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 nature and the damped oscillation behavior of the solutions of the positive critical point of system (1) was presented. 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

\[
\begin{align*}
\frac{dx}{dt} &= px(t) + r_1 x(t)(R_1 - \alpha_1 x(t) - \alpha_2 x([t - 1])) - \gamma_1 x(t)y([t - 1]) - d_1 x(t)x([t]) \\
\frac{dy}{dt} &= r_2 y(t)(R_2 - \beta_1 y(t) - \beta_2 y([t - 1])) + \gamma_1 x([t])y(t) - d_2 y(t)y([t])
\end{align*}
\]

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 \( \beta_2 \) are parameters to construct logistic differential equations, \( \gamma_1 \) is the converting rate of sensitive cells to resistant cells. The parameters \( d_1 \) and \( d_2 \) are their death 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

\[
\begin{align*}
x(n + 1) &= x(n) \cdot \left( p + r_1 R_1 - \alpha_2 x(n - 1) - \gamma_1 y(n - 1) - d_1 x(n) \right) \\
&\quad - \gamma_1 x(n - 1) y(n) - d_1 x(n) x(n) \\
y(n + 1) &= y(n) \cdot \left( r_2 R_2 - \beta_2 y(n - 1) + \gamma_1 x(n - 1) - d_2 y(n) \right) \\
&\quad - \gamma_1 x(n - 1) y(n) - d_2 y(n) y(n)
\end{align*}
\]

where hereafter

\[
\begin{align*}
&\left( p + r_1 R_1 - \alpha_2 x(n - 1) - \gamma_1 y(n - 1) - d_1 x(n) \right) \neq 0 \\
&\left( r_2 R_2 - \beta_2 y(n - 1) + \gamma_1 x(n - 1) - d_2 y(n) \right) \neq 0.
\end{align*}
\]

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

\[
\mu = (\bar{x}, \bar{y}) = \left( \frac{(p + r_1 R_1)(d_2 + \beta_1 r_2 + \beta_2 r_2) - r_2 R_2 \gamma_1}{(d_1 + \alpha_2 r_1 + \alpha_1 r_1)(d_2 + \beta_2 r_2 + \beta_1 r_2) + r_1 \gamma_1} \right)
\]

where \( \gamma_1 = \gamma_1 d_1 / (d_1 + \gamma_1 x(n - 1)) \), \( r_1 \) 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 \( \beta_2 \) are parameters to construct logistic differential equations, \( \gamma_1 \) is the converting rate of sensitive cells to resistant cells. The parameters \( d_1 \) and \( d_2 \) are their death 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.
where $\gamma_1 < \frac{(p+\alpha R_1)(d_1+\beta r_1+\beta r_2)}{r_2}$. Hereafter, let

\[
\begin{align*}
(A = p + r_1R_1 - (\alpha x_1 + d_1)x - \gamma_1y > 0) \\
(B = r_2R_2 - (\beta x_2 + d_2)y + \gamma_1x > 0).
\end{align*}
\]

(5)

Linearizing (2) about $\mu$, we obtain

\[
\begin{align*}
u_1 &= \frac{d_1 + ax_1r_1}{\alpha x_1} \exp(-\beta x_1) - d_1 - \frac{1}{\alpha x_1} \\
u_2 &= \frac{d_2 + ax_2r_2}{\alpha x_2} \exp(-\beta x_2) - d_2 - \frac{1}{\alpha x_2} \\
u_3 &= \frac{d_1 + ax_1r_1}{\beta x_1} \exp(-\beta x_1) - d_1 - \frac{1}{\alpha x_1} \\
u_4 &= \frac{d_2 + ax_2r_2}{\beta x_2} \exp(-\beta x_2) - d_2 - \frac{1}{\alpha x_2}
\end{align*}
\]

(6)

where

\[
\lambda^4 - (u_1 + v_2)\lambda^3 + (u_1v_3 - v_4 - u_2)\lambda^2 + (u_1v_4 + u_2v_3 - u_4v_1)\lambda + u_2v_4 = 0.
\]

(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 $ax_1r_1 - d_1 < \frac{a}{a_1+\alpha_1}$ and $r_2 > \frac{d_2}{\beta_1+\alpha_1}$ and $\gamma_1 < \frac{d_2}{\beta_1+\alpha_1}$ hold, where $\alpha_2 > a_1$ and $\beta_2 > \beta_1$.

