Identifiability analysis of an epidemiological PDE model

Antoine Perasso, Béatrice Laroche and Suzanne Touzeau

***Abstract*— We investigate the parameter identifiability problem for a SIR system of nonlinear integro-partial differential equations of transport type, representing the spread of a disease with a long infectious but undetectable period in an animal population. After obtaining the expression of the model input-output (IO) relationships, we give sufficient conditions on the boundary conditions of the system that guarantee the parameter identifiability on a finite time horizon. We finally illustrate our findings with numerical simulations.**

I. INTRODUCTION

Epidemiological models are useful tools to describe the spread of a disease in a population, to predict its evolution and control its outbreak. They usually derive from the classical SIR model, a compartmental model in which the population is structured in susceptible, infected and recovered individuals.

The model we investigate in this paper is a SIR-like model, a simplified version of a model developed to study the spread of scrapie in a sheep flock [5]. It is characterised by a long and variable incubation period, during which individuals are infectious but cannot be detected. At the end of this period, detectable clinical signs appear. Then, either infected individuals recover and become immune or they die from the disease. Vertical (in utero) transmission is neglected. The population is assumed to be a well-mixed population confined on a limited territory, so the space dimension can be omitted. It is however structured in age ($a \in [0, A]$) and infection load ($\theta \in [0, 1]$). Newly infected individuals are distributed along θ according to a probability density function Θ (support $[0, 1]$). The infection load θ then grows exponentially with time during the incubation period, which ends when θ reaches 1. An alternative option would have been to structure the infected population according to an age of infection instead, leading to a model similar to [1]. Whatever the modelling, it yields a distributed delay structure. At the end of the incubation period, a fraction $\alpha \in]0, 1[$ of infected individuals die. The other individuals recover and become immune. The resulting susceptible (S), infected (I) and recovered (R) population densities evolve with time ($t \in [0, +\infty[$) according to the following nonlinear integro-partial differential dynamical system of transport reaction type

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) S(t,a) = -\mu S(t,a) - \beta\, S(t,a)\, \mathbf{I}(t), \tag{1}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a} + c\theta \frac{\partial}{\partial \theta}\right) I(t,a,\theta) = -(\mu + c)\, I(t,a,\theta) + \Theta(\theta)\beta\, S(t,a)\, \mathbf{I}(t), \tag{2}$$

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) R(t,a) = -\mu R(t,a) + (1-\alpha)\, c\, I(t,a,1), \tag{3}$$

where $\mathbf{I}(t) = \int_0^A \int_0^1 I(t,a,\theta)\, d\theta\, da$ denotes the force of infection defined as the total number of infected individuals. All parameters are positive: basic mortality rate μ, unitary horizontal transmission rate β, infection load growth rate c ($\frac{d\theta}{dt} = c\theta$), and disease-induced mortality proportion $\alpha \in [0, 1]$. Boundary conditions are given by

$$S(t,0) = B(t), \quad I(t,0,\theta) = I(t,a,0) = 0, \quad R(t,0) = 0 \tag{4}$$

where B is the birth function, and initial conditions by

$$S(0,a) = S_0(a), \quad I(0,a,\theta) = I_0(a,\theta) \quad R(0,a) = 0. \tag{5}$$

The system input is the birth function B. Infected individuals cannot be distinguished from susceptible individuals during their infectious incubation period. The system outputs are observed on a given finite time horizon $T > 0$ and consist of the age density of the total population

$$N(t,a) = S(t,a) + R(t,a) + \int_0^1 I(t,a,\theta)\ d\theta, \tag{6}$$

the total basic mortality outflow

$$\mathfrak{m}(t,a) = \mu\, N(t,a), \tag{7}$$

the case incidence outflow

$$\mathfrak{i}(t,a) = \alpha c\, I(t,a,1), \tag{8}$$

the recovered inflow

$$\mathfrak{r}(t,a) = (1-\alpha)\, c\, I(t,a,1). \tag{9}$$

Function B is known. The uniqueness of mortality rate μ is a direct consequence of (6) and (7) and can be estimated [2]. Similarly, disease-induced mortality proportion α can be deduced from (8) and (9). Since $\mathfrak{r}(t,a)$ is known and since boundary and initial conditions on R are zero, $R(t,a)$ is known for all $(t,a) \in [0,T] \times [0,A]$. Let us denote

$$\mathfrak{j} = \mathfrak{r} + \mathfrak{i} = cI(t,a,1). \tag{10}$$

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Unlike the other parameters, epidemiological parameters c, β and function Θ need to be identified from output observations.

An important issue is therefore to check whether these epidemiological parameters are identifiable, i.e. whether they can be uniquely determined from the input, initial conditions and observed outputs. It is an inverse problem that consists in establishing that the map from parameters to outputs is into, the input and initial conditions being known. This property is a prerequisite to the model identification, in which parameters are estimated from observed data.

The paper is organised as follows: identifiability results are stated in Section II; Section III establishes an input-output (IO) relation for the model; the proofs, based on algebro-differential elimination are given in Section IV. Finally, results are illustrated by simulations in Section V.

II. Identifiability results

The parameters of interest are gathered into a vector $p = (c, \beta, \Theta)^T$ belonging to $\mathbf{P} = (\mathbb{R}^{+*})^2 \times \mathcal{A}_0$, where $\mathcal{A}_0$ is the set of real-analytic functions on $]0,1[$, continuous on $[0,1]$, with zero values at 0 and 1.

