Injectivity Analysis using Interval Analysis. Application to Structural Identifiability ⋆

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Abstract

This paper presents a new numerical algorithm based on interval analysis able to prove that a differentiable function $\mathbf{f} : \mathcal{A} \subset \mathbb{R}^n \to \mathbb{R}^n$ is injective. This algorithm also performs a partition of the domain $\mathcal{A}$ in subsets $\mathcal{A}_i$ where, for all $\mathbf{x} \in \mathcal{A}_i$, the cardinality of $\mathbf{f}^{-1}(\mathbf{f}(\mathbf{x}))$ is constant. In the context of parameter estimation, we show how this algorithm provides an efficient and numerical method to study the structural identifiability of parametric models.

Key words: Injectivity, parametric system, structural identifiability, interval analysis.

1 Introduction

1.1 Structural identifiability

The notion of *(structural) identifiability* is the question of whether one can hope uniquely to estimate the parameters of a model from experimental data that can be collected. This question is particulary relevant since the parameters have a concrete meaning and whenever decisions have to be taken on the basis of their numerical values [2]. Consider the model structure $\mathcal{M}(.)$ for which the vector of parameters $\mathbf{p}$ belongs to a prior set $\mathcal{P}$ and denote by $\mathcal{M}(\tilde{\mathbf{p}}) = \mathcal{M}(\mathbf{p})$ the identical input-output behavior generated by the models $\mathcal{M}(\tilde{\mathbf{p}})$ and $\mathcal{M}(\mathbf{p})$. The structural identifiability of $\mathcal{M}(.)$ depends to the number of solutions of $\mathcal{M}(\tilde{\mathbf{p}}) = \mathcal{M}(\mathbf{p})$. Define $\mathbb{S}_{\mathbf{p}} = \{\tilde{\mathbf{p}} \in \mathcal{P} \mid \mathcal{M}(\mathbf{p}) = \mathcal{M}(\tilde{\mathbf{p}})\}$. If, for almost any $\mathbf{p} \in \mathcal{P}, \mathbb{S}_{\mathbf{p}}$ is a singleton, the vector of parameters $\mathbf{p}$ is *structurally globally identifiable* (*s.g.i*); if, for almost any $\mathbf{p} \in \mathcal{P}, \mathbb{S}_{\mathbf{p}}$ is finite or countable, $\mathbf{p}$ is *structurally locally identifiable* (*s.l.i*). Otherwise, $\mathbf{p}$ is *structurally unidentifiable* [10]. When testing model for identifiability, the standard approach is in two steps.

During the first step, equations of the form $\mathbf{f}(\tilde{\mathbf{p}}) = \mathbf{f}(\mathbf{p})$ equivalent to $\mathcal{M}(\tilde{\mathbf{p}}) = \mathcal{M}(\mathbf{p})$ are established. According to the structure $\mathcal{M}(\cdot)$, various methods can be used to obtain $\mathbf{f}$ [6,8–10]. In the following, we consider that the function $\mathbf{f}$ is available.

During the second step, the set of all solutions $\tilde{\mathbf{p}}$ of $\mathbf{f}(\tilde{\mathbf{p}}) = \mathbf{f}(\mathbf{p})$ is sought for any $\mathbf{p}$. When each component of $\mathbf{f}$ is polynomial in the entries of $\mathbf{p}$; elimination theory can be used to put this set of polynomial equations into a triangular form. Then, it becomes possible (at least in principle) to solve $\mathbf{f}(\tilde{\mathbf{p}}) = \mathbf{f}(\mathbf{p})$ by solving a succession of polynomial equations in a single unknown and thus to obtain the set of all the parameter vectors $\tilde{\mathbf{p}}$ that satisfy these equations. However, formal approaches may turn out to be unsatisfactory for different reasons: i) If Equation $\mathbf{f}(\tilde{\mathbf{p}}) = \mathbf{f}(\mathbf{p})$ is not polynomial, formal calculus often fails to reach a solution. ii) The complexity of the formal manipulations is high. iii) The number of solutions $\tilde{\mathbf{p}}$ depends on the value of $\mathbf{p}$. It is then difficult to reach a structural conclusion. The following example illustrates the points i) and iii). It will be treated with the new approach advocated in this paper.

