Carleman discretization of impulsive systems: application to the optimal control problem of anti-angiogenic tumor therapies

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Abstract— **Impulsive systems model continuous-time frameworks with control actions occurring at discrete time instants. Among the others, such models assume relevance in medical situations, where the physical system under control evolves continuously in time, whilst the control therapy is instantaneously administered, e.g. by means of intra-venous injections. This note proposes a discretization algorithm for an impulsive system, whose methods relies on the Carleman embedding techinique. The discretization times are given by the impulsive control action and do not require to have a fixed discretization period. On the ground of the resulting discrete-time system (which can be computed with arbitrary level of accuracy) we propose an optimal control algorithm on a finite horizon. Simulations are carried out on a model exploited for anti-angiogenic tumor therapies and show the effectiveness of the theoretical results.**

I. Introduction

Impulsive systems are continuous-time systems characterized by instantaneous variations of the state at given time instants [?], [?]. These systems have been exploited in many different frameworks, such as mechanical systems [?], sampled-data systems [?], chaotic secure communication systems [?] and biochemistry [?]. They have recently gained an increasing interest in physiologically-based pharmacokinetic models, where the instantaneous jumps model the kind of drug delivery in the proper compartment (subcutaneous or intravenous injections, oral ingestion, etc.) [?].

Several researchers have studied the control problem of impulsive systems by means of Lyapunov functions [?], [?], [?], [?], [?]. In [?] some sufficient conditions for the impulsive control of a class of nonlinear systems are derived by using the results in [?]. Less conservative conditions have been derived in [?], [?] by using similar approaches.

Necessary conditions for the existence of a solution of the optimal control problem for systems with impulsive control as well as the characterization of these solutions has been studied, among the others, by [?], [?], [?], [?], [?], [?], [?], [?].

Differently from these approaches, in this paper we aim at reducing the optimal control problem of an impulsive system to the corresponding problem for discrete-time systems by means of a discretization procedure for the continuous part of the impulsive system. The discretization times are given by the impulsive control action and do not require to have a fixed

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discretization period. The resulting discrete-time system is, then, exploited to design an optimal control strategy on a finite horizon. To the aim of discretization, the Carleman embedding technique is exploited [?]. Based on the Taylor expansion of the nonlinear map of the system, the algorithm provides the exact solution to the discretization problem, whose implementation is based on a suitable truncation of the involved series expansion. The Carleman technique is exploited as well to compute the gradient (with respect to the state variables) of the nonlinear map associated to the discretized system, which is required in the computation of the optimal control. Though the Carleman technique relies in the embedding of the original system into an infinite-dimensional one, each term of the series can be computed from a finite number of block matrices, thus allowing to achieve an arbitrary chosen level of accuracy.

The second part of the note is dedicated to carry out simulations of the proposed optimal control strategy for an anti-angiogenic tumor therapy. The reference model for tumor growth is [?], already exploited in the literature to validate open- and closed-loop control laws [?], [?], [?]. Coherently with the provided methodology, crucial parameters to validate the proposed control strategy are the interval between any two impulses of drug administration and the order of truncation of the involved Taylor series. Numerical results show the effectiveness of the proposed algorithm with respect to three different targets such as the closeness to a desired reference level of the tumor volume, the total and the average daily amount of the delivered drug.

A. Notation

The symbol $\otimes$ denotes the Kronecker product. $M^{[i]}$ is the i-th Kronecker power of the matrix M, recursively defined by $M^{[i]} = M \otimes M^{[i-1]}$ and $M^{[0]} = 1$. Given $f \in C^\infty(\mathbb{R}^a; \mathbb{R}^b)$, and $x_1, \ldots, x_c$, $c \leq a$, some of the variables in f, $\nabla_x \otimes f$ is the function $\mathbb{R}^a \to \mathbb{R}^{b \times c}$ defined by $[\partial f/\partial x_1 \ldots \partial f/\partial x_c]$. $\nabla_x^{[i]} \otimes f$ denotes the same operation repeated i times and it is a function $\mathbb{R}^a \to \mathbb{R}^{b \times c^i}$.

