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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 consortia 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 the model. 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. 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 the 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; 90C31; 90C48

Background

The microbiome refers to the complex community of microorganisms that live in and on the human body, as well as the collective genetic material they carry. This vast population of bacteria, fungi, viruses, archaea, and protozoa inhabits almost every surface and cavity, from the skin to the oral cavity, the respiratory tract, and the urogenital system, but it is in the gut that the microbiome reaches its greatest density and diversity. It has become increasingly clear that this ecosystem is not a passive passenger but an active participant in the maintenance of health, influencing metabolism, immunity, and even neurological processes. For a long time, microbes were primarily associated with disease, but advances in sequencing technologies and computational biology have revolutionized our understanding, revealing that the relationship between humans and microbes is symbiotic and, in many respects, and indispensable.

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The human gut alone harbors trillions of microorganisms, with their genes vastly outnumbering human genes, creating what has been described as a second genome. The composition of the microbiome is highly variable and influenced by factors such as diet, age, lifestyle, geography, genetics, and even the mode of birth. Infants born vaginally are initially colonized by microbes resembling their mother's vaginal and gut flora, while those born by cesarean section often acquire microbes from the skin and hospital environment. Early nutrition also plays a role, with breast milk promoting the growth of beneficial species such as bifidobacteria through the presence of specialized sugars known as human milk oligosaccharides. As solid foods are introduced, microbial diversity increases, and by the time childhood ends, the microbial community resembles that of an adult. In adulthood, the microbiome is relatively stable but remains sensitive to changes in diet, stress, environment, and medical interventions such as antibiotics. With aging, microbial diversity often declines, accompanied by the loss of beneficial species and a rise in potentially harmful microbes, which can contribute to inflammation, frailty, and disease.

The microbiome performs countless vital functions that extend beyond digestion. One of its central roles is in nutrient metabolism. Microbes in the gut ferment complex carbohydrates that humans cannot digest on their own, producing short-chain fatty acids such as acetate, propionate, and butyrate. These metabolites not only provide energy for colon cells but also regulate immune function, reduce inflammation, and influence metabolic pathways throughout the body. The microbiome also contributes to the synthesis of vitamins such as vitamin K and several B vitamins, participates in the metabolism of bile acids and cholesterol, and plays a part in processing xenobiotics, including certain medications.

Equally important is the microbiome's role in shaping and regulating the immune system. From early life, microbial exposure teaches the immune system how to differentiate between harmless and harmful stimuli, reducing the likelihood of autoimmune responses. Microbial products stimulate the production of antimicrobial peptides, enhance the function of immune cells, and help maintain immune tolerance. The microbiome strengthens the intestinal barrier, promoting the secretion of protective mucus and the integrity of tight junctions between epithelial cells, thus preventing pathogens from breaching the gut wall.

The influence of microbes extends even further, into areas once considered exclusively human, such as mood, cognition, and behavior. Through what is now known as the gut–brain axis, microbial metabolites, immune signaling molecules, and even microbial neurotransmitter precursors affect the nervous system. For example, certain gut bacteria produce precursors of serotonin, dopamine, and gamma-aminobutyric acid, all of which play roles in mood regulation and mental health. Communication between the gut and the brain occurs through neural pathways such as the vagus nerve as well as through systemic circulation. Growing evidence links microbial imbalances to conditions such as depression, anxiety, autism spectrum disorder, and neurodegenerative diseases, illustrating the depth of the microbiome's reach.

When the delicate balance of microbial communities is disrupted, a state known as dysbiosis occurs. Dysbiosis can involve a loss of beneficial microbes, the overgrowth of harmful species, or a general reduction in diversity. This imbalance has been implicated in a wide range of diseases. In the gastrointestinal tract, dysbiosis is strongly associated with inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, as well as irritable bowel syndrome and colorectal cancer. Mechanisms include disruption of the mucosal barrier, inappropriate immune activation, and chronic inflammation. Metabolic diseases also show microbial signatures. Obesity, for instance, has been linked to a higher ratio of Firmicutes to Bacteroidetes and an increased capacity

