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Analysis and control of a tuberculosis model

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Abstract

In this study, bifurcation analysis and multi objective nonlinear model predictive control is performed on a tuberculosis disease model. 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. 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 branch points. The MNLMC converged to the utopia solution. The branch points (which cause multiple steady-state solutions from a singular point) are very beneficial because they enable the Multi objective nonlinear model predictive control calculations to converge to the Utopia point (the best possible solution) in the model.

Keywords: bifurcation, optimization, control, tuberculosis

Background

Tuberculosis is one of the most ancient and persistent infectious diseases known to humanity, affecting millions of people each year and remaining a leading cause of death worldwide despite being preventable and curable. It is primarily caused by the bacterium *Mycobacterium tuberculosis*, which was discovered by Robert Koch in 1882, a landmark event that revolutionized the understanding of infectious diseases. The bacterium primarily infects the lungs, causing pulmonary tuberculosis, though it can also affect other parts of the body such as the lymph nodes, bones, kidneys, and brain, resulting in extra pulmonary forms. Tuberculosis is a complex disease, not only medically but also socially and economically, reflecting inequalities in living conditions, healthcare access, and nutrition. It thrives in environments where poverty, malnutrition, overcrowding, and inadequate medical care are prevalent, making it a symbol of global health inequity. The transmission of tuberculosis occurs through airborne particles expelled by infected individuals when they cough, sneeze, speak, or sing. When a person inhales these droplets, the bacteria can lodge in the lungs and may remain dormant for years before causing active disease. This distinction between latent tuberculosis infection and active tuberculosis is a defining feature of the disease's epidemiology. In latent infection, the immune system controls the bacteria but does not eliminate them, leading to a state where the person shows no symptoms and is not contagious. However, if the immune system weakens, such as in cases of HIV infection, malnutrition, or chronic illnesses, the bacteria can reactivate, causing active tuberculosis and making the person infectious. This reactivation contributes to the persistence of tuberculosis in the population and complicates eradication efforts.

The symptoms of active tuberculosis are often insidious, developing gradually over weeks or months. The most characteristic symptom is a chronic cough that lasts more than three weeks, often producing sputum and occasionally blood. Other symptoms include fever, night sweats, weight loss, fatigue, and loss of appetite. Because these signs overlap with other respiratory diseases, tuberculosis is sometimes misdiagnosed, leading to delays in treatment. Diagnosis typically involves a combination of clinical evaluation, radiographic imaging such as chest X-rays, and microbiological tests to detect *Mycobacterium tuberculosis*. Traditional methods include sputum smear microscopy and culture, the latter being the gold standard but requiring weeks to yield results. Advances in molecular diagnostics, such as the GeneXpert MTB/RIF assay, have dramatically improved the speed and accuracy of tuberculosis detection, while also identifying resistance to rifampicin, one of the key drugs in tuberculosis therapy. Treatment of tuberculosis relies on a combination of antibiotics taken over a long duration, typically six months for drug-susceptible cases. The standard regimen includes isoniazid, rifampicin, pyrazinamide, and ethambutol, used together to prevent the emergence of resistant strains. The long treatment course poses challenges for patient adherence, and interruptions can lead to relapse or the development of drug-resistant tuberculosis. Multidrug-resistant tuberculosis (MDR-TB), resistant to at least isoniazid and rifampicin, and extensively drug-resistant tuberculosis (XDR-TB), resistant to even more antibiotics, have emerged as serious global health threats. Treating these forms requires newer and more toxic drugs, prolonged therapy, and close monitoring. The emergence of resistance underscores the importance of proper diagnosis, complete adherence to treatment, and robust public health infrastructure to track and support patients through therapy.

