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# Bifurcation Analysis and Optimal Control of the Tumor Macrophage Interactions

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**ABSTRACT**

Bifurcation analysis and optimal control was performed on a model describing the interaction between tumors and macrophages. The MATLAB program MATCONT was used to perform the bifurcation analysis and the optimization language promo is used in conjunction with the state-of-the-art global optimization solvers IPOPT and BARON for the optimal control calculations. Both single and multi-objective nonlinear model predictive control (that involves Multi objective optimal control) calculations were performed. The bifurcation analysis revealed oscillation causing Hopf bifurcations while the optimal control showed the existence of spikes in the control profiles. Both were eliminated using an activation factor involving the hyperbolic tangent function.

**Keywords:** Bifurcation; Optimization; Control; Macrophage; Tumor

## Introduction

Genetically engineered macrophages that kill tumor cells cause inflammation, leading to DNA and tissue damage. This is remedied by alternatively activated macrophages that can reduce inflammation and repair tissue damage. The interaction between the tumor cells and the two macrophages demonstrates oscillatory behavior that from a mathematical standpoint arises from the existence of a Hopf bifurcation. Oscillations are similar to the existence of spikes in a control profile. Traditionally spikes in optimal control problems are eliminated using a Tanh activation factor. This raises the question of whether using the tanh activation factor will eliminate the unwanted oscillatory behavior that exists because of a Hopf bifurcation. In this work, both bifurcation analysis and optimal control are performed on a scaled dynamic model involving tumor cells and macrophages and it is shown that just as in optimal control, the tanh factor is effective in the elimination of spikes, it also eliminates the Hopf bifurcation that causes oscillatory behavior.

## Background

Mantovani and co-workers [1-3] studied tumor immunity, macrophage polarization, and the effect of Macrophage immunity on cancer. Wilke and Hahnfeldtt [4] developed a model studying the dichotomy of the immune response to cancer: Rakoff-Nahoum [5] studied the interaction between cancer and inflammation Prehn [6] studied investigated the effect of the immune reaction on the as a stimulator of tumor growth. Sica and co-workers [7] investigated Macrophage polarization in tumor progression. The two macrophages' phenotypes are divided into M1 and M2 macrophages. M1 cells have anti-tumor properties that can produce pro-inflammatory cytokines to eradicate pathogens but can cause tissue and DNA damage. M2 cells can reduce the pro-inflammatory response and stimulate tissue repair. Allavena and Mantovani [8] suggested a re-polarization of macrophages towards the classically activated M1 cells, as an effective treatment approach to ensure tumor elimination. A considerable amount of computational work has been done dealing with tumor macrophage interactions. As early as 1985, De Boer, et al. [9] presented a mod-

el of the interactions between macrophages and T lymphocytes that generate an anti-tumor immune response. Owen and Sherratt [10] developed a five-dimensional differential equations model to study the roles of macrophages presence, influx, and ability to selectively kill tumor cells in avascular tumors. They verified that the proportion of macrophages in tumors increases with the chemotactic activity of the mutant cell line. Byrne, et al. [11] proposed a mathematical model that describes the interactions between normal cells, tumor cells and infiltrating macrophages, to evaluate the ability of the engineered macrophages to eliminate the tumor changes as model parameters vary Owen, et al. [12] investigated the role of chemotaxis, chemokine production and the efficacy of macrophages as vehicles for drug delivery to hypoxic tumor sites.

Webb, et al. [13] extended the model of Owen [12] to show that limited-diffusivity or non-cell- cycle dependent drugs help macrophages effectively target hypoxic tumor cells. Eftimie [14-16] studied the complex dynamics in the interactions between the macrophages and tumor cells. Dong, et al. [17] and Ghosh [18] and Liu, et al. [19] show that the models describing the dynamics of macrophage and tumor interactions exhibit periodic oscillations which indicate the presence of Hopf bifurcations. Shu, et al. [20] show the existence of Hopf bifurcations in the model describing the interaction between tumor cells, M1 and M2 macrophages. Sridhar [21] showed that the use of the hyperbolic tangent activation factor was effective in removing spikes in a control profile. Repeated spikes are similar to oscillatory behavior and the aim of this paper is to use a similar hyperbolic tangent activation factor on the tumor macrophage interaction model and demonstrate that the oscillation causing Hopf bifurcation can be eliminated. This paper is organized as follows. First, the tumor macrophage interaction model Shu, et al. [20] is described. This is followed by a discussion of the bifurcation analysis and the multi-objective nonlinear model predictive control strategy that involves optimal control. The results are then presented and discussed followed by conclusions.

