Sufficiently Exciting Inputs for Structurally Identifiable Systems Biology Models*

Alejandro F. Villaverde * Neil D. Evans **
Michael J. Chappell ** Julio R. Banga *

* Bioprocess Engineering Group, IIM-CSIC, Vigo 36208, Spain (e-mail: avillaverde@iim.csic.es).
** School of Engineering, University of Warwick, Coventry CV4 7AL, UK

Abstract: A parameter is structurally identifiable if its value can theoretically be estimated by observing the model output. Structural identifiability is a desirable property in biological modelling: if a parameter is structurally unidentifiable, its estimated numerical value is meaningless, and model predictions of unmeasured state variables can be wrong, compromising the ability of the model to provide biological insight. Structural identifiability depends on the system dynamics, observation function (model output), initial conditions, and external inputs. In this paper we focus on the last factor. Methods for structural identifiability analysis typically classify a model as identifiable provided that it is fed with sufficiently exciting inputs. For example, a given model may require a time-varying input to be structurally identifiable, while for another model a constant non-zero input may be enough. Here we present a method that determines how sufficiently exciting an input should be. The approach builds on the STRIKE-GOLDD toolbox, which considers structural identifiability as generalized observability. The approach incorporates extended Lie derivatives, which correctly assess structural identifiability in the case of time-varying inputs. The procedure can also be used to determine the type of input profile that is required to make the parameters identifiable. This capability is helpful when designing new experiments for the purpose of parameter estimation.

© 2018, IFAC (International Federation of Automatic Control) Hosting by Elsevier Ltd. All rights reserved.

Keywords: Identifiability, Structural Identifiability, Structural properties, Observability, Parameter identification, Parameter estimation, Inputs.

1. INTRODUCTION

A parameter is structurally identifiable if it is theoretically possible to determine its true value from noiseless data (Cobelli and DiStefano, 1980). Since identifiability depends, among other things, on the system’s inputs and outputs, it can vary as a result of the experiment design. The term qualitative experiment design refers to the selection of input and output ports in order to maximize the number of structurally identifiable parameters (Walter and Pronzato, 1990).

Some structural identifiability methods, such as the similarity transformation approach (Evans et al., 2002; Yates et al., 2009) and direct test (Denis-Vidal and Joly-Blanchard, 2000) are applicable to autonomous systems, i.e. systems with no input. Other approaches, such as those based on power series (Polujanpaloo, 1978), differential algebra (Ljung and Glad, 1994; Bellu et al., 2007), implicit functions (Xia and Moog, 2003), or differential geometry (Villaverde et al., 2016), can be applied to systems with external inputs. Additionally, it is possible (for a given set of experiments with defined inputs) to assess identifiability with numerical approaches based on profile likelihoods (Raue et al., 2009) or the sensitivity matrix (Stigter and Molenaar, 2015). There are a number of software tools implementing some of the aforementioned methodologies, such as DAISY (Bellu et al., 2007), GenSSI (Chiş et al., 2011), EAR (Karlsson et al., 2012), COMBOS (Meshkat et al., 2014), STRIKE-GOLDD (Villaverde et al., 2016), and Data2Dynamics (Raue et al., 2015). These methods assess whether a given input-output configuration is in principle sufficient to obtain a structurally identifiable model (Saccomani and Cobelli, 1992). Algorithms that automate the search for the subsets of outputs that guarantee structural identifiability are also available (Auguste, 2009; Anguelova et al., 2012).

Determining the necessary set of inputs and outputs is only part of experiment design. Additionally, it is necessary to define aspects such as the number and timing of the samples, the system’s initial state, and characterization of the inputs. This task is known as quantitative experiment design, and aims at maximizing practical identifiability. In the present paper we address a different, although related, problem. We seek to determine, a priori, what mathematical form the inputs must have in order to guarantee structural identifiability. For example, for a given model structure a non-zero constant input may not be sufficiently exciting and a ramp input may be necessary. To a certain extent, this situation resembles the relationship between structural identifiability and initial conditions: generally, methods that analyse structural identifiability

---

---
yield results that are valid for almost all initial conditions; however, a model classified as structurally identifiable may lose structural identifiability when started from particular initial conditions (Denis-Vidal et al., 2001; Saccomani et al., 2003; Villaverde and Banga, 2017). Likewise, for the case of the inputs, structural identifiability analysis methods can determine whether a model is structurally identifiable provided that sufficiently exciting inputs are applied – but it is not straightforward to characterize the necessary inputs with the existing implementations of said methods. Our aim is to determine this qualitative property holds for all initial conditions; (Ljung and Glad, 1994):

\[ \dot{y}(t, \tilde{p}) = y(t, p^*) \Rightarrow \tilde{p}_i = p_i^* \]  

