Differential algebra methods for the study of the structural identifiability of biological rational polynomial models

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Abstract

In this paper methods from differential algebra are used to study the structural identifiability of biological models expressed in state-space form and with rational polynomial structure. The focus is on the examples and on efficient, automatic methods to test identifiability for various input-output experiments. Differential algebra is coupled with Gröbner basis, Lie derivatives and the Taylor series expansion in order to obtain efficient algorithms. Two algorithms are discussed in details. In particular an upper bound on the number of derivatives needed for the Taylor series approach is given.

Keywords: State-space models, structural identifiability, differential algebra, Taylor series.

1 Introduction

In this paper we show that differential algebra techniques are useful for the structural identifiability analysis of a large class of biological models, with non-zero input and time-dependent parameters. We consider state-space models defined by the state equations

$$\begin{cases} x'(t,p) &= f(x(t,p),u(t),p) \\ y(t,p) &= g(x(t,p),p) \\ x(0,p) &= x_0(p) \end{cases} \tag{1}$$

where $x(t,p) \in \mathbf{R}^n$, $u(t) \in \mathbf{R}^s$ and $y(t,p) \in \mathbf{R}^m$ are the state variables, the input functions and the observation functions respectively, and $'$ indicates the vector of first derivatives. The entries of the vectors f and g are polynomials or fractions of polynomials in x, u and p. In general the parameter vector p is assumed to belong to an open set $\Omega \subset \mathbf{R}^l$, and the aim is to determine whether the parameter vector p is structurally identifiable, that is whether with perfect input-output data from a specified experiment the parameter vector can be uniquely determined. As we deal with rational polynomials a statement of identifiability true on an open set is valid on all $\mathbf{R}^l$ except for the set of Lebesgue measure zero where the rational polynomials are not defined. The techniques used in identifiability testing differ depending, for example, on whether the model output is linear with respect to the input. In the literature several approaches are established for linear systems, see [27] and [13] for a review. In contrast relatively few methods are available for the identifiability analysis of non-linear models [2, 25, 27].

The differential algebra method considered here requires that all the functions involved are polynomial or rational polynomial in form and deals with both linear and non-linear models. Differential algebra has already proved to be an interesting and useful tool in the study of identifiability (see [5, 17, 21]) when applied alone or together with techniques like the similarity transformation approach and the Taylor series method. The technique requires that the input function u is differentiable while other methods may only require that it is piecewise constant or measurable. This is a drawback of the differential algebra method which on other hand can handle models that proved too difficult for other approaches. An example is the model in Section 7 which could not be solved with the Taylor series method (see [12]).

A major advantage of the differential algebra method is that, once the model to be studied is presented in polynomial form, the study of identifiability is an automatic procedure limited only by the power of the computer. The differential algebra method returns polynomial differential equations in the unknown parameters and the identifiable quantities which define algebraic varieties.

The starting point is to transform a rational polynomial model to one in pure polynomial form that is equivalent from a structural identifiability point of view. Initially we assume that in Model (1) g is a polynomial in the indicated variables and $f_i = \dfrac{r_i(x,p,u)}{q(x,p,u)}$, where q is a polynomial. Then we can write $x_{n+1}(t,p) = q^{-1}(x,p,u)$. The state-space vector $(x_1,\dots,x_{n+1})$ satisfies a system of differential equations and thus Model (1) can be written in a polynomial form as

$$\left\{\begin{array}{lcl} x'(t,p) & = & x_{n+1}(t,p)r(x(t,p),u(t),p) \\ x'_{n+1}(t,p) & = & -x_{n+1}(t,p)^2 \sum_{i=1}^{n} \dfrac{\partial q}{\partial x_i} x_{n+1}(t,p) r_i(x(t,p),u(t),p) \\ y(t,p) & = & g(x(t,p),p) \\ x(0,p) & = & x_0(p) \\ x_{n+1}(0,p) & = & q^{-1}(x(0),p,u). \end{array}\right. \tag{2}$$

For the equivalence of Model (1) and Model (2) from a structural identifiability viewpoint see Vajda [25]. Note that the general case of $f_i = \dfrac{r_i(x,p,u)}{q_i(x,p,u)}$ can be dealt similarly to the case of one common denominator by reducing the model to a common denominator or introducing more than one variable of the type x_{n+1}.

In Section 2 the relevant notions from differential algebra are introduced. Section 3 describes the differential algebra method for identifiability. Sections 4 and 5 present two algorithms for the determination of the identifiability of Model (1) expressed in form (2). The second algorithm allows us to determine an upper-bound for the number of derivatives necessary for the identifiability analysis with the Taylor series approach. Section 6 where various examples are presented is the main section of this paper.

2 Characteristic sets

We first introduce some notions leading to the definition of characteristic sets, crucial to the differential algebra approach to structural identifiability. References are [15, 16, 19, 22]. The aim of this application of differential algebra is to determine a basis of the set of (rational) polynomial functions of the parameters which are indentifiable by a given input-output experiment and to deduce model idenfiability from such a basis.

Definition 1 *1. The* differential ring $\mathbf{R}\{x_1,\dots,x_n\}$ *is the set of all polynomials in the infinite set of indeterminates* $x_i, x'_i, \dots, x_i^{(m)}, \dots$ *for* $i = 1,\dots,n$*, where* $x_i^{(m)}$ *represents the* m*-th derivative of* x_i *with respect to* t*, that is* $\dfrac{\partial^{(m)} x_i}{\partial t^{(m)}}$ *and the coefficients of the polynomials are real numbers.*

2. A differential polynomial *is an element of* $\mathbf{R}\{x_1,\dots,x_n\}$*.*

3. A differential ideal *is a subset I of $\mathbf{R}\{x_1, \dots, x_n\}$ such that*

(i) $f + g \in I$ *for all* $f, g \in I$,

(ii) $fg \in I$ *for all* $f \in I$ *and* $g \in \mathbf{R}\{x_1, \dots, x_n\}$,

(iii) $f^{(m)} \in I$ *for all* $f \in I$.

An example is the ring $\mathbf{R}[x_1, \dots, x_n]$ of all polynomials in the indeterminates $x_1, \dots, x_n$ with coefficients in the field $\mathbf{R}$. It is a differential ring with the trivial derivation that maps a polynomial to zero.

In this paper the elements of $\mathbf{R}\{x_1, \dots, x_n\}$ are called *differential polynomials* and the elements of $\mathbf{R}[x_1, x_1', \dots, x_1^{(l_1)}, \dots, x_n, x_n', \dots, x_n^{(l_n)}]$ are called *polynomials*, where $l_1, \dots, l_n$ are non-negative integers.

The differential ring $\mathbf{R}\{x\}$ represents the set of all polynomial functions in the state variable $x(t)$ and its derivatives with coefficients in $\mathbf{R}$. For example the polynomial $x'' - \frac{1}{2}x' - 3x$ is in $\mathbf{R}\{x\}$ and an example of differential ideal in $\mathbf{R}\{x\}$ is $\left\{\sum_{i\geq 1} \alpha_i x^i + \sum_{j \geq 1} \beta_j x^{(j)} : \alpha_i, \beta_j \in \mathbf{R}\right\}$.

As an example, the state-space model (see Vajda [26])

$$\left\{ \begin{array}{l} x_1' = p_1 x_1^2 + p_2 x_1 x_2 \\ x_2' = p_3 x_1^2 + p_4 x_1 x_2 \\ y = x_1 \end{array} \right. \tag{3}$$

corresponds to the ideal of $\mathbf{R}\{x_1, x_2, y\}$ generated by the following three differential polynomials

$$\begin{array}{l} x_1' - p_1 x_1^2 - p_2 x_1 x_2, \\ x_2' - p_3 x_1^2 - p_4 x_1 x_2, \\ y - x_1 \end{array} \tag{4}$$

where the parameters p_1, p_2, p_3, p_4 are in $\mathbf{R}$. In order to consider unknown constant parameters we might need to extend the coefficient field to the set of all rational polynomials in the parameters, namely as a coefficient field we consider $\mathbf{R}(p_1, p_2, p_3, p_4)$. At times it is convenient to consider the parameters as differential indeterminates and the differential polynomials p_i' are added to indicate that p is an unknown constant. We shall come back to this.

Definition 2 *A ranking of $(x_1, \dots, x_n)$ is a total ordering on the set of all derivatives $x_i^{(m)}$ such that*

(i) $x_i^{(m)} < x_i^{(m+k)}$ *and*

(ii) $x_i^{(m)} < x_j^{(l)}$ *implies* $x_i^{(m+k)} < x_j^{(l+k)}$

for all $i, j = 1, \dots, n$ and for m, l, k non-negative integers.

Note that a ranking of $(x_1, \ldots, x_n)$ induces in a natural way a ranking or term-ordering over the monomials of $\mathbf{R}[x_1, {x_1}', \ldots, x_1^{(l_1)}, \ldots, x_n, {x_n}', \ldots, x_n^{(l_n)}]$. Namely for v, w monomials in $\mathbf{R}[x_1, {x_1}', \ldots, x_1^{(l_1)}, \ldots, x_n, {x_n}', \ldots, x_n^{(l_n)}]$, v is smaller than w if v is smaller than w with respect to the ranking of $(x_1, \ldots, x_n)$. We use the same notation for the two rankings, in the differential framework and in the polynomial framework.

