A Viscoelastic Model for Glioma Growth

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Abstract: In this paper we propose a mathematical model to describe the evolution of glioma cells in the brain taking into account the viscoelastic properties of brain tissue. The mathematical model is established considering that the glioma cells are of two phenotypes: migratory and proliferative. The evolution of the migratory cells is described by a diffusion-reaction equation of non Fickian type deduced considering a mass conservation law with a non Fickian migratory mass flux. The evolution of the proliferation cells is described by a reaction equation. Numerical simulations that illustrate the behaviour of the mathematical model are included.

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. There are different stages at tumor development of varying duration, starting from genetic changes at the cell level and finishing with detachment of metastases and invasion. Tumor cell transport and proliferation are the main contributors to the malignant dissemination ((Swanson et al., 2003)).

Extensive research has been done to model cancerous growth, specially on solid tumors, in which growth primarily comes from cellular proliferation. It is far beyond the aim of the present paper to list exhaustively the many significant contribution in the topic. References (Fedotov and Iomin, 2007), (Giese et al., 1996), (Habib et al., 2003), (Harpold et al., 2007), (Mur, 2002), (Swanson et al., 2000), (Swanson et al., 2003) and the references therein represent some of these contributions.

However the understanding of malignant gliomas is much less complete, mostly because gliomas proliferate as solid tumors and invade the surrounding brain parenchyma actively. Proliferation and specially migration of gliomas represent a very challenging problem from mathematical viewpoint.

Gliomas are diffusive and highly invasive brain tumors accounting for about 50% of all primary brain tumors and, 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. Theorists and experimentalists believe that inefficiency of treatments results from the high mobility of glioma cells. Additionally gliomas can exhibit very high proliferation rates.

Cancer research has been a fertile ground for mathematical modeling, beginning with the early concept of simple exponential growth of solid tumors doubling at a constant rate. The introduction of logistic or gompertzian growth (there is increased doubling time and decreased growth fraction as a function of time) allowed to slow the growth in the later stages. With 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, the mathematical concepts necessarily became more complicated than those used in the original simple models for solid tumors.

The initial answer to the question of how to measure the growth of an infiltrating glioma was provided by Murray in the early 90s ((Mur, 2002)). 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

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

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, and ∇ defines the spatial gradient operator. Un-

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der the assumption of the classical Fick's law for the mass flux J_F

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

where D is the diffusion tensor, the model can be written as

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

The mathematical model is complemented by boundary conditions which impose no migration of cells beyond the brain boundary, that is,

$$J_F.\eta = 0,$$

on the boundary, where η denotes the exterior unit normal to the brain region, and by initial conditions $c(x,0) = c_0(x), x \in \Omega$, where c_0 defines the initial spatial distribution of malignant cells.

Tumor growth is generally assumed to be exponential, so that the cell growth term is given by $f(c) = \rho c$, where the net proliferation rate ρ is constant. However, logistic and gompertzian growths have been considered but found to be unnecessary in the time frames considered for gliomas ((Harpold et al., 2007)). To apply the modeling approach to specific patients, a more realistic look at the brain geometry and structure was necessary. Swanson *et al.* introduced in (Swanson et al., 2000) the complex geometry of the brain and allowed diffusion to be a function of the spatial variable to reflect the observation that glioma cells exhibit higher motility in the white matter than in grey matter.

Finally we observe that the most popular treatments used to combat gliomas are chemotherapy and radiation. Mathematical models to describe the effect of the previous treatments were proposed in the literature. Without being exhaustive we mention (Rockne et al., 2009) and (Tracqui et al., 1995).

The partial differential equation (3), of parabolic type,was established combing the mass conservation law (1) with Fick's law (2) for mass flux. It is well known that, in this case, 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 physically observable. To avoid the limitation of Fickian models an hyperbolic correction has been proposed in different contexts (see (Edwards and Cohen, 1995), (Joseph and Preziosi, 1989), (Fedotov, 1998), (Fedotov, 1999), (Hassanizadeh, 1996), (Neuman and Tartakovsky, 2009) and the references cited in those papers).

