On upper bounds for compact invariant sets of nonlinear bladder cancer system with BCG immunotherapy

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Abstract. In this work upper bounds for all variables of the nonlinear bladder cancer system with BCG immunotherapy are derived. These bounds characterize ultimate health conditions in the ideal situation of infinite time interval and may be used in studies of global dynamics. Some nonexistence conditions of compact invariant sets are presented as well.
Key words: Upper Bounds, Bladder Cancer, Immunotherapy, Compact Invariant Sets

1 Introduction

The dynamic of cancerous tumor growth and immunological response can be described by a nonlinear model. The analysis of these models are necessary to understand in short and long time behavior how the tumor invades surrounding organs (this processes is called metastases) or simply growth *in situ*. Analysis of nonlinear mathematical biological ordinary differential equation (ODE) system is relatively a new area to investigate, the advantage over the PDE mathematical biological systems which is most common to find these analysis in literature is the simplicity that carry at the moment of visualize a whole framework with the main variables. Analyzing a high degree mathematical biological ODE system can present a better interaction framework of the whole system, and with a proper anti-tumor treatment may reduce as many side effects possible if a key variable is identified. In order to reduce cancerous tumor significantly several treatments must by combine. Latency may occur if a non proper serious care is taken, see e.g. paper [1].

Bladder Cancer is a tumor that growths in the inner surface of the bladder, it originated at first in the epithelium as *carcinoma in-situ (*CIS*)* and after some time the tumor begins to invade the superficial muscle layer. According to the TNM classification of Cancer if tumor is not eradicated by surgery on T2a stage the tumor will penetrated into the deep muscle leading to a more aggressive treatment. Cystectomy consist in removal of the bladder which is an aggressive treatment,this is usually made when the tumor has growth up to stage T3a.

If no surgery or treatment are applied up to stage T3a, the tumor next stage is invasion of the surrounding organs , for example lungs, liver, bone, etc. If metastasis is detected no treatment or surgery can be able to eradicate the tumor, see e.g. paper [2].

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Hence we can say that in a short time of period the tumor is *in-situ* and there is absence of metastasis therefore it can be removed with local surgery, better known as transurethral resection (TUR). This procedure consist on identifying cancerous regions in the bladder cavity and remove the damage tissue by making small cuts heating the circular point of the probe. The probe is introduced directly by the urethra. In this case to avoid latency, immunotherapy has proved to be more effective with less side effects in comparison with quimiotherapy after a tumor surgery has been made. The immunotherapy BCG (Bacillus-Calmette-Guerin) -*an attenuated strain of Mycobacterium bovis (M. bovis) used for anti tuberculosis immunization* - clinically has proven to be a reliable procedure to avoid latency after TUR surgery in 50-70 [3]. Immunotherapy is a treatment which enhances the immune response against a pathogen, in this case cancer cells are known to be a pathogen because a set of cancerous cells make a cancerous tumor.

The mathematical model under study was presented by Svetlana in 2007, [4], where it describe the interaction between tumor cells within the bladder, immune system response and BCG immunotherapy with a system of nonlinear ODEs. To describe the model slightly, we have that the model is divided into two subpopulation of tumor cells, we have those that have been infected (T_i) by BCG (B) and those who have not been infected by BCG (Tu), but the total tumor cells is given by the sum of T_u and T_i. The effector cells (E) are the set of the immune system response cells (APC, natural killer cells, lymphocyte-activated killer) defined by one single term. Also the model describe two types of tumor growth behavior, exponential and logistic. Is called exponential growth because the rate proportional to the product $T_u r$ is constant , hence there is no death of tumor cells as a result of self-limiting competition for resources such as oxygen and glucose , thus the product $-p_2 T_u B$ where p_2 is the coefficient of infection rate of tumor cells by BCG will continue growing at the rate $T_u r$ indicating that the BCG treatment has a low effect on the tumorous cells. Is called logistic growth when the tumor carrying capacity (β^{-1}) may be viewed as the maximum carry capacity of the tumor where is prevail the competition for resources (β).

