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Dynamics of Chemotherapy Models

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ABSTRACT

Chemotherapy is a drug treatment that uses powerful chemicals to kill fast-growing cancer cells. Cancer cells grow and multiply much more quickly than most cells in the body and it is necessary to destroy the cancerous cells to prevent the loss of life. Many different chemotherapy drugs are available. Since cancer cells multiply rapidly, the interaction dynamics between the drugs and the cancer cells need to be understood and controlled. Bifurcation analysis is a powerful mathematical tool used to describe the dynamics of any process. Several factors must be considered and multiple objectives need to be met simultaneously. Bifurcation analysis and multi objective nonlinear model predictive control (MNLMPC) calculations were performed on two chemotherapy models. 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 branch points in both models. The branch points were beneficial because they enabled the multi objective nonlinear model predictive control calculations to converge to the Utopia point, which is the best solution.

Keywords: Bifurcation Optimization; Control; Cancer tumor; Chemotherapy

Background

Agur, et al[1]. developed mathematical models for cancer immunotherapy. Robertson-Tessi, et al[2]. developed a mathematical model of tumor-immune interactions. Batmani, et al[3]. determined optimal drug regimens in cancer chemotherapy using a multi-objective approach. Wang, et al[4], introduced mathematical modeling in cancer drug discovery. Lopez, et al[5]. developed a validated mathematical model of tumor growth including tumor-host interaction, cell-mediated immune response and chemotherapy. Liu, et al[6]. developed a mathematical model of cancer treatment by radiotherapy. Roesch, et al[7]. performed modelling work involving lymphoma therapy. Michor, et al[8]. used mathematical modelling to improve cancer treatment. Robertson-Tessi, et al[9]. developed a model for studying adaptive immunity on tumor response to chemotherapy and chemoimmunotherapy.

Pang, et al[10]. developed a mathematical model and analyzed tumor treatment regimens with pulsed immunotherapy and chemotherapy. Feizabadi, et al[11]. modeled multi-mutation and drug resistance. Heesterman, et al[12]. discussed mathematical models for tumor growth and the reduction of overtreatment. Lestari, et al[13], discussed the dynamics of a mathematical model of cancer cells with Chemotherapy. Akhmetzhanov, et al[14], modeled bistable tumor population dynamics to design effective treatment strategies.

Subramanian, et al[15]. studied glioblastoma growth using a 3D multispecies tumor model with mass effect. Shu, et al[16]. performed mathematical modeling and bifurcation analysis of pro- and anti-tumor macrophages. Pang, et al[17]. performed a dynamic analysis of anti-tumor immune response. Magee, et al[18]. compared immunotherapy agents with chemotherapy in solid organ tumors.

Abernathy, et al[19]. developed a mathematical model for tumor growth and treatment using virotherapy. Yousef, et al[20], performed mathematical modeling of the immune-chemotherapeutic breast cancer treatment under some control parameters. Song, et al[21]. developed a mathematical model of cell-mediated immune response to tumors. Song, et al[22], performed mathematical Modeling and Analysis of Tumor Chemotherapy. Bashkirtseva, et al[23], modeled and analyzed tumor-immune interaction under chemotherapy and radiotherapy. Alqahtani, et al[24]. developed an Effector-cell Interactions under chemotherapy model.

Bifurcation analysis and single-objective optimal control calculations were performed disjointly on chemotherapy problems. This work involves the development of an integrating mathematical framework where Mult objective nonlinear model predictive control calculations (MNLMPC) are performed in conjunction with bifurcation analysis on two chemotherapy models described in Song, et al[22] and Alqahtani, et al[24].

This manuscript is organized as follows: First, the two models are presented, followed by a description of the numerical techniques (Bifurcation analysis and MNLMPC). The results, discussion and conclusions are then presented.

Chemotherapy Models

The chemotherapy models are very complex, with considerable differences in values of the variables and parameters involved. Hence, they are often scaled to make them more tractable. Two of the scaled models that will be used for the calculations are described in Song, et al[22] and Alqahtani, et al[24].