A parameter \( p_i \) is structurally locally identifiable (s.l.i.) if for almost any \( p^* \) there is a neighbourhood \( V(p^*) \) in which (2) holds. If (2) does not hold in any neighbourhood of \( p^* \), then \( p_i \) is structurally unidentifiable (s.u.). A model \( M \) is s.g.i. if all its parameters are s.g.i.; it is s.u. if at least one of its parameters is s.u.; and it is s.i. if all its parameters are s.i. or s.g.i. and at least one of them is not s.g.i.

\[ \text{2.2 Structural identifiability as generalized observability} \]

Local structural identifiability can be considered as a generalization of observability. A model is observable if it is possible to determine its internal state \( x \) by observing its output \( y \). Observability can be evaluated by calculating the rank of an observability matrix, \( O_1 \), which represents a map between the model output \( y \) (and its derivatives \( \ddot{y}, \dot{y}, \ldots \)) on the one hand, and its state \( x \) on the other. For nonlinear models with constant input \( O_1 \) can be calculated using Lie derivatives, as follows:

\[ O(x) = \begin{pmatrix} \frac{\partial}{\partial x^1} y(t) \\ \frac{\partial}{\partial x^2} \dot{y}(t) \\ \vdots \\ \frac{\partial}{\partial x^n} y^{(n-1)}(t) \end{pmatrix} = \begin{pmatrix} \frac{\partial}{\partial x^1} g(x) \\ \frac{\partial}{\partial x} (L_f g(x)) \\ \vdots \\ \frac{\partial}{\partial x} (L_f^{n-1} g(x)) \end{pmatrix} \]  

where \( L_f g(x) \) is the Lie derivative of \( g \) with respect to \( f \):

\[ L_f g(x) = \frac{\partial g(x)}{\partial x} f(x,u). \]  

Subsequent derivatives can be recursively calculated:

\[ L_f^2 g(x) = \frac{\partial^2 L_f g(x)}{\partial x} f(x,u), \]

\[ L_f^3 g(x) = \frac{\partial^3 L_f g(x)}{\partial x} f(x,u). \]  

The observability rank condition (ORC) states that, if the system given by (1) with constant input \( u \) satisfies rank\( (O(x_0)) = n \), with \( O \) defined by (3), then it is (locally) observable around \( x_0 \) (Hermann and Krener, 1977).

The model’s structural identifiability can be evaluated in the same way as its observability. To this end, we consider the parameters \( p_i \) as additional states with zero dynamics \( \ddot{p}_i = 0 \), i.e., we augment the state variable vector as \( \tilde{x} = (x, p) \). The augmented (or generalized) observability-identifiability matrix, \( O_1(\tilde{x}) \), is then defined as:

\[ O_1(\tilde{x}) = \begin{pmatrix} \frac{\partial}{\partial x} g(\tilde{x}) \\ \frac{\partial}{\partial x} (L_f g(\tilde{x})) \\ \vdots \\ \frac{\partial}{\partial x} (L_f^{n+q-1} g(\tilde{x})) \end{pmatrix} \]  

The corresponding observability-identifiability condition (OIC) states that, if the system (1) with constant input \( u \) satisfies rank\( (O_1(\tilde{x}_0)) = n + q \), with \( O_1(\tilde{x}_0) \) given by (6), then it is locally observable and structurally locally identifiable in a neighbourhood \( N(\tilde{x}_0) \) of \( \tilde{x}_0 \).
2.3 Time-varying inputs and extended Lie derivatives

The input vector \( u(t) \) in (1) can in general be time-varying. However, the expressions for the Lie derivatives used in (4) and (5) implicitly assume that it is constant. For time-varying inputs, the definition of the Lie derivative must be modified in order to correspond to the output derivative. To this end we use an extended Lie derivative (Karlsson et al., 2012), which is defined by:

\[
L_f g(\tilde{x}) = \frac{\partial g(\tilde{x})}{\partial \tilde{x}} f(\tilde{x}, u) + \sum_{j=0}^{j=\infty} \frac{\partial g(\tilde{x})}{\partial u^{(j)}} u^{(j+1)}.
\]

In the second term of the sum within (7), \( u^{(j)} \) and \( u^{(j+1)} \) denote the \( j^{th} \) and \( (j+1)^{th} \) derivatives of the input, respectively (note that we write \( u \) instead of \( u(t) \) to ease the notation). Clearly, since the output function \( g \) does not depend on the input directly (i.e. it is \( g(\tilde{x}) \), not \( g(\tilde{x}, u) \)), it holds that

\[
\sum_{j=0}^{j=\infty} \frac{\partial g(\tilde{x})}{\partial u^{(j)}} u^{(j+1)} = 0
\]

and the extended Lie derivative defined above is identical to its non-extended counterpart. However, the summation term is not necessarily zero in higher order extended Lie derivatives, which are calculated as:

\[
L_f^j g(\tilde{x}) = \frac{\partial L_f^{j-1} g(\tilde{x})}{\partial \tilde{x}} f(\tilde{x}, u) + \sum_{j=0}^{j=\infty} \frac{\partial L_f^{j-1} g(\tilde{x})}{\partial u^{(j)}} u^{(j+1)}
\]

