STABILITY ANALYSIS OF SWITCHED SYSTEMS FOR CANCER TREATMENT BY ANTI-ANGIOGENESIS VIA MINIMUM DWELL TIME (MDT)

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Abstract. Anti-angiogenic therapy is a novel treatment approach for cancer that aims at preventing a tumor from developing its own blood supply system that it needs for growth. In this paper we consider a mathematical model for cancer with treatment by using Lotka-Volterra Competition model. In order to minimize the side effects for treatment, we propose a switched system to determine the duration of treatments by using the MDT method and provide an analytical insight into the effectiveness of such method. An illustrative example is presented to show the validity of the results.

Keywords: Lotka-Volterra competition; cancer anti-angiogenics; switched systems; minimum dwell time; multiple Lyapunov functions; stability.

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1. INTRODUCTION

According to the World Health Organization, cancer is the second leading cause of death globally, and is responsible for an estimated 9.6 million deaths in 2018. Globally, about 1 in 6 deaths is due to cancer [1].

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The best treatment for cancer is early detection and then the use of suitable treatment such as chemotherapy, surgery,immunotherapy, radiotherapy or anti-angiogenics therapy. In this paper, we focus on cancer treatment by anti-angiogenics therapy. In order for the cancer to grow and survive, it needs oxygen and nutrients which can be found in nearby blood vessels. So, to reduce the growth of the cancer, anti-angiogenics drugs are used to prevent the cancer from forming new blood vessels. Many angiogenesis inhibitors also affect other ways that cancers grow, people may also receive these drugs with other types of treatment. For each type of cancer, certain types of drugs have been used for treatment, but these drugs have many side effects such as hypertension, delayed wound healing, bleeding and more. So we look for a way to minimize these effects.

Mathematicians are trying to help the medical community in search for a cure for cancer. For that, many mathematicians have developed mathematical models to help scientists predict how different cancer types grow, and how to eliminate them [9, 10, 11]. Of those models Lotka–Volterra model. [12, 13, 14, 15, 17] have been used to describe the interactions between normal cells and cancer cells and the effect of treatment on them.

Some researchers [5, 6, 7, 8] have been studying cancer therapy strategies, which are based on switching between successive parameter dependent domains of attraction. They used switched system to model these strategies.

In this paper, we aim to propose a switched system to determine the duration of treatments by using the MDT method and provide an analytical insight into the effectiveness of such method. Specifically, time-driven switching control is used. The Lotka-Volterra model is discussed in Section 2. The cancer dynamics are discussed in Section 3. Section 4 presents the model with treatment. The proposed switching signal is defined in Section 5. An example illustrating the results are presented in Section 6.

2. THE LOTKA-VOLTERRA COMPETITION MODEL [3]

A competition model is a system of differential equations used to describe the dynamics of two or more species living in the same environment and sharing the same resources. If one species is more efficient in finding resources, then it will increase in population and win the competition driving the other species to extinction. But if there are enough resources to

support all species then they can share the environment and coexist together. The Lotka-Volterra competition model describes the competition between two species and assumes logistic growth for each population which are reduced due to the competition between them. The mathematical model is given by:

$$\dot{x}_1 = \alpha_1 x_1 \left(1 - \frac{x_1}{K_1}\right) - \beta_1 x_1 x_2$$

(2.1)
$$\dot{x}_2 = \alpha_2 x_2 \left(1 - \frac{x_2}{K_2}\right) - \beta_2 x_1 x_2$$

where x_1 and x_2 are populations of species 1 and 2, respectively; α_1 and α_2 are the growth rates of species 1 and 2, respectively; K_1 and K_2 are the carrying capacities of the populations; β_1 is the competition coefficient that measures the competitive effect that population 2 has on population 1 and β_2 is the competition coefficient that measures the competitive effect that population 1 has on population 2.

To study the behavior of the model we will find the equilibria (steady states) and determine their stability. There are four equilibria, as follows

$$(0,0), (K_1,0), (0,K_2), (\bar{x}_1, \bar{x}_2)$$

where

$$\bar{x}_1 = \frac{\alpha_1 \alpha_2 K_1 - \alpha_2 \beta_1 K_1 K_2}{\alpha_1 \alpha_2 - \beta_1 \beta_2 K_1 K_2}, \quad \bar{x}_2 = \frac{\alpha_1 \alpha_2 K_2 - \alpha_1 \beta_2 K_1 K_2}{\alpha_1 \alpha_2 - \beta_1 \beta_2 K_1 K_2}$$

Note that $(\bar{x}_1, \bar{x}_2)$ exists if either

$$\alpha_1 > \beta_1 K_2, \ \alpha_2 > \beta_2 K_1$$

or

$$\alpha_1 < \beta_1 K_2, \ \alpha_2 < \beta_2 K_1$$

The stability of the equilibrium is determined by the eigenvalues of the Jacobian

(2.2)
$$J = \begin{bmatrix} \alpha_1 - \frac{2\alpha_1}{K_1} x_1 - \beta_1 x_2 & -\beta_1 x_1 \\ -\beta_2 x_2 & \alpha_2 - \frac{2\alpha_2}{K_2} x_2 - \beta_2 x_1 \end{bmatrix}$$

For $E_1 = (0,0)$ the matrix (2.2) is

$$J_1 = \begin{bmatrix} \alpha_1 & 0 \\ 0 & \alpha_2 \end{bmatrix}$$

This matrix has two positive eigenvalues and (0,0) is always an unstable.

