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Analysis and Control of an Asthma Transmission Model

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Abstract

In this study, bifurcation analysis and multi-objective nonlinear model predictive control are performed on an asthma transmission 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 of branch points. 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 Multi objective nonlinear model predictive control calculations to converge to the Utopia point (the best possible solution) in the model.

Keywords: Bifurcation; Optimization; Control; Asthma; Pollution

Background

Ghosh [1], developed a mathematical model concerning industrial pollution and Asthma. D'amato et al. [2], discussed the environmental risk factors (outdoor air pollution and climatic changes) and the increasing trend of respiratory allergy. Martinez FD [3], researched the relationship between genes, environments, development, and asthma. Gauderman et al. [4] studied the effect of traffic on lung development. Ionescu et al. [5,6], developed parametric models characterizing respiratory input impedance and investigated the relationship between fractional-order model parameters and lung pathology in chronic obstructive pulmonary disease. Epton et al. [7] studied the effect of ambient air pollution on the respiratory health of school children. Ram et al. [8] developed a nonlinear mathematical model for Asthma. Strickland et al. [9] studied the short-term associations between ambient air pollutants and pediatric asthma emergency department visits. Ionescu et al. [10,11] performed theoretical work using fractional order models of asthma and respiration. Tawhai et al. [12], developed multi-scale lung models. Annesi-Maesano et al. [13] studied indoor air quality and sources in schools and related health effects. Ionescu et al. [14], developed a respiratory impedance model with a lumped fractional order diffusion compartment. Kim et al. [15] investigated the regulation of Th1/Th2 cells in asthma development. Lim et al. [16], studied the short-term effect of fine particulate matter on children's hospital admissions and emergency department visits for asthma. Faria et al. [17], studied forced oscillation, integer and fractional-order modelling in asthma. Alejo et al. [18] modelled the association between the seasonal asthma prevalence and upper respiratory infections. Cohen et al. [19] studied the trends of the global burden of disease attributable to ambient air pollution. Ionescu et al. [20] investigated the role of fractional calculus in modeling biological phenomena. Landrigan et al. [21] studied the effect of pollution on children's health. Whittle et al. [22] studied the molecular characterisation of human dust-mite-associated allergic asthma. Shah et al. [23] developed a mathematical model for Asthma due to Air Pollution. In this work, bifurcation analysis and multiobjective nonlinear model predictive control are performed on a dynamic model describing asthma due to air pollution [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 Multiobjective Nonlinear Model Predictive Control (MNLMPC). The results and discussion are then presented, followed by the conclusions.

Model equations

In this model, individuals experiencing an asthma exacerbation are av, individuals affected by indoor smoke are sv, and individuals affected by air pollution are pv. Indoor smoke increases the intensity of pollution in the air at a rate of $\beta 1$ Asthma-infected individuals infect their surrounding environment at a rate of $\beta 3$ while the rate at which asthma exacerbation is caused by indoor smoke and outdoor air pollution is $\beta 2$ and $\beta 4$. μa and μ represent the death rate because of asthma exacerbation and a natural degradation rate for all three variables.

$$\begin{aligned}
\frac{d(sv)}{dt} &= bpar - \beta 1(sv)pv - \beta 2(sv)av + \beta 3(av) - \mu(sv) \\
\frac{d(pv)}{dt} &= \beta 1(sv)pv - \beta 4(av)pv - \mu(pv) \\
\frac{d(av)}{dt} &= \beta 4(av)pv - \beta 3(av) + \beta 2(sv)av - \mu(av) - \mu a(av)
\end{aligned} \quad (1)$$

The base parameter values are

$bpar = 0.1; \beta 1 = 0.15; \beta 2 = 0.25; \beta 3 = 0.3; \beta 4 = 0.35; \mu = 0.3; \mu a = 0.2.$

The variables and parameters can be summarized as

a) individuals experiencing an asthma exacerbation av

b) individuals affected by indoor smoke sv

c) individuals affected by air pollution pv

d) Indoor smoke increases the intensity of pollution in the air at a rate $\beta 1$

e) Asthma-infected individuals infect their surrounding environment at a rate $\beta 3$

f) rate at which asthma exacerbation is caused by indoor smoke $\beta 2$

g) rate at which asthma exacerbation is caused by outdoor air pollution $\beta 4$

h) represent the death rate because of asthma exacerbation μa

i) natural degradation rate for all three variables μ

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 [24,25]. This program detects Limit Points (LP), Branch Points (BP) and Hopf bifurcation points(H) for an ODE system

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

$x \in R^n$ 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

$$Aw = 0 \quad (3)$$

Where A is

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

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

$$J\hat{w} = Aw = 0 \quad (5)$$

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

$$\begin{aligned} Az &= 0 \\ Aw &= 0 \end{aligned} \quad (6)$$

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,

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

@ indicates the bialternate product while 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 [26,27] & Govaerts [28].

