

Controlling Human Microbiota

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Brigham and Women's Hospital
Harvard Medical School*



The Invisible Universe of The Human Microbiome



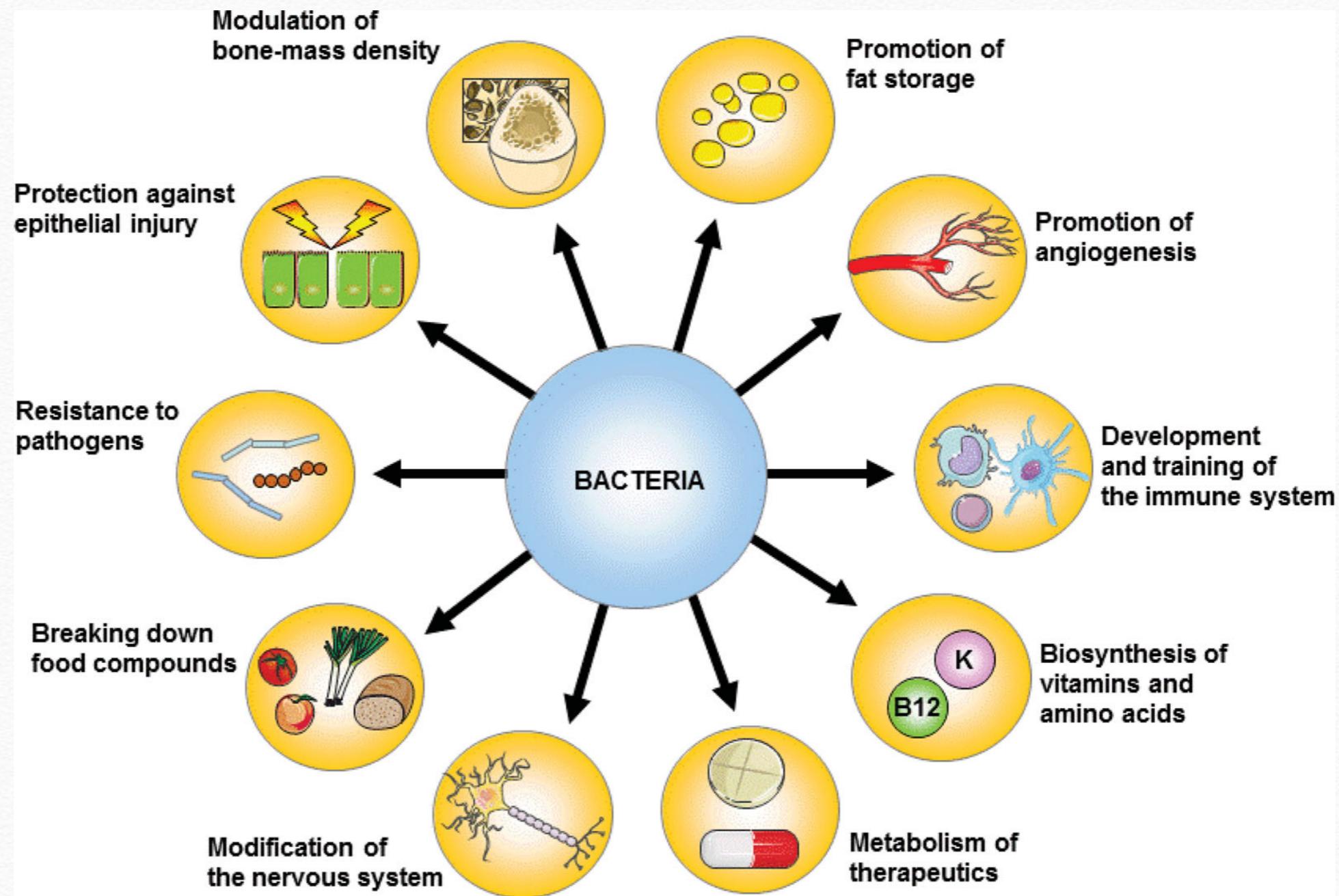
Credit: Benjamin Arthur and Rob Stein/NPR. Produced by Ben de la Cruz/NPR

We Are Our Bacteria!



Erody, *The New York Times* (2014)

Main functions of bacteria in the gut.

