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Including Errata: Fig. 2 and its caption on page 393.

Extending a sensitivity based algorithm to detect local structural identifiability

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Abstract: Output sensitivities to parameters underly a highly efficient sensitivity based algorithm to compute local structural identifiability of possibly large-scale nonlinear dynamic systems. By means of simple examples, this paper explores exceptional cases where this algorithm fails. That is, if one applies the common definition of local structural identifiability. As also shown in this paper, when applying a closely related definition of identifiability, based on sensitivities, the sensitivity based algorithm always provides the correct answer. The subtle difference between these two definitions, that seems to have been overlooked in the literature, is further explored and explained in this paper. For the common definition of local structural identifiability, an extension of the sensitivity based algorithm is presented that approximately doubles the computation time. This extension is shown to work along non-singular trajectories.

Keywords: Local structural identifiability, Local sensitivity identifiability, Large-scale nonlinear dynamic systems, Sensitivity rank condition (SERC), Sensitivity based algorithm.

1. INTRODUCTION

In building mathematical models of dynamic systems, estimating unknown model parameters from measurements, is a common important task. Local structural identifiability is a system property that tells whether parameters can be uniquely determined locally from such measurements. Therefore, local structural identifiability is often considered a prerequisite to properly perform parameter estimation.

Within a sensitivity based algorithm to detect local structural identifiability of possibly large-scale dynamic systems, output sensitivities to parameters are fundamental (Stigter and Molenaar 2015; Stigter et al., 2017a, 2017b; Joubert et al., 2020; van Willigenburg et al., 2021). In comparing algorithms detecting local structural identifiability, this algorithm was even called incredibly fast (Wieland et al. 2021). By computing output sensitivities from a trajectory of a dynamic system, the sensitivity based algorithm produces a sensitivity matrix. A rank condition applied to this sensitivity matrix, called a sensitivity rank condition (SERC), represents a condition for local structural identifiability to hold. This condition has been presented both as sufficient (Stigter and Molenaar, 2015), and necessary and sufficient (van Willigenburg et al., 2021).

Of course, the nature of the condition concerning local structural identifiability relates to its definition. The development of different definitions of identifiability is extensively described in the literature (Bellman and Åström, 1970; Reid, 1977; Cobelli and DiStefano, 1980; Tunali and Tarn, 1987; Saccomani et al. 2003; Miao et al. 2011; Villaverde et al. 2018; Wieland et al. 2021). One contribution of this paper is to reconsider two definitions being local sensitivity identifiability and local structural identifiability and pinpoint a subtle difference between the two that seems to have been overlooked in the literature (Cobelli and DiStefano, 1980). A further contribution is to show that the condition computed by the sensitivity based algorithm decides on local sensitivity identifiability. An argument is presented why local structural identifiability is to be preferred over local sensitivity identifiability. A further major contribution is to present an extension of the algorithm, that makes the algorithm decide on local structural identifiability from non-singular trajectories. Because this extension approximately doubles the computation time, the sensitivity based algorithm still detects local structural identifiability in the order of seconds, even for large-scale systems (Stigter and Molenaar 2015; Stigter et al., 2017a, 2017b; Joubert et al., 2020; van Willigenburg et al., 2021).

The outline of the paper is as follows. Since our major objective is to extend the sensitivity based algorithm, this algorithm is presented first, in section 2. In section 3 a simple and exceptional example illustrating the failure of the algorithm is presented and analyzed. Based on the analysis, in section 4, the extension of the algorithm is presented. Finally, in section 5, the original algorithm is shown to decide on local sensitivity identifiability, whereas with the extension, it is shown to decide on local structural identifiability from non-singular trajectories. The difference between these two definitions of identifiability is pinpointed and shown to exactly relate to the extension. Finally, an argument is presented why local structural identifiability is to be preferred over local sensitivity identifiability. Short conclusions are presented in section 6.

