IMMUNOTHERAPY CONTROL : A SET-VALUED APPROACH [*]

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Abstract. Immunotherapy control is set as a target control problem under state-control constraints, taking into account a general ODE tumor dynamics. Then a set-valued approach based on viability theory is used to enable building feedback protocol laws by which cancer cells may be asymptotically destroyed.

1. Introduction and statement of the problem. Cancer development and the dynamics of the immune system have been a significant focus of mathematical modeling in recent decades, see [6, 13]. Immunotherapy, a treatment approach that enhances the body's natural ability to fight cancers, is becoming increasingly prevalent in many multi-stage treatment programs. Models of such a process abound in the literature, see [4], [9], [10] and [12] and the references therein. They give rise to numerous works which take on immunotherapy control, by using the well-known methods of control theory ([2], [5], [7], [11]).

In this paper we investigate an ODE tumor dynamics versus the immune system, given in general form as follows,

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

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

with initial data,

$$x(0) = x_0 \text{ and } \tau(0) = \tau_0. \tag{1.1c}$$

where $x \doteq (x_1, \ldots, x_n)'$ denote densities of cells that interact with tumor cells such as effector cells, interleukin-2, antibodies, etc. The control (protocol) is denoted by $u = (u_1, \ldots, u_p)'$ and consists of the rates of the administered cells. Density of tumor cells is denoted by τ. The functions f and ψ map $\mathbb{R}^n \times \mathbb{R}$ into $\mathbb{R}$ and $\mathbb{R}^n$ respectively and are smooth. The operator G maps $\mathbb{R}^n \times \mathbb{R}$ into $\mathcal{L}(\mathbb{R}^p, \mathbb{R}^n)$.

In this context we conceive a successful therapy as follows : Find a protocol u such that,

(a) u ranges in the constraints subset $K \doteq \prod_{i=1}^{p} \; [0, u_i^{\max}]$, to preserve patient's quality of life.

(b) $\lim_{t\to\infty} \tau(t) = 0$, to clean cancer.

(c) $\tau(\cdot)$ decreases, as one wishes.

2. A set-valued approach. Let $D_\nu \doteq \{(x,\tau) \in \mathbb{R}_+^{n+1} \mid \psi(x,\tau) \le -\nu\}$ for $\nu > 0$. If the trajectory (x,τ) is viable in D_ν then condition (c) is fulfilled. It follows by using viability theory [1] that u can be given as a selection of the feedback map given as follows,

$$\mathcal{F}_\nu(x,\tau) \doteq \{u \in K \mid (f(x,\tau) + G(x,\tau)u, \tau\psi(x,\tau))' \in T_{D_\nu}(x,\tau)\}, \tag{2.1}$$

where T_{D_ν} denotes the cotangent cone of D_ν, see [3]. Then we have the following basic result.

THEOREM 2.1. *If $\sigma : D_\nu \to K$ is a selection of the map $\mathcal{F}_\nu$ (ie. $\sigma(x,\tau) \in \mathcal{F}_\nu(x,\tau)$ for all $(x,\tau) \in D_\nu$) and system (1.1) with $u = \sigma(x,\tau)$ has a solution on $[0,\infty)$ then protocol u solves problem (a-b-c) and $\tau(t) \le e^{-\nu t}\tau_0$ for all $t \ge 0$.*

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DEFINITION 2.2. *Such σ in Theorem 2.1 is said to be an immunotherapy protocol law, in short,* itp *law.* By computing the cotangent cone $T_{D_\nu}(x,\tau)$ we get for all $(x,\tau) \in D_\nu$,

$$\mathcal{F}_\nu(x,\tau) = \left| \begin{array}{lll} K & \text{if} & \psi(x,\tau) < -\nu \\ C(x,\tau) & \text{if} & \psi(x,\tau) = -\nu, \end{array} \right. \tag{2.2}$$

where,

$$C(x,\tau) \doteq \{u \in K \mid \langle h(x,\tau), u\rangle \geq \ell(x,\tau)\}, \tag{2.3}$$

and the functions h and ℓ are given by,

$$h(x,\tau) \doteq -G^\star(x,\tau)\nabla_x\psi(x,\tau) \tag{2.4a}$$

and,

$$\ell(x,\tau) \doteq \langle \nabla_x\psi(x,\tau), f(x,\tau)\rangle + \tau\psi(x,\tau)\frac{\partial\psi}{\partial\tau}(x,\tau). \tag{2.4b}$$

