Estimation of domains of attraction of tumor dormancy equilibriums

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***Abstract*—In the last years many models have been proposed to study the behavior of tumor development. Among them those based in a prey-predator approach provide a framework to analyze the interaction between malignant and immune system cells within the body. Since stochastic perturbations of the state variables can be externally induced on the system, an estimation of the region where tumor dormancy is recovered might be clinically useful. In this contribution, a Lyapunov based approach for the estimation of the domain of attraction of a dormancy equilibrium of a tumor growth model is proposed. An analysis of the effect of the value of a therapeutic related parameter is also provided.**

***Key words*—Tumor growth model, Dormancy equilibrium, Domain of attraction, Lyapunov stability.**

I. Introduction

TUMOR development models have received considerable attention in the last years [1], [2]. Although low dimension models are insufficient to accurately describe the complex phenomena of cancer, they can be useful to analyze partial effects and gain some biological insight. Among the many modeling approaches, prey-predator systems provide a conceptual and biologically sound framework to address the interaction between cancerous cells and immune system cells.

The resulting nonlinear systems usually have several equilibrium points which represent possible clinical states. In particular, asymptotically stable equilibrium points constitute desirable blocked-growth situations in which the amount of the malignant cells does not increase with time. Moreover, in the face of certain disturbances, the system would return back to this dormancy state. Since the levels of the cells can be significantly disturbed by external sources such as changes in hemodynamic perfusion of the tumor, radiation and chemotherapy [3], it is desirable to have some estimation of this region of asymptotic stability, also known as the Domain of Attraction (DA) of the equilibrium under study.

The estimation of DAs of nonlinear dynamic systems has been largely addressed so far. Among the many existing approaches [4], a particularly important family of techniques is based on the Lyapunov stability theory.

Lyapunov based approaches have been recently applied in the study of cancer models [3]. Specifically, it is proposed in [3] a methodology to determine whether a box shaped subspace which contains the dormancy equilibrium belongs to the DA of such equilibrium. The methodology is restricted to nonlinearities of the quadratic type.

In this contribution an optimization based methodology for the estimation of DAs which makes use of rational Lyapunov functions [5] is applied to a tumor growth model of the prey-predator type [6]. The proposed methodology can address any type of nonlinearity and the obtained estimations are larger than those calculated with other types of Lyapunov functions. The size and shape of the estimations are analyzed in terms of the resulting dormancy equilibrium which depends on a therapeutic related parameter of the model.

II. Tumor Growth Model

In this section the model proposed in [6] is introduced. In such model the tumor dynamics is described as a prey-depredator system. Malignant cells are modeled as a prey population which is destroyed by the immune system cells (cytotoxic T-lymphocites and macrophages). The immune system cells have two stages, hunting and resting. Cells in the resting form can become active hunting predators when activation signals are triggered. The model is presented in Eq. (1).

$$
\begin{aligned}
\frac{\mathrm{d}M}{\mathrm{d}t} &= q + rM\left(1-\frac{M}{k_1}\right) - \alpha MN \\
\frac{\mathrm{d}N}{\mathrm{d}t} &= \beta NZ - d_1 N \\
\frac{\mathrm{d}Z}{\mathrm{d}t} & sZ\left(1-\frac{Z}{k_2}\right) - \beta NZ - d_2 Z
\end{aligned}
\tag{1}
$$

The model possesses three state variables: density of tumor cells M, density of hunting cells, N, and density of resting predator cells Z. The parameters are as follows: r is the growth rate of the tumor cells, q is the rate of conversion of the normal cells to the malignant cells, α is the rate of predation of the tumor cells by the hunting cells, β is the rate of conversion of the resting cells to the hunting cells, s is the growth rate of the resting predator cells, d_1 is the natural death of the hunting cells, d_2 is the natural death of the resting cells, k_1 is the maximum carrying or packing capacity of the tumor cells and k_2 is the maximum carrying capacity of the resting cells. Artificial values for the parameters [6] are presented in Table I. The type and location of the resulting equilibrium points are shown in Table II.

