**Title**

Baseline microbiota composition modulates the dynamics of murine gut microbiota and SCFA metabolism in response to dietary fibers

Running title: Dietary fibers induce dynamical and baseline-dependent response in murine gut microbiota and short-chain fatty acids production

**Abstract (Chen Liao)**

Dietary fibers are commonly used as an intervention of gut microbiota to promote the production of short-chain fatty acids (SCFA), which are important for host health. The underlying processes are poorly understood due to the systems, dynamic, and individualized nature of microbiome metabolism. To address the challenge, we performed longitudinal analysis of quantitative microbiome profiles and targeted metabolomics of adult mice with distinct baseline microbiota undergoing intervention of inulin and resistant starch. Inulin stimulus normally shifts both gut microbiota composition and SCFA concentration away from baseline into new steady states after transient overshoot responses, which can be explained by initial rapid growth of several inulin responders (e.g., Bacteroides acidifaciens and unclassified Muribaculaceae) and their competitions inferred from ecological network model. Using a new computational framework based on time series factor analysis, we showed that 10% bacterial species (including all inulin responders) and two major SCFAs (butyrate and propionate) exhibit positive and significant baseline-dependent dynamical responses to inulin. Add a sentence for resistant starch. Due to the baseline differences, SCFA dynamics were, however, only marginally predictable from microbiota compositions using machine learning models, which also challenges robust identification of SCFA producers. This work provides a generic systems biology approach for studying gut microbiome under external perturbations and reveals inter-individual differences as a major limitation for predicting personalized responses to nutritional therapies in preventive health care.

**Lei Dai**

Dietary fibers are commonly used as an intervention of gut microbiome to promote the production of short-chain fatty acids (SCFA), which are important for host health. However, the response after dietary fiber interventions is still poorly understood due to the lack of time series data on both microbiome and metabolome. Here we used adult mice with different baseline microbiota to study the dynamical and individualized response of gut microbiota following interventions of inulin and resistant starch. We found dramatic shifts dynamics in mice gut microbiome composition and SCFA metabolism over four weeks. We used gLV to infer microbial ecology and successfully identified primary degraders. Furthermore, we used machine learning models to identify bacteria taxa associated with SCFA production, which can explain the individualized response to some degree but fails to predict the response of gut microbiome with a different baseline composition. Finally, we propose that SCFA production of gut microbiome in response to dietary fiber may have different phases. Our work underscores the importance of understanding the dynamical and individualized response in gut microbiome.

**Hongbin Liu**

(*Background*)

Longitudinal microbiome-metabolome monitoring at an individual level enables deep physiological and mechanistic profiling and may provide an important tool for precision nutrition, which aims to prevent and manage chronic diseases by tailoring dietary interventions or recommendations.

(*Goal*)

Using mice that harboring different gut microbiome as model hosts, we assess the dynamic response of the gut ecosystem to dietary fiber intervention by integrating analyze longitudinal data from the gut microbiome and SCFA metabolome.

(*Result*)

Regardless of the different baseline microbiome, we identified a strong short-term response and long-term adaptation of the gut microbiome in response to inulin intervention, representing by the substantial changes in the microbial structure and total SCFAs metabolism that happened a few days after the start of the intervention diminished before approach a final stable state. This biphasic response was consistent observed when reanalyzed another published dataset. However, the magnitudes and rates of the biphasic response dynamics of individual SCFAs and specific microbes were variable and identifiable influenced by pre-treatment microbiota. By coupling microbial quantity data and inferring with dynamic models, we verified multiple SCFAs producers that previously reported (*Parabacteroides goldsteinii*, *Lachnospiraceae bacterium 28-4*, *unclassified\_**Desulfovibrionaceae*, *Bacteroides-acidifaciens*), with their dynamics significantly correlated with the temporal changes of SCFAs concentrations. Furthermore, *Bacteroides-acidifaciens*, a species that previously reported for its involvement of inulin’s primary degradation, was again identified as inulin-responder here, along with a novel identified inulin-responder family *Muribaculaceae*. The different preintervention abundance of these two inulin-responders could result in distinct dynamic responses to inulin intervention. Through applying the quantitative modeling analysis to published human longitudinal microbiome data, we identified previously reported bacteria that may engage in the primary degradation of inulin or resistant starch. Our study highlights the importance of longitudinal sampling and integrating complementary multi-omics data to identify temporal dynamics of the microbiome. Serving as a widely-applied framework, this quantitative modeling method reveals insights into the ecologic mechanisms that how dietary fiber reshape the gut microbial structure and SCFA metabolism, which will help improve existing dietary treatments and guide precisely manipulation of the gut microbiome for optimal medical care.