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Utilizing Sparse Optimal Linear Feedback Control to Design Targeted Therapeutic Strategies for Enhancing Gut Microbiome Stability

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Abstract

According to the 2024 *American Cancer Risk* Survey, one in 24 individuals is at high risk of developing colon cancer. This condition is linked to gut microbiome instability. Consequently, there is a pressing need for a more effective and precise approach to maintaining gut microbiome stability, which this research aims to solve by finding the most crucial bacteria species in maintaining the stability of the gut microbiome through the application of Optimal Linear Feedback Control. Two of its variants being applied in this research are Sparsity Promoting Linear Quadratic Regulator (LQRSP) with a variety range of γ (0.05, 44.58, and 49.84) and Linear Quadratic Regulator (LQR) ($\gamma = 0$) along with other supporting methods; Controllability Gramian and Network Theory (graph analysis).

The finding in this research shows that bacteria species *Bacteroides hydrogenotrophica, Bacteroides uniformis, Bacteroides vulgaris, Bacteroides thetaiotaomicron, Escherichia lenta, and Dorea formicigenerans* have an important role for preventing and medicating a variety of gut-related diseases. This conclusion is reinforced by the analysis conducted using the Controllability Gramian, displaying five of the chosen bacteria with the highest controllability index, which demonstrates that the system can be effectively controlled. This finding suggests a potential for enhancing therapeutic strategies, rendering them more precise and systematic. To gain deeper insights into the relationship between each bacteria and the rationale behind the selection of these bacteria by LQRSP, this study also employs network theory, which successfully elucidates the choice of *Bacteroides uniformis* despite its low controllability index. Additionally, to further validate the efficacy of these bacteria, the research develops a simulation that compares the controlled system with the uncontrolled system, utilizing two types of disturbances. The results indicate a significant difference in robustness against disturbances between the controlled and uncontrolled systems.

The findings from this research can be used as a foundation for a more efficient and systematic intervention strategy findings. By researching gut microbiome composition regulation using a mathematical approach, it opens new opportunities for new method discoveries aiming to increase the health of the gut microbiome which is beneficial for the medical field and prevention of gut related diseases.

Keywords:

Gut microbiome
Optimal Linear Feedback Control
Sparse Quadratic Regulator
Controllability
Graph analysis

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1. Introduction

1.1 Background

The human gut microbiome is a complex dynamical system consisting of myriads of bacterial species with various symbiotic interactions between species and the host gut. The bacterial composition of the gut microbiome dictates a variety of physiological processes, including digestion, immune regulation, and even mental health through the gut-brain axis [1,2,3]. Ultimately, bacterial composition in the human gut plays an important role in the health of its human host.

The bacterial composition of the gut microbiome is influenced by numerous factors, such as diet, lifestyle, genetics, and environmental exposures. Disruptions to this delicate microbial balance—known as dysbiosis—have been associated with various diseases, including inflammatory bowel disease, obesity, diabetes, and neurodegenerative disorders [4]. Therefore, maintaining a healthy and stable gut microbiome composition is critical to preventing disease and supporting overall health [5]. However, recent studies indicate an increasing prevalence of chronic diseases associated with dysbiosis, such as colon cancer, diabetes, inflammatory bowel disease, and cardiovascular diseases [6,7,8]. This highlights the importance of interventive treatment that moderates gut microbiome composition to mitigate or prevent dysbiosis.

In the medical field, there have been extensive studies to develop methods aimed at modulating and maintaining the stability of the human gut microbiome. One common approach is transplanting feces obtained from healthy donors to reintroduce beneficial bacteria to the gut, also known as *Fecal Matter Transplant* (FMT) therapy. However, FMT poses a high risk of pathogenic transmission, infection, and rejection of the host gut microbiome [9,10]. Another common method is to use specific drugs, such as antibiotics, prebiotics, and probiotics, to modulate the interactions and composition of intestinal microbes [11]. However, these drug-induced changes in the digestive tract environment can potentially exacerbate microbiome instability, leading to antibiotic-induced diarrhea, bloating, and infections [11]. The side effects of both approaches can be attributed to the lack of precision and non-specific targeting mechanisms of these treatments. Furthermore, the inherent complexity of the human gut microbiome makes it challenging to design low-risk therapeutic interventions to stabilize and modulate bacterial compositions properly. A more rigorous and quantitative approach is required to develop such therapy.

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This study will leverage concepts from optimal control theory to help develop robust strategies for modulating and stabilizing the gut microbiome as a networked system. More specifically, this research will apply sparse optimal feedback control to a dynamical model of the human gut microbiome to identify critical bacterial species and interactions responsible for regulating and maintaining the ecosystem's balance, which can be specifically targeted for therapeutic interventions.

This study is organized as follows: Section 2 discusses the gut microbiome model this research assumed and discusses several preliminary concepts in control theory and network science. Section 3 elaborates on our method of analyzing and applying sparse optimal feedback control to the gut microbiome. Section 4 elaborates on the implications of our results. Section 5 concludes our study. Sections 6 and 7 evaluate the scope of our study and potential future works.