This means that, if we calculate the matrix \( O_I \) in (6) using extended Lie derivatives, we may encounter first order derivatives of the input \( u \) in the third and subsequent rows (for one-dimensional outputs), second order derivatives \( \dot{u} \) in the fourth and subsequent rows, and so on. Thus, when the structural identifiability analysis of a model requires two or more Lie derivatives, the result may indeed be affected by the presence of time-varying inputs.

It should also be noted that, in practice, the calculation of \( \sum_{j=0}^{j=\infty} \frac{\partial L_f^{j-1} g(\tilde{x})}{\partial u^{(j)}} u^{(j+1)} \) can be truncated, since the \( i^{th} \) Lie derivative, \( L_f^i \), depends on \( u, \dot{u}, \ldots, u^{(i-2)} \) but not on higher derivatives of the input. Hence, for \( i > 1 \) it suffices to calculate the extended Lie derivative as:

\[
L_f^i g(\tilde{x}) = \frac{\partial L_f^{i-1} g(\tilde{x})}{\partial \tilde{x}} f(\tilde{x}, u) + \sum_{j=0}^{j=i-2} \frac{\partial L_f^{i-1} g(\tilde{x})}{\partial u^{(j)}} u^{(j+1)}
\]

2.4 Use of extended Lie derivatives for input design

Using extended Lie derivatives (9, 10) we can characterize the type of time dependency that is needed for the input to enable structural identifiability. We can do this by setting to zero in \( O_I \) (6) the derivatives of the input of order higher than a given one, and then recalculating rank\((O_I)\). For example, if \( O_I \) has full rank for \( \dot{u} = 0 \), a constant input is sufficient for structural identifiability. If, however, \( O_I \) is full rank for \( \{ \dot{u} \neq 0, \ddot{u} = 0 \} \), but not for \( \dot{u} = 0 \), then a ramp input is necessary and sufficient, and a constant input is not. The effect of a specific input can be tested by entering the corresponding expression for \( u(t) \) in (6).

3. EXAMPLE: TWO COMPARTMENT MODEL

We illustrate the effect of using extended Lie derivatives with a biological model of a physiological system with two compartments (i.e. two states, of which one is measured). We illustrate the effect of using extended Lie derivatives.

\[
M_1 : \begin{cases}
\dot{x}_1 &= -(k_{1e} + k_{12}) \cdot x_1 + k_{21} \cdot x_2 + b \cdot u, \\
\dot{x}_2 &= k_{12} \cdot x_1 - k_{21} \cdot x_2, \\
y &= x_1
\end{cases}
\]

where the unknown parameter vector is \( p = (k_{1e}, k_{12}, k_{21}, b) \); the initial condition \( x_2(0) \) is also unknown. A diagram of the model is shown in the left hand side of Fig. 1.

Calculating the \( O_I \) matrix of Eq. (6) for \( M_1 \) with 5 extended Lie derivatives, as in (7–9), yields a \( 6 \times 6 \) matrix with rank\((O_I)\) = 6. Therefore the observability-identifiability rank condition (OIC) is satisfied. This means that the model is structurally identifiable. In contrast, the parameters \( (k_{1e}, k_{12}, k_{21}, b) \) by measuring the model output \( y(=x_1) \), it is necessary to perform an experiment with time-varying input \( \dot{u} \neq 0 \). Moreover, we can characterize the type of time dependency that is needed for the input to enable structural identifiability. We can do this by replacing in \( O_I \) higher order derivatives of the input with zero and recalculating rank\((O_I)\). For the model \( M_1 \) this procedure yields that rank\((O_I) \) = 6 even if \( \dot{u} = 0 \), as long as \( \ddot{u} \neq 0 \); however, rank\((O_I) \) reduces to 5 if \( \dot{u} = 0 \). Thus we know that a ramp input \( u(t) = k_1 \cdot t + k_2 \) suffices for structural identifiability of the parameters, but a constant one \( u(t) = k \) does not. Fig. 1 illustrates this fact.

