Mathematical Modeling and Stability Analysis of the Brain Tumor Glioblastoma Multiforme (GBM)

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Abstract—**In this paper, a brain tumor growth that is known as Glioblastoma Multiforme (GBM) is modeled, which has two sub-population; the sensitive tumor cell and the resistant tumor cell. Within a single tumor of monoclonal origin, the sensitive cell produces another population, the resistant cell population, that has more resistance to the drug than the sensitive tumor population. In this work, the local and global stability of the positive equilibrium point of the constructed system was investigated based on specific conditions. The boundedness nature and the damped oscillation behavior of the solutions were also analyzed. The obtained stability relations depend to the growth rates of the tumor population and the drug treatment, that was considered in the discussion part of this work.**

Index Terms—**Difference equations, local stability, global stability, damped oscillation.**

I. Introduction

The most severe grade of astrocytic brain tumor glioblastoma multiforme (GBM) is one of the deadliest forms of human cancer [1]. Within a single tumor of monoclonal origin, there can develop multiple sub-populations, each of which may be characterized by different growth-rates and treatment susceptibilities [2]-[5]. Mathematical approaches to tumor treatment offer a perspective that current in vivo/in vitro techniques cannot [6]-[7].

Mathematical approximation for population growth involves in some biological situations nonlinear differential equations. For an overlapping generation of a single species, a model with a differential equation is preferred. If there is a non-overlapping generation of a single species, then it is convenient to construct a model with a difference equation. For both time situations, continuous and discrete, there are some population which need the properties of both differential and difference equations, where the use of piecewise constant arguments come into question. Some works about constructing population dynamics in view of the time step can be shown in [8]-[13], [14]-[25].

In this paper, two sub-population of a GBM, sensitive cells and resistant cells, is modeled such as

$$\begin{cases} \frac{dx}{dt} = px(t) + r_1 x(t)\big(R_1 - \alpha_1 x(t) - \alpha_2 x([\![t-1]\!])\big) \\ \qquad -\gamma_1 x(t) y([\![t-1]\!]) - d_1 x(t) x([\![t]\!]) \\ \frac{dy}{dt} = r_2 y(t)\big(R_2 - \beta_1 y(t) - \beta_2 y([\![t-1]\!])\big) \\ \qquad +\gamma_1 x([\![t]\!]) y(t) - d_2 y(t) y([\![t]\!]) \end{cases} \tag{1}$$

where $t \geq 0$ the parameters $\alpha_1, \alpha_2, \beta_1, \beta_2, \gamma_1, p, d_1, d_2, R_1, R_2, r_1$ and r_2 denote positive numbers and $[\![t]\!]$ denotes the integer part of $t \in [0, \infty)$. p is the division rate of the sensitive cells. R_1 and R_2 are the capacities of the sensitive (including negrotic part) and resistant cell, respectively. It can be shown that $\alpha_1, \alpha_2, \beta_1$ and β_2 are parameters to construct logistic differential equations. γ_1 is the converting rate of sensitive cells to resistant cells. The parameters d_1 and d_2 are their dead rate caused from drugs, respectively. In Section II the local and global stability of the positive equilibrium point of system (1) and the boundedness nature of the positive solutions were investigated based on specific conditions. The damped oscillation behavior of the solutions was analyzed in Section III. Examples show the behavior of the constructed model. The discussion part in Section V will take in account the relation between the growth rate of the tumors and the drug treatment.

II. Local and Global Asymptotic Stability

In this section, the local and global stability analysis of the positive critical point of system (1) was presented.

On an interval of the form $t \in [n, n+1)$ and taking $t \to n+1$ one can write the solutions of (1) as

$$\begin{cases} x(n+1) = x(\mathrm{n}) \cdot \{p + r_1 R_1 - \alpha_2 r_1 x(n-1) - \gamma_1 y(n-1) - d_1 x(n)\} \\ (\{p + r_1 R_1 - \alpha_2 r_1 x(n-1) - \gamma_1 y(n-1) - (\alpha_1 r_1 + d_1) x(n)\} \\ \exp(-\{p + r_1 R_1 - \alpha_2 r_1 x(n-1) - \gamma_1 y(n-1) - d_1 x(n)\}) + \alpha_1 r_1 x(n))^{-1} \\ \\ y(n+1) = y(n) \cdot \{r_2 R_2 - \beta_2 r_2 y(n-1) + \gamma_1 x(n) - d_2 y(n)\} \\ (\{r_2 R_2 - \beta_2 r_2 y(n-1) + \gamma_1 x(n) - (\beta_1 r_2 + d_2) y(n)\} \\ \cdot \exp(-\{r_2 R_2 - \beta_2 r_2 y(n-1) + \gamma_1 x(n) - d_2 y(n)\}) + \beta_1 r_2 y(n))^{-1}, \end{cases} \tag{2}$$

where hereafter

$$\begin{cases} p + r_1 R_1 - \alpha_2 r_1 x(n-1) - \gamma_1 y(n-1) - d_1 x(n) \neq 0 \\ r_2 R_2 - \beta_2 r_2 y(n-1) + \gamma_1 x(n) - d_2 y(n) \neq 0. \end{cases} \tag{3}$$

