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Analysis and Control of a Microbiome Dynamic Model

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ABSTRACT

The complex dynamics of the interacting species in a microbial consortium needs to be fully analyzed and controlled effectively. 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 multi-objective nonlinear model predictive control (MNLMPC) calculations are performed on a dynamic model involving microbiomes. 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 both models. 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. It is proved (with computational validation) that the branch points were caused because of the existence of two distinct separable functions in one of the equations in each dynamic model. A theorem was developed to demonstrate this fact for any dynamic model.

Keywords: Bifurcation; Optimization; Control; Microbiome,

MSC Codes 65P30, 65P40, 37M20, 65K10, 49M41, 93C10, 93C15 and 90C31, 90C48

Background

Brenner, et al.[1] showed that engineering microbial consortia was a new frontier in synthetic biology. Davies, et al.[2] discussed the origins and evolution of antibiotic resistance. Faith, et al.[3] predicted the human gut microbiotaś response to diet in gnotobiotic mice. Faust and Raes[4] discussed microbial interactions from networks to models. Minty, et al.[5] discussed the design and characterization of synthetic fungal-bacterial consortia for direct production of isobutanol from cellulosic biomass. Stein, et al[6] performed ecological modeling from time-series inference with an insight into dynamics and stability of intestinal microbiota. Schwabe and Jobin[7] discussed the connection between the microbiome and cancer. Song, et al.[8] studied models of microbial community.

Youngster, et al.[9] researched microbiota transplant for relapsing clostridium difficile infection using a frozen inoculum from unrelated donors. Stefka, et al.[10] showed that commensal bacteria protect against food allergen sensitization. Larimer, et al.[11] investigated the synergism and context dependency of interactions between arbuscular mycorrhizal fungi and rhizobia with a prairie legume. Lima-Mendez, et al.[12] studied the determinants of community structure in the global plankton interactome. Kostic, et al.[13] investigated the dynamics of the human infant gut microbiome in development and in progression toward type 1 diabetes. Wlodarska, et al.[14] researched microbiome-host interactions in inflammatory

bowel diseases. Coyte[15] studied the ecology of the microbiome in terms of networks, competition and stability. Zhang and Wang[16] developed modular co-culture engineering, which is a new approach for metabolic engineering. Widder, et al.[17] investigated the challenges in microbial ecology: building predictive understanding of community function and dynamics. Gonze, et al.[18] performed research on multi-stability and the origin of microbial community types. Hall, et al.[19] investigated the human genetic variation and the gut microbiome in disease. Vos, et al.[20] investigated interaction networks, ecological stability and collective antibiotic tolerance in polymicrobial infections. Hassani[21] investigated the microbial interactions within the plant holobiont. McCarty, et al.[22] developed synthetic biology tools to engineer microbial communities for biotechnology. Rugbjerg, et al.[23], showed that synthetic addiction extends the productive lifetime of engineered Escherichia coli populations. Kong, et al.[24] designed microbial consortia with defined social interactions. Succurro and Ebenhöh[25] reviewed mathematical models of microbial ecosystems. Stephens, et al.[26] developed bacterial co-cultures with cell signaling translator and growth controller modules for autonomously regulated culture composition.

Tsoi, et al.[27] discussed the emerging strategies for engineering microbial communities. Lv, et al.[28] investigated coupling feedback genetic circuits with growth phenotype for dynamic population control and intelligent bioproduction. Dai, et al.[29] discussed e biomanufacturing through stimulus-responsive cell-material feedback. Jawed, et al.[30], discussed the advances in the development and application of microbial consortia for metabolic engineering. Du, et al.[31], developed a de novo design of an intercellular signaling toolbox for multi-channel cell–cell communication and biological computation. Arora, et al.[32] discussed the current status of the chemical diversity through microorganisms co-culture.

Wang, et al.[33] discussed the recent advances in modular co-culture engineering for synthesis of natural products. Marsafari, et al.[34], conducted research on genetically encoded biosensors for analyzing and controlling cellular processes in yeast. Lv, et al.[35] discussed about coupling metabolic addiction with negative autoregulation to improve strain stability and pathway yield. Ben Said, et al[36] discussed the engineering of spatially linked microbial consortia. Xu[37] studied the dynamics of microbial competition, commensalism and cooperation and its implications for coculture and microbiome engineering.

This work aims to perform bifurcation analysis and multiobjective nonlinear control (MNLMPC) studies on a microbiome dynamic model described in Xu[37]. 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.

