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Optimal Initial State for Fast Parameter Estimation in Nonlinear Dynamical Systems

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Abstract:

Background and Objective:

This paper deals with the improvement of parameter estimation in terms of precision and computational time for dynamical models in a bounded error context.

Methods:

To improve parameter estimation, an optimal initial state design is proposed combined with a contractor. This contractor is based on a volumetric criterion and an original condition initializing this contractor is given. Based on a sensitivity analysis, our optimal initial state design methodology consists in searching the minimum value of a proposed criterion for the interested parameters. In our framework, the uncertainty (on measurement noise and parameters) is supposed unknown but belongs to known bounded intervals. Thus guaranteed state and sensitivity estimation have been considered. An elementary effect analysis on the number of sampling times is also implemented to achieve the fast and guaranteed parameter estimation.

Results:

The whole procedure is applied to a pharmacokinetics model and simulation results are given.

Conclusions:

The good improvement of parameter estimation in terms of computational time and precision for the case study highlights the potential of the proposed methodology.

Keywords: Optimal initial state; Parameter estimation; Nonlinear systems; Contractor; Bounded noise; Interval analysis

1. INTRODUCTION

Providing models representing physical systems is a common concern spread over all scientific and engineering communities. Models are essential to predict the behaviour of systems, or to control them (for example Van Den Bosch and Van Der Klauw (1994)). Actual systems are often described by ordinary differential equations which can contain unknown parameters to be estimated. State and/or parameter estimation problems are usually solved by probabilistic methods (Aster et al. (2005); Keesman (2011); Walter and Young (2003); Walter and Pronzato (1994)) when noises and perturbations can be reasonably assumed to be random variables. However, often in practice, an explicit characterization of noise and perturbation variables is not available, making difficult to assess proper stochastic hypotheses.

An alternative approach consists in assuming that uncertain variable values belong to sets, hence modeling bounded uncertainty. Thus, state and/or parameter estimation problems are now placed into a bounded-error

context. Bounded-error approaches permit the characterization of the set of all values of the state/parameter vector that are consistent with the measured data, the model structure and the prior known error bounds. Available methods based on set-membership approaches exist for linear and nonlinear models. Bounded error parameter estimation assumes that the uncertainty on the measured data is bounded but otherwise unknown, which has been known as a guaranteed estimation by Jaulin et al. (2001b), Walter et al. (2001).

Numerous approaches have been investigated for the case of linear models. We can characterize the solution set by a convex polyhedron. But in practice, this set is very difficult to obtain. Thus it may be preferable to compute other geometric shapes, such as for example ellipsoids Durieu and Walter (2001), Lesecq et al. (2003) or zonotopes Guerra et al. (2006) guaranteed to contain the exact solution set. The first work has been done by Schweppe (1968) on state estimation for linear models. Ellipsoids have been used in this context.

When the model is nonlinear, the set of values of the state vector to be characterized is usually non convex and may consist of several disconnected components. The previous methods are no longer relevant and other algorithms based on interval analysis have been developed Jaulin et al. (2001b).

Interval analysis and an enclosure of the solutions of the ordinary differential equations allow to compute guaranteed solutions to the state estimation problem. Then, guaranteed numerical methods for solving the ordinary differential equation are applied. These methods use high-order interval Taylor models Nedialkov (2010), Raïssi et al. (2004) to compute intervals which are guaranteed to contain the solution of ordinary differential equations.

Concerning parameter estimation and to improve it, experimental design is important for identifying mathematical models of complex systems. The overall goal is to design an experiment that produces data from which model parameters can be estimated accurately.

The conventional approach for the experimental design is based on stochastic models for uncertain parameters and measurement errors (see for example Rojas et al. (2007); Wahlberg et al. (2010); Keesman and Stigter (2012, 2002) or Rosenwasser and Yusupov (2000)). However, as was mentioned above, some sources of uncertainty are not well-suited to the stochastic approach and are better modeled as bounded uncertainty. This is the case of parameter uncertainties that generally arise from design tolerances and from aging. Some works consider that the parameters belong to some prior domain, on which no probability function is defined (for example Pronzato and Walter (1988), Belforte and Gay (2000)). The first aim at optimizing is the worst possible performance of the experiment over the prior domain for the parameters. In Pronzato and Walter (1988), this maximin approach to synthesize the optimal input is described and the specific criteria are developed.

In case of stochastic models the study is based on Fisher information matrix. Several criteria are taken from this matrix. For example the A-criterion: this criterion is based on the trace of the Fisher information matrix inverse which minimizes, in the linear case, the average variance of the estimates of parameters. Another criterion widely used is the D-criterion which is based on the determinant of the matrix of Fisher. This criterion minimizes the volume of the confidence ellipsoid.

In case of bounded but unknown errors, experiment design has been much less studied. In Li et al. (2015a), the authors have showed that the search for an optimal input in nonlinear dynamical systems can be made with the Gram matrix of sensitivity functions in a context only bounded intervals : measurement noise and parameters to be estimated.

This paper is an extended version of Li et al. (2015c) in which an optimal initial state design for fast parameter estimation is proposed in a bounded-error context. This approach combines a sensitivity analysis and a contractor based on a volumetric start criterion.