1.2 Research Question

1. How can we utilize linear optimal control theory as a quantitative approach to analyze compositions of the human gut microbiome to develop a more systematic therapeutic design?
2. Based on the Sparsity Promoting Linear Quadratic Regulator, which bacterial species play an important role in maintaining the stability of the gut microbiome?

1.3 Objectives

This research aims to find the best modulation strategy for a more targeted and systematic medication development aiming to stabilize the gut microbiome. This can be accomplished through the use of tools from optimal control theory, including Sparsity Promoting Linear Quadratic Regulator, Controllability Grammian, and Network Theory (Graph analysis) to find the most influential bacteria in modulating and maintaining the stability of the gut microbiome.

2. Literature Review

2.1 Dynamical Model of the Human Gut-Microbiome

To model the human gut microbiome, this research adopts the generalized Lotka-Volterra (gLV) model, a widely used approach for representing the dynamics of interacting microbial communities. The gLV has been previously utilized to model various dynamic systems, such as stock market fluctuations, infection patterns of RNA viruses, and gut microbiome [12,13,14]. The gLV model can capture the population dynamics of microbial species through a set of coupled differential equations, where the growth rate of each species depends not only on its intrinsic properties but also on its interactions with other species in the system. The gLV model is given by Equation 1.

$$\frac{dx_i}{dt} = f_i(x_1, \ldots, x_n) = r_i x_i + \sum_{j=1}^{n} A_{ij} x_i x_j, \qquad (1)$$

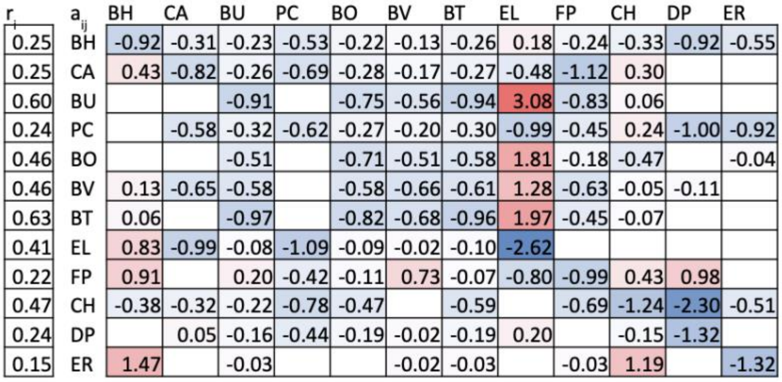
where the vector $x \in \mathbb{R}^n$ represents the population densities of n microbial species over time, the coefficient vector $r \in \mathbb{R}^n$ is the intrinsic growth rate of each species, and the matrix $A \in \mathbb{R}^{n \times n}$ is the interspecies interaction matrix. The value $A_{ij} > 0$ indicates that species j facilitates the growth of species i, and $A_{ij} < 0$ indicates that species j inhibits the growth of species i. In this study, this research adopt the version of the generalized Lotka-Volterra (gLV) model presented by Hromada and Venturelli [14], which includes the following 12 microbial species shown in Table 1:

Table 1. Abbreviation indices of bacterial species in [14]

No.	Bacteria Species Name	
1.	BH	*Bacteroides hydrogenotrophica*
2.	CA	*Clostridium aerofaciens*
3.	BU	*Bacteroides uniformis*
4.	PC	*Prevotella copri*
5.	BO	*Bacteroides ovatus*
6.	BV	*Bacteroides vulgatus*
7.	BT	*Bacteroides thetaiotaomicron*
8.	EL	*Escherichia lenta*
9.	FP	*Faecalibacterium prausnitzii*
10.	CH	*Clostridium hiranonsis*
11.	DP	*Dorea formicigernerans*
12	ER	*Escherichia rectale*

Their experimentally determined growth rates (r) and interaction matrix coefficients (A) are given in Table 2.

Table 2. Coefficients of the general Lotka-Volterra model [14]



r_i	a_{ij}	BH	CA	BU	PC	BO	BV	BT	EL	FP	CH	DP	ER
0.25	BH	-0.92	-0.31	-0.23	-0.53	-0.22	-0.13	-0.26	0.18	-0.24	-0.33	-0.92	-0.55
0.25	CA	0.43	-0.82	-0.26	-0.69	-0.28	-0.17	-0.27	-0.48	-1.12	0.30		
0.60	BU			-0.91		-0.75	-0.56	-0.94	3.08	-0.83	0.06		
0.24	PC		-0.58	-0.32	-0.62	-0.27	-0.20	-0.30	-0.99	-0.45	0.24	-1.00	-0.92
0.46	BO			-0.51		-0.71	-0.51	-0.58	1.81	-0.18	-0.47		-0.04
0.46	BV	0.13	-0.65	-0.58		-0.58	-0.66	-0.61	1.28	-0.63	-0.05	-0.11	
0.63	BT	0.06		-0.97		-0.82	-0.68	-0.96	1.97	-0.45	-0.07		
0.41	EL	0.83	-0.99	-0.08	-1.09	-0.09	-0.02	-0.10	-2.62				
0.22	FP	0.91		0.20	-0.42	-0.11	0.73	-0.07	-0.80	-0.99	0.43	0.98	
0.47	CH	-0.38	-0.32	-0.22	-0.78	-0.47		-0.59		-0.69	-1.24	-2.30	-0.51
0.24	DP		0.05	-0.16	-0.44	-0.19	-0.02	-0.19	0.20		-0.15	-1.32	
0.15	ER	1.47		-0.03			-0.02	-0.03		-0.03	1.19		-1.32

The model provides a comprehensive framework to study the interdependencies among these microbial populations, making it ideal for exploring strategies to stabilize the gut microbiome. The following section will discuss concepts and techniques for analyzing the gLV model.