Multiobjective Nonlinear Model Predictive Control (MNLMPC)

The rigorous Multiobjective 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

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

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 Multiobjective Optimal Control (MOOC) problem that will be solved is

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

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 And Biegler [31] and confirmed as a global solution with BARON Tawarmalani M et al. [32].

The steps of the algorithm are as follows

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

b) 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 at various times.

c) Implement the first obtained control values

d) 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 multiobjective optimal control problem is

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

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 [34] is

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

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 optimal solution is the Utopia solution.

Results and Discussion

Theoretical development

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

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

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

$$A=\begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \frac{\partial f_1}{\partial x_3} & \frac{\partial f_1}{\partial x_4} \cdots\cdots & \frac{\partial f_1}{\partial x_n} & \frac{\partial f_1}{\partial \alpha} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \frac{\partial f_2}{\partial x_3} & \frac{\partial f_2}{\partial x_4} \cdots\cdots & \frac{\partial f_2}{\partial x_n} & \frac{\partial f_2}{\partial \alpha} \\ \cdots\cdots & & & & & \\ \cdots\cdots & & & & & \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \frac{\partial f_n}{\partial x_3} & \frac{\partial f_n}{\partial x_4} \cdots\cdots & \frac{\partial f_n}{\partial x_n} & \frac{\partial f_n}{\partial \alpha} \end{bmatrix} \quad (3)$$

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

$$A=[\frac{\partial f_p}{\partial x_q}.| \ \frac{\partial f_p}{\partial \alpha}] \quad (4)$$

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

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

The matrix $\{\frac{\partial f_p}{\partial x_q}\}$ must be singular at both limit and branch points. The n+1th 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

$$Az=0 \quad (6)$$

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

$$Az=0$$
$$Aw=0 \quad (7)$$

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,

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

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

$$f_i = \phi_1 \phi_2 \quad (8)$$

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

$$[\frac{\partial f_i}{\partial x_k} | \frac{\partial f_i}{\partial \alpha}] \quad (9)$$

However,

$$[\frac{\partial f_i}{\partial x_k} = \phi_1(=0)\frac{\partial \phi_2}{\partial x_k} + \phi_2(=0)\frac{\partial \phi_1}{\partial x_k} = 0 (\forall k = 1.,,n)$$
$$\frac{\partial f_i}{\partial \alpha} = \phi_1(=0)\frac{\partial \phi_2}{\partial \alpha} + \phi_2(=0)\frac{\partial \phi_1}{\partial \alpha}] = 0 \quad (10)$$

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.

Numerical results

Bifurcation results: When $\beta 1$ is the bifurcation parameter a branch point occurs at (sv,pv,av, $\beta 1$) values of (0.333333 0, 0, 0.9) (Figure 1a)

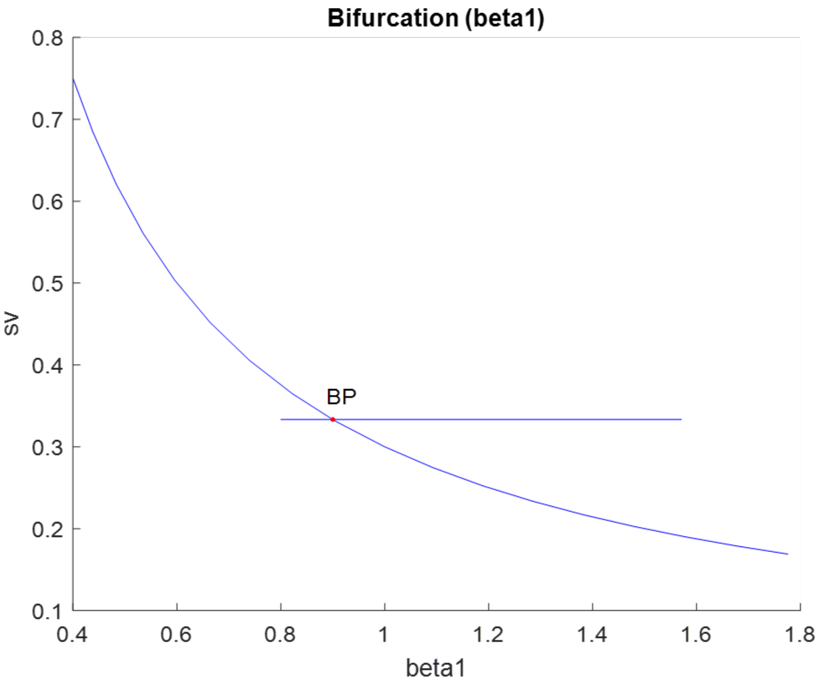

Figure 1a: Bifurcation diagram ($\beta 1$ is the bifurcation parameter) revealing a branch point at (sv,pv,av, $\beta 1$) values of (0.333333 0, 0, 0.9).

