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Chemotherapy for brain tumour: balance between frequency and intensity

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Abstract

In this paper we present a mathematical model to describe the evolution of brain tumour cells under the effect of a chemotherapy drug. A theoretical analysis on the total mass of cells in the system provides useful information to design treatment protocols, relating the frequency of treatments with the dosage of drug in each treatment. Their efficiency is theoretically and numerically illustrated and discussed.

Key words: Glioma, chemotherapy, numerical simulation.

1 Introduction

Cancer is a disease that involves abnormal cell growth which can spread to other parts of the body. Many mathematical models have been introduced in the literature to simulate the growth of this disease, incorporating different aspects of the phenomena, see [1, 2, 3, 6, 7, 8, 10, 14, 15].

One particular case of cancer are gliomas which are highly invasive brain tumours. These tumours, if left untreated, give the patient a median survival time between 6 months to 1 year. Even if treatment is applied (usually chemotherapy or radiotherapy), it can rarely be cured. It is believed that the reason why treatments are ineffective lies with the high mobility of glioma cells in the brain tissue.

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Modelling glioma growth has been a challenge from a mathematical point of view. The first model to measure the growth of an infiltrating glioma was provided in [10]. The approach considered a mass conservation principle for the cells. An equation of the type

$$\frac{\partial w}{\partial t} = \nabla \cdot (D_w \nabla w) + f(w) \text{ in } \Omega \times (0, \infty) \tag{1}$$

was deduced, where $\Omega \subset \mathbb{R}^n, n = 1, 2, 3$, is the glioma domain, $w(x, t)$ denotes the tumour cell density at location x and time t, $f(w)$ denotes net proliferation of tumour cells and D_w is the diffusion tensor.

To apply the modelling approach to specific patients, Swanson *et al.* [14] introduced the complex geometry of the brain and allowed diffusion to be a function of the spatial variable x to reflect the observation that glioma cells exhibit higher motility in the white matter than in grey matter ([6]).

Treatment with chemotherapy involves the use of drugs to disrupt the cell cycle and to block proliferation. The incorporation of this effect in the growth of glioma cells can be considered by adding an extra equation for the concentration of drug that couples with the equations for the cells. The chemical treatment effect can be included by introducing cell death as a loss term. In [16] this term was considered independent of the concentration of drug, being simply a on/off mechanism to control the death of cells (at constant rate). The approach followed by [11], which considered a term for the death of cells dependent on the concentration of drug, lead to an equation of the type

$$\frac{\partial w}{\partial t} = \nabla \cdot (D_w \nabla w) + f(w) - k(c)w \text{ in } \Omega \times (0, T]\,. \tag{2}$$

where c denotes the concentration of the drug and $k(c)w$ describes the rate of cell death due to the exposure to a drug of concentration c. The behaviour of c was described by a diffusion-reaction equation.

The aim of this paper is to establish a model that takes into account the evolution and growth of glioma cells during a chemotherapy treatment. The novelty of this contribution lies in the use of a cells' mass estimation to design chemotherapy protocols. In Section 2 the total mass of cells is analysed providing a tool to devise protocols for the control and treatment of glioma growth, relating the frequency of the treatments with the dose intensity in each treatment. In Section 3, some numerical examples are given to illustrate different protocols.Finally, in Section 4, the main outcome of the paper is summarized.

2 Chemotherapy: mathematical model and protocol analysis

In this section we study the behaviour of the glioma mass when chemotherapy is considered and we establish criteria to define protocols that lead to control the tumour. Our goal is to prove that for the same total dose a higher frequency of treatments leads to better

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results, i.e., we obtain a better glioma control if we use a protocol of m monthly sessions with dosage d/m than if we use a one only monthly session with dosage d. Theoretically, this means that if a patient is submitted to multiple monthly sessions we use a smaller global drug dosage to obtain the same results that would be obtained with a single monthly session.

