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Bifurcation Analysis and Multiobjective Nonlinear Model Predictive Control of the Cancer Model with Tumor-Immune Interactions

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ABSTRACT

Bifurcation analysis and Nonlinear model predictive control were performed on a cancer model with tumor-immune interactions. It is also demonstrated (both numerically and analytically) that the presence of the branch and limit points was instrumental in obtaining the Utopia solution when the multiobjective nonlinear model predictive control calculations were performed. Bifurcation analysis was performed using the MATLAB software MATCONT while the multi-objective nonlinear model predictive control was performed by using the optimization language PYOMO.

Keywords: Optimal Control; Bifurcation; Cancer Remission; Immunotherapy

Introduction and Background

The models involving cancer remission and immunotherapy are extremely nonlinear and exhibit singularities that affect optimization and control strategies. Several researchers have investigated the nonlinearity of the cancer models. Swan [1] studied applications of optimal control theory in cancer chemotherapy. Dunn, et al. [2] discuss Cancer immunoediting; Pillis, et al. [3] studied the dynamics of an optimally controlled tumor model and Gatenby, et al. [4] discussed the mathematical oncology pertaining to cancer. Albini, et al. [5] studied tumor inflammatory angiogenesis and its chemoprevention and Merlo, et al. [6] studied cancer as an evolutionary and ecological process, De Pillis, et al. [7] performed an analysis of the dynamics and a study of quadratic and linear optimal controls regarding chemotherapy for tumors; while Castiglione and Piccoli, et al. [8] performed mathematical modeling and optimal control of Cancer immunotherapy. Grivennikov, et al. [9] discuss the effect of immunity on inflammation, and cancer and Hanahan, et al. [10] presented the main hallmarks of the cancer cell while Weinberg [11] studied the biology of Cancer. Ghosh, et al. [12] showed how delayed interactions between cancer cells and the microenvironment can influence tumor growth. Letellier, et al. [13] investigated chemotherapy combined with an anti- angiogenic drug applied to a cancer model.

Khajanchi, et al. [14] discussed the influence of time delay in a chaotic cancer model and Das, et al. [15] demonstrated the dynamical complexity in a time-delayed tumor-immune model. Das, et al. [16] developed optimal treatment strategies for delayed cancer-immune system with multiple therapeutic approach. Das et al (2021) developed an optimal control strategy for cancer remission using combinatorial therapy. All the optimal control work involving cancer remission and immunotherapy involved single objective optimization. In this work, multiobjective nonlinear model predictive control calculations (MNLMPC) are performed in conjunction with bifurcation analysis. The effect of the bifurcations on the MNLMPC is shown. The cancer remission model described in the work of Das, et al. [17] is used. The paper is organized as follows. First the details of the cancer remission model (Das, et al. [17]) are presented, followed by a

description of the bifurcation analysis methods and the strategy used for performing the Multiobjective nonlinear model predictive control calculations (MNLMPC) . This is followed by an analysis of the effect of the singularities (Limit Point (LP) and Branch Point (BP)) on MNLMPC. The numerical results validating the analysis is then presented followed by the conclusions.

Model Description

The differential equations that constitute the cancer remission model (Das, et al. [17]) are

$$\frac{dT_A}{dt} = a_1 T_A(1-b_1 T_A) - m_1 T_A H_A - \frac{n_1 T_A I_A}{\alpha_1 + T_A} - r_1(1-e^{-V_A})T_A$$

$$\frac{dH_A}{dt} = a_1 H_A(1-b_2 H_A) - m_2 T_A H_A - r_2(1-e^{-V_A})H_A$$

$$\frac{dI_A}{dt} = \frac{n_2 T_A I_A}{\alpha_2 + T_A} - r_3(1-e^{-V_A})I_A - \delta I + u\sigma$$

$$\frac{dV_A}{dt} = w - d_1 V_A \quad (1)$$

T_A , H_A , I_A ,V_A represent tumor cells, host cells, immune-effector cells, and chemotherapy. The parameter values and units are