The aim of the present paper is the establishment of a class of non Fickian models that take into account the viscoelastic behavior of the brain tissue. The paper is organized as follows. Since the brain tissue presents a viscoelastic behaviour that can be described by the Voigt-Kelvin model (see for instance (G.Franceschini, 2006), (Humphrey, 2003), (Mehrabian and Abousleiman, 2011)), we present in Section 2 a class of non Fickian models to describe the space and time evolution of glioma cancer cells constructed by combining the diffusion process with the viscoelastic properties of the brain tissue. In Section 3 we study the behaviour of the glioma mass. In Section 4 we introduce the numerical method that will be used to obtain numerical approximations for the density of proliferation and migratory glioma cells. Plots illustrating the evolution of gliomas are included in Section 5. Finally, in Section 6 we present some conclusions.

2 A VISCOELASTIC MODEL

The class of non Fickian models that we present in what follows is established taking into account the viscoelastic nature of the brain tissue. Following (Edwards and Cohen, 1995), (Edward and Cohen, 1995), (Edwards, 1996), (Edwards, 2001) and (Shaw and Whiteman, 1998), if a diffusion process occurs in a medium that has a viscoelastic behaviour, then this behaviour should be included in the diffusion equation which leads to a modified diffusion equation

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

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

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

$$\frac{\partial \sigma}{\partial t} + \beta\sigma = \alpha_1\varepsilon + \alpha_2\frac{\partial \varepsilon}{\partial t}, \tag{5}$$

where ε stands for the strain. Equation (5) 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 (5) 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 (G.Franceschini, 2006), (Humphrey, 2003), (Mehrabian and Abousleiman, 2011)).

Equation (5) leads to the following expression for σ

$$\sigma(t) = \int_0^t e^{-\beta(t-s)}\big(\alpha_1\varepsilon(s) + \alpha_2\frac{\partial \varepsilon}{\partial t}(s)\big)ds + e^{-\beta t}\sigma(0). \tag{6}$$

If we assume that the strain ε satisfies $\varepsilon = \lambda c$ where λ is a positive constant(see (Edwards and Cohen, 1995), (Edward and Cohen, 1995), (Edwards, 1996) and (Edwards, 2001)) we obtain from (4) and (6) an integro-differential equation of type

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

where $k_{er}(s) = e^{-\beta s}$.

To establish a mathematical model to describe the space-time evolution of the gliomas some medical information is needed. According to (Fedotov and Iomin, 2007) and (Fedotov and Iomin, 2008) the following assumptions are considered in our model:

- the glioma cells are of two phenotypes - proliferation (state 1) and migratory (state 2);
- in state 1 (migratory phenotype) the cells randomly move but there is no cell fission;
- in state 2 (proliferation phenotype) the 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. The dynamics of glioma cells is then described by

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

where D and D_v denote square matrices of order n and β_1 is the switching rate from migratory phenotype to proliferation phenotype and β_2 is the switching rate from proliferation phenotype to migratory phenotype. The set of equations (8) is complemented with initial conditions

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

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 and the non Fickian flux J is given by

$$J(t) = -D\nabla u(t) - \int_0^t e^{-\beta(t-s)} D_v\nabla u(s)\,ds.$$

Condition (9) means that the glioma is located inside of the brain and the cancer cells do not cross the pia mater.

We observe that the first equation of (8) can be deduced considering the mass conservation law (1) and a modified Fick's law for the mass flux. In fact, if we assume that the mass flux J has two contributions, a Fickian and a non Fickian, that is

$$J = J_F + J_{NF},$$

where J_{NF} is given by

$$J_{NF}(t) = -\int_0^t e^{-\beta(t-s)} D_v\nabla u(s)\,ds, \tag{10}$$

we obtain (8) from (1). We note that (10) satisfies the following IVP

$$\begin{cases} \dfrac{\partial J_{NF}}{\partial t} + \beta J_{NF} = -D_v\nabla u \text{ in } \Omega\times(0,+\infty), \\ J_{NF}(0) = 0 \text{ in } \Omega, \end{cases} \tag{11}$$

where the first equation of (11) is a first order approximation of the equality

$$J_{NF}(x,t+\frac{1}{\beta}) = -\frac{1}{\beta} D_v\nabla u(x,t). \tag{12}$$

This equation establishes that non Fickian mass flux at time $t+\dfrac{1}{\beta}$, where $\dfrac{1}{\beta}$ is the relaxation time, is related with the gradient of the concentration u at a previous time. This observation means that system (8) incorporates a certain memory effect induced by the behaviour of migratory cells.

