July 11, 2021

Dear editorial board of *Nature Ecology & Evolution*,  
  
Please find enclosed the manuscript entitled “**Ecological dynamics of the gut microbiome in response to dietary fiber**”. All authors have contributed to, read and approved this manuscript. It has not been submitted or accepted for publication elsewhere.

Our manuscript addresses an important yet rarely-addressed question of microbiome ecology: what are the ecological mechanisms underpin the dynamical responses of gut bacteria to dietary fiber intervention? A better understanding of the underlying ecology would show great promise for advancing human health through targeted modulation of gut microbiome towards controlled production of beneficial metabolites such as short-chain fatty acids. Previous studies on the fiber-induced shifts in gut microbiome have been mostly devoted to identifying fibe-degrading bacteria with sigificant responses *in vivo*, but their finidngs vary from study to study due to the lack of ecological interactions in their framework. We hypothesize that, the responses of gut bacteria— including those capable of degrading fibers *in vitro*—depend on the ecological network and thus the composition of baseline community before intervention. A recent research has revealed early insights into the role of ecological interactions in determining the microbial response to dietary fiber (Patnode *et al.* *Cell*, 2019). However, a system-level, quantitative understanding of the fiber-induced ecological dynamics and its baseline dependence remains very limited.

To bridge this gap, we used statistical and ecological modeling to analyze longitudinal profiles of gut microbiota (both relative and absolute abundances) after inulin intervention in mice—an animal model that has better controls over confounding variations caused by factors other than microbiome. A highlight of our study is that mice were purchased from multiple vendors: the mice from different vendors show distinct baseline gut microbiome compositions while those from the same vendor are essentially biological replicates. Such a microbiome-stratified experimental model system, along with computational modeling and Bayesian regression, has provided the following insights:

* Sustained inulin intake induces a rapid but transient dynamical response of gut microbiota composition that stabilizes to new equilibria in 4 weeks
* Ecology model parameterized from the time series data reveals a limited number of bacterial taxa with known ability to degrade inulin or resistant starch *in vitro*
* The initial abundance of a few fiber-induced responders and their intertaxa competitions explain the baseline-dependent dynamics of microbiome density and composition
* The strong correlation between bacterial load and propionate concentration suggests that the fiber responders are also propionate producers

In multiple aspects, we believe the longitudinal data and ecological network analysis should interest the broad readership of *Nature Ecology & Evolution*. First, our results emphasize the importance of understanding the outcomes of dietary fiber intervention from an ecological perspective. Furthermore, the ecological inference framework (generalized Lotka-Volterra model plus Bayesian regression) can be in principle applied to other microbiome-targeting interventions and therapies, such as probiotics and drugs. Finally, since the the individualized response of gut microbiome has impeded tailored dietary interventions, our paper may indirectly contribute to the development of precision intervention strategy based on baseline gut microbiota.

The paper that we are submitting contains 246 words in the abstract, 2180 words in the main text, 901 words in the Methods (298 words in the Methods Summary), 375 words in the figure legends and 497 words in the Box. There are 4 figures with a total of 12 panels in the main text. The supplementary information contains 8 supplementary figures, 1 supplementary table and 4 supplementary notes. We expect the paper to occupy ~4 pages in Nature.

Below, we suggest several possible reviewers, each of whom has published influential work in the field of gut microbiome and quantitative ecology. Please let me know if you need any additional information.

Sincerely,

Lei Dai

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**Suggested reviewers**

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