## Tumor Macrophage Interaction Model

The model and its scaled version Shu, et al. [20] is presented in this section. The model includes three variables: the population of tumor cells (T), the population of M1 macrophages (M1) and the population of M2 macrophages (M2). The interactions among these three cells is described by the following differential equations:

$$\frac{Tt}{dt} = \alpha T\left(1-bT\right) - fTM_1 + GTM_2 \quad (1)$$

$$\frac{dM_1}{dt} = e_1 TM_1 - d_1 M_1 - r_1 M_1 - r_2 M_2 \quad (2)$$

$$\frac{dM_2}{dt} = e_2 TM_2 - d_2 M_2 + r_1 M_1 - r_2 M_2 \quad (3)$$

The model parameter values are : $t(0)=10^6$, $M1(0)=10^6$, $M2(0)=10^6$, $a=0.565$, $b^{-1}=2X10^{-9}$, $d_1=0.2$, $d_2=0.2$, $f=2X10^{-9}$, $q=10^{-7}$, $e_1=10^{-6}$, $e_2=9X10^{-7}$, $r_1=0.05$, $r_2=0.04$,

Owing to the large variation of parameters convergence for bifurcation analysis and optimal control is difficult. Hence a scaled model is developed. The scaled model non-dimensional variables are $x=\frac{T}{T(0)}$, $y=\frac{M_1}{M_1(0)}$, $z=\frac{M_2}{M_{2(0)}}$, $\alpha=\frac{a}{e_1 T(0)}$, $\beta=bt(0)$, $\delta=\frac{f}{e_1}$, and

the equations are:

$$\frac{dx}{dt} = \alpha x\left(1-\beta y\right) - \delta xy + \eta xz \quad (4)$$

$$\frac{dy}{dt} = xy - \mu_1 y - r_1 y + r_1 z \quad (5)$$

$$\frac{dz}{dt} = \zeta xz - \mu_2 z + r_1 y - r_2 z \quad (6)$$

$\alpha=0.5650$, $\beta=0.505$, $\delta=2$, $r_1=0.05$, $r_2=0.0444$, $\mu_1=0.2$, $\mu_2=0.2222$,

$\zeta$ is the bifurcation parameter and the control variable.

## Bifurcation Analysis

There has been a lot of work in chemical engineering involving bifurcation analysis throughout the years, The existence of multiple steady-states and oscillatory behavior in chemical processes has led to a lot of computational and analytical work to explain the causes for these nonlinear phenomena. Multiple steady states are caused by the existence of branch and limit points while oscillatory behavior is caused by the existence of Hopf bifurcations points. In the case of branch points and limit points the Jacobian matrix of the set of steady-state equations is singular. However, at a branch point, there are 2 distinct tangents at the singular point while at a limit point, there is only one tangent at the singular point. Singularities in the Jacobian matrix is often indicative of an optimal solution, and this motivates the investigation of how the singular points in the Jacobian matrix, indicated by branch and limit points would affect the multi-objective dynamic optimization. One of the most used software to locate limit points, branch points, and Hopf bifurcation points is MATCONT Dhooge, et al. [22,23]. This software detects Limit points, branch points and Hopf

bifurcation points. Consider an ODE system:

$$x = f(x, \beta)$$

Where $x \in R^n$ Let the tangent plane at any point $x$ be $[v_1, v_2, v_3, v_4, ....v_{n+1}]$. Define matrix A given by

$$A = \begin{bmatrix} \frac{\partial f_1}{\partial x_1}\frac{\partial f_1}{\partial x_1}\frac{\partial f_1}{\partial x_1}\frac{\partial f_1}{\partial x_1}.....\frac{\partial f_1}{\partial x}\frac{\partial f_1}{\partial \beta} \\ \frac{\partial f_2^1}{\partial x_1}\frac{\partial f_2^2}{\partial x_2}\frac{\partial f_2^3}{\partial x_3}\frac{\partial f_2^4}{\partial x_4}.....\frac{\partial f_2^n}{\partial x_n}\frac{\partial f_2}{\partial \beta} \\ ..... \\ ..... \\ \frac{\partial f_n}{\partial x_1}\frac{\partial f_n}{\partial x_2}\frac{\partial f_n}{\partial x_3}\frac{\partial f_n}{\partial x_4}.....\frac{\partial f_n}{\partial x_n}\frac{\partial f_n}{\partial \beta} \end{bmatrix} \quad (8)$$