For $E_2 = (K_1, 0)$ the matrix (2.2) is

$$J_2 = \begin{bmatrix} -\alpha_1 & -\beta_1 K_1 \\ 0 & \alpha_2 - \beta_2 K_1 \end{bmatrix}$$

This matrix has eigenvalues $\{-\alpha_1, \alpha_2 - \beta_2 K_1\}$. It follows that $(K_1, 0)$ is a saddle if

$$K_1 < \frac{\alpha_2}{\beta_2},$$

but asymptotically stable if

$$K_1 > \frac{\alpha_2}{\beta_2}.$$

For $E_3 = (0, K_2)$ the matrix (2.2) is

$$J_3 = \begin{bmatrix} \alpha_1 - \beta_1 K_2 & 0 \\ -\beta_2 K_2 & -\alpha_2 \end{bmatrix}$$

This matrix has eigenvalues $\{\alpha_1 - \beta_1 K_2, -\alpha_2\}$. It follows that $(0, K_2)$ is a saddle if

$$K_2 < \frac{\alpha_1}{\beta_1},$$

but asymptotically stable if

$$K_2 > \frac{\alpha_1}{\beta_1}.$$

For $E_4 = (\bar{x}_1, \bar{x}_2)$ the matrix (2.2) is

$$J_4 = \begin{bmatrix} \alpha_1 - \frac{2\alpha_1}{K_1}\bar{x}_1 - \beta_1 \bar{x}_2 & -\beta_1 \bar{x}_1 \\ -\beta_2 \bar{x}_2 & \alpha_2 - \frac{2\alpha_2}{K_2}\bar{x}_2 - \beta_2 \bar{x}_1 \end{bmatrix}$$

From equation (2.1) , $(\bar{x}_1, \bar{x}_2)$ satisfies the equations

$$\alpha_1 \left(1 - \frac{\bar{x}_1}{K_1} \right) - \beta_1 \bar{x}_2 = 0$$

$$\alpha_2 \left(1 - \frac{\bar{x}_2}{K_2} \right) - \beta_2 \bar{x}_1 = 0$$

and so

$$J_4 = \begin{bmatrix} \frac{-\alpha_1}{K_1} \bar{x}_1 & -\beta_1 \bar{x}_1 \\ -\beta_2 \bar{x}_2 & \frac{-\alpha_2}{K_2} \bar{x}_2 \end{bmatrix}$$

Then

$$\det (J_4) = \bar{x}_1 \bar{x}_2 \left(\frac{\alpha_1 \alpha_2}{K_1 K_2} - \beta_1 \beta_2 \right),$$

$$\mathrm{tr}\, (J_4) = -\frac{\alpha_1}{K_1} \bar{x}_1 - \frac{\alpha_2}{K_2} \bar{x}_2.$$

It follows that E_4 is a saddle if

$$K_1 K_2 > \frac{\alpha_1 \alpha_2}{\beta_1 \beta_2},$$

but asymptotically stable if

$$K_1 K_2 < \frac{\alpha_1 \alpha_2}{\beta_1 \beta_2}.$$

Theorem 2.1. *For the Lotka-Volterra two species competition model we have four cases,*

A. *If $K_1 > \frac{\alpha_2}{\beta_2}$ and $K_2 < \frac{\alpha_1}{\beta_1}$ then $(K_1, 0)$ is asymptotically stable and $(0, K_2)$ is unstable, so x_1 gains the competition.*

B. *If $K_1 < \frac{\alpha_2}{\beta_2}$ and $K_2 > \frac{\alpha_1}{\beta_1}$ then $(0, K_2)$ is asymptotically stable and $(K_1, 0)$ is unstable, so x_2 gains the competition.*

C. *If $K_1 < \frac{\alpha_2}{\beta_2}$ and $K_2 < \frac{\alpha_1}{\beta_1}$ then the two species coexist at $(\bar{x}_1, \bar{x}_2)$ which is asymptotically stable. In this case both $(K_1, 0)$ and $(0, K_2)$ are unstable.*

D. *If $K_1 > \frac{\alpha_2}{\beta_2}$ and $K_2 > \frac{\alpha_1}{\beta_1}$ then $(K_1, 0)$ and $(0, K_2)$ are both asymptotically stable and the bistability occurs for the two species.* [2]

3. CANCER DYNAMICS

In this section we use Lotka-Volterra model (2.1) to describe the competition between normal cells x_1 and cancer cells x_2. The model parameters have the following biological meaning: β_1 represents the negative effect of the cancer cells on normal cells, while β_2 represents the effect of the normal cells on cancer cells, α_1 and α_2 are the maximum growth rates of normal and cancer cells respectively, K_1 and K_2 denote the carrying capacities of normal and cancer cells. This

system contains four equilibria each with different stability properties based on the conditions
mentioned in Theorem (2.1).

1. $E = (0,0)$ will always exist and unstable, so it is not biologically important.

