Switching microbial steady states by changing interaction parameters guided by dimensionally-reduced model

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Abstract

Author summary

Introduction

Composed of a large number of microorganisms , gut microbiome has great influence on health of human body. In a healthy person's body, these microorganisms decompose food molecules and produce beneficial substances. However, gut microbiome can be disturbed by environment factors such as food and medicine. In some cases, such as using of antibiotics, the disturbance is too strong for the microbiome community to restore its original healthy composition. Varying with time, microbiome composition will stabilize at a state different from the healthy one, causing the gut to be susceptible to infection. Treatments of this unhealthy state include Fecal Microbial Transplant(FMT), which brings the microbiome composition of a healthy donor to the infected patient's microbiome, restoring its normal community.

For instance, the use of Clindamycin could change the composition of gut microbiome to a state susceptible to *Clostridium difficile* infection (cite Buffie 2011). Clinically, this situation is frequently seen in senior patients who take antibiotics which introduces a *C. difficile* infection, causing diarrhea and abdominal pain. An experiment done on mice shows that directly giving *C. difficile* to mice does not change the gut microbiome significantly. On the other hand, after receiving clindamycin, the microbiome changes to a susceptible state which could develop into an infected state after receiving *C. difficle*.

Modelling the dynamics of gut microbiome requires understanding the dynamics of microbial ecosystem. The gut microbiome is composed of a large number of bacteria species, each of them constantly consuming and producing different substances. One bacteria species might consume another species' production; a different species might be damaged by another species' production. In addition, species' population are simultaneously growing and dying, forming a complex system.

Based on the aforementioned mice experiment, Stein *et al.* developed a model that captures the phenomena discovered in the experiment. This model sorts microorganisms in gut into 11 categories, and simulates the change in amount of a certain category using generalized Lotka-Volterra equations. In addition, they assigned a susceptibility coefficient to each category in order to model the change brought by antibiotics. This model's predicted dynamic system steady states include normal, healthy states of gut microbiome, as well as the susceptible state and the *C. difficile* infected state.

Antibiotics can drastically affect the state of microbiome by killing many microorganisms. Studies have shown that many other factors can also influence state of gut microbiome, including gastrointestinal transit time, amount of consumed dietary fiber, emulsifiers in food additives, and Roux-en-Y gastric bypass surgery used to reduce obesity. The factors mentioned above changes the environment of the gut microbiome, thus changing the way different microorganisms interact with each other. Based on clinical interest, we seek a principled way of qualitatively making these environmental changes to improve one's health. Therefore, inspired by the generalized Lotka-Volterra model, we model these environmental changes by changing the interaction coefficients between different categories. By changing these interaction coefficients we change the dynamical landscape of the generalized Lotka-Volterra system.

Specifically, two steady states in this 11-dimensional system, usually one diseased or disease-susceptible steady state and another healthy state are considered, as well as an initial microbiome state in between. Using a method called "steady states reduction"(SSR), we are able to closely estimate this 11-dimensional system using a well-studied 2-dimensional generalized Lotka-Volterra system. If the initial condition of interest goes to the undesirable steady state, a coordinated change in the interaction matrix of this reduced 2-dimensional system can be made to change the dynamical landscape so that the concerned initial condition goes to the desirable steady state. This change of 2-D interaction coefficient could be projected back to the 11-dimensional original interaction matrix according the formulae of SSR method. Therefore, we can mathematically estimate a coordinated change in these interaction coefficients sufficient to change the trajectory of microbiome state from going to unwanted steady state to going to a healthy one. In stead of randomly trying, this method gives a computationally quick way to change the interaction matrix in the benefit of healthy steady states. This method could potentially enhance treatment of disease related to gut microbiome. In addition, this mathematical method could also be applied to other complex systems with favorable and unfavorable steady states.

Materials and methods

Generalized Lotka-Volterra equations are used model the growth and interactions of the gut microbial community. They are given by

$$\frac{d}{dt}y_i(t) = y_i(t)\Big(\rho_i + \sum_{j=1}^{N} K_{ij}y_i(t)\Big) \tag{1}$$

where $y_i(t)$ denotes the number of microbes in a certain species at a given time t, ρ_i is the growth rate of each species, and K_{ij} is the interaction coefficient between two populations i and j. In the model used by Stein *et al.*, a large number of speices in the whole gut microbiome is categorized into 11 categories, and each y_i in the generalized Lotka-Volterra(gLV) equations represent a category instead of a specific species.