II. Discretization of impulsive systems

Consider a finite set of time instants $\mathcal{T} = \{\tau_k \geq 0, \ \tau_{k+1} > \tau_k, \ k = 0, 1, \ldots, N\}$ and an impulsive differential system [?], with impulses occurring at times $\tau_k \in \mathcal{T}$, $k \in \mathcal{I} = \{1, \ldots, N\}$, defined by

$$\dot{z}(t) = f(z(t)), \qquad t \in [\tau_k, \tau_{k+1}), \quad k \in \mathcal{I}, \quad (1)$$

$$z(\tau_k^+) = z(\tau_k^-) + Bv_k \qquad (2)$$

where $z(t) \in \mathbb{R}^n$, $v_k \in \mathbb{R}^p$ and $f : \mathbb{R}^n \to \mathbb{R}^n$ is an analytic map. Eq.(**??**) holds also in $t \in [\tau_0, \tau_1)$, with the initial condition $z(\tau_0) = z_0$. In the sequel we will denote with $\delta_k = \tau_{k+1} - \tau_k$ intervals between any two impulses.

Let $x_k = z(\tau_k^+)$ and $u_k = v_{k+1}$. System (**??**)–(**??**) can be written at the discrete times τ_k as

$$x_{k+1} = x_k + \int_{\tau_k}^{\tau_{k+1}} f(z(t))dt + Bu_k. \tag{3}$$

In the time interval $[\tau_k, \tau_{k+1})$, system (**??**) is autonomous with initial condition x_k. We can therefore represent the integral in (**??**) as a function $F_k(x_k)$. The analytical computation of $F_k(x_k)$ may be hard or even not possible Therefore we will use the Carleman discretization approach described in [**?**] to obtain the series expansion of $F_k(x_k)$. We briefly summarize this approach in order to derive some further properties of (**??**).

III. Carleman discretization of autonomous systems

Let $\zeta_k(t) : [0, \delta_k] \to \mathbb{R}^n$ be defined as

$$\zeta_k(t) = z(\tau_k + t) - x_k = \int_{\tau_k}^{\tau_k + t} f(z(s))\, ds. \tag{4}$$

Consequently,

$$\zeta_k(0) = 0, \quad \zeta_k(\delta_k) = F_k(x_k), \quad \dot{\zeta}_k(t) = f(z(\tau_k+t)). \tag{5}$$

Since f is analytic, we can write its Taylor expansion in the neighborhood of x_k as

$$\dot{\zeta}_k(t) = \sum_{j=0}^{\infty} \frac{(\nabla_z^{[j]} \otimes f)(x_k)}{j!} \zeta_k^{[j]}(t) = \sum_{j=0}^{\infty} A_j^1(x_k) \zeta_k^{[j]}(t), \tag{6}$$

where $A_0^1 = f$, A_1^1 is the standard Jacobian of f, and, for $j > 1$, $A_j^1 : \mathbb{R}^n \to \mathbb{R}^{n \times n^j}$ depends on the higher-order Jacobian, $A_j^1(x) = (\nabla_z^{[j]} \otimes f)(x)/j!$.

The Carleman linearization procedure consists in extending the system (**??**) with the time derivatives of the Kronecker powers $\zeta_k^{[i]}(t)$ expressed as

$$\frac{d}{dt}\zeta_k^{[i]}(t) = \sum_{j=0}^{\infty} A_j^i(x_k)\zeta_k^{[j+i-1]}(t), \tag{7}$$

where the coefficients $A_j^i(x) \in \mathbb{R}^{n^i \times n^{j+i-1}}$ can be computed from the $A_j^1(x)$ through the recursive expression

$$A_j^i = A_j^1 \otimes I_n^{[i-1]} + I_n \otimes A_j^{i-1}, \tag{8}$$

and I_n is the identity matrix of dimension n (see [**?**] for the details).