2. $E = (K_1,0)$ represents normal cells and no cancer cells. If $K_1 > \frac{\alpha_2}{\beta_2}$ and $K_2 < \frac{\alpha_1}{\beta_1}$ then
   this is an asymptotically stable equilibrium point which means that the cancer will be
   eliminated.

3. $E = (0,K_2)$ represents an invasive cancer. If $K_1 < \frac{\alpha_2}{\beta_2}$ and $K_2 > \frac{\alpha_1}{\beta_1}$ then this is an asymp-
   totically stable equilibrium point which means that the cancer will destroy all normal
   cells.

4. $E = (\bar{x}_1, \bar{x}_2)$ represents a stable coexistence of both cancer and normal cells. If $K_1 < \frac{\alpha_2}{\beta_2}$
   and $K_2 < \frac{\alpha_1}{\beta_1}$ then this is an asymptotically stable equilibrium point which means that
   the cancer is controlled at a certain level.

4. CANCER MODEL WITH TREATMENT

In this section we will consider using an anti-angiogenic drug to stop the cancer from having
its own blood vessels. This treatment will slow the growth of the cancer or sometimes shrink it.
In order to study the cancer model with treatment we will use the following model :

$$\dot{x}_1 = \alpha_1 x_1 \left(1 - \frac{x_1}{K_1} \right) - \beta_1 x_1 x_2$$

(4.1)

$$\dot{x}_2 = x_2 \left(\alpha_2 - \gamma - \frac{\alpha_2 x_2}{K_2} \right) - \beta_2 x_1 x_2$$

where $\gamma < \alpha_2$ denotes the anti-angiogenic treatment rate.

4.1. Existence of Equilibrium. We will have four equilibria as follows:

$$E_1 = (0,0), E_2 = (K_1,0), E_3 = (0,K_2(1 - \frac{\gamma}{\alpha_2})), E_4 = (x_1^*, x_2^*)$$

where

$$x_1^* = \frac{\alpha_1 \alpha_2 K_1 - (\alpha_2 - \gamma)\beta_1 K_1 K_2}{\alpha_1 \alpha_2 - \beta_1 \beta_2 K_1 K_2}, \quad x_2^* = \frac{\alpha_1(\alpha_2 - \gamma)K_2 - \alpha_1 \beta_2 K_1 K_2}{\alpha_1 \alpha_2 - \beta_1 \beta_2 K_1 K_2}$$

E_1, E_2, always exists, but E_3 exists if $\gamma < \alpha_2$ and E_4 exists if either

$$\alpha_1 > \frac{\alpha_2 - \gamma}{\alpha_2} \beta_1 K_2, \ (\alpha_2 - \gamma) > \beta_2 K_1$$

or

$$\alpha_1 < \frac{\alpha_2 - \gamma}{\alpha_2} \beta_1 K_2, \ (\alpha_2 - \gamma) < \beta_2 K_1.$$

4.2. Stability Analysis. The stability of the equilibria is determined by the eigenvalues of the Jacobian,

(4.2)
$$J = \begin{bmatrix} \alpha_1 - 2\frac{\alpha_1}{K_1}x_1 - \beta_1 x_2 & -\beta_1 x_1 \\ -\beta_2 x_2 & \alpha_2 - \gamma - 2\frac{\alpha_2}{K_2}x_2 - \beta_2 x_1 \end{bmatrix}$$

For $E_1 = (0,0)$ the matrix (4.2) is

$$J_1 = \begin{bmatrix} \alpha_1 & 0 \\ 0 & \alpha_2 - \gamma \end{bmatrix}$$

Since $\gamma < \alpha_2$, then this matrix has two positive eigenvalues and $(0,0)$ is always an unstable.

For $E_2 = (K_1,0)$ the matrix (4.2) is

$$J_2 = \begin{bmatrix} -\alpha_1 & -\beta_1 K_1 \\ 0 & \alpha_2 - \gamma - \beta_2 K_1 \end{bmatrix}$$

with eigenvalues $\{-\alpha_1, \alpha_2 - \gamma - \beta_2 K_1\}$. It follows that $(K_1,0)$ is a saddle if

$$K_1 < \frac{\alpha_2 - \gamma}{\beta_2},$$

and asymptotically stable if

$$K_1 > \frac{\alpha_2 - \gamma}{\beta_2}.$$

For $E_3 = \left(0, K_2\left(1 - \frac{\gamma}{\alpha_2}\right)\right)$ the matrix (4.2) is

$$J_3 = \begin{bmatrix} \alpha_1 - \frac{\beta_1 K_2}{\alpha_2}(\alpha_2 - \gamma) & 0 \\ -\frac{\beta_2 K_2}{\alpha_2}(\alpha_2 - \gamma) & \gamma - \alpha_2 \end{bmatrix}$$

with eigenvalues $\left\{\alpha_1 - \frac{\beta_1 K_2}{\alpha_2}(\alpha_2 - \gamma), \gamma - \alpha_2\right\}$. It follows that $\left(0, K_2\left(1 - \frac{\gamma}{\alpha_2}\right)\right)$ is a saddle if

$$K_2 < \frac{\alpha_1 \alpha_2}{\beta_1(\alpha_2 - \gamma)},$$

and asymptotically stable if

$$K_2 > \frac{\alpha_1 \alpha_2}{\beta_1 (\alpha_2 - \gamma)}.$$

For $E_4 = (x_1^*, x_2^*)$

$$J_4 = \begin{bmatrix} \alpha_1 - 2\frac{\alpha_1}{K_1}x_1^* - \beta_1 x_2^* & -\beta_1 x_1^* \\ -\beta_2 x_2^* & \alpha_2 - \gamma - \frac{\alpha_2}{K_2}x_2^* - \beta_2 x_1^* \end{bmatrix}$$

