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A mathematical model of pre-diagnostic glioma growth

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Abstract

Due to their location, the malignant gliomas of the brain in humans are very difficult to treat in advanced stages. Blood-based biomarkers for glioma are needed for more accurate evaluation of treatment response as well as early diagnosis. However, biomarker research in primary brain tumors is challenging given their relative rarity and genetic diversity. It is further complicated by variations in the permeability of the blood brain barrier that affects the amount of marker released into the bloodstream. Inspired by recent temporal data indicating a possible decrease in serum glucose levels in patients with gliomas yet to be diagnosed, we present an ordinary differential equation model to capture early stage glioma growth. The model contains glioma-glucose-immune interactions and poses a potential mechanism by which this glucose drop can be explained. We present numerical simulations, parameter sensitivity analysis, linear stability analysis and a numerical experiment whereby we show how a dormant glioma can become malignant.

Keywords

glioma; blood biomarker; glucose; parameter sensitivity analysis

1. Introduction

Gliomas, the most common primary brain tumors, are thought to arise from the supporting glial cells of the brain or their precursors (Sanai et al. 2005). They generally grow and invade extensively before the patient experiences any symptoms, which makes gliomas almost impossible to cure. Glioblastomas are the most malignant and most common gliomas in adults, accounting for about 50% of all gliomas. Glioblastomas are distinguished by necrosis, which may be massive centrally or more irregular between vascular supplies, and peripheral cells that diffusely invade the surrounding tissue. The aggressive behavior of these tumors is reflected in their nearly 100% fatality rate within six to twelve months from the time of diagnosis (Stylli et al. 2005; Lonardi et al. 2005). Surgery is the main treatment

option and is generally followed by radiotherapy and chemotherapy but these treatments typically merely prolong the patient's life by a few weeks. Recent observational data (see Table 1) as well as some cell culture studies (Flavahan et al. 2013) has revealed that patients with lower serum glucose levels are at higher risk of developing high-grade gliomas. The data presented in Table 1 is taken from Edlinger et al. (2012) who studied a large cohort of over half a million participants in the Metabolic Syndrome and Cancer Project. These participants ranged between 15 to 99 years of age at baseline (between 1972 and 2005) from several European countries. The glioma patients in that cohort showed a general trend where the lower the pre-diagnostic serum glucose levels, the higher the hazard ratio of the glioma occurrence. In fact, more recent data has revealed that a decline in serum glucose levels is correlated with probability of subsequent diagnosis with glioma and that this decline can appear up to 9 years prior to the diagnosis (see, e.g., Schwartzbaum et al. 2005) – suggesting that a new blood-based screening process may aid in the early detection of these deadly tumors. Indeed, recent advancements in technology have made the non-invasive daily monitoring of serum glucose levels a real possibility in the near future – see Vashist (2012) for a review. In this paper, we consider a mathematical model of the early growth of gliomas in order to delineate the mechanism underlying the drop in glucose levels in the blood associated with glioma growth.

Mathematical modeling of glioma growth has had a long and rich history and we direct the reader to Hatzikirou et al. (2005) and Harpold et al. (2007) for detailed reviews. These mathematical models can be extremely helpful in analyzing factors that may contribute to the complexity intrinsic to glioma growth and in optimising treatment protocols. Some of these models have investigated spatial aspects of glioma growth through the use of partial differential equations that utilise MRI scans to make the domain more realistic (Powathil et al. 2007; Swanson et al. 2003; Toma et al. 2012) while others have used ordinary differential equations (ODEs) to solely look at the temporal evolution of gliomas (Ribba et al. 2012). Lattice-gas cellular automaton models have also been used to model glioma progression in a spatially explicit manner (Tektonidis et al. 2011). Recent efforts have been concentrated on multi-scale approaches that keep track of intracellular processes as well as macroscopic features such as oxygen distributions (Powathil et al. 2012; Schütz et al. 2012; Deroulers et al. 2009). We wish to highlight that a common feature of all these previous mathematical models is the fact that they are primarily interested in the evolution of a post-diagnosed glioma. The major difference in the model we present here is that it is of a pre-diagnosed glioma and we are interested in how the glioma growth influences serum-glucose levels.

One of the reasons for the slow growth of tumors and, in some cases, for their regression, may be the reaction of the host immune system to the nascent tumor cells. It has been demonstrated that tumor-associated antigens can be found on tumor cells at very early stages of tumor progression (Flavahan et al. 2013). These changes are sufficient for intensive lymphoid, granulocyte and monocyte infiltration of a tumor. Especially pronounced infiltration may correlate with a favourable prognosis (Lord and Burkhardt 1984). The early stage and the subsequent stages of tumor growth are characterized by a chronic inflammatory infiltration of neutrophils, eosinophils, basophils, monocytes/macrophages, T-lymphocytes, B-lymphocytes and natural killer (NK) cells (Lord and Wilson 1987). These cells drill deep into the interior of the tumor and accumulate in it due to attractants secreted

from the tumor tissue and the high locomotive ability of activated immune cells (Ratner and Heppner 1986). Indeed during the avascular stage, tumor development can be effectively eliminated by tumor-infiltrating cytotoxic lymphocytes (TLs) (Loeffler and Ratner 1989).

