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The role of stiffness in the proliferation of brain tumors

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Abstract

In this paper we present a mathematical model to describe the evolution of glioma cells taking into account the viscoelastic properties of brain tissue. A theoretical stability analysis gives information to design protocols which efficiency is illustrated by a number of numerical simulations.

Key words: Glioma, viscoelastic behaviour, chemotherapy, numerical simulation.

1 Introduction

Cancer is a complex disease which leads to the uncontrolled growth of abnormal cells, destruction of normal tissues and invasion of vital organs. Extensive research has been done to model cancerous growth, however the understanding of malignant gliomas is much less complete, mostly because migration of gliomas represent a very challenging problem from a mathematical viewpoint.

Gliomas are diffusive and highly invasive brain tumors. Median untreated survival time for high grade gliomas ranges from 6 months to 1 year and even lower grade gliomas can rarely be cured. Theorists and experimentalists believe that inefficiency of treatments results from the high mobility of glioma cells, which is partly driven by the mechanical properties of brain tissue.

The first model to measure the growth of an infiltrating glioma was provided by Murray in the early 90s ([19]). He formulated the problem as a conservation law where the rate of change of tumor cell population results from mobility and net proliferation of cells. An equation of type

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

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was used, where $\Omega \subset \mathbb{R}^n, n = 1, 2, 3$, is the glioma domain, $c(x, t)$ denotes the tumor cell density at location x and time t, $f(c)$ denotes net proliferation of tumor cells (generally assumed to be exponential, $f(c) = \rho\, c$ where the net proliferation rate ρ is constant), $\tilde{D}$ is the diffusion tensor and ∇ defines the spatial gradient operator.

The partial differential equation (1), of parabolic type, was established combing the mass conservation law with Fick's law for the mass flux J_F,

$$J_F = -\tilde{D}\,\nabla c\,. \tag{2}$$

It is well known that that Fickian approach gives rise to infinite speed of propagation which is not physically observable. To avoid the limitation of Fickian models an hyperbolic correction has been proposed in different contexts (see [1], [6], [9], [10], [15], [17], and [20]).

The aim of this paper is to establish a class of non Fickian models that take into account the viscoelastic behavior of the brain tissue and to present a stable numerical method for this class of models. A simplified version of this model was considered [2] using a simple geometry. To apply the modeling approach to specific patients a more realistic look at the brain geometry and structure is necessary. In this case we can follow [23] where a complex geometry of the brain and a space dependent diffusion coefficient were considered to reflect the observation that glioma cells exhibit higher motility in the white matter than in grey matter ([14]).

We observe that the most popular treatments used to combat gliomas are chemotherapy and radiotherapy. Chemotherapy involves the use of drugs to disrupt the cell cycle and to block proliferation. Tracqui *et al.* [24] incorporated chemotherapy by introducing cell death as a loss term. If $G(t)$ defines the rate of cells death then, assuming a loss proportional to the tumour cells density, equation (1) is replaced by

$$\frac{\partial c}{\partial t} = \nabla.(\tilde{D}\nabla c) + f(c) - G(t)c \ \text{ in } \Omega \times (0, T]\,, \tag{3}$$

where

$$G(t) = \begin{cases} k, & \text{when chemotherapy is being administered} \\ 0, & \text{otherwise}\,. \end{cases} \tag{4}$$

Here k describes the rate of cell death due to exposure to the drug. The main question is how to define k and the periods of chemotherapy applications that lead to control the glioma mass.

2 A viscoelastic model

The brain tissue presents a viscoelastic behaviour that can be described by the Voigt-Kelvin model ([13], [16], [18]). In this section we present a class of non Fickian models to describe

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the space and time evolution of glioma cancer cells, combining the diffusion process with the viscoelastic properties of the brain tissue.

Several authors have studied the diffusion in a viscoelastic medium ([5], [7], [8] and [22]), using a modified diffusion equation of type

$$\frac{\partial c}{\partial t} = \nabla.(\tilde{D}\nabla c) + \nabla.(\tilde{D}_v\nabla\sigma) + f(c) \text{ in } \Omega \times (0,\infty), \tag{5}$$

where σ represents the stress exerted by the medium on the diffusing molecules and $\tilde{D}$ represents a diagonal tensor with positive entries.

