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Dynamic Studies of Glioma Models

Lakshmi N Sridhar*

Chemical Engineering Department, University of Puerto Rico, Mayaguez, PR 00681-9046, USA

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***Corresponding author:** Lakshmi N Sridhar, Chemical Engineering Department, University of Puerto Rico, Mayaguez, PR 00681-9046, USA

ABSTRACT

The dynamics of Glioma are very complex and the mathematical models involving glioma are highly nonlinear This work describes a rigorous mathematical framework to deal with the high degree of nonlinearity in Glioma models. Bifurcation analysis and Mult objective nonlinear model predictive control (MNLMPC) calculations were was performed on two models describing the dynamics of Glioma. The MATLAB program MATCONT was used to perform the bifurcation analysis. The MNLMPC calculations were performed using the optimization language PYOMO in conjunction with the state-of-the-art global optimization solvers IPOPT and BARON. The bifurcation analysis revealed limit points the limit were beneficial because they allowed the Mult objective nonlinear model predictive control calculations to converge to the Utopia point which is the best possible solution.

Keywords: Bifurcation; Optimization; Control; Cancer tumor; Glioma

Introduction

Gliomas are life-threatening brain tumors that recur despite a lot of efforts to control and prevent their recurrence and spreading. To eliminate the glioma, one needs to understand the dynamics of how the glioma reacts to therapy and develop strategies to eradicate them. The behavior of the glioma is very complicated and nonlinear. This motivated researchers to perform theoretical work involving bifurcation analysis and dynamic optimization of Glioma models.

This work involves Mult objective nonlinear model predictive control (MNLMPC) calculations performed with bifurcation analysis on Glioma models. It is shown that the presence of limit bifurcation points is beneficial because they enable the MNLMPC calculations to converge to the Utopia point which is the best possible solution.

Bifurcation analysis and MNLMPC calculations are performed on two different Glioma models. The bifurcation analysis reveals the presence of limit points. The MNLMPC calculations are shown to converge to the Utopia solution.

Background

Swanson, et al[1], used mathematical modeling to quantify glioma growth invasion. Farin, et al[2], demonstrated that transplanted glioma cells migrate and proliferate on host brain vasculature using dynamic analysis. Hardie[3] showed that AMP-activated/SNF1 protein kinases were guardians of cellular energy. Godlewski J, et al[4], demonstrated that targeting the Bmi-1 oncogene/stem cell renewal factor by microRNA-128 inhibits glioma proliferation and self-renewal. Kronik, et al[5], used a simulation model to Improve alloreactive CTL immunotherapy for malignant gliomas. Kim, et al[6], developed a mathematical model for the pattern formation of glioma cells outside the tumor

spheroid core. Lawler, et al[7], discussed the emerging functions of microRNAs in glioblastoma.

Derr, et al[8], discussed the association between hyperglycemia and survival in patients with newly diagnosed glioblastoma. Godlewski, et al[9,10], showed that microRNA-451 regulates LKB1/AMPK signaling and allows adaptation to metabolic stress in glioma cells and microRNA-451: was a conditional switch controlling glioma cell proliferation and migration. Wesseling[11], discussed the pathological diagnosis of diffuse gliomas in a multidisciplinary context.

Using a mathematical model, Kim Y, et al[12], discovered the mutual antagonism of miR451 and AMPK in glioma cell migration and proliferation. Gerlee, et al[13], discuss the impact of phenotypic switching on glioblastoma growth and invasion, Kim, et al[14,15], developed a hybrid model for cell proliferation and migration in glioblastoma and discussed the regulation of cell proliferation and migration in glioblastoma: Song, et al[16] showed that MiR-18a regulates the proliferation, migration and invasion of human glioblastoma cell by targeting neogenin. Guo, et al[17], demonstrated that miR-656 inhibits glioma tumorigenesis through repression of BMPR1A. Yang, et al[18], showed that MicroRNA-16 inhibits glioma cell growth and invasion by suppressing BCL2 and the nuclear factor-kB1/MMP9 signaling pathway. Ma, et al[19], showed that MiR-152 functions as a tumor suppressor in glioblastoma stem cells. Wang L, et al[20], showed that MiR-143 acts as a tumor suppressor by targeting N-RAS and enhances temozolomide-induced apoptosis in glioma. Shi, et al[21], showed that miR-145 inhibits migration and invasion of glioma stem cells by targeting ABCG2. De los Reyes, et al[22], performed optimal control calculations eradicating invisible glioblastoma cells after conventional surgery. Khajanchi, et al[23], explained the role of the immunotherapeutic drug T11 target structure in the progression of malignant gliomas. Khajanchi[24], modeled the dynamics of glioma-immune surveillance. Khajanchi, et al[25], performed the stability analysis of a Mathematical Model for Glioma-Immune interaction under optimal therapy.