If

\[
\ln\left(\frac{a_2x_1r_1 + a_1x_1r_1 + a_2x_2r_2 + a_1x_2r_2 + a_1d_1 + d_1d_2}{a_2x_1r_1 + a_1x_1r_1 + a_2x_2r_2 + a_1x_2r_2 + a_2d_1 + d_1d_2}ight) < B
\]

\[
\ln\left(\frac{a_2x_1r_1 + a_1x_1r_1 + a_2x_2r_2 + a_1x_2r_2 + a_1d_1 + d_1d_2}{a_2x_1r_1 + a_1x_1r_1 + a_2x_2r_2 + a_1x_2r_2 + a_2d_1 + d_1d_2}ight) < B
\]

(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) $p(1) = 1 - (u_1 + v_2) + (u_1v_3 - v_4 - u_2) + (u_1v_4 + u_2v_3 - u_4v_1 + u_2v_4) > 0$

(b) $(-1)^p(-1) = 1 + (u_1 + v_2) + (u_1v_3 - v_4 - u_2) - (u_1v_4 + u_2v_3 - u_4v_1 + u_2v_4) > 0$

(c) $|u_2v_4| < 1$

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

\[
1 + u_1v_3 + u_2v_4 > v_4 + u_2.
\]

(9)

Using (6) in (9), we have

\[
1 + \frac{(d_1 + ax_1r_1)e^{-\beta x_1} - d_1}{\alpha x_1} + \frac{(d_2 + ax_2r_2)e^{-\beta x_2} - d_2}{\alpha x_2} > \frac{\beta x_1}{1 - \exp(-\beta x_1)} + a \frac{(e^{-\beta x_1} - 1)}{\alpha x_1}.
\]

By ordering and computing (10), we obtain

\[
\ln\left(\frac{a_2x_1r_1 + a_1x_1r_1 + a_2x_2r_2 + a_1x_2r_2 + a_1d_1 + d_1d_2}{a_2x_1r_1 + a_1x_1r_1 + a_2x_2r_2 + a_1x_2r_2 + a_2d_1 + d_1d_2}ight) < B
\]

\[
\ln\left(\frac{a_2x_1r_1 + a_1x_1r_1 + a_2x_2r_2 + a_1x_2r_2 + a_1d_1 + d_1d_2}{a_2x_1r_1 + a_1x_1r_1 + a_2x_2r_2 + a_1x_2r_2 + a_2d_1 + d_1d_2}ight) < B
\]

(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

\[
\frac{a_2(1-e^{-\beta_1})}{\alpha_2}, \frac{a_2(1-e^{-\beta_1})}{\beta_2} < 1
\]

(12)

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

\[
\frac{\beta_2y_1}{\alpha_2} < 1 - e^{-\beta_2} \frac{\beta_2r_2d_1 + a_1(\alpha_2 + \alpha_1)r_1}{\alpha_2(\alpha_2 + \alpha_1)r_1} + \frac{a_1(\alpha_2 + \alpha_1)r_1}{\alpha_2(\alpha_2 + \alpha_1)r_1} < e^{-\beta_2}
\]

(13)

Using (13) in (12), we obtain

\[
\frac{a_2(1-e^{-\beta_1})}{\alpha_2} < 1 - e^{-\beta_2} < \frac{a_2(1-e^{-\beta_1})}{\alpha_2}
\]

(14)

which lead us to the inequality

\[
\frac{a_2r_2d_1 - (a_2 - a_1)r_1}{e^{-\beta_2}} < \frac{a_2r_2d_1 - (a_2 - a_1)r_1}{e^{-\beta_2}} < e^{-\beta_2}
\]

(15)

This is simplify such as

\[
\frac{\alpha_1}{\alpha_2} < \frac{r_1}{r_2}, \frac{\beta_1}{\beta_2}
\]

And $\frac{a_2}{\alpha_1} > \frac{\beta_1}{\beta_2}$, where

\[
\frac{a_2r_2d_1 - (a_2 - a_1)r_1}{e^{-\beta_2}} < \frac{a_2r_2d_1 - (a_2 - a_1)r_1}{e^{-\beta_2}} < e^{-\beta_2}
\]

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 $n=0, 1, \ldots$ the conditions

\[
\begin{align*}
\alpha_1 x(n) < p + r_1R_1 - a_2x(n-1) \\
y(n-1) - d_1x(n) < \alpha_1 x(n) \\
\beta_1 y(n) < \alpha_2 R_2 - \beta_2 y(n-1) + y(n) - d_2y(n)
\end{align*}
\]

(16)

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

\[
\frac{\alpha_1 R_1}{\alpha_1} \leq x(n) < p + r_1R_1
\]

And

\[
y(n) < \frac{\alpha_1 R_1}{\alpha_1} y(n)
\]

(17)

The solution of system (2) increase monotonic.