This paper is organized as follows. Section 2 presents some preliminaries composed of basic tools of interval analysis.

The notions of interval, box, interval matrix and inclusion function are given. In Section 3, the problem statement and the design of an optimal initial state are presented. In Section 4, the parameter estimation method is proposed and the construction of the contractor is developed. In Section 5, the case study is presented. It is taken from pharmacokinetics domain and describes the variation of enzyme concentration in plasma. The estimation results obtained on this case study are presented and discussed. Finally, some conclusions are outlined in Section 6.

2. PRELIMINARIES

Interval analysis provides tools for computing with sets which are described using outer-approximations formed by union of non-overlapping boxes. The following results are mainly taken from Jaulin et al. (2001b).

2.1 Basic tools

A real interval $[u] = [\underline{u}, \bar{u}]$ is a closed and connected subset of \mathbb{R} where \underline{u} represents the lower bound of $[u]$ and \bar{u} represents the upper bound. The width of an interval $[u]$ is defined by $w([u]) = \bar{u} - \underline{u}$, and its midpoint by $m([u]) = (\bar{u} + \underline{u})/2$.

The magnitude of an interval $[x]$, noted $mag([x])$ or $|[x]|$ is given by the largest absolute value of $[x]$ that means the absolute value of the real with the largest value in $[x]$.

The mignitude of an interval is $mig([u]) = \min(|\underline{u}|, |\bar{u}|)$ if $0 \notin [u]$, else $mig([u]) = 0$.

The set of all real intervals of \mathbb{R} is denoted \mathbb{IR} .

Two intervals $[u]$ and $[v]$ are equal if and only if $\underline{u} = \underline{v}$ and $\bar{u} = \bar{v}$. Real arithmetic operations are extended to intervals by Moore (1966).

Arithmetic operations on two intervals $[u]$ and $[v]$ can be defined by:

$$\circ \in \{+, -, *, /\}, \quad [u] \circ [v] = \{x \circ y \mid x \in [u], y \in [v]\}.$$

An interval vector (or box) $[x]$ is a vector with interval components and may equivalently be seen as a cartesian product of scalar intervals:

$$[x] = [x_1] \times [x_2] \dots \times [x_n].$$

The set of n -dimensional real interval vectors is denoted by \mathbb{IR}^n . The width $w(\cdot)$ of an interval vector is the maximum of the widths of its interval components. The midpoint $m(\cdot)$ of an interval vector is a vector composed of the midpoint of its interval components. The magnitude $mag(\cdot)$, respectively mignitude $mig(\cdot)$, of an interval vector is a vector composed of the magnitude, respectively mignitude, of its interval components.

Classical operations for interval vectors are direct extensions of the same operations for scalar vectors by Moore (1966).

Let $f : \mathbb{IR}^n \rightarrow \mathbb{IR}^m$, the range of the function f over an interval vector $[u]$ is given by:

$$f([u]) = \{f(x) \mid x \in [u]\}.$$

The interval function $[f]$ from \mathbb{IR}^n to \mathbb{IR}^m is an inclusion function for f if:

$$\forall [u] \in \mathbb{IR}^n, \quad f([u]) \subseteq [f]([u]).$$

An inclusion function of f can be obtained by replacing each occurrence of a real variable by its corresponding interval and by replacing each standard function by its interval evaluation. Such a function is called the natural inclusion function. In practice the inclusion function is not unique, it depends on the syntax of f .

In order to perform state estimation, an algorithm generally based on alternative prediction-correction steps must be developed.

2.2 State Estimation by using Taylor expansions

This section concerns the integration of ordinary differential equations as described in Equation (3). Thus, the objective of this section is to estimate the state vector x at the sampling times $\{t_1, t_2, \dots, t_N\}$ corresponding to the measurement times of the outputs. We note x_j the box $x(t_j)$ where t_j represents the sampling time, $j = 1, \dots, N$ and \tilde{x}_j represents the solution of (3) at t_j . State estimation for dynamical nonlinear systems can be solved efficiently by considering methods based on Taylor expansions, e.g. Berz and Makino (1998), Moore (1966), Nedialkov et al. (2001), and Rihm (1994). These methods consist in two parts: the first one verifies the existence and uniqueness of the solution by using the fixed point theorem and the Picard-Lindelöf operator. At a time t_{j+1} , an a priori box \tilde{x}_j containing all solutions corresponding to all possible trajectories between t_j and t_{j+1} is computed. In the second part, the solution at t_{j+1} is computed by using a Taylor expansion, where the remainder term is \tilde{x}_j .

However, in practice, the box $[\tilde{x}_j]$ often fails to contain the true solution according to Nedialkov et al. (1999). Thus, a classical technique used consists in inflating this set until it verifies the following inclusion (Lohner (1987)):

$$[x_j] + [0, h_j]f([\tilde{x}_j]) \subseteq [\tilde{x}_j], \quad (1)$$

where h_j denotes the integration step and $[x_j]$ the first solution.

This method is performed in the *Enclosure algorithm* and developed by Nedialkov (2002).