3 QUALITATIVE BEHAVIOUR

In what follows we 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

$$0 < d_i, d_{v,i} \text{ in } \quad \overline{\Omega}, i = 1,\ldots,n. \tag{13}$$

Let $\mathcal{M}(t)$ be the mass of glioma cells in Ω,

$$\mathcal{M}_1(t) = \int_\Omega (u(t)+v(t))dx.$$

We study in what follows the behaviour of $\mathcal{M}_1(t)$. We start by remarking that

$$\mathcal{M}_1'(t) = \int_\Omega \Big(\frac{\partial u}{\partial t}(t) + \frac{\partial v}{\partial t}(t)\Big)\, dx. \tag{14}$$

As u and v are defined by the system of equations (8), from (14) we obtain

$$\mathcal{M}_1'(t) = \int_\Omega (-\nabla.J(t) + \rho v(t))dx,$$

that leads to

$$\mathcal{M}_1'(t) = -\int_{\partial\Omega} J(t).\eta ds + \rho \int_\Omega v(t)dx. \tag{15}$$

From (9) we conclude that

$$\mathcal{M}_1'(t) = \rho \int_\Omega v(t)dx,$$

which means that the instantaneous time variation of the cancer mass depends only on the mass of the proliferation cells and on the proliferation rate ρ. Assuming the positivity of u, we finally obtain the upper bound

$$\mathcal{M}_1(t) \leq e^{\rho t}\mathcal{M}_1(0). \tag{16}$$

To avoid the positivity assumption on u we establish in what follows an upper bound for

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

where $\|.\|$ denotes the usual L^2 norm and which is induced by the usual L^2 inner product $(.,.)$.
We have

$$\frac{1}{2}\mathcal{M}_2'(t) = (\frac{\partial u}{\partial t}(t), u(t)) + (\frac{\partial v}{\partial t}(t), v(t))$$

As (8) holds we obtain

$$\begin{aligned}\frac{1}{2}\mathcal{M}_2'(t) &= \int_{\partial\Omega} -J(t).\eta u(s)\, ds - \|\sqrt{D}\nabla u(t)\|^2 \\ &-((\int_0^t k_{er}(t-s)D_v\nabla u(s)\, ds, \nabla u(t))) \\ &-\beta_1\|u(t)\|^2 + (-\beta_2+\rho)\|v(t)\|^2 \\ &+(\beta_1+\beta_2)(u(t), v(t)),\end{aligned} \tag{17}$$

where the inner product in $L^2(\Omega)\times L^2(\Omega)$ is denoted by $((.,.))$ and represents $\|.\|$ the induced norm.
Considering the boundary condition (9), the Cauchy-Schwarz inequality and the following equality

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

we deduce from (17) that

$$E'(t) \leq \max\{\beta_2-\beta_1, \beta_1-\beta_2+2\rho, -2\beta\}E(t), t>0, \tag{18}$$

where

$$E(t) = \mathcal{M}_2(t) + \|\int_0^t k_{er}(t-s)\sqrt{D_v}\nabla u(s)\, ds\|^2.$$

Inequality (18) leads to

$$\mathcal{M}_2(t) \leq e^{\max\{\beta_2-\beta_1, \beta_1-\beta_2+2\rho, -2\beta\}t}\mathcal{M}_2(0). \tag{19}$$

The upper bound for the glioma mass defined by inequality (19) depends on the parameters of the model: the switching rate β_1 from migratory state to proliferation state; the switching rate β_2 from proliferation state to migratory state, the proliferation rate ρ of the cells of type 2 and the viscoelastic characteristic time β. If $\beta_2 = \beta_1$ then the upper bound is $e^{2\rho t}\mathcal{M}_2(0)$ which is analogous to the one obtained for $\mathcal{M}_1(t)$ with arbitrary β_1, β_2. Moreover, if $0 < \beta_2 - \beta_1 < \rho$, then the upper bound is $e^{(2\rho-(\beta_2-\beta_1))t}\mathcal{M}_2(0)$ being the amplification factor $e^{(2\rho-(\beta_2-\beta_1))t}$ greater than $e^{\rho t}$ obtained for $\mathcal{M}_1(t)$. However as expected, under these assumptions, we can not select parameter β_2, β_1, ρ such that the increasing of migratory cells is bounded.

