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A UNIFIED SET-VALUED APPROACH TO CONTROL IMMUNOTHERAPY*

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Abstract. Immunotherapy is set as an asymptotic target control problem under mixed state-control constraints with tumor dynamics given by a general ODE. Then a set-valued approach based on Aubin viability theory is used to design feedback protocols with which density of cancer cells may decrease to zero. Existence of such protocols involves a condition C on initial data; otherwise it is shown that either cancer cells cannot be eliminated or condition C may be achieved at a certain instant, in which case the above protocols can then be used. In order to illustrate the approach two examples are studied.

Key words. feedback control, set-valued analysis, viability theory, immunotherapy protocols

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1. Introduction and statement of the problem.

Nowadays, there is a growing recognition that mathematical modeling [10, 20, 21] can play a central role in cancer research. It can guide laboratory investigations and give scientists deeper insight into how tumors develop and spread.

Immunotherapy, also referred to as biological therapy, stands for a treatment that stimulates the body's immune system to produce antibodies to fight cancer or lessen the side effects associated with some cancer treatments. Mathematical models of such a process abound in the literature and are submitted to continuous improvements; see, for instance, [5, 7, 14, 15, 17, 18, 19] and the references therein. They give rise to numerous studies which investigate immunotherapy control by using the well-known methods of control theory.

For instance, in [4, 9] the authors state an adequate objective functional and use Hamilton–Jacobi equations to derive a bang-bang optimal protocol. An ODE system of five equations is considered in [5] as a model for tumor-immune interaction and vaccine, then the immunotherapy control problem is set and solved in the Bolza context. In [16] geometric methods of nonlinear control are applied to deal with a mathematical model for antiangiogenic treatments.

Moreover, we refer to [8], which uses spreading control techniques [12] in order to deal with the PDE model of [17] by seeking to expand the zones without tumor cells to the entire tissue.

Alternatively to the approaches cited above, a set-valued method is applied in [13] to show, in the particular case of the model established in [14], that feedback protocol laws can be provided as selections of a parameter set-valued map. Unfortunately, the method works only for the initial data that satisfy a condition, interpreted there as *the cancer is less developed at the beginning of the therapy.*

The aim of this paper is to investigate a general class of immunotherapy ODE models in the framework of the set-valued approach which was developed by [13].

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Furthermore, it addresses the issue of how initial data can condition existence of protocols with which cancer cells may be eliminated.

Most of the ODE models of immunotherapy, encountered in the literature [5, 7, 13, 14, 19], can be expressed as the nonlinear control system

$$\dot{x} = f(x, \tau) + G(x, \tau)u, \tag{1.1a}$$

$$\dot{\tau} = \tau\psi(x, \tau), \tag{1.1b}$$

where $x \doteq (x_1, \ldots, x_n)', u = (u_1, \ldots, u_p)'$, and $f \doteq (f_1, \ldots, f_n)'$ for integers n, p with $p \leq n$. The x_i's denote densities of cell populations which compete with tumor cells. Among them, an external source of p populations are infused in the cancerous tissue with rates u_i. Density of tumor cells is denoted by τ.

The operator G maps $\mathbb{R}_+^n \times \mathbb{R}_+$ into $\mathcal{L}(\mathbb{R}^p, \mathbb{R}^n)$. Both functions f_i and ψ map $\mathbb{R}_+^n \times \mathbb{R}_+$ into $\mathbb{R}$ and are continuous. The initial data are given by

$$\begin{aligned} &x_i(0) = x_i^0 \text{ for each } i = 1, \ldots, n, \\ &\tau(0) = \tau_0, \end{aligned} \tag{1.2}$$

where all numbers x_i^0 and τ_0 are positive.

In this context, a successful immunotherapy consists of finding a protocol u_θ which satisfies

$$u_\theta : [0, \infty) \to K, \tag{1.3a}$$

$$\tau_\theta \text{ decreases on } [0, \infty), \tag{1.3b}$$

$$\lim_{t \to \infty} \tau_\theta(t) = 0, \tag{1.3c}$$

where (x_θ, τ_θ) denotes a solution to system (1.1) for control u_θ and

$$K \doteq \prod_{i=1}^{p} [0, u_i^{\max}]$$

for positive numbers $u_i^{\max}$.

Condition (1.3a) allows one to keep the toxicity to the normal tissue acceptable and (1.3c) expresses that cancer cells are destroyed at a terminal time, while (1.3b) may be optional and aims at reducing undesirable effects on the patient.

Throughout this paper, the Euclidean norm is denoted $\|\|$, and $\langle , \rangle$ is the usual inner product. For a vector z we denote by z_i its ith component. Let T be a linear operator, and we denote its adjoint operator by $T^\star$ and its norm by $\|T\|$. Furthermore we consider the notation

$$\nabla_x \psi \doteq \left(\frac{\partial \psi}{\partial x_1}, \ldots, \frac{\partial \psi}{\partial x_n} \right)',$$

such that for each (x, τ) and (y, ξ) in $\mathbb{R}_+^n \times \mathbb{R}_+$ we have

$$\dot{\psi}(x, \tau)(y, \xi) = \langle \nabla_x \psi(x, \tau), y \rangle + \xi \frac{\partial \psi}{\partial \tau}(x, \tau).$$

Given a set-valued map $Q : D \to 2^{\mathbb{R}^m}$ and an integer m, the mapping $s : D \to \mathbb{R}^m$ is called a selection of Q if $s(p) \in Q(p)$ for each p. The minimal selection of the map Q is given by

$$s^\star(p) = \pi_{Q(p)}(0) \text{ for all } p \in D.$$

Here π stands for the operator of best approximation.

The layout of this paper is as follows: In the next section we give some background on viability theory along with some facts from set-valued analysis, and an exposition of the main elements of our approach is provided in section 3. In section 4 we prove some topological properties of the feedback map. In section 5 we focus on protocol laws, and section 6 contains the main results on immunotherapy control. Finally in section 7 two models of immunotherapy are studied in order to illustrate the results established.

2. Definitions and preliminary results. Let D denote a subset of the Euclidean space $\mathbb{R}^k$ with $k \geq 1$. The contingent cone [6] at $p \in D$ is defined by

$$T_D(p) \doteq \left\{ q \in \mathbb{R}^k \mid \liminf_{h \downarrow 0} \frac{d(p + hq, D)}{h} = 0 \right\},$$

where

$$d(r, D) \doteq \inf_{q \in D} \|q - r\| \quad \text{ for each } r \in \mathbb{R}^k.$$

We need to recall the following facts we will use throughout the paper.

