Simulations results show that the proposed scheme can be effectively used in closed loop, and that the combined effect of discretization and measurement noise preserve the convergence properties which are demonstrated in the continuous time domain.

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Identifiability of Nonlinear Systems With Application to HIV/AIDS Models

X. Xia and C. H. Moog

***Abstract*—In this note, we investigate different concepts of nonlinear identifiability in the generic sense. We work in the linear algebraic framework. Necessary and sufficient conditions are found for geometrical identifiability, algebraic identifiability and identifiability with known initial conditions. Relationships between different concepts are characterized. Constructive procedures are worked out for both generic geometrical and algebraic identifiability of nonlinear systems. As an application of the theory developed, we study the identifiability properties of a four dimensional model of HIV/AIDS. The questions answered in this study include the minimal number of measurement of the variables for a complete determination of all parameters and the best period of time to make such measurements. This information will be useful in formulating guidelines for the clinical practice.**

***Index Terms*—AIDS, algebraic framework, HIV, identifiability, nonlinear systems.**

I. INTRODUCTION

Identifiability of nonlinear systems has been studied in different contexts. The first systematic treatment of the topic was probablyin [20]. In that paper, the authors investigated the structural properties, in particular, the one-to-one property, of the map from the parameter to be identified and the measured output of the system. The question under investigation was whether or not it was possible to distinguish different sets of parameters from the measurement of the output. The one-to-one property was shown to be a characterization of such distinguishability of parameters. The authors worked in the *differential geometrical* framework which was very popular around the time of the publication of the note. So, the results carry a strong differential geometrical flavor. Nevertheless, necessary and sufficient conditions were only found for some special cases of regularity.

The usefulness of the identifiability lies in the practical requirement that parameters can be expressed as functions of the known quantities of the system, such as input and output. In this aspect, an algebraic definition, its relationship to observability, and algorithmic procedures based on differential algebraic polynomial systems were rigourously studied in [5], [7], [14]. The paper by Ljung and Glad [14] is trendsetting. Most of the later developments apply to polynomial systems and are of differential algebraic in nature.

It has long been recognized that initial conditions play a role in identifying the parameters [5], [20], [14]. As indicated in [14], the dependence of the output on the initial state is not a simple algebraic relation. The relationship between the geometric identifiability which accommodates the initial conditions as defined in [20] and the algebraic one is not clear, as many other studies of nonlinear system properties,e.g., invertibility [6], [9].

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A recent effort to include the effect of known initial conditions into identifiability is [4] where a slightly different differential algebraic algorithm was suggested to present a characterization of polynomial systems without input. Little systematic study exists, however. The relationship with the algebraic and the geometric ones has not been clear.

In this note, we will show the following. 1) In a generic sense, the structural identifiability is equivalent to identifiability with known initial conditions, i.e., the parameters can be determined by the known initial conditions, the available input and output, if and only if, the map between the parameter and the output is one-to-one. We also obtain necessary and sufficient conditions for all three kinds of identifiability of nonlinear systems. 2) The relationship between the structural concept and the algebraic concept is completely characterized. 3) Identifiability with partially known initial conditions is also easily characterized.

Another distinct feature of the note is that both the structural concept and the algebraic one are dealt with in a single framework: the linear algebraic framework [2]. Constructive procedures are worked out for both geometric and algebraic identifiability of nonlinear systems. Though we present generic results, the results can also be used to check the singularities of the system for parameter identification.

As an application, we study the identifiability properties of the HIV/AIDS models. We will show in this note that the theorems developed in this note lend themselves to characterizations of whether all the parameters in the 4 D HIV/AIDS model are determinable from the measurement of $\mathrm{CD4+}$ T cells and virus load, and if not, what else one has to measure. Another question answered by this study is the minimal number of measurement of the variables that a first estimation of all ten parameters is possible. This gives guidelines for the clinical practice.

The organization of the note is as follows. In Section II, we review different concepts of nonlinear identifiability. Algebraic characterizations are given in Section III. Section IV is devoted to the calculation procedures. Section V contains our study of the identifiability properties of the HIV/AIDS model. Some concluding remarks are given in Section VI.

II. Concepts

Consider a nonlinear system

$$\Sigma_\theta : \begin{cases} \dot{x} = f(x, \theta, u), & x(0, \theta) = x_0, \\ y = h(x, \theta, u) \end{cases} \tag{1}$$

where $x \in R^n$, $u \in R^m$ and $y \in R^p$ are the state, input, and output variables of the system. Assume that

$$\operatorname{rank} \frac{\partial h(x, \theta, u)}{\partial x} = p. \tag{2}$$

θ is the parameter to be identified. θ is assumed to belong to $\mathcal{P}$ which is a simply connected open subset of R^q. The functions $f(x, \theta, u)$ and $h(x, \theta, u)$ are meromorphic functions on a simply connected open subset $\mathcal{M} \times \mathcal{P} \times \mathcal{U}$ of $R^n \times R^q \times R^m$. Moreover, without loss of generality, x_0 is assumed to be independent of θ and not an equilibrium point of the system. We do not assume there are model uncertainties.

An input function $u(t) : [0, T] \to \mathcal{U}$, where $\mathcal{U}$ is a simply connected open subset of R^m, is called an admissible input (on $[0, T]$) if the differential equation in (1) admits a unique (local) solution. For any initial condition x_0 and an admissible input $u(t)$ on $[0, T]$, there exists, on a possibly smaller time interval, $[0, \bar{T}]$, $\bar{T} \leq T$, a parameterized solution $x(t, \theta, x_0, u)$. The corresponding output is denoted by $y(t, \theta, x_0, u)$.

A classical definition of identifiability can be found in [20].

Definition 1: The system Σ_θ is said to be x_0 identifiable at θ through an admissible input u (on $[0, T]$) if there exists an open set $\mathcal{P}^0 \subset \mathcal{P}$ containing θ such that for any two $\theta_1, \theta_2 \in \mathcal{P}^0$, $\theta_1 \neq \theta_2$, the solutions $x(t, \theta_1, x_0, u)$ and $x(t, \theta_2, x_0, u)$ exist on $[0, \epsilon]$, $0 < \epsilon \leq T$, and their corresponding outputs satisfy, on $t \in [0, \epsilon]$, $y(t, \theta_1, x_0, u) \neq y(t, \theta_2, x_0, u)$.