In this paper we consider two types of ranking:

1. $x < y$ stands for the ranking

$$x_1 < \ldots < x_n < y_1 < \ldots < y_m < x'_1 < \ldots < x'_n < y'_1 < \ldots$$

2. $x << y$ stands for the ranking

$$x_1 < \ldots < x_n < x'_1 < \ldots < y_1 < \ldots < y_m < y'_1 < \ldots .$$

For example in $\mathbf{R}\{x_1, x_2, y\}$, if we assume that x_1 is smaller than x_2 then the ranking $x < y$ is

$$x_1 < x_2 < y < x'_1 < x'_2 < y' < \ldots < x_1^{(l)} < x_2^{(l)} < y^{(l)} \ldots$$

and the ranking $x << y$ is

$$x_1 < x_2 < x'_1 < x'_2 < \ldots < x_1^{(l)} < x_2^{(l)} < \ldots < y < y' < \ldots < y^{(l)} \ldots$$

Definition 3 *1. Given a ranking of $(x_1, \ldots, x_n)$ and a differential polynomial f in $\mathbf{R}\{x_1, \ldots, x_n\}$, the* leader *$v$ of f is the largest derivative in f with respect to the ranking.*

2. Let d be the degree of v in f. The rank *of f is v^d and the differential polynomial f can be written as a polynomial in v, i.e. $f = \sum_{i=0}^{d} I_i v^i$ where the I_i's are differential polynomials.*

With respect to both rankings $<$ and $<<$ the leaders of the polynomials in Model (4) are x'_1, x'_2 and y. The degree of both leaders is 1. In particular the rank and the leader coincide.

Definition 4 *Let f and g be differential polynomials and let v and d be as in Definition 3 above, then*

1. *g is said to be* partially reduced *with respect to f if no proper derivative of v appears in g,*

2. *g is said to be* reduced *with respect to f if g is partially reduced with respect to f and its degree in v is less than d.*

3. *A set of differential polynomials $\mathcal{A}$ is called* autoreduced *if $\mathcal{A} \cap \mathbf{R} = \emptyset$ and each element of $\mathcal{A}$ is reduced with respect to all the other elements.*

For example the polynomial $y - x_1$ is reduced with respect to the first two polynomials in Model (4).

Definition 5 *An autoreduced subset $\mathcal{A}$ of a set E of polynomials is called a* characteristic set *if E does not contain any non-zero element reduced with respect to $\mathcal{A}$.*

The three polynomials in (4) form a characteristic set of the differential ideal they generate with respect to the ranking $x < y$.

Characteristic sets can be computed in Maple with the package `diffalg` in the differential case [1] and with the package `charset` in the non-differential case [28]. We prefer to use the `charset` package as it turns out to be faster for our kind of computation. Alternative algorithms are proposed in [5] and [18].

3 Identifiability and Differential Algebra

Given the differential polynomial Model (2) we consider the differential ideal I in $\mathbf{R}\{u, x, y, p\}$ generated by the following differential polynomials

$$\begin{array}{l} x'(t,p) - f(t,x,p,u), \\ p', \\ y(t,p) - g(t,x,p,u). \end{array} \tag{5}$$

where now the vector x represents the extended set of state-space variables. We call I the *model ideal*. Note that a differential polynomial model is characterised by its ideal.

The differential equations $p' = 0$ are adjoined to the model according to the hypothesis that the parameters are time-independent. Likewise the equations $p' = h(p)$ are adjoined in the case of time-dependent parameters, where $h(p)$ is a vector of polynomials in p.

Cobelli et al. [5] consider the following time-dependent model to assess glucose metabolism in the brain (see Schmidt et al. 1991 [24])

$$\left\{ \begin{array}{l} x_1' = p_1 u - [p_2(t) + p_3(t)]x_1 \\ x_2' = p_3(t)x_1 \\ y = x_1 + x_2 \end{array} \right.$$

with $p_2(t) = p_2(1 + p_4 e^{-p_5 t})$ and $p_3(t) = p_3(1 + p_4 e^{-p_5 t})$. The model can be reparameterised as follows:

$$\left\{ \begin{array}{l} x_1' = p_1 u - [p_2(1 + x_3) + p_3(1 + x_3)]x_1 \\ x_2' = p_3(1 + x_3)x_1 \\ x_3' = -p_5 x_3 \\ y = x_1 + x_2 \end{array} \right. \tag{6}$$

where $x_3 = p_4 e^{-p_5 t}$ and the parameters p_i are now time-independent.

Structural identifiability is a minimal, necessary condition for achieving a successful estimation of a model from real input-output data. A classical definition of structural identifiability from control theory is as follows.

Definition 6 *Let $p \in \Omega \subseteq \mathbf{R}^l$ and let $x_0(p)$ be the initial condition. Assume that the solution of Model (1) with initial condition $x_0(p)$ exists and consider the input-output map, $\mathcal{T}_p^{x_0(p)} : u(\cdot) \longmapsto y(\cdot, p)$. The parameter values p and $\bar{p}$ are said to be* equivalent, *$p \sim \bar{p}$ if and only if $\mathcal{T}_p^{x_0(p)}(u) = \mathcal{T}_{\bar{p}}^{x_0(\bar{p})}(u)$ for all $u \in \mathcal{U} \subseteq \mathbf{R}^s$.*

1. *Model (1) is said to be* globally identifiable at p *if $p \sim \bar{p}$ for all $\bar{p} \in \Omega$ implies $p = \bar{p}$. It is* locally identifiable at p *if there exists an open set W, $p \in W \subset \Omega$ (with respect to the Euclidean topology) such that $p \sim \bar{p}$ for all $\bar{p} \in W$ implies $p = \bar{p}$. Otherwise it is said* unidentifiable at p.

2. *Model (1) is said to be* globally (locally) structurally identifiable *if it is* globally (locally) identifiable at p *for almost all parameter value $p \in \Omega$. Otherwise it is said* structurally unidentifiable.

For the algebraic counterpart of Definition 6 we follow the approach of Fliess and Diop [6].

Definition 7 *Consider Model (1) and its characterisation as a differential ideal (5).*

1. *The parameter vector p is* locally identifiable *if, for each unknown parameter p_i, $i = 1, \ldots, l$, there exists a differential polynomial in p_i, u, y in the ideal I. Moreover the polynomial does not contain derivatives of p_i.*

2. *The unknown parameter vector p is* globally identifiable *if for each i, $i = 1, \ldots, l$ there exists a differential polynomial in p_i, u, y which is linear in p_i and free of derivatives of p_i in the ideal I.*

Fliess and Glad [17] give a clarifying interpretation of identifiability in terms of non-linear observability of the parameters. Indeed if a parameter p is globally identifiable according to Definition 7, then that same parameter is structurally identifiable, Definition 6. This is because, with perfect data for a given input-output experiment, derivatives of u and y are known and there are algebraic relationships that allow us to "measure" p. If a parameter is unidentifiable then by algebraic manipulation of the model equations it is not possible to determine the parameter uniquely or locally. An example of an unidentifiable model is Model (3). Indeed it is sufficient to consider the simplest polynomial in the corresponding differential ideal that does not involve x_1 and x_2, namely

$$y''y - (p_1 + p_4)y^2y' - y'^2 - (p_3 - p_1p_4)y^4$$

It does not contain the parameter p_2 which, as a consequence, is unidentifiable. Other references on the algebraic differential "translation" of the notion of structural identifiability are [6], [8], [9].

Theorem 1 gives the main properties of model ideals.

Theorem 1 *1. The differential ideal I defined by (5) is prime, that is if $fg \in I$ then $f \in I$ or $g \in I$.*

2. The three sets of polynomials in (5) form a characteristic set with respect to the ranking $u << p < x < y$.

For a proof see [3].

Ljung and Glad [17] have shown that a characteristic set with respect to a ranking eliminating the variables x and p solves the identifiability problem. An example of such a ranking is $u << y << p < x$. The characteristic set with respect to $u << y << p < x$ has the structure given by Equation (7) in Theorem 2.

Theorem 2 *Consider a model of type (2) with n state-space variables, l parameters and m observation functions. There are $m + l + n$ differential polynomials in the characteristic set with respect to the ranking $u << y << p < x$, namely*

$$\begin{array}{l} A_1(u,y), \ldots, A_m(u,y), \\ B_1(u,y,p), \ldots, B_l(u,y,p), \\ C_1(u,y,p,x), \ldots, C_n(u,y,p,x) \end{array} \tag{7}$$

Moreover y_i is the leading variable of A_i, p_k is the leading variable of B_k and x_j is the leading variable of C_j.

Three different situations can arise.

(i) If there exists an i such that $B_i = p_i'$ then the model is not identifiable at any p.

(ii) If all of the B_i, $i = 1, \ldots, l$ are of order zero and degree one in p_i then the model is globally identifiable at p_i. If the model is globally identifiable at each parameter then we can write B_i in the linear regression form $B_i(u, y, p_i) = P_i(u, y)p_i + Q_i(u, y)$.

(iii) If all of the B_i, $i = 1, \ldots, l$ are of order zero in p_i and some B_j is of degree larger than one in p_j then the model is locally, but not globally, identifiable at p_j.

Ollivier [20], [21] proposes a different ranking for the study of identifiability. The method by Ollivier is applied when the ideal defined by equations (5) has a generic solution. Eva Here we simply observe that a solution is generic if it does not satisfy any polynomial in the differential ideal For a deeper insight see Ollivier (1998) [21]. In the method proposed by Ollivier the elimination of the variable x suffices in order to determine identifiability results. In fact we determine the $m+n$ differential polynomials

$$A_1(u,y,p),\dots,A_m(u,y,p),C_1(u,y,p,x),\dots,C_n(u,y,p,x)$$

where the set

$$\begin{array}{l} A_1(u,y,p),\dots,A_m(u,y,p),\\ p_1',\dots,p_l',\\ C_1(u,y,p,x),\dots,C_n(u,y,p,x) \end{array} \tag{8}$$

is a characteristic set with respect to the ranking $u << y < p << x$. The differential polynomials A_j are considered as polynomials having coefficients in $\mathbf{R}(p)$, rational polynomials in p, and their leading monomials are taken to have coefficient one. The coefficients of A_j are polynomial (or rational polynomial) functions of the parameters. The analysis of the coefficients of A_j allows us to establish the identifiability of the parameter vector p. Note that the testing for identifiability does not depend on the ranking, but only rankings that eliminate the variables x can be considered. This fact allows us to choose a ranking for which the calculation is less computationally intensive.

