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Research Article

Dynamics of Leukemia Models

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Abstract:

Millions of people are affected by leukemia. It is important to understand the progression dynamics of this disease to be able to minimize the damage that is caused by it. This article provides a mathematical framework to develop strategies to control leukemia. Bifurcation analysis is a powerful mathematical tool used to deal with the nonlinear dynamics of any process. Several factors must be considered, and multiple objectives must be met simultaneously. Bifurcation analysis and multiobjective nonlinear model predictive control (MNLMPC) calculations are performed on three leukemia 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 the existence of limit points and branch in the models. The limit and branch points were beneficial because they enabled the multiobjective nonlinear model predictive control calculations to converge to the Utopia point in both problems, which is the most beneficial solution. A combination of bifurcation analysis and multiobjective nonlinear model predictive control for leukemia models is the main contribution of this paper.

Key words: leukemia; bifurcation; optimization; control

Introduction

Deininger et al (2000)[1] investigated the molecular biology of chronic myeloid leukemia. Topaly et al [2] researched the synergistic activity of the new ANL-specific tyrosine kinase inhibitor STI571 and the effect of chemotherapeutic drugs on BCR-ABL-positive chronic myelogenous leukemia cells. Deininger and co-workers(2003)[3,4] studied the effect of imatinib on patients with chronic myeloid leukemia. Goldman and Melo(2003) [5] described the treatments for chronic myeloid leukemia patients. Mackey et al (2004)[6] studied the periodic behavior of chronic myelogenous leukemia. Baccarani et al [7] studied the effect of Imatinib and pegylated human recombinant interferon-alpha2 b on early chronic-phase chronic myeloid leukemia. Moore and Li(2004)[8] developed a mathematical model of chronic myelogenous leukemia. Adimy et al (2005)[9] performed a mathematical study of the hematopoiesis process with applications to chronic myelogenous leukemia. Michor et al (2005)[10], studied the dynamics of chronic myeloid leukemia. Nanda et al (2007)[11] , performed single objective optimal control of a mathematical model of chronic myelogenous leukemia. Liso et al and Ommen et al (2008)[12,13] and Cucuianu et al (2010)[14] performed theoretical studies of mathematical models involving myelogenous leukemia. Dohner et al (2010)[15] provided recommendations for the diagnosis and management of acute myeloid leukemia in adults. Komarova(2011)[16], Stiehl(2012)[17], Maclean et al (2013,2014) [18,19], Agarwal (2015)[20], and Clapp(2015)[21] performed mathematical investigations of problems involving leukaemia. Crowell et al (2016)[22] studied feedback mechanisms control coexistence in a stem cell model of acute myeloid leukaemia. Austin et al (2016)[23] , described harnessing the immune system in acute myeloid leukaemia. Zeidan et al (2016)[24] described the economic burden associated with acute myeloid leukemia treatment.Masarova et al (2017) [25] performed additional investigations about harnessing the immune system against leukemia. Lichtenegger et al (2017) [26] presented more developments in immunotherapy of acute myeloid leukemia. Krupar et al (2018) [27], provided an analysis of anti-leukemia immune response and immune evasion in acute myeloid leukemia. Sharp et al (2019)[28] and Khatun et al (2020) [29] performed single-objewctive optimal control studies of ,myeloid leukaemia treatment , Journal of Theoretical Biology, Volume 470, 2019, Pages 30-42, ISSN 0022-5193. In this work, bifurcation analysis is performed in conjunction with multiobjective nonlinear model predictive control (MNLMPC) for three leukemia models that are described in Nanda et al (2007)[11] , Khatun et al (2020), and Sharp et al (2019) (Model 1, Model 2, and Model 3). This paper is organized as follows. First, the leukemia models are presented. The numerical procedures (bifurcation analysis and multiobjective nonlinear model predictive control (MNLMPC) are then described. This is followed by the results and discussion, and conclusions.