In this paper localizations analysis of compact invariant sets for the bladder cancer system and bounds for the bounded positively invariant domain were made under the logistic tumorous growth cells due to the complexity that encompasses the dynamics of all the variables. The model is presented below:

$$\begin{aligned}
\frac{dB}{dt} &= -\mu_1 B - p_1 EB - p_2 BT_u + b \\
\frac{dE}{dt} &= -\mu_2 E + \alpha T_i + p_4 EB - p_5 ET_i \\
\frac{dT_i}{dt} &= -p_3 ET_i + p_2 BT_u \\
\frac{dT_u}{dt} &= T_u(-p_2 B + r[1 - \beta T_u])
\end{aligned} \tag{1}$$

On the model we can see that the BCG immunotherapy have a parameter b which is a constant dose of the treatment BCG, then some free BCG binds to tumorous cells at a coefficient p_2 infecting them but other BCG is lost at a rate p_1 due to the effector cells recognized them as pathogens cells. The coefficient μ_1 indicates the rate of BCG decay. From here we can say that b is our free parameter that can be manipulated in

order to be considered as a proper doses of BCG with lower side effects if bounds are apply.

The effector cells on the other hand have two complex dynamic, the first one is to deal with BCG at a rate p_4 and the second one is to eliminate the tumor infected cells by BCG at a rate p_5. The μ_2 coefficient is the effector cells mortality rate and α be the rate of effector stimulations due to infected tumor cells. The advantage of the effector cells on eliminate first the BCG is that strengthens their cells against these tumorous cells. The Ti is attacked at a rate p_3 by the effectors strengthens cells and continuously infected by BCG at a rate p_2 on new regions of the tumor area uninfected, see e.g. paper [Svetlana, 2007].

The method of *Localization analysis of Compact Invariant Sets* is a powerful mathematical tool for finding trapping regions given a localizing function, this is important because it gives a solution to the localization problem of all compact invariant sets that the system have. Localizing functions are tricky to find using a general methodology because each localizing function is customized for each system under study. In literature some of these function were apply on physic systems [5], mechanical systems [6], chaotic systems [7],[8] for mention some few of them. The model (1) differs from other models in literature, see e.g. paper [9] by the fact of considering the interaction terms of αT_i and $p_4 EB$ instead of analyzing the explicit effects of one citokine.

In this work we present result concern to the solution to the localization problem of all compact invariant contained in the positive orthant for the bladder cancer with BCG immunotherapy under a logistic growth and a nonexistence conditions where the boundaries positive domains are presented with some inequalities depending of the parameters of the system.

2 Biological sense of the system,its parameters

Svetlana in 2007 presents for the first time the system (1) where the parameters value are compiled from peer-reviewed mathematical models of cancer growth and immunotherapy BCG. The list of all the parameters of the system (1) are presented in Table 1,[4]. There main idea of using values from literature was to obtain a generic qualitative results that are intrinsic to the models structure. This leads to results that are not tied to any specific growth rates if mathematical analysis is made. In our case the biological interpretation once is located all compact invariant sets will depend of the parameters value of the system (1). Notwithstanding the parameter ranges are realistic and agree with values from the literature this leads to our results to have biologic sense after our mathematical analysis. The parameter range for tumor growth rate presented in Table 1 is presented in vitro, from mice or from humans. In this case is consider the in vitro parameter, proposed by Aranha in 2000, [10]. If a parameter is obtained in a laboratory under an artificial control environment, isolated from living organisms or systems but artificially maintained in a test tube for continuous surveillance is called in vitro parameter. According to Andrea in 2004 studies in vitro leads to a greater understanding with all the variables of the bladder cancer system. The system 1 which has a complex dynamics between the immunotherapy BCG and the tumor growth, the in vitro parameter value will be for the tumor growth. [11]

3 Some preliminaries and necessary notations

We consider a $C^\infty-$ differentiable system

$$\dot{x} = F(x), \tag{2}$$

with $x \in \mathbf{R}^n$, $F(x) = (F_1(x), \ldots, F_n(x))^T$ and $F_i(x) \in C^\infty(\mathbf{R}^n)$, $i = 1, \ldots, n$.

