**Main text figures:**

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**Figure 1.** **Experimental design and computational framework to study the dynamic and individualized response of mouse gut microbiome to dietary fiber intervention. A.** Schematic view of the experiments performed on a mouse model. Gray points indicate the days on which longitudinal fecal samples, microbiome and metabolomics data were collected. SCFA: short-chain fatty acid. **B.** Baseline gut microbiota composition of isogenic mice purchased from four different vendors. **C.** PCoA (principal coordinate analysis) biplot of the baseline microbiota in (**B**). Points represent baseline samples and gray arrows represent dominant bacterial species in the samples. The sample whose point projects furthest in the direction of a species has the highest relative abundance of that species. R2 and P-value were obtained from Adonis analysis, which tests for baseline differences across the four vendors. **D.** Illustrative overview of our systems biology approaches for data analysis. We used ecological modeling to infer keystone dietary fiber responders, time series factor analysis to visualize and test significance of individualized responses of both microbiome and SCFA (two P-values for each variable, Pr for responsiveness and Pi for individuality), and machine learning models to predict SCFA concentration from microbiome predictors and infer SCFA producers.

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**Figure 2.** **Dynamical responses of short-chain fatty acid (SCFA) metabolism and gut microbiome to dietary fiber intervention. A**-**C.** Temporal changes in fecal concentration of three major SCFAs (**A**) as well as microbiota composition (**B**) and alpha diversity (**C**) within four weeks’ intervention of two dietary fibers (inulin and resistant starch). Both SCFA concentration and microbiota diversity show short-term overshoot and long-term steady-state responses to inulin treatment. **D.** Inulin-stimulated response trajectories in PCoA (principal coordinate analysis) ordination scatter plot also indicate compositional convergence of gut microbiota to different steady states from the baseline. **E**. Total bacterial density measured by quantitative PCR. **F**. PCoA ordination scatter plot of gene abundances in inulin-fed mice metagenome. R2 and P-value were obtained from Adonis analysis, which tests for gene abundance differences among different response phases (day 0 for baseline, day 5 for short-term and, day 31 for long-term). For **A** and **B**, the heights of stacked bands represent averages across individual mouse. For **C-E**, lines or points represent mean and shading areas or error bars represent standard error of the mean.

**Diagram

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**Figure 3. Microbiota dynamics in response to inulin is driven by several key** **responders****. A.** Increased expression of inulinase genes following inulin treatment. Each dotted line represents an individual mouse. \*: P < 0.05; \*\*: P < 0.01; \*\*\*: P < 0.001. **B-F**. Inference of inulin responders. **B.** A schematic diagram showing our hypothesis that the observed overshoot dynamic responses of gut microbiota to inulin are predominately caused by growth and ecological interactions of several key responder species. **C.** Posterior distribution of five bacterial species with significant growth responses. **D.** Core ecological interaction network constituted by significant interspecific interactions (self-interactions not shown). Point and blunt arrows represent positive and negative interactions respectively. The arrow thickness is proportional to the posterior mean of the corresponding interaction coefficient. For C and D, significance was determined when 95% credible interval does not include 0. **E.** Absolute abundance of the five inulin responders shown in **(C)**. **F**. The inulin responders together dominate the short-term responses of gut microbiota. **G**,**H.** Predict total bacterial density (i.e., absolute abundance) from relative abundance of inulin responders. **G**. Pearson correlation for different combinations of inulin responders. **F**. Scatter plot showing the positive correlation of the combined relative abundance of *Bacteroides acidifaciens* (B.a.) and *unclassified Muribaculaceae* (Un. Mu.) with total bacterial density. Gray line: linear regression; shading area: standard error of the regression.

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**Figure 4.** **Visualization and quantitative significance test of individualized responses of bacterial species (A) and short-chain fatty acids (SCFAs) (B) to inulin supplement.** The scatter plot in (A) distinguishes four different scenarios of individualized responses depending on the P-values for significance test of responsiveness (Pr) and individuality (Pi). The bacterial species whose responses to inulin are both non-responsive and non-individualized are marked as gray dots, which are otherwise colored by the ratio of their time-and-individual-averaged absolute abundances (abs. abun.) between inulin and cellulose group. We displayed the inulin-stimulated longitudinal responses of bacterial species and SCFAs, relative to their corresponding responses in the cellulose group, in a reduced two-dimensional space spanned by factor 1 and factor 2 extracted using sequential non-negative matrix factorization (see Methods for details). In the simplified visualizations, each symbol represents a mouse (dots: cellulose group, crosses: inulin group) and all mice data from the same vendor under the same dietary fiber treatment was used to fit an eclipse. For each vendor, an arrow was drawn from the eclipse center of the vendor under cellulose treatment (standardized to the origin) to that under the inulin treatment. Numbers in parentheses indicate factor loadings.

