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A New Computational Tool for Establishing Model Parameter Identifiability

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ABSTRACT

We describe a novel method to establish *a priori* whether the parameters of a nonlinear dynamical system are identifiable—that is, whether they can be deduced from output data (experimental observations). This is an important question as usually identifiability is assumed, and parameters are sought without first establishing whether these can be inferred from a set of measurements. We highlight the connections between parameter identifiability and state observability. We show how observability criteria can be used to check for identifiability, and we use new, state of the art computational tools to implement our approach. Nonlinear dynamical systems are prevalent in systems biology, where they are often used to represent a biological system. Thus, examples from biology are used to illustrate our method.

Key words: parameter identifiability, sum of squares decomposition, systems biology.

1. INTRODUCTION

Determining interactions and their strength in large-scale biochemical networks has been an active area of research for some time now. Typical models for such systems are based on physical and biological knowledge, and take the form of differential equations that involve polynomial and rational functions; the network structure is encoded in these equations through appropriate system parameters. To determine the latter from experimental data, one often disturbs the system, for example, by artificially changing chemical concentrations, and observes the transient response. The recorded information is then used to extract model parameters such as reaction rate constants (Feng and Rabitz, 2004). Often, because of the difficulty of establishing whether parameters can be deduced from the experimental observations, parameter *identifiability* is assumed (Farina et al., 2006; Geffen et al., 2007). In this article, we consider the problem of parameter identifiability and provide a novel approach to check *a priori* whether the proposed measurements allow us to identify all unknown system parameters—that is, before any resources are committed to identifying them.

The notion of identifiability is strongly connected to the notion of *observability* (Vajda and Rabitz, 1994). In dynamical systems and control theory, we say that a system is observable if at any given point in time we can deduce the values of all system states through previous output measurements (experimental data). For linear systems, there exist several methods to check that a state-space system representation is observable (Zhou et al., 1996). These methods can be easily implemented computationally, however, they cannot be readily extended to nonlinear systems. Hermann and Krener (1977) provide a fundamental result

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on (local) nonlinear observability that requires to check the rank of the so called *observability matrix*, which is constant for linear systems but state-dependent for nonlinear systems and therefore makes checking the condition nontrivial (see also (Respondek, 2002; Chaves, 2003; Anguelova, 2004)). Related results on identifiability based on differential algebra or Taylor series expansion (Fitch, 1984; Ljung and Glad, 1994; Denis-Vidal et al., 2001; Audoly et al., 2001) do not provide an easily implementable and verifiable condition. In this article, we show how the criterion of Hermann and Krener can be directly applied to check for identifiability. We implement it computationally using new, state of the art tools in order to check for local observability and identifiability in the case of models of biological systems that are represented by dynamical systems involving polynomial and rational functions. For example, *chemical reaction networks* with *mass action* or *Michaelis Menten kinetics*, are well-known systems that have such a structure.

In Farina et al. (2006), a result is presented that shows that identifiability of parameters in the case of linear or linearized models of chemical reaction networks requires full state observability (measuring the concentrations of all chemicals). However, it is known that conditions for linear observability/identifiability can be different from the conditions for nonlinear observability/identifiability. Indeed, in this article we present a simple two dimensional nonlinear chemical reaction network whose parameters are identifiable despite the fact that we observe only one of the two states. (The result based on linear observability in Farina et al. (2006) requires that we observe both states for parameter identifiability.) Sedoglavic (2002) and Anguelova (2004) briefly discuss a methodology to establish non-identifiable parameters (see Remark 1 below). Recent papers that deal with estimating parameters when not all are identifiable are Balsa-Canto et al. (2007) and Quaiser et al. (2007).

The structure of this article is as follows: In Section 2, we describe the different methods used in this paper to first establish a model for a biological system and then check whether the model parameters can be identified from a set of experimental measurements. In Section 2.1, we introduce *chemical reaction network theory*, which is often used to describe and understand biological processes. Section 2.2 introduces the notions of and criteria for observability and identifiability of a system. We show how the conditions can be implemented computationally using new, state of the art tools, which we briefly describe in Section 2.3. Section 3 provides examples validating our approach to parameter identifiability. We conclude the paper in Section 4.