Let us denote $H_1^+ = L^2([0,A],\mathbb{R}^+)$, $H_2^+ = L^2([0,A]\times[0,1],\mathbb{R}^+)$ and let $C_p(J_1,J_2)$ be the set of piecewise continuous functions from J_1 to J_2. It has been shown in [3] that for $T > 0$, $(S_0, I_0) \in H_1^+ \times H_2^+$, $B \in C_p([0,T],\mathbb{R}^+)$, and $p \in \mathbf{P}$ system (1-5) has a unique mild solution (S,R,I) in $C([0,T],(H_1^+)^2 \times H_2^+)$, with outputs (N, j) in $C([0,T],(H_1^+)^2)$.

Moreover, with stronger regularity assumptions on the initial conditions, namely $(S_0, I_0) \in C_p([0,A],\mathbb{R}^+) \times C_p([0,A]\times[0,1],\mathbb{R}^+)$, the solutions are such that $(S(t), I(t)) \in C_p([0,A],\mathbb{R}^+) \times C_p([0,A]\times[0,1],\mathbb{R}^+)$. Consequently, the outputs $N(t,\cdot)$ and $\mathrm{j}(t,\cdot)$ are both in $C_p([0,A],\mathbb{R}^+)$.

We assume in the sequel that all these assumptions are verified. Hence the parameter to output map O is defined from $\mathbf{P}$ to the set

$$\begin{aligned}\mathcal{O} = &\{(N,\mathrm{j}) \in C([0,T],(H_1^+)^2)\ / \\ &\forall\, t \in [0,T], (N(t),\mathrm{j}(t)) \in C_p([0,A],\mathbb{R}^+)^2\}.\end{aligned}$$

A subset $\mathbf{Q}$ of $\mathbf{P}$ is said to be identifiable if the restriction $O|_{\mathbf{Q}}$ is into.

We are now in a position to state our first identifiability result.

To this end, we define the following notations

- for $B \in C_p([0,T],\mathbb{R}^+)$, $\mathcal{B}$ and $\underline{B}$, are defined as

$$\mathcal{B} = \{t \in [0,T],\ B(t) \neq 0\}, \quad \underline{B} = \inf \mathcal{B}, \tag{11}$$

- for $\Theta \in \mathcal{A}_0$ and $c \in \mathbb{R}^{+*}$, $\Psi(c,\Theta) \in \mathcal{A}_0$ is defined as

$$\forall \theta \in [0,1],\ \Psi(c,\Theta)(\theta) = c\theta^c \Theta(\theta^c) \tag{12}$$

and $\mathcal{F}(c,\Theta)$ is defined as

$$\forall \theta \in [0,1],\ \mathcal{F}(c,\Theta)(\theta) = \int_0^{\theta^c} \Theta(\xi) d\xi. \tag{13}$$

We assume that the initial conditions (S_0, I_0) are fixed, but they are not known. Then we have

Theorem 1: Let $\mathcal{G} \subset \mathcal{A}_0$ be such that for all $(\Theta, \bar\Theta) \in \mathcal{G}^2$, $\forall (c, \bar c) \in (\mathbb{R}^{+*})^2$, $\forall (\alpha, \bar\alpha) \in (\mathbb{R}^{+*})^2$,

$$(\Psi(c,\Theta) = \Psi(\bar c, \bar\Theta)) \Rightarrow (\bar c = c,\ \bar\Theta = \Theta) \tag{14}$$

and

$$\begin{gathered}\frac{\Psi(\bar c,\bar\Theta)}{\alpha} - \frac{\Psi(c,\Theta)}{\bar\alpha} = \mathcal{F}(c,\Theta) - \mathcal{F}(\bar c,\bar\Theta) \\ \Downarrow \\ (\alpha = \bar\alpha,\ c = \bar c \text{ and } \Theta = \bar\Theta).\end{gathered} \tag{15}$$

Then $\mathbf{Q}_{\mathcal{G}}^\star = (\mathbb{R}^{+*})^2 \times \mathcal{G}$ is identifiable.

Theorem 1 ensures that, given a suitable parametric family for the first infection load distribution, $\mathbf{Q}_{\mathcal{G}}^\star$ is identifiable under the realistic hypothesis that the birth function is piecewise continuous, and the initial conditions are piecewise continuous, fixed and unknown.This theorem has a very strong practical interest, because when dealing with parameter identification on experimental data, Θ is indeed restricted to a parametric family of p.d.f., such as for instance the two-parameter family of Beta p.d.f. with support in $[0,1]$. For this family, it is easily checked that conditions (14) and (15) hold.

Note that in Theorem 1, the initial conditions are assumed to be fixed but unknown. Assuming now that they are not fixed, they have to be included in the unknown parameter vector. Hence the "extended parameter" to output map is now defined on $\mathbf{P_E} = \mathbf{P} \times C_p([0,A],\mathbb{R}^+) \times C_p([0,A]\times[0,1],\mathbb{R}^+)$.

Theorem 2: Let $\mathcal{G} \subset \mathcal{A}_0$ be as in Theorem 1, and assume that $\underline{B} = 0$. Then for all $p = (c, \beta, \Theta, S_0, I_0)^T \in \mathbf{P_E}$, $\bar p = (\bar c, \bar\beta, \bar\Theta, \bar S_0, \bar I_0)^T \in \mathbf{P_E}$ such that $\mathbf{I}(0) = \bar{\mathbf{I}}(0)$,

$$O(p) = O(\bar p) \Rightarrow (c = \bar c,\ \beta = \bar\beta,\ \Theta = \bar\Theta).$$