Leukemia models

Model 1

The model equations are

$$\frac{dT_n}{dt} = sn - u2(dnT_n) - \frac{knT_n(c)}{c+\eta}$$
$$\frac{dT_e}{dt} = \alpha n\frac{knT_n(c)}{c+\eta} + \alpha e\frac{knT_e(c)}{c+\eta} - u2(deT_e) - \gamma_e C(T_e)$$
$$\frac{dC}{dt} = (1-u1)r_c C\ln(\frac{C_{\max}}{C}) - u2(dcC) - \gamma_c C(T_e) \quad (1)$$

Here (T_n, T_e, C) represent the naive T cell population and the effector T cell population and the cancer cell population, respectively.The base values of the parameters are sn=0.29; dn=0.35; de=0.40; dc=0.012; kn=0.066; η =140; α_n =0.39; α_e =0.65; Cmax=16000; rc=0.011; γ_e =0.079; γ_c =0.058. u1 and u2 are the bifurcation and control parameters.

Model 2

$$\frac{d(Sval)}{dt} = A - \alpha_0(Sval) - \beta(Sval(Ival) - u1Sval$$
$$\frac{d(Ival)}{dt} = \beta(Sval(Ival) - (\beta_0 + \alpha)Ival - (u2(Ival))$$
$$\frac{d(Wval)}{dt} = \alpha(Ival) - b0(Wval) + u1(Sval) + u2(Ival) \quad (2)$$

Here Sval, Ival, Wval represent susceptible cells, infected cells and immune cells. The base values of the parameters areA=1.5; α_0 =0.01; β =0.0005; β_0 =0.003; α =0.0001;b0=0.03. u1 and u2 are the bifurcation and control parameters.

Model 3

The model equations are

$$\frac{d(Sval)}{dt} = \rho_s Sval(k1 - sval) - \delta_s(Sval);$$
$$\frac{d(Aval)}{dt} = \delta_s(Sval) - \delta_a(Aval) + \rho_a Aval(k2 - (Aval + Lval));$$
$$\frac{d(Dval)}{dt} = \rho_a Aval - \mu_d Dval$$
$$\frac{d(Lval)}{dt} = -\delta_l(Lval) + \rho_l Lval(k2 - (Aval + Lval))...$$
$$-\frac{\alpha Lval}{(\gamma + Lval)} - (u(Lval));$$
$$\frac{d(Tval)}{dt} = \delta_l(Lval) - \mu_t Tval \quad (3)$$

Here $(Sval, Aval, Dval, Lval, Tval)$ represent haematopoietic stem cells, progenitor cells, terminally differentiated cells, leukaemia stem cells, and fully differentiated leukaemia cells.

The base parameter values are

ρ_s =0.5; ρ_a =0.43; ρ_l =0.27; δ_s =0.14; δ_a =0.44; δ_l =0.05; μ_d =0.275; μ_t =0.3; k1=1;k2=1; α =0.015; γ =0.01. u is the bifurcation parameter and 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(Dhooge Govearts, and Kuznetsov, 2003[30]; Dhooge Govearts, Kuznetsov, Mestrom and Riet, 2004[31]). This program detects Limit points(LP), branch points(BP), and Hopf bifurcation points(H) for an ODE system

$$\frac{dx}{dt} = f(x, \alpha) \quad (4)$$

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

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

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

Where A is $A = [\partial f / \partial x \quad | \partial f / \partial \alpha]$ (6)

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,

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

@ 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 (1998[32]; 2009[33]) and Govaerts [2000] [34]

Multiobjective Nonlinear Model Predictive Control (MNLMPC)

Flores Tlacuahuaz et al (2012)[35] developed a multiobjective 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=1, 2..n) represents the variables that need to be minimized/maximized simultaneously for a problem involving a set of ODE

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

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

$$\min(\sum_{j=1}^{n}(\sum_{t_{i=0}}^{t_i=t_f} q_j(t_i) - q_j^*))^2 \quad (9)$$

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

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 (Hart et al, 2017)[36] 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 (Wächter And Biegler, 2006)[37]and confirmed as a global solution with BARON (Tawarmalani, M. and N. V. Sahinidis 2005)[38].

The steps of the algorithm are as follows

1. 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.
2. 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.
3. Implement the first obtained control values
4. 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 (2024)[39] 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 (Upreti, 2013)[40]. 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 multiobjective optimal control problem is

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

Differentiating the objective function results in

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

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

Hence

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

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

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

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

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

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 $[\lambda_i] = 0$ This makes the problem an unconstrained optimization problem, and the only solution is the Utopia solution.

