Identifiability and Observability via decoupled variables: Application to a malaria intra-host model

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Abstract: For a class of systems for which identifiability is difficult to be proved in the original set of coordinates, we show that when there exists a change of variables which decouples some variables i.e., whose dynamics is independent of the parameters, identifiability can then be assessed without having to compute derivatives. Moreover, we show that this allows to consider an observer to reconstruct the state of the system without having to estimate the unknown parameters. The effectiveness of this approach is illustrated on an intra-host model of malaria infection.

Keywords: Parameters estimation, identifiability, observability, parameters identification, observer.

1. INTRODUCTION

Identifiability of dynamical models, as described for instance in the textbook Walter and Pronzato (1997), is of crucial importance in epidemiological models Hadeler (2011); Lintusaari et al. (2016); Miao et al. (2011); Tuncer and Le (2018). It has been studied on several virus transmission models (e.g. Cantó et al. (2017); Capaldi et al. (2012); Capistrán et al. (2009); Cintrón-Arias et al. (2009); Eisenberg et al. (2013); Nguyen et al. (2015); Tuncer et al. (2018)). However, it might be difficult to prove identifiability of a model in the original set of coordinates, especially when the dimension of the system is not small. This is typically the case of models of the malaria transmission which is quite complex Gravenor et al. (2002, 1998, 1995). The aim of the present work is to show the interest of considering other variables, that possess "good" properties.

We first study the identifiability problem and then the state reconstruction. We shall see that these two problems can be completely decoupled for a class of systems that we make explicit. Finally, these results are illustrated on a case study of a model of within-host malaria population dynamics proposed in Gravenor and Lloyd (1998); Iggidr et al. (2006); Bichara et al. (2014).

2. THE IDENTIFIABILITY PROBLEM

We consider a system in $\mathbb{R}^n$ parameterized by $\theta \in \Theta \subset \mathbb{R}^p$, with an observation in $\mathbb{R}^q$:

$$\begin{cases} \dot{x} = f(x,\theta), \quad x(0) = x_0 \in X \\ y = h(x) \end{cases} \tag{1}$$

where $X \subset \mathbb{R}^n$ is a positively invariant set for any $\theta \in \Theta$. Posit $Y = h(X) \subset \mathbb{R}^q$.

Proposition 1. Assume that the following properties hold.

(1) The map f verifies
$$\forall \theta_1, \theta_2 \in \Theta,\ \forall x \in X,\quad \theta_1 \neq \theta_2 \Longrightarrow f(x,\theta_1) \neq f(x,\theta_2). \tag{2}$$
(2) There exist smooth maps $g : X \times Y \mapsto W$, $\tilde{g} : W \times Y \mapsto X$ and $l : W \times Y \mapsto \mathbb{R}^m$, where $W \subset \mathbb{R}^m$, such that
   (a) for any solution $x(\cdot)$ of (1) in X, the variable
   $$w(t) := g(x(t), y(t))$$
   verifies
   $$\dot{w}(t) = l(w(t), y(t)), \quad t \geq 0 \tag{3}$$
   (b) for any $x \in X$, one has
   $$w = g(x, h(x))) \Longleftrightarrow x = \tilde{g}(w, h(x)) \tag{4}$$

Then the system (1) is identifiable over Θ for any initial condition in X.

Proof. Fix $x_0 \in X$ and denote by $x_\theta(\cdot)$ the solution of (1) for the parameter $\theta \in \Theta$. Consider θ_1, θ_2 in Θ that give the same output function: $h(x_{\theta_1}(t)) = h(x_{\theta_2}(t)) = y(t)$ for any $t \geq 0$.