1. If a subset D is closed and convex, then it is a sleek subset. The latter property consists of that the map $T_D : D \to 2^{\mathbb{R}^k}$ is lower semicontinuous (in short, *lsc*), i.e., for each $p \in D$ and any sequence $(p_n)_n \subset D$ which converges to p, then for each $q \in T_D(p)$ there exists a sequence $q_n \in T_D(p_n)$ that converges to q.

2. The result below is due to [2, section 11.2.5].

LEMMA 2.1. *Let $L \subset \mathbb{R}^l$ and $M \subset \mathbb{R}^m$ (for integers l, m) be two closed sleek subsets and let $\varphi : \mathbb{R}^l \to \mathbb{R}^m$ be a continuously differentiable mapping. If $p \in L \cap \varphi^{-1}(M)$ satisfies the transversality condition*

$$\dot{\varphi}(p) T_L(p) - T_M(\varphi(p)) = \mathbb{R}^m, \tag{2.1}$$

then

$$T_{L \cap \varphi^{-1}(M)}(p) = T_L(p) \cap \dot{\varphi}(p)^{-1} T_M(\varphi(p)). \tag{2.2}$$

3. Let $\varphi : \mathbb{R}^k \to \mathbb{R}^k$. Then D is said to be locally viable under the system

$$\begin{aligned} \dot{\xi} &= \varphi(\xi), \\ \xi(0) &= \xi_0 \end{aligned} \tag{2.3}$$

if for all $\xi_0 \in D$ there exist $\bar{t} > 0$ and a solution to system (2.3), $\bar{\xi}(\cdot)$ on $[0, \bar{t})$ which is viable in D (i.e., satisfies $\bar{\xi}(t) \in D$ for all t). Such a property can be characterized in terms of contingent subsets.

LEMMA 2.2 (see [1]). *Assume that φ is continuous on the closed subset D. Then D is locally viable under system* (2.3) *if and only if*

$$\varphi(\xi) \in T_D(\xi) \text{ for each } \xi \in D. \tag{2.4}$$

4. Next, given the control system

$$\dot{\xi} = \varphi(\xi) + B(\xi)w, \\ w \in W(\xi), \tag{2.5}$$

where w takes values in $\mathbb{R}^m$ and denotes the control, $B : \mathbb{R}^k \to \mathcal{L}(\mathbb{R}^m, \mathbb{R}^k)$, and $W(\cdot)$ stands for the set-valued map of constraints, define the feedback map

$$\mathcal{F}(p) \doteq \{w \in W(p) \mid \varphi(p) + B(p)w \in T_D(p)\}. \tag{2.6}$$

Assume that φ and $B(\cdot)$ are continuous on D; then any continuous selection of the feedback map $\mathcal{F}$ provides a control law that leads to a viable solution to system (2.5) in D. This is so for the minimal selection whenever it is continuous. Otherwise we can use [2, Theorem 4.3.2] as follows.

LEMMA 2.3. *Assume that the feedback map $\mathcal{F}(\cdot)$ is* lsc *with nonempty closed convex values. Then system* (2.5) *with feedback control $w = \pi_{\mathcal{F}(\xi)}(0)$ has a locally viable solution in D.*

5. Let F be a set-valued map from $\mathbb{R}^k$ to $\mathbb{R}^k$. Then consider the differential inclusion

$$\left| \begin{array}{l} \dot{z} \in F(z), \\ z(0) = z_0. \end{array} \right. \tag{2.7}$$

DEFINITION 2.4 (see [2]). *The* capture basin *of D under F is denoted by* $\text{capt}_F(D)$ *and stands for the set of all initial states $z_0 \in \mathbb{R}^k$ such that subset D is reached by one solution to differential inclusion* (2.7).

3. A set-valued approach. In a ready manner we verify that condition (1.3b) can be written as $\psi(x(t), \tau(t)) \leq 0$ for each $t \in [0, \infty)$. Thereby it reduces to the viability of the subset

$$D_0 \doteq \left\{(x, \tau) \in \mathbb{R}_+^n \times \mathbb{R}_+ \mid \psi(x, \tau) \leq 0\right\}.$$

Being inspired by the theory of Lyapunov functions as studied in [1, section 9.2], we introduce the family of subsets

$$D_\nu \doteq \left\{(x, \tau) \in \mathbb{R}_+^n \times \mathbb{R}_+ \mid \psi(x, \tau) \leq -\nu\right\} \quad \text{for each } \nu \geq 0. \tag{3.1}$$

Now, let $\nu > 0$ and suppose that protocol $u_\theta : [0, \infty) \to K$ leads to a solution (x_θ, τ_θ) which is globally viable in D_ν; then u_θ solves Problem (1.3). Indeed, it is obvious that u_θ and τ_θ satisfy (1.3a) and (1.3b), respectively. As for (1.3c), thanks to (1.1b) we have

$$\tau_\theta(t) = \tau_\theta(0) \exp\left(\int_0^t \psi(x_\theta(s), \tau_\theta(s)) ds\right) \text{ for each } t \geq 0,$$

which yields the estimate

$$0 \leq \tau_\theta(t) \leq \tau_0 \exp(-\nu t) \text{ for each } t \geq 0. \tag{3.2}$$

Remark 3.1. We notice that the parameter ν in formula (3.2) can be interpreted as the average speed of the therapy. The greater it is, the smaller the therapy horizon.

Definition 3.2. *The mapping* $\sigma : D_\nu \to K$ *is said to be an immunotherapy protocol law (in short,* itp *law) if the feedback control* $u = \sigma(x,\tau)$ *is a solution to problem* (1.3) *for all* $(x_0, \tau_0) \in D_\nu$.

According to (2.6) the feedback map can be given for each $\nu > 0$ by

$$\mathcal{F}_\nu(x,\tau) \doteq \{u \in K \mid (f(x,\tau) + G(x,\tau)u, \tau\psi(x,\tau))' \in T_{D_\nu}(x,\tau)\} \tag{3.3}$$

for each $(x,\tau) \in D_\nu$.

