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Impulsive control of single-input nonlinear systems with application to HIV dynamics

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ABSTRACT

In this paper, some fundamental analysis and results are introduced for the accessibility of impulsive control systems (ICS). The main result is the characterization of accessibility for nonlinear ICS based on the 'number of impulses' which is required. These results naturally generalize and correct some earlier results obtained for linear ICS. The theory developed is applied to an impulsive model of the dynamics of human immunodeficiency virus (HIV) subject to medication. It is shown that HIV system fulfills the accessibility criterion. Finally, an impulsive control strategy is designed based on exact linearization to improve the response immune system of a patient of HIV.

1. Introduction

This paper tackles impulsive nonlinear control systems and introduces some basic properties like controllability, reachability, and accessibility for this class of systems.

Such problems arise naturally from a wide variety of applications, such as spacecraft [1], ecosystems management [2], pharmacokinetics [3], and chaotic systems [4]. In contrast with continuous control systems, where there already is a significant body of literature, impulsive control systems is attracting an increasing number of researchers.

The basic mathematical tools for studying impulsive control systems is the theory of impulsive differential equations [5]. The theory of linear ICS has been developed during this last decade through the investigation of fundamental properties such as stability and controllability [6]. The results available for the class of nonlinear ICS are much less advanced, even for the characterization of controllability/accessibility. Actually, accessibility is the structural property that in the nonlinear case plays a role similar to that of controllability in the linear case. Instead of that, many researchers have studied this property in continuous systems and they have given useful criteria to characterize it (see for instance [7,8]), in nonlinear impulsive control systems, this subject is a field to explore.

As regard to the design of feedback control laws for ICS, several control problems (like pole placement problem, optimal control, and the others) have been fully developed for linear impulsive systems. In [6], a feedback control strategy is explained in detail for nonlinear ICS based on comparison methods. Here, the problem of exact linearization via feedback is attacked for single-input single-output nonlinear ICS. It is shown that under specific conditions related to the notion of relative degree (see [8]), a nonlinear ICS can be locally transformed into a linear one, by an impulsive state feedback control at each control instant τ_k, where the impulse is applied, and by a nonlinear state transformation.

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Mathematical modeling has made a substantial impact on our thinking and understanding of HIV-1 infection. A large number of deterministic models have been developed to describe the immune system and its interaction with HIV-1 as well as the effects of drug therapy (see [9–13] and their references). In most cases, their mathematical expression are based in relatively complex systems of non-linear differential equations. Population models are the most commonly used.

Using these models, therapeutic strategies can be simulated with the purpose of reducing the viral load. Also, different control problems can be posed and solved when the dynamics is known. Control theory have already been used to develop anti-HIV treatment strategies based on the efficiency of the drugs. However, the resulting strategies are quite hard to put into practice since drug efficiency is typically not expressed in terms of prescribed drug amounts (see [11,14–16]). To circumvent this drawback, pharmacokinetics and pharmacodynamics models have been included in the model in order to relate efficiency with drug dosage [17,11].

Here, a pragmatic point of view for the control of the HIV dynamics will be considered, subject to a standard therapy. The intake of drugs twice a day can be interpreted as an impulse input (as it is observed in [3]), with a time interval of 12 h. The absorption time is neglected as regards this time interval and the time characteristics of pharmacokinetics are much smaller as well [17]. As a consequence, it is appropriate to develop the analysis and control of the HIV dynamics in the framework of ICS.

The contribution of this paper is twofold. First, a new theoretical setting is introduced for nonlinear ICS, where accessibility is defined and characterized in terms of the number of required control impulses. Second, a novel feedback control law based on exact linearization for nonlinear ICS is designed and applied to HIV dynamics in a more realistic way than existing control strategies [18,11,15].

The paper is organized as follows: the state of art and problem statement are given in Section 2. Also, it is shown by a counter example that a statement on the controllability property of linear ICS in [19] is not correct and the correction is included. The theoretical framework and the main results for nonlinear ICS are developed in Section 3. A new control algorithm is introduced and its results are illustrated in Section 4. Those results are applied to the analysis of the HIV dynamics in Section 5. Finally, the last Section is devoted to conclusions and perspectives.

2. Preliminaries

A plant is an impulsive control system when there is a set of control instants $T = \{\tau_k\},\ \tau_k \in \mathbb{R},\ \tau_k < \tau_{k+1}$, and a set of inputs $U_k \in \mathbb{R}^n,\ k = 1, 2, \ldots$, such that the state $x \in \mathbb{R}^n$ at each τ_k is changed impulsively by $x(\tau_k^+) = x(\tau_k) + U(k, x)$. Note that the control instants are not necessarily equidistant and the control $U(k, x)$ yields a discontinuity of x at instant τ_k.

The class of dynamic systems of interest basically consists of objects defined by a set of impulsive first-order differential equations of the form

$$\begin{cases} \dot{x}(t) = f(x(t)), & t \neq \tau_k, \\ \Delta x(\tau_k) = g(x(\tau_k))u(\tau_k), & k \in \mathbb{N}, \\ x(t_0^+) = x(t_0) = x_0, \end{cases} \tag{1}$$

where the independent variable $t \in \mathbb{R}$ denotes time, the state $x \in \mathcal{M} \subset \mathbb{R}^n$, and the input $u(\tau_k) = u_k \in \mathbb{R}^m,\ 1 \leqslant m < n$. The functions $f(x) \in \mathbb{R}^n$ and $g(x) \in \mathbb{R}^{n \times m}$ are analytic vector fields and— $\mathcal{M}$ is an analytic manifold.

Definition 1. System (1) is said to be impulsively controllable if for all vectors $x_0,\ \bar{x} \in \mathcal{M}$, and $t_f > t_0 \in \mathbb{R}$, there are real numbers $\tau_k \in [t_0, t_f],\ t_0 < \tau_1 < \tau_2 \cdots < \tau_p = t_f$, and vectors $u_k \in \mathbb{R}^m,\ k = 1, \ldots, p < \infty$ such that (1) has a solution $x(t) = x(t, x_0, u_k)$ existing on $[t_0, t_f]$ satisfying $x(t_f^+) = \bar{x}$.

For the special case of impulsive linear systems [6], a criterion of controllability has been established in [19]:

Theorem 1. *If $f(x) = Ax$ and $g(x) = B$, where A, B are constant matrices, then system (1) is impulsively controllable if and only if*

$$Rank\left[B, AB, A^2B, \ldots, A^{n-1}B\right] = n. \tag{2}$$

The proof of the Theorem 1 can be found in [19]. It is claimed in [19] that the maximum number of impulses required to reach any desired final state for a controllable linear ICS is $p = \lceil \frac{n}{m} \rceil$, where $\lceil z \rceil$ denotes the smallest integer greater than or equal to z. The following linear example is developed as an illustration of this theorem.

Example. Consider the linear ICS:

$$\begin{cases} \dot{x}_1(t) = x_2(t), \\ \dot{x}_2(t) = 0, & t \neq \tau_k, \\ \Delta x_2(\tau_k) = u(\tau_k), & k \in \mathbb{N}, \end{cases} \tag{3}$$

System (3) is controllable from Theorem 1. The maximum number of required impulses to reach any final states $(\bar{x}_1, \bar{x}_2)$ is $p = 2$ according to the statement in [19]. In addition, applying the control sequence $u(\tau_k) = \{u(\tau_1) = \frac{\bar{x}_1}{\tau_2},\ u(\tau_2) = \bar{x}_2 - u(\tau_1)\}$ is enough for reaching these final states.