The set of coefficients A_j can contain a large number of (rational) polynomials in the parameters which can make the analysis difficult by hand. D'Angio et al. [5] propose the use of Gröbner bases in the analysis of the coefficients. Their method is justified by the Implicit Function theorem for algebraic varieties. We shall discuss this further. In Section 6.1 computational aspects are discussed.

The straightforward calculation of differential characteristic sets in Theorem 2 is generally very computationally intensive. In the next sections we present two new algorithms that somewhat simplify the computation.

4 Algorithm 1

So far we have seen that the differential polynomials in (8) form a characteristic set of the differential ideal I generated by the differential polynomials (5) with respect to the ranking $u << y < p << x$. Note that the derivatives of the parameters p_i do not appear in the differential polynomials A_i and C_i because of the conditions $p_i'{=}0$. By analysis of the coefficients of A_j it is possible to establish the identifiability of the parameter vector

p. It will turn out that is is sufficient to determine $y_i^{(e_i)}$, the leader of A_i, $i = 1, \dots, m$.

In this section we introduce efficient ways to find the differential polynomials A_i and to perform the analysis of the coefficients. For this we need to consider the Lie-derivative operator (see for example [10]).

Let f be a differential polynomial in $\mathbf{R}\{x_1, \dots, x_n\}$. The Lie-derivative operator L_f with respect to f is defined as

$$L_f = \sum_{i=1}^{n} f_i \frac{\partial}{\partial x_i} + \sum_{i=1}^{\infty} u^{(i)} \frac{\partial}{\partial u^{(i-1)}}.$$

Note that the definition of the Lie-derivative operator involves an infinite number of derivatives with respect to the variables u but for each polynomial h in $\mathbf{R}[x, p, u, u', \dots, u^{(s)}]$, $L_f h(x, p, u)$ involves only the variables $x, p, u, u', \dots, u^{(s+1)}$. For positive integers $a_1, \dots, a_m$ let $I(a_1, \dots, a_m)$ be the polynomial ideal generated by

$$y_i - g_i, \dots, y_i^{(a_i)} - L_f^{a_i} g_i, \quad \text{for } i = 1, \dots, m. \tag{9}$$

The ideal $I(a_1, \dots, a_m)$ is contained in the polynomial ring

$$\mathbf{R}[u, u', \dots, y_1, \dots, y_1^{(a_1)}, \dots, y_m, \dots, y_m^{(a_m)}, x, p].$$

Recall that the ranking $u << y < p << x$ over the differential ring $\mathbf{R}\{u, x, y, p\}$ induces in a natural way a ranking or term-ordering over the polynomial ring above.

In Theorem 3 we determine the non-negative integers $e_1, \dots, e_m$ by computing characteristic sets of suitable ideals of type $I(a_1, \dots, a_m)$.

Theorem 3 *Let $e_1^k, \dots, e_m^k$, $k = 0, 1, \dots$ be the sequence of non-negative integers defined recursively as follows:*

1. $e_1^0 = 0, \dots, e_m^0 = 0.$

2. *Let I_k be the ideal $I(e_1^k, \dots, e_m^k)$. Let T_k be a characteristic set of I_k with respect to the ranking $u << y < p << x$ and let Y_k be the set of leaders of*

$$T_k \cap \mathbf{R}[u, u', \dots, y_1, \dots, y_1^{(e_1^k)}, \dots, y_m, \dots, y_m^{(e_m^k)}].$$

   (i) *If there exists a positive integer d_i, such that $y_i^{(d_i)}$ is the derivative of y_i of lowest order in Y_k, i.e. $y_i^{(d_i)}$ is a leader of the characteristic set T_k and $y_i^{(d_i-1)}$ is not a leader of T_k, then $e_i^{k+1} = d_i$.*

   (ii) *If there is no positive integer d_i, i.e. $y_i^{(e_i^k)}$ is not a leader of the characteristic set T_k, then $e_i^{k+1} = e_i^k + 1$.*

Then there exists an integer r such that for all i and for all $s \geq r$, $e_i^s = e_i$, where the e_i's are the leaders of the A_i's, $i = 1, \ldots, m$.

Note that the polynomial ideal $I(e_1, \ldots, e_m)$ contains all the information we need for an identifiability analysis. In fact, for all i, the polynomials A_i of Theorem 3 are in $I(e_1, \ldots, e_m)$. Thus a characteristic set of $I(e_1, \ldots, e_m)$ with respect to the ranking $u << y < p << x$ allows us to find A_i, $i = 1, \ldots, m$. See [18] and [23]. The analysis of the coefficients of the A_i's can be performed using Gröbner basis methods or by choosing a random point in the parameter space Ω.

Example 1 As a simple example consider again Model (3). The ideal I_0 is the ideal generated by $y - x_1$. The ideal I_1 is generated by $y - x_1$ and $y' - p_1 x_1^2 + p_2 x_1 x_2$, its characteristic set as for Item 2 of Theorem 3 is

$$y - x_1, \quad y' - y p_2 x_2 - y^2 p_1$$

and the leaders are x_1 and x_2. Note that since $p_i' = 0$ for all parameters p_i and in Theorem 3 we are interested to determine the polynomials A_i only, then the computation of the above characteristic set is done with respect to the polynomial ranking $y < y' < y'' < x_1 < x_2$. The ideal I_2 is generated by

$$\begin{aligned}
&y - x_1, \\
&y' - p_1 x_1^2 + p_2 x_1 x_2, \\
&y'' - 2{p_1}^2 {x_1}^3 - 3 p_1 {x_1}^2 p_2 x_2 - {p_2}^2 x_1 {x_2}^2 - p_2 {x_1}^3 p_3 - p_2 {x_1}^2 p_4 x_2
\end{aligned}$$

and has the following characteristic set

$$\begin{aligned}
\{ &-yy'' + {y'}^2 + (p_2 p_3 - p_1 p_4) y^4 + (p_1 + p_4) y' y^2, \\
&y - x_1, \\
&y' - y p_2 x_2 - y^2 p_1 \,\} .
\end{aligned}$$

In the first polynomial above there is no x_i variable and thus, according to the method by Ollivier, we consider its coefficients, which are

$$p_2 p_3 - p_1 p_4, \quad p_1 + p_4, \quad -1, \quad 1. \tag{10}$$

Since we have only two coefficients involving the parameters and there are four parameters we deduce that the model is unidentifiable.

The algorithm is outlined as follows.

1. Reparameterise the model as described in Section 3 and derive a differential polynomial formulation.

2. Find the sequence $e_1^k, \ldots, e_m^k$, $k = 0, 1, \ldots, r$ of non-negative integers as described in Theorem 3.

3. Compute the characteristic set with respect to the ranking $u << y < p << x$ of $I(e_1^r, \ldots, e_m^r)$. Consider the polynomials with leaders $y_i^{(e_i)}$, for $i = 1, \ldots, m$ as polynomials in $\mathbf{R}(p)$ and reduce them to monic form, i.e. with leading coefficient one. Consider the set C of coefficients of the polynomials so obtained. Note that the elements of C are identifiable quantities and are a basis of the ideal of all identifiable quantities.

4. Each polynomial in the set C is set equal to a new variable c_j and the set Ψ of the resultant equations is formed. There are two alternatives:

   4a. A Gröbner basis of the set Ψ is computed with an ordering eliminating p, for example the lexicographic ordering with the p_i variables bigger than the c_i variables. That is, one could try and rewrite the set of polynomial equations in Ψ so that the parameters p_i are functions of the c_i's. If this is possible then the system is uniquely identifiable.

   4b. A numerical point p^0 is randomly chosen in the parameter space Ω and each polynomial in the set C is evaluated at the numerical point p^0. Each polynomial is set equal to its corresponding numerical value and the set Φ of the resultant equations is formed. A Gröbner basis of the set Φ is computed. A system of polynomial equations is obtained by setting each element of the Gröbner basis equal to zero. The number of solutions for each parameter is derived. For almost all points p^0, if the system has infinite solutions, finite but more than one, only one, the model is unidentifiable, locally identifiable or globally identifiable respectively.

In Step 4b we use the idea in D'Angio et al. [5] which as mentioned is justified by the Implicit Function Theorem. In fact the set of coefficients defines a polynomial map $\bar{\Phi}$ for which we want to find the rational polynomial inverse. If $\bar{\Phi}$ admits a rational inverse then, for almost all points of the domain, the map $\bar{\Phi}$ is one-to-one. Since the point p^0 is generic, with probability 1 it is in the domain where the map $\bar{\Phi}$ is one-to-one if the model is globally identifiable.

Example 2 To illustrate Step 4 we use again Model (3). Since there is only one observation $m = 1$, the polynomials in (10) give the set C. The set Ψ is

$$\Psi = \{c_1 - p_2p_3 + p_1p_4, \;\; c_2 - p_1 - p_4\}$$

and its (reduced) Gröbner basis with respect to the lexicographic ordering with $c_2 < c_1 < p_4 < p_3 < p_2 < p_1$ is

$$\{ -c_2 + p_4 + p_1, \;\; -c_1 - c_2p_4 + p_4^2 + p_2p_3 \}.$$

The model is unidentifiable because it is not possible to express all the parameters p_i as functions of the c_i's.

