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A population model of two-strains tumors with piecewise constant arguments

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ABSTRACT

In this study, the population growth of the brain tumor GBM, is constructed such as

$$\begin{cases} \dfrac{dx}{dt} = px(t) + r_1 x(t)\left(R_1 - \alpha_1 x(t) - \alpha_2 x([[t]])\right) - \gamma_1 x(t) y([[t]]) - d_1 x(t) x([[t]]) \\ \dfrac{dy}{dt} = r_2 y(t)\left(R_2 - \beta_1 y(t) - \beta_2 y([[t]])\right) + \gamma_1 x([[t]]) y(t) - d_2 y(t) y([[t]]) \end{cases} \quad \text{(A)}$$

where $t = 0$, 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 are positive real numbers and $[[t]]$ denotes the integer part of $t \in [0,8)$. System (A) explains a tumor growth, that produces after a specific time another tumor population with different growth rate and different treatment susceptibilities. The local and global stability of this model is analyzed by using the theory of differential and difference equations. Simulations and data of GBM give a detailed description of system (A) at the end of the paper.

Keywords: Differential equation; difference equations; local stability; global stability; boundedness

INTRODUCTION

Glioblastoma multiforme is the most aggressive of the gliomas, a collection of tumors arising from glia or their precursors within the central nervous system. Most patients with GBMs die of their disease in less than a year and essentially none has long-term survival, Holland (2000). In the first stage of GBM, the tumor has a monoclonal origin, which changes after reaching a specific density. This kind of tumor can develop multiple sub-population with different growth rates and treatments susceptibilities. For this, during the treatment process a formidable obstacle can be obtained. Various papers about the characteristic behavior of GBM or tumor population with multiform are written, where some of them are Berkmann *et al*. (1992); Coons & Johnson (1993); Paulus & Peiffer (1989); Yung *et al*. (1982). Brain tumors are ideal candidates for theoretical modeling. Mathematical approaches to tumor treatment offer a perspective that current in vivo/in vitro techniques cannot, Coldman & Goldie (1979); Panetta (1998).

By describing the tumor phenomena the best known modeling is the Gompertz's model,

$$V = V_0 \exp\left(\frac{A \cdot (1 - \exp(-Bt))}{B} \right), \tag{1.1}$$

where V describes the volume of the tumor, t denotes the time, V_0 is the volume at time t=0, A and B are parameters that have to be specified, Birkhead (1987).

Coldman & Goldie (1979) proposed a model, which links a Tumor's drug sensitivity to its rate of spontaneous resistance mutations such as

$$\frac{d\mu}{dt} = \frac{\mu}{N} + \alpha\left(1 - \frac{\mu}{N}\right) \tag{1.2}$$

where μ is the mean volume of the resistant strain and N the total volume of the tumor. The parameter α is the mutation rate per cell generation.

Panetta (1998) modeled the size of two sub-populations in time such as

$$\begin{cases} \dfrac{dx}{dt} = (r_1 - d_1(t))x \\ \dfrac{dy}{dt} = b_1 d_1(t)x + (r_2 - d_2(t))y \end{cases} \tag{1.3}$$

where x represents the sensitive cell population, y the resistant cell population, r_1 and r_2 are the growth rates, d_1 and d_2 are their drug sensitivities, respectively.

Birkhead *et al*. (1987), have considered both cycling and resting tumor cells in their study. The difference between the two models is that sensitive cells could convert to resistant cells, while cycling and resting cells could inter-convert. Similar works about modeling tumor behaviors can be found in Schmitz *et al*. (2002); De Vlader & Gonzalez (2004); Gevertz & Toquato (2006); Mansury *et al*. (2006).

In some biological situations Mathematical approximation for population growth involves nonlinear differential equations, May (1975); May & Oester (1976). It is generally known that for an overlapping generation of a single species, a model with a differential equation is preferred. If there is a non-overlapping generation of single species, then it is convenient to construct a model with a difference equation, Allen (2007); Hoppenstead (2004); Rubinow (2002). For both time situations, continuous and discrete, there is some population dynamics in ecosystem, which combine the properties of both differential and difference equations, where the use of piecewise constant arguments come into question. For such biological events it may be suitable to construct a model with piecewise constant arguments, see Cooke & Huang (1991); Gopalsamy & Liu (1998); Gurcan & Bozkurt (2009); Liu & Gopalsamy (1999); Ozturk & Bozkurt (2011).