To investigate more about the behavior of (1) we continue the analysis, since (2) is a system of difference equations. Computations reveal that the positive equilibrium points of (2) is

$$\mu = (\bar{x}, \bar{y}) = \left(\frac{(p + r_1 R_1)(d_2 + \beta_1 r_2 + \beta_2 r_2) - r_2 R_2 \gamma_1}{(d_1 + \alpha_2 r_1 + \alpha_1 r_1)(d_2 + \beta_2 r_2 + \beta_1 r_2) + \gamma_1^2}, \right.$$
$$\left. \frac{r_2 R_2 (d_1 + \alpha_2 r_1 + \alpha_1 r_1) + (p + r_1 R_1)\gamma_1}{(d_1 + \alpha_2 r_1 + \alpha_1 r_1)(d_2 + \beta_2 r_2 + \beta_1 r_2) + \gamma_1^2} \right) \tag{4}$$

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where $\gamma_1 < \frac{(p+r_1R_1)(d_2+\beta_1r_2+\beta_2r_2)}{r_2R_2}$. Hereafter, let

$$\begin{cases} A = p + r_1R_1 - (\alpha_2 r_1 + d_1)\bar{x} - \gamma_1\bar{y} > 0 \\ B = r_2R_2 - (\beta_2 r_2 + d_2)\bar{y} + \gamma_1\bar{x} > 0. \end{cases} \quad (5)$$

Linearizing (2) about μ, we obtain

$$\begin{cases} u_1 = \frac{(d_1+\alpha_1 r_1)\exp(-A)-d_1}{\alpha_1 r_1} \\ u_2 = \frac{\alpha_2(\exp(-A)-1)}{\alpha_1} \\ u_4 = \frac{\gamma_1(\exp(-A)-1)}{\alpha_1 r_1} \end{cases}, \begin{cases} v_1 = \frac{\gamma_1(1-\exp(-B))}{\beta_1 r_2} \\ v_3 = \frac{(\beta_1 r_2+d_2)\exp(-B)-d_2}{\beta_1 r_2} \\ v_4 = \frac{\beta_2(\exp(-B)-1)}{\beta_1} \end{cases} \quad (6)$$

where

$$\lambda^4 - (u_1+v_3)\lambda^3 + (u_1v_3 - v_4 - u_2)\lambda^2 + (u_1v_4 + u_2v_3 - u_4v_1)\lambda + u_2v_4 = 0. \quad (7)$$

is the characteristic equation of (2).

Theorem 2.1. Let $(\bar{x}, \bar{y})$ be the equilibrium point of (2) and assume that the conditions $\frac{\alpha_2\beta_2 d_1 - \alpha_1\beta_1}{\alpha_2^2\beta_2 + \alpha_1^2\beta_1} < r_1 < \frac{d_1}{\alpha_2+\alpha_1}$, $r_2 > \frac{d_2}{\beta_2+\beta_1}$ and $\frac{\alpha_1\beta_1}{\alpha_2\beta_2} < d_1 < \frac{(\alpha_1+\alpha_2)\beta_1}{\alpha_2\beta_2 - \alpha_1\beta_1}$ hold, where $\alpha_2 > \alpha_1$ and $\frac{\alpha_2}{\alpha_1} > \frac{\beta_1}{\beta_2}$. If

$$\ln\left(\frac{\alpha_2\beta_2r_1r_2 + \alpha_1\beta_2r_1r_2 + \beta_1r_2d_1 + d_1d_2}{\alpha_1\beta_1r_1r_2 + \alpha_1\beta_2r_1r_2 + \alpha_2\beta_1r_1r_2 + \alpha_2\beta_2r_1r_2 + d_1d_2}\right) < B < \ln\left(\frac{\alpha_1\beta_1r_1r_2 + \alpha_2\beta_2r_1r_2 + \alpha_1r_1d_2 + \beta_1r_2d_1 + d_1d_2}{\alpha_2\beta_2r_1r_2 + \alpha_2\beta_1r_1r_2 + \alpha_1r_1d_2 + d_1d_2}\right), \quad (8)$$

Then the positive equilibrium point of (2) is locally asymptotically stable.

Proof. By the Jury Condition (or Schur-Cohn criteria, see [26]) we get that the positive equilibrium point of system (2) is locally asymptotically stable if

(a) $p(1) = 1 - (u_1+v_3) + (u_1v_3 - v_4 - u_2) + (u_1v_4 + u_2v_3 - u_4v_1) + u_2v_4 > 0$

(b) $(-1)^4 p(-1) = 1 + (u_1+v_3) + (u_1v_3 - v_4 - u_2) - (u_1v_4 + u_2v_3 - u_4v_1) + u_2v_4 > 0$

(c) $|u_2v_4| < 1$

Hold. From (a) and (b), we can write

$$1 + u_1v_3 + u_2v_4 > v_4 + u_2. \quad (9)$$

Using (6) in (9), we have

$$1 + \left(\frac{(d_1+\alpha_1r_1)e^{-A} - d_1}{\alpha_1 r_1}\right)\left(\frac{(\beta_1r_2+d_2)e^{-B} - d_2}{\beta_1 r_2}\right) + \left(\frac{\alpha_2(e^{-A}-1)}{\alpha_1}\right)\left(\frac{\beta_2(e^{-B}-1)}{\beta_1}\right) > \frac{\beta_2(e^{-B}-1)}{\beta_1} + \frac{\alpha_2(e^{-A}-1)}{\alpha_1}. \quad (10)$$

By ordering and computing (10), we obtain

$$\ln\left(\frac{\alpha_2\beta_2r_1r_2 + \alpha_1\beta_2r_1r_2 + \beta_1r_2d_1 + d_1d_2}{\alpha_1\beta_1r_1r_2 + \alpha_1\beta_2r_1r_2 + \alpha_2\beta_1r_1r_2 + \alpha_2\beta_2r_1r_2 + d_1d_2}\right) < B < \ln\left(\frac{\alpha_1\beta_1r_1r_2 + \alpha_2\beta_2r_1r_2 + \alpha_1r_1d_2 + \beta_1r_2d_1 + d_1d_2}{\alpha_2\beta_2r_1r_2 + \alpha_2\beta_1r_1r_2 + \alpha_1r_1d_2 + d_1d_2}\right), \quad (11)$$

where $r_1 < \frac{d_1}{\alpha_2+\alpha_1} < \frac{d_1}{\alpha_2-\alpha_1}$, $r_2 > \frac{d_2}{\beta_2+\beta_1}$ and $\alpha_2 > \alpha_1$.