Motivation and Objectives

All the optimal control work involving Glioma models involved single-objective optimal control. Bifurcation analysis involving the Glioma models, especially the work of De los Reyes, et al[22] and Khajanchi, et al[25], showed the existence of limit points that cause multiple steady-states. This work aims to perform multiobjective nonlinear model predictive control (MNLMPC) calculations in conjunction with bifurcation analysis and demonstrate that the presence of limit points is beneficial because they enable the MNLMPC calculations to converge to the Utopia point which is the best possible solution. This paper is organized as follows. The Glioma models of De los Reyes, et al[22] and Khajanchi, et al[25], are first described followed by the numerical procedures for the bifurcation analysis and the MNLMPC calculations. The results, discussion and conclusions are then presented.

Model Equations

Model 1

The model equations[22] are

$$\begin{aligned}
\frac{dG}{dt} &= u_1(t) - \mu G \\
\frac{dM}{dt} &= G - M + \frac{k_1 k_2^2}{k_2^2 + \alpha e^{-D} A^2} \\
\varepsilon \frac{dA}{dt} &= S - A + \frac{k_3 k_4^2}{k_4^2 + \beta M^2} \\
\frac{dD}{dt} &= u_2(t) - \delta D
\end{aligned} \tag{1}$$

The glucose, miR-451, AMPK complex and drug activity are represented by G, M, A and D, respectively. The parameter values are.

$$k_1 = 4, k_2 = 1, \alpha = 1.6, k_3 = 4, k_4 = 1, \beta = 1, s = 0.2, \varepsilon = 0.02, \mu = 0.5, \delta = 1.316$$

These parameters represent the miR-451 autocatalytic production rate, Hill-type coefficient, inhibition strength of miR-451 by the AMPK complex, signaling source of AMPK, scaling factor (slow-dynamics), glucose consumption rate and drug decay rate. u_1, u_2 are both bifurcation parameters and control values.

Model 2

The model equations[25]are

$$\begin{aligned}
\frac{du}{dt} &= r_1 \mathrm{u(t)(1- u(t))} - \frac{(\alpha_1 v(t) + \alpha_2 w(t))}{u(t) + k_1} \mathrm{u(t)} \\
\frac{dv}{dt} &= r_2 \mathrm{v(t)(1- v(t))} - \alpha_3 \frac{(v(t))\mathrm{u(t)}}{u(t) + k_2} \\
\frac{dw}{dt} &= \gamma_1 \frac{(w(t))\mathrm{u(t)}}{u(t) + k_3} - \alpha_4 \frac{(w(t))\mathrm{u(t)}}{u(t) + k_4} - \mu_1 w(t) + uc(t)
\end{aligned} \tag{2}$$

Here u(t) represents the number of glioma cells while v(t) and w(t) represent the number of macrophages and tumor-specific CD8+T cells. Uc is the control value and bifurcation parameter.

The parameter values are

$$r_1 = 0.4822, \alpha_1 = 0.069943, \alpha_2 = 2.74492, k_1 = 0.90305, r_2 = 0.3307, \alpha_3 = 0.0194,$$
$$k_2 = 0.030584, \gamma_1 = 0.1245, k_3 = 2.8743, \mu_1 = 0.0074, \alpha_4 = 0.01694, k_4 = 0.378918$$

These parameters represent the proliferation rate of glioma cells, decay rate of gliomas due to macrophages, decay rate of gliomas due to CD8+T cells, steepness coefficient of glioma cells, growth rate of macrophages, loss of macrophages due to malignant gliomas, steepness coefficient of macrophages, recruitment of activated CD8+T cells by glioma cells, maximum recruitment of CD8+T cells by glioma cells, natural death rate of CD8+T cells, deactivation rate of CD8+T cells by glioma cells and the Michaelis-Menton constant.