2.2 Optimal Control of Dynamical Networked Systems

2.2.1 Linear Time-Invariant System

This research begin with the simplest dynamical networked system in the form of a square multivariate linear differential equation given by the *Linear Time-Invariant* (LTI) system defined (Equation 2):

$$\frac{dx}{dt} = Ax + Bu + d, \tag{2}$$

where $x \in \mathbb{R}^n$ is the state vector, $u \in \mathbb{R}^n$ is the control input vector, $d \in \mathbb{R}^n$ is the disturbance vector, $A \in \mathbb{R}^{n \times n}$ is the state transition matrix, and $B \in \mathbb{R}^{n \times n}$ is the control input matrix.

The term Ax captures the intrinsic dynamics, where A_{ij} defines how the j-th state influences the i-th state. The structure of A reflects the network's connectivity, while its eigenvalues indicate stability: negative real parts signify stability and return to equilibrium, while positive real parts

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indicate instability. The magnitude of the eigenvalues determines the speed of these dynamics. The term Bu represents the influence of control inputs u on the system. and d accounts for disturbances or external factors that perturb the system, representing environmental changes or noise. Together, these terms describe the balance between intrinsic dynamics, external interventions, and disruptions, providing a comprehensive framework for analyzing and influencing the system's behavior.

2.2.2 Controllability and H_2 norm of Networked Systems

Controllability is a fundamental concept in analyzing LTI systems, determining whether it can steer the system's state vector x from any initial state to any desired final state using appropriate control inputs u. For the LTI system, the structure of both A and B plays a critical role in ensuring controllability. The controllability Gramian, W_c, provides an energetic perspective on controllability by quantifying the energy required to move the system between states given A and B. The controllability Gramian is defined as Equation 3 [15]:

$$W_c(A,B) = \int_0^\infty e^{A\tau}BB^Te^{A^T\tau}d\tau. \qquad (3)$$

The overall controllability of the LTI given A and B can be measured by computing for the trace of $W_c(A,B)$ [15] (Equation 4:

$$H_2(A,B) = trace(W_c(A,B)). \qquad (4)$$

This value is also known as the H_2 norm. Larger values of $H_2(A,B)$ indicate that less energy is required to steer the system, while smaller values suggest that the system is inherently harder to control.

Supplemental to measuring the H_2 norm, the degree centrality measure can also help reveal structural insights into the gut microbiome system [16]. By generating a directed graph from the interconnection matrix A in Eq. (1) showcn in Figure 1, the in and out-degree centrality can be computed by counting the number of incoming and outgoing directed edges out of every species i.

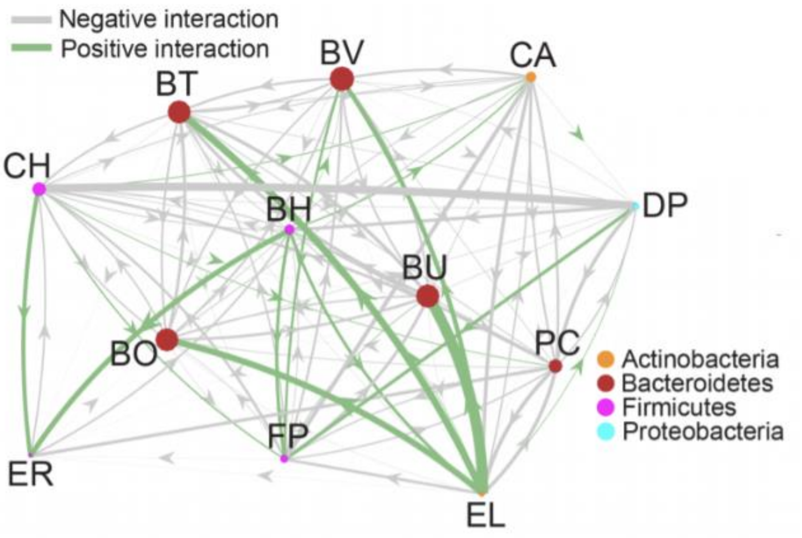


Figure 1. Graphical representation of inter-species connectivity based on the matrix A in Eq. (1) [14].

2.2.3 Linear Feedback Control System

Linear feedback control is used extensively in engineering to regulate the behavior of dynamic systems. It is based on the idea of using information from the current state of the system to modify its control input and achieve stability and responsiveness. A linear feedback controller for the LTI in Eq. (2) is given by Equation 5:

$$u = -Kx, \tag{5}$$

where $K \in \mathbb{R}^{n \times n}$ is the feedback gain matrix. The resulting controlled system then becomes (Equation 6):

$$\frac{dx}{dt} = (A - BK)x + d \tag{6}$$

The box diagram in Figure 2. illustrates the linear feedback control of an LTI.