Let $w(\cdot)$ be the (unique) solution of the Cauchy problem

$$\dot{w} = l(w, y(t)), \quad w(0) = g(x_0, h(x_0)).$$

Then, one has

$$w(t) = g(x_{\theta_i}(t), y(t)) \quad t \geq 0, \quad i = 1, 2,$$

and from property (4), one obtains

$$\tilde{g}(w(t), y(t)) = x_{\theta_i}(t) \quad t \geq 0, \quad i = 1, 2,$$

that is $x_{\theta_1}(t) = x_{\theta_2}(t)$ for any $t > 0$. Therefore, for any $t > 0$ one has also $\dot{x}_{\theta_1}(t) = \dot{x}_{\theta_2}(t)$ or $f(x(t), \theta_1) = f(x(t), \theta_2)$ where $x(t) = x_{\theta_1}(t) = x_{\theta_2}(t)$. Finally, from condition (2), we deduce that one has necessarily $\theta_1 = \theta_2$, which shows the identifiability of the system.

This result states that when a system is identifiable when measuring the whole state x (condition (2)), and there exits a variable w whose dynamics is *decoupled* in the sense that it depends on w and y only (condition (3)) such that the map $(x, y) \mapsto w$ is invertible with respect to x (condition (4)), then the system is identifiable when measuring y only. This result is illustrated on an intra-host model for malaria infection in Section 4

3. THE STATE RECONSTRUCTION

We study now how to exploit the properties of Proposition 1 to propose an observer to reconstruct the state x.

For convenience, we define the map $k : W \times Y \mapsto Y$ as

$$k(w, y) := h \circ \tilde{g}(w, y), \quad (w, y) \in W \times Y.$$

Proposition 2. Under Assumptions of Proposition 1, let us assume

(1) The maps l and k can be extended as smooth maps on $\mathbb{R}^m \times \mathbb{R}^q$, resp. $\mathbb{R}^m \times \mathbb{R}^q$.
(2) The map $\tilde{g}$ is globally Lipschitz w.r.t. $w \in W$, uniformly w.r.t. $y \in Y$.

Then, for a dynamics of the form

$$\frac{d}{dt}\hat{w} = \hat{l}(\hat{w}, k(\hat{w}, y) - y), \quad \hat{w} \in \mathbb{R}^q \tag{5}$$

which is an exponential observer of the parameter-free system

$$\begin{cases} \dot{w} = l(w, y) \\ y = h(x) \end{cases} \tag{6}$$

the estimator of x defined as

$$\hat{x} = \tilde{g}^{\dagger}(\hat{w}, y)$$

(where $\tilde{g}^{\dagger}$ is any extension of $\tilde{g}$ on $\mathbb{R}^m \times Y$ that is globally Lipschitz w.r.t. w uniformly w.r.t. y) has an exponential convergence of the error, whatever is the unknown parameter $\theta \in \Theta$.

Proof. Let $x(\cdot)$ be a solution of system (1) for a certain $\theta \in \Theta$. Then, $y(t) = h(x(t))$, $w(t) = g(x(t), y(t))$ are necessarily solutions of system (6) for any $t \geq 0$. Therefore an estimator $\hat{w}(\cdot)$ which verifies

$$||\hat{w}(t) - w(t)|| \leq (A + B|\hat{w}(0) - w(0)|)e^{-\alpha t}, \quad t > 0$$

for some positive numbers A, B, α provides the inequality

$$\begin{aligned} ||\hat{x}(t) - x(t)|| &= ||\tilde{g}^{\dagger}(\hat{w}(t), y(t) - \tilde{g}(w(t), y(t))|| \\ &\leq L||\hat{w}(t) - w(t)|| \\ &\leq (LA + LB|\hat{w}(0) - w(0)|)e^{-\alpha t}, \quad t > 0 \end{aligned}$$

where L is the Lipschitz rank of $\tilde{g}^{\dagger}$ (let us recall the existence of a Lipschitz extension of $\tilde{g}$ preserving the same rank from for instance MacShane (1934)), and thus the exponential convergence of the estimator $\hat{x}$.

Remark 3. In the expression (5) of the observer, the quantity $k(\hat{w}, y) - y$ is playing the role of the innovation i.e. $\hat{y} - y$. Typically, one may look for an observer of Luenbeger form

$$\frac{d}{dt}\hat{w} = l(\hat{w}) + G(k(\hat{w}, y) - y)$$

where G is a gains matrix to be chosen to ensure an exponential convergence of the error $\hat{w} - w$ (but other forms of observers are possible).