This property was termed in [20] as (instantaneously) locally strongly identifiable. A property of distinguishability as defined by the inequality in Definition 1 is the kernel for observability and identifiability. Refer also to [20] for connections and comparisons between identifiability and observability of an extended system in which the constant parameters are considered as states with zero derivatives.

We are more interested in a generic property of identifiability. This property was studied in [4] for polynomial systems.

To introduce such a concept, we need a topology for the input function space. For any $T > 0$ and a positive integer N, the space $C^N[0, T]$ is the space of all functions on $[0, T]$ which have continuous derivatives up to the order N. A topology of the space $C^N[0, T]$ is the one associated with following well-defined norm: for $r(t) \in C^N[0, T]$, $\|r(t)\| = \sum_{i=0}^{N} \max_{t \in [0,T]} |r^{(i)}(t)|$.

For any $T > 0$ and positive integer N, denote $C_{\mathcal{U}}^N[0, T]$ the set of all admissible inputs (on $[0, T]$) that have continuous derivatives up to the order N. The topology of $C_{\mathcal{U}}^N[0, T]$ is defined to be the m-fold product topology of $C^N[0, T]$. The topology of $C_{\mathcal{U}}^N[0, T] \times C_{\mathcal{U}}^N[0, T]$ is defined to be the product topology of $C_{\mathcal{U}}^N[0, T]$. The M-fold product of $C_{\mathcal{U}}^N[0, T]$ is denoted as $(C_{\mathcal{U}}^N[0, T])^M$.

Definition 2: The system Σ_θ is said to be structurally identifiable if there exist a $T > 0$, and a positive integer N, and open and dense subsets $\mathcal{M}^0 \subset \mathcal{M}$, $\mathcal{P}^0 \subset \mathcal{P}$, $\mathcal{U}^0 \subset C_{\mathcal{U}}^N[0, T]$ such that the system Σ_θ is x_0-identifiable at θ through u, for every $x_0 \in \mathcal{M}^0$, $\theta \in \mathcal{P}^0$ and $u \in \mathcal{U}^0$.

The structural identifiability is also interchangeably called geometric identifiability in this note, because Definition 2 is the generic version of the definition of [20] (Definition 1). The structural identifiability is used to characterize the one-to-one property of the map from the parameter to the system output. The algebraic identifiability is about construction of parameters from algebraic equations of the system input and output. This concept was first employed in [7] and [14], and later formally defined in [5] in the differential algebraic framework. We adapt the definition into the following one.

Definition 3: The system Σ_θ is said to be algebraically identifiable if there exist a $T > 0$, a positive integer k, and a meromorphic function $\Phi : R^q \times R^{(k+1)m} \times R^{(k+1)p} \to R^q$ such that

$$\det \frac{\partial \Phi}{\partial \theta} \neq 0 \tag{3}$$

and

$$\Phi\left(\theta, u, \dot{u}, \ldots, u^{(k)}, y, \dot{y}, \ldots, y^{(k)}\right) = 0 \tag{4}$$

hold, on $[0, T]$, for all $\left(\theta, u, \dot{u}, \ldots, u^{(k)}, y, \dot{y}, \ldots, y^{(k)}\right)$ where (θ, x_0, u) belong to an open and dense subset of $\mathcal{P} \times \mathcal{M} \times C_{\mathcal{U}}^k[0, T]$, and $\dot{u}, \ldots, u^{(k)}$ are the corresponding derivatives of u, and $y, \dot{y}, \ldots, y^{(k)}$ are the derivatives of the corresponding output $y(t, \theta, x_0, u)$.

Algebraic identifiability enables one to construct the parameters from solving algebraic equations depending only on the information of the input and output. As a matter of fact, under (3), one can locally solve (4) with respect to the parameter θ invoking the implicit function theorem.

Sometimes, an initial condition is known for a system. The information of the known initial state may provide additional help in determining the parameters. This phenomenon was recognized in [7], [20], [14]. The following definition formalizes this.

Definition 4: The system Σ_θ is said to be identifiable with known initial conditions if there exist a positive integer k and a meromorphic function $\Phi : R^q \times R^n \times R^{(k+1)m} \times R^{(k+1)p} \to R^q$ such that $\det(\partial\Phi/\partial\theta) \neq 0$, and

$$\Phi\left(\theta, x_0, u\left(0^+\right), \dot{u}\left(0^+\right), \ldots, u^{(k)}\left(0^+\right), y\left(0^+\right), \dot{y}\left(0^+\right), \ldots, y^{(k)}\left(0^+\right)\right) = 0 \quad (5)$$

hold for all $\left(\theta, x_0, u(0^+), \dot{u}(0^+), \ldots, u^{(k)}(0^+), y(0^+\right), \dot{y}(0^+), \ldots, y^{(k)}(0^+))$, where $(\theta, x_0, u(0^+), \dot{u}(0^+), \ldots, u^{(k)}(0^+)$ belong to an open and dense subset of $\mathcal{P} \times \mathcal{M} \times \mathcal{U}^{(k+1)m}$, and $y(0^+)$, $\dot{y}(0^+), \ldots, y^{(k)}(0^+))$ are the derivatives of the corresponding output $y(t, \theta, x_0, u)$ evaluated at $t = 0^+$.

III. Characterizations

We will give characterizations of the algebraic identifiability and structural identifiability in the linear algebraic framework of nonlinear systems [2]. The characterizations also lend themselves to isolate the initial conditions and inputs that are not persistently exciting, i.e., where the system parameters can not be determined.

