_d = K_{d13}$
14	$\text{CaM} + \text{CaMKII} \rightleftharpoons \text{CaMKII_CaM}$	$k_f = k_{f14}$	$k_r = k_{r14}$	$K_d = K_{d14}$
15	$\text{CaM_Ca1} + \text{CaMKII} \rightleftharpoons \text{CaMKII_CaM_Ca1}$	$k_f = k_{f15}$	$k_r = k_{r15}$	$K_d = K_{d15}$
16	$\text{CaM_Ca2} + \text{CaMKII} \rightleftharpoons \text{CaMKII_CaM_Ca2}$	$k_f = k_{f16}$	$k_r = k_{r16}$	$K_d = K_{d16}$
17	$\text{CaM_Ca3} + \text{CaMKII} \rightleftharpoons \text{CaMKII_CaM_Ca3}$	$k_f = k_{f17}$	$k_r = k_{r17}$	$K_d = K_{d17}$
18	$\text{CaM_Ca4} + \text{CaMKII} \rightleftharpoons \text{CaMKIIc}$	$k_f = k_{f18}$	$k_r = k_{r18}$	$K_d = K_{d18}$
19	$\text{Ca} + \text{CaMKII_CaM} \rightleftharpoons \text{CaMKII_CaM_Ca1}$	$k_f = k_{f19}$	$k_r = k_{r19}$	$K_d = K_{d19}$
20	$\text{CaMKII_CaM_Ca1} + \text{Ca} \rightleftharpoons \text{CaMKII_CaM_Ca2}$	$k_f = k_{f20}$	$k_r = k_{r20}$	$K_d = K_{d20}$
21	$\text{CaMKII_CaM_Ca2} + \text{Ca} \rightleftharpoons \text{CaMKII_CaM_Ca3}$	$k_f = k_{f21}$	$k_r = k_{r21}$	$K_d = K_{d21}$
22	$\text{CaMKII_CaM_Ca3} + \text{Ca} \rightleftharpoons \text{CaMKIIc}$	$k_f = k_{f22}$	$k_r = k_{r22}$	$K_d = K_{d22}$
23	$\text{CaM_Ca4} + \text{pCaMKIIaut} \rightleftharpoons \text{pCaMKII}$	$k_f = k_{f23}$	$k_r = k_{r23}$	$K_d = K_{d23}$
24	$\text{CaM_Ca3} + \text{pCaMKIIaut} \rightleftharpoons \text{pCaMKII_Ca3}$	$k_f = k_{f24}$	$k_r = k_{r24}$	$K_d = K_{d24}$
25	$\text{CaM_Ca2} + \text{pCaMKIIaut} \rightleftharpoons \text{pCaMKII_Ca2}$	$k_f = k_{f25}$	$k_r = k_{r25}$	$K_d = K_{d25}$
26	$\text{CaM_Ca1} + \text{pCaMKIIaut} \rightleftharpoons \text{pCaMKII_Ca1}$	$k_f = k_{f26}$	$k_r = k_{r26}$	$K_d = K_{d26}$
27	$\text{CaM} + \text{pCaMKIIaut} \rightleftharpoons \text{pCaMKII_Ca0}$	$k_f = k_{f27}$	$k_r = k_{r27}$	$K_d = K_{d27}$
28	$\text{pCaMKII_Ca0} + \text{Ca} \rightleftharpoons \text{pCaMKII_Ca1}$	$k_f = k_{f28}$	$k_r = k_{r28}$	$K_d = K_{d28}$
29	$\text{pCaMKII_Ca1} + \text{Ca} \rightleftharpoons \text{pCaMKII_Ca2}$	$k_f = k_{f29}$	$k_r = k_{r29}$	$K_d = K_{d29}$
30	$\text{pCaMKII_Ca2} + \text{Ca} \rightleftharpoons \text{pCaMKII_Ca3}$	$k_f = k_{f30}$	$k_r = k_{r30}$	$K_d = K_{d30}$
31	$\text{pCaMKII_Ca3} + \text{Ca} \rightleftharpoons \text{pCaMKII}$	$k_f = k_{f31}$	$k_r = k_{r31}$	$K_d = K_{d31}$
32	$\text{pairedCaMKIIc} + \text{CaMKIIc} \rightarrow \text{pCaMKII}$	$k_f = k_{f32}$	-	-

TABLE 2. The chemical reactions in Nair et al.'s system [1], where paired-CaMKIIc denotes a non-linear function of CaMKIIc.

This system has conservation laws corresponding to each of the elements Ca, CaM, CaMKII and PP2B, which can be derived from the stoichiometry matrix N , as in Section 4.7.

Another thing to notice about this system is that there exist several cyclic reactions. This means that there are multiple paths from one substance to another in the chemical reaction network. The Wegscheider condition for these cycles are listed in Table 3.

$$\begin{aligned}
(32) \quad & K_{d8} \cdot K_{d13} = K_{d4} \cdot K_{d9} \\
& K_{d7} \cdot K_{d12} = K_{d3} \cdot K_{d8} \\
& K_{d6} \cdot K_{d11} = K_{d2} \cdot K_{d7} \\
& K_{d5} \cdot K_{d10} = K_{d1} \cdot K_{d6} \\
& K_{d14} \cdot K_{d19} = K_{d1} \cdot K_{d15} \\
& K_{d15} \cdot K_{d20} = K_{d2} \cdot K_{d16} \\
& K_{d16} \cdot K_{d21} = K_{d3} \cdot K_{d17} \\
& K_{d17} \cdot K_{d22} = K_{d4} \cdot K_{d18} \\
& K_{d24} \cdot K_{d31} = K_{d4} \cdot K_{d23} \\
& K_{d25} \cdot K_{d30} = K_{d3} \cdot K_{d24} \\
& K_{d26} \cdot K_{d29} = K_{d2} \cdot K_{d25} \\
& K_{d27} \cdot K_{d28} = K_{d1} \cdot K_{d26}
\end{aligned}$$

TABLE 3. The relations for the equilibrium constants for the cyclic reactions at equilibrium [1].

6. SOLVING $\mathbf{v}(X, \{k_f, k_r\}) = 0$ WHEN ALL REACTIONS ARE ELEMENTARY AND REVERSIBLE

When all chemical reactions are elementary and reversible, the reaction rate equations will have the form $v_i = k_{fi}[A_i][B_i] - k_{ri}[C_i]$. Here we want to solve the equilibrium equations $\mathbf{v} = 0$ which in vector form are

$$(33) \quad \begin{bmatrix} k_{f1}[A_1][B_1] - k_{r1}[C_1] \\ k_{f2}[A_2][B_2] - k_{r2}[C_2] \\ \vdots \\ k_{fm}[A_m][B_m] - k_{rm}[C_m] \end{bmatrix} = 0,$$

where $[A_i], [B_i], [C_i]$ are concentrations for the substances occurring in reaction i and m is the number of reactions. First we substitute k_r by $k_f \cdot K_d$ in every equation. Then we get the equations

$$(34) \quad \begin{bmatrix} k_{f1}[A_1][B_1] - k_{f1}K_{d1}[C_1] \\ k_{f2}[A_2][B_2] - k_{f2}K_{d2}[C_2] \\ \vdots \\ k_{fm}[A_m][B_m] - k_{fm}K_{dm}[C_m] \end{bmatrix} = 0.$$

We know that $k_{fi} \neq 0$ for all i , because all reactions are reversible. This is used to simplify the equations to

$$(35) \quad \begin{bmatrix} [A_1][B_1] - K_{d1}[C_1] \\ [A_2][B_2] - K_{d2}[C_2] \\ \vdots \\ [A_m][B_m] - K_{dm}[C_m] \end{bmatrix} = 0.$$