The infinite dimensional linear system associated to system (**??**) in $[\tau_k, \tau_{k+1}]$ defines the evolution of the *extended state* $\Phi_k(t) = [\Phi_{k1}^T(t), \Phi_{k2}^T(t), \dots]^T$, where $\Phi_{ki}(t) = \zeta_k^{[i]}(t)$. From (**??**) we have

$$\dot{\Phi}_k(t) = L(x_k) + M(x_k)\Phi_k(t), \quad t \in [0, \delta_k),$$
$$\Phi(0) = [0_{n \times 1}^T, 0_{n^2 \times 1}^T, \dots]^T. \tag{9}$$

where the infinite dimensional matrices $L(x_k)$ and $M(x_k)$ have the following block structure

$$L = \begin{bmatrix} A_0^1 \\ 0_{n^2 \times 1} \\ 0_{n^3 \times 1} \\ \dots \end{bmatrix}, \quad M = \begin{bmatrix} A_1^1 & A_2^1 & A_3^1 & \dots \\ A_0^2 & A_1^2 & A_2^2 & \dots \\ 0_{n^3 \times 1} & A_0^3 & A_1^3 & \dots \\ 0_{n^4 \times 1} & 0_{n^3 \times n} & A_0^4 & \dots \\ \dots & \dots & \dots & \dots \end{bmatrix}. \tag{10}$$

The solution of (**??**) for $t \in [0, \delta_k]$ can be written as

$$\Phi_k(t) = \sum_{j=0}^{\infty} P_j(x_k) \frac{t^{j+1}}{(j+1)!}, \tag{11}$$

with $P_j(x_k) = M^j(x_k)L(x_k)$. Notice that $P_0(x_k) = L(x_k)$ and $P_{j+1}(x_k) = M(x_k)P_j(x_k)$. We are interested in

$$F_k(x_k) = \zeta_k(\delta_k) = \Phi_{k1}(\delta_k) = \Pi_n \Phi_k(\delta_k), \tag{12}$$

where $\Pi_n = [I_n \ 0_{n \times n^2} \ \dots]$ is a linear operator that selects the first n components of a vector. Then, (**??**) yields

$$F_k(x_k) = \sum_{j=0}^{\infty} \Pi_n P_j(x_k) \frac{\delta_k^{j+1}}{(j+1)!} = \sum_{j=0}^{\infty} P_j^1(x_k) \frac{\delta_k^{j+1}}{(j+1)!}, \tag{13}$$

where $P_j^1(x_k)$ are the first n elements of $P_j(x_k)$ and $P_0^1(x_k) = A_0^1(x_k) = f(x_k)$. Since in the infinite dimensional vector $P_j(x_k)$ only the first $\sum_{i=1}^{j+1} n^i$ elements are non-null, $P_j^1(x_k) \in \mathbb{R}^n$ can be computed from a finite number of blocks of M and L.

Notice that (**??**) corresponds to the Taylor series of the solution of (**??**) in $[\tau_k, \tau_k + \delta_k]$ with initial point x_k. Due to the uniqueness of the Taylor series of a function, (**??**) implies that

$$P_j^1(x_k) = P_j^1(z(\tau_k)) = (\nabla_t^{[j+1]} \otimes z)(\tau_k). \tag{14}$$

In order to compute the coefficients $P_j^1(x_k)$ of the series expansion in (**??**), divide P_j into blocks P_j^i of size $n^i \times 1$, $i \geq 1$ as $P_j^T = [P_j^{1T}, P_j^{2T}, \dots]$ where, as stated above, only the first $j+1$ blocks are non-null. When $j = 0$, $P_0^1 = A_0^1 = f$ and $P_0^i = 0$, $i \geq 2$. Then, because of property $P_{j+1} = MP_j$, the following recursive equation is readily achieved:

$$P_j^1 = \sum_{l=1}^{j} A_l^1 P_{j-1}^l \tag{15}$$

Eq.(**??**) can indeed be generalized as follows:

$$P_j^i = \sum_{l=\max\{1, i-1\}}^{j} A_{l-i+1}^i P_{j-1}^l \tag{16}$$

(**??**) will be exploited in the next section for further computations involved in the optimal control algorithm related to the discretization of the impulsive system.