According to Gopalsamy & Liu (1998), the differential equation

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t}=rN(\mathrm{t})\left\{1-\mathrm{a}N(\mathrm{t})-\mathrm{b}N([[\mathrm{t}]])\right\} \tag{1.4}$$

was considered, where N(t) denotes the biomass (or population density) of a single species, r, a, b and t are positive numbers. Using the Lyapunov function, they proved sufficient condition for all positive solutions of equation (1.4). A general differential equation of (1.4) can be shown in Liu & Gopalsamy, (1999), were by using the lemma of Cooke and Huang, see Cooke & Huang (1991) the global attractivity of the positive equilibrium point are proven.

Gurcan & Bozkurt (2009), considered the logistic equation

$$\frac{\mathrm{d}x}{\mathrm{d}t}=rx(\mathrm{t})\left(1-\alpha\mathrm{x}(\mathrm{t})-\beta_0\mathrm{x}([[\mathrm{t}]])-\beta_1\mathrm{x}([[\mathrm{t}-1]])\right), \tag{1.5}$$

where $t\geq 0$ and the parameters $\alpha,\ \beta_0,\ \beta_1$ and r denote positive numbers. The local asymptotic stability of the positive equilibrium point of equation (1.5) was proven by using the Linearized Stability Theorem and the global asymptotic stability by using a suitable Lyapunov function. A general differential equation (1.5) was shown in Ozturk & Bozkurt (2011), where additionally a detailed description and condition of semicycle and damped oscillation of the positive solutions are proved.

In this paper, the growth of GBM has been considered. This tumor has two sub-populations, the sensitive cells and the resistant cells, where the model is constructed such as

$$\begin{cases}\dfrac{\mathrm{d}x}{\mathrm{d}t}=px(t)+\mathrm{r}_1\mathrm{x}(\mathrm{t})\left(\mathrm{R}_1-\alpha_1\mathrm{x}(\mathrm{t})-\alpha_2\mathrm{x}([[\mathrm{t}]])\right)-\gamma_1\mathrm{x}(\mathrm{t})\mathrm{y}([[\mathrm{t}]])-\mathrm{d}_1\mathrm{x}(\mathrm{t})\mathrm{x}([[\mathrm{t}]])\\ \quad\dfrac{\mathrm{d}y}{\mathrm{d}t}=\mathrm{r}_2\mathrm{y}(\mathrm{t})\left(\mathrm{R}_2-\beta_1\mathrm{y}(\mathrm{t})-\beta_2\mathrm{y}([[\mathrm{t}]])\right)+\gamma_1\mathrm{x}([[\mathrm{t}]])\mathrm{y}(\mathrm{t})-\mathrm{d}_2\mathrm{y}(\mathrm{t})\mathrm{y}([[\mathrm{t}]]).\end{cases} \tag{1.6}$$

Here, $t\geq 0$ and the parameters $\alpha_1,\alpha_2,\beta_1,\beta_2,\gamma_1,p,\mathrm{d}_1,\mathrm{d}_2,\mathrm{r}_1$ and r_2 denote positive numbers. p is the division rate of the sensitive cells and the parameter $\alpha_1,\alpha_2,\beta_1$ and β_2 are necessary parameters for the logistic differential equations of the tumor populations. 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 2, we investigate the local and global behavior of the nonlinear difference solutions of (1.6) based on specific conditions. Furthermore, the boundedness nature of the positive solutions of (1.6) was considered. Simulations and the data of GBM give a detailed description of the behavior of system (1.6) at the end of the paper.

LOCAL STABILITY AND GLOBAL ASYMPTOTIC STABILITY

On an interval of the form $t \in [n, n+1)$, one can write (6) as

$$\begin{cases} \dfrac{dx}{dt} - \{p + r_1R_1 - (\alpha_2 r_1 + d_1)x(n) - \gamma_1 y(n)\}x(t) = -\alpha_1 r_1 (x(t))^2 \\ \dfrac{dy}{dt} - \{r_2R_2 - (\beta_2 r_2 + d_2)y(n) + \gamma_1 x(n)\}y(t) = -\beta_1 r_2 (y(t))^2, \end{cases} \tag{2.1}$$

where for n = 0,1,2, and $t \to n+1$ the solution is

$$\begin{cases} x(n+1) = \dfrac{x(n)\cdot\{p + r_1R_1 - (\alpha_2 r_1 + d_1)x(n) - \gamma_1 y(n)\}}{\{p + r_1R_1 - (\alpha_2 r_1 + d_1 + \alpha_1 r_1)x(n) - \gamma_1 y(n)\}\cdot exp\left(-\{p + r_1R_1 - (\alpha_2 r_1 + d_1)x(n) - \gamma_1 y(n)\}\right) + \alpha_1 r_1 x(n)} \\ \\ y(n+1) = \dfrac{y(n)\cdot\{r_2R_2 - (\beta_2 r_2 + d_2)y(n) + \gamma_1 x(n)\}}{\{r_2R_2 - (\beta_2 r_2 + d_2 + \beta_1 r_2)y(n) + \gamma_1 x(n)\}\cdot exp\left(-\{r_2R_2 - (\beta_2 r_2 + d_2)y(n) + \gamma_1 x(n)\}\right) + \beta_1 r_2 y(n)}. \end{cases} \tag{2.2}$$