We reorganize the equations to

$$(36) \quad \begin{bmatrix} \frac{[A_1][B_1]}{[C_1]} \\ \frac{[A_2][B_2]}{[C_2]} \\ \vdots \\ \frac{[A_m][B_m]}{[C_m]} \end{bmatrix} = \begin{bmatrix} K_{d1} \\ K_{d2} \\ \vdots \\ K_{dm} \end{bmatrix},$$

for which we take the logarithm of both sides, to get the equations

$$(37) \quad \begin{bmatrix} \log[A_1] + \log[B_1] - \log[C_1] \\ \log[A_2] + \log[B_2] - \log[C_2] \\ \vdots \\ \log[A_m] + \log[B_m] - \log[C_m] \end{bmatrix} = \begin{bmatrix} \log(K_{d1}) \\ \log(K_{d2}) \\ \vdots \\ \log(K_{dm}) \end{bmatrix}.$$

Now we want to rewrite the equations into a linear system with logarithms of the concentrations as variables. The equations have the form $\sum_{j=1}^n \gamma_{ji} \log(X_j) = \log(K_{di})$ where

$$(38) \quad \gamma_{ji} = \begin{cases} 1 & \text{if substance } X_j \text{ is one of reaction } i\text{'s reactants} \\ -1 & \text{if substance } X_j \text{ is reaction } i\text{'s product} \\ 0 & \text{if } X_j \text{ does not occur in reaction } i \end{cases}$$

for every reaction $i = 1, \dots, m$. γ is according to its structure equal to $-N$, where N is the stoichiometry matrix. This gives us that the system we want to solve for the logarithm of the

concentrations is

$$(39) \quad -N^T \begin{bmatrix} \log(X_1) \\ \log(X_2) \\ \vdots \\ \log(X_n) \end{bmatrix} = \begin{bmatrix} \log(K_{d1}) \\ \log(K_{d2}) \\ \vdots \\ \log(K_{dn}) \end{bmatrix}.$$

This is a linear system in the logarithms of the concentrations, which can be solved to get the concentration of the substances. The system has a solution if and only if

$$(40) \quad \begin{bmatrix} \log(K_{d1}) \\ \log(K_{d2}) \\ \vdots \\ \log(K_{dn}) \end{bmatrix} \in \ker(N)^\perp.$$

From this Wegscheider's conditions can be derived [5].

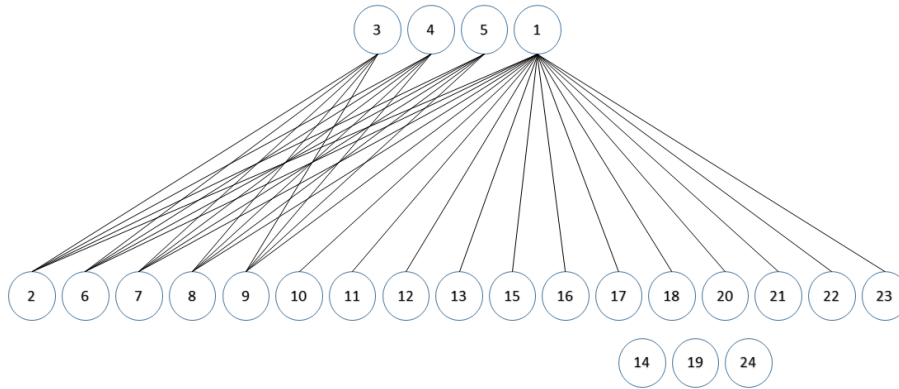
The linearity makes this a fast solution method for mass action systems at equilibrium and it works if every reaction in the system is reversible and elementary.

7. TRANSFORMING $0 = N\mathbf{v}$ INTO A LINEAR SYSTEM

In our system all equations are on the form of (31) except for one equation with a more complicated non-linearity. This section shows how an approach described by E. Feliu and C. Wiuf [6] can be used to transform our system into a linear system.

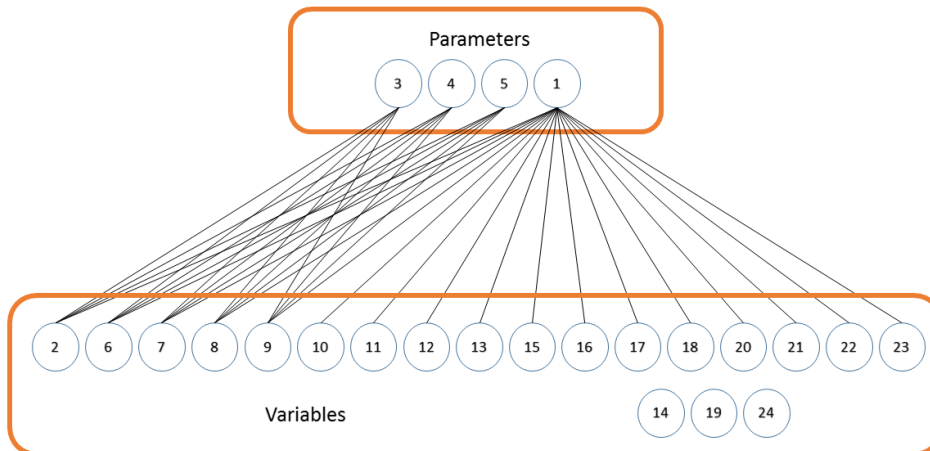
The basic idea is to decompose the problem into two parts, one linear part and one non-linear part. Then we first solve the linear part and then the non-linear part. The reason why this is easier is that if the non-linear part is small (here it will be zero or one equation), this method would make it possible to solve the whole system symbolically.

The way to transform this system into a linear one is the following; we view some of the variables as parameters and these variables will be chosen in such a way that the resulting system is linear. This is done by creating a graph where each variable is represented by a node and there is an edge between two nodes if and only if the corresponding substances are reactants in the same reaction in the system. For our system, this creates the following graph:



Here the number represents the corresponding substance in Table 1.

In the graph we want to find the largest set of nodes that do not have any edges between each other. We let this set be the variables and the rest of the nodes to be the parameters. In our system, we get:



Here we can see that the substances Ca, PP2B, CaMKII and pCaMKIIaut should be treated as parameters and the rest as variables. This makes it possible to write $\mathbf{v}(X, \{k_f, k_r\})$ as a product of $R(\{k_f, k_r, \text{Ca}, \text{PP2B}, \text{CaMKII}, \text{pCaMKIIaut}\})$ and a vector X , where X is a vector of the variables:

$$(41) \quad \mathbf{v}(X, \{k_f, k_r\}) = R(\{k_f, k_r, \text{Ca}, \text{PP2B}, \text{CaMKII}, \text{pCaMKIIaut}\})X$$

We then let S denote the submatrix of the stoichiometry matrix N that correspond to the variables in X . This gives us that the system we want to solve is

$$(42) \quad 0 = SRX,$$

which is a linear system.

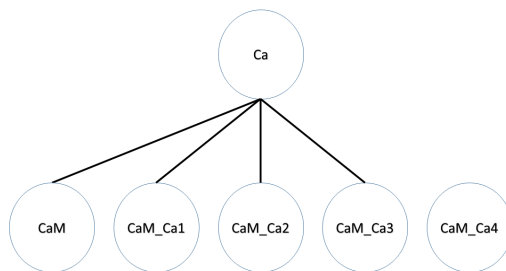
This method can be used both to solve the steady state system $SRX = 0$, but can also be used to solve the equilibrium system $RX = 0$, which gives us an alternative method to solve the equilibrium system $v = 0$.