IV. ADDITIONAL PROPERTIES OF CARLEMAN DISCRETIZATION

By exploiting expression (**??**), system (**??**) can be written as:

$$x_{k+1} = \Psi_k(x_k, u_k) = x_k + \sum_{j=0}^{\infty} P_j^1(x_k) \frac{\delta_k^{j+1}}{(j+1)!} + Bu_k. \tag{17}$$

In view of the application to optimal control, is of interest to compute the derivatives of Ψ_k with respect to u_k and x_k. The former is immediately obtained as $\nabla_u \otimes \Psi_k = B$. The latter can be computed as

$$\nabla_x \otimes \Psi_k = I_n + \sum_{j=0}^{\infty} (\nabla_x \otimes P_j^1) \frac{\delta_k^{j+1}}{(j+1)!}. \tag{18}$$

Notice that, due to the particular structure of the impulsive system (**??**)–(**??**), $\nabla_u \otimes \Psi_k$ does not depends on x_k (it is a constant) and $\nabla_x \otimes \Psi_k$ does not depend on u_k.

It is useful for the applications to have $\nabla_x \otimes \Psi_k$ in (**??**) expressed as a recursive function of the blocks A_j^1.

To this end, the following preliminary Lemma is required.

Lemma 1: For any $j \geq 0$ and $i > 0$ it is:

$$\nabla_x \otimes A_j^i = (j+1)\left(A_{j+1}^1 \otimes I_n^{[i-1]}\right) + [I_n \otimes \mathcal{A}_1, \dots I_n \otimes \mathcal{A}_n] \tag{19}$$

with

$$\mathcal{A}_l = \nabla_{x_l} \otimes A_j^{i-1} = \frac{\partial A_j^{i-1}}{\partial x_l} \tag{20}$$

and x_l is the l-th component of vector x. In case of $i = 1$:

$$\nabla_x \otimes A_j^1 = (j+1)A_{j+1}^1. \tag{21}$$

Proof. For $i = 1$ the result descends from:

$$\nabla_x \otimes A_j^1 = \left.\frac{\nabla_z^{[j+1]} \otimes f}{j!}\right|_{z=x} = (j+1)A_{j+1}^1. \tag{22}$$

For $k > 1$ (**??**) is obtained from (**??**) together with the following property of the nabla operator for any matrix function $A : \mathbb{R}^n \to \mathbb{R}^{m \times p}$ and any matrix B,

$$\nabla_x \otimes \left(A(x) \otimes B\right) = \left(\nabla_x \otimes A(x)\right) \otimes B. \tag{23}$$

Lemma 2: For $j \geq 1$, then for $i = 1$ it is

$$\nabla_x \otimes P_j^1 = \sum_{l=1}^{j} \left[(l+1)A_{l+1}^1(I_n \otimes P_{j-1}^l) + A_l^1(\nabla_x \otimes P_{j-1}^l)\right] \tag{24}$$

$$\tag{25}$$

and for $i > 1$ it is ...

$$\nabla_x \otimes P_j^i = \sum_{l=0}^{j-i+1} \left[(\nabla \otimes A_l^i)(I_n \otimes P_{j-1}^{l+i-1}) + A_l^i(\nabla_x \otimes P_{j-1}^{l+i-1})\right] \tag{26}$$

Proof. The thesis follows from (**??**) and (**??**) together with the following property of the nabla operator for any matrix functions $A : \mathbb{R}^n \to \mathbb{R}^{m \times p}$, $D : \mathbb{R}^n \to \mathbb{R}^{p \times q}$,

$$\nabla_x \otimes \left(A(x) \cdot D(x)\right) = \left(\nabla_x \otimes A(x)\right)\left(I_n \otimes D(x)\right) + A(x) \cdot \left(\nabla_x \otimes D(x)\right). \tag{27}$$

Remark 1: Since $\nabla_x \otimes P_0^1 = \nabla_x \otimes f = A_1^1$ is the Jacobian, Lemma **??** allows to recursively compute all the remaining $(\nabla_x \otimes P_j^1)$ in (**??**) as a function of the matrices A_j^1.

V. OPTIMAL CONTROL PROBLEM

Consider the impulsive system (**??**)-(**??**) and its discretized version:

$$x_{k+1} = \Psi_k(x_k, u_k), \quad x_0 = z_0, \quad k = 0, 1, \dots, N-1 \tag{28}$$

where

$$\Psi_k(x_k, u_k) = x_k + F_k(x_k) + Bu_k \tag{29}$$

and $F_k(x_k)$ can be written according to the Carleman discretization as in (**??**) with P_j^1 recursively computed according to (**??**).