This result shows that the original observation problem on system (1) with unkwown parameter θ can be transformed into an observation problem of system (6) fully decoupled from the parameter θ.

In Section 4, we illustrate this construction on an intra-host model for malaria infection.

4. A CASE STUDY

We consider a generic intra-host model for malaria in dimension $n = m + 2$ (with $m > 2$) with one unknown parameter, and a single scalar observation variable. The state vector is $x = (S,\ I_1, \ldots\ , I_m\ , M)$ in $\mathbb{R}^n_+$, where S is the concentration of uninfected erythrocytes in the blood, I_i are the concentrations of infected erythrocytes in different age classes, and M is the concentration of free merozoites. The dynamics is given by the following system

$$\begin{cases} \dot{S} = \Lambda - \mu_S\, S - \beta\, SM, \\ \dot{I}_1 = \beta\, SM - (\gamma_1 + \mu_1)\, I_1, \\ \dot{I}_2 = \gamma_1\, I_1 - (\gamma_2 + \mu_2)\, I_2, \\ \vdots \\ \dot{I}_m = \gamma_{m-1}\, I_{m-1} - (\gamma_m + \mu_m)\, I_m, \\ \dot{M} = r\, \gamma_m\, I_m - \mu_M\, M - \beta\, SM, \end{cases} \tag{7}$$

where the different parameters are

Λ: recruitment of the healthy red blood cells (RBC).
β: rate of infection of RBC by merozoites.
μ_S: natural death rate of healthy cells.
μ_i: natural death rate of i-th stage of infected cells.
γ_i: transition rate from i-th stage to $(i+1)$-th stage of infected cells.
r : number of merozoites released by the late stage of infected cells.
μ_M : natural death rate of merozoites.

The first k stages of infected erythrocytes $(I_1, \ldots, I_k)$ with $k \in (2, m)$ correspond to the concentrations of free

circulating parasitized erythrocytes than can be observed (seen on peripheral blood smears). Typically, the quantity

$$y(t) = h(x(t)) = \sum_{i=1}^{k} I_i(t)$$

is measured at any time t. Among parameters in (7), most of them (μ_i, γ_i, and r) are known or at least widely accepted by the community, but the infection rate β, which is playing a crucial role, is unknown and cannot be estimated by biological considerations. This estimation problem has already been studied in Bichara et al. (2014) for the particular case of $m = 5$. We show here how to generalize to any $m > 2$ with the systematic approach we propose here.

Let us then write the dynamics (7) as $\dot{x} = f(x, \beta)$, which takes the form

$$\begin{cases} \dot{x} = f(x,\beta) := A\,x + (\beta\, SM)E + \Lambda\, e_1, \\ y = C\,x \end{cases} \tag{8}$$

with the matrices A, E, C as follows:

$$A = \begin{bmatrix} -\mu_S & 0 & 0 & \cdots & \cdots & 0 \\ 0 & -\gamma_1 - \mu_1 & 0 & \cdots & \cdots & 0 \\ 0 & \gamma_1 & -\gamma_2 - \mu_2 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & 0 & \gamma_{m-1} & -\gamma_m - \mu_m & 0 \\ 0 & 0 & 0 & 0 & r\gamma_m & -\mu_M \end{bmatrix}$$

$$E = \begin{bmatrix} -1 \\ 1 \\ 0 \\ \vdots \\ 0 \\ -1 \end{bmatrix}, \quad e_1 = \begin{bmatrix} 1 \\ 0 \\ \vdots \\ \vdots \\ 0 \end{bmatrix}, \quad C = [0, \underbrace{1, \cdots, 1}_{k \text{ times}}, 0, \cdots, 0]$$

4.1 Identifiability

Due to the dimension of the dynamics, it is not easy to check the identifiability of he parameter β. However, on the domain $X = (\mathbb{R}_+ \setminus \{0\})^n$, one has $SM \neq 0$, which implies the property

$$f_1(x, \beta_1) = f_1(x, \beta_2) \Rightarrow \beta_1 = \beta_2, \quad x \in X.$$