Example 1. *We here use the system described above and look at the subsystem of the system described in section 5 that arises when the concentrations of PP2B, CaMKII and pCaMKIIaut is zero. We then only have four reactions (1-4 in Figure 2) and six substances (1,2,6-9 in Figure 1). This gives us the matrices*

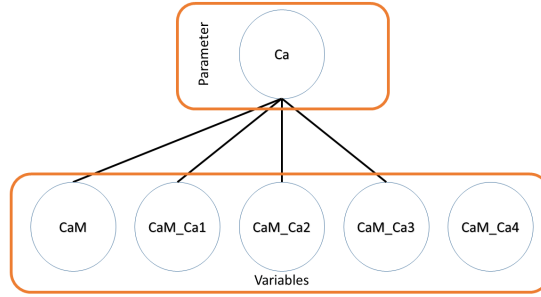
$$(43) \quad N = \begin{bmatrix} 1 & 1 & 1 & 1 \\ 1 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 \\ 0 & -1 & 1 & 0 \\ 0 & 0 & -1 & 1 \\ 0 & 0 & 0 & -1 \end{bmatrix}$$

$$\mathbf{v} = \begin{bmatrix} k_{f1} \cdot \text{Ca} \cdot \text{CaM} & - & k_{r1} \cdot \text{CaM} _ \text{Ca} 1 \\ k_{f2} \cdot \text{Ca} \cdot \text{CaM} _ \text{Ca} 1 & - & k_{r2} \cdot \text{CaM} _ \text{Ca} 2 \\ k_{f3} \cdot \text{Ca} \cdot \text{CaM} _ \text{Ca} 2 & - & k_{r3} \cdot \text{CaM} _ \text{Ca} 3 \\ k_{f4} \cdot \text{Ca} \cdot \text{CaM} _ \text{Ca} 3 & - & k_{r4} \cdot \text{CaM} _ \text{Ca} 4 \end{bmatrix}.$$

The graph over the products in this subsystem is:



This gives that if we view Ca as a parameter, \mathbf{v} becomes linear in the other substances:



Then we have $X = [\text{CaM}, \text{CaM_Ca 1}, \text{CaM_Ca 2}, \text{CaM_Ca 3}, \text{CaM_Ca 4}]^T$, which we use to rewrite \mathbf{v} :

$$(44) \quad \mathbf{v} = RX = \begin{bmatrix} k_{f1} \cdot \text{Ca} & -k_{r1} & 0 & 0 & 0 \\ 0 & k_{f2} \cdot \text{Ca} & -k_{r2} & 0 & 0 \\ 0 & 0 & k_{f3} \cdot \text{Ca} & -k_{r3} & 0 \\ 0 & 0 & 0 & k_{f4} \cdot \text{Ca} & -k_{r4} \end{bmatrix} \begin{bmatrix} \text{CaM} \\ \text{CaM_Ca 1} \\ \text{CaM_Ca 2} \\ \text{CaM_Ca 3} \\ \text{CaM_Ca 4} \end{bmatrix}$$

The rows of the matrix S are the rows of N corresponding to the substances in X . This gives us that the rows of S are all rows in N except the one corresponding to Ca (the first one):

$$(45) \quad S = \begin{bmatrix} 1 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 \\ 0 & -1 & 1 & 0 \\ 0 & 0 & -1 & 1 \\ 0 & 0 & 0 & -1 \end{bmatrix}$$

This implies that we can solve the system $SRX = 0$ for X and then use the conservation laws to solve our original system. $SRX = 0$ is a linear system, which makes it simpler to solve than our original system.

8. SIMPLIFYING $SRX = 0$

In this section we want to simplify $SRX = 0$ as much as possible to make the computations of X as fast as possible. ¹

8.1. Reducing the problem to $RX = 0$ when there are no cycles in the network. We have the system $SRX = 0$ and want to find X . S is an $n \times m$ matrix, where n is the number of variables in the system and m is the number of reactions in the system. The system can be rewritten to the following:

$$(46) \quad \begin{cases} SY = 0 \\ RX = Y. \end{cases}$$

If the kernel of S only consist of the null vector, the only solution to $SY = 0$ is $Y = 0$, which gives us that (46) can be reduced to the following system in some cases:

$$(47) \quad RX = 0$$

This system has an easier structure and will be computed faster. So the conclusion of this section is that if $\ker(S) = \{0\}$, the problem can be reduced to $RX = 0$. This happens in the subsystems in the model that do not contain any cyclic reactions.

Example 2. Here we use the system described in Example 1 and look at the subsystem that arises when the concentration of PP2B, CaMKII and pCaMKIIaut are zero. We then only have four reactions (1-4 in Table 2) and six substances (1,2,6-9 in Table 1). The matrices S, R and X are in this case (see Example 1)

$$(48) \quad S = \begin{bmatrix} 1 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 \\ 0 & -1 & 1 & 0 \\ 0 & 0 & -1 & 1 \\ 0 & 0 & 0 & -1 \end{bmatrix},$$

$$(49) \quad R = \begin{bmatrix} k_{f1} \cdot \text{Ca} & -k_{r1} & 0 & 0 & 0 \\ 0 & k_{f2} \cdot \text{Ca} & -k_{r2} & 0 & 0 \\ 0 & 0 & k_{f3} \cdot \text{Ca} & -k_{r3} & 0 \\ 0 & 0 & 0 & k_{f4} \cdot \text{Ca} & -k_{r4} \end{bmatrix}$$

and

$$(50) \quad X = \begin{bmatrix} \text{CaM} \\ \text{CaM_Ca1} \\ \text{CaM_Ca2} \\ \text{CaM_Ca3} \\ \text{CaM_Ca4} \end{bmatrix}.$$

Here $\ker(S) = \{0\}$, which means that instead of solving $SRX = 0$ we can solve $RX = 0$.

If we run this in Matlab, we can compare the time it takes to compute X . Solving $SRX = 0$ directly took 0.023 seconds and solving $RX = 0$ took 0.007 seconds. Both methods are fast (because the example is small), but solving the simplified system is faster.

¹The content of this chapter is mostly relevant for systems where Wegscheider's conditions are not satisfied, since if these conditions are satisfied we would rather solve the system $RX = 0$.

9. SOLVING THE STEADY STATE SYSTEM $SRX = 0$

Presented here is a solution method for the linear equation system $SRX = 0$ ². First we decompose the equation into the equivalent formulation

$$(51) \quad \begin{cases} SY &= 0 \\ Y &= RX. \end{cases}$$

From (51) we can conclude that $Y \in \ker(S) \cap \text{Ran}(R)$. By Corollary 1, this is equivalent to $Y \in (\text{Ran}(S^T))^\perp \cap \text{Ran}(R)$, which is equivalent to

$$(52) \quad Y \in \text{Ran}(R) \text{ and } Y \perp \text{Ran}(S^T).$$

Let S_1 be a matrix, whose columns are all the basis vectors for $\text{Ran}(S^T)$. S_1 can be computed using the `colspace` command in Matlab. We also construct a matrix S_2 , whose columns are basis vectors for $\text{Ran}(R)$. S_2 can also be computed using the `colspace` command.

Using S_1 and S_2 , our system can be rewritten. Y can then be expressed as $Y = S_2\mathbf{a}$, where \mathbf{a} is a column vector of the same size as the number of columns in S_2 . This gives us that $S_2\mathbf{a} \perp S_1$, which is equivalent to $S_2\mathbf{a} \cdot S_1 = 0$, which is equivalent to $S_1^T S_2\mathbf{a} = 0$, according to Definition 7. Now we have the following system:

$$(53) \quad \begin{cases} Y &= RX \\ Y &= S_2\mathbf{a} \\ S_1^T S_2\mathbf{a} &= 0 \end{cases}$$

This can be solved for X , since S_1 has full rank by construction:

$$\begin{aligned} RX &= Y \iff \\ RX &= S_2\mathbf{a} \iff \\ S_1^T RX &= S_1^T S_2\mathbf{a} \iff \\ S_1^T RX &= 0 \end{aligned}$$

This means that instead of solving $SRX = 0$, we can solve $S_1^T RX = 0$. This is faster, because the matrix $S_1^T R$ is smaller than the matrix SR .

