GLIOBLASTOMA GROWTH COMPUTATIONAL SIMULATION: A MINIMAL MODEL OF MULTISCALE ANGIOGENESIS

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Abstract. The tumor growth computational simulation is a fundamental step for the cancer management future, especially in this work the glioblastoma is modeled by a reaction-diffusion system. It is shown that the following mathematical models can simulate tumor behavior, analyzing the control parameters of the model that could help to avoid the tumor aiming to increase the percentage of survivors of this ailment.

Key words: *Cancer, Computational simulation, Glioblastoma, Tumor growth.*

INTRODUCTION

Cancer or neoplasm is defined as a phenomenon originating when a group of cells grows without control with certain characteristics like: proliferative, invasive and migratory advantages. This ailment is one of the most lethal diseases that takes millions of lives every year. Indeed, the number of people suffering from cancer is increasing annually, therefore it is important to analyze the factors that could contribute to the spread of tumors.

Glioblastoma is the most common malignant primary brain tumor, representing approximately 57% of all gliomas and 48% of all primary malignant central nervous system (CNS) tumors. Despite recent advances in multimodality therapy for glioblastoma incorporating surgery, radiotherapy, systemic therapy (chemotherapy, targeted therapy), and supportive care, the overall prognosis remains poor and long-term survival is rare, just with less 22% survivors after 5 years and in most cases 14 months is the life expectancy. If the biologic processes that characterize this illness are known, new molecular techniques will be put in clinical practice, improving the prevention strategies and patient management. However, it is still difficult to integrate computational oncology in clinic practice, and *requires different professional profile collaboration to achieve it.*

At this point, the computational dimensional (2D) simulations are considered as a powerful tool. There are certain mathematical models that help to understand the way glioblastoma grows: continue models and discrete models. The cellular automata discrete models are useful to model effects at cellular level and interactions based on agents. Nevertheless, continuous models are more appropriate if it is intended to model interactions and temporal effects at very different scales, helping to advance toward growth models more personalized.

A new minimal model of glioblastoma growth.

It is important to know the dynamics of cancer cell growth in order to propose new in-silico research methodologies to understand the underlying mechanisms. This future knowledge could help improve current brain cancer treatment techniques. Mathematical models of tumor growth try to represent, through functions and laws, the complex mechanisms of oncogenesis. In this research work, a multiscale mathematical model of angiogenesis is proposed based on the continuous Proliferation Invasion Hypoxia Necrosis Angiogenesis (PIHNA) model [1-9]. The new model considers the production and consumption of angiogenic factors, cell diffusion, chemotaxis, and macroscopic tissue processes such as tumor invasion and growth.

The reaction-diffusion equations of the proposed model are the following:

$$\frac{\partial g}{\partial t} = \nabla \cdot \left(D_g \nabla g\right) + \rho_g g(1-T) + \left(\theta_{mg} H_{mg}\right)m - \left(\theta_{gm} H_{gm}\right)g \quad (1)$$

$$\frac{\partial m}{\partial t} = \nabla \cdot (D_m \nabla m) + \rho_m m(1-T) + \left(\theta_{gm} H_{gm}\right)g - \left(\theta_{mg} H_{mg}\right)m - (\theta_{mN} H_{mN})m \quad (2)$$

$$\frac{\partial a}{\partial t} = \nabla \cdot (D_a \nabla a) + \rho_{am} m - \gamma v \quad (3)$$

$$\frac{\partial v}{\partial t} = \nabla \cdot (\chi v \nabla a) + \rho_v v m(1-N) + (\theta_{vN} H_v)v \quad (4)$$

g (cell/cm^3) is the proliferating cell density, m (cell/cm^3) is the invasive cell density, a (mol/cm^3) is the concentration of angiogenic factors and v (cell/cm^3) is the vascularization density. From these variables, the total tumor density T can be defined such that: $T=g+m$. The terms of Eq. (1) take into account respectively: the cellular diffusion of proliferating cells, the cell proliferation due to the tumor growth and the phenotype change from one population to another that is mediated by the local availability of oxygen. This change is controlled by the Heaviside function such that: $H_{mg}=1$ if there is hypoxia and $H_{mg}=0$ if there is not hypoxia. So: $H_{gm}=1-H_{mg}$. While the terms of Eq. (2) only considers the cellular diffusion and the cell proliferation of the invasive cells. At this point, two cases are distinguished regarding the diffusion between g and m: when invasive cells are capable of greater mobility than proliferative cells ($D_m > D_g$), and vice versa ($D_m < D_g$). The terms of Eqs. (3) and (4) modeling that: Invasive m cells produce angiogenic factors a, which attract endothelial cells v