Thus, thanks to Lemma 2.2, *itp* laws can be provided by selections σ of the map $\mathcal{F}_\nu(\cdot)$ for which system (1.1) with $u = \sigma(x,\tau)$ has a globally viable solution in D_ν.

Next we proceed to express the contingent cone $T_{D_\nu}(\cdot)$. First of all, by considering (3.1) we get $D_\nu = L \cap \psi^{-1}(M_\nu)$, where

$$L \doteq \mathbb{R}^n_+ \times \mathbb{R}_+ \quad \text{and} \quad M_\nu \doteq (-\infty, -\nu].$$

Since L and M_ν are closed and convex, they are sleek subsets as required by Lemma 2.1, and their contingent cones are given by

$$(y,\xi) \in T_L(x,\tau) \iff \left| \begin{array}{l} y_i \geq 0 \text{ if } x_i = 0 \text{ for } i = 1,\dots,n, \\ \xi \geq 0 \text{ if } \tau = 0 \end{array} \right.$$

and

$$z \in T_{M_\nu}(m) \iff z \leq 0 \text{ if } m = -\nu$$

for all $(x,\tau) \in L$ and $m \in M_\nu$. Moreover, we can easily see that the transversality condition in Lemma 2.1 is satisfied whenever the following conditions hold:

$$\psi \text{ is of class } \mathcal{C}^1 \text{ on } D_\nu, \tag{3.4a}$$

and

$$\left| \begin{array}{l} \text{for all } (x,\tau) \in D_\nu \text{ there exists} \\ j \in \{1,\dots,n+1\} \text{ such that } \dfrac{\partial\psi}{\partial\zeta_j}(x,\tau) < 0, \\ \text{where } \zeta = (x,\tau). \end{array} \right. \tag{3.4b}$$

Lemma 3.3. *Let* $\nu > 0$ *and suppose that condition* (3.4) *is satisfied. Then for each* $(x,\tau) \in D_\nu$ *we have*

$$(y,\xi) \in T_{D_\nu}(x,\tau) \iff \left| \begin{array}{l} y_i \geq 0 \textit{ if } x_i = 0 \textit{ for } i = 1,\dots,n, \\ \xi \geq 0 \textit{ if } \tau = 0 \textit{ and} \\ \langle \nabla_x \psi(x,\tau), y \rangle + \xi \dfrac{\partial\psi}{\partial\tau}(x,\tau) \leq 0 \textit{ if } \psi(x,\tau) = -\nu. \end{array} \right. \tag{3.5}$$

4. The feedback map. This section involves the main results we need in order to carry out our approach. First of all, we seek to determine a useful expression of the feedback map $\mathcal{F}_\nu(\cdot)$ given by (3.3). Define the functions

$$h(x,\tau) \doteq -G^\star(x,\tau)\nabla_x\psi(x,\tau), \tag{4.1a}$$

$$\ell(x,\tau) \doteq \langle \nabla_x\psi(x,\tau), f(x,\tau) \rangle + \tau\psi(x,\tau)\frac{\partial\psi}{\partial\tau}(x,\tau) \tag{4.1b}$$

and the map

$$C(x,\tau) \doteq \{u \in K \mid \langle h(x,\tau), u\rangle \geq \ell(x,\tau)\} \tag{4.1c}$$

for each $(x,\tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+$. In addition we consider the assumption

$$\left| \begin{array}{l} x = (x_1,\dots,x_n)' \\ x_i = 0 \text{ and } \tau \geq 0 \end{array} \right. \Rightarrow f_i(x,\tau) + (G(x,\tau)u)_i \geq 0 \text{ for all } u \in K \tag{4.2}$$

for all $i = 1,\dots,n$.

Proposition 4.1. *Let $\nu > 0$ be such that* (3.4) *and* (4.2) *hold true. Then for each $(x,\tau) \in D_\nu$ we have*

$$\mathcal{F}_\nu(x,\tau) = \left| \begin{array}{lll} K & \text{if} & \psi(x,\tau) < -\nu, \\ C(x,\tau) & \text{if} & \psi(x,\tau) = -\nu. \end{array} \right. \tag{4.3}$$

Proof. First, by (4.1) we remark that

$$\dot{\psi}(x,\tau)(f(x,\tau) + G(x,\tau)u, \tau\psi(x,\tau))' = -\langle h(x,\tau), u\rangle + \ell(x,\tau).$$

By (3.3) and Lemma 3.3 we get

$$u \in \mathcal{F}_\nu(x,\tau) \Longleftrightarrow \left| \begin{array}{lll} f_i(x,\tau) + (G(x,\tau)u)_i \geq 0 & \text{if} & x_i = 0 \text{ for } i = 1,\dots,n, \\ \tau\psi(x,\tau) \geq 0 & \text{if} & \tau = 0, \\ -\langle h(x,\tau), u\rangle + \ell(x,\tau) \leq 0 & \text{if} & \psi(x,\tau) = -\nu. \end{array} \right.$$

Thanks to (4.2), it follows that

$$u \in \mathcal{F}_\nu(x,\tau) \Longleftrightarrow \langle h(x,\tau), u\rangle \geq \ell(x,\tau) \text{ if } \psi(x,\tau) = -\nu,$$

ending the proof of the proposition. □

Subsequently, let us consider the assumption

$$\left| \begin{array}{l} \text{for each } (x,\tau) \in D_\nu \text{ there exists} \\ u \in K \text{ such that } \langle h(x,\tau), u\rangle > \ell(x,\tau), \end{array} \right. \tag{4.4}$$

where the functions h and ℓ are given by (4.1).

Lemma 4.2. *The map $C(\cdot)$ given by* (4.1c) *is lsc on D_ν whenever condition* (4.4) *is satisfied.*

Proof. We rewrite the map C in the context of [3, Proposition 1.5.2]. We get

$$C(x,\tau) = \{u \in \bar{F}(x,\tau) \mid \bar{f}(x,\tau,u) \in \bar{G}(x,\tau)\},$$

where, for each $(x,\tau) \in D_\nu$, we have

$$\bar{F}(x,\tau) \doteq K, \quad \bar{f}(x,\tau,u) \doteq \langle h(x,\tau), u\rangle, \quad \text{and} \quad \bar{G}(x,\tau) \doteq [\ell(x,\tau), \infty).$$

Thereafter, we easily check the hypotheses of the cited proposition as follows:

(i) The map $\bar{F}$ is lsc with convex values.
(ii) $\bar{f}$ is continuous.
(iii) For all $(x,\tau) \in D_\nu$, the mapping $u \to \bar{f}(x,\tau,u)$ is affine.
(iv) For all (x,τ), $\bar{G}(x,\tau)$ is convex and its interior is nonempty.