2. THE SENSITIVITY BASED ALGORITHM TO DETECT LOCAL STRUCTURAL IDENTIFIABILITY

A dynamic system is called structural identifiable if parameters can be uniquely determined from measured data. Because dynamic systems may be nonlinear, structural identifiability is generally considered as a local property in the parameter space. In this paper, dynamic systems are represented by ordinary differential equations written in state-space format

$$\frac{dx(t)}{dt} = f\left(x(t),u(t),\theta\right),\ f,x\in\mathbb{R}^n,\ u\in\mathbb{R}^r,\theta\in\mathbb{R}^p, \quad (2.1)$$

$$y(t) = h\left(x(t),\theta\right),\ y,h\in\mathbb{R}^m. \quad (2.2)$$

Here variable t denotes continuous time, x is a vector containing the state variables, u a vector containing the input variables of the system, θ represents the vector of parameters and f is a vector function also referred to as the system dynamics. Furthermore y is a vector containing the output variables available for observation, identification and control and h is a vector function that determines how the output variables depend on the state variables and parameters. The sensitivity based algorithm (Stigter and Molenaar, 2015) computes output sensitivities to parameters from an *a-priori specified trajectory* governed by equations (2.1), (2.2) for $t\in[t_0,t_N]$, $t_N > t_0$. This trajectory is fixed if we fully specify the initial conditions, the parameter values and input

$$x(t_0) = x_0,\ \theta=\theta_0,\ u(t)=u_0(t),\ t\in[t_0,t_N]. \quad (2.3)$$

All results obtained from the sensitivity based algorithm are therefore conditioned on *a choice of* (2.3). Vector functions f,h are assumed to be analytic. This guarantees that no changes of local structural identifiability occur along the trajectory (2.3).

The sensitivity based algorithm computes parametric state and output *sensitivity matrix functions* $\frac{\partial x}{\partial\theta}(t)$, $\frac{\partial y}{\partial\theta}(t)$ associated with system (2.1), (2.2). For notational convenience, these matrix functions will be written as $x_\theta(t)$ and $y_\theta(t)$ having dimensions $n\times p$ and $m\times p$ respectively. Straightforward differentiation of equations (2.1), (2.2) with respect to parameter vector θ, and interchanging differentiation with respect to different, independent parameters, reveals that the dynamics of these sensitivity matrix functions is governed by

$$\frac{dx_\theta}{dt} = \frac{\partial f}{\partial x}x_\theta + \frac{\partial f}{\partial\theta}, \quad (2.4)$$

$$y_\theta = \frac{\partial h}{\partial x}x_\theta + \frac{\partial h}{\partial\theta}. \quad (2.5)$$

Simultaneous integration of differential equations (2.1), (2.4) along trajectory (2.3) with the additional initial condition,

$$x_\theta(t_0) = 0\in\mathbb{R}^{n\times p} \quad (2.6)$$

provides $x(t)$, $x_\theta(t)$. Substitution of these in equation (2.5) then yields $y_\theta(t)$. By sampling matrix function $y_\theta(t)$, $t\in[t_0,t_N]$ at times t_i, $i=0,1,..,N,$ the sensitivity based algorithm computes a sensitivity matrix

$$Y_\theta = \begin{bmatrix} y_\theta(t_0) \\ y_\theta(t_1) \\ \vdots \\ y_\theta(t_N) \end{bmatrix} \in \mathbb{R}^{(N+1)m\times p},\ (N+1)m > p. \quad (2.7)$$

The sensitivity rank condition (SERC), that is a major part of the sensitivity based algorithm, then reads $rank(Y_\theta) = p$. To avoid rank deficiency in equation (2.7), the number of samples N is chosen such that $(N+1)m > p$. As we shall further explore in section 5, SERC is a necessary and sufficient condition for local sensitivity identifiability and a sufficient condition for local structural identifiability of the parameters θ from trajectory (2.3). The rank is computed from a singular value decomposition of the sensitivity matrix Y_θ

$$\begin{aligned} &Y_\theta = \sum_{i=1}^{p} u_i\sigma_i v_i^T,\ Y_\theta\in\mathbb{R}^{(N+1)m\times p}, \\ &u_i\in\mathbb{R}^{(N+1)m},\ \sigma_i\in\mathbb{R}^1,\ v_i\in\mathbb{R}^p. \end{aligned} \quad (2.8)$$

