MATHEMATICAL MODEL DESCRIBING TUMOR GROWTH UNDER A TREATMENT BY CHEMOTHERAPY

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Abstract

In this work we study a mathematical model describing tumor growth considering a treatment by chemotherapy. We use values for the parameters according to experimental results and mathematical considerations. We verify that the our model presents dynamical behavior relate to suppression of the cancerous cells. Due to a time delay the system may produce oscillations of the cells number, where the time delay is considered in the conversion of resting to hunting cells. The cancerous cells can be disappear when the chemotherapy is inserted in the model.

Key words

Tumor, delay, chemotherapy

1 Introduction

Cancer is a disorderly growth of cells that invade tissues and organs [Anderson, 2001; Bru, 2003]. Moreover, these cells are able to spread to others regions of the body [Baserga, 1965]. A mechanism of the body against virus, bacteria and tumor is the destruction of cells infected or tumors by cytotoxic T-lymphocytes (CTL) actived or hunter lymphocytes. CTL may annihilate cells inducing apoptosis. The biological activation occurs when the CTLs receive impulses from T-helper cells (T_H cells). This activation is not instantaneous, not only there is the conversion of resting cells in hunter cells, but also a natural delay of the cytological process [Wodarz, 1998; Iarosz, 2011]. Banerjee and Sarkar studied the dynamical behavior between tumor and immune cells using delay differential equations [Banerjee, 2008].

It is possible to stop the growing of the cancer cells using chemotherapy. There are many studies about the effects of the chemotherapy on the cells. Moreover, mathematical models have been considered to simulate the growth of cancerous cells [Liu, 2012], and tumor-immune interactions with chemotherapy [Pillis, 2007].

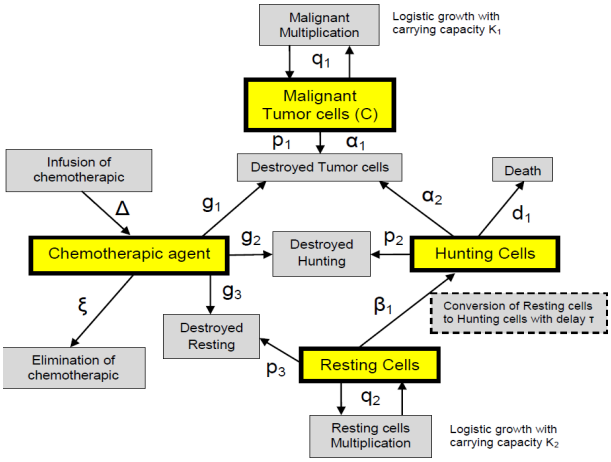

Figure 1. Schematic representation of the interactions in the system.

In this work we analyse a mathematical model that consider the treatment by chemotherapy. We modify the model of Banerjee and Sarkar [Banerjee, 2008] adding a chemotherapy. According to experimental protocols we have used a constant amplitude for the control inputs [Ahn, 2011] and an oscillatory amplitude [Kuebler, 2007]. Moreover, we also show a model of brain tumor.

This paper is organized as follows: Section 2 shows the mathematical model, Section 3 presenst the cancer suppression, Section 4 deals with the brain tumor. Our conclusions are left to the last Section.

2 The mathematical model

We modify a mathematical model proposed by Banerjee and Sarkar [Sarkar, 2005] considering a chemotherapy agent. This agent is input in equations as a predator on both lymphocytes and cancerous cells. Fig. 1 shows the schema the interactions. There is a time delay in activation and conversion of resting into hunting cells. The model is given by

$$\left.\begin{array}{l} \frac{dC(t)}{dt} = q_1 C(t)\left(1-\frac{C(t)}{K_1}\right) \\ -\alpha_1 C(t)H(t)\left(\frac{p_1 C(t)}{a_1+C(t)}\right)Z(t) \\ \\ \frac{dH(t)}{dt} = \beta_1 H(t)R(t-\tau) - d_1 H(t) \\ -\alpha_2 C(t)H(t) - \left(\frac{p_2 H(t)}{a_2+H(t)}\right)Z(t) \\ \\ \frac{dR(t)}{dt} = q_2 R(t)\left(1-\frac{R(t)}{K_2}\right) - \beta_1 H(t) \\ R(t-\tau) - \left(\frac{p_3 R(t)}{a_3+R(t)}\right)Z(t) \\ \\ \frac{dZ(t)}{dt} = \Delta - \left(\xi + \frac{g_1 C(t)}{a_1+C(t)} + \frac{g_2 H(t)}{a_2+H(t)}\right. \\ \left. + \frac{g_3 R(t)}{a_3+R(t)}\right)Z(t), \end{array}\right\} \quad (1)$$

where C, H and R are the number of cancerous, hunting and resting cells, respectively, t is the time and Z is the concentration of the chemotherapy agent.