According to [3] and [4] we will consider the following assumptions: glioma cells are of two phenotypes - proliferation (state 1) and migratory (state 2); in state 2 cells randomly move but there is no cell fission; in state 1 cancer cells do not migrate and only proliferation takes place with rate ρ; a cell of type 1 remains in state 1 during a time period and then switches to a cell of type 2; β_1 is the switching rate from state 1 to 2; a cell of type 2 remains in state 2 during a time period and then switches to a cell of type 1; β_2 is the switching rate from state 2 to 1. Let $u(x,t)$ and $v(x,t)$ represent the density of migratory and proliferation cells at x and t, respectively. Then the dynamics of glioma cells is described by the following system:

$$\begin{cases} \dfrac{\partial u}{\partial t} = \nabla \cdot (D_m \nabla u) - \beta_1 u + \beta_2 v - k(c)\, u & \text{in } \Omega \times (0,T]\,, \\ \dfrac{\partial v}{\partial t} = \rho\, v + \beta_1\, u - \beta_2\, v - k(c)\, v, & \text{in } \Omega \times (0,T]\,. \end{cases} \tag{3}$$

where

$$D_m(x) = \begin{cases} D_g, & x \text{ in grey matter} \\ D_w, & x \text{ in white matter}\,, \end{cases} \tag{4}$$

and D_g and D_w are constants such that $D_w > D_g$. In system (3), $k(c)$ represents the concentration dependent rate of cell's death. Estimates of the difference in the diffusion coefficients in grey and white matter can range from 2 to 100 fold ([14]).

In this context, the interaction of glioma mass with the drug concentration, $c(x,t)$, is described by

$$\frac{\partial c}{\partial t} = \nabla \cdot (D\, \nabla c) - \frac{k(c)}{\alpha}\,(u+v) + g(t) - M\, c \quad \text{in } \Omega \times (0,T]\,, \tag{5}$$

where D stands for the diffusion coefficient associated with the drug. In equation (5), $\frac{1}{\alpha}$ represents the part of drug concentration per unit time consumed by tumour cells; the term $g(t)$ stands for the concentration rate of drug inoculated and M measures how the drug is consumed per unit time by the metabolic activity.

System (3)-(5) is completed by the initial conditions

$$\begin{aligned} u(x,0) = c(x,0) = 0, &\qquad x \in \Omega \\ v(x,0) = v_0(x), &\qquad x \in \Omega \end{aligned} \tag{6}$$

and no flux boundary conditions.

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The fully dynamics of glioma mass is now described by the system (3), (5) and (6).

Let us define

$$\text{Mass}(t) \;=\; \int_\Omega \big(u+v\big)\, d\Omega\,, \tag{7}$$

as the total mass of tumour cells at time t.

From equations of system (3) and the no flux boundary conditions, we can prove that

$$\text{Mass}' \;=\; \rho \int_\Omega v\, d\Omega - k \int_\Omega c\,(u+v)\, d\Omega \tag{8}$$

where we have taken $k(c)$ as a linear function of c ([11]). Assuming the positivity of the solution of (3), we have

$$\text{Mass}(t) \;\leq\; \text{Mass}(0)\; e^{\int_0^t (\rho - k\cdot c(s))\, ds}\,. \tag{9}$$

When chemotherapy is applied, condition (9) can be used to determine an effective dosage such that the total amount of tumour cells do not increase. In fact, if

$$\int_0^t \Big(\rho - k\cdot c(s)\Big)\, ds \;\leq 0\,, \tag{10}$$

then we can conclude that $\text{Mass}(t) \leq \text{Mass}(0)$, at any time t.

For simulation purposes we use system (3),(5) to describe the dynamics of glioma mass and drug delivery. However, for estimation purposes we considerer some simplifications. Firstly we admit that drug dynamics will be dominated by delivery. In fact, brain is a densely irrigated organ so drug diffusion is less significative compared with drug delivery through the circulatory system. Secondly, and according to real data, $\frac{k}{\alpha} \approx 0$. Consequently, the dynamics of the drug is described by the simplified equation

$$\frac{\partial c}{\partial t} = g(t) - M\, c \quad \text{ in } \Omega \times (0,T]\,, \tag{11}$$

which account for the drug injection and the drug wash-out effects.