2.3 Set inversion via interval analysis

Consider the problem of determining a solution set for the unknown quantities u defined by:

$$S = \{u \in U \mid \Phi(u) \in [y]\} = \Phi^{-1}([y]) \cap U, \quad (2)$$

where $[y]$ is known a priori, U is an a priori search set for u and Φ a nonlinear function not necessarily invertible in the classical sense. Equation (2) involves computing the reciprocal image of Φ and is known as a set inversion problem which can be solved using the algorithm Set Inverter Via Interval Analysis (denoted SIVIA). The algorithm SIVIA proposed in Jaulin and Walter (1993) is a recursive algorithm which explores all the search space without losing any solution. This algorithm makes it possible to derive a guaranteed enclosure of the solution set S as follows:

$$\underline{S} \subseteq S \subseteq \bar{S}.$$

The inner enclosure \underline{S} is composed of the boxes that have been proved feasible. To prove that a box $[u]$ is feasible it is sufficient to prove that $\Phi([u]) \subseteq [y]$. Conversely, if it can be proved that $\Phi([u]) \cap [y] = \emptyset$, then the box $[u]$ is unfeasible. Otherwise, no conclusion can be reached and the box $[u]$ is said undetermined. The latter is then bisected and tested again until its size reaches a user-specified precision threshold $\varepsilon > 0$. Such a termination criterion ensures that SIVIA terminates after a finite number of iterations.

2.4 Constraint satisfaction

To solve a problem described as an interval equation system, we can use constraint propagation Jaulin et al. (2001a). In fact, the inclusion relations and equations can be interpreted as constraints and the *resolution* of such a system can then be taken into a Constraint Satisfaction Problem (*CSP*). Let us recall the basic definitions:

A Constraint Network (*CN*) $H = (\mathcal{X}, \mathcal{D}, \mathcal{C})$ is defined by:

- a set of variables $\mathcal{X} = \{x_1, \dots, x_n\}$,
- a set of value domains $\mathcal{D} = \{D_1, \dots, D_n\}$ where D_i is the domain associated to the variable x_i ,
- a set of constraints $\mathcal{C} = \{C_1, \dots, C_m\}$, linking the variables \mathcal{X} . The resolution of a *CN* is a *CSP*.

The solution S of the *CSP* : $H = (\mathcal{X}, \mathcal{D}, \mathcal{C})$ is the set of all the values affected to the corresponding variables at the same time.

Contraction and consistency of a CSP: The resolution of a *CSP* starts from an infinite domain or a bounded domain. The reduction of the domain is known as a local consistency problem, which can take the form of node consistency, arc consistency, or path consistency (Chabert et al. (2009); Lhomme (1993)). The operation is called constraint propagation or contraction, which is based on the equivalent relation below:

Two CSP \mathcal{H}_1 and \mathcal{H}_2 are equivalent if and only if they have the same set of solutions.

Remark 2.1. For the same set of variables \mathcal{X} and the same set of constraints \mathcal{C} , different sets of variable domains \mathcal{D}_i define different *CSP* \mathcal{H}_i .

A contractor \mathcal{R} for a *CSP* $\mathcal{H}_1 = (\mathcal{X}, \mathcal{D}_1, \mathcal{C})$ is an operator that can shrink the domain \mathcal{D}_1 into a domain \mathcal{D}_2 without losing any solution, such that:

$$\mathcal{D}_2 \subset \mathcal{D}_1.$$

The new *CSP* \mathcal{H}_2 is equivalent to \mathcal{H}_1 .

A *CSP* is solvable when it is equivalent to a *CSP* in which the infinite quantity domain is replaced by a larger value in computation. The contractor aims to reduce the initial domain into an as small as possible domain. The principle is to reject the parts of the domain which are not consistent with the constraints.

A *CSP* : $\mathcal{H} = (\mathcal{X}, \mathcal{D}, \mathcal{C})$ is globally consistent if and only if:

$$\forall x_i \in D_i, \exists (x_1, \dots, x_i, \dots, x_n) \in \mathcal{D} \mid \forall C(x_1, \dots, x_i, \dots, x_n) \in \mathcal{C}, C(x_1, \dots, x_i, \dots, x_n) \text{ is verified,}$$

in which $C(x_1, \dots, x_i, \dots, x_n)$ is a single constraint with a set of variables.

Global consistency can be interpreted as the correspondence between the defined domain and the variation of the

constraints for all the variables. In such a case, a globally consistent *CSP* gives a minimal exterior estimation of the equivalent system equation of the solution.

There is a large choice of contractors. Each has its own advantages and shortcomings, system characteristics and available information. We use these criteria to classify different contractors: constraint linearity, constraints, and size of $[x]$, which is $w([x])$. The first criterion to consider is the linearity of the constraints, which defines two categories, linear *CSPs* and nonlinear *CSPs*. More information on *CSPs* can be found in Chabert and Jaulin (2009) or in Xiong (2013).