Considering (c), we have

$$\frac{\alpha_2(1-e^{-A})}{\alpha_1} \cdot \frac{\beta_2(1-e^{-B})}{\beta_1} < 1 \quad (12)$$

where A>0 and B>0. In view of (11), we can write

$$\frac{\beta_1r_2(d_1 - (\alpha_2+\alpha_1)r_1)}{\alpha_2\beta_2r_1r_2 + \alpha_1\beta_2r_1r_2 + \beta_1r_2d_1 + d_1d_2} < 1 - e^{-B} < \frac{\beta_1r_2(d_1 - (\alpha_2-\alpha_1)r_1)}{\alpha_1\beta_1r_1r_2 + \alpha_2\beta_2r_1r_2 + \alpha_1r_1d_2 + \beta_1r_2d_1 + d_1d_2}. \quad (13)$$

Using (13) in (12), we obtain

$$\frac{\alpha_2\beta_2(1-e^{-A})(1-e^{-B})}{\alpha_1\beta_1} < \frac{\alpha_2\beta_2r_2(d_1 - (\alpha_2-\alpha_1)r_1)(1-e^{-A})}{\alpha_1(\alpha_1\beta_1r_1r_2 + \alpha_2\beta_2r_1r_2 + \alpha_1r_1d_2 + \beta_1r_2d_1 + d_1d_2)} < 1 \quad (14)$$

which lead us to the inequality

$$\frac{\alpha_2\beta_2r_2(d_1 - (\alpha_2-\alpha_1)r_1)}{\alpha_1(\alpha_1\beta_1r_1r_2 + \alpha_2\beta_2r_1r_2 + \alpha_1r_1d_2 + \beta_1r_2d_1 + d_1d_2)} - 1 < \frac{\alpha_2\beta_2r_2(d_1 - (\alpha_2-\alpha_1)r_1)}{\alpha_1(\alpha_1\beta_1r_1r_2 + \alpha_2\beta_2r_1r_2 + \alpha_1r_1d_2 + \beta_1r_2d_1 + d_1d_2)} e^{-A}.$$

This is simplify such as

$$\alpha_2\beta_2r_2(d_1 - (\alpha_2-\alpha_1)r_1) - \alpha_1\begin{pmatrix}\alpha_1\beta_1r_1r_2 + \alpha_2\beta_2r_1r_2 + \\ \alpha_1r_1d_2 + \beta_1r_2d_1 + d_1d_2\end{pmatrix} < \alpha_2\beta_2r_2(d_1 - (\alpha_2-\alpha_1)r_1)e^{-A}. \quad (15)$$

Since

$$\frac{\alpha_1\beta_1}{\alpha_2\beta_2} < d_1 < \frac{(\alpha_1+\alpha_2)\beta_1}{\alpha_2\beta_2 - \alpha_1\beta_1}$$

And $\frac{\alpha_2}{\alpha_1} > \frac{\beta_1}{\beta_2}$,
where

$$\frac{\alpha_2\beta_2d_1 - \alpha_1\beta_1}{\alpha_2^2\beta_2 + \alpha_1^2\beta_1} < r_1 < \frac{d_1}{\alpha_2+\alpha_1},$$

The left side of the inequality (15) will be negative. This completes the proof.

Theorem 2.2. Let $\{(x(n), y(n))\}_{n=0}^{\infty}$ be a positive solution of (2). Assume that for n=0, 1,… the conditions

$$\begin{cases} \alpha_1r_1x(n) < p + r_1R_1 - \alpha_2r_1x(n-1) - \gamma_1y(n-1) - d_1x(n) \\ \beta_1r_2y(n) < r_2R_2 - \beta_2r_2y(n-1) + \gamma_1x(n) - d_2y(n) \end{cases} \quad (16)$$

Holds. The following statements are true.
All positive solutions of (2) are in the interval

$$x(n) \in \left(0, \frac{p+r_1R_1}{\alpha_1 r_1}\right)$$

And

$$y(n) \in \left(0, \frac{\alpha_1R_2r_1r_2 + \gamma_1(p+r_1R_1)}{\alpha_1\beta_1r_1r_2}\right).$$

The solution of system (2) increase monotonic.