Bifurcation Analysis

The existence of multiple steady-states and limit cycles in various processes has led to much research involving bifurcation analysis. Multiple steady states occur because of the existence of branch and limit points. Hopf bifurcation points cause limit cycles. One of the most commonly used software to locate limit points, branch points and Hopf bifurcation points is the

MATLAB program MATCONT[26,27]. This software detects Limit points (LP), branch points (BP) and Hopf bifurcation points(H). Consider an ODE system.

$$\frac{dx}{dt} = f(x,\alpha) \qquad (3)$$

$x \in R^n$ Let the tangent plane at any point x be $W = [W_1, W_2, W_3, W_4, ...W_{n+1}]$. The bifurcation parameter is α . Define matrix A as

$$A = [\partial f / \partial x \quad | \partial f / \partial \alpha] \qquad (4)$$

where $\partial f / \partial x$ is the Jacobian matrix. Since the gradient is orthogonal to the tangent vector,

$$Aw = 0 \qquad (5)$$

For both limit and branch points the matrix $[\partial f / \partial x]$ must be singular. For a limit point (LP) the n+1 th component of the tangent vector $w_{n+1} = 0$ and for a branch point (BP) the matrix

$\begin{bmatrix} A \\ w^T \end{bmatrix}$ must be singular. At a Hopf bifurcation point,

$$\det(2f_x(x,\alpha) @ I_n) = 0 \qquad (6)$$

@ indicates the bialternate product while I_n is the n-square identity matrix. Hopf bifurcations cause limit cycles and should be eliminated because limit cycles make optimization and control tasks very difficult. More details can be found in Kuznetsov[28,29] and Govaerts[30].

Mult objective Nonlinear Model Predictive Control

The Mult objective nonlinear model predictive control (MNLMPC) method[31] used in these calculations is rigorous and does not involve weighting functions or additional constraints. Let $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ (j=12.n) be the variables that need to be minimized/maximized simultaneously for a problem involving a set of ODE

$$\frac{dx}{dt} = F(x,u) \qquad (7)$$

t_f being the final time value and n the total number of objective variables. u is the control parameter. The MNLMPC method first solves the single objective optimal control problem independently optimizing each of the variables $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ individually. The minimization/maximization of $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ will lead to the values q_j^* . Then the optimization problem that will be solved is

$$\min\left(\sum_{j=1}^{n}\left(\sum_{t_i=0}^{t_i=t_f} q_j(t_i) - q_j^*\right)\right)^2$$

$$subject\ to\ \frac{dx}{dt} = F(x,u); \qquad (8)$$

This will provide the values of u at various times. The first obtained control value of u is implemented and the rest are discarded. This procedure is repeated until the implemented and the first obtained control values are the same or if the Utopia point where $\left(\sum_{t_i=0}^{t_i=t_f} q_j(t_i) = q_j^*\right.$ for all j) is obtained. The optimization package in Python, Pyomo[32], where the differential equations are automatically converted to a Nonlinear Program (NLP) using the orthogonal collocation method will be used. The resulting nonlinear optimization problem was solved using the solvers IPOPT[33] and confirmed as a global solution with BARON[34]. To summarize the steps of the algorithm are as follows

- Optimize $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ subject to the differential and algebraic equations that govern the process using Pyomo with IPOPT and BARON. This will lead to the value q_j^* at various time intervals t_i. The subscript *i* is the index for each time step.
- Minimize $\left(\sum_{j=1}^{n}\left(\sum_{t_i=0}^{t_i=t_f} q_j(t_i) - q_j^*\right)\right)^2$ subject to the differential and algebraic equations that govern the process using Pyomo with IPOPT and BARON. This will provide the control values for various times.
- Implement the first obtained control values and discard the remaining.

Repeat steps 1 to 3 until there is an insignificant difference between the implemented and the first obtained value of the control variables or if the Utopia point is achieved. The Utopia point is when $\sum_{t_i=0}^{t_i=t_f} q_j(t_i) = q_j^*$ or for all j. This implies that $\left(\sum_{j=1}^{n}\left(\sum_{t_i=0}^{t_i=t_f} q_j(t_i) - q_j^*\right)\right)^2 = 0$. Sridhar[35] proved that the MNLMPC calculations to converge to the Utopia solution when the bifurcation analysis revealed the presence of limit and branch points. This was done by imposing the singularity condition on the co-state equation[36].