III. Input-Output relationships

A standard strategy to investigate identifiability problems is to seek differential IO relationships of the model. To this end, we use an alternative expression of the incidence (10). It can be deduced from the mild solution of (1-5) given in [3] by

$$S(t,a) = \begin{cases} S_0(a-t)e^{-(\mu t + \beta\int_0^t \mathbf{I}(s)\ ds)} & \text{for } a \geqslant t, \\ B(t-a)e^{-(\mu a + \beta\int_{t-a}^t \mathbf{I}(s)\ ds)} & \text{for } a \leqslant t, \end{cases} \tag{16}$$

$$I(t,a,\theta) = \tag{17}$$

$$\begin{cases} S_0(a-t)e^{-\mu t}\int_0^t e^{c(s-t)}\Theta\left(\theta e^{c(s-t)}\right)\beta\mathbf{I}(s)e^{-\beta\int_0^s \mathbf{I}(u)du}ds \\ \quad +I_0(a-t,\theta e^{-ct})e^{-(\mu+c)t} \quad \text{for } a \geqslant t, \\ B(t-a)e^{-\mu a}\int_{t-a}^t e^{c(s-t)}\Theta\left(\theta e^{c(s-t)}\right)\beta\mathbf{I}(s)e^{-\beta\int_{t-a}^s \mathbf{I}(u)du}ds \\ \quad \text{for } a \leqslant t. \end{cases}$$

Let us define the non-negative real-analytic function on $\mathbb{R}^{+*}$, continuous on $\mathbb{R}^+$

$$X(\tau) = \Psi(c,\Theta)(e^{-\tau}). \tag{18}$$

Note that X is the p.d.f. corresponding to the incubation period ($\tau = \frac{-1}{c}\ln\theta$). Then, for $(t,a) \in [0,T]\times[0,A]$ and $t \leqslant a$, one has

$$\begin{aligned}\mathrm{j}(t,a) =& S_0(a-t)e^{-\mu t}\int_0^t X(t-s)\beta\mathbf{I}(s)e^{-\beta\int_0^s \mathbf{I}(u)du}ds\\ &+ cI_0(a-t,e^{-ct})e^{-(\mu+c)t},\end{aligned} \tag{19}$$

and, for $(t,a) \in [0,T]\times[0,A]$ and $t \geqslant a$,

$$\mathrm{j}(t,a) = B(t-a)e^{-\mu a}\int_{t-a}^t X(t-s)\beta\mathbf{I}(s)e^{-\beta\int_{t-a}^s \mathbf{I}(u)du}ds. \tag{20}$$

We now define $\mathcal{D} = \{(t,a) \in [0,T]\times[0,A],\ a \leqslant t\}$ and introduce the function y defined on $\mathcal{D}$ by

$$y(t,a) = \int_{t-a}^t X(t-s)\beta\mathbf{I}(s)e^{-\beta\int_{t-a}^s \mathbf{I}(u)du}\ ds. \tag{21}$$

In the sequel we shall also denote

$$\mathcal{D}_{\mathcal{B}} = \{(t,a) \in \mathcal{D},\ t-a \in \mathcal{B}\}, \quad D = \partial_a + \partial_t\ .$$

Therefore, y is known on $\mathcal{D}_{\mathcal{B}}$ since $y(t,a) = \frac{\mathrm{j}(t,a)}{B(t-a)e^{-\mu a}}$ on $\mathcal{D}_{\mathcal{B}}$. Moreover, the following key result holds.

Proposition 1: On $\mathcal{D}$, y and Dy are C^1, $\partial_a y$ is differentiable and

$$D\partial_a y(X(a)-y) = \partial_a y(X'(a)-Dy). \tag{22}$$

On $\mathcal{D}_{\mathcal{B}}$, Eq. (22) defines an IO relation for the system.

Proof 1: Consider $\tilde{y}$ defined on $\mathcal{D}$ by

$$\tilde{y}(t,a) = c\int_{t-a}^t e^{2c(s-t)}\,\Theta'(e^{c(s-t)})\,\beta\,\mathbf{I}(s)\,e^{-\beta\int_{t-a}^s \mathbf{I}(u)du}\,ds.$$

From Eq. (17) the function $t \mapsto \mathbf{I}(t)$ is differentiable on $[0,T]$ and has a piecewise continuous derivative. Consequently, $t \mapsto e^{-\beta\int_0^t \mathbf{I}(u)du} \in C^1([0,T])$ and $y(t,a)$ has partial derivatives in a and t on $\mathcal{D}$, expressed as

$$\begin{aligned}\partial_a y &= X(a)\beta\mathbf{I}(t-a)\\ &\quad - \beta\mathbf{I}(t-a)\int_{t-a}^t X(t-s)\beta\mathbf{I}(s)e^{-\beta\int_{t-a}^s \mathbf{I}(u)du}ds\\ &= X(a)\beta\mathbf{I}(t-a) - \beta\mathbf{I}(t-a)y(t,a)\\ &= \beta\mathbf{I}(t-a)\,(X(a)-y)\,,\end{aligned} \tag{23}$$

and

$$\begin{aligned}\partial_t y =& -X(a)\beta\mathbf{I}(t-a) - c\int_{t-a}^t X(t-s)\beta\mathbf{I}(s)e^{-\beta\int_{t-a}^s \mathbf{I}(u)du}ds\\ &- c^2\int_{t-a}^t e^{2c(s-t)}\,\Theta'(e^{c(s-t)})\,\beta\,\mathbf{I}(s)\,e^{-\beta\int_{t-a}^s \mathbf{I}(u)du}\ ds\\ &+ \beta\mathbf{I}(t-a)\int_{t-a}^t X(t-s)\beta\mathbf{I}(s)e^{-\beta\int_{t-a}^s \mathbf{I}(u)du}ds\\ &= -X(a)\beta\mathbf{I}(t-a) - cy + \beta\mathbf{I}(t-a)y - c\tilde{y}.\end{aligned} \tag{24}$$

Moreover, standard results on integrals depending on parameters imply that the functions y and $\tilde{y}$ are continuous on $\mathcal{D}$. From Eq. (23,24) we deduce that $\partial_a y$ and $\partial_t y$ are continuous functions on $\mathcal{D}$ and consequently y is C^1 on this set. Similar arguments prove that $\tilde{y}$ is also C^1. Summing (23) and (24) leads to $Dy = -c\,y - c\,\tilde{y}$, which proves that Dy is C^1. Since y is C^1 and $t \mapsto \mathbf{I}(t)$ is differentiable, Eq. (23) implies that $\partial_a y$ is differentiable. Applying the operator D to (23), since $D\big(\mathbf{I}(t-a)\big) = 0$, leads to

$$D\partial_a y = \beta\,\mathbf{I}(t-a)\,(X'(a) - Dy). \tag{25}$$

Eq. (22) is obtained by combination on $\mathcal{D}$ of Eq. (23) and (25).