Theorem 2.3. Let system (2) be

$$F\big(x(n),y(n),x(n-1),y(n-1)\big)=\begin{cases}x(n+1)=f(x(n),y(n),x(n-1),y(n-1))\\ y(n+1)=g(x(n),y(n),x(n-1),y(n-1))\end{cases}\tag{17}$$

where the first order partial derivatives of the functions f and g regard to x and y are continuous in $I\subset R^+$ and f, g: $V\subset(\mathbb{R}^+)^4\to I\subset R^+$. Furthermore assume that

$$\alpha_1 r_1 x(n)<p+r_1R_1-\alpha_2 r_1 x(n-1)\\ -\gamma_1 y(n-1)-d_1x(n)\tag{18}$$

And

$$\beta_1 r_2 y(n)<r_2R_2-\beta_2 r_2 y(n-1)+\gamma_1 x(n)\\ -d_2y(n),\tag{19}$$

That $2\alpha_1>\alpha_2>\alpha_1, 2\beta_1>\beta_2>\beta_1$ and $\gamma_1<d_1$. If

$$\frac{\alpha_1 r_1 x(n)}{1-\alpha_2 r_1 x(n)}<A<\ln\left(\frac{A-\alpha_1 r_1 x(n)}{\alpha_2 r_1 A x(n)}\right),\tag{20}$$

And

$$\frac{\beta_1 r_2 y(n)}{1-\beta_2 r_2 y(n)}<B<\ln\left(\frac{B-\beta_1 r_2 y(n)}{\beta_2 r_2 B y(n)}\right)\tag{21}$$

where $r_1>\frac{d_1}{\alpha_1}$, $r_2>\frac{d_2}{\beta_1}$, $x(n)<\frac{1}{\alpha_2 r_1}$ and $y(n)<\frac{1}{\beta_1 r_2}$, then (17) has no 2-cycle in I.

Proof. For some

$$\begin{cases}s(2)=\big(x(1),y(1),x(0),y(0)\big),\\ s(3)=\big(x(2),y(2),x(1),y(1)\big)\\ r(2)=\big(x(1),y(1),x(0),y(0)\big),\\ r(3)=\big(x(2),y(2),x(1),y(1)\big),\end{cases}\tag{22}$$

A_2-cycle will be hold the condition

$$\begin{cases}s(2)=f\big(s(3)\big)=f\Big(f\big(x(1),y(1),x(0),y(0)\big)\Big)\\ r(2)=g\big(r(3)\big)=g\Big(g\big(x(1),y(1),x(0),y(0)\big)\Big).\end{cases}\tag{23}$$

In this case, we must have $\int_{s(2)}^{s(3)}(1+\frac{\partial f}{\partial x})dx\neq 0$, $\int_{s(2)}^{s(3)}(1+\frac{\partial f}{\partial y})dy\neq 0$ $\int_{r(2)}^{r(3)}(1+\frac{\partial g}{\partial x})dx\neq 0$ and $\int_{r(2)}^{r(3)}(1+\frac{\partial g}{\partial y})dy\neq 0$. This lead us to the following cases:

The partial derivative of $f(x(n),y(n),x(n-1),y(n-1))$ regard to $x(n)$, $x(n\text{-}1)$, $y(n)$ and $y(n\text{-}1)$ will give the following results:

For the partial derivative of function f regard to $x(n)$, we get

$$1+\frac{\partial f}{\partial x(n)}=\frac{1}{\Big(\big(A-\alpha_1 r_1 x(n)\big)e^{-A}+\alpha_1 r_1 x(n)\Big)^2}\\ \times\{\big(A-\alpha_1 r_1 x(n)\big)e^{-A}x(n)(2\alpha_1 r_1-d_1)\\ +\big(A-\alpha_1 r_1 x(n)\big)e^{-A}\Big(\big(A-\alpha_1 r_1 x(n)\big)e^{-A}-d_1Ax(n)\Big)\\ +\alpha_1 r_1\big(x(n)\big)^2(\alpha_1 r_1-d_1)+\big(A-\alpha_1 r_1 x(n)\big)Ae^{-A}\\ +(\alpha_1 r_1+d_1)Ax(n)e^{-A}\}.\tag{24}$$

Since $r_1>\frac{d_1}{\alpha_1}$, if

$$\big(A-\alpha_1 r_1 x(n)\big)e^{-A}-d_1Ax(n)>0,\tag{25}$$

Then $1+\frac{\partial f}{\partial x(n)}>0$. The inequality (25) leads to the condition

$$\frac{\alpha_1 r_1 x(n)}{1-d_1 x(n)}<A<\ln\left(\frac{A-\alpha_1 r_1 x(n)}{d_1 A x(n)}\right),\tag{26}$$

where $x(n)<\frac{1}{d_1}$. Showing the partial derivative of function f regard to $x(n\text{-}1)$, give that $1+\frac{\partial f}{\partial x(n-1)}>0$, if

$$\frac{\alpha_1 r_1 x(n)(\alpha_2-\alpha_1)}{\alpha_2}<A<\ln\left(\frac{\alpha_2 A}{\alpha_1 r_1 x(n)(\alpha_2-\alpha_1)}\right)\tag{27}$$

And

$$\frac{\alpha_1 r_1 x(n)}{1-\alpha_2 r_1 x(n)}<A<\ln\left(\frac{A-\alpha_1 r_1 x(n)}{\alpha_2 r_1 A x(n)}\right),\tag{28}$$

where $2\alpha_1>\alpha_2>\alpha_1$ and $x(n)<\frac{1}{\alpha_2 r_1}$. Considering both (27) and (28), since $\alpha_2>\alpha_1$, we get

$$\frac{\alpha_1 r_1 x(n)(\alpha_2-\alpha_1)}{\alpha_2}<\frac{\alpha_1 r_1 x(n)}{1-\alpha_2 r_1 x(n)}<A\\ <\ln\left(\frac{A-\alpha_1 r_1 x(n)}{\alpha_2 r_1 A x(n)}\right)<\ln\left(\frac{\alpha_2 A}{\alpha_1 r_1 x(n)(\alpha_2-\alpha_1)}\right).\tag{29}$$