**Theorem 2.3.** Let system (2) be...
\[ F(x(n), y(n), x(n-1), y(n-1)) = \\
(\begin{align*}
(\sigma f) & = f(x(n), y(n), x(n-1), y(n-1)) \\
(\sigma g) & = g(x(n), y(n), x(n-1), y(n-1))
\end{align*})
\]

where the first order partial derivatives of the functions \( f \) and \( g \) with respect to \( x \) and \( y \) are continuous in \( I \subseteq \mathbb{R}^* \) and \( f, g: V \subseteq (\mathbb{R}^*)^4 \rightarrow I \subseteq \mathbb{R}^* \). Furthermore assume that

\[ \alpha_1 r_1 x(n) < p + r_1 R_1 - \alpha_2 F_1 x(n-1) - y_1 y(n-1) - d_1 x(n) \]

(17)

And

\[ \beta_1 r_2 y(n) < r_2 R_2 - \beta_2 y_2 y(n-1) + y_1 x(n) - d_2 y(n) \]

(18)

That \( 2\alpha_1 > \alpha_2 > a_2, 2\beta_1 > \beta_2 > \beta_1 \) and \( y_1 < d_1 \). If

\[ \frac{\alpha_1 r_1 x(n)}{1 - \alpha_2 r_1 x(n)} < A < \ln \left( \frac{A - \alpha_2 r_1 x(n)}{\alpha_2 r_1 Ax(n)} \right) \]

(20)

And

\[ \frac{\beta_1 r_2 y(n)}{1 - \beta_2 r_2 y(n)} < B < \ln \left( \frac{B - \beta_2 r_2 y(n)}{\beta_2 r_2 By(n)} \right) \]

(21)

where \( r_1 > \frac{a_1}{a_2}, r_2 > \frac{a_1}{a_1} \), \( x(n) < \frac{1}{\alpha_2 r_1} \) and \( y(n) < \frac{1}{\beta_2 r_2} \), then (17) has no 2-cycle in \( I \).

**Proof.** For some

\[ s(2) = (x(1), y(1), x(0), y(0)) \]

\[ s(3) = (x(2), y(2), x(1), y(1)) \]

\[ r(2) = (x(1), y(1), x(0), y(0)) \]

\[ r(3) = (x(2), y(2), x(1), y(1)) \]

(22)

\[ A_2 \text{-cycle will be the condition} \]

\[ \begin{cases} 
  s(2) = f(s(3)) = f(f(x(1), y(1), x(0), y(0))) \\
  r(2) = g(r(3)) = g(g(x(1), y(1), x(0), y(0))) 
\end{cases} \]

(23)

In this case, we must have \( f(s(2)) (1 + \frac{\partial f}{\partial x}) dx \neq 0 \), \( g(s(3)) (1 + \frac{\partial g}{\partial y}) dy \neq 0 \), \( f(s(2)) (1 + \frac{\partial f}{\partial x}) dx \neq 0 \) and \( f(r(2)) (1 + \frac{\partial f}{\partial x}) dx \neq 0 \).

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

For the partial derivative of function \( f \) with respect to \( x(n) \), we get

\[ 1 + \frac{\partial f}{\partial x(n)} = \frac{1}{(A - \alpha_1 r_1 x(n)) e^{-A} - d_1 Ax(n))} \]

\[ \times \left( (A - \alpha_1 r_1 x(n)) e^{-A} - d_1 Ax(n)) (2\alpha_1 r_1 - d_1) + \alpha_1 r_1 x(n) e^{-A} + (\alpha_1 r_1 - d_1) Ax(n) e^{-A} \right) \]

(24)

Since \( r_1 > \frac{a_1}{a_1} \), if

\[ (A - \alpha_1 r_1 x(n)) e^{-A} - d_1 Ax(n)) > 0 \]

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

\[ \frac{\alpha_1 r_1 x(n)}{1 - d_1 x(n)} < A < \ln \left( \frac{A - \alpha_2 r_1 x(n)}{d_2 x(n)} \right) \]

(26)

where \( x(n) < \frac{1}{a_2} \). Showing the partial derivative of function \( f \) with respect to \( x(n-1) \), give that \( 1 + \frac{\partial f}{\partial x(n-1)} > 0 \), if

\[ \frac{\alpha_1 r_1 x(n)(\alpha_2 - a_1)}{a_2} < A < \ln \left( \frac{\alpha_2 A}{\alpha_1 r_1 x(n)(\alpha_2 - a_1)} \right) \]

(27)

And

\[ \frac{\alpha_1 r_1 x(n)}{1 - \alpha_2 r_1 x(n)} < A < \ln \left( \frac{\alpha_2 A}{\alpha_1 r_1 x(n)(\alpha_2 - a_1)} \right) \]

(28)

where \( 2\alpha_1 > \alpha_2 > a_1 \) and \( x(n) < \frac{1}{a_2} \). Considering both (27) and (28), when \( a_2 > a_1 \), we get

\[ \frac{\alpha_1 r_1 x(n)(\alpha_2 - a_1)}{a_2} < \frac{\alpha_1 r_1 x(n)}{1 - \alpha_2 r_1 x(n)} < A < \ln \left( \frac{\alpha_2 A}{\alpha_1 r_1 x(n)(\alpha_2 - a_1)} \right) \]

