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Efficient protocols to control glioma growth

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Abstract

In this paper we consider a mathematical model to describe glioma evolution. The model is established combining the viscoelastic behaviour of the brain tissue with a mass conservation law that takes into account the effect of chemotherapy. For the non Fickian model we establish an upper bound for the tumor mass that leads to a sufficient condition to control tumor growth. Based on the theoretical upper bound, protocol for chemotherapy treatment are proposed. Numerical experiments are included to illustrate the behaviour of the model as well as the efficiency of the presented protocols.

Key words: Viscoelastic behaviour, tumor growth, glioma, chemotherapy.

1 Introduction

Gliomas are the most common type of brain tumors. They begin in the glial cells and thus diffuse and highly invade the brain tissue, often intermixing with normal brain tissue. Unfortunately, the prognosis for patients with gliomas is very poor. Median untreated survival time for high grade gliomas ranges from 6 months to 1 year and even lower grade gliomas can rarely be cured. Tumor cell transport and proliferation are the main contributors to the malignant dissemination [21]. Theorists and experimentalists believe that inefficiency of treatments results of the highly mobility capacity and high proliferation rates presented by glioma cells.

Research activity in the mathematical modelling of tumor growth has been very fruitful specially in solid tumors where the growth primarily comes from cellular proliferation. Glioma's growth is characterized by proliferation (as solid tumors) but also by invasion of

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the surrounding brain tissue. The recognition that tumor cells might spread outside the grossly visible mass, invading locally and metastasizing distantly, and that some cells die during the development process, lead to more complex mathematical concepts than those used in the original simple models for solid tumors ([8], [11], [12], [14], [18], [20], [21]).

The most popular model used to measure the glioma growth is characterized by an equation of type

$$\frac{\partial c}{\partial t} = \nabla(D\nabla c) + f(c)\,, \text{ in } \Omega \times (0, +\infty)\,. \tag{1}$$

where $\Omega \subset \mathbb{R}^n$, $n = 1, 2, 3,$ is the spatial domain of the glioma, $c(x,t)$ denotes the tumor cell density at location x and time t, $f(c)$ denotes net proliferation of tumor cells, D represents the diffusion tensor and ∇ defines the spatial gradient operator (see [18]). The proliferation term f is assumed to be exponential, and so cell growth term is given by $f(c) = \rho\, c$, where the net proliferation rate ρ is constant. Logistic and gompertzian growths are also possible choices for f but found to be unnecessary in the time frames considered for gliomas [14].

Equation (1) is established combining the mass conservation law

$$\frac{\partial c}{\partial t} + \nabla J_F = f(c)\,, \text{ in } \Omega \times (0, +\infty), \tag{2}$$

with the classical Fick's law for the mass flux J_F,

$$J_F = -D\nabla c\,. \tag{3}$$

The partial differential equation (1) is of parabolic type and it is well known that if a sudden change on the cell concentration takes place somewhere in the space, it will be felt instantaneously everywhere. This means that Fickian approach gives rise to infinite speed of propagation which is not a physical property. To avoid this limitation of Fickian models an hyperbolic correction has been proposed in different contexts ([1], [2], [6], [7], [13], [16], and the references cited therein).

In this paper we consider a mathematical model to describe glioma growth of non Fickian type that takes into account the viscoelastic behaviour of the brain tissue ([10], [15] and [17]). Following [2], [3], [4], [5] and [19], the viscoelastic behaviour of the brain tissue is included in the definition of the mass flux considering the effect of the stress exerted by the brain tissue on the tumor cells.

Chemotherapy is one of the most popular treatments used on gliomas. This therapy involves the use of drugs to disrupt the cell cycle and to block proliferation. The success of chemotherapy agents varies widely, depending on cell type and the type of drug being used. The effectiveness of a particular drug is dependent on the concentration of drug reaching the tumor, the duration of exposure and the sensitivity of the tumor cells to the drug.