From equation (11) we can easily conclude that drug concentration is space independent and that

$$c(t) \;=\; \int_0^t e^{-M(t-s)} g(s)\, ds + c(0)\, e^{-M\,t}\,. \tag{12}$$

The typical bang-bang protocol corresponds to a treatment which alternates maximum doses of chemotherapy with rest periods when no drug is administered. According to this scheduling, the function $g(t)$ is defined by

$$g(t) = \begin{cases} d, \text{ when chemotherapy is being administered} \\ 0, \text{ otherwise}\,. \end{cases} \tag{13}$$

To design chemotherapy protocols we assume that the following conditions are verified

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- each treatment cycle (chemotherapy sessions and rest period) has P_t days
- the patient is submitted to m chemotherapy sessions during each treatment cycle, on the first $m\,(\leq P_t)$ consecutive days of the latter;
- each chemotherapy session has a time duration $\Delta t\,(\leq 24h)$;
- in each chemotherapy session the patient receives a drug dose d;
- the chemotherapy protocol will be repeated for n months.

In Figure 1 we present an example of a protocol with $m = 6$ chemotherapy sessions each month.

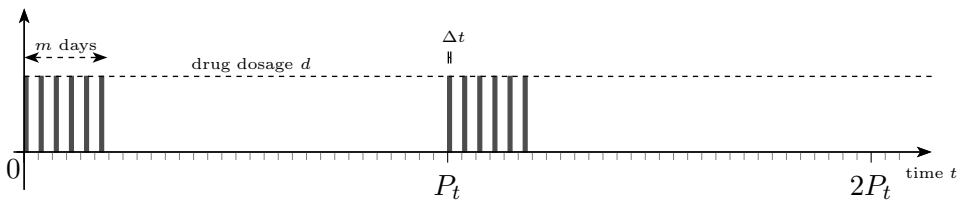

Figure 1: Chemotherapy protocol.

For $t = nP_t$, let us represent the first member of (10) by $P_e(n)$. We have

$$P_e(n) = \int_0^{nP_t} \left(\rho - k \int_0^s g(\tau) e^{M(\tau - s)} d\tau\right) ds.$$

A straightforward calculation of the protocol efficiency leads to

$$P_e(n) \;=\; P_t\,\rho\,n - d\,k\,\left(\frac{n\,\Delta t\,m}{M} - \frac{e^{m\,M}-1}{e^{P_t\,M}-1}\,\frac{e^{\Delta t\,M}-1}{e^{M}-1}\,\frac{1-e^{-P_t\,m\,M}}{M^2}\right). \qquad (14)$$

To guarantee that $P_e(n) \leq 0$, we can use (14) to determine an effective dosage d and the frequency of treatments that allows to control the total tumour mass. Obviously the value of d depends on the chemotherapy protocol.

3 Numerical results

In this section we illustrate numerically the behaviour of solutions of system (3),(5) using the domain described in Figure 2 (approximately $14.4\,cm \times 9.2\,cm$). The coordinate system has its origin at the lower left corner of the image.

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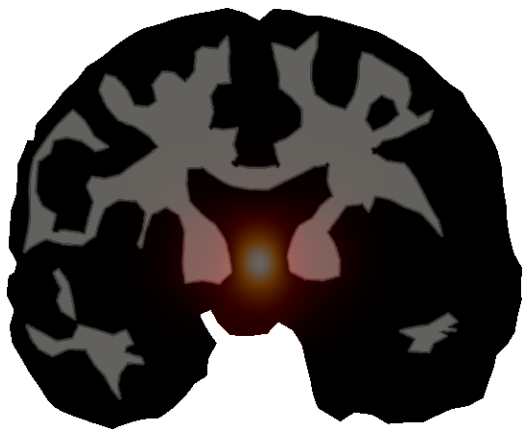

Figure 2: Computational representation of the brain: white matter (dark grey) and grey matter (black) and initial gaussian profile for tumour cells (v_0).

We consider a growth rate $\rho = 0.012\,/day$ and switching parameters $\beta_1 = 10^{-6}/day$ and $\beta_2 = 0.036/day$. These values are physiological and have been obtained from [12].

According to [9] the initial condition is defined by a Gaussian profile with a maximum $10^5\,cells/cm^2$, centered at $(7.2,\, 4.6)$. The diffusion coefficients are $D_w = 0.026\,cm^2/day$ and $D_g = 0.0052\,cm^2/day$.

Finally, according to [11], $k(c) = \frac{\mu\, c}{c_0}$, where μ is a measure of the efficiency of the drug and c_0 is the maximum external drug concentration. For simulation purposes we took $\alpha = 24 \times 10^{10}\,ml/(g\,cm^2)$.