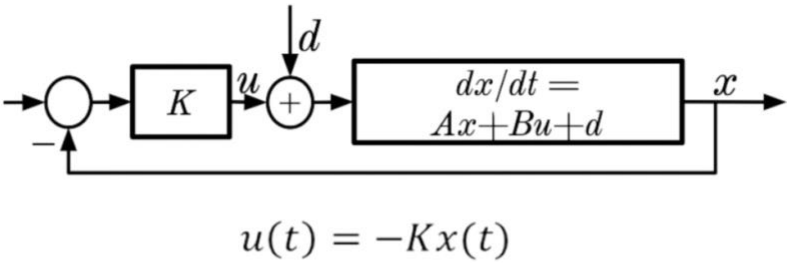


Figure 2. A schematic for a linear Feedback control of an LTI system.

The design of the feedback gain matrix K is critical to achieve system stability and responsiveness. The following section will discuss several criteria for selecting the optimal design for the feedback gain matrix K.

2.2.4 Sparsity-Promoting Linear Quadratic Regulator (LQRSP)

Optimal control techniques are commonly used to help design feedback control laws for a system by systematically optimizing a performance criterion. These techniques aim to determine the best control actions to achieve specific objectives, such as minimizing energy usage, ensuring stability, or achieving fast and precise tracking of desired trajectories.

In this study, Sparsity Promoting Linear Quadratic Regulator (LQRSP) is utilized to design an optimal feedback control law [17]. LQRSP considers three key factors in determining the optimal K: 1) control performance, 2) control effort, and 3) feedback costs. It is an extension of the traditional Linear Quadratic Regulator (LQR) framework by incorporating sparsity-promoting penalties into the optimization process, making it particularly useful for systems where feedback control channels can be limited or resource-intensive or difficult to control, such as in applications like controlling a gut microbiome.

The output feedback gain matrix K of the LQRSP is determined by solving Equation 7a-c optimization problem:

$$minimize_K \int_0^\infty \quad x^T(t)Qx(t) + u^T(t)Ru(t)dt + \gamma|K|_0 \tag{7a}$$

$$subject\ to: \ \ dx/dt = Ax + Bu + d \tag{7b}$$

.

$$u(t) = -Kx(t), \tag{7c}$$

where x and u are the same state and control input vectors found in Eq. (2) and K is the feedback gain matrix found in Eq. (5). The matrices $Q \in \mathbb{R}^{n\times n}$ and $R \in \mathbb{R}^{n\times n}$ are symmetric and positive semidefinite weight matrices that this study set as the identity matrix of size $n \times n$ for this study ($Q = R = I_n$). The coefficient $\gamma > 0$ is the sparsity penalty for the term $|K|_0$, which $|K|_0$ is the number of non-zero entries in the matrix K. Note that when $\gamma = 0$, the classical LQR formulation is recovered.

A feature of the LQRSP that is particularly relevant to this study is its ability to identify frugal control actions by selecting the most critical entries of K for achieving desired system performance while simultaneously minimizing control energy. By promoting sparsity in the feedback gain matrix, LQRSP effectively prioritizes impactful control channels based on the inherent structure and connections of the system being controlled. This makes it suitable for control applications of highly interconnected systems that require resource-efficient interventions, such as gut microbiome control.

3. Research Methodology

3.1. Linearization of the gLV model

To allow the application of the tools discussed in section 2, this study must first proceed by linearizing the gLV model to resemble an LTI. The linearization is done by computing for the Jacobian of Eq. (8):

$$J_{ij}(x) = \frac{\partial f_I}{\partial x_j} = A_{ij}x_i + \delta_{ij}(r_i + \textstyle\sum_{k\neq i} \quad A_{ik}x_k), \tag{8}$$

where δ_{ij} is the Kronecker delta ($\delta_{ij} = 0$ if $i \neq j$ and $\delta_{ij} = 1$ if $i = j$). To obtain the linear approximation of the gLV, the Jacobian is computed at the non-trivial steady state of Eq.(8), x_{ss}. The heatmap for the Jacobian coefficients is shown in Figure 3.

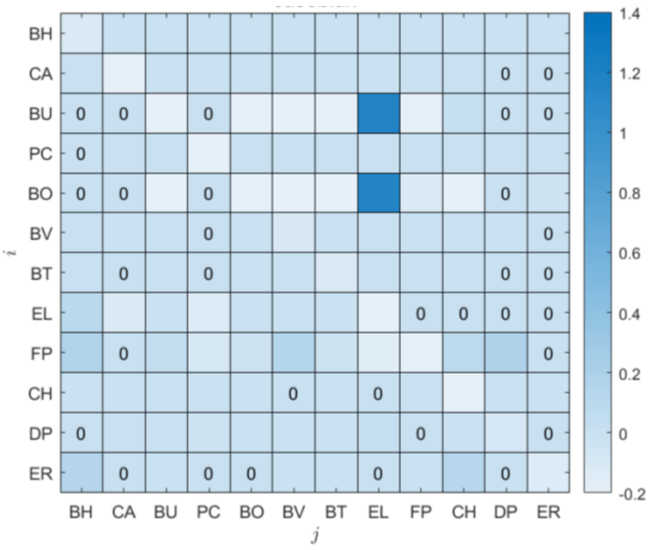


Figure 3. Heatmap of Jacobian Coefficients. Zero entries are annotated as “0” in the heatmap.

