Mathematical Biosciences xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

A switching control law approach for cancer immunotherapy of an evolutionary tumor growth model

Q1 Alina I. Doban*, Mircea Lazar

Department of Electrical Engineering, Eindhoven University of Technology, P.O. Box 513, Eindhoven 5600 MB, The Netherlands

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Mathematical biology
Nonlinear systems
Stability domains
Lyapunov methods
Tumor dynamics

ABSTRACT

We propose a new approach for tumor immunotherapy which is based on a switching control strategy defined on domains of attraction of equilibria of interest. For this, we consider a recently derived model which captures the effects of the tumor cells on the immune system and viceversa, through predator–prey competition terms. Additionally, it incorporates the immune system's mechanism for producing hunting immune cells, which makes the model suitable for immunotherapy strategies analysis and design. For computing domains of attraction for the tumor nonlinear dynamics, and thus, for deriving immunotherapeutic strategies we employ rational Lyapunov functions. Finally, we apply the switching control strategy to destabilize an invasive tumor equilibrium and steer the system trajectories to tumor dormancy.

1. Introduction

Developing dynamical models which can be employed to describe and predict tumor evolution has been the focus of a considerable amount of research work in the past decades. The majority of this work is based on capturing the competition interaction between the immune cells and cancer cells, which turns out to be dynamical and nonlinear. See [1] for a collection of such models, or the more recent [2] for a more specific survey focused on tumor dormancy. This interaction is best understood if seen from an evolutionary perspective, as the competition of two populations for space in the tissue. Such models have been developed and studied previously in the literature [3,4]. Although the model proposed therein is a two states Lotka–Volterra model, it is able to effectively capture certain phases in tumor development and growth. Some other type of models take into account also the immune system's mechanism of producing hunting immune cells (killer T-cells) by conversion from resting immune cells (helper T-cells [5]. This kind of models is particularly interesting for immunotherapy.

Immunotherapy is a type of treatment which uses certain parts of the immune system to fight tumor growth and can act towards boosting the immune system in a general way or by helping it to attack cancer cells specifically. If the mechanism which produces hunting immune cells acts optimally, this has great influence on helping eradicating cancer or at least on driving it to dormancy. The usefulness of a dynamical model which incorporates this mechanism comes from the fact that such a model allows for assessment of immunotherapy effectiveness and for designing new strategies.

In this work we consider the model proposed in [6] for describing the tumor–immune system predator–prey interaction, which also incorporates the dynamics driving the immune system itself, i.e. the conversion of resting cells to hunting ones. The considered model is polynomial of order two and has three states, which represent the tumor population, the hunting immune cells population and the resting immune cells population. For predicting treatment outcome or designing treatment strategies, it is not sufficient to assess whether a certain equilibrium becomes stable or unstable under treatment. On one hand, it is also necessary to be able to say from which set of initial conditions the system will converge to that certain equilibrium, i.e. by computing the domain of attraction. And on the other hand, treatment strategies should take into account destabilizing an unhealthy equilibria and adapting therapies until the desired equilibrium is reached, with minimal side effects to the patient. Thus, the focus on immunotherapies, and consequently on the model parameters which are responsible for boosting the immune response against cancer.

The idea that maintaining a stable dormant tumor might actually increase a patient's survival chances more than by trying to completely eradicate the tumor was previously proposed [7]. In terms of tumor dynamical models, this implies that the optimal treatment tactic would be to try to maintain the stable tumor

* Corresponding author.
E-mail addresses: a.i.doban@tue.nl (A.I. Doban), m.lazar@tue.nl (M. Lazar).

http://dx.doi.org/10.1016/j.mbs.2016.09.008
0025-5564/© 2016 Published by Elsevier Inc.

dormancy equilibrium. Therefore, the goal of the proposed domain of attraction based immunotherapy strategy is to steer the tumor growth dynamics to the tumor dormancy equilibrium of the proposed model.