3. FORMULATION AND DEVELOPMENT OF OPTIMAL INITIAL STATE DESIGN

3.1 Problem statement

In this article, we use the notations introduced in Kearfott et al. (2005). We consider nonlinear dynamical systems described by the following form:

$$\begin{cases} \dot{x}(t, p, x_0) = f(x(t, p, x_0), p, x_0), \\ y^{\text{mod}}(t, p, x_0) = h(x(t, p, x_0)), \\ x_0 = x(0) \in [\mathbb{X}_0], \quad p \in [\mathbb{P}_0], \end{cases} \quad (3)$$

where $x(t, p, x_0) \in \mathbb{R}^{n_x}$ and $y^{\text{mod}}(t, p, x_0) \in \mathbb{R}^{n_y}$ denote the state variables and the model outputs respectively. The initial conditions $x(0)$ is supposed to belong to an initial bounded box $[\mathbb{X}_0]$. The parameter vector $p \in \mathbb{R}^{n_p}$ is constant and is assumed to belong to a bounded box $[\mathbb{P}_0]$. Time t is assumed to belong to $[0, t_{\text{max}}]$. The functions f and h are nonlinear functions. f is real and analytic on M for every $p \in [\mathbb{P}_0]$ and every $x(0) \in [\mathbb{X}_0]$, where M is an open set of \mathbb{R}^{n_x} such that $x(t, p, x_0) \in M$ for every $p \in [\mathbb{P}_0]$, $x(0) \in [\mathbb{X}_0]$ and $t \in [0, t_{\text{max}}]$.

The model output at sampling time t_k is denoted $y_k^{\text{mod}}(p, x_0) = y^{\text{mod}}(t_k, p, x_0)$, $y_k^{\text{mod}}(p, x_0)$ is a vector with components $y_{l,k}^{\text{mod}}(p, x_0)$ for $l = 1, \dots, n_y$, $k = 1, \dots, N$. The integer N is the total number of sample times. Let $y(t_k, x_0)$ be the vector of the measurements at sampling time t_k . The output error is assumed to be given by:

$$v(t_k) = y(t_k, x_0) - y^{\text{mod}}(t_k, p, x_0), \quad k = 1, \dots, N. \quad (4)$$

Finally $[y^k] = [y(t_k, x_0) - \bar{v}(t_k), y(t_k, x_0) - \underline{v}(t_k)]$ where $[y^k]$ is a vector with components $[y_l^k]$ for $k = 1, \dots, N$ and $l = 1, \dots, n_y$.

We assume that for each experimental data $y(t_k, x_0)$, $\underline{v}(t_k)$ and $\bar{v}(t_k)$ are known as lower and upper bounds for the acceptable output errors. Such bounds may, for instance, correspond to a bounded measurement noise.

3.2 Optimal initial state design

Consider parameter estimation in a bounded error framework. A parameter vector p is acceptable if and only if the error between the measured data y and the model output y^{mod} is bounded in a known way. To estimate parameters, we have to get the set \mathbb{P} of all parameters p enclosed in the a priori search set $[\mathbb{P}_0]$ such that the error $v(t_k)$ between real data and model outputs belongs to $[\underline{v}(t_k), \bar{v}(t_k)]$:

$$\mathbb{P} = \{p \in [\mathbb{P}_0], y^{\text{mod}}(t_k, p, x_0) \in [y^k], \forall k = 1, \dots, N\}. \quad (5)$$

In order to obtain the most accurate estimates, the volume of the set \mathbb{P} must be made as small as possible. This volume

may generally depend on the values of the input Li et al. (2015b), the initial time, sampling times, etc. In this paper only the initial state is considered. This is a question of experiment design. We must therefore find a criterion J solving this issue in the context of bounded errors.

Then the optimal initial state design problem can be stated as follows:

Find an initial state x_0^* such that:

$$x_0^* = \arg \min_{x_0 \in [\mathbb{X}_0]} J(\mathbb{P}, x_0). \quad (6)$$

In fact, due to the possible non convexity and perhaps non connectivity of \mathbb{P} , the optimal input design problem is considered in a context more restrictive as follows:

Given $[p]$ such that $\mathbb{P} \subset [p] \subset [\mathbb{P}_0]$

$$x_0^* = \arg \min_{x_0 \in [\mathbb{X}_0]} J([p], x_0). \quad (7)$$

The following part is devoted to the research of such a criterion.

To obtain a contractor similar to the contractor proposed in Kieffer and Walter (2011), we use a centered form for $[y^{\text{mod}}(t_k, [p], x_0)]$ as inclusion function. For all $[p]$ such that $\mathbb{P} \subset [p] \subset [\mathbb{P}_0]$ and $m \in [p]$, we have for the l^{th} component of $[y^{\text{mod}}(t_k, [p], x_0)]$:

$$y_{l,k}^{\text{mod}}(m, x_0) + \sum_{j=1}^{n_p} ([p_j] - m_j) \left[\frac{\partial y_{l,k}^{\text{mod}}}{\partial p_j} \right] ([p], x_0) \subset [y_l^k]. \quad (8)$$

Thus, for all $l = 1, \dots, n_y$, $[p_i] - m_i$ is a subset of:

$$\frac{[y_l^k] - y_{l,k}^{\text{mod}}(m, x_0) - \sum_{j \neq i} ([p_j] - m_j) \left[\frac{\partial y_{l,k}^{\text{mod}}}{\partial p_j} \right] ([p], x_0)}{\left[\frac{\partial y_{l,k}^{\text{mod}}}{\partial p_i} \right] ([p], x_0)}. \quad (9)$$

Now by taking m equal to the middle of $[p]$, then the interval $[p_j] - m_j$ is a symmetric interval.