Let $h(x) \in C^\infty(\mathbf{R}^n)$ be a function such that h is not the first integral of the system (2).

The function h is used in the solution of the localization problem of compact invariant sets and is called a localizing function. Suppose that we are interested in the localization of all compact invariant sets located in some set $N \subset \mathbf{R}^n$ where N is an invariant set for the system (2) or a domain. By $S(h)$ we denote the set $\{x \in \mathbf{R}^n : L_F h(x) = 0\}$, where $L_F h(x)$ is a Lie derivative with respect to F. Further, we define $h_{\inf}(N) := \inf\{h(x) \mid x \in N \cap S(h)\}$, $h_{\sup}(N) := \sup\{h(x) \mid x \in N \cap S(h)\}$.

Proposition 1. *If $N \cap S(h) = \emptyset$ then the system (2) has no compact invariant sets located in N.*

Theorem 1. *For any $h(x) \in C^\infty(\mathbf{R}^n)$ all compact invariant sets of the system (2) located in N are contained in the set defined by the formula*

$$K(N) = \{x \in N : h_{\inf}(N) \leq h(x) \leq h_{\sup}(N)\}$$

as well.

Theorem 2. *Let $h_m(x), m = 1, 2, \ldots$ be a sequence of functions from $C^\infty(\mathbf{R}^n)$. Sets*

$$K_1 = K_{h_1}, K_m = K_{m-1} \cap K_{m-1,m}, m > 1,$$

with

$$\begin{aligned} K_{m-1,m} &= \{x : h_{m,\inf} \leq h_m(x) \leq h_{m,\sup}\}, \\ h_{m,\sup} &= \sup_{S_{h_m} \cap K_{m-1}} h_m(x), \\ h_{m,\inf} &= \inf_{S_{h_m} \cap K_{m-1}} h_m(x), \end{aligned}$$

contain all compact invariant sets of the system (2) and $K_1 \supseteq K_2 \supseteq \cdots \supseteq K_m \supseteq \ldots$.

4 Main result: polytopic localization for all compact invariant sets

In order to study the system (1) we took the a dimensionless blader cancer system from Svetlana in 2007. The system is below:

$$\begin{aligned}\dot{x} &= x(-1 - p_1 y - p_2 w) + b \\ \dot{y} &= y(-\mu + p_4 x - p_5 z) + \alpha z \\ \dot{z} &= -p_3 yz + p_2 xw \\ \dot{w} &= w(-p_2 x + r - r\beta w)\end{aligned} \tag{3}$$

where x represent the treatment BCG and the parameter b is the continuous doses of BCG, y represent the set of effector cells (APC, natural killer cells, lymphocyte-activated killer), z represents the tumor infected cells and w is the tumor uninfected cells via endocytosis after administration of the BCG in the bladder. All variables are considered in the positive orthant $\mathbf{R}^4_+ = \{\, x > 0; y > 0; z > 0; w > 0\}$ because of its biological nature. Also, let $\mathbf{R}^4_{+,0}$ be the closure of $\mathbf{R}^4_+ : \mathbf{R}^4_{+,0} = \{x \geq 0; y \geq 0; z \geq 0; w \geq 0\}$.

By using results in Section 2 and the localizing function $h_1 = x$ we can derive the localization set

$$K_1(h_1) = \{x \leq b\}$$

From this we concluded that the upper bound for the treatment will depend of the BCG doses administrated, according to Svetlana in 2007 a optimal doses of BCG is with less side effects.

