

Guaranteed numerical alternatives to structural identifiability testing

I. Braems¹, L. Jaulin², M. Kieffer¹ and E. Walter¹

¹Laboratoire des Signaux et Systèmes, CNRS-Supélec-Université Paris-Sud
91192 Gif-sur-Yvette, France

{braems, kieffer, walter}@lss.supelec.fr

²Laboratoire d'Ingénierie des Systèmes Automatisés, Université d'Angers

2 bld Lavoisier, 49045 Angers, France

luc.jaulin@univ-angers.fr

Abstract

Testing models for structural identifiability is particularly important for knowledge-based models. If several values of the parameter vector lead to the same observed behavior of the model, then one may try to modify the experimental setup to eliminate this ambiguity (qualitative experiment design). The tediousness of the algebraic manipulations involved makes computer algebra particularly attractive. The purpose of this paper is to explore an alternative route based on guaranteed numerical computation. A new definition of identifiability in a domain allows testing to be cast into the framework of constraint-satisfaction problems, and makes it possible to use the tools of interval analysis and interval constraint propagation to get guaranteed answers. When the data have already been collected, the notion of structural identifiability may not be the most pertinent concept. This paper shows how interval analysis and interval constraint propagation can again be used to bypass the identifiability study and estimate even parameters that are not identifiable uniquely.

Keywords: constraint satisfaction problems, compartmental models, experiment design, guaranteed numerical computation, identifiability, identification, interval analysis, parameter estimation.

1 Introduction

Underlying the notion of identifiability is the question of whether one can hope uniquely to estimate the parameters of a model from the experimental data that can be collected. This question is particularly relevant for knowledge-based models, where these parameters have a concrete meaning, and whenever decisions are to be taken on the basis of their numerical values. The importance of the notion has been recognized more than 50 years ago [1], but much remains to be done to convince potential users and to provide them with tools to test their models for identifiability. As the algebraic manipulations involved in identifiability testing can become

really tedious, the use of computer algebra and elimination theory to obtain reliable results is particularly attractive, see, *e.g.*, [2]-[7].

The purpose of the present paper is to explore an alternative route, mainly based on numerical computation, and discuss its advantages and disadvantages. The paper is organized as follows. The notion of structural identifiability is briefly recalled in Section 2, where some limits of a formal approach are also mentioned. These limits are the rationale for the development of an alternative numerical approach based on interval analysis and interval constraint propagation in Section 3. Section 4 shows that these tools may make it possible to bypass the structural identifiability study altogether by allowing one to characterize, in a guaranteed way, the set of *all* values of the parameter vector that are consistent with the experimental data collected on the system to be modeled. It thus becomes possible to identify unidentifiable models.

2 Formal approach to structural identifiability

Structural identifiability is studied in an idealized context where the data are assumed to be generated by a model with the same structure $\mathcal{M}(\cdot)$ as the model to be identified. The *unknown* true value of the parameter vector is denoted by \mathbf{p}^* , and is assumed to belong to some prior feasible set $\mathbb{P} \subset \mathbb{R}^{\dim \mathbf{p}}$. From noise-free data generated by $\mathcal{M}(\mathbf{p}^*)$, one wants to estimate the parameters of a model $\mathcal{M}(\hat{\mathbf{p}})$. In these idealized conditions, it is always possible to tune $\hat{\mathbf{p}}$ so as to ensure that the outputs generated by the “model” $\mathcal{M}(\hat{\mathbf{p}})$ are identical to those generated by the “process” $\mathcal{M}(\mathbf{p}^*)$ for all inputs and times. The identity of these external behaviors will then be expressed concisely by

$$\mathcal{M}(\hat{\mathbf{p}}) = \mathcal{M}(\mathbf{p}^*). \quad (1)$$

The identifiability of $\hat{\mathbf{p}}$ only depends on the number of solutions of (1) for $\hat{\mathbf{p}}$ in \mathbb{P} . If the set \mathbb{S} of all these solutions reduces to the singleton $\{\mathbf{p}^*\}$, then $\hat{\mathbf{p}}$ is *globally* (or

uniquely) identifiable at \mathbf{p}^* . If \mathbb{S} is denumerable (most often finite), then $\hat{\mathbf{p}}$ is *locally* (or *countably*) *identifiable* at \mathbf{p}^* . If \mathbb{S} is not denumerable, then $\hat{\mathbf{p}}$ is *unidentifiable* at \mathbf{p}^* . Of course, a given entry \hat{p}_i of $\hat{\mathbf{p}}$ may be locally or globally identifiable even when the entire parameter vector is unidentifiable.

