Thrombosis and High Cellular Density Impact on Glioma Growth: A Revised Mathematical Model

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Contents

Abstract

A glioma is a tumor that forms when glial cells grow out of control. All its treatments typically merely prolong the patient's life by a few weeks. Helping to solve this problem, several studies were made to predict glioma growth, including Sturrock et al. In 2015, Sturrock et al. [1] utilized the several literatures that exhibited a relation between pre-diagnostic serum glucose levels and the hazard ratio of glioma occurrence. Thus, making 4 differential equations, describing pre-diagnostic glioma interactions, unlike other models. In this paper, Sturrock et al. work is revised, including the effect of microenvironmental factors, thrombosis and high cellular density, on glioma growth, showing how they lead to further complications. Providing further data of the effects of more microenvironmental phenomena is also shown, helping in better diagnosis of glioma. To overcome the lack of data of pre-diagnostic glioma, further work is needed, advancing our understanding of tumor-microenvironment interactions.

1. Background/ Introduction

Eighty percent of malignant brain tumors are gliomas, which are believed to originate from neuroglial stem or progenitor cells. They are almost impossible to treat, due to their location, biological complexity, and adaptive resistance to therapies. Besides, some grow very quickly before patients experience any symptoms [2]. Its several types, including astrocytomas, ependymomas and oligodendrogliomas account for 24% of all primary brain and CNS tumors; these tumors vary greatly in histology from benign ependymomal tumors to the most aggressive and deadly grade IV GBM [3]. 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. Sturrock et al. (2015) highlight that pre-diagnosed gliomas have received less attention, which has resulted in a shortage of data, although the efforts that has been towards studying glioma growth and applying it mathematically. The lack of data on pre-diagnosed gliomas is due to a combination of subtle early symptoms, rapid progression of the disease, lack of routine screening, challenges in early detection technologies, and limited focus on early stages. Despite this lack of data, there have been several literatures that exhibited a relation between pre- diagnostic serum glucose levels and the hazard ratio of the glioma occurrence, indicating that metabolism may influence glioma [4][5]. This has inspired Sturrock et al., to make a mathematical model of pre-diagnosed glioma, making better understanding of glioma-glucose interactions, optimizing treatment strategies, and facilitating early detection.

The immune system starts it journey with the glioma after the detection through mechanisms such as recognizing abnormal tumor-associated antigens on

glioma cells or responding to stress signals from damaged cells. As immune cells get activated, they use energy from glucose metabolism, increasing serum glucose levels. As well as when glioma grows, it affects the overall glucose availability in the brain, altering the glucose movement between serum and brain. Nevertheless, those relations are affected by the tumor microenvironment (TME), the complex and dynamic ecosystem surrounding tumor cells, consisting of various non-cancerous cells, signaling molecules, and extracellular components [6]. In addition to TME, tumor mutations, microbiomes, and stress play a critical role in altering those mutations. After the immune system begins its attack on glioma, the tumor often counteracts through several strategies to evade destruction and continue growing, inducing physical barriers to continue growing and spreading and creating an immunosuppressive microenvironment. Some tumors even escape immune recognition by losing or altering their antigens or markers [7].

Current glioma models usually focus on limited properties of glioma cells, neglecting the surrounding intrinsic microenvironment due to the lack of data that integrate microenvironmental factors, especially thrombosis and high cellular density, as shown in Sturrock et al. (2015). This exclusion creates a significant gap in research and results in an incomplete understanding of tumor dynamics, potentially leading to inaccurate predictions of tumor growth and treatment response. For instance, Thrombosis, the formation of blood clots, and high cellular density both significantly accelerate glioma growth. Thrombosis induces hypoxia, stimulating angiogenesis and inflammation, which in turn promotes tumor expansion. High cellular density, large number of cells packed closely together. increases cell signaling and invasion, further driving angiogenesis and worsening hypoxia, creating a vicious cycle that supports tumor growth. Both factors can be

modeled mathematically to quantify their impact on glioma progression [8].

It is also stated in [9], that in patients with diabetes, where insulin levels can be high or low, not incorporating hormonal variations might lead to incorrect predictions of tumor growth dynamics. High insulin levels can accelerate tumor growth, leading to underestimation of the aggressiveness of the tumor. Low insulin levels, associated with reduced metabolic activity, might lead to an overestimation of tumor stability. This oversight can result in ineffective treatment strategies and a lack of personalized therapeutic approaches for diabetic patients. This highlights the importance of considering the microenvironment when trying to understand the interactions between glioma growth and the body.

Sturrock et al., unlike other models which are primarily interested in the evolution of post diagnosed glioma, produce a mathematical model of pre-diagnostic glioma, interested in how glioma growth influences serum-glucose levels. Some models have investigated glioma growth using partial differential equations [10] [11] [12], while Sturrock et al. have used ordinary differential equations. Thus, providing simplicity and computational efficiency. The basic assumptions regarding the interactions between Sturrock et al. model variables follow previous modelling efforts [13] [14] [15]. The format of this paper is as follows. First the mistake in the manuscript of Sturrock et al will be shown, and the steady states will be reproduced, guided by [16]. The unexpected glioma behavior will also be discussed. Then, the effect of different microenvironmental factors on developing glioma will be discussed, incorporating the effect of thrombosis and high cellular density on glioma growth.

