Guaranteed Numerical Computation as an Alternative to Computer Algebra for Testing Models for Identifiability

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Abstract. Testing parametric models for identifiability is particularly important for knowledge-based models. If several values of the parameter vector lead to the same observed behavior, then one may try to modify the experimental set-up to eliminate this ambiguity (which corresponds to performing qualitative experiment design). The tediousness of the algebraic operations involved in such tests makes computer algebra particularly attractive. This paper describes some limitations of this classical approach and explores an alternative route based on new definitions of identifiability and numerical tests implemented in a guaranteed way. The new approach is illustrated in the context of compartmental modeling, widely used in biology.

1 Introduction

In many domains of pure and applied sciences, one would like to build a mathematical model from input-output experimental data. Sometimes, the only purpose of modeling is to mimic these observations, with no physical interpretation in mind. One then speaks of a *black-box model*. The situation considered in this paper is different. It is assumed that some prior knowledge is used to build a mathematical model that depends on a vector of parameters to be estimated from the data. If the model is entirely based on such a prior knowledge, one speaks of a *white-box model*. This is an idealized situation seldom encountered and the model is often a mixture of knowledge-based and black-box parts. One then speaks of a *gray-box model*. For white-box and gray-box models, all or some of the parameters receive a physical interpretation, and one would like to make sure that these parameters can be estimated meaningfully.

Let $\mathbf{u}$ be the (known) vector of the inputs of the system, which is usually a function of time t, and let $\mathbf{y}(t)$ be the corresponding vector of the outputs of the system at time t. A typical set-up for estimating the vector $\mathbf{p}$ of the parameters

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of the model of this system (see, for instance, [1], [2] or [3]) is to give the system and model the same input (one then speaks of a *parallel model*), and to look for the estimate $\widehat{\mathbf{p}}$ that minimizes the sum of the squares of the differences between the system and model outputs

$$\widehat{\mathbf{p}} = \arg\min_{\mathbf{p}} \sum_{i=1}^{f} (\mathbf{y}(t_i) - \mathbf{y}_{\mathrm{m}}(t_i, \mathbf{p}))^{\mathrm{T}} (\mathbf{y}(t_i) - \mathbf{y}_{\mathrm{m}}(t_i, \mathbf{p})).$$

In this equation, the t_is are the instants of time at which the outputs of the system are measured and $\mathbf{y}_{\mathrm{m}}(t, \mathbf{p})$ is the vector of the outputs of the model at time t when the parameter vector takes the value $\mathbf{p}$. The dependence of $\mathbf{y}$ and $\mathbf{y}_{\mathrm{m}}$ on the input $\mathbf{u}$ is omitted to simplify notation. When $\mathbf{p}$ has a physical meaning, one would like to know whether finding a numerical value for $\widehat{\mathbf{p}}$ gives any indication about the actual values of the physical parameters of the system under investigation. If not, one may try to modify the experimental set-up in order to remove the ambiguity. This is why it is desirable to reach a conclusion *as soon as possible* (if possible before performing any actual experimentation). A partial answer is found, under idealized conditions, with the concept of *identifiability*. We shall start by presenting the classical notion of identifiability before pointing out some of its limitations and proposing alternative definitions of identifiability and a guaranteed numerical method of test consistent with these new definitions.

2 Classical Approach to Identifiability Testing

Assume that there are no measurement noise or system perturbations, that the input and measurement times can be chosen in the most informative manner and that the system is actually described by a model with output $\mathbf{y}_{\mathrm{m}}(t_i, \mathbf{p}^*)$, where $\mathbf{p}^*$ is the (unknown) true value of the parameter vector. Under these idealized conditions, it is always possible to find at least one $\widehat{\mathbf{p}}$ such that the "system" with parameters $\mathbf{p}^*$ and the "model" with parameters $\widehat{\mathbf{p}}$ behave in *exactly* the same manner for all inputs and times, which we shall denote by

$$\mathbf{y}_{\mathrm{m}}(t, \widehat{\mathbf{p}}) \equiv \mathbf{y}_{\mathrm{m}}(t, \mathbf{p}^*). \tag{1}$$