Now this identifiability study may take place before data collection. This is actually advisable, as the results of the identifiability study may impact on the experiments to be conducted [8]. No numerical value is then available for \mathbf{p}^* , and we would like our conclusions to be valid whatever the value of \mathbf{p}^* may be. Unfortunately, this is not always possible, which led to the notion of *structural* (or *generic*) identifiability. A parameter p_i is *structurally globally identifiable* (*s.g.i.*) if, for almost any \mathbf{p}^* in \mathbb{P} , the set \mathbb{S} of the solutions of (1) for \hat{p}_i reduces to the singleton p_i^* . It is *structurally locally identifiable* (*s.l.i.*) if, for almost any \mathbf{p}^* in \mathbb{P} , \mathbb{S} is denumerable or finite. If \mathbb{S} is not denumerable, for almost any \mathbf{p}^* in \mathbb{P} , then p_i is *structurally unidentifiable*. Of course, \mathbf{p} is *s.g.i.* or *s.l.i.* if all of its components are *s.g.i.* or *s.l.i.*

When testing model structures for identifiability, the standard approach is in two steps. During the first step, the equations to be satisfied by $\hat{\mathbf{p}}$ for (1) to hold true are established, and this is usually much facilitated by the use of computer algebra. Very often, (1) translates into a set of equations:

$$\mathbf{r}(\hat{\mathbf{p}}) = \mathbf{r}(\mathbf{p}^*). \quad (2)$$

During the second step, the set of all solutions of (2) for $\hat{\mathbf{p}}$ is sought for. When each component of $\mathbf{r}(\mathbf{p})$ is polynomial in the entries of \mathbf{p} , elimination theory can be used to put this set of polynomial equations into a triangular form

$$\mathbf{t}(\hat{\mathbf{p}}) = \mathbf{t}(\mathbf{p}^*), \quad (3)$$

where again each component of $\mathbf{t}(\mathbf{p})$ is polynomial in the entries of \mathbf{p} . It then becomes possible, at least in principle, to solve (3) by solving a succession of polynomial equations in a single unknown, in a way similar to that used to solve linear systems of equations by triangularization, and thus to obtain the set \mathbb{S} of all the parameter vectors $\hat{\mathbf{p}}$ that satisfy these equations. The method used to build (3) from (2) guarantees that no solution can be lost, so if the degree of each of the polynomial equations to be solved in the process is generically one, then it has been proven that \mathbf{p} is *s.g.i.* Even when this is not so, it is sometimes possible to generate the set of all solutions of (2) for $\hat{\mathbf{p}}$ as an explicit function of \mathbf{p}^* , what has been called *exhaustive modeling* [9]. Provided that the cardinal of this set keeps the same value for almost any value of \mathbf{p}^* , this formal approach allows one to conclude about the structural identifiability of the model under study.

Testing models for structural identifiability is a very interesting domain of application for computer algebra,

because one looks for a simple answer to the simple qualitative question of whether the model is *s.g.i.* There are, however several reasons why the approach may turn out not to be satisfactory.

- (1) may not translate into polynomial equations, or the translation may make the problem exceedingly complicated to solve.
- Reaching a conclusion may require formal manipulations that are much more complicated than allowed by present-day computers.
- The degree of some of the univariate polynomials to be solved may be too large for an analytic expression to exist, which then imposes the use of numerical methods and the loss of the formal nature of the solution.
- The number of *real* solutions for the \hat{p}_i 's (the only ones in which we are interested) may depend on the value of \mathbf{p}^* in such a way that no conclusion of a structural nature can be reached. The following example will serve to illustrate this point. It will be treated in Section 3 with the alternative approach advocated in this paper.