(v) The graph of the map $(x,\tau) \in D_\nu \to \mathrm{int}(\bar{G}(x,\tau))$ is open.

(vi) For all $(x,\tau) \in D_\nu$, there exists $u \in \bar{F}(x,\tau)$ such that $\bar{f}(x,\tau,u) \in \mathrm{int}(\bar{G}(x,\tau))$.

Note that (vi) is due to condition (4.4), whence the map C is lsc. ∎

LEMMA 4.3. *Let $\nu > 0$ be such that condition* (4.4) *holds true. Then the minimal selection of the map C is continuous on D_ν.*

Proof. By Lemma 4.2 the map C is lsc. Then we can use [11, Theorem 4.1] by verifying that the subset

$$K_\epsilon \doteq \{(x,\tau) \in D_\nu \mid \exists u \in C(x,\tau) \text{ s.t. } \|u\| \leq \epsilon\}$$

is closed in D_ν for all $\epsilon > 0$. Indeed, let $((x_n,\tau_n))_n$ be a sequence in K_ϵ which converges to $(\bar{x},\bar{\tau})$. Then there exists a sequence $(u_n)_n \subset K$ such that

$$\|u_n\| \leq \epsilon \quad \text{and} \quad \langle h(x_n,\tau_n), u_n\rangle \geq \ell(x_n,\tau_n) \text{ for all } n. \tag{4.5}$$

Now, as $(u_n)_n$ is bounded it has a subsequence $(u_k)_k$ which converges to $\bar{u}$. Then by noting that h and ℓ are continuous and letting $k \to \infty$ in (4.5), we get

$$\|\bar{u}\| \leq \epsilon \quad \text{and} \quad \langle h(\bar{x},\bar{\tau}), \bar{u}\rangle \geq \ell(\bar{x},\bar{\tau}).$$

This implies that $(\bar{x},\bar{\tau}) \in K_\epsilon$ and therefore K_ϵ is closed. ∎

LEMMA 4.4. *Let $\nu > 0$ and suppose that condition* (4.4) *holds true. Then the map $\mathcal{F}_\nu(\cdot)$ as given by* (4.3) *is lsc on D_ν.*

Proof. Let $(x_n,\tau_n)_n$ be a sequence of D_ν that converges to $(x,\tau) \in D_\nu$ and $u \in \mathcal{F}_\nu(x,\tau)$. We have to seek a sequence $(u_n)_n$ that satisfies

$$\left| \begin{array}{l} u_n \in \mathcal{F}_\nu(x_n,\tau_n) \text{ for each } n, \\ \text{and } u_n \to u. \end{array} \right. \tag{4.6}$$

Assume that $\psi(x,\tau) < -\nu$. Since the function ψ is continuous and $(x_n,\tau_n) \to (x,\tau)$ we can consider the smallest number n_0 such that

$$\psi(x_n,\tau_n) < -\nu \text{ for all } n \geq n_0.$$

Then the sequence defined by

$$u_n \doteq \left| \begin{array}{ll} u & \text{if } n \geq n_0, \\ v_n & \text{if } n < n_0, \end{array} \right.$$

where

$$v_n \in C(x_n,\tau_n) \text{ for all } n < n_0,$$

merely satisfies (4.6) due to the fact that $\psi(x_n,\tau_n) = -\nu$ whenever $n < n_0$.

Now suppose that $\psi(x,\tau) = -\nu$; then $u \in C(x,\tau)$. By Lemma 4.2 the map $C(\cdot)$ is lsc as condition (4.4) holds true. It follows that there exists a sequence $(u_n)_n$ such that $u_n \in C(x_n,\tau_n)$ for each n and $u_n \to u$. Thanks to (4.3) we get $u_n \in \mathcal{F}_\nu(x_n,\tau_n)$ for all n, as required in (4.6). ∎

5. Immunotherapy protocol laws. This section is entirely dedicated to itp laws. We know from section 3 that these laws can be provided as selections of the feedback map $\mathcal{F}_\nu(\cdot)$, which lead to global solutions to the system. For that end, we consider the linear growth assumption on D_ν,

$$\|f(x,\tau)\| \le m_1(\tau)(\|x\|+1) \quad \text{and} \quad \|G(x,\tau)\| \le m_2(\tau), \tag{5.1}$$

where m_1 and m_2 denote positive functions that map bounded subsets into bounded images.

LEMMA 5.1. *Assume that* (5.1) *holds and let* $\sigma : D_\nu \to K$ *be such that feedback control* $u = \sigma(x,\tau)$ *leads to a locally viable solution* $(\bar{x},\bar{\tau})$ *to system* (1.1) *for all* $(x_0,\tau_0) \in D_\nu$. *Then that solution is global for all* $(x_0,\tau_0) \in D_\nu$.

Proof. Let $(\bar{x},\bar{\tau})$ be defined over a maximal interval $[0,t_1)$. We have to show that $t_1 = \infty$. Indeed, assume that $t_1 < \infty$. As the nonnegative function $\bar{\tau}$ is decreasing on $[0,t_1)$ it follows that $\bar{\tau}(t) \le \tau_0$ for all $t \in [0,t_1)$. Then there exists $\bar{m} > 0$ such that

$$m_1(\tau(t)) \le \bar{m} \quad \text{and} \quad m_2(\tau(t)) \le \bar{m} \text{ on } [0,\bar{t}) \,.$$

It follows that the right-hand side of (1.1a) satisfies the estimate

$$\|f(x,\tau) + G(x,\tau)\sigma(x,\tau)\| \le \bar{m}\left(\|x\| + \sup_{0\le i\le p}(u_i^{\max}) + 1\right),$$

which yields a linear growth for (1.1a). This implies that

$$\bar{x}(t) \to x_1 \text{ when } t \to t_1.$$

As $\bar{\tau}(\cdot)$ is a nonnegative decreasing function, we have

$$\bar{\tau}(t) \to \tau_1 \text{ when } t \to t_1.$$

Therefore

$$(\bar{x}(t),\bar{\tau}(t)) \to (x_1,\tau_1) \text{ when } t \to t_1,$$

and $(x_1,\tau_1) \in D_\nu$ because D_ν is closed. Now, by considering (x_1,τ_1) as an initial data, it follows that system (1.1) admits a viable solution in D_ν, which starts from (x_1,τ_1) at time t_1, contradicting the fact that the interval $[0,t_1)$ is maximal. ∎