Alternatively the point $p^0 = (23, 155, 6678, 90)$ is chosen arbitrarily and the set

$$\Phi = \{p_2 p_3 - p_1 p_4 - 1033020, \;\; p_1 + p_4 - 113\}$$

is derived, with Gröbner basis with respect to the term-ordering $p_4 < p_3 < p_2 < p_1$

$$\{p_1 + p_4 - 113, \;\; p_2 p_3 - 1033020 + p_4^2 - 113 p_4\}$$

The corresponding system of polynomial equations has infinitely many solutions and thus the model is unidentifiable.

5 The Taylor series approach

The Taylor series approach is based on the Taylor series expansion of the observation functions around $t = 0$

$$y_i(t) = y_i(0) + t y_i'(0) + \frac{t^2}{2!} y_i^{(2)}(0) + \dots .$$

The successive derivatives $y_i^{(j)}(0)$ are assumed measurable and contain information about the parameter vector p. The idea is to study the number of possible solutions for the parameter vector from knowledge of each term of the Taylor series, namely the solutions with respect to p of the system of polynomials $y_i^{(j)}(0) = \alpha_j$ where the α_j's are known. In particular the parameter vector is locally identifiable if the set of solutions is finite, it is globally identifiable if there is a unique solution, otherwise it is unidentifiable. To determine the upper bound on the number of successive derivatives of $y(t,p)$ needed, however, becomes a problem. According to Chappell et al. [2] the following upper bounds have been established:

$2n - 1$ for linear systems [25],

$2^{2n} - 1$ for bilinear systems [26],

$(q^{2n} - 1)/(q - 1)$ for homogeneous polynomial systems, where q is the degree of the polynomials [26].

One of the main results presented here is an upper bound for a generic state-space model of the form in (1), equivalently (5), obtained with differential algebra methods. Let $L_f h(x(0), p, u)$ be the Lie-derivative $L_f h(x, p, u)$ in which the initial conditions $x(0)$ is used instead of x. Next consider $y^{(j)}(0) - L_f^{(j)} g(x(0), p)$, for $j = 0, 1, \dots,$ instead of successive derivatives.

This will not effect the Taylor series analysis but enables us to avoid the derivatives of the state variables x. Consider the ideal $J(e_1, \ldots, e_m)$ generated by

$$y_i(0) - g_i(x(0), p), \ldots, y_i^{(e_i)}(0) - L_f^{e_i} g_i(x(0), p), \qquad (11)$$

for $i = 1, \ldots, m$. The proofs of the following theorems are given in [18].

Theorem 4 *Consider the characteristic set of the model ideal I with respect to the ranking $u << y << p < x$ given in Theorem 2, Equations (7). Let:*

1. *$y_i^{(e_i)}$ be the leader of A_i, $i = 1, \ldots, m$,*
2. *T be a characteristic set of $J(e_1, \ldots, e_m)$ with respect to the ranking $u << y << p$,*
3. *X be the set of ranks of T and Y be the set of leaders of T.*

Then three situations can arise.

(i) If there exists an index i such that the parameter p_i is not a leader of T, i.e. $p_i \notin Y$, then the model is not structurally identifiable for any p.

(ii) If all parameters p_i are ranks of T, i.e. $p_i \in X$, $i = 1, \ldots, l$, then the model is globally structurally identifiable at p.

(iii) If all parameters p_j are in Y, but p_i is not in X, for some i, then the model is locally structurally identifiable at p_i.

Theorem 5 *For $m = 1$, the single output model, $n + l$ derivatives are sufficient to determine the identifiability structure with the Taylor series method, that is, it is enough to consider $J(n + l)$, where n is the number of state variables in the polynomial model (2).*

Example 3 Consider again Model (3) with the initial conditions $x_1(0) = 1, x_2(0) = 0$ and $n+l = 6$. The set $J(6)$, that contains the first six derivatives of y, is

$$\begin{aligned}
\{\ & y - 1, \\
& y' - p_1, \\
& y'' - 2p_1^2 - p_2p_3, \\
& y^{(3)} - 6p_1^3 - 6p_1p_2p_3 - p_3p_2p_4, \\
& y^{(4)} - 24p_1^4 - p_3p_4^2p_2 - 9p_1p_3p_2p_4 - 36p_1^2p_2p_3 - 5p_3^2p_2^2, \\
& y^{(5)} - 13p_1p_3p_4^2p_2 - 78p_1p_3^2p_2^2 - 72p_1^2p_3p_2p_4 - 240p_1^3p_2p_3 - 17p_3^2p_2^2p_4 \\
& \quad -p_3p_4^3p_2 - 120p_1^5, \\
& y^{(6)} - 1800p_1^4p_2p_3 - p_3p_4^4p_2 - 137p_1^2p_3p_4^2p_2 - 960p_1^2p_3^2p_2^2 - 720p_1^6 - 61p_3^3p_2^3 \\
& \quad -600p_1^3p_3p_2p_4 - 18p_1p_3p_4^3p_2 - 44p_3^2p_2^2p_4^2 - 342p_1p_3^2p_2^2p_4\ \}.
\end{aligned}$$

The model is unidentifiable because the parameters p_2 and p_3 always appear as the product $p_2 p_3$ and cannot be written in regression form. Again Gröbner bases will allow us to formalise this intuitive idea.

5.1 Algorithm 2

The principal steps of the proposed algorithm for the Taylor series approach are as follows.

1. Rewrite the model to a differential polynomial formulation.

2. Find non-negative integers $(e_1, \ldots, e_m)$ such that $y_i^{(e_i)}$ is one of the leaders of the characteristic set with respect to the ranking $u << y << p < x$ of the differential ideal I.

3. Construct the set

$$J(e_1, \ldots, e_m) = \Big\{ y_i - g_i(x(0), p), \ldots, y_i^{(e_i)} - L_f^{e_i} g_i(x(0), p) : \text{for } i = 1, \ldots, m \}$$

4. Compute a characteristic set with respect to the ranking $u << y << p$ of $J(e_1, \ldots, e_m)$. If it is not possible to compute a characteristic set of the ideal $J(e_1, \ldots, e_m)$ because the computations are too complex then go to Step 5.

5. Chose at random a numerical point p^0 in the space Ω of the admissible parameters and evaluate each polynomial in the set $J(e_1, \ldots, e_m)$ at p^0. Set each polynomial equal to its corresponding numerical value and consider the set Φ of the obtained equations.

6. Compute the Gröbner basis of the set Φ and find the number of solutions for each parameter. For almost all points p^0, if the system has infinite solutions, finite but more than one solution or only one solution, the model is unidentifiable, locally identifiable or globally identifiable respectively.

There are two main differences between this and the algorithm in Section 4, one a consequence of the other. The first one is in the choice of the ranking and the second one is the characteristic set derived. Note that the rationales behind the algorithms are different as in Algorithm 2 the initial conditions are used. Note also that in general Algorithm 2 uses more derivatives of the output function y.

The characteristic set of Step 2 can be computed in Maple with the package `diffalg`. The computations of the characteristic set can be very difficult to perform and note that only the numbers $e_1, \ldots, e_m$ are necessary for the algorithm. If it is not possible to find such a characteristic set then Step 2 can be avoided in several ways, as follows.

It is known that

$$\sum_{i=1}^{m} e_i \leq n + l \tag{12}$$

(see [11]) where l is the number of the parameters and n is the number of the states in the polynomial formulation. In particular $e_i \leq n + l$.

In the single output case, $m = 1$, by Theorem 4 we can chose $e_1 = n + l$.

In the case of more outputs, divide $n + l$ by m, i.e. $n + l = qm + r$ and $r < m$. Then define e_i^0 for all $i = 1, \dots, m$ as follows:

$$\begin{array}{ll} \text{if } r = 0 & \text{then } e_i^0 = q \text{ for } i = 1, \dots, m, \\ \text{if } r \neq 0 & \text{then } e_i^0 = \begin{cases} q & \text{for } i = 1, \dots, r \\ q + 1 & \text{for } i = r + 1, \dots, m. \end{cases} \end{array}$$

It is reasonable to chose the above values as there exists a j such that $e_j \leq e_j^0$ and then $\sum_{i=1}^{m} e_i^0 = n + l$ [18]. Then a characteristic set for $J(e_1^0, \dots, e_m^0)$ is computed and the lowest leader $y_t^{(s)}$ $(s > 0)$ found. It follows that $e_i \geq s$ for all $i = 1, \dots, m$. Furthermore from the other derivatives of y that are leaders and from Equation (12) it is possible to find an integer b_i, for all $i = 1, \dots, m$, as small as possible such that $e_i \leq b_i$.

Algorithm 2 has been implemented in Maple V Release 5 and can be found in [19]. The computation of the characteristic set in Step 4 is performed using the package `charset`.

6 Case Study 1

Consider the following model that has been derived to model the interaction of E.coli and somatic cells during persistent and acute bovine mastitis (Dörte Döpfer 2000 [7])

$$\begin{cases} x_1' = p_1 x_1 - \dfrac{p_2 x_1 x_2}{x_1 + p_3} \\ x_2' = \left(1 - \dfrac{x_2}{K(x_1)}\right) x_2 \left(p_7 + p_8 x_1\right) \\ x_1(0) = x_1^0 \\ x_2(0) = x_2^0 \\ y_1 = x_1 \\ y_2 = x_2 \end{cases} \tag{13}$$

where $K(x_1) = p_4 - \dfrac{p_5(p_4 - p_6)}{x_1 + p_5}$, $x_1^0, x_2^0 \geq 0$ and the parameter set is $\{p_1 \dots, p_8\}$.