Results and Discussion

For the bifurcation analysis of model 1, u1 is the bifurcation parameter and the other parameter values are sn=0.29; dn=0.35; de=0.40; dc=0.012; kn=0.066; η =0.0020; α_n =0.39; α_e =0.65; Cmax=16000; rc=0.011; γ_e =0.079; γ_c =0.158; u2=1.62; a limit point was found at $[T_n, T_e, C, u1]$ values of (0.458808 0.639024 0.140437 0.059894). This is shown in Fig. 1a.

When u2 is the bifurcation parameter and the other parameter values are

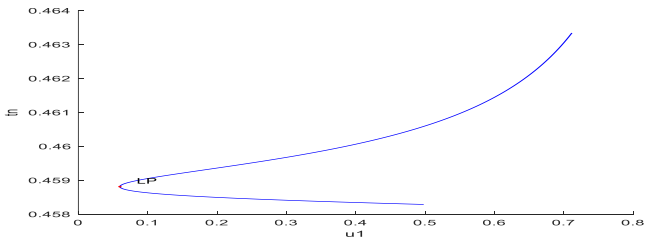

Figure. 1a (Bifurcation analysis model 1 u1 is bifurcation parameter)

sn=0.29; dn=0.35; de=0.40; dc=0.012; kn=0.066; η =0.0020; α_n =0.39; α_e =0.65; Cmax=16000; rc=0.011; γ_e =0.079; γ_c =0.1; u1=0.059894; a limit point was found at $[T_n, T_e, C, u2]$ values of (0.463059 1.015647 0.135093 1.603523). This is shown in Figure. 1b.

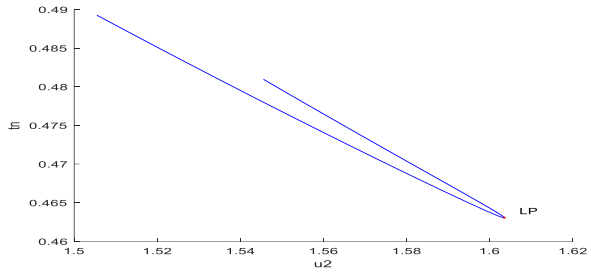

Figure. 1b: (Bifurcation analysis model 1 u2 is bifurcation parameter)

For the bifurcation analysis of model 2, when u1 is the bifurcation parameter and the other parameter values are

A=0.082; α_0 =0.01; β =0.0005; β_0 =0.003; α =0.0001;b0=0.03; u2=0;

A branch point occurred at [sval, ival, wval, u1] values of (6.200000 0.000000 0.666667 0.003226). This is shown in Figure. 2a.

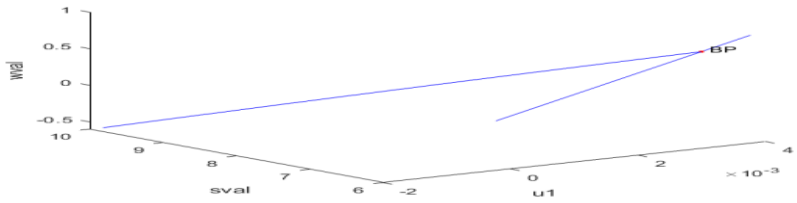

Figure. 2a: (Bifurcation analysis model 2 u1 is bifurcation parameter)

When u2 is the bifurcation parameter and the other parameter values are

A=0.082; α_0 =0.01; β =0.0005; β_0 =0.003; α =0.0001;b0=0.03; u1=0;

A branch point occurred at [sval, ival, wval, u2] values of (8.200000 0.0 0.0 0.0010). This is shown in Figure. 2b.

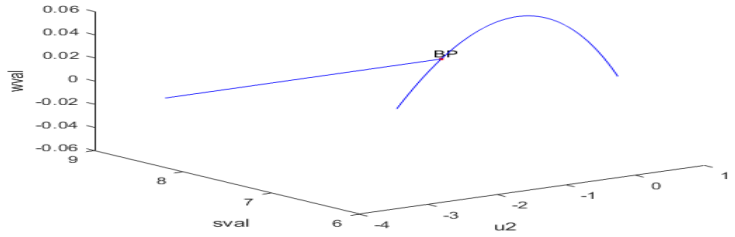

Figure. 2b: (Bifurcation analysis model 2 u2 is bifurcation parameter)