The rank equals the number of singular values σ_i that are (numerically) non-zero. The column vectors v_i corresponding to zero singular values σ_i, span the nullspace. This nullspace has the following important interpretation. It represents all directions at θ_0 in the parameter space along which small changes of parameters θ have no influence on the output $y(t)$. The column vectors v_i make up what is called the local identifiability signature (Stigter and Molenaar, 2015). These column vectors and the corresponding nullspace they span, will play a major role in establishing the main result of this paper, to be developed in the next sections.

3. WHEN AND WHY THE SENSITIVITY BASED ALGORITHM FAILS

In exceptional cases, explored in this section by means of a single example, the sensitivity based algorithm is shown to fail. A subsequent analysis reveals the cause of these exceptional failures.

Example 1
Consider the system (2.1), (2.2) without inputs given by

$$f(x,\theta) = \left(1+\theta^3\right)x,\ h(x) = x,\ x\in\mathbb{R}^1,\ \theta\in\mathbb{R}^1 \quad (3.1)$$

and the trajectory (2.3) given by

$$x_0 = 1,\ \theta_0 = 0,\ t_0 = 0,\ t_N = 1. \quad (3.2)$$

From equations (3.1), (3.2), $\frac{\partial f}{\partial \theta} = 3\theta^2 x = 0$, $\frac{\partial h}{\partial \theta} = 0$ for $\theta = \theta_0 = 0$. Substitution of these into equations (2.4), (2.5) and considering the zero initial condition (2.6) yields $x_\theta(t) = 0,\ y_\theta(t) = 0,\ t \in [t_0, t_N]$. Through equations (2.7) this results in a single and zero singular value in equation (2.8). Thus the sensitivity rank condition (SERC) reads $rank(Y_\theta) = 0 \neq p = 1$ implying identifiability does not hold. On the other hand, for any parameter value $\theta \neq \theta_0 = 0$, we obtain $\frac{\partial f}{\partial \theta} = 3\theta^2 x \neq 0$ since $x \neq 0$ given $x_0 = 1$ in (3.2). Then a non-zero output sensitivity $y_\theta(t)$, $t \in [t_0, t_N]$ is obtained and SERC reads $rank(Y_\theta) = p = 1$, implying identifiability. So $rank(Y_\theta)$ is zero for $\theta = \theta_0 = 0$ but non-zero in any neighborhood of θ_0 in the parameter space implying that $\theta = \theta_0 = 0$ is an *isolated* output sensitivity singularity, i.e. an isolated point in the parameter space where $rank(Y_\theta)$ has a reduced value compared to its neighborhood. Also observe that the output $y(t)$, $t \in [t_0, t_N]$ is different for different values of θ. This tells us that the system is actually globally structural identifiable. From this analysis, *isolated* output sensitivity singularities explain the exceptional sensitivity based algorithm failure. These occur if sensitivities are zero to first-order but nonzero when higher-order terms are considered.

Example 1 concerns a system with just one state, one output and one parameter. Then the output sensitivity $y_\theta(t)$, $t \in [t_0, t_N]$ is a scalar function and $rank(Y_\theta)$ can be either zero or one. In the general case of systems having more states, parameters and outputs, the output sensitivity $y_\theta(t)$, $t \in [t_0, t_N]$ is a matrix function having dimensions $m \times p$ and $rank(Y_\theta)$ in (2.7) can take on values in between zero and p. To fix the outcome of the algorithm for isolated output sensitivity singularities, detection of these is required, together with an appropriate correction. These will be considered in the next section.

