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Analysis and Control of HIV Dynamic Models

Lakshmi. N. Sridhar*

Chemical Engineering Department, University of Puerto Rico, Mayaguez, PR 00681, USA

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***Corresponding author:** Lakshmi. N. Sridhar, Chemical Engineering Department, University of Puerto Rico, Mayaguez, PR 00681, USA, Email: lakshmin.sridhar@upr.edu

ABSTRACT

HIV/AIDS has significantly impacted universities, affecting young students through increased illness, mortality and absenteeism, as well as impacting institutional functioning and resources. Universities, particularly in regions with high HIV prevalence, have had to develop strategies to address the epidemic, including prevention, care and support programs, as well as integrating HIV/AIDS education into the curriculum. In this work, bifurcation analysis and multiobjective nonlinear model predictive control is performed on three HIV dynamic models, 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 oncolytic dynamic 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 branch and limit points in the models. The branch and limit points (which cause multiple steady-state solutions from a singular point) are very beneficial because they enable the Multiobjective nonlinear model predictive control calculations to converge to the Utopia point (the best possible solution) in all the models.

Keywords: Bifurcation; Optimization; Control; HIV

Background

Kirschne, et al[1] investigated the optimal control of the chemotherapy of HIV. Samanta[2], analyzed a nonautonomous HIV/AIDS model. Nyabadza, et al.[3] developed a rigorous of an HIV/AIDS model with public health information campaigns and individual withdrawal. Samanta[4] conducted research on the permanence and extinction of a nonautonomous HIV/AIDS epidemic model with distributed time delay. Waziri, et al.[5] modelled HIV/AIDS dynamics with treatment and vertical transmission," Hattaf and N. Yousfi[6,7], researched optimal treatments of HIV infection models. Lungu, et al.[8], modelled the HIV/Kaposi's sarcoma coinfection dynamics in areas of high HIV prevalence. Huo and Feng[9] investigated the global stability for an HIV/AIDS epidemic model with different latent stages and treatment. Balasubramaniam, et al.[10], showed the presence of Hopf bifurcations and periodic solutions for delay differential model of HIV infection of CD4+ T-cells. Silva and Torres[11] developed a SICA compartmental model in epidemiology applied to HIV/AIDS in Cape Verde. Ali, et al.[12] developed an optimal control strategy of the HIV-1 epidemic model regarding a recombinant virus. Aldila[13], developed a mathematical model for an HIV spread control program with ART treatment. Marsudi, et al.[14] performed optimal control and sensitivity analysis of HIV model with public health education campaign and antiretroviral therapy. Ghosh, et al.[15] described a simple SI-type model for HIV/AIDS with media and self-imposed psychological fear.

Akudibillah, et al.[16] described optimal control techniques for HIV treatment. Lawi, et al.[17] studied in vivo HIV dynamics under combined antiretroviral treatment. Ilahi and Nurhalimah[18] studied global stability and sensitivity analysis of the SIA model for the AIDS disease. Saha and Samanta[19], conducted optimal control studies of HIV/AIDS prevention through PrEP and limited treatment. Widyaningsih, et al[20] developed a susceptible infected AIDS treatment (SIAT) model. Mayanja, et al.[21], modelled the HIV-HCV coinfection dynamics in the absence of therapy. Rana and Sharma[22], modelled and analyzed a SI-type model for HIV/AIDS. Ayele, et al.[23] modelled the HIV/AIDS with optimal control. Marsudi, et al.[24] performed optimal control of an HIV/AIDS epidemic model with behavioral change and treatment. Cheneke, et al.[25] performed bifurcation and stability analysis of a HIV transmission model with optimal control. Cheneke, et al.[26] performed single-objective optimal control with bifurcation analysis of a HIV Model.

This work aims to perform bifurcation analysis and multiobjective nonlinear control (MNLMPC) studies in three HIV models, which are discussed in Akudibillah, et al.[16] (model 1); Cheneke, et al.[26] (model 2) and Kirschne, et al.[1] (model 3). The paper is organized as follows. First, the model equations are presented, followed by a discussion of the numerical techniques involving bifurcation analysis and multiobjective nonlinear model predictive control (MNLMPC). The results and discussion are then presented, followed by the conclusions.