Example 1 *Consider the model $f(p) = p\cos(p)$ where the parameter p belongs to $\mathcal{P} = [-3, 3]$ and no input. For any $(\tilde{p}, p) \in \mathcal{P}^2$, $\mathcal{M}(\tilde{p}) = \mathcal{M}(p)$ iff $\tilde{p}\cos\tilde{p} = p\cos p$. Let a and b be the real numbers defined in Figure 1. The set of feasible values for $\tilde{p}$ is a triple for $p \in]-a, -b[\cup]-b, b[\cup]b, a[$, a pair for $p \in \{-a, -b, b, a\}$ and a singleton for $p \in [-3; -a[\cup]a, 3]$ (see Figure 1).*

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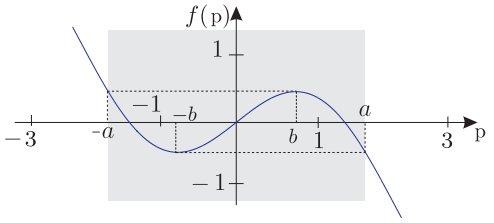

Fig. 1. The grey zone corresponds to the values of x for which the equation $f(x) = f(\tilde{x})$ has more than one solution.

1.2 Contents of the paper

The purpose of the paper is to present an alternative route, based on guaranteed numerical computation, able to study the structural identifiability. Concisely, consider a differentiable function $\mathbf{f}$ defined from $\mathcal{A} \subset \mathbb{R}^n$ to $\mathbb{R}^n$, we define the *injectivity function of* $\mathbf{f}$ by

$$\mu : \begin{cases} \mathcal{A} \rightarrow \mathbb{N} \cup \{+\infty\} \\ \mathbf{x} \rightarrow |\{\tilde{\mathbf{x}} \in \mathcal{A} \mid \mathbf{f}(\tilde{\mathbf{x}}) = \mathbf{f}(\mathbf{x})\}| \end{cases}$$

where $|\cdot|$ denotes the cardinality of a set. The function μ associates to each vector $\mathbf{x}$ the number of solutions $\tilde{\mathbf{x}}$ of the equation $\mathbf{f}(\tilde{\mathbf{x}}) = \mathbf{f}(\mathbf{x})$. This paper proposes a new algorithm able to enclose the function μ between two functions μ^- and μ^+ such that $\mu^-(\mathbf{x}) \leq \mu(\mathbf{x}) \leq \mu^+(\mathbf{x})$. This algorithm is relevant for identifiability analysis of parametric models as previously illustrated. It can decompose the parametric space into different domains. In each of this domains the number of feasible vectors of parameters is constant (and known). To our knowledge, it does not exist any numerical and guaranteed approaches to enclose μ. This paper presents the first attempt in that direction. Note that Braems and al. have presented in [3] an approximated (numerical) method to test whether the function μ is equal to one.

The paper is organized as follows. Section 2 presents interval analysis and some possibilities of this tool. Section 3 defines the injectivity function restricted to a domain and points out its main properties. By a combination of interval analysis and the properties of the injectivity function, an effective algorithm is built in Section 4. In Section 5, an illustrative example shows the efficiency of the algorithm to test models for structural identifiability. A C++ solver called IAVIA is made available. Note that the proposed technique only works for low dimensional problems since the proposed algorithm takes an exponential amount of time in terms of the dimension.