- a_1 a=4.31e-01 [cells /day] {Intrinsic growth rate of tumor cells};
- b_1 =1.02e-09 [1/cells] {1/(the carrying capacity of tumor cells)};
- m_1 =6.41e-11 [1/(cell day)] { Inactivation of tumor cell by host cell};
- n_1 =10e-01 [1/(cell day)] {Clarence of tumor cell by immune cell};
- α_1 =2e+05 [cell ^{2}] { Steepness coefficient of immune cell};
- R_1 =8e-01 [1/(cell day)] { Killing rate of tumor cell by chemotherapy};
- a_2 =11e-01[1/(day)] { Intrinsic growth rate of host cells};
- b_2 =1.02e-09[1/(cells)] {1/(the carrying capacity of host cells)};
- m_2 =15e-01[1/(cell day)] { Inactivation of host cell by tumor cell};
- r_2 =6.0e-01 [1/(cell day)] { Killing rate of host cell by chemotherapy cell};
- n_2 =1.245e-01 [1/(day)]{ Recruitment rate of immune cell};
- α_2 =1.e+07 [cell2] { Steepness coefficient of immune cell};
- ρ =2.e-01[1/(cell day)] {Inactivation of immune cell by tumor cell};
- δ =4.12e-02 [1/(day)] { Death rate of immune cell};
- R_3 =6.0e-01[1/(cell day)] { Killing rate of immune cell by chemotherapy};
- d_1 =9.0e-01[1/day] { Decay rate of drug};

σ represents the adoptive cellular immunotherapy (aci) (value = 60) and u is the amount of dose of ACI (value = 0.2). w refers to the dose of chemo injected into the system and is utilised as the bifurcation parameter and control variable.

Bifurcation Analysis

The existence of bifurcations in engineering problems that lead to multiple steady-state solutions is well known. Bifurcations that lead to multiple steady-state solutions are a) Branch Points and b) limit points. Both these bifurcation points are singularities where 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 One of the most commonly used software to locate these bifurcations is CL_MATCONT (Dhooge, et al. [18,19]) CL_MATCONT uses a continuation procedure implementing the Moore-Penrose matrix pseudo-inverse. A stationary solution of the model under is used to obtain, a set of points that corresponds to the equilibria of the ordinary differential equations. CL_MATCONT detects the singularities and bifurcation points in the solution path and obtains all the branches of the solutions starting from the bifurcation points. CL_MATCONT detects singular points which are limit points, branch points and Hopf bifurcation points . Hopf bifurcation points do not cause multiple steady-states and therefore do not result in the formation of a maxima or minima. Limit and Branch points cause the existence of multiple solutions. Consider an ODE system

$$\dot{x} = f(x,\beta) \quad (2)$$

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 as

$$A = \begin{bmatrix} \frac{\partial f_1}{\partial x_1}\frac{\partial f_1}{\partial x_2}\frac{\partial f_1}{\partial x_3}\frac{\partial f_1}{\partial x_4}.....\frac{\partial f_1}{\partial x_n}\frac{\partial f_1}{\partial \beta} \\ \frac{\partial f_2}{\partial x_1}\frac{\partial f_2}{\partial x_2}\frac{\partial f_2}{\partial x_3}\frac{\partial f_2}{\partial x_4}.....\frac{\partial f_2}{\partial x_n}\frac{\partial f_2}{\partial \beta} \\ ..... \\ ..... \\ \frac{\partial f_n}{\partial x_1}\frac{\partial f_n}{\partial x_2}\frac{\partial f_n}{\partial x_3}\frac{\partial f_n}{\partial x_4}.....\frac{\partial f_n}{\partial x_n}\frac{\partial f_n}{\partial \beta} \end{bmatrix} \quad (3)$$

The matrix A can be written in a compact form as

$$A = [B \mid \frac{\partial f}{\partial \beta}] \quad (4)$$

The tangent surface must satisfy the equation

$$Av = 0 \quad (5)$$

For both limit and branch points the matrix B must be singular. For a limit point (LP) the n+1th 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 (Kuzenetsov, et al. [20-22]).