2. Methodology

Sturrock is seeking to explain how glioma grows and interacts with glucose and the immune system in the early stages of its development, not seeking to explain the mechanisms by which a single glioma cell first originates. Sturrock assumes that glioma maintains a consistent shape with no migration and glucose is the main source for energy, excluding the microenvironmental influences.

2.1 The Mathematical Model:

Sturrock et al. shows glioma properties by providing these systems of differential equation:

$$\frac{dT}{dt} = \alpha_T \sigma_{brain} T\left(1 - \frac{T}{K_T}\right) - d_T T - d_{TI} \quad (1)$$

$$\frac{dT}{dt} = \alpha_\sigma(\sigma_{serum} - \sigma_{brain}) - d_{T\sigma} T \sigma_{brain} - (d_{\sigma 1} + \alpha_s(\nu + 1))\sigma_{brain} \quad (2)$$

$$\frac{dI}{dt} = \alpha_s(\nu + 1)\sigma_{brain} + \alpha_{TI} TI - d_I I - d_{TT} TI \quad (3)$$

$$\frac{d\sigma_{serum}}{dt} = \alpha_\sigma(\sigma_{brain} - \sigma_{serum}) + F(t) - d_{\sigma 2}\sigma_{serum} \quad (4)$$

Subject to the following initial conditions:

$T(0) = T_0$, $\sigma_{brain}(0) = \sigma_{brain,0}$, $I(0) = I_0$, $\sigma_{serum}(0) = \sigma_{serum,0}$ that are 4 positive constants. The glucose intake function is defined by:

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

Following mass-action kinetics, equation 1 states Tumor the temporal evolution of glioma growth. Sturrock et al. assume that glioma undergoes logistic growth with parameter α_T and carrying capacity K_T, and this growth depends on the

amount of glucose available in the brain. The glioma is also supposed to undergo apoptosis at a rate d_T as well as degradation at a rate d_{TI}.

Equation 2 describes the evolution of glucose concentration in the brain. Based on the difference in glucose levels between the serum and brain compartments, Sturrock et al. assume that there is an exchange of glucose from the serum to the brain at a rate α_σ. Glucose in the brain is also supposed to be consumed at the rates of $d_{T\sigma}$ for gliomas, $d_{\sigma 1}$ for typical brain activity, and αsv for the immune system. The glucose consumption rate by glioma ($d_{T\sigma}$) is one of the parameters that more influences the dynamics, and the model is very sensitive to this parameter. There is also an immune system dependent rate of consumption of glucose in the brain at a rate αs.

Equation 3 models the evolution of immune system activity in the brain. Both immune system dependent production at rates and basal production rate of immune system cells at rate α_{sv} are assumed. Immune system cells are also supposed to be recruited to the growing glioma at a rate α_{TI}. Furthermore, it is believed that immune system cells degrade naturally (at rate d_I) and in reaction to interactions with glioma cells (at rate d_{TT}).

Equation 4 represents the interactions of serum glucose. The exchange of glucose between the brain and serum compartments is assumed to be at a rate α_σ. Serum glucose interactions are also affected by glucose intake function. Lastly, the final term captures the metabolic consumption of serum glucose, which happens at a rate of $d_{\sigma 2}$. The parameters are given by Table 1.

Parameter	Description	Range (unit)
α_T	Growth rate of glioma	1.575 ($ml^2\ g^{-2}\ day^{-1}$)
K_T	Carrying capacity of glioma	2 (g/ml)
d_{TI}	Decay rate of glioma due to immune response	0.072 (day^{-1})
α_{TI}	Recruitment rate of immune systems cells due to glioma	3×10^{-4} (day^{-1})
d_T	Natural decay rate of glioma	1×10^{-4} (day^{-1})
d_I	Natural decay rate of immune system cells	0.01 (day^{-1})
α_s	Immune system cell recruitment rate	0.7 (day^{-1})
ν	Baseline immune system cell production rate	0.7 (day^{-1})
$d_{T\sigma}$	Glucose consumption rate by glioma	1 (day^{-1})
α_σ	Transfer rate of glucose from serum to brain	20.0 (day^{-1})
σ_{min}	Minimum glucose intake rate to serum	8.00×10^{-4} (g/ml)
σ_0	Maximum variation in glucose intake rate	1.6×10^{-3} (g/ml)
d_σ	Glucose consumption in brain by healthy cells	0.01 (day^{-1})
d_{TT}	Rate of glioma cells killing immune cells	0.72 (day^{-1})

***Table 1**: Shows the original parameters as stated in Sturrock et al.*

2.2 The Model Steady States:

Sturrock et al. considers three different initial conditions or steady states, presented in units of g/ml, where the volume of one glioma cell is around 10,000 fl, or 1 x 10^{-8} ml, and the number of cells in 1 g is approximately 1 x 10^9:

$$T_1, \sigma_{brain,1}, I_1, \sigma_{serum,1} \approx (0.14, 3.92 \times 10^{-4}, 2.84 \times 10^{-4}, 4.39 \times 10^{-4}) \quad (1)$$

$$T_2, \sigma_{brain2}, I_2, \sigma_{serum,2} \approx (0.0498, 8.28 \times 10^{-4}, 0.016, 8.86 \times 10^{-4}) \quad (2)$$

$$T_3, \sigma_{brain,3}, I_3, \sigma_{serum,3} \approx (0, 8.45 \times 10^{-4}, 0.061, 8.81 \times 10^{-4}) \quad (3)$$