For the bifurcatiom analysis of model 3, u is the bifurcation parameter and the other parameter values are

ρ_s =0.5; ρ_a =0.43; ρ_l =0.27; δ_s =0.14; δ_a =0.44; δ_l =0.04; μ_d =0.275; μ_t =0.3; k1=1;k2=1; α =0.015; γ =0.01; a limit point at [sval;aval;dval;lval;tval,u] values of (0.72 0.354939 0.554995 0.282254 0.037634 0.006633). This is shown in Figure. 3

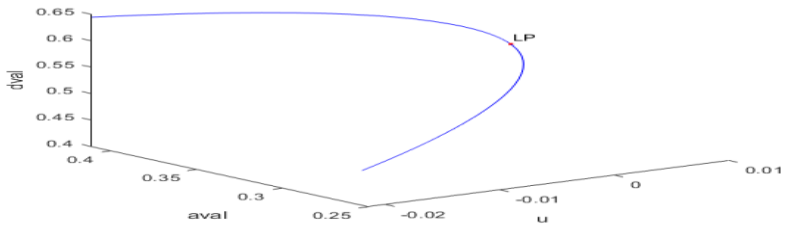

Figure. 3: (Bifurcation analysis model 3 u is bifurcation parameter)

For the MNLMPC calculations involving model 1, $\sum_{t_{i=0}}^{t_i=t_f} c(t_i)$ was minimized $\sum_{t_{i=0}}^{t_i=t_f} T_n(t_i)$ was maximized individually and resulted in values of 0 and 2000. The overall optimal control problem will involve the minimization of $(\sum_{t_{i=0}}^{t_i=t_f} c(t_i)-0)^2+(\sum_{t_{i=0}}^{t_i=t_f} T_n(t_i)-2000)^2$ was minimized subject to the equations governing the model. This led to a value of zero (the Utopia solution. The various concentration profiles for this MNLMPC calculation are shown in Figure. 4a-4c.

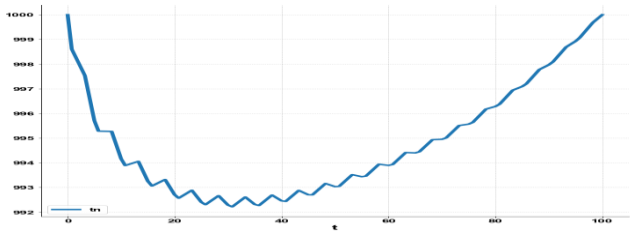

Figure 4a:(MNLMPC for model 1 tn vs t)

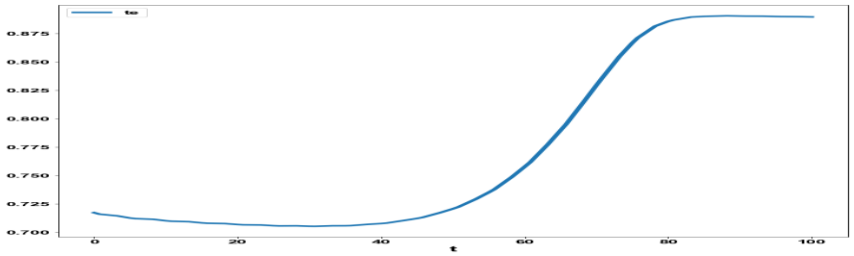

Figure 4b:(MNLMPC for model 1 tn vs t)

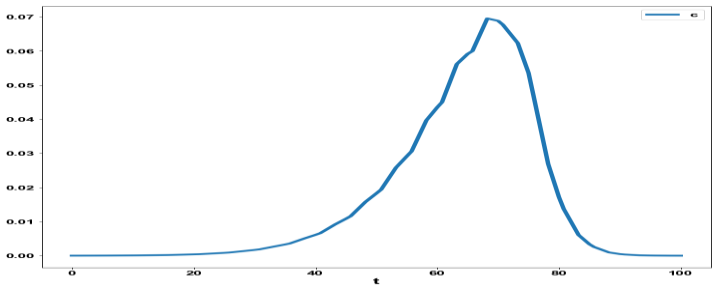

Figure 4c: (MNLMPC for model 1 c vs t)

The obtained control profile of u1 and u2 exhibited noise (Figure. 4d and Figure. 4e). This issue was addressed using the Savitzky-Golay Filter. The smoothed version of this profile is shown in Figure 4f and 4g. The MNLMPC control values obtained for u1 and u2 are 0.0624 and 0.00443. The MNLMPC calculations converged to the Utopia solution, validating the analysis by Sridhar (2024), which demonstrated that the presence of a limit point/branch point enables the MNLMPC calculations to reach the optimal (Utopia) solution.