Notation

$\mathbb{R}, \mathbb{R}^n, \mathbb{R}^{m\times n}$	real numbers, real vector of length n, $m\times n$ real matrices
A_{ij}	(i,j)th entry of matrix $A \in \mathbb{R}^{m\times n}$
$\mathbb{R}^n_+, \overline{\mathbb{R}}^n_+$	$\{x \in \mathbb{R}^n : x_i > 0, \forall i, i=1, \ldots, n\}, \{x \in \mathbb{R}^n : x_i \geq 0, \forall i, i=1, \ldots, n\}$
e	$[1, 1, \ldots, 1]^{\mathrm{T}}$
$I(I_n)$	the Identity matrix (of dimension $n\times n$)
$\mathrm{diag}(x), x \in \mathbb{R}^n$	an $n\times n$ matrix whose diagonal is given by x
$\dot{x}$	derivative of x with respect to the time variable t

2. METHODS

2.1. Chemical reaction networks

Chemical reaction networks are used to describe and understand biological processes (Feinberg, 1979, 1987). The general form for a chemical reaction is given by

$$aA + bB + \ldots \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} xX + yY + \ldots. \tag{1}$$

We denote by $[A]$, $[B]$, $[X]$, and $[Y]$ the concentrations of the chemicals or *species* A, B, X and Y. The objects that appear before and after the reaction arrows in (1) are called *complexes*. Note that complexes are made up of species (Guberman, 2003). The positive constants k_1 and k_{-1} are the forward and reverse *reaction rate constant* respectively.

The law of mass action assumes that if reactions take place at constant temperature in a homogenous and well-mixed solution then the probability of a collision between molecules is proportional to the product of their concentrations. Now, consider a simple chemical reaction of the form

$$A + B \xrightarrow{k} C. \tag{2}$$

Then, it follows from the law of mass action that

$$\frac{d[C]}{dt} = k[A][B]. \tag{3}$$

Moreover, most chemical reactions do not proceed in one direction only and in these cases we have to include the reverse reactions:

$$A + B \underset{k_-}{\overset{k_+}{\rightleftarrows}} C, \tag{4}$$

In this case, Equation (3) becomes

$$\frac{d[C]}{dt} = -k_-[C] + k_+[A][B]. \tag{5}$$

The law of mass action can be generalized to larger networks using chemical reaction network theory. We consider here an illustrative example; the following reaction scheme proposed by Michaelis and Menten for chemical reactions involving enzymes, which we will use in the sequel:

$$E + S \underset{p_2}{\overset{p_1}{\rightleftarrows}} ES \xrightarrow{p_3} E + P, \; P \xrightarrow{p_4} \emptyset, \tag{6}$$

where S denotes the substrate, E the enzyme, ES the enzyme-substrate complex and P the final product. The symbol $\emptyset$ represents the *null-complex*, which functions as a sink/source for the system.

In the chemical reaction network given by (6), *edges* represent chemical reactions and *vertices* represent complexes. We denote the concentration vector of the different complexes by $\Psi(x)$, where x is the concentration vector of the different species. For the Michaelis-Menten reaction, the vectors of complexes and species are given by

$$\Psi(x) = \begin{bmatrix} \emptyset \\ [E][S] \\ [ES] \\ [E][P] \\ [P] \end{bmatrix} \text{ and } x = \begin{bmatrix} [S] \\ [E] \\ [ES] \\ [P] \end{bmatrix}$$

respectively. Now, the so-called *bookkeeping matrix* Y maps the space of complexes into the space of species. Its entries are nonnegative integers. The elements of the ith row of Y tell us in which complexes species i appears; or, equivalently, the entries to the jth column tell us of which species complex j is made of. For (6),

$$Y = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 \end{bmatrix}.$$

Let $K \in \overline{\mathbb{R}}_+^m$ be the transpose of the *weighted adjacency matrix* of the weighted *digraph* representing the chemical reaction network. The entry K_{ij} corresponds to the rate constant associated with the reaction from complex j to i. Thus, for (6),

$$K = \begin{bmatrix} 0 & 0 & 0 & 0 & p_4 \\ 0 & 0 & p_2 & 0 & 0 \\ 0 & p_1 & 0 & 0 & 0 \\ 0 & 0 & p_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

The transpose of the *weighted Laplacian matrix* is given by

$$L = \text{diag}\ (K^{\mathrm{T}} e) - K.$$

The matrix $A_\kappa = -L$ is the so-called *kinetic matrix*. For (6),

$$A_\kappa = \begin{bmatrix} 0 & 0 & 0 & 0 & p_4 \\ 0 & -p_1 & p_2 & 0 & 0 \\ 0 & p_1 & -(p_2+p_3) & 0 & 0 \\ 0 & 0 & p_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & -p_4 \end{bmatrix}.$$

