Control of brain tumour through chemotherapy

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Abstract

In recent years, the studies about cancer treatment have intensified, mainly studies for the control of tumour growth. In this work we propose coupled differential equations that model brain tumour. There are different types of brain tumour, and a malignant brain tumour is a fast growing cancer. We analyse the effect of a control on the cell behaviour, where the control is simulated according to chemotherapeutic agents. We verify the possibility of the tumour growth to be controlled. Moreover, we identify values of the parameters in that the tumour growth inhibition is arrived with a minimal loss of normal cells.

Keywords: control, tumour, brain

1. Introduction

Cells growth is a phenomenon that has been studied in the fields of the mathematics, biology, physics, etc [1]. Unregulated cells growth may be associated with a wide group of diseases, where the cells become a lump or cause illness. As a result, several growth models related to tumours have appeared in the literature [2, 3], such as models for the metastasis [4], the lack of nutrients [5], the competition for resources, and the cytotoxic activity produced by the immune response [6, 7].

The most common malignant intrinsic primary tumours of the adult human brain are the gliomas [8]. It is called of glioma due to the fact that the cancer cells attack the glial cells, and the neurons are not attacked. However, the death of the glial cells affects the neurons, because they are the responsible for

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delivering nutrients and provide support to them [9]. Chemotherapeutic agent affects all the cells [10].

The glial cells provide nutrients for neurons and control the biochemical compositions of the fluid surrounding the neurons. The neurons are the main responsible by the information processing from external and internal environments [11, 12, 13]. However, glial cells are also responsible for processing of information by mediating the neural signal. The communication among neurons and glial cells is bidirectional, and there are an average number of ten glial cells connected to a neuron [14].

In this paper, we propose a mathematical model for the growth of brain cancer, where the cancer only attacks the glial cells, causing a glioma [15, 16]. The cancer cells arise from normal cells. The transformation is permanent. A cancerous cell never returns to be normal again, resulting in invasion and destruction of surrounding healthy tissue by cancer cells [17, 18]. Neurons and their synapses fail to function without the glial cells. The glias also contribute to the pruning of synapses during brain development. However, an abnormal pruning may be a factor in Alzheimer’s disease [19]. In our model, we consider interactions among glial cells, neurons, cancer cells, and the chemotherapeutic agent. The novelty of our model is to describe the action of chemotherapeutic agent in controlling brain cancer growth, minimising the death of neurons and glial cells.

This paper is organized as follows: in Section 2 we introduce the coupled differential equations modelling the control of glioma by a chemotherapeutic agent. In Section 3, we discuss about equilibria and local stabilities of our model. An equilibria point for example is the one that describes a successful chemotherapy result in a controlled number of cancer cells. Section 4, we study how the variations of parameters in the model influence its dynamic behaviour. In the last section, we present the conclusions.

2. Brain tumour model

Figure 1 shows a diagram illustrating the many agents, their interactions, and their behaviours being considered in our model. The cancer cells only attack the glial cells. Neurons are not attacked by cancer cells, and they have interactions with glial cells. Then, a decrease in the number of glial cells has an influence on the neuron concentration. In order to control the cancer growth we added a chemotherapeutic agent as a predator acting on all cells.
Our model is described by

\[
\begin{align*}
\frac{dG(t)}{dt} &= \Omega_1 G(t) \left(1 - \frac{G(t)}{K}\right) - \Psi_1 G(t) C(t) - \frac{P_1 G(t) Q(t)}{A_1 + G(t)}, \\
\frac{dC(t)}{dt} &= \Omega_2 C(t) \left(1 - \frac{C(t)}{K}\right) - \Psi_2 G(t) C(t) - \frac{P_2 C(t) Q(t)}{A_2 + C(t)}, \\
\frac{dN(t)}{dt} &= \psi \dot{G}(t) \Gamma(-\dot{G}) N(t) - \frac{P_3 N(t) Q(t)}{A_3 + N(t)}, \\
\frac{dQ(t)}{dt} &= \Phi - \zeta Q(t),
\end{align*}
\]

where \( G \) represents the glial cells concentration, \( C \) represents the cancerous cells concentration, \( N \) the neurons cells concentration, \( Q \) is the chemotherapeutic agent concentration, and \( \Gamma(x) \) is the Heaviside function, defined as

\[
\Gamma(x) = \begin{cases} 
0, & x < 0, \\
\frac{1}{2}, & x = 0, \\
1, & x > 0.
\end{cases}
\]

Table 1 shows the parameters that we consider. In Eq. (1) and Eq. (2) the first term is the logistic growth, the second term is the interaction between glial and cancer cells, and the last term is the effect of the chemotherapeutic agent. The first term of the Eq. (3) is related with the decrease in the neuronal population due to glial cells death, and the second term is the interaction with the chemotherapeutic agent. Eq. (4) describes the dynamics of the chemotherapeutic agent, presenting an exponential decay in concentration.
Table 1: Description of the parameters according to literature.