It suffices to take the trivial solution $\widehat{\mathbf{p}} = \mathbf{p}^*$ for (1) to be satisfied. If this solution is unique, then the model is said to be *globally* (or *uniquely*) identifiable. This is of course desirable. Unfortunately, there may be parasitic solutions. If the number of solutions of (1) for $\widehat{\mathbf{p}}$ is greater than one, then we know that even under idealized conditions it will not be possible to estimate meaningfully all components of $\mathbf{p}^*$ with a single point estimate such as $\widehat{\mathbf{p}}$. As an illustrative example, consider the compartmental model described by Figure 1. Each circle represents a tank. The ith tank contains a quantity x_i of material. These tanks exchange material between themselves and with the exterior as indicated by arrows. A usual assumption in linear compartmental modeling is that the flow of material leaving a compartment via an arrow is proportional to the quantity of material in this compartment. The constants of proportionality of these exchanges are then

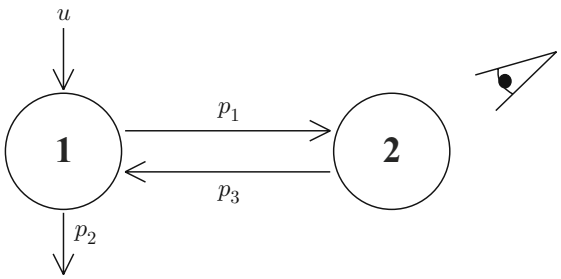

Fig. 1. Compartmental model

parameters to be estimated. Note that even when the compartmental model is linear, its output is nonlinear in these parameters, which significantly complicates their estimation. The dynamical state-space equations associated with a given compartmental model are very simple to obtain by writing down mass balances for each compartment. Such models, or variants of them, are widely used in biology and find applications in other experimental sciences such as pharmacokinetics, chemistry or ecology [4], [5]. For the model of Figure 1, mass balances in Compartments 1 and 2 lead to

$$\frac{\mathrm{d}x_1}{\mathrm{d}t} = -(p_1 + p_2)x_1 + p_3 x_2 + u$$

and

$$\frac{\mathrm{d}x_2}{\mathrm{d}t} = p_1 x_1 - p_3 x_2.$$

Assume that there is no material in the system at time 0, so $\mathbf{x}(0) = \mathbf{0}$, and that the quantity of material in Compartment 2 can be measured at any positive time, so

$$\mathbf{y}_{\mathrm{m}}(t, \mathbf{p}) = x_2(t, \mathbf{p}).$$

The question we are interested in is as follows: assuming that noise-free data are generated by a compartmental model with the structure described by Figure 1 and parameters $\mathbf{p}^*$, can the value of $\mathbf{p}^*$ be recovered from an analysis of the input-output data?

An obvious difficulty with this question is that the numerical value of $\mathbf{p}^*$ is unknown (since the very purpose of the exercise is to estimate it!), so we would like to reach a conclusion that would not depend on this value. Unfortunately, this is impossible in general, because there are usually atypical hypersurfaces in parameter space for which the conclusion is not the same as for all other values of the parameter vector. An example of such an atypical hypersurface is the plane defined by $p_1^* = 0$ for the model of Figure 1. Indeed, if there is no flow from Compartment 1 to Compartment 2 then no material ever reaches Compartment 2 and $y(t) = y_{\mathrm{m}}(t, \mathbf{p}^*) \equiv 0$, so there is no information in the

system output about p_2^* and p_3^*. This is of course pathological and one would not use such a model if one had reasons to believe that there is no exchange from Compartment 1 to Compartment 2. The existence of such pathological situations led to the following usual definition of *structural* (or *generic*) *identifiability* [6]: a model is *structurally globally identifiable* (s.g.i. for short) if *for almost any value of* $\mathbf{p}^*$

$$\mathbf{y}_\mathrm{m}(t, \widehat{\mathbf{p}}) \equiv \mathbf{y}_\mathrm{m}(t, \mathbf{p}^*) \Rightarrow \widehat{\mathbf{p}} = \mathbf{p}^*.$$

If a model is not s.g.i., then there are several values of $\widehat{\mathbf{p}}$ for the same input-output behavior, and it is impossible to find out which one of them corresponds to $\mathbf{p}^*$ even in our idealized noise-free experimental set-up. The situation can only get worse in the presence of noise or perturbations. Moreover since there are several models with the same behavior, there are several ways of reconstructing non-measured state variables, *e.g.*, by Kalman filtering, with different results. So it is important to test models for identifiability whenever unknown parameters or state variables have a physical meaning or when decisions are to be taken on the basis of the numerical values of the estimates of these quantities.