For all $\nu > 0$, the minimal selection of the map $\mathcal{F}_\nu(\cdot)$ of (4.3) is given for all $(x,\tau) \in D_\nu$ by

$$s_\nu^\star(x,\tau) \doteq \left| \begin{array}{lll} 0 & \text{if} & \psi(x,\tau) < -\nu, \\ \pi_{C(x,\tau)}(0) & \text{if} & \psi(x,\tau) = -\nu. \end{array} \right. \tag{5.2}$$

Although $s_\nu^\star$ is not continuous, we will see next that it can provide an itp law.

THEOREM 5.2. *Let* $\nu > 0$ *and assume both conditions* (4.4) *and* (5.1). *Then* $s_\nu^\star$ *given by* (5.2) *stands for an itp law.*

Proof. Lemma 4.4 implies that $\mathcal{F}_\nu(\cdot)$ is lsc. Since it has closed convex values, we can use Lemma 2.3. Thus, by using feedback control $u = s_\nu^\star(x,\tau)$, system (1.1) has a local solution which is viable in D_ν. Now, by virtue of Lemma 5.1, $s_\nu^\star(\cdot)$ is an itp law. ∎

We now establish a result on continuous itp laws.

THEOREM 5.3. *Assume that conditions* (4.4) *and* (5.1) *are satisfied. Let* σ *be a continuous selection of the map* C *and let* $\zeta : \mathbb{R}^+ \to [0,1]$ *be continuous such that* $\zeta(0) = 1$. *Then a continuous itp law can be given by*

$$s_\nu(x,\tau) \doteq \zeta(-\psi(x,\tau) - \nu)\sigma(x,\tau) \quad \textit{for each } (x,\tau) \in D_\nu. \tag{5.3}$$

Proof. We notice first that s_ν is continuous as being the composite of continuous functions. Since $0 \le \zeta(-\psi(x,\tau) - \nu) \le 1$ for all $(x,\tau) \in D_\nu$, then $s_\nu(x,\tau) \in K$ if $\psi(x,\tau) < -\nu$. Otherwise we get $s_\nu(x,\tau) = \sigma(x,\tau) \in C(x,\tau)$, whence s_ν is a selection of the map $\mathcal{F}_\nu(\cdot)$. Now we use Lemma 5.1 to conclude that s_ν is an itp law. ∎

Remark 5.4. As an application of Theorem 5.3, let $\zeta(z) = e^{-\mu z}$ for some positive parameter μ and let σ stand for the minimal selection of the map C (continuous thanks to Lemma 4.3). Then we get an important family of continuous itp laws on D_ν as follows:

$$\sigma_\nu(x,\tau) \doteq e^{\mu(\psi(x,\tau)+\nu)}\pi_{C(x,\tau)}(0) \quad \text{for each } (x,\tau) \in D_\nu. \tag{5.4}$$

We emphasize that these laws are slightly higher than the minimal itp law $s_\nu^\star$ given by (5.2). This is due to the exponential decay in formula (5.4).

6. Immunotherapy control. In this section we examine the implications of our set-valued approach on the treatment of the immunotherapy control problem (1.3a)–(1.3c). First of all, we define the set-valued map

$$F(x,\tau) \doteq \{(f(x,\tau) + G(x,\tau)u, \tau\psi(x,\tau))' \mid u \in K\} \tag{6.1a}$$

for all $(x,\tau) \in \mathbb{R}_+^n \times \mathbb{R}_+$. Therefore solutions to system (1.1) are also given as solutions to the differential inclusion

$$\left| \begin{array}{l} (\dot{x},\dot{\tau}) \in F(x,\tau), \\ x(0) = x_0, \tau(0) = \tau_0, \end{array} \right. \tag{6.1b}$$

and vice versa. Then we let

$$\Sigma \doteq \Omega_+ \cap \operatorname{capt}_F(\Omega_-), \tag{6.2}$$

where the subset $\operatorname{capt}_F(\cdot)$ stands for the capture basin as provided by Definition 2.4, and the subsets Ω_- and Ω_+ are given by

$$\Omega_- \doteq \left\{(x,\tau) \in \mathbb{R}_+^n \times \mathbb{R}_+ \mid \psi(x,\tau) < 0\right\} \tag{6.3a}$$

and

$$\Omega_+ \doteq \left\{(x,\tau) \in \mathbb{R}_+^n \times \mathbb{R}_+ \mid \psi(x,\tau) \ge 0\right\}. \tag{6.3b}$$

Then we can state the following result.

THEOREM 6.1. *Consider system* (1.1) *with initial data* (x_0,τ_0), *and let* $\nu_0 \doteq -\psi(x_0,\tau_0)$. *Then either of the following situations may hold:*

(i) $(x_0,\tau_0) \in \Omega_-$*: in this case* $s_{\nu_0}^\star(\cdot)$ *and* $s_{\nu_0}(\cdot)$ *as given by* (5.2) *and* (5.3), *respectively, are itp laws whenever conditions* (4.4) *and* (5.1) *hold true for* ν_0.

(ii) $(x_0,\tau_0) \in \Sigma$*: if condition* (4.4) *is satisfied on* D_0, *then a protocol which satisfies* (1.3a) *and* (1.3c) *exists, and it is given by an itp law after an instant* t_{im}.

(iii) $(x_0, \tau_0) \in \Omega_+ \setminus \Sigma$*: then there is no protocol which solves problem* (1.3a)–(1.3c).

Proof. (i) We are in a position to apply Theorems 5.2 and 5.3, respectively.