The partial derivative of function f regard to $y(n)$ leads to $1+\frac{\partial f}{\partial y(n)}=1>0$. At last, we can write

$$1+\frac{\partial f}{\partial y(n-1)}=\frac{1}{\Big(\big(A-\alpha_1 r_1 x(n)\big)e^{-A}+\alpha_1 r_1 x(n)\Big)^2}\\ \times\{\big(A-\alpha_1 r_1 x(n)\big)e^{-A}\Big(\big(A-\alpha_1 r_1 x(n)\big)e^{-A}-\gamma_1 Ax(n)\Big)\\ +\alpha_1 r_1\big(x(n)\big)^2(\alpha_1 r_1-\gamma_1)+\big(A-\alpha_1 r_1 x(n)\big)\\ e^{-A}x(n)(2\alpha_1 r_1-\gamma_1)+\gamma_1 Ax(n)e^{-A}\}.\tag{30}$$

Since $x(n)<\frac{1}{\gamma_1}$ and $r_1>\frac{\gamma_1}{2\alpha_1}$, if

$$\frac{\alpha_1 r_1 x(n)}{1-\gamma_1 x(n)}<A<ln\left(\frac{A-\alpha_1 r_1 x(n)}{\gamma_1 A x(n)}\right),\tag{31}$$

Then we get $1+\frac{\partial f}{\partial y(n-1)}>0$. Taking in view (26), (29) and (31), we obtain

$$\frac{\alpha_1 r_1 x(n)}{1-\gamma_1 x(n)}<\frac{\alpha_1 r_1 x(n)}{1-d_1 x(n)}<\frac{\alpha_1 r_1 x(n)}{1-\alpha_2 r_1 x(n)}<A\\ <ln\left(\frac{A-\alpha_1 r_1 x(n)}{\alpha_2 r_1 A x(n)}\right)<ln\left(\frac{A-\alpha_1 r_1 x(n)}{d_1 A x(n)}\right)<ln\left(\frac{A-\alpha_1 r_1 x(n)}{\gamma_1 A x(n)}\right)\tag{32}$$

where $\gamma_1<d_1$, $r_1>\frac{d_1}{\alpha_2}>\frac{\gamma_1}{\alpha_2}$ and $x(n)<\frac{1}{\alpha_2 r_1}<\frac{1}{d_1}<\frac{1}{\gamma_1}$.

The partial Derivative of $g(x(n),y(n),x(n-1),y(n-1))$ regard to $x(n)$, $x(n\text{-}1)$, $y(n)$ and $y(n\text{-}1)$ will give the following results: For

$$1+\frac{\partial g}{\partial y(n)}=\beta_1 r_2\big(y(n)\big)^2(\beta_1 r_2-d_2)+\big(B-\beta_1 r_2 y(n)\big)$$

$$e^{-B}y(n)(2\beta_1 r_2 - d_2) + \big(B - \beta_1 r_2 y(n)\big)e^{-B}$$
$$\Big(\big(B - \beta_1 r_2 y(n)\big)e^{-B} - d_2 B y(n)\Big) + (\beta_1 r_2 + d_2)e^{-B}By(n)$$
$$+B\big(B - \beta_1 r_2 y(n)\big)e^{-B},$$

if

$$\frac{\beta_1 r_2 y(n)}{1-d_2 y(n)} < B < \ln\left(\frac{B-\beta_1 r_2 y(n)}{d_2 B y(n)}\right), \tag{33}$$

where $r_2 > \frac{d_2}{\beta_1}$ *and* $y(n) < \frac{1}{d_2}$, then one can obtain

$$1 + \frac{\partial g}{\partial y(n)} > 0.$$

Considering

$$1 + \frac{\partial g}{\partial y(n-1)} = \big(B - \beta_1 r_2 y(n)\big)e^{-B}$$
$$\Big(\big(B - \beta_1 r_2 y(n)\big)e^{-B} - \beta_2 r_2 B y(n)\Big)$$
$$+\beta_1 {r_2}^2 y(n)^2(\beta_1 - \beta_2) + \beta_2 r_2 e^{-B} B y(n)$$
$$+\big(B - \beta_1 r_2 y(n)\big)e^{-B} y(n) r_2 (2\beta_1 - \beta_2),$$

We obtain that since $2\beta_1 > \beta_2 > \beta_1$ and $y(n) < \frac{1}{\beta_1 r_2}$, if

$$\frac{(\beta_2-\beta_1)\beta_1 r_2 y(n)}{\beta_2} < B < ln\left(\frac{\beta_2 B}{(\beta_2-\beta_1)\beta_1 r_2 y(n)}\right) \tag{34}$$

And

$$\frac{\beta_1 r_2 y(n)}{1-\beta_2 r_2 y(n)} < B < \ln\left(\frac{B-\beta_1 r_2 y(n)}{\beta_2 r_2 B y(n)}\right), \tag{35}$$

Then $1 + \frac{\partial g}{\partial y(n-1)} > 0$. Considering both (34) and (35), since $\beta_2 > \beta_1$, we obtain

$$\frac{(\beta_2 - \beta_1)\beta_1 r_2 y(n)}{\beta_2} < \frac{\beta_1 r_2 y(n)}{1 - \beta_2 r_2 y(n)} < B$$
$$< \ln\left(\frac{B-\beta_1 r_2 y(n)}{\beta_2 r_2 B y(n)}\right) < \ln\left(\frac{\beta_2 B}{(\beta_2-\beta_1)\beta_1 r_2 y(n)}\right). \tag{36}$$

Showing similarly $1 + \frac{\partial g}{\partial x(n)}$ and $1 + \frac{\partial g}{\partial x(n-1)}$, one can see that both are always positive. Considering at last (33) and (36), we get

$$\frac{\beta_1 r_2 y(n)}{1-d_2 y(n)} < \frac{\beta_1 r_2 y(n)}{1-\beta_2 r_2 y(n)} < B < \ln\left(\frac{B-\beta_1 r_2 y(n)}{\beta_2 r_2 B y(n)}\right) <$$
$$\ln\left(\frac{B-\beta_1 r_2 y(n)}{d_2 B y(n)}\right),$$

where $r_2 > \frac{d_2}{\beta_1} > \frac{d_2}{\beta_2}$ and $y(n) < \frac{1}{\beta_1 r_2} < \frac{1}{d_2}$.