The resulting LTI that approximates the dynamics of the gLV model around the steady state is then given by Equation 9:

$$\frac{d\bar{x}}{dt} = J(x_{ss})\bar{x} + Bu(t) + d\ , \tag{9}$$

where $\bar{x} = x - x_{ss}$. Given Eq. (9), this study can apply the tools discussed in Section 2.

3.2. Calculating H_2-Norm and Degree Centralities

The linear approximation of the gLV allows the computation of the H_2 norm representing the total influence of each microbial species in steering the system. To separately measure the potential control influence of every species k, this study compute the H_2 norm using Eq. (4) with $A = J(x_{ss})$ and the following control input matrices (Equation 10):

$$B_{BH} = \begin{bmatrix} 1 & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 \end{bmatrix}, B_{CA} = \begin{bmatrix} 0 & 0 & \cdots & 0 \\ 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 \end{bmatrix}, \dots, B_{ER} = \begin{bmatrix} 0 & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 1 \end{bmatrix}. \tag{10}$$

Each value of $H_2(J(x_{ss}), B_k)$ for species $k = BH, CA, \dots, ER$ indicates the control influence each species k has on the rest of the system. Similarly, the in and out-degree centrality for each species $k = BH, CA, \dots, ER$ is calculated based on the graph in Figure 1.

3.3. Application of the Sparsity Promoting Linear Quadratic Regulator

To design the feedback gain matrix K using the LQRSP, this research apply the LQRSP solver in MATLAB to the LTI in Eq. (9) [18], with $J(x_{ss})$ as the state transition matrix and $B = I_n$as the control input matrix. To explore the effects of γ on the structure of the output feedback gain matrix K, this research solve Eq. (7) for $\gamma \in [0,100]$, discretized into forty values that generate forty different values of $K(\gamma)$.

3.4. Feedback Control Model Simulation under Known Disturbance

Using the resulting feedback gain matrices $K(\gamma)$ with various sparsity patterns produced by LQRSP, this research simulate the feedback-controlled gLV model using $K(\gamma)$ is given by Equation 11:

$$\frac{d\bar{x}_i(t)}{dt} = f_i(\bar{x}(t)) + Bu(t) + d(t), \tag{11}$$

where f_i is the differential equation governing the dynamics of species i defined in Eq. (1). This research simulate Eq. (11) using the forward Euler method to obtain a time series with $T = 10{,}000$ time points with iteration step of $h = 0.01$ [19]. This research employ two types of disturbances $d(t)$ in Eq. (2) to illustrate the stabilizing effect of the controllers:

$$d_{step}(t) = \{0, t < 0 |\ \underline{1}, t \geq 0\} \tag{12}$$

$$d_{impulse}(t) = \{1, t = 0 |\ 0, t \neq\ 0\}. \tag{13}$$

.

where Eq. (12) is known as the step disturbance where, and Eq. (13) is known as the impulse disturbance.

3.5. Measure of Controller’s Performance under Known Disturbances

To quantify the stabilizing effect of $K(\gamma)$ at different values of γ, this research employ the L_1 norm to measure the deviation of the simulated dynamics from the steady state x_{ss}. The L_1 norm for a set of time series $x(t)$ is defined as Equation 14:

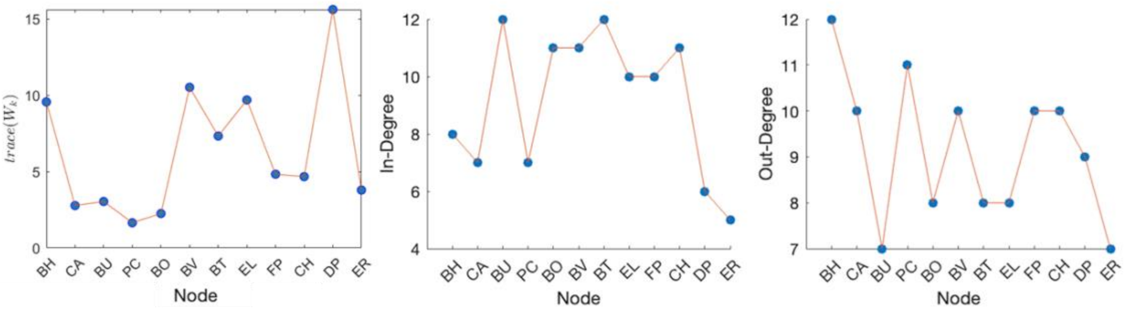
$$L_1(\bar{x}(t)) = \sum_{i=1}^{n} \int_0^T |\bar{x}_i(t)|dt. \qquad (14)$$

$L_1(x(t))$ can interpreted as the magnitude of deviation of $x(t)$ from $x_{ss}(t)$. The $L_1(\bar{x}(t))$ will be calculated for different feedback gain matrices $K(\gamma)$ and disturbances. Therefore, higher values of $L_1(\bar{x}(t))$ indicate poorer control performance and lower values indicate otherwise.