Microbiome Model[37]

The equations that govern the microbiome model are

$$\frac{dx_A}{dt} = (\mu_A - D)x_A$$

$$\frac{dx_B}{dt} = (\mu_B - D)x_B$$

$$\frac{dS}{dt} = D(S_0 - S(t)) - \frac{\mu_A x_A(t)}{Y_{AS}} - \frac{\mu_B x_B(t)}{Y_{BS}} - \frac{(\alpha\mu_A + \beta)x_A(t)}{Y_{PS}}$$

$$\frac{dP_A}{dt} = (\alpha\mu_A + \beta)x_A(t) - DP_A(t) - \frac{kx_B(t)P_A(t)}{Y_{BA}(k_m + P_A(t))}$$

$$\frac{dP_B}{dt} = -DP_B(t) + \frac{kx_B(t)P_A(t)}{(k_m + P_A(t))}$$

$$\mu_A = \frac{\mu_{A\_\max} S}{K_{SA} + S}\left(1 + \frac{\gamma_{BA} x_B}{S_0 y_{BS}}\right)$$

$$\mu_B = \frac{\mu_{B\_\max} S}{K_{SB} + S}\left(1 + \frac{\gamma_{AB} x_A}{S_0 y_{AS}}\right)$$

- The nomenclature in these equations is given by
- $\mu_{A\_\max}$ maximal specific growth rate for species A (1/h)
- μ_A specific growth rate for species A (1/h)
- $\mu_{B\_\max}$ maximal specific growth rate for species B (1/h)
- μ_B specific growth rate for species B (1/h)
- K_{SA} substrate saturation constant for species A (g/L)
- K_{SB} substrate saturation constant for species B (g/L)
- Y_{AS} species A biomass yield from substrate S (g/g)
- Y_{BS} species B biomass yield from substrate S (g/g)
- Y_{BA} product B (PB) yield from intermediate A (PA) (g/g)
- Y_{PS} intermediate A (PA) yield from substrate S (g/g)
- α growth-associated intermediate A (PA) formation coefficient (dimensionless)
- β growth-unassociated intermediate A (PA) formation rate (1/h)
- γ_{AB} interaction coefficient of species A imposes on species B (dimensionless)
- γ_{BA} interaction coefficient of species B imposes on species A (dimensionless)
- k rate constant of intermediate A (PA) converted to product B (PB) (1/h)
- Km intermediate A saturation constant for species B (g/L)
- x_A species A biomass in the CSTR (g/L)
- x_B species B biomass in the CSTR (g/L)
- P_A intermediate A concentration in the CSTR (g/L)
- P_B product B concentration in the CSTR (g/L)
- S substrate concentration in the CSTR (g/L)
- S_0 substrate concentration in the feeding stream (g/L)
- D dilution rate in the CSTR (1/h)

The parameter values are $\mu_{A\_\max}$ = 1.6/h; $\mu_{B\_\max}$ = 1.2/h; K_{SA} = 1.0 g/L; K_{SB} = 0.8 g/L; S_0 = 50g/L; Y_{AS} = 0.5 g/g; Y_{BS} = 0.8 g/g; Y_{BA} = 0.8 g/g; Y_{PS} = 0.4 g/g; α = 0.5 and β = 0.5; $\gamma_{AB} = \gamma_{BA} = 1$

Bifurcation analysis

Bifurcation analysis is performed using the MATLAB software MATCONT which locates branch points limit points and Hopf bifurcation points[38,39]. 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

$$Az \quad (9)$$

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,

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

$@$ 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[40-42].

Hopf bifurcations cause limit cycles. The tanh activation function (where a control value u is replaced by) $(u \tanh u / \varepsilon)$ is used to eliminate spikes in the optimal control profiles[43-46]. Sridhar[47] explained with several examples how the activation factor involving the tanh function also eliminates the Hopf bifurcation points. This was because the tanh function increases the oscillation time period in the limit cycle.

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[49] 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[50] and confirmed as a global solution with BARON[51].

Sridhar[52] 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[53]. This makes the constrained problem an unconstrained optimization problem and the only solution is the Utopia solution. More details can be found in Sridhar[52].

Results

Bifurcation analysis revealed the existence of two branch points at $(x_A; x_B; S, p_A; p_B; D)$ values of (0;0; 50; 0; 0; 1.568627) and (0; 0; 50; 0; 0;1.181102). D is the bifurcation parameter. This is shown in **(Figure 1a)**.