Model Description

Model 1

The variables $(s, iua; iu1, iu2, iu3, iu4, ida, id1, id2, id3, id4, it2, it3, it4)$ stands for susceptible individuals, infected undiagnosed acute, infected undiagnosed stage1, infected undiagnosed stage 2, infected undiagnosed stage3, infected undiagnosed stage 4, infected diagnosed acute, infected diagnosed stage1, infected diagnosed stage 2, infected diagnosed stage3, infected diagnosed stage 4 or infected treated stage 2, infected treated stage3, infected treated stage 4. The model equations are

$$\begin{aligned}
\frac{ds}{dt} &= b(nval) - \mu(s) - \lambda(s)\\
\frac{d(iua)}{dt} &= \lambda(s) - (d + ra + \mu) iua\\
\frac{d(iu1)}{dt} &= ra(iua) - (d + r1 + \mu) iu1\\
\frac{d(iu2)}{dt} &= r1(iu1) - (d + r2 + \mu) iu2\\
\frac{d(iu3)}{dt} &= r2(iu2) - (d + r3 + \mu + \gamma 3) iu3\\
\frac{d(iu4)}{dt} &= r3(iu3) - (d4 + \gamma 4 + \mu) iu4\\
\frac{d(ida)}{dt} &= d(iua) - (ra + \mu) ida\\
\frac{d(id1)}{dt} &= ra(ida) + d(iu1) - (r1 + \mu) id1\\
\frac{d(id2)}{dt} &= r1(id1) + d(iu2) + \tau(it2) - (u2 + r2 + \mu) id2\\
\frac{d(id3)}{dt} &= r2(id2) + d(iu3) + \tau(it3) - (u3 + r3 + \mu + \gamma 3) id3\\
\frac{d(id4)}{dt} &= r3(id3) + d4(iu4) + \tau(it4) - (u4 + \mu + \gamma 4) id4\\
\frac{d(it2)}{dt} &= u2(id2) + y3(it3) - (\tau + \mu) it2\\
\frac{d(it3)}{dt} &= u3(id3) + y4(it4) - (\tau + \mu + y3) it3\\
\frac{d(it4)}{dt} &= u4(id4) - (\tau + \mu + y4 + \gamma 4) it4
\end{aligned} \tag{1}$$

With

$$\begin{aligned}
nval &= s + iua + iu1 + iu2 + iu3 + iu4 + ida + id1 + id2 + id3 + id4 + it2 + it3 + it4\\
\lambda a &= \frac{\beta a(iua + \xi(ida))}{nval}\\
\lambda 1 &= \frac{\beta 1(iu1 + \xi(id1))}{nval}\\
\lambda 2 &= \frac{\beta 2(iu2 + \xi(id2) + \xi(1-\alpha) it2)}{nval}\\
\lambda 3 &= \frac{\beta 3(iu3 + \xi(id3) + \xi(1-\alpha) it3)}{nval}\\
\lambda &= \lambda a + \lambda 1 + \lambda 2 + \lambda 3
\end{aligned} \tag{2}$$

The base parameter values are

$$b = 0.0309; \mu = 0.0244; \gamma 4 = 0.9091; \gamma 3 = 0.9091; \alpha = 0.960; \xi = 0.68;$$
$$\beta a = 0.656; \beta 1 = 0.096; \beta 2 = 0.654; \beta 3 = 0.248; r = 0.03; ra = 4.8;$$
$$r1 = 0.3235; r2 = 0.6667; r3 = 0.1538; y3 = 1; y4 = 1; da = 0; d = 0.3333;$$
$$\tau = 0.2;\ u2 = 0.2; u3 = 0.1; u4 = 0.1; d4 = 0.9;$$

Model 2

The variables s, w, iv, u and a represent the susceptible population, HIV untested population, Size of HIV tested pre-AIDS population with transmissible virus, pre-AIDS population with untransmissible virus and AIDS population. The model equations are

$$\begin{aligned}
\frac{ds}{dt} &= \lambda - (1-u_1) s\left(\left((\beta_1 w) + (\beta_2 iv)\right)/nv\right) - \mu s\\
\frac{dw}{dt} &= (1-u_1) s\left(\left((\beta_1 w) + (\beta_2 iv)\right)/nv\right) - (\xi + \mu) w\\
\frac{d(iv)}{dt} &= (\xi w) + (u_2 ka) + (\phi u) - \left(\left(\left((1-u_2)\eta\right) + \left((u_2\theta) + \mu\right)\right) iv\right)\\
\frac{du}{dt} &= (u_2 \theta iv) - \left((\Phi + \mu) u\right)\\
\frac{da}{dt} &= \left((1-u_2)\eta iv\right) - \left(\left((u_2 ka) + \delta + \mu\right) a\right)
\end{aligned} \tag{3}$$

The base parameter values are

$$\lambda = 200; \beta_1 = 0.9815; \beta_2 = 0.866; \xi = 0.8;\ \Phi = 0.75;$$
$$\mu = 0.02; \eta = 0.1; \phi = 0.1; \theta = 0.5; k = 0.1; \delta = 1; u_1 = 0; u_2 = 0$$

Model 3

In this model, the variables tv tv1, tv2, v represents the concentration of uninfected CD4+ T Cells, the concentrations of latently infected and actively infectedCD4+ T cells and the concentration of free infectious virus particles.

