DISCRETIZATION OF A MATHEMATICAL MODEL FOR TUMOR-IMMUNE SYSTEM INTERACTION WITH PIECEWISE CONSTANT ARGUMENTS

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ABSTRACT

The present study deals with the analysis of a Lotka-Volterra model describing competition between tumor and immune cells. The model consists of differential equations with piecewise constant arguments and based on metamodel constructed by Stepanova. Using the method of reduction to discrete equations, it is obtained a system of difference equations from the system of differential equations. In order to get local and global stability conditions of the positive equilibrium point of the system, we use Schur-Cohn criterion and Lyapunov function that is constructed. Moreover, it is shown that periodic solutions occur as a consequence of Neimark-Sacker bifurcation.

KEYWORDS

piecewise constant arguments; difference equation; stability; bifurcation

1. INTRODUCTION

In population dynamics, the simplest and most widely used model describing the competition of two species is of the Lotka-Volterra type. In addition, there exist numerous extensions and generalizations of this type model in tumor growth model [1-8]. In 1995, Gatenby [1] used Lotka-Volterra competition model describing competition between tumor cells and normal cells for space and other resources in an arbitrarily small volume of tissue within an organ. On the other hand, Onofrio [2] has presented a general class of Lotka-Volterra competition model as follows:

$$\begin{cases} x^{\cdot} = x(f(x) - \phi(x)y), \\ y^{\cdot} = \beta(x)y - \mu(x)y + \sigma q(x) + \theta(t). \end{cases} \quad (1)$$

Here x and y denote tumor cell and effector cell sizes respectively. The function $f(x)$ represents tumor growth rates and there are many versions of this term. For example, in Gompertz model: $f(x) = \alpha Log(A/x)$ [3], the logistic model: $f(x) = \alpha(1 - x/A)$ [4].

The metamodel (1) also includes following exponential model which has been constructed by Stepanova [6].

$$\begin{cases} \dot{x} = \mu_C x(t) - \gamma x(t)y(t), \\ \dot{y} = \mu_I (x(t) - \beta x(t)^2) y(t) - \delta y(t) + \kappa, \end{cases} \qquad (2)$$

where x and y denote tumor and T-cell densities respectively. In this model, μ_C is the multiplication rate of tumors, γ is the rate of elimination of cancer cells by activity of T-cells, μ_I represents the production of T-cells which are stimulated by tumor cells, β^{-1} denotes the saturation density up from which the immunological system is suppressed, δ is the natural death rate of T cell and κ is the natural rate of influx of T cells from the primary organs [3].

Recently, it has been observed that the differential equations with piecewise constant arguments play an important role in modeling of biological problems. By using a first-order linear differential equation with piecewise constant arguments, Busenberg and Cooke [9] presented a model to investigate vertically transmitted. Following this work, using the method of reduction to discrete equations, many authors have analyzed various types of differential equations with piecewise constant arguments [10-19]. The local and global behavior of differential equation

$$\frac{dx(t)}{dt} = rx(t)\{1 - \alpha x(t) - \beta_0 x([t]) - \beta_1 x([t-1])\} \qquad (3)$$

has been analyzed by Gurcan and Bozkurt [10]. Using the equation (3), Ozturk et al [11] have modeled a population density of a bacteria species in a microcosm. Stability and oscillatory characteristics of difference solutions of the equation

$$\frac{dx(t)}{dt} = x(t)\{r(1 - \alpha x(t) - \beta_0 x([t]) - \beta_1 x([t-1])) + \gamma_1 x([t]) + \gamma_2 x([t-1])\} \qquad (4)$$

has been investigated in [12]. This equation has also been used for modeling an early brain tumor growth by Bozkurt [13].

In the present paper, we have modified model (2) by adding piecewise constant arguments such as

$$\begin{cases} \dot{x} = \mu_C x(t) - \gamma x(t)y([t]), \\ \dot{y} = \mu_I (x([t]) - \beta x([t])^2) y(t) - \delta y(t) + \kappa, \end{cases} \qquad (5)$$

where $[t]$ denotes the integer part of $t \in [0, \infty)$ and all these parameters are positive.