For the parameter $\theta = \beta$, condition (2) of Proposition 1 is thus fulfilled. Note that one has $ECE = E$. Therefore one can consider the variable

$$w = g(x, y) := x - Ey = (I - EC)x$$

whose dynamics is independent of the non-linear term βSM:

$$\dot{w} = l(w, y) := \bar{A}w + \bar{A}Ey + \Lambda\, e_1$$

where we posit $\bar{A} = A - ECA$. Given w and y, the state x is then given by

$$x = \tilde{g}(w, y) := w + Ey.$$

Conditions (3) and (4) of Proposition 1 are thus also satisfied, which allows to conclude without any other calculation, that the parameter β is identifiable.

4.2 State reconstruction

Conditions (1) and (2) of Proposition 2 are naturally satisfied, the maps l, g and $\tilde{g}$ being all linear with respect to their arguments. As suggested in Remark 3, we look for an observer of w of the system

$$\begin{cases} \dot{w} = \bar{A}w + \bar{A}Ey + \Lambda\, e_1 \\ y = Cx \end{cases}$$

in Luenberger form:

$$\begin{aligned} \dot{\hat{w}} &= \bar{A}\hat{w} + \bar{A}Ey + \Lambda\, e_1 + L(y(t) - C(\hat{w} + Ey(t)) \\ &= (\bar{A} - LC)\,\hat{w} + \big(L + (\bar{A} - LC)E\big)\,y(t) + \Lambda\, e_1, \end{aligned} \tag{9}$$

where L is a vector in $\mathbb{R}^n$ to be chosen, which is completely decoupled from the unknown parameter β. The estimator of x is then given by

$$\hat{x}(t) = \hat{w}(t) + E\,y(t).$$

The dynamics of the error $e(t) = \hat{x}(t) - x(t)$ is given by

$$\dot{e} = (\bar{A} - LC)e$$

Note that one has $C\bar{A} = 0$. Therefore the rank of the observability matrix of the pair $(\bar{A}, C)$ is equal to one, and 0 is an eigenvalue of $\bar{A}$. The matrix $\bar{A}$ has the block structure

$$\bar{A} = \left[\begin{array}{c|c} U & 0 \\ \hline * & T \end{array}\right] \text{ with } U = \left[\begin{array}{c|c} -\mu_S & \star\ \cdots\ \star \\ \hline 0 & \\ \vdots & W \\ 0 & \end{array}\right]$$

and

$$W = \begin{bmatrix} -\gamma_1 & \mu_2 & \cdots & \mu_{k-1} & \gamma_k + \mu_k \\ \gamma_1 & -\gamma_2 - \mu_2 & 0 & \cdots & 0 \\ 0 & \gamma_2 & \ddots & & \vdots \\ \vdots & & \ddots & & \\ & & \gamma_{k-2} & -\gamma_{k-1} - \mu_{k-1} & \\ & & & \gamma_{k-1} & -\gamma_k - \mu_k \end{bmatrix}$$

$$T = \begin{bmatrix} -\gamma_{k+1} - \mu_{k+1} & & & & & \\ \gamma_{k+1} & \ddots & & & & \\ 0 & \ddots & & & & \\ \vdots & & \ddots & & & \\ \vdots & \cdots & 0 & \gamma_{n-1} & -\gamma_n - \mu_n & 0 \\ 0 & & \cdots & 0 & r\gamma_n & -\mu_M \end{bmatrix}$$

If one considers a vector L with $L_i = 0$ for $i \neq 2$, $\bar{A} - LC$ has the same block structure than $\bar{A}$ where the sub-matrix W is replaced by $W - L_2K$ with

$$K = \begin{bmatrix} 0 & \cdots & \cdots & 0 \\ 1 & \cdots & \cdots & 1 \\ 0 & \cdots & \cdots & 0 \\ \vdots & & & \vdots \end{bmatrix}$$

Then, for $0 < L_2 < \min_i \mu_i$, the matrix $(W - L_2K)^\top$ is strictly diagonally dominant with negative diagonal and thus Hurwitz. The other eigenvalues of $\bar{A} - L_2C$ are $-\mu_S$ and those on the diagonal of the triangular matrix T,

which are all negative. Therefore, for this choice of L, (9) is an observer for system (8) with exponential convergence, that does not use the unknown parameter β.