The relationship between tuberculosis and HIV/AIDS has had devastating consequences in many parts of the world. HIV weakens the immune system, making co-infected individuals far more likely to develop active tuberculosis and suffer severe outcomes. In regions such as sub-Saharan Africa, the dual epidemic of HIV and tuberculosis has strained health systems and caused enormous suffering. Integrating tuberculosis and HIV care, including routine screening and preventive therapy for co-infected patients, has been a cornerstone of modern control strategies. The use of antiretroviral therapy not only prolongs the lives of HIV patients but also reduces their risk of developing tuberculosis, demonstrating how interconnected global health interventions must be. Prevention of tuberculosis involves both medical and social measures. The Bacillus Calmette-Guérin (BCG) vaccine, developed in the early twentieth century, remains the only available vaccine and is widely used in newborns to prevent severe forms of childhood tuberculosis, such as meningitis and miliary disease. However, its effectiveness against adult pulmonary tuberculosis is limited, prompting on-going research to develop more effective vaccines. Public health efforts also focus on early detection, isolation of infectious cases, contact tracing, and improving living conditions to reduce transmission. Addressing the social determinants of tuberculosis—poverty, malnutrition, and inadequate housing-is as essential as medical treatment, because these factors create conditions under which the disease thrives.

The global response to tuberculosis has evolved through international collaboration and sustained public health programs. The World Health Organization launched the "End TB Strategy," aiming to reduce tuberculosis deaths by 95% and new cases by 90% by 2035 compared to 2015 levels. Achieving these targets requires not only advances in medicine but also political commitment, funding, and social change. Many countries have made significant progress, but challenges remain, particularly in low- and middle-income regions where health systems are weak and social inequality is high. The COVID-19 pandemic further disrupted tuberculosis control programs by diverting resources and reducing access to diagnostic and treatment services, leading to a resurgence of cases in several regions. The setback highlights the fragility of global health progress and the need for resilient systems capable of managing multiple infectious threats simultaneously.

At the scientific level, on-going research seeks to deepen understanding of Mycobacterium tuberculosis biology, host-pathogen interactions, and immune responses. The bacterium's ability to persist in a dormant state for years remains one of the greatest puzzles in microbiology. Its thick, waxy cell wall provides resistance too many environmental stresses and contributes to its slow growth rate, which complicates treatment. Modern tools in genomics, proteomics, and immunology are being used to identify new drug targets and vaccine candidates. Promising developments include shorter treatment regimens for both drug-sensitive and drug-resistant tuberculosis, as well as novel drugs like bed aquiline and pretomanid that offer new hope for patients with few options. However, scientific advances must be matched by efforts to make treatments affordable and accessible to those most in need. Tuberculosis also carries a profound social and psychological burden. Stigma and discrimination against those infected can lead to isolation, loss of employment, and reluctance to seek care. Historically, tuberculosis was romanticized as the "disease of poets" in the nineteenth century, but in modern times it has become associated with poverty and marginalization. Combating stigma is therefore part of the broader fight against the disease. Education, awareness, and community involvement are crucial to breaking myths and encouraging early diagnosis and treatment. Empowering patients and communities fosters trust and ensures that prevention and treatment efforts are sustainable.

Blower et al,[1] discussed the intrinsic transmission dynamics of the tuberculosis epidemic. Blower et al.[2] researched control strategies for tuberculosis epidemics using new models for old problems. Vynnycky et al.[3] discussed the natural history of tuberculosis, emphasizing the implications of age-dependent risks of disease and the role of reinfection. Raviglione et al.[4] provided an assessment of worldwide tuberculosis control. Dye et al.[5] Investigated the prospects for worldwide tuberculosis control under the WHO DOTS strategy. Feng et.[6] developed a model for tuberculosis with exogenous reinfection. Jung et al.[7] Investigated optimal control of treatments in a two-strain tuberculosis model, Frieden et al,[8] reviewed a lot of the work on tuberculosis control. Castillo-chavez et al,[9] discussed several dynamical models of tuberculosis and their applications. Gomes et al,[10] showed that the reinfection threshold promotes variability in tuberculosis epidemiology and vaccine efficacy. Cohen et al[11] modelled the epidemics of multidrug-resistant tuberculosis of heterogeneous fitness. Chiang et al[12] described the exogenous reinfection in tuberculosis. Verver et al[13] 0\][-09tuberculosis.