The aim of parameter bounding is to find the smallest possible domain for parameter under estimation, thus we have to maximize the denominator and to minimize the numerator of (9).

If we note:

$$\left[\frac{\partial y_{l,k}^{\text{mod}}}{\partial p_i} \right] ([p], x_0) = [S_{lki}] = [\underline{S}_{lki}, \bar{S}_{lki}]. \quad (10)$$

For the sensitivities such as $0 \notin [\underline{S}_{lki}, \bar{S}_{lki}]$, we have:

$$[\underline{S}_{lki}, \bar{S}_{lki}]^{-1} = \left[\frac{1}{\bar{S}_{lki}}, \frac{1}{\underline{S}_{lki}} \right]. \quad (11)$$

And:

- If $\underline{S}_{lki} > 0$ and we have to maximize $|\underline{S}_{lki}| = \text{mig}(S_{lki})$, so we can minimize $\frac{1}{\underline{S}_{lki}}$.
- If $\bar{S}_{lki} < 0$, we have to maximize $|\bar{S}_{lki}| = \text{mig}(S_{lki})$, so we can minimize $\left| \frac{1}{\bar{S}_{lki}} \right|$.

If $0 \in [\underline{S}_{lki}, \bar{S}_{lki}]$, so we implement an extended interval algorithm to calculate separately the positive part and the negative part of this interval.

For the numerator, we minimize the magnitude of the sum

$$\sum_{j \neq i} ([p_j] - m_j) \left[\frac{\partial y_k^{\text{mod}}}{\partial p_j} \right] ([p], x_0),$$

but $[p_j] - m_j$ is symmetric, then we minimize the magnitude of the sensitivities $[S_{lkj}]$ for all $j \neq i$.

Then, for the denominator, we maximize the magnitude of the sensitivities $[S_{lki}]$ for all $l = 1, \dots, n_y$, $k = 1, \dots, N$, $j = 1, \dots, n_p$ and $i = 1, \dots, n_p$.

Then the following Theorem leads.

Theorem 3.1. A criterion J for optimal initial state design may be defined as follows:

$$J([p], x_0) = \frac{\sum_{k=1}^N \sum_{l=1}^{n_y} \sum_{i=1}^{n_p} \sum_{j=1, j \neq i}^{n_p} \text{mag}([S_{lkj}])}{\sum_{k=1}^N \sum_{l=1}^{n_y} \sum_{i=1}^{n_p} \text{mig}([S_{lki}])}, \quad (12)$$

$$\text{with } S_{lki} = \frac{\partial y_{l,k}^{\text{mod}}}{\partial p_i}.$$

Then this leads to the following definitions:

Definition 3.1. The criterion J is called the set-membership-MIGMAG-optimality criterion.

Definition 3.2. An initial state x_0^* is said to be set-membership-MIGMAG-optimal when:

$$x_0^* = \arg \min_{x_0 \in [x_0]} J([p], x_0).$$

4. PARAMETER ESTIMATION WITH CONTRACTOR

4.1 Proposed contractor

The differential contractor which is proposed in Kieffer and Walter (2011) is obtained with formula (9). Using simplified expressions, the interval parameter given by this contractor is equal to the intersection of $[p_i]$ with:

$$\frac{[y_l^k] - y_{l,k}^{\text{mod}}(m, x_0) - \sum_{j \neq i} ([p_j] - m_j) \left[\frac{\partial y_{l,k}^{\text{mod}}}{\partial p_j} \right] ([p], x_0)}{\left[\frac{\partial y_{l,k}^{\text{mod}}}{\partial p_i} \right] ([p], x_0)} + m_i. \quad (13)$$

This expression uses the computation of the sensitivity for each parameter. If the parameter interval widths are large, a lot of sets are eliminated by this contractor with one computation. If the widths are close to the stop criterion, the contractor is not sufficiently efficient to eliminate unfeasible boxes. In this last case, we should not use the contractor all the time long. Thus, we propose the following criterion to decide when the contractor needs to be used.

The criterion CondContract is true when the following formula described by a volumetric product is verified:

$$\prod_{i=1}^{n_p} w([p_i]) > \prod_{i=1}^{n_p} (C_i \times \varepsilon_i). \quad (14)$$

where ε_i is a bisection parameter for the parameter p_i ($i = 1, \dots, n_p$) and each element of $C = (C_i)_{i=1, \dots, n_p}$ is chosen bigger than 2.

In the following algorithm, for starting the contractor, the criterion CondContract is proposed.