In view to the application to the control of therapies, we formulate a finite horizon optimal control with respect to the input and the final state. The extension to more general situations can be accomplished by using the same technique. Let N be the time horizon for the control problem, x_r be a reference final value of the state, $\mathbf{x}$ denote the sequence of states $x_1, \dots, x_N$, $\mathbf{u}$ be the sequence of inputs $u_0, \dots, u_{N-1}$. Recall that $u_k = v_{k+1}$, so that control action occurs from time instant t_1 up to the final time instant t_N.

The optimal control problem is to minimize the quadratic index

$$J(x_N, \mathbf{u}) = (x_N - x_r)^T Q_N (x_N - x_r) + \sum_{k=0}^{N-1} u_k^T R_k u_k \tag{30}$$

where $Q_N \geq 0$, $R_k > 0$, are weight matrices. The Lagrangian associated to the cost function is:

$$\mathcal{L}(\mathbf{x}, \lambda, \mathbf{u}) = J(x_N, \mathbf{u}) + \sum_{k=0}^{N-1} \lambda_{k+1}^T \left(\Psi_k(x_k, u_k) - x_{k+1}\right) \tag{31}$$

where λ is the sequence of multipliers $\lambda_1, \dots, \lambda_N$, $\lambda_k \in \mathbb{R}^n$. Let $\mathcal{I}_0 = [0, \dots, N-1]$ and $\mathcal{I}_1 = [1, \dots, N-1]$. The following constraints are obtained from (**??**)

$$k \in I_0 : \nabla_{u_k} \otimes \mathcal{L} = 2u_k^T R_k + \lambda_{k+1}^T B = 0, \tag{32}$$

$$k \in I_0 : \nabla_{\lambda_k} \otimes \mathcal{L} = \Psi_k(x_k, u_k) - x_{k+1} = 0, \tag{33}$$

$$k \in I_1 : \nabla_{x_k} \otimes \mathcal{L} = \lambda_{k+1}^T \left(\nabla_x \otimes \Psi_k(x_k, u_k)\right) - \lambda_k^T = 0, \tag{34}$$

$$\nabla_{x_N} \otimes \mathcal{L} = 2(x_N - x_r)^T Q_N - \lambda_N^T = 0. \tag{35}$$

Eq.(**??**) allows to write the control law as a function of λ:

$$u_k = \frac{1}{2} R_k^{-1} B^T \lambda_{k+1} \tag{36}$$

and eqs.(**??**)–(**??**) are a system of $2nN$ nonlinear equations with $\mathbf{x}$ and λ as unknowns. Following the Carleman discretization procedure the functions $\Psi_k(x_k, u_k)$ and $\nabla_x \otimes \Psi_k(x_k, u_k)$ that are needed for the numerical solution of the problem can be computed as in (**??**) and (**??**), by means of Lemma **??**.

A. Receding horizon approach

As it usually happens in nonlinear optimal control problems, the forward/backward expression of (**??**)–(**??**) prevents to have recursive analytical solution like in the linear case. As a matter of fact, numerical solutions are sought. In practice, a compromise to obtain an approximate solution to (**??**)–(**??**) with a reasonable computational effort is to resort to a *receding horizon* approach in which a solution is computed on the first $N' < N$ steps, but only the first input of the computed solution is applied before iterating the procedure on the new state. This is well suited to a discretization scheme, that may introduce errors on a large time horizon but is arbitrarily precise on a shorter one.

B. Backward discretization

Another computational scheme exploits the possibility of inverting the system evolution, provided by the Carleman discretization method. From (**??**) and (**??**) it is clear that the evolution of the autonomous part of the system trajectory can be discretized backward by using as initial point $x_{k+1} - Bu_k$. The "final" value x_k can be expressed as

$$
\begin{aligned}
x_k &= x_{k+1} - Bu_k + \sum_{j=0}^{\infty} P_j^1(x_{k+1} - Bu_k)\frac{(-\delta_k)^{j+1}}{(j+1)!} \\
&= x_{k+1} - Bu_k + F_k^{(-)}(x_{k+1} - Bu_k).
\end{aligned} \tag{37}
$$