If we assume that the chemical system given by (6) obeys the law of mass action, then its time evolution is given through the following set of nonlinear ODEs (Gunawardena, 2003):

$$\dot{x} = Af(x) = YA_\kappa \Psi(x),\ A = YA_\kappa,\ f(x) = \Psi(x),\ \ln \Psi(x) = Y^{\mathrm{T}}\ \ln x. \tag{7}$$

For clarity, we also provide the expanded ODE representation of the Michaelis-Menten reaction system (6):

$$\begin{aligned} [\dot{S}] &= -p_1[E][S] + p_3[ES], \\ [\dot{E}] &= -p_1[E][S] + (p_2+p_3)[ES], \\ [\dot{E}S] &= p_1[E][S] - (p_2+p_3)[ES], \\ [\dot{P}] &= p_3[ES] - p_4[P]. \end{aligned} \tag{8}$$

In general, we assume that a chemical reaction network has n species and m complexes. Thus, in (7): $x \in \bar{\mathbb{R}}^n_+$, $\Psi(x) \in \bar{\mathbb{R}}^m_+$, $A_\kappa \in \mathbb{R}^{m\times m}$, and $Y \in \mathbb{R}^{n\times m}_+$.

2.2. *Observability and identifiability*

In this section, we establish a connection between the notions of observability and identifiability. Consider a linear time-invariant system of the form

$$\begin{aligned} \dot{x} &= Ax + Bu \\ y &= Cx \end{aligned} \tag{9}$$

where $x \in \mathbb{R}^n$ is the state, $u \in \mathbb{R}^k$ is the input and $y \in \mathbb{R}^m$ is the output. In general, we assume that the time history of $u(t)$ is known and say that a state of the system is observable at time t_0 if we can deduce its value $x(t_0)$ through the time history (up to t_0) of output measurements (experimental data) y_j, $j = 1, \ldots, m$. In particular, the linear system (9) is observable if the observability matrix

$$\mathcal{O} = \begin{bmatrix} C \\ CA \\ CA^2 \\ \vdots \\ CA^{n-1} \end{bmatrix}$$

has full column rank (Zhou et al., 1996). To see this, notice that we observe $y = Cx$ and its time derivatives. That is, we observe (for simplicity, we let $u = 0$):

$$\mathcal{Y} = \begin{bmatrix} y \\ \dot{y} \\ \ddot{y} \\ \vdots \\ y^{(n-1)} \end{bmatrix} = \begin{bmatrix} C \\ CA \\ CA^2 \\ \vdots \\ CA^{n-1} \end{bmatrix} x = \mathcal{O}x.$$

If $\mathcal{O}$ has full column rank then the inverse of $\mathcal{O}^{\mathrm{T}}\mathcal{O}$ exists and it follows that $x = (\mathcal{O}^{\mathrm{T}}\mathcal{O})^{-1}\ \mathcal{O}^{\mathrm{T}}\mathcal{Y}$.

Now, consider the case when some elements of A, the parameter matrix, are unknown. Then, we rewrite (9) as:

$$\begin{aligned} \dot{x} &= Ax + Bu \\ \dot{A}_{ij} &= 0 \ \forall i,\ j,\ i,j = 1, \ldots, n \\ y &= Cx. \end{aligned} \tag{10}$$

Note that (10) is a nonlinear dynamical system. In general, we assume that the time history of $u(t)$ is known and say that system parameters are identifiable if at any given point of time we can deduce the values of all system states and parameters through a finite number of previous output measurements. Consider a nonlinear dynamical system of the form:

$$\begin{aligned} \dot{x} &= f(x,p,u),\ x \in \mathbb{R}^n,\ p \in \mathbb{R}^q,\ u \in \mathbb{R}^k \\ \dot{p} &= 0 \\ y &= h(x),\ y \in \mathbb{R}^m \end{aligned} \tag{11}$$

Let

$$\tilde{x} = \begin{bmatrix} x \\ p \end{bmatrix}$$

and

$$O_N(\tilde{x}) = \begin{pmatrix} \frac{\partial}{\partial \tilde{x}} h(x) \\ \frac{\partial}{\partial \tilde{x}} (L_f h(x)) \\ \vdots \\ \frac{\partial}{\partial \tilde{x}} (L_f^{n+q-1} h(x)) \end{pmatrix}, \tag{12}$$

where $L_f h = \frac{\partial h(x)}{\partial \tilde{x}} f(\tilde{x}, u)$ is the so-called *Lie derivative* (Respondek, 2002). Then, (11) is *locally identifiable* if

$$\operatorname{rank}(O_N(\tilde{x})) = n + q,\ \tilde{x} \in \mathcal{D}, \mathcal{D} \subset \mathbb{R}^{n+q}. \tag{13}$$