Actually, this number of impulses p is correct when m equals 1. For a multi-input system, this statement is not true in general, as it is shown in the following counter example:

Example.

$$\begin{cases} \dot{x}_1(t) = x_2(t), \\ \dot{x}_2(t) = x_3(t), \\ \vdots \\ \dot{x}_9(t) = x_{10}(t), \qquad t \neq \tau_k, \\ \dot{x}_{10}(t) = 0, \\ \dot{x}_{11}(t) = 0, \\ \Delta x_{10}(\tau_k) = u_1(\tau_k), \quad k \in \mathbb{N}, \\ \Delta x_{11}(\tau_k) = u_2(\tau_k), \end{cases} \tag{4}$$

where $n = 11$, and $m = 2$. From Theorem 1, system (4) is controllable. Thus, in [19], six impulses ($p = 6$) are claimed to be required to steer the system (4) from x_0 to any final state $\bar{x}$. However, the input u_2 only has influence on x_{11}. Accordingly, the number of required impulses to achieve any $\bar{x}$ for the system (4) is at least $p = 10$. The standard notion of controllability indices of the pair (A, B) describes the number of required impulses (see [8,7]). The controllability indices associated to system (4) are $\{1, 10\}$.

For the class of nonlinear ICS, to the best of our knowledge, there is no available result equivalent to Theorem 1. Next section introduces a theoretical setting which allows to define accessibility and generalize the accessibility criterion.

3. Accessibility of impulsive single-input systems

Two basic notions in control systems theory are that of reachable states and controllability. Controllability is about the possibility of steering the system from a state x_1 to another state x_2. For linear systems, controllability is a structural property (which is described for linear ICS in the first section, and in [19]). Any linear system can be split into a controllable subsystem and an autonomous one. The structural property that in the nonlinear case plays a role similar to that of controllability in the linear case and can be given a similar characterization is the accessibility property. For its definition, we will start with the notion of an impulsively reachable state.

Definition 2. For system (1), $x(t_1) = x_1$ is said to be impulsively reachable from the initial state x_0 if there is a finite set of control instants $T = \{\tau_k\}$ $\tau_1 < \tau_2 \cdots < \tau_k = t_1$, and a finite control sequence $U = \{u(\tau_k)\}$, so that $x(x_0, U, t_1^+) = x_1$.

Accessibility is now characterized through the notion of autonomous elements [7,8]. From a technical point of view, the notion impulse relative degree of a given function of the state is defined at first place. After that, a relationship between this notion an autonomous elements will be established. For simplicity, single-input systems will be considered, i.e the dimension of u in system (1) will be equal to 1.

Given system (1), consider a scalar function $y(t) = h(x(t)),\ y \in \mathcal{Q} \subset \mathbb{R}$ of the state $x(t)$. This function can be thought as an output of the system. Let $y_0 = h(x_0)$. Let $\dot{y}$, and $y^{(i)}$ denote the first and i-th derivative of y with respect to time, respectively. Let $\mathcal{Y}_1$ denote the set of points in $\mathbb{R}$, which can be reached by y from $h(x_0)$ with one single impulse control at time τ_1. More generally, let $\mathcal{Y}_k$ denote the set of points in $\mathbb{R}^k$, which can be reached by $(y, \dot{y}, \ldots, y^{(k-1)})$ from $\left(h(x_0), L_f h(x_0), \ldots, L_f^{k-1} h(x_0)\right)$ with k control impulses at times $\tau_1 < \tau_2 < \cdots < \tau_k$.

Example. Consider the following linear system

$$\begin{cases} \dot{x}_1(t) = x_2(t), \\ \dot{x}_2(t) = x_3(t), \qquad t \neq \tau_k, \\ \dot{x}_3(t) = 0, \\ \Delta x_3(\tau_k) = u(\tau_k), \quad k \in \mathbb{N}. \end{cases} \tag{5}$$

From Theorem 1, at least 3 impulses are required to reach any point of $\mathbb{R}^3$. In order to describe the set of points $\mathcal{Y}_3$, the output $y = x_1$ is taken into account. Then, at control instant τ_1, when the first impulse is applied, we have

$$\begin{aligned} y(\tau_1^+) &= x_1(0) + x_2(0)\tau_1 + x_3(0)\frac{\tau_1^2}{2}, \\ \dot{y}(\tau_1^+) &= x_2(0) + x_3(0)\tau_1, \\ y^{(2)}(\tau_1^+) &= x_3(0) + u_1. \end{aligned} \tag{6}$$

The space reachable by $(y, \dot{y}, y^{(2)})$ with a single impulse is a line in $\mathbb{R}^3$, i.e $dim\{\mathcal{Y}_3\} = 1$. At τ_2, the second impulse is applied, then

$$
\begin{aligned}
y(\tau_2^+) &= x_1(0) + x_2(0)\tau_2 + x_3(0)\frac{\tau_2^2 + \tau_1^2}{2} + \frac{(\tau_2 - \tau_1)^2}{2}u_1, \\
\dot{y}(\tau_2^+) &= x_2(0) + x_3(0)\tau_2 + (\tau_2 - \tau_1)u_1, \\
y^{(2)}(\tau_2^+) &= x_3(0) + u_1 + u_2.
\end{aligned} \tag{7}
$$

Now, the set of points that can be reached by $(y, \dot{y}, y^{(2)})$ with two impulses $\mathcal{Y}_3$ is a plane in $\mathbb{R}^3$. At $t = \tau_3$, the third impulse is applied and the output and its derivatives are

$$
\begin{aligned}
y(\tau_3^+) &= x_1(0) + x_2(0)\tau_3 + x_3(0)\frac{\tau_1^2 + \tau_3^2}{2} + \frac{(\tau_3 - \tau_1)^2}{2}u_1 + \frac{(\tau_3 - \tau_2)^2}{2}u_2, \\
\dot{y}(\tau_3^+) &= x_2(0) + x_3(0)\tau_3 + (\tau_3 - \tau_1)u_1 + (\tau_3 - \tau_2)u_2, \\
y^{(2)}(\tau_3^+) &= x_3(0) + u_1 + u_2 + u_3.
\end{aligned} \tag{8}
$$

The space reachable by $(y, \dot{y}, y^{(2)})$ with three impulses is $\mathcal{Y}_3 = \mathbb{R}^3$ since the system (5) is linear and controllable.

From these notations, the impulse relative degree can now be defined.

Definition 3. Given system (1), and the scalar function $y(t) = h(x), y \in \mathcal{Q} \subset \mathbb{R}$. The impulse relative degree $d^0(y)$ of y is defined to be the smallest number r of impulses required so that $\mathcal{Y}_r$ contains a locally dense subset of $\mathbb{R}^r$. If for any $r \in \mathbb{N}$, this dense subset does not exist, then set $d^0(y) = \infty$.

Note that in general, the impulse relative degree depends on the initial state x_0. For a linear ICS, it is defined independently of x_0, and if $d^0(y) = r$ then $\dim\{\mathcal{Y}_r\} = Rank[B, AB, \ldots, A^{r-1}B] = r$.