<table>
<thead>
<tr>
<th>Description</th>
<th>Parameter</th>
<th>Values</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation rate</td>
<td>$\Omega$</td>
<td>0.0068 day$^{-1}$</td>
<td>$\Omega_1 &lt; \Omega_2$ [20]</td>
</tr>
<tr>
<td>$\Omega_2$ for CCs</td>
<td></td>
<td>0.012 day$^{-1}$</td>
<td>Reference [21]</td>
</tr>
<tr>
<td>Loss influences</td>
<td>$\psi$</td>
<td>0 - 0.02</td>
<td>Reference [20]</td>
</tr>
<tr>
<td>for N due GCs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predation coefficients</td>
<td>$P_1$</td>
<td>$2.4 \times 10^{-5}$ m$^2$(day.mg)$^{-1}$</td>
<td>Reference [20]</td>
</tr>
<tr>
<td>$P_2$ for CCs</td>
<td></td>
<td>$2.4 \times 10^{-2}$ m$^2$(day.mg)$^{-1}$</td>
<td>$P_3 &gt; P_1$ [23]</td>
</tr>
<tr>
<td>$P_3$ for N</td>
<td></td>
<td>$2.4 \times 10^{-5}$ m$^2$(day.mg)$^{-1}$</td>
<td>$P_3 = P_1$</td>
</tr>
<tr>
<td>Chemotherapy agent rate</td>
<td>$\Phi$</td>
<td>0 - 100 mg (day.m$^2$)</td>
<td>Daily doses [24]</td>
</tr>
<tr>
<td>$\zeta$ for washout</td>
<td></td>
<td>0.2 day$^{-1}$</td>
<td>Reference [25, 26]</td>
</tr>
<tr>
<td>Saturation rate</td>
<td>$A_1$, $A_2$, $A_3$</td>
<td>510</td>
<td></td>
</tr>
<tr>
<td>Competition coefficients</td>
<td>$\Psi_1$</td>
<td>$3.6 \times 10^{-6}$ day$^{-1}$</td>
<td>Cancer hypothesis [20]</td>
</tr>
<tr>
<td>$\Psi_2$ between CCs and GCs</td>
<td></td>
<td>$3.6 \times 10^{-6}$ day$^{-1}$</td>
<td>$\Psi_2 &lt; \Psi_1$</td>
</tr>
<tr>
<td>Carrying capacity</td>
<td>$K$</td>
<td>510</td>
<td>Reference [22]</td>
</tr>
</tbody>
</table>

Introducing the normalized variables

$$g = \frac{G}{K_1}, \ c = \frac{C}{K_2}, \ n = \frac{N}{K_3},$$

where $K$ is the carrying capacity of the cells. We obtain the normalized mathematical model

$$\frac{dg(t)}{dt} = \Omega_1 g(t)(1 - g(t)) - \beta_1 g(t) c(t) - \frac{p_1 g(t)Q(t)}{a_1 + g(t)},$$
$$\frac{dc(t)}{dt} = \Omega_2 c(t)(1 - c(t)) - \beta_2 g(t) c(t) - \frac{p_2 c(t)Q(t)}{a_2 + c(t)},$$
$$\frac{dn(t)}{dt} = \alpha \dot{g}(t) \Gamma(\dot{g}) n(t) - \frac{p_3 n(t)Q(t)}{a_3 + n(t)},$$
$$\frac{dQ(t)}{dt} = \Phi - \zeta Q(T),$$

with

$$\beta_1 = \Psi_1 K_2, \ \beta_2 = \Psi_2 K_1, \ \alpha = \psi K_1,$$
$$a_1 = \frac{A_1}{K_1}, \ a_2 = \frac{A_2}{K_2}, \ a_3 = \frac{A_3}{K_3},$$
$$p_1 = \frac{P_1}{K_1}, \ p_2 = \frac{P_2}{K_2}, \ p_3 = \frac{P_3}{K_3},$$

where Table 2 exhibits the values of the normalized parameters.