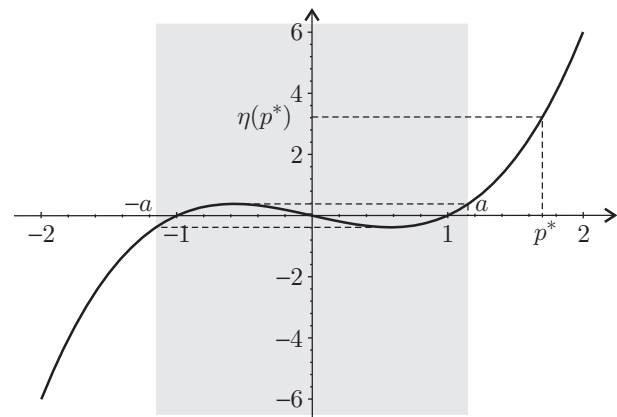


Figure 1: Output of the polynomial model of Example 1; the grey zone corresponds to the values of p^* for which the model is not uniquely identifiable

Example 1 Consider the model

$$\eta(p) = p(p-1)(p+1),$$

with one parameter p in $\mathbb{P} = [-2, 2]$ and no input. For any (\hat{p}, p^*) in $\mathbb{P} \times \mathbb{P}$, $\mathcal{M}(\hat{\mathbf{p}}) = \mathcal{M}(\mathbf{p}^*)$ if and only if

$$p^*(p^* - 1)(p^* + 1) - \hat{p}(\hat{p} - 1)(\hat{p} + 1) = 0.$$

The set of feasible values for \hat{p} is a singleton for $p^* \in]-2, -a[\cup]a, 2[$, a pair for $p^* = a$ or $p^* = -a$, and a triple for p^* in $]-a, a[$, with $a = \frac{2}{\sqrt{3}}$ (see Figure 1). So unique identifiability is not a structural property in \mathbb{P} . ■

3 Alternative guaranteed numerical approaches

The route to be followed will depend on whether a numerical value can be given to \mathbf{p}^* .

3.1 A numerical value can be given to \mathbf{p}^*

This will be the case, for instance, when a satisfactory model with structure $\mathcal{M}(\cdot)$ has already been identified from experimental data and one is interested in estimating all the models with the same structure and the same external behavior. It then suffices to take for \mathbf{p}^* the numerical value of the vector of the estimated parameters, and to get a reliable estimate of the number of solutions of (2) for $\hat{\mathbf{p}}$ by using a guaranteed solver. This can be done by means of interval analysis [10], [11]. Solving (2) amounts to finding the zeros of the function \mathbf{f} defined in \mathbb{P} by

$$\mathbf{f}(\hat{\mathbf{p}}) = \mathbf{r}(\hat{\mathbf{p}}) - \mathbf{r}(\mathbf{p}^*). \quad (4)$$

When $\dim \mathbf{p} = \dim \mathbf{f}(\mathbf{p})$, under the hypothesis that \mathbf{f} is continuously differentiable, an interval Newton solver can be employed to enclose *all* these zeros in a union \mathbb{L} of interval vectors (or *boxes*) $[\hat{\mathbf{p}}]$ [12]. The width of these boxes depends on a tuning parameter with a direct impact on the amount of computation required. In this solver we used the Newton-Gauss-Seidel operator $N_{\text{GS}}([\mathbf{p}])$ [12], which has the following properties:

- (i) each zero $\hat{\mathbf{p}}$ of (4) in any box $[\mathbf{p}]$ satisfies $\hat{\mathbf{p}} \in N_{\text{GS}}([\mathbf{p}])$;
- (ii) if $N_{\text{GS}}([\mathbf{p}]) = \emptyset$, then there is no zero of (4) in $[\mathbf{p}]$;
- (iii) if $N_{\text{GS}}([\mathbf{p}])$ is strictly inside $[\mathbf{p}]$, then $[\mathbf{p}]$ contains exactly one zero of \mathbf{f} .

Properties (i) and (ii) indicate that the result is reliable in the sense that no zero can be lost. Property (iii) is used to evaluate the actual number of zeros. If \mathbb{L} is reduced to a single box $[\hat{\mathbf{p}}]$ and (iii) is satisfied for $[\hat{\mathbf{p}}]$, then the model is globally identifiable at \mathbf{p}^* . Else, $[\hat{\mathbf{p}}]$ may contain one or more zeros. A solution is then to split $[\hat{\mathbf{p}}]$ into two subboxes $[\mathbf{p}_1]$ and $[\mathbf{p}_2]$ and to apply N_{GS} again on $[\mathbf{p}_1]$ and $[\mathbf{p}_2]$. If all boxes in \mathbb{L} are such that (iii) is satisfied, then the model is locally identifiable at \mathbf{p}^* .

