Analysis and Control of a Drug Delivery Model

Abstract:
Many chronic diseases require continuous treatment, and the interaction between drug exposure and pharmacological response is very complex and nonlinear. It is important to understand the nonlinear complexity and use this nonlinearity effectively to obtain the best advantage. Several factors must be considered, and multiple objectives must be achieved simultaneously. Bifurcation analysis and multi-objective nonlinear model predictive control (MNLMPC) calculations are performed on a dynamic model involving drug delivery. The MATLAB program MATCONT was used to perform the bifurcation analysis. The MNLMPC calculations were carried out using the optimization language PYOMO in conjunction with the advanced global optimization solvers IPOPT and BARON. The bifurcation analysis revealed the existence of a branch point in the system. These branch point (which causes multiple steady-state solutions from a single point) is beneficial because it enables the multi-objective nonlinear model predictive control calculations to converge to the Utopia point, which is the best possible solution. It has been demonstrated (with computational validation) that the branch point results from the presence of two distinct separable functions in one of the equations of the dynamic model. A theorem was developed to prove this fact for any dynamic model..

Key Words: Bifurcation, optimization, control, drug-delivery

Author Information

Lakshmi. N. Sridhar*
Chemical Engineering Department University of Puerto Rico Mayaguez

***Corresponding Author:** Lakshmi. N. Sridhar, Chemical Engineering Department University of Puerto Rico Mayaguez

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Introduction:

Background

Coldman and Murray (2000)[1] performed optimal control studies for a stochastic model of cancer chemotherapy. Oefelein et al (2000)[2] reassessed the definition of castrate levels of testosterone and investigated the implications for clinical decision-making. Stengel et al (2002)[3] investigated the optimal enhancement of immune responses. Oefelein and Resnick (2003)[4] studied testosterone suppression for patients with prostate cancer. Kimmel and Swierniak(2006)[5] provided a control Theory approach to cancer chemotherapy, benefiting from Phase Dependence and Overcoming Drug Resistance. Gu and Moore(2006)[6] studied optimal therapy regimens for treatment-resistant mutations. Tornøe et al (2007)[7] developed Population pharmacokinetic/pharmacodynamic (PK/PD) models of the hypothalamic-pituitary-gonadal axis following treatment with GnRH analogues.

Scher et al (2008)[8] researched design and endpoints of Clinical Trials for Patients With Progressive Prostate Cancer and

Castrate Levels of Testosterone. Woodcock et al (2008)[9] studied the FDA Critical Path Initiative and Its Influence on New Drug Development. De Pillis et al (2008)[10] performed optimal control studies of mixed Immunotherapy and chemotherapy of tumors. Engelhart et al (2011)[11] performed optimal control computation for selected cancer chemotherapy ODE models with a view to the potential of optimal schedules and choice of objective function. Romero et al (2012)[12] developed a pharmacokinetic/pharmacodynamic model of the testosterone effects of triptorelin administered in sustained release formulations in patients with prostate cancer.

Shi et al (2014)[13] conducted a survey of optimization models on cancer chemotherapy treatment planning. Buil-Bruna et al (2016)[14] performed a population pharmacokinetic analysis of Lanreotide Autogel/Depot in the Treatment of Neuroendocrine Tumors. Ledzewicz and Moore (2016)[15] studied the dynamical systems properties of a mathematical model for the treatment of CML. Almeida et al (2016) developed a simplified control scheme for the depth of anesthesia. Almeida et al (2016)[17] developed a simplified control approach for neuromuscular blockade levels. He et al (2016)[18] developed optimized treatment schedules for chronic myeloid leukemia. Irurzun-Arana et al (2018)[19] used an optimal dynamic control approach in a multi-objective therapeutic scenario with an application to drug delivery in the treatment of prostate cancer.

This work aims to perform bifurcation analysis and multiobjective nonlinear control (MNLMPC) studies in a drug-delivery dynamics model (Irurzun-Arana et al ;2018[19]). 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 are then presented, followed by the discussion and conclusions.