IV. Proof of Theorems 1 and 2

Let (S_0, I_0) and B be given and consider $(p,\bar{p}) \in \mathbf{P}^2$ such that

$$O(p) = O(\bar{p}). \tag{26}$$

In the sequel, the population densities, the p.d.f. of first infection load and incubation period, the output vector associated to $\bar{p}$ shall be denoted as $\bar{S}$, $\bar{I}$, $\bar{\Theta}$, $\bar{X}$, $\bar{\mathrm{j}}$ and $\bar{N}$; more generally, all the quantities wearing a bar will be related to $\bar{p}$. The same quantities without bar will be related to p. Note that (26) implies $\bar{y} = y$ on $\mathcal{D}_{\mathcal{B}}$.

As mentioned in the introduction, we start with an algebro-differential elimination step where $\bar{y} = y$ is combined with Eq. (22) in order to obtain some relationships between p and $\bar{p}$.

We obtained the following fundamental result.

Proposition 2: If (26) holds, then

$$\begin{aligned}&\text{either} \quad X = \bar{X},\\ &\text{or} \quad \exists\,(\alpha,\bar{\alpha}) \in (\mathbb{R}^{+*})^2\ /\\ &\qquad \alpha \neq \bar{\alpha} \text{ and } \frac{1}{\alpha}\bar{X}' - \frac{1}{\bar{\alpha}}X' = X - \bar{X}.\end{aligned}$$

In this last case, $t \mapsto \beta\mathbf{I}(t)$ and $t \mapsto \bar{\beta}\bar{\mathbf{I}}(t)$ are non zero constant functions on $\mathcal{B}$, whose values are α and $\bar{\alpha}$ respectively.

Let us define $M_y(t,a) = (Dy,\ y)^T$, and also $M_{\partial_a y}$, $Y(a) = (X'(a),\ X(a))^T$ and $\bar{Y}(a) = \big(\bar{X}'(a),\ \bar{X}(a)\big)^T$ and finally for $x > 0$,

$$R(x) = \begin{vmatrix} X'(x) & \bar{X}'(x) & \Delta(x)\\ X^{(2)}(x) & \bar{X}^{(2)}(x) & \Delta'(x)\\ X^{(3)}(x) & \bar{X}^{(3)}(x) & \Delta^{(2)}(x)\end{vmatrix}, \tag{27}$$

where we set $\Delta = X - \bar{X}$ on $\mathbb{R}^+$.

Note that from (26), $M_y(t,a) = M_{\bar{y}}(t,a)$ and $M_{\partial_a y} = M_{\partial_a \bar{y}}$ on $\mathcal{D}_{\mathcal{B}}$.

We sketch the proof of Proposition 2, the detailed proofs can be founded in [4]. Proposition 2 follows from three technical lemmas that make an extensive use of the following remark.

Remark 1: Since Θ and $\bar{\Theta}$ are analytic on $]0,1[$, X, $\bar{X}$, Δ and all their derivatives are real-analytic functions on $\mathbb{R}^{+*}$. Consequently, either they have isolated zeros in $\mathbb{R}^{+*}$ or they are identically equal to zero.

The first lemma is

Lemma 1: If (26) holds one gets for all $(t,a) \in \mathcal{D}_{\mathcal{B}}$

$$D\partial_a y(X(a) - \bar{X}(a)) - \partial_a y(X'(a) - \bar{X}'(a)) = 0 \tag{28}$$

$$[X'\bar{X} - X\bar{X}'] - y\,[X' - \bar{X}'] + Dy\,[X - \bar{X}] = 0. \tag{29}$$

Then the second lemma is

Lemma 2: If (26) holds one gets for all $(t,a) \in \mathcal{D}_{\mathcal{B}}$

$$[X'\bar{X} - X\bar{X}'] [X' - \bar{X}'] - [X^{(2)}\bar{X} - X\bar{X}^{(2)}] [X - \bar{X}] \\ -y \left([X' - \bar{X}']^2 - [X^{(2)} - \bar{X}^{(2)}] [X - \bar{X}] \right) = 0. \quad (30)$$

And finally,

Lemma 3: If (26) holds then $R(x) = 0$ for all $x \in \mathbb{R}^{+*}$.

We now proceed with the proof of Proposition 2. Lemma 3 and (26) imply that, for all $x > 0$, there exists $\lambda(x), \mu(x), \nu(x) \in \mathbb{R}$ such that

$$\begin{cases} \lambda X' + \mu \bar{X}' + \nu \Delta = 0, \\ \lambda X^{(2)} + \mu \bar{X}^{(2)} + \nu \Delta' = 0, \\ \lambda X^{(3)} + \mu \bar{X}^{(3)} + \nu \Delta^{(2)} = 0, \end{cases} \quad (31)$$

where λ, μ, ν are minors of determinant (27). We can choose ν associated to $\Delta^{(2)}$, given by $\nu = X'\bar{X}^{(2)} - \bar{X}'X^{(2)}$. Then two cases may arise.