Table 1. Values for the control parameters taken for the glioblastoma simulation

Da	ρ_{am}	ρ_v	θ_{mN}	θ_{vN}	O_{2hyp}	O_{2death}	$[O_2]_a$	α_g	α_m	γ	φ	x	k_{max}
$1x10^{-5}$ cm^2/s	$1x10^{-9}$ mol/s	$\frac{\rho_g}{10}$	1.2 day s^{-1}	$\frac{\theta_{mN}}{10}$	7 mmHg	0.7 mmHg	60 mmHg	$1x10^{-17}$ mol/cells ·s	$\frac{\alpha_g}{5}$	α_g	0.3	0.1	$1x10^8$ cell/cm^3

by chemotaxis. As a consequence, vascular density increases. To avoid introducing another non-linear term, we assume that the consumption of angiogenic factors by endothelial cells occurs at a constant ratio γ, where H_{vN}=1 if there is hypoxia and H_{vN}=0 if there is not hypoxia. Nevertheless, γ can be a function of *a, m,* or both. Also, the Eqs. (3) and (4) considers the chemical diffusion of concentration of angiogenic factors and the proliferation of invasive cells. The rest of control parameters are defined in the Table 1.

The numerical simulation results show evidence of glioblastoma growth inhibition in at least one case for the control parameter values of Table 1. The model presents a situation under which the growth of a brain tumor is viable, which is promising for new methods or treatments of this type of brain pathology.

Stability linear analysis.

The *Fixed points* were obtained of the following equations:

$$\rho_g g(1-T) + (\theta_{mg}H_{mg})m - (\theta_{gm}H_{gm})g = 0$$
$$\rho_m m(1-T) + (\theta_{gm}H_{gm})g - (\theta_{mg}H_{mg})m - (\theta_{mN}H_{mN})m = 0$$
$$\rho_{am} m - \gamma v = 0$$
$$\rho_v v m(1-N) + (\theta_{vN}H_v)v = 0$$

And its results, respectively:

$$g = -m\frac{(\theta_{mg}H_{mg})}{((\theta_{gm}H_{gm}))} \quad (5)$$
$$T = 1 \text{ ó } m = 0 \quad (6)$$
$$m = \frac{(\theta_{vN}H_{vn})}{\rho_v(1-N)} \quad (7)$$
$$v = \frac{(\theta_{vN}H_{vn})\rho_{am}}{\rho_v(1-N)\gamma} \quad (8)$$

The *Jacobian* of the model is:

$$J(g,m,a,v) = \begin{pmatrix} \rho_g(1-T) + (\theta_{gm}H_{gm}) & (\theta_{mg}H_{mg}) & 0 & \rho_m(1-T) & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \rho_{am} & 0 & \rho_v v(1-N) & 0 & \\ 0 & \gamma & 0 & \rho_v m(1-N) - \theta_{mg}H_{vN} & \end{pmatrix}$$

And their trace and determinant are respectively:

$$TrJ = \rho_g(1-T) + (\theta_{gm}H_{gm}) + \rho_m(1-T) + \rho_v m(1-N) - \theta_{mg}H_{vN}$$
$$|J(g,m,a,v)| = 0$$

At consider the diffusion effect in Eqs. (1) to (4), the extended determinant is:

$$\left| \lambda \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} - J(g,m,a,v) + k^2 \begin{pmatrix} D_g & 0 & 0 & 0 \\ 0 & D_m & 0 & 0 \\ 0 & 0 & D_a & 0 \\ 0 & 0 & 0 & \chi+1 \end{pmatrix} \right| = 0$$

And from here the eigenvalues are:

$$\lambda_1 = \rho_g(1-T) - (\theta_{gm}H_{gm}) - k^2 D_g$$
$$\lambda_2 = \rho_m(1-T) - k^2 D_m$$
$$\lambda_3 = -k^2 D_a$$
$$\lambda_4 = -k^2(\chi+1)$$

To finalize the section are presents the graphs of eigenvalues in ***Fig 1***, using the control parameters values of Table 1 and the fixed points given for Eqs. (5) to (6). In these graphs are presents the regions where there are instability zones and here are solved numerically the Eqs. (1) to (4). The 2D simulations are presented in the next section employing the numerical solution obtained previously.

