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Mathematical model of brain tumour with glia–neuron interactions and chemotherapy treatment

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HIGHLIGHTS

- We have analysed a mathematical model of brain tumour.
- We study a system of coupled differential equations.
- We consider in our model the interactions among glial cells, glioma, neurons, and chemotherapy.
- Glioma is studied aiming to identify values of the parameter for which the inhibition of the glioma cells is obtained with a minimal loss of healthy cells.
- We present a model of glioma with glia–neuron interactions.

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ABSTRACT

In recent years, it became clear that a better understanding of the interactions among the main elements involved in the cancer network is necessary for the treatment of cancer and the suppression of cancer growth. In this work we propose a system of coupled differential equations that model brain tumour under treatment by chemotherapy, which considers interactions among the glial cells, the glioma, the neurons, and the chemotherapeutic agents. We study the conditions for the glioma growth to be eliminated, and identify values of the parameters for which the inhibition of the glioma growth is obtained with a minimal loss of healthy cells.

1. Introduction

Cells growth is a phenomenon that has been studied in the fields of mathematics, biology, and physics (Adam and Bellomo, 1996; Wolpert et al., 2002; Hirt et al., 2014). Unregulated cells growth may be associated with a wide group of diseases, where cells become a lump or cause illness. As a result, several growth models related to tumours have appeared in the literature (Menchón and Condat, 2008; Aroesty et al., 1973), such as models for the metastasis (Pinho et al., 2002), the lack of nutrients (Scaleranpdi et al., 1999), the competition for resources, and the cytotoxic activity produced by the immune response (Cattani and Ciancio, 2008; Wheldon, 1988).

The most common malignant intrinsic primary tumours of the adult human brain are the gliomas (Inaba et al., 2011). Gliomas are tumours of the neoplastic glial cells. They are classified by the World Health Organisation as oligodendroglioma, astrocytoma, mixed oligoastrocytoma, and ependymoma (Louis et al., 2007; Goodenberger and Jenkins, 2012). Glioma causes regional effects by invasion, compression, and destruction of brain parenchyma, arterial and venous hypoxia (Cuddapah et al., 2014). There is release and recruitment of cellular mediators which disrupt normal parenchymal function (Ye and Sontheimer, 1999). Glioma cells migrate along blood vessels, displacing the junction among glial cells and blood vessels. This way, the glioma cells can extract nutrients from the bloodstream. Displacements produce disruptions of glial functions, compromising adequate delivery of glucose and oxygen to neurons (Cuddapah et al., 2014). Moreover, disruptions of glial cells affect the neurons, because they are responsible for delivering nutrients, to provide structural support to them

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(Glees, 1955), and to control the biochemical compositions of the fluid surrounding the neurons. The neurons are mainly responsible for the information processing from external and internal environments (Otis and Sofronie, 2008; Fieldes, 2006; Shaham, 2005). However, glial cells are also responsible for the processing of information by mediating the neural signal. Neurons and their synapses fail to function without glial cells.

Mathematical modelling of glioma is an extensively explored area with a large variety of mathematical models exploring multiple complexities. An approach to modelling glioma is to use differential equations for the total of cells. In this case, the model ignores the spatial aspects. Kronik et al. (2008) proposed a mathematical model using differential equations for glioma and the immune system interactions. They incorporated studies about improved immunotherapy schedules and interventions which can lead to a cure of glioma. There are models that consider the spatio-temporal evolution, such as partial differential equations (Harpold et al., 2007) and cellular automaton (Alarcón et al., 2003) since the evolution of glioma critically depends on spatial geometry.

In this paper, we propose a mathematical model using differential equations for the growth of glioma, where the glioma cells attack the glial cells (Bulstrode et al., 2012). Glioma rises from glial cells (Weille, 2014), and glioma cells never return to be glial cells, resulting in invasion and destruction of surrounding healthy tissue (Alberts et al., 1994; Hahn and Weinberg, 2002). In our model, we consider interactions among glial cells, neurons, glioma cells, and the chemotherapeutic agent. The novelty of our model was to introduce the interaction between glial cells and neurons. This interaction is biologically relevant since glial cells make crucial contributions to the formation, operation and adaptation of neural cells. Glial cells are essential for neuronal survival, once their removal causes neuronal death (Allen and Barres, 2009). With this in mind, the main features of our model are: (i) treatment will likely preserve glial cells, (ii) glioma can be eliminated, but not without also destroying neurons. If the treatment is ceased without the complete elimination of glioma cells, concentration of glioma cells increases, (iii) there is an optimal duration for the treatment that reduces significantly the number of glioma cells by preserving the levels of glial cells and minimising the impact on the neural populations.