In the following, we assume that

$$p + r_1R_1 - (\alpha_2 r_1 + d_1)x(n) - \gamma_1 y(n) \neq 0 \tag{2.3}$$

and

$$r_2R_2 - (\beta_2 r_2 + d_2)y(n) + \gamma_1 x(n) \neq 0. \tag{2.4}$$

To investigate more about the behavior of (1.6) we continue the analysis, since (2.2) is a system of difference equations. First, we need to obtain the positive equilibrium point of (2.2), which is also the critical points of (1.6). Computations reveal that the positive equilibrium points of (8) is

$$\mu = (\bar{x}, \bar{y}) = \left(\frac{(p + r_1R_1)(d_2 + \beta_1 r_2 + \beta_2 r_2) - r_2R_2\gamma_1}{(d_1 + \alpha_2 r_1 + \alpha_1 r_1)(d_2 + \beta_2 r_2 + \beta_1 r_2) + \gamma_1^2}, \frac{r_2R_2(d_1 + \alpha_2 r_1 + \alpha_1 r_1) + (p + r_1R_1)\gamma_1}{(d_1 + \alpha_2 r_1 + \alpha_1 r_1)(d_2 + \beta_2 r_2 + \beta_1 r_2) + \gamma_1^2} \right) \tag{2.5}$$

where

$$\gamma_1 < \frac{(p + r_1R_1)(d_2 + \beta_1 r_2 + \beta_2 r_2)}{r_2R_2} \tag{2.6}$$

and

$$\begin{cases} A = p + r_1R_1 - (\alpha_2 r_1 + d_1)\bar{x} - \gamma_1 \bar{y} = \dfrac{\alpha_1 r_1 (p + r_1R_1)(d_2 + \beta_1 r_2 + \beta_2 r_2) - \alpha_1 r_1 r_2 R_2 \gamma_1}{(d_1 + \alpha_2 r_1 + \alpha_1 r_1)(d_2 + \beta_2 r_2 + \beta_1 r_2) + \gamma_1^2} > 0 \\ B = r_2R_2 - (\beta_2 r_2 + d_2)\bar{y} + \gamma_1 \bar{x} = \dfrac{\beta_1 R_2 r_2^2 (d_1 + \alpha_2 r_1 + \alpha_1 r_1) + (p + r_1R_1)\gamma_1 \beta_1 r_2}{(d_1 + \alpha_2 r_1 + \alpha_1 r_1)(d_2 + \beta_2 r_2 + \beta_1 r_2) + \gamma_1^2} > 0 \end{cases}$$

Linearizing system (2.2) about the positive equilibrium point, we obtain for $n = 0, 1, 2, \ldots$ the associated characteristic equation of (2.2) as

$$\lambda^2-(a_{11}+a_{22})\lambda+(a_{11}a_{22}-a_{12}a_{21})=0, \tag{2.7}$$

where

$$\begin{cases} a_{11}=\dfrac{(d_1+\alpha_2 r_1+\alpha_1 r_1)e^{-A}-(d_1+\alpha_2 r_1)}{\alpha_1 r_1} \\ a_{12}=\dfrac{\gamma_1(e^{-A}-1)}{\alpha_1 r_1} \\ a_{21}=\dfrac{\gamma_1(1-e^{-B})}{\beta_1 r_2} \\ a_{22}=\dfrac{(d_2+\beta_2 r_2+\beta_1 r_2)e^{-B}-(d_2+\beta_2 r_2)}{\beta_1 r_2}. \end{cases} \tag{2.8}$$

Theorem 2.1. Let $\alpha_2>\alpha_1$ and $r_1 r_2>\dfrac{2(\gamma_1)^2}{\alpha_1\beta_1}$. If

$$\ln\left(\frac{d_1+\alpha_2 r_1+\alpha_1 r_1}{d_1+\alpha_2 r_1}\right)<A<\ln\left(\frac{d_1+\alpha_2 r_1+\alpha_1 r_1}{d_1+\alpha_2 r_1-\alpha_1 r_1}\right) \tag{2.9}$$

and

$$B<\ln\left(\frac{d_2+\beta_2 r_2+\beta_1 r_2}{d_2+\beta_2 r_2}\right), \tag{2.10}$$

then the positive equilibrium point of system (8) is locally asymptotically stable.