Steady State 2 and 3 describe small dormant tumors and healthy patients with no tumor respectively. Steady State 1 appears in a later section in Sturrock et al. as:

$$T_4, \sigma_{brain,4}, I_4, \sigma_{serum,4} \approx (1.53, 3.27 \times 10^{-4}, 2.84 \times 10^{-4}, 3.65 \times 10^{-4}) \quad (4)$$

What makes it clear there is a typo in Sturrock et al. study is that Steady State 1 describes an unstable tumor growth, with tumor neither at dormancy nor at a large, aggressive state, as stated in Figure 1 and Steady State 4 describes a large stable tumor growth that is most related to the aggressive tumor, as stated in Figure 2.

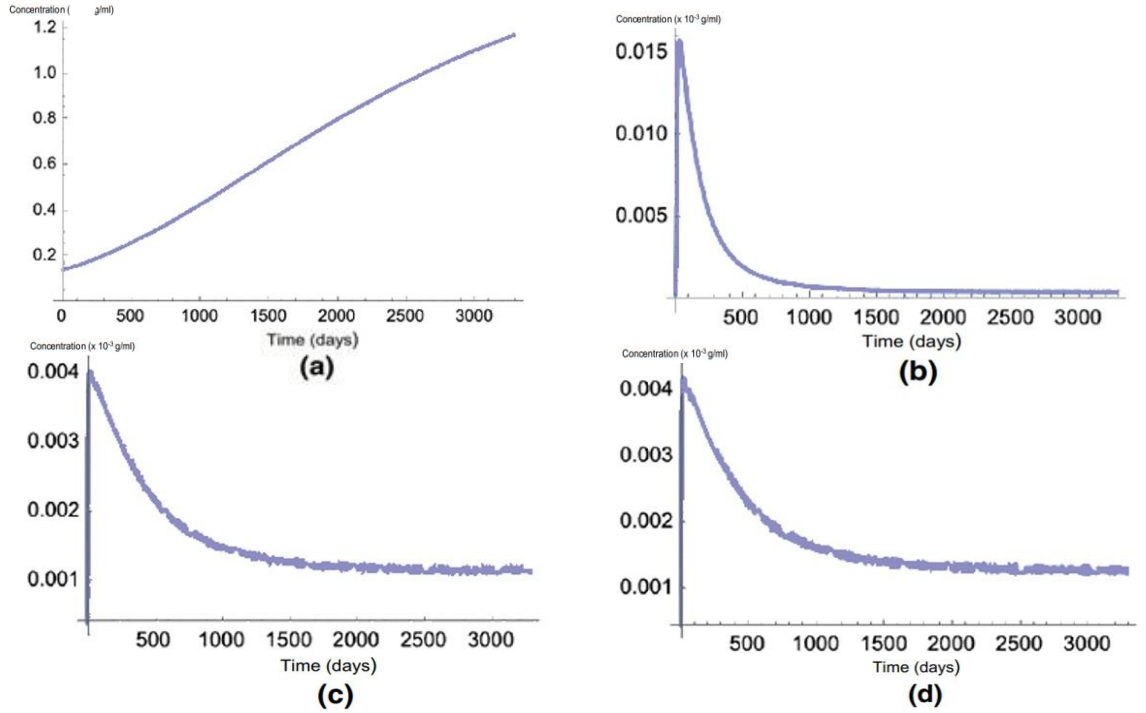

Figure 1: Steady State 1is modeled to 9 years. (a) Evolution of glioma, (b) Evolution of immune system activity, (c) Glucose levels in the brain, (d) Glucose levels in serum.