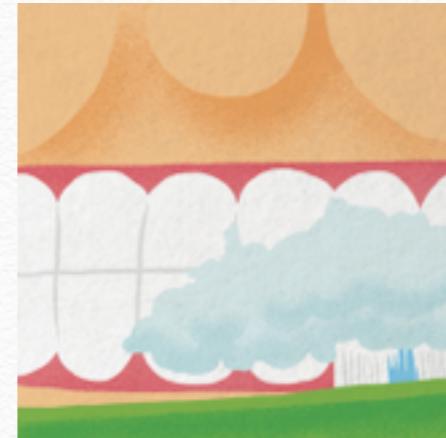




Acne



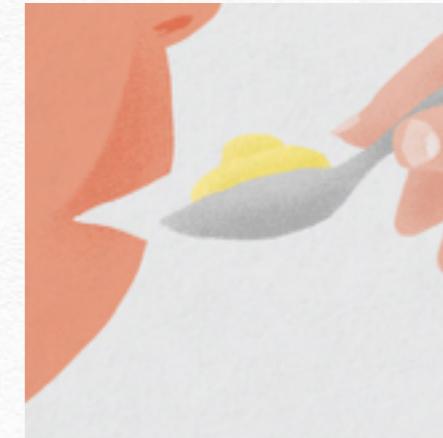
Eczema



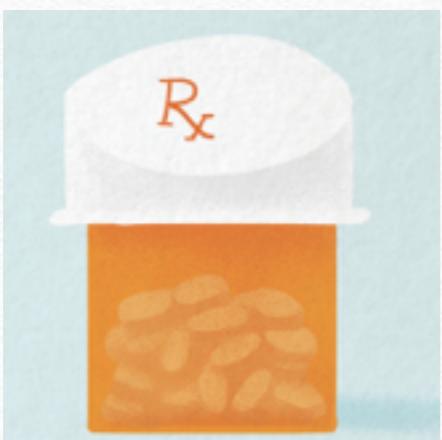
Dental cavities



Obesity



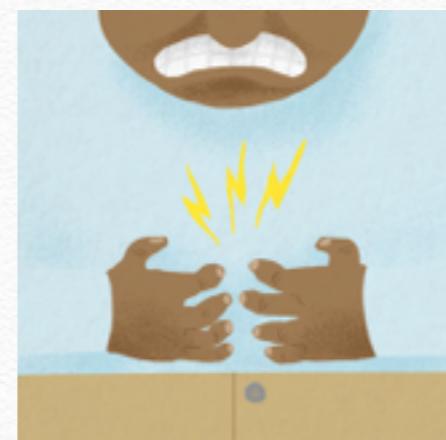
Malnutrition



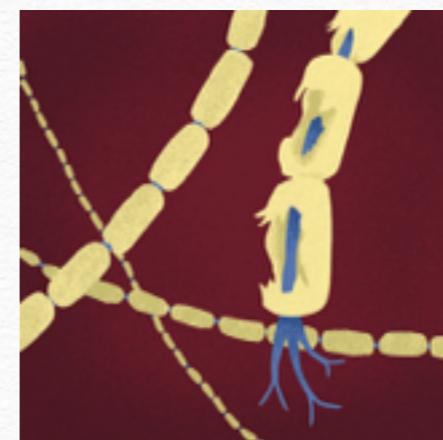
**Antibiotic-
associated
diarrhea**



Gastric ulcers