4. EXTENDING THE SENSITIVITY BASED ALGORITHM

Recall that the column vectors v_i corresponding to zero singular values σ_i in equation (2.8), obtained from the singular value decomposition of sensitivity matrix Y_θ in equation (2.7), span the nullspace. Also recall that this nullspace represents all directions at θ_0 in the parameter space, along which *small* changes of parameters θ have no influence on both the output $y(t)$ and $rank(Y_\theta)$, that is, if θ_0 is not an isolated output sensitivity singularity. This is due to output sensitivities being zero in these directions. But if θ_0 is an isolated output sensitivity singularity, all small parameter changes in the nullspace *will* change the output $y(t)$ and *will increase* $rank(Y_\theta)$. This increase happens in Example 1, where the nullspace is the full parameter space that is one dimensional. Any very small change of θ away from $\theta = \theta_0 = 0$ increases $rank(Y_\theta)$ from zero to one. So in general, our task is to search for directions in the nullspace along which $rank(Y_\theta)$ increases, if any.

Let $r_{\max}$ denote the maximum of $rank(Y_\theta)$ when searching for such directions in the nullspace and r_0 the rank initially obtained from the sensitivity based algorithm. The outcome of the search may be twofold. 1) There are no such directions and $rank(Y_\theta)$ remains unchanged. Then $r_{\max} = r_0$ implying the sensitivity based algorithm already found the correct result. 2) There are directions in which $rank(Y_\theta)$ *increases*. Then $r_{\max} > r_0$. Let $v_{\max}$ denote a vector pointing in a direction of the small parameter change that realizes $r_{\max}$. To find $r_{\max}$, suppose the small parameter change away from θ_0 is chosen in an *arbitrary direction* of the nullspace. Then, *with probability one*, this vector will have a component in the direction $v_{\max}$. As a result, when running the sensitivity based algorithm again, we will obtain $r_{\max} = rank(Y_\theta)$. Finally note that an arbitrary direction in the nullspace is a linear combination of its basis vectors v_i corresponding to zero singular values σ_i, $i = 1, 2, .., p - r_0$ obtained from equation (2.8). As the arbitrary direction we will take the sum of these basis vectors. If in doubt about this choice, one can make several choices and select the one with the highest outcome of $rank(Y_\theta)$.

Extended sensitivity based algorithm

1. Execute the sensitivity based algorithm to determine $r_0 = rank(Y_\theta)$.
2. Change θ_0 into $\theta_0 + \varepsilon\Delta\Theta,\ \Delta\Theta = \sum_{i=1}^{p-r_0} v_i,\ \varepsilon = 10^{-2}\frac{\|\theta_0\|}{\|\Delta\theta\|}$, with v_i singular vectors corresponding to (numerically) zero singular values σ_i, $i = 1, 2, .., p - r_0$ obtained from step 1 and equation (2.8).
3. Execute the sensitivity based algorithm again to obtain the proper $r_{\max} = rank(Y_\theta) \geq r_0 \leq p$.
4. SERC: $r_{\max} = rank(Y_\theta) = p$.

Remark 1

Steps 2-4 above extend the sensitivity based algorithm by taking a small step in the parameter nullspace, away from θ_0. Now what is considered *small*, is a subtle issue in our extension. The small step in the parameter nullspace should be *large enough* to increase the *numerical rank* of Y_θ. This is represented by a numerically zero singular value turning into a non-zero one in equation (2.8). On the other hand, the small step in the parameter nullspace should be *small enough* not to be affected by the change of the entire nullspace as we change parameters. This change of the entire nullspace relates to nonlinearities in the output sensitivities $y_\theta(t)$. So deciding on what is a small step is a *compromise*. Step 2 implements this compromise. It works well for the two small-scale examples in this paper, see Table 1, and several others that we tested. Also we successfully applied step 2 to a large-scale system having many states, parameters and $r_{\max} > r_0$. But obviously, this issue deserves further investigation and testing.

Table 1: *Single singular value for Example 1 and Example 2 obtained from the extended algorithm after step 1 and after step 3 respectively. A numerically zero value is in the order of the machine constant being* 2.22e-16.