Generating an efficient and effective immune response involves large increases in cellular proliferative, biosynthetic, and secretory activities, which all require high energy consumption. Adaptive as well as innate immune cells must be able to rapidly respond to the presence of pathogens, shifting from a quiescent phenotype to a highly active state within hours after stimulation. For that purpose, cells must dramatically alter their metabolism in order to support these increased synthetic activities based on extracellular signals and various fuels, amongst which glucose is the most essential one (Wolowczuk et al. 2008). In addition, one of the primary sources of nutrients for gliomas is glucose and indeed it was reported in (Ishikawa et al. 1993) that higher glucose consumption indicated poorer prognosis in patients with high-grade gliomas, regardless of the treatments given. Similar finding for prostate cancer is described in Van Hemelrijck et al. (2011) and, more recently, in Häggström et al. (2014) who found that the prostate tumors are inversely related to prediagnostic metabolic syndrome, a condition which also includes elevated serum glucose concentration. To our knowledge though, the prostate cancer is the only cancer besides glioma which growth has been found to be negatively related to serum glucose levels.

The format of this paper is as follows. In the next section we introduce the mathematical model, detailing our modeling assumptions as well as introducing parameter values and initial conditions. In the subsequent section, we present numerical simulations of our model showing how the initial conditions can lead to different behaviors. Next, we perform a parameter sensitivity analysis in order to bring to light which model parameters are important and sensitive to change. We then perform a linear stability analysis of the steady states of the model. Motivated by our analysis, we suggest a mechanism by which a dormant glioma can become large and aggressive. We conclude with a discussion and place our work within the context of a bigger ongoing project which seeks to unearth blood-biomarkers for early detection of gliomas.

2. The mathematical model

We consider a simplified process of a small glioma growing in the brain which elicits a response from the host immune system. Both the host immune system and the glioma require energy to sustain their functions. Therefore, we also keep track of an energy source in our model, specifically in the form of glucose (which can exist in the brain or blood). Our model consists of four variables denoted T , σ_{brain} , I and σ_{serum} which represent the concentration of glioma cells, the concentration of glucose in the brain, the concentration of immune system cells and the concentration of serum glucose levels respectively. The basic assumptions regarding the interactions between our model variables follow previous modelling efforts (Kim 2013; Matzavinos and Chaplain 2003; Man et al. 2007). Figure 1 shows a schematic diagram of the interactions we consider which are also described by the following system of differential equations

$$\frac{dT}{dt} = \underbrace{\alpha_T \sigma_{\text{brain}} T (1 - T/K_T)}_{\text{production}} - \underbrace{d_{TT}}_{\text{apoptosis}} T - \underbrace{d_{TI} TI}_{\text{immuneresponse}}, \quad (1)$$

$$\frac{d\sigma_{\text{brain}}}{dt} = \underbrace{\alpha_\sigma (\sigma_{\text{serum}} - \sigma_{\text{brain}})}_{\text{glucose exchange}} - \underbrace{d_{T\sigma} T \sigma_{\text{brain}}}_{\text{glioma consumption}} - \underbrace{(d_{\sigma_1} + \alpha_s (\nu + I)) \sigma_{\text{brain}}}_{\text{natural consumption}}, \quad (2)$$

$$\frac{dI}{dt} = \underbrace{\alpha_s (\nu + I) \sigma_{\text{brain}} + \alpha_{TI} TI}_{\text{production/recruitment}} - \underbrace{d_I I}_{\text{natural decay}} - \underbrace{d_{TI} TI}_{\text{glioma response}}, \quad (3)$$

$$\frac{d\sigma_{\text{serum}}}{dt} = \underbrace{\alpha_\sigma (\sigma_{\text{brain}} - \sigma_{\text{serum}})}_{\text{glucose exchange}} + \underbrace{F(t)}_{\text{glucose intake}} - \underbrace{d_{\sigma_2} \sigma_{\text{serum}}}_{\text{natural consumption}}, \quad (4)$$

subject to the following initial conditions:

$$T(0) = T_0, \quad \sigma_{\text{brain}}(0) = \sigma_{\text{brain}_0}, \quad I(0) = I_0, \quad \sigma_{\text{serum}}(0) = \sigma_{\text{serum}_0}$$

where T_0 , σ_0 , and I_0 are positive constants. The initial conditions are particularly important in our model – as stated earlier, we are not seeking to explain the mechanisms by which a single glioma cell first originates but rather how a glioma grows and interacts with glucose and the immune system in the early stages of its development. Hence we choose a non-zero value for the glioma concentration at time $t = 0$. The equations in our model follow mass-action kinetics. Equation (1) is an ODE which governs the temporal evolution of glioma growth. We assume the glioma undergoes logistic growth with parameter α_T and carrying capacity K_T and we also assume this growth depends on the amount of glucose available in the brain. The glioma is also assumed to undergo apoptosis at a rate d_T as well as enhanced degradation due to the immune system response at a rate d_{TI} . The ODE given by equation (2) governs the evolution of the glucose concentration in the brain. The first term in this equation represents the transfer of glucose from the blood to the brain (which occurs via the blood-brain barrier). We assume there is an exchange of glucose from the serum to the brain at a rate α_σ which depends on the difference in the glucose levels in the serum and brain compartments. Glucose in the brain is also assumed to be consumed by the glioma at rate $d_{T\sigma}$ (see, e.g., Flavahan et al. 2013), by the brain for natural brain activity at rate d_{σ_1} and by the immune system at rate $\alpha_s \nu$. There is also an immune system dependent rate of consumption of glucose in the brain at a rate α_s . The third ODE given by equation (3) models the evolution of immune system activity in the brain. We assume that there is a basal production rate of immune system cells at rate $\alpha_s \nu$ as well as an immune system dependent production at rate α_s . Immune system cells are also assumed to be recruited to the growing glioma at a rate α_{TI} . We also assume the immune system cells undergo some natural degradation (at rate d_I) and degradation in response to interacting with glioma cells (at rate d_{TI}). The final ODE captures the evolution of serum glucose levels. As in equation (2), the first term represents the exchange of glucose between the brain and serum compartments (at

a rate α_0). The second term captures glucose intake and we chose the glucose intake function, $F(t)$, to follow Man et al. (2007), i.e.