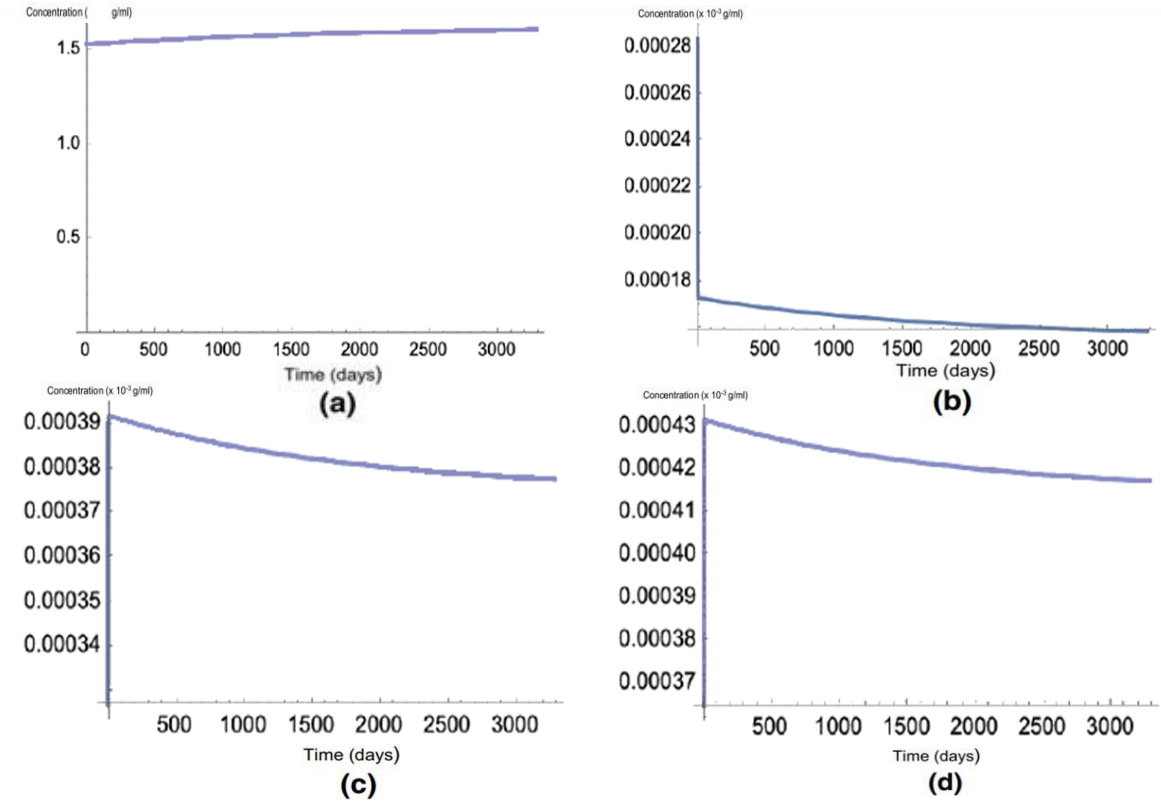

Figure 2: Steady State 4 is modeled to 9 years. (a) Evolution of glioma, (b) Evolution of immune system activity, (c) Glucose levels in the brain, (d) Glucose levels in serum

Following the reproduction of the steady states of [6], 6 steady states were produced. They correspond to Sturrock et al steady states, but not quantitively matching it. This is due to the glucose intake function, which propagated negative values at extremely small values, unlike minimizing allowed value of glucose to remove the possibility of F(t) giving negative values in Sturrock et al.:

$$T_5, \sigma_{brain,5}, I_5, \sigma_{serum,5} \approx (0.26, 10 \times 10^{-4}, 180 \times 10^{-4}, 10 \times 10^{-4}) \quad (5)$$

$$T_6, \sigma_{brain,6}, I_6, \sigma_{serum,6} \approx (1.27, 4.49 \times 10^{-4}, 20 \times 10^{-4}, 4.9 \times 10^{-4}) \quad (6)$$

$$T_7, \sigma_{brain,7}, I_7, \sigma_{serum,7} \approx (0, 14 \times 10^{-4}, 776.5 \times 10^{-4}, 14.7 \times 10^{-4}) \quad (7)$$

$$T_8, \sigma_{brain,8}, I_8, \sigma_{serum,8} \approx (-0.1, -267 \times 10^{-4}, -617 \times 10^{-4}, -267 \times 10^{-4}) \quad (8)$$

$$T_9, \sigma_{brain,9}, I_9, \sigma_{serum,9} \approx (0, 49 \times 10^{-4}, -72 \times 10^{-4}, 49 \times 10^{-4}) \quad (9)$$

$$T_{10}, \sigma_{brain,10}, I_{10}, \sigma_{serum,10} \approx (3.2, 397 \times 10^{-4}, -5331 \times 10^{-4}, 40 \times 10^{-4}) \quad (10)$$

It is worthwhile noting that Steady States 8, 9, and 10 are biologically unrealistic due to the negative values of some of the variables, so they are discarded. The other three were used as initial conditions in the numerical simulations. They provide a foundation for benchmarking and further stability and sensitivity analysis. Clearly, Steady State 5, as shown in Figure 3, refers to a large stable tumor growth, proving the error in the manuscript of Sturrock et al. Steady State 6 refers to an advanced stage glioma, as shown in in Figure 4. Steady State 7 refers to a healthy patient with no tumor, as shown in Figure 5.