of the microbiome to harvest energy from food. Type 2 diabetes has been associated with reduced butyrate-producing bacteria, which normally help maintain insulin sensitivity and metabolic stability. Neurological and psychiatric conditions show microbial alterations as well, with studies pointing to distinctive microbial patterns in individuals with autism, Parkinson's disease, or Alzheimer's disease. Immune-mediated conditions such as asthma, allergies, and autoimmune disorders have been tied to early-life dysbiosis, supporting the so-called hygiene hypothesis, which suggests that reduced microbial exposure in modern environments contributes to rising immune-related conditions. Opportunistic infections such as Clostridioides difficile are perhaps the clearest example of dysbiosis, often arising after antibiotic use wipes out protective bacteria, allowing harmful strains to dominate.

The study of the microbiome has been propelled by technological advances. Traditional culture-based approaches were limited because most microbes cannot be grown under standard laboratory conditions. Sequencing methods such as 16S ribosomal RNA analysis allowed researchers to identify bacterial taxa without culturing, while whole metagenomic sequencing revealed the functional potential of entire microbial communities. Beyond identifying who is present, scientists now examine microbial activity through metatranscriptomics, metaproteomics, and metabolomics, which track microbial RNA, proteins, and metabolites. These tools provide a more dynamic picture of how microbes interact with their host. Experimental models, particularly germ-free animals raised without microbes, have been instrumental in proving causal relationships between specific microbes and host traits. Computational modeling and machine learning now play central roles in analyzing the massive datasets generated by microbiome research, allowing researchers to predict interactions, identify biomarkers, and suggest therapeutic strategies.

Therapeutic applications of microbiome science are rapidly expanding. Probiotics, defined as live microorganisms that confer health benefits when consumed in adequate amounts, are already widely used, with strains of Lactobacillus, Bifidobacterium, and the yeast Saccharomyces boulardii being among the most common. These can help restore balance, particularly after antibiotic treatment or in cases of mild digestive disturbances. Prebiotics, non-digestible fibers that selectively stimulate beneficial microbes, complement this approach by providing the substrates microbes need to thrive. Synbiotics combine probiotics and prebiotics, aiming to optimize colonization and effectiveness.

One of the most striking therapeutic successes has been fecal microbiota transplantation, in which stool from a healthy donor is introduced into the gut of a patient. This has proven highly effective for recurrent Clostridioides difficile infections, with cure rates far exceeding those of conventional antibiotic therapies. Research is now exploring fecal transplants for conditions such as inflammatory bowel disease, obesity, and metabolic syndrome, although long-term safety and standardization remain challenges. Newer approaches focus on so-called next-generation probiotics, which go beyond traditional lactobacilli and bifidobacteria to include promising species such as Akkermansia muciniphila and Faecalibacterium prausnitzii, both associated with metabolic and anti-inflammatory benefits. Advances in biotechnology also open the possibility of engineering microbes to deliver drugs, modulate immune responses, or correct metabolic imbalances. Targeted interventions using bacteriophages or CRISPR-based editing may one day allow precise modification of the microbiome without the broad disruptions caused by antibiotics.

The variability of the microbiome between individuals underlines its potential for personalized medicine. The way a person responds to diet, drugs, or disease can be partly predicted by the structure and function of their

microbial community. Personalized nutrition programs have shown that tailoring diets based on microbiome composition can improve glycemic control. Similarly, the microbiome influences drug metabolism, altering the effectiveness and toxicity of medications ranging from cardiac drugs like digoxin to chemotherapy agents. Microbial signatures are also being investigated as diagnostic biomarkers, providing non-invasive tools for the early detection of colorectal cancer, liver disease, and other conditions.

The importance of the microbiome extends beyond human health. Plants rely on root-associated microbial communities to enhance nutrient uptake, protect against pathogens, and tolerate environmental stress. In animals, the microbiome shapes growth, immune defense, and disease susceptibility, influencing agriculture and aquaculture practices. Environmental microbiomes regulate nutrient cycles in soil and oceans and play central roles in carbon and nitrogen cycling, underscoring their significance for global ecology and climate.