A typical method of test consists of two steps. The first one is the obtention of algebraic equations that $\widehat{\mathbf{p}}$ and $\mathbf{p}^*$ must satisfy for (1) to hold true. For the model of Figure 1, it is easy to show that its transfer function is

$$\frac{Y(s)}{U(s)} = \frac{p_1}{s^2 + (p_1 + p_2 + p_3)s + p_2 p_3},$$

or equivalently that

$$\frac{\mathrm{d}^2 y}{\mathrm{d}t^2} + (p_1 + p_2 + p_3)\frac{\mathrm{d}y}{\mathrm{d}t} + p_2 p_3 y = p_1 u.$$

So, for almost any value of $\mathbf{p}^*$, (1) holds true if and only if

$$\begin{cases} \widehat{p}_1 = p_1^*, \\ \widehat{p}_1 + \widehat{p}_2 + \widehat{p}_3 = p_1^* + p_2^* + p_3^*, \\ \widehat{p}_2 \widehat{p}_3 = p_2^* p_3^*. \end{cases}$$

The second step is then the search for all solutions of these equations for $\widehat{\mathbf{p}}$. In the case of the model of Figure 1, these solutions are the trivial solution $\widehat{\mathbf{p}} = \mathbf{p}^*$ and

$$\begin{cases} \widehat{p}_1 = p_1^*, \\ \widehat{p}_2 = p_3^*, \\ \widehat{p}_3 = p_2^*. \end{cases}$$

The model of Figure 1 is therefore not s.g.i. The roles of p_2 and p_3 can be interchanged, and it is impossible to know which is which. Moreover, since there are two models with the same input-output behavior, there are two ways of reconstructing x_1 from measurements of x_2, even in a noise-free situation, leading to different values of $\widehat{x}_1$. Note that the parameter p_1, which takes the same values in the two solutions is s.g.i., and recall that most of this analysis becomes false if $p_1^* = 0$.

3 Limitations of This Classical Approach

Steps 1 and 2 of structural identifiability testing require algebraic manipulations that may become exceedingly complicated for models of a more realistic size. Both are facilitated by computer algebra [7], but these algebraic manipulations may become so complex that they are no longer feasible even on present-day computers. Moreover taking into account the fact that only real solutions are of interest is still a subject of research with computer algebra. Failing to detect that all solutions for $\widehat{\mathbf{p}}$ but one are complex would mean failing to detect that the parameters are actually globally identifiable.

Consider, for example, the (static) one-parameter model

$$y_{\mathrm{m}}(p) = p(p-1)(p+1).$$

Equation (1) translates into

$$\widehat{p}(\widehat{p}-1)(\widehat{p}+1) = p^*(p^*-1)(p^*+1),$$

and the set of real solutions for $\widehat{p}$ is a singleton, a pair or a triple depending on the value taken by p^*. So global identifiability is *not* a structural property for this model.

These shortcomings call for new definitions of identifiability, first presented in [8].

4 New Definitions and Method of Test

The parameter p_i will be said to be *globally identifiable in* $\mathbb{P}$ (g.i.i.$\mathbb{P}$) if for all $(\mathbf{p}^*, \widehat{\mathbf{p}})$ in $\mathbb{P} \times \mathbb{P}$, $\mathbf{y}_{\mathrm{m}}(t, \widehat{\mathbf{p}}) \equiv \mathbf{y}_{\mathrm{m}}(t, \mathbf{p}^*)$ implies that $\widehat{p}_i = p_i^*$. The model will be g.i.i.$\mathbb{P}$ if all of its parameters are g.i.i.$\mathbb{P}$. With this new definition of identifiability, atypical hypersurfaces are no longer allowed in $\mathbb{P}$ and unique identifiability can be established even if the model is not structurally globally identifiable. It makes sense to study identifiability in a specific region $\mathbb{P}$ of parameter space, if only because some information is usually available on the sign and possible range for each physical parameter.

It does not suffice to have realistic new definitions of identifiability, methods of test are also needed. A model will be g.i.i.$\mathbb{P}$ if and only if

$$\nexists(\mathbf{p}^*, \widehat{\mathbf{p}}) \in \mathbb{P} \times \mathbb{P} \text{ such that } \mathbf{y}_{\mathrm{m}}(t, \widehat{\mathbf{p}}) \equiv \mathbf{y}_{\mathrm{m}}(t, \mathbf{p}^*) \text{ and } \|\widehat{\mathbf{p}} - \mathbf{p}^*\|_\infty > 0.$$

