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Identifiability Problems of Time-delay HIV Models

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Abstract: *In vivo* modelling of the pathogenesis of HIV-1 in plasma captures the interplay of the virus and CD4 cells in the cell-free viral spread process. Modelling is also done for both *in vitro* cell-to-cell and cell-to-free viral spread of HIV-1 and its kinetics in tissue cultures. Upon infection with HIV-1, there is a short intracellular "eclipse phase" or "latency", during which the cell is infected but has not yet begun producing virus. One approach to account for the "eclipse phase" or "latency" is to introduce an intracellular delay in the models. This paper focuses on the identifiability of the parameters in the most popular HIV models with time delay, *in vivo* and *in vitro*. The identifiability of such parameters as the time-delay parameter; the effective reproductive rate of healthy cells; death rate of infected cells; average life time of productively infected cells; viral burst size; etc, is studied by the linear algebraic method based on differential 1-form. Medical interpretation for the identifiability results is given, and it provides guidelines in data collection for the identification of these parameters.

Keywords: identifiability; HIV model; time-delay; differential 1-form.

1. INTRODUCTION AND A REVIEW OF HIV MODELS

The markers of the disease progression due to the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS) are the CD4 cell and viral levels in the plasma. The interplay of the CD4 cells and virus is better revealed during the early process of cellular infection and viral production as well as the post therapeutical period of viral suppression and immunological recovery. Mathematical models have been proposed to describe the immunological response to HIV infection, with HIV dynamics *in vivo* data verification and extraction of key parameters of the dynamics (see Ho et al [1995], Wei, et al [1995], Nowak and May [2000], Perelson and Nelson [1999] and references therein).

The need of a full set of HIV model parameters is recognized in the approach of model identifiability and parameter identification taken by Xia and Moog [2003], Jeffrey and Xia [2005], Jeffrey et al [2003], as well as the applications in studies of vaccine readiness in Southern Africa (Filter et al [2003], Gray et al [2005]), drug effectiveness and therapy failures on existing patients in France (Ouattara [2005], Ouattara et al [2004] (see also the summary report given in Xia [2007])).

Investigation of *in vitro* cell-to-cell spread of HIV is important since majority of infection occurs in the lymphatic tissues where 98% of CD 4+ lymphocytes reside (Rosenberg and Janossy [1999]) on the one hand, and many features are easier to determine experimentally in tissue cultures than in plasma (Culshaw et al [2003]) on the other hand. A modeling approach was proposed by Spouge et al [1996] to simulate the infection and progression of HIV, the "infected equilibrium" of the co-existence of healthy cells and infected cells, under realistic parameter ranges.

A short intracellular "eclipse phase" or "latency" is observed during the infection stage and post therapeutical response. During early infection, the cell is infected but has not yet started producing virus. While in response to therapeutical treatment with highly active antiretroviral therapy (HAART), the virus is not suppressed until a "shoulder period" of time. There are two approaches to model this eclipse phase, by a time delay or by an explicit class of latently infected cells, and Perelson and Nelson [1999] has taken the approach of modeling with an explicit class of latently infected cells. The first paper of taking the "delay" approach is Herz et al [1996] where it is assumed that cells become productively infected τ time units after initial infection. Tam [1999] has taken up the investigation of introducing a delay in modeling the interaction between the replicating virus and host cells. Properties of these models in terms of stability and steady states are studied for clinically reported parameter values (Culshaw and Ruan [2000], Lloyd [2001]). Extensions are done in Mittler et al [1998] for a distributed delay, and in Nelson et al [2001, 2000], Nelson and Perelson [2002], Dixit and Perelson [2004] to include delays in HIV infection and treatment for more general cases of combination antiviral drugs with/without reduced efficacy. A "delayed" version of the cell-to-cell *in vitra* model of Spouge et al [1996] was also proposed by Culshaw et al [2003].

At the theoretical front of identifiability, concepts and algorithmic procedures are developed (Zhang et al [2006]) for non-linear models with pointwise delays under the general framework of non-commutative module approach (Xia et

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al [2002]). This paper focuses on the identifiability of the parameters in the most popular HIV models with time delay, *in vivo* and *in vitro*. These parameters, which include the time-delay parameter; the effective reproductive rate of healthy cells; death rate of infected cells; viral burst size; etc, are studied by the algebraic method in Zhang et al [2006]. After deriving the identifiability results, the corresponding medical interpretations, which give guidelines in data collection for parameter identification, are provided.

The layout of the paper is as follows. The next section gives a quick review on the parameter identifiability results for nonlinear time-delay systems. Section 3 provides the identifiability of delay and other parameters of three HIV models. The last section is the conclusion.

2. PRELIMINARIES

For the readers' convenience, some results on the identifiability of delay parameter, and the algebraic and geometric identifiability of other system parameters from Anguelova and Wennberg [2006] and Zhang et al [2006] are recalled. Consider the following nonlinear time-delay system

$$\begin{array}{l}\dot{x}(t) = f(\theta, x(t-i\tau), u(t-i\tau) : i = 0, 1, 2, \cdots, s),\\ \dot{y}(t) = h(\theta, x(t-i\tau), u(t-i\tau) : i = 0, 1, 2, \cdots, s),\\ x(t) = \phi(t), t \in [-s\tau, 0],\\ u(t) = u_0(t), t \in [-sT, 0],\end{array} \quad (1)$$

where $x \in \mathbb{R}^n, u \in \mathbb{R}^m, y \in \mathbb{R}^p, \theta \in \mathbb{R}^q, \tau \in [0, T)$, f, h, ϕ, u_0 are meromorphic, and θ is a parameter. When θ is known and $s = 1$, Anguelova and Wennberg [2006] defines the identifiability of the delay parameter under the framework of non-commutative modules (Xia et al [2002]) as the following.

Definition 1. (Anguelova and Wennberg [2006]) Assume that $s = 1$ and θ is known in (1). The delay parameter τ is said to be locally identifiable at $\tau_0 \in [0, T)$ if there exists an open set $U \ni \tau_0, U \subset [0, T)$, such that $\forall \tau_1 \in U : \tau_1 \neq \tau_0, \forall \phi_0, \phi_1 \in C([-\tau, 0], \mathbb{R}^n)$, there exist $t \geqslant 0$ and a smooth input u such that $y(t; \phi_1, u, \tau_1) \neq y(t; \phi_0, u, \tau_0)$, where $y(t; \phi, u, \tau)$ denotes the output for the initial function ϕ, the input u and delay τ.

Let $\mathbb{Z}_{\geqslant 0}$ be the set of nonnegative integers, and $\mathcal{K}$ the field of meromorphic functions of a finite number of variables in the set $\{x(t-i\tau), \theta, u^{(j)}(t-i\tau) : i, j \in \mathbb{Z}_{\geqslant 0}\}$. Define δ to be the shift operator such that $\delta(a(t)) = a(t-\tau)$. Let $\mathcal{K}(\delta)$ be the noncommutative ring which is defined as the set of polynomials in δ with coefficients in $\mathcal{K}$ (Xia et al [2002]).