3.2 A prior domain can be given to \mathbf{p}^*

One of the interest of structural identifiability is that it can be tested before experimentation and thus serve as a tool for qualitative experiment design [8]. On the other hand, the experimenter may feel uncomfortable with the fact that global identifiability is not necessarily a structural property (as shown in Example 1) and that, even if the model is s.g.i., there may be atypical regions where the conclusion reached may be false. This motivates the following new definition.

Definition 1 *The parameter p_i is globally identifiable in \mathbb{P} (g.i.i. \mathbb{P}) if*

$$\forall (\mathbf{p}^*, \hat{\mathbf{p}}) \in \mathbb{P} \times \mathbb{P}, \quad \mathcal{M}(\hat{\mathbf{p}}) = \mathcal{M}(\mathbf{p}^*) \Rightarrow \hat{p}_i = p_i^*, \quad (5)$$

and the parameter vector \mathbf{p} is g.i.i. \mathbb{P} if all its components are g.i.i. \mathbb{P} .

Definition 1 no longer allows the existence of atypical regions in \mathbb{P} and underlines the importance of the search domain \mathbb{P} . If the problem

$$\mathcal{M}(\hat{\mathbf{p}}) = \mathcal{M}(\mathbf{p}^*), \quad \|\hat{\mathbf{p}} - \mathbf{p}^*\|_\infty > 0 \quad (6)$$

has no solution for $(\hat{\mathbf{p}}, \mathbf{p}^*)$ in $\mathbb{P} \times \mathbb{P}$, then \mathbf{p} is *g.i.i. \mathbb{P}* . This makes it easy to express the test of global identifiability as a *constraint satisfaction problem* (CSP). A CSP consists of a set of variables (here, $\{\hat{p}_1, \dots, \hat{p}_n, p_1^*, \dots, p_n^*\}$), a set of domains assumed to contain these variables (here we shall consider intervals, and \mathbb{P} will be taken as a box, but more sophisticated search domains, such as unions of boxes, could also be considered), and a set of constraints to be satisfied (here, those in (6)). *Interval constraint propagation* (ICP) has been developed to deliver guaranteed outer approximations of the solutions of CSP's (see, e.g., [13] and the references therein). ICP contracts the initial domains into smaller ones. If a deadlock is reached, bisection of the domain of interest can once again be applied, at the cost of an increase in complexity.

In practice, (6) is replaced by

$$\mathcal{M}(\hat{\mathbf{p}}) = \mathcal{M}(\mathbf{p}^*), \quad \|\hat{\mathbf{p}} - \mathbf{p}^*\|_\infty > \varepsilon, \quad (7)$$

where ε is some positive coefficient to be set by the user to express a distance below which parameter vectors will not be distinguished. We shall then talk of ε -g.i.i. \mathbb{P} parameters or models. For ε -g.i.i. \mathbb{P} models, ICP may allow a conclusion to be reached without a single bisection, which is particularly attractive for large-dimensional problems.

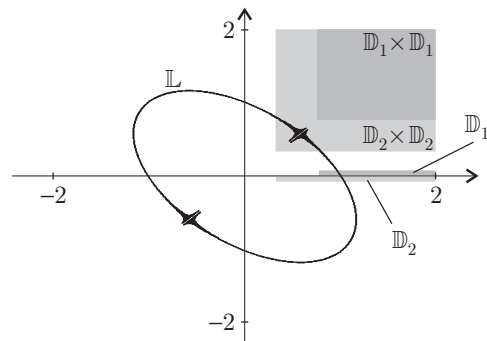


Figure 2: \mathbb{L} , as computed in the $(\hat{p} \times p^*)$ space for Example 2, and the domains \mathbb{D}_1 and \mathbb{D}_2 ; since $\mathbb{D}_2 \times \mathbb{D}_2$ intersects \mathbb{L} , \mathcal{M} may not be ε -g.i.i. \mathbb{D}_2 , whereas it is ε -g.i.i. \mathbb{D}_1

