

Analysis and Control of an Influenza Transmission Model

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ABSTRACT

Influenza is a global health challenge and effective strategies must be implemented to minimize the damage. The dynamics of influenza transmission must be understood and control methods that are beneficial and cost-effective must be implemented.

In this work, bifurcation analysis and multiobjective nonlinear model predictive control are performed on a dynamic model involving influenza. 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 of branch points in the influenza model for two different bifurcation parameters. The MNLMPC 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 Multiobjective nonlinear model predictive control calculations to converge to the Utopia point (the best possible solution) in the model.

Keywords: Bifurcation; Optimization; Control; Influenza

Background

Stilianakis, et al.¹, researched the emergence of drug resistance during an influenza epidemic using insights from a mathematical model. Alexander, et al.² developed a vaccination model for transmission dynamics of influenza. Nuno et al.³ studied the dynamics of two-strain influenza with isolation and partial cross-immunity. Xu, et al.⁴ developed a stochastic model of an influenza epidemic with drug resistance. Rambaut, et al.⁵ studied the genomic and epidemiological dynamics of human influenza. Lee, et al.⁶, researched optimal control for a pandemic influenza model involving the role of limited antiviral treatment and isolation. Qiu, et al.⁷ studied the transmission dynamics of an influenza model with vaccination and antiviral

treatment. Tchuente et al.⁸, performed optimal control and sensitivity analysis studies of an influenza model with treatment and vaccination. Lee, et al.⁹ modeled the optimal age-specific vaccination strategies against pandemic influenza. Guan, et al.¹⁰ investigated the global stability of an influenza A model with vaccination. Prasad, et al.¹¹, used a multi-modeling approach to evaluate the efficacy of layering pharmaceutical and nonpharmaceutical interventions for influenza pandemics. Chen, et al.¹², performed optimal control studies of an influenza model with mixed cross-infection by age group. Le Sage, et al.¹³, discussed the barriers to transmission of influenza viruses. Han, et al.¹⁴, investigated the co-evolution of immunity and seasonal influenza viruses. Wang, et al. performed optimal

control of an influenza model incorporating pharmacological and non-pharmacological interventions. This work aims to perform bifurcation analysis and multiobjective nonlinear control (MNLMP) studies in the influenza transmission model. The paper is organized as follows¹⁵. First, the model equations are presented, followed by a discussion of the numerical techniques involving bifurcation analysis and multiobjective nonlinear model predictive control (MNLMP). The results and discussion are then presented, followed by the conclusions.

Model Equations for the influenza transmission model¹⁵

The variables (s,v, is,ir,istr,irtr, r) represent the susceptible population, vaccinated population, the population untreated with drug-sensitive strains, people untreated with drug-resistant strains, those treated with drug-sensitive strains, those treated with drug-resistant strains and the recovered population.

The model equations are

$$rval = \beta r(ir) + \beta rtr(irtr)$$

$$sval = \beta s(is) + \beta str(istr)$$

$$tval = rval + sval$$

$$\frac{ds}{dt} = \Lambda - (tval(s)) - (\phi(s)) + ((1-u1)\omega(v)) + (\gamma(r)) - (\mu(s));$$

$$\frac{dv}{dt} = (\phi(s)) - ((1-u1)\omega(v)) - ((1-\sigma)(tval)v) - (\mu v);$$

$$\frac{d(is)}{dt} = (sval(s)) + ((1-\sigma)svalv) - ((1+u2)k1is) - (is(\xi1 + \mu + u4));$$

$$\frac{d(ir)}{dt} = (rval(s)) + ((1-\sigma)rvalv) - ((1+u3)k2ir) - (ir(\xi2 + \mu + u4));$$

$$\frac{d(istr)}{dt} = ((1+u2)k1(is)) - (istr(ppar + \alpha1 + \mu + u5));$$

$$\frac{d(irtr)}{dt} = ((1+u3)k2(ir)) + (ppar(istr)) - (irtr(\alpha2 + \mu + u5));$$

$$\frac{d(r)}{dt} = (\xi1(is)) + (\xi2(ir)) + (istr(\alpha1)) + (\alpha2(irtr)) - (r(\gamma + \mu))$$

The base parameter value are

$$\Lambda = 0.0137; \mu = 3.4247e-05; \beta s = 6.e-03; \beta rtr = 4.02e-03; \beta r = 1.2e-03; \beta rtr = 1.2e-03; \phi = 0.03; \omega = 0.003; \gamma = 0.011; \sigma = 0.85; k1=0.7; \xi1 = 0.25; k2=0.7; \xi2 = 0.25; \alpha1 = 0.3325; \alpha2 = 0.25; ppar=0.05;$$

u1, u2, u3, u4 and u5 are control parameters and are set to 0 for the bifurcation analysis.