Multiobjective Nonlinear Model Predictive Control Algorithm

The multiobjective nonlinear model predictive control strategy (MNLMPC) method was first proposed by Flores Tlacuahuaz, et al. [23] and used by Sridhar [24]. This method does not involve the use of weighting functions, nor does it impose additional constraints on the problem unlike the weighted function or the epsilon correction method (Miettinen [25]). For a problem that is posed as

$$\begin{aligned} &\min J(x,u) = (x_1, x_2 .... x_k) \\ &Subject\ to \frac{dx}{dt} = F(x,u) \\ &h(x,u) \le 0 \\ &x^L \le x \le x^U \\ &u^L \le u \le u^U \end{aligned} \quad (6)$$

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

$$\begin{aligned} &\min \{p_i - p_i^*\}^2 \\ &Subject\ to \frac{dx}{dt} = F(x,u) \\ &h(x,u) \le 0 \\ &x^L \le x \le x^U \\ &u^L \le u \le u^U \end{aligned} \quad (7)$$

This 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. [26]), where the differential equations are automatically converted to a Nonlinear Program (NLP) using the orthogonal collocation method . The Lagrange-Radau quadrature with three collocation points is used and 10 finite elements are chosen to solve the optimal control problems. The resulting nonlinear optimization problem was solved using the solvers IPOPT (Wächter, et al. [27]) and confirmed as global solutions with Baron (Tawaralmani, et al. [28]). To summarize the steps of the algorithm are as follows

1. Minimize/maximize p_i subject to the differential and algebraic equations that govern the process using Pyomo with IPOPT and Baron. This will lead to the value p_i^* at various time intervals t_i. The subscript i is the index for each time step.

2. Minimize $\{p_i - p_i^*\}^2$ 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.

3. Implement the first obtained control values and discard the remaining.

Repeat steps 1 to 4 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 $p_i = p_i^*$ for all i.

Effect of Singularities (Limit Point (LP) and Branch Point (BP)) on MNLMPC

Let the minimization be of the variable p_1 lead to the value M_1 and the minimization of function p_2 lead to the value M_2 . This is equivalent to minimizing $(p_1\text{-}M_1)^2$ and $(p_2\text{-}M_2)^2$.The subsequent multiobjective minimization will be of the function

$$(p_1 - M_1)^2 + (p_2 - M_2)^2 .$$

The multiobjective optimal control problem is

$$\begin{aligned} &\min (p_1 - M_1)^2 + (p_2 - M_2)^2 \\ &Subject\ to \frac{dx}{dt} = F(x,u) \end{aligned} \quad (1)$$

For all i,

$$\frac{d}{dx_i}((p_1 - M_1)^2 + (p_2 - M_2)^2) = 2(p_1 - M_1)\frac{d}{dx_i}(p_1 - M_1) + 2(p_2 - M_2)\frac{d}{dx_i}(p_2 - M_2)$$

(2)

At the Utopia point both $(p_1 - M_1)$ and $(p_2 - M_2)$ are zero. Hence

$$\frac{d}{dx_i}((p_1 - M_1)^2 + (p_2 - M_2)^2) = 0 \quad (3)$$

Now let us look at the co-state equation

$$\frac{d}{dt}(\lambda_i) = -\frac{d}{dx_i}((p_1 - M_1)^2 + (p_2 - M_2)^2) - g_x\lambda_i \quad (4)$$

The first term in this equation is 0 and hence

$$\frac{d}{dt}(\lambda_i) = -g_x\lambda_i \quad (5)$$
$$\lambda(t_f) = 0$$

If the set of ODE $\frac{d}{dt}(\lambda_i) = g(x,u)$ has a limit or a branch point, g_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 which will make the problem an unconstrained optimization problem and the one and only solution for the unconstrained problem is the Utopia solution

Numerical Results

The MATLAB software MATCONT was used to perform the bifurcation analysis which revealed the existence of a limit point and a branch point on the same curve. For the co-ordinates [T_A, H_A, I_A, V_A, w] a branch point(BP) occurred at a value of [0, 0, 16.465953, 0.773592, 0.696233] and a limit point (LP) occurred at a value of (581.150790 0, 0.051460, 0.773814, 0.696432). Both these points are shown in Figure 1.