1. Model Equations(Irurzun-Arana et al ;2018[19])

$$
\begin{aligned}
\frac{dc1}{dt} &= \left(-cld1/vt1\right)c1 + cld1\left(ctrp/vc\right)\\
\frac{dc2}{dt} &= \left(-cld2/vt2\right)c2 + cld2\left(ctrp/vc\right)\\
\frac{dctrp}{dt} &= \left(cld1/vt1\right)c1 - cld1\left(ctrp/vc\right) + \left(cld2/vt2\right)c2 - cld2\left(ctrp/vc\right) - cl\left(ctrp/vc\right) + u\\
\frac{drt}{dt} &= ksr\left(\frac{dr50}{\left(dr50 + frc - frc0\right)}\right)\left(\frac{rt}{rt0}\right)\left(2 - \left(\frac{rt}{rt0}\right)\right) - kdr\left(rt\right)\\
\frac{dtst}{dt} &= kst\left(frc\right)rt + kin - kdt\left(tst\right)\\
frc &= \frac{\left(agn + (ctrp/kd)\right)}{\left(1 + agn + (ctrp/kd)\right)}
\end{aligned}
\qquad (1)
$$

The parameter values are

$$
\begin{aligned}
&cl = 274.3; vc = 8.1; vt1 = 12; vt2 = 33.8; cld1 = 832.3; cld2 = 159.5; tst0 = 3.98; kd = 0.931;\\
&dr50 = 0.0124; ksr = 0.185; kin = 0.041; kdt = 0.55; agn = 0.31; \ frc0 = 0.2366; rt0 = 1; u = 0.5;\\
&kdr = 0.5; kst = 0.5;
\end{aligned}
$$

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[20]; Dhooge Govearts, Kuznetsov, Mestrom and Riet, 2004[21]). This program detects Limit points(LP), branch points(BP), and Hopf bifurcation points(H) for an ODE system

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

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

The tangent plane at any point $z = [z_1, z_2, z_3, z_4, ...z_{n+1}]$ must satisfy

$$Az = 0 \qquad (3)$$

Where A is

$$A = [\partial f / \partial x \quad | \partial f / \partial \alpha] \qquad (4)$$

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 z_{n+1} = 0 for a limit point (LP)and for a branch point (BP) the matrix $\begin{bmatrix} A \\ z^T \end{bmatrix}$ must be singular.

At a Hopf bifurcation point,

$$\det(2 f_x(x, \alpha) @ I_n) = 0 \qquad (5)$$

@ 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[22]; 2009[23]) and Govaerts [2000] [24].

2. Multiobjective Nonlinear Model Predictive Control (MNLMPC)

Flores Tlacuahuaz et al (2012)[25] 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

$$\frac{dx}{dt} = F(x, u) \qquad (6)$$

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

$$\min\left(\sum_{j=1}^{n} \left(\sum_{t_{i=0}}^{t_i = t_f} q_j(t_i) - q_j^*\right)\right)^2$$
$$subject\ to\ \frac{dx}{dt} = F(x, u); \qquad (7)$$

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)[26] 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)[27]and confirmed as a global solution with BARON (Tawarmalani, M. and N. V. Sahinidis 2005)[28].

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)[29] 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)[30]. 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

$$\min \quad (q_1 - q_1^*)^2 + (q_2 - q_2^*)^2 \quad subject\ to \ \frac{dx}{dt} = F(x,u) \tag{8}$$

Differentiating the objective function results in

$$\frac{d}{dx_i}((q_1 - q_1^*)^2 + (q_2 - q_2^*)^2) = 2(q_1 - q_1^*)\frac{d}{dx_i}(q_1 - q_1^*) + 2(q_2 - q_2^*)\frac{d}{dx_i}(q_2 - q_2^*) \tag{9}$$

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

$$\frac{d}{dx_i}((q_1 - q_1^*)^2 + (q_2 - q_2^*)^2) = 0 \tag{10}$$

the optimal control co-state equation (Upreti; 2013)[30] is

$$\frac{d}{dt}(\lambda_i) = -\frac{d}{dx_i}((q_1 - q_1^*)^2 + (q_2 - q_2^*)^2) - f_x \lambda_i; \quad \lambda_i(t_f) = 0 \tag{11}$$

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

$$\frac{d}{dt}(\lambda_i) = -f_x \lambda_i ; \lambda_i(t_f) = 0 \quad (12)$$

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 vector-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 :