A. Algebraic Framework

To recall the linear algebraic framework, let $\mathcal{K}$ be the field consisting of meromorphic functions of x, θ, u and finite derivatives of u, and define $E = \mathrm{span}_{\mathcal{K}}\{d\mathcal{K}\}$, that is, a vector in E is a linear combination of a finite number of one-forms from $dx, d\theta, du, d\dot{u}, \ldots, du^{(k)}, \ldots$, with coefficients in $\mathcal{K}$. The vectors in E are called one-forms. The differentiation of a function $\phi\left(x, \theta, u, \ldots, u^{(k)}\right)$ along the dynamics of (1) is defined as

$$\dot{\phi} = \frac{\partial\phi}{\partial x} f(x, \theta, u) + \sum_{i=0}^{k} \frac{\partial\phi}{\partial u^{(i)}} u^{(i+1)}$$

and this operation can be extended to differential one-forms $\omega = \kappa_x dx + \kappa_\theta d\theta + \sum \eta_i du^{(i)} \in E$ as the following:

$$\dot{\omega} = \dot{\kappa}_x dx + \dot{\kappa}_\theta d\theta + \sum \dot{\eta}_i du^{(i)} + \kappa_x df(x, \theta, u) + \sum \eta_i du^{(i+1)}$$

where $\dot{\kappa}_x$ and $\dot{\kappa}_\theta$ are the derivatives of κ_x and κ_θ, respectively, along the dynamics of (1). Note that $\dot{\omega} \in E$.

B. Algebraic Identifiability

Denote $\mathcal{Y} = \bigcup_{k=0}^{\infty} \mathrm{span}\left\{dy, d\dot{y}, \ldots, dy^{(k)}\right\}$, $\mathcal{X} = \mathrm{span}\{dx\}$, $\mathcal{U} = \bigcup_{k=0}^{\infty} \mathrm{span}\left\{du, d\dot{u}, \ldots, du^{(k)}\right\}$, $\Theta = \mathrm{span}\{d\theta\}$, then one has immediately the following result on algebraic identifiability.

Theorem 1: The system is algebraically identifiable if and only if $\Theta \subset (\mathcal{Y} + \mathcal{U})$.

Proof: (necessity) When (4) holds for some Φ, then $d\theta \in \mathcal{Y} + \mathcal{U}$, or $\Theta \subset \mathcal{Y} + \mathcal{U}$.

(sufficiency) If $d\theta = \sum_{i=0}^{N}\left(\xi_i dy^{(i)} + \eta_i du^{(i)}\right)$, denoting $\omega = d\theta - \sum_{i=0}^{N}\left(\xi_i dy^{(i)} + \eta_i du^{(i)}\right)$, then $\omega (= 0)$ is exact. Hence there exists a function $\Phi\left(\theta, u, \ldots, u^{(N)}, y, \ldots, y^{(N)}\right)$ such that $\omega = d\Phi$. Since $\omega = 0$, one can choose, without loss of generality, that

$$\Phi\left(\theta, u, \ldots, u^{(N)}, y, \ldots, y^{(N)}\right) = 0 \quad (6)$$

and Φ satisfying (3). By the Brown Theorem [15], there is a $T > 0$ such that the previous equation and (3) hold on an open and dense subset, denoted as S, of $\mathcal{P} \times (C_{\mathcal{U}}[0, T])^{N+1} \times (C_y[0, T])^{N+1}$, in which $C_{\mathcal{U}}[0, T] = C_{\mathcal{U}}^1[0, T]$, and $C_y[0, T] = C_y^1[0, T]$ is the space of all functions from $[0, T]$ to R^p with continuous differentiations.

Denote as Ψ the map from $\mathcal{P} \times \mathcal{M} \times C_{\mathcal{U}}^N[0, T]$ to $\mathcal{P} \times (C_{\mathcal{U}}[0, T])^{N+1} \times (C_y[0, T])^{N+1}$, defined by

$$(\theta, x_0, u) \to \left(\theta, u, \ldots, u^{(N)}, y, \ldots, y^{(N)}\right)$$

then it can be easily verified that the map Ψ is continuous with respect to the previously defined topology, therefore $\Psi^{-1}(S)$ is an open and dense subset of $\mathcal{P} \times \mathcal{M} \times C_{\mathcal{U}}^N[0, T]$ [3]. This shows that (6) and (3) hold for all $\left(\theta, u, \dot{u}, \ldots, u^{(N)}, y, \dot{y}, \ldots, y^{(N)}\right)$ where (θ, x_0, u) belong to the open and dense subset $\Psi^{-1}(S)$ of $\mathcal{P} \times \mathcal{M} \times C_{\mathcal{U}}^N[0, T]$, and $\dot{u}, \ldots, u^{(N)}$ are the corresponding derivatives of u, and $y, \dot{y}, \ldots, y^{(N)}$ are the derivatives of the corresponding output $y(t, \theta, x_0, u)$.

That is, the system is algebraically identifiable.

C. Structural Identifiability and Identifiability With Known Initial Conditions

In the following theorem, we give characterizations for the structural identifiability and the identifiability with known initial conditions. We also prove that the structural identifiability is equivalent to the identifiability with known initial conditions. Denote $\mathcal{Y}_k = \mathrm{span}\left\{dy, d\dot{y}, \ldots, dy^{(k)}\right\}$ and $\mathcal{U}_k = \mathrm{span}\left\{du, d\dot{u}, \ldots, du^{(k)}\right\}$.

Theorem 2: The following statements are equivalent:

i) the system Σ_θ is structurally identifiable;
ii) $\Theta \subset \mathcal{X} + \mathcal{Y} + \mathcal{U}$;
iii) $\dim(\mathcal{Y}_k + \mathcal{X} + \mathcal{U}_k)/(\mathcal{X} + \mathcal{U}_k) = q$, for some integer k; the left-hand side of the equation denotes the quotient space;
iv) the system Σ_θ is identifiable with known initial conditions.

Proof: i)$\Rightarrow$ ii): If the system is x_0-identifiable at θ through the input u, then the mapping

$$\begin{bmatrix} \phi_0 \\ \phi_1 \\ \vdots \\ \phi_{k+1} \end{bmatrix} = \begin{bmatrix} y(x(0^+, \theta, u(0^+)), \theta, u(0^+)) \\ \dot{y}(x(0^+, \theta, u(0^+)), \theta, u(0^+), \dot{u}(0^+)) \\ \vdots \\ y^{(k)}\left(x(0^+, \theta, u(0^+)), \theta, u(0^+), \dot{u}(0^+), \ldots, u^{(k)}(0^+)\right) \end{bmatrix}$$

is one-to-one, for some k, from θ to $\left(y, \dot{y}, \ldots, y^{(k)}\right)$. One has that $\mathrm{rank}\,(\partial\Phi/\partial\theta) = q$, where $\Phi = (\phi_0, \phi_1, \ldots, \phi_{k+1})^T$.