2 Interval Newton Method

The purpose of this section is to give a sufficient condition to verify the proposition : $\forall \mathbf{y} \in [\mathbf{y}], \exists \mathbf{x} \in [\mathbf{x}]$ such that

$$\begin{cases} \mathbf{h}(\mathbf{x}, \mathbf{y}) = \mathbf{0} \\ \forall \mathbf{x}' \in [\mathbf{x}], (\mathbf{h}(\mathbf{x}', \mathbf{y}) = \mathbf{0} \Rightarrow \mathbf{x} = \mathbf{x}') \end{cases}$$

where $\mathbf{h} : \mathbb{R}^n \times \mathbb{R}^m \rightarrow \mathbb{R}^n$ is a differentiable function and $[\mathbf{x}], [\mathbf{y}]$ are two boxes of $\mathbb{R}^n$ and $\mathbb{R}^m$. The implication means that for all $\mathbf{y}$ there exists a *unique* $\mathbf{x}$ (denoted $\exists!\mathbf{x}$) such that $\mathbf{h}(\mathbf{x}, \mathbf{y}) = \mathbf{0}$. Thus, the proposition can be rewritten $\forall \mathbf{y} \in [\mathbf{y}], \exists! \mathbf{x} \in [\mathbf{x}], \mathbf{h}(\mathbf{x}, \mathbf{y}) = \mathbf{0}$. To perform this test, we generalize the interval Newton method [4,5,7] and define an extension of the unicity operators. This new result will be exploited in the next section in order to show that a function $\mathbf{f} : \mathbb{R}^n \rightarrow \mathbb{R}^n$ satifies $\forall \mathbf{y} \in [\mathbf{y}], \exists! \mathbf{x} \in [\mathbf{x}]$ such that $\mathbf{f}(\mathbf{x}) = \mathbf{y}$ (by setting $\mathbf{h}(\mathbf{x}, \mathbf{y}) = \mathbf{f}(\mathbf{x}) - \mathbf{y}$).

Let us recall the definition of an (interval) unicity operator. Consider a function $\mathbf{f} : \mathbb{R}^n \rightarrow \mathbb{R}^n$ and $[\mathbf{x}] \subset \mathbb{R}^n$. An operator $\mathcal{N} : \mathbb{R}^n \rightarrow \{\text{true}, \text{false}\}$ is a unicity operator of $\mathbf{f}$ if $\mathcal{N}(\mathbf{f}, [\mathbf{x}]) \Rightarrow \exists! \mathbf{x} \in [\mathbf{x}], \mathbf{f}(\mathbf{x}) = \mathbf{0}$. The standard (interval) unicity operator is the unicity operator of Newton [1,4].

We extend the unicity operator defined for functions from $\mathbb{R}^n$ to $\mathbb{R}^n$ to functions defined from $\mathbb{R}^n \times \mathbb{R}^m$ to $\mathbb{R}^n$. These extended operators will be named *generalized unicity operators*. Consider a function $\mathbf{h} : \mathbb{R}^n \times \mathbb{R}^m \rightarrow \mathbb{R}^n$ and two boxes $[\mathbf{x}] \subset \mathbb{R}^n, [\mathbf{y}] \subset \mathbb{R}^m$. For $\mathbf{y} \in [\mathbf{y}]$, one defines $\mathbf{h}_\mathbf{y} : \mathbb{R}^n \ni \mathbf{x} \mapsto \mathbf{h}_\mathbf{y}(\mathbf{x}) = \mathbf{h}(\mathbf{x}, \mathbf{y}) \in \mathbb{R}^n$. Now, let $\mathcal{N}(\mathbf{h}_\mathbf{y}, [\mathbf{x}])$ be a unicity operator of $\mathbf{h}_\mathbf{y}$ then we get $\mathcal{N}(\mathbf{h}_\mathbf{y}, [\mathbf{x}]) \Rightarrow \exists! \mathbf{x} \in [\mathbf{x}], \mathbf{h}_\mathbf{y}(\mathbf{x}) = \mathbf{0}$. Since $\overline{\mathcal{N}}(\mathbf{h}, [\mathbf{x}], \mathbf{y}) \triangleq \mathcal{N}(\mathbf{h}_\mathbf{y}, [\mathbf{x}])$, $\overline{\mathcal{N}}$ is a unicity operator of the function $\mathbf{h}$ at the point $\mathbf{y}$. Therefore $\overline{\mathcal{N}}(\mathbf{h}, [\mathbf{x}], [\mathbf{y}]) \Rightarrow \forall \mathbf{y} \in [\mathbf{y}], \exists! \mathbf{x} \in [\mathbf{x}], \mathbf{h}(\mathbf{x}, \mathbf{y}) = \mathbf{0}$.