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^{16,17}. This program detects Limit points (LP), branch points (BP) and Hopf bifurcation points(H) for an ODE system

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

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

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

$$Aw = 0$$

Where A is

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

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

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

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

the n+1th 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

$$Az = 0$$

$$Aw = 0$$

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,

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

@ 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 Kuznetsov¹⁸⁻²⁰.

Multiobjective Nonlinear Model Predictive Control (MNLMP)

The rigorous multiobjective nonlinear model predictive control (MNLMP) method developed by Flores Tlacuahuaz, et al.²¹ was used.

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

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

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

multiobjective optimal control (MOOC) problem that will be solved is

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

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

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

Pyomo²² 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 IPOPT²³ and confirmed as a global solution with BARON²⁴.

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

Sridhar²⁵ 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 equation²⁶. 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 MNLMPC calculations will minimize the function $(q_1 - q_1^*)^2 + (q_2 - q_2^*)^2$. The multiobjective optimal control problem is

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

Differentiating the objective function results in

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

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

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

The optimal control co-state equation is

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

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

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

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

The bifurcation analysis of the influenza model revealed branch points when βr and βrtr are bifurcation parameters. When βr was the bifurcation parameter the branch point occurred at

(s, v, is, ir, istr, irtr, r, βr) values of (42.757781, 189.151848, 0, 1.870419, 0, 5.236455, 161.018538, 0.009997) (**Figure 1**).

When βrtr was the bifurcation parameter the branch point occurred at (s, v, is, ir, istr, irtr, r, βrtr) values of (42.757781, 189.151848, 0, 1.870419, 0, 5.236455, 161.018538, 0.004342) (**Figures 2, 3 and 4**).

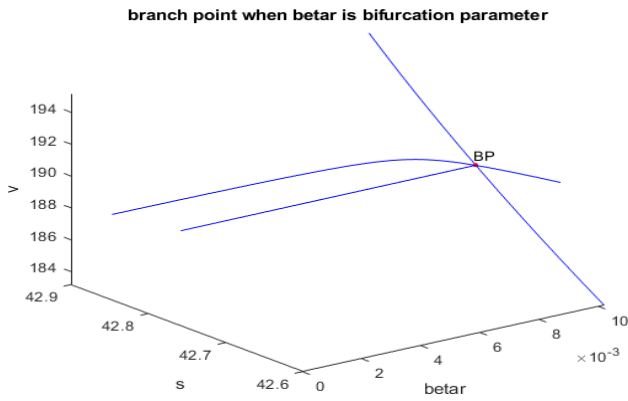


Figure 1: Branch point (βr is the bifurcation parameter).

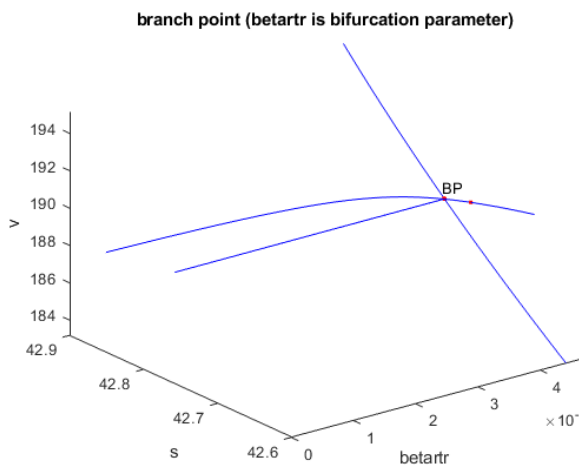


Figure 2: Branch point (βrtr is the bifurcation parameter).

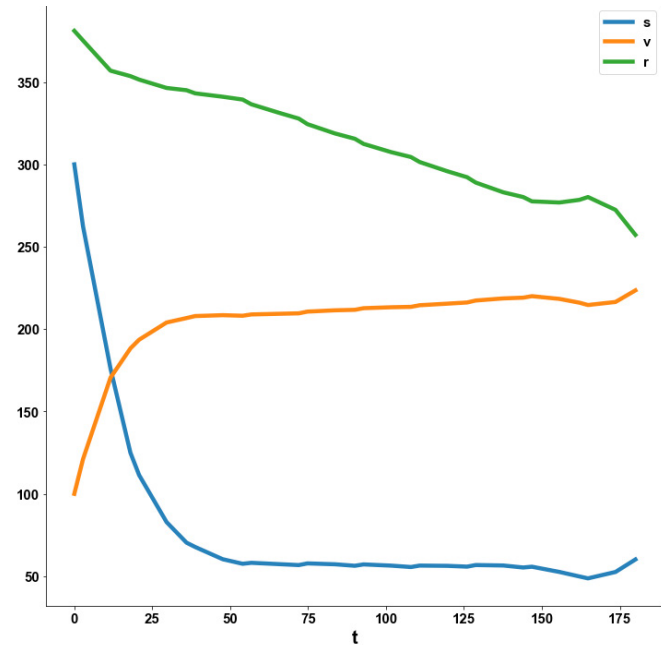


Figure 3: MNLMPc (s v r profiles).