2. STABILITY ANALYSIS

In this section, we investigate local and global stability behavior of the system (5). The system can be written in the interval $t \in [n, n+1)$ as

$$\begin{cases} \frac{dx}{x(t)} = (\mu_C - \gamma y(n))\, d(t), \\ \frac{dy}{dt} + (\beta\mu_I x(n)^2 + \delta - \mu_I x(n))\, y(t) = \kappa. \end{cases} \qquad (6)$$

Integrating each equations of system (6) with respect to t on $[n, t)$ and letting $t \to n+1$, one can obtain a system of difference equations

$$\begin{cases} x(n+1) = x(n)e^{\mu_C - \gamma y(n)}, \\ y(n+1) = \dfrac{e^{[\mu_I x(n) - \beta\mu_I x(n)^2 - \delta]}\left[\beta\mu_I x(n)^2 y(n) + \delta y(n) - \mu_I x(n)y(n) - \kappa\right] + \kappa}{\beta\mu_I x(n)^2 + \delta - \mu_I x(n)}. \end{cases} \tag{7}$$

Computations give us that the positive equilibrium point of the system is

$$(\bar{x},\bar{y}) = \left(\frac{1 - \frac{\sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}}{\sqrt{\mu_I}\sqrt{\mu_C}}}{2\beta}, \frac{\mu_C}{\gamma} \right).$$

Hereafter,

$$\gamma < \frac{\delta\mu_C}{\kappa} \text{ and } \beta \le \frac{\mu_I\mu_C}{-4\gamma\kappa + 4\delta\mu_C}. \tag{8}$$

The linearized system of (7) about the positive equilibrium point is $w(n+1) = Aw(n)$, where A is a matrix as;

$$A = \begin{pmatrix} 1 & -\dfrac{\gamma\left(1 - \frac{\sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}}{\sqrt{\mu_I}\sqrt{\mu_C}}\right)}{2\beta} \\ \dfrac{e^{-\frac{\gamma\kappa}{\mu_C}}\left(-1 + e^{\frac{\gamma\kappa}{\mu_C}}\right)\sqrt{\mu_I}\mu_C^{3/2}\sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}}{\gamma^2\kappa} & e^{-\frac{\gamma\kappa}{\mu_C}} \end{pmatrix}. \tag{9}$$

The characteristic equation of the matrix A is

$$p(\lambda) = \lambda^2 + \lambda\left(-1 - e^{-\frac{\gamma\kappa}{\mu_C}}\right) + e^{-\frac{\gamma\kappa}{\mu_C}} - \frac{e^{-\frac{\gamma\kappa}{\mu_C}}\left(-1 + e^{\frac{\gamma\kappa}{\mu_C}}\right)\mu_C\sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}\left(-\sqrt{\mu_I}\sqrt{\mu_C} + \sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}\right)}{2\beta\gamma\kappa}. \tag{10}$$

Now we can determine the stability conditions of system (7) with the characteristic equation (10). Hence, we use following theorem that is called Schur-Chon criterion.

Theorem A ([20]). The characteristic polynomial

$$p(\lambda) = \lambda^2 + p_1\lambda + p_0 \tag{11}$$

has all its roots inside the unit open disk $(|\lambda| < 1)$ if and only if

(a) $p(1) = 1 + p_1 + p_0 > 0$,
(b) $p(-1) = 1 - p_1 + p_0 > 0$,

(c) $D_1^+ = 1 + p_0 > 0$,
(d) $D_1^- = 1 - p_0 > 0$.

Theorem 1. The positive equilibrium point $(\bar{x}, \bar{y})$ of system (7) is local asymptotically stable if $\frac{\delta\mu_C^2}{\kappa + \kappa\mu_C} < \gamma < \frac{\delta\mu_C}{\kappa}$ and $\beta \le \frac{\mu_I\mu_C}{-4\gamma\kappa + 4\delta\mu_C}$.

Proof. From characteristic equations (10), we have

$$p_1 = -1 - e^{-\frac{\gamma\kappa}{\mu_C}},$$
$$p_0 = e^{-\frac{\gamma\kappa}{\mu_C}} - \frac{e^{-\frac{\gamma\kappa}{\mu_C}}(-1 + e^{\frac{\gamma\kappa}{\mu_C}})\mu_C\sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}\left(-\sqrt{\mu_I}\sqrt{\mu_C} + \sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}\right)}{2\beta\gamma\kappa}.$$

From Theorem A/a we get

$$p(1) = \frac{2\beta\gamma\kappa - (-1 + e^{\frac{\gamma\kappa}{\mu_C}})\mu_C\sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}\left(-\sqrt{\mu_I}\sqrt{\mu_C} + \sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}\right)}{2\beta\gamma\kappa}.$$