From equation (4.1) ,we get

$$J_4 = \begin{bmatrix} -\frac{\alpha_1}{K_1}x_1^* & -\beta_1 x_1^* \\ -\beta_2 x_2^* & -\frac{\alpha_2 - \gamma}{K_2}x_2^* \end{bmatrix}$$

Then

$$\det (J_4) = (x_1^* x_2^*) \left(\frac{\alpha_1 (\alpha_2 - \gamma)}{K_1 K_2} - \beta_1 \beta_2 \right),$$

$$\operatorname{tr} (J_4) = -\frac{\alpha_1}{K_1}x_1^* - \frac{\alpha_2 - \gamma}{K_2}x_2^*.$$

It follows that E_4 is a saddle if

$$K_1 K_2 > \frac{\alpha_1 (\alpha_2 - \gamma)}{\beta_1 \beta_2},$$

and asymptotically stable if

$$K_1 K_2 < \frac{\alpha_1 (\alpha_2 - \gamma)}{\beta_1 \beta_2}.$$

In order to destroy all the cancer cells we need to focus on the equilibrium point $E_2 = (K_1, 0)$ and try to satisfy the conditions that make it asymptotically stable and make E_3 unstable (i.e.) $\gamma > m$, where $m = max \left\{ \alpha_2 - \beta_2 K_1, \alpha_2 - \frac{\alpha_1 \alpha_2}{\beta_1 K_2} \right\}$.

5. DESIGN OF THE SWITCHING SIGNAL

As mentioned in section 1, the treatment can have many side effects especially for high dosage of the drugs. So, in order to minimize these side effects, doctors need to reduce the dosage for periods of time or even stop the treatment. Our purpose is to determine the best duration for different dosages that would maintain the effectiveness of the treatment by introducing switching into model (4.1). Assume that the treatment γ is a parameter which varies over time in a simple way: it is a piecewise constant that switches its value at some certain times t_k, where $t_0 = 0 < t_1 < t_2 < \cdots < t_m < \cdots < \infty$, as $k = 0,1,2,\cdots$. Assume there are n different treatment rates γ_i where γ_i is a piecewise constant parameter, $i \in \{1,2,3,\cdots,n\}$. Consider a switching signal $\sigma(t) : [t_0,\infty) \to I = \{1,2,3,\cdots,n\}, n \in \mathbb{N}$ which is a piecewise right-continuous function. Let $\tau_k = t_{k+1} - t_k$ denotes the dwell time. This leads to the following model:

$$\dot{x}_1 = \alpha_1 x_1 \left(1 - \frac{x_1}{K_1} \right) - \beta_1 x_1 x_2$$

(5.1)
$$\dot{x}_2 = x_2 \left(\alpha_2 - \gamma_i - \frac{\alpha_2 x_2}{K_2} \right) - \beta_2 x_1 x_2$$

where $i \in \{1,2,3,\cdots,n\}$ follows the switching signal $\sigma(t)$, $m < \gamma_i < \alpha_2$. In order to destroy cancer cells and reduce the side effects of the treatment, we use MDT method in [16] and theorem in [20] which we state for convenience of the reader:

Theorem 5.1. [16] *Consider the nonlinear switched system*

(5.2)
$$\dot{x} = f_{\sigma(t)}(x)$$

with n = 2, and the two subsystems are active in turn. If $\dot{x} = f_1(x)$ is exponentially asymptotically stable, and there exists a Lyapunov function $V_1(x)$ such that

$$\dot{V}_1(x)|_{(1)} = \frac{\partial V_1}{\partial x} f_1(x) \leq -\lambda_1 V_1(x)$$

where

$$a_1 \|x\|^2 \leq V_1(x) \leqslant b_1 \|x\|^2, \ 0 < a_1 < b_1$$

and the subsystem $\dot{x} = f_2(x)$ is unstable and there exists a Lyapunov function $V_2(x)$ such that

$$\dot{V}_2(x)|_{(2)} = \frac{\partial V_2}{\partial x} f_2(x) \leq \lambda_2 V_2(x)$$

where

$$a_2 \|x\|^2 \leq V_2 \leqslant b_2 \|x\|^2, \ 0 < a_2 < b_2$$

then we have three cases

(i) *If* $\lambda_2 < \lambda_1$, *then system (5.2) is asymptotically stable under arbitrary switching with* $\tau_k^{(1)} \geq \tau_0$, $\tau_k^{(2)} \leq \tau_0$, *where* $\tau_k^{(i)}$ *is the dwell time of the* i^{th} *subsystem* $\dot{x} = f_i(x), i \in I$, *and the MDT is given by*

$$(5.3) \qquad\qquad \tau_0 = \frac{ln(\mu_1 \mu_2)}{\lambda_1 - \lambda_2}, \ \mu_i = \frac{b_i}{a_i}, \ i \in I$$