9.1. **Example $SRX = 0$.** Here we will consider a subsystem of our network with the S matrix

$$(54) \quad \begin{bmatrix} -1, & 0, & 0, & 0, & -1, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 1, & -1, & 0, & 0, & 0, & -1, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & 1, & -1, & 0, & 0, & 0, & -1, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & 1, & -1, & 0, & 0, & 0, & -1, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & -1, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & -1, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 1, & -1, & 0, & 0 \\ 0, & 0, & 0, & 0, & -1, & -1, & -1, & -1, & -1, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 1, & -1, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 1, & -1 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 1 \end{bmatrix}$$

²The content of this chapter is mostly relevant for systems where Wegscheider's conditions are not satisfied, since if these conditions are satisfied we would rather solve the system $RX = 0$.

and the R matrix

$$(55) \begin{bmatrix} \text{Ca} \cdot k_{f1}, & -K_{d1} \cdot k_{f1}, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & \text{Ca} \cdot k_{f2}, & -K_{d2} \cdot k_{f2}, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & \text{Ca} \cdot k_{f3}, & -K_{d3} \cdot k_{f3}, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & \text{Ca} \cdot k_{f4}, & -K_{d4} \cdot k_{f4}, & 0, & 0, & 0, & 0, & 0, & 0 \\ \text{CaMKII} \cdot k_{f14}, & 0, & 0, & 0, & 0, & -K_{d14} \cdot k_{f14}, & 0, & 0, & 0, & 0, & 0 \\ 0, \text{CaMKII} \cdot k_{f15}, & 0, & 0, & 0, & 0, & 0, & -K_{d15} \cdot k_{f15}, & 0, & 0, & 0, & 0 \\ 0, & 0, \text{CaMKII} \cdot k_{f16}, & 0, & 0, & 0, & 0, & 0, & -K_{d16} \cdot k_{f16}, & 0, & 0, & 0 \\ 0, & 0, & 0, \text{CaMKII} \cdot k_{f17}, & 0, & 0, & 0, & 0, & 0, & -K_{d17} \cdot k_{f17}, & 0, & 0 \\ 0, & 0, & 0, & 0, \text{CaMKII} \cdot k_{f18}, & 0, & 0, & 0, & 0, & 0, & 0, & -K_{d18} \cdot k_{f18} \\ 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca} \cdot k_{f19}, & -K_{d19} \cdot k_{f19}, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca} \cdot k_{f20}, & -K_{d20} \cdot k_{f20}, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca} \cdot k_{f21}, & -K_{d21} \cdot k_{f21}, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca} \cdot k_{f22}, & -K_{d22} \cdot k_{f22} \end{bmatrix}$$

Now we want to compute X from the system $SRX = 0$. In this case S has not full rank, which means that we can not simplify this system to $RX = 0$. The computation is done using two different approaches, then we compare the time it took.

9.1.1. *The naive approach.* We know that $X \in \ker(SR)$. This is used to calculate X :

```
tic;
X = null(S*R);
toc
```

The time it took Matlab to execute this was 7.72 seconds.

9.1.2. *The Dot Product Method.* Here we use the approach described in this section. We know that $X \in \ker(S_1^T R)$, which can be used to calculate X in Matlab:

```
tic;
S1 = colspace(S');
X = null(S1'*R);
toc
```

The time it took Matlab to execute this was 5.64 seconds.

The second approach is faster. This is because we are calculating the kernel of a smaller matrix.

10. VARIABLE DEPENDENCY

In this section we will present our method for testing if it is possible to simplify a linear system of the form $A(\mu)X = 0$ by removing one or several parameters. $A(\mu)$ can for instance be R or SR and μ could be one of the parameters k_f, k_r or K_d . This is done by checking if the value of the output X is independent of a specific parameter μ . In this section we let μ denote *one* of the parameters (for example k_{r1}, k_{r2}, k_{f1} or K_{d1} et cetera). We assume that A is continuously differentiable with respect to μ , for μ in some subinterval of \mathbb{R} . Since $A(\mu)$ depends on μ , in most cases X should also depend on μ . Despite this it can happen that X does not depend on μ , in which case $X'(\mu) = 0$. The purpose of this section is to find out if $X'(\mu) = 0$ *without solving the system*. This can be used to simplify the system, which could make solving the system faster.

Assume that $A(\mu)$ is an $(n - 1) \times n$ matrix, with a one-dimensional kernel and that the system has a conservation law $cX = b$. We assume that $\begin{bmatrix} A(\mu) \\ c \end{bmatrix}$ has full rank. Then the system

$$(56) \quad \begin{bmatrix} A(\mu) \\ c \end{bmatrix} X = \begin{bmatrix} 0 \\ b \end{bmatrix}$$

has an unique solution (for every specific μ). Let us denote this solution by $X(\mu)$.

The general idea is to create a matrix containing $A(\mu)$ and $A'(\mu)$ and then compute the rank of the matrix and use the rank to draw conclusions about whether or not X is dependent on μ .

Theorem 2. *Assume that (56) has a unique solution, $X(\mu)$. If the matrix*

$$(57) \quad \begin{bmatrix} A'(\mu) & A(\mu) \\ A(\mu) & 0 \\ 0 & c \\ 0 & I \end{bmatrix}$$

has rank $2n - 1$, then $X'(\mu) = 0$.

Proof. We start with an observation. Assume that we have two matrices M and N , with sizes $(n - 1) \times n$ and $m_2 \times n$ respectively. If the rank of the matrix $\begin{bmatrix} M \\ N \end{bmatrix}$ is the same as the rank of the matrix M , then the matrices also have the same kernel. In other words

$$(58) \quad \begin{bmatrix} M \\ N \end{bmatrix} Y = 0 \quad \text{if and only if} \quad MY = 0.$$

Now we look at the system $\begin{bmatrix} M \\ C \end{bmatrix} Y = \begin{bmatrix} 0 \\ b \end{bmatrix}$, where $\begin{bmatrix} M \\ C \end{bmatrix}$ has full rank. Then this system has a unique solution. From the observation above it follows that the system

$$(59) \quad \begin{bmatrix} M \\ N \\ C \end{bmatrix} Y = \begin{bmatrix} 0 \\ 0 \\ b \end{bmatrix}$$

also has a unique solution, and this has to be the same solution.

Now we study the system (56), which has the unique solution $X(\mu)$. Hence $A(\mu)X(\mu) = 0$. We compute the derivative of this equation with respect to μ . We also differentiate

the conservation law $cX(\mu) = b$ with respect to μ . Then we get the system (ignoring the conservation law $cX(\mu) = b$ for now)

$$(60) \quad \begin{bmatrix} A'(\mu) & A(\mu) \\ A(\mu) & 0 \\ 0 & c \end{bmatrix} \begin{bmatrix} X(\mu) \\ X'(\mu) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

Since $\begin{bmatrix} A(\mu) \\ c \end{bmatrix}$ has full rank, the rank of the matrix in the system (60) is equal to the rank of the system $\begin{bmatrix} A(\mu) & 0 \\ 0 & I \end{bmatrix}$, which is $2n - 1$, because we assumed that $A(\mu)$ had rank $n - 1$.

Assume that the matrices of (57) and (60) have the same rank. Then by the observation above, they have the same kernel. We now add the conservation law $cX(\mu) = b$ to the system (60), which leads to that the system has a unique solution according to the assumptions of the system. Then according to the argument above, the systems

$$(61) \quad \begin{bmatrix} A'(\mu) & A(\mu) \\ A(\mu) & 0 \\ 0 & c \\ c & 0 \end{bmatrix} \begin{bmatrix} X(\mu) \\ X'(\mu) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ b \end{bmatrix}$$

and

$$(62) \quad \begin{bmatrix} A'(\mu) & A(\mu) \\ A(\mu) & 0 \\ 0 & c \\ 0 & I \\ c & 0 \end{bmatrix} \begin{bmatrix} X(\mu) \\ Y(\mu) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ b \end{bmatrix}$$

have the same solution. But we already know that $\begin{bmatrix} X(\mu) \\ X'(\mu) \end{bmatrix}$ satisfies (61). Hence it also satisfies (62). This gives us that $Y(\mu) = X'(\mu)$. But (62) implies that $Y(\mu) = 0$ and hence $X'(\mu) = 0$. This shows that $X'(\mu) = 0$ if (57) has rank $2n - 1$. \square

Corollary 1. *Assume that (56) has a unique solution, $X(\mu)$. If the matrix*

$$(63) \quad \begin{bmatrix} A'(\mu) \\ A(\mu) \end{bmatrix}$$

has rank $n - 1$, then $X'(\mu) = 0$.

Proof. We know that the rank of a matrix is the number of linearly independent columns.