The following is a partial result on the identifiability of τ in Anguelova and Wennberg [2006] which will be used in this paper.

Theorem 1. (Anguelova and Wennberg [2006]) Assume that $s = 1$, θ is known, and the observability index of system (1) is $(s_1, s_2, \cdots, s_p)$, then the delay parameter τ is locally identifiable if the rank of

$$\frac{\partial(h_1, \dot{h_1}, \cdots, h_1^{(s_1-1)}, h_2, \cdots, h_2^{(s_2-1)}, \cdots, h_p, \cdots, h_p^{(s_p-1)})}{\partial x}$$

over $\mathcal{K}(\delta)$ is not equal to the rank of

$$\frac{\partial((h_1, \dot{h_1}, \cdots, h_1^{(s_1)}, h_2, \cdots, h_2^{(s_2)}, \cdots, h_p, \cdots, h_p^{(s_p)})}{\partial x}$$

over $\mathcal{K}$.

For any $T' > 0$ and any integer $N > 0$, the following basic definitions such as the function space $C^N[-s\tau, T']$ and its topology, the set $C^N_{\mathcal{U}}[-s\tau, T']$ of all admissible inputs on $[-s\tau, T']$, the topology of $C^N_{\mathcal{U}}[-s\tau, T'] \times C^N_{\mathcal{U}}[-s\tau, T']$, and the topology of M-fold product $(C^N_{\mathcal{U}}[-s\tau, T'])^M$, are referred to Xia and Moog [2003]. Let $\mathcal{P}$ be the range of θ and define $W_k := \mathcal{P} \times \mathcal{M} \times C^k_{\mathcal{U}}[-s\tau, T']$.

Definition 2. (Zhang et al [2006]) The parameter θ in system (1) is said to be geometrically identifiable if there exist a $T' > 0$, an integer $k \geqslant 0$, an open subset S_1 of W_k, a function ϕ which is meromorphic in its arguments, such that $\theta = \phi(y^{(i)}(t-j\tau), u^{(i)}(t-j\tau), x(t-j\tau) : i, j = 0, 1, \ldots, k)$ holds for all $(\theta, x_0, u) \in S_1$.

Definition 3. (Zhang et al [2006]) The parameter θ in system (1) is said to be algebraically identifiable if there exist an integer $k \geqslant 0$, a $T' > 0$, an open subset S_1 of W_k, a meromorphic function ψ, such that

$$\theta = \psi(y^{(i)}(t-j\tau), u^{(i)}(t-j\tau) : i, j = 0, 1, \ldots, k) \quad (2)$$

holds for all $(\theta, x_0, u) \in S_1$.

Denote $\mathcal{Y} = \text{span}_{\mathcal{K}(\delta)}\{\mathrm{d}y^{(j)} : j \in \mathbb{Z}_{\geqslant 0}\}$, $\mathcal{X} = \text{span}_{\mathcal{K}(\delta)}\{\mathrm{d}x\}$, $\mathcal{U} = \text{span}_{\mathcal{K}(\delta)}\{\mathrm{d}u^{(j)} : j \in \mathbb{Z}_{\geqslant 0}\}$,$\Theta = \text{span}_{\mathcal{K}(\delta)}\{\mathrm{d}\theta\}$, that is, $\mathcal{Y}, \mathcal{X}, \mathcal{U}$ and Θ are the linear combinations of their generators with row vector coefficients whose elements are in $\mathcal{K}(\delta)$. The notation $\mathcal{X} + \Theta$ means the span of $\{\mathrm{d}x, \mathrm{d}\theta\}$ with suitable row vector coefficients.

Theorem 2. (Zhang et al [2006]) (i) The parameter θ in (1) is algebraically identifiable if and only if $\mathrm{d}\theta \in \mathcal{Y} + \mathcal{U}$ holds for all $(\theta, x_0, u) \in S_1$, where S_1 is an open subset of some W_k.

(ii) The parameter θ in (1) is geometrically identifiable if and only if $\mathrm{d}\theta \in (\mathcal{X} + \mathcal{Y} + \mathcal{U})$ holds for all $(\theta, x_0, u) \in S$, where S is an open subset of some W_k.

Roughly speaking, the algebraic identifiability of the parameter θ means that θ can be represented by some meromorphic function of the output y and its derivatives and delays, while the geometric identifiability of θ means θ can be represented as a function of x and y, and their derivatives and delays. Therefore the algebraic and geometric identifiability can be tested by the computation of derivatives of y, or equivalently, the derivatives of $\mathrm{d}y$, to see if the conditions in the above Theorem 2 hold (see Theorem 2 and 3 of Zhang et al [2006] for computing details). That is, one needs to compute $y_i^{(j)}$ or $\mathrm{d}y_i^{(j)}$ and try to solve θ or $\mathrm{d}\theta$ from the obtained equations.

3. MAIN RESULTS

This section considers two dimensional *in vitro* HIV model, and three and four dimensional *in vivo* HIV models. The detailed computation for the two and three dimensional models is omitted since the technique is similar to the four dimensional case in subsection 3.3 and Xia and Moog [2003].

3.1 2-dimensional in vitro model

The following is a 2-dimensional HIV *in vitro* model from Culshaw et al [2003]:

$$\begin{aligned}\dot{C} &= r_C C(t)(1-\frac{C(t)+I(t)}{C_M}) - k_I I(t)C(t),\\ \dot{I} &= k_I' I(t-\tau)C(t-\tau) - \mu_I I(t),\end{aligned} \tag{3}$$

where $C(t)$ is the concentration of healthy cells, $I(t)$ is the concentration of infected cells, r_C is the effective reproductive rate of healthy cells, C_M is the effective carrying capacity of the system, k_I is the infection of healthy cells by the infected cells, $\frac{k_I'}{k_I}$ is the fraction of cells surviving the incubation period, μ_I is the death rate of infected cells, and τ is the time delay. The output is $y(t) = C(t) + I(t)$. Let $x_1 = C, x_2 = I, \theta_1 = r_C, \theta_2 = \frac{\theta_1}{C_M}, \theta_3 = k_I, \theta_4 = k_I', \theta_5 = \mu_I$, and $\theta = (\theta_1, \theta_2, \cdots, \theta_5)^T$.

The delay τ can be identified by using Theorem 1.

Proposition 1. Assume that θ is known and the following persistent exciting conditions hold:

$$\begin{vmatrix} \theta_1 - (\theta_2+\theta_3)x_2 - 2\theta_2 x_1 & \theta_4 x_2(t-\tau) \\ -(\theta_2+\theta_3)x_1 - \theta_5 & \theta_4 x_1(t-\tau)\end{vmatrix} \neq 0, \tag{4}$$

$(\theta_4 x_1(t-\tau)x_2(t-2\tau))^2 + (\theta_4 x_1(t-\tau)x_1(t-2\tau))^2 \neq 0$, then the delay parameter τ of system (3) is locally identifiable.