Case 1. Assume that $\nu(x) = 0$ for all $x > 0$. The function $\bar{X}'$ is a non zero function on $\mathbb{R}^{+*}$, otherwise, by continuity, $\bar{X}$ would be constant and equal to zero on $\mathbb{R}^+$. Therefore, we can find $x_1 > 0$ such that $\bar{X}'(x_1) \neq 0$. By continuity, this is still true in a neighbourhood $\mathcal{V}(x_1)$ of x_1. Then, for all $x \in \mathcal{V}(x_1)$,

$$\left(\bar{X}'(x)\right)^2 \times \frac{d}{dx} \left(\frac{X'}{\bar{X}'} \right) = 0,$$

which implies that there exists a constant c_0 such that $X' = c_0\, \bar{X}'$ on $\mathcal{V}(x_1)$. From Remark 1, we get $X' = c_0\, \bar{X}'$ on $\mathbb{R}^{+*}$ and $X = c_0\, \bar{X}$ on $\mathbb{R}^{+*}$ since $X(0) = \bar{X}(0) = 0$. Taking into account that $\int_0^{+\infty} X(x)dx = \int_0^{+\infty} \bar{X}(x)dx = 1$, we have $c_0 = 1$ and finally $X = \bar{X}$ on $\mathbb{R}^{+*}$.

Case 2. Assume that there exists $x_2 > 0$ and a neighbourhood $\mathcal{V}(x_2) \subset \mathbb{R}^{+*}$ such that $\nu(x) \neq 0$ for all $x \in \mathcal{V}(x_2)$. Then, from system (31), we deduce that the following equations are satisfied on $\mathcal{V}(x_2)$,

$$\tilde{\lambda} X' + \tilde{\mu} \bar{X}' = \Delta, \quad (32)$$

$$\tilde{\lambda} X^{(2)} + \tilde{\mu} \bar{X}^{(2)} = \Delta', \quad (33)$$

$$\tilde{\lambda} X^{(3)} + \tilde{\mu} \bar{X}^{(3)} = \Delta^{(2)}, \quad (34)$$

where $\tilde{\lambda} = -\frac{\lambda}{\nu}$, $\tilde{\mu} = -\frac{\mu}{\nu}$. Differentiating (32) and subtracting (33) yields, for $x \in \mathcal{V}(x_2)$,

$$\tilde{\lambda}' X' + \tilde{\mu}' \bar{X}' = 0. \quad (35)$$

In the same way, differentiating (32) twice and subtracting (34) yields

$$\tilde{\lambda}^{(2)} X' + \tilde{\mu}^{(2)} \bar{X}' + 2(\tilde{\lambda}' X^{(2)} + \tilde{\mu}' \bar{X}^{(2)}) = 0. \quad (36)$$

Finally, differentiating (35) and combining it (36), we get

$$\tilde{\lambda}^{(2)} X' + \tilde{\mu}^{(2)} \bar{X}' = 0 \text{ on } \mathcal{V}(x_2). \quad (37)$$

From (35) and (37), we have $W = 0$ on $\mathcal{V}(x_2)$ where

$$W = \begin{vmatrix} \tilde{\lambda}' & \tilde{\mu}' \\ \tilde{\lambda}^{(2)} & \tilde{\mu}^{(2)} \end{vmatrix}.$$

Otherwise, there would exist an open subset $\mathcal{V} \subset \mathcal{V}(x_2)$ such that $W(x) \neq 0$ for $x \in \mathcal{V}$. The unique solution of system (35,37) would be $\left(X', \bar{X}'\right) = (0,0)$ on $\mathcal{V}$. This would imply $\nu(x) = 0$ on $\mathcal{V}$, which is impossible. We now distinguish the two following subcases.

Case 2.1. If there exists an open subset $\mathcal{V} \subset \mathcal{V}(x_2)$ on which $\tilde{\lambda}'(x) \neq 0$, then $W = 0$ on $\mathcal{V}(x_2)$ implies that $\frac{d}{dx}(\tilde{\mu}'/\tilde{\lambda}') = 0$ in $\mathcal{V}$. Consequently, there exists a constant c_0 such that $X' = c_0\, \bar{X}'$ on $\mathcal{V}$ and we can conclude as in *Case 1* that $X = \bar{X}$ on $\mathbb{R}^+$.

Case 2.2. If $\tilde{\lambda}' = 0$ on $\mathcal{V}(x_2)$, then $\tilde{\lambda}$ is a constant function on $\mathcal{V}(x_2)$ whose value is denoted $\tilde{\lambda}_0$. Since $\bar{X}'$ has isolated zeros, Remark 1 and (35) imply that $\tilde{\mu}$ is also a constant function on $\mathcal{V}(x_2)$ whose value is denoted $\tilde{\mu}_0$. Consequently, on $\mathcal{V}(x_2)$, equalities (32) and (33) become respectively

$$\begin{aligned} \tilde{\lambda}_0 X' + \tilde{\mu}_0 \bar{X}' &= \Delta, \\ \tilde{\lambda}_0 X^{(2)} + \tilde{\mu}_0 \bar{X}^{(2)} &= \Delta'. \end{aligned} \quad (38)$$

By Remark 1, these equalities can be extended to $\mathbb{R}^{+*}$ and can be used to simplify (30). On $\mathcal{D}_{\mathcal{B}}$ one therefore has

$$\begin{aligned} [X'\bar{X} - X\bar{X}']\Delta' - [X^{(2)}\bar{X} - X\bar{X}^{(2)}]\Delta \\ = (\tilde{\lambda}_0 X + \tilde{\mu}_0 \bar{X})(\bar{X}^{(2)}X' - \bar{X}'X^{(2)}), \\ (\Delta')^2 - \Delta\, \Delta^{(2)} = (\tilde{\lambda}_0 + \tilde{\mu}_0)\, (\bar{X}^{(2)}X' - \bar{X}'X^{(2)}), \end{aligned}$$

and

$$\left(-y(\tilde{\lambda}_0 + \tilde{\mu}_0) + \tilde{\lambda}_0 X + \tilde{\mu}_0 \bar{X} \right) \left(\bar{X}^{(2)}X' - \bar{X}'X^{(2)} \right) = 0.$$