The system of equations for the solution of the optimal control problem becomes then

$$
x_k = x_{k+1} - Bu_k + F_k^{(-)}(x_{k+1} - Bu_k), \tag{38}
$$
$$
\lambda_k = \left(\nabla_x \otimes \Psi_k(x_k, u_k)\right)^T \lambda_{k+1}, \tag{39}
$$
$$
\lambda_N = 2Q_N(x_N - x_r). \tag{40}
$$

where u_k is obtained from (**??**). Notice that the variables in (**??**)–(**??**) can now be computed starting from x_N, since (**??**) specifies λ_N, (**??**) allows to compute x_{N-1}, (**??**) provides λ_{N-1} and so on. Eq. (**??**) for $k = 0$ is the constraint that the initial value of the sequence provides the parameter x_0. Therefore, (**??**)–(**??**) is a system of equations in the unknown x_N only.

VI. Application to anti-angiogenic tumor therapies

As mentioned before, impulsive control systems arise quite naturally when modeling therapies, due to the different time scales of therapy administration (the control) and of the patient response to it (the controlled system). We chose to apply the proposed algorithm to a model of tumor growth in presence of anti-angiogenic treatment [**?**]. The aim of the treatment is to control the tumor size by reducing the vascular network on which it depends. In [**?**], Hahnfeld and coworkers, in addition to introducing the concept of vascular carrying capacity, propose a comparison between the model and experimental data concerning anti-angiogenically treated and untreated Lewis lung tumors in mice.

The Hahnfeldt model is a nonlinear model accounting for angiogenic stimulation and inhibition. It is composed by three ordinary differential equations which describe the evolution of the tumor volume (x_1, mm^3), the carrying capacity (x_2, mm^3) and the drug amount of the administered angiogenic inhibitor (x_3, mg/kg).

$$
\begin{aligned}
\dot{x}_1(t) &= -\lambda x_1(t) \ln\left(\frac{x_1(t)}{x_2(t)}\right) \\
\dot{x}_2(t) &= bx_1(t) - (\mu + dx_1(t)^{2/3})x_2(t) - cx_2(t)x_3(t) \\
\dot{x}_3(t) &= -\eta x_3(t) + u(t)
\end{aligned} \tag{41}
$$

In particular, the parameters in (**??**) describe: the carcinoma growth rate λ, the vascular birth rate b, the endothelial cell death d, the spontaneous vascular inactivation rate μ, the sensitivity to the drug c and the diffusion rate into serum η. The values are referred to an estimation based on experimental data of Lewis lung carcinoma implanted in C57BL/6 mice under angiostatin drug and are reported in Table I. Note that, according to the original model, μ was set to 0 because this parameter was found to be negligible, i.e., vascular inactivation rate does not play a major role in this system.

TABLE I
ANGIOSTATIN MODEL PARAMETERS

λ	b	d	c	η
day^{-1}	day^{-1}	day^{-1} mm^{-2}	day^{-1} (mg/kg)$^{-1}$	day^{-1}
0.192	5.85	0.00873	0.15	0.38

The drug administration is modeled as an impulsive process taking place at uniform intervals. The choice of uniform administration intervals is not mandatory, the algorithm can use any sequence of such intervals as remarked in Section **??**.

The first step of the method is to represent the continuous-time system (**??**) with impulsive input as the discrete-time system (**??**)–(**??**) where, in our case, $B = [0, 0, 1]^T$. This step requires to derive the series expansion of $F_k(x_k)$ in (**??**) and, in particular, to calculate the elements $P_j^1(x_k)$ in (**??**). Table **??** shows the terms P_j^1 for $j \in \{1, 2, 3, 4\}$, whose computation is reported in Appendix. Of course Table II is general and holds for any system undergoing Carleman discretization. Obviously a larger number of terms in (**??**) guarantees a better approximation of $F_k(x_k)$.

After representing the controlled system (**??**) as a discrete-time system (the notation adopted for component i of the discretized state vector at time τ_k is $(x_k)_i$), the optimal control problem can be formulated in order to compute the optimal control law. Here the aim is to reduce the tumor size to a target dimension in a fixed time interval while minimizing the total amount of anti-angiogenic drug. An additional constraint is that each administration (the control impulse) should not exceed a given threshold.