Now suppose the delay parameter τ is known and consider the identifiability of θ. It is obvious that $\mathrm{d}\dot{y} = a_1\mathrm{d}\theta + (a_2 + a_3\delta)\mathrm{d}x_1 + (a_4 + a_5\delta)\mathrm{d}y$, where $a_1 = (x_1, -x_1 y, -x_1 x_2, x_1(t-\tau)x_2(t-\tau), -x_2), a_2 = \theta_1 - \theta_2 y - \theta_3 y + \theta_5 + 2x_1\theta_3, a_3 = \theta_4 y(t-\tau) - 2\theta_4 x_1(t-\tau), a_4 = -\theta_2 x_1 - x_1\theta_3 - \theta_5, a_5 = \theta_4 x_1(t-\tau)$. Let $\alpha_1 = (x_1, -x_1 y, -x_1 y + x_1^2, 0, 0)$, $\alpha_2 = \theta_1 - \theta_2 y - \theta_3 y + 2\theta_3 x_1$, and $\alpha_3 = -\theta_2 x_1 - \theta_3 x_1$, then $\mathrm{d}\dot{x}_1 = \alpha_1\mathrm{d}\theta + \alpha_2\mathrm{d}x_1 + \alpha_3\mathrm{d}y$. Now

$$\mathrm{d}\ddot{y} = b_1\mathrm{d}\theta + b_2\mathrm{d}x_1 + b_3\mathrm{d}\delta x_1 + b_4\mathrm{d}y + b_5\mathrm{d}\dot{y},$$

with $b_1 = \dot{a_1} + a_2\alpha_1 + a_3\delta(\alpha_1), b_2 = \dot{a}_2 + a_2\alpha_2, b_3 = \dot{a}_3 + a_3\delta(\alpha_2), b_4 = \dot{a}_4 + a_2\alpha_3 + [\dot{a}_5 + a_3\delta(\alpha_3)]\delta, b_5 = a_4 + a_5\delta$. When $a_2 b_3 - b_2 a_3 \neq 0$, one has

$$\begin{aligned}&\begin{pmatrix}\mathrm{d}x_1\\ \mathrm{d}\delta x_1\end{pmatrix} = \begin{pmatrix}a_2 & a_3\\ b_2 & b_3\end{pmatrix}^{-1}\begin{pmatrix}\mathrm{d}\dot{y} - a_1\mathrm{d}\theta - (a_4+a_5\delta)\mathrm{d}y\\ \mathrm{d}\ddot{y} - b_1\mathrm{d}\theta - b_4\mathrm{d}y - b_5\mathrm{d}\dot{y}\end{pmatrix}\\ &:= \begin{pmatrix} c_1\mathrm{d}\theta + c_2\mathrm{d}y + c_3\mathrm{d}\dot{y}\\ c_4\mathrm{d}\theta + c_5\mathrm{d}y + c_6\mathrm{d}\delta y + c_7\mathrm{d}\dot{y} + c_8\mathrm{d}\delta\dot{y} + c_9\mathrm{d}\ddot{y}\end{pmatrix},\end{aligned}$$

where $c_1, \cdots, c_9 \in \mathcal{K}$ are defined obviously by the above equality, and $c_9 \neq 0$. By using $\mathrm{d}\delta x_1 = \delta(\mathrm{d}x_1)$ one has

$$\begin{aligned}\mathrm{d}\ddot{y} =& \frac{(\delta(c_3) - c_8)\mathrm{d}\delta\dot{y} - c_7\mathrm{d}\dot{y} + (\delta(c_2) - c_6)\mathrm{d}\delta y - c_5\mathrm{d}y}{c_9}\\ &+\frac{(\delta(c_1) - c_4)\mathrm{d}\theta}{c_9},\\ :=& \quad e_1\mathrm{d}\theta + e_2\mathrm{d}y + e_3\mathrm{d}\delta y + e_4\mathrm{d}\dot{y} + e_5\mathrm{d}\delta\dot{y}.\end{aligned}$$

For $k \geqslant 3$, it is easy to compute that

$$\mathrm{d}y^{(k)} = e_1^{(k-2)}\mathrm{d}\theta + [e_2\mathrm{d}y + e_3\mathrm{d}\delta y + e_4\mathrm{d}\dot{y} + e_5\mathrm{d}\delta\dot{y}]^{(k-2)}.$$

Now the following proposition follows.

Proposition 2. Assume that the delay parameter τ in system (3) is known, $a_2 b_3 - a_3 b_2 \neq 0$, and the matrix

$$\left(e_1^T, (e_1^{(1)})^T, \cdots, (e_1^{(4)})^T\right)$$

is of rank 5, then the five parameters r_C, C_M, k_I, k_I' and μ_I are all algebraically identifiable and hence geometrically identifiable.

Remark 1. The above proposition means that when the delay parameter τ is given and some persistent exciting conditions hold, then the five parameters in (3) can be determined by the measured values $\{y^{(i)}(t), y^{(j)}(t-\tau) : i = 0, 1, \cdots, 6; j = 0, 1, \cdots, 5\}$ for any fixed time t. Even if the delays are ignored, one has to measure 7 times to obtain $y, \dot{y}, \cdots, y^{(6)}$. Therefore the measurement has to be taken at least 7 times. These persistent exciting conditions are satisfied roughly at the rapid changing infection and replication stages. Model (3) describes an infection taking place in the culture tissues in a well-controlled laboratory environment, and the above needed measurements of the derivatives and delays of the output can usually be completed within one or two days, therefore the five parameters are determined accordingly.

3.2 3-dimensional in vivo model

The following is a 3-dimensional HIV *in vivo* model with time delay:

$$\begin{aligned}\dot{T}(t) &= \lambda - dT(t) - kT(t)V(t),\\ \dot{T}^*(t) &= kT(t-\tau)V(t-\tau)e^{-m\tau} - \delta T^*(t),\\ \dot{V}(t) &= N\delta T^*(t) - cV(t),\end{aligned} \tag{5}$$

where T is the density of uninfected CD4 cell lymphocytes (or target cells), which are generated at a rate λ and die with a first order rate constant d when there is no infection. When there is virus, T^* is the density of infected cells, k is the second order rate constant of infection, V is the viral load. The parameter $\frac{1}{\delta}$ is average lifetime of productively infected cells, N is the viral burst size, c is a first order rate constant that free virions are cleared with, $\frac{1}{m}$ is the average lifetime of infected cells before they become productive, and τ is the fixed intracellular delay (see Dixit and Perelson [2004]). The following are the outputs

$$y_1(t) = T(t),\ y_2(t) = V(t). \tag{6}$$

Let $x_1 = T, x_2 = T^*, x_3 = V, \theta_1 = \lambda, \theta_2 = d, \theta_3 = k, \theta_4 = \delta, \theta_5 = N, \theta_6 = c, \theta_7 = m$, $\theta = (\theta_1, \theta_2, \cdots, \theta_7)^T$, then system (5) can be rewritten as

$$\begin{aligned}\dot{x}_1(t) &= \theta_1 - \theta_2 x_1(t) - \theta_3 x_1(t)x_3(t),\\ \dot{x}_2(t) &= \theta_3 x_1(t-\tau)x_3(t-\tau)e^{-\theta_7\tau} - \theta_4 x_2(t),\\ \dot{x}_3(t) &= \theta_5\theta_4 x_2(t) - \theta_6 x_3(t).\end{aligned} \tag{7}$$

By computing $\operatorname{rank}_{\mathcal{K}} \frac{\partial(y_1, y_2, \dot{y}_2, \ddot{y}_2)}{\partial(x_1, x_2, x_3, x_1(t-\tau), x_3(t-\tau))}$ and $\operatorname{rank}_{\mathcal{K}(\delta)} \frac{\partial(y_1, y_2, \dot{y}_2)}{\partial(x_1, x_2, x_3)}$, one has the following result.