Model 1[22]

The scaled model variables are tumor cell population at time t (tval (t)), nval (t) the NK cell population, lval (t) for cytotoxic tval cell (CTLs) population and uval(t) the amount of drug at the tumor site. Natural killer cells (NK) are innate lymphocytes endowed with the ability to recognize and kill cancer cells.

$$\frac{d(nval)}{dt} = 10(nval)(1-0.018(nval)) - nval(tval+uval)$$

$$\frac{d(lval)}{dt} = nval(tval) - lval - (3.42(10^{-03})(lval)tval) - uval(lval);$$

$$\frac{d(tval)}{dt} = 25.7(tval(1-(2.04(10^{-04})tval))) - (nval(tval))$$

$$-6.02(10^{3})(lval)(tval) - 0.4(uval(tval))$$

$$\frac{d(uval)}{dt} s - 0.1(uval)$$

s is the ratio of the product of the Immune cell killed and drug Influx of drug divided by the square of the CTL death rate. It is used as the bifurcation parameter and the control variable. More details of this model are in Song, et al[22].

Model 2[24]

The scaled model equations are

$$\frac{d(eval)}{dt} = 0.12 + \frac{(1.13(eval)tval))}{(gval+tval)} \ldots$$

$$-(mval(eval)tval) - (0.37eval) - (450mval(eval))$$

$$\frac{d(tval)}{dt} = 1.636tval(1-0.002tval) - (eval(tval)) - (450mval(tval))$$

$$\frac{d(mval)}{dt} = -(8.18*mval) + vcont;$$

The effector cells are represented by eval (predator) and tumor cells by tval. The concentration of the chemotherapy drug is denoted mval. The amount of drug administered to the body is represented by vcont, which is used as the bifurcation parameter and the control variable.

Bifurcation Analysis

The MATLAB software MATCONT is used to perform the bifurcation calculations. Bifurcation analysis deals with multiple steady-states and limit cycles. Multiple steady states occur because of the existence of branch and limit points. Hopf bifurcation points cause limit cycles. A commonly used MATLAB program that locates limit points, branch points and Hopf bifurcation points is MATCONT[25,26]. This program detects Limit points (LP), branch points (BP) and Hopf bifurcation points(H) for an ODE system

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

$x \in R^n$ Let the bifurcation parameter be α Since the gradient is orthogonal to the tangent vector,

The tangent plane at any point $w = [w_1, w_2, w_3, w_4, \ldots w_{n+1}]$ must satisfy

$$Aw = 0$$

Where A is

$$A = [\partial f / \partial x \quad | \partial f / \partial \alpha]$$

where $\partial f / \partial x$ is the Jacobian matrix.

For both limit and branch points, the matrix $[\partial f / \partial x]$ must be singular. The n+1 th component of the tangent vector w_{n+1} = 0 for a limit point (LP)and for a branch point (BP) the matrix $\begin{bmatrix} A \\ w^T \end{bmatrix}$ must be singular. At a Hopf bifurcation point,

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

@ 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[27,28] and Govaerts[29].

Mult objective nonlinear model predictive control

Flores Tlacuahuaz, et al[30], developed a Mult objective nonlinear model predictive control (MNLMPC) method that is rigorous and does not involve weighting functions or additional constraints. This procedure is used for performing the MNLMPC calculations.

Here $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ (j=12.n) represents the variables that need to be minimized/maximized simultaneously for a problem involving a set of ODES

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

t_f being the final time value and n the total number of objective variables and . u the control parameter. This MNLMPC procedure 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

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

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

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 ($\sum_{t_{i=0}}^{t_i=t_f} q_j(t_i)=q_j^*$ for all j) is obtained.

Pyomo[31], is used for these calculations. Here, the differential equations are converted to a Nonlinear Program (NLP) using the orthogonal collocation method The NLP is solved using IPOPT[32] and confirmed as a global solution with BARON[33].