TABLE II

TAYLOR SERIE COEFFICIENTS

j	$P_j^1(x_k)$
0	$A_0^1 = f(x)$
1	$A_1^1 A_0^1 = J(x)f(x)$
2	$\left(A_1^1\right)^2 A_0^1 + 2A_2^1 \left(A_0^1\right)^{[2]}$
3	$\left(A_1^1\right)^3 A_0^1 + \left(2A_1^1 A_2^1 + 3A_2^1 A_1^2\right)\left(A_0^1\right)^{[2]} + 6A_3^1 \left(A_0^1\right)^{[3]}$

In our case we set the initial condition to $x_0 = [200,\ 630,\ 0]^T$, in order to compare the outcome with the experimental outcomes of the therapies described in [?]. For the same reason, the reference final value of the tumor volume is $x_r = 100$ mm^3 and the simulation total time $T = 13$ days.

The goal is to find the optimal control that satisfy the following targets:

1) to bring the final value of the tumor volume within 15% of variation of the reference level (x_r):

$$(x_N)_1 \in [0.85,\ 1.15] \cdot x_r$$

2) to keep the average daily amount of the administered drug smaller than 20 mg/kg/day. If δ is the interval between any two drug administrations, $\nu = \lceil 1/\delta \rceil$ is the maximum number of daily administrations and the constrained can be expressed as $U_i < 25$ mg/kg/day for $i = 1, \ldots, T$, where

$$U_i = \sum_{k=(i-1)\nu+1}^{i\nu} u_{k-1}$$

3) to minimize the total amount U_T of administered drug,

$$U_T = \sum_{k=0}^{N} u_k = \sum_{i=1}^{T} U_i, \quad N = \lfloor T/\delta \rfloor \quad (42)$$

The problem is formulated as the minimization of the index (??) with $Q =$ diag[5, 3.5, 0] and $R_k = 250$.

The algorithm was tested in a wide range of situations by varying:

- the interval between two inputs $\delta = [0.1,\ 0.3]$ day, and the corresponding discrete-time horizon for the control problem $N = \lfloor T/\delta \rfloor$,
- the *receding horizon* $N' = [4,\ 10]$ (as described in ??),
- the Taylor order $j_{\max} \in \{4, 5, 6\}$.

In these scenarios the method shows excellent results both in terms of the final tumor volume and minimization of the administered drug. The algorithm is sensitive to the choice of the parameters. A smaller δ as well as a higher order of the Carleman approximation leads to a more precise discretization and consequently to a better control performance. For a given N, a decrease of J is obtained with a larger N' at the expense of a larger computational time.

Figs. ??–?? illustrate the results obtained with $\delta = 0.25$ day, $N = 52$, $N' = 10$ and $j_{\max} = 4$.

Fig. ?? shows the evolution of the continuous state (??) using the input calculated by the algorithm and in particular that the tumor volume arrives to the desired value, $(x_N)_1 = 111, 79$ with respect to the reference value $x_r = 100$, while in Fig. ?? the comparison between the continuous state and the model discretized with Carleman is reported.
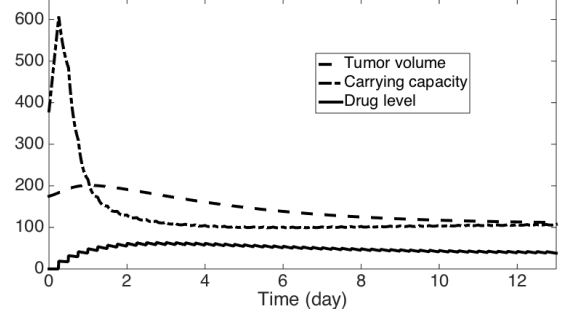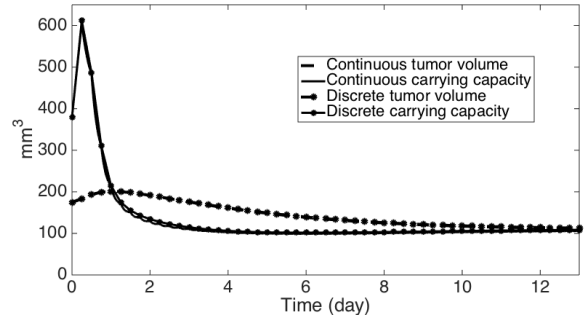

Fig. 1. Continuous Hahnfeldt model evolution

Fig. 2. Comparison between continuous and discrete Hahnfeldt model evolution

Figure ?? shows the input computed by the optimization algorithm u_k and the daily amount U_i.