Proposition 3. Assume that θ is known in (5), and $k\delta N x_1(t-\tau) \neq 0$ or $k\delta N x_3(t-\tau) \neq 0$, then the delay parameter τ in system (5)-(6) is locally identifiable.

Now consider the algebraic identifiability of θ when τ is given. Since

$$\begin{aligned}\dot{y}_1 &= \theta_1 - \theta_2 y_1 - \theta_3 y_1 y_2,\\ y_1^{(i+1)} &= -\theta_2 y_1^{(i)} - \theta_3 (y_1 y_2)^{(i)}, i \geqslant 1,\end{aligned}$$

the parameters $\theta_1, \theta_2, \theta_3$ are algebraically identifiable when

$$\operatorname{rank}_{\mathcal{K}} \begin{pmatrix} 1 & -y_1 & -y_1 y_2\\ 0 & -\dot{y}_1 & -(y_1 y_2)^{(1)}\\ 0 & -\ddot{y}_1 & -(y_1 y_2)^{(2)}\end{pmatrix} = 3. \tag{8}$$

The identifiability of the remaining parameters $\theta_4, \theta_5, \cdots, \theta_7$ follows from

$$\begin{aligned}\ddot{y}_2(t) =& \theta_3\theta_4\theta_5 e^{-\theta_7\tau} y_1(t-\tau)y_2(t-\tau) - (\theta_4+\theta_6)\dot{y}_2\\ &-\theta_4\theta_6 y_2.\end{aligned}$$

Proposition 4. Suppose the persistent exciting conditions (8) and

$$\text{rank}_{\mathcal{K}} \begin{pmatrix} y_1(t-\tau)y_2(t-\tau) & \dot{y}_2 & y_2 \\ (y_1(t-\tau)y_2(t-\tau))^{(1)} & \ddot{y}_2 & \dot{y}_2 \\ (y_1(t-\tau)y_2(t-\tau))^{(2)} & y_2^{(3)} & \ddot{y}_2 \end{pmatrix} = 3 \qquad (9)$$

hold for system (5)-(6).

(i) If m and τ are given, then all the remaining parameters $\lambda, d, k, \delta, N, C$ are algebraically identifiable;

(ii) If τ is given, then all the parameters $m, \lambda, d, k, \delta, N, C$ are geometrically identifiable.

Remark 2. The above proposition shows that when m and τ are given and some persistent exciting conditions hold, then all the parameters in (5) can be determined by the measurement of $\{y^{(i)}(t), y^{(j)}(t-\tau) : i = 0, 1, \cdots, 4; j = 0, 1, 2\}$ for any fixed time t. Even if the delays are ignored, one has to measure at least five times to obtain $y, \dot{y}, \cdots, y^{(4)}$.

Although the output (6) for system (5) is often available for post-treatment, the following output is easier to be measured and hence studied here:

$$y_1 = T + T^*, \; y_2 = V. \qquad (10)$$

The identifiability of the delay parameter τ can be considered similarly as above, and the following result is obtained.

Proposition 5. If $k\delta N x_3(t-\tau) \neq 0$ or $k\delta N x_1(t-\tau) \neq 0$ in system (5)-(10), and the parameter θ is given, then the delay parameter τ is locally identifiable.

Now consider the identifiability of θ under the output (10). The following relation is obtained by some computation:

$$\begin{aligned} \ddot{y}_2 = {} & \xi_1 + \xi_2 y_1 + \xi_3 y_1 y_2 + \xi_4 y_2 + \xi_5 y_2^2 + \xi_6 \dot{y}_2 + \xi_7 y_2 \dot{y}_2 \\ & + \xi_8 \ddot{y}_1, \end{aligned}$$

where $\xi_1 = -\theta_1\theta_4\theta_5, \xi_2 = \theta_2\theta_4\theta_5, \xi_3 = \theta_3\theta_4\theta_5, \xi_4 = -\theta_2\theta_6, \xi_5 = -\theta_3\theta_6, \xi_6 = -(\theta_2 + \theta_6), \xi_7 = -\theta_3, \xi_8 = \theta_4\theta_5$. Therefore

$$\begin{aligned} y_2^{(k+2)} = {} & \xi_2 y_1^{(k)} + \xi_3 (y_1 y_2)^{(k)} + \xi_4 y_2^{(k)} + \xi_5 (y_2^2)^{(k)} \\ & + \xi_6 y_2^{(k+1)} + \xi_7 (y_2 \dot{y}_2)^{(k)} + \xi_8 y_1^{(k+1)}, \quad k \geqslant 1. \end{aligned}$$

Proposition 6. Assume that τ is given in system (5) with output (10). If the rank of the following matrix

$$\begin{pmatrix} \dot{y}_1 & (y_1y_2)^{(1)} & \dot{y}_2 & (y_2^2)^{(1)} & \ddot{y}_2 & (y_2\dot{y}_2)^{(1)} & \ddot{y}_1 \\ y_1^{(2)} & (y_1y_2)^{(2)} & y_2^{(2)} & (y_2^2)^{(2)} & y_2^{(3)} & (y_2\dot{y}_2)^{(2)} & y_1^{(2)} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ y_1^{(7)} & (y_1y_2)^{(7)} & y_2^{(7)} & (y_2^2)^{(7)} & y_2^{(8)} & (y_2\dot{y}_2)^{(7)} & y_1^{(8)} \end{pmatrix} \qquad (11)$$

over $\mathcal{K}$ is 7, then $\theta_1, \theta_2, \theta_3, \theta_4\theta_5, \theta_6$ are algebraically identifiable. If furthermore θ_7 is given and $\theta_4\theta_5 \neq 0$, then all the parameters $\theta_1, \theta_2, \theta_3, \theta_4, \theta_5, \theta_6$ are algebraically identifiable and hence geometrically identifiable.

Remark 3. The condition $\theta_4\theta_5 = N\delta \neq 0$ holds in general. Now it follows from the above proposition that when m is given, then the parameters $\lambda, d, k, N\delta, c, m$ in (5) can be determined by the measured values $\{y^{(i)}(t) : i = 0, 1, \cdots, 9\}$ for any fixed time t. If, furthermore, $y_1(t-\tau), y_2(t-\tau), \dot{y}_2(t-\tau)$ are known for some time t, then it is easy to show that N and δ can be determined.