Algorithm 1 Contractor start condition (p, C, ε)

Require: $p(0)$;
Ensure: true, false;
1: $Cond1 := \prod_{i=1}^{n_p} w([p_i])$;
2: $Cond2 := \prod_{i=1}^{n_p} C_i \varepsilon_i$
3: **if** $Cond1 > Cond2$ **then**
4: CondContract := true;
5: **else**
6: CondContract := false;
7: **end if**

4.2 Parameter estimation algorithm

Based on contractor properties, we propose the following algorithm as a tradeoff between the precision and efficiency when applying a contractor. Added in a parameter estimation algorithm, this kind of indicator for application of contractor could be summarized as follows:

Algorithm 2 Parameter estimation with contractor control $(y, \mathcal{P}_{admis}, C, \varepsilon)$

Require: $x(0), p(0)$;
Ensure: $\mathcal{P}_{admis}, \mathcal{P}_{uncertain}, \mathcal{P}_{rejected}$;
1: initialization: $P_{list} := p(0), x_e(0) := (x(0), p(0)), C$;
2: **while** $P_{list} \neq \emptyset$ **do**
3: $p := Pop(\mathcal{P}_{list})$;
4: $CondContract := Contract(p, C, \varepsilon)$
5: **if** CondContract = true **then**
6: **Contract**(p);
7: **end if**
8: $i := 1$;
9: **while** $i \leq N$ **do**
10: $x_e(i) := VNODE - LP(x_e(i-1))$;
11: $j := i$;
12: $i := i + 1$;
13: **end while**
14: **if** $h(x_e(1:j)) \subseteq y(1:j)$ **then**
15: $\mathcal{P}_{admis} := \mathcal{P}_{admis} \cup p$;
16: **else if** $h(x_e(1:j)) \cap y(1:j) = \emptyset$ **then**
17: $\mathcal{P}_{rejected} := \mathcal{P}_{rejected} \cup p$;
18: **else if** $w(p) < \varepsilon$ **then**
19: $\mathcal{P}_{uncertain} := \mathcal{P}_{uncertain} \cup p$;
20: **else**
21: $bisectBox(p) \rightarrow \{p_1, p_2 \mid p_1 \cup p_2 = p\}$;
22: $\mathcal{P}_{list} := \mathcal{P}_{list} \cup p_1, \mathcal{P}_{list} := \mathcal{P}_{list} \cup p_2$;
23: **end if**
24: **end while**

In the previous algorithm, we note $VNODE - LP$ the call to the guaranteed state estimation package. $VNODE-LP$ is a C^{++} package for computing bounds of solutions in initial value problem for ordinary differential equation. This package implements particularly algorithms corresponding to high order enclosure and Hermite-Obreschkoff method by Nedialkov (2011) which gives a way to obtain tighter enclosure.

The following section is dedicated to the application. We use the package $VNODE-LP$ to generate the guaranteed

results with uncertain variables. Many initial state candidates are calculated with their sensitivities. Only the largest one is used in the next parameter estimation process. Besides, the total number of sampling times is searched to reduce the computation time of set inversion.

5. APPLICATION

This section is devoted to parameter estimation of a case study including optimal initial state design. The case study is a pharmacokinetics model (15) developed below.

5.1 Case study

The case study considered in this paper is a model of glucose-oxidase pharmacokinetics developed in Verdière et al. (2005). Intracellular infections are an important worldwide health problem. For instance, it is estimated that tuberculosis, caused by the optional intracellular bacterium *Mycobacterium tuberculosis*, kills 2-3 million people each year. Macrophage lifetime is much longer than the lifetime of granulocytes, the latter cells forming the body first line of defense against infectious organisms. Thus, bacteria which evolved resistance against the macrophage defense mechanisms can survive for a long time in the body, being protected from the immune responses. Moreover, antibiotic concentrations are often lower inside cells than in extracellular fluids. Consequently, intracellular infections determine diseases difficult to cure. Targeting anti-infectious drugs toward macrophages could bring the drugs in close contact with intracellular bacteria and thus help to fight the diseases they determine. In order to reach this goal, macromolecular carriers bearing the drug and a homing device directed toward the mannose receptor of macrophages were used.

Before synthesizing macromolecular conjugates and studying their in vivo efficacy, it was necessary to explore the capacity of the macrophage mannose receptor to endocytose soluble macromolecules and to quantify the different aspects of such a process. Glucose oxidase, a mannose-lyated enzyme easily detected in biological samples through spectrophotometric, potentiometric or immunologic techniques, was used for a first pharmacokinetic study of mannose receptor activity in vivo Demignot and Domurado (1987). After bolus intravenous administration of glucose oxidase, its pharmacokinetic behavior is represented by the following system in which to simplify the description we omit the variables t , p and x_0 :

$$\begin{cases} \dot{x}_1 = k_{12}(x_2 - x_1) - k_v \frac{x_1}{1 + x_1}, & x_1(0) = x_{10}, \\ \dot{x}_2 = k_{21}(x_1 - x_2), & x_2(0) = 0, \\ y = x_1. \end{cases} \quad (15)$$

In this model, x_1 is the enzyme concentration in plasma, x_2 its concentration in compartment 2, and k_{12} is the rate constant of the transfer from compartment 1 (or the central compartment), practically plasma, to compartment 2 (or the peripheral compartment), which represents in the model the part of extravascular extracellular fluid accessible to glucose oxidase. Concretely, this transfer occurs through the capillary walls, more or less rapidly depending on the different permeabilities of the capillary beds in the different organs. Therefore k_{12} is the sum of all the transcapillary transfers in all the organs. Furthermore, k_{21}

is the rate constant of the transfer from compartment 2 to compartment 1. For a macromolecule such as glucose oxidase, this transfer corresponds to return from extracellular fluid to blood through lymphatic circulation. k_v is the maximum rate of an uptake by macrophages through the mannose receptor. The receptor-mediated uptake is a cellular process taking place at the level of the macrophage membrane. The ratio $\frac{k_{12}}{k_{21}}$ of these two parameters is equal to the ratio of the volume of the peripheral compartment to the volume of the central compartment. From the equations of system (15), it is possible to calculate the amount of a mannose receptor ligand taken up by macrophages at any given time after intravenous injection.