It can be shown that if

$$-\sqrt{\mu_I}\sqrt{\mu_C} + \sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C} < 0, \quad (12)$$

then $p(1) > 0$. On the other hand, the inequality (12) always holds under the condition (8). When we consider Theorem A/b and Theorem A/c with the fact (12), we have respectively

$$p(-1) = 2 + 2e^{-\frac{\gamma\kappa}{\mu_C}} - \frac{e^{-\frac{\gamma\kappa}{\mu_C}}(-1 + e^{\frac{\gamma\kappa}{\mu_C}})\mu_C\sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}\left(-\sqrt{\mu_I}\sqrt{\mu_C} + \sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}\right)}{2\beta\gamma\kappa} > 0$$

And

$$D_1^+ = 1 + e^{-\frac{\gamma\kappa}{\mu_C}} - \frac{e^{-\frac{\gamma\kappa}{\mu_C}}(-1 + e^{\frac{\gamma\kappa}{\mu_C}})\mu_C\sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}\left(-\sqrt{\mu_I}\sqrt{\mu_C} + \sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}\right)}{2\beta\gamma\kappa} > 0.$$

From Theorem A/d, we get

$$D_1^- = e^{-\frac{\gamma\kappa}{\mu_C}}(-1 + e^{\frac{\gamma\kappa}{\mu_C}})\left(2\beta\gamma\kappa + 4\beta\gamma\kappa\mu_C + (-4\beta\delta + \mu_I)\mu_C^2 - \sqrt{\mu_I}\mu_C^{\frac{3}{2}}\sqrt{4\beta\gamma\kappa + (-4\beta\delta + \mu_I)\mu_C}\right).$$

By using the conditions of Theorem 1, we can also see that $D_1^- > 0$. This completes the proof.

Now we can use parameters value in Table 1 for the testing the conditions of Theorem 1. Using these parameter values, it is observed that the positive equilibrium point $(\bar{x},\bar{y}) = (7.41019, 0.5599)$ is local asymptotically stable where blue and red graphs represent $x(n)$ and $y(n)$ population densities respectively (see Figure 1).

Table 1. Parameters values used for numerical analysis

Parameters	Numerical Values	Ref
μ_C tumor growth parameter	0.5549	[8]
γ interaction rate	1	[8]
μ_I tumor stimulated proliferation rate	0.00484	[8]
β inverse threshold for tumor suppression	0.00264	[8]
δ death rate	0.37451	[8]
κ rate of influx	0.19	

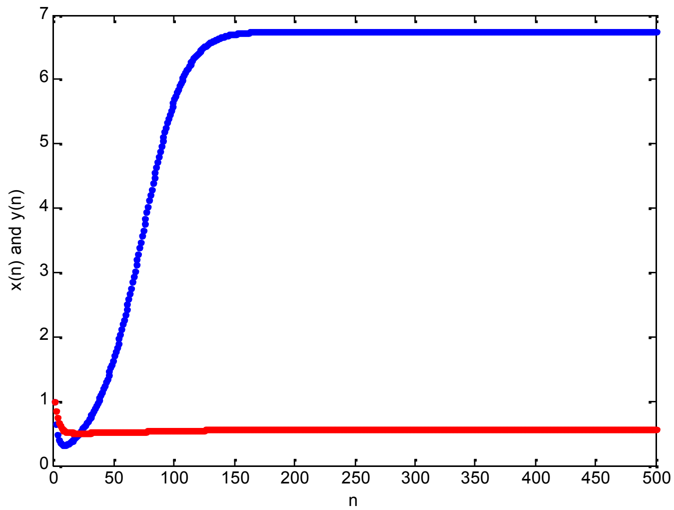

Figure 1. Graph of the iteration solution of $x(n)$ and $y(n)$, where $x(1) = y(1) = 1$

Theorem 2. Let $\{x(n), y(n)\}_{n=-1}^{\infty}$ be a positive solution of the system. Suppose that $\mu_C - \gamma y(n) < 0$, $\beta x(n) - 1 > 0$ and $\beta\mu_I x(n)^2 y(n) + \delta y(n) - \mu_I x(n) y(n) - \kappa < 0$ for $n = 0,1,2,3 \ldots$. Then every solution of (7) is bounded, that is,

$$x(n) \in (0, x(0)) \text{ and } y(n) \in \left(0, \frac{\kappa}{\delta}\right).$$