Here, the two distinct functions can be obtained from the second ODE in the model

$$\frac{d(pv)}{dt} = \beta 1(sv)pv - \beta 4(av)pv - \mu(pv) \quad (11)$$

The two distinct equations are

$$pv = 0$$
$$\beta 1(sv) - \beta 4(av) - \mu = 0 \quad (12)$$

With pv=0, $\beta 1$=0.9, av=0, μ=0.3; sv =0.33333 both distinct equations are satisfied, validating the theorem.

When $\beta 2$ is the bifurcation parameter a branch point occurs at (sv,pv,av, $\beta 2$) values of (0.333333 0 0 2.4) (Figure 1b). Here, the two distinct functions can be obtained from the third ODE in the model

$$\frac{d(av)}{dt} = \beta 4(av)pv - \beta 3(av) + \beta 2(sv)av - \mu(av) - \mu a(av) \quad (13)$$

The two distinct equations are

$$av = 0$$
$$\beta 4(pv) - \beta 3 + \beta 2(sv) - \mu - \mu a = 0 \quad (14)$$

With pv=0, $\beta 2$=2.4, $\beta 3$=0.3; μa=0.2; pv=0, μ=0.3; sv =0.33333, both distinct equations are satisfied, validating the theorem.

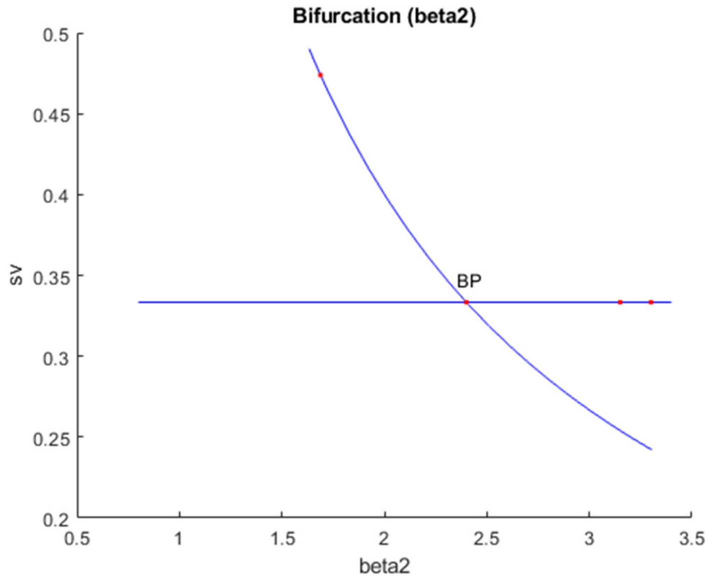

Figure 1b: Bifurcation diagram ($\beta 2$ is the bifurcation parameter) revealing a Branch Point (BP) at (sv,pv,av, $\beta 2$) values of (0.333333 0 0 2.4).

MNLMPC results: For the MNLMPC, $\beta 1, \beta 2,$ are the control parameters, and $\sum_{t_i=0}^{t_i=t_f} pv(t_i), \sum_{t_i=0}^{t_i=t_f} sv(t_i)$ were minimized individually, and each led to a value of 0. The overall optimal control problem will involve the minimization of $(\sum_{t_i=0}^{t_i=t_f} pv(t_i)-0)^2+(\sum_{t_i=0}^{t_i=t_f} sv(t_i)-0)^2$ subject to the equations governing the model. This led to a value of zero (the Utopia point). The MNLMPC values of the control variables, $\beta 1, \beta 2,$ were 0.505, 0.00578. The MNLMPC profiles are shown in Figure 2a-2d. The control profiles of $\beta 1, \beta 2,$ were exhibited noise (Figure 2c) and this was remedied using the Savitzky-Golay filter to produce the smooth profiles $\beta 1sg, \beta 2sg$ (Figure 2d).