The steps of the algorithm are as follows

Optimize $\sum_{t_{i=0}}^{t_i=t_f} q_j(t_i)$ and obtain q_j^* at various time intervals t_i. The subscript *i* is the index for each time step.

Minimize $(\sum_{j=1}^{n}(\sum_{t_{i=0}}^{t_i=t_f} q_j(t_i)-q_j^*))^2$ and get the control values for various times.

Implement the first obtained control values

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 $\sum_{t_{i=0}}^{t_i=t_f} q_j(t_i)=q_j^*$ for all j.

Sridhar[34], 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[35]. If the minimization of q_1 lead to the value q_1^* and the minimization of q_2 lead to the value q_2^* The MNLPMC calculations will minimize the function $(q_1-q_1^*)^2+(q_2-q_2^*)^2$. The Mult objective optimal control problem is

$$\min\ (q_1-q_1^*)^2+(q_2-q_2^*)^2\quad subject\ to\ \frac{dx}{dt}=F(x,u)$$

Differentiating the objective function results in

$$\frac{d}{dx_i}((q_1-q_1^*)^2+(q_2-q_2^*)^2)=2(q_1-q_1^*)\frac{d}{dx_i}(q_1-q_1^*)+2(q_2-q$$

The Utopia point requires that both $(q_1-q_1^*)$ and $(q_2-q_2^*)$ are zero. Hence

$$\frac{d}{dx_i}((q_1-q_1^*)^2+(q_2-q_2^*)^2)=0$$

the optimal control co-state equation (Upreti; 2013) is

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

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

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

At a limit or a branch point, for the set of ODE $\frac{dx}{dt}=f(x,u)$ 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.

Hopf bifurcations cause unwanted oscillatory behavior and limit cycles. The tanh activation function (where a control value u is replaced by) $(u\tanh u/\varepsilon)$ is commonly used in neural nets[36-38] and optimal control problems[39] to eliminate spikes in the optimal control profile. Hopf bifurcation points cause oscillatory behavior. Oscillations are similar to spikes and the results in Sridhar(2024b) demonstrate that the tanh factor also eliminates the Hopf bifurcation by preventing the occurrence of oscillations. Sridhar[40], explained with several examples how the activation factor involving the tanh function successfully eliminates the limit cycle causing Hopf bifurcation points. This was because the tanh function increases the time period of the oscillatory behavior, which occurs in the form of a limit cycle caused by Hopf bifurcations.

Results and Discussion

The bifurcation analysis performed with MATCONT on model 1 revealed a branch point at (nval, lval, tval, uval, s) = (0,0, 0, 10, 1). The bifurcation parameter is s. This branch point BP resulted in 2 solution branches as shown in **(Figure 1)**.

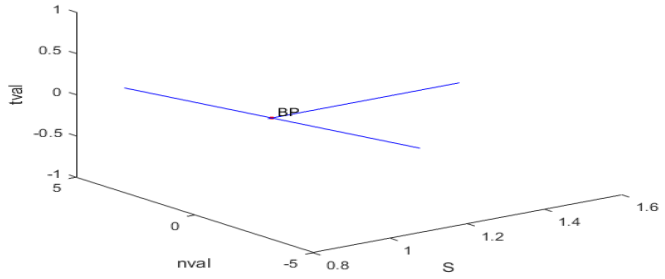

Figure 1: Bifurcation Diagram (Model 1).