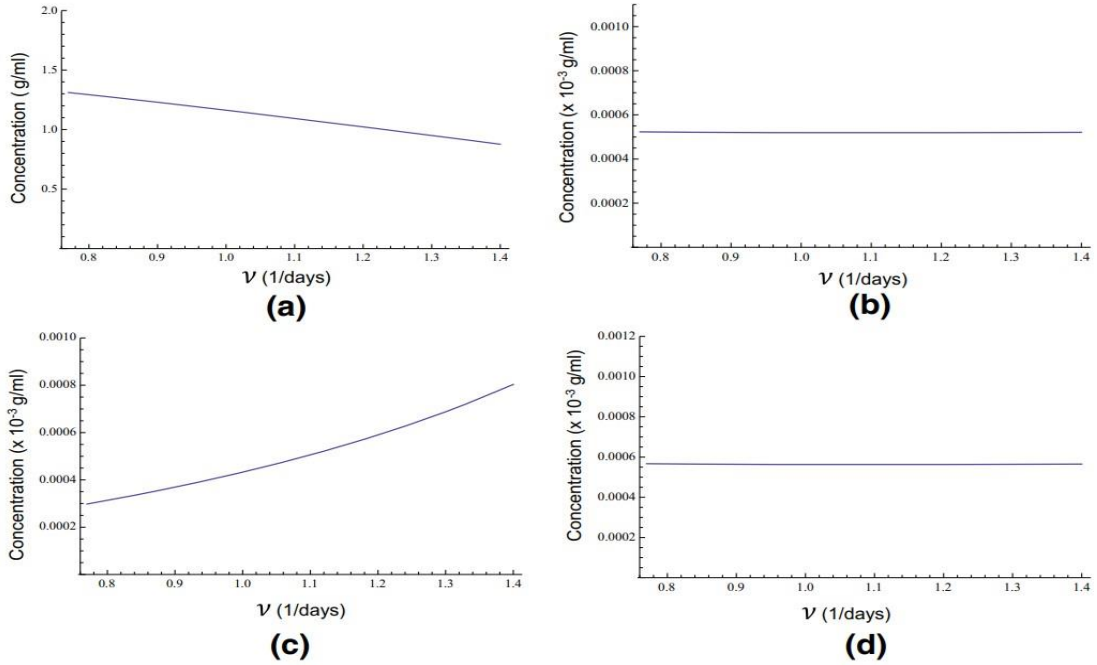

Figure 5: Steady State 5 is modeled to 9 years. (a) Evolution of glioma, (b) Glucose levels in the brain, (c) Evolution of immune system activity, (d) Glucose levels in serum.

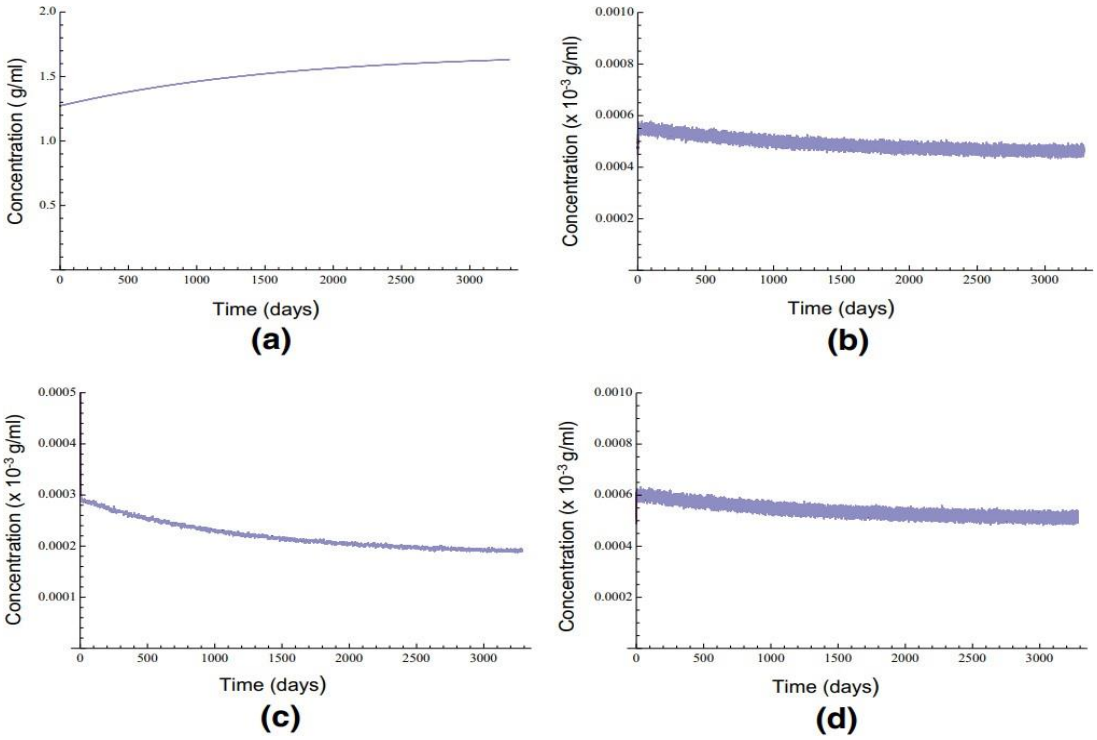

Figure 4: Steady State 6 is modeled to 9 years. (a) Evolution of glioma, (b) Glucose levels in the brain, (c) Evolution of immune system activity, (d) Glucose levels in serum.