4. Results and Discussion

4.1. Identification of Influential Gut Bacteria

Figure 4 shows the result of $H_2(J, B^{(k)})$, in-degree and out-degree centrality for each $k = BH, CA, BU, PC, BO, BV, BT, EL, FP, CH, DP, ER$:



a)   b)   c)

Figure 4. a) Controllability index $H_2(J, B^{(i)})$*. b) out-degree centralities, and c) in-degree centralities for each 12 gut microbial species*

Observation of Figure 4a reveals that species BH, BV, BT, EL, FP, and DP represent the six bacterial strains with the highest $H_2(J, B^{(k)})$ value, indicating that these species have a strong dynamical influence over the rest of the gut microbial species. The difference in $H_2(J, B^{(k)})$ values across different strains implies that only certain species can be specifically targeted to effectively modulate gut microbiome dynamics. This measurement can be used as a data-driven pre-assessment to design a more informed specific therapeutic program.

In addition, the degree centrality measures in Figures 4a and b reveal the direct relationships between species. For example, BU and BT are the two strains that have the highest out-degree and lowest in-degree centrality, indicating that BU and BT are directly responsible for influencing the dynamics of the largest number of other species in the network but are themselves minimally influenced by other species. This highlights their potential role as dominant regulators or drivers within the system, which is suitable for targeted interventions or manipulations to steer the overall network dynamics.

4.2. Sparse Control Action via Influential Gut Bacteria

Figure 5 represents the variation of the feedback gain matrix $K(\gamma)$ with increasing sparsity penalty parameter γ:

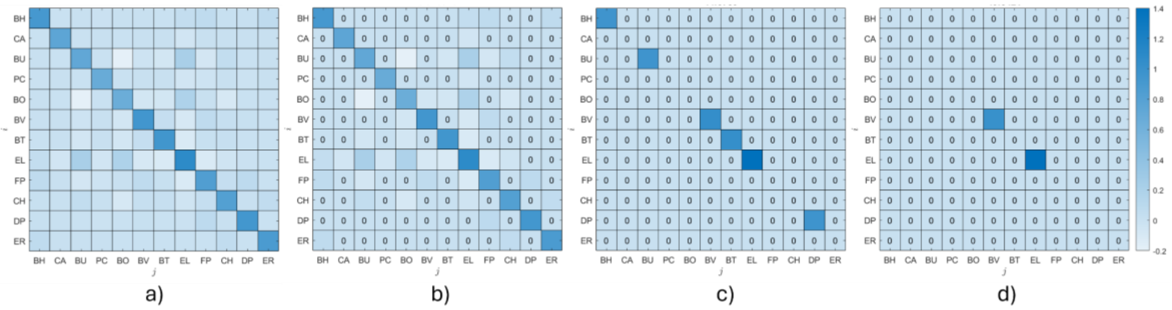


Figure 5. Structural variation of the feedback gain matrix K with increasing values of γ: a) $\gamma = 0$, b) $\gamma = 0.05$, c) $\gamma = 44.58$, and d) $\gamma = 49.81$.

An increase in γ leads to a more sparse $K(\gamma)$ structure, ultimately resulting in the retention of only the diagonal coefficients. When the value of γ reaches 44.58, all non-diagonal coefficients are reduced to zero, leaving only the diagonals of BH, BU, BV, BT, EL, and DP unchanged. An increase in the value of γ to 49.84 causes the matrix to become more sparse, leaving only two diagonals which are located at the indices of the strains BV and EL.

Furthermore, the progression of $K(\gamma)$ the matrix structure as the value of γ increases has several implications. Firstly, the rising cost of creating feedback control prompts LQRSP to select the most efficient feedback control channel by eliminating variables with minimal coefficients found in the LQR output of the K matrix. The controlled node at $\gamma = 44.58$ corresponds well with the species with higher values of $H_2(J, B^{(i)})$, such as BH, BV, BT, EL, FP, and DP. BU is also seen as one of the controlled nodes at $\gamma = 44.58$ even with relatively low value of $H_2(J, B^{(BU)})$. However, the decision to control BU can be explained by its high out-degree centrality. This implies that the controlled channels selected by LQRSP may also depend on the topology of the inter-species connections. This correspondence provides a stronger case for the effectiveness of LQRSP in identifying and prioritizing influential species within the network, ensuring that limited feedback control resources are allocated to nodes with the highest impact on system dynamics. Therefore, the LQRSP provides a promising framework for the automation of the identification of influential strains and the selection of frugal control actions of the gut microbiome.

4.3. Gut Microbiome Stability Analysis Under Disturbance

Comparison of the simulation results of Eq. (11) when no control action is applied and when different gain matrices K with different levels of sparsities are used as feedback control are visualized in Figure 6.