For the MNLMPc calculations, $s(0)$ is set to 300 and $v(0)$ is set to 100

$\sum_{t_i=0}^{t_i=t_f} is(t_i), \sum_{t_i=0}^{t_i=t_f} ir(t_i), \sum_{t_i=0}^{t_i=t_f} istr(t_i), \sum_{t_i=0}^{t_i=t_f} irtr(t_i)$ were minimized individually and each of them led to a value 0. The overall optimal control problem will involve the minimization of

$$\left(\sum_{t_i=0}^{t_i=t_f} is(t_i) \right)^2 + \left(\sum_{t_i=0}^{t_i=t_f} ir(t_i) \right)^2 + \left(\sum_{t_i=0}^{t_i=t_f} istr(t_i) \right)^2 + \left(\sum_{t_i=0}^{t_i=t_f} irtr(t_i) \right)^2$$

was minimized subject to the equations governing the model. This led to a value of zero (the Utopia)

The MNLMPc values of the control variables, u_1, u_2, u_3, u_4, u_5 were 0.5498, 0.7725, 0.4696, 0.92579, 0.8467. The various MNMPC figures are shown in figures 3--6. The control profiles u_1, u_2, u_3, u_4, u_5 (**Figure 5**) exhibited noise and this was remedied using the Savitzky-Golay filter (**Figure 6**). It is seen that the presence of the limit and branch points is beneficial because it allows the MNLMPc calculations to attain the Utopia solution, validating the analysis of Sridhar²⁵.

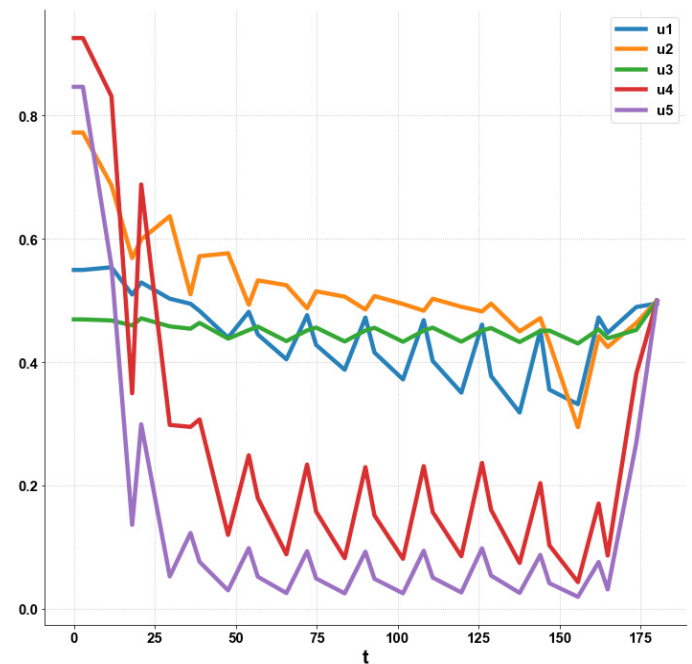


Figure 5: MNLMPc (control profiles with noise).

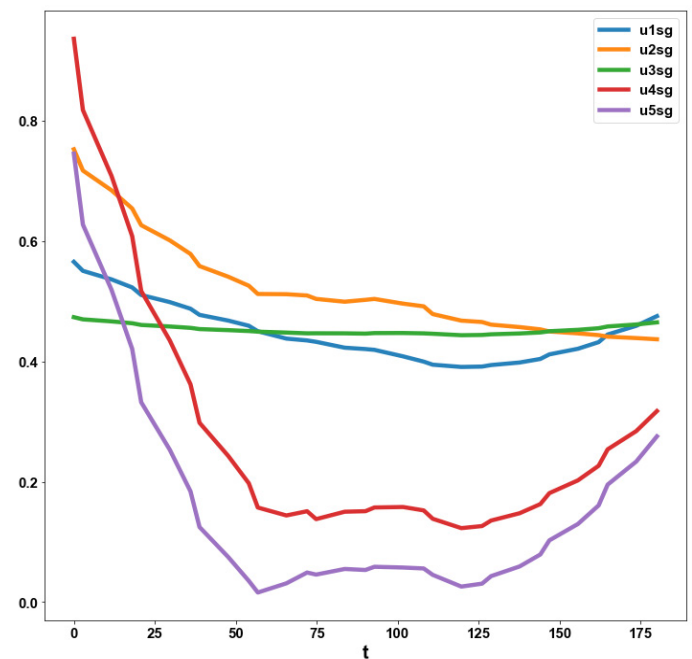


Figure 6: MNLMPc (smooth control profiles; noise removed by Savitzky-Golay filter).

Conclusions

Bifurcation analysis and multiobjective nonlinear control (MNLMP) studies a dynamic influenza transmission model. The bifurcation analysis revealed the existence of branch points for two different bifurcation parameters. The branch and 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 (MNLMP) for dynamic influenza transmission 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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