$$F(t) = \max\{\sigma_{\min}, \sigma_0 \sin(6\pi t)\}. \quad (5)$$

A visualisation of this function is presented in the subplot of Figure 8. To remove the possibility of $F(t)$ giving negative values we set a minimal allowed value of glucose ($\sigma_{\min}$). This reflects the fact that the human body needs a certain amount of energy each day in order to function. We also set a maximum amount of variation in daily glucose levels which is given by parameter σ_0 . We note that this function can take a variety of different forms to reflect different diets and we explore this idea in section 6. Finally, the metabolic consumption of serum glucose is captured in the final term and occurs at rate d_{o2} . The baseline parameter set we use for exploring the behavior of our model is presented in Table 2 along with descriptions and a reference (where possible).

3. Numerical simulations

In this section, we present numerical simulations of our model, i.e., equations (1)–(4). For all numerical simulations we used the MATLAB ODE solver ‘ode45’ and solve for a time corresponding to 9 years. We note that, for comparison, we have also tried a range of different solvers such as ‘ode23s’ and ‘ode15s’ and found no quantitative change in the numerical solution. As indicated earlier, this value is consistent with the recent observational data and the parameter estimates presented in Table 2. We consider three different initial conditions which are motivated by the steady states of the model. These steady states are discussed in Section 5.

$$(T_1, \sigma_{\text{brain}_1}, I_1, \sigma_{\text{serum}_1}) \approx (0.14, 3.92 \times 10^{-4}, 2.84 \times 10^{-4}, 4.39 \times 10^{-4}), \quad (6)$$

$$(T_2, \sigma_{\text{brain}_2}, I_2, \sigma_{\text{brain}_2}) \approx (0.0498, 8.28 \times 10^{-4}, 0.016, 8.86 \times 10^{-4}), \quad (7)$$

$$(T_3, \sigma_{\text{brain}_3}, I_3, \sigma_{\text{brain}_3}) \approx (0, 8.45 \times 10^{-4}, 0.061, 8.81 \times 10^{-4}), \quad (8)$$

The initial conditions are presented in units of *g/ml*. We note that using the fact that 1 glioma cell has a volume of approximately 10,000 *fl* or $1 \times 10^{-8} \text{ml}$ (Watkins and Sontheimer 2011) and also the fact that within 1 g there are approximately 1×10^9 cells (Monte 2009) then initial condition (6) corresponds to a glioma of size 1.4×10^8 cells and initial condition (7) corresponds to a glioma of size 4.98×10^7 cells. Figure 2 shows how the numerical solution evolves when the first initial condition is used. The glioma grows slowly over the course of 9 years which in turn causes the glucose levels in the brain to decrease as the glioma consumes the glucose. The immune system activity increases initially in response to the growing glioma but then decreases as the glioma cells attack the immune system cells. As a result of the glioma increasing in concentration, the serum glucose levels show a marked drop (more glucose must be delivered to the brain to feed the growing glioma and immune system activity). For this initial condition, we can interpret the system as evolving

to an ‘aggressive glioma’ steady state. We highlight healthy serum glucose levels using two horizontal lines (values given by $7 \times 10^{-4} \text{g/ml}$ and $11 \times 10^{-4} \text{g/ml}$) in the lower right panel. It can be observed that the serum glucose levels drop below the healthy range at approximately 5.5 years in response to the growing glioma.

In Figure 3 we show how the system evolves when subject to the second initial condition. Here, in contrast to Figure 2 the glioma does not grow with respect to time but remains at a low level. As a result of this, both the immune system activity and glucose levels in the brain remain unchanged. The serum glucose levels remain high throughout the simulation, there is no discernible drop. This steady state can be interpreted as a ‘glioma dormancy’ steady state, in which the glioma is kept under control by the immune system. Our model suggests that using serum glucose levels as a blood-based biomarker may not be able to aid in the detection of such a dormant glioma. This highlighted by the fact that the serum glucose levels always remain within the dotted lines which indicate healthy serum glucose levels.

Finally we show in Figure 4 how the model variables evolve subject to the third initial condition. For this case, there is no glioma present in the system. The glucose levels in the brain and immune system activity do not vary and may be associated with those of a healthy host. Serum glucose levels remain relatively high throughout the simulation but are still within the normal range marked by horizontal lines. This initial condition gives rise to what we interpret as a ‘healthy steady state’.