Example. Consider the linear ICS (4), if $y = x_i$ for some i with $1 \leqslant i \leqslant 10$, then the impulse relative degree $d^0(y)$ is $11 - i$.

Example. Given the following nonlinear ICS,

$$
\begin{cases}
\dot{x}_1(t) = x_2^2(t), & \\
\dot{x}_2(t) = 0, & t \neq \tau_k, \\
\Delta x_2(\tau_k) = x_2(\tau_k)u(\tau_k), & k \in \mathbb{N},
\end{cases} \tag{9}
$$

and the scalar function $y = x_1(t)$, it is easy check that $d^0(y) = 2$ for any $x_2(0) \neq 0$. When $x_2(0) = 0$, then $d^0(y) = \infty$. The conclusion is that two impulses are required to reach any final states $x_1(\tau_2) = \bar{x}_1$, and $x_2(\tau_2) = \bar{x}_2$ from $(x_1(0), x_2(0))$, provided that $\bar{x}_1 \geqslant (x_2^2(0)\tau_1 + x_1(0))$. That sequence of controls can be computed as

$$
u(\tau_1) = \frac{x_2(\tau_1^+) - x_2(0)}{x_2(0)}, \quad x_2(\tau_1^+) = \left(\frac{\bar{x}_1 - (x_2^2(0)\tau_1 + x_1(0))}{\tau_2 - \tau_1}\right)^{\frac{1}{2}}, \tag{10}
$$

$$
u(\tau_2) = \frac{\bar{x}_2 - x_2(\tau_2)}{x_2(\tau_2)}. \tag{11}
$$

Based on the arguments described above, the accessible space for system (9) is drawn in Fig. 1. Note that the reachable set is not dense everywhere in $\mathbb{R}^2$.

Now, two useful differential operations will be introduced for describing the impulse relative degree (see [7] for more details). The first operation involves a real-valued function $\lambda : \mathcal{M} \to \mathbb{R}$ and a vector field $f : \mathcal{M} \to \mathcal{M}$, where $\mathcal{M}$ is a subset of $\mathbb{R}^n$. From these, a new smooth real-valued function is defined, whose value at each $x \in \mathcal{M}$ is equal to the inner product

$$
\langle \mathrm{d}\lambda(x), f(x) \rangle = \frac{\partial \lambda}{\partial x} f(x) = \sum_{i=1}^{n} \frac{\partial \lambda}{\partial x_i} f_i(x) = L_f \lambda(x), \tag{12}
$$

where $\mathrm{d}\lambda(x) = \frac{\partial \lambda}{\partial x} = (\frac{\partial \lambda}{\partial x_1}, \frac{\partial \lambda}{\partial x_2}, \ldots, \frac{\partial \lambda}{\partial x_n})$. This function is called the derivative of λ along f and is denoted $L_f \lambda(x)$.

It is possible to repeat this operation. For instance, by taking the derivative of λ first along a vector field f and then along a vector field g one defines the function

$$
L_g L_f \lambda(x) = \frac{\partial (L_f \lambda)}{\partial x} g(x) = \langle \mathrm{d}L_f \lambda(x), g(x) \rangle, \tag{13}
$$

If λ is differentiated k times along f, the function $L_f^k \lambda(x)$ satisfies the recursion

$$
L_f^k \lambda(x) = \frac{\partial (L_f^{k-1} \lambda)}{\partial x} f(x) = \langle \mathrm{d}L_f^{k-1} \lambda(x), f(x) \rangle, \tag{14}
$$

with $L_f^0 \lambda(x) = \lambda(x)$. Some practical properties are described in [7]. The second operation involves two vector fields f, g and is called the Lie bracket of f and g. It is defined as

$$
[f, g](x) = \frac{\partial g}{\partial x} f(x) - \frac{\partial f}{\partial x} g(x), \tag{15}
$$

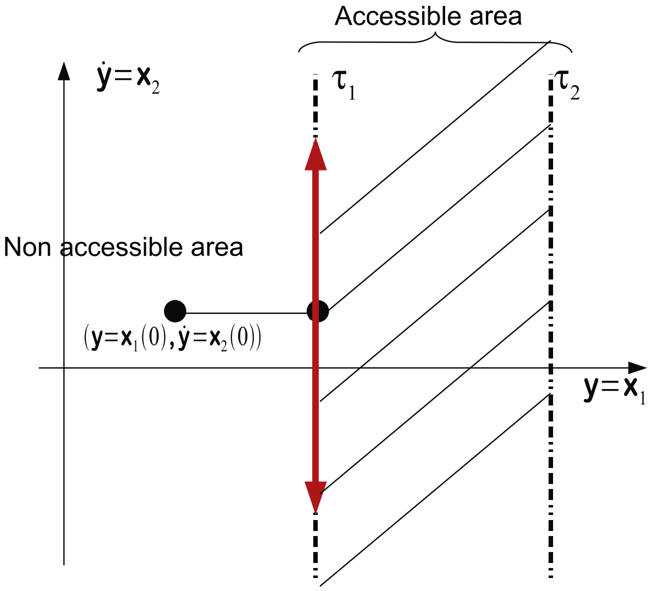

Fig. 1. Accessibility characterization for system (9).

at each $x \in \mathcal{M}$, where $\frac{\partial g}{\partial x}$ and $\frac{\partial f}{\partial x}$ denote the Jacobian matrices of the mappings g and f, respectively. The repetition of this operation yields the following recursion

$$\mathrm{ad}_f^k g(x) = [f, \mathrm{ad}_f^{k-1} g](x), \tag{16}$$

for any $k \geqslant 1$, setting $\mathrm{ad}_f^0 g(x) = g(x)$.

The following Proposition will provide a simple way to compute the impulse relative degree for nonlinear ICS and a scalar function $y = h(x)$, namely.

Proposition 1. *The three following statements are equivalent*

(i) $d^0 = \min\{r \in \mathbb{N} | y \text{ is differentiable, i.e. } y^{(r-1)} \text{ exists}\}$,
(ii) $d^0 = \min\{r \in \mathbb{N} | \langle dL_f^{r-1} h(x), g(x)\rangle \neq 0\}$, *and*
(iii) d^0 *is the impulse relative degree according to Definition 3.*

In particular, y has finite impulse relative degree if d^0 *belongs to* $\mathbb{N}$ *and y has infinite impulse relative degree if* $d^0 = \infty$.

Sketch of proof: In order to illustrate the equivalence, consider the system (1), which can be written alternatively as $\dot{x}(t) = f(x(t)) + g(x(t))u\delta(t - \tau_k)$. Denote the state $x(0) = x_0$ and the initial output $y(0) = h(x_0)$.

Case $d^0 = 1$. **(i)**⇒ **(ii)**. Assume that at some control instant time $\tau_p > 0$, the system has evolved to state $x(\tau_p^+) = x_p$. We wish to compute the value of the output $y(t)$ and its time derivatives $y^{(r)}$, for $r = 1, 2, \ldots$, around at fixed time $t = \tau_p$.