CONDITION 2.3. *For all $(x,\tau) \in D_\nu$ there exists $u \in K$ such that*

$$\langle h(x,\tau), u\rangle > \ell(x,\tau).$$

CONDITION 2.4. *There exist non-negative real functions m_1, m_2 which map bounded subsets into bounded images and satisfy the linear growth :*

$$\|f(x,\tau)\| \leq m_1(\tau)(\|x\| + 1) \textit{ and } \|G(x,\tau)\| \leq m_2(\tau),$$

for all $(x,\tau) \in D_\nu$. Then we can generate *itp* laws from the map (2.1) by using the result below. For that end we need the notation,

$$c_\star(x,\tau) \doteq \pi_{C(x,\tau)}(0) \text{ and } \sigma_\star^\nu(x,\tau) \doteq \left| \begin{array}{l} 0 \text{ if } \psi(x,\tau) < -\nu \\ c_\star(x,\tau) \text{ if } \psi(x,\tau) = -\nu, \end{array} \right.$$

where $\pi_C(\cdot)$ denotes the operator of best approximation on a convex closed subset C.

THEOREM 2.5. *Assume that conditions 2.3 and 2.4 hold true then :*

(i) The minimal selection of the feedback map (2.1), $\sigma_\star^\nu$ stands for an itp *law.*

(ii) Continuous itp *laws σ can be provided on D_ν by $\sigma(x,\tau) \doteq e^{\psi(x,\tau)+\nu}c_\star(x,\tau)$.*

EXAMPLE 1. *To illustrate the above results we consider the Kuznetsov immunotherapy model as given in [4],*

$$\begin{array}{l} \dot{x} = \beta(\tau)x - \mu(\tau)x + \sigma q(\tau) + u(t), \\ \dot{\tau} = \tau(g(\tau) - \phi(\tau)x), \end{array}$$

where

$$\left| \begin{array}{l} g(\tau) = 1.636(1 - \tau/100),\ \beta(\tau) = 1.131\tau/(20.19 + \tau),\ \phi(\tau) = 1, \\ \mu(\tau) = 0.347 + 0.0311\tau,\ q(\tau) = 1,\ \textit{and}\ \sigma = 0.6, x_0 = 1, \tau_0 = 70. \end{array} \right.$$

In the figures below we represent simulation results which correspond to the continuous itp *law (ii) with $\nu = -\psi(x_0,\tau_0) = 0.5092$.*

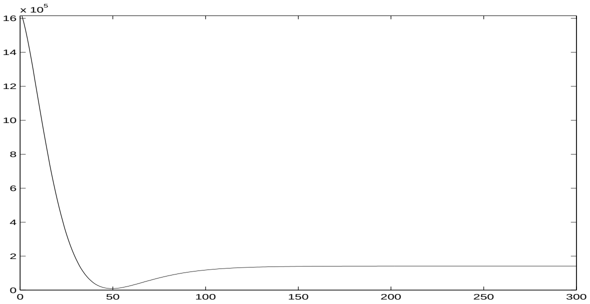

FIG. 2.1. *Dose of the infused effector cells.*

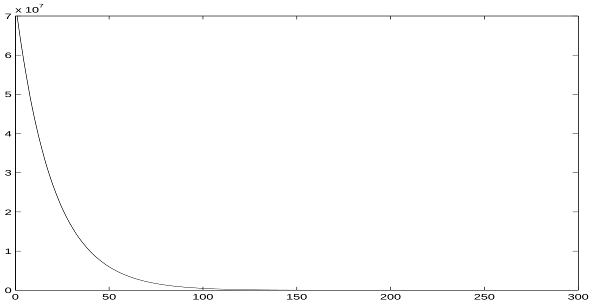

FIG. 2.2. *Density of tumor cells.*

3. Concluding remarks. In this note we state a framework by which protocol laws can be designed to solve the immunotherapy control problem.

These laws have the advantage that they let the cancer cells decrease over the therapy session, providing that the initial stage of the cancer is less developed, ie. $\psi(x_0, \tau_0) < 0$. Although it is discontinuous the minimal law (i) involves minimal doses to destroy cancer. Note also that the continuous *itp* laws (ii) are slightly higher then the minimal law, due to its exponential decay. In a forthcoming study we will investigate stage developed cancers which initially satisfy $\psi(x_0, \tau_0) \geq 0$.

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