The first two equations can be rewritten as

$$\begin{aligned} x_1' &= p_1x_1 - p_2x_2 + \frac{p_3p_2x_2}{x_1+p_3}, \\ x_2' &= \frac{(p_4x_1+p_5p_6-x_2x_1-x_2p_5)x_2(p_7+p_8x_1)}{p_4x_1+p_5p_6}. \end{aligned}$$

As there are two different denominators, it is convenient from a computational point of view to introduce two new variables, one for each denominator. Thus the set of differential equations becomes

$$\begin{aligned} x_1' &= p_1x_1 - p_2x_2 + p_3p_2x_2x_3 \\ x_2' &= (p_4x_1+p_5p_6-x_2x_1-x_2p_5)x_2(p_7+p_8x_1)x_4 \\ x_3' &= -x_3^2x_1' \\ x_4' &= -p_4x_4^2x_1'. \end{aligned}$$

We use Algorithm 1 to determine the differential polynomials involving the derivatives of the observations $y_1 = x_1$ and $y_2 = x_2$ and the parameters. We obtain the following six polynomials of which only the first two polynomials are input/output relations:

$$\begin{aligned} T_1 &= -y_{11}y_{21}p_3p_2 + \boxed{y_{11}^3} + y_{20}p_3p_2y_{12} - y_{20}y_{11}p_1p_3p_2 + 2y_{20}y_{11}^2p_2 \\ &\quad + y_{20}^2{p_2}^2y_{11} - 2y_{10}y_{11}^2p_1 + y_{10}p_1y_{21}p_3p_2 - 2y_{10}y_{20}p_1y_{11}p_2 + y_{10}^2{p_1}^2y_{11} \\ T_2 &= -y_{11}y_{21}^2p_4 + y_{21}^2p_5p_6p_7 - y_{20}y_{22}p_5p_6p_7 - 2y_{20}y_{21}^2p_5p_7 + y_{20}y_{11}y_{21}p_4p_7 \\ &\quad + y_{20}y_{11}y_{21}p_5p_6p_8 + y_{20}^2y_{22}p_5p_7 - y_{20}^2y_{11}y_{21}p_5p_8 - y_{20}^2y_{11}y_{21}p_7 \\ &\quad + y_{10}y_{21}^2p_5p_6p_8 + y_{10}y_{21}^2p_4p_7 - 2y_{10}y_{20}y_{21}^2p_5p_8 - y_{10}y_{20}y_{22}p_4p_7 \\ &\quad - y_{10}y_{20}y_{22}p_5p_6p_8 - 2y_{10}y_{20}y_{21}^2p_7 + 2y_{10}y_{20}y_{11}y_{21}p_4p_8 + y_{10}y_{20}^2y_{22}p_5p_8 \\ &\quad + y_{10}y_{20}^2y_{22}p_7 - \boxed{2y_{10}y_{20}^2y_{11}y_{21}p_8} + y_{10}^2y_{21}^2p_4p_8 - y_{10}^2y_{20}y_{22}p_4p_8 \\ &\quad - 2y_{10}^2y_{20}y_{21}^2p_8 + y_{10}^2y_{20}^2y_{22}p_8 \\ T_3 &= y_{10} - x_1 \\ T_4 &= y_{20} - x_2 \\ T_5 &= y_{11} - p_1y_{10} + p_2y_{20} - p_3p_2y_{20}x_3 \\ T_6 &= y_{21} - y_{20}x_4p_4y_{10}p_7 - y_{20}x_4p_4{y_{10}}^2p_8 - y_{20}x_4p_5p_6p_7 - y_{20}x_4p_5p_6p_8y_{10} \\ &\quad + {y_{20}}^2x_4y_{10}p_7 + {y_{20}}^2x_4{y_{10}}^2p_8 + {y_{20}}^2x_4p_5p_7 + {y_{20}}^2x_4p_5p_8y_{10}. \end{aligned}$$

The symbol y_{ij} stands for the jth derivative of the ith variable. For example y_{20} is y_2 and y_{21} is y_2'.

Next we consider the leading terms of T_1 and T_2 with respect to the term-ordering $y_{22} > y_{12} > y_{21} > y_{11} > y_{20} > y_{10}$ according to Theorem 3. The leading monomial of T_1 is y_{11}^3 and of T_2 is $y_{10}y_{20}^2y_{11}y_{21}$ with leading coefficients 1 and $2p_8$ respectively. The coefficients of T_1 and $T_2/(2p_8)$ give a basis for the identifiable quantities. The coefficients of T_1 are

$$-p_1p_3p_2, \quad -p_3p_2, \quad -2p_1p_2, \quad p_1p_3p_2, \quad 1, \quad 2p_2, \quad p_2^2, \quad -2p_1, \quad p_1^2, \quad p_3p_2$$

and the coefficients of $T_2/(2p_8)$ are the following seventeen relationships

$$\begin{array}{lll}
-\dfrac{1}{2}p_4, & \dfrac{1}{2}\dfrac{p_5p_6p_7}{p_8}, & \dfrac{1}{2}p_4, \\
-\dfrac{1}{2}, & -\dfrac{1}{2}\dfrac{p_5p_6p_7}{p_8}, & -\dfrac{p_7}{2p_8}+\dfrac{p_5}{2}, \\
\dfrac{p_5p_7}{p_8}, & -\dfrac{1}{2}\dfrac{p_5p_7}{p_8}, & -\dfrac{p_4p_7}{2p_8}+\dfrac{p_5p_6}{2}, \\
\dfrac{p_7}{p_8}+p_5, & \dfrac{p_4p_7}{2p_8}+\dfrac{p_5p_6}{2}, & -\dfrac{p_4p_7}{2p_8}+\dfrac{p_5p_6}{2}, \\
\dfrac{p_7}{2p_8}+\dfrac{p_5}{2}, & 1, & -p_4, \\
1, & \dfrac{1}{2}\dfrac{p_4}{p_8}. &
\end{array}$$

Notice that some of the relationships above are redundant as they are either repeated or easily deduced from other relationships. In this example we included them all for completeness. A minimal generating set for "the T_1 coefficients" is

$$A_1 = -2p_1, \quad A_2 = 2p_2, \quad A_3 = -p_3p_2.$$

There we mean generating set in the sense of polynomial ideals. For example the coefficient $p_1p_2p_3$ can be rewritten using ideal operations as $A_1A_3/2$. The parameters p_1, p_2, p_3 are identifiable because p_1 appears in the coefficient A_1, p_2 in A_2. The identifiability of p_3 follows from A_3 as p_2 is identifiable.

The analysis of the $T_2/(2p_8)$ coefficients is slightly more complicated. We still perform it by hand. Clearly p_4 is identifiable as it appears alone in a coefficient expression. The identifiability of p_8 follows from the last relationship. The parameter p_6 is identifiable as it comes from the ratio of the second and eighth relationships. The parameter p_7 can be written in terms of identifiable quantities as

$$p_7 = \frac{\dfrac{-p_5p_7}{2p_8}\left(\dfrac{p_5p_6}{2}+\dfrac{p_4p_7}{2p_8}\right)+\left(\dfrac{p_7}{2p_8}+\dfrac{p_5}{2}\right)\left(\dfrac{p_5p_6p_7}{2p_8}\right)}{\left(\dfrac{-p_5p_7}{2p_8}\right)\left(\dfrac{p_4}{2p_8}\right)+\left(\dfrac{p_5p_6p_7}{2p_8}\right)}$$

and p_5 is identifiable from the second coefficient. In conclusion the model in Equation (13) is globally identifiable.

6.1 Coefficient analysis

In this section we detail Item 4 of Algorithm 1 and Items 5 and 6 of Algorithm 2 using the above example. We concentrate on the analysis of the second set of coefficients, those involving the parameters $p_4, \dots, p_8$.

For each "$T_2/(2p_8)$ coefficient" (excluding the two 1 values) a new variable c_i, $i = 1, \ldots, 17$ is introduced. Thus the c_i's are a basis for the set of identifiable quantities. In this way a map $\mathcal{M}$ from $\mathbf{R}[p_4, \ldots, p_8]$ into $\mathbf{R}[c_1, \ldots, c_{17}]$ has been defined. The aim is to invert this map. If we can express each parameter in terms of $c_1, \ldots, c_{17}$ then the model is globally identifiable. If the map is only locally invertible, then the model is locally identifiable and if the map is not invertible then the model is unidentifiable. The first three relationships are as follows

$$-\frac{1}{2}p_4 - c_1, \quad \frac{1}{2}\frac{p_5p_6p_7}{p_8} - c_2, \quad \frac{1}{2}p_4 - c_3, \quad \ldots \tag{14}$$

The invertibility of the complete map is here performed using a symbolic computation method from algebraic geometry based on Gröbner bases with respect to the lexicographic term-ordering. A general reference to the theory of Gröbner bases for polynomials is [4]. Here we simply say that given a set of polynomials and a ranking, Gröbner bases are special representation of the set of polynomials with respect to the ranking. That is the system of polynomial equations obtained by setting to zero the elements of the Gröbner basis has the same solutions as the original set of polynomials. Moreover each polynomial in the original set can be rewritten as a polynomial combination of elements of a Gröbner basis, and vice-versa. In particular the Gröbner basis with respect to a lexicographic term-ordering rewrites the original system of equations in a triangular form. From this form it is easier to check whether the corresponding system of polynomial equations admits solutions and it can be solved by backwards substitution.