To see this, consider $\tilde{x}_0 \in \mathcal{D}$ and note that for all $\tilde{x}$ in a neighborhood of $\tilde{x}_0$ (i.e., $\tilde{x} \in \mathcal{N}(\tilde{x}_0)$):

$$\mathcal{Y} = O_N(\tilde{x})\tilde{x}. \tag{14}$$

Then, condition (13) implies that for $\tilde{x} \in \mathcal{N}(\tilde{x}_0)$:

$$\tilde{x} = (O_N(\tilde{x})^{\mathrm{T}} O_N(\tilde{x}))^{-1} O_N(\tilde{x})^{\mathrm{T}} \mathcal{Y}. \tag{15}$$

It follows from (15) that we can observe all states and identify all parameters in $\mathcal{N}(\tilde{x}_0)$. Now, note that in order to check rank condition (13) it is not necessary to compute all Lie derivatives. Moreover, it was shown in Anguelova (2004) that if the equality in (13) does not hold in a particular case then increasing the number of Lie derivatives in (12) beyond $n + q - 1$ will not make (13) hold. (In the linear case, this follows from the Caley-Hamilton Theorem.)

A numerical test that provides an $\tilde{x}_0$ for which rank $(O_N(\tilde{x}_0)) < n + q$ would establish non-identifiability of model parameters. Formally, it is given by:

- There exist vectors $\tilde{x}_0 \in \mathcal{D}$ and $z \in \mathbb{R}^{n+q}, z \neq 0,$ such that the set

$$\{z^{\mathrm{T}} O_N(\tilde{x}_0) = 0\} \neq \emptyset; \tag{16}$$

i.e., the set is nonempty. Note that this is, by definition, the linear dependence of the columns of $O_N(\tilde{x}_0)$.

The result in the following remark provides means to identify non-observable states and non-identifiable parameters, it follows directly from (15).

Remark 1 *(Anguelova, 2004). If deleting the ith column of $O_N(\tilde{x})$ does not change the rank of the matrix then the ith state (parameter) is non-observable (non-identifiable).*

Now, establishing identifiability of model parameters is a much harder task. Formally, condition (13) can be rewritten as follows:

$$\{\tilde{x} \in \mathcal{D},\ z \in \mathbb{R}^{n+q},\ z \neq 0,\ z^{\mathrm{T}} O_N(\tilde{x}) = 0\} = \emptyset. \tag{17}$$

Unfortunately, it is not easy to check condition (17) analytically. The result of the next remark, which follows from *Sylvester's inequality*, provides a conservative[1] means to perform such a test.

Remark 2. *If*

$$Q(\tilde{x}) = O_N(\tilde{x})^{\mathrm{T}} O_N(\tilde{x}) > 0, \tilde{x} \in \mathcal{D} \tag{18}$$

then (13) holds, which implies local identifiability of (11).

Note that, in general, it is not easy to check condition (18) analytically either. Indeed, it is a polynomial non-negativity condition which can be NP hard to test (Murty and Kabadi, 1987). The standard approach is to grid region $\mathcal{D}$, to check whether (18) holds at the chosen grid points and from this to deduce whether it holds everywhere in $\mathcal{D}$ or not. Not only is this method computationally expensive but it also does not provide guarantees that (18) indeed holds everywhere in $\mathcal{D}$. Using the *sum of squares decomposition*, which we discuss in the next section, inequality (18) can be efficiently checked computationally in $\mathcal{D}$ using a *semidefinite program*.

The following remark presents an alternative means to establish identifiability of model parameters, which at times can be performed more efficiently than (18).

Remark 3. *Note that $O_N(\tilde{x}) \in \mathbb{R}^{w \times (n+q)}$ and $w \geq n+q$. If there exists a matrix $M(\tilde{x}) \in \mathbb{R}^{w \times (n+q)}$ such that*

$$\tilde{Q}(\tilde{x}) = M(\tilde{x})^{\mathrm{T}} O_N(\tilde{x}) > 0 \text{ (or } O_N(\tilde{x})^{\mathrm{T}} M(\tilde{x}) > 0 \text{ if } w = n+q),\ \tilde{x} \in \mathcal{D} \tag{19}$$

then it follows that (13) holds.