This is illustrated with a simple two-variable example. Let $\sum_{t_i=0}^{t_i=t_f} q_1(t_i) = \hat{q}_1$ and $\sum_{t_i=0}^{t_i=t_f} q_2(t_i) = \hat{q}_2$ If the minimization of $\hat{q}_1$ lead to the value q_1^* and the minimization of $\hat{q}_2$ lead to the value q_2^* The MNLPMC calculations will minimize the function $(\hat{q}_1 - q_1^*)^2 + (\hat{q}_2 - q_2^*)^2$. The Mult objective optimal control problem is

$$\min \quad (\hat{q}_1 - q_1^*)^2 + (\hat{q}_2 - q_2^*)^2 \quad subject\ to\ \frac{dx}{dt} = f(x,u) \tag{9}$$

Simple differentiation shows that

$$\frac{d}{dx_i}((\hat{q}_1 - q_1^*)^2 + (\hat{q}_2 - q_2^*)^2) = 2(\hat{q}_1 - q_1^*)\frac{d}{dx_i}(\hat{q}_1 - q_1^*) + 2(\hat{q}_2 - q_2^*)\frac{d}{dx_i}(\hat{q}_2 - q_2^*) \tag{10}$$

The Utopia point requires that both $(\hat{q}_1 - q_1^*)$ and $(\hat{q}_2 - q_2^*)$ are zero. Hence

$$\frac{d}{dx_i}((\hat{q}_1 - q_1^*)^2 + (\hat{q}_2 - q_2^*)^2) = 0 \tag{11}$$

The optimal control co-state equation (Upreti; 2013)[36] is

$$\frac{d}{dt}(\lambda_i) = -\frac{d}{dx_i}((\hat{q}_1 - q_1^*)^2 + (\hat{q}_2 - q_2^*)^2) - f_x\lambda_i; \quad \lambda_i(t_f) = 0 \tag{12}$$

λ_i is the Lagrangian multiplier. t_f is the final time. The first term in this equation is 0 and hence

$$\frac{d}{dt}(\lambda_i) = -f_x\lambda_i; \lambda_i(t_f) = 0 \tag{13}$$

At a limit or a branch point, for the set of ODES $\frac{dx}{dt} = f(x,u)$ f_x is singular. Hence there are two different vectors-values for $[\lambda_i]$ where $\frac{d}{dt}(\lambda_i) > 0$ and $\frac{d}{dt}(\lambda_i) < 0$. In between there is a vector $[\lambda_i]$ where $\frac{d}{dt}(\lambda_i) = 0$. This coupled with the boundary condition $\lambda_i(t_f) = 0$ will lead to $[\lambda_i] = 0$ This makes the problem an unconstrained optimization problem and the only solution is the Utopia solution.

Results and Discussion

For the bifurcation analysis, in Model 1 (De los Reyes et al 2015)[22], u_1 and u_2 were individually used as bifurcation parameters. Each of them revealed 2 limit points. The co-ordinates of the limit points when u_1 was used as the bifurcation parameter were

[G,M.A,D, u_1]= (0.575313 1.285863 1.707475 0.007599 0.287656) and

[G,M.A,D, u_1]=(0.391657 2.517528 0.745112 0.007599 0.195828).

Both these limit points are shown in **(Figure 1)**.

The co-ordinates of the limit points when u_2 was used as the bifurcation parameter were [G,M.A,D, u_2]= (0.100000 0.770733 2.709363 0.861295 1.133465) and

[G,M.A,D, u_2]=(0.100000 2.457335 0.768303 0.304074 0.400161).

Both these limit points are shown in **(Figure 2)**.