If $d^0(y) = 1$, and by using the theorem of existence and uniqueness of solutions of impulsive differential systems (see [5,6] for details), we can write

$$\dot{y} = \frac{\mathrm{d}y}{\mathrm{d}t} = \frac{\partial h}{\partial x}\frac{\mathrm{d}x}{\mathrm{d}t} = L_f h(x(t)) + L_g h(x(t))u\delta(t - \tau_p).$$

If $\langle \mathrm{d}h(x), g(x)\rangle = L_g h(x) \neq 0$, it is easy check that y is no longer differentiable at τ_p for any nonzero u.

(ii)⇒ **(iii)**. Now, we wish to determine the number of impulses for reaching a dense subset in $\mathbb{R}$, as a matter of fact that $d^0(y) = 1$. In the interval $[0, \tau_1[$, where τ_1 is a control instant and $0 < \tau_1 < \tau_2$, no impulse control is applied and $y(t) = h(x(t))$ is the free response. At $t = \tau_1$, an impulse is applied and the output becomes $y(\tau_1^+) = h(x(\tau_1)) + L_g h(x(\tau_1))u_1$. As the amplitude of u_1 is free, then only one impulse is required so that $\mathcal{Y}_1$ contains a locally dense set of values in $\mathbb{R}$.

Case $d^0 = 2$. **(i)**⇒ **(ii)**. At $t = \tau_p$, As $d^0 = 2$, then $\langle \mathrm{d}h(x), g(x)\rangle = 0$, and the first and second time derivatives of y are

$$\dot{y} = \frac{\mathrm{d}y}{\mathrm{d}t} = L_f h(x(t)), \tag{17}$$

$$y^{(2)} = \frac{\mathrm{d}^{(2)}y}{\mathrm{d}t^{(2)}} = \frac{\partial L_f h}{\partial x}\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{\partial L_f h}{\partial x}(f(x(t)) + g(x(t))u\delta(t - \tau_p)), \tag{18}$$

$$= L_f^2 h(x(t)) + L_g L_f h(x(t))u\delta(t - \tau_p). \tag{19}$$

If $\langle dL_f h(x), g(x)\rangle = L_g L_f h(x) \neq 0$, then y is not differentiable at τ_p. Otherwise, y is again differentiable, and we can conclude that $d^0(y) > 2$.

(ii)⇒ (iii). Consider the intervals $[0, \tau_1[$ and $[\tau_1, \tau_2[$ in order to find the number of impulses required so that $\mathcal{Y}_2$ contains a dense subset in $\mathbb{R}^2$. In the first interval, we get

$$y = h(x(t)), \quad \dot{y} = L_f h(x(t)), \quad y^{(2)} = L_f^2 h(x(t)). \tag{20}$$

At $t = \tau_1$, the impulse u_1 is applied and the output y and its first time derivative $\dot{y}$ are

$$y(\tau_1^+) = h(x(\tau_1)), \tag{21}$$
$$\dot{y}(\tau_1^+) = L_f h(x(\tau_1)) + L_g L_f h(x(\tau_1))u_1. \tag{22}$$

Since the output y is not affected by u_1, so just one impulse is not enough to reach a locally dense set in $\mathbb{R}^2$. In the next interval $[\tau_1, \tau_2[$, we get

$$y(t) = h(x(\tau_1)) + L_g L_f h(x(\tau_1))u_1(t - \tau_1), \tag{23}$$
$$\dot{y}(t) = L_f h(x(\tau_1)) + L_g L_f h(x(\tau_1))u_1, \tag{24}$$
$$y^{(2)}(t) = L_f^2 h(x(t)). \tag{25}$$

At $t = \tau_2$, a second impulse is applied and

$$y(\tau_2^+) = h(x(\tau_2)) + L_g L_f h(x(\tau_1))u_1(\tau_2 - \tau_1), \tag{26}$$
$$\dot{y}(\tau_2^+) = L_f h(x(\tau_2)) + L_g L_f h(x(\tau_1))u_1 + L_g L_f h(x(\tau_2))u_2. \tag{27}$$

From Eqs. (26) and (27), we can conclude that it is just required to apply only two impulses so that $\mathcal{Y}_2$ contains a locally dense set of values in $\mathbb{R}^2$.

Case $d^0 = r$. **(i)⇒ (ii)**. Continuing in this way, at some control instant $t = \tau_p$, when we set $d^0 = r$, then y is differentiable r times (i.e. $y^{(r-1)}$ exits), and $\langle dL_f^{r-1} h(x), g(x)\rangle \neq 0$.

(ii)⇒ (iii). For $\tau_r \leqslant t < \tau_{r+1}$, and $r = \min\{j \mid L_g L_f^{j-1} \neq 0\}$, at $t = \tau_r$, when r impulses have been already applied, it is possible to find r equations for the r unknowns u_r in the space spanned by $\{y, \dot{y}, \ldots, y^{(r-1)}\}$, namely

$$\begin{aligned}
y^{(r-1)}(\tau_r^+) &= L_f^{r-1} h(x(\tau_r)) + L_g L_f^{r-1} h(x(\tau_1))u_1 + \cdots + L_g L_f^{r-1} h(x(\tau_r))u_r,\\
y^{(r-2)}(\tau_r^+) &= L_f^{r-2} h(x(\tau_r)) + L_g L_f^{r-1} h(x(\tau_1))(\tau_r - \tau_1)u_1 + \cdots + L_g L_f^{r-1} h(x(\tau_{r-1}))(\tau_r - \tau_{r-1})u_{r-1},\\
&\vdots\\
y^{(1)}(\tau_r^+) &= L_f h(x(\tau_r)) + L_g L_f^{r-1} h(x(\tau_1))\frac{(\tau_r - \tau_1)^{r-2}}{r-2}u_1 + \cdots + L_g L_f^{r-1} h(x(\tau_{r-1}))\frac{(\tau_r - \tau_{r-1})^{r-2}}{(r-2)!}u_{r-1},\\
y(\tau_r^+) &= h(x(\tau_r)) + L_g L_f^{r-1} h(x(\tau_1))\frac{(\tau_r - \tau_1)^{r-1}}{(r-1)!}u_1 + \cdots + L_g L_f^{r-1} h(x(\tau_{r-1}))\frac{(\tau_r - \tau_{r-1})^{r-1}}{(r-1)!}u_{r-1}.
\end{aligned} \tag{28}$$

In other words, if Eqs. (28) are seen as a linear algebraic system $\mathcal{A}u = \mathcal{B}$, where $u = (u_1, u_2, \ldots, u_r)'$, then the matrix $\mathcal{A}$

$$\mathcal{A} = \begin{pmatrix}
L_g L_f^{r-1} h(\tau_1) & \cdots & L_g L_f^{r-1} h(\tau_{r-1}) & L_g L_f^{r-1} h(\tau_r)\\
L_g L_f^{r-1} h(\tau_1)(\tau_r - \tau_1) & \cdots & L_g L_f^{r-1} h(\tau_1)(\tau_r - \tau_{r-1}) & 0\\
\vdots & \ddots & \vdots & \vdots\\
L_g L_f^{r-1} h(\tau_1)\frac{(\tau_r-\tau_1)^{r-2}}{(r-2)!} & \cdots & L_g L_f^{r-1} h(\tau_1)\frac{(\tau_r-\tau_{r-1})^{r-2}}{(r-2)!} & 0\\
L_g L_f^{r-1} h(\tau_1)\frac{(\tau_r-\tau_1)^{r-1}}{(r-1)!} & \cdots & L_g L_f^{r-1} h(\tau_{r-1})\frac{(\tau_r-\tau_{r-1})^{r-1}}{(r-1)!} & 0
\end{pmatrix}$$

has determinant

$$\det \mathcal{A} = \frac{(-1)^r}{\prod_{i=1}^{r-1} i!}\prod_{j=1}^{r}\left[L_g L_f^{r-1} h(x(\tau_j))\prod_{k=j+1}^{r}(\tau_j - \tau_k)\right] \tag{29}$$

different from zero. As a result, the number of impulses required so that $\mathcal{Y}_r$ contains a locally dense subset of $\mathbb{R}^r$ is equal to r.