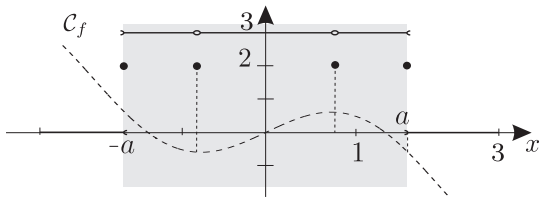

Fig. 2. Graph $\mu_{[-a,a]} : [-3, 3] \rightarrow \mathbb{N} \cup \{+\infty\}$ of $f(x) = x\cos(x)$. The graph of f has been superposed as dotted-lines.

Definition 1 *An operator* $\overline{\mathcal{N}} : \mathbb{R}^n \times \mathbb{R}^m \rightarrow \{true, false\}$ *is a generalized unicity operator of* $\mathbf{h} : \mathbb{R}^n \times \mathbb{R}^m \rightarrow \mathbb{R}^n$ *if* $\overline{\mathcal{N}}(\mathbf{h}, [\mathbf{x}], [\mathbf{y}]) \Rightarrow \forall \mathbf{y} \in [\mathbf{y}], \exists! \mathbf{x} \in [\mathbf{x}], \mathbf{h}(\mathbf{x}, \mathbf{y}) = \mathbf{0}$.

3 Injectivity function

This section presents some properties of μ. This will motivate the implementation of the algorithm presented in the next section.

Let $[\tilde{\mathbf{x}}]$ be a box included in $[\mathbf{x}]$, we define *the injectivity function (of* $\mathbf{f}$*) restricted to* $[\tilde{\mathbf{x}}]$, denoted $\mu_{[\tilde{\mathbf{x}}]}$, by

$$\mu_{[\tilde{\mathbf{x}}]} : \begin{cases} [\mathbf{x}] \rightarrow \mathbb{N} \cup \{+\infty\} \\ \mathbf{x} \rightarrow |\{\tilde{\mathbf{x}} \in [\tilde{\mathbf{x}}] \mid \mathbf{f}(\tilde{\mathbf{x}}) = \mathbf{f}(\mathbf{x})\}| . \end{cases}$$

$\mu_{[\tilde{\mathbf{x}}]}(\mathbf{x})$ is the number of solutions $\tilde{\mathbf{x}}$ of the equation $\mathbf{f}(\tilde{\mathbf{x}}) = \mathbf{f}(\mathbf{x})$ that belongs to $[\tilde{\mathbf{x}}]$ (see example of Figure 2). Note that, since we only consider the injectivity function of $\mathbf{f}$, we omit to specify it in the following.

Proposition 1 *Consider a function* $\mathbf{f} : [\mathbf{x}] \subset \mathbb{R}^n \rightarrow \mathbb{R}^n$ *and a collection* $[\tilde{\mathbf{x}}_1], \ldots, [\tilde{\mathbf{x}}_q]$ *of boxes of* $[\mathbf{x}]$*. For* $I = \{1, \ldots, q\}$*, we get* $\mu_{\bigcup\limits_{i \in I} [\tilde{\mathbf{x}}_i]}(\mathbf{x}) = \sum\limits_{J \subset I} (-1)^{|J|-1} \mu_{\bigcap\limits_{i \in J} [\tilde{\mathbf{x}}_i]}(\mathbf{x})$.