Firstly, we check the behaviour of the cancer without the infusion of a chemotherapeutic agent. Due to absence of treatment the cancer cells kill all
Table 2: Values of the normalized parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_1$</td>
<td>$1.8 \times 10^{-4}$ day$^{-1}$</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>$1.8 \times 10^{-3}$ day$^{-1}$</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>$0.0 - 10.0$</td>
</tr>
<tr>
<td>$a_1 = a_2 = a_3$</td>
<td>$1$</td>
</tr>
<tr>
<td>$p_1 = p_3$</td>
<td>$4.7 \times 10^{-8}$ m$^2$(day.mg)$^{-1}$</td>
</tr>
<tr>
<td>$p_2$</td>
<td>$4.7 \times 10^{-5}$ m$^2$(day.mg)$^{-1}$</td>
</tr>
</tbody>
</table>

the glial cells (Fig. 2a), while the cancer cells grow (Fig. 2b). As time goes by, the neurons dead without the glial support (Fig. 2c). For $t = 500$ there are around 35% of glial cells, and approximately 28% of neurons. Due to the logistic growth of the glial cells, they resist longer than the neurons from the attack of cancer. As a result, we can see that without the chemotherapy (Fig. 2d) the cancer cells are going to kill all the cells (Fig. 2a,b, and c).

Then, we use the infusion of a chemotherapeutic agent in order to control the cancer growth. Figure 3 shows a case where our model exhibits a controlled state. In the interval $0 < t < 50$ the glial cells concentration decreases (Fig. 3a) due to cancer cells and chemotherapeutic agent. However, for $t > 50$ we have $c < 0.005$ (Fig. 3b). Glial cells recover their normal concentration level
after sometime. Figure 3c exhibits a fast decay of the neurons due to the effect of the chemotherapeutic agent and the cancer cells on the neuron population. After the rapid decrease of cancer cells the decay of neurons slows down. If the chemotherapeutic agent is not suspended if eventually kill all neurons, since in our model we are not considering the neurogenesis.

3. Local stability

The study of the local stability is important to verify if the suppression of cancer is stable or unstable, or to understand whether a non desired state (e.g. $n = 0$) is stable. The model has some equilibria $E(\pi, c, n, Q)$, and we consider the equilibria physiologically feasible.

Now, we analyse the local stability for an undesirable equilibrium $E_0(0, 0, 0, \Phi \xi^{-1})$. For this equilibrium the Jacobian matrix is given by

$$J_0 = \begin{bmatrix}
\Omega_1 - \frac{\mu_1 \Phi}{\xi a_1} & 0 & 0 & 0 \\
0 & \Omega_2 - \frac{\mu_2 \Phi}{\xi a_2} & 0 & 0 \\
0 & 0 & -\frac{\nu_3 \Phi}{\xi a_3} & 0 \\
0 & 0 & 0 & -\xi
\end{bmatrix},$$
and the eigenvalues are

\[
\begin{align*}
\lambda_1^{(0)} &= \Omega_1 - \frac{p_1 \Phi}{\xi a_1}, \\
\lambda_2^{(0)} &= \Omega_2 - \frac{p_2 \Phi}{\xi a_2}, \\
\lambda_3^{(0)} &= -\frac{p_3 \Phi}{\xi a_3}, \\
\lambda_4^{(0)} &= -\xi.
\end{align*}
\]

Through the sign of the real part of each eigenvalue we can check the stability of the equilibrium. In a hyperbolic equilibrium, if the real part of each eigenvalue is strictly negative, then the equilibrium is asymptotically stable. If positive, then the equilibrium is unstable. In order to ensure the stability of the equilibrium \( E_0(0, 0, 0, \Phi \xi^{-1}) \) it is necessary that

\[
\Phi > \frac{\Omega_1 a_1 \xi}{p_1},
\]

and

\[
\Phi > \frac{\Omega_2 a_2 \xi}{p_2},
\]

where these results are obtained through \( \lambda_1^{(0)} < 0 \), and \( \lambda_2^{(0)} < 0 \). The values of the normalized parameters are positive, then the eigenvalues \( \lambda_3^{(0)} \), and \( \lambda_4^{(0)} \) are negative. We consider \( a_1 = a_2 = 1, \ \Omega_1 = 0.0068, \ \Omega_2 = 0.012, \ p_1 = 4.7 \times 10^{-8}, \ p_2 = 4.7 \times 10^{-5}, \) and \( \xi = 0.2 \) (table 2). With these values we obtain that \( E_0 \) is linearly asymptotically stable for \( \Phi > 28936.17 \). In other words, if the chemotherapeutic agent kills all cells, they will never recover.