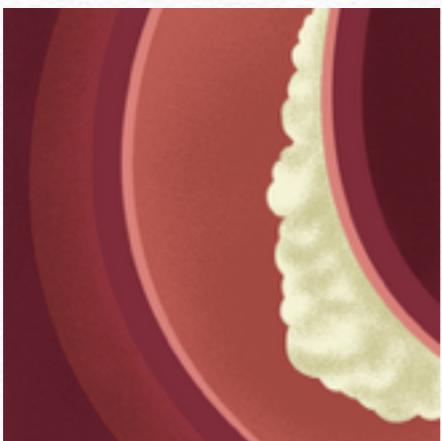
**Inflammatory
bowel diseases**



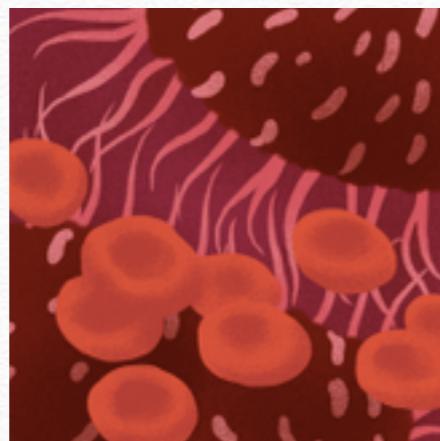
**Autoimmune
disease**



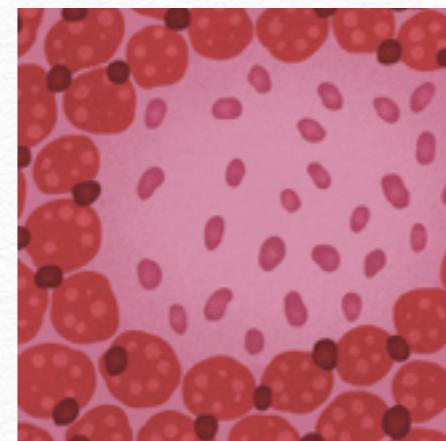
Asthma/allergies



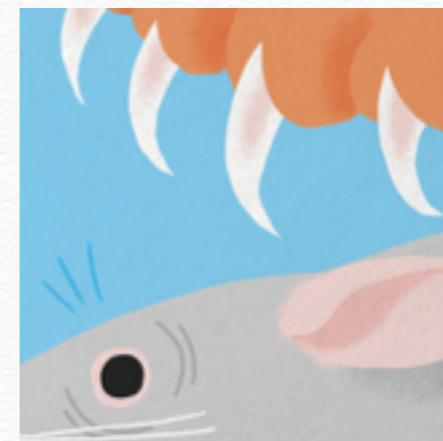
**Hardening of
the arteries**



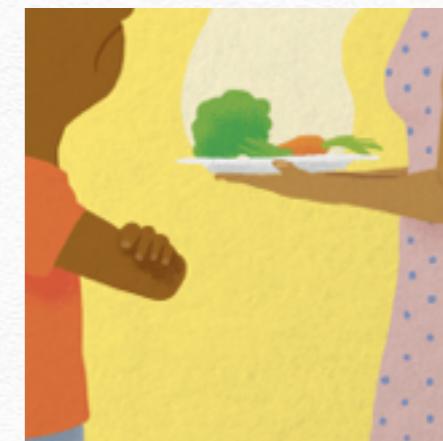
Cancer



Diabetes