A technique of dimensional reduction, called "Steady State Reduction"(SSR), can be applied to high-dimensional generalized Lotka-Volterra equations to reduce the model into 2 dimensions. As shown in Fig 3, in the high-dimensional dynamic system, we

choose two steady states of interest, a healthy steady state $\vec{y_a}$and a diseased state $\vec{y_b}$. These two steady state vectors span a plane in the high-dimensional space, and we aim to find a 2-D gLV dynamics that captures the original high-dimensional dynamics on this plane as close as possible, with the assumption that the plane spanned by $\vec{y_a}$ and $\vec{y_b}$ is a slow manifold. Explicitly, the newly-created 2-D gLV system has the form

$$\frac{dx_a}{dt} = x_a(\mu_a + M_{aa}x_a + M_{ab}x_b) \tag{2}$$

$$\frac{dx_b}{dt} = x_b(\mu_b + M_{ba}x_a + M_{bb}x_b) \tag{3}$$

where x_a corresponds to the high-dimensional gLV system's component on the direction $\hat{x_a} = \frac{\vec{y_a}}{\|\vec{y_a}\|_2}$ and x_b correspond to the direction $\hat{x_b} = \frac{\vec{y_b}}{\|\vec{y_b}\|_2}$, and $\|\vec{v}\|_2$ represents the 2-norm of $\vec{v}$. Assuming two steady states $\vec{y_a}$ and $\vec{y_b}$ are orthogonal, SSR method gives the parameter value as follows:

$$\mu_\gamma = \frac{\vec{\rho} \cdot \vec{y_\gamma}^2}{\|\vec{y_\gamma}\|_2^2} \tag{4}$$

$$M_{\gamma\delta} = \frac{(\vec{y_\gamma^2})^T K \vec{y_\gamma}}{\|\vec{y_\gamma}\|_2^2 \|\vec{y_\delta}\|_2} \tag{5}$$

where $\gamma, \delta \in a, b$ and $\vec{y}^2 \equiv diag(\vec{y})\vec{y}$ is the element-wise square of $\vec{y}$. This SSR method is mathematically proven to be the gLV dynamic system with the smallest variation from the original high-dimensional dynamics.

In this study, we are interested in modifying parameters to achieve the goal of switching steady states. In a high-dimensional gLV model, interaction parameters are many. Due to the complexity of dynamical landscape, it is hard to find the most effective interaction parameters and determine the minimum change value enough to switch steady states. When simplifying the high-dimensional system using SSR, we obtain a 2-D dynamic landscape with four interaction parameters, M_{aa}, M_{ab}, M_{ba} and M_{bb}. These four parameters can be further non-dimensionalized into only two parameters, called new M_{ab} and M_{ba}. These two parameters , generated from SSR, determines the dynamical landscape in the 2-D gLV system. Bifurcation analysis shows that as the parameter M_{ab} and M_{ba} changes, a third steady state, marking the position of separatrix, changes its position in the phase space. As shown in Fig 4, there are two steady states, corresponding to $\vec{y_a}$ and $\vec{y_b}$ in the high-dimensional system, at $(0, 1)$ and $(1, 0)$. Changing interaction parameters M_{ab} and M_{ba} will move the separatrix close to one of the fixed steady states $(0, 1)$ and $(1, 0)$, thus making more points on the phase space evolve to the other one.

This bifurcation analysis shows a general direction to change the parameters in order to switch steady states. By numerically trying, the minimal change enough to switch steady states in parameter M_{ab} or M_{ba} can be found. As a guide to change the interaction parameters in the original high-dimensional system, this parameter change in the steady state reduced system can be projected back using Eq (5). There are more than one way to change K in eq (5) to change parameter $M_{\gamma\delta}$ the same amount, and we aim to find a minimal change. Generally, Eq (5) can be rewritten as

$$M_{\gamma\delta} = \sum_{i,j} \alpha_{ij} K_{ij} \tag{6}$$

where α_{ij} is determined by $\vec{y_\gamma}$ and $\vec{y_\delta}$. The biggest α_{ij} coefficient means the smallest change in K_{ij} parameter. Therefore, we are able to find the minimal change in K that corresponds to change in parameters in the steady state reduced 2-D model.