Proof. Since $\{x(n), y(n)\}_{n=-1}^{\infty} > 0$ and $\mu_C - \gamma y(n) < 0$, we have

$$x(n+1) = x(n) e^{\mu_C - \gamma y(n)} < x(n).$$

In addition, if we use $\beta\mu_I x(n)^2 y(n) + \delta y(n) - \mu_I x(n) y(n) - \kappa < 0$ and $\beta x(n) - 1 > 0$, we have

$$y(n+1) = \frac{e^{[\mu_I x(n) - \beta\mu_I x(n)^2 - \delta]}\left[y(n)(\beta\mu_I x(n)^2 + \delta - \mu_I x(n)) - \kappa\right] + \kappa}{\mu_I x(n)(\beta x(n) - 1) + \delta}$$

$$< \frac{\kappa}{\mu_I x(n)(\beta x(n) - 1) + \delta} < \frac{\kappa}{\delta}.$$

This completes the proof.

Theorem 3. Let the conditions of Theorem 1 hold and assume that

$$\bar{x} < \frac{1}{2\beta} \quad \text{and} \quad \bar{y} < \frac{\kappa}{2\mu_I x(n)(\beta x(n) - 1) + 2\delta}.$$

If

$$x(n) > \frac{1}{\beta} \quad \text{and} \quad y(n) > \frac{\kappa}{\mu_I x(n)(\beta x(n) - 1) + \delta},$$

then the positive equilibrium point of the system is global asymptotically stable.

Proof. Let $\bar{E} = (\bar{x}, \bar{y})$ is a positive equilibrium point of system (7) and we consider a Lyapunov function $V(n)$ defined by

$$V(n) = [E(n) - \bar{E}]^2, \; n = 0,1,2 \ldots$$

The change along the solutions of the system is

$$\Delta V(n) = V(n+1) - V(n) = \{E(n+1) - E(n)\}\{E(n+1) + E(n) - 2\bar{E}\}.$$

Let $A_1 = \mu_C - \gamma y(n) < 0$ which gives us that $y(n) > \frac{\mu_C}{\gamma} = \bar{y}$. If we consider first equation in (7) with the fact $x(n) > 2\bar{x}$, we get

$$\begin{aligned} \Delta V_1(n) &= \{x(n+1) - x(n)\}\{x(n+1) + x(n) - 2\bar{x}\} \\ &= \{x(n)(e^{A_1} - 1)\}\{x(n)e^{A_1} + x(n) - 2\bar{x}\} < 0. \end{aligned}$$

Similarly, Suppose that $A_2 = \beta\mu_I x(n)^2 + \delta - \mu_I x(n) > 0$ which yields $x(n) > \frac{1}{\beta}$. Computations give us that if $y(n) > \frac{\kappa}{A_2}$ and $y(n) > 2\bar{y}$, we have

$$\begin{aligned} \Delta V_2(n) &= \{y(n+1) - y(n)\}\{y(n+1) + y(n) - 2\bar{y}\} \\ &= \left\{\frac{(1 - e^{-A_2})(\kappa - y(n)A_2)}{A_2}\right\}\left\{\frac{y(n)A_2(e^{-A_2} + 1) + \kappa(1 - e^{-A_2}) - 2\bar{y}A_2}{A_2}\right\} < 0. \end{aligned}$$

Under the conditions

$$\bar{x} < \frac{1}{2\beta} \quad \text{and} \quad \bar{y} < \frac{\kappa}{2\mu_I x(n)(\beta x(n) - 1) + 2\delta},$$

we can write

$$x(n) > \frac{1}{\beta} > 2\bar{x} \;\text{ and } y(n) > \frac{\kappa}{A_2} = \frac{\kappa}{\mu_I x(n)(\beta x(n) - 1) + \delta} > 2\bar{y}.$$

As a result, we obtain $\Delta V(n) = (\Delta V_1(n), \Delta V_2(n)) < 0$.

3. NEIMARK-SACKER BIFURCATION ANALYSIS

In this section, we discuss the periodic solutions of the system through Neimark-Sacker bifurcation. This bifurcation occurs of a closed invariant curve from a equilibrium point in discrete dynamical systems, when the equilibrium point changes stability via a pair of complex eigenvalues with unit modulus. These complex eigenvalues lead to periodic solution as a result of limit cycle. In order to study Neimark-Sacker bifurcation we use the following theorem that is called Schur-Cohn criterion.