For the MNLMPC calculation, with s is the control variable, $\sum_{t_{i=0}}^{t_i=t_f} tval_j(t_i)$ was minimized, leading to a value of 0 and $\sum_{t_{i=0}}^{t_i=t_f} nval_j(t_i)$ was maximized resulting in a value of 20. The overall optimal control problem will involve the minimization of $(\sum_{t_{i=0}}^{t_i=t_f} tval_j(t_i)-0)^2+(\sum_{t_{i=0}}^{t_i=t_f} nval_j(t_i)-20)^2$ subject to the ODE describing Model 1. This minimization resulted in the Utopia point (0) confirming the analysis of Sridhar[34], which showed that the presence of a branch point enables the MNLMPC calculations to reach the best possible (Utopia) solution. The first of the control variable is implemented and the rest are discarded. The process is repeated until the difference between the first and second values of the control variables are the same. This MNLMPC control value was 0.8409. The various MNLMPC profiles are shown in **(Figure 2)**. The obtained control profile of s exhibited a lot of noise **(Figure 3)**. This was remedied using the Savitzky-Golay Filter. The smoothed-out version of this profile is shown in **(Figure 4)**.

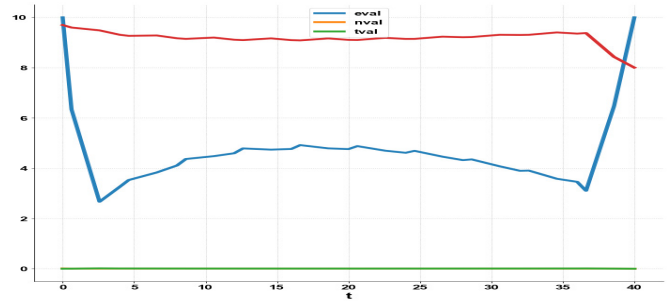

Figure 2: eval, nval , tval (MNLMPC model 1).

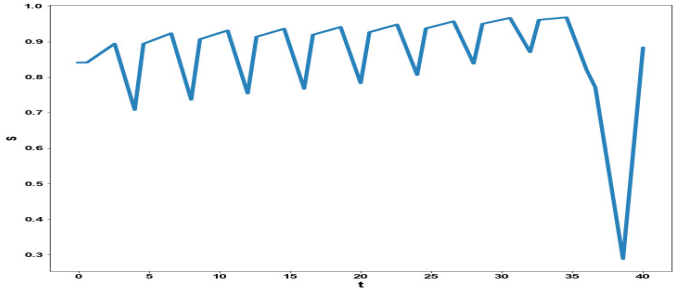

Figure 3: s profile (MNLMPC model 1).

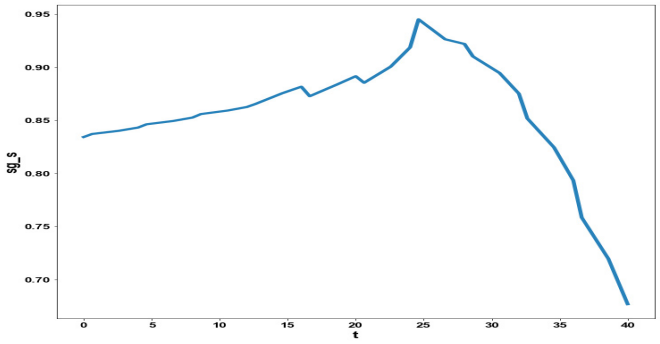

Figure 4: s profile with Savitsky Golay filter MNLMPC model 1).

In model 2, a branch point was obtained at (eval, tval, mval, vcont) = (0.061719 0.0, 0.003498, 0.028617). This is shown in **(Figure 5)**.

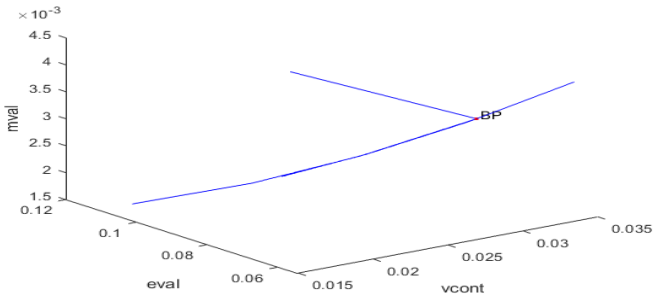

Figure 5: Bifurcation Diagram (Model 2).