(ii) Since $(x_0, \tau_0) \in \text{capt}_F(\Omega_-)$ then there exists a solution $(\bar{x}, \bar{\tau})$ to differential inclusion (6.1b), which satisfies

$$(\bar{x}(t_{\text{im}}), \bar{\tau}(t_{\text{im}})) \in \Omega_- \text{ at an instant } t_{\text{im}}.$$

Let $\bar{u} : [0, \infty) \to K$ be a control which leads to such a solution in accord with (6.1). Let $x_{\text{im}} \doteq \bar{x}(t_{\text{im}})$ and $\tau_{\text{im}} \doteq \bar{\tau}(t_{\text{im}})$. Then as $(x_{\text{im}}, \tau_{\text{im}}) \in \Omega_-$ one can use (i) to get an itp law for $(x_{\text{im}}, \tau_{\text{im}})$ as initial data, say $s_{\text{im}} : D_{\nu_m} \to K$, with $\nu_m \doteq -\psi(x_{\text{im}}, \tau_{\text{im}})$. Subsequently, a control that solves problem (1.3a)–(1.3c) can be given by

$$\left| \begin{array}{lll} \bar{u}(t) & \text{if} & 0 \le t < t_{\text{im}}, \\ s_{\text{im}}(x(t), \tau(t)) & \text{if} & t \ge t_{\text{im}}. \end{array} \right. \tag{6.4}$$

(iii) For such initial data (x_0, τ_0) all solutions $(\bar{x}, \bar{\tau})$ to differential inclusion (6.1b) are viable in subset Ω_+, that is to say,

$$\psi(\bar{x}(t), \bar{\tau}(t)) \ge 0 \text{ for all } t \ge 0. \tag{6.5}$$

As a result, any control u taking values in K will lead to such a solution. Now by using (1.1b) and (6.5) we get

$$\bar{\tau}(t) \ge \tau_0 \text{ for each } t \ge 0;$$

therefore $\bar{\tau}(t) \not\to 0$ when $t \to \infty$. ∎

Next, we show how protocol $\bar{u}$ and instant t_{im}, which are involved by the proof of Theorem 6.1 (ii), can be determined. For each $\alpha > 0$, let us define the set-valued map

$$C_\alpha(x, \tau) \doteq \{v \in K \mid \langle h(x, \tau), v\rangle - \ell(x, \tau) \ge \alpha\} \tag{6.6}$$

for all $(x, \tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+$, where h and ℓ are as in (4.1a) and (4.1b).

PROPOSITION 6.2. *Let* $(x_0, \tau_0) \in \Omega_+$ *and assume the statements below:*

(i) σ *is a continuous selection of the map* $C_\alpha(\cdot)$ *given by* (6.6) *for some* $\alpha > 0$.

(ii) *System* (1.1) *with feedback control* $u = \sigma(x, \tau)$ *admits a solution on an interval* $[0, t_{\text{im}}]$, *where* t_{im} *satisfies*

$$t_{\text{im}} > \frac{\psi(x_0, \tau_0)}{\alpha}. \tag{6.7}$$

Then the protocol given by $u \doteq \sigma(x, \tau)$ *steers system* (1.1) *from* (x_0, τ_0) *to* Ω_- *at time* t_{im}, *that is,* $(x_0, \tau_0) \in \Sigma$.

Proof. Let $(\bar{x}, \bar{\tau})$ denote the solution which is provided by (ii). Then we get

$$\psi(\bar{x}(t_{\text{im}}), \bar{\tau}(t_{\text{im}})) = \psi(x_0, \tau_0) + \int_0^{t_{\text{im}}} \left[\langle \nabla_x \psi(\bar{x}(s), \bar{\tau}(s)), \dot{\bar{x}}(s)\rangle + \dot{\bar{\tau}}(s) \frac{\partial \psi}{\partial \tau}(\bar{x}(s), \bar{\tau}(s)) \right] ds.$$

Next, by putting $\bar{u} \doteq \sigma(\bar{x}, \bar{\tau})$, we use formulas (4.1a) and (4.1b) to get

$$\psi(\bar{x}(t_{\text{im}}), \bar{\tau}(t_{\text{im}})) = \psi(x_0, \tau_0) - \int_0^{t_{\text{im}}} [\langle h(\bar{x}(s), \bar{\tau}(s)), \bar{u}(s)\rangle - \ell(\bar{x}(s), \bar{\tau}(s))] \, ds.$$

Since σ is a selection of the map $C_\alpha(\cdot)$ then (6.6) yields

$$\psi(\bar{x}(t_{\mathrm{im}}), \bar{\tau}(t_{\mathrm{im}})) \leq \psi(x_0, \tau_0) - \alpha t_{\mathrm{im}}.$$

Thanks to (6.7) it follows that $\psi(\bar{x}(t_{\mathrm{im}}), \bar{\tau}(t_{\mathrm{im}})) < 0$. $\square$

Remark 6.3. We can adapt Lemmas 4.3 and 4.2 to get similar results relative to the map $C_\alpha(\cdot)$. We need to replace condition (4.4) by

$$\left| \begin{array}{l} \text{For all } (x, \tau) \in \mathbb{R}^n_+ \times \mathbb{R}_+ \text{ there exists} \\ u \in K \text{ such that } \langle h(x, \tau), u\rangle - \ell(x, \tau) > \alpha, \end{array} \right.$$

and then use $\alpha + \ell$ instead of ℓ.

Ultimately, as a noteworthy fact in cancer modeling, the results above show that any one of the three instances below may arise for a patient having a cancer at the stage (x_0, τ_0) (see Figure 6.1):

(A) $(x_0, \tau_0) \in \Omega_-$: This means that the tumor is less developed with respect to the immune system. It can be cured with an itp law as derived from Theorem 6.1 (i). The notable advantage is that tumor cells will decrease during the therapy, in keeping with the patient's quality of life. Moreover, one may either use the minimal itp law (5.2) in order to reduce the amounts of the administered cells or else be interested in the continuous protocols provided in Remark 5.4 whenever smoothness is required to avoid undesirable effects.

(B) $(x_0, \tau_0) \in \Sigma$: The cancer is more developed. The protocol law σ given by Proposition 6.2 will bring the cancer to a better stage $(x_1, \tau_1) \in \Omega_-$ at an instant t_{im}. This hereby allows one to use an itp law after t_{im}, as in instance (A). Note that a sudden change in the variation of tumor cells may occur within horizon t_{im}, as their density is not necessarily decreasing.

(C) $(x_0, \tau_0) \in \Omega_+ \setminus \Sigma$: The cancer is so advanced that it is not curable, as shown by Theorem 6.1 (iii).