Note that $M(\tilde{x})^{\mathrm{T}} O_N(\tilde{x}) > 0$ means that it is of size $n+q$ and rank $n+q$. Thus, it follows from Sylvester's inequality that rank $(O_N(\tilde{x})) = n+q$ (and also rank $(M(\tilde{x})) = n+q$).

2.3. Semidefinite programming and the sum of squares decomposition

In this section, we provide some mathematical background on the computational tools we use in this article to solve (18) and (19). These tools can also be used to computationally implement and solve other problems that arise in the field of biological systems modelling analysis (El Samad et al., 2006). The main computational tool is *semidefinite programming* (Vandenberghe and Boyd, 1996), which can be solved efficiently using interior-point methods (Vandenberghe and Boyd,1996; Boyd and Vandenberghe, 2004). In semidefinite programming, we replace the nonnegative orthant constraint of linear programming by the cone of positive semidefinite matrices and pose the following minimisation problem:

$$\begin{aligned} \text{minimise} \quad & c^T x \\ \text{subject to} \quad & F(x) \geq 0, \text{where} \\ & F(x) = F_0 + \sum_{i=1}^{n} x_i F_i. \end{aligned} \tag{20}$$

Here, $x \in \mathbb{R}^n$ is the free variable. The so-called problem data, which are given, are the vector $c \in \mathbb{R}^n$ and the matrices $F_j \in \mathbb{R}^{m \times m}, j = 0, \ldots, n$. Note that convexity of the set of symmetric positive semidefinite matrices in (20) implies that the minimisation problem has a global minimum.

2.3.1. Sum of squares decomposition. For problem data that consists of polynomials of any degree the requirement of positivity can be relaxed to the condition that the polynomial function is a *sum of*

[1]That is, establishing that (18) holds guarantees (17), but it is not necessarily true that (18) holds whenever the condition in (17) is fulfilled.

squares. On one hand, this is only a sufficient condition for positivity it can at times be quite conservative; in other words, a function can be positive without being a sum of squares. On the other hand, as mentioned previously, testing positivity of a polynomial, is NP hard.

Consider the real-valued polynomial function $F(x)$ of degree $2d$, $x \in \mathbb{R}^n$. A sufficient condition for $F(x)$ to be nonnegative is that it can be decomposed into a sum of squares (Parrilo, 2003):

$$F(x) = \sum_i f_i^2(x) \geq 0,$$

where f_i are polynomial functions. Now, $F(x)$ is a sum of squares if and only if there exists a positive semidefinite matrix Q and

$$F(x) = z^{\mathrm{T}} Q z, \; z = [1, x_1, x_2, \ldots, x_n, x_1 x_2, \ldots, x_n^d].$$

The length of vector z is $l = \binom{n+d}{d}$. Note that Q is not necessarily unique. However, $\sum_i f_i^2(x) = z^{\mathrm{T}} Q z$ poses certain constraints on Q of the form trace $(A_j Q) = c_j$, where A_j and c_j are appropriate matrices and constants respectively. (For an illustration, see Example 3.5 in Parrilo [2003]).

In general, in order to find Q, we solve the optimization problem associated with the following semidefinite program:

$$\begin{array}{ll} \text{minimize} & \text{trace}(A_0 Q) \\ \text{subject to} & \text{trace}(A_j Q) = c_j, j = 1, \ldots, m \\ & Q \geq 0. \end{array} \tag{21}$$

In this paper, to solve sum of squares programs, we use SOSTOOLS (Prajna et al., 2002), a free, third-party MATLAB toolbox, which relies on the solver SeDuMi (Sturm, 1999). For instance, we use SOSTOOLS to check whether (18) (or (19)) holds. Finally, here are some additional remarks:

- Consider a rational function $F(x)$; that is, $F(x) = \frac{f(x)}{g(x)}$, where $f(x)$ and $g(x)$ are polynomial functions. Then, $F(x) \geq 0$ if $g(x) > 0$ and (21) is feasible with $z^{\mathrm{T}} Q z = F(x) g(x)$.
- If

$$F(x) + p(x) h(x) = \sum_i g_i^2(x) \geq 0, \; p(x) \geq 0, h(x) = \begin{cases} \leq 0 \text{ if } a_i \leq x_i \leq b_i \; \forall i \\ > 0 \; \textit{otherwise} \end{cases},$$

then $F(x) \geq 0$ if $a_i \leq x_i \leq b_i$ for all i, where a, b are vectors. This can be used to show that $F(x)$ is nonnegative in a specific region of the state or/and parameter space.