The three equilibrium points determines a complex phase diagram. The asymptotically stable equilibrium, E_3, represents a dormancy condition desirable from a clinical point of view. Such equilibrium possesses a certain DA which is the region of the states space where trajectories that evolve to such dormancy condition originate. From outside this region the system may present an unbounded increase of the malignant cells. An estimation of the size and shape of this region is desirable therefore to analyze the robustness of this healthy state.

TABLE I
PARAMETERS OF SYSTEM (1)

Parameter	Value
q	10 *cells/day*
r	0.9/ *day*
k_1	0.8 */cells*
k_2	0.7 */cells*
α	0.3 */cells/day*
β	0.1 */cells/day*
s	0.8 */day*
d_1	0.02 */day*
d_2	0.03/*day*

TABLE II
EQUILIBRIUM POINTS OF SYSTEM (1)

Point	M	N	Z	Type
E_1	3.4081	0	0	Saddle
E_2	3.4081	0	0.673 7	Saddle
E_3	2.6768	5.4142	0.2	Stable

It should be stressed that the location of the three equilibriums depends on the values of the parameters of the model. In particular, parameter α has a significant effect on the position of equilibrium E_3 as shown in [3]. Since this parameter represents the rate of predation of the tumor cells by the hunting cells, it can be related to the amount of immunotherapeutic drug injected into the patient. Therefore, an analysis of the estimations of the domains for several values of parameter α may provide some insight in the design of a therapeutic strategy.

III. DETERMINATION OF DAS

The problem of determination of the DAs of nonlinear dynamic systems has been largely addressed due to the important theoretical and practical implications [7]. For general nonlinear systems, DAs are complex sets which do not admit analytical representation, therefore effort has been devoted to estimate them. Among the many existing approaches [4], a particularly important family of techniques is based on the Lyapunov stability theory. In the following, the fundamentals of the Lyapunov based method for DA estimation will be briefly outlined. For a rigorous and comprehensive treatment, see for example [7].

Consider the following autonomous nonlinear dynamic system $d\mathbf{x}/dt=\mathbf{f}(\mathbf{x})$ being the origin of the states space, $\mathbf{x}=\mathbf{0}$, an asymptotically stable equilibrium point. The DA of the origin is defined by the set of initial conditions $\mathbf{x}_0$, such that the trajectories initiated at $\mathbf{x}_0$ converge to the origin as time increases. Lyapunov stability theory [7], provides the basis of a family of techniques whose rationale is to approximate the DA by a level set of a Lyapunov function of the equilibrium point. Such a level set is an invariant set meaning that any trajectory starting within it remains in the set for $t \to \infty$. Consider that a function $V(\mathbf{x})$ exists such that i) $V(\mathbf{x})>0$ in some region $R(\mathbf{0})$ around the origin and ii) $dV(\mathbf{x})/dt<0$ in such region $R(\mathbf{0})$. Condition i) means that $V(\mathbf{x})$ is positive definite in region $R(\mathbf{0})$ around the origin and condition ii) that the time derivative of $V(\mathbf{x})$ is negative definite in that region. Positive (negative) definiteness of a function in some region of the states space implies that the function is strictly positive (negative) in all $\mathbf{x}\neq\mathbf{0}$ in $R(\mathbf{0})$ and $\mathbf{0}$ in $\mathbf{x}=\mathbf{0}$. If conditions i) and ii) hold for the dynamic system under study then $V(\mathbf{x})$ is known as a Lyapunov function for such system at the origin.

Let $V(\mathbf{x})=c$ be the level set of $V(\mathbf{x})$ at value c, this is, the projection on the states space of $V(\mathbf{x})$ at value c. Such projection determines the region $S(\mathbf{0})=\{\mathbf{x}\colon V(\mathbf{x}) - c \leq 0\}$. Consider that $S(\mathbf{0})$ is contained in $R(\mathbf{0})$, then $S(\mathbf{0})$ belongs to the DA of the origin and can be considered an estimation of $DA(\mathbf{0})$. Clearly, the larger the c, the better the estimation of the DA for some couple $d\mathbf{x}/dt=\mathbf{f}(\mathbf{x})$ and $V(\mathbf{x})$.