Next, by using results in Section 2 and the localizing function $h_2 = w$ we can obtain the localization set

$$K_2(h_2) = \left\{ w \leq \frac{1}{\beta} \right\}$$

Now let

$$\frac{\mu}{\alpha} \leq \frac{p_3}{p_5} \tag{4}$$

Then by using results in Section 2 and the localizing function $h_3 = z - qy$ we can obtain the localization set

$$K_3(h_3) = \left\{ z - qy \leq \frac{p_2 p_5 b}{p_3 \alpha \beta} \right\},$$

with $q \in \left[\frac{\mu}{\alpha}, \frac{P_3}{P_5} \right]$.

Further, by using results in Section 2 and the localizing function $h_4 = z + w$ we can obtain the localization set

$$K_4(h_4; q) := \left\{ z \leq z_{\max}(q) := \frac{1}{\beta} + \frac{bp_2}{2q\alpha\beta} + \sqrt{\frac{b^2 p_2^2}{4q^2\alpha^2\beta^2} + \frac{rq}{4\beta p_3}} \right\}$$

under condition (4).

The best bound $z_{\max}(q_{\min})$ may be found from the solution of the minimization problem

$$\min\left\{z_{\max}(q); q \in \left[\frac{\mu}{\alpha}, \frac{P_3}{P_5}\right]\right\}$$

and we introduce

$$K(h_4) := K(h_4; q_{\min})$$

Now let

$$\mu - p_4 b > 0 \tag{5}$$

Finally, by using results in Section 2 and the localizing function $h_5 = y$ we can obtain the localization set

$$K(h_5) = \left\{y \leq y_{max} := \frac{\alpha z_{\max}}{\mu - P_4 b}\right\}$$

As a result, we come to

Theorem 3. *Suppose that conditions 4 and 5 hold. Then all compact invariant sets are located in the set*

$$K := \cap_{i=1;2;4;5} K(h_i)$$

5 Conditions of non existence of compact invariant sets in $\mathbf{R}^4_{+,0} \cap \{w > 0\}$

Conditions of non existence in the domain $\mathbf{R}^4_{+,0} \cap \{w > 0\}$ can be derived by exploiting the next rational localization function.

$$h_6 = \frac{x}{w}$$

We have

Theorem 4. *Let*

$$(1 + r)^2 > 4 p_2 b \tag{6}$$

Then there are no compact invariant sets contained in $\mathbf{R}^4_{+,0} \cap \{w > 0\}$.

We notice that the condition (6) holds according with parameters from Table 1 in [4].

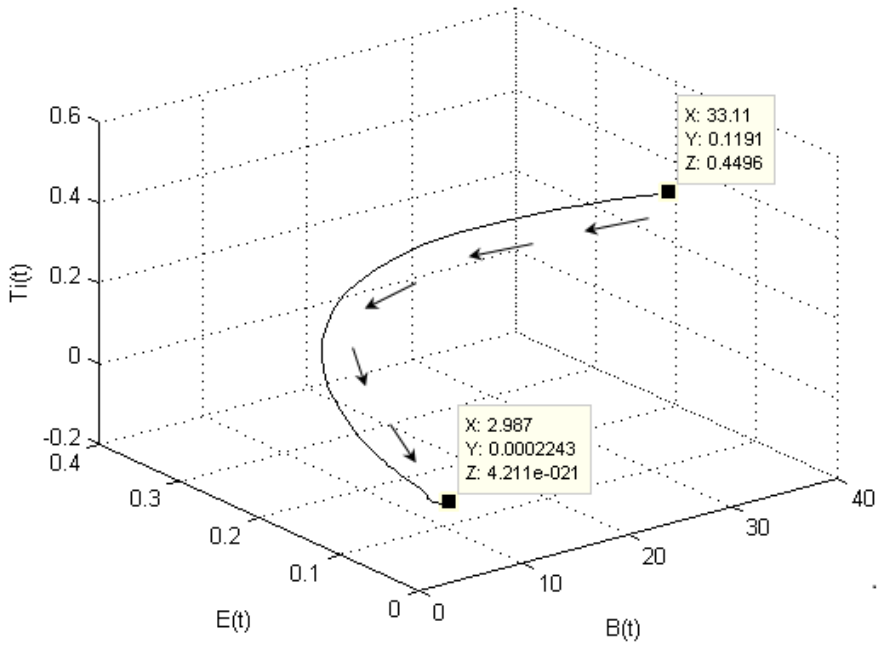

Fig. 1. Trajectory converging to an equilibrium point (b, 0,0,0).