(ii) *If* $\lambda_1 = \lambda_2$, *then system (5.2) is asymptotically stable under arbitrary switching with* $\tau_k^{(1)} - \tau_k^{(2)} \geq \tau_0$, *and the MDT is given by*

$$(5.4) \qquad\qquad \tau_0 = \frac{ln(\mu_1 \mu_2)}{\lambda_1)}, \ \mu_i = \frac{b_i}{a_i}, \ i \in I$$

(iii) *If* $\lambda_2 > \lambda_1$, *then system (5.1) is asymptotically stable under arbitrary switching with* $\tau_k^{(1)} \geq \frac{\lambda_2 + \varepsilon}{\lambda_1} \tau_0, \tau_k^{(2)} \leq \tau_0$, *and the MDT is given by*

$$(5.5) \qquad\qquad \tau_0 = \frac{ln(\mu_1 \mu_2)}{\varepsilon}, \ \mu_i = \frac{b_i}{a_i}, \ i \in I$$

where $\varepsilon > 0$ *is an arbitrary positive real number.*

Theorem 5.2. [20] *Consider the nonlinear switched system (5.2) with* $n = 3$, *and the three subsystems are active in turn. If* $\dot{x} = f_1(x)$ *and* $\dot{x} = f_2(x)$ *are exponentially asymptotically stable, and there exists a Lyapunov function* $V_i(x)$ *such that*

$$\dot{V}_i(x)|_{(i)} = \frac{\partial V_i}{\partial x} f_i(x) \leq -\lambda_i V_i(x)$$

where

$$a_i \|x\|^2 \leq V_i(x) \leqslant b_i \|x\|^2, \ 0 < a_i < b_i \ for \ i = \{1, 2\}$$

and the subsystem $\dot{x} = f_3(x)$ *is unstable and there exists a Lyapunov function* $V_3(x)$ *such that*

$$\dot{V}_3(x)|_{(3)} = \frac{\partial V_3}{\partial x} f_3(x) \leq \lambda_3 V_3(x)$$

where

$$a_3 \|x\|^2 \leq V_3 \leqslant b_3 \|x\|^2, \ 0 < a_3 < b_3$$

then we have three cases

(i) If $\lambda_3 < \lambda_1 + \lambda_2$, then system (5.2) is asymptotically stable under arbitrary switching with $\tau_k^{(1)} \geq \tau_0$, $\tau_k^{(2)} \geq \tau_0$ and $\tau_k^{(3)} \leq \tau_0$, where $\tau_k^{(i)}$ is the dwell time of the ith subsystem $\dot{x} = f_i(x), i \in I$, and the MDT is given by

(5.6)
$$\tau_0 = \frac{ln(\mu_1\mu_2\mu_3)}{\lambda_1 + \lambda_2 - \lambda_3}, \ \mu_i = \frac{b_i}{a_i}, \ i \in I$$

(ii) If $\lambda_1 = \lambda_2 = \lambda_3$, then system (5.2) is asymptotically stable under arbitrary switching with $\tau_k^{(1)} + \tau_k^{(2)} - \tau_k^{(3)} \geq \tau_0$, and the MDT is given by

(5.7)
$$\tau_0 = \frac{ln(\mu_1\mu_2\mu_3)}{\lambda_1}, \ \mu_i = \frac{b_i}{a_i}, \ i \in I$$

(iii) If $\lambda_3 > \lambda_1 + \lambda_2$, then system (5.2) is asymptotically stable under arbitrary switching with $\tau_k^{(1)} \geq \frac{\lambda_3 + \varepsilon}{\lambda_1 + \lambda_2}\tau_0, \tau_k^{(2)} \geq \frac{\lambda_3 + \varepsilon}{\lambda_1 + \lambda_2}\tau_0, \tau_k^{(3)} \leq \tau_0$, and the MDT is given by

(5.8)
$$\tau_0 = \frac{ln(\mu_1\mu_2\mu_3)}{\varepsilon}, \ \mu_i = \frac{b_i}{a_i}, \ i \in I$$

where $\varepsilon > 0$ is an arbitrary positive real number.

6. NUMERICAL ILLUSTRATIONS

In this section, we apply the method from Theorem (5.1) on two subsystems, the second subsystem represents the interaction between cancer and normal cells without treatment while in the first subsystem we introduce treatment using anti-angiogenic drugs. Also the method from Theorem (5.2) on three subsystems is applied in the second example, where we introduce a third subsystem with a lower dosage of the drug to minimize the side effects. To illustrate these method, we assume the following values for fixed parameters $\alpha_1 = 0.9, \alpha_2 = 0.9, K_1 = K_2 = 10, \beta_1 = 0.18, \beta_2 = 0.045$. In the first example , we choose $\gamma_1 = 0.6, \gamma_2 = 0$, and for the second example, we choose $\gamma_1 = 0.75, \gamma_2 = 0.5, \gamma_3 = 0$.