Example 2 *Consider again the model of Example 1, and the domains $\mathbb{D}_1 = [0.8, 2]$ and $\mathbb{D}_2 = [0.3, 2]$. With $\varepsilon = 0.02$, in 1 ms on a Pentium 350, ICP proved that \mathcal{M} is ε -g.i.i. \mathbb{D}_1 , but could not conclude about whether \mathcal{M} is ε -g.i.i. \mathbb{D}_2 . Figure 2 presents an outer approximation \mathbb{L} of all solutions of (7) for $(\hat{\mathbf{p}}, \mathbf{p}^*)$ in $[-2, 2] \times [-2, 2]$, as*

computed in 2.2 s by ICP. Since $\mathbb{D}_2 \times \mathbb{D}_2$ intersects \mathbb{L} , it may exist $(\hat{\mathbf{p}}, \mathbf{p}^*)$ in $\mathbb{D}_2 \times \mathbb{D}_2$ satisfying (7). It can be shown on this simple example that the actual solution set \mathbb{S} of (7) is included in the ellipse defined by $(\hat{\mathbf{p}} + \mathbf{p}^*)^2 - \hat{\mathbf{p}} \times \mathbf{p}^* = 1$. The constraint $\|\hat{\mathbf{p}} - \mathbf{p}^*\|_\infty > \varepsilon$ in (7) implies that a part of this ellipse does not belong to \mathbb{S} . This analysis confirms that \mathcal{M} is not ε -g.i.i. \mathbb{D}_2 . ■

Example 3 Consider the following compartmental model, used to describe the behavior of a drug such as Glafenine administered orally:

$$\mathcal{M}(\mathbf{p}) : \begin{cases} \dot{q}_1 &= -(p_1 + p_2)q_1 + u, \\ \dot{q}_2 &= p_1q_1 - (p_3 + p_5)q_2, \\ \dot{q}_3 &= p_2q_1 + p_3q_2 - p_4q_3, \\ \eta_1 &= p_6q_2, \\ \eta_2 &= p_7q_3. \end{cases} \quad (8)$$

The initial conditions on the state variables q_i are all taken to be zero. $\mathcal{M}(\hat{\mathbf{p}}) = \mathcal{M}(\mathbf{p}^*)$ translates into (2) where the components of $\mathbf{r}(\mathbf{p})$ are the coefficients of the transfer matrix associated with (8). For this to be valid, the entries of this matrix should be expressed in some canonical form. For $\mathbb{P} = [0.6, 1]^{7 \times 7}$ and $\varepsilon = 10^{-9}$, ICP finds in 0.01 s that the model is ε -g.i.i. \mathbb{P} . On $\mathbb{P} = \mathbb{R}^7$, the model is not s.g.i. [8]. ■

4 Bypassing the identifiability study

When the data have already been collected, it is no longer so important to obtain conclusions that are valid for all (or almost all) possible values of \mathbf{p}^* . Instead, one would like to characterize the set \mathbb{S} of all values of $\hat{\mathbf{p}}$ that are consistent with these data, in a sense to be specified. Interval analysis can also be used for this purpose, as illustrated by the next two sections. The identifiability analysis is thus bypassed, to address the actual problem of interest directly, namely finding all optimal or acceptable models based on the data. The results are guaranteed, irrespective of whether the model structure is globally identifiable, contrary to those provided by traditional local numerical methods.

4.1 Global optimization

Assume that the set \mathbb{S} of interest is the set of all global minimizers of a suitable cost function $J(\cdot, \cdot)$, obtained, e.g., by a maximum-likelihood approach based on hypotheses about the noise corrupting the data

$$\mathbb{S} = \{\hat{\mathbf{p}} \in \mathbb{P} \mid J(\hat{\mathbf{p}}, \mathbf{y}) \leq J(\mathbf{p}, \mathbf{y}) \quad \forall \mathbf{p} \in \mathbb{P}\}, \quad (9)$$

where \mathbf{y} is the (numerically known) vector of all the data containing information about \mathbf{p} .