4. Parameter sensitivity analysis

In this section, we explore the significance of our model parameters by using sensitivity analysis. The baseline parameters chosen (see Table 2) were either taken from similar cancer models in the literature or estimated. We did not obtain our parameters directly from patients with gliomas, hence there is uncertainty regarding their precise values. Sensitivity analysis is a powerful tool in ranking the importance of random inputs and quantifying their interactions. We applied the uncertainty quantification method – SGPCM (Xiu and Hesthaven 2005) to achieve faster convergence in the uncertainty quantification process. The general procedure of the PCM approach is similar to that of the MC method except that different sampling points and corresponding weights are selected. The procedure of the PCM consists of the following three main steps:

1. Generate N_c collocation points in the probability space of random parameters ξ as independent random inputs based on a quadrature formula (see Xiu and Hesthaven 2005);
2. Solve a deterministic problem at each collocation point;
3. Estimate the solution statistics (typically its mean and variance) using the corresponding quadrature rule.

Global sensitivity analysis is obtained from PCEs in order to identify the dominant sources of uncertain parameters and their attributes. Generally, PCEs of a second-order stochastic processes with d number of independent random variables can be expressed as

$$g(x_1, \dots, x_d) = \sum_{k=0}^{K-1} c_k \Psi_k(\mathbf{x}),$$

where $\mathbf{x} = (x_1, \dots, x_d)$ is a set of independent random variables, $\Psi_k(\mathbf{x})$ are multidimensional orthogonal polynomials with regard to the inner product, and c_k are the deterministic polynomial chaos coefficients of g . In our model, we take g as the steady-state tumor size T^* or serum glucose level G^* , $\mathbf{x}$ as the random variable supported on the d -dimensional cube centered at the literature-based parameter values from Table 2, and $\Psi_k(\mathbf{x})$'s are the system of Legendre polynomials. For this model the global sensitivity analysis based on variance decomposition is employed with the total variance defined as

$$\text{Var}[g(\mathbf{x})] = \sum_{k>0} c_k^2 \|\Psi_k(\mathbf{x})\|^2,$$

where $\|\Psi_k(\mathbf{x})\|$ can be pre-computed, and c_k is calculated using the sparse grid probabilistic collocation method and the orthogonal property of polynomial chaos. Then the first-order (or main) effect sensitivity indices of S_i are

$$S_i = \frac{\text{Var}[\mathbb{E}(g(\mathbf{x}|x_i))]}{\text{Var}[g(\mathbf{x})]} = \frac{\sum_{k \in \mathbb{I}_i} c_k^2 \|\Psi_k(\mathbf{x})\|^2}{\sum_{k>0} c_k^2 \|\Psi_k(\mathbf{x})\|^2},$$

where $\mathbb{I}_i$ is the set of bases with only x_i involved. S_i is the uncertainty contribution that is due to i -th parameter only. Similarly, the joint sensitivity indices can be written as

$$S_{ij} = \frac{\text{Var}[\mathbb{E}(g(\mathbf{x}|x_i, x_j))]}{\text{Var}[g(\mathbf{x})]} - S_i - S_j = \frac{\sum_{k \in \mathbb{I}_{ij}} c_k^2 \|\Psi_k(\mathbf{x})\|^2}{\sum_{k>0} c_k^2 \|\Psi_k(\mathbf{x})\|^2},$$

where $\mathbb{I}_{ij}$ is the set of bases with only x_i and x_j involved. S_{ij} is the uncertainty contribution that is due to (i, j) parameter pair.

The outputs we are interested in are the glioma and serum glucose concentrations at steady state. We use sensitivity analysis to understand how input uncertainties propagate through the model equations (1)–(4) and how the model responds to variation in values of these parameters. The total variance of glioma concentration is decomposed by using an Analysis Of Variance technique (ANOVA). We remark that the sensitivity analysis performed in the present paper can be extended to inverse modeling and calibration of model parameters to improve its predictive power. The relationships between the output responses and input parameters (response curves or surfaces) can also be used to develop reduced-order models for the subset of processes, which can then be used to perform more extensive uncertainty quantification of the complete model. In this study, we apply the Sparse Grid Probabilistic Collocation Method (SGPCM) (Xiu and Hesthaven 2005) to study the uncertainty quantification process which has a fast convergence rate. We made use of the SGPCM and generated 1024 samples to calculate the first-order effect sensitivity indices and the joint (or second-order) sensitivity indices. The sensitivity analysis results are shown in Figures 5 and

6. A positive correlation means that an increase in the parameter value will increase the glioma or serum glucose concentration while a negative correlation means an increase in the parameter will decrease the glioma or serum glucose concentration.

As can be seen from Figure 5, d_{TT} (the rate at which glioma cells kill immune system cells) is the most sensitive parameter with respect to changing glioma concentration. This can be understood because the glioma growth will be unimpeded by immune system cells if there are less immune system cells to attack the glioma cells. Our sensitivity analysis suggests that if the rate of destruction of immune system cells by glioma cells is increased a small amount, then the glioma will increase in size significantly. We also highlight the co-sensitivity of parameter pairs (σ_0, d_{TT}) , (d_{TI}, ν) and (d_{TT}, a_T) . These three co-sensitive pairs are consistent with intuition and can be understood by the following reasoning. If the parameters σ_0 and d_{TT} are increased a small amount then this will result in an increase in the overall glioma size as the glioma will have more glucose to consume and less degradation due to the immune system cells. Similarly, if the parameters d_{TI} and ν are increased a small amount then this will result in a decrease in the overall glioma concentration as the glioma cells will be destroyed more often by immune system cells and there will be more immune system cells available to do this. Lastly, we note that if the parameters d_{TT} and a_T are increased a small amount then this will result in an increase in the overall glioma concentration due to the fact that glioma cell production will be increased and the destruction of immune system cells will also be increased.