Consider the following switched system:

$$\dot{x}_1 = 0.9x_1(1 - 0.1x_1) - 0.18x_1x_2$$

(6.1)
$$\dot{x}_2 = x_2(0.9 - \gamma_i - 0.09x_2) - 0.045x_1x_2$$

Example 6.1. *Consider the following subsystems:*

$$(6.2) \qquad subsystem1 : \begin{cases} \dot{x}_1 & = 0.9x_1 \left(1 - 0.1x_1\right) - 0.18x_1x_2 \\ \dot{x}_2 & = x_2 \left(0.3 - 0.09x_2\right) - 0.045x_1x_2 \end{cases}$$

$$(6.3) \qquad subsystem2 : \begin{cases} \dot{x}_1 & = 0.9x_1 \left(1 - 0.1x_1\right) - 0.18x_1x_2 \\ \dot{x}_2 & = 0.9x_2 \left(1 - 0.1x_2\right) - 0.045x_1x_2 \end{cases}$$

where subsystem 1 is the competition model between normal and cancer cells with treatment $(\gamma_1 = 0.6)$ and in subsystem 2 we stop using the treatment $(\gamma_2 = 0)$. we will use numerical simulations to prove that the switched system is asymptotically stable if we use the MDT method found in Theorem (5.1) even though subsystem 2 is unstable. This shows that we can stop using the drugs for a specific time period and then use it again for another time period and repeat this process without loosing stability, so the cancer would still be decreasing in size and we can minimize the side effects of the drug.

Analysing system (6.2) and (6.3) by using Linearization method, we find that the equilibrium point $(10,0)$ is unstable for subsystem 2 and asymptotically stable for subsystem 1. To use Theorem (5.1) to find the MDT for the switched system (6.1), we need to translate the point $(10,0)$ to the origin by using the transformation $x_1 = u_1 + 10$, $x_2 = u_2$ and get the switched system

$$(6.4) \qquad subsystem3 : \begin{cases} \dot{u}_1 & = -0.09u_1^2 - 0.9u_1 - 0.18u_1u_2 - 1.8u_2 \\ \dot{u}_2 & = -0.15u_2 - 0.09u_2^2 - 0.045u_1u_2 \end{cases}$$

$$(6.5) \qquad subsystem4 : \begin{cases} \dot{u}_1 & = -0.09u_1^2 - 0.9u_1 - 0.18u_1u_2 - 1.8u_2 \\ \dot{u}_2 & = 0.45u_2 - 0.09u_2^2 - 0.045u_1u_2 \end{cases}$$

Let $V_1 = \frac{1}{3}u_1^2 + u_2^2$ be a Lyapunov function for the 3rd subsystem, and $V_2 = \frac{1}{2}u_1^2 + u_2^2$ be a Lyapunov function for the 4th subsystem. Next;

$$\dot{V}_1|_{(1)} = \frac{2}{3}u_1\left(-0.09u_1^2 - 0.9u_1 - 0.18u_1u_2 - 1.8u_2\right) + 2u_2\left(-0.15u_2 - 0.09u_2^2 - 0.045u_1u_2\right)$$

$$= -0.06u_1^3 - 0.6u_1^2 - 0.12u_1^2u_2 - 1.2u_1u_2 - 0.3u_2^2 - 0.18u_2^3 - 0.09u_1u_2^2$$

$$\leq -0.6u_1^2 - 0.3u_2^2 = -0.3\left(2u_1^2 + u_2^2\right) \leq -0.3V_1$$

$$\dot{V}_2|_{(2)} = u_1\left(-0.09u_1^2 - 0.9u_1 - 0.18u_1u_2 - 1.8u_2\right) + 2u_2\left(0.45u_2 - 0.09u_2^2 - 0.045u_1u_2\right)$$

$$= -0.09u_1^3 - 0.9u_1^2 - 0.18u_1^2u_2 - 1.8u_1u_2 + 0.9u_2^2 - 0.18u_2^3 - 0.09u_1u_2^2$$

$$\leq -0.9u_1^2 + 0.9u_2^2 = 0.9\left(-u_1^2 + u_2^2\right) \leq 0.9V_2$$

then, $\lambda_1 = 0.3, \lambda_2 = 0.9$, and

$$\frac{1}{5}\|u\|^2 \leq V_1(u) \leq \|u\|^2$$

$$\frac{1}{4}\|u\|^2 \leq V_2(u) \leq \|u\|^2$$

where $\|u\|^2 = u_1^2 + u_2^2$, and then $\mu_1 = 5, \mu_2 = 4$. Since $\lambda_2 > \lambda_1$, choose $\varepsilon = 0.8$, then

$$\tau_0 = \frac{ln(5 \times 4)}{0.8} = \frac{ln(20)}{0.8} = 3.744665$$

The simulation is presented in Figure 1,with initial Condition: $[x_1(0), x_2(0)] = [12, 4]$, and switching signal:

$$\sigma(t) = \begin{cases} 2, t \in [t_{2k+1}, t_{2k+2}), t_{2k+2} - t_{2k+1} = 3.5 \\ \\ 1, t \in [t_{2k}, t_{2k+1}), t_{2k+1} - t_{2k} = 22 \text{ where k=0,1,2,...} \end{cases}$$