The paper is structured as follows. In Section 2 the notation and instrumental tools which are used for analysis and control law design are introduced. In Section 3 the tumor growth model derived in [6], as well as a classical predator–prey tumor growth model are presented. The proposed therapy strategy is described in Section 4. The analysis carried out in [6] is briefly recalled in Section 4.1, while the application of the switching control law on the newly proposed model is illustrated for one scenario example in Section 4.2. Summarizing remarks are drawn in Section 5.

2. Tools

For constructing the procedure developed in this paper, some concepts and tools from nonlinear systems theory, and in particular Lyapunov theory are required. These tools will be elaborated in this section.

2.1. Tools for analysis

We proceed by introducing the notation and formally defining the theoretical tools that will be used to compute domains of attraction of equilibria of interest of a considered dynamical system. (See also [8]).

The set of non–negative reals is denoted by $\mathbb{R}_+$. For a vector $x \in \mathbb{R}^n$, let $\|x\|$ denote an arbitrary Hölder norm. Let $\mathbb{B}_\rho(p)$ denote the ball of radius ρ centered in $p \in \mathbb{R}^n$, defined as $\mathbb{B}_\rho(p) = \{x \in \mathbb{R}^n \mid \|x - p\| \leq \rho\}$. Given a point $p \in \mathbb{R}^n$ we define a neighborhood of p, $\mathcal{N}(p)$, as the ball $\mathbb{B}_\rho(p)$ for some radius ρ. By $\mathcal{N}(p)^+$ the projection of $\mathcal{N}(p)$ on $\mathbb{R}^n_+$ is denoted, where $\mathbb{R}^n_+$ denotes the positive orthant in $\mathbb{R}^n$.

Consider the continuous–time nonlinear autonomous system

$$\dot{x} = f(x), \tag{1}$$

where $f : \mathbb{X} \to \mathbb{R}^n$ is a locally Lipschitz map from the domain $\mathbb{X} \subset \mathbb{R}^n$ into $\mathbb{R}^n$.

Assumption 2.1. $x = 0$ is an asymptotically stable equilibrium point of the system (1).

Note that for systems with nonzero equilibria, a transformation can be defined to translate the nonzero equilibria to the origin [9].

Consider the concept of *domain of attraction* [10,11].

Definition 2.2. The domain of attraction (DOA) of the origin for the system (1) is the set

$$\mathcal{S} := \{x_0 \in \mathbb{R}^n : \lim_{t\to\infty} x(t, x_0, t_0) = 0\}, \tag{2}$$

where $x(\cdot, x_0, t_0)$ denotes the solution of (1) corresponding to the initial condition x_0 at time $t_0 = 0$.

Definition 2.3. A set $\mathcal{S} \in \mathbb{R}^n$ is called an invariant set w.r.t. (1) if for any initial condition $x_0 \in \mathcal{S}$, it holds that $x(t, x_0, t_0) \in \mathcal{S}$ for all $t \geq t_0$.

The DOA of an equilibrium for a given system is inherently an invariant set. Next, we will formally define positive systems [12], as they are relevant for biological systems, such as the tumor growth system.

Definition 2.4. The system defined by (1) is called *positive* if for any initial state x_0 in $\mathbb{R}^n_+$, the solution $x(t, x_0, t_0)$ will remain in $\mathbb{R}^n_+$, for any $t > t_0 = 0$.

Therefore, the positive orthant is an invariant set for a positive system. A system is positive if the vector field at any state on the boundary of the positive orthant points into the interior of the positive orthant or along the boundary of the positive orthant.

Definition 2.5. A function $V : \mathcal{A} \to \mathbb{R}$, where $\mathcal{A} \subseteq \mathbb{R}^n$ and the origin is in its interior, is called positive definite (positive semidefinite) on $\mathcal{A}$ if

$$V(0) = 0 \quad \text{and} \quad V(x) > 0\,(V(x) \geq 0), \tag{3}$$

for any $x \in \mathcal{A}\backslash\{0\}$. $V(x)$ is called negative definite (negative semidefinite) if $-V(x)$ is positive definite (positive semidefinite).