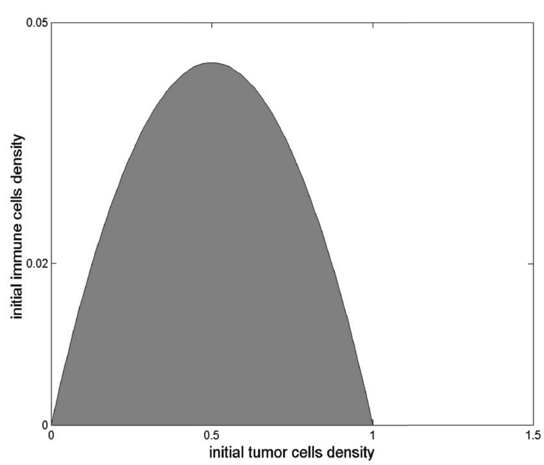

FIG. 6.1. *In gray: plot of the zone* Ω_+ *which corresponds to immunotherapy model* (7.1), *described by both cases* (B) *and* (C) *above. The complimentary zone provides instance* (A).

7. Examples. We begin by investigating the model of [14], which is given by

$$\dot{y} = c\tau - \mu_2 y + \frac{p_1 yz}{g_1 + z} + s_1 u_1, \tag{7.1a}$$

$$\dot{z} = \frac{p_3 y\tau}{g_3 + \tau} - \mu_3 z + s_2 u_2, \tag{7.1b}$$

$$\dot{\tau} = r_2 \tau(1 - b\tau) - \frac{ay\tau}{g_2 + \tau}, \tag{7.1c}$$

with normalized initial conditions

$$y(0) = 1, \; z(0) = 1, \; \tau(0) = 1, \tag{7.1d}$$

where $y(\cdot)$ stands for density of the activated immune system cells, or effector cells (ECs). Concentration of Interleukin-2 (IL-2) is denoted by $z(\cdot)$ and tumor cells (TCs) by $\tau(\cdot)$. All parameters are positive constants; see [14] for their values and units.

In the first differential equation the parameter c models the antigenicity of the tumor, the second term represents the natural death of the effector cells at the rate of μ_2, the third term is of Michaelis–Menton form to indicate the saturated effects of the immune response whereby effector cells are stimulated by IL-2, and the final term involves the strength of the treatment s_1 and the control $u_1(\cdot)$ that represent an external source of ECs.

The second equation gives the rate of change for the concentration of IL-2, the IL-2 source is modeled by another Michaelis–Menton term in which the TCs stimulate the interaction with the ECs to produce more IL-2, the second term represents the loss of these cells at the rate of μ_3, and the last term involves both the strength of the treatment s_2 and the supply rate of IL-2, $u_2(\cdot)$.

The third equation includes a logistic term in order to model the rate of change of TCs. The loss of tumor cells is represented by a Michaelis–Menton term to indicate the limited interaction between the tumor and ECs.

We then see that model (7.1) is involved in our approach by taking $n = p = 2$, and the functions f, ψ, and G in system (1.1) are given by

$$f(x, \tau) \doteq \left(c\tau - \mu_2 y + \frac{p_1 yz}{g_1 + z} \;,\; \frac{p_3 y\tau}{g_3 + \tau} - \mu_3 z \right)'$$

and

$$\psi(x, \tau) \doteq r_2(1 - b\tau) - \frac{ay}{g_2 + \tau}, \qquad G(x, \tau) \doteq \operatorname{diag}(s_1, s_2)$$

for all $(x, \tau) \in \mathbb{R}_+^2 \times \mathbb{R}_+$ and $x = (y, z)'$. We have

$$\nabla_x \psi(x, \tau) = \left(-\frac{a}{g_2 + \tau} \;,\; 0 \right)',$$

$$\frac{\partial \psi}{\partial \tau}(x, \tau) = -r_2 b + \frac{ay}{(g_2 + \tau)^2}$$

for each $(x, \tau) \in \mathbb{R}_+^2 \times \mathbb{R}_+$. It follows that condition (3.4b), which is needed in Lemma 3.3, is satisfied because

$$\frac{\partial \psi}{\partial y}(x, \tau) = -\frac{a}{g_2 + \tau} < 0.$$

The functions h and ℓ of formulas (4.1) are given by

$$h(x,\tau) \doteq \left(\frac{s_1 a}{g_2+\tau} \ , \ 0 \right)'$$

and

$$\ell(x,\tau) \doteq -\frac{a}{g_2+\tau}\left(c\tau - \mu_2 y + \frac{p_1 yz}{g_1+z} \right) + \tau \left(r_2(1-b\tau) - \frac{ay}{g_2+\tau} \right)\left(-r_2 b + \frac{ay}{(g_2+\tau)^2} \right).$$

Then the map C of (4.1c) can be expressed by

$$C(x,\tau) \doteq \left\{ u \in [0, u^1_{\max}] \mid uh(x,\tau) \ge \ell(x,\tau) \right\} \times \left[0, u^2_{\max}\right],$$

and thereby the minimal selection of $\mathcal{F}_\nu(\cdot)$ is as follows:

$$s^\star_\nu(x,\tau) \doteq \left| \begin{array}{lll} (0,0)' & \text{if} & \psi(x,\tau) < -\nu, \\ (\varrho(x,\tau),0)' & \text{if} & \psi(x,\tau) = -\nu, \end{array} \right.$$

where

$$\varrho(x,\tau) \doteq \max\left(-\frac{1}{s_1}\left(c\tau - \mu_2 y + \frac{p_1 yz}{g_1+z} \right) - \frac{\nu\tau}{s_1 a}\left(-r_2 b(g_2+\tau) + \frac{ay}{(g_2+\tau)} \right), 0 \right).$$

As a result, the map $\mathcal{F}_\nu(\cdot)$ admits a continuous selection given by

$$s_\nu(x,\tau) \doteq \left(\min\left(\frac{(g_2+\tau)\exp(\psi(x,\tau)+\nu)\max(\ell(x,\tau),0)}{s_1 a}, u_1^{\max} \right), 0 \right)'.$$

As for condition (5.1), it is also satisfied by taking

$$m_1(\tau) \doteq \max(p_1+p_3+\mu_2, \mu_3, c\tau) \quad \text{and} \quad m_2(\tau) \doteq \max(s_1, s_2).$$

It follows that the conditions of Theorem 6.1 hold true whenever $(x_0,\tau_0) \in D_\nu$.