The matrix A can be written in a compact form as

$$A = [B | \frac{\partial f}{\partial \beta} \quad (9)$$

The tangent surface must satisfy the equation:

$$Av = 0 \quad (10)$$

for both limit and branch point the matrix B must be singular. For a limit point (LP) the $n+1^{th}$ component of the tangent vector $v_{n+1} = 0$ and for a branch point (BP) the matrix $\begin{bmatrix} A \\ v^T \end{bmatrix}$ must be singular. For a Hopf bifurcation, the function should be zero. $\square$ indicates the biternate product while $I_n$ is the n-square identity matrix. More details can be found in Kuznetsov [24,25] and Govaerts [26]. The PI has published several articles where bifurcation analysis was used in chemical engineering problems such as reactive distillation and fermentation Ruiz, et al. [27-30]. Hopf bifurcation points cause unwanted oscillatory behavior which makes control tasks difficult.

### Multi-Objective Nonlinear Model Predictive Control (MNLMPC) Method

The multi-objective nonlinear model predictive control (MNLMPC) method was first proposed by Flores Tlacuahuaz, et al. [31] and used by Sridhar [32-36]. This method is rigorous, and it does not involve the use of weighting functions do not do it impose additional parameters or additional constraints on the problem unlike the weighted function or the epsilon correction method (Miettinen; 1999). For a problem that is posed as

$$\min J(x,u) = (x_1, x_1.....x_k) \text{ Subject to}$$

$$\frac{dx}{dt} = F(x,u); h(x,u) \le 0; x^L \le x \le x^U; u^L \le u \le u^U \quad (11)$$

The MNLMPC method first solves dynamic optimization problems independently minimizing/maximizing each $x_i$ individually. The minimization/maximization of $x_i$ will lead to the values $x_i^*$ Then the optimization problem that will be solved is:

$$\min \sqrt{\{x_i - x_i^*\}^2} \text{ Subject to}$$

$$\frac{dx}{dt} = F(x,u); h(x,u) \le 0; x^L \le x \le x^U; u^L \le u \le u^U \quad (12)$$

This is the MOOC calculation. It will provide the control values for various times. The first obtained control value is implemented and the remaining discarded. This procedure is repeated until the implemented and the first obtained control value are the same. The optimization package in Python, Pyomo Hart, et al. [37] where the differential equations are automatically converted to a Nonlinear Program (NLP) using the orthogonal collocation method Biegler, [38] is commonly used for these calculations. The state-of-the-art solvers like IPOPT Wachter and Biegler [39] and BARON Tawaralmani and Sahinidis [40] are normally used in conjunction with PYOMO. To summarize the steps of the algorithm are as follows.

1. Minimize/maximize $x_i$ subject to the differential and algebraic equations that govern the process using Pyomo and Baron. This will lead to the value $x_i^*$
2. Minimize $\min \sqrt{\{x_i - x_i^*\}^2}$ (multi-objective function) subject to the differential and algebraic equations that govern the process. This is the MOOC calculation and provides the control values for various times. If this calculation results in obtaining a value of zero for the multi-objective function, then the Utopia point is obtained, and the calculations are terminated. Otherwise, we proceed to step 3.
3. Implement the first obtained control values and discard the remaining.
4. Repeat steps 1 to 3 until there is an insignificant difference between the implemented and the first obtained value of the control variables.
5. This strategy was used in Sridhar [30-34].

## Results and Discussion

First, the bifurcation analysis was performed on a scaled model describing the tumor macrophage interactions. As shown by Shu [20], the model exhibits Hopf bifurcations when $\zeta$ is the bifurcation parameter. However, when the activation factor $\tanh(\zeta)$ is introduced and the resulting bifurcation parameter is $\frac{\zeta \tanh(\zeta)}{\varepsilon}$ the Hopf bifurcation point disappears. $\varepsilon$ is taken as $10^{-3}$.Such an activation factor is commonly used to control spikes or miniature waves in optimal control problems. Figures 1a & 1b show the two profiles with and without the activation factor $\tanh(\zeta)$. It can be seen that the use of the activation factor eliminated the Hopf bifurcation point. Figures 2a & 2b show the optimal control profiles for the single objective opti-