For the MNLMPC calculations, $\sum_{t_i=0}^{t_i=t_f} p_B(t_i)$ was maximized and produced a value of 40 and $\sum_{t_i=0}^{t_i=t_f} p_A(t_i)$ was minimized led to value a of. D was the control parameter. The multiobjective optimal control problem will involve the minimization of $(\sum_{t_i=0}^{t_i=t_f} p_B(t_i) - 40)^2 + (\sum_{t_i=0}^{t_i=t_f} p_A(t_i) - 0)^2$ subject to the equations governing microbiome model. This led to a value of zero (the Utopia solution). The MNLMPC control value (D) was 0.61754 **(Figures 1b,1c and 1d)**. show the various MNLMPC profiles **(Figures 1b,1c and 1d)**. show the various MNLMPC profiles. The profile of the control variable D exhibited a lot of noise, which was remedied using the Savitzky-Golay filter. Both the original and the modified profiles are shown in **(Figure 1e)**.

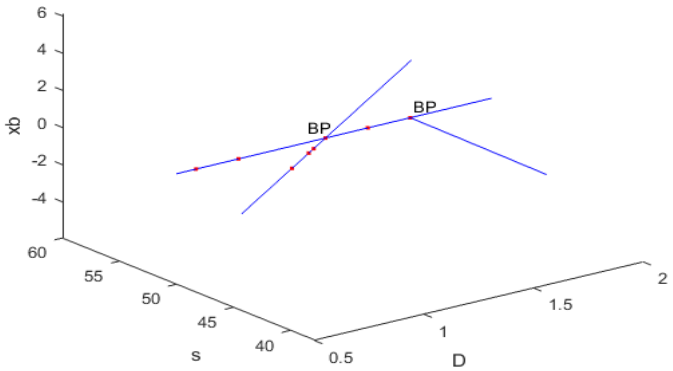

Figure 1a: Bifurcation analysis of Microbiome model showing two branch points

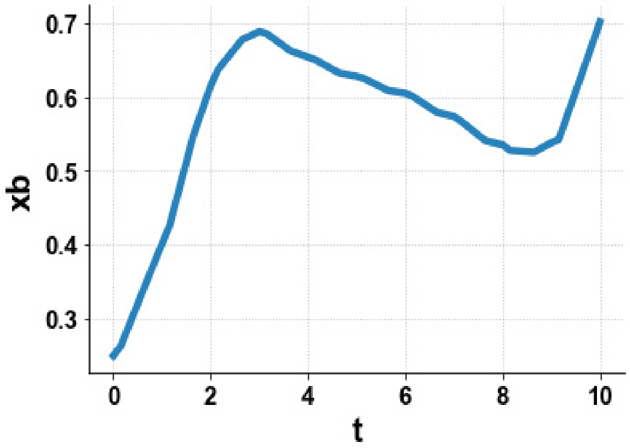

Figure 1b: MNLMPC Microbiome model xb vs t.

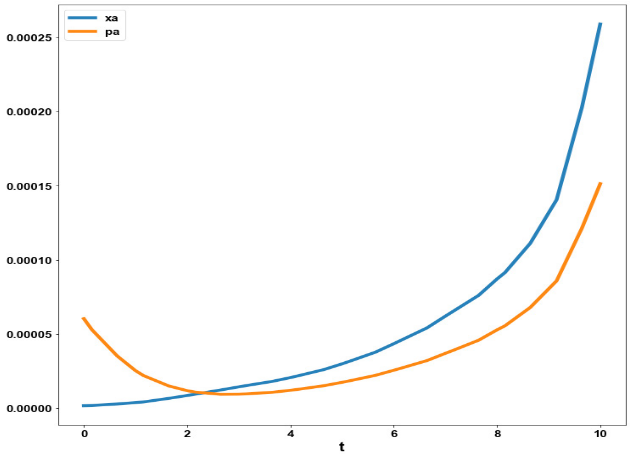

Figure 1c: MNLMPC Microbiome model xa,pa vs t.

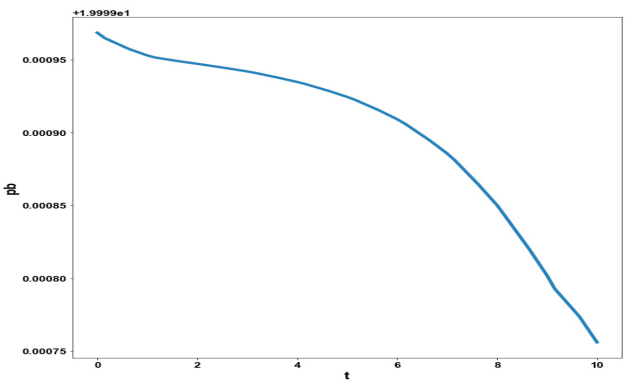

Figure 1d: MNLMPC Microbiome model pb vs t.