Theorem B. ([20]) A pair of complex conjugate roots of equation (11) lie on the unit circle and the other roots of equation (11) all lie inside the unit circle if and only if

(a) $p(1) = 1 + p_1 + p_0 > 0$,
(b) $p(-1) = 1 - p_1 + p_0 > 0$,
(c) $D_1^+ = 1 + p_0 > 0$,
(d) $D_1^- = 1 - p_0 = 0$.

In stability analysis, we have shown that Theorem B/a, Theorem B/b and Theorem B/c always holds. Therefore, to determine bifurcation point we can only analyze Theorem B/d. Solving equation d of Theorem B, we have $\bar{\kappa} = 0.0635352$. Furthermore, Figure 2 shows that $\bar{\kappa}$ is the Neimark-Sacker bifurcation point of the system with eigenvalues $|\lambda_{1,2}| = |0.945907 \pm 0.324439i| = 1$, where blue, and red graphs represent $x(n)$ and $y(n)$ population densities respectively.

As seen in Figure 2, a stable limit cycle occurs around the positive equilibrium point at the Neimark-Sacker bifurcation point. This limit cycle leads to periodic solution which means that tumor and immune cell undergo oscillations (Figure 3). This oscillatory behavior has also occurred in continuous biological model as a result of Hopf bifurcation and has observed clinically.

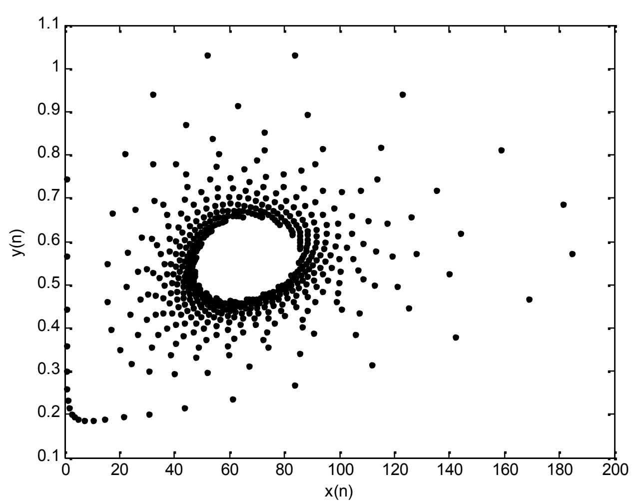

Figure 2. Graph of Neimark-Sacker bifurcation of system (7) for $\bar{\kappa} = 0.0635352$. Initial conditions and other parameters are the same as Figure 1

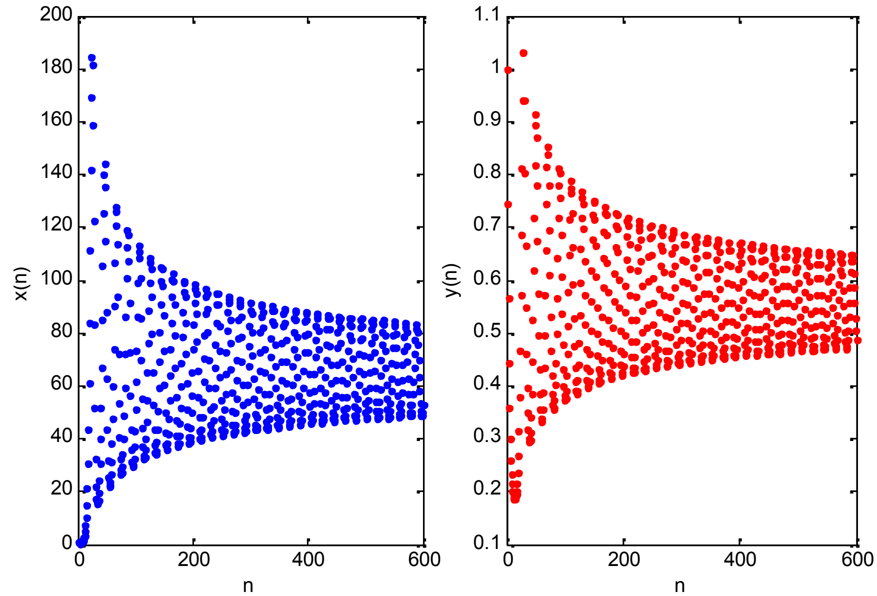

Figure 3. Graph of the iteration solution of x(n) and y(n) for $\bar{\kappa} = 0.063535$. Initial conditions and other parameters are the same as Figure 1

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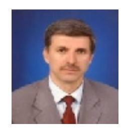

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