For the MNLMPC calculation, using vcont is the control variable, $\sum_{t_{i=0}}^{t_i=t_f} tval_j(t_i)$ and $\sum_{t_{i=0}}^{t_i=t_f} eval_j(t_i)$ are both minimized, each leading to a value of 0 The overall optimal control problem will involve the minimization of $(\sum_{t_{i=0}}^{t_i=t_f} tval_j(t_i)-0)^2+(\sum_{t_{i=0}}^{t_i=t_f} eval_j(t_i)-0)^2$ subject to the ODE describing Model 2. This minimization resulted in the Utopia point (0) confirming the analysis of Sridhar[34], which showed that the presence of a branch point enables the MNLMPC calculations to reach the best possible (Utopia) solution. The first of the control variable is implemented and the rest are discarded. The process is repeated until the difference between the first and second values of the control variables are the same. This MNLMPC control value was .2385. The various MNLMPC profiles are shown in **(Figure 6)**. The obtained control profile of s exhibited noise **(Figure 7)**. This was remedied using the Savitzky-Golay Filter. The smoothed-out version of this profile is shown in **(Figure 8)**. Although one of the branches is in an infeasible region **(Figure 2)** the branch point in the feasible region indicates a singularity of the Jacobian matrix. This singularity causes the MNLMPC calculations to converge to the Utopia point.

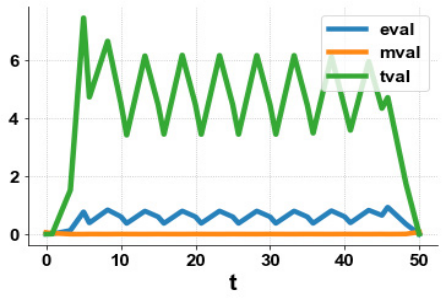

Figure 6: eval, mval, tval profiles MNLMPC model 2).

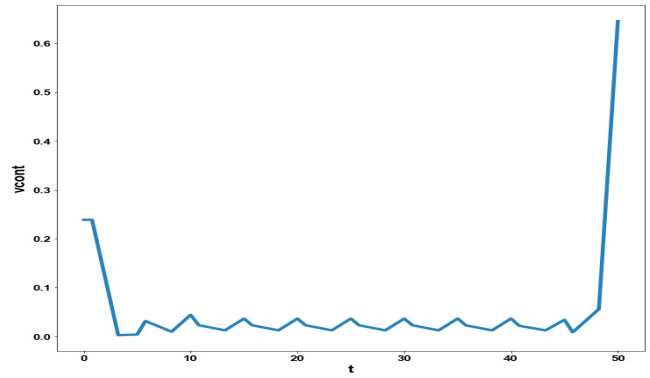

Figure 7: vcont profile MNLMPC model 2)

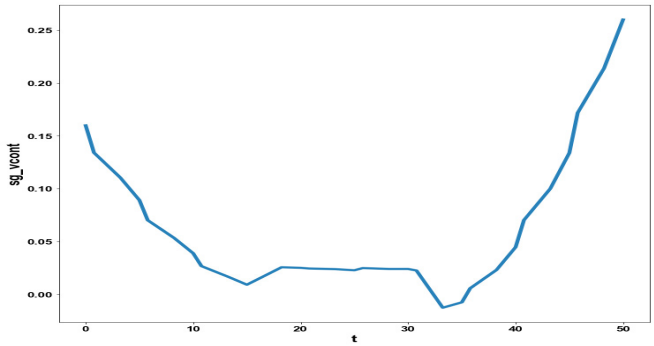

Figure 8: vcont profile with Savitsky Golay filter MNLMPC model 2).

Conclusion

Mult objective nonlinear model predictive control calculations were performed along with bifurcation analysis on scaled chemotherapy models. The bifurcation analysis revealed the existence of brach points that produced different solution branches originating from a singular point. The presence of a branch point is very beneficial as it caused the Mult objective nonlinear model predictive calculations to converge to the Utopia point, which is the best possible solution.

Data Availability Statement

All data used is presented in the paper.

Conflict of interest

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

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