When rt0 is the bifurcation parameter, we get BP ar (c1,c2,ctrp,rt,tst,rt0) values of
(0.021874 0.061611 0.014765 0 0.074545 0.425365) (Fig. 1a)
When frc0 is the bifurcation parameter, we get BP ar (c1,c2,ctrp,rt,tst,frc0) values of
(0.021874 0.061611 0.014765 0 0.074545 0.248996) (Fig. 1b)

For the MNLMPC calculations, $\sum_{t_{i=0}}^{t_i=t_f} c1(t_i), \sum_{t_{i=0}}^{t_i=t_f} c2(t_i), \sum_{t_{i=0}}^{t_i=t_f} ctrp(t_i)$ were minimized individually and each minimization led to a value of 0. $\sum_{t_{i=0}}^{t_i=t_f} tst(t_i)$ was maximized and resulted in a value of 1.5284. The multiobjective optimal control problem will involve the minimization of $(\sum_{t_{i=0}}^{t_i=t_f} ctrp(t_i))^2 + (\sum_{t_{i=0}}^{t_i=t_f} c2(t_i))^2 + (\sum_{t_{i=0}}^{t_i=t_f} tst(t_i) - 1.5284)^2 + (\sum_{t_{i=0}}^{t_i=t_f} c1(t_i))^2$ subject to the equations of the listeriosis model. This led to a value of zero (the Utopia solution). The MNLMPC control values of u, was 0.0010016175523356997. Figs 1c -1e. The control profile u vs t exhibited a lot of noise. This was remedied using the Savitzky-Golay filter to produce a smoother control profile (usg vs t) . Both u and usg profiles are shown in fig. 1e.