Now that $\left\{dy, d\dot{y}, \ldots, dy^{(k)}\right\} \subset \mathrm{span}\,\left\{dx, d\theta, du, \ldots, du^{(k)}\right\}$, there is a matrix $\Gamma = \left(\gamma_0^T, \gamma_1^T, \ldots, \gamma_k^T\right)^T \in \mathcal{K}^{k \times q}$ such that

$$\left\{dy - \gamma_0 d\theta, d\dot{y} - \gamma_1 d\theta, \ldots, dy^{(k)} - \gamma_k d\theta\right\} \subset \mathrm{span}\,\left\{dx, du, \ldots, du^{(k)}\right\}. \quad (7)$$

By the definition of derivatives along the dynamics of the system (1), one knows immediately that $\Gamma_{0^+} = \partial\Phi/\partial\theta$, where Γ_{0^+} is the evaluation of Γ at $x_0, \theta, u(0^+), \ldots, u^{(k)}(0^+), \ldots$. So, $\mathrm{rank}\,\Gamma_0 = q$. This implies, by the Brown Theorem [15], that Γ has the maximal rank q for an open and dense subset of x, θ and $u, \ldots, u^{(k)}, \ldots$. Thus, one has

$$\mathrm{rank}_{\mathcal{K}}\Gamma = q. \quad (8)$$

From (7) and (8), one solves for $d\theta$ and $\Theta \subset \mathcal{X} + \mathcal{Y} + \mathcal{U}$.

ii)$\Leftrightarrow$ iii): To prove the equivalence of ii) and iii), note that, for all $k \geq 0$

$$\mathcal{Y}_k \subset \mathcal{X} + \Theta + \mathcal{U}_k \quad (9)$$

and when ii) holds, it holds for some finite integer k (abusing the notation). So, ii) is equivalent to $\mathcal{X}+\mathcal{Y}_k+\mathcal{U}_k=\mathcal{X}+\Theta+\mathcal{U}_k$, for some k, and the result follows.

ii) $\Rightarrow$ iv): If $\Theta \subset \mathcal{X}+\mathcal{Y}+\mathcal{U}$, then $d\theta = \kappa dx + \sum_{i=0}^{k}\left(\xi_i dy^{i)} + \eta_i du^{(i)}\right)$, for suitable matrices κ, ξ_1, η_i, whose components belong to $\mathcal{K}$. Define $\omega = d\theta - \kappa dx - \sum_{i=0}^{k}(\xi_i dy^{(i)} + \eta_i du^{i)})$, then similar to the proof of sufficiency of Theorem 1, there exists a function $\Phi(\theta, x, y, \ldots, y^{(k)}, u, \ldots, u^{(k)})$ such that $\Phi = 0$ and $\det(\partial\Phi/\partial\theta) = 1$ hold on an open and dense subset. Therefore, they must also hold for all values of x_0, $y(0^+), \ldots, y^{(k)}(0^+)$, $u(0^+), \ldots, u^{(k)}(0^+)$ in an open and dense subset.

That is, the system Σ_θ is identifiable with known initial conditions.

iv) $\Rightarrow$ i): If the system is identifiable with known initial condition, then for every θ, there is an open set $\mathcal{P}$ containing θ, such that $\det(\partial\Phi/\partial\theta) \neq 0$, and

$$\Phi\left(\theta, x_0, u(0^+), \dot{u}(0^+), \ldots, u^{(k)}(0^+), y(0^+), \dot{y}(0^+), \ldots, y^{(k)}(0^+)\right) = 0.$$

Thus, on an open subset of $\mathcal{P}$, by solving the previous equation for θ, one has

$$\theta = \phi\left(x_0, u(0^+), \dot{u}(0^+), \ldots, u^{(k)}(0^+), y(0^+), \dot{y}(0^+), \ldots, y^{(k)}(0^+)\right).$$

From here, one can see that the map from the parameter θ to the output y must be one-to-one.

D. Relationship Between Algebraic and Structural Identifiability

First of all, algebraic identifiability implies structural identifiability.

Corollary 1: If a system is algebraically identifiable, then it is structurally identifiable.

Proof: The proof follows from Theorem 1, Theorem 2, and $\mathcal{Y}+\mathcal{U} \subset \mathcal{X}+\mathcal{Y}+\mathcal{U}$.

A complete characterization of the relationship between algebraic identifiability and structural identifiability is described by the following theorem.

Theorem 3:

1) If

$$\mathcal{X} \cap (\mathcal{Y}+\Theta+\mathcal{U}) = \mathcal{X} \cap (\mathcal{Y}+\mathcal{U}) \tag{10}$$

then the system is algebraically identifiable if and only if it is structurally identifiable.

2) If the system is algebraically identifiable, then (10) holds.

Proof:

1) We only need to show that if (10) holds and $\Theta \subset \mathcal{X}+\mathcal{Y}+\mathcal{U}$, then $\Theta \subset \mathcal{Y}+\mathcal{U}$.

To see this, for any $\omega \in \Theta$, there is an $\omega_x \in \mathcal{X}$, an $\omega_y \in \mathcal{Y}$ and an $\omega_u \in \mathcal{U}$, such that $\omega = \omega_x + \omega_y + \omega_u$, so $\omega_x = \omega - \omega_y - \omega_u \in \mathcal{X} \cap (\mathcal{Y}+\Theta+\mathcal{U})$. Hence, by (10), there is an $\omega_y^1 \in \mathcal{Y}$ and an $\omega_u^1 \in \mathcal{U}$ such that $\omega_x = \omega_y^1 + \omega_u^1$. Therefore, one has, $\omega = \omega_y + \omega_y^1 + \omega_u + \omega_u^1 \in \mathcal{Y}+\mathcal{U}$, proving that $\Theta \subset \mathcal{Y}+\mathcal{U}$.

2) The proof is straightforward, thus omitted.