Tracqui *et al.* [22] incorporated chemotherapy by introducing cell death as a loss term. If $G(t)$ defines the time profile of the chemotherapy treatments then, assuming a loss pro-

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portional to the amount of therapy at a given time, equation (1) is replaced by

$$\frac{\partial c}{\partial t} = \nabla(D\nabla c) + f(c) - G(t)c\,, \text{ in } \Omega \times (0, +\infty)\,, \tag{4}$$

where

$$G(t) = \begin{cases} k, & \text{when chemotherapy is being administered} \\ 0, & \text{otherwise}\,. \end{cases} \tag{5}$$

Here k describes the rate of cell death due to exposure to the drug. If $f(c) = \rho c$, for a tumor to decrease in size during chemotherapy, k must be larger than the growth rate ρ of the cell population. The main question is to define k and the periods of chemotherapy applications that lead to control the glioma mass.

The mathematical model that we consider is defined in a simple geometry. To apply the modeling approach to specific patients, a more realistic look at the brain geometry and structure was necessary. In [20] Swanson *et al.* 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 ([11]).

The paper is organized as follow. In Section 2 we present a class of non Fickian models that describe the space and time evolution of glioma cells constructed combining the diffusion process with the viscoelastic properties of the brain tissue. In Section 3 we study the behaviour of the glioma mass and we establish sufficient conditions on the parameters of the model that lead to control glioma growth. These sufficient conditions allow us to define the standard bang-bang chemotherapy protocol. In Section 4 we present numerical experiments that illustrate the effect of several protocols. Finally, in Section 5 we include some conclusions.

2 A viscoelastic model

In this section we present the mathematical model that will be considered in this work. Following [2], [3], [4], [5] and [19], if a diffusion process occurs in a medium that has a viscoelastic behaviour then this behaviour should be included in the mass flux. This fact means that the mass flux J admits the representation

$$J = J_F + J_{nF}, \tag{6}$$

where the Fickian flux J_F is given by (3) and the non Fickian mass flux J_{nF} is defined by

$$J_{nF}(t) = -D_v \nabla\sigma(t), \tag{7}$$

where σ represents the stress exerted by the brain tissue on the tumor cells.

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We will assume that the viscoelastic behaviour of the brain tissue is described by

$$\frac{\partial \sigma}{\partial t} + \beta \sigma = \alpha_1 \epsilon + \alpha_2 \frac{\partial \epsilon}{\partial t}, \tag{8}$$

where ϵ stands for the strain. Equation (8) is based on a mechanistic model which is represented by a spring (restorative force component) and a dashpot (damping component) in parallel connected with a free spring. In (8) the viscoelastic characteristic time β is given by $\beta = \frac{E_0+E_1}{\mu_1}$, and $\alpha_1 = \frac{E_0 E_1}{\mu_1}$, $\alpha_2 = E_0$, where E_1 is the Young modulus of the spring element, μ_1 represents the viscosity and E_0 stands for the Young modulus of the free spring (see for instance [10], [15] and [17]).

Equation (8) leads to the following expression for σ

$$\sigma(t) = \int_0^t e^{-\beta(t-s)}(\alpha_1 \epsilon(s) + \alpha_2 \frac{\partial \epsilon}{\partial t}(s))ds + e^{-\beta t}\sigma(0). \tag{9}$$

If we assume that the strain ϵ satisfies $\epsilon = \lambda c$ where λ is a positive constant (see [2], [3], [4] and [5]) from (9) we obtain

$$\sigma(t) = \lambda \int_0^t e^{-\beta(t-s)}(\alpha_1 c(s) + \alpha_2 \frac{\partial c}{\partial t}(s))ds + e^{-\beta t}\sigma(0). \tag{10}$$

Mass conservation equation (2) with J_F replaced by J, given by (6), leads to the integro-differential equation

$$\frac{\partial c}{\partial t} = \nabla(D^* \nabla c) + \int_0^t k_{er}(t-s)\nabla(D_v^* \nabla c(s)) + f(c)\,, \text{ in } \Omega \times (0, +\infty)\,, \tag{11}$$

where $D^* = D + \lambda \alpha_2 D_v\,,\ D_v^* = \lambda(\alpha_1 + \alpha_2)D_v$ and $k_{er}(t) = e^{-\beta t}\,.$