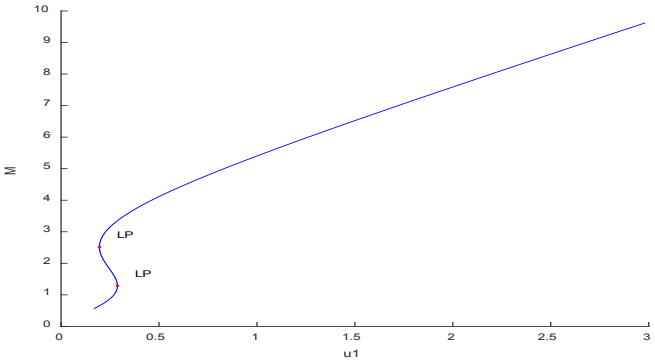

Figure 1: Limit points for model 1 when u1 was used as the bifurcation parameter.

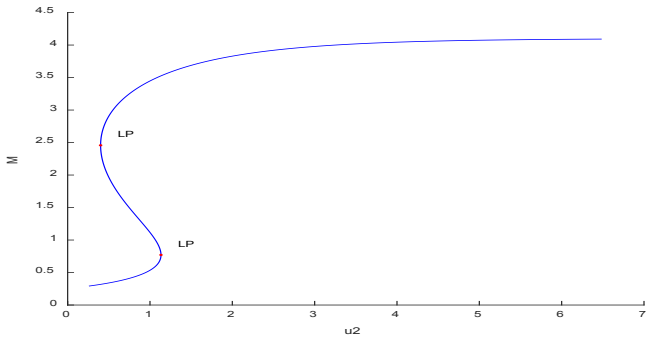

Figure 2: Limit points for model 1 when u2 was used as the bifurcation parameter.

For the MNLMPC calculations in this model $\sum_{t_i=0}^{t_i=t_f} M(t_i)$ and $\sum_{t_i=0}^{t_i=t_f} D(t_i)$ was maximized and resulted in a value of 10 each. $\sum_{t_i=0}^{t_i=t_f} u_1(t_i)$ and $\sum_{t_i=0}^{t_i=t_f} u_2(t_i)$ were minimized individually and resulted in a value of 0 each. The overall minimization that was done for the multiobjective calculation was done by minimizing $(\sum_{t_i=0}^{t_i=t_f} M(t_i) - 10)^2 + \sum_{t_i=0}^{t_i=t_f} D(t_i) - 10)^2 + (\sum_{t_i=0}^{t_i=t_f} u_1(t_i) - 0)^2 + (\sum_{t_i=0}^{t_i=t_f} u_2(t$. The first obtained control value was implemented and the remaing were discarded. This procedure was repeated until the first obtained and implemented control values were the same. The resulting MNLMPC control values of u_1 and u_2 were 0.30028 and 0.529579 respectively. The resulting minimized objective function value was 0 (the Utopia point) confirming the theorem in Sridhar (2024). The MNLMPC profiles for GMAD are shown in **(Figure 3)**. The obtained control profiles of u_1 and u_2 exhibited noise **(Figure 4)**. This was remedied using the Savitzky-Golay Filter. The smoothed-out version of this profile is shown in **(Figure 5)**.

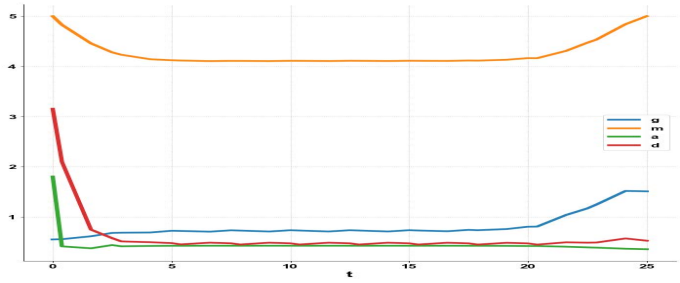

Figure 3: GMAD MNLMPC profiles (model 1).

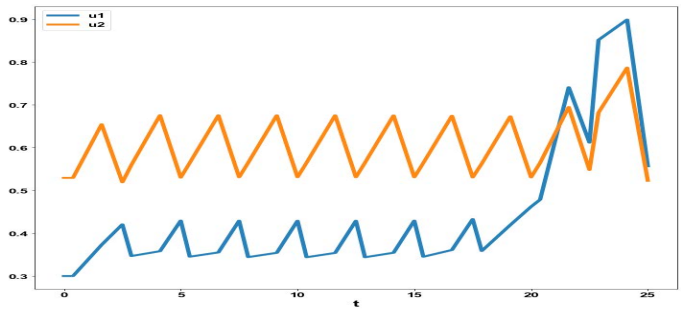

Figure 4: Noisy u1 and u2 MNLMPC profiles (model 1).