Since the columns of $\begin{bmatrix} A'(\mu) \\ A(\mu) \\ 0 \\ 0 \end{bmatrix}$ does not belong to the span of $\begin{bmatrix} A(\mu) \\ 0 \\ c \\ I \end{bmatrix}$, it follows that

$$(64) \quad \text{Rank} \left(\begin{bmatrix} A'(\mu) & A(\mu) \\ A(\mu) & 0 \\ 0 & c \\ 0 & I \end{bmatrix} \right) = \text{Rank} \left(\begin{bmatrix} A'(\mu) \\ A(\mu) \\ 0 \\ 0 \end{bmatrix} \right) + \text{Rank} \left(\begin{bmatrix} A(\mu) \\ 0 \\ c \\ I \end{bmatrix} \right).$$

The rank of $\begin{bmatrix} A(\mu) \\ 0 \\ c \\ I \end{bmatrix}$ is n , since I has rank n . Hence

$$(65) \quad \text{Rank} \left(\begin{bmatrix} A'(\mu) & A(\mu) \\ A(\mu) & 0 \\ 0 & c \\ 0 & I \end{bmatrix} \right) = \text{Rank} \left(\begin{bmatrix} A'(\mu) \\ A(\mu) \\ 0 \\ 0 \end{bmatrix} \right) + n.$$

This implies that the matrix $\begin{bmatrix} A'(\mu) \\ A(\mu) \end{bmatrix}$ has rank $n-1$ if and only if the matrix $\begin{bmatrix} A'(\mu) & A(\mu) \\ A(\mu) & 0 \\ 0 & c \\ 0 & I \end{bmatrix}$ has rank $2n-1$. We know from Theorem 2 that $X'(\mu) = 0$ if the matrix $\begin{bmatrix} A'(\mu) & A(\mu) \\ A(\mu) & 0 \\ 0 & c \\ 0 & I \end{bmatrix}$ has rank $2n-1$. Hence $X'(\mu) = 0$ if $\begin{bmatrix} A'(\mu) \\ A(\mu) \end{bmatrix}$ has rank $n-1$. \square

10.1. **Example** $\mu = k_{f1}$. In this example we investigate the dependence X has on the parameter k_{f1} . We will work with a small system $RX = 0$, where R is a 4×5 matrix with rank 4. The conservation law in this system is $\sum_{i=1}^5 X_i = b$.

$$(66) \quad R = \begin{bmatrix} \text{Ca} \cdot k_{f1}, & -K_{d1} \cdot k_{f1}, & 0, & 0, & 0 \\ 0, & \text{Ca} \cdot k_{f2}, & -K_{d2} \cdot k_{f2}, & 0, & 0 \\ 0, & 0, & \text{Ca} \cdot k_{f3}, & -K_{d3} \cdot k_{f3}, & 0 \\ 0, & 0, & 0, & \text{Ca} \cdot k_{f4}, & -K_{d4} \cdot k_{f4} \end{bmatrix}$$

The goal in this section is to find out if the parameter k_{f1} that occurs in R occurs in X , without calculating X .

We want to use Corollary 1, which means that we want to compute the rank of the matrix $\begin{bmatrix} R'(\mu) \\ R(\mu) \end{bmatrix}$. This matrix is in our case:

$$(67) \quad \begin{bmatrix} \text{Ca} & -K_{d1} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \text{Ca} \cdot k_{f1}, & -K_{d1} \cdot k_{f1}, & 0, & 0, & 0 \\ 0, & \text{Ca} \cdot k_{f2}, & -K_{d2} \cdot k_{f2}, & 0, & 0 \\ 0, & 0, & \text{Ca} \cdot k_{f3}, & -K_{d3} \cdot k_{f3}, & 0 \\ 0, & 0, & 0, & \text{Ca} \cdot k_{f4}, & -K_{d4} \cdot k_{f4} \end{bmatrix}$$

This matrix has rank 4, which is not full rank. This means that X is not dependent on k_{f1} . This is correct, because X can be found explicitly in this example:

$$(68) \quad X = \frac{Ca^4 b}{Ca^4 + K_{d4}(Ca^3 + K_{d3}(Ca^2 + K_{d2}(Ca + K_{d1})))} \begin{bmatrix} \frac{K_{d1} \cdot K_{d2} \cdot K_{d3} \cdot K_{d4}}{Ca^4} \\ \frac{K_{d2} \cdot K_{d3} \cdot K_{d4}}{Ca^3} \\ \frac{K_{d3} \cdot K_{d4}}{Ca^2} \\ \frac{K_{d4}}{Ca} \\ 1 \end{bmatrix}$$

10.2. Useful output. Sometimes we only need the concentration of a few of the substances. This happens when the concentrations are used to calculate some sort of output, which can for example be a quotient of linear combination of X_i 's. This model reduction method can be modified, so that only the important information in the X vector is kept. This is done by replacing I in (57) by rows corresponding to the linear combinations which are needed in the output. Lets denote that matrix by \tilde{I} .

Theorem 3. *Assume that (56) has a unique solution, $X(\mu)$, and that the rows in \tilde{I} is rows corresponding to the linear combinations which are needed in the output. If the matrix*

$$(69) \quad \begin{bmatrix} A'(\mu) & A(\mu) \\ A(\mu) & 0 \\ 0 & c \\ 0 & \tilde{I} \end{bmatrix}$$

has rank $2n - 1$, then the output is not dependent on μ .

Proof. We study the system (56), which has the unique solution $X(\mu)$, and compute its derivative with respect to μ . Then we get the following system (excluding the conservation law $cX(\mu) = b$):

$$(70) \quad \begin{bmatrix} A'(\mu) & A(\mu) \\ A(\mu) & 0 \\ 0 & c \end{bmatrix} \begin{bmatrix} X(\mu) \\ X'(\mu) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

The rank of the left matrix in this system is equal to the rank of the system $\begin{bmatrix} A(\mu) & 0 \\ 0 & I \end{bmatrix}$, which is $2n - 1$.

Assume that the matrices (69) and (70) have the same rank. Then by the observation in Theorem 2, they have the same kernel. Then according to the argument in the proof of Theorem 2, the systems

$$(71) \quad \begin{bmatrix} A'(\mu) & A(\mu) \\ A(\mu) & 0 \\ 0 & c \\ c & 0 \end{bmatrix} \begin{bmatrix} X(\mu) \\ X'(\mu) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ b \end{bmatrix}$$

and

$$(72) \quad \begin{bmatrix} A'(\mu) & A(\mu) \\ A(\mu) & 0 \\ 0 & c \\ 0 & \tilde{I} \\ c & 0 \end{bmatrix} \begin{bmatrix} X(\mu) \\ Y(\mu) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ b \end{bmatrix}$$

have the same solution. But we already know that $\begin{bmatrix} X(\mu) \\ X'(\mu) \end{bmatrix}$ satisfies (71). Hence it also satisfies (72). This gives us that $Y(\mu) = X'(\mu)$. But (72) implies that $\tilde{I}Y(\mu) = 0$, which gives us that $\tilde{I}X'(\mu) = 0$. This shows that the concentraions in X that is in the output is not dependent on μ . Hence the output is not dependent on μ if the matrix (69) has rank $2n - 1$. \square

10.3. **Example** $\mu = K_{d5}$. Assume that we have the system $RX = 0$, with conservation law $\sum_{i=7}^{10} X_i = b$, where R is

$$(73) \quad \begin{bmatrix} 0, & 0, & 0, & \text{Ca} \cdot k_{f4}, -K_{d4} \cdot k_{f4}, & 0, & 0, & 0, & 0, & 0, & 0 \\ \text{PP2B} \cdot k_{f5}, & 0, & 0, & 0, & 0, -K_{d5} \cdot k_{f5}, & 0, & 0, & 0, & 0, & 0 \\ 0, \text{PP2B} \cdot k_{f6}, & 0, & 0, & 0, & 0, & 0, & -K_{d6} \cdot k_{f6}, & 0, & 0, & 0, & 0 \\ 0, & 0, \text{PP2B} \cdot k_{f7}, & 0, & 0, & 0, & 0, & 0, & -K_{d7} \cdot k_{f7}, & 0, & 0, & 0 \\ 0, & 0, & 0, \text{PP2B} \cdot k_{f8}, & 0, & 0, & 0, & 0, & 0, & -K_{d8} \cdot k_{f8}, & 0, & 0 \\ 0, & 0, & 0, & 0, \text{PP2B} \cdot k_{f9}, & 0, & 0, & 0, & 0, & 0, & -K_{d9} \cdot k_{f9}, & 0 \\ 0, & 0, & 0, & 0, & 0, & \text{Ca} \cdot k_{f10}, -\frac{K_{d1} \cdot K_{d6} \cdot k_{f10}}{K_{d5}}, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca} \cdot k_{f11}, -\frac{K_{d2} \cdot K_{d7} \cdot k_{f11}}{K_{d6}}, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca} \cdot k_{f12}, -\frac{K_{d3} \cdot K_{d8} \cdot k_{f12}}{K_{d7}}, & 0, & 0, & 0 \end{bmatrix}.$$

R is an 9×10 matrix, with rank 9. Assume that we are interested in if the output $\frac{X_7}{X_9}$ is independent of the parameter K_{d5} . First we try and use Corollary 1, by computing the rank of the matrix $\begin{bmatrix} R'(\mu) \\ R(\mu) \end{bmatrix}$, which is 10. Hence we can not use Corollary 1.