We remark that inequality (19) allow us to conclude the stability of the proposed mathematical model with respect to perturbations of the initial conditions.

4 NUMERICAL METHOD

We assume in what follows that $n = 2$, Ω is the square $[0,L]\times[0,L]$ and $H = (h,k)$ with $h > 0, k > 0$. In $\overline{\Omega}$ we introduce the spatial grid

$$\overline{\Omega}_H = \{(x_{1,i}, x_{2,j}), i = 0,\ldots,N_h, j = 0,\ldots,N_k\}$$

where $x_{1,i} = x_{1,i-1} + h$, $i = 1,\ldots,N_h$, $x_0 = 0, x_{1,N_h} = L$, and $x_{2,j} = x_{2,j-1} + k$, $j = 1,\ldots,N_k$, $x_{2,0} = 0, x_{2,N_k} = L$. By $\partial\Omega_H$ we represent the set of boundary points. We introduce the following auxiliary points

$$x_{1,-1} = x_{1,0} - h,\ x_{1,N_h+1} = x_{1,N_h} + h,$$

and

$$x_{2,-1} = x_{2,0} - k,\ x_{2,N_k+1} = x_{2,N_k} + k.$$

By $\partial\Omega_H'$ we denote the following set of auxiliary points

$$\begin{aligned}\partial\Omega_H' &= \{(x_{1,-1}, x_{2,j}), (x_{1,N_h+1}, x_{2,j}), j = 0,\ldots,N_k, \\ &(x_{1,i}, x_{2,-1}), (x_{1,i}, x_{2,N_k+1}), i = 0,\ldots,N_h\}.\end{aligned}$$

In $[0,T]$ we introduce the grid $\{t_n, n = 0,\ldots,M\}$ with $t_n = t_{n-1} + \Delta t, n = 1,\ldots,M$, $t_0 = 0, t_M = T$. We

discretize the integral term of (8) using a rectangular rule and the second order partial derivatives $\frac{\partial}{\partial x}(a\frac{\partial u}{\partial x}), \frac{\partial}{\partial y}(b\frac{\partial u}{\partial y})$, where a and b are scalar functions, using the usual second order finite difference operators

$$\nabla_h^*(a\nabla_h u_H)(x_{1,i},x_{2,j}) = \frac{1}{h}\Big(a_{i+1/2,j}D_{-x_1}u_{i+1,j} - a_{i-1/2,j}D_{-x_1}u_{i,j}\Big) \quad (20)$$

$$\nabla_k^*(b\nabla_k u_H)(x_{1,i},x_{2,j}) = \frac{1}{k}\Big(b_{i,j+1/2}D_{-x_2}u_{i,j+1} - b_{i,j-1/2}D_{-x_2}u_{i,j}\Big) \quad (21)$$

where $a_{i\pm1/2,j} = a(x_{1,i} \pm \frac{h}{2}, x_{2,j}), b_{i,j\pm1/2} = b(x_{1,i},x_{2,j}\pm\frac{k}{2})$, D_{-x_i} denotes the usual backward finite difference operator in x_i direction, $i = 1,2$.
To compute numerical approximations for u and v in $(x_{1,i},x_{2,j})$ at time level t_n, $u_H^n(x_{1,i},x_{2,j})$, $v_H^n(x_{1,i},x_{2,j})$, respectively, we introduce the implicit-explicit finite difference scheme