TABLE I
IDENTIFIABILITY CHARACTERIZATIONS

Definition of identifiability	Characterization
Algebraic identifiability	$\Theta \subset \mathcal{Y}+\mathcal{U}$
Identifiability with partially known initial conditions	$\Theta \subset \mathcal{X}_p+\mathcal{Y}+\mathcal{U}$
Identifiability with known initial conditions	$\Theta \subset \mathcal{X}+\mathcal{Y}+\mathcal{U}$
Geometric identifiability	$\Theta \subset \mathcal{X}+\mathcal{Y}+\mathcal{U}$

E. Identifiability With Partially Known Initial Condition

Assume that initial conditions are partially known for $x_i(0)$, $i = i_1, \ldots, i_s, i_s \in \{1, \ldots, n\}$, and the identifiability problem in this case is to find whether the parameter θ can be expressed as a meromorphic function of $x_i(0)$, $i = i_1, \ldots, i_s$, and u, y and their derivatives.

Definition 5: The system Σ_θ is said to be identifiable with partially known initial conditions $x_i(0), i = i_1, \ldots, i_s, i_s \in \{1, \ldots, n\}$ if there exist a positive integer k and a meromorphic function $\Phi: R^q \times R^s \times R^{(k+1)m} \times R^{(k+1)p} \rightarrow R^q$ such that $\det \partial\Phi/\partial\theta \neq 0$, and

$$\Phi\left(\theta, x_{i_1}(0), \ldots, x_{i_s}(0), u(0^+), \dot{u}(0^+), \ldots, u^{(k)}(0^+), y(0^+), \dot{y}(0^+), \ldots, y^{(k)}(0^+)\right) = 0 \tag{11}$$

hold for all $(\theta, x_{i_1}(0), \ldots, x_{i_s}(0), u(0^+), \dot{u}(0^+), \ldots, u^{(k)}(0^+), y(0^+), \dot{y}(0^+), \ldots, y^{(k)}(0^+))$ belonging to an open and dense subset of $R^q \times R^s \times R^{(k+1)m} \times R^{(k+1)p}$.

Define $\mathcal{X}_p = \operatorname{span}\{dx_i, i = 1, \ldots, i_s\}$. Then quite analogous to the aforementioned development, one has the following characterization.

Theorem 4: The system is identifiable with known $x_i(0)$, $i = i_1, \ldots, i_s$ if and only if $\Theta \subset \mathcal{Y}+\mathcal{U}+\mathcal{X}_p$, or equivalently $\Theta \cap (\mathcal{Y}+\mathcal{U}+\mathcal{X}_p) = \Theta$.

A proof of the result is left for the interested readers.

If we have two sets of known initial conditions $\mathcal{X}_p^1$ and $\mathcal{X}_p^2$, and one is larger than the other $\mathcal{X}_p^1 \supset \mathcal{X}_p^2$, then the following corollary is implied by Theorem 4.

Corollary 2: If the system is identifiable with $\mathcal{X}_p^2$, then it is identifiable with $\mathcal{X}_p^1$.

The characterizations of the different notions of identifiability are summarized in Table I.

IV. CALCULATION

Section III was devoted to the characterization of various notions of identifiability and their relationships. Let us now investigate the computational issues for the determination of the parameter identifiability.

Note that $\mathcal{X} \cap (\mathcal{Y}+\mathcal{U})$ is the observation cospace of the system (1) [2], while $\mathcal{X} \cap (\mathcal{Y}+\Theta+\mathcal{U})$ can be regarded as the observation cospace with parameter. One checks the identifiability through calculating the input-output relations of the system. One way of doing this is first to eliminate x through observability properties of the system.

Define for (1) the so-called observability indexes. Let

$$\mathcal{F}_k := \mathcal{X} \cap \left(\operatorname{span}\left\{dy, d\dot{y}, \ldots, dy^{(k-1)}\right\} + \mathcal{U} + \Theta\right)$$

for $k = 1, \ldots, n$. Consider the filtration $\mathcal{F}_1 \subset \mathcal{F}_2 \subset \cdots \subset \mathcal{F}_n$. Then, as done in [13] for nonlinear systems without parameters and which are linearizable by output injections, define $d_1 := \dim \mathcal{F}_1$ and $d_k :=$

$$\operatorname{rank}\frac{\partial\left(y, \dot{y}, \ldots, y^{(n-1)}\right)}{\partial x} = \operatorname{rank}\frac{\partial\left(y_1, \dot{y_1}, \ldots, y_1^{(k_1-1)}, y_2, \ldots, y_2^{(k_2-1)}, \ldots, y_p, \dot{y_p}, \ldots, y_p^{(k_p-1)}\right)}{\partial x} = k_1 + k_2 + \cdots + k_p. \tag{12}$$

$\dim \mathcal{F}_k - \dim \mathcal{F}_{k-1}$, for $k = 2, \ldots, n$. Let $k_i := \max\{k \mid d_k \geq i\}$. Then the list $\{k_1, k_2, \ldots, k_p\}$ is the list of observability indices and d_k represents the number of observability indices which are greater than or equal to k, for $k = 1, \ldots, n$.

Reorder, if necessary, the output components such that (12), as shown at the bottom of the page, holds. Thanks to (2), the p observability indices are well defined. Compute

$$\begin{aligned} dy_1 =& \xi_{11} dx + \gamma_{11} d\theta (\mathrm{mod} \mathcal{U}) \\ &\vdots \\ dy_p =& \xi_{p1} dx + \gamma_{p1} d\theta (\mathrm{mod}\, \mathcal{U}). \end{aligned}$$

By assumption, $\mathrm{rank}\, \left[\xi_{11}^T, \ldots, \xi_{p1}^T\right]^T = q$. More generally, compute

$$dy_i^{(j-1)} = \xi_{ij} dx + \gamma_{ij} d\theta (\mathrm{mod}\, \mathcal{U})$$

for $i = 1, \ldots, p$ and $j = 1, \ldots, k_i$. From (12), any ξ_{ij} can be written as linear combination of $\{\xi_{11}, \ldots, \xi_{1,k_1}, \ldots, \xi_{p1}, \ldots, \xi_{p,k_p}\}$.