Now we use Theorem 3 instead. Here we are interested in the values of X_7 and X_9 . This gives us that

$$(74) \quad \tilde{I} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \end{bmatrix}.$$

Now we compute the rank of the matrix (69), with $A(\mu) = R(\mu)$ and $\mu = K_{d5}$ with the rank command in Matlab. The rank of this matrix is 19, which means that the output is independent of K_{d5} .

11. EXACT MODEL REDUCTION

We will in this section generalize the approach from the last section to figure out how the output is dependent on the parameters, all of them at the same time. For example there may exist other parameters that we can substitute our parameters with and still get the same solution.

Let us denote the parameters by

$$(75) \quad \mu = \begin{bmatrix} \mu_1 \\ \mu_2 \\ \vdots \\ \mu_m \end{bmatrix}.$$

Then the goal of this section is to find one (or several) curve(s) $\mu(t)$, parametrized by t , in the parameter space that satisfies $\frac{d}{dt}X(\mu(t)) = 0$, where $X(\mu(t))$ is a solution of $A(\mu(t))X = 0$, with the conservation law $cX = b$. The matrix $A(\mu(t))$ is an $(n-1) \times n$ matrix, which has the rank $n-1$.

Theorem 4. *Assume that $X(\mu)$ is a solution to the system $A(\mu)X = 0$, where $A(\mu)$ is an $(n-1) \times n$ matrix, that has the rank $n-1$. Assume that $X(\mu)$ satisfies the conservation law $cX(\mu) = b$. Assume that*

$$(76) \quad \frac{d\mu}{dt} \in \ker \left(\begin{bmatrix} \frac{\partial A}{\partial \mu_1}(\mu_1(t))X(\mu) & \frac{\partial A}{\partial \mu_2}(\mu_2(t))X(\mu) & \dots & \frac{\partial A}{\partial \mu_m}(\mu_m(t))X(\mu) \end{bmatrix} \right).$$

Then $\frac{d}{dt}X(\mu(t)) = 0$.

Proof. According to Corollary 1, $\frac{d}{dt}X(\mu(t)) = 0$ if the matrix $\begin{bmatrix} A(\mu(t)) \\ \frac{d}{dt}A(\mu(t)) \end{bmatrix}$ has rank $n-1$.

This matrix is equal to

$$(77) \quad \begin{bmatrix} A(\mu(t)) \\ \frac{\partial A}{\partial \mu_1}(\mu_1(t))\mu_1'(t) + \frac{\partial A}{\partial \mu_2}(\mu_2(t))\mu_2'(t) + \dots + \frac{\partial A}{\partial \mu_m}(\mu_m(t))\mu_m'(t) \end{bmatrix}.$$

Rewriting $A(\mu(t))$ as $\begin{bmatrix} A_1 \\ A_2 \\ \vdots \\ A_{n-1} \end{bmatrix}$ and introducing the notation $v(\mu(t)) = \frac{d\mu}{dt}$ the matrix is

equal to

$$(78) \quad \begin{bmatrix} A(\mu(t)) \\ \frac{\partial A_1}{\partial \mu_1}(\mu_1(t))v_1 + \frac{\partial A_1}{\partial \mu_2}(\mu_2(t))v_2 + \dots + \frac{\partial A_1}{\partial \mu_m}(\mu_m(t))v_m \\ \frac{\partial A_2}{\partial \mu_1}(\mu_1(t))v_1 + \frac{\partial A_2}{\partial \mu_2}(\mu_2(t))v_2 + \dots + \frac{\partial A_2}{\partial \mu_m}(\mu_m(t))v_m \\ \vdots \\ \frac{\partial A_{n-1}}{\partial \mu_1}(\mu_1(t))v_1 + \frac{\partial A_{n-1}}{\partial \mu_2}(\mu_2(t))v_2 + \dots + \frac{\partial A_{n-1}}{\partial \mu_m}(\mu_m(t))v_m \end{bmatrix}.$$

The rank of this matrix has to be equal to the rank of $A(\mu(t))$ (which is $n-1$), according to Corollary 1. This happens if and only if every row of the second part of the system belongs

to the row space of $A(\mu(t))$ (which is equal to the range of $A(\mu(t))^T$)

$$(79) \quad \left(\frac{\partial A_k}{\partial \mu_1}(\mu_1(t))v_1 + \frac{\partial A_k}{\partial \mu_2}(\mu_2(t))v_2 + \cdots + \frac{\partial A_k}{\partial \mu_m}(\mu_m(t))v_m \right) \in \text{Ran}(A(\mu(t))^T)$$

for every row $k = 1, \dots, n-1$. According to Theorem 1, this is equivalent to

$$(80) \quad \left(\frac{\partial A_k}{\partial \mu_1}(\mu_1(t))v_1 + \frac{\partial A_k}{\partial \mu_2}(\mu_2(t))v_2 + \cdots + \frac{\partial A_k}{\partial \mu_m}(\mu_m(t))v_m \right) \in \ker(A(\mu(t)))^\perp$$

for every row $k = 1, \dots, n-1$.

$X(\mu)$ belongs to the kernel of $A(\mu)$. We also know that the kernel is one-dimensional, so every vector in the kernel can be written as $\alpha X(\mu)$, where α is a constant. Hence (80) is equivalent to

$$(81) \quad \left(\frac{\partial A_k}{\partial \mu_1}(\mu_1(t))v_1 + \frac{\partial A_k}{\partial \mu_2}(\mu_2(t))v_2 + \cdots + \frac{\partial A_k}{\partial \mu_m}(\mu_m(t))v_m \right) \perp X(\mu(t))$$

for every row $k = 1 \dots n-1$.

This is, according to Definition 7, equivalent to

$$(82) \quad \begin{bmatrix} X(\mu(t)) \cdot \left(\frac{\partial A_1}{\partial \mu_1}(\mu_1(t))v_1 + \frac{\partial A_1}{\partial \mu_2}(\mu_2(t))v_2 + \cdots + \frac{\partial A_1}{\partial \mu_m}(\mu_m(t))v_m \right)^T \\ X(\mu(t)) \cdot \left(\frac{\partial A_2}{\partial \mu_1}(\mu_1(t))v_1 + \frac{\partial A_2}{\partial \mu_2}(\mu_2(t))v_2 + \cdots + \frac{\partial A_2}{\partial \mu_m}(\mu_m(t))v_m \right)^T \\ \vdots \\ X(\mu(t)) \cdot \left(\frac{\partial A_{n-1}}{\partial \mu_1}(\mu_1(t))v_1 + \frac{\partial A_{n-1}}{\partial \mu_2}(\mu_2(t))v_2 + \cdots + \frac{\partial A_{n-1}}{\partial \mu_m}(\mu_m(t))v_m \right)^T \end{bmatrix} = 0,$$

