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Structural Identifiability Analysis via Extended Observability and Decomposition

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Abstract: Structural identifiability analysis of nonlinear dynamic models requires symbolic manipulations, whose computational cost rises very fast with problem size. This hampers the application of these techniques to the large models which are increasingly common in systems biology. Here we present a method to assess parametric identifiability based on the framework of nonlinear observability. Essentially, our method considers model parameters as particular cases of state variables with zero dynamics, and evaluates structural identifiability by calculating the rank of a generalized observability-identifiability matrix. If a model is unidentifiable as a whole, the method determines the identifiability of its individual parameters. For models whose size or complexity prevents the direct application of this procedure, an optimization approach is used to decompose them into tractable subsystems. We demonstrate the feasibility of this approach by applying it to three well-known case studies.

Keywords: structural identifiability, observability, parameter identification, model decomposition, optimization, systems biology

1. INTRODUCTION

Structural identifiability analysis determines whether the parameters in a model can be identified from knowledge of the system dynamics, observable functions, external stimuli, and initial conditions (Walter and Pronzato, 1997). The concept of structural identifiability was introduced by Bellman and Åström (1970). A wide variety of methods, reviewed e.g. in (Miao et al., 2011; Chiş et al., 2011b; Villaverde and Barreiro, 2016), have been proposed for assessing the structural identifiability of nonlinear dynamic models. We can distinguish between symbolic (Pohjanpalo, 1978; Walter and Lecourtier, 1982; Vajda et al., 1989; Ljung and Glad, 1994; Bellu et al., 2007; Balsa-Canto et al., 2010), semi-numerical (Sedoglavic, 2002; Karlsson et al., 2012; Stigter and Molenaar, 2016), and numerical approaches (Raue et al., 2009) for structural identifiability. Symbolic manipulations can provide exact (as opposed to probabilistic) results, and in some cases they can determine global (as opposed to local) identifiability. However, they quickly give rise to long expressions as the system size increases, and are hardly applicable to large-scale or even medium-size models (Miao et al., 2011; Chiş et al., 2011b; Grandjean et al., 2014). Numerical methods can be more efficient, although at the expense of generality. The two approaches can be seen as complementary (Raue et al., 2014).

The existing methodologies have different strengths and weaknesses, and when choosing one it is necessary to take into account trade-offs between generality (some methods are only valid for certain types of systems, such as rational or polynomial expressions (Sedoglavic, 2002; Bellu et al., 2007; Karlsson et al., 2012; Merkt et al., 2015), while others are more generally applicable), computational cost (application of some methods to large-scale problems is infeasible), and level of detail of the results. For example, most methods not only classify the model as identifiable or unidentifiable as a whole, but also determine the identifiability of individual parameters. Additionally, other methods distinguish between local and global identifiability (Bellu et al., 2007; Chiş et al., 2011a), find symmetries between parameters (Yates et al., 2009; Merkt et al., 2015), or provide identifiable reparameterizations (Meshkat et al., 2014).

A conclusion from the aforementioned studies is that structural identifiability analysis is still a challenging task, particularly for large models. Hence it is seldom performed before undertaking parameter estimation, due to its complexity (Miao et al., 2011). In summary, despite recent advances there is still a need for structural identifiability methods that have the sufficient generality and efficiency to be applicable to the increasingly complex models being developed in the systems biology community.

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Here we present a method that approaches local structural identifiability as a generalized version of observability. A system is observable at time t_1 if it is possible to determine its state $x(t_1)$ from future measurements, that is, from $y(t)$ such that $t_1 < t < t_2$, where t_2 is a finite time. Tools for determining observability have been developed for both linear and nonlinear systems. If the model parameters p are considered as state variables with dynamics $\dot{p} = 0$, structural identifiability analysis can be recast as a generalization of observability analysis (Tunali and Tarn, 1987). By adopting this point of view it is possible to assess the structural identifiability of nonlinear systems of small and medium size (Chatzis et al., 2015). We show that larger models can be analysed by decomposing them into smaller and more tractable submodels, using an optimization algorithm. For models which are diagnosed as unidentifiable the method determines the subset of identifiable parameters. If all or some of the initial conditions of the state variables are unknown, their identifiability can also be assessed. The methodology proposed here is of broad applicability, since it is not restricted to systems in polynomial or rational form.

The structure of this paper is as follows: in section 2 we define mathematically the structural identifiability problem, and describe how its analysis can be recast as a generalization of nonlinear observability analysis. In section 3 we present a methodology based in this approach, and apply it to several case studies in section 4. Finally, in section 5 we provide some conclusions and guidelines for future work.