The study of the invertibility of the map $\mathcal{M}$ is a specialisation of the above arguments. Firstly we multiply the set in (14) by $2p_8$ in order to have polynomials instead of rational polynomials and add the equation $1 - p_8T$ to record the fact that p_8 cannot be zero. We obtain the set of polynomials in (15)

$$\begin{array}{lll}
-p_4 - 2c_1, & p_5p_6p_7 - 2c_2p_8, & p_4 - 2c_3, \\
-1 - 2c_4, & -p_5p_6p_7 - 2c_5p_8, & -p_7 - p_5p_8 - 2c_6p_8, \\
p_5p_7 - c_7p_8, & -p_5p_7 - 2c_8p_8, & -p_4p_7 - p_5p_6p_8 - 2c_9p_8, \\
p_7 + p_5p_8 - c_{10}p_8, & p_4p_7 + p_5p_6p_8 - 2c_{11}p_8, & -p_4p_7 - p_5p_6p_8 - 2c_{12}p_8, \\
p_7 + p_5p_8 - 2c_{13}p_8, & 1 - c_{14}, & -p_4 - c_{15}, \\
1 - c_{16}, & p_4 - 2c_{17}p_8, & 1 - p_8T.
\end{array} \tag{15}$$

Next we consider (15) as a set of polynomials in T, $p_4, \ldots, p_8$ and $c_1, \ldots, c_{17}$. Its Gröbner basis with respect to the lexicographic ordering for which $T > p_4 > \ldots > p_8 > c_1 \ldots > c_{17}$ (which is an elimination ordering of the T variable) is given by the polynomials in (16) below

$$\begin{array}{llll}
Tp_7 + p_5 - 2c_{13}, & -1 + p_8 T, & 2c_{17} + Tc_{15}, & \boxed{p_4 + c_{15}}, \\
-2c_8 + {p_5}^2 - 2p_5 c_{13}, & \boxed{2c_{12} + 2c_{17}p_7 + p_5 p_6}, & p_5 p_7 + 2c_8 p_8, & p_7 + p_5 p_8 - 2c_{13}p_8, \\
2c_8 c_{12} + 2c_8 c_{17} p_7 + c_5 p_5, & \multicolumn{3}{l}{c_8 c_{15} + c_5 - 2c_{13}c_{17}p_7 + c_{12}p_5 - 2c_{13}c_{12},} \\
p_5 c_{15} - 2c_{17}p_7 - 2c_{13}c_{15}, & \multicolumn{3}{l}{p_6 p_7 - 2p_6 c_{13} p_8 + c_{15}p_7 - 2c_{12}p_8,} \\
\multicolumn{4}{l}{2c_{13}c_{15}c_{12} - 2{c_{12}}^2 + {c_{15}}^2 c_8 + 2c_5 c_{15} + 2{c_{13}}^2 c_{15} p_6 - 2c_{12}p_6 c_{13} + p_6 c_5,} \\
\boxed{-c_5 + p_6 c_8}, & \multicolumn{3}{l}{-2c_8 {p_8}^2 + {p_7}^2 - 2p_7 c_{13} p_8,} \\
\multicolumn{4}{l}{\boxed{c_8 c_{15} p_7 - 2c_8 c_{12} p_8 + p_7 c_5 - 2c_5 c_{13} p_8},} \\
\multicolumn{2}{l}{-c_5 p_8 - p_7 c_{13} c_{15} + c_{12} p_7 - c_{15} c_8 p_8,} & \boxed{2c_{17}p_8 + c_{15}}, & \\
-c_{15} + 2c_1, & c_5 + c_2, & c_{15} + 2c_3, & 1 + 2c_4 \\
\multicolumn{4}{l}{2c_{13}c_8 c_{15} c_{12} - 2c_8 {c_{12}}^2 + {c_8}^2 {c_{15}}^2 + 2{c_{13}}^2 c_{15} c_5 - 2c_{12}c_{13}c_5 + 2c_5 c_8 c_{15} + {c_5}^2,} \\
c_{13} + c_6, & 2c_8 + c_7, & -c_{12} + c_9, & -2c_{13} + c_{10} \\
c_{12} + c_{11}, & -1 + c_{14}, & -1 + c_{16}. &
\end{array} \tag{16}$$

From the fourth polynomial of (16) we have that p_4 is identifiable as we can write $p_4 = -c_{15}$. From the fourteenth polynomial of (16) we have that p_6 is identifiable as $p_6 = c_5/c_8$. From the eighteenth polynomial we have that p_8 is identifiable as $p_8 = c_{15}/2c_{17}$. The identifiability of p_7 follows from the sixteenth polynomial as p_8 is identifiable and

$$p_7 = \frac{2c_8 c_{12} p_8 + 2c_5 c_{13} p_8}{c_5 + c_8 c_{15}}.$$

Note that $c_5 + c_8 c_{15} = 0$ occurs when $p_5 p_6 p_7 (p_6 - p_4) = 0$. That is either when $p_5 = 0$, $p_6 = 0$, $p_7 = 0$ or $p_4 = p_6$. All these cases cannot happen as the parameters are supposed to be positive and distinct. In general the set where as above zero denominators occurs has Lebesgue measure zero. Finally the identifiability of p_5 follows from the sixth polynomial $p_5 = (c_{12} - c_{13}p_7)/p_6$ as both p_7 and p_6 are identifiable. In conclusion the model is globally structurally identifiable.

In theory the computation of a lexicographic Gröbner basis is always possible. But in some cases it is too computationally intensive. An alternative method to study the invertibility of the map $\mathcal{M}$ with Gröbner basis methods is as in Items 5 and 6 of Algorithm 2. Some values for the parameters are chosen randomly within the admissible region, namely $p_1^0 = 123$, $p_2^0 = 345$, $p_3^0 = 789$, $p_4^0 = 1983$, $p_5^0 = 6753$, $p_6^0 = 9803$, $p_7^0 = 121$ and $p_8^0 = 88912$. The corresponding Gröbner basis is

$$\begin{array}{lllll}
\{ \quad -1 + 24202290960T, & p_1 - 123, & p_2 - 345, & -789 + p_3, & \\
\quad\; p_4 - 1983, & p_5 - 6753, & p_6 - 9803, & p_7 - 121, & p_8 - 88912 \quad \}
\end{array}$$

where again T is the product of the denominators.

If in p^0 we had chosen equal values for p_4 and p_6 then the Gröbner basis method would have returned that the model is unidentifiable. For example

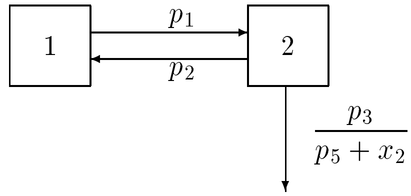

Figure 1: A two compartment model with Michaelis-Menten elimination kinetics.

for the point $p_1^0 = 8, p_2^0 = 33, p_3^0 = 7, p_4^0 = 345, p_5^0 = 13, p_6^0 = 345, p_7^0 = 22, p_8^0 = 12$ the Gröbner basis below has an infinite number of solutions as p_3 is missing

$$\{-1 + 396T,\ \ p_1 - 8,\ \ -33 + p_2,\ \ p_4 - 345,\ \ p_5 - 13,\ \ p_7 - 22,\ \ p_8 - 12\}\,.$$

A way to prevent the miss-determination of identifiability because of a bad choice of the point $p^{(0)}$ is by trying a full grid of points.

For the application of Algorithm 2 we have assumed that $x_1(0) = 1$ and $x_2(0) = 1$. But the computation was too intensive for the platform and the software used and the result crashed. The experiment was performed in Maple V Release 5 under a OS Solaris SparcStation 4. This is a further confirmation that algorithms to study identifiability are efficient for some models but not for other models.

7 Case Study 2

Consider the pharmacokinetic model studied in [12] and shown in Figure 1. The state-space equations of the system are

$$\begin{cases} x_1' = -p_1 x_1 + p_2 x_2 \\ x_2' = p_1 x_1 - \dfrac{p_3 x_2}{p_4 + x_2} - p_2 x_2 \\ x_1(0) = a \\ x_2(0) = 0. \end{cases}$$

First the system is reformulated as follows

$$\begin{cases} x_1' = -p_1 x_1 + p_2 x_2 \\ x_2' = p_1 x_1 - p_2 x_2 - p_3 x_2 x_3 \\ x_3' = -p_1 x_1 x_3^2 + p_2 x_2 x_3^2 + p_3 x_2 x_3^3 \\ x_1(0) = a \\ x_2(0) = 0 \\ x_3(0) = p_5 \end{cases}$$

where $x_3 = \dfrac{1}{p_4 + x_2}$. Furthermore, $p_5 = \dfrac{1}{p_4}$ so that if the parameter p_5 is identifiable then the same holds for the parameter p_4 in the original model.

A first experiment consists of observing compartment 1 only, that is $y = x_1$. The initial condition, a is assumed to be known and the set of unknown parameters is $\{p_1, p_2, p_3, p_5\}$.