With the rapid expansion of microbiome science come ethical and social considerations. Microbiome data are highly personal, capable of serving as unique identifiers, raising questions about privacy. Access to microbiome-based therapies may be unequal, creating disparities in global health. Long-term safety is still unknown for many interventions, especially those involving engineered microbes or repeated fecal transplants. Regulatory frameworks are evolving, but clearer guidelines are needed to balance innovation with safety.

Looking ahead, microbiome research is expected to move toward precision and integration. Precision microbiome editing using phages and CRISPR tools promises selective targeting of harmful microbes. Standardization of sequencing and analytical methods will improve reproducibility across studies. Synthetic microbial communities may be designed for specific therapeutic purposes, offering a new generation of living medicines. Integrating microbiome data with genomics, metabolomics, and other layers of biological information will provide a more complete understanding of host-microbe interactions. Clinical translation will require rigorous trials to move discoveries from bench to bedside.

The microbiome has emerged as one of the most exciting frontiers in science. Its influence on digestion, immunity, metabolism, and even mental health underscores the idea that humans are not solitary organisms but superorganisms, ecosystems of human and microbial cells working in concert. Dysbiosis can tip the balance toward disease, while targeted interventions hold the potential to restore health in ways that conventional medicine has struggled to achieve. In the coming decades, microbiome research may reshape how we approach nutrition, disease prevention, and therapy, while also reminding us of our profound interconnectedness with the microbial world.

Literature Review

Brenner et al. (2008)[1] showed that engineering microbial consortia was a new frontier in synthetic biology. Davies et al. (2010)[2] discussed the origins and evolution of antibiotic resistance. Faith et al. (2011)[3] predicted the human gut microbiotaś response to diet in gnotobiotic mice. Faust and Raes (2012)[4] discussed microbial interactions from networks to models. Minty et al (2013)[5] discussed the design and characterization of synthetic fungal-bacterial consortia for direct production of isobutanol from cellulosic biomass. Stein et al (2013)[6] performed ecological modeling from time-series inference with an insight into dynamics and stability of intestinal microbiota. Schwabe and Jobin (2013)[7] discussed the connection between the microbiome and cancer. Song et al . (2014)[8] studied models of microbial community.

Youngster et al (2014)[9] researched microbiota transplant for relapsing clostridium difficile infection using a frozen inoculum from unrelated donors. Stefka et al (2014)[10] showed that commensal bacteria protect against food allergen sensitization. Larimer et al (2014)[11] investigated the synergism and context dependency of interactions between arbuscular mycorrhizal fungi and rhizobia with a prairie legume. Lima-Mendez et al (2015)[12] studied the determinants of community structure in the global plankton interactome. Kostic et al (2015)[13] investigated the dynamics of the human infant gut microbiome in development and in progression toward type 1 diabetes. Wlodarska et al (2015)[14] researched microbiome-host interactions in inflammatory bowel diseases. Coyte (2015)[15] studied the ecology of the microbiome in terms of networks, competition, and stability. Zhang and Wang,(2016)[16] developed modular co-culture engineering, which is a new approach for metabolic engineering. Widder et al (2016) [17] investigated the challenges in microbial ecology: building predictive understanding of community function and dynamics. Gonze et al (2017)[18] performed research on multi-stability and the origin of microbial community types. Hall et al (2017)[19] investigated the human genetic variation and the gut microbiome in disease. Vos et al (2017)[20] investigated interaction networks, ecological stability, and collective antibiotic tolerance in polymicrobial infections. Hassani (2018)[21] investigated the microbial interactions within the plant holobiont. McCarty et al (2018)[22] developed synthetic biology tools to engineer microbial communities for biotechnology. Rugbjerg et al (2018)[23], showed that synthetic addiction extends the productive lifetime of engineered Escherichia coli populations. Kong et al (2018) [24] designed microbial consortia with defined social interactions. Succurro and Ebenhöh (2018)[25] reviewed mathematical models of microbial ecosystems. Stephens et al (2019)[26] developed bacterial co-cultures with cell signaling translator and growth controller modules for autonomously regulated culture composition.