Some additional assumptions of (18) are needed to verify global asymptotic stability for the positive equilibrium point $(\bar{x}, \bar{y})$.

f and *g* are continuous functions.

$$f: \left(0, \frac{p + r_1 R_1}{\alpha_1 r_1}\right) \times \left(0, \frac{\alpha_1 R_2 r_1 r_2 + \gamma_1 (p + r_1 R_1)}{\alpha_1 \beta_1 r_1 r_2}\right)$$
$$\to \left(0, \frac{p + r_1 R_1}{\alpha_1 r_1}\right)$$
$$g: \left(0, \frac{p + r_1 R_1}{\alpha_1 r_1}\right) \times \left(0, \frac{\alpha_1 R_2 r_1 r_2 + \gamma_1 (p + r_1 R_1)}{\alpha_1 \beta_1 r_1 r_2}\right)$$
$$\to \left(0, \frac{\alpha_1 R_2 r_1 r_2 + \gamma_1 (p + r_1 R_1)}{\alpha_1 \beta_1 r_1 r_2}\right)$$

Corollary 2.1. Let $(\bar{x}, \bar{y})$ be a positive equilibrium point of system (2). Suppose that Theorem 2.1-Theorem 2.3 hold. Then the positive equilibrium point of system (2) is globally asymptotically stable.

III. Oscillation

In this section is the damped oscillation behavior of the solutions of system (2) was considered.

Theorem 3.1. Let $\{(x(n), y(n))\}_{n=0}^{\infty}$ be a positive solution of system (2). Assume that

$$\alpha_1 r_1 x(2n) < p + r_1 R_1 - \alpha_2 r_1 x(2n-1) - \gamma_1 y(2n-1) -$$
$$d_1 x(2n) < ln\left(\frac{x(2n-1)}{x(2n)}\right) \tag{37}$$

And

$$\beta_1 r_2 y(2n) < r_2 R_2 - \beta_2 r_2 y(2n-1) + \gamma_1 x(2n) -$$
$$d_2 y(2n) < ln\left(\frac{y(n-1)}{y(n)}\right) \tag{38}$$

Hold, where $r_1 > \frac{d_1}{\alpha_2}$ and $r_2 > \frac{d_2}{\beta_2}$. If

$$x(2n) < \bar{x} < x(2n-1)$$

And

$$y(2n) < \bar{y} < y(2n-1) \tag{39}$$

Then the solution of (2) has damped oscillations.

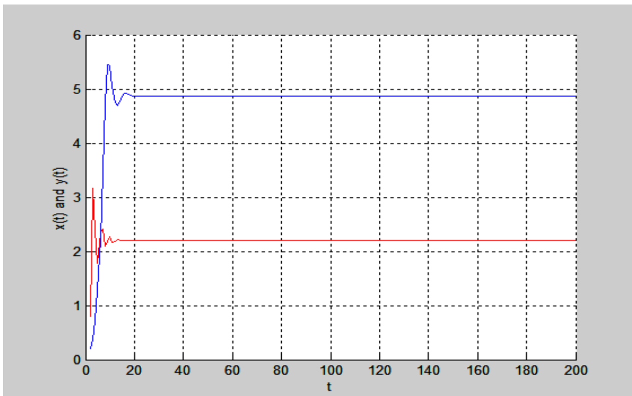

Fig. 1. Local stability of the solutions of system (2.2).

IV. Example

The values of the parameters of (2.2) are as selected as given in [9] and in view the obtained results. p=0.192 give the division rate of the sensitive cells. $R_1 = 0.42 \times 38^{2/3} = 4.704$ Is the carrying capacity of the negrotic and sensitive cells together, $R_2 = 0.11 \times 38^{2/3} = 1.232$ give the carrying capacity of the resistant tumor population. The mutation rate of the sensitive cells to resistant cells is in the interval $[10^{-5}, 10^{-2}]$. In [9] the parameters for the resistant population is given as $\beta_1 = 0.05$ and $\beta_2 = 0.2$. The same parameters are used for the resistant tumor population. The sensitive tumor cells have population rates in the interval $[0.5, 0.95]$, which lead to select $\alpha_1 = 0.51$ and $\alpha_2 = 0.555$. The causes of drug treatment to the sensitive and resistant cells are selected as $d_1 = 0.6$ and $d_2 = 0.006$, respectively. Both populations have different population rates. In this example a relation between both population are constricted such as $r = r_1$ and $(1.05) \times r = r_2$. Fig. 1 and Fig. 2 show the behavior of the sensitive and resistant tumor cells in view of the conditions of Theorem 2.1. The mutation rate is selected $\gamma_1 = 0.01$.