The parameters to be estimated are k_{12} , k_{21} , k_v which are assumed to be uncertain. Parameter and state estimation is conducted in simulation with the exact values of parameters given by $p = (k_{12}, k_{21}, k_v) = (0.011, 0.02, 0.1)$. The total number of sampling times N is fixed as 117 (by using a sampling period of 1s).

5.2 Optimal initial state design

To implement the calculus of MIGMAG criterion, estimation of Equation (15) is coupled with estimation of sensitivities. Sensitivities of each parameter are calculated and the sensitivity functions are written as (16):

$$\begin{cases} \dot{s}_{11} = \left(-\frac{k_v}{(x_1 + 1)^2} - k_{12} \right) s_{11} + k_{12}s_{21} + (x_2 - x_1), \\ \dot{s}_{21} = k_{21}s_{11} - k_{21}s_{21}, \\ \dot{s}_{12} = \left(-\frac{k_v}{(x_1 + 1)^2} - k_{12} \right) s_{12} + k_{12}s_{22}, \\ \dot{s}_{22} = k_{21}s_{12} - k_{21}s_{22} + (x_1 - x_2), \\ \dot{s}_{13} = \left(-\frac{k_v}{(x_1 + 1)^2} - k_{12} \right) s_{13} + k_{12}s_{23} - \frac{x_1}{1 + x_1}, \\ \dot{s}_{23} = k_{21}s_{13} - k_{21}s_{23}. \end{cases} \quad (16)$$

The initial condition is supposed to belong to $[0.1, 1.0]$ (only the state x_1 is measured). Equation (12) is used to calculate every possible value influence $S = S_{1\alpha}$ where $\alpha = 1, \dots, n_p$. The initial parameter box is given by:

$$[\mathbb{P}_0] = \begin{bmatrix} 0.0099, & 0.0121 \\ 0.018, & 0.022 \\ 0.09, & 0.11 \end{bmatrix}. \quad (17)$$

To see which initial state minimizes the criterion, we take a discretization of the interval for $x_1(0)$ ($x_1(0) \in [0.1, 1]$) with a sampling period fixed at 0.01s. The influence of initial state value is represented in Figure 1.

Through this figure, we can see that the set-membership MIGMAG criterion is a decreasing function with respect to $x_1(0)$. This result indicates that if we can increase the initial enzyme concentration, this model will be more informative for parameter estimation.

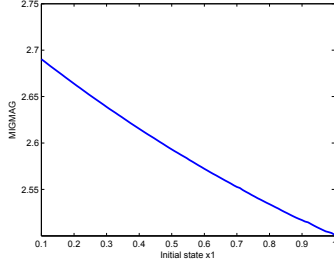


Fig. 1. Influence of initial state value of x_1 .

Then for the numerical results, two initial conditions are considered: the worst case $x_1(0) = 0.1$ and $x_1(0) = 0.9$ which is close to $x_1(0) = 1$, in order to avoid the problems of boundary conditions.

5.3 Elementary effect analysis

A problem of parameter estimation by using set inversion is the number of measurements used in the estimation procedure. It is well-known that an estimation algorithm based on set-inversion is a time consuming process. Thus an elementary effect analysis on the number of sample points is carried out. The proposed method has been introduced to evaluate whether a quantity of measurements is sufficient to implement our parameter estimation Saltelli et al. (2008).

The variation of MIGMAG criterion with different sampling time period is represented in Figure 2.

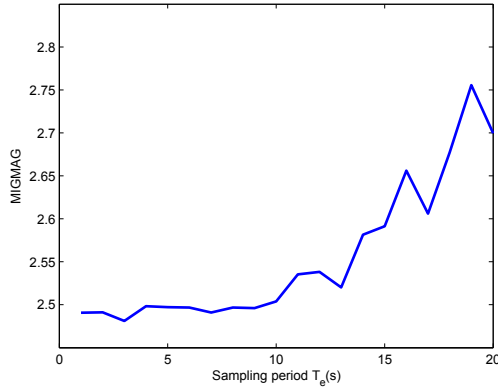


Fig. 2. Variation of MIGMAG criterion with different sampling time period T_e .

This Figure indicates that the results of the set-membership MIGMAG criterion are closed enough when the sampling period T_e is given by 1 second or 3 seconds and for larger periods ($T_e > 10$) the results are deteriorating. Then two sampling periods are considered : 1 second (thus $N = 117$) and 3 seconds (thus $N = 39$).

5.4 Parameter estimation

In the following part, we consider parameter estimation for the pharmacokinetics model. The bounded measurement error is fixed at $v \in [-5, 5] \times 10^{-3}$ for x_1 . The initial

parameter domain is given with 5% relative error over the true parameters. To estimate parameter, Algorithm 2 is used.