In particular, if for any $r \in \mathbb{N}$, $\langle dL_f^{r-1} h(x), g(x)\rangle$ always is identically zero then we will say that the impulsively relative degree will be $d^0 = \infty$ and a locally dense subset of $\mathbb{R}^r$ does not exist. □

Note that if $L_g L_f^k h(x) = 0,\ \forall\, k \geqslant 0$ then the output of the system is not affected by the input for all t. As a matter of fact, the previous calculations show that at the point $t = \tau_p$, the output has the form $y(t) \approx \sum_{i=1}^{\infty}(L_f^i h(x(0))\frac{t^i}{i!})$, i.e the output is a function depending only on the initial state and not on the input.

Lemma 1. *If* $d^0(y) = r < \infty$, *then* $\dim\{dh, dL_f h, \ldots, dL_f^{r-1}h\} = r \leqslant n$.

Proof. If $\dim\{dh, dL_f h, \ldots, dL_f^{r-1}h\} < r$, then $\exists j \mid dL_f^j h = \sum_{i=0}^{j-1}\alpha_i dL_f^i h$, and $\forall k \geqslant j$ $dL_f^k h = \sum_{i=0}^{j-1}\tilde{\alpha}_i dL_f^i h$. By item (*ii*) of the Proposition 1, the inner product $\langle dL_f^i h(x), g(x)\rangle = 0$ for all $i = 1, \ldots, j-1$, and $\forall k \geqslant 0$ we get that $\langle dL_f^k h(x), g(x)\rangle = 0$. As a result, the impulsively relative degree $d^0(y)$ is infinite, which stands in contradiction. Now, as the dimension of the matrix $[dh, dL_f h, \ldots, dL_f^{r-1}h]' = n \times r$, then $\dim\{dh, dL_f h, \ldots, dL_f^{r-1}h\} \leqslant n$. □

Lemma 2. *If the impulse relative degree* $d^0(y) > r$ *then dh is orthogonal to the involutive closure of* $\overline{\{g, ad_f g, \ldots, ad_f^{r-1} g\}}$.

Proof. From Proposition 1, when $d^0(y) > 1$, we get that $\langle dh, g\rangle = 0$, then dh is orthogonal to g. Now, $\forall y$ such that $d^0(y) > 2$,

$$\langle dL_f h, g\rangle = \langle L_f dh, g\rangle, \tag{30}$$

by the Leibniz's rule property [7]

$$\langle L_f dh, g\rangle = L_f\langle dh, g\rangle - \langle dh, \mathrm{ad}_f g\rangle. \tag{31}$$

Since $d^0 > 2$, the last equation becomes $\langle dh, \mathrm{ad}_f g\rangle = -\langle L_f dh, g(x)\rangle = 0$. As a consequence, d$h$ is orthogonal to $\mathrm{ad}_f g$. Since dh is an exact differential then dy is orthogonal to the involutive closure of $\overline{\{g, \mathrm{ad}_f g\}}$ (see [7] for more details).

Again, for any $y = h(x)$ such that $d^0(y) > 3$, applying the Leibniz's rule property in the following inner product, we get

$$\langle dL_f^2 h, g\rangle = \langle L_f dL_f h, g\rangle = -\langle dL_f h, \mathrm{ad}_f g\rangle + L_f\langle dL_f h, g\rangle. \tag{32}$$

Since $\langle dL_f h, g\rangle = 0$ and once more using the Leibniz's rule property in the left-hand side of the last equation

$$\langle dL_f^2 h, g\rangle = -L_f\langle dh, \mathrm{ad}_f g\rangle + \langle dh, \mathrm{ad}_f^2 g\rangle, \tag{33}$$

and by the fact that $\langle dL_f^2 h, g\rangle$, and $\langle dh, \mathrm{ad}_f g\rangle$ are zero, dh is orthogonal to $\mathrm{ad}_f^2 g$. As dh is an exact differential, then dh is orthogonal to the involutive closure of $\overline{\{g, \mathrm{ad}_f g, \mathrm{ad}_f^2 g\}}$.

Continuing in this way, it is easy to show that for any $y = h(x)$ such that $d^0(y) > r$, dh is orthogonal to the involutive closure $\overline{\{g, \mathrm{ad}_f g, \ldots, \mathrm{ad}_f^{r-1} g\}}$. □

So far, a fully description of the impulse relative degree has been developed. Summarizing, if system (1) has impulse relative degree $d^0(y)$ equal to r, then the output y is affected by the single-input after at least the r-th impulse.

Definition 4. The function y is said to be an autonomous element of system (1) if $d^0 = \infty$.

Definition 5. The system (1) is said impulsively accessible if there is no autonomous element.

Based on the notions explained above, a useful criterion for characterizing the accessibility property in ICS can be claimed, namely.

Theorem 2. *The system (1) satisfies the accessibility condition if*

$$\dim\overline{\{g, \mathrm{ad}_f g, \ldots, \mathrm{ad}_f^{n-1} g\}} = n. \tag{34}$$

Proof. It follows from Lemma 1 and Lemma 2. □

4. Impulsive linearizing control

One of the main purposes of checking accessibility is the analysis and the design of a impulsive feedback control law for nonlinear ICS. The objective of this section is to show how an accessible single input–output nonlinear ICS can be transformed into a linear system at control instants $t = \tau_k$, $k = 1, 2, \ldots, p$ by means of a suitable change of coordinates in the state space, and an impulsive state feedback. Specific tools are developed for the class of nonlinear ICS.

Problem Statement. Given system (1), $m = 1$, and a controllable pair (A, B) find if possible, a diffeomorphism $z = \Phi(x)$ and an impulsive state feedback $u(\tau_k) = \alpha(x(\tau_k)) + \beta(x(\tau_k))v(\tau_k)$, where $v(\cdot) \in \mathbb{R}$, and $k \in \mathbb{N}$, so that the trajectory $z(t)$ of the closed-loop system coincides with the trajectory $p(t)$ of the linear ICS

$$\begin{cases} \dot{p}(t) = Ap(t), & t \neq \tau_k, \\ \Delta p(\tau_k) = Bv(\tau_k), & k \in \mathbb{N}, \end{cases} \tag{35}$$

at each $t = \tau_k$, $\forall k \in \mathbb{N}$.

Theorem 3. *The impulsive state space linearization via feedback at each* $t = \tau_k$ *problem is solvable if and only if the following conditions are satisfied*

(i) *the distribution* $\overline{\{g, ad_f g, \ldots, ad_f^{n-2} g\}}$ *has dimension* $n-1$, *and*
(ii) *the distribution* $(g, ad_f g, \ldots, ad_f^{n-1} g)$ *has dimension* n.