By Remark 1, since $\nu \neq 0$, we conclude that

$$-y(\tilde{\lambda}_0 + \tilde{\mu}_0) + \tilde{\lambda}_0 X + \tilde{\mu}_0 \bar{X} = 0 \quad \text{on } \mathcal{D}_{\mathcal{B}}. \quad (39)$$

Then, either $\tilde{\lambda}_0 + \tilde{\mu}_0 = 0$, and integrating (38) yields $\Delta = X - \bar{X} = 0$. Or $\tilde{\lambda}_0 + \tilde{\mu}_0 \neq 0$ and consequently for all $(t,a) \in \mathcal{D}_{\mathcal{B}}$

$$y(t,a) = \frac{\tilde{\lambda}_0 X(a) + \tilde{\mu}_0 \bar{X}(a)}{\tilde{\lambda}_0 + \tilde{\mu}_0}.$$

This expression used in (23) yields, for all $(t,a) \in \mathcal{D}_{\mathcal{B}}$,

$$\tilde{\lambda}_0 X'(a) + \tilde{\mu}_0 \bar{X}'(a) = \tilde{\mu}_0\, \beta\, \mathbf{I}(t-a)\, (X(a) - \bar{X}(a)). \quad (40)$$

Denoting $\mathcal{E} = \{a \in [0,A],\, \Delta(a) \neq 0\}$, we easily check that 0 is in the closure of $\mathcal{E}$. Moreover, equation (40) implies that $(t,a) \mapsto \beta\, \mathbf{I}(t-a)$ is a constant on $\{(t,a) \in \mathcal{D}_{\mathcal{B}},\, a \in \mathcal{E}\}$ and consequently, for all $a \in \mathcal{E} \cap [0,T]$, $t \mapsto \beta\, \mathbf{I}(t)$ is constant on $\mathcal{B} \cap [0, T-a]$. Since 0 is in the closure of $\mathcal{E}$, we conclude that $t \mapsto \beta\, \mathbf{I}(t)$ is constant on $\mathcal{B}$. We denote α this constant, which is positive, as already mentioned. By the same arguments we also prove that $t \mapsto \bar{\beta}\, \bar{\mathbf{I}}(t)$ is a positive constant on $\mathcal{B}$ that we denote $\bar{\alpha}$. Then (32) and (40) yield $\alpha = \frac{1}{\tilde{\mu}_0}$. Similarly, $\bar{\alpha}$ is positive and such that $\bar{\alpha} = -\frac{1}{\tilde{\lambda}_0}$. Substituting these values in (38) yields the desired result.

Applying Proposition 2, the assumptions (14) and (15) on $\mathcal{G}$ immediately yields $c = \bar{c}$ and $\Theta = \bar{\Theta}$.

Substituting $X = \bar{X}$ in Eq. (23), one has for all $(\xi, a) \in \mathcal{B} \times [0, A]$

$$\partial_a y(\xi + a, a) = \beta \mathbf{I}(\xi) \left(X(a) - y(\xi + a, a)\right),$$
$$\partial_a y(\xi + a, a) = \bar{\beta} \bar{\mathbf{I}}(\xi) \left(X(a) - y(\xi + a, a)\right).$$

Term to term subtraction yields

$$\left(\beta \mathbf{I}(\xi) - \bar{\beta} \bar{\mathbf{I}}(\xi)\right) \left(X(a) - y(\xi + a, a)\right) = 0. \qquad (41)$$

By contradiction, assume that there exists $\xi_0 \in \mathcal{B}$ such that $\beta \mathbf{I}(\xi_0) \neq \bar{\beta} \bar{\mathbf{I}}(\xi_0)$. Since B is piecewise continuous and $\xi \mapsto (\beta \mathbf{I} - \bar{\beta} \bar{\mathbf{I}})(\xi)$ is continuous, there exists an interval $\mathcal{V}(\xi_0)$ included in $\mathcal{B}$, containing ξ_0, not reduced to a singleton set, such that $(\beta \mathbf{I} - \bar{\beta} \bar{\mathbf{I}})(\xi) \neq 0$ for all $\xi \in \mathcal{V}(\xi_0)$. Therefore, (41) reduces to

$$X(a) = y(\xi + a, a), \quad \forall (\xi, a) \in \mathcal{V}(\xi_0) \times [0, A]. \qquad (42)$$

This implies that $\partial_t y(\xi + a, a) = 0$ for $(\xi, a) \in \mathcal{V}(\xi_0) \times [0, A]$. Consequently, Eq.(23) becomes $\partial_a y(\xi + a, a) = 0$ on $\mathcal{V}(\xi_0)$ and differentiating (42) w.r.t a yields

$$X'(a) = \partial_t y(\xi + a, a) + \partial_a y(\xi + a, a) = 0,$$

for all $a \in [0, A]$. It follows that $X \equiv 0$ on $[0, A]$. Then Remark 1 implies that X is null on $\mathbb{R}^+$, which contradicts its definition as a p.d.f., and consequently yields

$$\beta\, \mathbf{I}(t) = \bar{\beta}\, \bar{\mathbf{I}}(t), \quad \forall t \in \mathcal{B}. \qquad (43)$$

If $\underline{B} = 0$, (43) immediately yields $\beta = \bar{\beta}$ and Theorem 1 is proved. Otherwise if $\underline{B} > 0$, we deduce from (26) and (6) that on $[0, \underline{B}]$

$$(\mathbf{I} - \bar{\mathbf{I}})(t) = \int_0^A \bar{S}(t, a) da - \int_0^A S(t, a) da, \ \forall t \in [0, T]. \qquad (44)$$