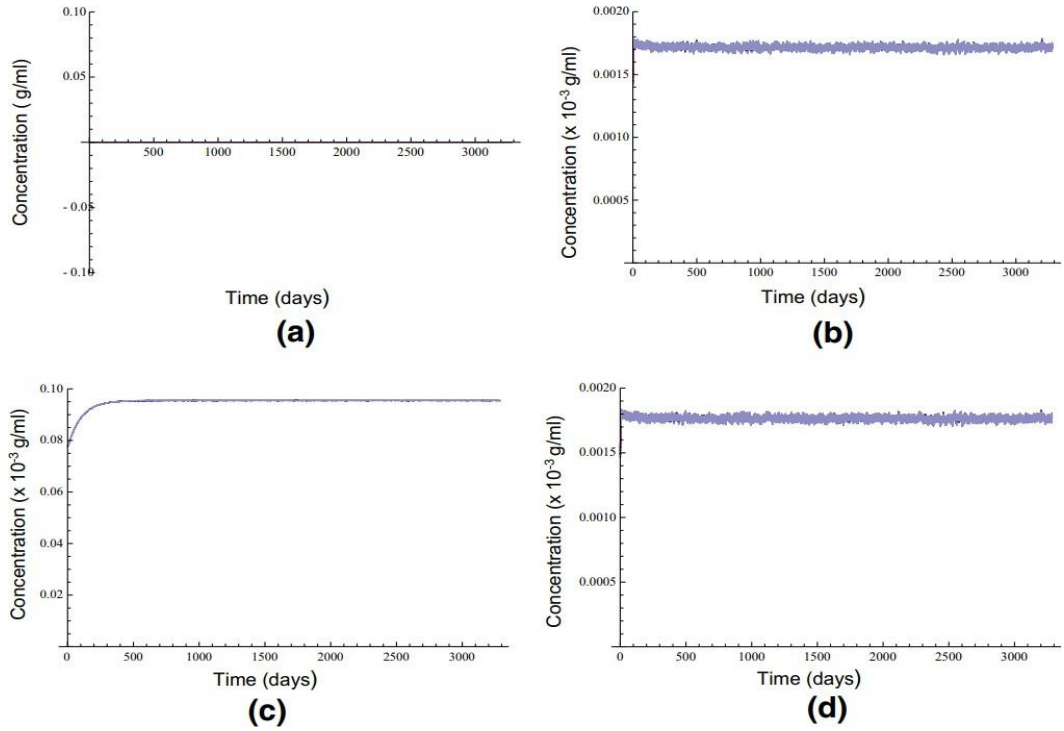

Figure 3: Steady State 7 is modeled to 9 years. (a) Evolution of glioma, (b) Glucose levels in the brain, (c) Evolution of immune system activity, (d) Glucose levels in serum.

2.3 Unexpected Glioma Behavior:

In Sturrock et al., d_{TT} represents the rate at which glioma cells eradicate immune system cells. The behavior of the steady states (represented in Steady States 1 and 3) showed an expected behavior, as stated in Sturrock et al. results. However, Sturrock et al. found an unexpected effect in the steady state (represented in Steady State 2) corresponding to a dormant tumor illustrated a decaying effect as its ability to destroy immune cells increased, when the parameter is increased from 0.5 day^{-1} to 1.5 day^{-1}. This may have occurred due to its complexity.

When the number of immune cells decreases, it usually leads to an increase in glioma concentration. This occurs because the immune system's ability to suppress or control the tumor is weakened, allowing the glioma to grow more freely [7]. However, there are several explanations for this unexpected effect. One possible explanation is that as the concentration of immune cells decreased, the body reduced the amount of glucose supplied to the brain to support them. This reduction in glucose availability could have led to a subsequent decrease in the number of glioma cells. The decrease in the immune cells may have influenced the tumor microenvironment in a way that inadvertently limits its growth or even entered a state of quiescence or dormancy in the absence of immune cell pressure [17] [18].

2.4 Microenvironmental Effects on Developing Glioma:

The model of Sturrock et al. is being revised to incorporate additional processes, developing their work. The revision includes showing the effect of different microenvironmental factors on the risk of glioma development, showing different coefficients from older studies (3.1). We further incorporate the concepts of thromboses and high cellular density, which are known for their effect on glioma growth. In addition, their effect on glioma growth is applied on Sturrock et al. models (3.2) and applied on graphs, showing how they alter glioma growth.

The microenvironment dramatically affects the risk of tumorigenesis by creating a supportive niche. This complex microenvironment is characterized by an array of cellular and molecular interactions that collectively enhance glioma development.

Key elements include HIF-1α, which is a transcription factor that is stabilized in response to hypoxia, a condition often found within rapidly growing tumors like gliomas. Under low oxygen levels, HIF-1α is translocated to the nucleus, where it activates genes that promote angiogenesis, including VEGF. This leads to the formation of new, but often abnormal, blood vessels that supply the tumor with the necessary oxygen and nutrients. These vessels are typically leaky and disorganized, contributing to the chaotic and invasive nature of gliomas [19].

Additionally, pre-diagnostic IgE levels and medically diagnosed allergies influence glioma development by creating an immune environment that supports tumor growth. The chronic inflammation linked to high IgE can either promote glioma progression directly or alter the tumor microenvironment in a way that favors glioma development [20].

Obesity is associated with a chronic inflammatory state and alterations in metabolism, creating a microenvironment that favors tumor development. Adipose tissue secretes inflammatory cytokines and growth factors that can promote tumorigenesis. Similarly, high birth weight might reflect early-life nutritional or hormonal exposures that predispose individuals to later metabolic disturbances, potentially increasing tumorigenesis [21] [22]

A high dietary insulin index, indicative of foods that rapidly raise blood insulin levels, can lead to insulin resistance, a condition linked to increased inflammation and metabolic dysregulation. These metabolic changes can promote glioma growth. Chronic stress also contributes by modulating immune responses and inducing the release of stress hormones like cortisol, which can suppress anti- tumor immune activity and promote tumor development [23] [24].

Exposure to excessive amounts of lead or calcium can disrupt various cellular processes, including signaling pathways involved in cell growth and survival. In addition, the dysregulation of calcium homeostasis may contribute to the altered signaling pathways that promote tumorigenesis [25] [26].