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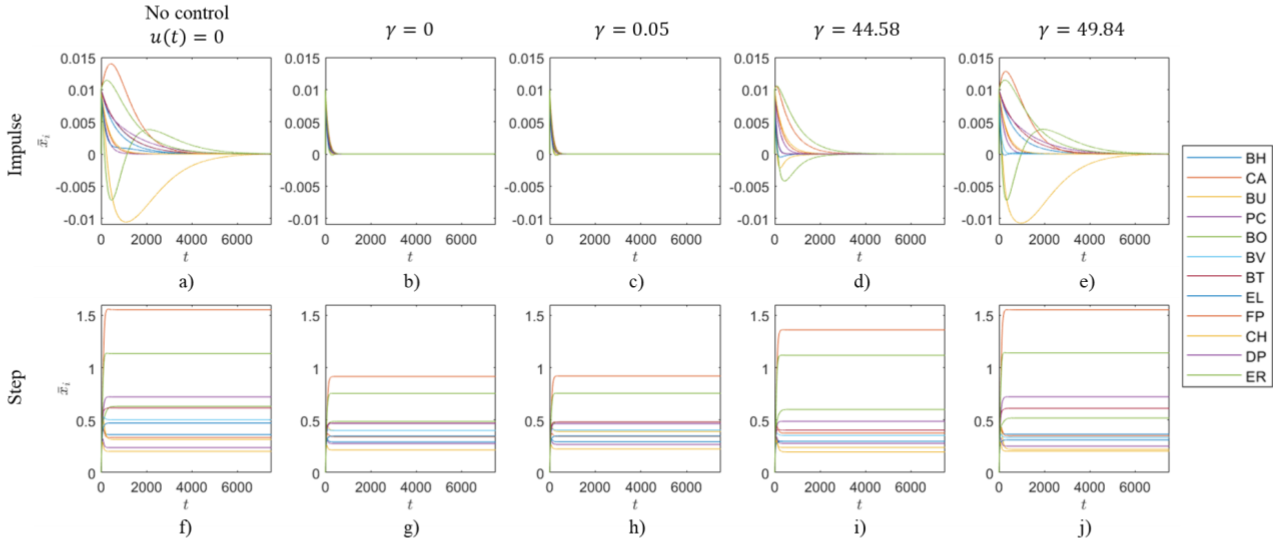

Figure 6. Simulation result of Eq. (10) with impulse disturbances $h_{impulse}(t)$ and step disturbances $h_{step}(t)$ at four different values of γ.

Observation of Figure 6a-e indicates the significance of the feedback gain matrix K in returning the gut microbiome dynamics to the steady state x_{ss}. As expected, the stabilizing effect of $K(\gamma)$ degrades with increasing γ as $K(\gamma)$ becomes sparser. At $\gamma = 49.84$, the controlled dynamics of the gut microbiome closely resemble the uncontrolled dynamics due to the negligible stabilizing effect of the feedback controller. This is evident when observing the extremely sparse feedback gain matrix $K(\gamma)$ shown in Figure 5d. A similar conclusion can be said in the case of the dynamics with step disturbances shown in Figures 6f-j. The offset from the steady state gradually becomes larger as $K(\gamma)$ becomes increasingly sparser. These results imply that there exists a tradeoff between control performance and frugality of the control channel being used to stabilize the system. This highlights the importance of selecting an ideal tradeoff when tuning for γ to obtain a significantly sparse $K(\gamma)$ that is significantly stabilizing.

To explore potential tradeoff points, the variations of the L_1 norm as a measure of controller performance with increasing forty values of γ for both types of disturbances are plotted in Figure 7:

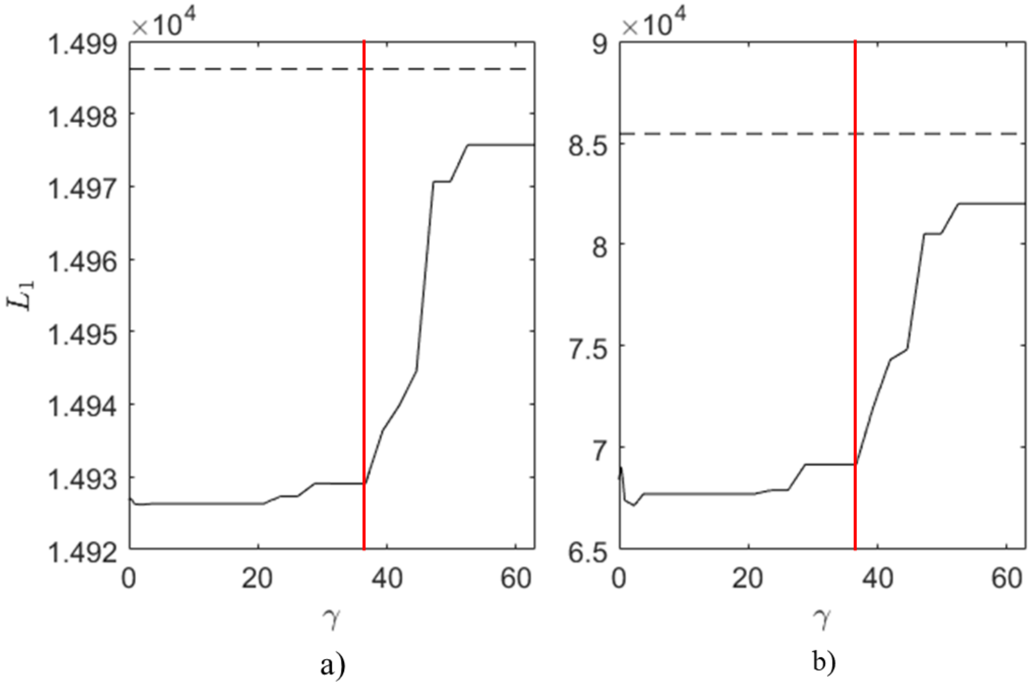

Figure 7. The variation of L_1 norm values with increasing γ for a) impulse and b) step disturbances. The dashed line indicates L_1norm values without control.

Similar to the results in Figure 6, both Figures 7a and b indicate the reduction in stabilizing effect (increasing L_1norms) of the feedback controller as γ increases. However, the finer distribution of γ reveals a critical value of sparsity penalty around $\gamma \approx 40$, where the value of L_1 increased drastically right after. Below this critical value, the system does not suffer a drastic decrease in performance with increasing sparsity. Overall, the sensitivity of L_1 norm and $K(\gamma)$ towards values of γ should depend strongly on the inherent interaction structure between bacterial species. The increasingly frugal controller design might prevent the selection of critical and influential species found in Sections 5.1 and 5.2, thus causing a significant drop in the stabilizing effect of the controller.

5. Conclusions

The results of this research provides a promising framework in aiding the process of designing therapeutic strategies that aims to maintain or improve the stability of the human gut microbiome. By applying control theoretic and network science approaches to identify critical bacterial species and design frugal control action, this research has introduced a more systematic and quantitative approach in modulating complex biological processes, such as the human gut microbiome, than existing therapeutic efforts.

The findings have shown that H_2 norms and graphical centrality index can be used to identify dynamically influential species that are suitable for control. This approach is further validated by the results of the sparse optimal linear feedback controller design via LQRSP, where it is found that the LQRSP is able to automatically select "favorable" microbial species to control based on the inherent structure and connectivities between microbial species. Thus, this findings have also shown a practical first step in utilizing LQRSP to design an exact interventive/preventive therapeutic strategies by identifying a critical value for γ, where the level of sparsity does not significantly decrease the stabilizing effect of the control action. Therefore, the quantitative insights obtained from the control theoretic framework can potentially propose a safer and more targeted approach for designing intervention strategies.

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6. Evaluations

The merit of this research is that all the findings regarding the most influential bacterial species and the frugal feedback controller design are derived from a purely data-driven and quantitative approach. This analytical automation can potentially streamline diagnosis processes to create a more reliable gut microbiome modulation therapy.

Nevertheless, the proposed framework is not without its limitations. Since this study focuses on the twelve most prevalent bacteria found in individuals, it relies on a specific working dynamical model. While gLV provides a well-established foundation for modeling microbial interactions, its assumptions, such as pairwise interactions and constant parameters, may oversimplify the complexity of real gut microbiomes. Furthermore, this framework does not account for rare or context-specific bacterial species, nor does it consider external environmental factors or host-related influences, which can significantly affect microbiome dynamics. Furthermore, real gut microbiomes rarely exhibit a linear and steady state dynamics due to the constantly changing and complex gut environment, suggesting that the resulting sparse optimal linear feedback controller might not be suitable.

7. Future Works

For future work, application of *Nonlinear control* and *Robust contro*l is intended as an alternative control technique to account for non-linearities and uncertainty of the model parameters. Furthermore, to further develop this research, support from the medical industry is very crucial in the form of direct in-vivo/in-vitro interventional experiments can provide greater insights regarding the true dynamics of the human gut microbiome, leading to more practical and reliable approaches that can be utilized in the medical field.

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The proposed research is important in the sense that it can be used to either replace, or reduce, or refine traditional cost/time-demanding human subject research. It aims to find bacteria species from gut microbiome that could help and/or medicate a variety of gut-related diseases such as colon cancer. A generalized Lotka-Volterra model for a set of 12 microbial species [14] is utilized to characterize the dynamics (growth rate of each and their interactions). Then, a feedback control with a gain matrix K is included and the object is to seek for the most dense gain matrix, satisfying the dynamics of the generalized Lotka-Volterra model, while the state variation and the control effort are minimized (LQRSP). The proposed research tries to simulate the optimization problem with, first a linearization to the generalized Lotka-Volterra model and then a neural network model for obtaining a steady state. In the end, with the criteria of the H_2-norm and degree centralities and the help of Matlab package, the author favors 6 species out of the 12 to have more important roles in gut microbiome stability. Overall speaking, the project is interesting and the data-driven model has important impact in medication. However, it lacks of real data from patients and hospitals to further tune the model. The author is also encouraged to find other optimization algorithms to directly solve the LQRSP, rather than a less precise simulation.