

Modelling the dynamics and long-term stability of perturbed gut microbiota

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INTRODUCTION

Gut microbiota are essential for maintaining host health, for example by providing protection against pathogens. This has prompted numerous studies to explore the composition and diversity of microbial communities using metagenomics techniques. Although this allows some degree of insight, there is still a shortcoming with regards to understanding the interactions and temporal dynamics of these communities in greater detail. Moreover, this knowledge gap becomes further pronounced if we also consider the impact of external perturbations, for example antibiotic treatment, on the long-term stability of these microbial communities. To address this, we propose a mechanistic modelling approach to predict microbial compositional changes over time and in response to external perturbation; hence, our aim is to model the resilience of gut microbial communities to changes in their environment.

METHODOLOGY

We used a mechanistic model to fit publicly available data derived from 16S rRNA sequencing as provided by Stein et. al. 2013 [1]. Specifically, for our predictive model we considered the generalised Lotka-Volterra (gLTV) model [1], which consists of a system of differential equations that describe the dynamics of microbial taxa with respect to their abundance counts. Crucially, this model relies on absolute abundance counts, which can be estimated from total microbial biomass measurements, and the data is organised into taxa at the genus level to avoid over-fitting. The gLTV is parameterised by microbial growth rates, mutual interactions, carrying capacity of the system (to account for depletion of resources), and a susceptibility term (to include the influence of an external perturbation signal), thereby making it amenable to biological interpretation. With respect to fitting, we used Bayesian inference to estimate model parameters from existing abundance counts. To model the impact of external perturbation on the modelled microbial community, we mathematically described the perturbation as a sinusoidal signal with given duration, frequency, and intensity.

RESULTS

To test this approach, we used the aforementioned data to infer bacterial growth, interaction, and susceptibility parameters for the gLV model. Here the dataset consists of absolute abundance counts for the top ten most abundant bacteria, grouped at the genus level, as determined from samples of mice intestinal microbiota. Notably, among these bacteria is the enteric pathogen, *Clostridioides difficile*. After fitting the gLV model to these data we explored different applications of the perturbation signal, mimicking antibiotic treatment, and evaluated its impact of the long-term stability of the community dynamics. In particular, we were able to identify a tipping point of the community in response to this signal: resulting in a distinct shift in its composition which corresponded to recovery from prior colonisation by *C. difficile*.

DISCUSSION

Modelling the dynamics of microbial communities using a mechanistic approach provides a more detailed understanding of their interactions and temporal dynamics; properties which are challenging to determine from experimental work alone. The main limitation of this computational approach, however, is the requirement for high resolution time-series sequencing data along with measurements of the total microbial biomass to estimate absolute abundance counts. Due to the scarcity of experimental data satisfying these conditions, we are currently exploring the use of individual-based models to generate in-silico data, which can be used for model validation. This will be used to inform the model design in preparation for fitting it to future data obtained from in-vitro gut model experiments. In summary, we have so far identified a model that is effective in describing the compositional changes of a microbial community, and which can be adapted to determining the resilience of such a community to environmental perturbations. This is a topic with strong relevance to healthcare, for example in this case antibiotic treatment regimen.