6 Simulations

In order to simulate we took the parameters values of Table 1 in [4]. First we simulate the trajectory around one of the equilibrium point (b,0,0,0) presented also in [4], where the equilibrium point will depend of the value of the treatment. In Figure 1 is presented the flow of the trajectory to the equilibrium point. The initial conditions are (33.11 1.778 0.1191 0.4496).

In Figure 2 in presented the the same trajectory inside the polytope, this is, restricted by the upper bound of the parameters x,z,w.

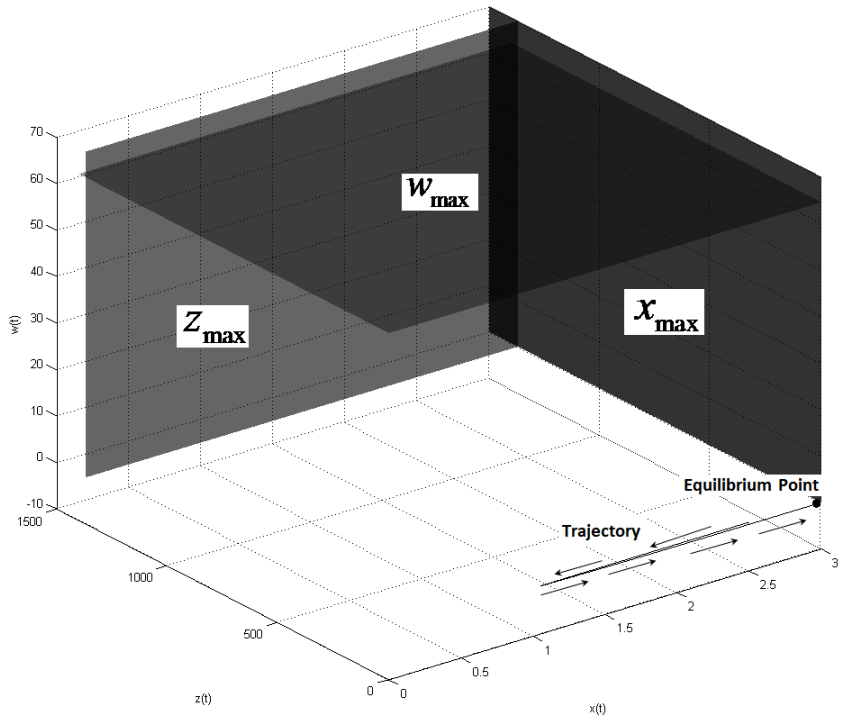

Fig. 2. Trajectory inside the positive polytope, $x_{max}, z_{max}, w_{max}$

7 Biological sense

The biological interpretation concerned to the mathematical analysis are the following:

1. The upper bound of the treatment BCG indicates the maximum carrying capacity of BCG infection to the tumor uninfected cells in the inner bladder.
2. The upper bound of the tumor logistic growth rate under the parameter value in vitro present the maximum carrying capacity of tumor growth of continuous feeding of glucose and oxygen for survival.
3. The upper bound of the effector cells will depend of the maximum bound of tumor infected cells by BCG, in order to eradicate the tumor in the bladder. In this case negligible the side effects by BCG.

8 Concluding remarks

In this paper we present results concerning upper bounds for all variables of the system (3) which characterize ultimate health conditions in the ideal situation of infinite time interval. These bounds are useful in studies of global dynamics of (3) and should be complemented by a proof that the system (3) has no escaping to infinity trajectories in $\mathbf{R}^4_+$. The corresponding work now is in a process.

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