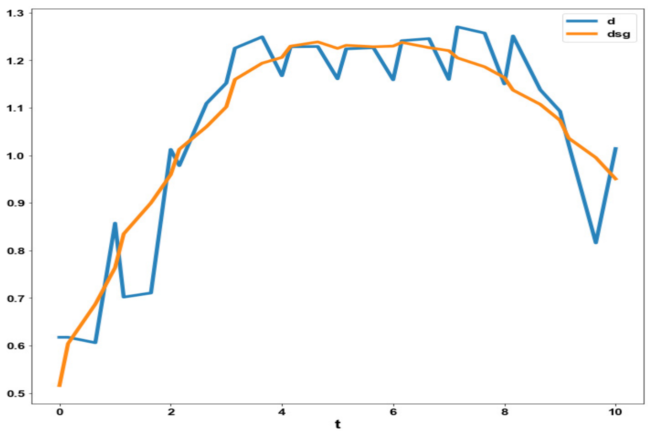

Figure 1e: MNLMPC microbiome model d with noise and dsg (with Savitzky Golay Filter) vs t.

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

$$\frac{dx}{dt} = f(x,\alpha) \qquad (14)$$

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

$$A = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \frac{\partial f_1}{\partial x_3} & \frac{\partial f_1}{\partial x_4} \cdots\cdots & \frac{\partial f_1}{\partial x_n} & \frac{\partial f_1}{\partial \alpha} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \frac{\partial f_2}{\partial x_3} & \frac{\partial f_2}{\partial x_4} \cdots\cdots & \frac{\partial f_2}{\partial x_n} & \frac{\partial f_2}{\partial \alpha} \\ \cdots\cdots & & & & & \\ \cdots\cdots & & & & & \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \frac{\partial f_n}{\partial x_3} & \frac{\partial f_n}{\partial x_4} \cdots\cdots & \frac{\partial f_n}{\partial x_n} & \frac{\partial f_n}{\partial \alpha} \end{bmatrix} \qquad (15)$$

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

$$A = [\frac{\partial f_p}{\partial x_q}. | \quad \frac{\partial f_p}{\partial \alpha}] \qquad (16)$$

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

$$Az = 0 \qquad (17)$$

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 $z = [z_1, z_2, z_3, z_4, \ldots z_{n+1}]$) must satisfy

$$Az = 0$$

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 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

$$f_i = \phi_1 \phi_2$$

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

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

However,

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

$$\frac{\partial f_i}{\partial \alpha} = \phi_1(=0)\frac{\partial \phi_2}{\partial \alpha} + \phi_2(=0)\frac{\partial \phi_1}{\partial \alpha}] = 0$$

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 first branch point occurred at $(x_A; x_B; S, p_A; p_B; D)$ = (0;0; 50; 0; 0; 1.568627) Here, the two distinct functions can be obtained from the first ODE in the microbiome model 1.

$$\frac{dx_A}{dt} = (\mu_A - D_A)x_A$$

The two distinct equations are

$$x_A = 0$$

$$\mu_A - D = 0$$

Since $\mu_A = \frac{\mu_{A\_\max} S}{K_{SA} + S}(1 + \frac{\gamma_{BA} x_B}{S_0 y_{BS}})$ and S=50; $\mu_{A\_\max}$ = 1.6; K_{SA} = 1.0; $x_A = x_B = 0$;D=1.568627

Both distinct equations are satisfied, validating the theorem.

The second branch point occurred at $(x_A; x_B; S, p_A; p_B; D)$ = (0;0; 50; 0; 0; 1.181102). Here, the two distinct functions can be obtained from the first ODE in the microbiome model.

$$\frac{dx_B}{dt} = (\mu_B - D)x$$

The two distinct equations are

$$x_B = 0$$

$$\mu_B - D = 0$$

Since $\mu_B = \frac{\mu_{B\_\max} S}{K_{SB} + S}(1 + \frac{\gamma_{AB} x_A}{S_0 y_{AS}})$ and S=50; $\mu_{B\_\max}$ = 1.2; K_{SB} =0.8; $x_A = x_B = 0$; D=1.181102

Both distinct equations are satisfied, validating the theorem. The MNLMPC calculations converge to the Utopia point, validating the analysis in Sridhar[52].

Conclusions

Bifurcation analysis and multiobjective nonlinear control (MNLMPC) studies were conducted on a microbiome dynamic model. The bifurcation analysis revealed the existence and 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. It is proved (with computational validation) that the branch points were caused because of the existence of two distinct separable functions in one of the equations in each 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 microbiomes 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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