Proof. By the Linearized Stability Theorem, see Gibbons *et al.* (2002), the positive equilibrium point of (8) is locally asymptotically stable if and only if

$$|a_{11}+a_{22}|<1+a_{11}a_{22}-a_{12}a_{21}<2 \tag{2.11}$$

holds. From condition (17), we can write

$$\begin{aligned}&\left((d_1+\alpha_2 r_1+\alpha_1 r_1)e^{-A}-(d_1+\alpha_2 r_1)\right)\cdot\left((d_2+\beta_2 r_2+\beta_1 r_2)e^{-B}\right.\\ &\left.-(d_2+\beta_2 r_2)\right)<\alpha_1\beta_1 r_1 r_2-(\gamma_1)^2\cdot(1-e^{-A})(1-e^{-B}).\end{aligned} \tag{2.12}$$

Since $A>0$ and $B>0$, if

$$A>\ln\left(\frac{d_1+\alpha_2 r_1+\alpha_1 r_1}{d_1+\alpha_2 r_1}\right) \tag{2.13}$$

and

$$B < \ln\left(\frac{d_2 + \beta_2 r_2 + \beta_1 r_2}{d_2 + \beta_2 r_2}\right), \tag{2.14}$$

then we have

$$\left(d_2 + \beta_2 r_2 + \beta_1 r_2\right)e^{-B} - \left(d_2 + \beta_2 r_2\right) > 0 \tag{2.15}$$

and

$$\left(d_1 + \alpha_2 r_1 + \alpha_1 r_1\right)e^{-A} - \left(d_1 + \alpha_2 r_1\right) < 0. \tag{2.16}$$

Additionally, we can write

$$\alpha_1 \beta_1 r_1 r_2 - (\gamma_1)^2 + (\gamma_1)^2 \cdot \left(e^{-A} + e^{-B}\right) > (\gamma_1)^2 e^{-(A+B)}, \tag{2.17}$$

since

$$e^{(A+B)} > 1 > \frac{(\gamma_1)^2}{\alpha_1 \beta_1 r_1 r_2 - (\gamma_1)^2} \tag{2.18}$$

and

$$r_1 r_2 > \frac{2(\gamma_1)^2}{\alpha_1 \beta_1} > \frac{(\gamma_1)^2}{\alpha_1 \beta_1}. \tag{2.19}$$

From (2.13)-(2.19), the conditions to hold the second part of the inequality in (2.11) are obtained. Furthermore, to consider the inequalities for the left side of (2.11), the following ones have to be considered;

(i) $\beta_1 r_2\left(\left(d_1 + \alpha_2 r_1 + \alpha_1 r_1\right)e^{-A} - \left(d_1 + \alpha_2 r_1\right)\right) + \alpha_1 r_1\left(\left(d_2 + \beta_2 r_2 + \beta_1 r_2\right)e^{-B} - \left(d_2 + \beta_2 r_2\right)\right) < \alpha_1 \beta_1 r_1 r_2 + \left(\left(d_1 + \alpha_2 r_1 + \alpha_1 r_1\right)e^{-A} - \left(d_1 + \alpha_2 r_1\right)\right) \cdot \left(\left(d_2 + \beta_2 r_2 + \beta_1 r_2\right)e^{-B} - \left(d_2 + \beta_2 r_2\right)\right) + (\gamma_1)^2 \cdot \left(1 - e^{-A}\right)\left(1 - e^{-B}\right)$

(ii) $-\alpha_1 \beta_1 r_1 r_2 - \left(\left(d_1 + \alpha_2 r_1 + \alpha_1 r_1\right)e^{-A} - \left(d_1 + \alpha_2 r_1\right)\right) \cdot \left(\left(d_2 + \beta_2 r_2 + \beta_1 r_2\right)e^{-B} - \left(d_2 + \beta_2 r_2\right)\right) - (\gamma_1)^2 \cdot \left(1 - e^{-A}\right)\left(1 - e^{-B}\right) < \beta_1 r_2\left(\left(d_1 + \alpha_2 r_1 + \alpha_1 r_1\right)e^{-A} - \left(d_1 + \alpha_2 r_1\right)\right) + \alpha_1 r_1\left(\left(d_2 + \beta_2 r_2 + \beta_1 r_2\right)e^{-B} - \left(d_2 + \beta_2 r_2\right)\right).$