Tsoi et al (2019)[27] discussed the emerging strategies for engineering microbial communities. Lv et al (2019)[28] investigated coupling feedback genetic circuits with growth phenotype for dynamic population control and intelligent bioproduction. Dai et al (2019)[29] discussed e biomanufacturing through stimulus-responsive cell-material feedback. Jawed et al (2019)[30], discussed the advances in the development and application of microbial consortia for metabolic engineering. Du et al (2020)[31], developed a de novo design of an intercellular signaling toolbox for multi-channel cell-cell communication and biological computation. Arora et al (2020)[32] discussed the current status of the chemical diversity through microorganisms co-culture.

Wang et al (2020)[33] discussed the recent advances in modular co-culture engineering for synthesis of natural products. Marsafari et al (2020)[34], conducted research on genetically encoded biosensors for analyzing and controlling cellular processes in yeast. Lv et al (2020)[35] discussed about coupling metabolic addiction with negative autoregulation to improve strain stability and pathway yield. Ben Said et al (2020)[36] discussed the engineering of spatially linked microbial consortia. Xu, 2020[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, 2020[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 ModelXu, 2020[37]

The equations that govern the microbiome model are

$$\frac{dx_A}{dt} = (\mu_A - D)x_A \quad (1)$$

$$\frac{dx_B}{dt} = (\mu_B - D)x_B \quad (2)$$

$$\frac{dS}{dt} = D(S_0 - S(t)) - \frac{\mu_A x_A(t)}{Y_{AS}} - \frac{\mu_B x_B(t)}{Y_{BS}} - \frac{(\alpha\mu_A + \beta)x_A(t)}{Y_{PS}} \quad (3)$$

$$\frac{dP_A}{dt} = (\alpha\mu_A + \beta)x_A(t) - DP_A(t) - \frac{kx_B(t)P_A(t)}{Y_{BA}(k_m + P_A(t))} \quad (4)$$

$$\frac{dP_B}{dt} = -DP_B(t) + \frac{kx_B(t)P_A(t)}{(k_m + P_A(t))} \quad (5)$$

$$\mu_A = \frac{\mu_{A\_\max} S}{K_{SA} + S}\left(1 + \frac{\gamma_{BA} x_B}{S_0 y_{BS}}\right) \quad (6)$$

$$\mu_B = \frac{\mu_{B\_\max} S}{K_{SB} + S}\left(1 + \frac{\gamma_{AB} x_A}{S_0 y_{AS}}\right) \quad (7)$$

The nomenclature in these equations is given by

- μ_{A_max} Maximal specific growth rate for species A (1/h)
- μ_A Specific growth rate for species A (1/h)
- μ_{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 μ_{A_max} = 1.6/h; μ_{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 (Dhooge Govearts, and Kuznetsov, 2003[38]; Dhooge Govearts, Kuznetsov, Mestrom and Riet, 2004[39]). Consider a set of ordinary differential equations

$$\frac{dx}{dt} = f(x, \alpha) \qquad (8)$$

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

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

$$Az = 0 \qquad (9)$$

A is given by

$$A = [\partial f / \partial x \quad | \partial f / \partial \alpha] \qquad (10)$$

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 $B = \begin{bmatrix} A \\ z^T \end{bmatrix}$ must be singular. At a Hopf bifurcation point,

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

@ 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 (1998[40]; 2009[41]) and Govaerts [2000] [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 (Dubey et al 2022[43]; Kamalov et al, 2021[44] and Szandała, 2020[45]; Sridhar 2023[46]). Sridhar (2024)[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 (2012)[48] 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.

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

$$\begin{aligned} &\min\left(\sum_{j=1}^{n}\left(\sum_{t_{i=0}}^{t_i=t_f} q_j(t_i) - q_j^*\right)\right)^2 \\ &subject\ to\ \frac{dx}{dt} = F(x,u); \end{aligned} \quad (13)$$

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)[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 (Wächter And Biegler, 2006)[50] and confirmed as a global solution with BARON (Tawarmalani, M. and N. V. Sahinidis 2005)[51].

Sridhar (2024)[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 (Upreti, 2013)[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 (2024)[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. 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.