To establish a mathematical model to describe the evolution in time and space of the glioma cells some medical information is needed. According to [8] and [9] the following assumptions are assumed in our model:

- glioma cells are of two phenotypes: proliferative (state 1) and migratory (state 2);
- in state 1 cells randomly move but there is no cell fission;
- in state 2 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 state 2;
- a cell of type 2 remains in state 2 during a time period and then switches to a cell of type 1;

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- β_2 is the switching rate from state 2 to state 1.

Let $u(x,t)$ and $v(x,t)$ be the densities of migratory and proliferation cells at position x and time t, respectively. The dynamics of glioma cells in $\Omega \times (0,T]$ is then described by (11), where we have dropped the asterisk in D^* and D_v^*, completed with an equation that describes the dynamic of proliferation cells

$$\begin{cases} \dfrac{\partial u}{\partial t} = \nabla(D\nabla u) + \displaystyle\int_0^t k_{er}(t-s)\nabla(D_v\nabla u(s)) - \beta_1 u + \beta_2 v\,, \\ \dfrac{\partial v}{\partial t} = \rho v + \beta_1 u - \beta_2 v\,, \end{cases} \tag{12}$$

where D and D_v denote square matrices of order n, β_1 is the switching rate from migratory phenotype to proliferative phenotype and β_2 is the switching rate from proliferative phenotype to migratory phenotype.

If chemotherapy is applied and $G(t)$ defines the time profile of the chemotherapy treatments then, assuming a loss proportional to the amount of therapy at a given time, system (12) is replaced by

$$\begin{cases} \dfrac{\partial u}{\partial t} = \nabla(D\nabla u) + \displaystyle\int_0^t e^{-\beta(t-s)}\nabla(D_v\nabla u(s)) - \beta_1 u + \beta_2 v - G(t)u\,, \\ \dfrac{\partial v}{\partial t} = \rho v + \beta_1 u - \beta_2 v - G(t)v\,, \end{cases} \tag{13}$$

where $G(t)$ is defined by (5).

System (13) is completed with initial conditions

$$u(0) = u_0,\ \ v(0) = v_0 \text{ in } \Omega, \tag{14}$$

and boundary conditions

$$u(t) = v(t) = 0 \text{ on } \partial\Omega, \tag{15}$$

where $\partial\Omega$ denotes the boundary for Ω. Condition (15) means that glioma is located inside the brain and cancer cells do not attain pia mater.

3 Control of glioma growth

We will assume that $D = [d_{ij}]$ and $D_v = [d_{v,ij}]$ are diagonal matrices such that

$$0 < \alpha_e \leq d_{ii}, d_{v,ii} \leq \alpha_b \text{ in } \overline{\Omega},\ i = 1, \ldots, n. \tag{16}$$

Let $\mathcal{M}_1(t)$ be the natural total mass of tumor cells in Ω,

$$\mathcal{M}_1(t) = \int_\Omega (u(t) + v(t))\, d\Omega \tag{17}$$

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and $\mathcal{M}_2(t)$ be an artificial mass of tumor cells, defined by the accumulated energy

$$\mathcal{M}_2(t) = \|u(t)\|^2 + \|v(t)\|^2\,, \tag{18}$$

where $\|.\|$ denotes the usual L^2 norm which is induced by the usual L^2 inner product $(.,.)$. For mathematical reasons we will study the behaviour of the artificial mass of tumor cells $\mathcal{M}_2(t)$, hoping to control the natural total mass $\mathcal{M}_1(t)$.