A major impediment to chemotherapy delivery for the glioma is the blood brain barrier (BBB). The BBB is a unique physiological structure that regulates the movement of ions, molecules, cells between the brain tissue and the blood (Gao and Li, 2014). It is necessary to deliver anti-glioma drugs across the intact BBB to obtain an efficient treatment of glioma (Srimanee et al., 2014). There are chemotherapeutic agents that are capable of penetrating the BBB (Friedman et al., 2000). Yang et al. (2014) showed blood-brain barrier disruption through ultrasound for targeted drug delivery. Moreover, phenotypic heterogeneity of glioma contributes to failure of chemotherapy (Burrel et al., 2013). Gerlee and Nelander (2012) studied the impact of phenotypic switching on glioma growth and invasion.

2. Brain tumour model

Fig. 1 shows a diagram illustrating the many agents, and their interactions being considered in our model. The glioma cells only attack the glial cells. Neurons are not attacked by glioma cells, and they interact with glial cells. The chemotherapeutic agent behaves as a predator acting on all cells (Schuette, 2004).

There have been relevant studies that model the time and space evolution of gliomas. However, as mixed effect modelling techniques cannot be yet applied to spatiotemporal equations (Ribba et al., 2012), we have considered differential equations aiming to yield a simplified description of the biological process

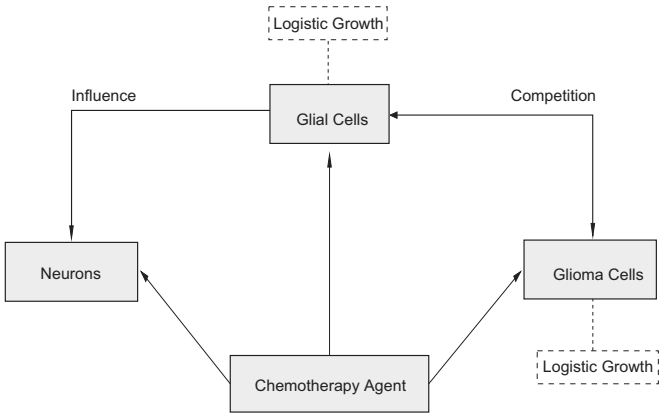

Fig. 1. Schematic representation of the agents (in grey coloured boxes), and their interactions (links) considered in our model.

according to schematic representation which is shown in Fig. 1. Our mathematical model describes the cells concentration, and the concentration of chemotherapeutic agent. Due to mixed effects we leave out spatial considerations, and our model is a new approach to modelling the dynamic evolution of the cells concentration in a brain tumour with glia–neuron interactions.

Our model is described by

$$\frac{dG(t)}{dt} = \Omega_1 G(t)\left(1-\frac{G(t)}{K}\right) - \Psi_1 G(t)C(t) - \frac{P_1 G(t)Q(t)}{A_1+G(t)}, \tag{1}$$

$$\frac{dC(t)}{dt} = \Omega_2 C(t)\left(1-\frac{C(t)}{K}\right) - \Psi_2 G(t)C(t) - \frac{P_2 C(t)Q(t)}{A_2+C(t)}, \tag{2}$$

$$\frac{dN(t)}{dt} = \psi \dot{G}(t)H(-\dot{G})N(t) - \frac{P_3 N(t)Q(t)}{A_3+N(t)}, \tag{3}$$

$$\frac{dQ(t)}{dt} = \Phi - \zeta Q(t), \tag{4}$$

where G represents the glial cells concentration (in kg/m^3), C represents the glioma cells concentration (in kg/m^3), N the neurons cells concentration (in kg/m^3), Q is the concentration of the chemotherapeutic agent (in mg/m^2), and $H(x)$ is the Heaviside function, defined as

$$H(x) = \begin{cases} 0, & x<0, \\ \frac{1}{2}, & x=0, \\ 1, & x>0. \end{cases} \tag{5}$$

Table 1 shows the parameters that we consider. In Eqs. (1) and (2), the first term is the logistic growth, the second term is the interaction between glial and glioma cells. This term is due to microglia cells, that are a type of glia, which act creating an active immune defense. They have the ability to generate innate and adaptive immune responses (Yang et al., 2010). The glioma is attacked by microglia, and as a result the glioma cells discharge immune suppressive factor to defend it by paralysing the immune effector mechanism (Ghosh and Chaudhuri, 2010). The last term of Eqs. (1) and (2) is the effect of the chemotherapeutic agent. We consider that the chemotherapy kills the cells with different intensities according to the Holling type 2 killing functions. Holling (1965) suggested kinds of functional responses to model phenomena of predation. Holling found that the predator has a Holling 2 functional response by taking into account the time a predator takes to handle the prey it has captured (Pei et al., 2005). The first term of Eq. (3) is related with the decrease in the neural population due to glial cells death, and the second term is the interaction with the chemotherapeutic agent. Eq. (4) describes the dynamics of the chemotherapeutic agent, presenting an exponential decay in concentration. The agent rate ζ in this equation is associated