One of the main numerical difficulties attached with this approach is the fact that $J(\mathbf{p}, \mathbf{y})$ is usually not convex with respect to \mathbf{p} , so there may be several global minimizers $\hat{\mathbf{p}}$, as well as parasitic local minimizers that may

trap any estimation algorithm based on local iterative search only. Even with more global tools such as simulated annealing, adaptive random search or genetic algorithms, one will never be sure in a finite time that all global minimizers have been located. Deterministic global optimization based on interval analysis, exemplified by Hansen's algorithm [11], does not suffer from the same limitations. It allows one to eliminate parts of the prior search space \mathbb{P} that cannot contain any global minimizer of the cost function, and to reduce the boxes of parameter space that cannot be eliminated. The results obtained are *guaranteed*, in the sense that an outer approximation of \mathbb{S} is obtained. It may even be possible to estimate parameters that are not globally identifiable, as evidenced by the following example.

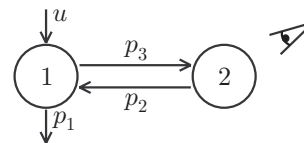


Figure 3: Two-compartment model of Example 4

Example 4 As in [14], consider the system described by Figure 3. The evolution of the vector $\mathbf{q} = (q_1, q_2)^T$ of the quantities of material in the two compartments is described by the linear time-invariant state equation

$$\begin{cases} \dot{q}_1 &= -(p_1 + p_3)q_1 + p_2q_2 + u, \\ \dot{q}_2 &= p_3q_1 - p_2q_2. \end{cases} \quad (10)$$

Take the system in zero initial condition ($\mathbf{q}(0_-) = \mathbf{0}$), and assume that a Dirac input $u(t) = \delta(t)$ is applied to Compartment 1, so $q_1(0_+) = 1$ and $q_2(0_+) = 0$. Assume also that the content of Compartment 2 is observed at 16 instants of time, according to

$$y_i = q_2(t_i) + n_i, \quad i = 1, \dots, 16, \quad (11)$$

where n_i is some measurement noise. It is trivial to show that the corresponding model outputs satisfy

$$\eta_i(\mathbf{p}) = \alpha (\exp(-\lambda_1 t_i) - \exp(-\lambda_2 t_i)), \quad i = 1, \dots, 16, \quad (12)$$

where α , λ_1 and λ_2 are simple functions of p_1, p_2 and p_3 . The parameter vector to be estimated is $\mathbf{p} = (p_1, p_2, p_3)^T$. The experimental data y_i , together with the times t_i at which they have been collected are given in Table 1. No prior information is available about \mathbf{p} , and the measurements y_i are all deemed equally reliable, so the cost function is chosen as

$$J(\mathbf{p}, \mathbf{y}) = \sum_{i=1}^{16} (y_i - \eta_i(\mathbf{p}))^2. \quad (13)$$

For $\mathbb{P} = [0.01, 2.0] \times [0.05, 3.0] \times [0.05, 3.0]$, and with its precision parameters ε_p and ε_J both equal to 10^{-9} ,

Hansen's algorithm guarantees that all global minimizers in \mathbb{P} are in the boxes

$$[1.925402, 1.925404] \times [0.232717, 0.232719] \\ \times [0.145075, 0.145077]$$

and

$$[0.232717, 0.232719] \times [1.925402, 1.925404] \\ \times [0.145075, 0.145077].$$

Note that these boxes can be deduced from one another by exchanging their interval values for p_1 and p_2 . This is consistent with the conclusion of an identifiability study. It seems important to stress that the conclusion of the present estimation was not based on such a study, which can therefore be dispensed with. Optimizing first with respect to α, λ_1 and λ_2 and then estimating \mathbf{p} with a guaranteed interval-based method, takes about one minute [14]. ■

Table 1: Experimental data

| t_i | y_i | t_i | y_i |
|-------|--------|-------|--------|
| 1 | 0.0532 | 9 | 0.0099 |
| 2 | 0.0478 | 10 | 0.0081 |
| 3 | 0.0410 | 11 | 0.0065 |
| 4 | 0.0328 | 12 | 0.0043 |
| 5 | 0.0323 | 13 | 0.0013 |
| 6 | 0.0148 | 14 | 0.0015 |
| 7 | 0.0216 | 15 | 0.0060 |
| 8 | 0.0127 | 16 | 0.0126 |

Instead of looking for all global minimizers of the cost function, one may look for the set \mathbb{S} of all values of \mathbf{p} such that the value of the cost function is below some threshold. This may be important in practice, as there does not seem to be any serious reason to eliminate values of \mathbf{p} that would correspond to values of the cost function almost equal to the absolute minimum. \mathbb{S} is then defined by an inequality, and the methods to be used are those of the next section. Note that such values of \mathbf{p} could not be obtained by a structural identifiability study based on purely algebraic manipulations.