By Theorem 5 it is sufficient to consider the ideal $J(5)$ and the polynomials of $J(5)$ of interest are

$$
\begin{aligned}
& y' + \boxed{p_1} a, \\
& a y^{(2)} + y' a \boxed{p_2} - (y')^2, \\
& y' a^3 (-(y')^3 y^{(4)} - (y^{(2)})^3 y' + 2(y')^2 y^{(3)} y^{(2)} - y' a (y^{(3)})^2 \\
& \qquad + a y^{(2)} y' y^{(4)}) \boxed{p_3} + y' a^3 (2a (y^{(2)})^4 - 4 y' a y^{(3)} (y^{(2)})^2 \\
& \qquad + 2(y')^2 a (y^{(3)})^2), \\
& y' a^4 (-2(y')^4 (y^{(3)})^2 + 2a (y')^2 (y^{(3)})^2 y^{(2)} + 4(y')^3 y^{(3)} (y^{(2)})^2 - 4 a y' y^{(3)} (y^{(2)})^3 \\
& \qquad - 2(y')^2 (y^{(2)})^4 + 2a (y^{(2)})^5) \boxed{p_5} + y' a^4 (-(y^{(2)})^5 \\
& \qquad + y^{(4)} (y')^3 y^{(3)} + a (y^{(2)})^3 y^{(4)} - y^{(4)} (y')^2 (y^{(2)})^2 \\
& \qquad - 2 (y^{(3)})^2 y^{(2)} (y')^2 + 3 y^{(3)} (y^{(2)})^3 y' + y' a (y^{(3)})^3 \\
& \qquad - a (y^{(3)})^2 (y^{(2)})^2 - y' a y^{(2)} y^{(4)} y^{(3)})
\end{aligned}
$$

Global identifiability follows readily.

A second experiment is considered as in [12] and compartment 2 is observed, that is $y = x_2$ and with initial conditions $x_1(0) = 0$ and $x_2(0) = 3$.

The computation of the characteristic set for Algorithm 2 did not produce a result as it proved computationally too intensive. Then we perform Steps 5-6, select the point $p^0 = (345, 657, 879, 876)$ and compute the Gröbner basis

$$\{p_1 - 345, \;\; p_2 - 657, \;\; p_3 - 879, \;\; p_5 - 876\}\,.$$

The system has one solution, thus, with probability one, the model is globally identifiable. Where possible we prefer the computation of the characteristic set rather than performing Steps 5-6 of Algorithm 2. This is because the characteristic set also gives information (although indirect) on where the model is unidentifiable and it shows which specific parameters are unidentifiable.

This case study has shown that, in some cases, as for the first experiment, the computation of the characteristic set requires a few seconds while for others, as in the second experiment, which is superficially very similar, it can prove very difficult.

8 Examples

Example 4 The non-linear differential equations

$$\begin{cases} x_1' = \dfrac{p_1 x_2}{p_2 + x_2} x_1 - p_3 x_1 \\ x_2' = -p_4 \dfrac{p_1 x_2}{p_2 + x_2} x_1 \\ x_1(0) = a \\ x_2(0) = b \end{cases}$$

have been used to describe microbial growth in a batch reactor [13], [14]. Both x_1 and x_2 are observed, that is $y_1 = x_1$ and $y_2 = x_2$ and an identifiability analysis of the unknown parameters $\{p_1, p_2, p_3, p_4\}$ is required.

By introducing the state variable $x_3 = \dfrac{1}{p_2 + x_2}$ the system becomes

$$\begin{cases} x_1' = p_1 x_1 x_2 x_3 - p_3 x_1 \\ x_2' = -p_1 p_4 x_1 x_2 x_3 \\ x_3' = p_1 p_4 x_1 x_2 x_3^3 \\ y_1 = x_1 \\ y_2 = x_2 \\ x_1(0) = a \\ x_2(0) = b \\ x_3(0) = p_5 \end{cases}$$

where $p_5 = \dfrac{1}{p_2 + b}$. The unknown parameter set becomes $\{p_1, p_3, p_4, p_5\}$. We perform the steps of Algorithm 2 automatically using Maple. The following polynomials of the characteristic set are linear in p_1, p_3, p_4 and p_5 respectively:

$$(a^2 b {y_{22}}^2 - 2ab y_{22} y_{21} y_{11} + {y_{21}}^2 {y_{11}}^2 b - a^2 y_{22} {y_{21}}^2 + a {y_{21}}^3 y_{11}) {y_{21}}^3 \boxed{p_1} \\ + {y_{21}}^3 (-{y_{21}}^3 {y_{11}}^2 + {y_{21}}^3 a y_{12}),$$

$${y_{21}}^5 a (y_{21} y_{11} - a y_{22}) \boxed{p_3} + {y_{21}}^5 a (-y_{22} y_{11} + y_{21} y_{12}),$$

$${y_{21}}^6 (a y_{12} - {y_{11}}^2) \boxed{p_4} + {y_{21}}^6 (-y_{21} y_{11} + a y_{22}),$$

$${y_{21}}^6 (-{y_{21}}^2 a^2 y_{12} b + {y_{11}}^2 {y_{21}}^2 ab) \boxed{p_5} + {y_{21}}^6 (-a^2 y_{12} b y_{22} + y_{21} a y_{12} y_{11} b \\ + {y_{21}}^2 a^2 y_{12} + {y_{11}}^2 ab y_{22} - {y_{11}}^3 y_{21} b - {y_{11}}^2 {y_{21}}^2 a)$$

and thus the parameters p_1, p_3, p_4, p_5 are globally identifiable. Hence in the original model p_1, p_2, p_3, p_4 are globally identifiable and the model is globally identifiable.

Example 5 Let us consider the one-compartment model with non-linear Michaelis-Menten elimination shown in Figure 2 and presented in [2]. The state-space equations are

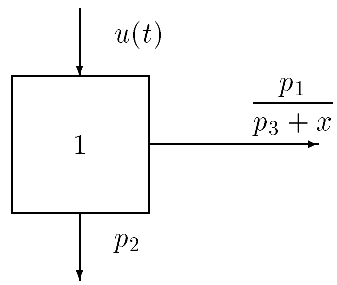

Figure 2: One-compartment model with parallel linear and non-linear elimination pathways

$$\begin{cases} x' = -\dfrac{p_1 x}{p_3 + x} - p_2 x \\ x(0) = a. \end{cases}$$

We rewrite them as follows

$$\begin{cases} x_1' = -p_1 x_1 x_2 - p_2 x_1 \\ x_2' = p_1 x_1 x_2^3 + p_2 x_1 x_2^2 \\ x_1(0) = a \\ x_2(0) = p_4 \end{cases}$$

with $x_1 = x$, $x_2 = \dfrac{1}{p_3 + x_1}$ and $p_4 = \dfrac{1}{p_3 + a}$. Only x_1 is observed, $y = x_1$ and the unknown parameter set is $\{p_1, p_2, p_4\}$. Applying Algorithm 2 yields

$$(2a^2 y_2 {y_1}^2 - 2a{y_1}^4)\boxed{p_4} + y_1 a^2 y_3 + 2{y_1}^4 - 2a y_2 {y_1}^2 - a^2 {y_2}^2,$$

$$\begin{aligned}&(a^4 {y_1}^2 {y_3}^2 + 4 y_3 {y_1}^5 a^2 - 4 y_3 y_2 {y_1}^3 a^3 - 2 y_3 {y_2}^2 y_1 a^4 + 4{y_1}^8 - 8{y_1}^6 a y_2 \\ &\quad + 4a^3 {y_2}^3 {y_1}^2 + a^4 {y_2}^4)\boxed{p_1} - 4a^3 {y_2}^3 {y_1}^3 + 12 a^2 {y_2}^2 {y_1}^5 - 12 a y_2 {y_1}^7 + 4{y_1}^9,\end{aligned}$$

$$a(y_1 a^2 y_3 + 2{y_1}^4 - 2a y_2 {y_1}^2 - a^2 {y_2}^2)\boxed{p_2} + a(-3{y_2}^2 y_1 a + 2 y_2 {y_1}^3 + {y_1}^2 a y_3).$$

From these linear equations in the p_i's we deduce that the model is globally identifiable.

We now consider the case of non-zero input u and zero initial conditions. An alternative and equivalent way to rewrite the model equations is by defining $x_2 = \dfrac{1}{1 + \frac{x_1}{p_3}}$ and $p_4 = \frac{1}{p_3}$. Thus the polynomials for which the characteristic set is computed are

$$x_1' + p_1 - p_1 x_2 + p_2 x_1 - u, \quad x_2' - p_4 p_1 x_2^2 + p_1 p_4 x_2^3 - p_4 p_2 x_1 x_2^2 + u p_4 x_2^2$$

and the initial condition for $x_2(0)$ is one. Algorithm 1 returns only one polynomial

$$\begin{array}{l}
-y_1p_4p_1^2+2y'p_1y^2p_2p_4-2y'p_1-yp_4u-y^3{p_2}^3p_4y'p_4u^2+2-{y'}^2p_4u+4y'up_4yp_2\\
+2uy^2{p_2}^2p_4+p_1{y'}^2yp_4-p_4{y'}^3+y^3{p_2}^2p_1p_4+p_1yp_4u^2-u^2p_4yp_2+2up_1p_4yp_2\\
-4y'p_1p_4yp_2-3{y'}^2p_4yp_2-2p_1p_4{y'}^2+2y^2p_2{p_1}^2p_4+2y'p_1p_4u+2y'{p_1}^2yp_4\\
-2y^2{p_2}^2p_1p_4+yp_4{p_1}^3-2yp_4{p_1}^2u+u'p_1-3y'y^2{p_2}^2p_4-2up_1y^2p_2p_4-y'p_2p_1\\
-yp_4{p_1}^2p_2-p_1y^{(2)}
\end{array}$$

with coefficients (divided by the leading term p_1)

$$\begin{array}{llll}
\boxed{2p_4}, & \boxed{\dfrac{p_4}{p_1}}, & \dfrac{-{p_2}^2p_4(-p_2+p_1)}{p_1}, & \boxed{-p_4p_1(-p_2+p_1)},\\
p_4p_1+p_2, & \dfrac{p_4}{p_1}, & \dfrac{-2p_4}{p_1}, & -2p_4(p_1-2p_2),\\
-2p_4, & \dfrac{-p_4(-p_2+p_1)}{p_1}, & 2p_4(-p_2+p_1), & \dfrac{2p_4(p_1-2p_2)}{p_1},\\
\dfrac{2p_4p_2(-p_2+p_1)}{p_1}, & \dfrac{-p_4(-3p_2+p_1)}{p_1}, & \dfrac{-p_4p_2(-3p_2+2p_1)}{p_1}, & -2p_4p_2(-p_2+p_1).
\end{array}$$