Therefore, since for $a \in [0, t]$, $B(t - a) = 0$, multiplying Eq. (44) by β and using Eq. (16), one gets

$$\begin{aligned}\beta(\mathbf{I} - \bar{\mathbf{I}})(t) = \beta e^{-\mu t} &\left(\int_0^{A - \min(t, A)} S_0(a) da\right) \times \\ &\left(e^{-\bar{\beta} \int_0^t \bar{\mathbf{I}}(\xi) d\xi} - e^{-\beta \int_0^t \mathbf{I}(\xi) d\xi}\right).\end{aligned} \qquad (45)$$

Consider the continuous functions $g : [0, T] \to]0, 1]$ defined by

$$\begin{aligned}g(t) = \exp \Bigg(- \int_0^t \beta e^{-\mu s} &\Bigg(\int_0^{A - \min(s, A)} S_0(a) da\Bigg) \times \\ f\Bigg(\int_0^s \bar{\beta} \bar{\mathbf{I}}(\xi) d\xi&, \int_0^s \beta \mathbf{I}(\xi) d\xi\Bigg) ds\Bigg),\end{aligned}$$

where the continuous function $f : \mathbb{R}^2 \to]0, 1]$ is defined by

$$f : (x, y) \mapsto \begin{cases} -\frac{e^{-x} - e^{-y}}{x - y} \text{ if } x \neq y, \\ e^{-x} \text{ if } x = y. \end{cases} \qquad (46)$$

Eq. (45) can be rewritten as

$$\beta \left(\mathbf{I} - \bar{\mathbf{I}}\right)(t) = \frac{g'(t)}{g(t)} \int_0^t \left(\bar{\beta} \bar{\mathbf{I}} - \beta \mathbf{I}\right)(\xi) d\xi. \qquad (47)$$

By contradiction, let us assume that $\beta > \bar{\beta}$. Then we have

$$\beta\big(\mathbf{I} - \bar{\mathbf{I}}\big)(t) \leqslant (\beta \mathbf{I} - \bar{\beta} \bar{\mathbf{I}})(t),$$

and, consequently to (47), we get

$$-\frac{g'(t)}{g(t)} \int_0^t \left(\beta \mathbf{I} - \bar{\beta} \bar{\mathbf{I}}\right)(\xi) d\xi \leqslant (\beta \mathbf{I} - \bar{\beta} \bar{\mathbf{I}})(t), \qquad (48)$$

which implies that $t \mapsto g(t) \int_0^t \big(\beta \mathbf{I} - \bar{\beta} \bar{\mathbf{I}}\big)(\xi) d\xi$ is increasing on $[0, \underline{B}]$. At $t = 0$, one has $(\beta \mathbf{I} - \bar{\beta} \bar{\mathbf{I}})(0) = (\beta - \bar{\beta}) \mathbf{I}(0) > 0$ and, by a continuity argument, there exists $0 < \varepsilon_0 < \underline{B}$ such that $\beta \mathbf{I} - \bar{\beta} \bar{\mathbf{I}}$ is positive on $[0, \varepsilon_0]$. Since $0 < g < 1$, for all $t \in [\varepsilon_0, \underline{B}]$

$$\int_0^t \big(\beta \mathbf{I} - \bar{\beta} \bar{\mathbf{I}}\big)(\xi) d\xi \geqslant g(t) \int_0^t \big(\beta \mathbf{I} - \bar{\beta} \bar{\mathbf{I}}\big)(\xi) d\xi \geqslant \Lambda_0,$$

where $\Lambda_0 = g(\varepsilon_0) \int_0^{\varepsilon_0} \big(\beta \mathbf{I}(\xi) - \bar{\beta} \bar{\mathbf{I}}(\xi)\big) d\xi > 0$. Using this inequality and the expression of $-\frac{g'(t)}{g(t)}$ in (48), we deduce that for all $t \in [\varepsilon_0, \underline{B}]$

$$\begin{aligned}&\beta e^{-\mu t} \left(\int_0^{A - \min(t, A)} S_0(a) da\right) \times \\ &\qquad f\left(\bar{\beta} \int_0^t \bar{\mathbf{I}}(\xi) d\xi, \beta \int_0^t \mathbf{I}(\xi) d\xi\right) \Lambda_0 \leqslant (\beta \mathbf{I} - \bar{\beta} \bar{\mathbf{I}})(t).\end{aligned}$$

Evaluating the above expression at $t = \underline{B}$ yields a contradiction with Eq. (43), and then $\beta = \bar{\beta}$, which ends proof of Theorem 1.

When the initial conditions are not fixed, using (43) and $\underline{B} = 0$, we get $\beta \mathbf{I}(0) = \bar{\beta} \bar{\mathbf{I}}(0)$. If $\mathbf{I}(0) = \bar{\mathbf{I}}(0)$, it follows that $\beta = \bar{\beta}$, which proves Theorem 2.

V. Numerical simulations

In this section, we illustrate our identifiability results through a simulation scenario that represents Theorem 1 for the Beta distribution family.

For this scenario, system $(1, 2, 3, 4, 5)$ is integrated with parameter values given in Table I. The birth function B is constant. The initial susceptible population density follows an exponential distribution $S_0(a) \propto e^{-\mu a}$. The initial infected population density $I_0(a, \theta)$ is uniformly distributed over $[a^{\min}, a^{\max}] \times [\theta^{\min}, \theta^{\max}]$. The initial recovered population density is 0. Scaling coefficients are adjusted to obtain the initial population sizes given in Table I. Parameter values are chosen to mimic realistic epidemiological situations.

