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Analysis and Control of CAR T Cell Therapy Model for Solid Tumors with by Stander Effects

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ABSTRACT

CAR T-cell therapy is a new type of cancer treatment that uses the immune system to kill cancer cells. In many situations, it has cured people where all other treatments have failed. The interaction between the CAR T cells and the cancer cells is very complex and highly nonlinear and to get the best results, one must consider several factors. This work involves the development of a rigorous mathematical framework to deal with the high degree of complexity in the model describing CAR T cell therapy for solid tumors with bystander effects. Bifurcation analysis and Mult objective nonlinear model predictive control (MNLMPC) calculations were was performed on this model that involves CAR T cell therapy for solid tumors with bystander effects 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 a limit point. This limit was beneficial because it enabled the Mult objective nonlinear model predictive control calculations to converge to the Utopia point which is the best solution.

Keywords: Bifurcation; Optimization; Control; Cancer tumor; CAR-T cells

Background

Martinez, et al[1], studied the effects of CAR T cells for solid tumors and provide new strategies for finding, infiltrating and surviving in the tumor microenvironment. Klampatsa, et al[2], describe the effects of the bystander cells on a syngeneic mouse cancer model. Sahoo, et al[3], studied the mathematical deconvolution of CAR-T cell proliferation and exhaustion from real-time killing assay data. Braendstru, et al[4], discussed the first approved gene therapy (chimeric antigen receptor t cells targeting cd19.). Lai, et al[5], researched the adoptive cellular therapy with t cells expressing the dendritic cell growth factor and Sterner, et al[6], studied the various limitations of CAR-T cell therapy. Marofi, et al[7], investigated the performance of CAR T cells in solid tumors. Cosenza, et al[8], researched the Cytokine release syndrome associated with t-cell-based therapies for hematological malignancies. Upadhyay, et al[9], demonstrated the critical role of fast-mediated off-target tumor killing in t-cell immunotherapy. León-Triana, et al[10], computationally Studied CAR T cell therapy in b-cell acute lymphoblastic leukemia. Barros, et al[11], developed Cartmath, a mathematical model of CAR-T immunotherapy in preclinical studies of hematological cancers. Owens et al[12], discussed the modeling of car t-cell therapy with patient preconditioning. Silveira, et al[13], showed that Cytokinesw as an important player in CAR-T cell therapy for cancer and discussed their role in tumor immunomodulation. Safarzadeh Kozani P, et al[14], reviewed the recent advances in solid tumor CAR-T cell therapy: Jia, et al[15], demonstrated the heterogeneity of the tumor immune microenvironment and its clinical relevance. Rotte, A, et al[16], studied the dose-response correlation for CAR-T cells with a systematic review of clinical

studies Liu L, et al[17], provided a computational model of car t-cell immunotherapy that dissects and predicts leukemia patient responses at remission, resistance and relapse. Santurio, et al[18], mathematically described the resistance mechanisms to CAR-T cell immunotherapy. Cappell, et al[19], discussed the. long-term outcomes following CAR-T cell therapy. Kara, et al[20], developed a mathematical model involving CAR T cell therapy for solid tumors with bystander effects. This work aims to perform rigorous bifurcation analysis and Mult objective nonlinear model predictive control (MNLMPC) calculations for the CAR-T cell therapy model described in Kara, et al (20240[20] and demonstrate that the presence of a limit point revealed by the bifurcation analysis is beneficial as it enables the MNLMPC calculations to yield the Utopia point which is the best possible solution. The paper is organized as follows. The model equations are first described. This is followed by the numerical methods (bifurcation analysis and MNLMPC). The results and discussion are then presented followed by the conclusions.