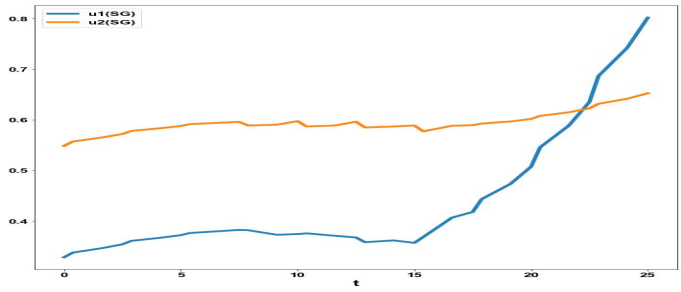

Figure 5: u1 and u2 MNLMPC profiles (model 1) with noise removed with Savitsky Golay Filter.

In Model 2[25], the bifurcation and control parameter was uc. The bifurcation analysis revealed a limit point at [u,v,w,uc]= (0.0146560.9809950.1338540.000990). This is shown in **(Figure 6)**. For the MNLMPC calculations in this model $\sum_{t_i=0}^{t_i=t_f} u(t_i)$ was minimized and resulted in a value of 0. To minimize control costs, $\sum_{t_i=0}^{t_i=t_f} v(t_i) + \sum_{t_i=0}^{t_i=t_f} w(t_i)$ was maximized and resulted in a value of 16.0002. The overall minimization that was done for the multiobjective calculation was done by minimizing $(\sum_{t_i=0}^{t_i=t_f} u(t_i) - 0)^2 + ((\sum_{t_i=0}^{t_i=t_f} v(t_i) + v(t_i)) - 16.002)^2$. This procedure was repeated until the first obtained and implemented control values were the same. The resulting MNLMPC control value of uc was 0.005496. The resulting minimized objective function value was 0 (the Utopia point) confirming the theorem in Sridhar[35]. The MNLMPC profiles for u v w are shown in **(Figure 7)**. The obtained control profiles of uc exhibited noise **(Figure 8)**. This was remedied using the Savitzky-Golay Filter. The smoothed-out version of this profile is shown in **(Figure 9)**.

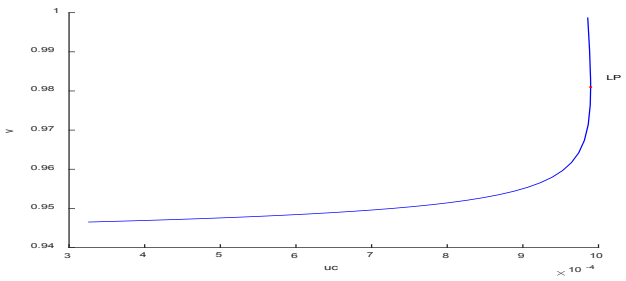

Figure 6: Bifurcation analysis for Model 2.

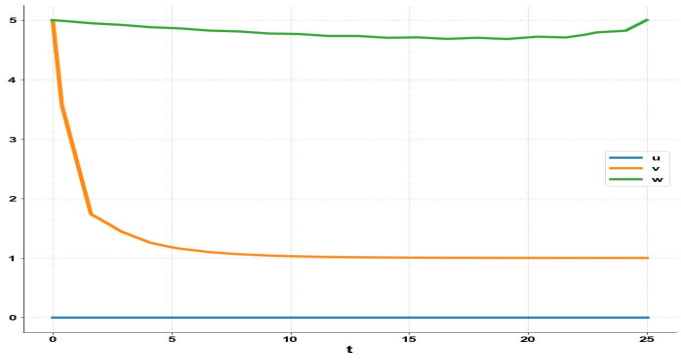

Figure 7: u,v,w MNLMPC profiles for Model 2.