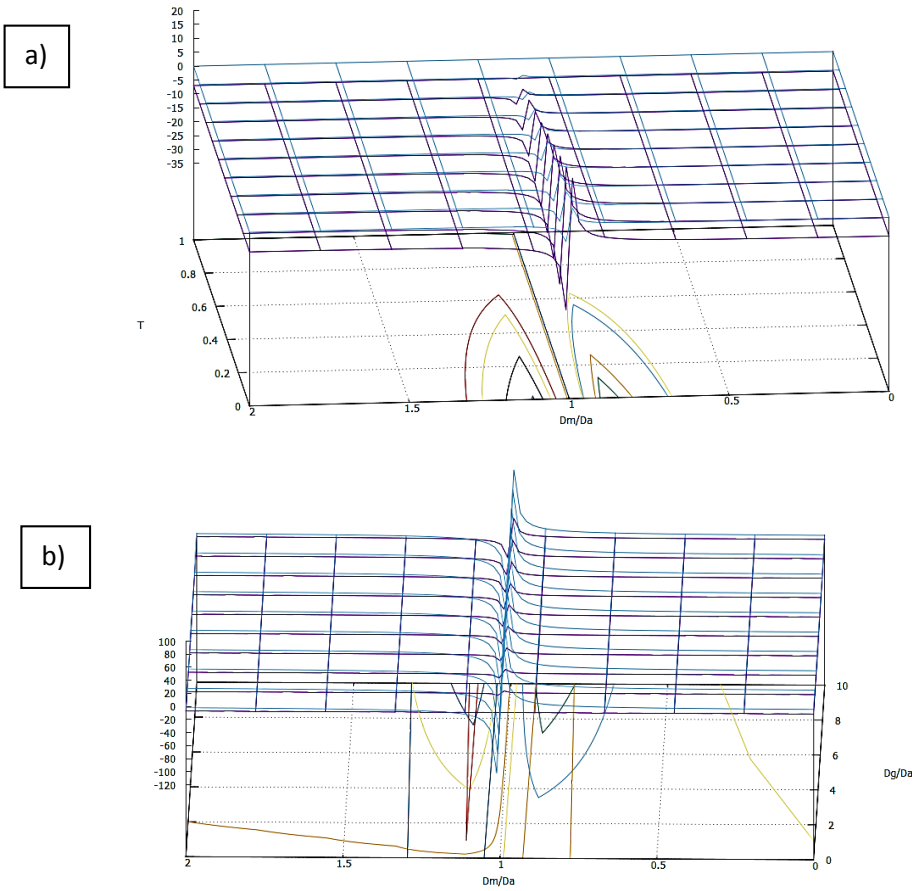


Figure 1. a) Eigenvalues graphs λ_1 and λ_2 for T vs d_m. b) Eigenvalues graphs λ_1 and λ_3 for d_m vs D_g/D_a

The graphs of Fig. 1 shows that the sensitive control parameters are *T*, d_m, and D_g / D_a. A similar behavior is found for the case of the eigenvalues 1 and 4. In all cases a saddle-type instability (Turing saddle points) is found

RESULTS OF COMPUTATIONAL

After taking those equations, the simulation was made with "Python 3.8" in its version of 32-Bit. The simulation development was possible due to 4 libraries called: math, numpy, random and pickle. It was just taken the first, second and third coupled reaction-diffusion space-time PDE to do the 1st and 2nd code and later it was made the third code, modifying the previous ones taking the entire model to compare if the is a variation considering different values. The numerical solution is obtained by means of difference finite algorithm in the space with a mesh step *dx=0.5* and the Euler ruler for the temporal evolution with step *dt=0.001*.

Considering time as dimensionless, were obtained the followings results from the simulations:

1. *First simulation* with Eqs. (1) to (3) where the parameter $d_m=D_m/D_a>1$ (associated with the diffusion of *m*) is defined with a value superior to general parameters (Fig. 2). The values are taken from control parameters are taken of Table 1 and the fixed points are given for Eqs. (5) to (8).
2. *Second simulation* with Eqs. (1) to (3) where the parameter $d_m=D_m/D_a$ (associated with the diffusion of m) is defined as with 0. It is: $D_m=0$ (Fig. 3). The values are taken from control parameters are taken of Table 1 and the fixed points are given for Eqs. (5) to (8).