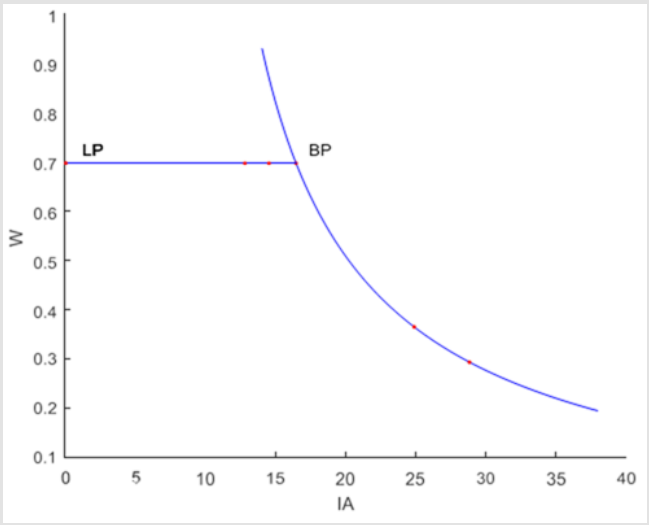

Figure 1: Bifurcation analysis for cancer remission problem.

For the MNLMPC calculations, I_A was maximized and V_A, T_A were individually minimized.

The maximization $\sum_0^{t_f} I_A$ of resulted in a value of 1.e+08 while the individual minimizations of $\sum_0^{t_f} I_A, \sum_0^{t_f} V_A$ each produced a value of 0. For the MNLMPC calculation the objective function $(\sum_0^{t_f} I_A - 1.e+08)^2 + (\sum_0^{t_f} V_A - 0)^2 + (\sum_0^{t_f} T_A - 0)^2$ was minimized subject to the differential equations representing the Cancer remission Model. This resulted in a value of 0 which is the Utopia solution and the obtained MNLMC value of the control variable of w was 0.0170410079149156. Figures 2-6 show the profiles obtained.

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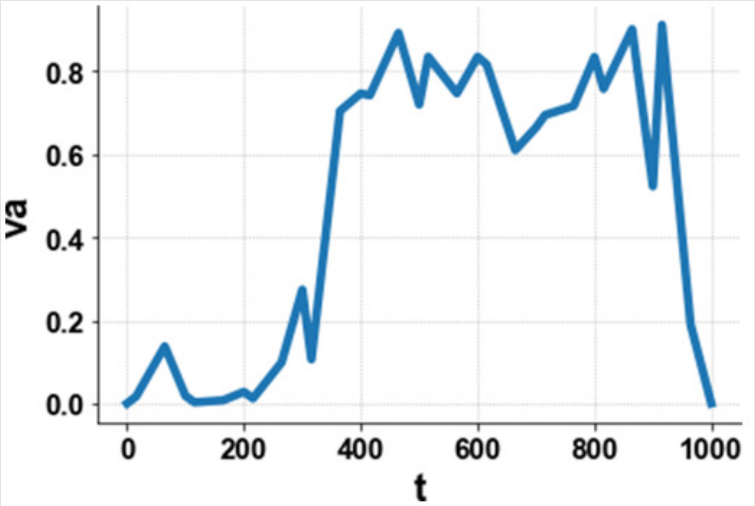

Figure 2: MNLMPC profile for cancer remission problem (va *vs* t).