Model Equations for Car-T Cell Tumor Interaction

The model equations are

$$\frac{dT_{POS}}{dt}=\left(r_1T_{POS}\frac{\left(1-\left(T_{POS}+T_{NEG}\right)\right)}{K_1}-\left(T_{POS}*db_{cap}\right)-\left(T_{POS}*dc_{cap}\right)\right);$$

$$\frac{dT_{NEG}}{dt}=\left(r_2T_{neg}\frac{\left(1-\left(T_{POS}+T_{NEG}\right)\right)}{K_1}-\left(T_{NEG}*dr_{cap}\right)\right);$$

$$\frac{dCval}{dt}=(\nu_C-(\gamma_cCval)-(\omega_cCvalT_{POS})$$

$$-(\mu_c*Cval*(dc_{cap}{}^2)/(k+(dc_{cap}{}^2))\frac{log((Bval+Cval)}{K_2})));$$

$$\frac{dBval}{dt}=(bpar-(\gamma_BBval)-(\omega_BBval(T_{POS}+T_{NEG}))-$$

$$(\mu_b*Bval*(db_{cap}{}^2)/(k+(db_{cap}{}^2))\frac{log((Bval+Cval)}{K_2})));\quad(1)$$

$$bp=(Bval/T_{POS})^l;$$

$$cp=(Cval/T_{POS})^l;$$

$$rp=(Bval/T_{NEG})^l;$$

$$db_{cap}=(db)bp/\left(s+bp\right);$$

$$dc_{cap}=(dc)cp/\left(s+cp\right);$$

$$dr_{cap}=(db)rp/\left(s+rp\right);\quad(2)$$

The parameter values are

$$r_1=0.18,r_2=0.21,K_1=5.1e+03,l=1.56,\mu_c=0.6,d_c0.41,s=0.305,$$
$$k=2.019e-07,\omega_c=3.e-05,K_2=1.65e+03,d_B=0.3,$$
$$\mu_B=0.89,bpar=1.4e-03,\gamma_B=7.e-03,\omega_B=3.42e-06$$

$r_1,r_2,K_1,l,\mu_c,d_c,s$ represent the Tpos proliferation rate (1/day), Tneg proliferation rate (1/day) ,Tpos and Tneg carrying capacity (mm^3), exponent of tumor lysis (unit-less), maximum recruitment rate of CAR T cells by antigen-positive tumor lysis(1/day) and the steepness of fractional antigen-negative tumor kill (unit-less). $\gamma_c,k,\omega_c,K_2,d_B$ represent CAR T cell death rate(1/day),steepness of CAR T cell/bystander recruitment(1/day^2), CAR T inhibition due to antigen-positive cells(1/day), immune cell carrying capacity (mm^3) and maximum killing rate of antigen-positive/antigen-negative cells via bystanders (1/day). $\mu_B,bpar,\gamma_B,\omega_B$ represent maximum recruitment rate of bystanders by antigen-positive tumor lysis (1/day), base recruitment rate of bystanders (mm^3/day), bystander death rate (1/day), bystander inhibition due to antigen-positive/antigen-negative cells (mm^3/day). T_{POS} and T_{NEG} , representing the quantities of target antigen-positive and target antigen-negative tumor cells measured in units of mm^3, respectively Cval and Bval are the quantities of CAR T cells and bystander cells present within the tumor micro-environment, also measured in units of mm^3. γ_c is the bifurcation parameter for the bifurcation analysis and the control variable for the MNLMPC calculations.

Numerical Methods

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 (Dhooge Govearts and Kuznetsov[21]; Dhooge Govearts, Kuznetsov, Mestrom and Riet[22]. This software detects Limit points (LP), branch points (BP) and Hopf bifurcation points(H). Consider an ODE system

