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Methods for checking structural identifiability of nonlinear biosystems: A critical comparison.

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Abstract: Model parametric identification is a critical yet often overlooked step for the modelling of biosystems. Modern experimental techniques can be used to obtain time-series data which may then be used to estimate model parameters. However, in many cases, a subset of model parameters may not be uniquely estimated, independently of the quantity and quality of data available or the numerical techniques used for estimation. This lack of identifiability is related to the structure of the model.
This work presents a review and a critical comparison of methods to analyze the structural identifiability of non-linear models. Three examples, of increasing level of complexity, related to the modelling of biochemical networks, will be used to illustrate advantages and disadvantages of the available techniques. Results reveal that the generating series approach combined with the identifiability *tableau* is the most promising to analyze large scale highly nonlinear models.

Keywords: biological models, (structural) identifiability, observability, controllability

1. INTRODUCTION

The analysis of the structure and dynamics of biosystems through data-based mathematical models has received major attention in recent years. Conferring a predictive character on a given mathematical formulation often relies on determining a number of non-measurable parameters that largely condition the response of the model.

However the solution of the so called parameter estimation problem is usually a very challenging task, due to the usual lack of identifiability. The identifiability problem is concerned with the possibility of calculating a unique solution for the parameters given a experimental scheme.

Practical identifiability analysis, which relies on given experimental data, has received significant attention lately (see for example, Hengl et al. [2007], Srinath and Gunawan [2010]) and optimal experimental design techniques have been suggested to improve practical identifiability (Balsa-Canto et al. [2008a]). Sensitivity-based identifiability lies between the structural and practical identifiability, but as this technique needs parameter values Miao et al. [2006], so it will be consider as part of practical identifiability.

Nevertheless the structural identifiability analysis, related to the model structure and possibly to the type of input and independent of the parameter values, has been often disregarded.

There are several reasons to asses structural identifiability. Possibly the most important is that the model parameters have a biological meaning, and we are interested in knowing whether it is possible to determine their values from experimental data. In fact several authors have reported difficulties in assessing unique and meaningful values for the parameters in the context of biosystems (see for example, Lipniacki et al. [2004], Brown et al. [2004], Achard and Schutter [2006], Piazza et al. [2008], among others).

There are a few methods for testing the structural identifiability of general nonlinear models. However there is no method amenable to every model, thus at some point we have to face the selection of one of the possibilities. Section 2 presents a review of available methods. For the sake of brevity, the most relevant or promising are discussed in more detail. Through the analysis of three illustrative examples related to biological networks - the Goodwin oscillator model (Goodwin [1965]) which describes oscillations in enzyme kinetics, the model of a glycolysis inspired metabolic pathway Bartl et al. [2010] and the model of the circadian clock of the Arabidopsis thaliana proposed by Locke et al. [2005]- the most promising techniques are critically compared in Section 3. Advantages and disadvantages of the different methods are discussed in Section 4.

2. STRUCTURAL IDENTIFIABILITY ANALYSIS

2.1 Structural identifiability definition

Currently, the most typical approach to representing biosystems is through a set of coupled deterministic ordinary differential equations as follows:

$$\Sigma(p) \begin{cases} \dot{x}(t) = f(x(t),p) + g(x(t),p)u(t),\ x(t_0) = x_0(p) \\ y(t,p) = h(x(t),p), \end{cases} \quad (1)$$

where $x \in \mathbf{R}^n$ is the $n-$dimensional state variable, $u \in \mathbf{R}^m$ a $m-$dimensional input (control) vector of smooth func-

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tions, $y \in \mathbf{R}^r$ is the $r-$dimensional output (experimentally observed quantities), and $x_0(p)$ are initial conditions chosen such that the model to be well defined. The model response will depend on a number of unknown parameters, denoted by $p \in \mathbf{P}$, where $\mathbf{P} \subset \mathbf{R}^q$, is an open and connected subset of $\mathbf{R}^q$. The entries of f, g, and h are supposed polynomial or rational functions of their arguments. These functions and the initial conditions may depend on the parameter vector $p \in \mathbf{P}$.

Structural identifiability analysis regards the question whether the parameters can be identified (uniquely or not) from the available measurements under ideal noise free experimental conditions.