By considering these, we obtain

$$\left(\left(d_1 + \alpha_2 r_1\right) - \left(d_1 + \alpha_2 r_1 + \alpha_1 r_1\right)e^{-A}\right) \cdot \left(\left(d_2 + \beta_2 r_2 + \beta_1 r_2\right)e^{-B} - \left(d_2 + \beta_2 r_2\right)\right) < \beta_1 r_2\left(\left(d_1 + \alpha_2 r_1 + \alpha_1 r_1\right)e^{-A} - \left(d_1 + \alpha_2 r_1\right)\right), \tag{2.20}$$

since $A > 0$. Furthermore, from

$$\alpha_1 r_1\left(\left(d_2+\beta_2 r_2+\beta_1 r_2\right)e^{-B}-\left(d_2+\beta_2 r_2\right)\right)<\alpha_1\beta_1 r_1 r_2, \tag{2.21}$$

we have $e^{-B}<1$, which is always true, since $B > 0$.

From (ii), if

$$\begin{aligned}&\left(\left(d_1+\alpha_2 r_1\right)-\left(d_1+\alpha_2 r_1+\alpha_1 r_1\right)e^{-A}\right)\left(\left(d_2+\beta_2 r_2+\beta_1 r_2\right)e^{-B}-\left(d_2+\beta_2 r_2\right)\right)\\&<\alpha_1 r_1\left(\left(d_2+\beta_2 r_2+\beta_1 r_2\right)e^{-B}-\left(d_2+\beta_2 r_2\right)\right),\end{aligned} \tag{2.22}$$

for $\alpha_2>\alpha_1$, we get

$$A< ln\left(\frac{d_1+\alpha_2 r_1+\alpha_1 r_1}{d_1+\alpha_2 r_1-\alpha_1 r_1}\right). \tag{2.23}$$

Considering both (2.13) and (2.23), the inequality (2.9) is obtained. In addition, from the inequality

$$\beta_1 r_2\left(\left(d_1+\alpha_2 r_1\right)-\left(d_1+\alpha_2 r_1+\alpha_1 r_1\right)e^{-A}\right)<\alpha_1\beta_1 r_1 r_2, \tag{2.24}$$

we get (2.23), which completes our proof.

Theorem 2.2. Suppose that the conditions in Theorem 2.1 hold. Furthermore, assume that

$$\alpha_1 r_1 x(n)<p+r_1 R_1-\left(\alpha_2 r_1+d_1\right)x(n)-\gamma_1 y(n)<ln\left(\frac{2\bar{x}-x(n)}{x(n)}\right) \tag{2.25}$$

and

$$\beta_1 r_2<r_2 R_2+\gamma_1 x(n)-\left(\beta_2 r_2+d_2\right)y(n)<ln\left(\frac{2\bar{y}-y(n)}{y(n)}\right). \tag{2.26}$$

For $n=0,1,2,\ldots$, if

$$x(n)<2\bar{x} \text{ and } y(n)<2\bar{y} \tag{2.27}$$

then the positive equilibrium point of system (8) is globally asymptotically stable.

Proof. We consider a Lyapunov function V(n) defined by

$$V(n)=\left(V_1(n),V_2(n)\right)=\left\{X(n)-\mu\right\}^2, \tag{2.28}$$

where n = 0,1,2, and $X(n)=\left(x(n),y(n)\right)$. From the change along the solutions of (32), we obtain

$$\Delta V_1(n)=\left\{x(n+1)-x(n)\right\}\left\{x(n+1)+x(n)-2\bar{x}\right\} \tag{2.29}$$

and

$$\Delta V_2(n)=\left\{y(n+1)-y(n)\right\}\left\{y(n+1)+y(n)-2\bar{y}\right\}. \tag{2.30}$$

By using (2.25), one can obtain

$$x(n+1)-x(n)>0. \tag{2.31}$$

Furthermore if (2.27) holds for x(n), then it is easy to obtain the following one;

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

$$=A\left(x(n)+\left(x(n)-2\bar{x}\right)e^{-A}\right)+\alpha_1 r_1 x(n)\left(1-e^{-A}\right)\left(x(n)-2\bar{x}\right)<0. \tag{2.32}$$

From (2.25) and (2.27), we get in this case $\Delta V_1(n)<0$. In similar way, for the condition (2.26), we have

$$y(n+1)-y(n)>0 \text{ and } y(n+1)+y(n)-2\bar{y}<0, \tag{2.33}$$

where, $y(n)<2\bar{y}$. This implies that $\Delta V_1(n)<0$. which completes the proof of global asymptotic stability.