Even if studies of glioma growth have essentially addressed biochemical and genetic factors, recent biomedical research has highlighted the role of mechanical properties. Our aim in this paper is the modelling and analysis of glioma growth under the effect of the rheological properties of the brain tissue.

Investigators have observed that the stiffness of extracellular matrix can either increase or decrease the diffusion of migration cells. These observations are explained by the fact that extracellular matrix stiffness induce complex biochemical phenomena that depend on the type of diffusive cells and microenvironment properties.

In [25] the authors observed in vitro migration of fibroblasts from soft to stiff regions of extracellular matrix. Following this paper we consider equation (5) where $\tilde{D}_v$ is a diagonal tensor with negative entries.

We assume that the viscoelastic behaviour of the brain tissue is described by the Voigt-Kelvin model

$$\frac{\partial \sigma}{\partial t} + \beta\sigma = \alpha_1\epsilon + \alpha_2\frac{\partial \epsilon}{\partial t}\,, \tag{6}$$

where ϵ stands for the strain. Equation (6) is based on a mechanistic model which is represented by a spring and a dashpot in parallel, connected with a free spring. In (6) the viscoelastic characteristic time β is given by $\beta = \frac{E_0+E_1}{\mu_1}$, and $\alpha_1 = \frac{E_0E_1}{\mu_1}$, $\alpha_2 = E_0$ 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 [13], [16], [18]).

If we assume that the strain ϵ satisfies $\epsilon = \lambda c$ where λ is a positive constant (see [5], [7] and [8]), from (6) we obtain

$$\frac{\partial c}{\partial t} = \nabla.(D\nabla c) + \int_0^t k_{er}(t-s)\nabla.(D_v\nabla c(s))\,ds + f(c) \text{ in } \Omega \times (0,\infty)\,, \tag{7}$$

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

According to [11] and [12] 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

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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. The dynamics of glioma cells is then described by

$$\begin{cases} \dfrac{\partial u}{\partial t} &= \nabla.(D\,\nabla u) + \displaystyle\int_0^t k_{er}(t-s)\,\nabla.(D_v \nabla u(s))\,ds - \beta_1 u + \beta_2 v \ \text{ in } \Omega \times (0,T], \\ \dfrac{\partial v}{\partial t} &= \rho v + \beta_1 u - \beta_2 v \ \text{ in } \Omega \times (0,T], \end{cases} \tag{8}$$

where D and D_v denote square matrices of order n. The set of equations (8) is complemented with initial conditions

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

where u_0 and v_0 define the initial spatial distribution of malignant cells, and boundary conditions

$$J.\eta = 0 \ \text{ on } \partial\Omega, \tag{9}$$

where $\partial\Omega$ denotes the boundary of Ω, η represents the exterior unit normal to the brain region and the non Fickian flux J is given by $J(t) = -D\nabla u(t) - \displaystyle\int_0^t e^{-\beta(t-s)} D_v \nabla u(s)\,ds\,.$ Condition (9) means that the glioma is located inside of the brain and the cancer cells do not cross the pia mater.

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

$$0 < d_i,\, d_{v,i} \ \text{ in } \quad \overline{\Omega},\, i = 1, \ldots, n. \tag{10}$$

If we consider the mass of glioma cells in Ω, $\quad M_1(t) = \displaystyle\int_\Omega (u(t) + v(t))\,dx$ we showed in [4] that $M_1(t) \le e^{\rho t} M_1(0)$, assuming the positivity of u, which means that mass $M_1(t)$ of cancer cells at time t depends on the initial mass, on time t and on the proliferation rate ρ.

To avoid the positivity assumption on u we consider the mass related functional $M_2(t) = \|u(t)\|^2 + \|v(t)\|^2$, where $\|.\|$ denotes the usual L^2. In this case we deduce that

$$M_2(t) \le e^{2\max\{\frac{\beta_2-\beta_1}{2}, \frac{\beta_1-\beta_2}{2}+\rho, -\beta\}t} M_2(0)\,. \tag{11}$$

If the tumor density is largen than 1 then an upper bound for $M_1(t)$ can be deduced from an estimate of $M_2(t)$. We observe that we can not select parameters β_1, β_2, ρ such that $M_2(t)$ is bounded in time. We also remark that inequality (11) allow us to conclude the stability of the proposed mathematical model with respect to perturbations of the initial conditions in $[0,T]$, for fixed $T > 0$.