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**Figure 5.** **Robust learning of microbiome-metabolome relationship** **is** **constrained by covariant shift. A,B.** Learning microbiome-metabolome relationships using machine learning models. **A**. Two data-split strategies to test model performance. Mice in the testing sets were randomly selected on a one-per-vendor basis for “interpolation” and exclusively selected from a single vendor for “extrapolation”. **B**.Training and testing accuracy in Random Forest regression models trained on absolute abundance of bacterial species. Data in day 0 were removed from the analysis. **C**,**D**. Covariant shift in cross-validation. **C**. Presence (threshold: 0.001%) and prevalence of bacterial species in baseline microbiota across mice and vendors. Species absent in any mouse baseline sample were not shown. The prevalence score of a species across mice was defined as the fraction of mice that contains this species in their baseline microbiota and that across vendors was the fraction of vendors whose mice all contain this species. **D**. Receiver operating characteristic (ROC) curve analysis of the similarity between training and testing datasets in (B). A Random Forest classifier trained to discriminate the two datasets outputs area under the ROC curve (auc) as a similarity score (see Methods for details). **E**-**H**. Potential producers and cross-feeding relationships for propionate production. **E**,**F**. Correlation of baseline unclassified (Un.) Parabacteroides absolute abundance with initial propionate production rates on day 0 (E) and rates in later days (F). R2 and P-value were obtained by linear regression. **G**,**H**. Simulated effects of cross-feeding (c.f.) (G) and inulin availability (H) on growth and propionate flux of two-genera Bacteroides-Parabacteroides community. w/ c.f.: mixing Bacteroides and Parabacteroides in 1:1 ratio; w/o c.f.: mixing Parabacteroides and its clone mate in 1:1 ratio.

**Supplementary figures:**

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**Figure S1**. Rarefaction analysis of 16S rRNA gene clone libraries in terms of species richness, Shannon diversity, and Simpson diversity. Rarefaction curves were generated using the iNEXT package. Solid lines represent the observed alpha diversity with the number of reads sampled, and dashed lines represent the extrapolation of the solid lines until 25% more reads. To avoid sample-to-sample bias due to variable sequencing depth (different number of reads per sample), all samples were rarefied to 38,980 sequences (read line) per sample before downstream analysis.

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**Figure S2**. Effects of inulin or resistant starch on (A) body weight, (B) daily food intake, (C) daily energy intake, and (D) 48-hr fecal sample weight of mice receiving diet supplementation used in this study. Data were analyzed by ordinary one-way ANOVA with Turkey post hoc test. \* *P* < 0.05, \*\* *P* < 0.01, and \*\*\* *P* < 0.001 vs cellulose group.

Q: star represents inulin or resistant starch? Not significant for all panels except one?

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**Figure S3**. Dynamical responses of fecal short-chain fatty acid (SCFA) concentration following dietary fiber intervention. Lines represent mean and shading areas represent standard error of the mean.

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**Figure S4**. Dynamics of gut microbiome (only for cellulose treatment) (A), relative abundance of the genus Bifidobacterium, evenness, number of observed ASVs, and beta diversity of the gut microbiome following dietary fiber intervention. For B-E, Lines represent mean and shading areas represent standard error of the mean.

Temporal changes in fecal concentration of three major SCFA in the cellulose group.

1. Temporal changes in fecal concentration of three major SCFA and total SCFA within one month’s intervention of two dietary fibers (inulin and resistant starch). Lines represent mean and shading areas represent standard error of the mean.

C. Compositional shifts in the predominant bacterial species of the cellulose-fed mice during the observation period.

D. Temporal changes in alpha diversity (Shannon index) of fecal microbiome. Lines represent mean and shading areas represent standard error of the mean.

E. Temporal changes in beta diversity (Aitchison distance after pairing using the “first distances” method) of fecal microbiome. Lines represent mean and shading areas represent standard error of the mean.

F. Principal coordinates analysis plot of Aitchison distance. After receiving the dietary fiber administration, the mice undergo a dramatic transition in their gut microbiomes. Each point represents the mean principal coordinate (PC) score of all mice in a group at one time point, and the error bar represents the SEM. The traces indicate the trajectory they follow over time.

G. The relative abundances of the *Bifidobacterium* over time within one month’s intervention of two dietary fibers (inulin and resistant starch).

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**Figure S5**. Fitting a harmonic oscillator model to the dynamics of short-chain fatty acids (A) and Shannon diversity (B). The best-fit parameter values for the short-term () and long-term () response time are shown in (C) and (D) for SCFA and Shannon diversity respectively.

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**Figure S5**. Alpha diversity (A), beta diversity (B) and trajectory of microbiota dynamcis (C) for a similar mouse experiment that are treated with inulin (Chijiwa 2020).

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**Figure S7**. Relationship between gut microbiome and total SCFA dynamics. We used the first principle coordinate from PCoA analysis to indicate the major change in microbiome.

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**Figure S8.** Relationship between gut microbiome and total SCFA dynamics. We used the first principle coordinate from PCoA analysis to indicate the major change in microbiome.

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**Supplementary Figure 12. Inference of inulin responders from human datasets. A.** Principle coordinate anlaysis (PCoA) of baseline human gut microbiota (Bray-Curtis distance matrix of 16S or shallow shotgun metagenomics) in four cohorts of literature studies with inulin intervention. **B.** Relative abundance of two major bacterial phyla in the same samples shown in J. **C.** Significant positive inulin responders identified from the four literature studies in J.