Theorem 2.3 Let $\{(x(n),y(n))\}_{n=0}^{8}$ be a positive solution of (2.2). Assume that for n=0, 1, the conditions

$$\alpha_1 r_1 x(n)<p+r_1R_1-(\alpha_2 r_1+d_1)x(n)-\gamma_1 y(n) \tag{2.34}$$

and

$$\beta_1 r_2 y(n)<r_2R_2+\gamma_1 x(n)-(\beta_2 r_2+d_2)y(n) \tag{2.35}$$

hold. Then all positive solutions of (2.2) are in the interval

$$x(n)\in\left(0,\ \frac{p+r_1R_1}{\alpha_1 r_1}\right) \text{ and } y(n)\in\left(0,\ \frac{\alpha_1 R_2 r_1 r_2+\gamma_1(p+r_1R_1)}{\alpha_1\beta_1 r_1 r_2}\right). \tag{2.36}$$

Proof. Let $\alpha_1 r_1 x(n)<p+r_1R_1-(\alpha_2 r_1+d_1)x(n)-\gamma_1 y(n)$. Then we can write

$$p+r_1R_1-(\alpha_2 r_1+d_1)x(n)-\gamma_1 y(n)<p+r_1R_1 \tag{2.37}$$

and from

$$-\left(p+r_1R_1-(\alpha_2 r_1+d_1)x(n)-\gamma_1 y(n)\right)>-(p+r_1R_1), \tag{2.38}$$

we have

$$e^{-\left(p+r_1R_1-(\alpha_2 r_1+d_1)x(n)-\gamma_1 y(n)\right)}>e^{-(p+r_1R_1)}. \tag{2.39}$$

By using both (2.37) and (2.39), the first equation of (2.2) satisfy

$$x(n+1)<\frac{x(n)(p+r_1R_1)}{\left\{p+r_1R_1-(\alpha_2 r_1+d_1)x(n)-\gamma_1 y(n)\right\}e^{-(p+r_1R_1)}+\alpha_1 r_1 x(n)\left(1-e^{-(p+r_1R_1)}\right)}. \tag{2.40}$$

Furthermore, since $\alpha_1 r_1 x(n) < p + r_1 R_1 - (\alpha_2 r_1 + d_1) x(n) - \gamma_1 y(n)$, we can write

$$\frac{1}{p + r_1 R_1 - (\alpha_2 r_1 + d_1) x(n) - \gamma_1 y(n)} < \frac{1}{\alpha_1 r_1 x(n)}. \tag{2.41}$$

Using (2.41) in (2.40), we get

$$x(n+1) < \frac{x(n)(p + r_1 R_1)}{\alpha_1 r_1 x(n) e^{-(p+r_1 R_1)} + \alpha_1 r_1 x(n)\left(1 - e^{-(p+r_1 R_1)}\right)} = \frac{p + r_1 R_1}{\alpha_1 r_1}. \tag{2.42}$$

In addition, since $\beta_1 r_2 y(n) < r_2 R_2 + \gamma_1 x(n) - (\beta_2 r_2 + d_2) y(n)$, we obtain

$$r_2 R_2 + \gamma_1 x(n) - (\beta_2 r_2 + d_2) y(n) < r_2 R_2 + \gamma_1 x(n) \tag{2.43}$$

and

$$\frac{1}{r_2 R_2 + \gamma_1 x(n) - (\beta_2 r_2 + d_2) y(n)} < \frac{1}{\beta_1 r_2 y(n)}. \tag{2.44}$$

Considering both (2.43) and (2.44), we get

$$y(n+1) < \frac{r_2 R_2 + \gamma_1 x(n)}{\beta_1 r_2} < \frac{\alpha_1 R_2 r_1 r_2 + \gamma_1 (p + r_1 R_1)}{\alpha_1 \beta_1 r_1 r_2}, \tag{2.45}$$

which completes the proof.