The model equations are

$$\begin{aligned}
\frac{d(tv)}{dt} &= \left(\frac{s}{1+v}\right) - (\mu_T tv) + r(tv)\left(1 - \left(\frac{(tv + tv1 + tv2)}{tmax}\right)\right) - (k_1(v) tv)\\
\frac{d(tv1)}{dt} &= (k1(v) tv) - (\mu_T(tv1)) - (k2(tv1))\\
\frac{d(tv2)}{dt} &= (k_2(tv1)) - (\mu_B tv2)\\
\frac{d(v)}{dt} &= (u1(n\mu_B) tv2) - (k_1(v) tv) - (\mu_V v)
\end{aligned} \tag{4}$$

The base parameter values are

$\mu_T = 0.02; \mu_B = 0.24; \mu_V = 2.4; k1 = 2.4e-05; k2 = 3e-03; r = 0.03; n = 1200;$
$tmax = 1.5e+03; s = 10; u1 = 1$

Bifurcation analysis

Bifurcation analysis is performed using the MATLAB software MATCONT which locates branch points limit points and Hopf bifurcation points[27,28]. Consider a set of ordinary differential equations

$$\frac{dx}{dt} = f(x,\alpha) \quad (8)$$

$x \in R^n$ Let the bifurcation parameter be α . Since the gradient is orthogonal to the tangent vector, The tangent plane at any point $z = [z_1, z_2, z_3, z_4, ...z_{n+1}]$ must satisfy

$$Az = 0 \quad (9)$$

Where A is

$$A = [\partial f / \partial x \quad | \partial f / \partial \alpha] \quad (10)$$

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

$$\det(2f_x(x,\alpha) @ I_n) = 0 \quad (11)$$

@ indicates the bialternate product and 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[29-31].

Multiobjective Nonlinear Model Predictive Control (MNLMPC)

The procedure developed by Flores Tlacuahuaz, et al.[32] is used for performing the MNLMPC calculations Let the objective function variables $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ (j=1, 2..n) for a problem involving a set of ODE

$$\frac{dx}{dt} = F(x,u) \quad (12)$$

Where t_f is the final time value and n the total number of objective variables and u the control parameter is parameter. First, the single objective optimal control problem independently and individually optimizing each of the variables $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ is solved. Leading to the values q_j^*. Then the multiobjective optimal control (MOOC) optimization problem that will be solved is

$$\min\left(\sum_{j=1}^{n}\left(\sum_{t_i=0}^{t_i=t_f} q_j(t_i) - q_j^*\right)\right)^2 \quad (13)$$

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[33] 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[34] and confirmed as a global solution with BARON[35]. Sridhar[36] 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[37]. This makes the constrained problem an unconstrained optimization problem and the only solution is the Utopia solution. More details can be found in Sridhar[36].

Results and Discussion

In model 1, the bifurcation analysis revealed several limit points for various bifurcation parameters. We provide an example of a limit point when is the bifurcation parameter. In this case the limit point occurred at $(s, iua; iu1, iu2, iu3, iu4, ida, id1, id2, id3, id4, it2, it3, it4, \tau)$ values of (15300176172.914, 23558640.2, 166003336.701, 41517249.721 ,27348556.3828, 2294086.703, 1627579.549, 181492652.947, 79629149.219, 71504204.973, 12754317.507, 99171199.0158, 6328187.215, 597811.929, 0.935788) **(Figure 1)**.

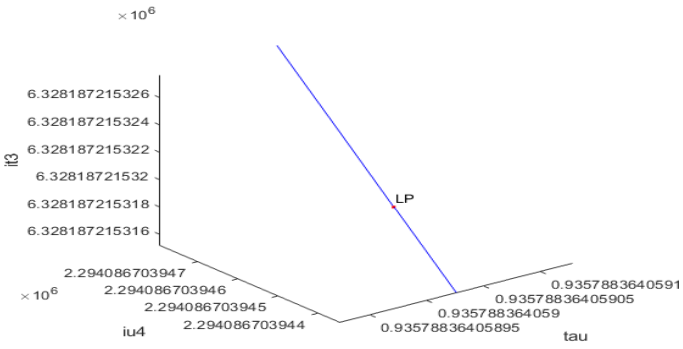

Figure 1: Bifurcation Diagram for HIV model 1(indicating limit point).