4.3 Estimation of β

As we know that the system is identifiable, the parameter β can be reconstructed by a least-square method. Alternatively, one may also consider an additional observer for its estimation. While the estimation error of the state reconstruction provided by the observer (9) is small, which is indicated by the innovation $y - \hat{y}$ remaining close to 0, one may consider that the state is (almost perfectly) known, and consider then the following observer for β

$$\begin{cases} \dot{\tilde{S}} = \Lambda - \mu_S \hat{S}(t) - \tilde{\beta}\hat{S}(t)\hat{M}(t) + G_1(\hat{S}(t) - \tilde{S}(t)) \\ \dot{\tilde{\beta}} = G_2(\hat{S}(t) - \tilde{S}(t)) \end{cases}$$

where $\hat{S}(t)$, $\hat{M}(t)$ are the estimated state variables given by the observer (9). The estimation error $\epsilon(t) = \begin{pmatrix} \tilde{S}(t) - \hat{S}(t) \\ \tilde{\beta}(t) - \beta \end{pmatrix}$ verifies

$$\dot{\epsilon} = \underbrace{\begin{bmatrix} -G_1 & -\hat{S}(t)\hat{M}(t) \\ -G_2 & 0 \end{bmatrix}}_{\Delta(t)} \epsilon$$

The time varying matrix $\Delta(t)$ converges asymptotically to

$$\Delta_\infty = \begin{bmatrix} -G_1 & -S^\star M^\star \\ -G_2 & 0 \end{bmatrix}$$

where $S^\star > 0$, $M^\star > 0$ are the steady-state values of (7). With $G_1 > 0$, $G_2 < 0$, Δ_∞ is Hurwitz guaranteeing the asymptotic convergence of the error ϵ to 0.

4.4 Numerical illustrations

Simulations have been conducted for $n = 5$ age classes and $k = 4$ first classes, with the values of the parameters given in Table 1.

β	Λ	μ_S	μ_M	r
10^{-4}	4.1710^4	8.3310^{-3}	72	16

μ_i	0	1.86	0	0.1	0
γ_i	1.96	3.78	2.85	1.76	2.35

Table 1. Parameters values for the simulation

Figure 1 shows a simulation of the observer (9) with $L_2 = 3$.

For the estimation of β, as the values of S are large and β is small, we have renormalized S by Λ i.e. we have considered the observer

$$\begin{cases} \dot{\hat{s}} = 1 - \mu_S \dfrac{\hat{S}(t)}{\Lambda} - \hat{\beta}\dfrac{\hat{S}(t)}{\Lambda}\hat{M}(t) + G_1\left(\dfrac{\hat{S}(t)}{\Lambda} - \hat{s}\right) \\ \dot{\hat{\beta}} = G_2\left(\dfrac{\hat{S}(t)}{\Lambda} - \hat{s}\right) \end{cases}$$

to avoid a peaking phenomenon. Figure 2 shows the estimation of β with $G_1 = 10$ and $G_2 = -0.5$ in *log* variables to better appreciate the small value of β.

