Ecological Modeling from Time-Series Inference: Insight into Dynamics and Stability of Intestinal Microbiota (2013)

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Outline

• Microbial effects on human health
• Previously shown methods and their shortcomings
• Overview of new method
• Results
• Discussion
Intestinal microbiome: Friend or foe

Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in Japan

The microbiome, cancer, and cancer therapy

Diet, Microbiota and Gut-Lung Connection
The methods discussed thus far

- Exclusively correlative (non-directional) inference of interaction
- No predictive power
- Limited to a single time-frame

**A: Current Analysis**

*Cross-sectional analysis*

- Correspondence analysis
  - + Statistical Tests (Kruskall–Wallis, Wilcoxon,…)
  - + PCoA/NMDS (Unifrac, Bray–Curtis, Euclidean)
  - + Diversity Indices (Shannon, Chao,…)
  - + Community Similarity Time Decay
  - + Co-occurrence (correlation) networks

**High-throughput community data and perturbation profiles**

- Log 16s rRNA/cm³
- Days
Static analyses
Microbes are alive

The microbiome is highly dynamic, effected by various factors:

• Diet
• Competition
• Drugs
• Infections
Lotka-Volterra Predator-prey model (1910)
Modelling an ecological community

\[
\frac{d}{dt} x_i(t) = \mu_i x_i(t) + x_i(t) \sum_{j=1}^{L} M_{ij} x_j(t) + x_i(t) \sum_{l=1}^{P} \varepsilon_{il} v_l(t)
\]

\(i = 1, \ldots, L\)  Species of interest

\(x_i(t)\)  Concentration of \(i\) at time point \(t\)

\(\mu_i\)  Growth rate of \(i\)

\(M_{ij}\)  Effect of \(j\) on \(i\) during interaction

\(\varepsilon_{il}\)  Susceptibility of \(i\) to perturbation \(l\)

\(v_l(t)\)  Susceptibility of \(i\) to perturbation \(l\).
Converting continuous to discrete

\[ \frac{\Delta \ln x_i(t_k)}{\Delta t_k} = \mu_i + \sum_{j=1}^{L} M_{ij} \ln x_j(t_k) + \sum_{l=1}^{P} \epsilon_i \nu_l(t_k) \]
Estimating parameters with regularized regression

$$\min \left\| (M \mu E)Y - F \right\|^2_{2+\lambda_M} \left\| M \right\|^2_{2+\lambda_\mu} \left\| \mu \right\|^2_{2+\lambda_\mu} \left\| \left\| E \right\| \right\|^2_{2+\lambda_E} \left\| E \right\|^2_{2}$$
K-Fold cross validation

Shown with $k=5$, authors used $k=3$
Mouse experiment

3 mice groups:
• Administration of Clostridium difficile, a bacterial pathogen.
• Administration of Clindamycin, an antibiotic.
• Administration of Clindamycin, followed by an administration of C. difficile the day after.
Effects of Clostridium difficile
Effects of Clindamycin
Effects of Clindamycin + Clostridium difficile
Predictive power

Spearman rank correlation = 0.62

\[ \log_{10} \text{of predicted abundance (Copies rRNA/cm}^3) \]

\[ \log_{10} \text{of Data (Copies rRNA/cm}^3) \]
The interplay between microbial taxa
The microbial drama unfolds
The microbial drama unfolds
The microbial drama unfolds
The microbial drama unfolds
Current shortcomings and possibilities for improvement

- Currently tested with absolute data only (antibiotically treated to extinction).
- Only supports with pairwise, second order interactions.
- Currently only works with roughly estimated and transformed count data.
- Works in a rough genus-level resolution and includes only the most common of those.
- More specific and gradual experimental data for empirical modeling of specific effects.
Discussion

• What is the best possible way to improve the current method (whether it’s a model improvement, addition, data consideration)?
• Are you more averse to antibiotic treatment after seeing the results of the experiment?