Definition 2.6. Let $V : \mathcal{A}^\dagger \to \mathbb{R}$, with $\mathcal{A}^\dagger \subseteq \mathbb{R}^n$ containing the origin, be a continuously differentiable function with $V(0) = 0$ and the following properties:

(a) $V(x)$ is positive definite on $\mathcal{A}^\dagger$ and radially unbounded, i.e. $V(x) \to \infty$ as $\|x\| \to \infty$
(b) its derivative along the trajectories of (1), $\dot{V}(x) = \nabla V^\top f(x)$, is negative definite on $\mathcal{A}^\dagger$.

Then V is called a Lyapunov function for the system (1).

The following result is a consequence of [13, Theorem 1] and will be instrumental in the procedure for estimating the DOA of the origin of the system (1).

Theorem 2.7. *Let $V(x)$ be a Lyapunov function for the system (1) and consider the region*

$$\mathcal{A} = \{x : \dot{V}(x) \leq 0\}. \tag{4}$$

Furthermore, let C^* be the largest positive value such that the level set $V(x) = C^*$ is contained in $\mathcal{A}$. Then, the set

$$\mathcal{S}_\mathcal{A} = \{x : V(x) < C^*\} \tag{5}$$

is contained in the DOA of the origin of (1), $\mathcal{S}$.

In [14], it is shown that if f is continuously differentiable in a neighborhood of the origin, then there exists a *maximal* Lyapunov function which can be used to estimate the DOA exactly [14, Theorem 2]. This function tends to infinity as x approaches the boundary $\partial\mathcal{S}$ of the DOA $\mathcal{S}$.

Definition 2.8 ([14]). A function $V_m : \mathbb{R}^n \to \mathbb{R}_+ \cup \{\infty\}$ is called a *maximal Lyapunov function* for the system (1) if

(a) $V_m(0) = 0$, $V_m(x) > 0$, for any $x \in \mathcal{S}\backslash\{0\}$
(b) $V_m(x) < \infty$ if and only if $x \in \mathcal{S}$
(c) $V_m(x) \to \infty$ as $x \to \partial\mathcal{S}$ and/or $\|x\| \to \infty$
(d) $\dot{V}_m$ is well defined and negative definite over $\mathcal{S}$.

When f is continuously differentiable, then $V_m(x) \to \infty$ as $x \to \partial\mathcal{S}$. If f is Lipschitz continuous on $\mathcal{S}$, then V_m can be taken continuously differentiable on $\mathcal{S}$ and then $V_m(x) \to \infty$ as $\|x\| \to \infty$.

Remark 2.9. In [14, Theorem 1] it is shown that if it is possible to find a set $\mathcal{A}$ containing the origin in its interior and a continuous function satisfying the properties of a maximal LF on that set, then $\mathcal{A}$ is the same as the DOA $\mathcal{S}$ defined in (2). This result implicitly assumes that there does not exist a $\xi \in \mathcal{S}^\circ$ such that $\lim_{x\to\xi} V(x) = \infty$. For any proper candidate LF, i.e. radially unbounded, this property obviously holds. As such, we consider in the definition above of a maximal LF, item c) the case when both $V_m(x) \to \infty$ as $x \to \partial\mathcal{S}$ and as $\|x\| \to \infty$ hold.

The next result will be of use with respect to the computation of DOA of positive systems.

Fact 2.10. Let the sets $\mathcal{S}_1, \mathcal{S}_2$ in $\mathbb{R}^n$ be two invariant sets for system (1). Then $\mathcal{S}_1 \cap \mathcal{S}_2$ is an invariant set for system (1).

Please cite this article as: A.I. Doban, M. Lazar, A switching control law approach for cancer immunotherapy of an evolutionary tumor growth model, Mathematical Biosciences (2016), http://dx.doi.org/10.1016/j.mbs.2016.09.008