So, we can use the treatment for $\tau_k = 22$, and then stop using it for $\tau_k = 3.5$, and repeat this process without loosing stability, and the cancer would still be decreasing in size.
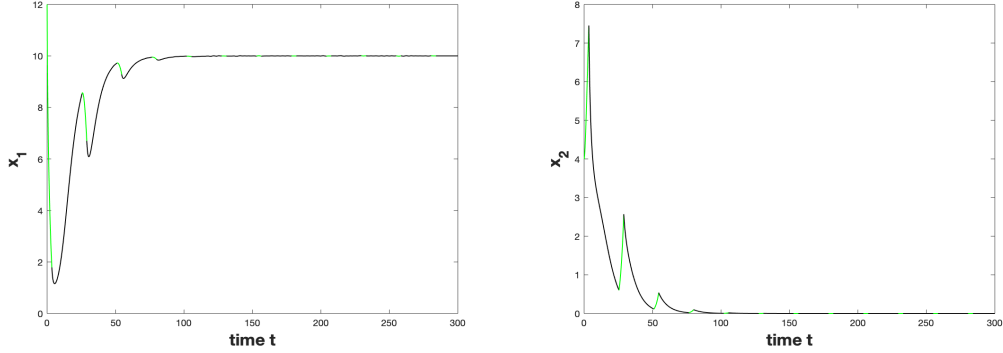
FIGURE 1. State response with MDT $\tau_0 = 3.744665$

Example 6.2. *Consider the following subsystems:*

$$(6.6) \qquad subsystem1 : \begin{cases} \dot{x}_1 & = 0.9x_1\,(1-0.1x_1) - 0.18x_1x_2 \\ \\ \dot{x}_2 & = x_2\,(0.15 - 0.09x_2) - 0.045x_1x_2 \end{cases}$$

$$(6.7) \qquad subsystem2 : \begin{cases} \dot{x}_1 & = 0.9x_1\,(1-0.1x_1) - 0.18x_1x_2 \\ \\ \dot{x}_2 & = x_2\,(0.4 - 0.09x_2) - 0.045x_1x_2 \end{cases}$$

$$(6.8) \qquad subsystem3 : \begin{cases} \dot{x}_1 & = 0.9x_1\,(1-0.1x_1) - 0.18x_1x_2 \\ \\ \dot{x}_2 & = 0.9x_2\,(1-0.1x_2) - 0.045x_1x_2 \end{cases}$$

where subsystem 1 is the competition model between normal and cancer cells with treatment $(\gamma_1 = 0.75)$, in subsystem 2 we use treatment with rate $(\gamma_2 = 0.5)$ and in subsystem 3 we stop using the treatment $(\gamma_3 = 0)$ Analysing system (6.6), (6.7) and (6.8) by using Linearization method, we find that the equilibrium point $(10,0)$ is unstable for subsystem 3, asymptotically stable for subsystems 1 and 2. Using Theorem (5.2) to find the MDT for the switched system (6.1), we need to translate the point $(10,0)$ to the origin by using the transformation $x_1 = u_1 + 10$, $x_2 = u_2$ and get the switched system

$$(6.9) \qquad subsystem4 : \begin{cases} \dot{u}_1 & = -0.09u_1^2 - 0.9u_1 - 0.18u_1u_2 - 1.8u_2 \\ \\ \dot{u}_2 & \quad = -0.3u_2 - 0.09u_2^2 - 0.045u_1u_2 \end{cases}$$

(6.10) $\qquad$ $subsystem5:$ $\begin{cases} \dot{u}_1 & = -0.09u_1^2 - 0.9u_1 - 0.18u_1u_2 - 1.8u_2 \\ \\ \dot{u}_2 & = -0.05u_2 - 0.09u_2^2 - 0.045u_1u_2 \end{cases}$

(6.11) $\qquad$ $subsystem6:$ $\begin{cases} \dot{u}_1 & = -0.09u_1^2 - 0.9u_1 - 0.18u_1x_2 - 1.8u_2 \\ \\ \dot{u}_2 & = 0.45u_2 - 0.09u_2^2 - 0.045u_1u_2 \end{cases}$

Let $V_1 = \frac{1}{6}u_1^2 + \frac{1}{2}u_2^2$ be a Lyapunov function for the 4th subsystem, $V_2 = \frac{1}{9}u_1^2 + u_2^2$ be a Lyapunov function for the 5th subsystem, and $V_3 = \frac{1}{2}u_1^2 + u_2^2$ be a Lyapunov function for the 6th subsystem. Next;

$$\dot{V}_1|_{(1)} = \frac{1}{3}u_1\left(-0.09u_1^2 - 0.9u_1 - 0.18u_1u_2 - 1.8u_2\right) + u_2\left(-0.3u_2 - 0.09u_2^2 - 0.045u_1u_2\right)$$

$$= -0.03u_1^3 - 0.3u_1^2 - 0.06u_1^2u_2 - 0.6u_1u_2 - 0.3u_2^2 - 0.09u_2^3 - 0.045u_1u_2^2$$