3.3 4-dimensional in vivo model

The following is the 4-dimensional *in vivo* HIV model from Dixit and Perelson [2004]

$$\begin{aligned} \dot{T} &= \lambda - dT - kTV_1, \\ \dot{T}^*(t) &= kT(t-\tau)V_1(t-\tau)e^{-m\tau} - \delta T^*(t), \\ \dot{V}_1 &= N\delta(1-\epsilon)T^* - CV_1, \\ \dot{V}_2 &= N\delta\epsilon T^* - CV_2, \end{aligned} \qquad (12)$$

with the output

$$y_1 = T, \; y_2 = V_1 + V_2, \qquad (13)$$

where V_1 and V_2 are infectious and non-infectious viral load respectively, ϵ is the instantaneous efficacy of the protease inhibitors and has been assumed to be constant in this paper, and all the other variables and parameters have the same meaning as the 3-dimensional *in vivo* model (5). Let $x_1 = T, x_2 = T^*, x_3 = V_1, x_4 = V_2, \theta_1 = \lambda, \theta_2 = d, \theta_3 = k, \theta_4 = \delta, \theta_5 = N, \theta_6 = C, \theta_7 = m, \theta_8 = \epsilon$, then the above system (12) is rewritten as

$$\begin{aligned} \dot{x}_1 &= \theta_1 - \theta_2 x_1 - \theta_3 x_1 x_3, \\ \dot{x}_2(t) &= \theta_3 x_1(t-\tau) x_3(t-\tau) e^{-\theta_7\tau} - \theta_4 x_2(t), \\ \dot{x}_3 &= \theta_5\theta_4(1-\theta_8)x_2 - \theta_6 x_3, \\ \dot{x}_4 &= \theta_5\theta_4\theta_8 x_2 - \theta_6 x_4. \end{aligned} \qquad (14)$$

The identifiability of the delay parameter τ follows from the following computation.

$$\begin{aligned} \dot{y}_1 &= \theta_1 - \theta_2 x_1 - \theta_3 x_1 x_3, \\ \dot{y}_2 &= \theta_5\theta_4 x_2 - \theta_6 x_3 - \theta_6 x_4, \\ \ddot{y}_2 &= \theta_3\theta_4\theta_5 x_1(t-\tau) x_3(t-\tau) e^{-\theta_7\tau} - (\theta_4^2\theta_5 + \theta_4\theta_5\theta_6) x_2 \\ &\quad + \theta_6^2 x_3 + \theta_6^2 x_4. \end{aligned}$$

The following matrix

$$\frac{\partial(y_1, y_2, \dot{y}_1, \dot{y}_2)}{\partial(x_1, x_2, x_3, x_4)} = \begin{pmatrix} 1 & 0 & -\theta_2 - \theta_3 x_3 & 0 \\ 0 & 0 & 0 & \theta_4\theta_5 \\ 0 & 1 & -\theta_3 x_1 & -\theta_6 \\ 0 & 1 & 0 & -\theta_6 \end{pmatrix}$$

has rank 4 over $\mathcal{K}(\delta]$ when $\theta_3\theta_4\theta_5 x_1 \neq 0$. Note that $\frac{\partial \ddot{y}_2}{\partial(x_1(t-\tau), x_3(t-\tau))} = \theta_3\theta_4\theta_5 e^{-\theta_7\tau}\,(x_3(t-\tau), x_1(t-\tau))$, therefore

$$\text{rank}_{\mathcal{K}} \frac{\partial(y_1, y_2, \dot{y}_1, \dot{y}_2, \ddot{y}_2)}{\partial(x_1, x_2, x_3, x_4, x_1(t-\tau), x_3(t-\tau))} = 4$$

when $\theta_3\theta_4\theta_5 x_1(t) x_3(t-\tau) \neq 0$ or $\theta_3\theta_4\theta_5 x_1(t)\, x_1(t-\tau) \neq 0$. It follows from Theorem 1 that τ is identifiable. Now the following result is obtained.

Proposition 7. Assume that the parameter θ is known in system (12)-(13), then the delay parameter τ is locally identifiable if $k\delta N x_1(t) x_3(t-\tau) \neq 0$ or $k\delta N x_1(t) x_1(t-\tau) \neq 0$.

Now consider the algebraically identifiability of θ under the condition that τ is given. It is easy to compute that

$$\begin{aligned} x_3 &= \frac{\theta_1 - \theta_2 y_1 - \dot{y}_1}{\theta_3 y_1}, \quad x_2 = \frac{\dot{y}_2 + \theta_6 y_2}{\theta_4\theta_5}, \\ \ddot{y}_1 &= -\theta_2\dot{y}_1 + (-\theta_3\dot{y}_1 + \theta_3 y_1\theta_6) x_3 \\ &\quad -\theta_3\theta_4\theta_5(1-\theta_8) y_1 x_2 \\ &= \theta_1\theta_6 - \theta_2\theta_6 y_1 - \theta_6\dot{y}_1 - \frac{\theta_1\dot{y}_1}{y_1} + \frac{\dot{y}_1^2}{y_1} - \\ &\quad \theta_3(1-\theta_8) y_1\dot{y}_2 - \theta_3(1-\theta_8)\theta_6 y_2, \end{aligned}$$

$$\begin{aligned}\ddot{y}_2 &= \theta_3\theta_4\theta_5 y_1(t-\tau)e^{-\theta_7\tau}x_3(t-\tau) - \theta_4^2\theta_5 x_2 - \theta_6\dot{y}_2\\ &= \theta_1\theta_4\theta_5 e^{-\theta_7\tau} - \theta_2\theta_4\theta_5 e^{-\theta_7\tau}y_1(t-\tau) -\\ &\quad \theta_4\theta_5 e^{-\theta_7\tau}\dot{y}_1(t-\tau) - (\theta_4+\theta_6)\dot{y}_2 - \theta_4\theta_6 y_2,\end{aligned}$$

$$y_2^{(k+2)} = -\theta_2\theta_4\theta_5 e^{-\theta_7\tau}y_1^{(k)}(t-\tau) - \theta_4\theta_5 e^{-\theta_7\tau}y_1^{(k+1)}(t-\tau) -(\theta_4+\theta_6)y_2^{(k+1)} - \theta_4\theta_6 y_2^{(k)}, k \geqslant 1.$$