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3 Chemotherapy: control of the glioma growth

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 the decreasing of the tumor mass. All the results of this section were carefully analyzed in [3].

To take into account the chemotherapy effect, the viscoelastic model for glioma growth (8) is modified as follows

$$\begin{cases} \dfrac{\partial u}{\partial t} &= \nabla.(D\,\nabla u) + \displaystyle\int_0^t k_{er}(t-s)\,\nabla.(D_v \nabla u(s))\,ds - \beta_1 u + \beta_2 v - G(t)u \ \text{ in } \Omega\times(0,T], \\ \dfrac{\partial v}{\partial t} &= \rho v + \beta_1 u - \beta_2 v - G(t)v \ \text{ in } \Omega\times(0,T], \end{cases} \tag{12}$$

where $G(t)$ is defined by (4).

Considering $E(t) = M_2(t) + \| \displaystyle\int_0^t k_{er}(t-s)\sqrt{D_v}\nabla u(s)\,ds\|^2$, it can be proved that

$$E'(t) \le 2\max\Big\{\frac{\beta_2-\beta_1}{2} - G(t), \frac{\beta_1-\beta_2}{2} + \rho - G(t), -\beta\Big\}E(t)\,. \tag{13}$$

From (13) some conditions on the parameters, that lead to a decreasing of $M_2(t)$, can be established:

1. If the net proliferation rate is greater than the switching proliferation rate

$$\rho > \beta_2 - \beta_1\,, \tag{14}$$

and the total amount of death cells until time t due to chemotherapy effect is such that

$$\Big(\frac{\beta_1-\beta_2}{2} + \rho\Big)t \;<\; \int_0^t G(s)\,ds \;<\; \big(\frac{\beta_2-\beta_1}{2} + \beta\big)\,t\,, \tag{15}$$

then we can conclude that $M_2(t)$ decreases.

From (15) we conclude that the difference between the net and switching proliferation rates should be less than the viscoelastic characteristic time, that is,

$$\rho - (\beta_2 - \beta_1) < \beta. \tag{16}$$

If no viscoelastic effects are considered ($\beta = 0$) we deduce from (15) that $\displaystyle\int_0^t G(s)\,ds$, which measures in some sese the intensity of the treatment, should be smaller.

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2. Otherwise, if the net proliferation rate is less than the switching proliferation rate

$$\rho < \beta_2 - \beta_1 \tag{17}$$

and the total amount of death cells until time t, due to chemotherapy effect, is such that

$$\Big(\frac{\beta_2 - \beta_1}{2}\Big)t < \int_0^t G(s)\,ds < \Big(\frac{\beta_1 - \beta_2}{2} + \rho + \beta\Big)t\,, \tag{18}$$

then we conclude that $M_2(t)$ decreases. Again we observe that the parameter β has influence on the admissible threshold of the chemotherapy treatment.

We note that condition (18) implies

$$\rho - (\beta_2 - \beta_1) > \beta\,. \tag{19}$$

When chemotherapy is applied, conditions (15) and (18) 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. 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 (4) and illustrated in Figure 1.

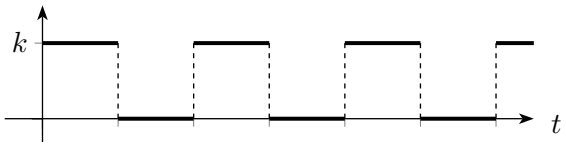

Figure 1: Chemotherapy protocol.

4 A fully discrete model

In this section we present a stable method to obtain numerical approximations for the density of proliferation and migratory glioma cells. We show that the method preserves the qualitative behaviour of the initial boundary value problem studied in the last section.