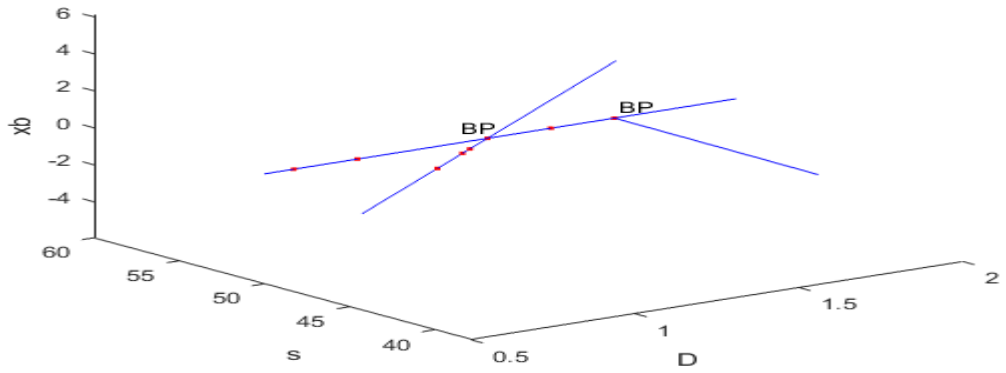

Figure 1a: Bifurcation analysis of Microbiome model showing two branch points.