Liu[14] investigated the global stability for a tuberculosis model. Silva t al[15,16] performed optimal control calculations for tuberculosis models. Bowong et al[17] discussed optimal interventions strategies for tuberculosis. Mushayabasa et al,[18] modelled the impact of early therapy for latent tuberculosis patients. Rodrigues et al,[19] did a cost-effectiveness analysis of optimal control measures for tuberculosis. Choi et al, [20] developed an optimal intervention strategy for prevention of tuberculosis using a smoking-tuberculosis model. Moualeu et al,[21] developed optimal control strategies for a tuberculosis model with undected cases. Yang et al,[22] studied global stability and performed optimal control for a tuberculosis model with vaccination and treatment. Gao et al,[23] did an optimal control analysis of a tuberculosis model. In this work, bifurcation analysis and multi objective nonlinear model predictive control is performed on a tuberculosis model described in Gao et al.[23] The paper is organized as follows. First, the model equations are presented, followed by a discussion of the numerical techniques involving bifurcation analysis and multi objective nonlinear model predictive control (MNLMPC). The results and discussion are then presented, followed by the conclusions.

Model equations[23]

In this model, sv, vv, lv, iv, tv represent the susceptible, vaccinated, later-stage infected , individuals infected, active-stage infected, and treated but infected individuals. The control parameters u1, u2, and u3, represent the constant vaccination rate, constant successfully treatment rate , and constant treatment rate. The model equations are

$$\begin{aligned}
\frac{d(sv)}{dt} &= \lambda - \beta(sv)\left(iv + \rho 1(tv)\right) - (\mu + u1)sv \\
\frac{d(vv)}{dt} &= u1(sv) - \rho 2\beta vv\left(iv + \rho 1(tv)\right) - \mu(vv) \\
\frac{d(lv)}{dt} &= lpar(\beta sv)\left(iv + \rho 1(tv)\right) + \rho 2\beta(vv)\left(iv + \left(\rho 1(tv)\right)\right) - (\mu + \delta)lv) + u2(tv) \\
\frac{d(iv)}{dt} &= (1 - lpar)\beta(sv)\left(iv + \rho 1(tv)\right) + \delta(lv) - (\mu + \alpha + u3)iv \\
\frac{d(tv)}{dt} &= u3(iv) - (\mu + u2)tv
\end{aligned} \tag{1}$$

The base parameters are

$$\lambda = 1428; \beta = 0.003; \rho 1 = 0.25;\ \mu = \frac{1}{70};\ \rho 2 = 0.3;\ lpar = 0.9; \delta = 0.00368; \alpha = 0.17; u1 = 0; u2 = 0; u3 = 0.$$

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, Govaerts, and Kuznetsov[24]; Dhooge, Govaerts, Kuznetsov, Mestrom and Riet[25]. This program detects Limit points (LP), branch points(BP), and Hopf bifurcation points(H) for an ODE system

$$\frac{dx}{dt} = f(x,\alpha) \tag{2}$$

$x \in R^n$ 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

$$Aw = 0 \tag{3}$$

Where A is

$$A = [\partial f / \partial x \quad | \partial f / \partial \alpha] \tag{4}$$

Where $\partial f / \partial x$ is the Jacobian matrix. For both limit and branch points, the Jacobian matrix

$J = [\partial f / \partial x]$ must be singular.

For a limit point, there is only one tangent at the point of singularity. At this singular point, there is a single non-zero vector, y, where Jy=0. This vector is of dimension n. Since there is only one tangent the vector

$y = (y_1, y_2, y_3, y_4, ...y_n)$ must align with $\hat{w} = (w_1, w_2, w_3, w_4, ...w_n)$. Since

$$J\hat{w} = Aw = 0 \tag{5}$$

the n+1 th component of the tangent vector w_{n+1} = 0 at a limit point (LP).