In what follows we compare three different treatment protocols, for treatment cycles of length $P_t = 28$ days:

	m	d
protocol I	1	0.1197
protocol II	5	0.0239
protocol III	28	0.0040

Using equation (14), we compute the protocol efficacy after three months, $P_e(3)$, considering three different values for drug efficiency, μ. We display, in Table 1, the obtained values, considering the same treatment window $\Delta t = 0.05\,days$.

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$P_e(3)$	$\mu = 1.5552$	$\mu = 7.7760$	$\mu = 15.5520$
protocol I	0.3354	−1.0108	−2.6935
protocol II	−1.0108	−7.7418	−16.1555
protocol III	−8.7514	−46.4450	−93.5619

Table 1: Protocol efficiency after 3 months, $P_e(3)$.

From the data gathered in Table 1 we observe that protocol III with more frequent treatments (even with a smaller dosage of drug) is more effective in controlling (and reducing) the glioma mass. This observation is further strengthened with the plots from Figure 3. Protocol I does not lead to an effective control of the glioma growth, while protocols II and II do. Indeed, protocol III is where the reduction of the tumour mass is more meaningful (whatever the drug efficiency we consider). We must observe that in protocol III there are very short rest periods. This corresponds to a new modality of drug administration called *metronomic chemotherapy*, see [13], characterised by equally spaced administration of low doses of drug without rest periods.

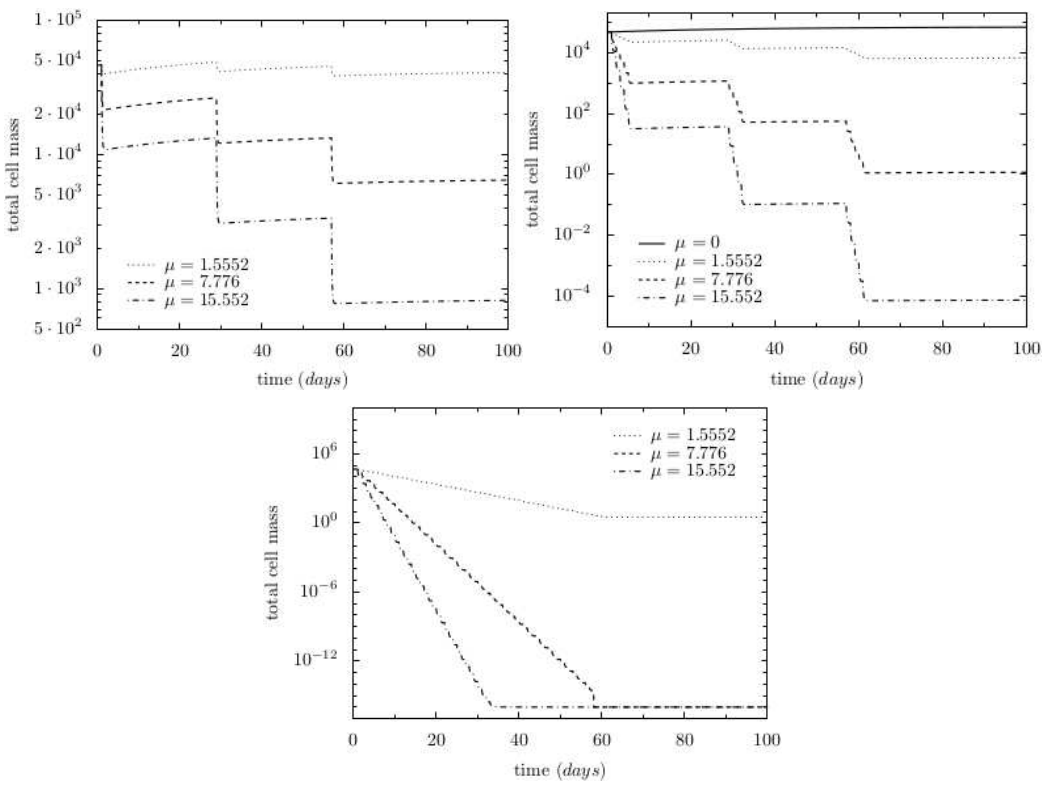

Figure 3: Total masses for protocols I (top left), II (top right) and III (bottom).

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All protocols were simulated with a numerical method using piecewise linear finite elements in space and an implicit-explicit approach in time. We plot, in Figure 4, the contour levels of the concentration c for two patients, one untreated (black) and another submitted to protocol II and protocol III (grey). These results are consistent with the respective protocol efficiency. Furthermore, simulation suggests that the tumour area decreases.