Definition 1. Walter and Prozato [1997]

(1) A parameter p is *structurally globally (or uniquely) identifiable* if for almost any $p^* \in \mathbf{P}$,
$$\Sigma(p) = \Sigma(p^*) \Rightarrow p = p^*,$$
(2) A parameter p is *structurally locally identifiable* if for almost any $p^* \in \mathbf{P}$, there exists a neighborhood $\mathbf{V}(p)$ of p such that
$$p^* \in \mathbf{V}(p) \, and \, \Sigma(p) = \Sigma(p^*) \Rightarrow p = p^*,$$
(3) A parameter p is *structurally unidentifiable* if for almost any $p^* \in \mathbf{P}$, there exists no neighborhood $\mathbf{V}(p)$ of p such that
$$p^* \in \mathbf{V}(p) \, and \, \Sigma(p) = \Sigma(p^*) \Rightarrow p = p^*.$$

2.2 Methods for testing structural identifiability

The conceptually simplest approach to test structural identifiability is the so called *direct test* which is no more than trying to directly solve the equality $f(x(t), p) = f(x(t), p^*) \Rightarrow p = p^*$. This method has been argued to have a number of limitations (Walter et al. [2004]), as it can be applied only for uncontrolled and autonomous systems. In general, reaching a conclusion may require excessively complicated formal manipulations or the equations to be solved may be too complicated for an analytic expression to exist, which then imposes the use of numerical methods and the loss of the formal nature of the solution.

More recently Xia and Moog [2003] proposed a new approach based on the *implicit function theorem*. Derivatives of the observables are computed with respect to the independent variable (time), to eliminate unobserved states. A differential system is obtained, depending on known system inputs, observable outputs and unknown parameters. An identification matrix is defined, consisting the partial derivatives of the differential equations with respect to the unknown parameters. Local identifiability is equivalent to non-singularity of the identification matrix. This method is hard to apply for high dimensional parameter space since it requires high order derivatives of the outputs. Alternatively Wu et al. [2008] propose an improved method, using multiple times instead of high order derivatives. Note that in this case it is in fact necessary to have some information of the state values in those times.

Also recently, Craciun and Pantea [2008], Davidescu and Jorgensen [2008], presented an approach to asses structural identifiability for *dynamic reaction networks*. The idea behind is to determine the structurally identifiable reaction rates using the stoichiometric matrix. Parameter identifiability is then computed for the considered independent reactions rates, by means of the generating series approach. Remark that the method is only applicable to models that are encoded in the chemical reaction network theory description of mass action kinetic networks.

For the sake of brevity, we will consider in more detail the methods maybe more promising: the power series based methods, the similarity transformation approach and the differential algebra based method.

Taylor series approach (Pohjanpalo [1978]). The method is based on the fact that observations are unique analytic functions of time and so all their derivatives with respect to time should also be unique. It is thus possible to represent the observables by the corresponding Maclaurin series expansion and it is the uniqueness of this representation that will guarantee the structural identifiability of the system. The idea is to establish a system of non-linear algebraic equations on the parameters, based on the calculation of the Taylor series coefficients, and to check whether the system has a unique solution.

In order to apply this method, $f(x(t), p) + g(x(t), p)u(t)$, should have infinitely many derivatives with respect to time, and $h(x(t), p)$ infinitely many derivatives with respect to the state vector components and the successive derivatives, $y_i^{(j)}(t_0)$, with j the derivative order, should be measurable. The Taylor series expansion of the observation functions is then given by:

$$y_i(t, p) = y_i(t_0, p) + t y_i^{(1)}(t_0, p) + \frac{t^2}{2!} y_i^{(2)}(t_0, p) + ..., \; i = 1, ..., r.$$

A sufficient condition for global structural identifiability is

$$a_k(p) = a_k(p^*), \; k = 1, 2, ..., k_{max}, \Rightarrow p = p^*, \qquad (2)$$

where $a_k(p) = \lim_{t \to 0} \frac{d^k}{dt^k} y(t, p)$, k_{max} is the smallest positive integer such that the symbolic computations give the solution of the parameters.

Generating series approach (Walter and Lecourtier [1981]). It allows to extend the analysis to the entire class of bounded and measurable inputs. In this case the output of the model is expanded in series with respect to the input u by means of Lie derivatives.

For the general model (1), f, g and h are assumed analytic on $\mathbf{R}^n$, with respect to the state variables $x \in \mathbf{R}^n$ and parametrized by the parameters p.

If $L_f h(x(t), p)$ is the Lie derivative of h, along the vector field f, then the coefficients of the series are given by $h(x_0(p))$, and its iterative Lie derivatives along g and/or f, evaluated at the initial conditions $x_0(p)$. The set of the resulting coefficients is used to compute the parametric solution and to decide upon the identifiability of the model.