Thus if

$$\text{rank}_{\mathcal{K}}\begin{pmatrix} \dot{y}_1(t-\tau) & \ddot{y}_1(t-\tau) & \ddot{y}_2(t) & \dot{y}_2(t)\\ \ddot{y}_1(t-\tau) & y_1^{(3)}(t-\tau) & y_2^{(3)}(t) & \ddot{y}_2(t)\\ y_1^{(3)}(t-\tau) & y_1^{(4)}(t-\tau) & y_2^{(4)}(t) & y_2^{(3)}(t)\\ y_1^{(4)}(t-\tau) & y_1^{(5)}(t-\tau) & y_2^{(5)}(t) & y_2^{(4)}(t)\end{pmatrix} = 4, \quad (15)$$

then the parameters

$$(\theta_2\theta_4\theta_5 e^{-\theta_7\tau}, \theta_4\theta_5 e^{-\theta_7\tau}, \theta_4+\theta_6, \theta_4\theta_6)$$

are algebraically identifiable. By the expression of $\ddot{y}_2$, the parameters $\theta_1, \theta_2, \theta_4, \theta_5 e^{-\theta_7\tau}, \theta_6$ are algebraically identifiable if $\theta_4\theta_5 \neq 0$. If, furthermore, $y_1\dot{y}_2 + \theta_6 y_2 \neq 0$, then $\theta_3(1-\theta_8)$ is also algebraically identifiable by the expression of $\ddot{y}_1$. The geometric identifiability of θ_3 and θ_5 follows from

$$\theta_3 = \frac{\theta_1 - \theta_2 y_1 - \dot{y}_1}{x_3 y_1}, \theta_5 = \frac{\dot{y}_2 + \theta_6 y_2}{\theta_4 x_2}.$$

Proposition 8. In the system (12)-(13), assume that τ is given, the persistent exciting condition (15) holds, then $\theta_2, \theta_4, \theta_6$ and $\theta_5 e^{-\theta_7\tau}$ are algebraically identifiable. If, furthermore, $\theta_4\theta_5 \neq 0$, then θ_1 is algebraically identifiable, and so is $\theta_3(1-\theta_8)$ when $y_1\dot{y}_2 + \theta_6 y_2 \neq 0$. When all the above conditions for algebraically identifiability hold, and $\theta_4 y_1 x_2 x_3 \neq 0$ for some time t, then all the parameters $\theta_1, \theta_2, \cdots, \theta_8$ are geometrically identifiable.

Remark 4. When m, ϵ and τ are given and some persistent exciting conditions hold, then all the parameters in (12) can be determined by the measurement of $\{y_2^{(i)}(t), y_1^{(j)}(t-\tau) : i = 0, 1, \cdots, 6; j = 0, 1, \cdots, 5\}$ for any fixed time t.

Now consider the second type of output for system (12):

$$y_1 = T + T^*, \ y_2 = V_1 + V_2. \quad (16)$$

The delay parameter τ is also identifiable by a similar computation.

Proposition 9. For system (12) with output (16) and known parameter θ, the delay parameter τ is locally identifiable if $k\delta N x_3(t)x_3(t-\tau) \neq 0$ or $k\delta N x_1(t)x_1(t-\tau) \neq 0$.

Now consider the identifiability of θ when τ is given. Let $\Gamma_{11} = \left(0, 0, 0, \frac{-x_2}{\theta_4}, \frac{-x_2}{\theta_5}, \frac{y_2}{\theta_4\theta_5}, 0, 0\right)$, then $\mathrm{d}x_2 = \Gamma_{11}\mathrm{d}\theta + \frac{1}{\theta_4\theta_5}\mathrm{d}\dot{y}_2 + \frac{\theta_6}{\theta_4\theta_5}\mathrm{d}y_2$. Since $\ddot{y}_2 = \theta_3\theta_4\theta_5 x_1(t-\tau)x_3(t-\tau)e^{-\theta_7\tau} - (\theta_4+\theta_6)\dot{y}_2 - \theta_4\theta_6 y_2$, one has

$$\theta_3 x_1(t-\tau)x_3(t-\tau)e^{-\theta_7\tau} = \frac{1}{\theta_4\theta_5}[\ddot{y}_2 + (\theta_4+\theta_6)\dot{y}_2 + \theta_4\theta_6 y_2].$$

Thus

$$\dot{y}_1 = \theta_1 - \theta_2 x_1 - \theta_3 x_1 x_3 - \theta_4 x_2 + \frac{\ddot{y}_2}{\theta_4\theta_5} + \frac{\theta_4+\theta_6}{\theta_4\theta_5}\dot{y}_2 + \frac{\theta_6}{\theta_5}y_2,$$

or equivalently

$$\begin{aligned}\ddot{y}_2 = &-\theta_1\theta_4\theta_5 + \theta_2\theta_4\theta_5 x_1 + \theta_3\theta_4\theta_5 x_1 x_3 + \theta_4^2\theta_5 x_2\\ &+\theta_4\theta_5\dot{y}_1 - (\theta_4+\theta_6)\dot{y}_2 - \theta_4\theta_6 y_2.\end{aligned}$$

If one computes $\ddot{y}_2$ directly by definition, then a delay parameter τ appears, while the above obtained $\ddot{y}_2$ does not contain τ, which simplifies some late computation.

By finding differentials of the above $\ddot{y}_2$, one has

$$\begin{aligned}\mathrm{d}\ddot{y}_2 &= \Gamma_{21}\mathrm{d}\theta + \Gamma_{22}\mathrm{d}x_1 + \theta_4^2\theta_5\mathrm{d}x_2 + \theta_3\theta_4\theta_5 x_1\mathrm{d}x_3\\ &\quad +\theta_4\theta_5\mathrm{d}\dot{y}_1 - (\theta_4+\theta_6)\mathrm{d}\dot{y}_2 - \theta_4\theta_6\mathrm{d}y_2\\ &= \Gamma_{31}\mathrm{d}\theta + \theta_3\theta_4\theta_5 x_1\mathrm{d}x_3 + \Gamma_{32}\mathrm{d}\dot{y}_2 + \Gamma_{33}\mathrm{d}y_2 + \Gamma_{34}\mathrm{d}\dot{y}_1\\ &\quad +\Gamma_{35}\mathrm{d}y_1,\end{aligned}$$

where

$$\begin{aligned}\Gamma_{21} &= (-\theta_4\theta_5, \theta_4\theta_5 x_1, \theta_4\theta_5 x_1 x_3, -\theta_1\theta_5 + \theta_2\theta_5 x_1 +\\ &\quad \theta_3\theta_5 x_1 x_3 + 2\theta_4\theta_5 x_2 + \theta_5\dot{y}_1 - \dot{y}_2 - \theta_6 y_2, -\theta_1\theta_4 +\\ &\quad \theta_2\theta_4 x_1 + \theta_3\theta_4 x_1 x_3 + \theta_4^2 x_2 + \theta_4\dot{y}_1, -\dot{y}_2 - \theta_4 y_2,\\ &\quad 0, 0),\\ \Gamma_{22} &= \theta_2\theta_4\theta_5 + \theta_3\theta_4\theta_5 x_3,\\ \Gamma_{31} &= \big(-\theta_4\theta_5, \theta_4\theta_5 x_1, \theta_4\theta_5 x_1 x_3, -\theta_1\theta_5 + \theta_2\theta_5 y_1 +\\ &\quad \theta_3\theta_5 x_3 y_1 + \theta_4\theta_5 x_2 + \theta_5\dot{y}_1 - \dot{y}_2 - \theta_6 y_2, -\theta_1\theta_4 +\\ &\quad \theta_2\theta_4 y_1 + \theta_3\theta_4 x_3 y_1 + \theta_4\dot{y}_1, -\dot{y}_2 - \theta_2 y_2 - \theta_3 y_2 x_3,\\ &\quad 0, 0\big),\\ \Gamma_{32} &= -\theta_6 - \theta_2 - \theta_3 x_3, \quad \Gamma_{33} = -\theta_2\theta_6 - \theta_3\theta_6 x_3,\\ \Gamma_{34} &= \theta_4\theta_5, \qquad\qquad \Gamma_{35} = \theta_4\theta_5(\theta_2 + \theta_3 x_3).\end{aligned}$$

