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A stochastic multiscale mathematical model for low grade Glioma spread

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Abstract

A stochastic multiscale mathematical model for glioma cell migration as well as proliferation is discussed, taking into consideration molecular markers such as isocitrate dehydrogenase (IDH) mutations which was highlighted in the recent updates of the world health organization (WHO) classification system of central nervous system (CNS).

1 Introduction

Gliomas are the most common primary brain tumors, arising from mutations in glial cells in the human brain. These fast growing tumors invade adjacent regions of the brain tissue and occur in all age groups. A number of experimental results have shown that invasion is facilitated by the directed movement of cells along the aligned neural fiber tracts that form much of the

white matter. A total resection of the malignant tissue is generally impossible due to the strong tumor infiltration of the healthy tissue and heterogenous rate of invasion that leads to a non-sharp edged border undetectable under current magnetic resonance imaging (MRI).

In fact the invasion of glioma cells in the human brain tissue involves several processes at different spatial and temporal scales: from the microscopic interactions between cancer cells and their micro-environement, through the intercellular level where individual cell behaviours are presented, up to the macroscopic setting for the cell population density description.

For these reasons being able to anticipate tumor behaviour, to then decide what medical approach to follow, can be helpful, time and life saver.

Therefore, using mathematical models can provide a valuable tool for including such detailed informations in the process, leading to enhanced forecasts of the tumor margins and thus an improvement of therapy planning.

Multiple mathematical models for glioma growth have been proposed in the literature ranging from purely discrete models such as cellular automata (CA) models which consist of a grid of cells involving only local rules for the evolution of the state of a given element (cancer cell) ie. the transition from one state to the other which defines the dynamics of the system only depends on the condition of its spatial neighborhood [2,11]. Totally continuous approaches [12,6,5] that involve a scheme of various types of reaction-diffusion partial differential equations that describe the evolution of tumor density in space and time while ignoring all the interactions that occur at the cellular level, but, despite that they are less detailed, they are able to capture the essential features of the modeled processes, and are better suited for efficient numerical simulations. Since there is no satisfactory representation of tumor growth by "pure" models, many hybrid models have been created, which are

essentially a combination of the two methods taking into account both a discrete system for cell-to-cell interactions and a continuous system for tumor mass growth [10,7,13,3].

We have reviewed a number of approaches to modelling gliomas and discussed them with Dr med Philip Rauch, who is a neurosurgeon at the NeuroMed Campus of the JKU.

In these discussions we have identified a number of issues that are not addressed in existing models, the construction of an easily scalable model of tumor growth, which can correctly describes both tumor growth while considering genetic markers, the invisible migration of certain tumor cells responsible for the switch from spreading along the white matter fibers to everywhere, patient specific data and the phenomena of cellular interactions, remains a real problem in theory and computational biology and related fields.

We chose the model in [1] by C. Surulescu and her group because first it covers all the the scales from the interactions happening in the cellular and subcellular level [8] to the macroscale where the tumor behaviour is studied, they also use diffusion tensor imaging (DTI) which measures the anisotropic diffusion of water molecules in the brain tissue to increase the precision in their modelling [9], all the more they integrate randomness into cell migaration without forgetting to take into consideration the particular geometry of the brain.

2 Description of the fundamental mathematical model

The aim of this project is to extend the work done in [1] where they consider a multi-scale approach for glioma modelling, starting from a description of the subcellular communication between cancer cells.

$$\begin{cases} dx = & vdt. \\ dv = & dS(t, x(t), v(t), z(t)). \\ dz = & -(k^+Q(x(t)) + k^-)z(t) - f^{'}(Q(x(t)))v(t).\nabla_x Q(x(t))dt. \end{cases}$$

Where $x(t)$ is the position of a single cell and $v(t)$ its corresponding velocity. $S(t)$ is a stochastic process depending on events occurring on the subcellular scale which depends on time, position, velocity, and the binding status $z(t)$ which measures the deviation from the steady state in the kinetic equation happening with a rate k, where k^+ and k^- denote respectively the attachment and detachment rates of the reversible binding of the surface receptors to the tissue fiber fraction.

$Q(x)$ is the volume fraction of tissue fibres, and the function f given by $f(s) = \frac{k^+ s}{k^+ s + k^-}$.