Singular value	After step 1	After step 3
Example 1:	0	1.4303e-04
Example 2:	0	1.1625e-02

5. RELATING THE SENSITIVITY BASED ALGORITHM AND ITS EXTENSION TO DEFINITIONS OF IDENTIFIABILITY

Following the early development in Bellman and Åström (1970), local identifiability concerns the ability to use least squares parameter estimation to uniquely determine parameters of the system (2.1), (2.2) from errorless measurements $y(t),\, t \in [t_0, t_N]$ obtained along a trajectory (2.3). Least squares parameter estimation varies the parameters θ of the system (2.1), (2.2) while minimizing

$$J(\theta) = \int_{t_0}^{t_N} \left(y(t,\theta) - y(t,\theta_0) \right)^2 dt \tag{5.1}$$

where $y(t,\theta)$ denotes errorless measurements along the trajectory (2.3), with θ_0 replaced with θ. Given the errorless nature of the measurements $y(t,\theta)$ and $y(t,\theta_0)$ in (5.1), local structural identifiability is a *system property*.

Definition 1
The parameters θ of system (2.1), (2.2) are *local structural identifiable from trajectory (2.3)*, if and only if $J(\theta)$ has a local isolated minimum $J(\theta_0) = 0$.

Consider small perturbations $\Delta y(t) = y(t,\theta) - y(t,\theta_0)$ and $\Delta\theta = \theta - \theta_0$. Then the following relation holds *to first-order*;

$$\Delta y(t) = y_\theta(t,\theta_0)\,\Delta\theta\,. \tag{5.2}$$

Based on this relation, in Reid (1977) sensitivity identifiability was introduced which closely relates to structural identifiability. Sensitivity identifiability was compared with other types of identifiability in Cobelli and DiStefano (1980).

Definition 2
The parameters θ are *local sensitivity identifiable from trajectory (2.3)*, if and only if $y_\theta(t,\theta_0)$ in (5.2) is one-to-one.

Definition 2 relies on the idea that any small perturbation $\Delta\theta$ of the parameters causes a corresponding unique small change $\Delta y(t)$ in the output according to equation (5.2). Since equation (5.2) only holds to first-order, sensitivity identifiability in Definition 2 only incorporates sensitivities to first-order, as clearly stated in Reid (1977) where it was introduced.

Example 2 (Example 4 from Tunali and Tarn (1987) concerning local structural identifiability)

$$f(x,u,\theta) = \begin{bmatrix} x_1 x_2 + u_1 \\ \theta_1^3 + x_1 u_1 \end{bmatrix},\; h(x,\theta) = x_1 + \theta_1^2 x_2 \tag{5.3}$$

$$x_0 = \begin{bmatrix} 0 \\ 0 \end{bmatrix},\; \theta_0 = 0,\; u_0(t) = \sin(2\pi t),\; t_0 = 0,\; t_N = 1. \tag{5.4}$$

One easily sees that along the trajectory (2.3), (5.4), $\dfrac{df}{d\theta} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}$, $\dfrac{dh}{d\theta} = 0$. As a result, from (2.4), (2.5) and (2.6), $y_\theta(t) = 0$. On the other hand, whenever $\theta \neq \theta_0$ in equation (5.4), $y_\theta(t)$ is non-zero implying that this example concerns another isolated output sensitivity singularity. From Definition 2, since $y_\theta(t,\theta_0) = 0$, parameters θ are not sensitivity identifiable from trajectory (2.3), (5.4). On the other hand, $J(\theta_0) = 0$ still is an isolated minimum, see Fig. 1. Then according to Definition 1, the parameters θ are local structural identifiable from trajectory (2.3), (5.4). This reveals that local structural identifiability in Definition 1 is weaker than sensitivity identifiability in Definition 2, and not equivalent as suggested in Cobelli and DiStefano (1980).

Theorem 1
SERC computed by the sensitivity based algorithm without the extension is:

a. A *sufficient condition* for the parameters θ to be local structural identifiable from trajectory (2.3).
b. A *necessary and sufficient condition* for the parameters θ to be local sensitivity identifiable from trajectory (2.3).