In Figure 6 we present the sensitivity analysis results using serum glucose levels as the output of interest. It can be observed the sensitivity shifts when considering serum glucose concentration as the output as opposed to glioma concentration. Notably, parameters α_s and ν are no longer sensitive to change, however, parameters σ_0 and d_{TT} remain sensitive to change. As with the previous figure, we highlight the co-sensitivity of certain parameter pairs. The parameter pair (σ_0, d_{TT}) is counter-intuitive and highlights the benefit of performing such a parameter sensitivity analysis. If the parameters σ_0 and d_{TT} are increased a small amount at the same time then the serum glucose concentration will decrease (despite σ_0 increasing the serum glucose concentration if increased by itself). We also note that the parameter pair (d_{TI}, a_{TI}) results in an overall decrease in the serum glucose concentration if increased. With the knowledge of the most sensitive parameters in our model, we can focus on obtaining experimental measurements for these specific parameters (σ_0 , d_{TT} , d_{TI} , a_T and α_s) as we know that they will have the biggest influence on the output of the model.

5. Local linear stability analysis

Steady states of our mathematical model can be written by setting the left hand side equal to zero, i.e.,

$$\begin{aligned} 0 &= \alpha_T \sigma_{\text{brain}}^* T^* (1 - T^*/K_T) - d_T T^* - d_{TI} T^* I^*, \\ 0 &= \alpha_\sigma (\sigma_{\text{serum}}^* - \sigma_{\text{brain}}^*) - d_{T\sigma} T^* \sigma_{\text{brain}}^* - (d_{\sigma_1} + \alpha_s (\nu + I^*)) \sigma_{\text{brain}}^*, \\ 0 &= \alpha_s (\nu + I^*) \sigma_{\text{brain}}^* + \alpha_{TI} T^* I^* - d_I I^* - d_{TT} T^* I^*, \\ 0 &= \alpha_\sigma (\sigma_{\text{brain}}^* - \sigma_{\text{serum}}^*) - d_{T\sigma} T^* \sigma_{\text{brain}}^* + F(t) - d_{\sigma_2} \sigma_{\text{serum}}^*, \end{aligned}$$

where asterisks denote system variables at steady state. For the case where $T^* = 0$, i.e., no glioma exists, we find the following steady state solutions

$$\begin{aligned} T^* &= 0, \\ 0 &= \alpha_\sigma (\sigma_{\text{serum}}^* - \sigma_{\text{brain}}^*) - (d_{\sigma_1} + \alpha_s (\nu + I^*)) \sigma_{\text{brain}}^*, \\ 0 &= \alpha_s (\nu + I^*) \sigma_{\text{brain}}^* - d_I I^*, \\ 0 &= \alpha_\sigma (\sigma_{\text{brain}}^* - \sigma_{\text{serum}}^*) + F(t) - d_{\sigma_2} \sigma_{\text{serum}}^*, \end{aligned}$$

This steady state system corresponds to a healthy patient who doesn't have a glioma and has a healthy immune system. It is possible to find a quadratic expression σ_{brain}^* which can be solved to yield two steady states. For the case in which $T^* > 0$ we find a quartic equation in terms of T^* . Therefore, each parameter set permits six distinct steady states. For a realistic parameter set (using values from the literature) we find that three of these steady states are biologically feasible and three are infeasible (due to being negative or complex).

As an example, for the parameter set presented in Table 2 it is straightforward to show that the system of equations (1)–(4) has 6 steady states given by

$$\begin{aligned} \begin{pmatrix} T_1^*, \sigma_{\text{brain}_1}^*, I_1^*, \sigma_{\text{serum}_1}^* \end{pmatrix} &\approx (0, 845 \times 10^{-4}, 0.061, 8.81 \times 10^{-4}), \\ \begin{pmatrix} T_2^*, \sigma_{\text{brain}_2}^*, I_2^*, \sigma_{\text{serum}_2}^* \end{pmatrix} &\approx (0.0498, 8.28 \times 10^{-4}, 0.016, 8.86 \times 10^{-4}), \\ \begin{pmatrix} T_3^*, \sigma_{\text{brain}_3}^*, I_3^*, \sigma_{\text{serum}_3}^* \end{pmatrix} &\approx (1.53, 3.27 \times 10^{-4}, 2.84 \times 10^{-4}, 3.65 \times 10^{-4}), \\ \begin{pmatrix} T_4^*, \sigma_{\text{brain}_4}^*, I_4^*, \sigma_{\text{serum}_4}^* \end{pmatrix} &\approx (0, 0.69, -1.27, 0.07), \\ \begin{pmatrix} T_5^*, \sigma_{\text{brain}_5}^*, I_5^*, \sigma_{\text{serum}_5}^* \end{pmatrix} &\approx (-0.04, -0.06, -1.25, -0.06), \\ \begin{pmatrix} T_6^*, \sigma_{\text{brain}_6}^*, I_6^*, \sigma_{\text{serum}_6}^* \end{pmatrix} &\approx (2.19, 2.12, -4.41, 2.11), \end{aligned} \quad (9)$$

It is clear that steady states $(T_4^*, \sigma_{\text{brain}_4}^*, I_4^*, \sigma_{\text{serum}_4}^*)$, $(T_5^*, \sigma_{\text{brain}_5}^*, I_5^*, \sigma_{\text{serum}_5}^*)$ and $(T_6^*, \sigma_{\text{brain}_6}^*, I_6^*, \sigma_{\text{serum}_6}^*)$ are biologically unrealistic (given the negative value for some of the steady states).