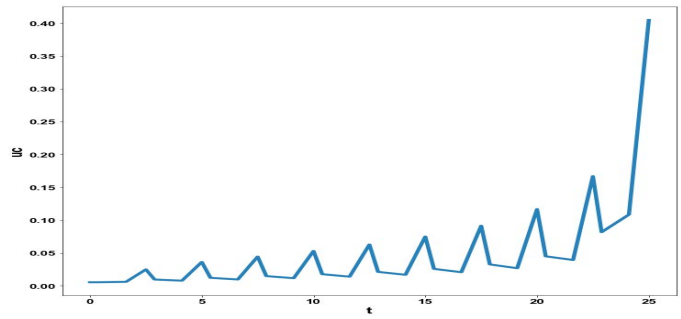

Figure 8: Noisy uc MNLMPC profiles (model 2).

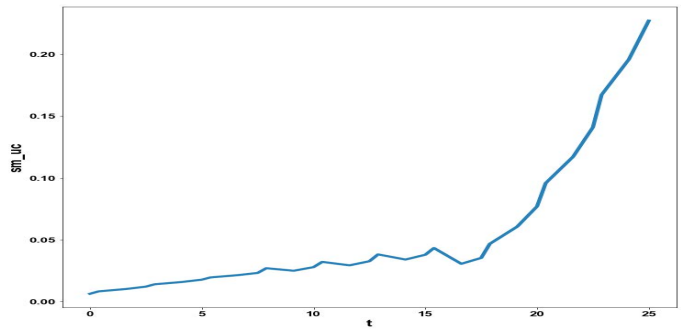

Figure 9: uc MNLMPC profiles (model 2) with noise removed with Savitsky Golay Filter.

Conclusion

Rigorous bifurcation analysis and Mult objective nonlinear model predictive control calculations were performed on models for glioma treatment. The bifurcation analysis revealed limit points which were beneficial because they allowed the Mult objective nonlinear model predictive control calculations to converge to the Utopia point which is the best solution.

Data Availability Statement

All data used is presented in the paper.

Conflicts of interest

The author, Dr. Lakshmi N Sridhar has no conflict of interest.