Proof. Necessity: from (35), the necessary condition **(ii)** is fulfilled as accessibility is unchanged under feedback, then from Theorem 2, the dimension of the distribution $(g, \mathrm{ad}_f g, \ldots, \mathrm{ad}_f^{n-1} g)$ is n. On the other hand, $\mathrm{d}\Phi_1(x)$ is orthogonal to $\overline{\{g, \mathrm{ad}_f g, \ldots, \mathrm{ad}_f^{n-2} g\}}$, thus $\dim \overline{\{g, \mathrm{ad}_f g, \ldots, \mathrm{ad}_f^{n-2} g\}} \leqslant n-1$. From (35), we get

$$\mathrm{d}\Phi_1(x) \perp \overline{\{g, \mathrm{ad}_f g, \ldots, \mathrm{ad}_f^{n-2} g\}} \tag{36}$$

$$\mathrm{d}\Phi_2(x) \perp \overline{\{g, \mathrm{ad}_f g, \ldots, \mathrm{ad}_f^{n-3} g\}} \tag{37}$$

$$\vdots \tag{38}$$

$$\mathrm{d}\Phi_{n-1}(x) \perp \overline{\{g\}}. \tag{39}$$

As the following sequence of involutive distributions

$$\overline{\{g\}} \subset \overline{\{g, \mathrm{ad}_f g\}} \subset \cdots \subset \overline{\{g, \mathrm{ad}_f g, \ldots, \mathrm{ad}_f^{n-2} g\}} \tag{40}$$

increases its dimension of one unit only, then condition **(i)** is satisfied.

Sufficiency: Conversely, suppose that conditions **(i)** and **(ii)** are satisfied, then pick $\mathrm{d}h$ orthogonal to $\{g, \mathrm{ad}_f g, \ldots, \mathrm{ad}_f^{n-2} g\}$, and set $y = h(x)$. Thus, from item **(i)**, $d^0(y) = n$. Now, define $\Phi_i(x) = L_f^{i-1} h(x)$, with $L_f^0 h(x) = h(x),\ i = 1, \ldots, n$, the dynamics of $z_i(t)$ follows easily,

$$\dot{z} = \frac{\mathrm{d}z_1}{\mathrm{d}t} = z_2(t); \quad \dot{z}_{n-1} = \frac{\mathrm{d}z_{n-1}}{\mathrm{d}t} = z_n(t). \tag{41}$$

Notice that z_i coincides with p_i with the exception of the last component z_n. Its dynamics turned to one more physically realizable form is

$$\dot{z}_n = L_f^n h(x(t)) + L_g L_f^{n-1} h(x(t)) U(\tau_k). \tag{42}$$

with $U(\tau_k) = \begin{cases} 0, & t \neq \tau_k \\ u(\tau_k), & t = \tau_k \end{cases}$.

For any $t \in]\tau_k, \tau_{k+1}[,\ \dot{z}_n = L_f^n h(x(t))$ is still nonlinear, but at each τ_k,

$$\dot{z}_n(\tau_k) = L_f^n h(x(\tau_k)) + L_g L_f^{n-1} h(x(\tau_k)) u(\tau_k) \tag{43}$$

can be transformed into a linear form. If on the right-hand side of Eq. (43), $x(\tau_k)$ is replaced by $x(\tau_k) = \Phi^{-1}(p(\tau_k))$, and the following impulsive state feedback control law is chosen

$$\begin{aligned} u(\tau_k) &= \frac{1}{a(p)}(-b(p) + v) = \frac{1}{L_g L_f^{n-1} h(\tau_k)}(-L_f^n h(\tau_k) + v(\tau_k)), \\ a(p) &= L_g L_f^{n-1} h(\Phi^{-1}(p((\tau_k)))), \quad b(p) = L_f^n h(\Phi^{-1}(p((\tau_k)))), \end{aligned} \tag{44}$$

$\dot{z}_n$ becomes equal to $v(\tau_k)$. As a result, the trajectory $z(t)$ of the closed-loop system coincides with the trajectory $p(t)$ of the linear ICS

$$\begin{cases} \dot{p}(t) = Ap(t), & t \neq \tau_k, \\ \Delta p(\tau_k) = Bv(\tau_k), & k \in \mathbb{N}, \end{cases} \tag{45}$$

where $A = \begin{pmatrix} 0 & 1 & 0 & \cdots & 0 \\ 0 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & 1 \\ 0 & 0 & 0 & \cdots & 0 \end{pmatrix}$ and $B = \begin{pmatrix} 0 \\ 0 \\ \vdots \\ 0 \\ 1 \end{pmatrix}$, at each $t = \tau_k$.

From Theorem 1, the linear ICS obtained (45) is controllable. □

Notice the linear ICS (45) is a virtual system that is only useful to design a new linear feedback controls, like for an instance $v(\tau_k) = Kp(\tau_k)$, with $K = (k_1, \ldots, k_n)$ chosen in order to assign a specific set of eigenvalues (see the pole-place problem for linear ICS developed in [6]), or satisfy an optimality criterion.

5. Impulsive HIV dynamics

Several nonlinear models have been developed to describe the dynamics of HIV-1 virus which take into account the kinetics of HIV infection with different cells populations *e.g.* macrophages, CTL cells, latently infected CD4 T cells as well the inclusion the lymphoid compartments in their models [15,14]. However, for the control and parameter estimation based on clinical data purposes, the dynamics of the infection can be modeled by relatively simple ordinary differential equations for the interactions of healthy CD4 + cells (T), infected CD4 + cells (y), free viruses (z) [11,12].

In this paper, the '3D model' (defined by T, y, z) is modified in order to incorporate the interaction of the intake of drugs and its concentration in blood according to the notions of pharmacokinetics and pharmacodynamics described in [17,11]. Consequently, the resulting impulsive model is:

$$\begin{cases} \dot{x}(t) = -\delta x(t) - \beta(x(t) + T_0)z(t), & \\ \dot{y}(t) = \beta(x(t) + T_0)z(t) - \mu y(t), & t \neq \tau_k, \\ \dot{z}(t) = \left(1 - \frac{w(t)}{w(t)+w_{50}}\right)ky(t) - cz(t), & \\ \dot{w}(t) = -Kw(t), & \\ \Delta w(\tau_k) = u(\tau_k), & k \in \mathbb{N}, \end{cases} \tag{46}$$

where healthy CD4 cells $x = T - T_0$ ($T_0 = s/\delta$ is an equilibrium) are produced from the thymus at a constant rate s and die with a half life time equal to $\frac{1}{\delta}$. The healthy cells are infected by the virus at a rate that is proportional to the product of their population and the amount of free virus particles. The proportionality constant β is an indication of the effectiveness of the infection process. The infected CD4 + cells (y) result from the infection of healthy CD4 cells and die at a rate μ. Free virus particles (z) are produced from infected CD4 cells at a rate k and die with a half life time equal to $\frac{1}{c}$.