3. RESULTS

3.1. A system that is locally identifiable but whose linearization is not identifiable

Consider the simple reaction mechanism

$$x_2 \xrightarrow{p} x_1 + x_2 \xrightarrow{1} x_1, \tag{22}$$

which we represent through the following dynamical system assuming mass action kinetics:

$$\begin{aligned} \dot{x}_1 &= p x_2, \\ \dot{x}_2 &= -x_1 x_2, \\ \dot{p} &= 0, \\ y &= x_2 (y = x_1). \end{aligned} \tag{23}$$

where $a_1 \le p \le b_1, a_2 \le x_2 \le b_2, a_3 \le x_1 \le b_3, b_i \ge a_i \ge 0$ and $i = 1,\ 2,\ 3$. Let $a_1 = 1, b_1 = 3, a_2 = 4$, $b_2 = 6, a_3 = 9$ and $b_3 = 11$). Then, with $Q = Q(\tilde{x})$ as in (18), the following feasibility problem provides means to check local identifiability of (23):

$$\begin{aligned} \text{search for} \quad & \text{polynomial functions of degree } 2 : q_1(z),\ q_2(z),\ q_3(z),\ z \in \mathbb{R}^3 \\ \text{such that} \quad & z^{\mathrm{T}}(Q - 0.01I)z + q_1(z)((p-2)^2 - 1) + q_2(z)((x_2 - 5)^2 - 1) \\ & + q_3(z)((x_1 - 10)^2 - 1) \text{ is SOS } \forall p,\ \forall x_1,\ \forall x_2,\ \forall z \\ & q_1(z),\ q_2(z) \text{ and } q_3(z) \text{ are SOS } \forall z \end{aligned} \tag{24}$$

We solve (24) and obtain

$$\begin{aligned} q_1 &= 0.058z_3^2 + 0.063z_2z_3 + 0.61z_2^2 - 0.324z_1z_3 + 0.275z_1z_2 + 0.551z_1^2, \\ q_2 &= 0.021z_3^2 + 0.032z_2z_3 + 0.154z_2^2 - 0.082z_1z_3 + 0.034z_1z_2 + 0.145z_1^2, \\ q_3 &= 0.006z_3^2 + 0.006z_2z_3 + 0.035z_2^2 - 0.021z_1z_3 + 0.011z_1z_2 + 0.037z_1^2 \end{aligned}$$

if $y = x_2$. This implies that the parameters in (23) are identifiable if $y = x_2$. If $y = x_1$ then we do not obtain a solution for (24), which we expected as it can be easily shown that $\text{rank}(Q) = 2$ for all x. Importantly, our result is less strict than the result presented in Farina et al. (2006). The result in this reference is based on the analysis of the linearization of dynamical systems representing chemical reaction networks with mass action kinetics—note that (23) is such a system—and requires full rank of matrix H_c, where $y = H_c x$, for identifiability.

Alternatively, for $y = x_2$, with $\tilde{Q} = \tilde{Q}(\tilde{x}) = M(\tilde{x})^{\mathrm{T}} O_N(\tilde{x})$ as in (19), we solve successfully the following feasibility problem:

$$\begin{aligned} \text{search for} \quad & \text{polynomial functions of degree } 2 : q_1(z),\ q_2(z),\ q_3(z),\ z \in \mathbb{R}^3 \\ & \text{and a constant matrix } M \\ \text{such that} \quad & z^{\mathrm{T}}(\tilde{Q} - 0.01I)z + q_1(z)((p-2)^2 - 1) + q_2(z)((x_2 - 5)^2 - 1) \\ & + q_3(z)((x_1 - 10)^2 - 1) \text{ is SOS } \forall p,\ \forall x_1,\ \forall x_2,\ \forall z \\ & q_1(z),\ q_2(z) \text{ and } q_3(z) \text{ are SOS } \forall z. \end{aligned} \tag{25}$$

We obtain the following solution for matrix M:

$$M = \begin{bmatrix} -4.345 & -0.904 & 0.004 \\ -0.904 & -1.071 & -0.006 \\ 0.004 & -0.006 & -0.006 \end{bmatrix}$$

Again, this shows that the parameters in (23) are identifiable if $y = x_2$. Moreover, algorithm (25) (cpusec: 0.39) performs faster than (24) (cpusec: 0.55).