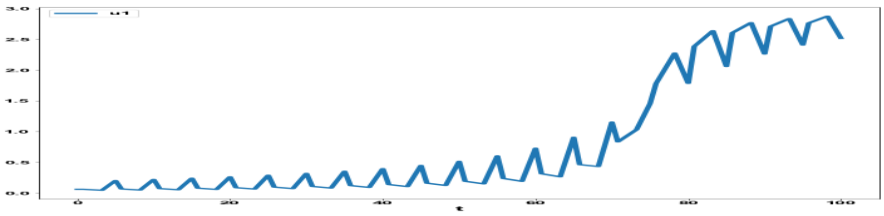

Figure 4d: (MNLMPC for model 1 u1 vs t)

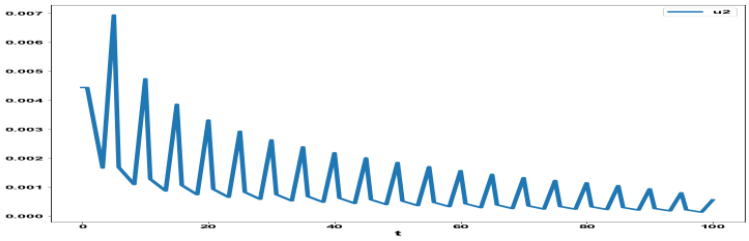

Figure 4e:(MNLMPC for model 1 u2 vs t)

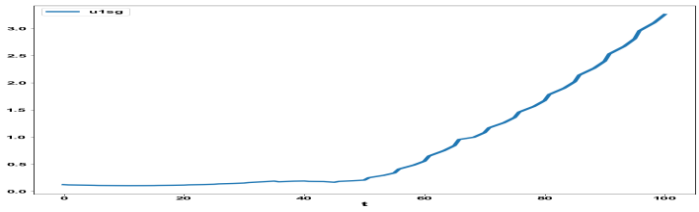

Figure 4f:(MNLMPC for model 1 u1 (Savitzky Golay) vs t)

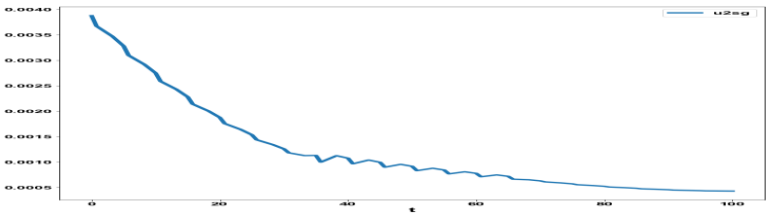

Figure 4g: MNLMPC for model 1 u2 (Savitzky Golay) vs t)

For the MNLMPC calculations involving model 2, $\sum_{t_i=0}^{t_i=t_f} ival(t_i)$ was minimized $\sum_{t_i=0}^{t_i=t_f} wval(t_i)$ was maximized individually and resulted in values of 0 and 200. The overall optimal control problem will involve the minimization of $(\sum_{t_i=0}^{t_i=t_f} ival(t_i)-0)^2+(\sum_{t_i=0}^{t_i=t_f} wval(t_i)-200)^2$ was minimized subject to the equations governing the model. This led to a value of zero (the Utopia solution. The various concentration profiles for this MNLMPC calculation are shown in Figure 5a-5c.