$$\begin{cases} D_{-t}u_H^{n+1} = \nabla_h^*(d_1\nabla_h u_H^{n+1}) + \nabla_k^*(d_2\nabla_k u_H^{n+1}) \\ +\Delta t\sum_{\ell=0}^{n} k_{er}(t_{n+1}-t_\ell)\Big(\nabla_h^*(d_{v,1}\nabla_h u_H^\ell) + \nabla_k^*(d_{v,2}\nabla_k u_H^\ell)\Big) \\ -\beta_1 u_H^{n+1} + \beta_2 v_H^n \ \text{ in } \overline{\Omega}_H, \\ D_{-t}v_H^{n+1} = (\rho-\beta_2)v_H^n + \beta_1 u_H^{n+1} \ \text{ in } \overline{\Omega}_H, \\ n = 0,\dots,M-1. \end{cases} \quad (22)$$

The finite difference method (22) is complemented with initial conditions

$$u_H^0 = u_0,\ v_H^0 = v_0 \text{ in } \overline{\Omega}_H, \quad (23)$$

and with the boundary conditions

$$\begin{aligned} D_{d,\eta_{x_1}}u_H^n(x_{1,i},x_{2,j}) + \Delta t\sum_{\ell=0}^{n} k_{er}(t_n-t_\ell)D_{v,\eta_{x_1}}u_H^\ell(x_{1,i},x_{2,j}) &= 0, \quad i = 0,N_h, j = 0,\dots,N_k, \\ D_{d,\eta_{x_2}}u_H^n(x_{1,i},x_{2,j}) + \Delta t\sum_{\ell=0}^{n} k_{er}(t_n-t_\ell)D_{v,\eta_{x_2}}u_H^\ell(x_{1,i},x_{2,j}) &= 0, \quad i = 0\dots,N_h, j = 0,N_k. \end{aligned} \quad (24)$$

In (24) the following notations were used

$$D_{d,\eta_{x_1}}u_H^n(x_{1,i},x_{2,j}) = \frac{1}{2}\Big(d_{1,i+1/2,j}D_{-x_1}u_{i+1,j}^n + d_{1,i-1/2,j}D_{-x_1}u_{i,j}^n\Big),$$

$$D_{v,\eta_{x_1}}u_H^\ell(x_{1,i},x_{2,j}) = \frac{1}{2}\Big(d_{v,1,i+1/2,j}D_{-x_1}u_{i+1,j}^\ell + d_{v,1,i-1/2,j}D_{-x_1}u_{i,j}^\ell\Big)$$

and

$$D_{d,\eta_{x_2}}u_H^n(x_{1,i},x_{2,j}) = \frac{1}{2}\Big(d_{2,i,j+1/2}D_{-x_2}u_{i,j+1}^n + d_{2,i,j-1/2}D_{-x_2}u_{i,j}^n\Big),$$

$$D_{v,\eta_{x_2}}u_H^\ell(x_{1,i},x_{2,j}) = \frac{1}{2}\Big(d_{v,2,i,j+1/2}D_{-x_2}u_{i,j+1}^\ell + d_{v,2,i,j-1/2}D_{-x_2}u_{i,j}^\ell\Big).$$

It can be shown that the truncation error T_H satisfies

$$\|T_H^\ell\|_\infty = O(h^2+k^2+\Delta t),$$

provided that $\frac{\partial^2 u}{\partial t^2}, \frac{\partial^3 u}{\partial t\partial x_1^2}, \frac{\partial^3 u}{\partial t\partial x_2^2}, \frac{\partial^4 u}{\partial x_1^4}, \frac{\partial^4 u}{\partial x_2^4}$ are bounded in $\overline{\Omega}\times[0,T]$. As it can be established a discrete version of the stability inequality (19) for the errors $E_u^\ell = u(t_\ell) - u_H^\ell, E_v = v(t_\ell) - v_H^\ell$, we conclude that method (22) is of second order in space and first order in time.

5 NUMERICAL SIMULATION

In what follows we consider $L = 15cm$, $T = 60$ days, $\rho = 0.05$/day, $\beta_1 = 10^{-6}$/day, $\beta_2 = 3.6\times10^{-2}$/day, $\beta = 1$, $u_0 = 0, v_0 = 10^6$ located at the square $(7,8)\times(7,8)$. The numerical solutions that we present were obtained with method (22), (23), (24). In Figures 1 and 2 we plot the density of migratory and proliferation cells defined by by the Fickian model that can be obtained from the previous model considering $D_v = 0$. In this case we took $d_1 = d_2 = 0.05cm^2$/day. An increasing of the glioma core is clearly observed.