We have

$$\frac{1}{2}\mathcal{M}_2'(t) = \int_\Omega \left(\frac{\partial u}{\partial t}(t)u(t) + \frac{\partial v}{\partial t}(t)v(t)\right) d\Omega.$$

From (13) and taking into account the boundary conditions (15) we deduce

$$\begin{aligned}\frac{1}{2}\mathcal{M}_2'(t) \;=\; & -\|\sqrt{D}\,\nabla u(t)\|^2 - \Big(\int_0^t e^{-\beta(t-s)} D_v \nabla u(s)\,ds, \nabla u(t)\Big) + (\,-\beta_1 - G(t))\|u(t)\|^2 \\ & +(\rho - \beta_2 - G(t))\|v(t)\|^2 + (\beta_1+\beta_2)(u(t),v(t)),\end{aligned} \tag{19}$$

where $\sqrt{D} = [\sqrt{d_{ii}}\,]$.

As

$$\begin{aligned}\Big(\int_0^t e^{-\beta(t-s)} D_v \nabla u(s)\,ds, \nabla u(t)\Big) \;=\; & \frac{1}{2}\frac{d}{dt}\|\int_0^t e^{-\beta(t-s)}\sqrt{D_v}\nabla u(s)\,ds\|^2 \\ & +\beta\,\|\int_0^t e^{-\beta(t-s)}\sqrt{D_v}\,\nabla u(s)\,ds\|^2,\end{aligned}$$

and

$$\alpha_e\|v\|^2 \le C_\Omega^2\|\sqrt{D}\,\nabla v\|^2,\ v\in H_0^1(\Omega), \tag{20}$$

then from (19) we get

$$\begin{aligned}\frac{d}{dt}\Big(\mathcal{M}_2(t) + \|\int_0^t e^{-\beta(t-s)}\sqrt{D_v}\nabla u(s)\,ds\|^2\Big) \le -2\beta\|\int_0^t e^{-\beta(t-s)}\sqrt{D_v}\nabla u(s)\,ds\|^2 \\ +2\max\Big\{\frac{\beta_2-\beta_1}{2} - \frac{\alpha_e}{C_\Omega^2} - G(t), \frac{\beta_1-\beta_2}{2} + \rho - G(t)\Big\}\mathcal{M}_2(t).\end{aligned} \tag{21}$$

If

$$\frac{\beta_1-\beta_2}{2} + \rho \;>\; \frac{\beta_2-\beta_1}{2} - \frac{\alpha_e}{C_\Omega^2} \tag{22}$$

and

$$\frac{\beta_2-\beta_1}{2} - \frac{\alpha_e}{C_\Omega^2} - G(t) > -\beta, \tag{23}$$

then equation (21) leads to

$$\mathcal{M}_2(t) \le e^{2\left((\frac{\beta_1-\beta_2}{2}+\rho)t - \int_0^t G(s)\,ds\right)}\mathcal{M}_2(0). \tag{24}$$

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As $\frac{\alpha_e}{C_\Omega^2}$ is a constant arising from mathematical analysis, conditions (22), (23) can be replaced by

$$\beta_1 - \beta_2 + \rho > 0$$

and

$$\beta_1 - \beta_2 < 2(\beta - G(t)),$$

respectively. Avoiding such constant, these last conditions assume a biological meaning. To conclude that the artificial mass $\mathcal{M}_2(t)$ is bounded by $\mathcal{M}_2(0)$, we need to combine conditions (22), (23) with

$$\Big(\frac{\beta_1 - \beta_2}{2} + \rho\Big)t \; < \; \int_0^t G(s)\, ds. \tag{25}$$

Condition (25) means that density of proliferation cells at time t, that is density of cells originated by cells of this type and cells that comes from state 1 and remains in state 2, is less than the total amount of death cells until time t due to chemotherapy effect.

From Schwarz inequality we have

$$\mathcal{M}_1(t) \leq \sqrt{|\Omega|}\,(\|u(t)\| + \|v(t)\|). \tag{26}$$

If we assume that $\sqrt{|\Omega|} \leq \|u(t)\|$ and $\sqrt{|\Omega|} \leq \|v(t)\|$, then we conclude that the upper bound (24) for $\mathcal{M}_2(t)$ is also an upper bound for the mass $\mathcal{M}_1(t)$. We note that inequality (26) has pure mathematical character and it is not obviously that it has a medical translation. However for the different simulations that we carried on, inequality (26) was verified and consequently we can use condition (25) to control tumoral mass.