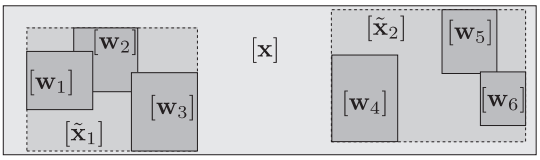

Fig. 3. Illustration of Step 11 with $\mathcal{L}_{\mathbf{w}} = \{[\mathbf{w}_1], \ldots, [\mathbf{w}_6]\}$. The $[\mathbf{w}_i]$'boxes are organized in order to obtain the two disjoint (and larger) boxes $[\tilde{\mathbf{x}}_1]$ and $[\tilde{\mathbf{x}}_2]$ stored in $\mathcal{L}_{\tilde{\mathbf{x}}}$.

Proof. Trivial (use the inclusion-exclusion principle). ■
Let us introduce the following theorem which gives a sufficient condition to enclose μ over a box $[\mathbf{x}_1] \subset [\mathbf{x}]$.

Theorem 1 *If $\mathbf{f} : [\mathbf{x}] \subset \mathbb{R}^n \to \mathbb{R}^n$ is differentiable (denote Df its Jacobian matrix), $\overline{\mathcal{N}}$ is a generalized unicity operator of $\mathbf{h}(\mathbf{x}, \mathbf{y}) \triangleq \mathbf{f}(\mathbf{x}) - \mathbf{y}$, $[\mathbf{x}_1] \subset [\mathbf{x}]$ and $\{[\tilde{\mathbf{x}}_i]\}_{i \in \{1,\ldots,q\}}$ be a set of boxes which satisfies*

i) $i \neq j \Rightarrow [\tilde{\mathbf{x}}_i] \cap [\tilde{\mathbf{x}}_j] = \emptyset$,

ii) $\mathbf{f}^{-1}(\mathbf{f}([\mathbf{x}_1])) \subset \bigcup_i [\tilde{\mathbf{x}}_i]$,

iii) $\forall i \in \{1, \ldots, q'\}, \overline{\mathcal{N}}(\mathbf{h}, [\tilde{\mathbf{x}}_i], \mathbf{f}([\mathbf{x}_1]))$ *is true*,

iv) $\forall i \in \{q'+1, \ldots, q\}, [D\mathbf{f}([\tilde{\mathbf{x}}_i])]$ *is full rank*

where $q' \in \mathbb{N}$, $1 \leq q' \leq q$, then $q' \leq \mu_{[\mathbf{x}]}([\mathbf{x}_1]) \leq q$.

Proof. $\mu_{[\mathbf{x}]}([\mathbf{x}_1]) = \mu_{\bigcup_i [\tilde{\mathbf{x}}_i]}([\mathbf{x}_1]) + \mu_{[\mathbf{x}] \setminus \bigcup_i [\tilde{\mathbf{x}}_i]}([\mathbf{x}_1])$ (see Proposition 1). Since ii), we get $\mu_{[\mathbf{x}]}([\mathbf{x}_1]) = \mu_{\bigcup_i [\tilde{\mathbf{x}}_i]}([\mathbf{x}_1])$. According to i), $\mu_{[\mathbf{x}]}([\mathbf{x}_1]) = \sum_{i=1}^{q} \mu_{[\tilde{\mathbf{x}}_i]}([\mathbf{x}_1])$ (see Proposition 1). Trivially, according to iii), one has $\forall i \in \{1, \ldots, q'\}$, $\mu_{[\tilde{\mathbf{x}}_i]}([\mathbf{x}_1]) = 1$. And, according to iv), one has $\forall i \in \{q'+1, \ldots, q\}$, $\mu_{[\tilde{\mathbf{x}}_i]}([\mathbf{x}_1]) \leq 1$ (this result can be proved by contradiction considering the Mean Value Theorem). Therefore Theorem 1 is proved. ■