The parameters according to experimental evidences are growth rate of malignant tumor cells (q_1 = 0.18 day^{-1}), carrying capacity of tumor cells (K_1 = 5 x 10^6 cells) [Siu, 1986], decay rate of tumor cells by hunting cells(α_1 = 1.101 x 10^{-7}cells^{-1} day^{-1}), decay rate of hunting cells by tumor cells (α_2 = 3.422 x 10^{-10} cells^{-1} day^{-1}), death rate of hunting cells (d_1 = 0.0412 day^{-1}), conversion rate from resting to hunting cells (β_1 = 6.2 x 10^{-9} cells^{-1} day^{-1}) [Kusnetsov, 1994], growth rate of resting cells (q_2 = 0.0245 day^{-1}), time delay in conversion of resting cells to hunting cells (τ = 45.6 day), carrying capacity of resting cells (K_2 = 1 x 10^7) [Banerjee, 2008], and the meaning of some parameters are predation coefficients of chemotherapy agent on cells (p_i), determine the rate at which C, H, R, in the absence of competition and predation, reach carrying capacities (a_i), combination rates of the chemotherapy agent with the cells (g_i), continuous infusion rate of chemotherapy (Δ) and washout rate of chemotherapy (ξ) [Pinho, 2002]. The presents the values which we also consider in our simulations nondimensional parameters q_1 = 0.18, K_1 = 1/3, α_1 = 1.6515, α_2 = 5.133 x 10^{-3}, d_1 = 0.0412, q_2 = 0.0245, τ = 45.6, K_2 = 2/3, β_1 = 9.3 x 10^{-2}, $p_1 = p_2 = p_3$ = 1 x 10^{-3}, $a_1 = a_2 = a_3$ = 1 x 10^{-4}, $g_1 = g_2 = g_3$ = 0.1, Δ = 0 - 10^4 and ξ = 0.2.

Considering the nondimensional variables $\bar{t} = t/day$, $\bar{C} = C/K_T$, $\bar{H} = H/K_T$, $\bar{R} = R/K_T$, $\bar{Z} = Z/\Delta_M\,\xi^{-1}$, with $K_T = K_1 + K_2$ is the total carrying capacity and Δ_M is equal 1 mg m^{-2}day^{-1}. Combining the variables up in equations 1, and renaming the variables $\bar{t}$, $\bar{C}$, $\bar{H}$, $\bar{R}$, $\bar{Z}$ as t, C, H, R, Z, respectively, and the parameters $\bar{q}_1$, $\bar{K}_1$, $\bar{\alpha}_1$, $\bar{p}_1$, $\bar{g}_1$, $\bar{a}_1$, $\bar{\beta}_1$, $\bar{d}_1$, $\bar{\alpha}_2$, $\bar{p}_2$, $\bar{g}_2$, $\bar{a}_2$, $\bar{q}_2$, $\bar{K}_2$, $\bar{p}_3$, $\bar{g}_3$, $\bar{a}_3$, $\bar{\Delta}$, $\bar{\xi}$ as q_1, K_1, α_1, p_1, g_1, a_1, β_1, d_1, α_2, p_2, g_2, a_2, q_2, K_2, p_3, g_3, a_3, Δ, ξ, respectively, we obtain the same equations for C, H and R. The equation for Z exhibits a alteration,

$$\left.\begin{array}{l} \frac{dZ(t)}{dt} = \Delta\xi - \left(\xi + \frac{g_1 C(t)}{a_1+C(t)} + \frac{g_2 H(t)}{a_2+H(t)}\right. \\ \left. + \frac{g_3 R(t)}{a_3+R(t)}\right)Z(t), \end{array}\right\} \quad (2)$$