4.2 Sets defined by inequalities

Assume now that

$$\mathbb{S} = \{\hat{\mathbf{p}} \in \mathbb{P} \mid \mathbf{g}(\hat{\mathbf{p}}, \mathbf{y}) \leq \mathbf{0}\}, \quad (14)$$

where $\mathbf{g}(\hat{\mathbf{p}}, \mathbf{y}) \leq \mathbf{0}$ is to be understood componentwise. \mathbb{S} may be a confidence region (at some level of confidence to be specified by the user). The (usually scalar) inequality $g(\hat{\mathbf{p}}, \mathbf{y}) \leq 0$ defining \mathbb{S} is then deduced by probabilistic considerations from hypotheses about the statistical distribution of the noise corrupting the data. The inequalities in (14) may also express that the errors

between the components y_i of the data vector and the corresponding model outputs $\eta_i(\mathbf{p})$ lie between known bounds. This corresponds to *parameter bounding* or *set-membership estimation* [15].

In both cases, characterizing \mathbb{S} can be cast into the framework of set inversion and performed using the algorithm SIVIA [16]. In this algorithm, a positive accuracy coefficient ε must also be tuned by the user, to choose the width below which uncertain boxes will not be bisected.

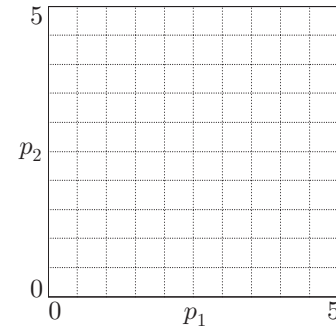


Figure 4: Projection of $\bar{\mathbb{S}}$ onto the plane (p_1, p_2)

Example 5 Consider again the problem of Example 4. Take $\mathbb{P} = [0, 5]^{\times 3}$. Assume now that $\hat{\mathbf{p}}$ is acceptable if the absolute deviations between the data y_i and corresponding model outputs η_i satisfy $|y_i - \eta_i(\hat{\mathbf{p}})| \leq 0.002$, $i = 1, \dots, 16$, which can of course be reformulated as $\mathbf{g}(\hat{\mathbf{p}}, \mathbf{y}) \leq \mathbf{0}$. For $\varepsilon = 0.0025$, in 2 mn on a Pentium 233, SIVIA computes an outer approximation $\bar{\mathbb{S}}$ of the set \mathbb{S} defined by (14). $\bar{\mathbb{S}}$ consists of two disconnected subsets contained in the boxes

$$[1.5046, 2.9546] \times [0.22245, 0.25954] \times [0.12061, 0.22069]$$

and

$$[0.22245, 0.25954] \times [1.5046, 2.9546] \times [0.12061, 0.22069].$$

The projection of $\bar{\mathbb{S}}$ onto the plane (p_1, p_2) is given in Figure 4. The fact that p_1 and p_2 can be exchanged without modifying the model behavior explains the symmetry of the figure. ■

5 Conclusions

Testing models for identifiability is important in at least three cases:

- when the parameters to be identified have a physical meaning and one wants to estimate their actual values,
- when state variables that cannot be measured directly are to be estimated from the available measurements and the model being built,
- when a decision is to be taken based on the numerical values of the parameters or state variables.

Two situations should then be distinguished.

When the data have not been collected yet, one is interested in a conclusion that is as independent as possible from the numerical value of \mathbf{p}^* . This conclusion may lead one to modify the location and nature of the sensors and actuators in an effort to improve identifiability [8]. We have shown here that it may depend on the value of \mathbf{p}^* in such a way that no generic conclusion can be reached. This led us to proposing an alternative approach based on a new definition of identifiability. A parameter vector \mathbf{p} is said to be globally identifiable in \mathbb{P} if it is globally identifiable for *all* values of \mathbf{p}^* in \mathbb{P} . We have briefly explained how interval analysis and interval constraint propagation can be used to test whether a model structure is globally identifiable in \mathbb{P} for a given set \mathbb{P} .

