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Modeling the dynamics of glioma-immune surveillance

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ABSTRACT

The proposed mathematical model describes how glioma cells evolve and survive the **brief** encounter with the immune system mediated by macrophages and the tumor specific CD8+T cells. We characterize the dynamics of the system by observing biologically realistic singular points and their stability analysis. The global asymptotic stability of the interior equilibrium point is studied with the help of Lyapunov method and we prove the uniform persistence by using the method of average Lyapunov function. The numerical **simulation** demonstrates that the model, with **the** parameter assumptions and values we used, is capable of reproducing glioma escape from immune surveillance in a biologically realistic time frame. We investigate the conditions under which **the macrophages can be infiltrated**, and identify the parameter values for which the inhibition of the gliomas proliferation is acquired.

1. Introduction

According to the National Brain Tumor Society, it has been estimated that around 7,00,000 peoples in the United states are living with primary brain tumors, and an estimated 78,980 will be diagnosed in the year 2018 [1]. It is not surprising that the researchers/scientists around the world have been trying to successfully model the brain tumor. The aim is to gain understanding of the complicated biological process, and to design better treatment strategies or improve existing strategies to eradicate the brain tumor or at least to improve the patients quality of life. Different types of mathematical models have already been developed, and each one contributes in their own way to a better understand the tumor and the dynamics which determine the patient's outcome.

Gliomas, the common name for a tumor arising from the supporting tissue of the brain, are highly diffuse and aggressive in primary brain tumors, accounting for about 50% brain tumors caused by malignancy of gliomas, and it has life expectancies 6th to 12th months. In most favorable conditions, the patients will die within 2 years [2]. Mathematical modeling is a viable tool provide realistic and quantitative representations of complex biological phenomena [6–12], and biological interpretation of their results could provide better insight to make realistic predictions of the state of gliomas under different conditions [10].

The World Health Organization (WHO) classified four grades of malignancy of gliomas: WHO grade I-IV. Among them Glioblastoma multiforme (GBM) WHO grade IV is the most frequent glioma and accounts for more than 50% of all primary brain tumors. Due to their genomic instability, heterogeneity, infiltrative behavior and the sequestered location beyond the blood brain barrier (BBB), malignant gliomas are difficult to conventional treatments, including chemotherapy, immunotherapy, surgery, radiation therapy and hormone therapy. The interesting thing is that, how our immune system responds to the development and progression of glioma cells, which is still an enigma in terms of its establishment and destruction [13].

Glioma cells use different ways to evade the surrounding normal tissues. One of them is a dramatic reduction in the expression of major histocompatibility complex (MHC) molecules on their surface, which weakens their detection by CD8+T cells. Gliomas secrete immunosuppressive factors, like TGF-β, prostaglandin E_2 and interleukin (IL)-10 can deactivate helper T cells (CD4+T), and stimulate the activity of regulatory T cells [23]. In the central nervous system (CNS), tumor-immune system cellular interactions are affected due to presence of the selective BBB. Only activated cytotoxic-T-lymphocytes (CD8+T cells) cross the BBB and enter into the brain [23]. Microglial cells are the brain resident macrophages which can protect the brain from the foreign antigen and destroy the foreign antibody by phagocytosis process [7,9].

The theoretical study of glioma-immune interactive dynamics has a long history. The substantial studies related to malignant gliomas modeling for invasion, proliferation and migration published before 2005 have been explored in the review article by Hatzikirou et al. [38]. There is a large body of work developed to study the tumor immune interaction through mathematical model [4,5,8,9,14,15,17–19,26–28,32,36,39], but few researchers worked on mathematical models to study the growth and control of malignant gliomas [2,6,7,10,11,16,20–22]. The interested reader is referred to

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see the references [3,10,29,34,35] for the mathematical description of the glioma-immune interactions through a system of reaction-diffusion equations, [37] for mathematical models of malignant gliomas growth through game theoretic approach, [21,31,33,41] to investigate the optimal treatment strategy in a glioma-immune model, [40] for the models to study glioma virotherapy to cure brain tumor, [30] for modelling the glioma-immune system interactions through Diffusion Tensor Imaging (DTI) data to predict the anisotropic pathways of brain tumor invasion. Leder et al. [41], employed a combined theoretical and experimental strategy with the aim of recognizing treatment protocols that would lead to superior survival in human models of gliomas by accounting the dynamic transitions of cells between radiosensitive and radioresistant pools. Painter and Hillen [30] constructed a microscopic phenomenological mathematical model for malignant gliomas proliferation and diffusion based on the isolated migration pathways of invading cells through the fibre tracts. Chakrabarty and Hanson [21] developed a mathematical model for the growth and control of malignant gliomas and applied the theory of optimal control techniques to minimize the cell count of malignant gliomas and reduce the detrimental effects of the drug by using Galerkin finite element method. Kronik et al. [6] considered the interactive dynamics of high grade malignant gliomas and their environment through a system of coupled nonlinear ordinary differential equations by exogenous administration of immune cells or immunoregulatory factor alloreactive cytotoxic-T-lymphocytes (aCTL) and they used computer simulations for model verification and retrieving putative treatment scenarios. Kim et al. [29] developed a mathematical model which elucidates the dynamics of glioblastomas multiforme (GBM) in presence of an immune system response using a coupled system of partial differential equations by considering the effects of cell-cell adhesion. They focused on the role of adhesion which gives an indispensable exposition for the numerous patterns of the cell migration. Basanta et al. [37] constructed a mathematical model of isocitrate dehydrogenase-1 (IDH-1) mutated secondary glioblastomas multiforme (GBM), by introducing evolutionary game theory to elucidate the interactive dynamics of the phenotypic population inside the malignant glioma cells.