Example: The values of the parameters of (2.2) are choosen as given in Schmitz *et al.* (2002) and in view the obtained results. The table is given as follows;

Table 1. Values of the parameter of system (2.1)

P	division rate of the sensitive cells	0.192
K_1	carriying capacity of the negrotic and sensitive cells together	$0.42 * 38^{2/3} = 4.704$
K_2	carriying capacity of the resistant tumor population	$0.11 * 38^{2/3} = 1.232$
Γ	mutation rate of the sensitive cells to resistant cells	$\gamma \in [10^{-5}, 10^{-2}]$
α_i	logistic population rate of sensitive cell population Here is $\alpha_1 = 0.51$ and $\alpha_2 = 0.555$	$\alpha_i \in [0.5, 0.95]$
β_i	logistic population rate of resistant cell population Here, $\beta_1 = 0.05$ and $\beta_2 = 0.2$.	$\beta_i \in [0.05, 0.2]$
d_1	causes of drug treatment to the sensitive cells	0.001
d_2	causes of drug treatment to the resistant cells	0.00001

We want to consider the behaviors for the converting rates $\gamma_1 = 0.01$ and $\gamma_1 = 0.00001$. Both populations have different growth rates. In this example, we have constructed a relation between both population such as $\mathrm{r} = \mathrm{r}_1$ and $(1.05) * \mathrm{r} = \mathrm{r}_2$. The initial conditions are x(0)=0.82 and y(0)=0.23, where the x-axis of the graph denotes the growth rate of the population and the y-axis the per capita growth of both population. The blue and the red graph sembolize the sensitive cells population ($x(n)$) and the resistant cells population ($\mathrm{y}(n)$), respectively. Figure 1 show the behavior of the sensitive cells and resistant cells, where the mutation rate is $\gamma_1 = 0.01$. Here, it is shown that at last the resistant cells will cover the sensitive cells, as also explained in Schmitz *et al*. (2002).

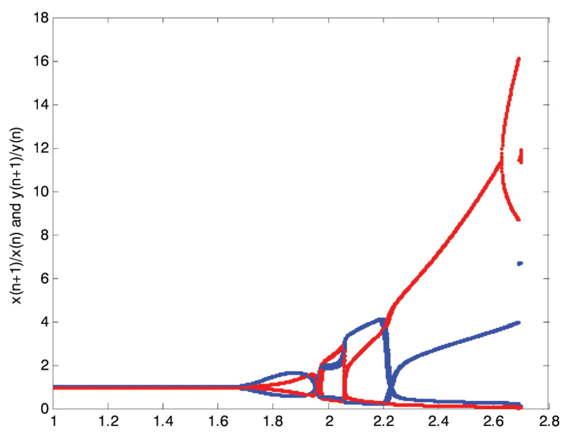

Fig. 1 Figure for the coordinates $(\mathrm{r}_1, x(\mathrm{n}+1)/x(n))$ and $(\mathrm{r}_2, y(\mathrm{n}+1)/y(n))$, where $\gamma_1 = 0.01$

Figure 2, show the behavior of the sensitive cells and resistant cells, where $\gamma_1 = 0.00001$. It is clear that during the initial phases, the volume of the sensitive cells are more than the resistant cells. But since the population growth rate of the resistant cells is greater than the sensitive cells, after a spesific time the resistant cells will occur on the wall of the sensitive tumor cells, see also Schmitz *et al*. (2002).

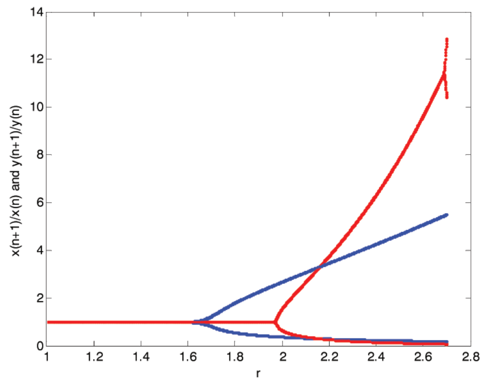

Fig. 2. Figure for the coordinates $(r_1, x(n+1)/x(n))$ and $(r_2, y(n+1)/y(n))$, where $\gamma_1 = 0.00001$.

NUMERICAL RESULTS AND COMMENTS

In section 2, the local and global asymptotic stability of the positive equilibrium point of system (8) have been analyzed in Theorem 2.1 and Theorem 2.2, respectively. Theorem 2.3 was an important proof to show the bound of both tumor structures. The parameters are used from the data of Schmitz, *et al*. (2002), where it has been shown that a sensitive tumor population with the mutation rate $\gamma_1 = 0.00001$, occur on the wall of the sensitive cells after a specific density and specific time. Furthermore, if the mutation rate is $\gamma_1 = 0.01$, then the resistant tumor population will cover the sensitive tumor cells, which makes the treatment process more difficult than the phenomena shown in Figure 1.

REFERENCES

Allen, L. 2007. An Introduction to Mathematical Biology, Pearson Prentice Hall, NJ.

Berkman, R., Clark, W., Saxena, A., Robertson, J., Oldfield, E. & Ali, I. 1992. Clonal composition of glioblastoma multiforme. Journal of Neurosurgery **77**: 432-437.