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

$x\in R^n$ Let the tangent plane at any point x be $W=\left[W_1,W_2,W_3,W_4,....W_{n+1}\right]$. Define matrix A given by

$$A=\begin{bmatrix}\frac{\partial f_1}{\partial x_1}&\frac{\partial f_1}{\partial x_2}&\frac{\partial f_1}{\partial x_3}&\frac{\partial f_1}{\partial x_4}.....&\frac{\partial f_1}{\partial x_n}&\frac{\partial f_1}{\partial \alpha}\\ \frac{\partial f_2}{\partial x_1}&\frac{\partial f_2}{\partial x_2}&\frac{\partial f_2}{\partial x_3}&\frac{\partial f_2}{\partial x_4}.....&\frac{\partial f_2}{\partial x_n}&\frac{\partial f_2}{\partial \alpha}\\ .....\\ .....\\ \frac{\partial f_n}{\partial x_1}&\frac{\partial f_n}{\partial x_2}&\frac{\partial f_n}{\partial x_3}&\frac{\partial f_n}{\partial x_4}.....&\frac{\partial f_n}{\partial x_n}&\frac{\partial f_n}{\partial \alpha}\end{bmatrix}\quad(4)$$

The bifurcation parameter is the matrix A can be expressed as

$$A=[\partial f/\partial x\ \ |\partial f/\partial\alpha]\quad(5)$$

Where is the Jacobian matrix. Since the gradient is orthogonal to the tangent vector,

$$Aw=0\quad(6)$$

For both limit and branch points the matrix $[\partial f/\partial x]$ must be singular. For a limit point (LP) the n+1th 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,

$$\det(2f_x(x,\alpha)@I_n)=0 \qquad (7)$$

@ indicates the bialternate product while 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[23,24] and Govaerts[25].

Nonlinear model predictive control

The Mult objective nonlinear model predictive control (MNLMPC) method[26] used in these calculations is rigorous and does not involve weighting functions, nor does it impose additional constraints on the problem unlike the weighted function or the epsilon correction method.

Let $q_j(t_f)$ (j=12.n) be the variables that need to be minimized/maximized simultaneously for a problem involving a set of ODES

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

t_f is 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 $q_j(t_f)$ individually. The minimization/maximization of $q_j(t_f)$ will lead to the values q_j^*. Then the optimization problem that will be solved is

$$\min\left(\sum_{j=1}^{n}(q_j(t_f)-q_j^*)\right)^2$$
$$subject\ to\ \frac{dx}{dt}=F(x,u); \qquad (9)$$

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 or if the Utopia point ($q_j(t_f)=q_j^*$) for all j. is obtained. The optimization package in Python, Pyomo[27], 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[28] and confirmed as a global solution with BARON[29]. To summarize the steps of the algorithm are as follows

- Optimize $q_j(t_f)$ 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^* . t_f is the final time.
- Minimize $\left(\sum^{n}(q_j(t_f)-q_j^*)\right)^2$ 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 $q_j(t_f)=q_j^*$ for all j.

Sridhar[30] proved that the MNLMPC calculations to converge to the Utopia solution when the bifurcation analysis revealed the presence of limit and branch points. The Utopia point is when $q_j(t_f)=q_j^*$ for all j. This was done by imposing the singularity condition on the co-state equation31. If the minimization be of the variable q_1 lead to the value q_1^* and the minimization of function 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

$$\min\quad (q_1-q_1^*)^2+(q_2-q_2^*)^2\quad subject\ to\ \frac{dx}{dt}=F(x,u) \qquad (10)$$

$$\frac{d}{dx_i}((q_1-q_1^*)^2+(q_2-q_2^*)^2)=2(q_1-q_1^*)\frac{d}{dx_i}(q_1-q_1^*)+2(q_2-q_2^*)\frac{d}{dx_i}(q_2-q_2^*) \qquad (11)$$

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

$$\frac{d}{dx_i}((q_1-q_1^*)^2+(q_2-q_2^*)^2)=0 \qquad (12)$$

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

$$\frac{d}{dt}(\lambda_i)=-\frac{d}{dx_i}((q_1-q_1^*)^2+(q_2-q_2^*)^2)-f_x\lambda_i;\quad \lambda_i(t_f)=0 \qquad (13)$$

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

$$\frac{d}{dt}(\lambda_i)=-f_x\lambda_i;\lambda_i(t_f)=0 \qquad (14)$$

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 [ ] 0 This makes the problem an unconstrained optimization problem and the only solution for the unconstrained problem is the Utopia solution.