Higher order time derivatives $dy_i^{(j)}$ can be computed and, from the implicit function theorem, dx can be substituted to obtain

$$dy_i^{(j)} = \left(\sum_{r=1}^{p} \sum_{s=1}^{k-r} \eta_{rs} dy_r^{(s-1)} \right) + \gamma_{i,j+1} d\theta (\mathrm{mod}\, \mathcal{U}).$$

Then, the system is geometrically identifiable if and only if there are integers k_i^*, for $i = 1, \ldots, p$, such that $\mathrm{rank}\, \Gamma_g = q$, where

$$\Gamma_g = \left[\gamma_{11}^T, \ldots, \gamma_{1k_1^*}^T, \gamma_{21}^T, \ldots, \gamma_{pk_p^*}^T\right]^T.$$

The system is algebraically identifiable if and only if there exist p integers l_i^*, for $i = 1, \ldots, p$, such that $\mathrm{rank}\, \Gamma_a = q$, where

$$\Gamma_a = \left[\gamma_{1,k_1+1}^T, \ldots, \gamma_{1l_1^*}^T, \gamma_{2,k_2+1}^T, \ldots, \gamma_{pl_p^*}^T\right]^T.$$

Definition 6: A pair $(x_0, u(t))$ is algebraically (geometrically) persistently exciting for θ_0 if Γ_a (Γ_g), as previously defined, is of rank q when evaluated at x_0, θ, and $u(t), \ldots, u^{(k)}(t)$.

From the aforementioned development, we see that when $(x_0, u(t))$ is algebraically (geometrically) persistently exciting, the parameters can be determined at least locally around $(x_0, u(t))$ as expressions of $u, \ldots, u^{(k)}$ and $y, \ldots, y^{(k)}$ (and x_0).

When $(x_0, u(t))$ is not algebraically (geometrically) persistently exciting for θ_0, it is referred to as an algebraic (a geometric) singular point for the identifiability of θ_0.

We can make use of the previous calculation procedures to check singularities.

V. Identifiability of HIV/AIDS Models

A three dimensional model of HIV/AIDS with six parameters was introduced for the study of virus dynamics in [8], [21], [16]. [22] presented on-line estimation methods for all these six parameters of the model which is easily verified to be algebraically identifiable.

A four-dimensional model is more accurate by incorporating both the actively infected $\mathrm{CD4+}$ T cells and the latently infected $\mathrm{CD4+}$ T cells [19]. The four state variables are: the population of sizes of uninfected cells, or healthy cells, T; the latently infected cells, T_1; the productively infected cells (also called as actively infected cells), T_2; and the free virus particles, v. T_1 is the population of cells which are infected by the virus, but which do not yet produce new virus particles. T_2 denotes the population of infected cells which do produce virus particles.

The latently infected cells T_1 are produced at a rate $q_1 \beta v T$, with $q_1 \leq 1$. μ_1 is their death rate constant. They are not producing new virus particles but they may produce such virus particles when activated; k_1 is the rate that latently infected cells convert to productively infected cells.

The productively infected cells T_2 are produced at a rate $q_2 \beta v T$, with $q_2 \leq 1$. μ_2 is their death rate constant.

The free virus particles v are produced by the actively infected T_2 cells at a constant rate k_2 and their death rate constant is c.

This is summarized in the following fourth-order model:

$$\dot{T} = s - dT - \beta v T \tag{13}$$
$$\dot{T}_1 = q_1 \beta v T - \mu_1 T_1 - k_1 T_1 \tag{14}$$
$$\dot{T}_2 = q_2 \beta v T + k_1 T_1 - \mu_2 T_2 \tag{15}$$
$$\dot{v} = k_2 T_2 - cv. \tag{16}$$

We assume that efficient monitoring of the healthy $\mathrm{CD4+}$ T cells and virus in blood samples is available, which is in accordance with the current medical practice,

$$\begin{aligned} y_1 =& T \\ y_2 =& v. \end{aligned}$$

This four-dimensional HIV model exhibits more interesting identifiability properties.

A. Algebraic Identifiability

Compute $\dot{y}_1 = s - dy_1 - \beta y_1 y_2$, thus, the output y_1 has an observability index equal to 1. Higher order derivatives yield $\ddot{y}_1 = -d\dot{y}_1 - \beta(y_1 y_2)^{(1)}$, $y_1^{(3)} = -d\ddot{y}_1 - \beta(y_1 y_2)^{(2)}$. Now, we have got three equations in three unknown parameters s, d and β. For any persistently exciting trajectory $y(t)$, i.e., such that

$$\mathrm{rank} \begin{bmatrix} 1 & -y_1 & -y_1 y_2 \\ 0 & -\dot{y}_1 & -(y_1 y_2)^{(1)} \\ 0 & -\ddot{y}_1 & -(y_1 y_2)^{(2)} \end{bmatrix} = 3 \tag{17}$$

the three equations can be solved to get a unique solution in s, d, β as functions of $y(t)$, $\dot{y}(t)$, $\ddot{y}(t)$ and $y_1^{(3)}(t)$. Therefore, these three parameters are identifiable. For the estimation of these three parameters, at least four measurements of y_1 and three measurements of y_2 are necessary.

For the rest of parameters, compute $\dot{y}_2 = k_2 T_2 - c y_2$, $\ddot{y}_2 = k_2 q_2 \beta y_1 y_2 + k_1 k_2 T_1 - k_2 \mu_2 T_2 - c\dot{y}_2$, and

$$\begin{aligned} y_2^{(3)} =& k_2 q_2 \beta (y_1 y_2)^{(1)} - (\mu_1 + \mu_2 + c + k_1)\ddot{y}_2 \\ & - (\mu_2 c + \mu_1 \mu_2 + \mu_1 c + k_1 c + k_1 \mu_2)\dot{y}_2 \\ & + (k_1 k_2 q_1 \beta + k_2 q_2 \beta(\mu_1 + k_1)) y_1 y_2 \\ & - c\mu_2(\mu_1 + k_1) y_2. \end{aligned} \tag{18}$$