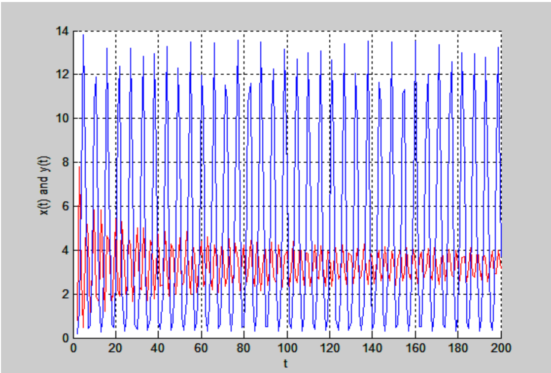

Fig. 2. Unstable behavior of the solutions of system (2.2).

To verify the conditions in Theorem 2.3, the parameter β_1 is selected as $\beta_1 = 0.15$ and $r = r_1 = 0.08$. The global behavior of the tumor population can be shown in Fig. 3.

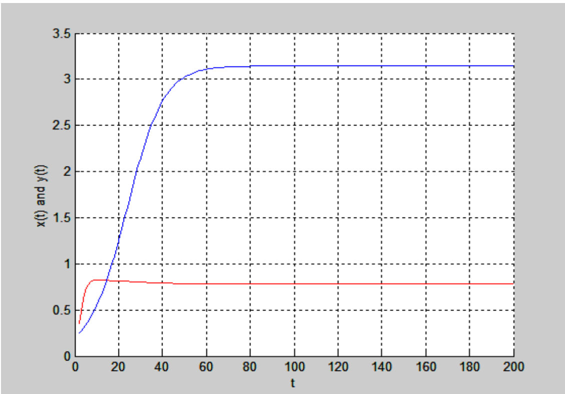

Fig. 3. Global asymptotic stability of the solution of system (2.2).

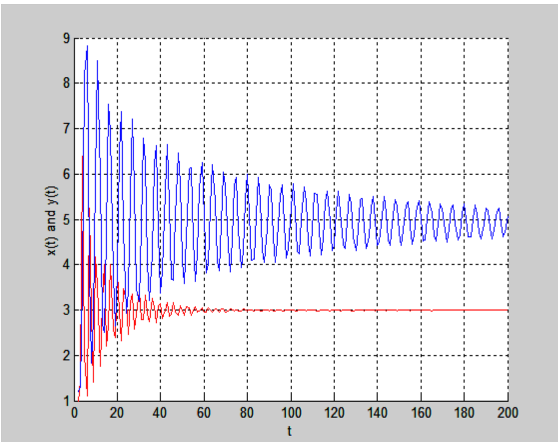

Fig. 4. Damped oscillation behavior of the solutions of system (2.2).

In view of Theorem 3.1, the growth rate is selected as $r = r_1 = 1.09$ and $\beta_1 = 0.05$. The obtained behavior can be shown in Fig. 4.

Fig. 5 and Fig. 6 show the bicurcation diagram of the tumor population where the mutation rate changed. The red and the blue graph sembolize the sensitive cells population $(x(t))$ and the resistant cells population $(y(t))$, respectively.

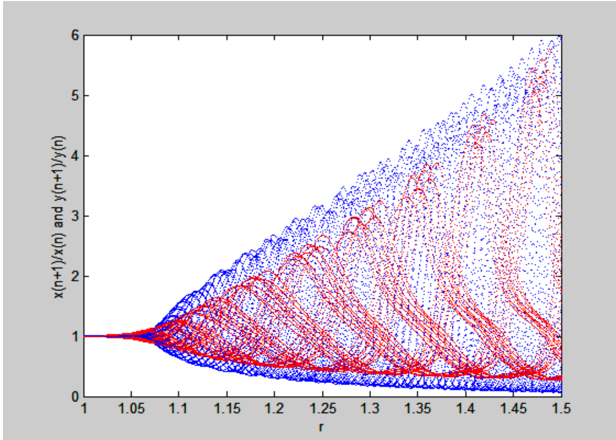

Fig. 5. Bifurcation diagram of the solutions of system (2.2).

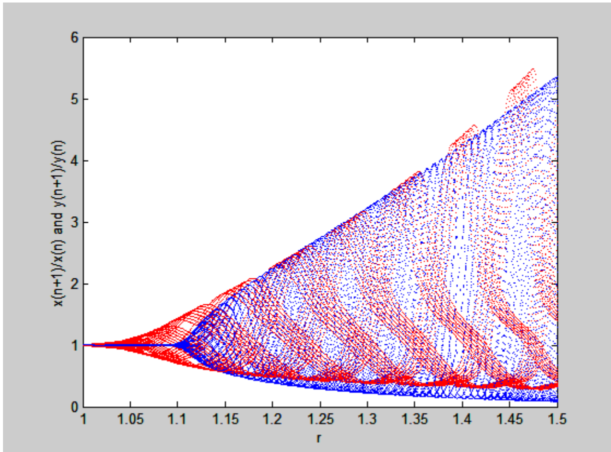

Fig. 6. Bifurcation diagram of the solutions of system (2.2).

V. Conclusion

To consider the model in (1), its solution (2) has been studied as a difference equation system. In section 2, the local and global asymptotic stability of the positive equilibrium point of system (2) was studied in Theorem 2.1-Theorem 2.3 and Corollary 2.1. Theorem 3.1 gives information of the damped oscillation behavior of system (2). It can be shown that with the mutation rate $\gamma_1 = 0.00001$ after a certain population rate a resistant tumor population occurs over the wall of the sensitive cells. Furthermore, if the mutation rate is $\gamma_1 = 0.01$, then the resistant tumor population will cover the sensitive tumor cells. It is interesting to see that for the local and global stability a relation between the growth rates and the drug treatment is obtained.