The problem of drug administration is classically divided into two phases, a so-called pharmacokinetics (PK) phase that is related to dosage, frequency and route of drug administration in the body, and a pharmacodynamics (PD) phase that is related to the concentration of drugs at the site of action to the magnitude of the effect produced (see [11] for more details). Mathematically, these phases are modeled by $\dot{w}(t) = -Kw(t) + u\delta(t - \tau_k)$, and $\eta = \frac{w(t)}{w(t)+w_{50}}$, respectively. The parameter w_{50} represents the concentration of drug that lowers the viral load by 50%, and the parameter η is the efficacy of an anti-HIV treatment (in general a cocktail drugs of RT and P inhibitors). However, only Zidovudine therapies will be considered. Although available pharmacokinetics and pharmacodynamics drug parameters are usually evaluated *in vitro*, the *in vivo* parameters for Zidovudine given in [17] are used in this work.

5.1. Accessibility characterization of HIV dynamics

In this section, the results about accessibility are applied to the impulsive HIV dynamics (46). The impulse relative degree is calculated based on the physical output $h = x + T_0 + y$, and using Theorem 2, it is shown that the model (46) satisfies the accessibility condition.

So, applying the condition **(ii)** of Proposition 1, we get

$$\begin{aligned} \langle dh(x), g(x)\rangle &= \frac{\partial h(x)}{\partial x} g(x) = (1 \quad 1 \quad 0 \quad 0)(0 \quad 0 \quad 0 \quad 1)' = 0, \\ \langle dL_f h(x), g(x)\rangle &= L_g L_f h(x) = (-\delta \quad -\mu \quad 0 \quad 0)(0 \quad 0 \quad 0 \quad 1)' = 0, \\ \langle dL_f^2 h(x), g(x)\rangle &= L_g L_f^2 h(x) = \begin{pmatrix} \delta^2 + (\delta - \mu)\beta z \\ \mu^2 \\ (\delta - \mu)\beta x \\ 0 \end{pmatrix}' \begin{pmatrix} 0 \\ 0 \\ 0 \\ 1 \end{pmatrix} = 0, \\ \langle dL_f^3 h(x), g(x)\rangle &= L_g L_f^3 h(x) = \begin{pmatrix} \frac{\partial L_f^3 h(x)}{\partial x} \\ \frac{\partial L_f^3 h(x)}{\partial y} \\ \frac{\partial L_f^3 h(x)}{\partial z} \\ \frac{\partial L_f^3 h(x)}{\partial w} \end{pmatrix} (0 \quad 0 \quad 0 \quad 1)', \\ \langle dL_f^3 h(x), g(x)\rangle &= -\frac{\beta k(\delta - \mu)(x + T_0)w_{50}y}{(w + w_{50})^2} \neq 0. \end{aligned} \tag{47}$$

From Eq. (47), we can conclude that the impulse relative degree is $d^0(y) = 4$, as a matter of fact $\langle dL_f^3 h(x), g(x)\rangle \neq 0$ for any $y > 0$ and $\delta \neq \mu$, i.e the impulsive input affects the output $h(x) = x + T_0 + y$ after at least the 4-th impulse, therefore $h(x)$

is not an autonomous element of system (46). However, this adds a constraint in the reachable space, which becomes the strictly positive subspace of $\mathbb{R}^4$. Now, from Theorem 2, we obtain

$$\mathrm{ad}_f g = \frac{\partial g}{\partial x} f - \frac{\partial f}{\partial x} g = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} - \begin{pmatrix} 0 \\ 0 \\ \frac{-kw_{50}y}{(w+w_{50})^2} \\ -K \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ \frac{kw_{50}y}{(w+w_{50})^2} \\ K \end{pmatrix},$$

$$\mathrm{ad}_f^2 g = \frac{\partial \mathrm{ad}_f g}{\partial x} f - \frac{\partial f}{\partial x} \mathrm{ad}_f g = \begin{pmatrix} \frac{\beta k w_{50}(x+T_0)y}{(w+w_{50})^2} \\ \frac{-\beta k w_{50}(x+T_0)y}{(w+w_{50})^2} \\ \frac{2kKw_{50}wy}{(w+w_{50})^3} + \frac{kw_{50}((K+c)y)+\dot{y})}{(w+w_{50})^2} \\ K^2 \end{pmatrix},$$

$$\mathrm{ad}_f^3 g = \frac{\partial \mathrm{ad}_f^2 g}{\partial x} f - \frac{\partial f}{\partial x} \mathrm{ad}_f^2 g = \begin{pmatrix} a_1(x) \\ -a_1(x) \\ a_3(x) \\ K^3 \end{pmatrix},$$

$$a_1(x) = \frac{\beta k w_{50}}{(w+w_{50})^2}\{(\delta T_0 y + c(T_0+x)y + 2\dot{y})(w+w_{50}) + (T_0+x) + K(5w+w_{50})y\},$$

$$a_3(x) = \frac{-6kK^2w^2w_{50}y}{(w+w_{50})^4} + \frac{\beta k^2(T_0+x)w_{50}^2 y}{(w+w_{50})^3} + \frac{kw_{50}}{(w+w_{50})^2}\{\beta\dot{x}z + (c^2+cK+K^2)y$$
$$+ (2c+K-\mu)\dot{y} + \beta(T_0+x)\dot{z}\}, \det\left(g, \mathrm{ad}_f g, \mathrm{ad}_f^2 g, \mathrm{ad}_f^3 g\right) = -\frac{\beta^2 k^3 w_{50}^3(\delta-\mu)(T_0+x)^2 y^3}{(w+w_{50})^6}. \quad (48)$$

Eq. (48) shows that the dimension of $\dim\overline{\{g, \mathrm{ad}_f g, \mathrm{ad}_f^2 g, \mathrm{ad}_f^3 g\}}$ is equal to 4 for any $y > 0$ and $\delta \neq \mu$. As a result, the subspace $\mathbb{R}_+^4$ is accessible.

5.2. Impulsive control of HIV dynamics

The aims of a standard therapy for a patient of HIV normally are [20]:

- The decrease of the viral load (z) by 90% of its initial value within 2–8 weeks of treatment.
- The drop of the viral load under the undetectability level (50 copies/ml) in six months of treatment maximum.
- The increase of the CD4 cells from its initial value to a neighborhood of its healthy equilibrium value $T_0 = \frac{s}{\delta}$.

The parameters of the impulsive model of HIV dynamics and its initial conditions used in simulations are the nominal values described in [11,12,17] and they can be seen in Table 1.

Table 1
Parameters and initial conditions used for simulations.

Parameter	Nominal value
s (*cells* mm^{-3} *day*$^{-1}$)	9
δ (*day*$^{-1}$)	0.009
β (ml*copies*$^{-1}$ *day*$^{-1}$))	4×10^{-6}
μ (*day*$^{-1}$)	0.3
k (*copies cells*$^{-1}$ mm^{-3} ml^{-1} *day*$^{-1}$)	80
c (*day*$^{-1}$)	0.6
K (*day*$^{-1}$)	8.4
X_{50} (mg)	89.6
Initial condition	Value
$T(0)$ (*cells* mm^{-3})	750
$y(0)$ (*cells* mm^{-3})	34
$z(0)$ (*copies* ml^{-1})	2800
$w(0)$ (mg)	350

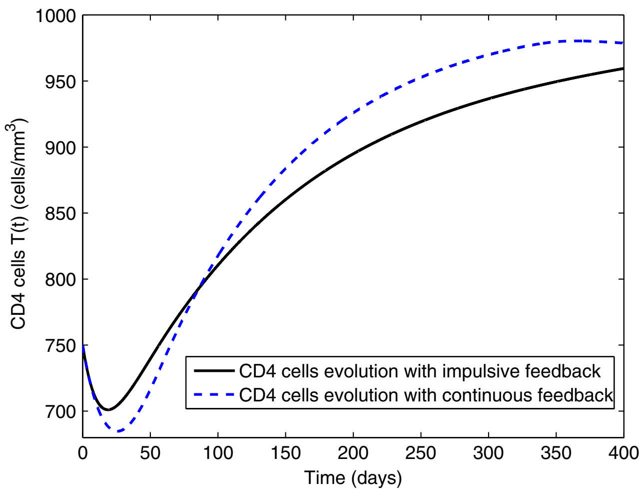

Fig. 2. Evolution of CD4 cells for the impulsive and continuous feedback control.