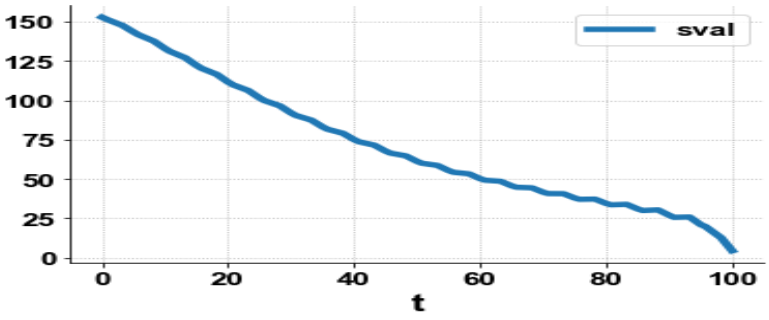

Figure 5a: (MNLMPC model 2, sval vs t)

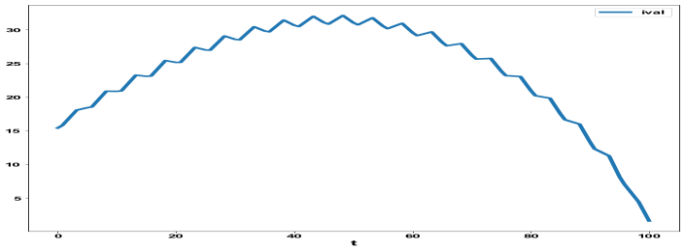

Figure 5b: (MNLMPC model 2, ival vs t)

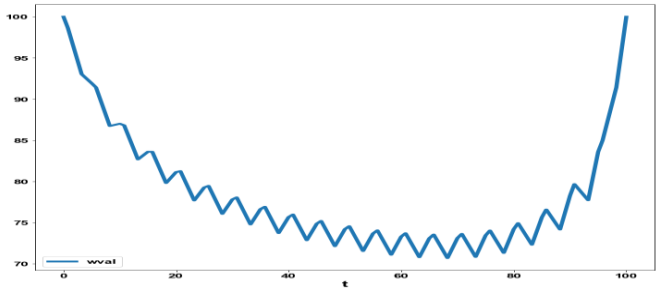

Figure 5c:(MNLMPC model 2, wval s t)

The obtained control profile of u1 and u2 exhibited noise (Figure. 5d and Figure. 5e). This issue was addressed using the Savitzky-Golay Filter. The smoothed version of this profile is shown in Figures 4f and 4g. The MNLMPC control values obtained for u1 and u2 are 0.002779 and 0.02749. The MNLMPC calculations converged to the Utopia solution, validating the analysis by Sridhar (2024), which demonstrated that the presence of a limit point/branch point enables the MNLMPC calculations to reach the optimal (Utopia) solution.

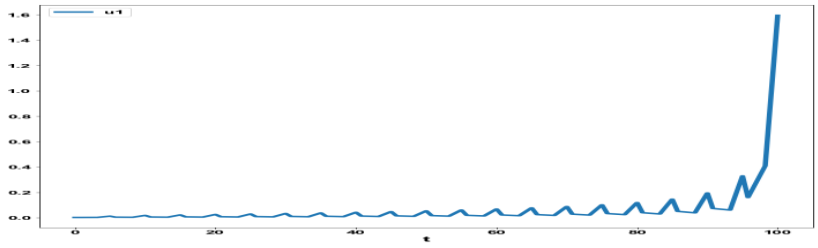

Figure 5d: (MNLMPC model 2, sval vs t)

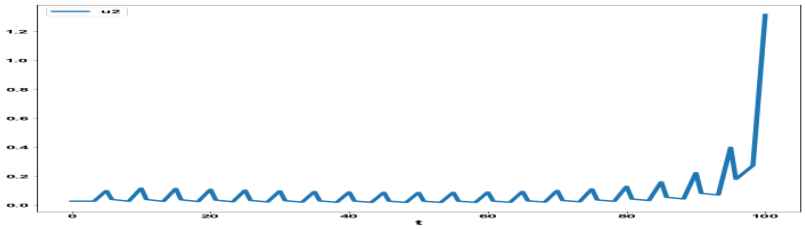

Figure 5e:(MNLMPC model 2, u2 vs t)

For the MNLMPC calculations involving model 3, $\sum_{t_{i=0}}^{t_i=t_f} lval(t_i)$ was minimized $\sum_{t_{i=0}}^{t_i=t_f} aval(t_i)$ was maximized individually and resulted in values of 0 and 5.47269. The overall optimal control problem will involve the minimization

$$(\sum_{t_{i=0}}^{t_i=t_f} lval(t_i)-0)^2+(\sum_{t_{i=0}}^{t_i=t_f} aval(t_i)-5.47269)^2$$

was minimized subject to the equations governing the model. This led to a value of zero (the Utopia solution. The MNLMPC control values obtained for u was 0.6345 The various concentration profiles for this MNLMPC calculation are shown in Figs. 6a-6f. The MNLMPC calculations converged to the Utopia solution, validating the analysis by Sridhar (2024)[39], which demonstrated that the presence of a limit point/branch point enables the MNLMPC calculations to reach the optimal (Utopia) solution.