where we consider

$$\left.\begin{array}{ll} \bar{q}_1 = q_1\,\text{day} & \bar{\alpha}_1 = \alpha_1 K_T\,\text{day} \\ \bar{K}_1 = \frac{K_1}{K_T} & \bar{p}_1 = \frac{p_1\,\Delta_M\,\text{day}}{K_T\,\xi} \\ \bar{a}_1 = \frac{a_1}{K_T} & \bar{\beta}_1 = \beta_1 K_T\,\text{day} \\ \bar{d}_1 = d_1\,\text{day} & \bar{\alpha}_2 = \alpha_2 K_T\,\text{day} \\ \bar{g}_1 = g_1\,\text{day} & \bar{g}_2 = g_2\,\text{day} \\ \bar{g}_3 = g_3\text{day} & \bar{p}_2 = \frac{p_2\,\Delta_M\,\text{day}}{K_T\,\xi} \\ \bar{a}_2 = \frac{a_2}{K_T} & \bar{K}_2 = \frac{K_2}{K_T} \\ \bar{p}_3 = \frac{p_3\,\Delta_M\text{day}}{K_T\,\xi} & \bar{a}_3 = \frac{a_3}{K_T} \\ \bar{\Delta} = \frac{\Delta}{\Delta_M} & \bar{q}_2 = q_2\,\text{day} \\ \bar{\xi} = \xi\,\text{day}. & \end{array}\right\} \quad (3)$$

3 Cancer suppression

In our simulations we consider: $C_0 = 0.18$, $H_0 = 0.0136$, $R_0 = 0.4786$ and $Z_0 = 0$, where one cancerous cell in the model (1) is 66×10^{-9} in the nondimensional model. In Fig. 2 we can see the time evolution of the nondimensional quantities. Fig. 2(a) shows the behavior of the infusion rate of chemotherapy. When $\Delta = 0.02$ there is not cancerous suppression and the system exhibits stable oscillatory state. Increasing the value of Δ the system may present cancerous suppression without the lymphocytes disappear. For a large Δ the lymphocytes and cancerous cells disappear. Then, we analyse the dependence of the cancer suppression on the chemotherapy and predation coefficient of chemotherapy agents on cancerous cells. Fig. 3 shows this dependence, where there are three regions. In the white region there are cancerous cells, and the suppression of cancer occurs for the parameters in black region. The grey region presents a non ideal situation, that is the s uppression of lymphocytes. It is possible to achieve suppression cancerous by increasing the chemotherapy to a high enough value, but the threshold depend on the predation coefficient of chemotherapy agent on cancerous cells p_1. Our main result is related with the values of Δ and p_1 in that the number of cancerous cells goes to zero preserving the immune cells (black region). When the number os cancerous cells is null the treatment can stop and the tumor will not return.

4 Brain tumor

There are many different tumor types that can be found in the human brain. A particular brain tumor is

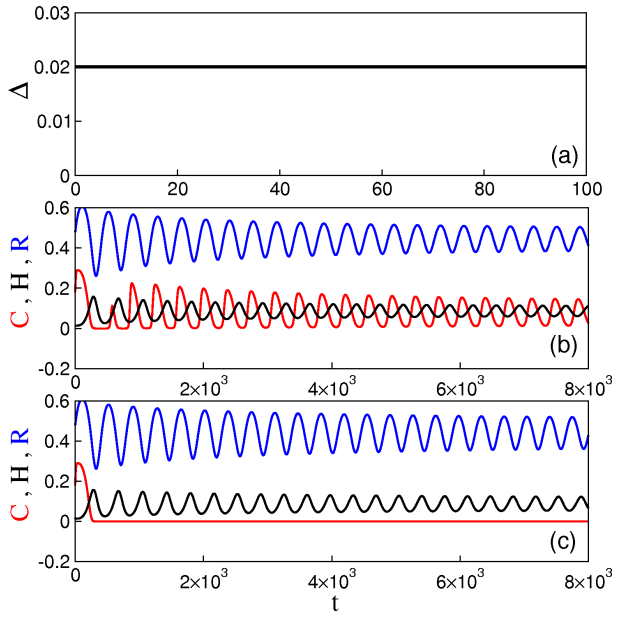

Figure 2. Time evolution of the nondimensional quantities. (a) Continuous infusion rate of chemotherapy, (b) $\Delta = 0.02$ and (c) $\Delta = 0.025$. The red line represents the cancerous cell, black line the hunter cells and blue line the resting cells.