When chemotherapy is applied, condition (25) can be used to determine an effective dosage that induces a rate k of cell death due to the exposure to the drug that allows to control the total tumor mass, provided that condition (22) holds. Obviously the value of k depends of the protocol of chemotherapy. The typical bang-bang protocol corresponds to treatment which alternate maximum doses of chemotherapy with rest periods when no drug is administered, as defined by (5) and illustrated in Figure 1.

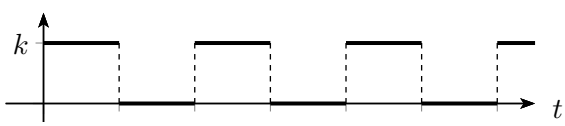

Figure 1: Chemotherapy protocol.

4 Numerical simulation

In this section we present some numerical results illustrating the behaviour of the glioma cells defined by (13). The numerical results were obtained using a standard numerical

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method defined combining the explicit Euler methods with second order centered difference operators and a rectangular rule to discretize the spatial derivatives and the time integral, respectively. We consider a homogeneous square domain $\Omega = [0, 15\,cm]\times[0, 15\,cm]$, diffusion coefficients $d_{11} = d_{22} = d_{v,11} = d_{v,22} = 0.025\,cm^2/day$, growth rate $\rho = 0.05\,/day$, switching parameters $\beta_1 = 10^{-6}/day$ and $\beta_2 = 0.036/day$, kernel such that $\beta = 1$ and initial condition defined by 10^6 proliferation tumor cells at middle square $[7, 8] \times [7, 8]$.

In Figure 2 we plot the numerical solutions at day 33 for an virtual untreated patient ($G(t) = 0$). We observe a decreasing on the highest values of the tumor cells concentration at initial times followed by an increase and very intense spreading of cells. The contour plots allow us to observe high gradients on the core of the tumor, defined by the proliferation cells, and that the migration cells are already quite far from the core!

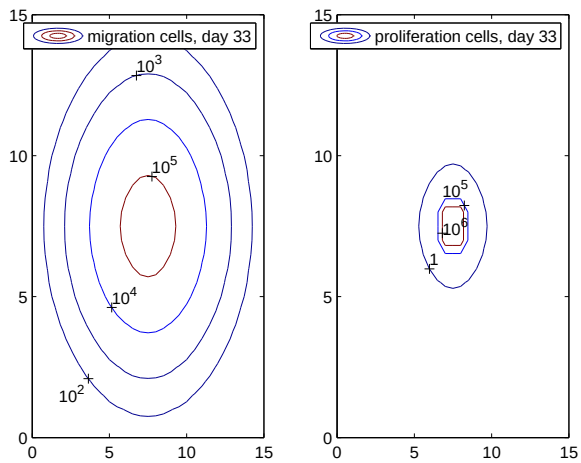

Figure 2: Numerical results at day 33, obtained with 2D model (13) for $k = 0/day$.

Let us consider now that the chemotherapy treatment defined by (5) is applied with a protocol as illustrated in Figure 1. Condition (25) is used to compute an effective drug that lead to control the total tumor mass. We consider a 24h dosage and different rest periods. In Table 1 we show the minimum value of k allowed by condition (25), for a virtual patient as defined in the beginning os this section. Here $\alpha_e = 0.025\,cm^2/day$ and $C_\Omega = \frac{1}{\sqrt{2}}$.

Protocol	$k_{\min}\,[./day]$
each 2 days	0.064
each 7 days	0.224
each 14 days	0.448

Table 1: $k_{\min}$ as (25), for a protocol of 24 consecutive hours of chemotherapy .