We also consider the equilibrium \( E_1(\bar{g}, 0, n, \bar{Q}) \), representing the complete elimination of cancer cells, but preserving glial and neuron cells. Then, the system (7) presents

\[
\begin{align*}
\Omega_1 \bar{g}(1 - \bar{g}) - \frac{p_1 \Phi \bar{Q}}{a_1 + \bar{g}} &= 0, \\
-\frac{p_3 \Phi \bar{Q}}{a_3 + \bar{n}} &= 0, \\
\Phi - \xi \bar{Q} &= 0,
\end{align*}
\]

where we obtain \( \bar{n} = 0 \) and \( \bar{Q} = \Phi \xi^{-1} \). Thus, the equilibrium \( E_1(\bar{g}, 0, 0, \Phi \xi^{-1}) \) is given by \( E_1(\bar{g}, 0, 0, \Phi \xi^{-1}) \).

The first equation of our proposed model can be rewritten as

\[
\bar{g}^2 + (a_1 - 1)\bar{g} - a_1 + \frac{p_1 \Phi}{\Omega_1 \xi} = 0,
\]

with solution \( \bar{g} = \left\{ 1 - a_1 \pm [(a_1 - 1)^2 + 4(a_1 - p_1 \Phi/\Omega_1 \xi)]^{1/2} \right\}/2 \). This way, we verify that \( \bar{g} \) has a null solution when \( p_1 \Phi/\Omega_1 \xi = a_1 \), and a real, positive
and not null solution when $p_1 \Phi / \Omega_1 \xi < a_1$. According to table 2, $\overline{g}$ has a real, positive and not null solution when $\Phi < 28936.17$.

Now, we analyse the local stability for the non cancer cells equilibrium $E_1(\overline{g}, 0, 0, \Phi^{-1})$. For this equilibrium the Jacobian matrix is given by

$$J_1 = \begin{bmatrix}
\Omega_1 (1 - 2\overline{g}) - \frac{p_1 a_1 \Phi}{\xi (a_1 + \overline{g})^2} & -\beta_1 \overline{g} & 0 & -\frac{p_1 \overline{g}}{a_1 + \overline{g}} \\
0 & \Omega_2 - \beta_2 \overline{g} - \frac{p_2 \Phi}{\xi a_2} & 0 & 0 \\
0 & 0 & -\frac{p_2 \Phi}{\xi a_3} & 0 \\
0 & 0 & 0 & -\xi
\end{bmatrix},$$

and the eigenvalues are

$$\lambda_1^{(1)} = \Omega_1 (1 - 2\overline{g}) - \frac{p_1 a_1 \Phi}{\xi (a_1 + \overline{g})^2},$$

$$\lambda_2^{(1)} = \Omega_2 - \beta_2 \overline{g} - \frac{p_2 \Phi}{\xi a_2},$$

$$\lambda_3^{(1)} = -\frac{p_2 \Phi}{\xi a_3},$$

$$\lambda_4^{(1)} = -\xi.$$ 

In order to ensure the stability of $E_1(\overline{g}, 0, 0, \Phi^{-1})$ it is necessary

$$p_1 \Phi \xi^{-1} > \frac{\Omega_1 (1 - 2\overline{g}) (a_1 - \overline{g})^2}{a_1},$$

and

$$p_2 \Phi \xi^{-1} > a_2 (\Omega_2 - \beta_2 \overline{g}),$$

where these results are obtained through $\lambda_1^{(1)} < 0$, and $\lambda_2^{(1)} < 0$. The values of the dimensionless parameters are positives, then the eigenvalues $\lambda_3^{(1)}$, and $\lambda_4^{(1)}$ are negatives. For $a_1 = 1.0$ (table 2) the equation (21) is satisfied for all $\overline{g} \geq 0.5$. Considering $a_2 = 1.0$, $\Omega_2 = 0.012$, $p_2 = 4.7 \times 10^{-5}$, $\xi = 0.2$, and $\beta_2 = 1.8 \times 10^{-3}$ (table 2) in equation 22 we have $\Phi > 51.064 - 7.660 \overline{g}$. As a result, for $E_1(\overline{g}, 0, 0, \Phi^{-1})$ the system presents an asymptotically stable equilibrium for $\Phi > 47.234$.