Rename the parametric coefficients in (18) as $y_2^{(3)} = \theta_1 (y_1 y_2)^{(1)} + \theta_2 \ddot{y}_2 + \theta_3 \dot{y}_2 + \theta_4 y_1 y_2 + \theta_5 y_2$, where

$$\begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \\ \theta_4 \\ \theta_5 \end{bmatrix} = \begin{bmatrix} k_2 q_2 \beta \\ -(\mu_1 + \mu_2 + c + k_1) \\ -(\mu_2 c + \mu_1 \mu_2 + \mu_1 c + k_1 c + k_1 \mu_2) \\ (k_1 k_2 q_1 \beta + k_2 q_2 \beta(\mu_1 + k_1)) \\ -c\mu_2(\mu_1 + k_1) \end{bmatrix} \tag{19}$$

then higher order derivatives of y_2 will just read as

$$\begin{aligned} y_2^{(i)} = \theta_1 (y_1 y_2)^{(i-2)} + \theta_2 y_2^{(i-1)} + \theta_3 y_2^{(i-2)} \\ + \theta_4 (y_1 y_2)^{(i-3)} + \theta_5 y_2^{(i-3)}. \end{aligned}$$

TABLE II
ALGEBRAIC INDENTIFIABILITY OF 4-D HIV MODEL

known	identifiability condition for the rest of the parameters	remark
(q_1, q_2)	(21)	
(q_1, μ_1)	(21)	
(q_1, k_1)	(21)	
(q_1, μ_2)	not identifiable	rank is ≤ 4
(q_1, k_2)	(21)	
(q_1, c)	not identifiable	rank is ≤ 4
(q_2, μ_1)	(21)	
(q_2, k_1)	(21)	
(q_2, μ_2)	not identifiable	rank is ≤ 4
(q_2, k_2)	(21)	
(q_2, c)	not identifiable	rank is ≤ 4
(μ_1, k_1)	not identifiable	rank is ≤ 3
(μ_1, μ_2)	not identifiable	rank is ≤ 4
(μ_1, k_2)	(21)	
(μ_1, c)	not identifiable	rank is ≤ 4
(k_1, μ_2)	not identifiable	rank is ≤ 4
(k_1, k_2)	(21)	
(k_1, c)	not identifiable	rank is ≤ 4
(μ_2, k_2)	not identifiable	rank is ≤ 4
(μ_2, c)	not identifiable	rank is ≤ 3

The five "parameters" $\theta_1, \ldots, \theta_5$ can be computed from any persistently exciting trajectory $y(t)$ such that $\operatorname{rank} \partial \left(y_2^{(3)}, \ldots, y_2^{(7)} \right) / \partial(\theta_1, \ldots, \theta_5) = 5$, i.e.,

$$\operatorname{rank} \begin{bmatrix} (y_1y_2)^{(1)} & \ddot{y}_2 & \dot{y}_2 & y_1y_2 & y_2 \\ (y_1y_2)^{(2)} & y_2^{(3)} & \ddot{y}_2 & (y_1y_2)^{(1)} & \dot{y}_2 \\ (y_1y_2)^{(3)} & y_2^{(4)} & y_2^{(3)} & (y_1y_2)^{(2)} & \ddot{y}_2 \\ (y_1y_2)^{(4)} & y_2^{(5)} & y_2^{(4)} & (y_1y_2)^{(3)} & y_2^{(3)} \\ (y_1y_2)^{(5)} & y_2^{(6)} & y_2^{(5)} & (y_1y_2)^{(4)} & y_2^{(4)} \end{bmatrix} = 5. \tag{20}$$

Anyhow, the system is not algebraically identifiable. Besides the identification of s, d, β, 5 over 7 remaining parameters can be computed in terms of the measurements and two remaining parameters, if the map defined by (19) has rank 5. It is noted that the map defined by (19) is of rank 5 if

$$q_1q_2\beta k_2(\mu_1 + k_1 - \mu_2)(\mu_2 - c)(\mu_1 + k_1 - c) \neq 0. \tag{21}$$

It is noted that some of the parameters can be determined by other methods. For example, through the experiment of [1], q_1 is found to be $q_1 = 0.01$, and [10] found that $q_2 = 0.02$. It is interesting to see whether (19) defines a map of rank 5 under the condition that two of the seven parameters $(q_1, q_2, k_1, \mu_1, k_2, \mu_2, c)$ are known ($\beta \neq 0$ is assumed to be known due to (17).) If this is the case, we can still claim that all the rest of the parameters are algebraically identifiable.

Table II is the exhaustive list of all the cases. These conclusions are drawn based on the analysis of the rank of the map defined by (19) by assuming two of the parameters are known.

B. Geometric Identifiability

Let us now inspect the geometric identifiability of the seven remaining parameters $\{q_1, q_2, \mu_1, \mu_2, k_1, k_2, c\}$. Introduce the notation $\Theta_1 := k_2q_2\beta$ and $\Theta_2 := k_1k_2q_1\beta$ and consider the new list of parameters $\{\Theta_1, \Theta_2, \mu_1, \mu_2, k_1, k_2, c\}$.

Compute $\ddot{y}_2$, $y_2^{(3)}$ and $y_2^{(4)}$ as

$$\ddot{y}_2 = \Theta_1 y_1 y_2 + k_1k_2T_1 - k_2\mu_2T_2 - c\dot{y}_2 \tag{22}$$

$$\begin{aligned} y_2^{(3)} =& \Theta_1(y_1y_2)^{(1)} + \Theta_2 y_1y_2 - (\mu_1 + k_1) \\ & \times [\ddot{y}_2 - \Theta_1 y_1 y_2 + \mu_2(\dot{y}_2 + cy_2) + c\dot{y}_2] \\ & - \mu_2(\ddot{y}_2 + c\dot{y}_2) - c\ddot{y}_2 \end{aligned} \tag{23}$$

$$\begin{aligned} y_2^{(4)} =& \Theta_1(y_1y_2)^{(2)} + \Theta_2(y_1y_2)^{(1)} - (\mu_1 + k_1) \\ & \times \left[y_2^{(3)} - \Theta_1(y_1y_2)^{(1)} + \mu_2(\ddot{y}_2 + c\dot{y}_2) + c\ddot{y}_2 \right] \\ & - \mu_2 \left(y_2^{(3)} + c\ddot{y}_2 \right) - cy_2^{(3)}. \end{aligned} \tag{24}$$

Higher order derivatives are easily obtained by differentiating (24).