Then

$$\mathrm{d}x_3 = \Gamma_{41}\mathrm{d}\theta + \Gamma_{42}\mathrm{d}\dot{y}_2 + \Gamma_{43}\mathrm{d}y_2 + \Gamma_{44}\mathrm{d}\dot{y}_1 + \Gamma_{45}\mathrm{d}y_1 + \Gamma_{46}\mathrm{d}\ddot{y}_2$$

with $\Gamma_{46} = \frac{1}{\theta_3\theta_4\theta_5 x_1}$, $\Gamma_{4i} = \frac{-\Gamma_{3i}}{\theta_3\theta_4\theta_5 x_1}$, $i = 1, 2, \cdots, 5$. Thus

$$\begin{aligned}\mathrm{d}\dot{x}_3 &= \theta_5(1-\theta_8)x_2\mathrm{d}\theta_4 + \theta_4(1-\theta_8)x_2\mathrm{d}\theta_5 - x_3\mathrm{d}\theta_6 -\\ &\quad \theta_5\theta_4 x_2\mathrm{d}\theta_8 + \theta_4\theta_5(1-\theta_8)\mathrm{d}x_2 - \theta_6\mathrm{d}x_3\\ &= [-x_3 + (1-\theta_8)y_2]\mathrm{d}\theta_6 - \theta_5\theta_4 x_2\mathrm{d}\theta_8 + (1-\theta_8)\mathrm{d}\dot{y}_2\\ &\quad +(1-\theta_8)\theta_6\mathrm{d}y_2 - \theta_6\mathrm{d}x_3\\ &= \Gamma_{51}\mathrm{d}\theta + \Gamma_{52}\mathrm{d}\dot{y}_2 + \Gamma_{53}\mathrm{d}y_2 + \Gamma_{54}\mathrm{d}\dot{y}_1 + \Gamma_{55}\mathrm{d}y_1\\ &\quad +\Gamma_{56}\mathrm{d}\ddot{y}_2,\end{aligned}$$

where $\Gamma_{50} = \big(0, 0, 0, 0, 0, -x_3 + (1-\theta_8)y_2, 0, \ -\theta_4\theta_5 x_2\big)$, $\Gamma_{51} = \Gamma_{50} - \theta_6\Gamma_{41}$, $\Gamma_{52} = 1 - \theta_8 - \theta_6\Gamma_{42}$, $\Gamma_{53} = (1-\theta_8)\theta_6 - \theta_6\Gamma_{43}$, $\Gamma_{54} = -\theta_6\Gamma_{44}$, $\Gamma_{55} = -\theta_6\Gamma_{45}$, $\Gamma_{56} = -\theta_6\Gamma_{46}$.

Now it is ready to compute $\mathrm{d}y_2^{(3)}$.

$$\begin{aligned}\mathrm{d}y_2^{(3)} &= \dot{\Gamma}_{31}\mathrm{d}\theta + \dot{\Gamma}_{35}\mathrm{d}y_1 + (\dot{\Gamma}_{34} + \Gamma_{35})\mathrm{d}\dot{y}_1 + \Gamma_{34}\mathrm{d}\ddot{y}_1 +\\ &\quad \dot{\Gamma}_{33}\mathrm{d}y_2 + (\Gamma_{33} + \dot{\Gamma}_{32})\mathrm{d}\dot{y}_2 + \Gamma_{32}\mathrm{d}\ddot{y}_2 +\\ &\quad \theta_3\theta_4\theta_5\dot{x}_1\mathrm{d}x_3 + \theta_3\theta_4\theta_5 x_1\mathrm{d}\dot{x}_3\\ &= \Gamma_{61}\mathrm{d}\theta + \Gamma_{62}\mathrm{d}\dot{y}_2 + \Gamma_{63}\mathrm{d}y_2 + \Gamma_{64}\mathrm{d}\dot{y}_1 + \Gamma_{65}\mathrm{d}y_1\\ &\quad +\Gamma_{66}\mathrm{d}\ddot{y}_2 + \Gamma_{67}\mathrm{d}\ddot{y}_1,\end{aligned}$$

where $\Gamma_{61} = \dot{\Gamma}_{31} + \theta_3\theta_4\theta_5\dot{x}_1\Gamma_{41} + \theta_3\theta_4\theta_5 x_1\Gamma_{51}, \Gamma_{62} = \Gamma_{33} + \dot{\Gamma}_{32} + \theta_3\theta_4\theta_5\dot{x}_1\Gamma_{42} + \theta_3\theta_4\theta_5 x_1\Gamma_{52}, \Gamma_{63} = \dot{\Gamma}_{33} + \theta_3\theta_4\theta_5\dot{x}_1\Gamma_{43} + \theta_3\theta_4\theta_5 x_1\Gamma_{53}, \Gamma_{64} = \dot{\Gamma}_{34} + \Gamma_{35} + \theta_3\theta_4\theta_5\dot{x}_1\Gamma_{44} + \theta_3\theta_4\theta_5 x_1\Gamma_{54}, \Gamma_{65} = \dot{\Gamma}_{35} + \theta_3\theta_4\theta_5\dot{x}_1\Gamma_{45} + \theta_3\theta_4\theta_5 x_1\Gamma_{55}, \Gamma_{66} = \Gamma_{32} + \theta_3\theta_4\theta_5\dot{x}_1\Gamma_{46} + \theta_3\theta_4\theta_5 x_1\Gamma_{56}, \Gamma_{67} = \Gamma_{34}$. For any $k \geqslant 1$, $\mathrm{d}y_2^{(k+3)}$ is easily computed by the above $\mathrm{d}y_2^{(3)}$:

$$\mathrm{d}y_2^{(k+3)} = \Gamma_{61}^{(k)}\mathrm{d}\theta + \sum_{j=0}^{k+2}(\mu_j\mathrm{d}y_1^{(j)} + \tau_j\mathrm{d}y_2^{(j)}),$$

where $\mu_j, \tau_j, j = 0, \cdots, k+2$, are coefficients which can be determined by $\Gamma_{6i}, i = 1, 2, \cdots, 7$. Note that $\Gamma_{61} = \dot{\Gamma}_{31} + \frac{\theta_6 x_1 - \dot{x}_1}{x_1}\Gamma_{31} + \theta_3\theta_4\theta_5 x_1\Gamma_{50}$, thus the 7-th column of Γ_{61} is zero, and the following result is obvious from Theorem 2.