We assume that $n = 2$, Ω is the square $[0, L] \times [0, L]$ and $H = (h_1, h_2)$ with $h_i > 0, i = 1, 2$. In $\overline{\Omega}$ we introduce the spatial grid $\overline{\Omega}_H = \{(x_{1,i}, x_{2,j}), i = 0, \ldots, N_{h_1}, j = 0, \ldots, N_{h_2}\}$,where $x_{\ell,i} = x_{\ell,i-1} + h_\ell$, $i = 1, \ldots, N_{h_\ell}$, $x_{\ell,0} = 0$, $x_{\ell,N_{h_\ell}} = L$, for $\ell = 1, 2$. By $\partial\Omega_H$ we represent the set of boundary points. We introduce the following auxiliary points $x_{\ell,-1} = x_{\ell,0} - h_\ell$, $x_{\ell,N_{h_\ell}+1} = x_{\ell,N_{h_\ell}} + h_\ell, \ell = 1, 2$.

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Let $w_H = (u_h,\, v_H)$ represent a semi-discrete aprocimation of $w = (u, v)$. To simplify the presentation we use the notation $w_{i,j} = w_H(x_{1,i}, x_{2,j})$. We discretize $\dfrac{\partial}{\partial x_1}(a\dfrac{\partial u}{\partial x_1})$, a is a scalar functions, using the usual second order finite difference discretization

$$\nabla^*_{h_1}(\hat{a}_H \nabla_{h_1} u_H)(x_{1,i}, x_{2,j}) = \frac{1}{h_1}\Big(a_{i+1/2,j} D_{-x_1} u_{i+1,j} - a_{i-1/2,j} D_{-x_1} u_{i,j}\Big), \tag{20}$$

where $a_{i\pm 1/2,j} = a(x_{1,i} \pm \frac{h_1}{2}, x_{2,j})$ and D_{-x_1} denotes the usual backward finite difference operator in x_1 direction. The second order finite difference discretization $\nabla^*_{h_2}(\hat{b}_H \nabla_{h_2} u_H)(x_{1,i}, x_{2,j})$ to discretize $\dfrac{\partial}{\partial x_2}(b\dfrac{\partial u}{\partial x_2})$ is defined analogously.

In $[0, T]$ we introduce the grid $\{t_n, n = 0, \ldots, M\}$ with $t_n = t_{n-1} + \Delta t, n = 1, \ldots, M$, $t_0 = 0, t_M = T$. To compute numerical approximations for u and v in $(x_{1,i}, x_{2,j})$ at time level t_n, $u^n_H(x_{1,i}, x_{2,j})$, $v^n_H(x_{1,i}, x_{2,j})$, respectively, we introduce the fully discrete initial boundary value problem

$$\begin{cases} D_{-t} u^{n+1}_H = \displaystyle\sum_{i=1,2} \nabla^*_{h_i}(d_i \nabla_{h_i} u^{n+1}_H) + \Delta t \sum_{\ell=1}^{n+1} k_{er}(t_{n+1} - t_\ell) \sum_{i=1,2} \nabla^*_{h_i}(d_{v,i} \nabla_{h_i} u^\ell_H) \\ \qquad\qquad -(\beta_1 + G(t_{n+1}) u^{n+1}_H + \beta_2 v^{n+1}_H \ \text{ in } \overline{\Omega}_H, \\ D_{-t} v^{n+1}_H = (\rho - \beta_2 - G(t_{n+1})) v^{n+1}_H + \beta_1 u^{n+1}_H \ \text{ in } \overline{\Omega}_H, \\ \qquad\qquad n = 0, \ldots, M-1, \end{cases} \tag{21}$$

$$u^0_H = u_0, \ \ v^0_H = v_0 \ \text{ in } \overline{\Omega}_H, \tag{22}$$

$$\begin{aligned} D_{\eta_{x_1}} u^{n+1}_H(x_{1,i}, x_{2,j}) = 0, \ i = 0, N_{h_1}, \ j = 0, \ldots, N_{h_2}, \\ D_{\eta_{x_2}} u^{n+1}_H(x_{1,i}, x_{2,j}) = 0, \ i = 0 \ldots, N_{h_1}, \ j = 0, N_{h_2}\,, \end{aligned} \tag{23}$$

where

$$D_{\eta_{x_1}} u^{n+1}_H(x_{1,i}; x_{2,j}) = D_{d_1, \eta_{x_1}} u_H(x_{1,i}; x_{2,j}) + \Delta t \sum_{l=1}^{n+1} k_{er}(t_{n+1} - t_l) D_{d_{v,1}, \eta_{x_1}} u^l_H(x_{1,i}; x_{2,j})\,, \tag{24}$$