VII. CONCLUSION

APPENDIX

In this section the explicit expression of the first (and only) nonzero block of $L(x_k)$ and of the blocks A_j^1, $j = 1, 2, 3, 4$ of matrix $M(x_k)$ (see (??)), required to compute Taylor series coefficients reported in Table II are reported.

$$A_0^1 = \begin{bmatrix} -\lambda x_1 \ln\left(\frac{x_1}{x_2}\right) \\ bx_1 - dx_1^{2/3} x_2 - cx_2 x_3 \\ -\eta x_3 \end{bmatrix}$$

$$A_1^1 = \begin{bmatrix} -\lambda(1+\ln(\frac{x_1}{x_2})) & \frac{\lambda x_1}{x_2} & 0 \\ b - \frac{2dx_2}{3x_1^{(1/3)}} & -cx_3 - dx_1^{(2/3)} & -cx_2 \\ 0 & 0 & -\eta \end{bmatrix}$$

$$A_2^1 = \begin{bmatrix} \frac{-\lambda}{x_1} & \frac{\lambda}{x_2} & 0 & \frac{\lambda}{x_2} & \frac{-\lambda x_1}{x_2^2} & 0 & 0 & 0 & 0 \\ \frac{2dx_2}{9x_1^{(4/3)}} & \frac{-2d}{3x_1^{(1/3)}} & 0 & \frac{-2d}{3x_1^{(1/3)}} & 0 & -c & 0 & -c & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$
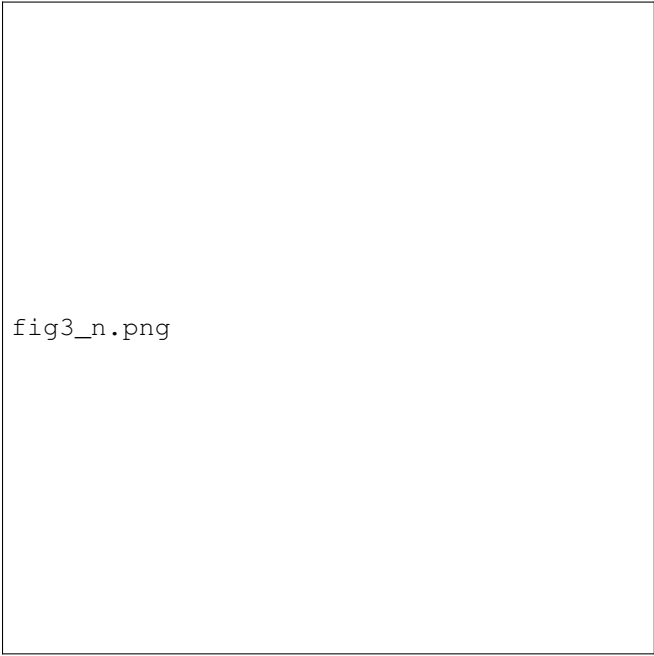
Fig. 3. Optimal control input

In particular, according (**??**), the block-element $M_{2,1}$ is calculated from previous terms as

$$A_0^2 = A_0^1 \otimes I_3 + I_3 \otimes A_0^1$$

and its explicit form is

$$A_0^2 = \begin{bmatrix} 2A_0^1(1) & 0 & 0 \\ A_0^1(2) & A_0^1(1) & 0 \\ A_0^1(3) & 0 & A_0^1(1) \\ A_0^1(2) & A_0^1(1) & 0 \\ 0 & 2A_0^1(2) & 0 \\ 0 & A_0^1(3) & A_0^1(2) \\ A_0^1(3) & 0 & A_0^1(1) \\ 0 & A_0^1(3) & A_0^1(2) \\ 0 & 0 & 2A_0^1(3) \end{bmatrix}$$