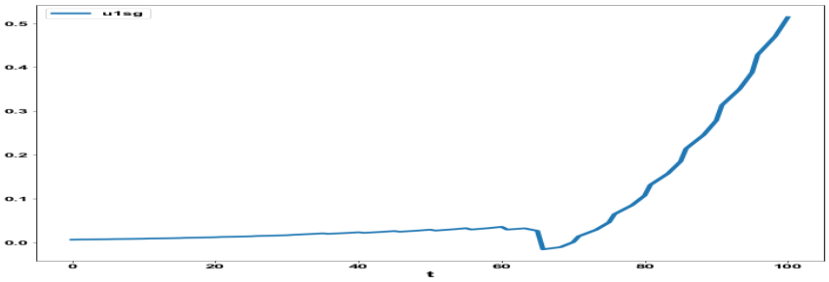

Figure 5f: (MNLMPC model 2, u1 (Savitzky Golay) vs t)

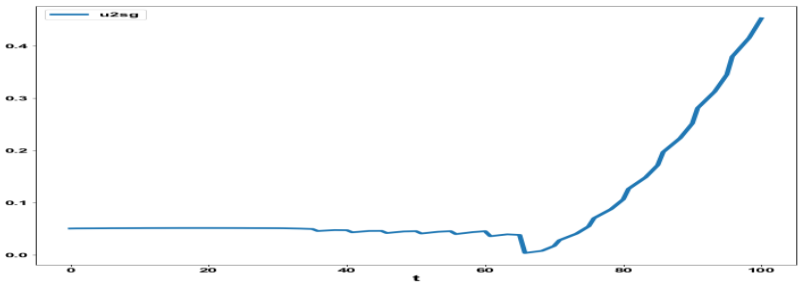

Figure 5g: (MNLMPC model 2, u2 (Savitzky Golay) vs t)

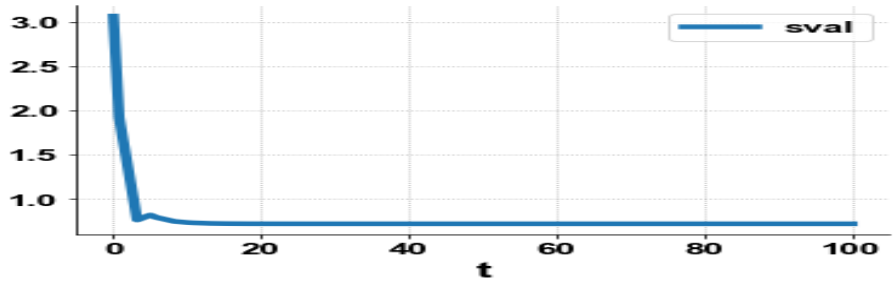

Figure 6a: (MNLMPC model 3, sval vs t)

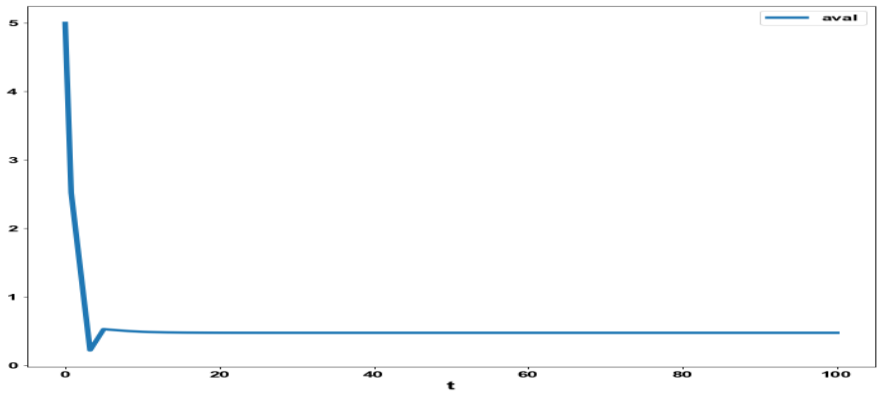

Figure 6b:(MNLMPC model 3, aval vs t)