In practice, it will usually suffice to prove that

$$\nexists(\mathbf{p}^*, \widehat{\mathbf{p}}) \in \mathbb{P} \times \mathbb{P} \text{ such that } \mathbf{y}_{\mathrm{m}}(t, \widehat{\mathbf{p}}) \equiv \mathbf{y}_{\mathrm{m}}(t, \mathbf{p}^*) \text{ and } \|\mathbf{p}^* - \widehat{\mathbf{p}}\|_\infty > \delta,$$

where δ is some small positive number to be chosen by the user. The model will then be said to be δ-g.i.i.$\mathbb{P}$. Testing whether a model is δ-g.i.i.$\mathbb{P}$ boils down to a constraint satisfaction problem (CSP). The algorithm SIVIA, combined with a

forward-backward contractor, can be used to bracket the solution set $\mathbb{S}$ of the CSP

$$(\mathbf{p}^*, \widehat{\mathbf{p}}) \in \mathbb{P} \times \mathbb{P},\ \mathbf{y}_{\mathrm{m}}(t, \widehat{\mathbf{p}}) \equiv \mathbf{y}_{\mathrm{m}}(t, \mathbf{p}^*),\ \left\|\mathbf{p}^* - \widehat{\mathbf{p}}\right\|_\infty > \delta$$

between inner and outer approximations:

$$\underline{\mathbb{S}} \subset \mathbb{S} \subset \overline{\mathbb{S}}.$$

If $\overline{\mathbb{S}}$ is empty, then the model is δ-g.i.i.$\mathbb{P}$. If $\underline{\mathbb{S}}$ is not empty, then the model is not δ-g.i.i.$\mathbb{P}$. Details about SIVIA can be found in the paper by Kieffer and Walter in this volume and in [9], where forward-backward contractors are also presented.

5 Benchmark Example

The model of Figure 2 could serve as a benchmark example. It has been proposed to describe the distribution of drugs such as Glafenine in the body [10], [11] after oral administration. Compartment 1 corresponds to the drug in the gastro-

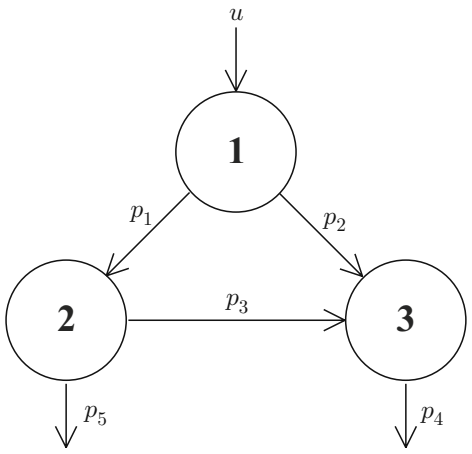

Fig. 2. Model of the distribution of Glafenine

intestinal tract, and Compartments 2 and 3 respectively correspond to the drug and its metabolite in the systemic circulation. The state equation of this model is

$$\begin{bmatrix} \frac{dx_1}{dt} \\ \frac{dx_2}{dt} \\ \frac{dx_3}{dt} \end{bmatrix} = \begin{bmatrix} -(p_1+p_2) & 0 & 0 \\ p_1 & -(p_3+p_5) & 0 \\ p_2 & p_3 & -p_4 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} u.$$

By measuring the plasma concentration of the drug and its metabolite, the quantities of drug in Compartments 2 and 3 are determined up to unknown multiplicative constants, so

$$\mathbf{y}_{\mathrm{m}}(t,\mathbf{p}) = \begin{pmatrix} p_6 x_2(t) \\ p_7 x_3(t) \end{pmatrix},$$

where p_6 and p_7 are respectively the inverses of the volumes of Compartments 2 and 3. The dimension of the parameter vector $\mathbf{p}$ is thus seven. The corresponding transfer matrix is trivial to obtain by taking the Laplace transform of the state and observation equations and then eliminating the state variables. The same approach as in the introductory example of Section 2 can then be used to obtain a set of nonlinear equations in $\widehat{\mathbf{p}}$ and $\mathbf{p}^*$ that are equivalent to

$$\mathbf{y}_{\mathrm{m}}(t,\widehat{\mathbf{p}}) \equiv \mathbf{y}_{\mathrm{m}}(t,\mathbf{p}^*).$$