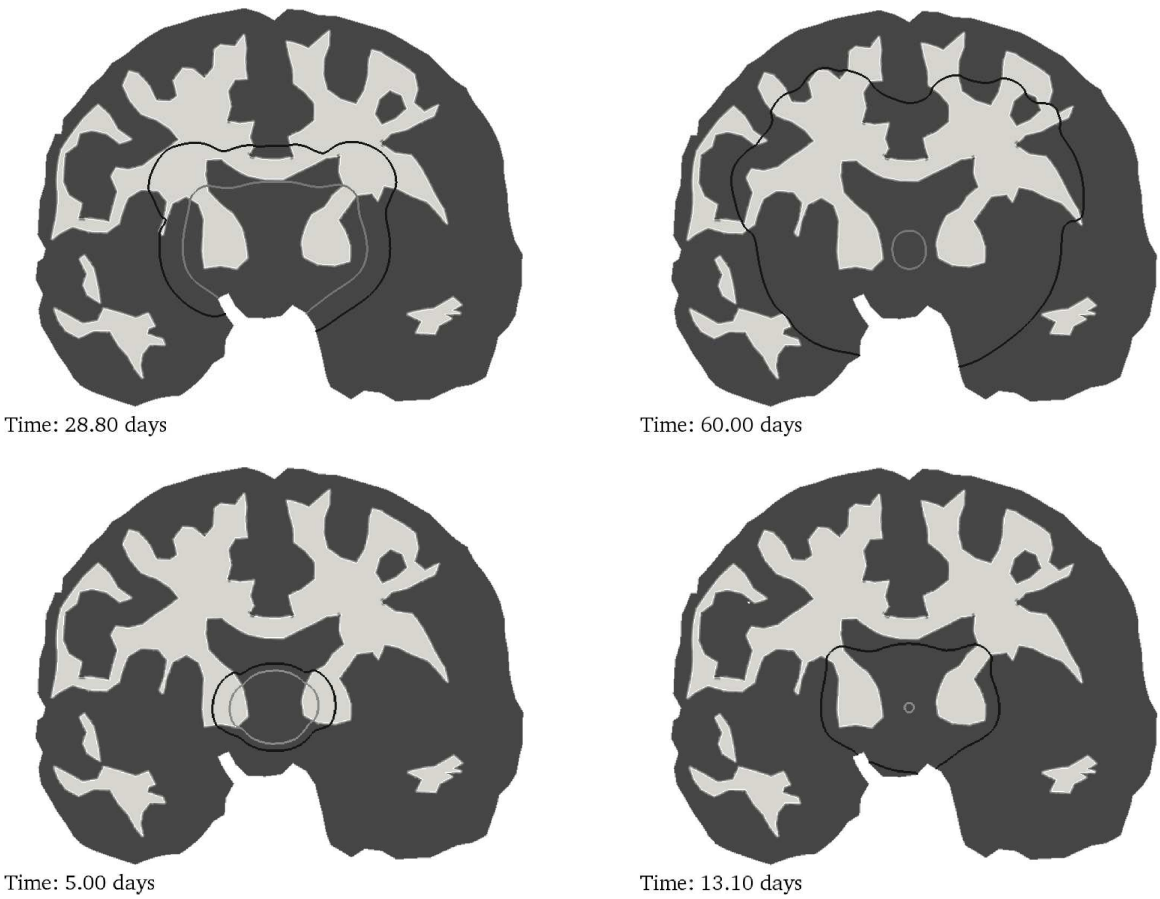

Figure 4: Total masses using $\mu = 7.7760$, for protocol II (top) and protocol III (bottom).

We observe in the white matter a deviation from the radial symmetry of the initial gaussian profile of the tumour. This deviation is explained by a more intensive spreading in the white matter.

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4 Conclusions

In this paper we proposed and studied a mathematical model to describe the evolution of glioma cells with and without chemotherapy. We deduced estimates that allowed to define sufficient conditions on the parameters that lead to control the glioma mass.

Our numerical results suggest that more frequent chemotherapy sessions with less aggressive dosages are preferable. These results are in agreement with new medical research in metronomics chemotherapy, based on more frequent treatments with low doses administration.

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