and $D_{a,\eta_{x_1}} u_H(x_{1,i}; x_{2,j})$ is defined by

$$\frac{1}{2}\Big(a(x_{1,i+1/2}; x_{2,j}) D_{-x_1} u^{n+1}_H(x_{1,i}; x_{2,j}) + a(x_{1,i-1/2}; x_{2,j}) D_{-x_1} u^{n+1}_H(x_{1,i}; x_{2,j})\Big)\,,$$

for $a = d_1,\, d_{v,1}\,,$ being $D_{a,\eta_{x_2}} u_H(x_{1,i}; x_{2,j})$ defined analogously.

We now study the stability of the discrete scheme (21), (22) and (23). It's easy to prove that

$$\min\{1, 1 - \Delta t \alpha_{n+1}\}\, E^{n+1}_H \le E^n_H, \ n = 0, \ldots, M, \tag{25}$$

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where

$$E_H^n = M_H^n + \sum_{i=1,2} \|\Delta t \sum_{\ell=0}^{n} k_{er}(t_n - t_\ell)\sqrt{\hat{d}_{v,i,H}} D_{-x_i} u_H^\ell\|_{\hat{h}_i}^2,$$

$M_H^n = \|u_H^n\|_H^2 + \|v_H^n\|_H^2$ represents a discretization of $M_2(t)$ and

$$\alpha_n = 2\Delta t \max\big\{\frac{\beta_2 - \beta_1}{2} - G(t_n), \rho + \frac{\beta_1 - \beta_2}{2} - G(t_n)\big\}.$$

From (25) we deduce the stability inequality

$$E_H^{n+1} \leq \prod_{\ell=1}^{n+1} \frac{1}{\min\{1, 1 - \alpha_\ell \Delta t\}} E_H^0\,, \tag{26}$$

provided that

$$1 - \Delta t\, \alpha_\ell \,>\, 0\,,\ \text{for all } \ell\,. \tag{27}$$

When G is defined by (4), if the administered dosage of drug is fixed such that

$$\frac{\beta_2 - \beta_1}{2} \,>\, k, \quad \rho + \frac{\beta_1 - \beta_2}{2} \,>\, k\,, \tag{28}$$

then condition (27) holds provided that time step size Δt satisfies

$$\Delta t < \frac{1}{\alpha_\beta}, \tag{29}$$

where

$$\alpha_\beta = 2\max\big\{\frac{\beta_2 - \beta_1}{2}, \frac{\beta_1 - \beta_2}{2} + \rho\big\}.$$

In this case (26) can be rewritten as follows

$$E_H^{n+1} \leq \frac{1}{\Big(1 - 2\Delta t \alpha_\beta\Big)^{(n+1)}}\, E_H^0\,,$$

and consequently

$$E_H^{n+1} \leq e^{\frac{2(n+1)\Delta t}{1 - 2\Delta t \alpha_\beta}}\, E_H^0\,, \tag{30}$$

which means that the numerical scheme (21), (22), (23) is conditionally stable under the condition (29) provided that the coefficients $\beta_i, i = 1, 2$, and ρ satisfy (28).

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5 Numerical results

In this section we illustrate the behaviour of (21), (22) and (23). We consider a homogeneous square domain $\Omega = [0, 15\,cm] \times [0, 15\,cm]$, 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 [21]. According to [18] the initial condition is defined by $10^5\,cells/cm^2$ proliferation tumor cells located at the middle point of the domain, $E_0 = 3156\,Pa$, $E_1 = 6E_0$ and $\mu = 8.9\times10^{-4}\,Pa{\cdot}s$. We also consider an isotropic behaviour with $\tilde{d}_{11} = \tilde{d}_{22} = 0.004\,cm^2/day$ and $\tilde{d}_{v,11} = \tilde{d}_{v,22} = -10^{-14}\,/Pa \cdot day$ (which leads to $d_{11} = d_{22} \sim 0.004\,cm^2/day$ and $d_{v,11} = d_{v,22} = 0.001\,cm^2/day^2$) and parameter $\lambda = 1\,cm^2$.