When the data have already been collected, the actual question of interest is: *what is the set of all values of the parameter vector that are acceptable, given the data and what we know about the noise?* Identifiability then becomes a way to get a partial answer to this question, in an idealized context. We have shown that interval analysis may make it possible to reach a guaranteed conclusion in a more realistic context. There are, of course, limitations to the complexity of the problems that can be handled, and one of the challenges of interval analysis is to enlarge the class of the problems that can be treated. The notion of interval constraint propagation, for instance, allows one to limit the number of bisections needed, which is an extremely important contribution to repelling the curse of dimensionality.

We have only considered the notion of *identifiability*, where the structures of the model and process are assumed to be identical. The same type of study could be conducted in the context of *distinguishability*, where it is assumed that the structure of the model may differ from that of the process [17]. The notion of structural distinguishability could similarly be replaced by a notion of distinguishability in \mathbb{P} , and the tools of interval analysis could again be used to test whether a given model structure is distinguishable from another one in this new sense.

References

- [1] T.C. Koopmans and O. Reiersol. The identification of structural characteristics. *Ann. Math. Stat.*, 21(2):165–181, 1950.
- [2] E. Walter and Y. Lecourtier. Global approaches to identifiability testing for linear and nonlinear state space models. *Mathematics and Computers in Simulation*, 24:472–482, 1982.
- [3] A. Raksanyi, Y. Lecourtier, E. Walter, and E. Venot. Identifiability and distinguishability testing in computer algebra. *Math. Biosci.*, 77(1-2):245–266, 1985.
- [4] S. Vajda, K. R. Godfrey, and H. Rabitz. Similarity transformation approach to identifiability analysis of nonlinear compartmental models. *Math. Biosci.*, 93(2):217–248, 1989.
- [5] F. Ollivier. *Le problème de l'identifiabilité structurelle globale : approche théorique, méthodes effectives et bornes de complexité*. PhD thesis, Ecole Polytechnique, 1990.
- [6] L. Ljung and T. Glad. On global identifiability of arbitrary model parametrizations. *Automatica*, 30:265–276, 1994.
- [7] M. P. Saccomani, S. Audoly, G. Bellu, L. D'Angio, and C. Cobelli. Global identifiability of nonlinear models parameters. In *Proc. IFAC Symp. on System Identification SYSID'97*, pages 219–224, Fukuoka, Japan, 1997.
- [8] E. Walter and L. Pronzato. Qualitative and quantitative experiment design for phenomenological models, a survey. *Automatica*, 26:195–213, 1990.
- [9] E. Walter and Y. Lecourtier. Unidentifiable compartmental models: What to do? *Math. Biosci.*, 56:1–25, 1981.
- [10] R. E. Moore. *Interval Analysis*. Prentice-Hall, Englewood Cliffs, NJ, 1966.
- [11] E. R. Hansen. *Global Optimization using Interval Analysis*. Marcel Dekker, New York, NY, 1992.
- [12] R. Hammer, M. Hocks, U. Kulish, and D. Ratz. *C++ Toolbox for Verified Computing*. Springer-Verlag, Berlin, Germany, 1995.
- [13] L. Jaulin, M. Kieffer, O. Didrit, and E. Walter. *Applied Interval Analysis*. Springer-Verlag, London, 2001.
- [14] M. Kieffer and E. Walter. Interval analysis for guaranteed nonlinear parameter estimation. In A. C. Atkinson, L. Pronzato, and H. P. Wynn, editors, *MODA 5-Advances in Model-Oriented Data Analysis and Experiment Design*, pages 115–125. Physica-Verlag, Heidelberg, Germany, 1998.
- [15] M. Milanese, J. Norton, H. Piet-Lahanier, and E. Walter, editors. *Bounding Approaches to System Identification*. Plenum Press, New York, NY, 1996.
- [16] L. Jaulin and E. Walter. Set inversion via interval analysis for nonlinear bounded-error estimation. *Automatica*, 29(4):1053–1064, 1993.
- [17] E. Walter, Y. Lecourtier, and J. Happel. On the structural output distinguishability of parametric models and its relation with structural identifiability. *IEEE Transactions on Automatic Control*, 29:56–57, 1984.