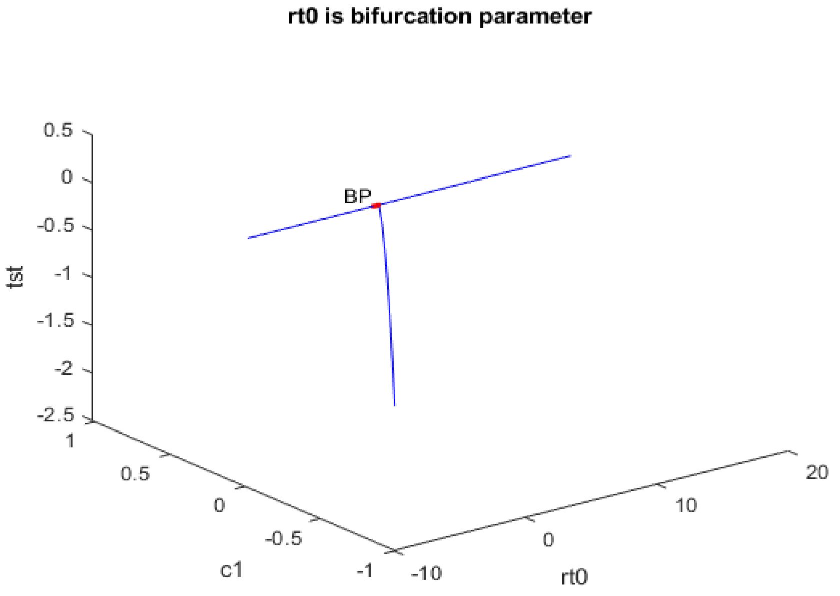

Figure 1: *a rt0 is the bifurcation parameter*

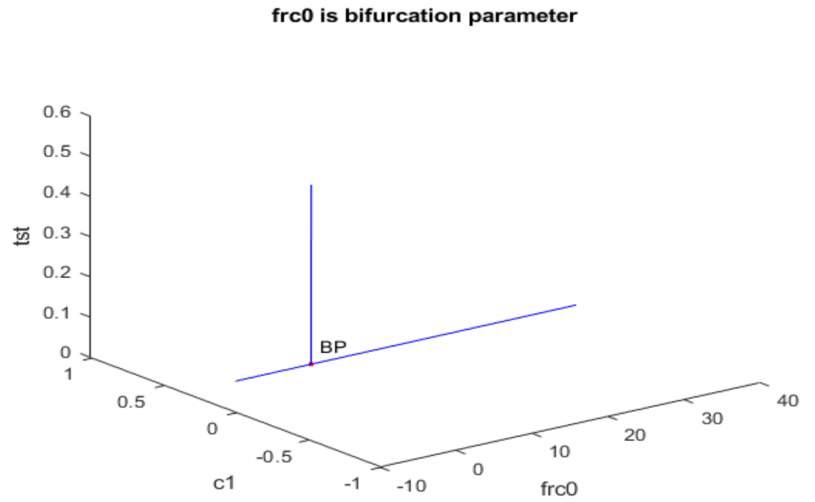

Figure 1b: *frc0 is bifurcation parameter*

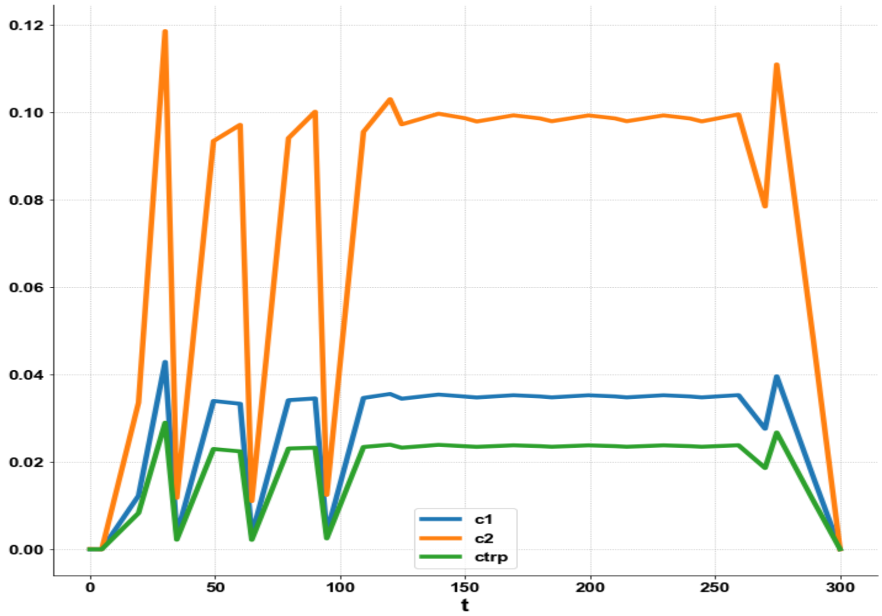

Figure 1c: *MNLMPC c1 c2 ctrp profiles*

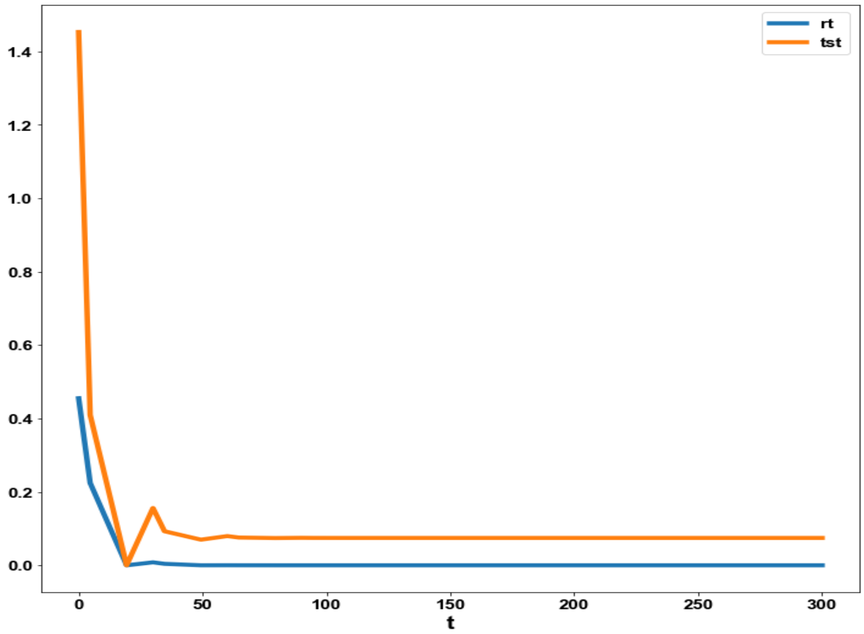

Figure 1d: *MNLMPC rt tst profiles*

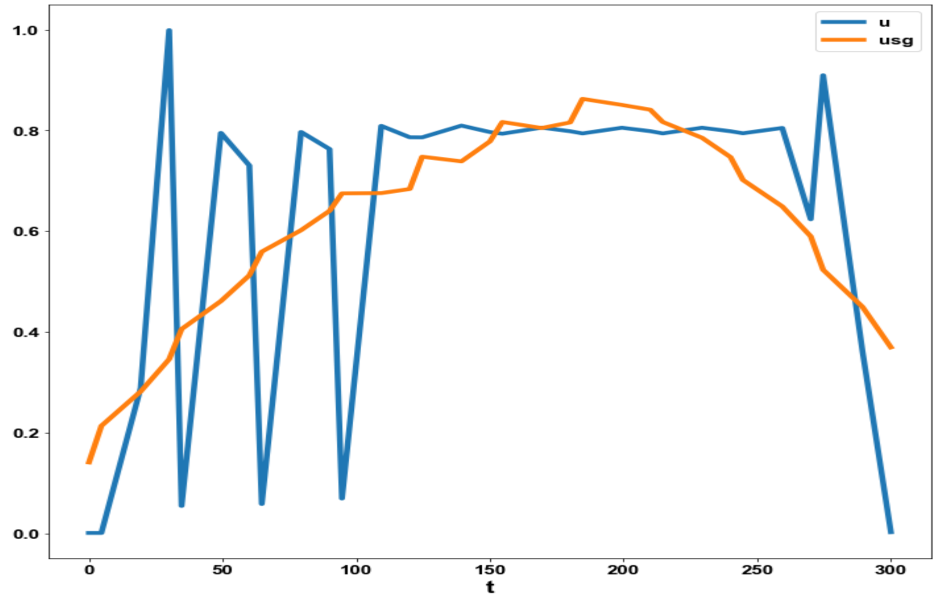

Figure 1e: *MNLMPC u vs t (noise exhibited) usg (noise eliminated with Savitzky Golay filter)*

Discussion of Results:

Theorem

If one of the functions in a dynamic system is separable into two distinct functions, a branch point singularity will occur in the system.

Proof

Consider a system of equations

$$\frac{dx}{dt} = f(x,\alpha) \qquad (13)$$

$x \in R^n$. Defining the matrix A as

$$A = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \frac{\partial f_1}{\partial x_3} & \frac{\partial f_1}{\partial x_4} \cdots\cdots & \frac{\partial f_1}{\partial x_n} & \frac{\partial f_1}{\partial \alpha} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \frac{\partial f_2}{\partial x_3} & \frac{\partial f_2}{\partial x_4} \cdots\cdots & \frac{\partial f_2}{\partial x_n} & \frac{\partial f_2}{\partial \alpha} \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \frac{\partial f_n}{\partial x_3} & \frac{\partial f_n}{\partial x_4} \cdots\cdots & \frac{\partial f_n}{\partial x_n} & \frac{\partial f_n}{\partial \alpha} \end{bmatrix} \qquad (14)$$

α is the bifurcation parameter. The matrix A can be written in a compact form as

$$A = [\frac{\partial f_p}{\partial x_q}.| \quad \frac{\partial f_p}{\partial \alpha}] \qquad (15)$$

The tangent at any point x; $(z = [z_1, z_2, z_3, z_4, ...z_{n+1}])$ must satisfy

$$Az = 0 \qquad (16)$$

The matrix $\{\frac{\partial f_p}{\partial x_q}\}$ must be singular at both limit and branch points.. The n+1 th component of the tangent vector $z_{n+1} = 0$ at a limit point (LP) and for a branch point (BP) the matrix $B = \begin{bmatrix} A \\ z^T \end{bmatrix}$ must be singular.

Any tangent at a point y that is defined by $z = [z_1, z_2, z_3, z_4, ...z_{n+1}]$) must satisfy

$$Az = 0 \tag{17}$$

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

$$\begin{aligned} Az &= 0 \\ Aw &= 0 \end{aligned} \tag{18}$$

Consider a vector v that is orthogonal to one of the tangents (say z). 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 z and v are orthogonal,

$z^T v = 0$. Hence $Bv = \begin{bmatrix} A \\ z^T \end{bmatrix} v = 0$ which implies that B is singular.