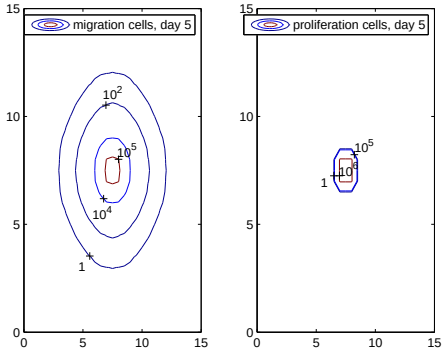

Figure 1: Fickian migratory and proliferation profiles at day 5.

The non Fickian migratory and proliferation profiles are plotted in Figures 3 and 4 when $d_1 = d_2 = d_{v,1} = d_{v,2} = 0.025cm^2$/day. We conclude, as expected, that viscoelastic effect does not change the behaviour of the proliferation cells. Moreover, the spatial distribution of such cells presents high gradients.

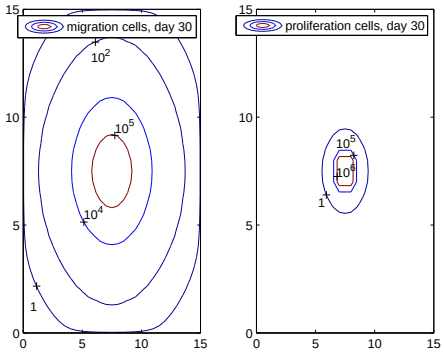

Figure 2: Fickian migratory and proliferation profiles at day 30.

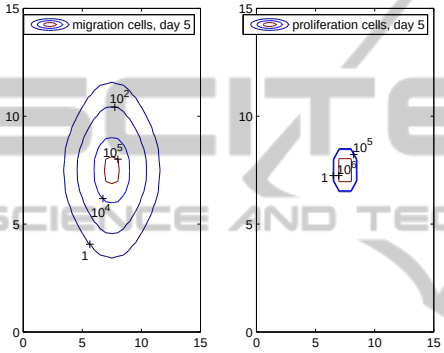

Figure 3: Non Fickian migratory and proliferation profiles at day 5.

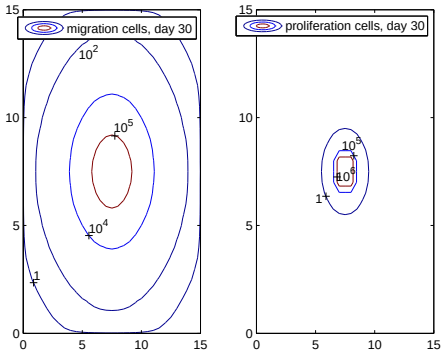

Figure 4: Non Fickian migratory and proliferation profiles at day 30.

From Figures 2 and 4 we conclude that the non Fickian migratory cells present higher spreading and lower concentration than the corresponding cells defined by the Fickian model.

6 CONCLUSIONS

In this paper a mathematical model to describe the evolution of gliomas cells that take into account the viscoelastic behaviour of the brain tissue was studied. Such mathematical model is characterized by an integro-differential equation of Volterra type that replaces the diffusion equation usually considered for the density of migratory cells. This equation was established assuming that the viscoelastic behaviour of the brain tissue is described by the Voigt-Kelvin model. An implicit-explicit numerical method to compute approximations for migratory and proliferation densities was presented and some numerical simulation illustrating the behaviour of the model is included. The numerical experiments allow us to conclude that the migratory cells defined by the non Fickian model present higher spreading and lower concentration than the corresponding cells defined by the Fickian model. However the behaviour of the proliferation cells seems not be sensitive to the viscoelastic properties of the brain tissue. In fact the evolution equation for such cells does not contain a diffusion part depending on the properties of the surrounding environment.

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