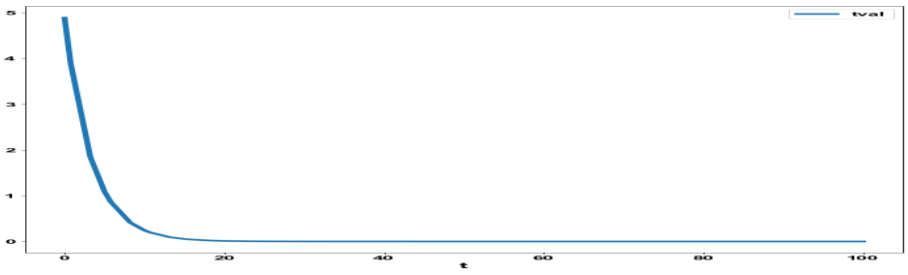

Figure 6c:(MNLMPC model 3, tval vs t)

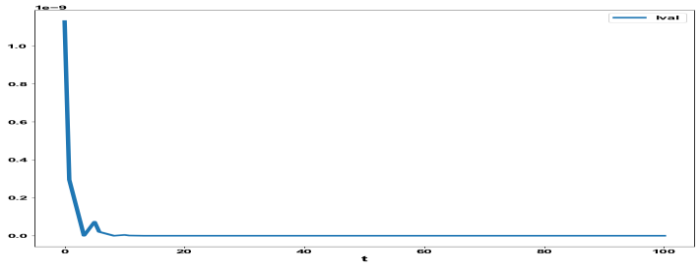

Figure 6d: (MNLMPC model 3, lval vs t)

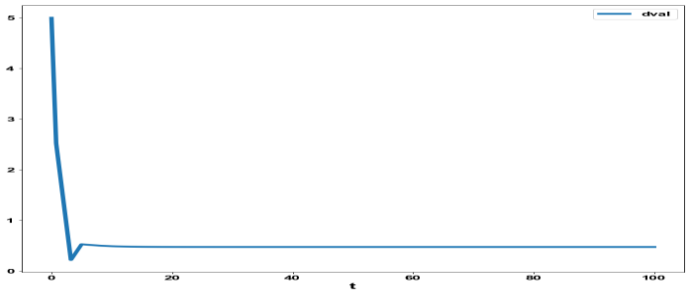

Figure 6e:(MNLMPC model 3, dval vs t)

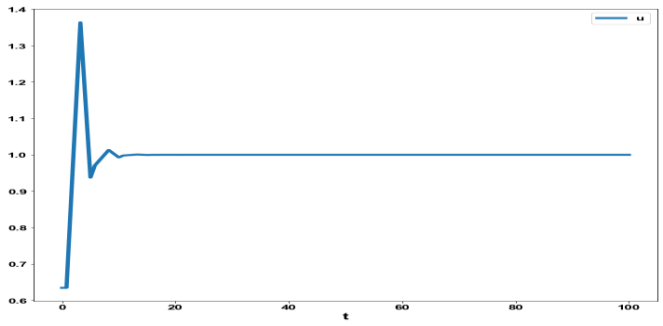

Figure 6f: (MNLMPC model 3, u vs t)

Model 1 and Model 3 displayed limit points, while Model 2 demonstrated a branch point. In all three instances, the MNLMPC calculations converged to the Utopia solution, validating the analysis of Sridhar (2024), which showed that the existence of a limit point or a branch point allows the MNLMPC calculations to achieve the best possible (Utopia) solution.

Conclusions

Bifurcation analysis and Multiobjective nonlinear model predictive control calculations were performed on three leukemia models. The bifurcation analysis revealed the existence of limit and branch points. The limit and branch points (which cause multiple steady-state solutions from a singular point) are very beneficial as they enable the Multiobjective nonlinear model predictive control calculations to converge to the Utopia point (the best possible solution) in both models. A combination of bifurcation analysis and multiobjective nonlinear model predictive control for leukemia disease models is the main contribution of this paper.

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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