From the first relationship above we deduce identifiability of p_4, from the second one the identifiability of p_1 and from the fourth one we see that p_2 is identifiable too. Thus we can conclude that the model is globally structurally identifiable. This result is confirmed by applying Algorithm 2: for example for the point $p_1 = 49, p_2 = 889, p_4 = 13$ the Gröbner basis is

$$\{p_4-13,\ \ p_2-889,\ \ -49+p_1\}\,.$$

Example 6 We now consider a purely polynomial model which is an immunological model for mastitis in diary cows introduced in [7]

$$\left\{\begin{array}{lcl} x_1' &=& p_1x_1-p_2x_1x_2\\ x_2' &=& p_3x_2(1-p_4x_2)+p_5x_1x_2. \end{array}\right.$$

If all the variables are observed, that is $y_1 = x_1$ and $y_2 = x_2$ then the model is structurally globally identifiable. Indeed from Algorithm 1 we have the following two polynomials

$$-y_{11}+y_{10}p_1-y_{10}y_{20}p_2,\quad y_{21}-y_{20}p_3+y_{20}^2p_3p_4-y_{10}y_{20}p_5.$$

The coefficient analysis is very straightforward and allows us to deduce global identifiability.

Next, we consider the experiment with only one observation $y_1 = x_1$. There is only one polynomial in the characteristic set of interest, namely:

$$\begin{array}{c}
y_{11}^2p_2+y_{11}^2p_3p_4-y_{10}p_2y_{12}+y_{10}y_{11}p_2p_3-2y_{10}y_{11}p_1p_3p_4\\
+y_{10}^2y_{11}p_2p_5-y_{10}^2p_1p_2p_3+y_{10}^2p_1^2p_3p_4-y_{10}^3p_1p_2p_5
\end{array}$$

and its coefficients divided by the leading term, p_2 are

$$
\begin{array}{lll}
c_1 = 2p_1p_3p_4/p_2 - p_3, & c_2 = 1, & c_3 = -p_5 \\
c_4 = p_1p_3 - p_1^2p_3p_4/p_2, & c_5 = p_1p_5, & c_6 = -1 - p_3p_4/p_2.
\end{array}
$$

The Gröbner basis computed according to Step 4a of Algorithm 1 yields

$$
\begin{array}{l}
\{ -p_3 - c_6p_3 - 4Tp_4c_4 - 4Tc_6p_4c_4 + Tp_4{c_1}^2, \quad 1 + p_2T, \\
-2c_4 - c_1p_1 + p_1p_3, \quad -c_1p_2 + 4p_4c_4 - p_2p_3 + 2p_1p_4c_1, \\
c_5 + \boxed{p_1}c_3, \quad c_1 + p_3 + 2p_1 + 2p_1c_6, \\
4c_4 + 4c_6c_4 - {c_1}^2 + {p_3}^2, \quad c_6p_2 + p_2 + p_3p_4, \\
-4p_4c_4 - 4c_6p_4c_4 + p_4{c_1}^2 + p_2p_3 + c_6p_2p_3, \\
-2c_5 - 2c_6c_5 + c_1c_3 + p_3c_3, \quad 2c_4c_3 - c_1c_5 + \boxed{p_3}c_5, \\
c_3 + \boxed{p_5}, \quad -{p_2}^2 - 2c_6{p_2}^2 - {c_6}^2{p_2}^2 - 4{p_4}^2c_4 - 4{p_4}^2c_6c_4 + {p_4}^2{c_1}^2, \\
-c_3p_2 - c_3c_6p_2 - 2p_4c_5 - 2p_4c_6c_5 + p_4c_1c_3, \\
c_5p_2 + c_6c_5p_2 - 2p_4c_3c_4 + p_4c_1c_5, \\
-c_3c_5p_2 - c_6c_5c_3p_2 - p_4{c_5}^2 - c_6{c_5}^2p_4 + p_4{c_3}^2c_4, \\
-{c_5}^2 - c_6{c_5}^2 - {c_3}^2c_4 + c_1c_3c_5, \quad -1 + c_2 \, \}
\end{array}
$$

where again the variable T takes into account the denominator, $-p_2$.

By performing Steps 4-5 of Algorithm 1, at the point $p_1^0 = 231, p_2^0 = 1999, p_3^0 = 1, p_4^0 = 23122, p_5^0 = 666$ we obtain

$$
23122 + 1999p_4T, \quad -231 + p_1, \quad 23122p_2 - 1999p_4, \quad p_3 - 1, \quad p_5 - 666
$$

and we find a relationship between p_2 and p_4. Thus, knowing p_2 or p_4 would make the model globally structurally identifiable.

For the experiment $y = x_2$ the parameter p_5 is not identifiable. Indeed in the characteristic set there is only the polynomial

$$
\begin{array}{l}
y_{10}y_{12} - y_{11}y_{10}p_1 + y_{11}y_{10}^2(p_2 + p_3p_4) - y_{11}^2 + y_{10}^2p_3p_1 \\
\quad -y_{10}^3(p_3p_2 + p_3p_4p_1) + y_{10}^4p_3p_4p_2.
\end{array}
$$

The coefficients are

$$
-p_1, \quad p_2 + p_3p_4, \quad p_3p_1, \quad -p_3p_2 - p_3p_4p_1, \quad p_3p_4p_2
$$

from which we deduce the identifiability of the parameters p_1, p_2, p_3 and p_4 but p_5 is not identifiable as it does not appear.

Example 7 The following example is similar to Example 6 and the extra variable models intra cellular reservoir (see [7])

$$
\left\{
\begin{array}{l}
x_1' = p_1x_1 - p_2x_1x_2 + p_6x_3 - p_7x_1 \\
x_2' = p_3x_2(1 - p_4x_2) + p_5x_1x_2 \\
x_3' = -p_6x_3 - p_7x_1.
\end{array}
\right.
$$

Both $y_1 = x_1$ and $y_2 = x_2$ are observed. The characteristic set contains the polynomial

$$y_{21} - y_{20}p_3 + y_{20}^2 p_3 p_4 - y_{10}y_{20}p_5$$

with coefficients

$$p_3p_4, \quad 1, \quad -p_5, \quad -p_3$$

and the polynomial

$$\begin{aligned}-y_{12} + y_{10}y_{20}^2 p_2p_3p_4 - y_{10}^2 y_{20}p_2p_5 + y_{11}(p_1 - p_7 - p_6) \\ -y_{11}y_{20}p_2 + y_{10}p_1p_6 - y_{10}y_{20}(p_2p_6 + p_2p_3)\end{aligned}$$

with coefficients

$$p_1 - p_7 - p_6, \quad p_2p_3p_4, \quad -p_2p_5, \quad -p_2, \quad -p_2p_3 - p_6p_2, \quad p_6p_1.$$

By performing Steps 4-5 of Algorithm 1 we deduce the structural global identifiability of the model.

Example 8 We conclude with the model in Equations (6) from Section 3. The set C of Algorithm 1, Step 3, has 114 elements, too many and too long to write here. None of them contain p_4 as expected because p_4 is incorporated in the state variable x_3. Thus p_4 is not identifiable. By the analysis of the set C we deduce that the other parameters are identifiable. Cobelli et al. [5] observes that p_4 can be identified by $x_3(0)$. It is a structural feature of the model that p_4 is problematic to deal with and not structurally globally identifiable in the way discussed in this paper. This is also shown by introducing $x_3(t) = e^{-p_5 t}$. Now the parameter p_4 is in the model equations but it is not in the set C obtained when running Algorithm 1.

9 Conclusions

Differential algebra techniques for non-linear control theory are presented in Fliess (1988) [8] and also by other authors. See the bibliographies in Margaria [19] and at the end of this paper.

In this paper we have presented two methods based on differential algebra techniques to study structural identifiability of biological models expressed in state-space form. We focus on (rational) polynomial systems. (Rational) polynomial systems of first order differential equations are translated into prime differential ideals. Convenient representations (characteristic sets) of these ideals are sought in order to determine identifiability of the original model. As computation in the differential environment is in general computationally intensive, we have developed a polynomial version of the method presented by Ollivier [21]. In addition when computation of the characteristic set in the polynomial ring proves too difficult, in Algorithm 1 the test of identifiability is performed locally at a point chosen randomly and by the

Implicit Function theorem for algebraic varieties the result is valid on the whole space with probability one.

The second algorithm presented is based on the Taylor series method for identifiability. It solves the problem of fixing an upper bound for the number of derivatives required and study the coefficients of the Taylor series expansion using characteristics sets. As typical in identifiability analysis whether to apply Algorithm 1 or 2 depends on the model studied. The authors found Algorithm 1 faster in most cases while Algorithm 2 has the advantage of returning algebraic relationships between the parameters and the identifiable quantities. An issue of interest is the comparison of the performances of the existing algorithms (not only those in this paper) for the study of identifiability.

Details on the implementation of Algorithm 1 and 2 can be found in Margaria [19].

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