We now turn to examine the family of immunotherapy models studied in [7]:

$$\dot{x} = \beta(\tau)x - \mu(\tau)x + \sigma q(\tau) + u(t), \tag{7.2a}$$

$$\dot{\tau} = \tau(g(\tau) - \phi(\tau)x), \tag{7.2b}$$

where $x(\cdot)$ and $\tau(\cdot)$, respectively, stand for the densities of ECs and TCs, and $g(\tau)$ summarizes many widely used models of tumor growth rates, such as the Stepanova model

$$\left| \begin{array}{l} g(\tau) \doteq \alpha > 0, \ \phi(\tau) \doteq 1, \ \beta(\tau) \doteq \beta_1 \tau, \\ q(\tau) \doteq 1 \text{ and } \mu(\tau) \doteq \mu_0 + \mu_2 \tau^2. \end{array} \right.$$

As regards the de Vladar–Gonzalez model, it is similar except that

$$g(\tau) \doteq \alpha \log(K/\tau).$$

The Kuznetsor model consists of taking

$$\left| \begin{array}{l} g(\tau) \doteq \alpha(1-\tau/K),\ \phi(\tau) \doteq 1,\ \beta(\tau) \doteq \beta_\infty \tau/(m+\tau), \\ \mu(\tau) \doteq \mu(0) + \mu_1 \tau,\ \text{and}\ q(\tau) \doteq 1, \end{array} \right.$$

We can easily see that system (7.2) represents a particular case of (1.1) where the functions f, ψ, and G are given as

$$f(x,\tau) \doteq \beta(\tau)x - \mu(\tau)x + \sigma q(\tau), \quad G(x,\tau) \doteq 1,$$

and

$$\psi(x,\tau) \doteq g(\tau) - \phi(\tau)x$$

for all $(x,\tau) \in \mathbb{R}_+ \times \mathbb{R}_+$. Thereby we can apply our set-valued approach by proceeding as in the preceding example. The partial derivatives of ψ are given by

$$\frac{\partial \psi}{\partial x}(x,\tau) = -\phi(\tau)$$

and

$$\frac{\partial \psi}{\partial \tau}(x,\tau) = \dot{g}(\tau) - \dot{\phi}(\tau)x.$$

We can see that conditions (4.2) and (3.4b) are satisfied. Consequently we get

$$\ell(x,\tau) \doteq -\phi(\tau)(\beta(\tau)x - \mu(\tau)x + \sigma q(\tau)) + \tau(\dot{g}(\tau) - \dot{\phi}(\tau)x)(g(\tau) - \phi(\tau)x)$$

and

$$h(x,\tau) \doteq \phi(\tau).$$

Then the map C of (4.1c) is given by

$$C(x,\tau) \doteq \{u \in [0, u_{\max}] \mid u\phi(\tau) \geq \ell(x,\tau)\}.$$

Therefore the minimal *itp* law can be expressed by

$$s^\star_\nu(x,\tau) \doteq \left| \begin{array}{lll} 0 & \text{if} & \psi(x,\tau) < -\nu, \\ \varrho(x,\tau) & \text{if} & \psi(x,\tau) = -\nu, \end{array} \right.$$

where

$$\varrho(x,\tau) \doteq \min\left(\max\left(\frac{\ell(x,\tau)}{\phi(\tau)}, 0\right), u_{\max}\right).$$

We can use Theorem 5.3 to get the continuous itp law

$$s_\nu(x,\tau) \doteq \exp(\psi(x,\tau) + \nu)\varrho(x,\tau). \tag{7.3}$$

In addition, we notice that condition (5.1) is also fulfilled. In Figures 7.1, 7.2, and 7.3 we summarize numerical results of the Kuznetsov model that represents a particular case of system (7.2) in which

$$\left| \begin{array}{l} g(\tau) = 1.636(1-\tau/100),\ \beta(\tau) = 1.131\tau/(20.19+\tau), \\ \mu(\tau) = 0.347 + 0.0311\tau,\ q(\tau) = 1,\ \text{and}\ \sigma = 0.6, \end{array} \right.$$

with the initial cells densities given by

$$x_0 = 1 \quad \text{and} \quad \tau_0 = 70,$$

where the function ψ takes the negative value -0.5092. We use the law $s_{0.5092}$ given by (7.3).

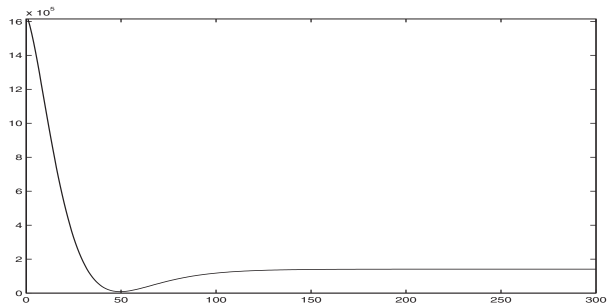

FIG. 7.1. *Dose of infused ECs.*

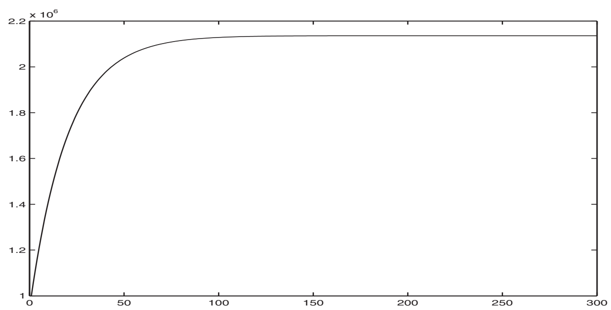

FIG. 7.2. *Density of ECs.*

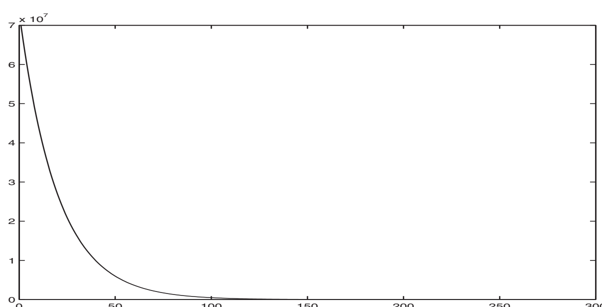

FIG. 7.3. *Density of TCs.*

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