Proof
a. Follows from Stigter, Molenaar (2015). b. If SERC is satisfied, sensitivity matrix Y_θ in (2.7), obtained by sampling the sensitivity matrix function $y_\theta(t)$, has full rank p. This implies $y_\theta(t)$ itself has p independent columns and $y_\theta(t)$ in (5.2) is one-to-one. According to Definition 2, this implies local sensitivity identifiability. If SERC is not satisfied, sensitivity matrix Y_θ in (2.7) does not have full rank p. Since in (2.7), the number of samples $(N+1)m > p$ this implies $y_\theta(t)$ does not have p independent columns and $y_\theta(t)$ in (5.2) is not one-to-one. Then, according to Definition 2, local sensitivity identifiability does not hold.

Example 2 and Theorem 1 clearly indicate that Definition 1 is to be preferred when it comes to the successful performance of parameter estimation using least squares. This can also be observed from Example 1. Given this preference, one would prefer necessary and sufficient conditions for local structural identifiability. One would expect SERC of the extended algorithm to be this necessary and sufficient condition if the small parameter change, mentioned in Remark 1, is a proper compromise and does not end up in another singularity. It is, apart from exceptional cases illustrated by the next example.

Example 3

$$f(x,\theta)=\begin{bmatrix}(1+\theta_1^3)x_2\\(\theta_2-\theta_3)x_1+\theta_3x_2\end{bmatrix},\ h(x)=x_2 \qquad (5.5)$$

$$x_0=[1,1]^T,\ \theta_0=[0,1,2]^T,\ t_0=0,\ t_N=1. \qquad (5.6)$$

Table 2: *Singular values for Example 3 obtained from the extended algorithm after step 1 and after step 3 respectively. A numerically zero value is in the order of the machine constant being* 2.22e-16.

After step 1: 5.3295e+00, 0, 0
After step 3: 5.3634e+00, 1.6188e-04, 8.7975e-08

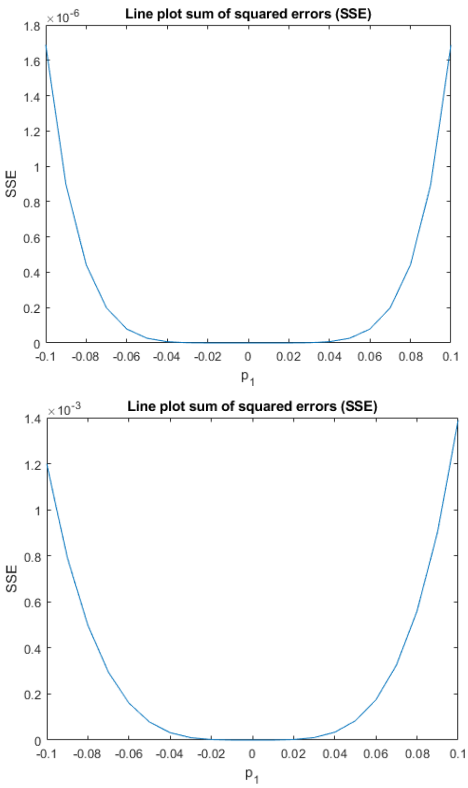

Fig. 1: *Sum of squared errors plot Example 1 and Example 2 respectively.*

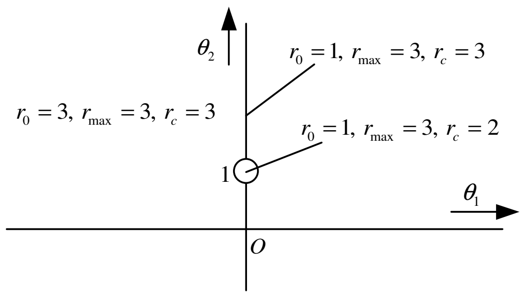

Fig. 2: *Example 3 has a local structural identifiability singularity at* $\theta_1=0$, $\theta_2=1$ *and an* isolated *output sensitivity singularity at* $\theta_1=0$. r_0, r_{max} *are obtained after step 1 and 3 of the extended algorithm and* r_c *indicates the correct rank.*