4 Algorithm IAVIA

This section presents the algorithm IAVIA (Injectivity Analysis Via Interval Analysis) whose aim is to enclose μ. IAVIA can be decomposed in two distinct sub-algorithms : Algorithm 1 exploits Theorem 1 in order to return an interval $[\mu^-, \mu^+]$ which encloses $\mu_{[\mathbf{x}]}$ over a box $[\mathbf{x}_1] \subset [\mathbf{x}]$. Algorithm 2 divides the initial box $[\mathbf{x}]$ into a paving $\{[\mathbf{x}_i]\}_i$ such that, for all i, Algorithm 1 succeeds in obtaining an enclosure of μ over the $[\mathbf{x}_i]$'boxes. Different domains are obtained : *an indeterminate domain* composed of the boxes of width lower than ε (stored in $\mathcal{U}$) and domains where the μ is perfectly known are stored in the list $\mathcal{S}$.

Remark 1 *Note that if $D\mathbf{f}(\mathbf{x})$ is not full rank, then every boxes $[\mathbf{x}]$ such that $\mathbf{x} \in [\mathbf{x}]$ verify $[D\mathbf{f}([\mathbf{x}])]$ is not full rank. Therefore, the condition at Step 13 of Algorithm 1 is never satisfied and the enclosure process fails. This implies that $\{\mathbf{x} \mid D\mathbf{f}(\mathbf{x})$ is not full rank $\}$ is included in $\mathcal{U}$. The proposed algorithm is not able to evaluate the injectivity (or the structural identifiability) for the values of $\mathbf{x}$ which are local maximizer/minimizer of $\mathbf{f}(\mathbf{x})$. This limitation of IAVIA also excludes the possibilities to proved that, for example, $f(x) = x^3$ is injective over $[-a, a], a \in \mathbb{R}$.*

Algorithm 1 Injectivity_Enclosure

Input: $\mathbf{f}$, $[\mathbf{x}]$ and $[\mathbf{x}_1] \subset [\mathbf{x}]$.
Output: μ^- and μ^+ such that $\mu^- \leq \mu_{[\mathbf{x}]}([\mathbf{x}_1]) \leq \mu^+$
1: Initialization : $\mathcal{L}_{stack} := \{[\mathbf{x}]\}$, $[\mu^-, \mu^+] = [0, 0]$.
2: **while** $\mathcal{L}_{stack} \neq \emptyset$ **do**
3: Pop $\mathcal{L}_{stack}$ into $[\mathbf{w}]$.
4: **if** $[\mathbf{f}]([\mathbf{w}]) \cap [\mathbf{f}]([\mathbf{x}_1]) \neq \emptyset$ **then**
5: **if** width$([\mathbf{w}])$ > width$([\mathbf{x}_1])$ **then**
6: Bisect $[\mathbf{w}]$ into $[\mathbf{w}_1]$ and $[\mathbf{w}_2]$.
7: Stack $[\mathbf{w}_1]$ and $[\mathbf{w}_2]$ in $\mathcal{L}_{stack}$
8: **else**
9: Push $[\mathbf{w}]$ in $\mathcal{L}_{\mathbf{w}}$.
10: **end while**
{here, $\mathbf{f}^{-1}(\mathbf{f}([\mathbf{x}_1])) \subset \cup_i [\mathbf{w}_i], [\mathbf{w}_i] in \mathcal{L}_{\mathbf{w}}$}
11: Build a partition $\mathcal{L}_{\tilde{\mathbf{x}}}$ from $\mathcal{L}_{\mathbf{w}}$ *{see Figure 3}*
12: **for** $i = 1$ to size of$(\mathcal{L}_{\tilde{\mathbf{x}}})$ **do**
13: **if** $[D\mathbf{f}([\tilde{\mathbf{x}}_i])]$ is full rank **then**
14: **if** $\overline{\mathcal{N}}(\mathbf{h}, [\tilde{\mathbf{x}}_i], \mathbf{f}([\mathbf{x}_1]))$ **then**
15: $\mu^- = \mu^- + 1$
16: **else**
17: Return $[0, +\infty]$ *{Enclosure failed}*
18: **end for**
19: Return $[\mu^-,$ size of $(\mathcal{L}_{\tilde{\mathbf{x}}})]$