The differences between the parameter vectors p and $\bar{p}$ are the infection load growth rates c and $\bar{c}$, and the first infection load distributions Θ and $\bar{\Theta}$. They are both Beta distributions with the same standard deviations $\sigma_\Theta = \sigma_{\bar{\Theta}}$, but different means $m_\Theta \neq m_{\bar{\Theta}}$. Parameters c and $\bar{c}$ are adjusted to obtain the same mean incubation period of 3 years for the distribution given in (18). First infection load and incubation period distributions are represented in Fig. 1.

With such similar incubation period distributions, one could fear the model not to be identifiable. However, Theorem 1 guarantees that the model is identifiable. This is illustrated in Fig. 2 that for both parameter sets represents output $\mathfrak{j}$, given by (10), integrated over age. These outputs

TABLE I

PARAMETER VALUES USED FOR THE SIMULATIONS.

Parameter definition	symbol	value
initial population size	–	600 indiv.
initial infected population size	–	30 indiv.
— age range	$[a^{\min}, a^{\max}]$	$[0.625, 1, 04]$ years
basic mortality rate	μ	0.15 year^{-1}
horizontal transmission rate	β	$3\,10^{-3}$ (indiv. year)$^{-1}$
disease-induced mortality proportion	α	0.5
birth rate	B	70 indiv./year
maximum lifespan	A	13 years
observation period	T	4 years
initial infection load range	$[\theta^{\min}, \theta^{\max}]$	$[0.68, 0.73]$
infection load growth rates	$(c, \bar{c})$	$(0.35, 0.12)$ year^{-1}
first infection load distribution Θ: mean	m_Θ	0.35
— : standard deviation	σ_Θ	0.05
first infection load distribution $\bar{\Theta}$: mean	$m_{\bar{\Theta}}$	0.7
— : standard deviation	$\sigma_{\bar{\Theta}}$	0.05

exhibit notable differences. It is even more obvious on the yearly cumulated outputs in Fig. 2.

REFERENCES

[1] O. Arino, A. Bertuzzi, A. Gandolfi, E. Sánchez, and C. Sinisgalli. A model with 'growth retardation' for the kinetic heterogeneity of tumour cell populations. *Math. Biosci.*, 206(2):185–199, 2007.

[2] B. Laroche and S. Touzeau. Parameter identification for a PDE model representing scrapie transmission in a sheep flock. In *44th IEEE Conference on Decision and Control & European Control Conference, Vols 1-8*, pages 1607–1612, Sevilla, Spain, December 2005.

[3] A. Perasso and B. Laroche. Well-posedness of an epidemiological problem described by an evolution PDE. *ESAIM:Proc.*, 25:29–43, December 2008.

[4] A. Perasso, B. Laroche, and S. Touzeau. Identifiability analysis of an epidemiological model in a structured population. Rapport technique 2009-5, INRA, UR341 Mathématiques et Informatique Appliquées, F-78350 Jouy-en-Josas, France, August 2009.

[5] S. M. Stringer, N. Hunter, and M. E. J. Woolhouse. A mathematical model of the dynamics of scrapie in a sheep flock. *Math. Biosci.*, 153(2):79–98, 1998.

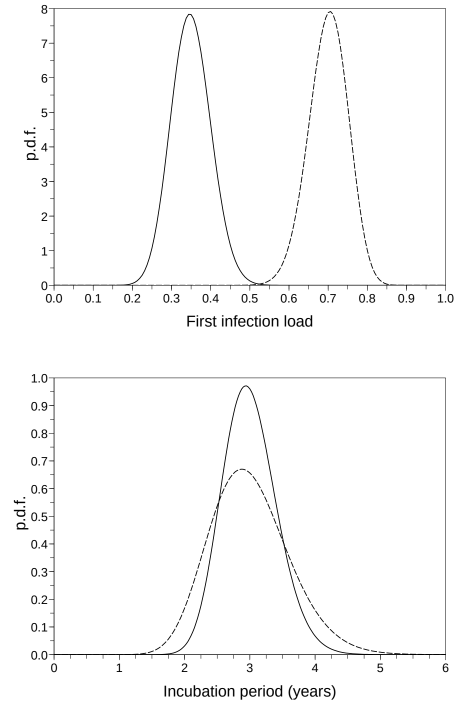
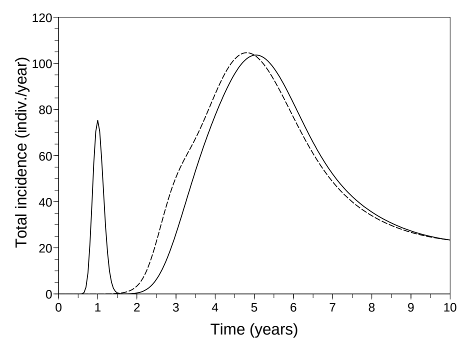
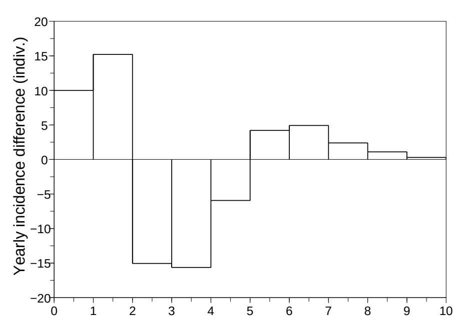


Fig. 1. Distributions represented for the two parameter sets given in Table I: (c, Θ) plain line & $(\bar{c}, \bar{\Theta})$ dashed line.



(a) Total output $\int_0^A \mathrm{j}(t, a)da$.



(b) Difference between the yearly cumulated outputs j.

Fig. 2. Outputs j corresponding to the two parameter sets given in Table I: (c, Θ) plain line & $(\bar{c}, \bar{\Theta})$ dashed line. The model is identifiable.