Followed by a mesoscopic description that illustrates the behavior of individual cells and their interactions with the underlying anisotropic tissue [2]. The kinetic equation for the density function $p(t, x, v, z)$, depending on time t, position $x \in \mathbb{R}^n$, velocity $v \in V \subset \mathbb{R}^n$ and internal state $z \in Z \subset \mathbb{R}^n$ is given by:

$$\partial_t p(t, x, v, z) + div_x(vp) - div_z\left(((k^+Q + k^-)z + f^{'}(Q)v.\nabla_x Q)p\right) = \mathcal{L}[\lambda(z)]p.$$

where λ is the turning rate such that $\lambda[z] = \lambda_0 + \lambda_1 z > 0$ with a change in the sign of λ_1 to compensate the sign change of z and $\mathcal{L}[\lambda(z)]$ denotes the turning

operator; a mathematical representation for modelling the velocity changes of the cells due to the oriented motility response of cells to the anisotropy in the environment given by $\mathcal{L}[\lambda]p = \lambda\left(q(x,v)\int_V p(v^{'})dv^{'} - p(v)\right)$, where $q : X \times V \to \mathbb{R}$ is the fiber probability density that describes the oriented structure of the environment.

At this intermediate scale, one can include a proliferation term $\mathcal{P}(p)$ via cell-tissue interactions.

$$\partial_t p(t,x,v,z) + div_x(vp) - div_z\left(((k^+Q + k^-)z + f^{'}(Q)v.\nabla_x Q)p\right) = \mathcal{L}[\lambda(z)]p + \mathcal{P}(p).$$

Finally, using the parabolic scaling technique, and the Hilbert expansion for the moment, they deduce the following macroscopic equation:

$$\partial_t M_0 - div_x div_x(DM_0) + div_x(gD\nabla_x Q M_0) = \mu(M_0)QM_0.$$

where M_0 is the macroscopic glioma density given by $M_0 = \frac{m_0}{q_0} - \frac{\lambda_1}{\lambda_0 q_0}(qM_0^z - m_0^z)$, D is the tumor diffusion tensor given by $D(x) = \int_V \frac{v\otimes v}{\lambda_0} q(x,\hat{v})dv$ (see [1,12] for details), $g(x) = \frac{\lambda_1}{\lambda_0 + k^+Q + k^-} f^{'}(Q)$, and μ is the growth function such that $\mu(s) = c_g(1-s)$, for all $s \geq 0$ where c_g is a growth parameter.

In particular, the tumor diffusion tensor can be made patient specific by incorporating data from the patient. The group of C. Surulescu has developed and implemented numerical methods approximating the solution of this deterministic partial differential equation.

3 Extension of the model in section 2

- Although the work in [1] covers a good part of tumor modeling such as the complex geometry of the brain, contact-guided migration where cells choose their new direction according to the given fiber network, the growth factor which depends on patient specific data, and taking into consideration different scales from the cellular level to the macroscopic description of the tumor, some fundamental issues are not addressed. For instance low grade glioma is considered an initially slow growing tumor with an irrevocable tendency to malignant transformation in 7 to 8 years.

- In particular, mutations in IDH1 / 2 are one of the main factors influencing the transition from slow growing low diffusing tumor to more aggressive deadly one according to the World Health Organization recent updates about the classification of tumors of the central nervous system (CNS).

- Moreover, based on a discussion with Doctor Philip-Rudolf Rauch, IDH mutations must be included in the growth factor term.
  First ideas in this direction result in the proliferation term becoming a stochastic process and thus, the whole system a hybrid stochastic/deterministic differential equation.

- Apart from this, statistics show that patients with the same histological diagnosis do not respond to the treatment in the same way and have a different outcome, so randomness in tumor behaviour arises in this context and the deterministic differential equation given above should be coupled with a stochastic process for better prediction of the tumor

upgrowth.

- Another problem that should be taken into account is the border of the tumor, unfortunately the glioma does not have the limited visible perfectly clear border but rather an irregular unsharped border due to the finger-like spreading, so a good mathematical model should in one hand describe the visible tumor density with all the characteristics which influence its growth, then predict the random branching-like spreading at the border of the visible mass, using stochastic branching processes.

- In order for this work to be useful in the context of medicine, the numerical analysis of this 3D model must be studied, for that I aim to collaborate with the team of DK14, who have expertise in numerical methods for partial differential equations, I will also collaborate with Luca Gerardo Giorda who in particular has already worked with a similar model in dimension 2.[1]

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