Proposition 10. Assume that τ is given in system (12)-(16). If $\text{rank}_{\mathcal{K}}\big(\Gamma_{61}^T, \dot{\Gamma}_{61}^T, \ddot{\Gamma}_{61}^T, \cdots, (\Gamma_{61}^{(6)})^T\big) = 7$, then $\theta_1, \theta_2, \theta_3, \theta_4, \theta_5, \theta_6, \theta_8$ are algebraically identifiable, and hence geometrically identifiable.

Remark 5. When m, ϵ and τ are given and some persistent exciting conditions hold, then all the parameters in (12) can be determined by the measurement of $\{y_2^{(i)}(t), y_1^{(j)}(t) : i = 0, 1, \cdots, 8; j = 0, 1, \cdots, 7\}$ for any fixed time t. One can measure nine times to know $y(t), \dot{y}(t), \cdots, y^{(8)}(t)$.

For the 3-dimensional and 4-dimensional *in vivo* models (5) and (12), the identifiability conditions of the delay parameter τ are given in Proposition 3, 5, 7, and 9, and the conditions are quite similar and have reasonable medical meanings. In fact, if $k = 0$, then infection does not take place; if $\delta N = 0$, then virus replication does not happen; $x_1 = 0$ corresponds to completely damaged immune system; and $x_3 = 0$ indicates no (infectious) free virus. In these cases, either the time delay does not matter or it is "invisible". Proposition 4, 6, 8, and 10 give persistent exciting conditions for the algebraic identifiability of θ. The most likely period for these conditions to hold is either the primary infection stage or the not-too-short period after disturbing the asymptomatic period through chemotherapy.

4. CONCLUSION

The identifiability of parameters in two dimensional HIV *in vitro* model, three and four dimensional HIV *in vivo* models are discussed in this paper by the linear algebraic method based on differential 1-form. For the *in vivo* models, two types of outputs are considered. The identifiability of delay parameters and the algebraic and geometric identifiability of other parameters are obtained. The results provide a guideline for data collection and parameter identification of these systems.

REFERENCES

M. Anguelova, B. Wennberg. State elimination and identifiability of the delay parameter for nonlinear time-delay systems, *Automatica* (to appear).

R. V. Culshaw, S. Ruan, G. Webb. A mathematical model of cell-to-cell spread of HIV-1 that includes a time delay, *Mathematical Biology* 46: 425–444, 2003.

R. V. Culshaw, S. Ruan. A delay-differential equation model of HIV infection of CD4+ T cells, *Math. Biosci.* 165: 27–39, 2000.

N. M. Dixit, A. S. Perelson. Complex patterns of viral load decay under antiretroviral therapy: influence of pharmacokinetics and intracellular delay, *Journal of Theoretical Biology* 226: 95–109, 2004.

R. Filter, X. Xia, C. Gray. Dynamic HIV/AIDS parameter estimation with application to a vaccine readiness study in Southern Africa, *IEEE Transactions on Biomedical Engineering* 52: 284–291, 2003.

C. Gray, C. Williamson, H. Bredell, A. Puren, X. Xia, et al. Viral dynamics and CD4+ T celll counts in subtype C human immunodeficiency virus type 1-infected individuals from Southern Africa, *Aids Research and Human Retroviruses* 21: 285–291, 2005.

A. V. M. Herz, S. Bonhoeffer, R. M. May, M. A. Nowak. Viral dynamics in vivo: limitations on estimates of intracellular delay and virus decay, *Proc. Natl. Acad. Sci. USA* 93: 7247–7251, 1996.

D. D. Ho, A. U. Neumann, et al. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection, *Nature* 273: 123-126, 1995.

M. Jeffrey, X. Xia. Identifiability of HIV/AIDS models, in: H. Wu and W. Y. Tan (Eds.), *Deterministic and Stochastic Models of AIDS and HIV with Intervention*, World Scientific Publications, Singapore, Chapter 11, 2005.

M. Jeffrey, X. Xia, I. Craig. Identifiability of an extended HIV model, *5th IFAC Symposium on Modelling and Control in Biomedical System*, Melbourne, Australia, 21–23 August 2003.

A. L. Lloyd. The dependence of viral parameter estimates on the assumed viral life cycle: limitations of studies of viral load data, *Proc. R. Soc. Lond. B*, 268: 847–854, 2001.

J. E. Mittler, B. Sulzer, A. U. Neumann, A. S. Perelson. Influence of delayed viral production on viral dynamics in HIV-1 infected patients, *Math. Boisci.* 152: 143–163, 1998.

P. W. Nelson, J. E. Mittler, A. S. Perlson. Effect of drug effcacy and eclipse phase of the viral life cycle on estimates of HIV viral dynamic parameters, *J AIDS* 26: 405–412, 2001.

P. W. Nelson, J. D. Murray, A. S. Perlson. A model of HIV-1 paghogenesis that includes an intrcellular delay, *Math. Biosci.* 163: 201-215, 2000.

P. W. Nelson, A. S. Perelson. Mathematical analysis of delay differential equation models of HIV-1 infection, *Math. Biosci.* 179: 73–94, 2002.

M. A. Nowak, R. M. May. *Virus Dynamics: mathematical principles of immunology and virology*, Oxford University Press, New York, 2000.

D. A. Ouattara. Mathematical analysis of the HIV-1 infection: parameter estimation, therapies effectiveness and therapeutical failures, *27th IEEE EMBS Annual International Conference*, 1–4 September 2005, Shanghai, China.

D. A. Ouattara, F. Bugnon, F. Raffi, C. H. Moog. Parameter identification of an HIV/AIDS model, *13th International Symposium on HIV and Emerging Infectious Diseases*, Toulon, France, September 2004.

A. S. Perelson, P. W. Nelson. Mathematical analysis of HIV-1 dynamics *in vivo*, *SIAM Review* 41: 3–44, 1999.

Y. Rosenberg, G. Janossy. The importance of lymphocyte trafficking in regularing blood lymphocyte levels during HIV and SIV infections, *Seminars in Immunol.* 11: 139–154, 1999.

J. L. Spouge, R. I. Shrager, D. S. Dimitrov. HIV-1 infection kinetics in tissue cultures, *Mathematical Biosciences* 138: 1782–1789, 1996.

J. Tam. Delay effect in a model for virus replication, *IMA J. Math. Appl. Med. Biol.* 16: 29–37, 1999.

X. Wei, S. K. Ghosh, et al. Viral dynamics in HIV-1 infection, *Nature* 273: 117–112, 1995.

X. Xia. Modelling of HIV infection: Vaccine readiness, drug effectiveness and therapeutical failures, *Journal of Process Control*, 17: 253–260, 2007.

X. Xia, L. A. Marquez, P. Zagalak, C. H. Moog. Analysis of nonlinear time-delay systems using modules over non-commutative rings, *Automatica*, 38: 1549–1555, 2002.

X. Xia, C. H. Moog. Identifiability of nonlinear systems with application to HIV/AIDS models, *IEEE Transactions on Automatatic Control* 48:330–336, 2003.

J. Zhang, X. Xia, C. H. Moog. Parameter identifiability of nonlinear systems with time-delay, *IEEE Transactions on Automatic Control*, 51:371–375, 2006.