For a branch point, there must exist two tangents at the singularity. Let the two tangents be z and w. This implies that

$$\begin{aligned} Az &= 0 \\ Aw &= 0 \end{aligned} \tag{6}$$

Consider a vector v that is orthogonal to one of the tangents (say w). v can be expressed as a linear combination of z and w ($v = \alpha z + \beta w$). Since $Az = Aw = 0$; $Av = 0$ and since w and v are orthogonal, $w^T v = 0$. Hence $Bv = \begin{bmatrix} A \\ w^T \end{bmatrix} v = 0$ which implies that B is singular?

Hence, for a branch point (BP) the matrix $B = \begin{bmatrix} A \\ w^T \end{bmatrix}$ must be singular.

At a Hopf bifurcation point,

$$\det(2 f_x(x,\alpha) @ I_n) = 0 \tag{7}$$

@ indicates the bi alternate 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 & Govaerts.[26-28]

Multi objective nonlinear model predictive control (MNLMPC)

The rigorous multi objective nonlinear model predictive control (MNLMPC) method developed by Flores Tlacuahuaz et al[29] was used.

Consider a problem where the variables $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ (j=1, 2..n) have to be optimized simultaneously for a dynamic problem

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

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

$$\begin{aligned} &\min\left(\sum_{j=1}^{n}\left(\sum_{t_i=0}^{t_i=t_f} q_j(t_i) - q_j^*\right)\right)^2 \\ &subject\ to\ \frac{dx}{dt} = F(x,u); \end{aligned} \tag{9}$$

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 where ($\sum_{t_i=0}^{t_i=t_f} q_j(t_i) = q_j^*$ for all j) is obtained.

Pyomo Hart et al,[30] 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 & Biegler[31] and confirmed as a global solution with BARON Tawarmalani, M. and N. V. Sahinidis[32].

The steps of the algorithm are as follows

Optimize $\sum_{t_i=0}^{t_i=t_f} q_j(t_i)$ and obtain q_j^*.

Minimize $\left(\sum_{j=1}^{n}\left(\sum_{t_i=0}^{t_i=t_f} q_j(t_i) - q_j^*\right)\right)^2$ and get the control values at various times

Implement the first obtained control values

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[33] demonstrated that when the bifurcation analysis revealed the presence of limit and branch points the MNLMPC calculations to converge to the Utopia solution. For this, the singularity condition, caused by the presence of the limit or branch points was imposed on the co-state equation (Upreti.[34] 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 multi objective optimal control problem is

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

Differentiating the objective function results in

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

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

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

The optimal control co-state equation Upreti;[34] is

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

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

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

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 optimal solution is the Utopia solution.

Results and discussion

Branch points were found when μ and α were used as bifurcation parameters. When μ is the bifurcation parameter a branch point was found at (sv, vv, lv, iv, tv, μ) values of (2408.908654, 0, 0, 0, 0,0.5928) Figure 1A. When α is the bifurcation parameter a branch point was found at(sv, vv, lv, iv, tv, α) values of (99960.0, 0, 0, 0, 0, 85.256936) Figure 1B.

For the MNLMPC, sv(0)=4500, vv(0)=3000, lv(0)]=(4000), iv(0)=(500) and tv(0)=480; u1, u u3 are the control parameters, and $\sum_{t_i=0}^{t_i=t_f} lv(t_i), \sum_{t_i=0}^{t_i=t_f} iv(t_i), \sum_{t_i=0}^{t_i=t_f} tv(t_i)$ were minimized individually, and led to

values of 6390.768, 500 and 480The overall optimal control problem will involve the minimization of

$$(\sum_{t_i=0}^{t_i=t_f} lv(t_i)-6390.768)^2+(\sum_{t_i=0}^{t_i=t_f} iv(t_i)-500)^2+(\sum_{t_i=0}^{t_i=t_f} iv(t_i)-480)^2$$