Collectively, microenvironmental factors are numerically affecting tumor development, as shown in the different coefficients calculated from the natural logarithm of the odds ratio, as shown in Table 2.

Microenvironmental Factor	Coefficient	Resource
HIF-1α	2.15	[19]
Allergy	-0.51	[20]
Pre-diagnostic IgE Levels	4.32	[27]
Obesity	0.36	[21]
Dietary insulin index	0.63	[23]
Stress	0.12	[24]
Angiogenesis	1.44	[28]
Calcium	-1.11	[25]
Lead	0.74	[26]
Medically diagnosed allergy	-0.48	[29]
Smoking more than 100 cigarettes	-0.8	[29]
AA versus GA/GG	0.04	[30]
EGFR haplotype	0.51	[31]
high birth weight	0.24	[22]
Epidermal Growth Factor (+61 G/A Polymorphism)	0.80	[32]
Diabetes mellites	-0.26	[33]

2.5 Thrombosis and High Cellular Density

Thrombosis is the formation of a blood clot within a blood vessel, which can obstruct or block the flow of blood through the circulatory system, leading to various medical complications [34]. Thrombosis and glioma growth are closely related. Thrombosis within the vessels supplying the tumor can lead to hypoxia in the tumor microenvironment, promoting glioma growth and invasiveness [35]. This can also stimulate the production of vascular endothelial growth factor (VEGF), leading to the formation of new blood vessels (angiogenesis) that support tumor growth and survival [35].

Thrombosis can also trigger an inflammatory response, which can further promote glioma growth contributing to the release of cytokines and growth factors that enhance tumor proliferation [36]. To show the effect of thrombosis on glioma growth, a variable P is produced to reflect the presence of thrombosis, while parameter β represents the coefficient between the presence of thrombosis and the rate of glioma growth, thus it is multiplied to the glioma growth parameter, as shown in Equation 6. As shown in Figure 6, equation 6 is also modeled to 9 years, incorporating the effect of thrombosis on the model of glioma growth.

High cellular density (HD) has a direct effect on tumor growth. It refers to the condition where a large number of cells are packed closely together within a given volume or area of tissue. The crowded environment can lead to increased cell-to-cell signaling, promoting further proliferation and invasion into surrounding brain tissue [28]. As the tumor grows and cellular density increases, the demand for nutrients and oxygen can stimulate angiogenesis. However, the new blood vessels formed are often abnormal and leaky, contributing to further hypoxia and an even more hostile microenvironment. HD in glioblastoma cells also down- regulates the cystine/glutamate transporter xCT, increasing cell viability under glucose deprivation [37]. To show the effect of HD on glioma growth, a variable P is produced to reflect the presence of the high density.

Multiplied to the glioma growth parameter, parameter γ represents the coefficient between the presence of high cellular density and rate of glioma growth, as shown in Equation 7. As shown in Figure 7, equation 7 is also modeled to 9 years, incorporating the effect of High Cellular Density on the model of glioma growth.

P is defined by: $\begin{cases} P = 0 \text{ (The microenvironmental factor is absent)} \\ P = 1 \text{ (The microenvironmental factor is present)} \end{cases}$

The new introduced parameters are shown in Table 3. The modified equations (6,7) are given, and tumor growth equation is repeated for clarity:

$$\frac{dT}{dt} = \alpha_T \sigma_{brain} T \left(1 - \frac{T}{K_T}\right) - d_T T - d_{TI} \quad (1)$$

$$\frac{dT}{dt} = \alpha_T \beta^P \sigma_{brain} T \left(1 - \frac{T}{K_T}\right) - d_T T - d_{TI} \quad (6)$$

$$\frac{dT}{dt} = \alpha_T \gamma^P \sigma_{brain} T \left(1 - \frac{T}{K_T}\right) - d_T T - d_{TI} \quad (7)$$

Microenvironmental Factor	Coefficient	Resource
Thromboses	1.46	[28]
High Cellular Density	1.10	[28]

Table 3: Shows the coefficients of the effect of thrombosis and high cellular density.

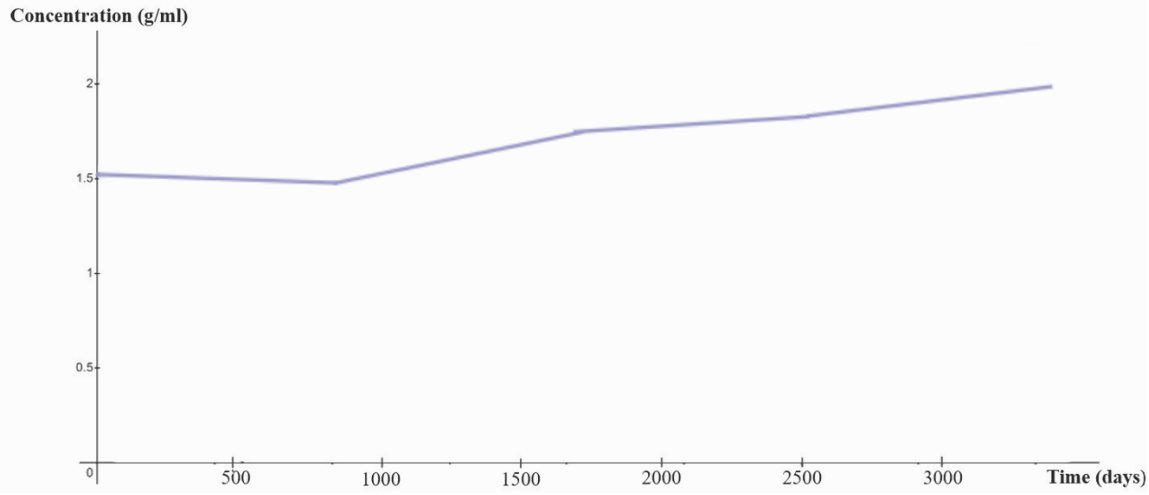

Figure 6: Equation 6 is modeled to 9 years, relating thrombosis to glioma growth.