In order to estimate the DA of the system under study the idea is therefore to find the maximum level set of some given $V(\mathbf{x})$ which is fully contained in the region of negative definiteness of $dV(\mathbf{x})/dt$. For Lyapunov functions of the rational type [8], an estimation of the $DA(\mathbf{0})$ can be obtained by solving problem (2) to global optimality as described in [5].

$$
\begin{aligned}
&\min_{\mathbf{x},\varepsilon,c} c\\
s.\,t.\quad & V(\mathbf{x})=\frac{N(\mathbf{x})}{D(\mathbf{x})}\\
& V(\mathbf{x})-c=0\\
& \dot{V}(\mathbf{x})=0\\
& c>0\\
& \mathbf{x}\neq\mathbf{0}\\
& \nabla\left(V(\mathbf{x})-c\right)=\varepsilon\nabla\left(\dot{V}(\mathbf{x})\right)\\
& N(\mathbf{x})>0\\
& D(\mathbf{x})>0\\
& \mathbf{x}^L\leq\mathbf{x}\leq\mathbf{x}^U
\end{aligned}
\tag{2}
$$

being $N(\mathbf{x})$ a numerator and $D(\mathbf{x})$ a denominator both of polynomial form and ε is an auxiliary variable.

IV. DA ESTIMATION OF TUMOR EQUILIBRIUMS

The procedure described in the previous section is applied here to the stable equilibrium E_3 of model (1). The first step is to calculate a Lyapunov function for such equilibrium according to the methodology proposed in [8]. Then problem (2) is solved to global optimality by using a global optimization solver of the branch and bound type as described in [5]. In Fig. 1 it is shown the obtained estimation. It should be stressed that the region of Fig. 1 is an approximation of the actual DA which can be much larger than this invariant set.

From a clinical point of view it can be useful however to count with such estimation since, for example, it can be graphically appreciated regions where trajectories that converge to the dormancy equilibrium initiate. Moreover, since the estimation is an invariant set it can be also ensured that such trajectories will not leave the region at any time. If it could be estimated where in the states space some disturbance will drive the system from the current dormancy equilibrium, it would be possible to assess if the system will return to such healthy state. For example, in Fig. 2 it is shown several views of the estimation of the DA in the (N, M) plane for different values of Z. Any trajectory initiated in any of the ellipse shaped curves will eventually reach equilibrium E_3 without leaving the closed surface shown in Fig. 1.

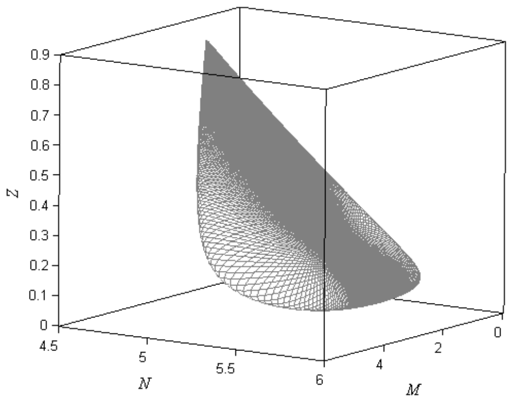

Fig. 1: DA around the equilibrium point E3.