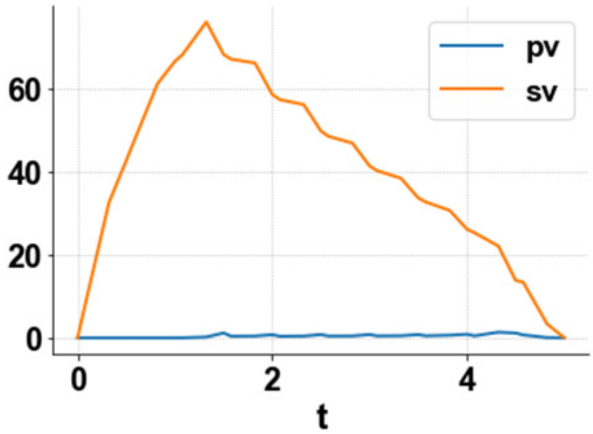

Figure 2a: MNLMPC pv, sv profiles for the combined minimization of $\sum_{t_i=0}^{t_i=t_f} pv(t_i), \sum_{t_i=0}^{t_i=t_f} sv(t_i)$

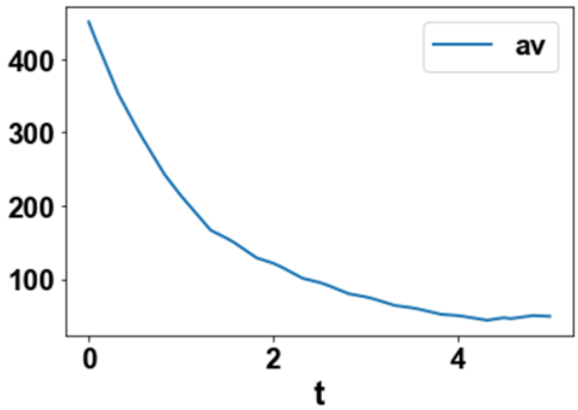

Figure 2b: MNLMPC av profile for the combined minimization of $\sum_{t_i=0}^{t_i=t_f} pv(t_i), \sum_{t_i=0}^{t_i=t_f} sv(t_i)$

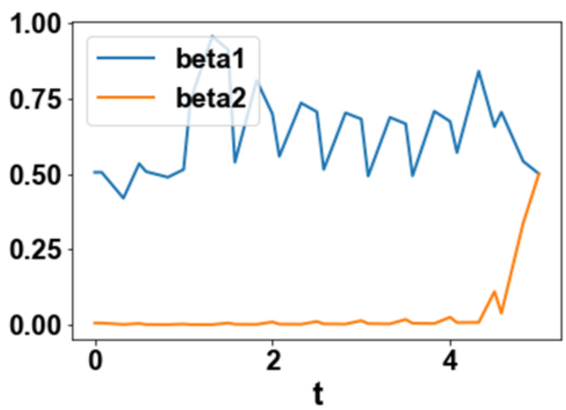

Figure 2c: MNLMPC noisy control profiles for $\beta 1, \beta 2$ before filtering.

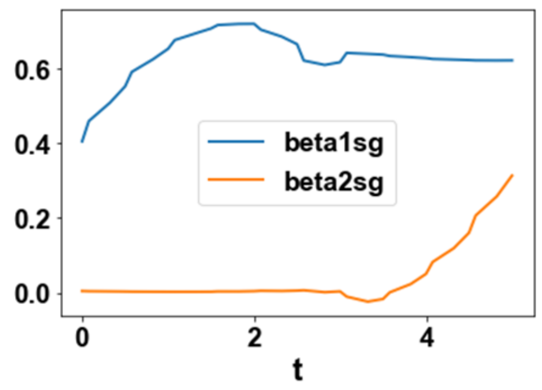

Figure 2d: MNLMPC $\beta 1sg, \beta 2sg$ which are filtered noisy profiles of $\beta 1, \beta 2$.

The presence of the branch point causes the MNLMPC calculations to attain the Utopia solution, validating the analysis of Sridhar [33].

Conclusion

It is of utmost importance to understand the dynamics of asthma transmission in order to control it effectively. This study demonstrates the application of integrated bifurcation analysis and MNLMPC to an asthma transmission model, revealing that this integrated approach enables us to understand the nonlinearity and obtain the most control profiles. The proposed link between branch points and optimal control convergence is the main contribution demonstrating a link between applied mathematics, systems biology, and control engineering. The bifurcation analysis revealed the existence of branch points. 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 models. A combination of bifurcation analysis and Multiobjective Nonlinear Model Predictive Control (MNLMPC) on an asthma transmission model is the main contribution of this paper.

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