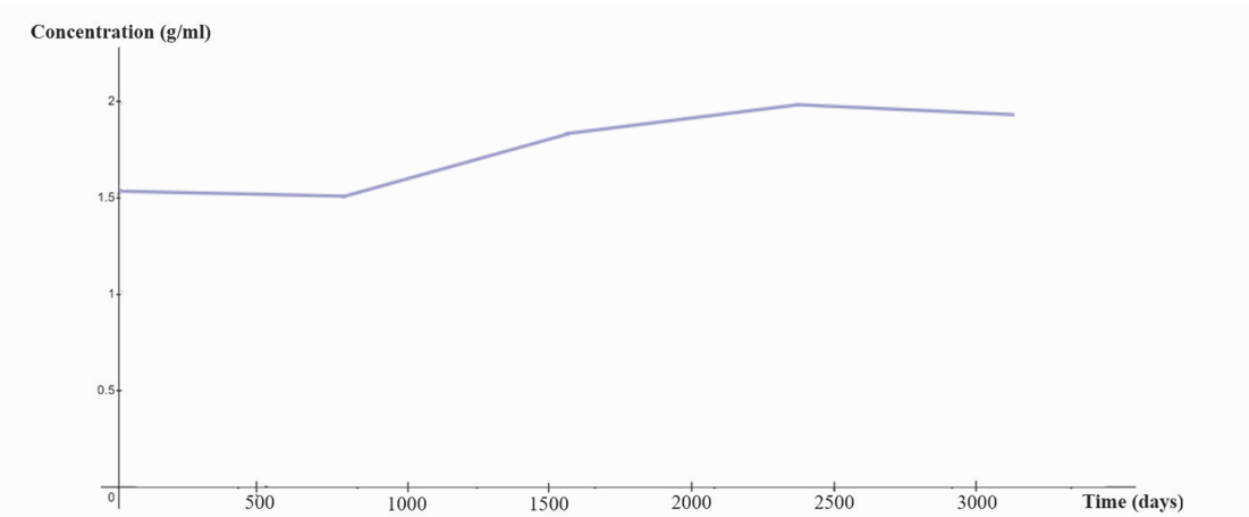

Figure 7: Equation 7 is modeled to 9 years, relating high cellular density to glioma growth.

3. Discussion

This paper reproduces Sturrock et al. mathematical model, showing the error in the manuscript. According to [16] methodology, 3 steady states were produced, qualitatively valid, quantitatively different from Sturrock et al. steady states. Thus, ensuring accuracy and providing a basis for further analysis. Furthermore, using a finite-difference method, the ordinary differential equations were discretized the in order to numerically implement the system of equations. The discretized system was also solved for 9 years, adding stochastic noise. The unexpected glioma behavior from Sturrock et al. results were also clarified, suggesting several explanations for it. We further show the microenvironmental roles in developing glioma, underlining it with odds ratios from past studied. Thrombosis and HD effects on glioma growth were also discussed, adding them as new parameters to the equation of growth. In general, it can be concluded that this model serves to determine the level of influence of the parameters in this system on pre- diagnostic glioma.

In Sturrock et al. study, the effect of sudden large glioma growth of the dormant glioma was modeled for 27 years as the glucose-rich diet that manifests after 3 years causes glucose levels to spike. This substantial growth increases the rate that glioma kills immune cells, which appears to be unrecoverable. As a result, the growth of glioma appears in Sturrock et al. to be increasing through the 27 years of the model. But this is different from the unexpected behavior Sturrock et al. presents in the dormant glioma; the glioma after the increase in killing immune cells does not present any kind of decaying effect. In addition, Sturrock et al. shows that

the glioma continues to grow beyond its carrying capacity at this point, even if the glucose levels are near zero.

Mathematical modeling of pre-diagnostic gliomas plays a vital role in advancing our understanding of tumor-microenvironment interactions and their impact on glioma. These models and its implications allow for personalized medicine by simulating patient-specific scenarios, high cellular density and thrombosis. By simulating these complex interactions, models help clinicians predict tumor aggressiveness and guide therapeutic strategies, improving patient outcomes. This causes timely and effective introversion and allows for better anticipation of the disease. For example, the work of Sturrock et al. focuses on searching for viable blood- based biomarkers for the early detection of gliomas, presenting a model which serum glucose levels. Furthermore, modeling the metabolic needs of gliomas, such as glucose intake, emphasizes the importance of nutrition in managing the disease. Overall, integrating multidisciplinary knowledge from biology, medicine, and mathematics, bridges gaps between different fields, ultimately guiding better therapeutic strategies and improving survivability for glioma patients.

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