Let us consider that the chemotherapy treatment is defined by (4) and applied with a protocol as illustrated in Figure 1. Conditions (15) are used to compute a profile for $G(t)$ 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.

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

Table 1: $k_{\min}$ as (15), for a protocol of 24 consecutive hours of chemotherapy.

In Figure 2 we compare glioma masses for tree patients: one untreated and two submitted to chemotherapy starting at day 7 and with 7 and 14 rest periods, respectively. The values of k were computed using conditions (15). We observe a significant reduction of glioma masses when compared to glioma's untreated patient. The results presented in this figure show the effectiveness of our approach to define chemotherapy protocols.

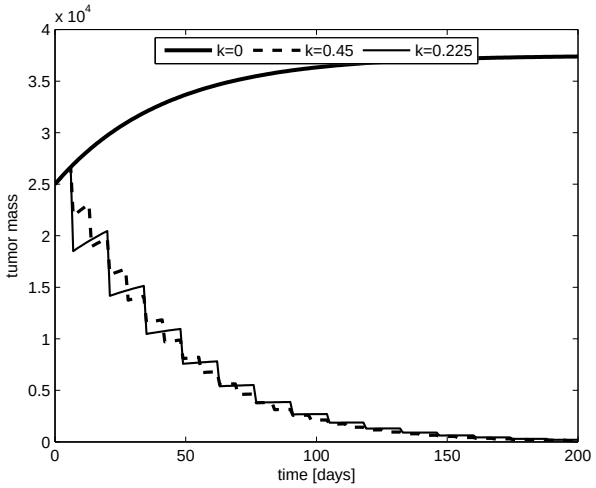

Figure 2: Glioma masses $M_1(t)$ for 200 days.

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In Figure 3 we plot the numerical solutions at day 104 for $E_0 = 3156\,Pa$ Solutions are presented in a logarithmic scale, which means that the contour plots represent the power of 10 of the density of tumor cells. For both cases we also present the distribution of proliferation cells for two patients submitted at chemotherapy protocol with a 24h dosage and 14 days of rest period (dosage at days 7, 21, 35, 49, etc). Values of k were computed using conditions (15) according to the weaker restriction. We observe a more intensive spreading when Young modulus (of the free spring) increases. This conclusion is in agreement with experimental results as stated in [25].

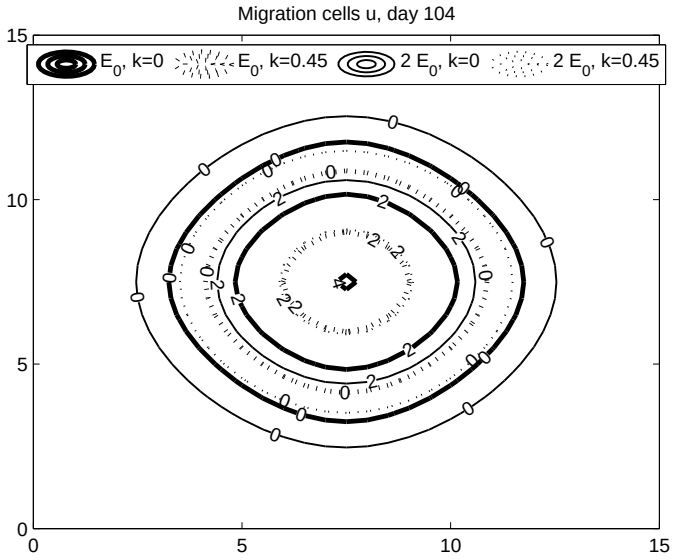

Figure 3: Distribution of proliferation cells results at day 104 ($E_0 = 3156\,Pa$).

6 Conclusions

In this paper we studied a mathematical model to describe the evolution of glioma cells with and without chemotherapy. The model was established combining a mass conservation law with a non Fickian mass flux that takes into account the viscoelastic behaviour of the brain tissue described by the Voigt-Kelvin model.

We deduced estimates that allowed to define sufficient conditions on the parameters that lead to control the glioma mass.

A fully discrete scheme was defined and the stability of such scheme was analyzed.

Numerical experiments suggest that our approach is a promising one. The behaviour of the mass of glioma cells was illustrated under the conditions deduced for the chemotherapy protocols.

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