Probably the major drawback of the power series approaches is that the necessary number of power series coefficients is usually unknown. In addition, solving the non-linear system of equations resulting from the power series approaches is usually not a trivial task, particularly when the number of parameters is large and the number of observables is reduced. We therefore propose the use of identifiability *tableaus* as defined in Balsa-Canto et al. [2010] to easily visualize the possible structural identifia-

bility problems and to assist in the solution of the non-linear system of equations.

The *tableau* represents the non-zero elements of the Jacobian of the series coefficients with respect to the parameters. It consists of a table with as many columns as parameters and as many rows as non-zero series coefficients, in principle, infinite. If the rank of the Jacobian coincides with the number of parameters, then it will be possible to, at least, locally identify the parameters. The rank may be deficient when empty rows appear (this may correspond to non-identifiable parameter), or if the number of Lie derivatives is not sufficient. From the generated tableau, a number of linear independent rows are selected tot guarantee the Jacobian rank condition. The new tableau is called "minimum" tableau.

If in the reduced tableau a row has just one non-zero element, then the corresponding parameter is structurally identifiable. These rows are then eliminated, generating a reduced tableau. Subsequent reductions may lead to the appearance of new unique non-zero elements and so on. Thus all possible reduced tableaus should be built first.

Once no more reductions are possible, one should try to solve the remaining equations. Since it is often the case that not all remaining power series coefficients depend on all parameters, the tableau will help to decide on how to select the equations to solve for particular parameters.

Similarity transformation approach (Vajda et al. [1989]) is based on the local state isomorphism theorem. It consists of solving a set of partial differential equations with respect to the parameters set. However, this may become difficult, if not impossible, if the model is complex. Denis-Vidal and Joly-Blanchard [1996] offer an alternative by eliminating the partial derivatives and combining equations such that direct relations between the components of the isomorphism could be found.

For the generic model (1) we should consider $f : M \to \mathbf{R}^n$ and $g : M \to \mathbf{R}^m$ real analytic vector fields on the state-space, open, connected domain $M \subseteq \mathbf{R}^n$, and $x_0(p) \in M$, h a real analytic output function and u a bounded and measurable control (Peeters and Hanzon [2005]). Structural identifiability can be obtained by using the local state isomorphism theorem.

Theorem 2. (Vajda et al. [1989]) Let us consider the parameter values p, $p^* \in \mathbf{P}$ such that the model (1) is locally reduced (observable and controllable) at the initial states $x_0(p)$, resp. $x_0(p^*)$, $V \subset \mathbf{R}^n$ an open neighborhood of $x_0(p)$, and an analytical mapping $\lambda : V \to \mathbf{R}^n$ with the following properties:

$$rank \frac{\partial \lambda(x^*)}{\partial x^*} = n, \; for\, all\, x^* \in V, \tag{3}$$

$$\lambda(x_0(p^*)) = x_0(p), \tag{4}$$

$$f(\lambda(x^*), p) = \frac{\partial \lambda(x^*)}{\partial x^*} f(x^*, p^*), \tag{5}$$

$$g(\lambda(x^*), p) = \frac{\partial \lambda(x^*)}{\partial x^*} g(x^*, p^*), \tag{6}$$

$$h(\lambda(x^*), p) = h(x^*, p^*) \tag{7}$$

for all $x^* \in V$. Then (1) is globally identifiable for every control u, if and only if conditions (3)-(7) imply $p = p^*$.

Vajda et al. [1989] claimed that λ must be linear. Peeters and Hanzon [2005] proved that this condition is not necessary if the initial state is considered different to the origin.

Differential algebra methods (Ljung and Glad [1994], Ollivier [1990], Saccomani et al. [2003]) are based on replacing the inputs-observables behavior of the system by some polynomial or rational mapping. Testing identifiability reduces then to testing whether that mapping is injective. In practice the problem is reduced to that of testing algebraic dependence of the parameters on the differential field generated by the inputs and the observables. This may be done by computing the characteristic set as, for example, in the Ritt's algorithm.

Let us consider the general model given by (1), with f, g, h polynomial or rational functions of their arguments, and the inputs u, differentiable. The model (1) can be written as polynomial differential equations that form a differential polynomial ring, having as entities the states x, the inputs u, outputs y and their derivatives. A differential ideal is a set of differential polynomials closed by addition, multiplication, scaling and differentiation, and it can be represented by a finite basis computed by applying a "ranking" of the variables and their derivatives. Usually the inputs have the lowest rank, then outputs, and the highest rank is attributed to the state variables Ljung and Glad [1994].