Let any of the functions f_i are separable into 2 functions ϕ_1, ϕ_2 as

$$f_i = \phi_1 \phi_2 \tag{19}$$

At steady-state $f_i(x, \alpha) = 0$ and this will imply that either $\phi_1 = 0$ or $\phi_2 = 0$ or both ϕ_1 and ϕ_2 must be 0. This implies that two branches $\phi_1 = 0$ and $\phi_2 = 0$ will meet at a point where both ϕ_1 and ϕ_2 are 0.

At this point, the matrix B will be singular as a row in this matrix would be

$$[\frac{\partial f_i}{\partial x_k} | \frac{\partial f_i}{\partial \alpha}] \tag{20}$$

However,

$$\begin{aligned} &[\frac{\partial f_i}{\partial x_k} = \phi_1(=0)\frac{\partial \phi_2}{\partial x_k} + \phi_2(=0)\frac{\partial \phi_1}{\partial x_k} = 0(\forall k = 1.,,n) \\ &\frac{\partial f_i}{\partial \alpha} = \phi_1(=0)\frac{\partial \phi_2}{\partial \alpha} + \phi_2(=0)\frac{\partial \phi_1}{\partial \alpha}] = 0 \end{aligned} \tag{21}$$

This implies that every element in the row $[\frac{\partial f_i}{\partial x_k} | \frac{\partial f_i}{\partial \alpha}]$ would be 0 and hence the matrix B would be singular. The singularity in B implies that there exists a branch point.

The two distinct equations (when rt0 is the bifurcation parameter) can be observed from the equation

$$\frac{drt}{dt} = ksr(\frac{dr50}{(dr50 + frc - frc0)})\left(\frac{rt}{rt0}\right)\left(2 - \left(\frac{rt}{rt0}\right)\right) - kdr(rt) \tag{22}$$

The two distinct equations are

$$rt = 0$$
$$ksr\left(\frac{dr50}{(dr50 + frc - frc0)}\right)\left(\frac{1}{rt0}\right)\left(2 - \left(\frac{rt}{rt0}\right)\right) - kdr = 0 \qquad (23)$$

With

$$ctrp = 0.014765; kd = 0.931; agn = 0.31;\ frc = \frac{(agn + (ctrp / kd))}{(1 + agn + (ctrp / kd))}; rt0 = 0.425365;$$
$$dr50 = 0.0124;\ frc0 = 0.2366; rt = 0; ksr = 0.185; kdr = 0.5$$

both the distinct equations are satisfied, validating the theorem.

The two distinct equations (when frc0 is the bifurcation parameter) can be observed from the equation

$$\frac{drt}{dt} = ksr\left(\frac{dr50}{(dr50 + frc - frc0)}\right)\left(\frac{rt}{rt0}\right)\left(2 - \left(\frac{rt}{rt0}\right)\right) - kdr(rt) \qquad (24)$$

The two distinct equations are

$$rt = 0$$
$$ksr\left(\frac{dr50}{(dr50 + frc - frc0)}\right)\left(\frac{1}{rt0}\right)\left(2 - \left(\frac{rt}{rt0}\right)\right) - kdr = 0 \qquad (25)$$

With

$$ctrp = 0.014765; kd = 0.931; agn = 0.31;\ frc = \frac{(agn + (ctrp / kd))}{(1 + agn + (ctrp / kd))}; rt0 = 1;$$
$$dr50 = 0.0124;\ frc0 = 0.248996; rt = 0; ksr = 0.185; kdr = 0.5$$

both the distinct equations are satisfied, validating the theorem.

The MNLMPC calculations converged to the Utopia solution, justifying the analysis of Sridhar(2024)[29].

Conclusions

Bifurcation analysis and multiobjective nonlinear control (MNLMPC) studies were performed in a drug-delivery model. The bifurcation analysis revealed the existence a branch point in the model. The branch point (which cause multiple steady-state solutions from a singular point) is very beneficial because it enables the Multiobjective nonlinear model predictive control calculations to converge to the Utopia point (the best possible solution) in the model. It is proved (with computational validation) that the branch point was caused by the existence of two distinct separable functions in one of the equations in the dynamic model. A theorem was developed to demonstrate this fact for any dynamic model. A combination of bifurcation analysis and Multiobjective Nonlinear Model Predictive Control(MNLMPC) for dynamic models involving listeriosis transmission 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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