Analysis of Example 3 reveals that $\theta_1=0$ causes $\frac{\partial f_1}{\partial \theta_1}$ and output sensitivity $\frac{\partial y}{\partial \theta_1}$ to be zero, but non-zero in any neighborhood of $\theta_1=0$ in the parameter space. This causes $\theta_1=0$ to be an isolated sensitivity singularity. Also, the initial condition $x_0=[1,1]^T$ together with $\theta_1=0$, $\theta_2=1$, causes $x_1(t)=x_2(t)$, $t\in[t_0,t_N]$ which prevents any influence of θ_3 on the state and output. Therefore, in Example 3, $\theta_1=0$ is part of *a structural identifiability singularity*, see Fig. 2, and the extended algorithm is going to make small changes in both the θ_1 and θ_3 direction. But any small change in the θ_1 direction also restores sensitivity of the state and output to θ_3, because $x_1(t)=x_2(t)$ no longer holds. As a result, SERC from the extended algorithm, i.e. after step 3, produces rank 3, as seen from Table 2, whereas it should produce rank 2, given the structural identifiability singularity. This very special example shows that if the isolated output sensitivity singularity is part of a structural identifiability singularity (θ_1 in Example 3), the algorithm extension may produce an erroneous result.

Conjecture 1

Assume the small parameter change, mentioned in Remark 1, is a proper compromise and does not end up in a singularity. Then the extended sensitivity based algorithm computes *necessary and sufficient conditions* for local structural identifiability from a trajectory (2.3) that is non-singular, i.e. with θ_0 not being a structural identifiability singularity.

6. CONCLUSIONS

The extension, presented in this paper, of the sensitivity based algorithm was shown to relate exactly to a subtle difference between two definitions of local identifiability. Because the sensitivity based algorithm relies on output sensitivities, these two definitions, being local sensitivity identifiability and local structural identifiability, were reconsidered in this paper, from the point of view of output sensitivities. They were shown to contain a subtle difference, that seems to have been overlooked in the literature. This subtle difference concerns *isolated sensitivity singularities*.

Isolated sensitivity singularities are singularities of local sensitivity identifiability, but they are not singularities of local structural identifiability. The original sensitivity based algorithm considers them as singularities, which is correct in the case of local sensitivity identifiability. According to Conjecture 1, the sensitivity based algorithm with the extension, no longer classifies them as singularities, which is correct in the case of local structural identifiability, as long as the isolated sensitivity singularity is not part of a singularity of local structural identifiability. An interesting continuation of this research is to proof this conjecture and see if singularities of local structural identifiability can also be included.

As also shown in this paper, local structural identifiability is to be preferred over local sensitivity identifiability because it corresponds with the most common method to estimate parameters being least-squares. On the other hand, Fig. 1 shows very small sensitivities around the isolated sensitivity singularity, implying poor parameter estimation whenever measurements are slightly erroneous. This holds for any isolated sensitivity singularity because the sensitivity is zero to first-order. So although in theory, isolated sensitivity singularities do not prevent local structural identifiability to hold, in practice they generally do.

Another common method to analyze local structural identifiability relies on Lie series expansion. This method is restricted to systems being linear in the input and in exceptional cases, such as Example 2 in this paper, it fails (Tunali and Tarn, 1987). These drawbacks are overcome by the extended sensitivity based algorithm presented in this paper. Because the sensitivity based algorithm extension approximately doubles its computation time, for large-scale systems the sensitivity based algorithm remains superior in terms of computational efficiency. On the other hand, the (extended) sensitivity based algorithm is numerical, requiring proper numerical conditioning of computations, that is not an issue when using Lie series expansions. Moreover, in some cases the outcome from Lie series expansions provides more insight. Therefore combining the two, as in Stigter and Molenaar (2015) and Joubert et al. (2020), provides an efficient powerful tool to analyze local structural identifiability. Finally, as indicated by Remark 1, the selection of appropriate small parameter changes within the algorithm extension requires further investigation and testing.

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