Results and Discussion

For the bifurcation analysis γ_c is the bifurcation parameter. The bifurcation analysis revealed a limit point at $[T_{POS},T_{NEG},Cval,Bval,\gamma_c]$ values of (5058.031223 3.544963 60.851452 0.057588 1.648362). This limit point causes multiple steady-states and is shown in **(Figure 1)**, For the MNLMPC

calculation, a γ_c is the control variable. $T_{POS}(t_f), T_{NEG}(t_f)$, are minimized individually and lead to the values of 0.071709 and 0 respectively. $(db_{cap}(t_f) + dC_{cap}(t_f))$ which is a factor that determines the killing of the antigen-positive tumor population is maximized. This maximization results in a value of 0.599. The overall optimal control problem will involve the minimization of $(db_{cap}(t_f) + dC_{cap}(f) - 0.599)^2 + (T_{NEG}(t_f))^2 + (T_{POS}(t_f) - 0.071709)^2$ subject to the equations governing this problem. This minimization resulted in the Utopia point value of 0. 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 variable, γ_c are the same. This MNLMPC control value was 0.15425. The result of obtaining the Utopia solution in the MNLMPC calculation confirms the analysis of Sridhar (2024) which stated that the presence of a limit point enables the MNLMPC calculation s to reach the best possible (Utopia) solution. The various MNLMPC profiles are shown in **(Figures 2-5)**.

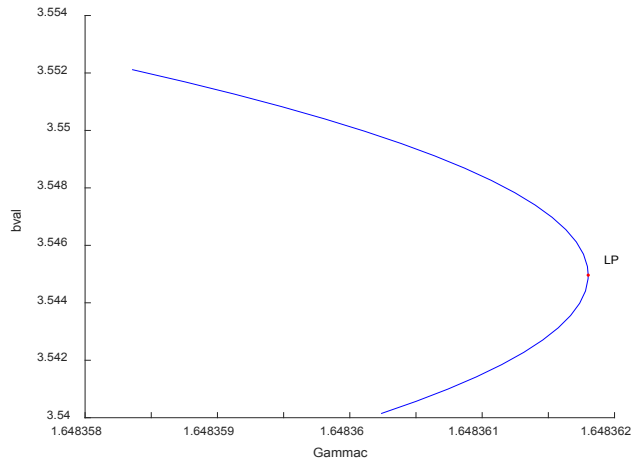

Figure 1: Bifurcation diagram for CART-cell tumor interaction model.

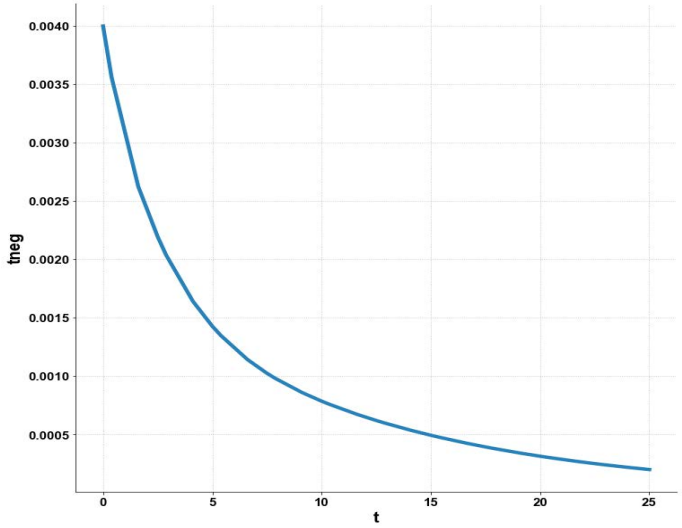

Figure 2: T_{NEG} vs t for MNLMPC calculation.