3.2. *Michaelis-Menten reaction*

Consider the following Michaelis-Menten reaction with product removal:

$$E + S \underset{p_2}{\overset{p_1}{\rightleftarrows}} ES \xrightarrow{p_3} E + P,\ P \xrightarrow{p_4} \emptyset. \tag{26}$$

We let x_1 denote the concentrations of substrate S, x_2 of enzyme E, x_3 of enzyme-substrate complex ES and x_4 of final product P. Under the assumption of mass action kinetics, we represent its dynamics by:

$$\begin{aligned} \dot{x}_1 &= -p_1x_1x_2 + p_2x_3, \\ \dot{x}_2 &= -p_1x_1x_2 + (p_2 + p_3)x_3, \\ \dot{x}_3 &= p_1x_1x_2 - (p_2 + p_3)x_3, \\ \dot{x}_4 &= -p_4x_4 + p_3x_3, \\ \dot{p}_1 &= 0,\ \dot{p}_2 = 0,\ \dot{p}_3 = 0,\ \dot{p}_4 = 0, \\ y_1 &= x_1,\ y_2 = x_4. \end{aligned} \tag{27}$$

We assume arbitrary units for concentrations and rates, and that $x_3 = 10 - x_2$. We normalize the reaction rates such that $p_1 = 1$. (Figure 1 depicts the time evolution of (27) for $p_2 = 6$, $p_3 = 10$ and $p_4 = 2$ with arbitrary time and concentration units.) Let

$$2 \le x_1 \le 4,\ 4 \le x_2 \le 6,\ 9 \le x_4 \le 11,\ 5 \le p_2 \le 7,\ 9 \le p_3 \le 11 \text{ and } 1 \le p_4 \le 3.$$

Recall that in order to check rank condition (13) it is not necessary to compute all Lie derivatives. Thus, we increase the number of derivatives δ one by one and check whether we can solve the following feasibility problem using SOSTOOLS:

$$\begin{aligned} \text{search for} \quad & \text{polynomial functions of degree } 2 : q_i(z), i = 1, \ldots, 6, z \in \mathbb{R}^3 \\ \text{such that} \quad & z^{\mathrm{T}}(Q - 0.01I)z + q_1((x_1 - 3)^2 - 1) + q_2((x_2 - 5)^2 - 1) + \\ & q_3((x_4 - 10)^2 - 1) \ + q_4(p_2 - 5)(p_2 - 7) + q_5(p_3 - 9)(p_3 - 11) + \\ & q_6(p_4 - 1)(p_4 - 3) \ \text{ is SOS } \forall p,\ \forall x,\ \forall z, \\ & q_i(z) \text{ is SOS } \forall i, \forall z, \end{aligned} \tag{28}$$

where

$$O_N(\tilde{x}) = \begin{pmatrix} \frac{\partial}{\partial \tilde{x}} h(x) \\ \frac{\partial}{\partial \tilde{x}} (L_f h(x)) \\ \vdots \\ \frac{\partial}{\partial \tilde{x}} (L_f^{\delta} h(x)) \end{pmatrix}, \tilde{x} = \begin{bmatrix} x_1 \\ x_2 \\ x_4 \\ p_2 \\ p_3 \\ p_4 \end{bmatrix}, \delta \le 5, Q(\tilde{x}) = O_N(\tilde{x})^{\mathrm{T}} O_N(\tilde{x}).$$

For $\delta = 3$, we solve (28), which proves that in order to identify the unknown parameters in (27) it is sufficient to measure the concentrations of the enzyme and of the final product.

Alternatively, we solve successfully the following feasibility problem:

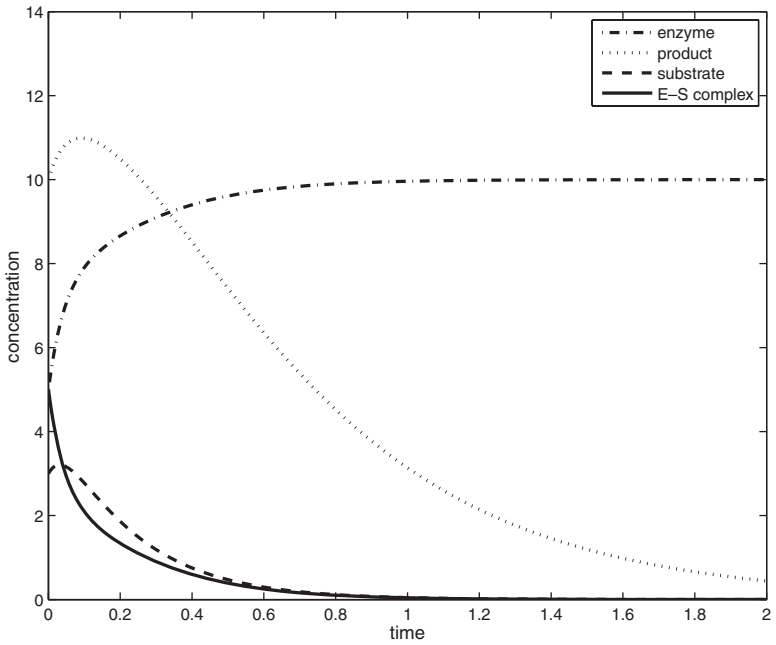

FIG. 1. Michaelis-Menten reaction. The parameters have arbitrary concentration and time units, and are $p_2 = 6, p_3 = 10$ and $p_4 = 2$. Solving (28) shows that we can identify parameters when measurements are taken at the start of the experiment when $2 \le x_1 \le 4, 4 \le x_2 \le 6$ and $9 \le x_4 \le 11$.

$$
\begin{aligned}
\text{search for} \quad & \text{polynomial function of degree } 2 : q_i(z), i = 1, \cdots, 6, z \in \mathbb{R}^6 \\
& \text{and a constant matrix } M \\
\text{such that} \quad & z^{\mathrm{T}}(MO_N(\tilde{x}) - 0.01I)z + q_1((x_1 - 3)^2 - 1) + q_2((x_2 - 5)^2 - 1) + \\
& q_3((x_4 - 10)^2 - 1) \; + q_4(p_2 - 5)(p_2 - 7) \; + q_5(p_3 - 9)(p_3 - 11) + \\
& q_6(p_4 - 1)(p_4 - 3) \;\; \text{is SOS } \forall p, \; \forall x, \; \forall z \\
& q_i(z) \text{ is SOS } \forall i, \forall z,
\end{aligned} \tag{29}
$$

We obtain the following solution for matrix M:

$$
M = \begin{bmatrix}
-0.339 & 0.043 & -0.842 & 0.107 & -0.013 & 0.019 \\
-1.670 & -0.134 & -0.030 & 0.168 & 0.032 & 0.038 \\
0.043 & 1.253 & -0.049 & -0.120 & -0.012 & -0.001 \\
0.822 & -0.063 & -0.239 & -0.768 & -0.004 & -0.013 \\
-2.137 & -0.150 & -1.126 & -0.139 & -0.071 & 0.019 \\
-1.519 & -0.050 & -0.456 & -0.377 & -0.013 & -0.034
\end{bmatrix}
$$

Again, this shows that the parameters in (27) are identifiable. Note that algorithm (29) (cpusec: 2.3) performs much faster than (28) (cpusec: 40.4).

4. CONCLUSION

In this article, we considered the problem of parameter identifiability. This is an important question as identifiability is often assumed in systems biology, and parameters are sought without first establishing whether these can be deduced from the set of measurements. Models of biological systems are based on physical and biological knowledge and often take the form of differential equations that involve polynomial and rational functions. We presented a method using novel computational tools to establish *a priori* whether the parameters of such models representing biological systems are identifiable.

We motivated and illustrated our method through examples from biology. In an earlier article (Farina et al. 2006), the problem of identifiability was approached by linearizing the model. While the authors of that article obtained that full state observability is necessary (that is, all chemical concentrations must be measured) for parameter identifiability of the linearized model, in the first example (Section 3.1) our approach, which applies to the nonlinear model directly, showed that at times partial state observability is sufficient. This is of high significance, because it allows us to choose the minimal set of experiments and thus, the least costly way, that will provide the values for the desired reaction rates or other model parameters. In the second example, we highlighted how our approach can be applied to identify the kind of output measurements that will provide full parameter identifiability in the case of a Michaelis-Menten system. Moreover, our algorithm is easily implementable and robust. It provides an attractive alternative to the more complicated methods based on differential algebra or Taylor series expansion, mentioned in the introduction, and which often require preprocessing.

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DISCLOSURE STATEMENT

No competing financial interests exist.

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