which, according to Definition 6, is equivalent to

$$(83) \quad \begin{bmatrix} \left(\frac{\partial A_1}{\partial \mu_1}(\mu_1(t))v_1 + \frac{\partial A_1}{\partial \mu_2}(\mu_2(t))v_2 + \cdots + \frac{\partial A_1}{\partial \mu_m}(\mu_m(t))v_m \right) X(\mu(t)) \\ \left(\frac{\partial A_2}{\partial \mu_1}(\mu_1(t))v_1 + \frac{\partial A_2}{\partial \mu_2}(\mu_2(t))v_2 + \cdots + \frac{\partial A_2}{\partial \mu_m}(\mu_m(t))v_m \right) X(\mu(t)) \\ \vdots \\ \left(\frac{\partial A_{n-1}}{\partial \mu_1}(\mu_1(t))v_1 + \frac{\partial A_{n-1}}{\partial \mu_2}(\mu_2(t))v_2 + \cdots + \frac{\partial A_{n-1}}{\partial \mu_m}(\mu_m(t))v_m \right) X(\mu(t)) \end{bmatrix} = 0,$$

which is the same as

$$(84) \quad \begin{bmatrix} v_1 \frac{\partial A_1}{\partial \mu_1}(\mu_1(t))X(\mu(t)) & + & v_2 \frac{\partial A_1}{\partial \mu_2}(\mu_2(t))X(\mu(t)) & + & \cdots & + & v_m \frac{\partial A_1}{\partial \mu_m}(\mu_m(t))X(\mu(t)) \\ v_1 \frac{\partial A_2}{\partial \mu_1}(\mu_1(t))X(\mu(t)) & + & v_2 \frac{\partial A_2}{\partial \mu_2}(\mu_2(t))X(\mu(t)) & + & \cdots & + & v_m \frac{\partial A_2}{\partial \mu_m}(\mu_m(t))X(\mu(t)) \\ \vdots & & & & & & \\ v_1 \frac{\partial A_{n-1}}{\partial \mu_1}(\mu_1(t))X(\mu(t)) & + & v_2 \frac{\partial A_{n-1}}{\partial \mu_2}(\mu_2(t))X(\mu(t)) & + & \cdots & + & v_m \frac{\partial A_{n-1}}{\partial \mu_m}(\mu_m(t))X(\mu(t)) \end{bmatrix} = 0.$$

This is equivalent to

$$(85) \quad \begin{bmatrix} \frac{\partial A_1}{\partial \mu_1}(\mu_1(t))X(\mu(t)) & \frac{\partial A_1}{\partial \mu_2}(\mu_2(t))X(\mu(t)) & \cdots & \frac{\partial A_1}{\partial \mu_m}(\mu_m(t))X(\mu(t)) \\ \frac{\partial A_2}{\partial \mu_1}(\mu_1(t))X(\mu(t)) & \frac{\partial A_2}{\partial \mu_2}(\mu_2(t))X(\mu(t)) & \cdots & \frac{\partial A_2}{\partial \mu_m}(\mu_m(t))X(\mu(t)) \\ \vdots & & & \\ \frac{\partial A_{n-1}}{\partial \mu_1}(\mu_1(t))X(\mu(t)) & \frac{\partial A_{n-1}}{\partial \mu_2}(\mu_2(t))X(\mu(t)) & \cdots & \frac{\partial A_{n-1}}{\partial \mu_m}(\mu_m(t))X(\mu(t)) \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ \vdots \\ v_m \end{bmatrix} = 0,$$

which is equivalent to

$$(86) \quad \left[\begin{array}{cccc} \frac{\partial A}{\partial \mu_1}(\mu_1(t))X(\mu(t)) & \frac{\partial A}{\partial \mu_2}(\mu_2(t))X(\mu(t)) & \dots & \frac{\partial A}{\partial \mu_m}(\mu_m(t))X(\mu(t)) \end{array} \right] v = 0.$$

This is equivalent to $v \in \ker \left(\left[\begin{array}{cccc} \frac{\partial A}{\partial \mu_1}(\mu_1(t))X(\mu) & \frac{\partial A}{\partial \mu_2}(\mu_2(t))X(\mu) & \dots & \frac{\partial A}{\partial \mu_m}(\mu_m(t))X(\mu) \end{array} \right] \right)$, which shows that $\frac{d}{dt}X(\mu(t)) = 0$ if and only if $\frac{d\mu}{dt} = v(\mu)$, where

$$(87) \quad v \in \ker \left(\left[\begin{array}{cccc} \frac{\partial A}{\partial \mu_1}(\mu_1(t))X(\mu) & \frac{\partial A}{\partial \mu_2}(\mu_2(t))X(\mu) & \dots & \frac{\partial A}{\partial \mu_m}(\mu_m(t))X(\mu) \end{array} \right] \right).$$

□

11.1. Example Exact Model Reduction. Here we will consider a subsystem of our system and show the method described above. Here we want to find dependencies of the parameters for the system $SRX = 0$,

$$(88) \quad S = \begin{bmatrix} -1, & 0, & 0, & 0, & -1, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 1, & -1, & 0, & 0, & 0, & -1, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & 1, & -1, & 0, & 0, & 0, & -1, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & 1, & -1, & 0, & 0, & 0, & -1, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & -1, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & -1, & -1, & -1, & -1, & -1, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & -1, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 1, & -1, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 1, & -1, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 1, & -1 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 1 \end{bmatrix}$$

and $R =$

$$(89) \quad \begin{bmatrix} \text{Ca} \cdot k_{f1}, -K_{d1} \cdot k_{f1}, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & \text{Ca} \cdot k_{f2}, -K_{d2} \cdot k_{f2}, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & \text{Ca} \cdot k_{f3}, -K_{d3} \cdot k_{f3}, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & \text{Ca} \cdot k_{f4}, -K_{d4} \cdot k_{f4}, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ \text{PP2B} \cdot k_{f5}, & 0, & 0, & 0, & 0, & -K_{d5} \cdot k_{f5}, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, \text{PP2B} \cdot k_{f6}, & 0, & 0, & 0, & 0, & 0, & -K_{d6} \cdot k_{f6}, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & \text{PP2B} \cdot k_{f7}, & 0, & 0, & 0, & 0, & -K_{d7} \cdot k_{f7}, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & \text{PP2B} \cdot k_{f8}, & 0, & 0, & 0, & 0, & -K_{d8} \cdot k_{f8}, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & \text{PP2B} \cdot k_{f9}, & 0, & 0, & 0, & 0, & 0, & -K_{d9} \cdot k_{f9}, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca} \cdot k_{f10}, -K_{d10} \cdot k_{f10}, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca} \cdot k_{f11}, -K_{d11} \cdot k_{f11}, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca} \cdot k_{f12}, -K_{d12} \cdot k_{f12}, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca} \cdot k_{f13}, -K_{d13} \cdot k_{f13}, & 0, & 0, & 0 \end{bmatrix}$$

This system is small enough to make it possible to compute $X(\mu)$ and use it to compute a basis for v , using Matlab, with the following code:

```
S;
R;
Matrix = colspace(S') * R;
nullspace = null(Matrix);

testmatrix = sym([]);
sizeMatrix = size(Matrix, 1);
```

```

for j = 1:sizeMatrix
    testmatrix(j,:) = nullspace' * jacobian(Matrix(j,:),parameters);
end

nullspace2 = null(testmatrix);

```

We get the following basis for this kernel:

(90)

$$\begin{bmatrix}
 \frac{k_{f1}}{k_{f10}}, & 0, & 0, & 0, & a1_5, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & a1_14, & 0, & 0, & 0 \\
 0, & \frac{k_{f2}}{k_{f11}}, & 0, & 0, & 0, & a2_6, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & a2_15, & 0, & 0 \\
 0, & 0, & \frac{k_{f3}}{k_{f12}}, & 0, & 0, & 0, & a3_7, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & a3_16, & 0 \\
 0, & 0, & 0, & \frac{k_{f4}}{k_{f13}}, & 0, & 0, & 0, & a4_8, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & a4_17 \\
 \frac{k_{f5}}{k_{f10}}, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & a5_9, & 0, & 0, & 0, & 0, & a5_14, & 0, & 0 \\
 a6_1, & a6_2, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & a6_10, & 0, & 0, & 0, & a6_14, & a6_15, & 0 \\
 0, & a7_2, & a7_3, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & a7_11, & 0, & 0, & 0, & a7_15, & a7_16 \\
 0, & 0, & a8_3, & a8_4, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & a8_12, & 0, & 0, & 0, & a8_16, & a8_17 \\
 0, & 0, & 0, & \frac{k_{f9}}{k_{f13}}, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & a9_13, & 0, & 0, & 0, & a9_17 \\
 1, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\
 0, & 1, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\
 0, & 0, & 1, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\
 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\
 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\
 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\
 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\
 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\
 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\
 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\
 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & 0, & 0 \\
 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0, & 0 \\
 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0, & 0 \\
 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0, & 0 \\
 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0, & 0 \\
 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1, & 0 \\
 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1 \\
 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 1
 \end{bmatrix}$$