These equations can be written as

$$\widehat{p}_1\widehat{p}_6 = p_1^* p_6^*$$

$$\widehat{p}_2\widehat{p}_7 = p_2^* p_7^*$$

$$\widehat{p}_7\left(\widehat{p}_1\widehat{p}_3 + \widehat{p}_2\widehat{p}_3 + \widehat{p}_2\widehat{p}_5\right) = p_7^*\left(p_1^* p_3^* + p_2^* p_3^* + p_2^* p_5^*\right)$$

$$\widehat{p}_1 + \widehat{p}_2 + \widehat{p}_3 + \widehat{p}_5 = p_1^* + p_2^* + p_3^* + p_5^*$$

$$\widehat{p}_1\widehat{p}_3 + \widehat{p}_1\widehat{p}_5 + \widehat{p}_2\widehat{p}_3 + \widehat{p}_2\widehat{p}_5 = p_1^* p_3^* + p_1^* p_5^* + p_2^* p_3^* + p_2^* p_5^*$$

$$\widehat{p}_1 + \widehat{p}_2 + \widehat{p}_3 + \widehat{p}_4 + \widehat{p}_5 = p_1^* + p_2^* + p_3^* + p_4^* + p_5^*$$

$$\begin{aligned}\widehat{p}_1\widehat{p}_3 + \widehat{p}_1\widehat{p}_4 + \widehat{p}_1\widehat{p}_5 + \widehat{p}_2\widehat{p}_3 + \widehat{p}_2\widehat{p}_4 + \widehat{p}_2\widehat{p}_5 + \widehat{p}_3\widehat{p}_4 + \widehat{p}_4\widehat{p}_5 = \\ p_1^* p_3^* + p_1^* p_4^* + p_1^* p_5^* + p_2^* p_3^* + p_2^* p_4^* + p_2^* p_5^* + p_3^* p_4^* + p_4^* p_5^*\end{aligned}$$

$$\widehat{p}_4\left(\widehat{p}_1\widehat{p}_3 + \widehat{p}_1\widehat{p}_5 + \widehat{p}_2\widehat{p}_3 + \widehat{p}_2\widehat{p}_5\right) = p_4^*\left(p_1^* p_3^* + p_1^* p_5^* + p_2^* p_3^* + p_2^* p_5^*\right)$$

Their obtention is facilitated by the use of computer algebra.

We said in [8] that this model was δ-g.i.i.$\mathbb{P}$ for $\mathbb{P} = [0.6, 1]^{\times 7}$ and $\delta = 10^{-9}$, but this remains to be confirmed, as this result may have been obtained with an incorrect software.

6 Conclusions

The concept of identifiability is important whenever physically meaningful parameters or state variables are to be estimated from experimental data. Testing models for structural global identifiability is not always possible, even with the help of computer algebra, and when a conclusion can be reached, it is not always relevant. This has led us to propose new definitions of global identifiability in a domain of parameter space. With this definition, it is possible to prove identifiability even in cases where the parameters are not structurally identifiable. The tests are performed via interval constraint satisfaction programming, with the use of contractors to avoid bisection as much as possible, thereby reducing the effect of the curse of dimensionality. We hope to have convinced the reader that identifiability testing is both a useful part of model building and an interesting challenge for interval analysts.

In this paper, it was assumed that there was a single model structure to be considered for the description of the data. When several model structures are in competition, a natural question to ask is whether it will be possible to select one that is more appropriate than the others. This question can be answered in the same type of idealized setting as considered for identifiability and corresponds then to the notion of *distinguishability*. The methodology advocated here for testing models for identifiability readily extends to the test of model structures for distinguishability.

References

1. Norton, J.P.: An Introduction to Identification. Academic Press, London (1986)
2. Ljung, L.: System Identification, Theory for the User, 2nd Edition. Prentice Hall, Englewood Cliffs (1999)
3. Walter, E., Pronzato, L.: Identification of Parametric Models from Experimental Data. Springer-Verlag, London (1997)
4. Jacquez, J.A.: Compartmental Analysis in Biology and Medecine. Elsevier, Amsterdam (1972)
5. Godfrey, K.: Compartimental Models and Their Application. Academic Press, London (1983)
6. Walter, E.: Identifiability of State Space Models. Springer-Verlag, Berlin (1982)
7. Raksanyi, A., Lecourtier, Y., Walter, E., Venot, E.: Identifiability and distinguishability testing in computer algebra. Math. Biosci. **77(1-2)** (1985) 245–266
8. Braems, I., Jaulin, L., Kieffer, M., Walter, E.: Guaranteed numerical alternatives to structural identifiability testing. In: Proceedings of the 40th IEEE Conference on Decision and Control, Orlando (2001) 3122–3128
9. Jaulin, L., Kieffer, M., Didrit, O., Walter, E.: Applied Interval Analysis. Springer-Verlag, London (2001)
10. Balant, L.: Applicability of different types of models in health and disease. Drug Metab. Rev. **15** (1984) 75–102
11. Venot, A., Walter, E., Lecourtier, Y., Raksanyi, A., Chauvelot-Moachon, L.: Structural identifiability of "first-pass" models. Journal of Pharmacokinetics and Biopharmaceutics **15** (1987) 179–189