(29)

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

\[ 1 + \frac{\partial f}{\partial y(n-1)} = \frac{1}{(A - \alpha_1 r_1 x(n)) e^{-A} + \alpha_1 r_1 x(n))^2} \]

\[ \times \left( (A - \alpha_1 r_1 x(n)) e^{-A} + \alpha_1 r_1 x(n))^2 \right) \]

\[ + \frac{\alpha_1 r_1 x(n)(\alpha_2 - a_1)}{a_2} \]

\[ + \frac{\alpha_1 r_1 x(n)(\alpha_2 - a_1)}{a_2} \]

\[ + \frac{\alpha_1 r_1 x(n)(\alpha_2 - a_1)}{a_2} \]

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\[ + \frac{\alpha_1 r_1 x(n)(\alpha_2 - a_1)}{a_2} \]

\[ + \frac{\alpha_1 r_1 x(n)(\alpha_2 - a_1)}{a_2} \]

(30)

Since \( x(n) < \frac{1}{a_2} \) and \( r_1 > \frac{a_1}{a_2} \) if

\[ \frac{\alpha_1 r_1 x(n)}{1 - \gamma_1 x(n)} < A < \ln \left( \frac{\alpha_2 A}{\gamma_1 r_1 x(n)} \right) \]

(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{\alpha_2 A}{\alpha_1 r_1 x(n)(\alpha_2 - a_1)} \right) < A \]

(32)

where \( \gamma_1 < d_1, r_1 > \frac{a_1}{a_2} \) and \( x(n) < \frac{1}{a_2} \). The partial derivative of \( g(x(n), y(n), x(n-1), y(n-1)) \) with respect to \( x(n), x(n-1), y(n) \) and \( y(n-1) \) will give the following results:

For

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


global asymptotic stability for the positive equilibrium point \( \Phi \), where both are always positive. Considering at last (33) and 

\[
\frac{\beta_1 r_2 y(n)}{1-d_2 y(n)} < B < \ln \left( \frac{\beta_2}{\beta_2 - \beta_1 \beta_1 r_2 y(n)} \right) \tag{34}
\]

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

\[
\frac{\beta_2 - \beta_1 \beta_1 r_2 y(n)}{\beta_2} < B < \ln \left( \frac{\beta_2 B}{\beta_2 - \beta_1 \beta_1 r_2 y(n)} \right) \tag{35}
\]

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

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

And 

\[
\frac{\beta_2 y(n)}{1 - \beta_1 r_2 y(n)} < B < \ln \left( \frac{\beta_2 B}{\beta_2 - \beta_1 \beta_1 r_2 y(n)} \right) \tag{37}
\]

where \( r_2 > \frac{d_2}{\beta_1} \) and \( y(n) < \frac{1}{\beta_1 r_2} \), we have 

\[
1 + \frac{\partial g}{\partial x(n)} > 0.
\]

Considering both (33) and (35), since \( \beta_2 > \beta_1 \), we obtain 

\[
\frac{\beta_2 y(n)}{1 - \beta_1 r_2 y(n)} < B < \ln \left( \frac{\beta_2 B}{\beta_2 - \beta_1 \beta_1 r_2 y(n)} \right) \tag{38}
\]

And 

\[
\frac{\beta_2 y(n)}{1 - \beta_1 r_2 y(n)} < B < \ln \left( \frac{\beta_2 B}{\beta_2 - \beta_1 \beta_1 r_2 y(n)} \right) \tag{39}
\]

Then the solution of (2) has damped oscillations.

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 

\[
\alpha_1 r_1 x(2n) + p + r_1 R_1 - \alpha_2 r_1 x(2n+1) + \gamma_1 y(2n+1) - d_1 x(2n) < \ln \left( \frac{x(2n+1)}{x(2n)} \right) \tag{40}
\]

And 

\[
\beta_1 r_2 y(2n) < r_2 R_2 - \beta_2 r_2 y(2n-1) + \gamma_1 x(2n) - d_2 y(2n) < \ln \left( \frac{y(2n)}{y(2n-1)} \right) \tag{41}
\]

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

\[
x(2n) < x_1 < x(2n+1)
\]

And 

\[
y(2n) < y_1 < y(2n+1)
\]

Then the solution of (2) has damped oscillations.

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. \( R_1 = 0.42 \times 10^2/3 = 4.704 \) is the carrying capacity of the syngiotic and sensitive cells together, \( R_2 = 0.11 \times 10^2/3 = 1.232 \) 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 $\beta_1$ 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 symbolize 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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