Hence if v is any linear combination of the columns of the matrix above and we solve the system of differential equation $\frac{du}{dt} = v$, then the solution is independent of t along the solution curves. In particular, we can use this for the columns themselves. Then we know a curve where $X(\mu)$ has the same value in all points. This means that we can choose a point on that curve; we did this so that one parameter had the value 1. This lead to that we could simplify our original system. In this example, the R matrix could be simplified to the following matrix:

$$(91) \quad \begin{bmatrix} \text{Ca} \cdot m1_5, & -m1_5, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & \text{Ca} \cdot m2_6, & -m2_6, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & \text{Ca} \cdot m3_7, & -m3_7, & 0, & 0, & 0, & 0, & 0, & 0, & 0 \\ 0, & 0, & 0, & \text{Ca} \cdot m4_8, & -m4_8, & 0, & 0, & 0, & 0, & 0, & 0 \\ \text{PP2B} \cdot m5_9, & 0, & 0, & 0, & 0, & -m5_9, & 0, & 0, & 0, & 0, & 0 \\ 0, & \text{PP2B} \cdot m6_10, & 0, & 0, & 0, & 0, & -m6_10, & 0, & 0, & 0, & 0 \\ 0, & 0, & \text{PP2B} \cdot m7_11, & 0, & 0, & 0, & 0, & -m7_11, & 0, & 0, & 0 \\ 0, & 0, & 0, & \text{PP2B} \cdot m8_12, & 0, & 0, & 0, & 0, & -m8_12, & 0, & 0 \\ 0, & 0, & 0, & 0, & \text{PP2B} \cdot m9_13, & 0, & 0, & 0, & 0, & -m9_13, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca}, & -K_{d10}, & 0, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca}, & -K_{d11}, & 0, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca}, & -K_{d12}, & 0 \\ 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & 0, & \text{Ca}, & -K_{d13} \end{bmatrix}$$

Here we introduced new variables m that stands for a complicated expression in the rest of the parameters. The reason that it can be a good idea to do this model reduction, despite that we introduce new complicated expressions, is that in some applications parameter values are chosen at random. So instead of choosing 22 parameter values, we can choose 10.

11.2. Useful output. Here we consider the case that we are only interested in a specific output, which is a function of some of the parameters (compare with Section 10.2).

Theorem 5. *Assume that $X(\mu)$ is a solution to the system $A(\mu)X = 0$, where $A(\mu)$ is an $(n-1) \times n$ matrix, that has the rank $n-1$. Assume that $X(\mu)$ satisfies the conservation law $cX(\mu) = b$ and that the rows in \tilde{I} is the rows of I for which the corresponding concentration of the substance in X occurs in the output. Assume that*

$$(92) \quad \left[\begin{array}{c} \frac{d\mu}{dt} \\ \frac{d}{dt}X(\mu(t)) \end{array} \right] \in \ker \left(\begin{bmatrix} \frac{\partial A}{\partial \mu}X(\mu(t)) & A \\ 0 & c \\ 0 & \tilde{I} \end{bmatrix} \right)$$

where $\frac{\partial A}{\partial \mu}X(\mu(t))$ is the left matrix in (85), then $\frac{d}{dt}\tilde{I}X(\mu(t)) = 0$.

Proof. According to Theorem 1, $\frac{d}{dt}\tilde{I}X(\mu(t)) = 0$ if the matrix $\begin{bmatrix} \frac{d}{dt}A(\mu(t)) & A(\mu(t)) \\ A(\mu(t)) & 0 \\ 0 & c \\ 0 & \tilde{I} \end{bmatrix}$ has

rank $2n-1$. We also have $cX(\mu(t)) = b$, which gives us that if the system

$$(93) \quad \begin{bmatrix} \frac{d}{dt}A(\mu(t)) & A(\mu(t)) \\ A(\mu(t)) & 0 \\ 0 & c \\ 0 & \tilde{I} \\ c & 0 \end{bmatrix} \begin{bmatrix} X(\mu(t)) \\ Y \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ b \end{bmatrix}$$

has a unique solution $\begin{bmatrix} X(\mu(t)) \\ Y \end{bmatrix}$, then $\tilde{I}\frac{d}{dt}X(\mu(t)) = 0$. Then according to the argument in

Theorem 1, $Y = \frac{d}{dt}X(\mu(t))$. Here we know that $X(\mu(t)) = [A(\mu(t))]^{-1} \begin{bmatrix} 0 \\ b \end{bmatrix}$, and so the

system (93) can be rewritten as

$$(94) \quad \begin{bmatrix} \frac{d}{dt}A(\mu(t)) & A(\mu(t)) \\ 0 & c \\ 0 & \tilde{I} \end{bmatrix} \begin{bmatrix} X(\mu(t)) \\ \frac{d}{dt}X(\mu(t)) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}.$$

This system is equivalent to

$$(95) \quad \begin{cases} \frac{d}{dt}A(\mu(t))X(\mu(t)) + A(\mu(t))\frac{d}{dt}X(\mu(t)) = 0 \\ c\frac{d}{dt}X(\mu(t)) = 0 \\ \tilde{I}\frac{d}{dt}X(\mu(t)) = 0, \end{cases}$$

which can be rewritten into

$$(96) \quad \begin{cases} \frac{\partial A}{\partial \mu}X(\mu(t))v + A(\mu(t))\frac{d}{dt}X(\mu(t)) = 0 \\ c\frac{d}{dt}X(\mu(t)) = 0 \\ \tilde{I}\frac{d}{dt}X(\mu(t)) = 0, \end{cases}$$

where $\frac{\partial A}{\partial \mu}X(\mu(t))v$ is the left hand side of (85). This is equivalent to the system

$$(97) \quad \begin{bmatrix} \frac{\partial A}{\partial \mu}X(\mu(t)) & A(\mu(t)) \\ 0 & c \\ 0 & \tilde{I} \end{bmatrix} \begin{bmatrix} v \\ \frac{d}{dt}X(\mu(t)) \end{bmatrix} = 0,$$

which is the same as

$$(98) \quad \begin{bmatrix} v \\ \frac{d}{dt}X(\mu(t)) \end{bmatrix} \in \ker \left(\begin{bmatrix} \frac{\partial A}{\partial \mu}X(\mu(t)) & A(\mu(t)) \\ 0 & c \\ 0 & \tilde{I} \end{bmatrix} \right).$$

Hence if (92), then $\tilde{I}\frac{d}{dt}X(\mu(t)) = 0$.

□

12. DISCUSSION AND FUTURE WORK

The exact model reduction area is a far greater subject than this thesis shows and there is a lot more that can be done. An aspect of exact model reduction that can be studied is to find a method to compute the variable dependencies without solving the system. This could help to solve larger chemical reaction networks faster, and also provide a method for analysing transient systems that are not steady state or equilibrium.

The method of Section 6 and Wegscheider's condition were not understood by us until a late stage. This method shows that when Wegscheider's conditions are satisfied, the system $N\mathbf{v} = 0$ and $\mathbf{v} = 0$ are equivalent. Since the system $\mathbf{v} = 0$ can be solved as a linear system in the logarithms of the concentrations, this system could have been studied instead of the more complicated system $N\mathbf{v} = 0$. It seems more difficult to solve this system in Matlab though, even if we have not yet understood why. It would be interesting to compare the two methods and also combine the logarithm method with the model reduction of Section 11.

Note that the method of the model reduction is quite general and applies to many other linear systems as well.

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