Now let, $X_i = (T - T_i^*, \sigma_{\text{brain}} - \sigma_{\text{brain}_i}^*, I - I_i^*)^T$, $i=1,2,3,4,5,6$. By linearizing about each steady state, $(T_i^*, \sigma_{\text{brain}_i}^*, I_i^*)$, we obtain the following linear system:

$$\frac{d\mathbf{X}_i}{dt} = \mathbf{A}_i \mathbf{X}_i$$

where $\mathbf{A}_i$ is the Jacobian matrix of the system evaluated at the corresponding steady state. It can be shown that for $i = 1$, there are three real eigenvalues of $\mathbf{A}_i$, which are all negative.

Thus, $(T_1^*, \sigma_{\text{brain}_1}^*, I_1^*, \sigma_{\text{serum}_1}^*)$, which represents the 'healthy' steady state, is stable. For $i = 2$, there are three real eigenvalues of $\mathbf{A}_i$, two negative and one positive. Hence, $(T_2^*, \sigma_{\text{brain}_2}^*, I_2^*)$, which could be interpreted as a 'small dormant glioma' steady state, is unstable. For $i = 3$, which we interpret as the 'aggressive glioma' steady state, we find three negative real eigenvalues. Therefore, $(T_3^*, \sigma_{\text{brain}_3}^*, I_3^*)$ is stable. Due to the fact that our model contains two stable steady states and one unstable steady state, it can be described as a bistable system. Finally, for $i = 4,5,6$, which are the biologically infeasible steady states, we find at least one positive eigenvalue for each of them rendering them all unstable.

The parameter d_{TT} represents the rate at which glioma cells eradicate immune system cells and our parameter sensitivity analysis highlighted this parameter as the most sensitive to change. Therefore, in Figure 7 we demonstrate the effect of varying the parameter d_{TT} on the value of the three biologically feasible steady states. The first column of Figure 7 shows the effect that varying d_{TT} has on the healthy steady state. As can be seen, this steady state is completely unchanged by varying parameter d_{TT} and this makes sense, because if there are no glioma cells, then there will exist no interaction between glioma and immune system cells. The glioma dormancy steady state is shown in column 2 of Figure 7. Interestingly, as d_{TT} is increased the concentration of the dormant glioma decreases and the three other model variables increase. We wish to highlight that the idea of the glioma diminishing in size as its ability to eradicate immune system cells increases is somewhat unexpected. The final column shows the aggressive glioma steady state and we find that, consistent with intuition, the glioma size increases with increasing d_{TT} at the expense of the other model variables. Specifically, the immune system levels diminish and glucose levels are consumed by the growing tumor causing their levels to diminish also. We also checked the stability of the steady states as d_{TT} was varied and note that the stability of the steady states were unchanged by varying this particular parameter.

6. Sudden large glioma growth: the effect of increasing variation in the host's glucose intake

In this section, we present a mechanism by which our model can jump from the unstable glioma dormancy steady state (see Figure 3) to the stable aggressive glioma steady state (see Figure 2). To do this, we change the form of the glucose intake function, $F(t)$ to take the following form

$$F_2(t) = \begin{cases} \sigma_0, & \text{if } t < 3 \text{ years,} \\ 2\sigma_0, & \text{if } 3 \text{ years} \leq t \leq 13 \text{ years,} \\ \sigma_0, & \text{if } t > 13 \text{ years.} \end{cases}$$

This step-function is visualised in Figure 8 along with the daily glucose intake for the increased glucose intake (depicted by a red line) and the baseline glucose intake (shown by a green line). The three peaks correspond to the three daily meals which the host consumes. One interpretation of this increased intake of glucose could be that the host adopts a glucose rich diet after 3 years for 10 years in total. We use initial condition 2 as defined in equation (7) which yields the glioma dormancy steady state using the baseline parameter set. In this scenario, time $t = 0$ corresponds to the age when the host develops a dormant glioma.

Interestingly, the solution now tends to the aggressive glioma steady state (even though the baseline levels of glucose are resumed after 13 years). The transient increase in the glucose variation is enough to perturb the system away from the glioma dormancy steady state (which is unstable). Again, our models shows a drop in serum glucose levels as the glioma grows in size (this is particularly evident from 24 to 27 years). This is consistent with what we observed in Figure 2. We also note that other researchers have found a link between diets

and cancer (see Key et al. (2002) for a review). Indeed, studies in animals have shown that energy restriction can substantially reduce incidence of cancer (Kari et al. 1999).

7. Discussion

In this paper, we have presented a mechanistic ordinary differential equation model of glioma growth. Motivated by the emergence of recent temporal data which appears to show a decline in serum glucose levels in the early years of glioma growth, we focussed on glioma-glucose-immune interactions. Our model captures a possible mechanism by which the serum glucose drop can be explained. Essentially, as a glioma begins to grow in the brain, an immune response is elicited which in turn combats the growth of the glioma. The combination of the growing glioma and the immune response requires a lot of energy (which we assume to be predominately in the form of glucose) to be transferred from the blood to the brain via the blood brain barrier. This shift in glucose from the serum to the brain causes a decline in serum levels.