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In Figure 3 we plot the cell distribution at day 33, when a protocol of chemotherapy of 24h is administered at days 5, 19 and 33 using $k = 0.5/day$. We observe that glioma mass at day 33 is less than its mass at day 4 (the day before the first administration of the chemotherapy).

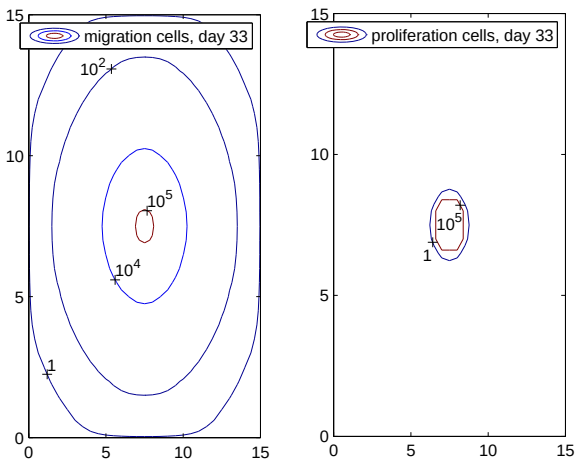

Figure 3: Numerical results at day 33, obtained with 2D model (13) for $k = 0.5/day$.

Finally, in Figure 4 we compare glioma masses of the virtual patient when no chemotherapy is administered and the results of the adminstration of 3 different chemotherapy protocols. The difference between the protocols is the rest period and the values of k were computed using condition (25). We observe that for all protocols glioma masses are less than the glioma mass at day 4 (the day before the first administration of the protocol). The results presented in this figure shows the effectiveness of the our approach to define chemotherapy protocols.

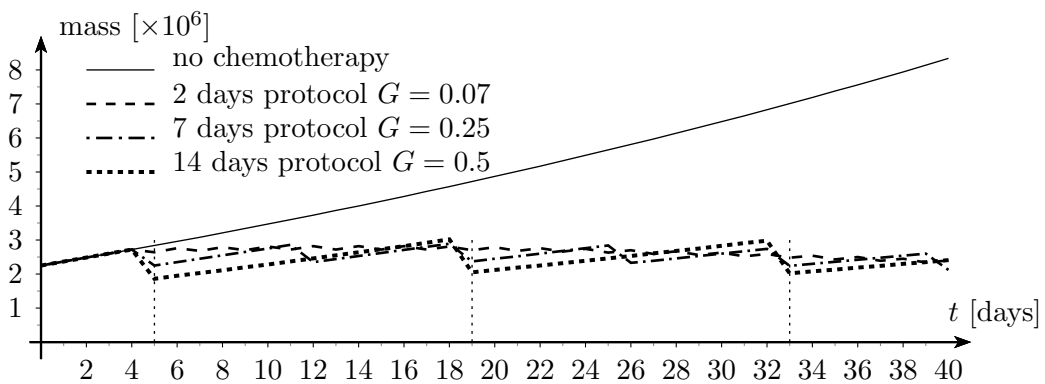

Figure 4: Glioma masses $\mathcal{M}_1(t)$.

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5 Conclusions

In this paper we studied a mathematical model to describe the evolution of glioma cells when chemotherapy is applied. The model was established combining a mass conservation with a non Fickian mass flux that takes into account the viscoelastic behaviour of the brain tissue described by the Voigt-Kelvin model.

Using the energy method we deduced an estimate for the glioma mass $\mathcal{M}_2(t)$, defined using L^2 norm. This estimate allowed us to define a sufficient condition on the parameters of the model that leads to the control of $\mathcal{M}_2(t)$, more precisely, to guarantee that $\mathcal{M}_2(t) < \mathcal{M}_2(0)$. Such condition was then used to define chemotherapy protocols. Numerical experiments illustrating the behaviour of the glioma mass under the conditions deduced for the chemotherapy protocols are also included. The results obtained suggest our approach is a promising one. Future work will address the comparison of the model with existing medical protocols.

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