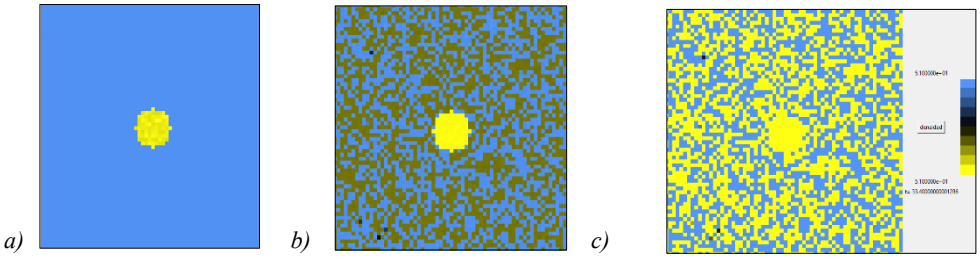
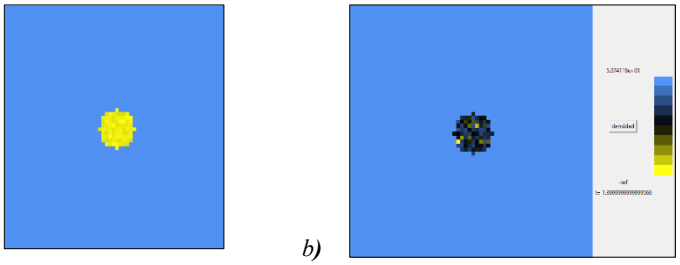
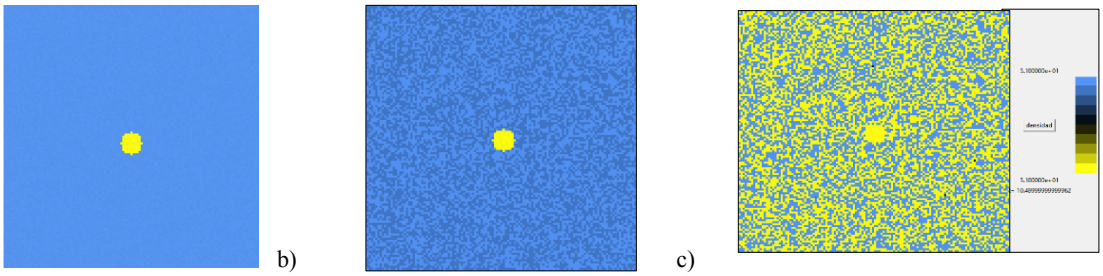


Figure 2. a) Growing tumor at t=1.9, b) Tumor starting its spread in the brain tissue at t=9.3, c) Tumor already spread in the brain tissue with t=33.4. When $d_m>1$



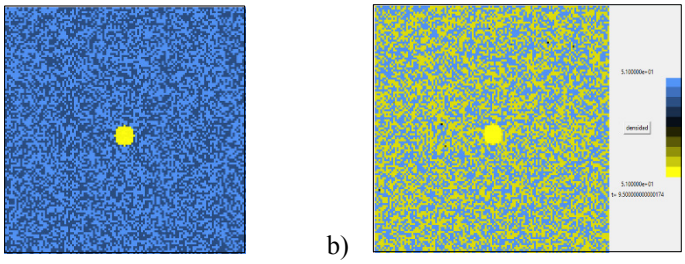
a) *b)*

Figure 3. a) Initial condition. b) Tumor that did not spread through the tissue and remains stable in time. When $d_m=0$



a) b) c)

Figure 4. a) Tumor growing at t=0.1, b) Tumor starting its spread in the brain tissue at t=8.5, c) Tumor already spread in the brain tissue at t=10.49. When $d_m>1$



a) b)

Figure 5. a) Tumor starting its spread in the brain tissue at t=8.8, b) Tumor already spread in the brain tissue at t=9.5. When $d_m>1$

3. *Third simulation* made with Eqs. (1) to (4) where the values are taken from control parameters are taken of Table 1 and the fixed points are given for Eqs. (5) to (8) (Fig. 4).

4. *Fourth simulation* made with Eqs. (1) to (4) where the values are taken from control parameters are taken of Table 1 and the fixed points are given for Eqs. (5) to (8). The *v* is taken is an inferior value than the third simulation (Fig. 5).

CONCLUSIONS

From the numerical experiments and their simulations 2D, it was seen that some parameters contribute to the tumor growth and ingrowth simulations as it follows:

- Increasing d_m (invasive cell density) in the first simulation employing Eqs. (1) to (3), it was seen that the growth increased when taking the general parameter with a difference of t=0.6.
- Taking D_m= 0, it's seen that the tumor isn't growing employing Eqs. (1) to (3). This means that by completely inhibiting the vascularization of the tumor, the lack of growth of the tumor is found.
- It is seen that the tumor grows faster if it is taken the Eqs. (1) to (4) model.
- In spite of decrease *v* (vascularization), the tumor spreads. It could be interpreted as metastasis.

Therefore, mathematical models can be used to simulate biological conditions under which the growth and decrease of a cerebral glioblastoma take place. This may be useful in future studies to find new treatments for this medical condition.

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