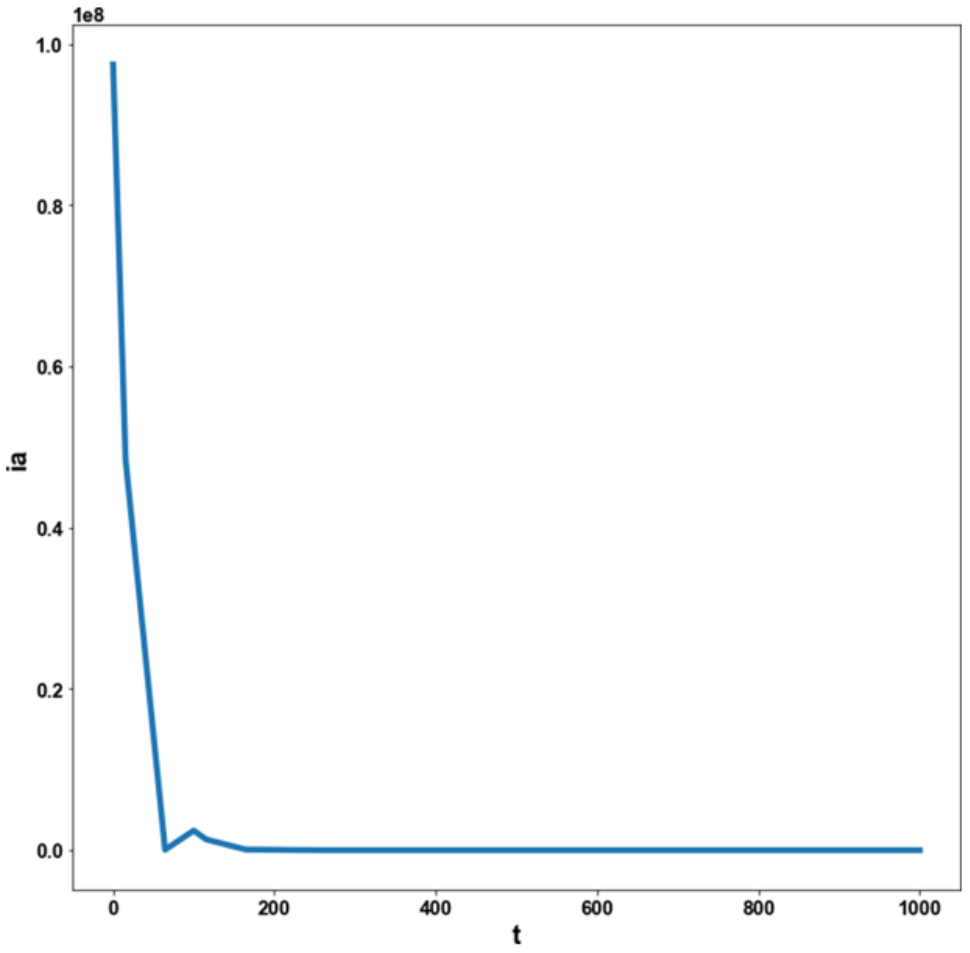

Figure 3: MNLMPC profile for cancer remission problem (ia *vs* t).

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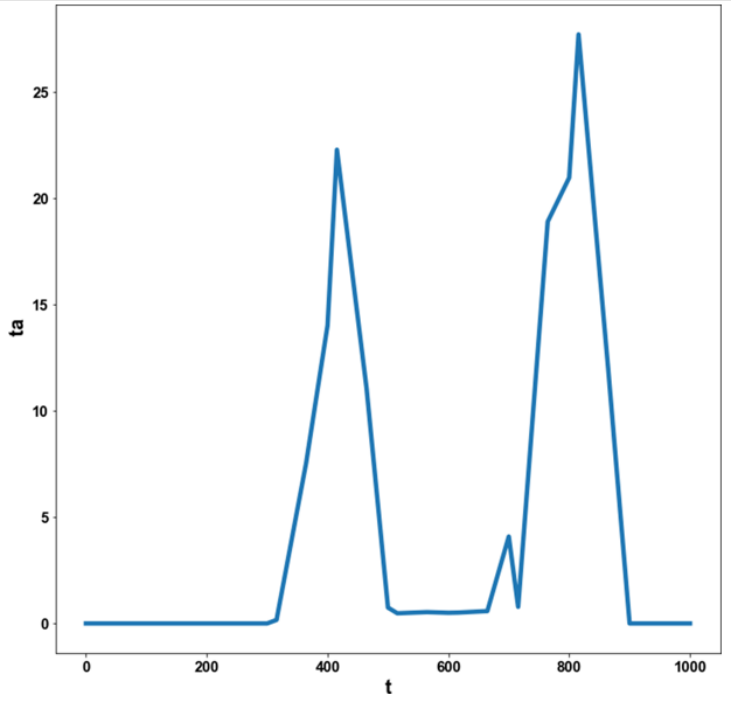

Figure 4: MNLMPC profile for cancer remission problem (ta *vs* t).