This ranking is used to derive an observable representation of the model which may be obtained by calculating the characteristic set as a representation of the differential ideal (Ljung and Glad [1994], Ollivier [1990]). The *characteristic set* is computed with respect to the chosen ranking and using Ritt's algorithm (Ljung and Glad [1994], Bellu et al. [2007]), or the (improved) Ritt-Kolchin or Rosenfeld-Gröebner algorithms (Denis-Vidal and Joly-Blanchard [2001]). All these algorithms are based on the same idea: eliminating the highest ranking variable, *pseudo-division*, such that differential polynomials in u, y, p can be obtained using symbolic computations.

After computing the characteristic set, the set of all coefficients of the input-output relations is used to check the identifiability. There are two ways to verify identifiability: one is calculating the unknown parameters by equating each component of the set of coefficients to unknown quantities (Margaria et al. [2001]), or equating to a pseudo-randomly chosen numerical values (Bellu et al. [2007]). To handle initial conditions the accessibility condition proposed by Saccomani et al. [2003] should be used.

2.3 Implementation of methods

The application of the different approaches requires symbolic manipulation. Power series based methods were implemented in MATHEMATICA. The similarity transformation approach was implemented in a combination of the MATLAB Symbolic Toolbox and MAPLE. The differential algebra method has been implemented using the modules Epsion and Linalg available in MAPLE. In addition, and for the purpose of differential algebra method, the software DAYSI (Bellu et al. [2007]) was also tested here.

3. CASE STUDIES

To allow for a critical comparison, the above mentioned methods will be applied to the structural identifiability analysis of three models related to biological systems.

Case study 1: Goodwin oscillator

The model describes the oscillations in enzyme kinetics (Goodwin [1965]). x_1 represents an enzyme concentration whose rate of synthesis is regulated by feedback control via a metabolite x_3, and x_2 regulates the synthesis of x_3:

$$\begin{cases} \dot{x}_1 = -bx_1 + \dfrac{a}{A + x_3^{\sigma}}, \\ \dot{x}_2 = \alpha x_1 - \beta x_2, \\ \dot{x}_3 = \gamma x_2 - \delta x_3 \end{cases} \tag{8}$$

Two scenarios will be considered, the typical case when only x_1 is measured ($y_1 = x_1$) and a hypothetical situation for which all states can be measured ($y_1 = x_1$, $y_2 = x_2$, $y_3 = x_3$).

For the case of one observable, the power series based methods are able to compute a full rank *tableau* for the case of fixing σ and A (Balsa-Canto et al. [2008b]), but it was not possible to solve the non linear system of equations on the parameters, so only local identifiability may be expected. The similarity transformation approach can not be applied in this case since controllability condition is not fulfilled (the model is uncontrolled). Differential algebra methods generate non-identifiability, with or without initial conditions, but a parametric solution was displayed, for a and b. If the parameter $\sigma = 10$, neither MAPLE, nor DAISY could finish the computations. For more precise results, the initial model is transformed into an equivalent polynomial one (Margaria et al. [2001]). DAISY software ends up with a computational error at the time of using initial conditions.

For the second scenario, the analysis is considerably easier. The power series methods generated a full rank *tableau* presented in Fig.1. But symbolic manipulation tools were not able to solve the non-linear parametric system. As posted above, the similarity transformation approach couldn't be applied. Similar result is obtained using differential algebra techniques, and for this scenario the parametric solution is given for $a, A, b, \alpha, \beta, \gamma$ and δ.

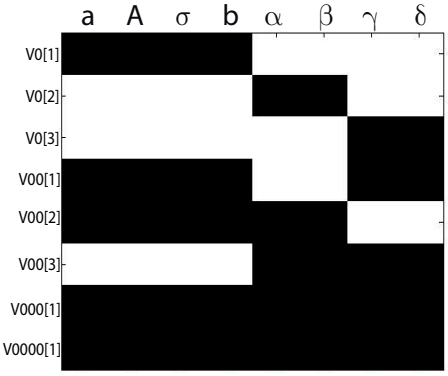

Fig.1. Reduced identifiability tableau for the Goodwin oscillator model

Case study 2: Glycolysis inspired metabolic pathway

This model represents a glycolysis inspired pathway (the upper part of the glycolysis) with different physiological constraints on enzyme synthesis as described in Bartl et al. 2010 Bartl et al. [2010]. Usually a specific enzyme (u) catalyzes a metabolic reaction denoted by x. The dynamical model can be written as:

$$\begin{cases} \dot{x}_1 = -\dfrac{k_1 x_1}{x_1 + k_M} u_1, \\ \dot{x}_2 = \dfrac{k_1 x_1}{x_1 + k_M} u_1 - \dfrac{k_2 x_2}{x_2 + k_M} u_2, \\ \dot{x}_3 = \dfrac{k_2 x_2}{x_2 + k_M} u_2 - \dfrac{k_3 x_3}{x_3 + k_M} u_3, \\ \dot{x}_4 = \dfrac{k_2 x_2}{x_2 + k_M} u_2 + \dfrac{k_3 x_3}{x_3 + k_M} u_3 - \dfrac{k_4 x_4}{x_4 + k_M} u_4, \\ \dot{x}_5 = \dfrac{k_4 x_4}{x_4 + k_M} u_4. \end{cases} \tag{9}$$

The model is considered fully observed ($y_1 = x_1$, $y_2 = x_2$, $y_3 = x_3$, $y_4 = x_4$, $y_5 = x_5$).

The Taylor series approach results into an identifiability tableau of rank 5 and multiple solutions of the parameters were found. Due to their complexity it was impossible to assess the uniqueness. The generating series approach concluded on the global identifiability of the model. The solution of the parameters is unique, fact that can be noticed from the reduced identifiability *tableau* (see Fig.2.). The similarity transformation approach can't be used for this example since the observability condition is not fulfilled. Using the differential algebra technique the model (9) was found globally identifiable, in DAISY the computations being done without the use of initial conditions.

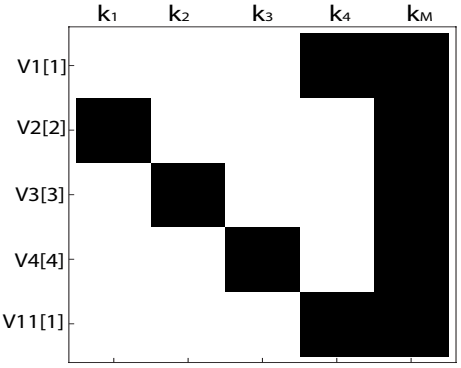

Fig.2. Reduced identifiability tableau for the Glycolysis metabolic pathway

Case study 3: Arabidopsis Thaliana model

The model describes the first multi-gene loop identified in the Arabidopsis circadian clock (Locke et al. [2005]) that comprises a negative feedback loop, in which two partially redundant genes Late Elongated Hypocotyl (LHY) and Circadian Clock Associanted 1 (CCA1) repress the expression of their activator, Timing of CAB Expression 1 (TOC1). A minimal mathematical representation of the system requires 7 coupled differential equations and 29 parameters. The differential equations involve Michaelis-Menten kinetics that describe enzyme-mediated protein degradation, and Hill functions that describe some transcriptional activation terms. The model is given by (Locke et al. [2005]):

$$\begin{cases} \dot{x}_1 = n_1 \dfrac{x_6}{g_1 + x_6} - m_1 \dfrac{x_1}{k_1 + x_1} + q_1 x_7 u(t), \\ \dot{x}_2 = p_1 x_1 - r_1 x_2 + r_2 x_3 - m_2 \dfrac{x_2}{k_2 + x_2}, \\ \dot{x}_3 = r_1 x_2 - r_2 x_3 - m_3 \dfrac{x_3}{k_3 + x_3}, \\ \dot{x}_4 = n_2 \dfrac{g_2^2}{g_2^2 + x_3^2} - m_4 \dfrac{x_4}{k_4 + x_4}, \\ \dot{x}_5 = p_2 x_4 - r_3 x_5 + r_4 x_6 - m_5 \dfrac{x_5}{k_5 + x_5}, \\ \dot{x}_6 = r_3 x_5 - r_4 x_6 - m_6 \dfrac{x_6}{k_6 + x_6}, \\ \dot{x}_7 = p_3 - m_7 \dfrac{x_7}{k_7 + x_7} - (p_3 + q_2 x_7) u(t) \end{cases} \tag{10}$$

with the measured states $y_1 = x_1$, $y_2 = x_4$.