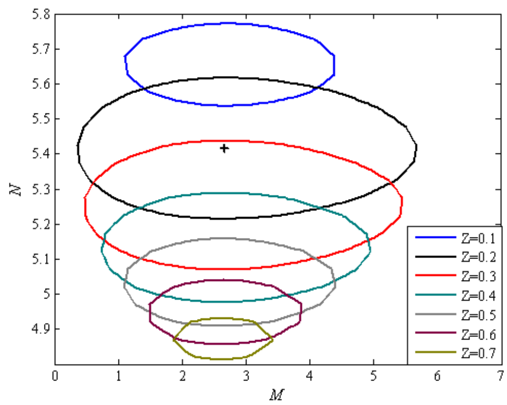

Fig. 2: DA projections on the (N,M) plane for several Z values (α=0.3, M=2.6768)

V. Effect of Therapeutic Strategies

The location of the dormancy equilibrium depends on the parameters of the model. For the studied instance, where parameter α takes the value of 0.3 (Table I), state M establishes in value 2.6768 (Table II). Parameter α is the rate of predation of the tumor cells by the hunting cells. Such parameter might be manipulated with the amount of immunotherapeutic drug injected into the patient [3]. Since it is desirable to keep medication levels as low as possible, a complex tradeoff exist between the robustness of the patient clinical situation and the aggressiveness of the treatment. In order to asses this tradeoff, estimations of the domains can be obtained for different values of parameter α within a range. In Figs. 3 and 4 there are shown estimations of the DA for $\alpha = 0.06$ and $\alpha = 0.16$, which may be understood as low and intermediate aggressive treatments, while the one corresponding to $\alpha = 0.3$ (Figs. 1, 2) is a highly aggressive one. Note that the density of malignant cells at the equilibrium decreases for larger values of α as shown in [3]. The size and shape of the estimations on the other hand do not vary significantly with such parameter.

VI. Conclusions

In this contribution the estimation of the DA of a stable equilibrium point of a cancer model was performed using a Lyapunov based methodology. The dynamic model describes the interactions of the different cell populations within the body based on a prey-predator approach. The equilibrium under study corresponded to a tumor dormancy state which is a clinically desirable condition. The estimation of the DA conservatively represents the set of initial conditions that determine trajectories that evolve to the equilibrium as time increases without leaving it. Such estimations might have some role in the design of therapeutic strategies since tradeoffs between therapeutic drug delivery and robustness of the clinical situation can be quantitatively evaluated.

It should be stressed that a complete description of tumor dynamics would require considering other effects, like diffusion of compounds through biological tissues, changes in the vascularization of the tumoral mass, etc. [3] which would increase the size and nonlinear complexity of the model. However, the proposed approach remains valid since problem (2) is general in the sense that it is not size or constrained and can address any type of nonlinerality.

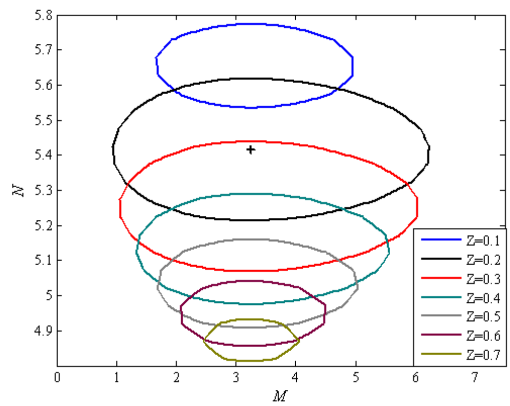

Fig. 3: DA projections on the (N,M) plane for several Z values ($\alpha = 0.06$, $M = 3.2480$)

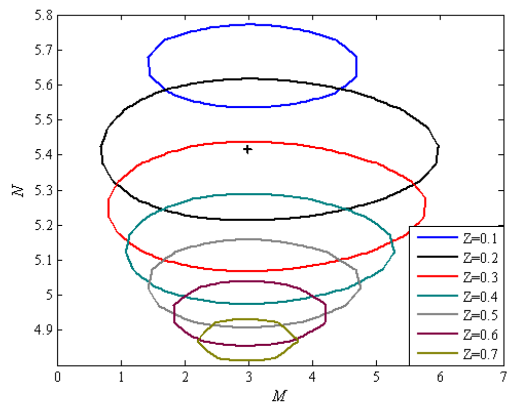

Fig. 4: DA projections on the (N,M) plane for several Z values ($\alpha = 0.16$, $M = 2.9964$)

VII. References

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