For the MNLMPC calculations, $\sum_{t_i=0}^{t_i=t_f} iu4(t_i), \sum_{t_i=0}^{t_i=t_f} id4(t_i), \sum_{t_i=0}^{t_i=t_f} it4(t_i)$ were minimized individually and each minimization yielded a value of 0. The multiobjective optimal control problem will involve the minimization of $(\sum_{t_i=0}^{t_i=t_f} iu4(t_i) - 0)^2 + (\sum_{t_i=0}^{t_i=t_f} id4(t_i) - 0)^2 + (\sum_{t_i=0}^{t_i=t_f} it4(t_i) - 0)^2$ subject to the equations governing Model 2. This led to a value of zero (the Utopia solution) validating the analysis of Sridhar (2024). The MNLMPC control values of u2, u3 and u4 were (0.2844, 0.02983, 0.6467).

(Figures 2-8) show the various MNLMPC profiles. **(Figure 7)** shows the control profiles (u2, u3, u4) exhibiting noise. The

noise was eliminated using the Savitzky-Golay filter to produce the smooth control profiles (u2sg, u3sg, u4sg) **(Figure 8)**.

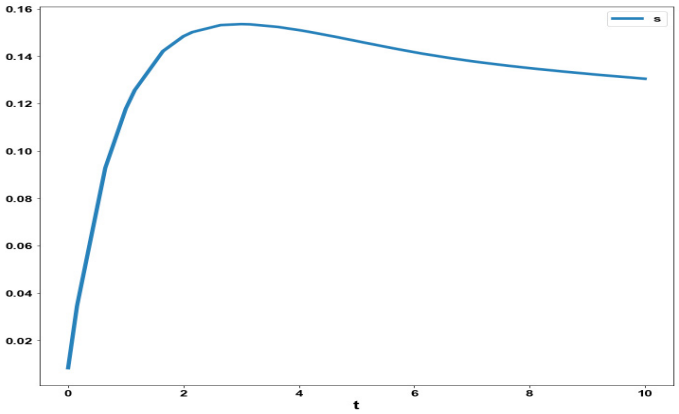

Figure 2: MNLMPC for HIV model 1(s vs t).

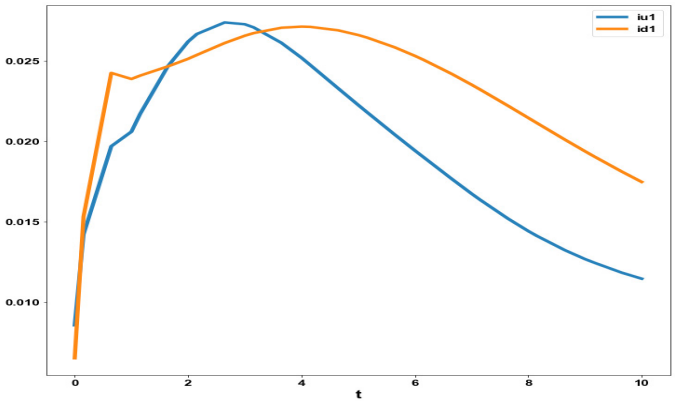

Figure 3: MNLMPC for HIV model 1(iu1, id1 vs t).

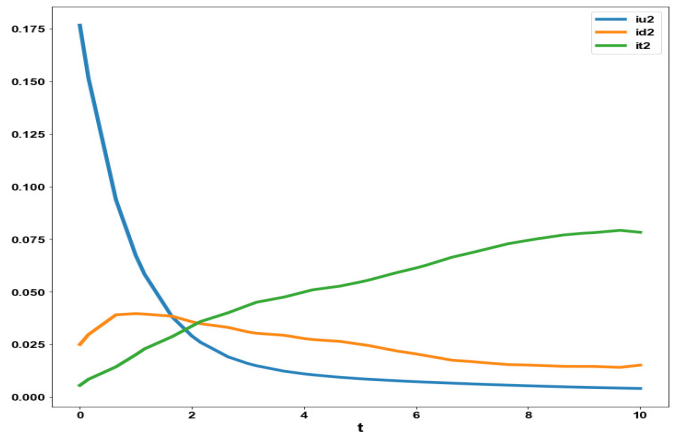

Figure 4: MNLMPC for HIV model 1(iu2, id2, it2 vs t).