For this example the Taylor series approach implemented in MATHEMATICA reached 10 derivatives, resulting into a rank 14 identifiability *tableau*. Therefore only partial results about local identifiability of parameters can be achieved. A complete solution of the parameters that characterize the reduced identifiability *tableau* couldn't be found because of the complexity. Using generating series approach a rank 16 *tableau* was obtained, using 11 derivatives (see Fig.3.). In this case a unique solution could be computed only for p_3, n_2, q_2, m_1, k_1. Regarding the application of the similarity transformation method, the model (10) results not to be observable, thus the approach could not be applied. Differential algebra was not successful in providing results for this example as the characteristic set couldn't be computed. In MAPLE no result was displayed, the software generating "Maple was unable to allocate enough memory" error, and DAISY also concluded the computation with an error message ("heap space low"), because of computational complexity.

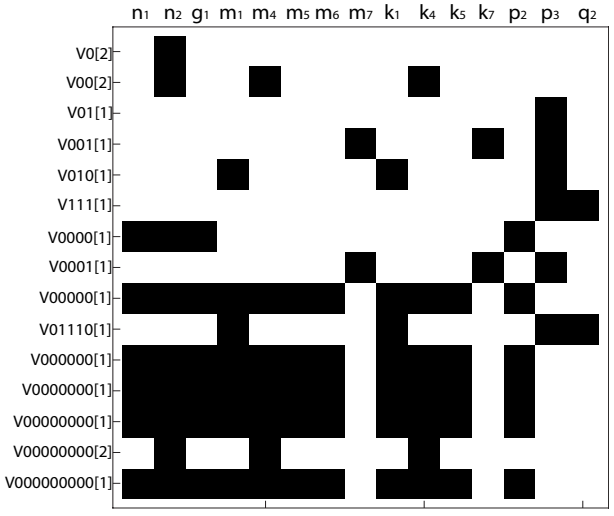

Fig.2. Reduced identifiability tableau for the model of the Arabidopsis thaliana clock

4. DISCUSSION AND CONCLUSIONS

This work presented a critical comparison of several methods for checking structural identifiability. First, an overview of available methods was presented including the *direct test*, the method by Xia and Moog [2003] based on the *implicit function theorem*, the one proposed by Craciun and Pantea [2008] for *dynamic reaction networks*, the *Taylor and generating series* approaches, the *similarity transformation* approach and the *differential algebra based method*. A more detailed description was presented for those that provided some representative, conclusive results for the illustrative examples considered.

Table 1 summarises the results achieved by the different methods for the three examples considered:

Table 1. Summary of results for the different methods and case studies. T.S.: Taylor series; G.S.: Generating series; S.T.: Similarity transformation and D.A.: Differential algebra based method

	Goodwin's model	Glycolysis metabolic pathway	Arabidopsis T. model
T.S.	local id. (fix param) global id.	can't decide local id.	local id. of some pars
G.S.	local id. (fix param) global id.	global id.	local id. of some pars
S.T.	not applicable not applicable	not applicable	not applicable
D.A.	not global id.	global id. without i.c.	comput. error

Complexity in testing structural identifiability is directly related to the size and nonlinear character of the model, the number of parameters to be considered and the observables that are amenable to experimentation.

The Taylor series method, although applicable to any non linear system, often requires a large number of coefficients, i.e. of derivatives, making the final system of equations (when the necessary terms may be computed) excessively complicated.

Same type of problems are faced by the differential algebra approach which often requires large computational facilities.

Note that both methods may be successful when most of the states of the model can be regarded as (or as part of) the observables, since this reduces the computational burden required. This is particularly true for the differential algebra approach, provided the model may be written in polynomial form.

The similarity transformation approach requires observability and controllability conditions which may be not fulfilled or may be impossible to asses. In those situations further results may not be obtained, being necessary to rely on other approaches to decide on the (local) identifiability of the parameters. In general, its applicability limits to small models.

From the results it may be concluded that the combination of the generating series approach (Walter and Lecourtier [1981]) with the identifiability tableau (Balsa-Canto et al. [2010]) is the most promising technique to test the struc-

tural identifiability of biosystems. It has been able to successfully handle all examples considered here. Computing Lie derivatives is highly efficient and further manipulations are doable as compared to the other methods.

Of course, and despite the necessity of knowing *a priori* whether we may or not be successful in identifying model parameters, much remains to be done to provide with tools to test models for identifiability, particularly for large scale models, as the algebraic manipulations involved in identifiability testing can become really tedious or even impossible.

The emphasis should be possibly paid in methods to detect which parameters may be identified (or at least locally identified) so as to help modellers to decide on whether to reformulate certain aspects of the model or to devise iterative procedures to estimate model parameters.

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