References

1. Swanson KR, Bridge C, Murray JD, Alvord Jr EC. Virtual and real brain tumors: Using mathematical modeling to quantify glioma growth invasion. J Neurol Sci 2003;216(1):1-10.
2. Farin A, Suzuki SO, Weiker M, Goldman JE, Bruce JN, Canoll P. Transplanted glioma cells migrate and proliferate on host brain vasculature: a dynamic analysis. Glia 2006;53:799-808.
3. Hardie DG. 2007 AMP-activated/SNF1 protein kinases: conserved guardians of cellular energy. Nat Rev Mol Cell Biol 2007;8:774-785.
4. Godlewski J, Nowicki MO, Bronisz A, et al. Targeting of the Bmi-1oncogene/stem cell renewal factor by microRNA-128 inhibits glioma proliferation and self-renewal. Cancer Res 2008;68:9125-9130.
5. Kronik N, Kogan Y, Vainstein V, Agur Z. Improving alloreactive CTL immunotherapy for malignant gliomas using a simulation model of their interactive dynamics, Cancer Immunol. Immunother 2008;57(3):425-439.
6. Kim Y, Lawler S, Nowicki MO, Chiocca EA, Friedman A. A mathematical model for pattern formation of glioma cells outside the tumor spheroid core. J Theor Biol 2009;260:359-371.
7. Lawler S, Chiocca EA. Emerging functions of microRNAs in glioblastoma. J Neurooncol 2009; 92:297-306.
8. Derr RL, Ye X, Islas MU, Desideri S, Saudek CD, Grossman SA. Association between hyperglycemia and survival in patients with newly diagnosed glioblastoma. J Clin Oncol 2009;27:1082-1086.
9. Godlewski J, Nowicki MO, Bronisz A, et al. MicroRNA-451 regulates LKB1/AMPK signaling and allows adaptation to metabolic stress in glioma cells. Mol Cell 2010;37:620-632.
10. Godlewski J, Bronisz A, Nowicki MO, Chiocca EA, Lawler S. microRNA-451: a conditional switch controlling glioma cell proliferation and migration. Cell Cycle 2010;9:2742-2748.
11. Wesseling P, Kros JM, Jeuken JWM. The pathological diagnosis of diffuse gliomas: towards a smart synthesis of microscopic and molecular information in a multidisciplinary context. Diagn Histopathol 2011;17:486-494.
12. Kim Y, Roh S, Lawler S, Friedman A. miR451 and AMPK mutual antagonism in glioma cell migration and proliferation: a mathematical model. PLOS ONE 2011;6:28293.
13. Gerlee P, Nelander S. The impact of phenotypic switching on glioblastoma growth and invasion. PLoS ONE Comput Biol 2012;8(6)**:**1002556.
14. Kim Y, Roh S. A hybrid model for cell proliferation and migration in glioblastoma. Discrete Contin Dyn Syst Ser B 2013;18:969-1015.
15. Kim Y. Regulation of cell proliferation and migration in glioblastoma: new therapeutic approach. Front Oncol 2013;3:53.
16. Song Y, Wang P, Zhao W, et al. MiR-18a regulates the proliferation, migration and invasion of human glioblastoma cell by targeting neogenin. Exp Cell Res 2014;324:54-64.
17. Guo M, Jiang Z, Zhnag X, et al. miR-656 inhibits glioma tumorigenesis through repression of BMPR1A. Carcinogenesis 2014;35:1698-1706.
18. Yang TQ, Lu XJ, Wu TF, et al. MicroRNA-16 inhibits glioma cell growth and invasion through suppression of BCL2 and the nuclear factor-kB1/MMP9 signaling pathway. Cancer Sci 2014;105:265-271.
19. Ma J, Yao Y, Wang P, et al. MiR-152 functions as a tumor suppressor in glioblastoma stem cells by targeting Kruppel-like factor 4. Cancer Lett 2014;355:85-95.
20. Wang L, Shi Z, Jiang C, et al. MiR-143 acts as a tumor suppressor by targeting N-RAS and enhances temozolomide-induced apoptosis in glioma. Oncotarget 2014;5:5416-5427.
21. Shi L, Wang Z, Sun G, Wan Y, Guo J, Fu X. miR-145 inhibits migration and invasion of glioma stem cells by targeting ABCG2. Neuromolecular Med 2014;16:517-528.
22. De los Reyes V AA, Jung E, Kim Y. Optimal control strategies of eradicating invisible glioblastoma cells after conventional surgery. J R Soc Interface 2015;12:20141392.
23. Khajanchi S, Banerjee S. Quantifying the role of immunotherapeutic drug T11 target structure in progression of malignant gliomas: mathematical modeling and dynamical perspective. Math Biosci 2017;289:69-77.
24. Khajanchi S. Modeling the dynamics of glioma-immune surveillance, Choas Solitons Fractals 2018;114:108-118.
25. Subhas K. Stability Analysis of a Mathematical Model for Glioma-Immune Interaction under Optimal Therapy. Int J Nonlinear Sci Numerical Simulation 2019;20(3-4):269-285.
26. Dhooge A, Govearts W, Kuznetsov AY. Matcont: A Matlab package for numerical bifurcation analysis of ODEs, ACM transactions on Mathematical software 2003;29(2):141-164.
27. Govaerts AW, Kuznetsov YA, Mestrom W, Riet AM. CL_ MATCONT; A continuation toolbox in Matlab 2004.
28. Kuznetsov YA. Elements of applied bifurcation theory. Springer, NY 1998.
29. Kuznetsov YA. Five lectures on numerical bifurcation analysis, Utrecht University 2009.
30. Govaerts WJF. Numerical Methods for Bifurcations of Dynamical Equilibria. SIAM 2000.
31. Flores-Tlacuahuac A. Morales P, Toledo MR. Mult objective Nonlinear model predictive control of a class of chemical reactors. I & EC research 2012:5891-5899.
32. William HE, Laird CD, Watson JP, et al. Siirola. Pyomo - Optimization Modeling in Python. Second Edition 2017;67.
33. Wächter A, Biegler L. On the implementation of an interior-point filter line-search algorithm for large-scale nonlinear programming. Math. Program 2006;106:25-57.
34. Tawarmalani M, Sahinidis NV. A polyhedral branch-and-cut approach to global optimization, Mathematical Programming 2005;103(2):225-249.
35. Sridhar LN. Coupling Bifurcation Analysis and Mult objective Nonlinear Model Predictive Control. Austin Chem Eng 2024;10(3):1107.
36. Ranjan US. Optimal control for chemical engineers. Taylor and Francis 2013