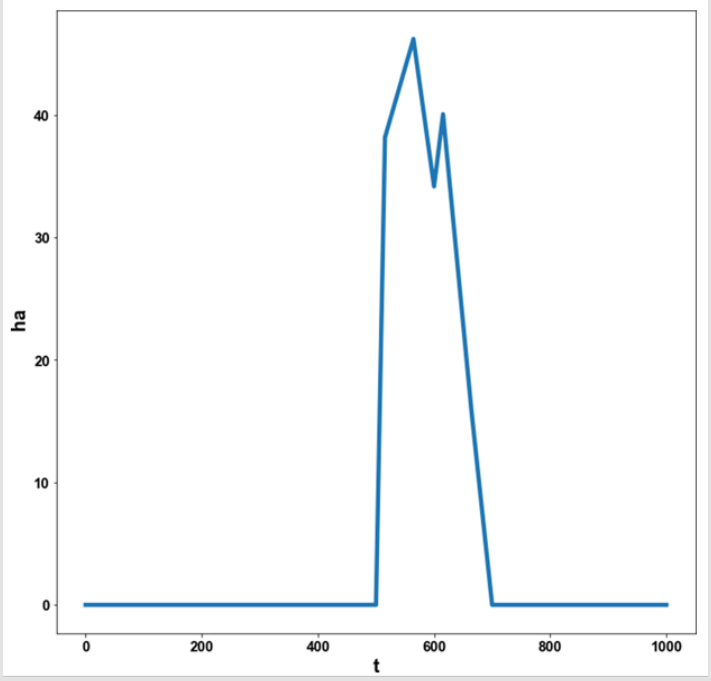

Figure 5: MNLMPC profile for cancer remission problem (ha *vs* t).

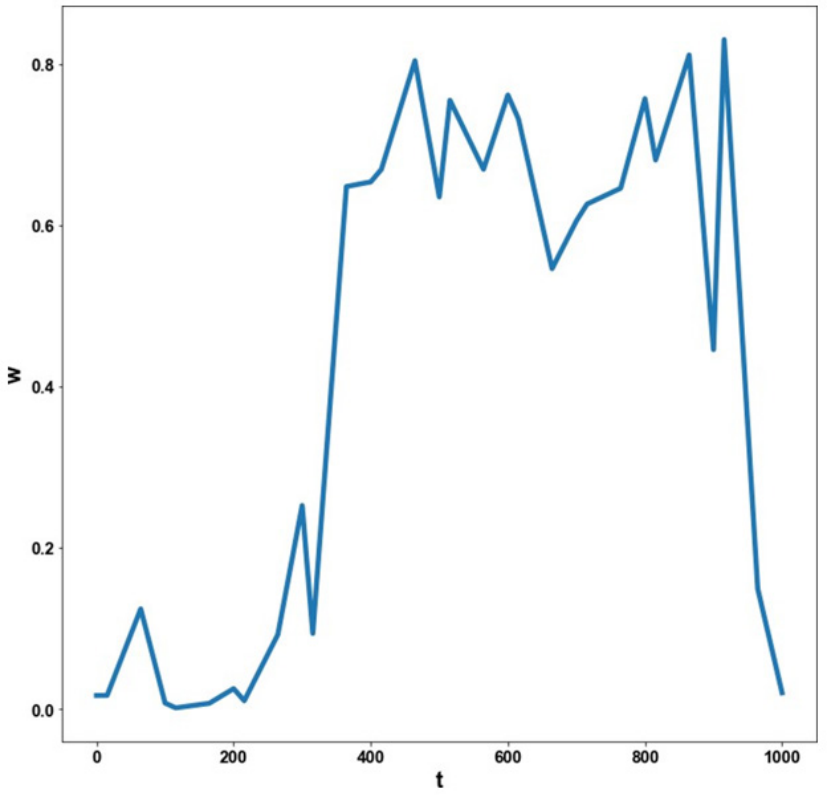

Figure 6: MNLMPC profile for cancer remission problem (w *vs* t).

Conclusion

This work demonstrates the highly nonlinear nature of the cancer remission model demonstrating the existence of the limit point and a branch point, point on the same curve and for the same bifurcation parameter. However, the existence of these bifurcation points is not a cause for concern as these singular points actually aid in the multiobjective nonlinear model predictive control calculations to converge to the best solution (Utopia point).

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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