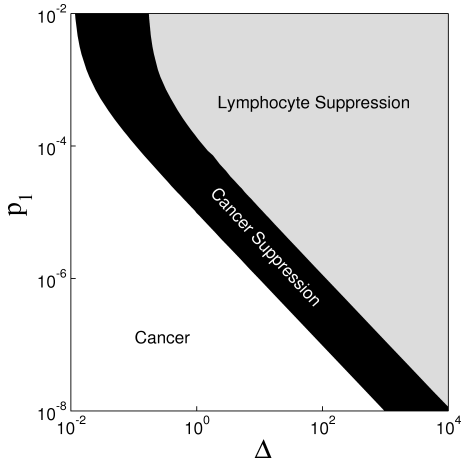

Figure 3. $p_1 \times \Delta$, the white region corresponds to existence of cancerous cells, cancer suppression in the black region and the grey region to the vanishing of the cancerous cells and lymphocytes.

the glioma, and it is considered to originate from glial cell.

We propose a dimensionless mathematical model that consider the interactions among cancerous cells c, glial cells g and neurons n. We also consider a chemotherapy q,

$$\left.\begin{array}{l} \frac{dg(t)}{dt} = \alpha_1 g(t)(1-g(t)) - \beta_1 g(t)c(t) \\ \quad - \frac{p_1 g(t) q(t)}{a_1 + g(t)} \\ \\ \frac{dc(t)}{dt} = \alpha_2 c(t)(1-c(t)) - \beta_2 g(t)c(t) \\ \quad - \frac{p_2 c(t) q(t)}{a_2 + c(t)} \\ \\ \frac{dn(t)}{dt} = -\beta_3 [g(t-\tau) - g(t)]\delta_{i0} n(t) \\ \quad - \frac{p_3 n(t) q(t)}{a_3 + n(t)} \\ \\ \frac{dq(t)}{dt} = \xi(\Delta - q(t)), \end{array}\right\} \quad (4)$$

where δ_{ij} is

$$\delta_{ij} = \begin{cases} 1, & \text{se} \quad i = j, \\ 0, & \text{se} \quad i \neq j, \end{cases}$$

$i, j \in Z$, for this case $j = 0$ and

$$\begin{cases} i = 1, & \text{se} \quad \dot{g} \geq 0, \\ i = 0. & \text{se} \quad \dot{g} < 0, \end{cases}$$

We used the values α_1 = 2.5, α_2 = 5, β_1 = 655, β_2 = 131, β_3 = 1.31, p_1 = 7.6×10^{-9}, p_2 = 4.7×10^{-6}, p_3 = 9.5×10^{-10}, a_1 = 7.6×10^{-6}, a_2 = 7.6×10^{-6}, a_3 = 7.6×10^{-6}, Δ = 40000, ξ = 0.8 in our simulation to obtain the Fig. 4. We can see through the Fig. 4(a) that the quantity of glial cells decreases when there are cancerous cells (b), as well as, the quantity of neurons also decreases (c) due to link with the glial cells. However, when the chemotherapy increases (d) it is possible to verify cancerous suppression.

5 Conclusion

In this paper we studied some aspects of the dynamics of cancerous growth displayed by a delay differential equation, we also analyzed the effect of the chemotherapy on the cancerous cells and lymphocytes. We modified a mathematical model adding a treatment by chemotherapy.

We studied a continuous administration of drugs. We found domains of cancer suppression for wide intervals in the parameters space of the predation coefficient of chemotherapy agent on cancerous cells and the continuous infusion rate of chemotherapy. More important, not only it was possible to obtain cancer suppression, but also to maintain the populations levels of lymphocytes. In the brain tumor, we considering a tumor in the glial cells and verify cancerous suppression when is applied a chemotherapy.

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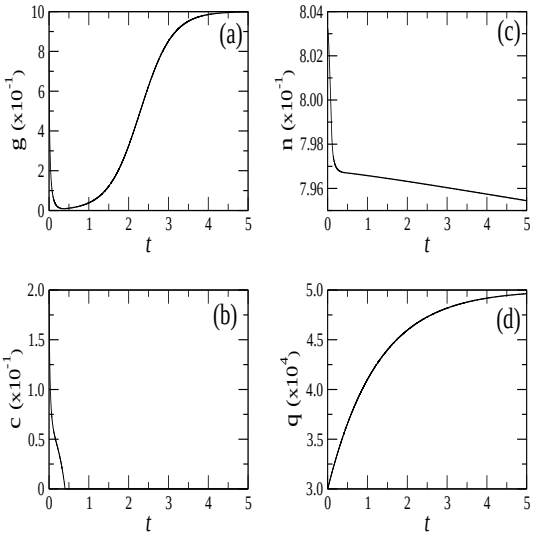

Figure 4. Time evolution of the dimensionless quantities (a) g, (b) c, (c) n and (d) q.

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