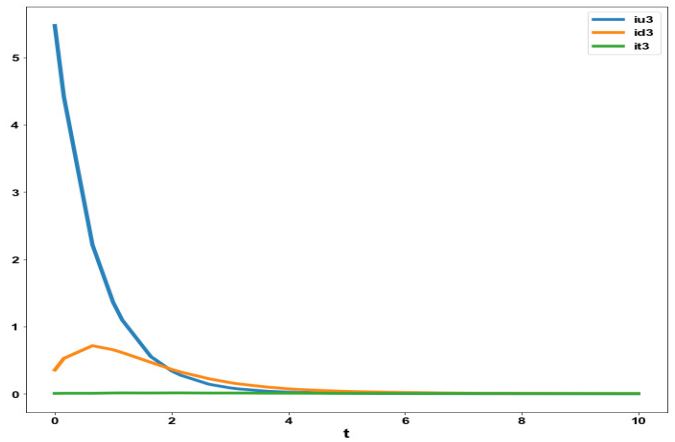

Figure 5: MNLMPC for HIV model 1(iu3, id3, it3 vs t).

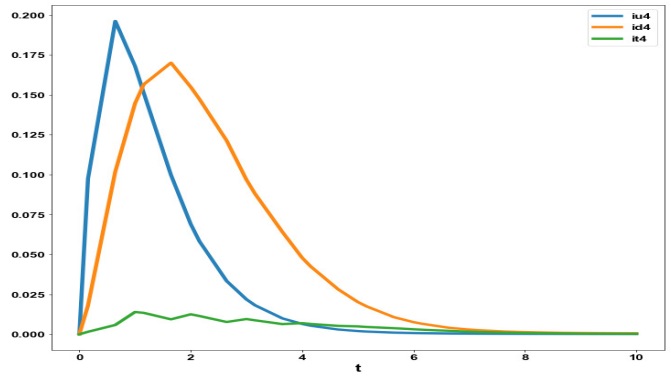

Figure 6: MNLMPC for HIV model 1(iu4, id4, it4 vs t).

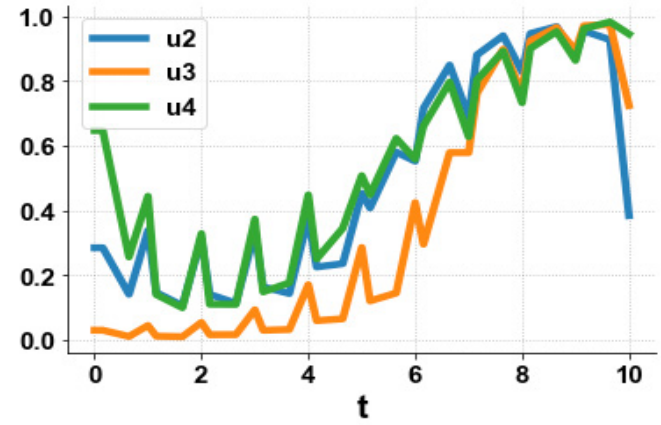

Figure 7: MNLMPC for HIV model 1(u2, u3, u4 vs t; control profiles exhibit noise).

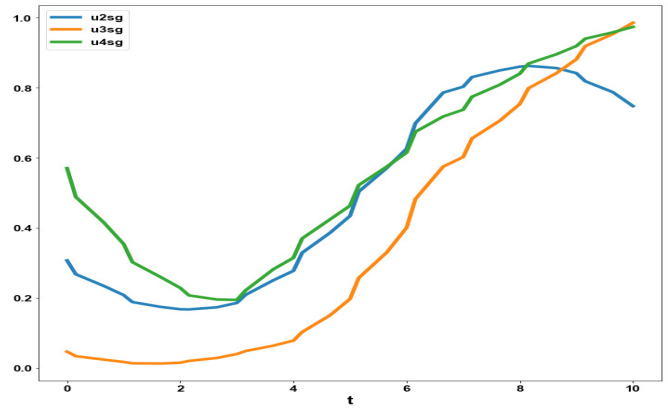

Figure 8: MNLMPC for HIV model 1(u2sg, u3sg, u4sg vs t; control profiles noise eliminated with Savitzky-Golay filter).

In model 2, the bifurcation analysis revealed both branch and limit points. With u1 as the bifurcation parameter, a branch point and limit point were found at (s, w, iv, u, a, u1) values of (10000, 0, 0, 0, 0, 0.878605) and (10000.009866, -0.000241, -0.001604, 0, -0.000157, 0.878605) **(Figure 9)**.

For the MNLMPC calculations, $\sum_{t_i=0}^{t_i=t_f} iv(t_i), \sum_{t_i=0}^{t_i=t_f} w(t_i), \sum_{t_i=0}^{t_i=t_f} a(t_i)$ were minimized individually and each minimization yielded a value of 0. The multiobjective optimal control problem will involve the minimization of $(\sum_{t_i=0}^{t_i=t_f} iv(t_i)-0)^2+(\sum_{t_i=0}^{t_i=t_f} w(t_i)-0)^2+(\sum_{t_i=0}^{t_i=t_f} a(t_i)-0)^2$ subject to the equations governing Model 2. This led to a value of zero

(the Utopia solution) validating the analysis of Sridhar (2024). The MNLMPC control values of u1, u2 and u4 were 0.44 and 0.3249.