Introduce the notation $A = y_1y_2$, $B = (y_1y_2)^{(1)} + (\mu_1 + k_1)(y_1y_2)$, $C = -[\ddot{y}_2 - \Theta_1 y_1y_2 + \mu_2(\dot{y}_2 + cy_2) + c\dot{y}_2]$, $D = -[(\mu_1 + k_1)(\dot{y}_2 + cy_2) + \ddot{y}_2 + c\dot{y}_2]$, $E = -[(\mu_1 + k_1)(\mu_2 y_2 + \dot{y}_2) + \mu_2\dot{y}_2 + \ddot{y}_2]$, compute $\partial \left(\dot{y}_2, \ddot{y}_2, y_2^{(3)}, y_2^{(4)}, y_2^{(5)}, y_2^{(6)}, y_2^{(7)} \right) / \partial(\Theta_1, \Theta_2, \mu_1, \mu_2, k_1, k_2, c)$ as the equation shown at the bottom of the page.

It is clear that this matrix has full rank if $k_2T_1T_2 \neq 0$ and

$$\operatorname{rank} \begin{bmatrix} \dot{B} & \dot{A} & \dot{C} & \dot{D} & \dot{E} \\ \ddot{B} & \ddot{A} & \ddot{C} & \ddot{D} & \ddot{E} \\ B^{(3)} & A^{(3)} & C^{(3)} & D^{(3)} & E^{(3)} \\ B^{(4)} & A^{(4)} & C^{(4)} & D^{(4)} & E^{(4)} \end{bmatrix} = 5. \tag{25}$$

Due to the relationship between (A, B, C, D, E) and $\left((y_1y_2)^{(1)}, \ddot{y}_2, \dot{y}_2, y_1y_2, y_2 \right)$, we can verify that (25) holds if and only if (20) and (21) are satisfied.

The system is, thus, fully geometrically identifiable, or equivalently, the parameters can be estimated if we know the initial condition and the plasma viral load and the $\mathrm{CD4+}$ T cell count.

Again this analysis provides guidelines for the clinical measurement. Note that apart from the higher order input-output equations (23) and (24), etc., one needs two extra equations (one of $\dot{y}_2$ and (22)) which depend on the availability of T_1 and T_2. Most likely that the persistent excitation condition (20) holds only during the acute infection stage and after sufficient disturbing the "set-point" with antiretroviral chemotherapies. Hence, for most HIV patents who are already in the asymptomatic stage, to determine all ten parameters, it is suggested to do at least one "comprehensive" test before the initiation of chemotherapy which includes the viral load, $\mathrm{CD4+}$ T cells, latently infected $\mathrm{CD4+}$ T cells and actively infected $\mathrm{CD4+}$ T cells. After the initiation of treatment, it is suggested to do at least seven measurement for the viral load and five measurements for the $\mathrm{CD4+}$ T cells. And for more accurate estimation of the parameters, one can repeat the above cycle of measurements. As an example, one cycle of one measurement daily will be accomplished in a week. With the advance of faster measuring device [17], it is envisaged that these measurements will be available cost effectively in a near future.

The actual estimation procedures of these ten parameters will be presented elsewhere.

$$\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & T_2 & -y_2 \\ A & 0 & 0 & -k_2T_2 & k_2T_1 & [k_1T_1 - \mu_2T_2] & -\dot{y}_2 \\ B & A & C & D & C & 0 & E \\ \dot{B} & \dot{A} & \dot{C} & \dot{D} & \dot{C} & 0 & \dot{E} \\ \ddot{B} & \ddot{A} & \ddot{C} & \ddot{D} & \ddot{C} & 0 & \ddot{E} \\ B^{(3)} & A^{(3)} & C^{(3)} & D^{(3)} & C^{(3)} & 0 & E^{(3)} \\ B^{(4)} & A^{(4)} & C^{(4)} & D^{(4)} & C^{(4)} & 0 & E^{(4)} \end{bmatrix}.$$

VI. Conclusion

In this note, we have studied different concepts of nonlinear identifiability in the linear algebraic framework. Constructive procedures have been worked out for both geometric and algebraic identifiability of nonlinear systems. Relationships between different concepts have been completely characterized. As an application of the theory developed, we investigated the identifiability properties of a four dimensional model of HIV/AIDS. The questions answered in this study include the minimal number of measurement of the variables for a complete determination of all parameters and the best period of time to make such measurements. This information will be useful in formulating guidelines for the clinical practice.

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Robust Control of Nonlinear Systems in the Presence of Unknown Exogenous Dynamics

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***Abstract*—A robust control is designed for a class of uncertain systems, and it is distinct and novel that the proposed control does not require any information of a bounding function on nonlinear uncertainties in the system. Instead, the uncertainties to be compensated for are generated by an exogenous system whose dynamics are either completely unknown or partially unknown. The only requirements on the exogenous system are that its unknown dynamics are bounded by a known function and that its output is bounded. The proposed robust control is based on a nonlinear observer that estimates the uncertainties. It is shown that, under different sets of conditions, local, semiglobal, or global stability of uniform ultimate boundedness or asymptotic stability can be achieved.**

***Index Terms*—Bounding function, estimation, Lyapunov direct method, nonlinear uncertainty, observer, robust control.**

I. Introduction

Robustness is one of the essential concepts in control theory. Roughly speaking, a control system is robust if stability and performance can be maintained under a specific class of uncertainties which could be unknown functionals, parameter variations, unmodeled dynamics, disturbances, etc. Robust control of nonlinear uncertain systems has attracted a lot of attention. Classes of stabilizable uncertain systems have been found, and several robust control design procedures have been proposed [4]–[7], [9], [10], [12], [15], [19]–[21], [24], [26].

In most of the existing results, robust controls are designed to deal with significant but bounded uncertainties by assuming a known bounding function on the size of uncertainties. While uncertainties being bounded ensures that a stabilizing control (if found) will be of finite magnitude, determining a known bounding function of uncertainties is a nontrivial issue in many applications. Without knowledge of the bounding function, robust control must be designed to learn the size of uncertainties while compensating for them. To this end, progress has been made by combining robust and adaptive control designs. In [6], the robust control design problem is investigated under the assumption that the bounding function has a known functional expression and it is parameterized in terms of finite unknown constants. In this case, an adaptive robust control was proposed to adaptively estimate the unknown parameters in the bounding function. In [22], an extension is made so that the bounding function can be parameterized in terms of time varying parameters. Specifically,

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