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mal control is performed minimizing $\zeta$ versus time minimizing the scaled variable $X$ subject to the equations 4 5 and 6. The resulting value of the objective function is 8e-05. However, the control profile exhibits a spike as seen in Figure 2a. When the activation factor is used the spikes disappear as seen in Figure 1b. Using this corrected value of $\zeta$ Oscillatory behavior is like the existence of spikes, and it is shown that the activation factor involving the tanh function is effective in eliminating both and this is the main message in this article. The Multi-Objective Nonlinear Model Predictive Control (MNLMPC) calculations were also performed. First, X was minimized while Y and Z were maximized individually [41-43]. The objective function values obtained are 0.0109, 8.95 and 2.156. The objective function for the MNLMPC calculations is $(X-0.0109)^2+(Y-0.95)^2+(Z-2.156)^2$ subject to the scaled differential equations. The first obtained control value of value of x was implemented and the process is repeated until there is no difference between the first obtained control value and the implemented control value. In this case tis value is 0.0292. Figures 3-6 show the profiles of the various variables where MNLMPC was used.

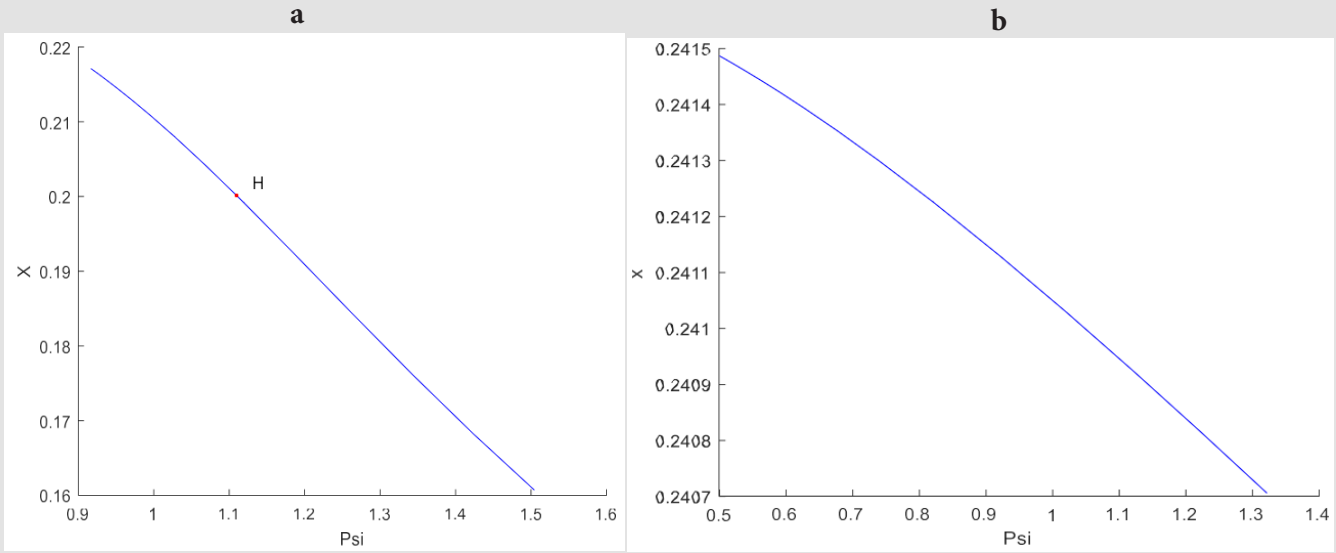


**Figure 1:**
a. Hopf Bifurcation point.
b. Hopf Bifurcation Point eliminated with use of activation factor.

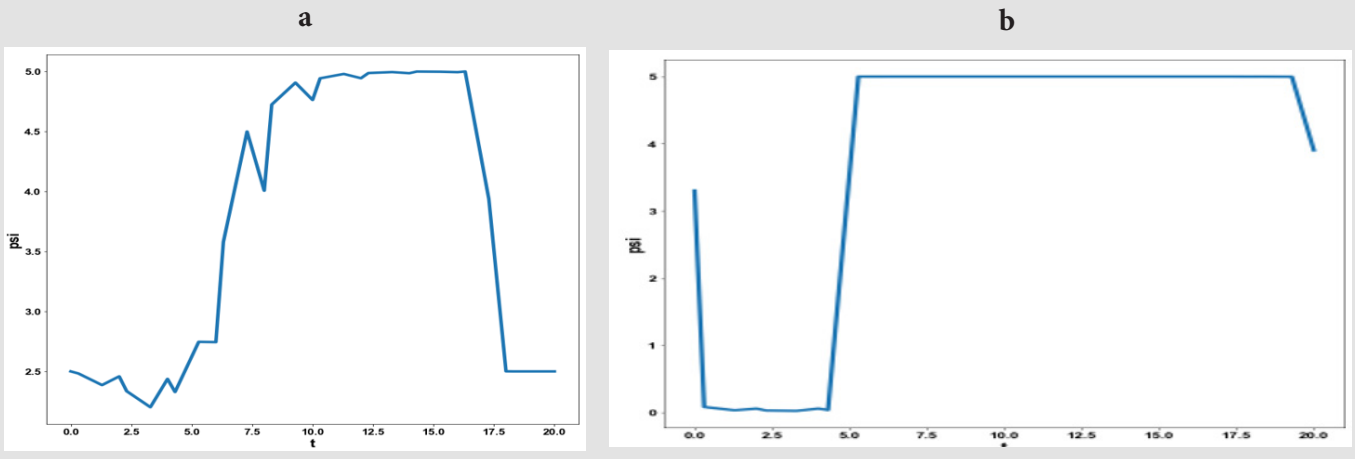


**Figure 2:**
a. Spikes in control profile when activation factor was not used.
b. No Spikes in control profile when activation factor was used.

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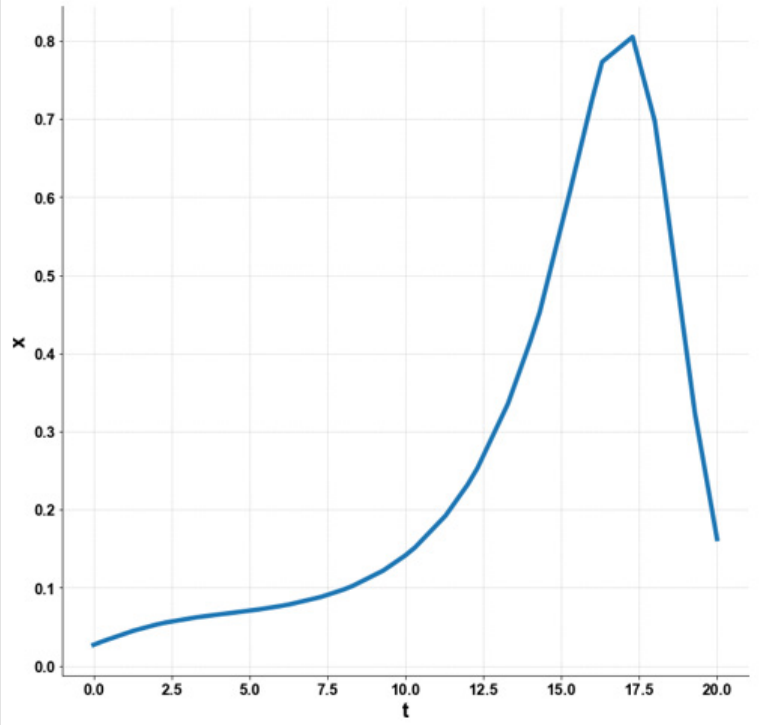