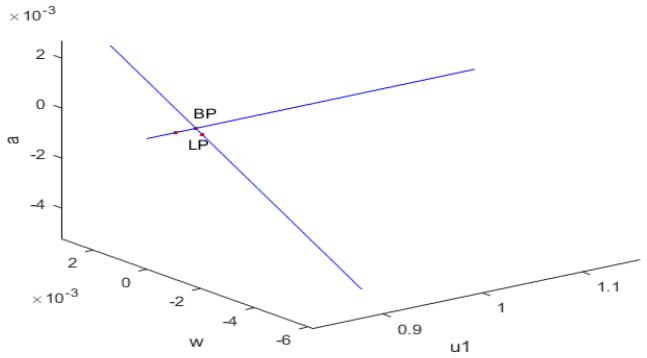

Figure 9: Bifurcation Diagram for Model 2.

(Figures 10-15) show the various MNLMPC profiles. **(Figure 14)** shows the control profiles (u1, u2) exhibiting noise. The noise was eliminated using the Savitzky-Golay filter to produce the smooth control profiles (u1sg, u2sg) **(Figure 15)**.

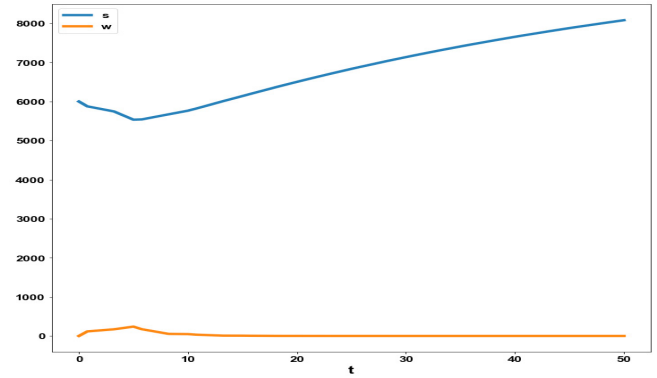

Figure 10: MNLMPC model 2 (s,w, vs t).

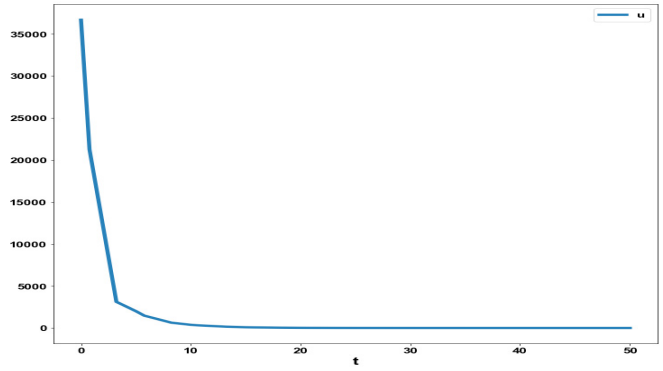

Figure 11: MNLMPC model 2 (u,vs t).

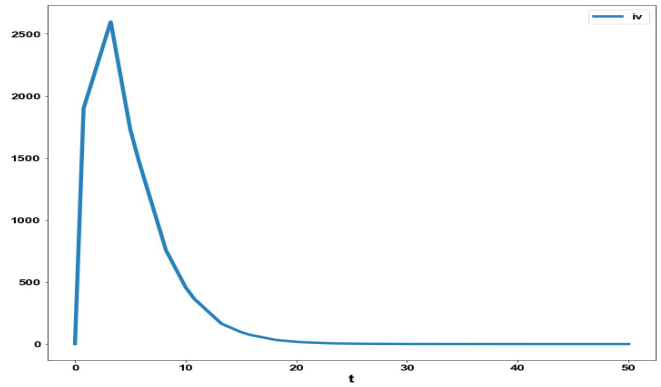

Figure 12: MNLMPC model 2 (iv vs t).