$$= -0.3u_1^2 - 0.3u_2^2 = -0.3\left(u_1^2 + u_2^2\right) \leq -0.3V_1$$

$$\dot{V}_2|_{(2)} = \frac{2}{9}u_1\left(-0.09u_1^2 - 0.9u_1 - 0.18u_1u_2 - 1.8u_2\right) + 2u_2\left(-0.05u_2 - 0.09u_2^2 - 0.045u_1u_2\right)$$

$$= -0.02u_1^3 - 0.2u_1^2 - 0.02u_1^2u_2 - 0.2u_1u_2 - 0.1u_2^2 - 0.18u_2^3 - 0.09u_1u_2^2$$

$$\leq -0.2u_1^2 - 0.1u_2^2 = -0.1\left(2u_1^2 + u_2^2\right) \leq -0.1V_2$$

$$\dot{V}_3|_{(3)} = u_1\left(-0.09u_1^2 - 0.9u_1 - 0.18u_1x_2 - 1.8u_2\right) + 2u_2\left(0.45u_2 - 0.09u_2^2 - 0.045u_1u_2\right)$$

$$= -0.09u_1^3 - 0.9u_1^2 - 0.18u_1^2u_2 - 1.8u_1u_2 + 0.9u_2^2 - 0.18u_2^3 - 0.09u_1u_2^2$$

$$\leq -0.9u_1^2 + 0.9u_2^2 = 0.9(-u_1^2 + u_2^2) \leq 0.9V_3$$

then, $\lambda_1 = 0.3, \lambda_2 = 0.1$, and $\lambda_3 = 0.9$, and

$$\frac{1}{7}\|u\|^2 \leq V_1(u) \leq \|u\|^2$$

$$\frac{1}{10}\|u\|^2 \leq V_2(u) \leq \|u\|^2$$

$$\frac{1}{4}\|u\|^2 \leq V_3(u) \leq \|u\|^2$$
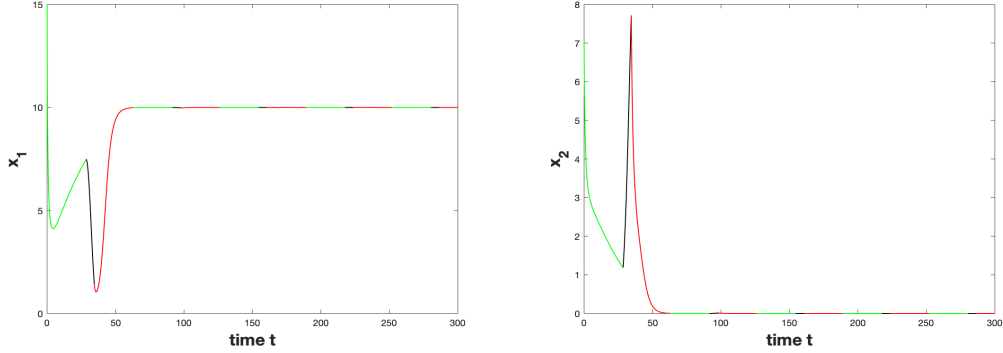
FIGURE 2. State response with MDT $\tau_0 = 6.26087$

where $\|u\|^2 = u_1^2 + u_2^2$, and then $\mu_1 = 7, \mu_2 = 10$ and $\mu_3 = 4$. Since $\lambda_1 + \lambda_2 < \lambda_3$, choose $\varepsilon = 0.9$, then

$$\tau_0 = \frac{ln(7 \times 10 \times 4)}{0.9} = \frac{ln(280)}{0.9} = 6.26087$$

The simulation is presented in Figure 2, with initial Condition: $[x_1(0), x_2(0)] = [15, 7]$, and switching signal:

$$\sigma(t) = \begin{cases} 2, t \in [t_{3k+1}, t_{3k+2}), t_{3k+2} - t_{3k+1} = 28.5 \\\\ 3, t \in [t_{3k+2}, t_{3k+3}), t_{3k+3} - t_{3k+2} = 6 \\\\ 1, t \in [t_{3k}, t_{3k+1}), t_{3k+1} - t_{3k} = 28.5 \text{ where k=0,1,2,...} \end{cases}$$

So, we can use the treatment for $\tau_k = 28.5$ with treatment rate of 0.5 and then stop using it for $\tau_k = 6$, and then with treatment rate of 0.75 for $\tau_k = 28.5$, and repeat this process without loosing stability, and the cancer would still be decreasing in size.

7. CONCLUSION

In this paper, we have considered a mathematical model using Lotka-Volterra Competition model to describe the competition between normal cells and cancer cells with treatmen, we have used an anti-angiogenic drug to stop the cancer from having its own blood vessels. This treatmen slows the growth of the cancer or sometimes shrinks it, but it can have many side effects especially for high dosage of the drugs. So, in order to minimize these side effects,

we determined the best duration for different dosages that would maintain the effectiveness of the treatment by introducing switching. We have proposed a switched system to determine the duration of treatments by using the MDT method and provide an analytical insight into the effectiveness of such method. Specifically, time-driven switching control is used. We proved that the drugs can be stopped for a specific time period and then used again for another time period and repeat this process without loosing stability, and the cancer would still decrease in size.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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