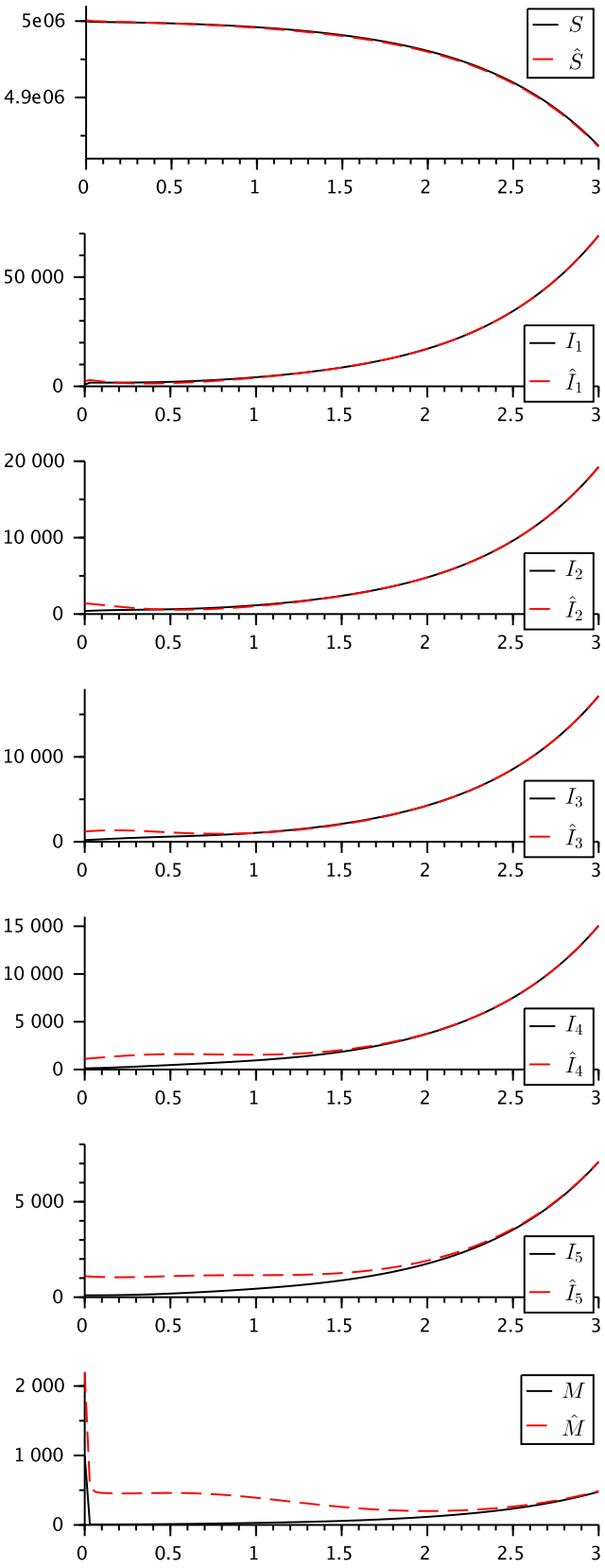

Fig. 1. Simulation of the state reconstruction

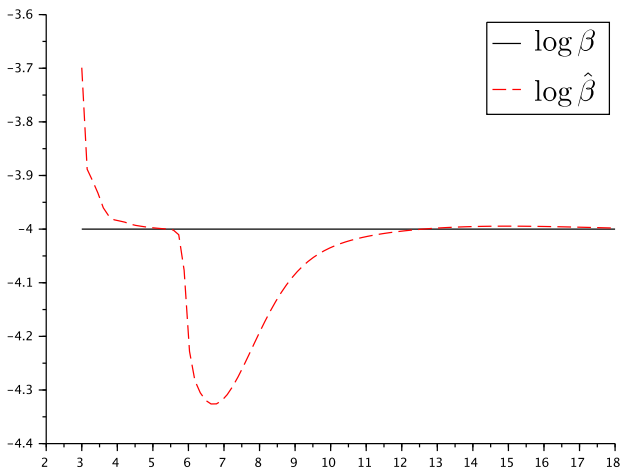

Fig. 2. Simulation of the estimation of the parameter β

5. CONCLUSION

In this work, the example of an intra-host malaria infection model illustrates the interest of exploiting conjointly identifiability and observability to solve the identifiability problem, as stated in Proposition 1. Moreover, this allows to reconstruct the state with an observer without having to estimate the unknown parameter (Proposition 2). The unknown parameter can then be estimated with an additional observer based on the state reconstruction.

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