was minimized subject to the

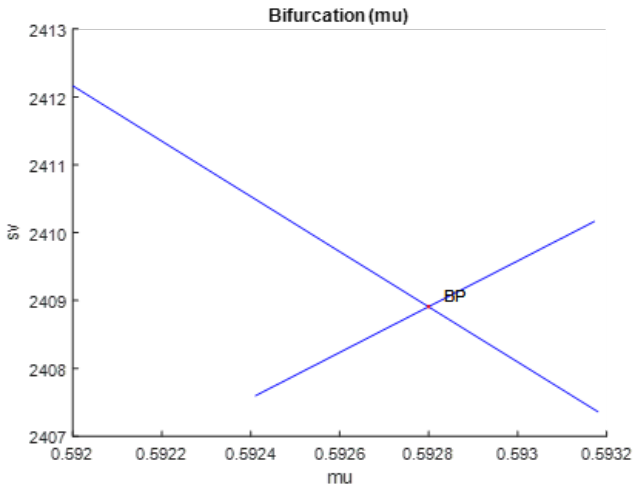

Figure 1A: Bifurcation Diagram when is the bifurcation parameter

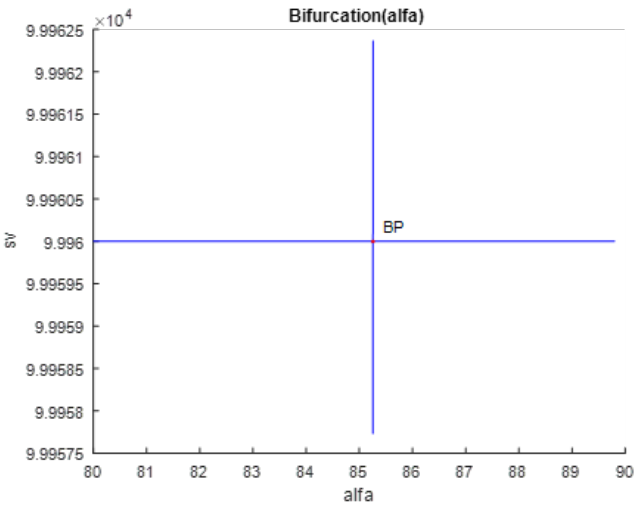

Figure 1B: Bifurcation Diagram when is the bifurcation parameter

Equations governing the model This led to a value of zero (the Utopia point). The MNLMPC values of the control variables, u1, u2, and u3 were 0.4021, 0.0172, and 0.7034. The MNLMPC profiles are shown in Figures 2A&2B. The control profiles of u1, u2, and u3 exhibited noise Figure 2C and this was remedied using the Savitzky-Golay filter to produce the smooth profiles u1sg, u2sg, and u3sg Figure 2D. The presence of the branch points causes the MNLMPC calculations to attain the Utopia solution, validating the analysis of Sridhar.[33]

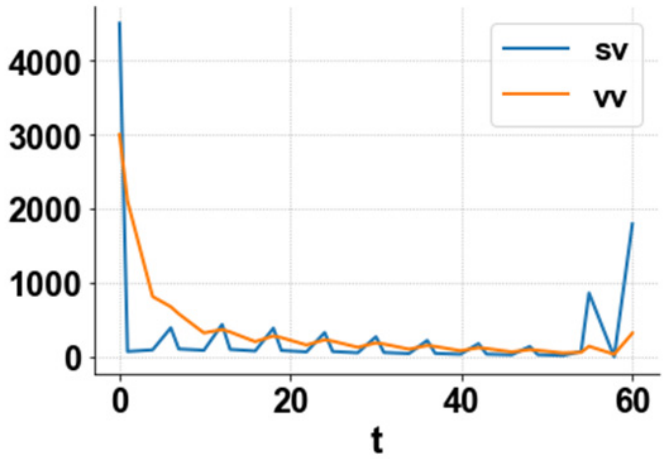

Figure 2A: MNLMPC sv vv profiles.