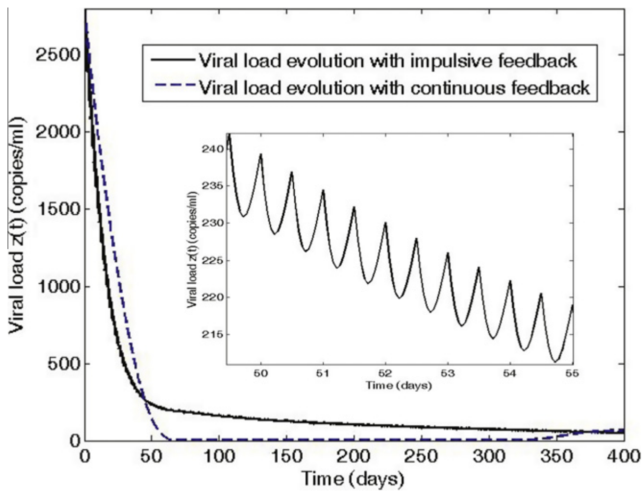

Fig. 3. Viral load behavior under impulsive and continuous feedback control strategies.

The conditions **(i)** and **(ii)** of Theorem 3 are fulfilled by the impulsive model of HIV dynamics (46) as it is shown in Subsection 5.1, then it is possible to apply the impulsive control strategy described in Section 4. Next, the diffeomorphism $\Phi(x)$ and the impulsive state feedback $u(\tau_k)$ are computed for HIV dynamics, namely

$$z_1(t) = h(x) = x + T_0 + y, \tag{49}$$

$$z_2(t) = L_f h(x) = -\delta x - \mu y, \tag{50}$$

$$z_3(t) = L_f^2 h(x) = \delta^2 x + (\delta - \mu)\beta(x + T_0)z + \mu^2 y, \tag{51}$$

$$z_4(t) = L_f^3 h(x) = \beta(\delta - \mu)(x + T_0)\dot{z} + (\delta^2 + \beta(\delta - \mu)z)\dot{x} + \mu^2 \dot{y}, \tag{52}$$

and

$$a(x) = L_g L_f^3 h(x) = -\frac{\beta k w_{50}(\delta - \mu)(x + T_0)y}{(w + w_{50})^2}, \tag{53}$$

$$b(x) = L_f^4 h(x) = \frac{\beta k(\delta - \mu)(x + T0)w_{50}(\dot{y}(w + X_{50}) + Kwy)}{(w + w_{50})^2} + -\mu^3\dot{y} + \dot{x}\big(\beta\mu^2 z + \beta(\delta - \mu)\dot{z} - (\delta + \beta z)(\delta^2 + \beta(\delta - \mu)z)\big)$$
$$+ \dot{z}(-\beta(\delta - \mu)(-\dot{x} + (x + T_0)(c + \delta + \mu + \beta z))). \tag{54}$$

For comparison purposes a continuous feedback control based on exact linearization [11] was applied using the '3D model' of HIV dynamics. In Figs. 2,3, the time evolution of the CD4 cells T and viral load z is depicted for both impulsive and continuous feedback therapies after suitable pole placement in both cases. Clearly, the clinical conditions of

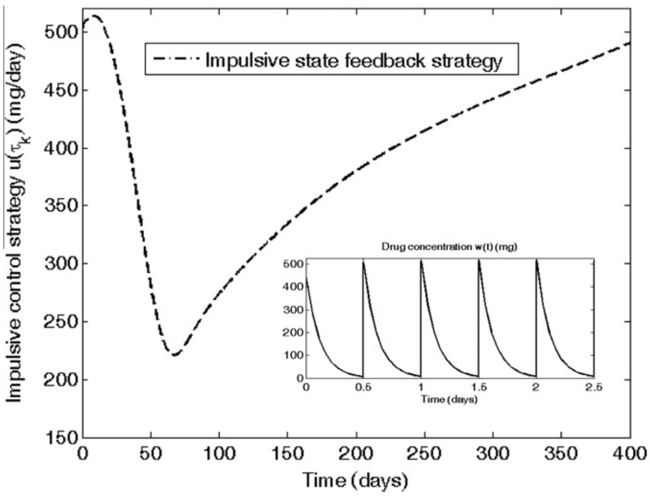

Fig. 4. Impulsive feedback control $u(\tau_k)$ and drug concentration $w(t)$.

an anti-HIV therapy imposed before are fulfilled by both strategies, but the 3D model is far from being implemented because of its lack of pharmacokinetics and pharmacodynamics knowledge. In the graphic inside Fig. 3, we can observe the influence on the impulsive input exerted in the states. In spite that the viral load z remains—continuous, it is not differentiable.

In Fig. 4, the impulsive state feedback trajectory and the evolution of drug concentration w are plotted. The medication ($u(\tau_k)$ mg) is an intake twice per day. The sudden jumps in $w(t)$ due to the impulsive input at each τ_k can be seen in the graphic inside this figure. One major advantage of this control scheme is its ability to minimize the viral load by the means of a time-varying dosage. This means that no full dosage is needed all the time.

6. Conclusions and perspectives

In this paper, the notions of impulse relative degree and accessibility for nonlinear ICS were introduced and explained in detail. Besides, it was shown that at each control instant $t = \tau_k$ there is a diffeomorphism depending on the states and an impulsive feedback so that the nonlinear ICS can be transformed into a linear one. The theoretic results were applied to the impulsive model of HIV dynamics.

The accessibility was fully characterized based on the physical interpretation of 'the number of impulses required' suggested by [19] in linear ICS. Thus, the impulse relative degree $d^0(y)$ is defined to represent this interpretation, and Proposition 1 is proposed as a simple way to compute it. After that, Lemma 1 and Lemma 2 are stated in order to establish Theorem 2 about accessibility for nonlinear ICS.

Sufficient and necessary conditions were provided to guarantee that at each control instant, a nonlinear ICS system can be transformed into a linear one by means of a suitable impulsive feedback control law. This result is summarized in Theorem 3, and allows the design of a realistic dosage regimen directly in mg of drug which drives the system near the healthy equilibrium state. This control approach is novel and represents the real situation of the control of HIV infection in a better way.

The analysis and control of nonlinear ICS remains being an open field of study. When describing basic properties of control theory such as controllability/accessibility, observability, among others for nonlinear ICS, the lack of more theoretic results is evident. About observability in ICS, there are questions such as the frequency of impulses required to identify parameters and to estimate states need to be studied. This subject will be explore in future works.

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