Birkhead, B., Ranken, E., Gallivan, S., Dones, L. & Rubens, R. 1987. A mathematical model of the development of drug resistance to cancer chemotherapy, European Journal of Cancer and Clinical Oncology **23**: 1421-1427.

Coldman, A. & Goldie, J. 1979. A mathematical model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treatment Reports **63**: 1727-1731.

Cooke, K. & Huang, W. 1991. In: Fink, A., Miller, R. & Kleman, W. (Eds.), A Theorem of George Seifert and an equation with State-Dependent Delay, Delay and Differential Equations. Pp. 65-77 World Scientific, Ames, Iowa.

Coons, S. & Johnson, P. 1993. Regional heterogeneity in the DNA content of human gliomas. Cancer, **72**: 3052-3060.

De Vladar, H. & Gonzalez, J. 2004. Dynamic response of cancer under the influence of immunological activity and therapy. Journal of Theoretical Biology, **227**: 335-348.

Gevertz, J. & Toquato, S. 2006. Modelig the effects of vasculature evolution on early brain tumor growth. Journal of Theoretical Biology, **243**: 517-531.

Gibbons, C., M. R. S. Kulenoviæ, M., G. Ladas, G. & Voulov, H. 2002. On the Trichotomy Character of $x_{n+1} = (\alpha + \beta x_n + \gamma x_{n-1}) / (A + x_n)$. J. Difference Equations and Applications, **8**: 75-92.

Gopalsamy, K. & Liu, P. 1998. Persistence and Global Stability in a population model. Journal of Mathematical Analysis and Applications **224**: 59-80.

Gurcan, F. & Bozkurt, F. 2009. Global stability in a population model with piecewise constant arguments. Journal of Mathematical Analysis and Applications, **360**(1): 334-342.

Holland, E.C. 2000. Glioblastoma multiforme: the termiator. Proceedings of the National Academy of Science, **97**: 6242-6244.

Hoppensteadt, F.C. 2004. Cambridge Studies in Mathematical Biology: Mathematical methods of population biology. Cambridge University Press, Cambridge.

Liu, P. & Gopalsamy, K. 1999. Global stability and chaos in a population model with piecewise constant arguments. Applied Mathematics and Computation, **101**: 63- 88.

Mansury, Y., Diggory, M. & Diesboeck, T. 2006. Evolutionary game theory in an agent-based brain tumor model: Exploring the `Genotype-Phenotype' link. Journal of Theoretical Biology, **238**: 146-156.

May, R. 1975. Biological populations obeying difference equations: Stable points, stable cycles and chaos. J. Theoret. Biol., **51**: 511-524.

May, R. & Oster, G. 1976. Bifurcations and dynamics complexity in simple ecological models. Amer. Nat., **110**: 573-599.

Ozturk, I. & Bozkurt, F., 2011. Stability analysis of a population model with piecewise constant arguments. Nonlinear analysis: Real World Applications, **12**(3): 1532-1545.

Panetta, J. 1998. A mathematical model of drug resistance: Heterogeneous tumors. Mathematical Biosciences, **147**: 41-61.

Paulus, W. & Peiffer, J. 1989. Intratumoral histologic heterogeneity of gliomas. A quantitative study. Cancer, **64**: 442-447.

Rubinow, S. 2002. Introduction to Mathematical Biology, Dover Publication, NY.

Schmitz, J., Kansal, A. & Torquato, S. 2002. A cellular Automaton of Brain Tumor Treatment and Resistance. Journal of Theoretical Medicine, **4**(4): 223-239.

Yung, Y., Shapiro, J. & Shapiro, W. 1982. Heterogeneous chemosensitivities of subpopulations of human glioma cells in culture. Cancer Research, **42**: 992-998.

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نموذج مجتمع إحصائي لأورام ثنائية السلالة لها عمد ثابتة قطعة – قطعة

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خلاصة

نبني في هذه الدراسة نموذجاً رياضياً لمجتمع إحصائي للنمو السرطاني لأورام الدماغ. يقوم النموذج الذي وصفناه بإيضاح النمو للأورام ثم يقوم بعد زمن محدد بإنتاج مجتمع إحصائي جديد له معدل نمو مختلف وله قابلية علاج مختلفة. نقوم بتحليل الاستقرار المحلي والاستقرار الشامل لهذا النموذج وذلك باستخدام نظرية المعادلات التفاضلية والمعادلات الفرقية. وتقدم المعطيات والمحاكاة وصفاً تفصيلياً للنموذج المبني على نظامنا وذلك في نهاية البحث.