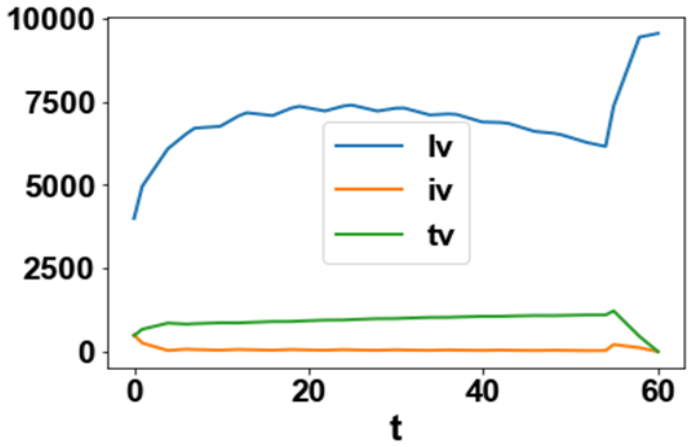

Figure 2B: MNLMPC lv iv tv profiles.

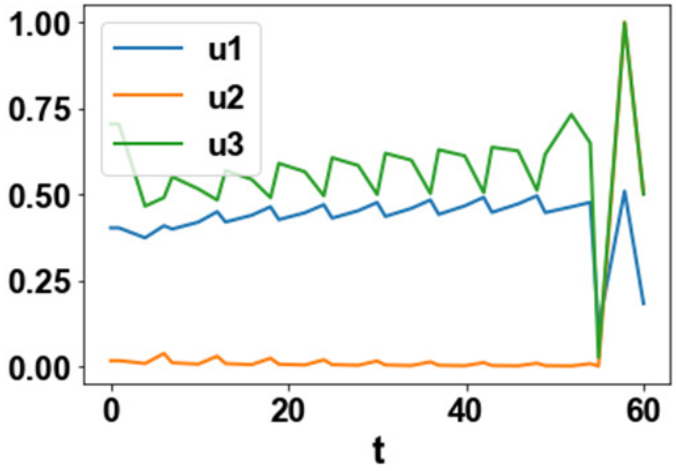

Figure 2C: MNLMPC u1 u2 u3 profiles

Conclusions

Bifurcation analysis and multi objective nonlinear control (MNLMPC) studies on a tuberculosis disease model. The bifurcation analysis revealed the existence of branch points. These branch points (which cause multiple steady-state solutions from a singular point) are very beneficial because they enable the Multi objective nonlinear model predictive control calculations to converge to the Utopia point (the best possible solution) in the models. A combination of bifurcation analysis and Multi objective Nonlinear Model Predictive Control (MNLMPC) for a tuberculosis disease model is the main contribution of this paper.

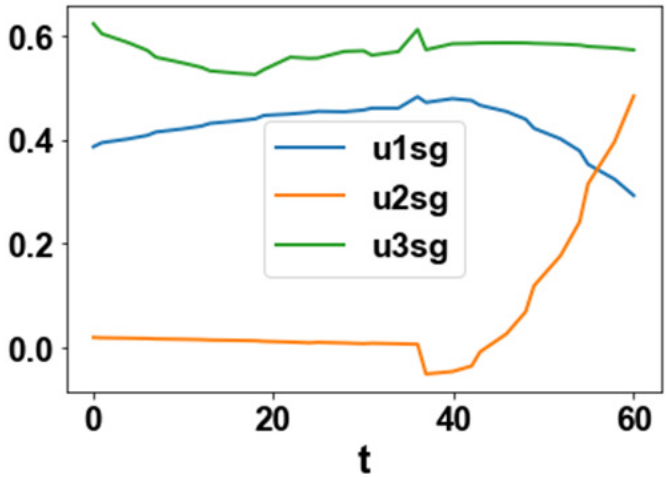

Figure 2D: MNLMPC u1sg u2sg u3sg profiles.

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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