The behavior of our model was sensitive to the initial conditions we adopted. In fact, by solving the steady state equations we showed that our model has six possible steady states and we interpreted these as the model exhibiting a healthy steady state (where the glioma levels were zero), a glioma dormancy steady state (small glioma level), an aggressive glioma steady state (high glioma concentration) and three biologically unfeasible steady states (negative value for at least one variable). We also performed a linear stability analysis for each of the six steady states.

Given the relative simplicity of our model, we were able to perform a thorough parameter sensitivity analysis. We used the glioma and serum glucose concentrations as measures of sensitivity. The result of this parameter sensitivity analysis unearthed the glucose intake rate as the most sensitive parameter with respect to glioma concentration and serum glucose concentration. We went on to confirm this by analyzing the effects of changing the glucose intake rate in Section 6. Essentially, we performed a simple numerical experiment to highlight the potential usefulness of having a mathematical model of early-stage glioma growth. By simply increasing the variation in the host's glucose intake for a finite time, we showed that our model could 'jump' from the glioma dormancy steady state to the aggressive glioma steady state. Our model can be used to test various hypothetical scenarios related to glioma-glucose-immune system interactions very cheaply which may be very expensive or unethical in a laboratory setting.

We also found that the parameter d_{TT} was sensitive to change with respect to glioma concentration and we investigated the effect of changing this in Figure 7. The analysis showed that even relatively small rate changes could profoundly influence the steady states. We wish to highlight here that our future work will aim at empirically confirming that fact by using some experimental data in tumor-bearing mice (which may also help us improve the model parametrization). We also considered the sensitivity of the corresponding tumor-free model to see which parameters influence the serum glucose levels in a healthy patient. This made it clear how the presence of a glioma influenced the sensitivities in the full model.

It has been hypothesized that the immune system can keep the tumor in a dormant state, but over time select for more aggressive variants with reduced immunogenicity (Dunn et al. 2002). This process, often referred to as immunoediting or tumor sculpting, may occur continuously and has major effects early in tumor progression and has been the subject of many modelling studies (see, for example, Enderling et al. (2012); Iwami et al. (2012)). As readily seen from the evolution trajectory of aggressive glioma presented in Figure 2, our model-based results seem consistent with the immunoediting hypothesis.

The focus of our future work is to search for viable blood-based biomarkers for the early detection of gliomas. In this paper, we presented a model which tracked one potential biomarker, namely serum glucose levels. The model helped elucidate a potential mechanism by which the serum glucose levels dropped in response to nascent glioma growth and if calibrated to individual patient data, it could be of use clinically. For any such clinical usage, we would need to gather patient specific information and feed it into our model initial conditions and individual-specific parameter values. More stable glucose measurements, as provided by the A1C test for example, could be perhaps more useful in determining these model parameters. The model could then potentially make a prediction about the likelihood of the patient developing an aggressive glioma in future. The patient-specific monitoring procedure has to come from statistical analyses of cohort data which is outside the scope of this current modeling paper. In calibration with experimentalists, we are presently in the process of developing an animal model to calibrate the model predictions in a real biological organism. Our current parameter sensitivity analysis highlights which parameter values should be prioritized for such procedure (σ_0 , d_{TT} , d_{IT} , a_T and a_S).

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Figure 1.

A schematic diagram of the interactions captured in our mathematical model of glioma growth. Serum glucose (σ_{serum}) exchanged with glucose in the brain via the blood-brain barrier. The glucose in the brain (σ_{brain}) feeds the immune system (I) and the glioma (T). The glioma elicits an immune response and we assume that the glioma and immune system mutually inhibit each other. Finally, the consumption of glucose in the brain by the glioma and immune system causes an increase in the flow of glucose from the serum to the brain.

Figure 2.

The evolution of the numerical solution of our model equations solved for a time corresponding to 9 years subject to an initial condition which represents a scenario for a patient with a small glioma already growing in the brain. The first subplot shows the evolution of the glioma (blue line), the second subplot shows glucose levels in the brain (red line), the third subplot shows the evolution of immune system activity in the brain (green line) and the final subplot shows the evolution of serum glucose levels (black line). All concentrations are expressed in units of g/ml . For better readability, we plot on a time grid of

332 days only. Healthy serum glucose levels are denoted in the lower right panel using two horizontal lines (values given by $7 \times 10^{-4}g/ml$ and $11 \times 10^{-4}g/ml$).

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Figure 3.

The evolution of the numerical solution of equations (1)–(3) solved for a time corresponding to 9 years subject to the second initial condition (see equation (7)). The first subplot shows the evolution of the glioma (blue line), the second subplot shows glucose levels in the brain (red line), the third subplot shows the evolution of immune system activity in the brain (green line) and the final subplot shows the evolution of serum glucose levels (black line). All concentrations are expressed in units of *g/ml*. For better readability, we plot on a time grid of 332 days only. Parameter set as per Table 2. Healthy serum glucose levels are

denoted in the lower right panel using two horizontal lines (values given by $7 \times 10^{-4} g/ml$ and $11 \times 10^{-4} g/ml$).

Figure 4.