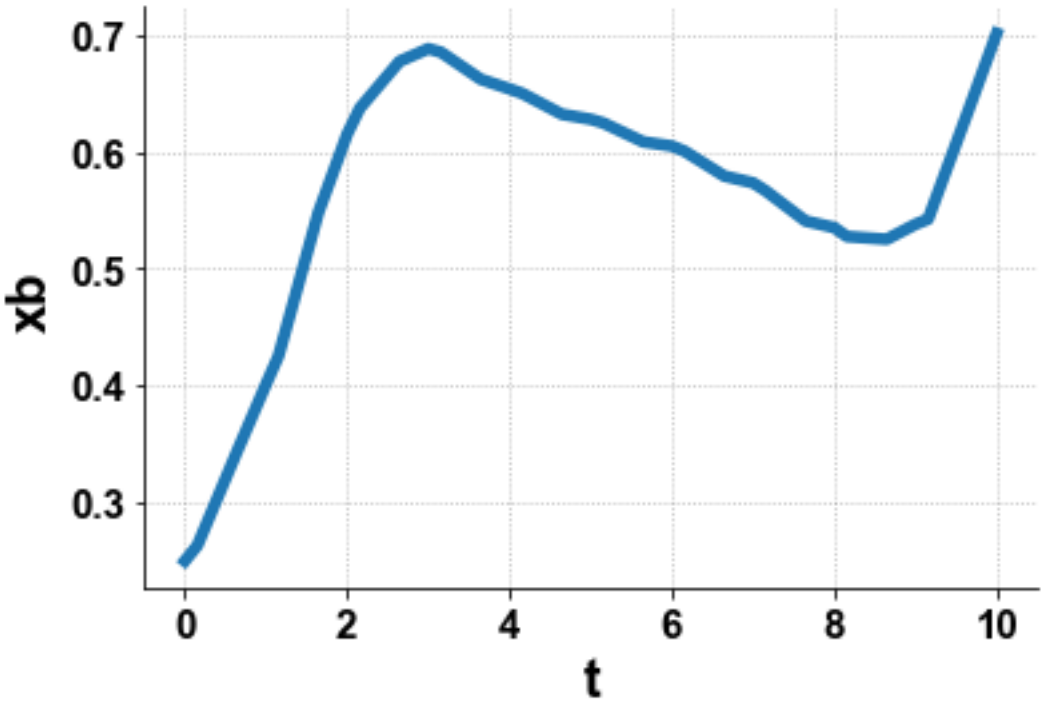

Figure 1b: MNLMPC Microbiome model xb vs t

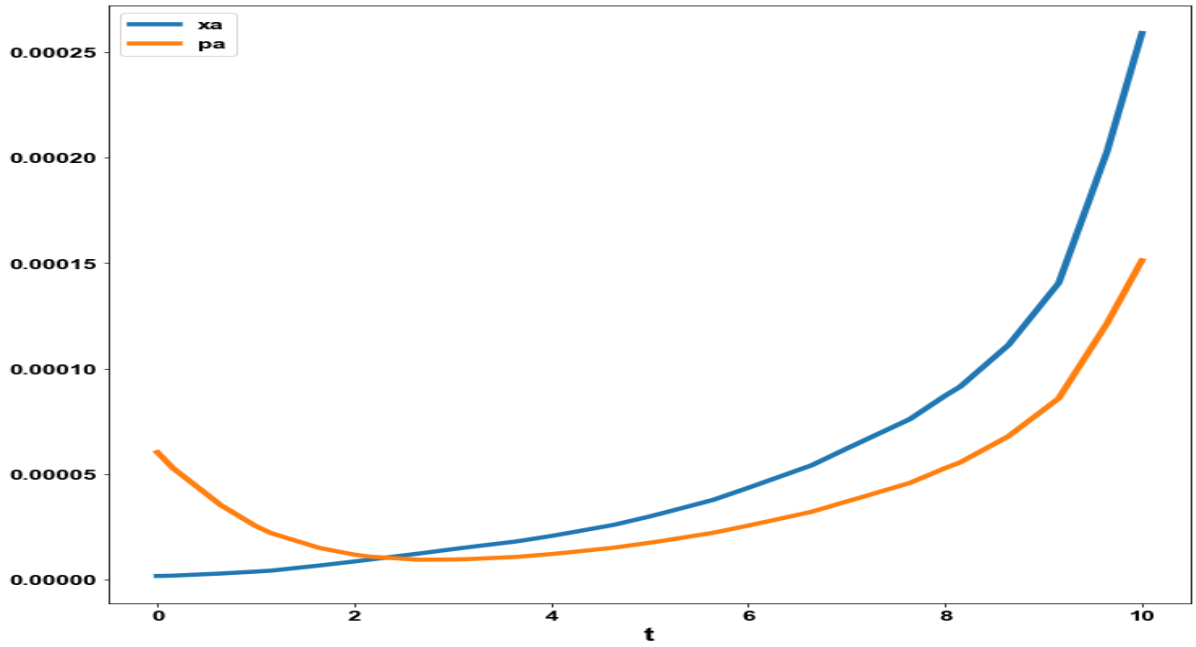

Figure 1c: MNLMPC Microbiome model xa, pa vs t

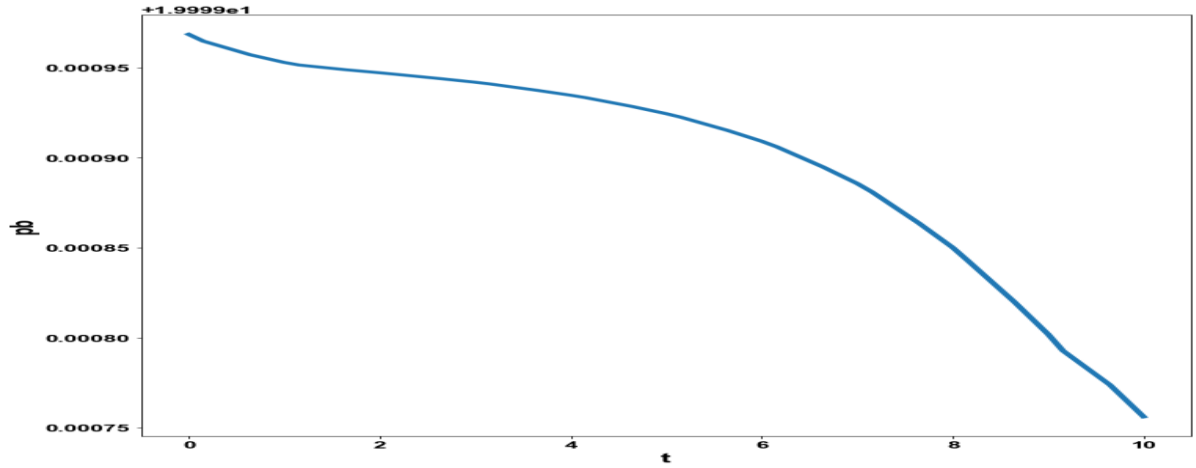

Figure 1d: MNLMPC Microbiome model pb vs t

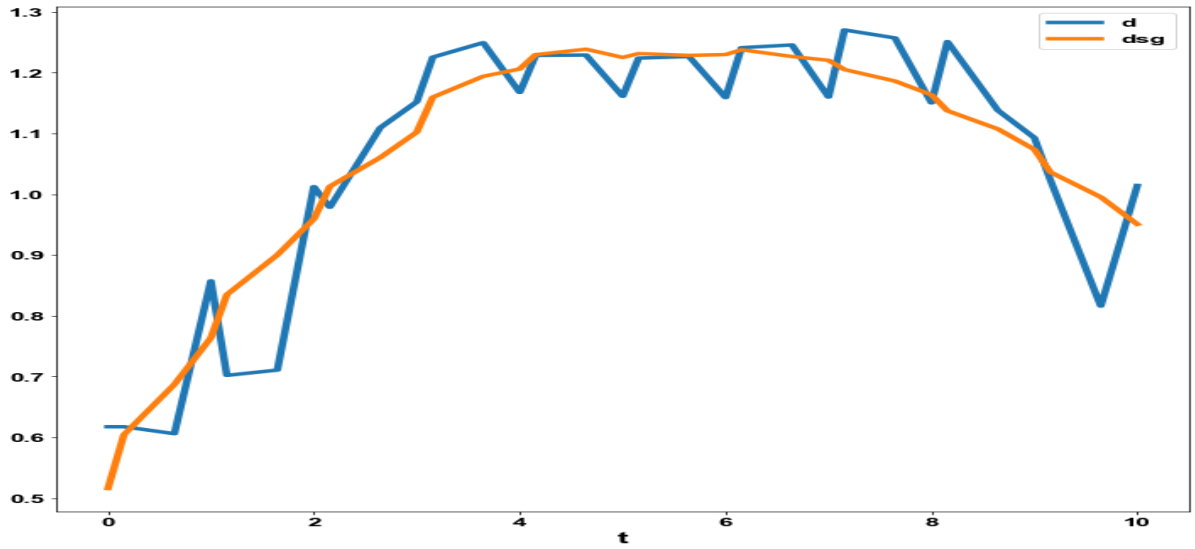

Figure 1e: MNLMPC microbiome model d with noise and dsg (with Savitzky Golay Filter) vs t

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

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

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

$$Az = 0 \qquad (18)$$

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

$$\begin{aligned} Az &= 0 \\ Aw &= 0 \end{aligned} \qquad (19)$$

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 where $B = \begin{bmatrix} A \\ z^T \end{bmatrix}$

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

$$f_i = \phi_1 \phi_2 \qquad (20)$$

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

$$[\frac{\partial f_i}{\partial x_k} | \frac{\partial f_i}{\partial \alpha}] \qquad (21)$$

However,