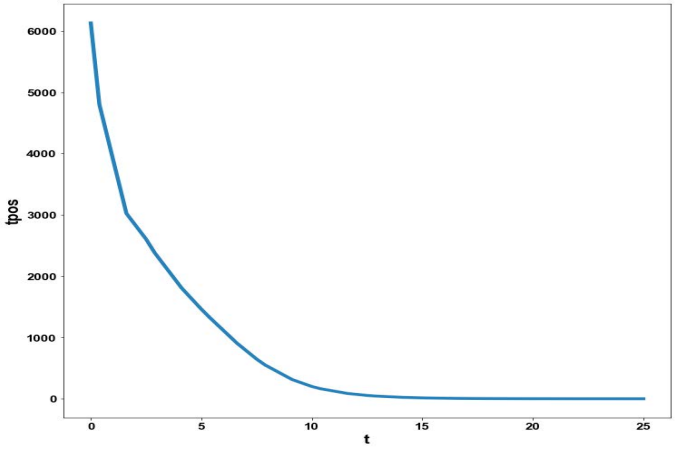

Figure 3: T_{POS} vs t for MNLMPC calculation.

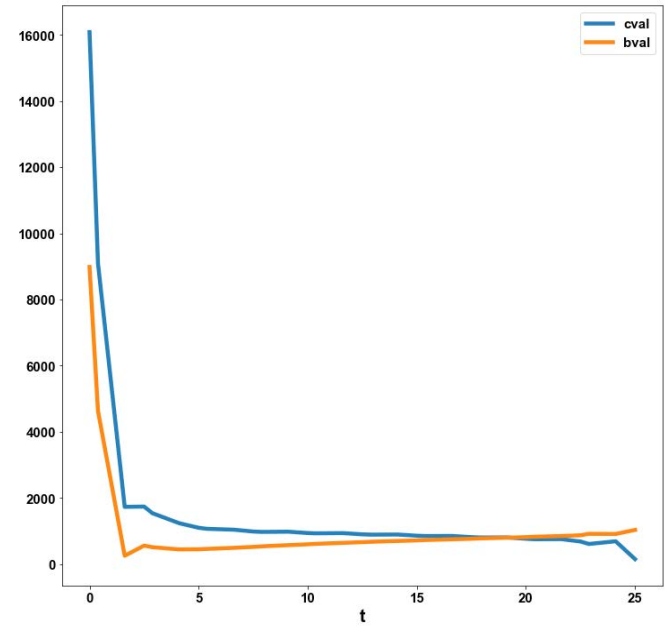

Figure 4: Cval, Bval profiles for MNLMPC calculation.

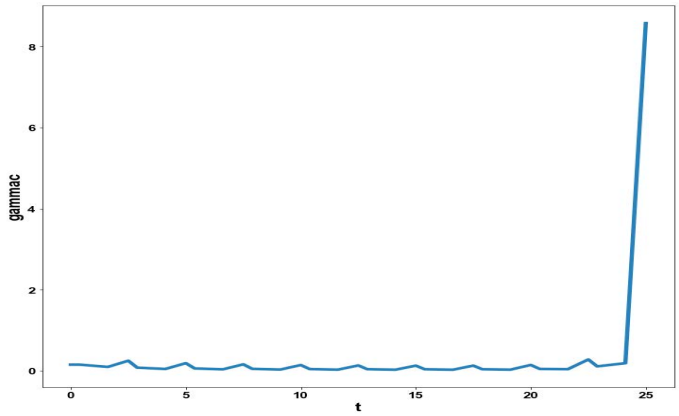

Figure 5: control value profile for MNLMPC calculation.

Conclusion

Rigorous bifurcation analysis and Mult objective nonlinear model predictive control calculations were performed on a model involving CAR T cell therapy for solid tumours with bystander effects The bifurcation analysis revealed a limit points. The limit point was beneficial because it enabled 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.

Conflict of interest

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

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