The bisection coefficient for the set inversion algorithm is given by $\varepsilon = [2, 2, 5] \times 10^{-5}$.

We have got the two following Figures in which the acceptable boxes are in black color.

By using a sampling period fixed at $T_e = 1s$ and $x_1(0) = 0.1$, the estimation procedure leads to $k_{12} \in [0.0099, 0.0121]$, $k_{21} \in [0.018, 0.022]$, $k_v \in [0.0974, 0.1026]$. These intervals contain the true values. The acceptable boxes are represented in Figure 3.

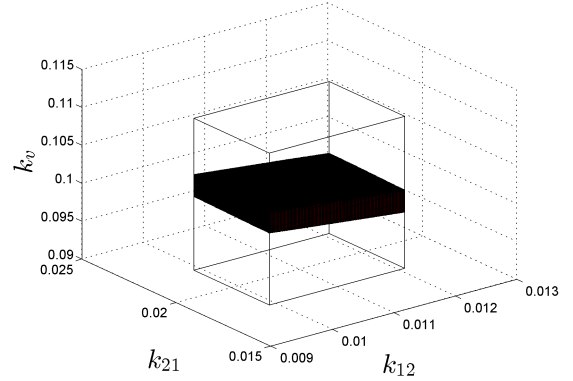


Fig. 3. Acceptable boxes $x_1(0) = 0.1$ and $T_e = 1s$.

By using a sampling period fixed at $T_e = 1s$ and $x_1(0) = 0.9$ the estimation procedure leads to $k_{12} \in [0.0107, 0.0113]$, $k_{21} \in [0.0187, 0.0213]$ and $k_v \in [0.0995, 0.1005]$. These intervals contain the true values of parameters. The acceptable boxes are represented in Figure 4.

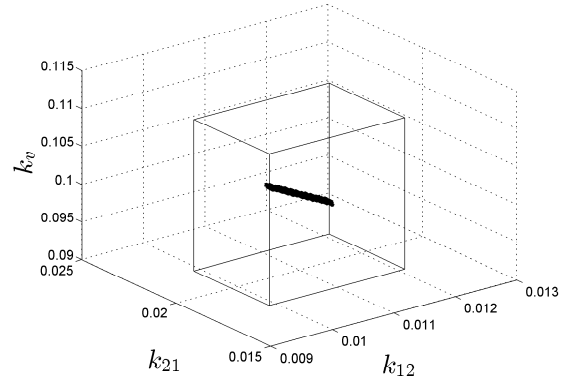


Fig. 4. Acceptable boxes with $x_1(0) = 0.9$ and $T_e = 1s$.

By using a sampling period fixed at $T_e = 3s$ and $x_1(0) = 0.9$, the acceptable box range is the same that those obtained with $T_e = 1s$.

Thus, we propose the following Table in which the estimation results are proposed:

Through this table, we see that the width of interval estimates are divided by about 4 for two parameters when

Table 1. Width of interval estimates for parameter of pharmacokinetics model.

T_e (s)	$x_1(0)$	width of estimate for k_{12}	width of estimate for k_{21}	width of estimate for k_v
1	0.1	0.0022	0.0040	0.0052
1	0.9	$6 \cdot 10^{-4}$	0.0026	0.0010

an optimal initial state is used and is divided by 2 for the other parameter.

In Table 2, the computational time of each configuration for parameter estimation is given. The time consuming is given in second.

Table 2. Computational time for parameter estimation process

T_e (s)	$x_1(0)$	Without contractor	Contractor	Contractor with volumetric criterion
1	0.1	42373	132773	32454
1	0.9	11013	9325	1507
3	0.9	4508	3501	621

The fastest method consists in combining the volumetric condition contractor and less sampling times. With the volumetric condition contractor, for all cases, we reduce the computational time of the parameter estimation process. The contractor accelerates the speed of elimination of non acceptable boxes, but an inappropriate use makes this tool not useful. Reducing the number of measurements and choosing the right time to launch the contractor are two important ways to minimize the computational time.

The previous simulation have not been made in a real-time context. But the computational requirement is compatible with the real-time constraints for the case study. Same algorithms were successful employed for example in robotics like in Walter et al. (2001) or in Braems et al. (2000).

6. CONCLUSION

In this contribution, original tools in a bounded-error context have been proposed to improve parameter estimation for a large class of nonlinear dynamical models. An optimal initial state criterion: the set-membership MIGMAG criterion has been highlighted. Then an algorithm based on an original criterion called CondContract has been proposed to reduce the use of contractors and consequently we reduce the computational time. Finally to increase efficiency in parameter estimation, the elementary effect analysis has been used.

Our tools have been tested on an example taken from the pharmacokinetics domain and they showed their efficiency.

We note that the set-membership MIGMAG criterion can also be used in the context of bounded errors for the input optimization of nonlinear controlled dynamical models.

This parameter estimation method has potential for being used for fault detection and diagnosis problems in continuous-time systems or hybrid systems. Fault detection mechanisms using bounded uncertainty models

present the advantage to guarantee absence of false alarms Armengol et al. (2000).

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