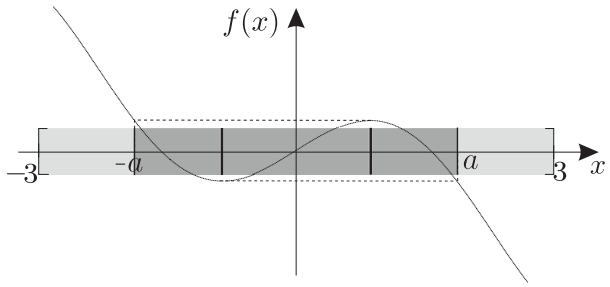

Fig. 4. Intervals from dark grey to light grey are respectively the domain where the injectivity function $\mu_{[-3,3]}$ is equal to 3 and 1. The black intervals correspond to the undeterminate domains (where the enclosure of $\mu_{[-3,3]}$ is $\mu^- = 0$ and $\mu^+ = +\infty$). The white intervals (close to black ones) correspond to the indeterminate domain where the function $\mu_{[-3,3]}$ belongs to $[1, 3]$.

Example 2 *Consider the function presented in Example 1. With a condition $\varepsilon = 10^{-3}$ and after 10 seconds on a Pentium III 1.8GHz, the solver IAVIA returns the boundaries presented in Figure 4.*

5 Numerical test for structural identifiability

This section gives an illustrative example which shows the efficiency of the (numerical) algorithm IAVIA to test models for structural identifiability. Consider the *ad hoc* parametric model $\mathcal{M}(\cdot)$ defined by the following state equations :

$$\begin{cases} \dot{x}(t) = [(1-p_2)\,p_1 c_1 - p_2 s_1 - 2p_2]\,x(t) + u(t) \\ y(t) = [p_1\,(1 + s_1 - p_2 s_1) + p_2 c_1]\,x(t) \end{cases}$$

Algorithm 2 IAVIA

Input: $\mathbf{f}$ a $\mathcal{C}^1$ function and $[\mathbf{x}]$ the initial box.
Output: A list $\mathcal{S}$ that contains sub-boxes of $[\mathbf{x}]$ and the corresponding bounds of the injectivity function.

1: Initialization : $\mathcal{L} := \{[\mathbf{x}]\}, \mathcal{S} = \emptyset, \mathcal{U} = \emptyset$.
2: **while** $\mathcal{L} \neq \emptyset$ **do**
3: Pull $[\mathbf{w}]$ in $\mathcal{L}$.
4: $[\mu^-, \mu^+]$ =Injectivity_Enclosure$(\mathbf{f}, [\mathbf{x}], [\mathbf{w}])$
5: **if** width$([\mathbf{w}]) > \varepsilon$ **then**
6: **if** $\mu^- = \mu^+$ **then**
7: Push $([\mathbf{w}], \mu^-)$ in $\mathcal{S}$
8: **else**
9: Bisect $[\mathbf{w}]$ into $[\mathbf{w}_1]$ and $[\mathbf{w}_2]$
10: Push $[\mathbf{w}_1]$ and $[\mathbf{w}_2]$ in $\mathcal{L}$
11: **else**
12: Push $([\mathbf{w}], [\mu^-, \mu^+])$ in $\mathcal{U}$
13: **end while**

Fig. 5. Enclosure of $\mu_{[\mathbf{p}]}$ obtained by IAVIA. In light gray, the value of the parameters for which the system is structurally identifiable ($\mu^+ = \mu^- = 1$). The two dark gray zones correspond to the value of the parameters for which the system is locally identifiable, 2 or 3 parameter vectors are possible ($\mu^+ = \mu^- = 2$ or $\mu^+ = \mu^- = 3$). In the white (tiny) domains, μ is proved to belong $[1, 3]$.