$$\begin{aligned} [\frac{\partial f_i}{\partial x_k} &= \phi_1 (=0) \frac{\partial \phi_2}{\partial x_k} + \phi_2 (=0) \frac{\partial \phi_1}{\partial x_k} = 0 (\forall k = 1.,, n) \\ \frac{\partial f_i}{\partial \alpha} &= \phi_1 (=0) \frac{\partial \phi_2}{\partial \alpha} + \phi_2 (=0) \frac{\partial \phi_1}{\partial \alpha}] = 0 \end{aligned} \qquad (22)$$

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.

$$\frac{dx_A}{dt} = (\mu_A - D_A) x_A \qquad (23)$$

The two distinct equations are

$$x_A = 0$$
$$\mu_A - D = 0 \qquad (24)$$

Since $\mu_A = \frac{\mu_{A\_max} S}{K_{SA} + S}(1 + \frac{\gamma_{BA} x_B}{S_0 y_{BS}})$, and S=50; μ_{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.

$$\frac{dx_B}{dt} = (\mu_B - D)x \qquad (25)$$

The two distinct equations are

$$x_B = 0$$
$$\mu_B - D = 0 \qquad (26)$$

Since $\mu_B = \frac{\mu_{B\_max} S}{K_{SB} + S}(1 + \frac{\gamma_{AB} x_A}{S_0 y_{AS}})$, and S=50; μ_{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 (2024)[52].

Conclusions

Bifurcation analysis and multiobjective nonlinear control (MNLMPC) studies were conducted on a microbiome dynamic model. 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 model. 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 the 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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