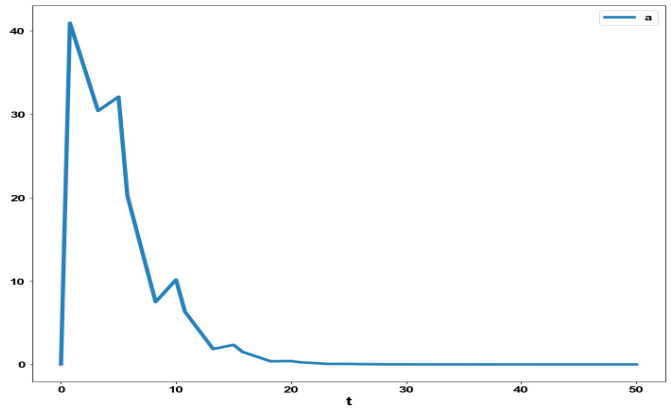

Figure 13: MNLMPC model 2 (a vs t).

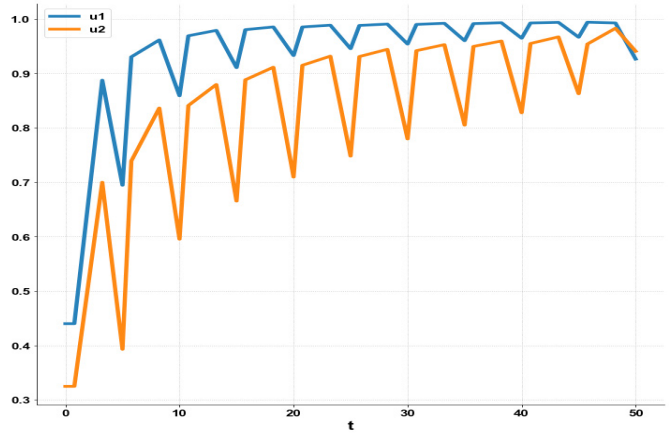

Figure 14: MNLMPC model 2 (u1, u2 vs t).

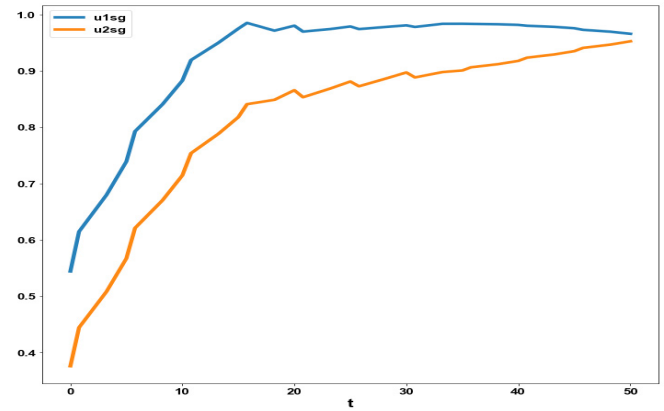

Figure 15: MNLMPC model 2 (u1sg, u2sg vs t).

In model 3, with as the bifurcation parameter a branch point and 2 limit points occurred at values of (1000, 0, 0, 0, 0); (999.977873, 0, 0.033191, 0, 0) and (999.965686, 0, 0.051471, 0, 0) **(Figure 16)**.

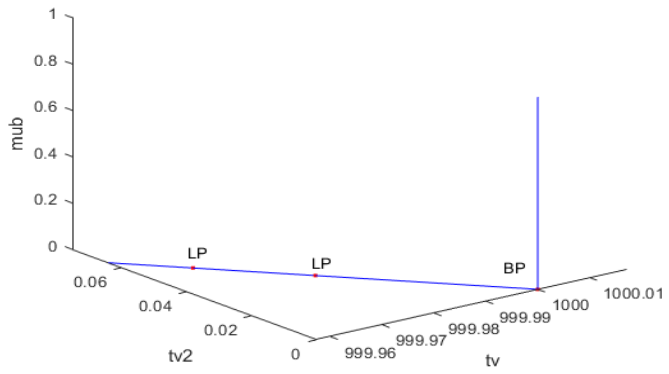

Figure 16: Bifurcation Diagram for Model 3.

For the MNLMPC calculations, $\sum_{t_i=0}^{t_i=t_f} tv1(t_i), \sum_{t_i=0}^{t_i=t_f} tv2(t_i)$ were minimized individually and each minimization yielded a value of 0. The multiobjective optimal control problem will involve the minimization of $(\sum_{t_i=0}^{t_i=t_f} tv1(t_i)-0)^2+(\sum_{t_i=0}^{t_i=t_f} tv2(t_i)-0)^2$ subject to the equations governing Model 3. This led to a value of zero (the Utopia solution) validating the analysis of Sridhar (2024). The MNLMPC control values of u1 was 0.7592.

(Figures 17-20) show the various MNLMPC profiles. **(Figure 20)** shows the control profile (u1) exhibiting noise. The noise was eliminated using the Savitzky-Golay filter to produce the smooth control profiles (u1sg) (also shown in **Figure 20**).