where $c_1 = \cos(p_1)$, $s_1 = \sin(p_1)$ and the vector of parameters $\mathbf{p} = (p_1, p_2)^T$ belongs to $[10, 26] \times [0, \frac{1}{10}]$. By the use of Laplace transform approach, $\mathcal{M}(\mathbf{p}) = \mathcal{M}(\tilde{\mathbf{p}})$ translates into $\mathbf{f}(\mathbf{p}) = \mathbf{f}(\tilde{\mathbf{p}})$ where the components of $\mathbf{f}$ are the coefficients of the transfer matrix of $\mathcal{M}$:

$$\mathbf{f}(\mathbf{p}) = \begin{pmatrix} (1 - p_2)\, p_1 \cos p_1 - p_2 \sin p_1 - 2p_2 \\ p_1\,(1 + \sin p_1 - p_2 \sin p_1) + p_2 \cos p_1 \end{pmatrix}.$$

The analysis of structural identifiability of $\mathcal{M}$ amounts to count the number of solutions of $\mathbf{f}(\mathbf{p}) = \mathbf{f}(\tilde{\mathbf{p}})$, for all $\mathbf{p} \in [\mathbf{p}]$. Or equivalently, it consists in studying the injectivity function $\mu_{[\mathbf{p}]}(\cdot)$ of $\mathbf{f}$. If $\mu_{[\mathbf{p}]}(\mathbf{p}) = 1$, $\mathbf{p}$ is *s.g.i*; if $\mu_{[\mathbf{p}]}(\mathbf{p})$ is bounded, $\mathbf{p}$ is *s.l.i*. Otherwise, $\mathbf{p}$ is unidentifiable. After $60\,\mathrm{min}$, the results of the enclosure of $\mu_{[\mathbf{p}]}$ are depicted in Figure 5. Note that in the context of structural identifiability test, the existence of a box $[\mathbf{x}_1]$ such that $\mu^-_{[\mathbf{x}]}([\mathbf{x}_1]) \geq 2$ could stop Algorithm IAVIA and no structural identifiability should be proved. It only consists to change the condition of Step 6 of IAVIA by "If $\mu^- \geq 2$". In this case, the structural unidentifiability of model $\mathcal{M}$ is proved in less than $1\,\mathrm{sec}$.

6 Conclusion

In this paper, we proposed a new numerical and guaranteed method to enclose the injectivity function of $\mathbf{f}$ defined by $\mu(\mathbf{x}) = |\{\tilde{\mathbf{x}} \in [\mathbf{x}] \mid \mathbf{f}(\tilde{\mathbf{x}}) = \mathbf{f}(\mathbf{x})\}|$. To our knowledge, it did not exist any numerical method able to perform this enclosure. Note that, in case of functions $\mathbf{f} : \mathbb{R} \to \mathbb{R}$ and $\mathbf{f} : \mathbb{R}^2 \to \mathbb{R}^2$, the solver IAVIA developed in C++ is made available at `http://www.istia.univ-angers.fr/~lagrange/`. In the context of parameter estimation, we have shown that the proposed algorithm is able to test models for structural identifiability. Table 6 gives comparaison with methods available in the literature. The method proposed by Ljung and Glad in [6] uses differential algebra to test global structural identifiability. However, it is impossible to take into account constraints on parameters (the natural non negativity of a (physical) parameter cannot be imposed). Our method is numerical and can prove *s.g.i.* with respect to a constrained parameter space. Moreover, IAVIA is able to decompose the parametric space into subspaces $\mathcal{P}_i$ such that *s.g.i.* with respect to $\mathcal{P}_i$ is proved.

Method	IAVIA	Ljung and Glad	Braems
Termination	no	yes	no
Guaranteed	yes	yes	no
Numeric	yes	no	yes
Constrained domains	yes	no	yes
limitations	few parameters	algebraic models	

Fig. 6. Comparaison between different approaches

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