This work shows investigations of the behavior of the tumor growth GBM. Future works will include studies about the stability of GBM in view of the density.

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REFERENCES

[1] E. C. Holland and G. Multiforme, "The terminator," *Nat. Acad. of Sci.*, 2000, vol. 97, pp. 6242-6244,.

[2] Y. A. Yung, J. R. Shapiro, and W. R. Shapiro, "Heterogeneous chemosensitivities of subpopulations of human glioma cells in culture," *Cancer Res.*, vol. 42, pp. 992-998, 1982.

[3] W. Paulus and J. Peiffer, "Intratumoral histologic heterogeneity of gliomas, A quantitative study," *Cancer*, vol. 64, pp. 442-447, 1989.

[4] R. A. Berkman *et al.*, "Clonal composition of glioblastoma multiforme," *J. of Neurosurgery*, vol. 77, pp. 432-437, 1992.

[5] S. W. Coons and P. C. Johnson, "Regional heterogeneity in the DNA content of human gliomas," *Cancer*, vol. 72, pp. 3052-3060, 1993.

[6] A. J. Coldman and J. H. Goldie, "A mathematical model for relating the drug sensitivity of tumors to their spontaneous mutation rate," *Cancer Treat. Rep.*, vol. 63, pp. 1727-1731, 1979.

[7] J. C. Panetta, "A mathematical model of drug resistance: Heterogeneous tumors," *Math. Biosci.*, vol. 147, pp. 41-61, 1998.

[8] B. G. Birkhead *et al*., A mathematical model of the development of drug resistance to cancer chemotherapy, Europe," *J. of Cancer and Clinical Oncology*, vol. 23, pp. 1421-1427, 1987.

[9] J. E. Schmitz, A. R. Kansal, and S. Torquato, "A cellular automaton of brain tumor treatment and resistance," *J. of Theoret. Med.*, vol. 4, no. 4, pp. 223-239, 2002.

[10] J.L. Gevertz and S. Toquato, "Modeling the effects of vasculature evolution on early brain tumor growth," *J. of Theoret. Biol.*, vol. 243, pp. 517-531, 2006.

[11] F. Gurcan and F. Bozkurt, "Global stability in a population model with piecewise constant arguments," *J. of Math. Anal. Appl.*, vol. 360, no. 1, pp. 334-342, 2009.

[12] I. Ozturk and F. Bozkurt, "Stability analysis of a population model with piecewise constant arguments," *Non. Anal.: RWA*, vol. 12, issue 3, pp. 1532-1545, 2011.

[13] I. Ozturk, F. Bozkurt, and F. Gurcan, "Stability analysis of a mathematical model in a microcosm with piecewise constant arguments," *Mathematical Biosciences*, vol. 240, no. 2, pp. 85-91, 2012.

[14] P. Mosayebi *et al*., "Tumor invasion margin on the Riemannian space of brain fibers," *Medical Image Analysis*, vol. 16, no. 2, pp. 361-373, 2012.

[15] C. Gh. Buzea, "Some implications of scale relativity theory in avascular stages of growth of solid tumors in the presence of an immune system response," *Journal of Theoretical Biology*, vol. 282, no. 1, pp. 52-64, 2011.

[16] F. Bozkurt, "Stability analysis of a logistic differential equation," *International Journal of Mathematics and Computation*, vol. 21, no. 4, pp. 1-14, 2013.

[17] F. Bozkurt, "Stability analysis of a nonlinear difference equation with delay," *International Journal of Modern Nonlinear Theory and Application*, vol. 2, no. 1, pp. 1-6, 2013.

[18] F. Bozkurt, "A mathematical model of the brain tumor Gliobalstoma Multiforme (GBM) and the Immune System (IS) interaction," *International Journal of Mathematics and Computation*, vol. 22, no. 1, pp. 47-56, 2014.

[19] F. Bozkurt, "Modeling a tumor growth with piecewise constant arguments," *Discrete Dynamics in Nature and Society*, vol. 2013, pp. 1-8, 2013.

[20] F. Bozkurt, "Hopf bifurcation and stability analysis for a delayed logistic equation," *International Journal of Modeling and Optimization*, vol. 3, pp. 288-292, 2013.

[21] F. Bozkurt, "Stability analysis of a fractional-order differential equation system of a GBM-IS interaction depending on the density," *Applied Mathematics and Information Science*, vol. 8, no. 3, pp. 1-8, 2014.

[22] F. Bozkurt and I. Ozturk, "A population model of two-strains tumors with piecewise constant arguments," *Kuwait Journal of Science*, vol. 1, pp. 1-11, 2015.

[23] E. I. Kulich *et al.*, "Phase transition in tumor growth: I avascular development," *Physica A: Statistical Mechanics and its Applications*, vol. 392, no. 24, pp. 6616-6623, 2013.

[24] N. C. Atuegwu *et al*., "Parameterizing the logistic model of tumor growth by dw-mri and dce-mri data to predict treatment response and changes in breast cancer cellularity during neoadjuvant chemotherapy," *Translational Oncology*, vol. 6, no. 3, pp. 256-264, 2013.

[25] M. Bodnar *et al*., "Logistic type equations with discrete delay and quasi-periodic suppression rate," *Applied Mathematics Letters*, vol. 26, no. 6, pp. 607-611, 2013.

[26] L. J. S. Allen, *An Introduction to Mathematical Biology*, NJ: Pearson Prentice Hall, 2007.

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