A highly desirable equilibrium is the $E_2(\overline{g}, 0, \pi, 0)$. In this case we have $\overline{g} = 1$ and $\pi$ has a constant value. The eigenvalues are $\lambda_1 = -\Omega_1$, $\lambda_2 = \Omega_2 - \beta_2$, $\lambda_3 = 0$, and $\lambda_4 = -\xi$. According to table 2 we obtain positive values for $\lambda_1$ and $\lambda_4$, $\lambda_2$ has a positive value, and $\lambda_3$ presents a null value. This equilibrium is an unstable saddle point. If it is considered the tumour immune interaction, the equilibrium will be stable. However, in this work we do not consider the immune system, as well as, our main aim is the control of cancer growth. Then, we consider a successful treatment when the results are closed this equilibrium $E_2(\overline{g}, 0, \pi, 0)$. 

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4. Control

In this section we analyse a control on the cancerous growth. The control is through chemotherapeutic agents according to Eq. (7). Our main aim is not only the controlled state, but also a reduction of the organ damage due to the chemotherapeutic agent.

Figure 3 shows the case for cancer suppression. However, the neurons concentration has decreased by 1.5% when the tumour has significantly decreased. In this case the controlled state is reached, but the neurons are badly damaged. For this reason we study the control on the system to obtain values of the chemotherapeutic agents not only to minimise effects on neurons but also to maximize drugs effects on cancer cells.

The state of cancer suppression is characterized by death of almost all cancer cells. Then, we have considered the cancer suppression for $c < 10^{-8}$, and when this occurs we identify the neurons concentration. The therapeutic implication for neurons is shown in Figure 4. We vary $\Phi$ and $\alpha$, in order to verify the situation of the neurons after a successful treatment by the chemotherapeutic agent. The colour bar exhibits the neurons concentration. The yellow region corresponds to a reduction of 1% in the neurons concentration, while the black region to 15%.

The black region is due to quick death of the glias in a short time (large $\dot{g}$), and also due to the chemotherapy. The chemotherapeutics induce neurons death is a side effect knew as neurotoxicity. Lomustine, cisplatin, topotecan, and vincristine are antitumor agents that induce cell death. Antje Wick and collaborators [27] analysed the effect these drugs on the neurons. They verified which drugs lead to cell death in cerebellar granule neurons in a concentration dependent manner.

![Figure 4: (Color online) $\alpha$ versus $\Phi$, where $g(0) = 0.99, c(0) = 0.01, n(0) = 0.99$, and $Q(0) = 0.0$. The colour bar represents the neurons concentration after a successful chemotherapy.](image)

For these parameter values the percentage of survived glial cells remains
larger than 95%. We can see in Equations 7 that the glial cells equation does not depend on the parameter $\alpha$, but it depends on the parameter $\Phi$ due to $Q$. When $\Phi$ increases we verify that $c$ decreases. However, there is not a significant variation in $g$ due to the lifetime cancer $\tau$ according to the chemotherapy agent rate. In other words, increasing the value of $\Phi$ the lifetime cancer quickly decreases, and in this time interval the glial cells concentration does not have a significantly alteration. Due to the fact that the glial cells are able to recover to their initial state.

Figure 5 shows the cancer lifetime when the system presents a successful treatment. We can see a slope of $-31.6$ for $\Phi \leq 50$ and $-1.4$ for $\Phi \geq 50$. This way, the cancer lifetime is minimised considering values of $\Phi$ larger than 50.

Figure 5: $\tau$ versus $\Phi$, considering $\alpha = 2$, and the same values as Figure 4. The slope for $\Phi \leq 50$ is about $-31.6$, and for $\Phi \geq 50$ the slope is about $-1.4$.

5. Conclusions

In conclusion, we proposed a mathematical model for brain cancer. The novelty is that our model describes the interactions among glial cells, neurons, and cancer, with a chemotherapy to control the brain tumour.

We studied some aspects of the dynamics of cancerous growth, as well as, we analysed a control varying parameters of the system. The main target of the control is the decrease in the number of cancer cells. A successful control is when the chemotherapy eliminates almost all the cancer cells minimising the neurons and glial cells injury, mainly the neurons that have no recovery from injuries.

We realised numerical simulations and obtained values of the infusion of chemotherapeutic agents in that the cancer is suppressed. We identified domains of cancer suppression for the parameters related with the influence of glial cells on neurons and the infusion of drugs. Our main result was to show that the
chemotherapy can be applied mitigating the side effects of drugs on the neurons death. Moreover, we found values of the infusion for minimising the cancer lifetime, where the anticancer activity has less toxicity.

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References