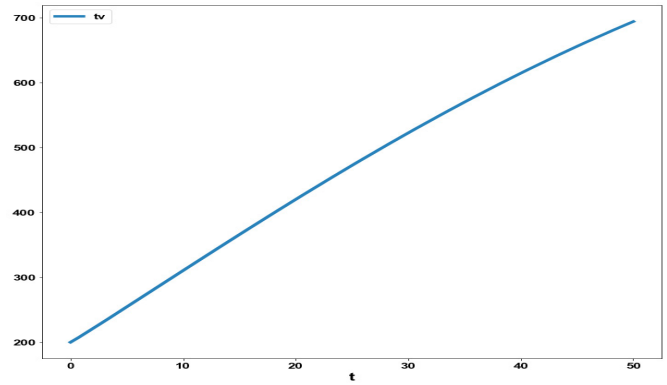

Figure 17: MNLMPC model 2 (tv vs t).

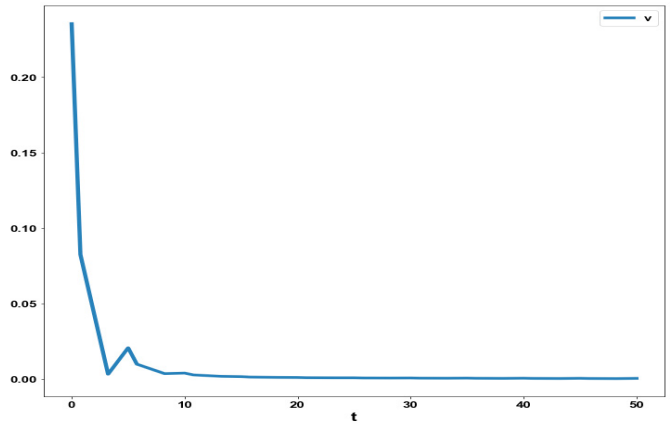

Figure 18: MNLMPC model 2 (v vs t).

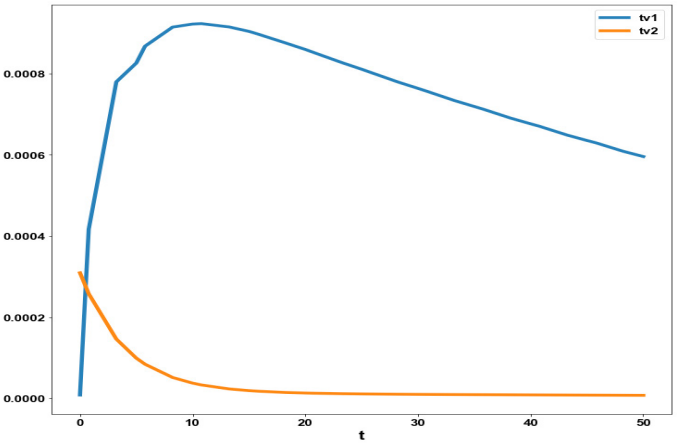

Figure 19: MNLMPC model 2 (tv1, tv2 vs t).

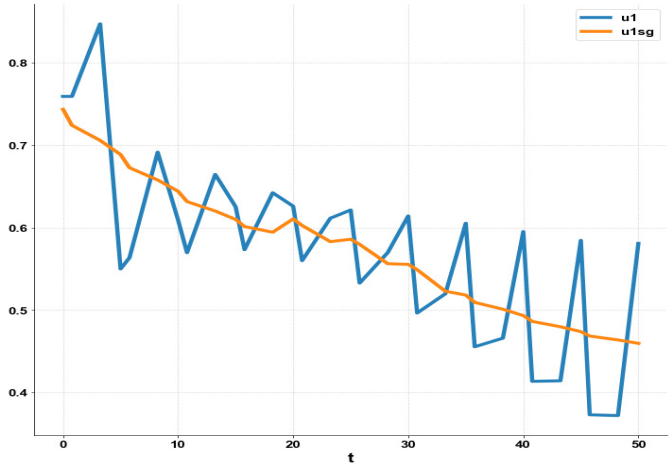

Figure 20: MNLMPC model 2 (u1, u1sg vs t)

Conclusions

Bifurcation analysis and multiobjective nonlinear control (MNLMPC) studies in dynamic HIV models. The bifurcation analysis revealed the existence of branch and limit points. The branch and limit points (which cause multiple steady-state solutions from a singular point) are very beneficial because they enable the Multiobjective nonlinear model predictive control calculations to converge to the Utopia point (the best possible solution) in the models. A combination of bifurcation analysis and Multiobjective Nonlinear Model Predictive Control (MNLMPC) for HIV 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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