4. CONCLUSION

The method presented here analyses the structural identifiability of models with continuously time-varying inputs. It does so by including the derivatives of the input in the identifiability matrix through extended Lie derivatives. In this way, the approach takes into account the ability (or lack thereof) of a given time-varying input to excite a dynamic behaviour in the system that leads to the resolution of structural non-identifiabilities. This is important because, in the case of structural unidentifiability, parameter estimates are biologically meaningless, and model predictions may be wrong. The method can inform the design of new experiments: it delimits the type of external inputs that are required to correctly estimate the model parameters from the resulting dataset – more specifically, it establishes which derivatives of the input must be non-zero. It can also test the effect of a particular input by introducing its expression into the identifiability
matrix. We have demonstrated the methodology with a compartmental model that is structurally unidentifiable if a constant input is used, but becomes identifiable with a time-varying input such as a ramp function.

REFERENCES

Anguelova, M., Karlsson, J., and Jirstrand, M. (2012). Minimal output sets for identifiability. *Math. Biosci.*, 239(1), 139–153.

August, E. (2009). Parameter identifiability and optimal experimental design. In *Int. Conf. on Computational Science and Engineering, CSE’09.*, volume 1, 277–284.

Bellu, G., Saccomani, M.P., Audoly, S., and D’Angio, L. (2007). DAISY: a new software tool to test global identifiability of biological and physiological systems. *Comput. Methods Programs Biomed.*, 88(1), 52–61.

Chiù, O., Banga, J.R., and Balsa-Canto, E. (2011). GenSSI: a software toolbox for structural identifiability analysis of biological models. *Bioinformatics*, 27(18), 2610–2611.

Cobelli, C. and DiStefano, J. (1980). Parameter and structural identifiability concepts and ambiguities: a critical review and analysis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 239(1), R7–R24.

Denis-Vidal, L. and Joly-Blanchard, G. (2000). An easy to check criterion for (un)identifiability of uncontrolled systems and its applications. *IEEE Trans. Autom. Control*, 45, 768–771.

Denis-Vidal, L., Joly-Blanchard, G., and Noiret, C. (2001). Some effective approaches to check the identifiability of uncontrolled nonlinear systems. *Math. Comput. Simul.*, 57(1), 35–44.

Evans, N.D., Chapman, M.J., Chappell, M.J., and Godfrey, K.R. (2002). Identifiability of uncontrolled nonlinear rational systems. *Automatica*, 38(10), 1799–1805.

Hermann, R. and Krener, A.J. (1977). Nonlinear controllability and observability. *IEEE Trans. Autom. Control*, 22(5), 728–740.

Karlsson, J., Anguelova, M., and Jirstrand, M. (2012). An efficient method for structural identifiability analysis of large dynamic systems. In *16th IFAC Symposium on System Identification*, volume 16, 941–946.

Ljung, L. and Glad, T. (1994). On global identifiability for arbitrary model parametrizations. *Automatica*, 30(2), 265–276.

Meshkat, N., Kuo, C.E.Z., and DiStefano III, J. (2014). On finding and using identifiable parameter combinations in nonlinear dynamic systems biology models and combos: A novel web implementation. *PLoS One*, 9(10).

Pohjantalo, H. (1978). System identifiability based on the power series expansion of the solution. *Math. Biosci.*, 41(1), 21–33.

Raue, A., Kreutz, C., Maiwald, T., Bachmann, J., et al. (2009). Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood. *Bioinformatics*, 25(15), 1923–1929.

Raue, A., Steiert, B., Schelker, M., Kreutz, C., et al. (2015). Data2dynamics: a modeling environment tailored to parameter estimation in dynamical systems. *Bioinformatics*, 31(21), 3558–3560.

Saccomani, M.P., Audoly, S., and D’Angiò, L. (2003). Parameter identifiability of nonlinear systems: the role of initial conditions. *Automatica*, 39(4), 619–632.

Saccomani, M.P. and Cobelli, C. (1992). Qualitative experiment design in physiological system identification. *IEEE Control Syst. Mag.*, 12(6), 18–23.

Stigter, J.D. and Molenaar, J. (2015). A fast algorithm to assess local structural identifiability. *Automatica*, 58, 118–124.

Villaverde, A.F. and Banga, J.R. (2017). Structural properties of dynamic systems biology models: Identifiability, reachability, and initial conditions. *Processes*, 5(2), 29.

Villaverde, A.F., Barreiro, A., and Papachristodoulou, A. (2016). Structural identifiability of dynamic systems biology models. *PLoS Comput. Biol.*, 12(10), e1005153.

Walter, É. and Pronzato, L. (1990). Qualitative and quantitative experiment design for phenomenological models—a survey. *Automatica*, 26(2), 195–213.

Xia, X. and Moog, C.H. (2003). Identifiability of nonlinear systems with application to HIV/AIDS models. *IEEE Trans. Autom. Control*, 48(2), 330–336.

Yates, J.W., Evans, N.D., and Chappell, M.J. (2009). Structural identifiability analysis via symmetries of differential equations. *Automatica*, 45(11), 2585–2591.