**Figure 3:** X vs. t MNLMPC.

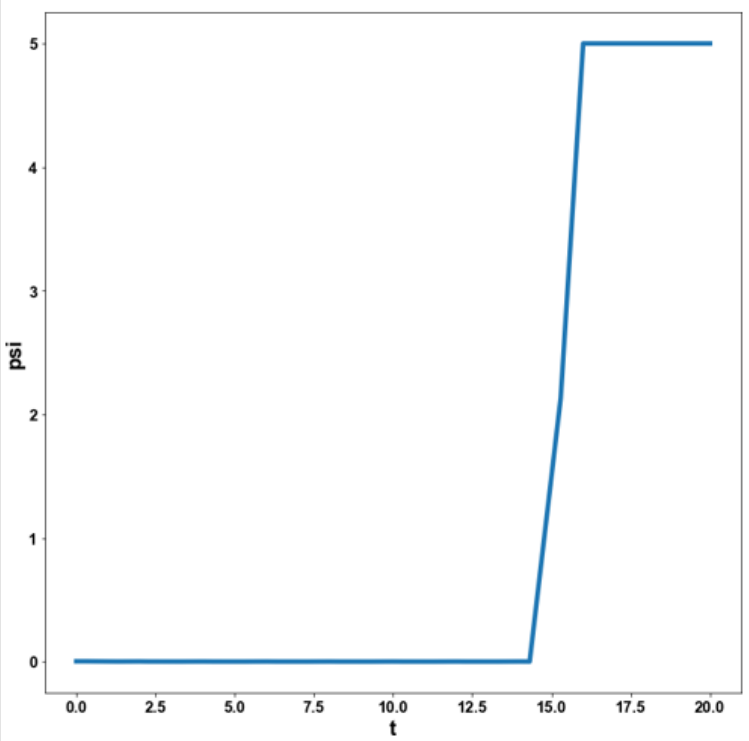


**Figure 4:** $\zeta$ VS t MNLMPC.

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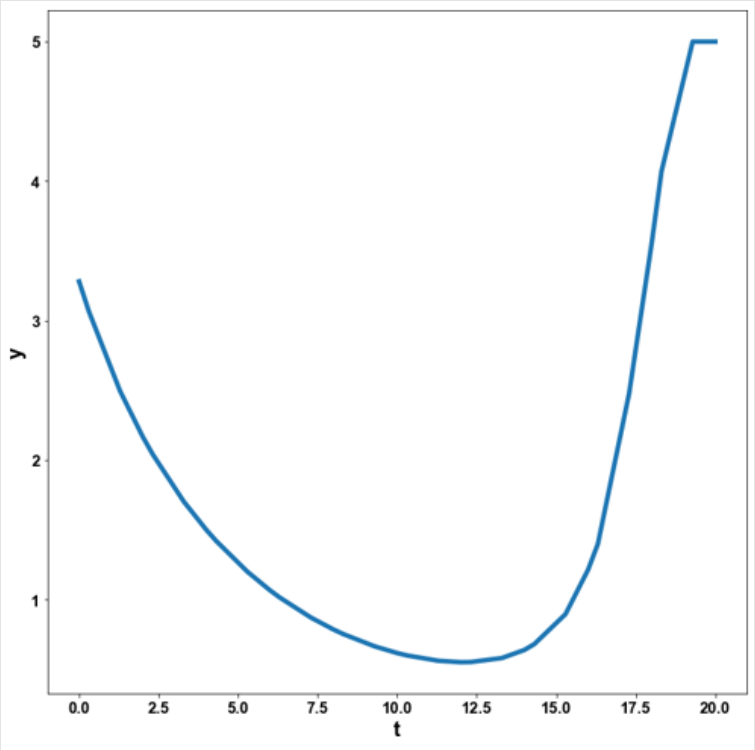


**Figure 5:** y VS t MNLMPC.

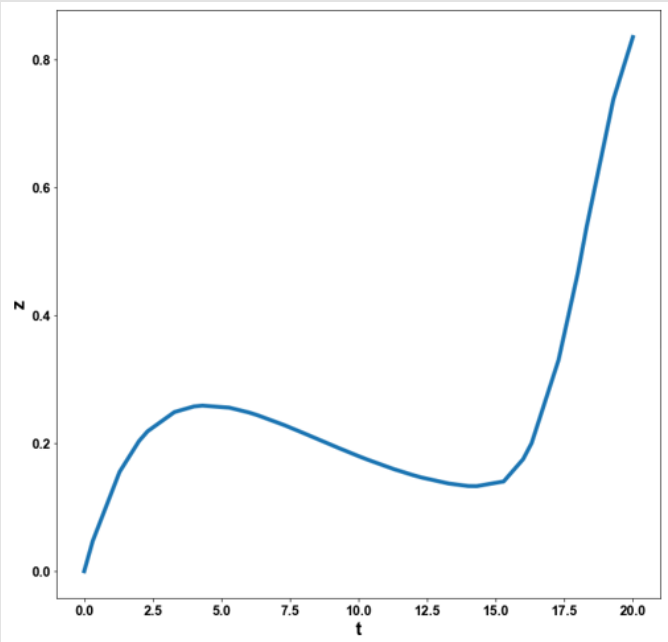


**Figure 6:** z VS t MNLMPC.

## Conclusion

Bifurcation analysis and optimal control was performed on a scaled model involving interactions between macrophages and tumors. Oscillation causing Hopf bifurcation points were found. It is shown that the incorporation of the hyperbolic tangent function (Tanh) that is normally used to eliminate spikes in optimal control profiles is also effective in the elimination of the unwanted oscillation causing Hopf bifurcation points.

## Data Availability Statement

All data used is presented on paper.

## Conflict of Interest

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

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