The administration of membrane glycoprotein T11 target structure as a therapeutic agent has been shown to reverse the immune-suppressed state of malignant gliomas by boosting the functional status of immune cells including macrophages and activated CD8+T cells in animals. Modeling this treatment computationally can predict that treatment with T11 target structure can allow effect or cells of the immune system to overcome blood-brain-barrier (BBB) impermeability and lead to enhanced phagocytic activity and diminishing of malignant gliomas [7]. Iarosz et al. [22] constructed a biologically based mathematical model of brain tumor in which they introduce the interaction between glial cells and neurons using heaviside step function. In their model, they used chemotherapeutic treatment to inhibit the proliferation of malignant glioma cells. Tektonidis et al. [35] investigated a computational data-driven study in vitro of the proliferation and invasion of malignant glioma cells based on cellular automaton model. They focused on the identification of intrinsic cellular structures which determine the aggressiveness of malignant gliomas in vitro culture. Gerlee and Nelander [11] developed a biologically based mathematical model to analyze how the phenotypic switching between proliferative and migratory states of individual cells affects the macroscopic growth of the malignant gliomas. From their model they derive a continuum approximation in the form of two coupled partial differential equations, which demonstrates traveling wave solutions whose speed of invasion depends on the system parameters. Papadogiorgaki et al. [34] developed a continuous three dimensional mathematical model for gliomas evolution which consists of four different phenotypes of malignant glioma cells, namely proliferation, hypoxia, hypoglychemic and necrotic, and the tissue micro-environment through a nonlinear system of reaction-diffusion equations.

In this article, we propose a biologically based mathematical model using a system of coupled nonlinear ordinary differential equations for the growth and control of malignant glioma cells, where the glioma cells attack macrophages [24]. In our model, we consider interaction among malignant glioma cells, macrophages and the glioma specific CD8+T cells. The main thrust of this paper is to introduce the dynamic relationship between glioma cells and macrophages. The special attention is paid to the local asymptotic stability of the total annihilation of the glioma cells, as well as the case of interior equilibrium point under which the tumor cells cannot be eliminated. This will provide a clearer idea to design better treatment strategies or to improve existing policies to eradicate the brain tumor or at least to improve the patients' quality of life which is the main goal of this paper.

The paper is organized in the following way: Section 2, briefly introduced the formulation of the mathematical model and its non-dimensional form. Section 3 is devoted to the basic properties of the mathematical model including positivity and boundedness of the system. In the same section, we provide the stability analysis of the feasible equilibrium points. Section 4 presents rigorous numerical simulations of different scenarios of the mathematical model. Finally, our paper ends with a brief discussion.

2. The mathematical model

The most popular mathematical models in theoretical immunology involve the system of ODEs to represent reaction kinetics. In general, the equations are used to represent concentration of cells and/or molecules and the parameters represent kinetic or affinity constants. PDEs are generally used to have a spatial representation of the diffusion of reagents or, as in the case of malignant glioblastoma, when one wants to investigate the glioma development and the scenarios of vascularization [3]. In this article, we formulate a simple mathematical model which shows a quite interesting and rich dynamics that fits reasonably to that of the glioma-immune interaction observed at the level of the cell population.

A mathematical model is aimed at yielding a simplified description of the complicated biological scenarios. By singling out the vital forces in the system and deliberately ignoring secondary effects, the analytical power of the model is importantly sharpened. Our mathematical model focuses on the main interaction between three cells concentration, namely, malignant glioma cells, macrophages and glioma-specific CD8+T cells. The mathematical expressions we have chosen for describing the model conform with standards of mathematical immunology set by works such as references [6–8,22]. Our mathematical model is described by

$$\begin{aligned}
\frac{dG(t)}{dt} &= r_1 G(t)\left(1-\frac{G(t)}{G_{\max}}\right) - \frac{(\overline{\alpha}_1 M(t)+\overline{\alpha}_2 C_T(t))}{G(t)+\overline{k}_1}G(t),\\
\frac{dM(t)}{dt} &= r_2 M(t)\left(1-\frac{M(t)}{M_{\max}}\right) - \alpha_3\frac{G(t)M(t)}{G(t)+\overline{k}_2},\\
\frac{dC_T(t)}{dt} &= \frac{\gamma_1 G(t)C_T(t)}{\overline{k}_3+G(t)} - \mu_1 C_T(t) - \alpha_4\frac{G(t)C_T(t)}{G(t)+\overline{k}_4},
\end{aligned} \tag{1}$$

where $G(t)$ represents the glioma cells concentration, $M(t)$ corresponds to the density of macrophages and $C_T(t)$ is the concentration of glioma specific CD8+T cells at any time t. The first term on the right hand side of the first Eq. (1) stands for gliomas growth with no immune intervention, using standard logistic growth fashion. The expression utilizes the concept of carrying capacity, that