The evolution of the numerical solution of equations (1)–(3) solved for a time corresponding to 9 years subject to the third initial condition (see equation (8)). The first subplot shows the evolution of the glioma (blue line), the second subplot shows glucose levels in the brain (red line), the third subplot shows the evolution of immune system activity in the brain (green line) and the final subplot shows the evolution of serum glucose levels (black line). All concentrations are expressed in units of *g/ml*. For better readability, we plot on a time grid of 332 days only. Parameter set as per Table 2. Healthy serum glucose levels are denoted in the

lower right panel using two horizontal lines (values given by $7 \times 10^{-4}g/ml$ and $11 \times 10^{-4}g/ml$).

Figure 5.

Network graph visualizing the importance of parameters and the interaction between reaction pairs with respect to glioma concentration. The radius of circles corresponds to the rank of sensitivity (the larger the radius, the greater the sensitivity) while the thickness of lines of any pair of parameters represents rank of their co-sensitivity (the thicker the line, the greater the co-sensitivity). The red color indicates the positive correlation while the blue one indicates the negative correlation between parameter values.

Figure 6.

Network graph visualizing the importance of parameters and the interaction between reaction pairs with respect to serum glucose levels. In both plots the radius of circles corresponds to the rank of sensitivity (the larger the radius, the greater the sensitivity) while the thickness of lines of any pair of parameters represents rank of their co-sensitivity (the thicker the line, the greater the co-sensitivity). The red color indicates the positive correlation while the blue one indicates the negative correlation between parameter values.

Figure 7.

Plots showing how the values of the three biologically realistic steady states shown in equation (9) (first three rows) are influenced by varying the parameter d_{TT} . The first row shows how the tumor steady states vary as the parameter d_{TT} is varied (blue lines), the second row shows how the glucose levels in the brain steady states vary as the parameter d_{TT} is varied (red lines), and the third row shows how the immune system level steady states vary as the parameter d_{TT} is varied (green lines). In the fourth row, the change in serum glucose levels is plotted with respect to variation of d_{TT} (black lines). All concentrations are expressed in units of g/ml . All other parameters as per Table 2.

Figure 8.

Plot showing $F_2(t)$ over a time period corresponding to 27 years (blue line). The concentration is expressed in units of g/ml . For better readability, we plot on a time grid of 166 days only. We also visualise the increased daily glucose intake (red line) and the baseline glucose intake (green line). The three peaks correspond to the three daily meals which the host consumes.

Figure 9.

The evolution of the numerical solution of equations (1)–(3) solved for a time corresponding to 27 years subject to the second initial condition (see equation (7)). The first subplot shows the evolution of the glioma (blue line), the second subplot shows glucose levels in the brain (red line), the third subplot shows the evolution of immune system activity in the brain (green line) and the final subplot shows the evolution of serum glucose levels (black line). All concentrations are expressed in units of *g/ml*. For better readability, we plot on a time grid of 332 days only. Parameter set as per Table 2 with the exception of σ_0 which is given

by the step-function $F_2(t)$. Healthy serum glucose levels are denoted in the lower right panel using two horizontal lines (values given by $7 \times 10^{-4} \text{g/ml}$ and $11 \times 10^{-4} \text{g/ml}$).

Table 1

Data taken from Edlinger et al. (2012) describing the risk of high-grade glioma incidents stratified by the pre-diagnostic glucose levels (*mmol/l*)

Glucose level quintile	Number of participants	Hazard ratio	95% confidence interval
1	88	1.00	(reference)
2	78	0.60	0.21 to 1.69
3	84	0.70	0.25 to 1.94
4	81	0.60	0.21 to 1.68
5	77	0.45	0.16 to 1.29

Table 2

Baseline parameter set, parameter descriptions and range of values as well as the literature sources.

Parameter	Description	Range (unit)	Sources
α_T	Growth rate of glioma	$1.575 \text{ (ml}^2\text{g}^{-2}\text{day}^{-1}\text{)}$	Giese et al. (1996); Swanson (1996)
K_T	Carrying capacity of glioma	2 (g/ml)	Matzavinos and Chaplain (2003)
d_{TI}	Decay rate of glioma due to immune response	$0.072 \text{ (day}^{-1}\text{)}$	Estimate
α_{TI}	Recruitment rate of immune systems cells due to glioma	$3 \times 10^{-4} \text{ (day}^{-1}\text{)}$	Estimate
d_T	Natural decay rate of glioma	$1 \times 10^{-4} \text{ (day}^{-1}\text{)}$	Tanaka et al. (2009)
d_I	Natural decay rate of immune system cells	$0.01 \text{ (day}^{-1}\text{)}$	Estimate
α_s	Immune system cell recruitment rate	$0.7 \text{ (day}^{-1}\text{)}$	Estimate
v	Baseline immune system cell production rate	$0.7 \text{ (day}^{-1}\text{)}$	Estimate
$d_{T\sigma}$	Glucose consumption rate by glioma	$1 \text{ (day}^{-1}\text{)}$	Estimate
α_σ	Transfer rate of glucose from serum to brain	$20.0 \text{ (day}^{-1}\text{)}$	Estimate
σ_{min}	Minimum glucose intake rate to serum	$8.00 \times 10^{-4} \text{ (g/ml)}$	Man et al. (2007)
σ_0	Maximum variation in glucose intake rate	$1.6 \times 10^{-3} \text{ (g/ml)}$	Man et al. (2007)
d_σ	Glucose consumption in brain by healthy cells	$0.01 \text{ (day}^{-1}\text{)}$	Man et al. (2007)
d_{TT}	Rate of glioma cells killing immune cells	$0.72 \text{ (day}^{-1}\text{)}$	Matzavinos and Chaplain (2003)