2. STRUCTURAL IDENTIFIABILITY AND OBSERVABILITY

2.1 Structural identifiability: definitions

Let us denote by M a general nonlinear model structure with the following dynamic equations:

$$\begin{aligned} \dot{x}(t) &= f[x(t,p), u(t), p] \\ y(t) &= g[x(t,p), p] \\ x_0 &= x(t_0, p) \end{aligned} \tag{1}$$

where f and g are nonlinear vector functions, $p \in \mathbb{R}^q$ is a real-valued vector of parameters, $u(t) \in \mathbb{R}^r$ is the input vector, $x(t) \in \mathbb{R}^n$ the state variable vector, and $y(t) \in \mathbb{R}^m$ the measurable output, also called observables vector.

Assuming that the model structure M is correct, that the data is noise-free, and that the inputs to the system can be chosen freely, it is always possible to choose an estimated parameter vector $\hat{p}$ such that the model output $M(\hat{p})$ equals the one obtained by the true parameter vector, $M(p^*)$. If $\hat{p} = p^*$ this is obviously the case.

Parameter p_i is structurally globally (or uniquely) identifiable (s.g.i.) if, for almost any p^*,

$$M(\hat{p}) = M(p^*) \Rightarrow \hat{p}_i = p_i^* \tag{2}$$

A model M is s.g.i. if all its parameters are s.g.i.

A parameter p_i is structurally locally identifiable (s.l.i.) if for almost any p^* there is a neighbourhood $V(p^*)$ such that

$$\hat{p} \in V(p^*) \text{ and } M(\hat{p}) = M(p^*) \Rightarrow \hat{p}_i = p_i^* \tag{3}$$

A model M is s.l.i. if all its parameters are s.l.i.

If equation (3) does not hold in any neighbourhood of p^*, parameter p_i is structurally unidentifiable (s.u.i.). A model M is s.u.i. if at least one of its parameters is s.u.i.

2.2 Nonlinear observability

Two states $x_0 \neq x_1$ are said to be distinguishable when there exists some input $u(t)$ such that $y(t, x_0, u(t)) \neq y(t, x_1, u(t))$, where $y(t, x_i, u(t))$ denotes the output function of the system for the input $u(t)$ and initial state $x_i (i = 0, 1)$. The system is said to be (locally) observable at x_0 if there exists a neighbourhood N of x_0 such that every other $x_1 \in N$ is distinguishable from x_0. The concept of observability was initially developed for linear systems, and was soon extended to the nonlinear case with the use of Lie algebra (Hermann and Krener, 1977).

A way to extract information about the state $x(t)$ from the output $y(t)$ of a system given by equations (1) is to build the derivatives $\dot{y}, \ddot{y}, \ldots$. In these differentiations, the so-called Lie derivatives of the output function appear. Given a smooth function $g(x)$ and a vector field $z(x)$, the Lie derivative of g with respect to z is:

$$L_z g = \frac{\partial}{\partial x} g(x) \cdot z(x), \tag{4}$$

where $\frac{\partial}{\partial x} g(x)$ is a row vector containing the partial derivatives of the smooth function $g(x)$. We are interested in the Lie derivative of g along f, which is defined as:

$$L_f g(x) = \frac{\partial g(x)}{\partial x} f(x, u) \tag{5}$$

For a generic system with n states and m outputs, $\frac{\partial}{\partial x} g(x)$ is a $m \times n$ matrix, and $L_f g(x) = \frac{\partial g(x)}{\partial x} f(x, u)$ is a $m \times 1$ column vector. The i^{th} order Lie derivatives are recursively defined as follows:

$$\begin{aligned} L_f^2 g(x) &= \frac{\partial L_f g(x)}{\partial x} f(x, u) \\ &\vdots \\ L_f^i g(x) &= \frac{\partial L_f^{i-1} g(x)}{\partial x} f(x, u) \end{aligned} \tag{6}$$

The observation space $\mathbf{O}$ of (1) is the space of linear combinations (with constant coefficients) of functions of the form:

$$L_f^k \; g(x) = \overbrace{L_f \ldots L_f L_f}^{k} \; g(x), \qquad k = 0, 1, 2, \ldots \tag{7}$$

where $L_f^0 g(x) = g(x)$. For each x, let $\mathbf{dO}(x)$ denote the subspace of rows consisting of all $\frac{\partial}{\partial x} \alpha(x)$ with $\alpha(x) \in \mathbf{O}$.