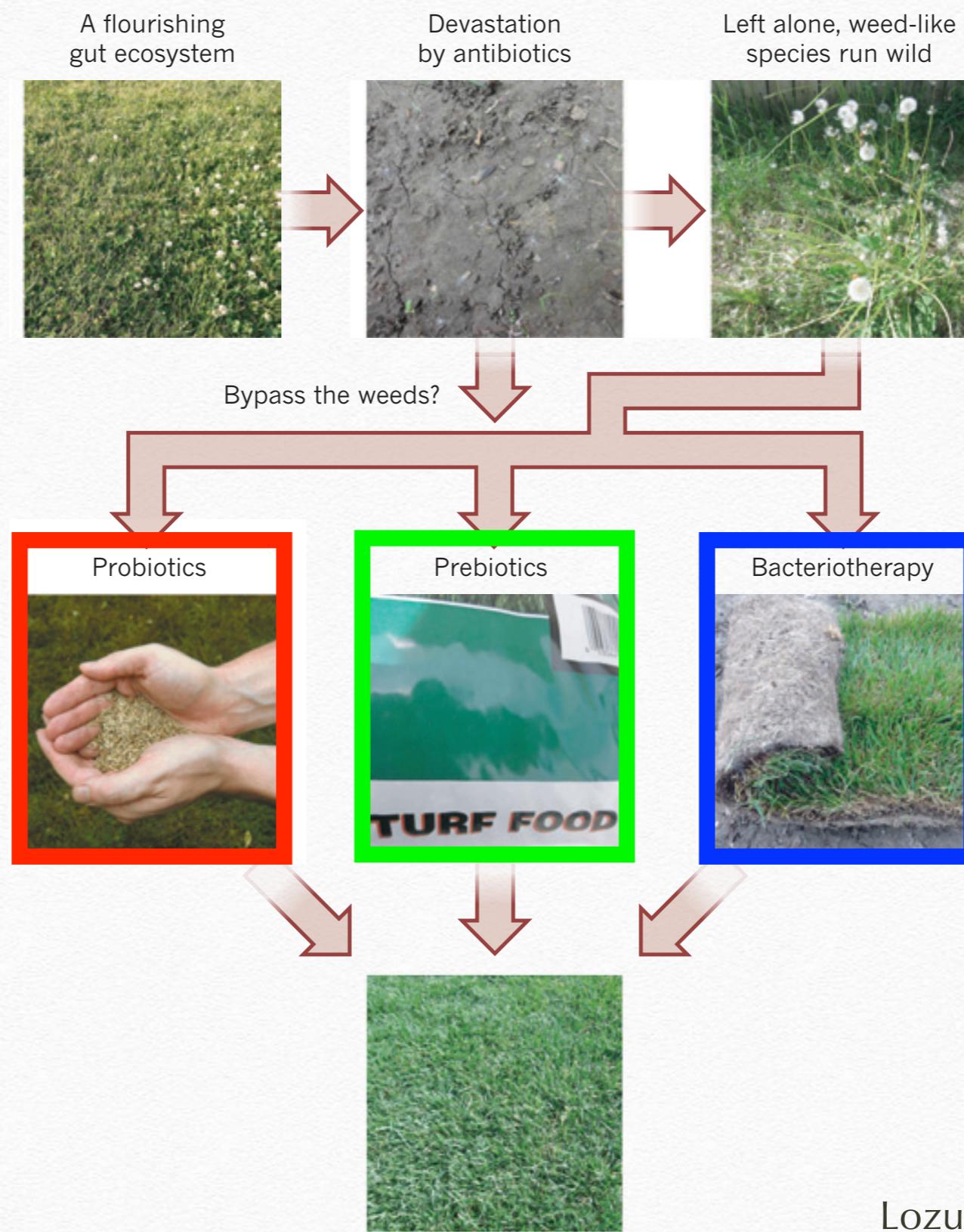


**Depression
anxiety**

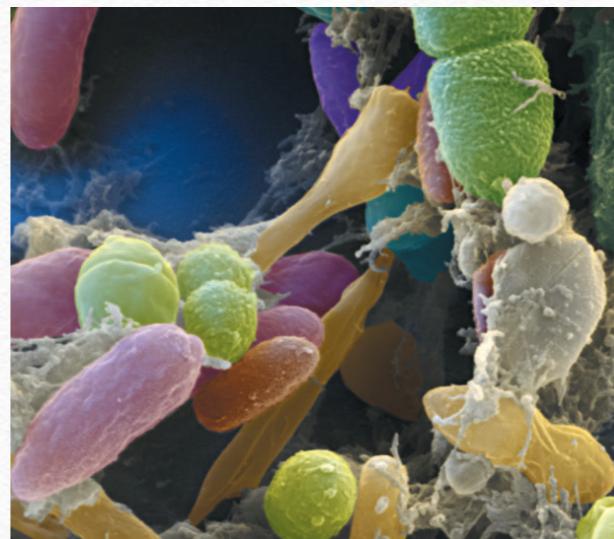


Autism

How to maintain/restore our healthy gut microbiota?



How to get real data?



A scanning electron micrograph (SEM)
of bacteria in human faeces

high-throughput
DNA sequencing

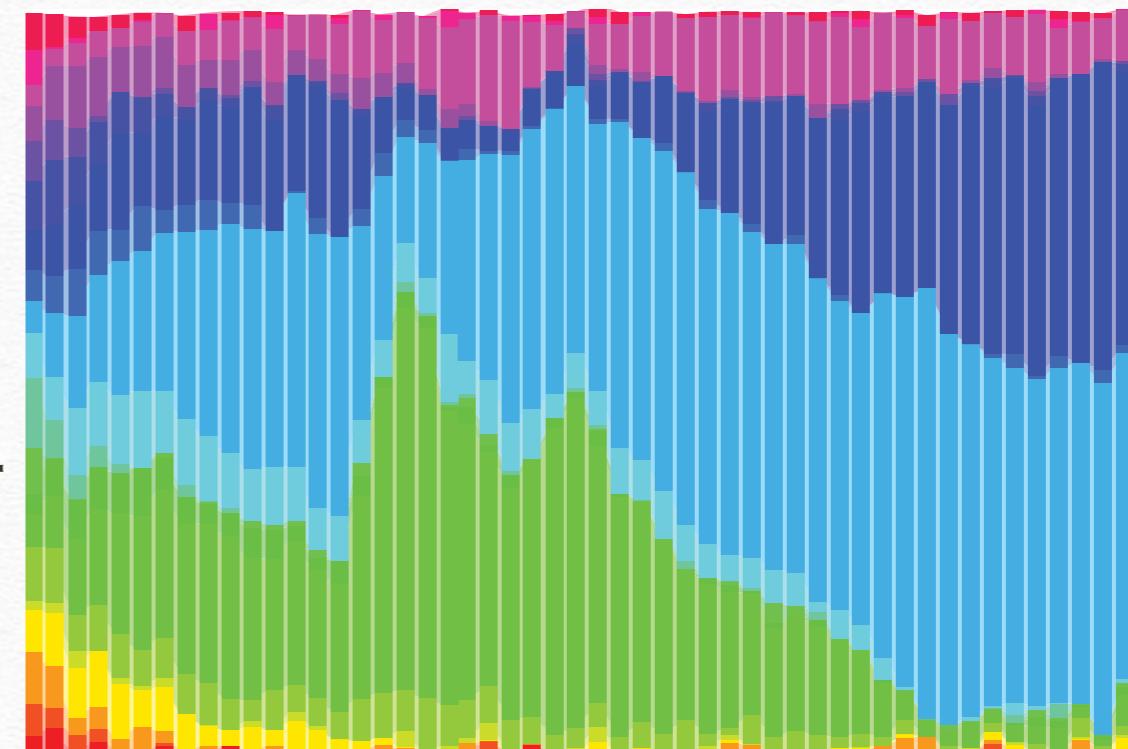


Abundance
profile

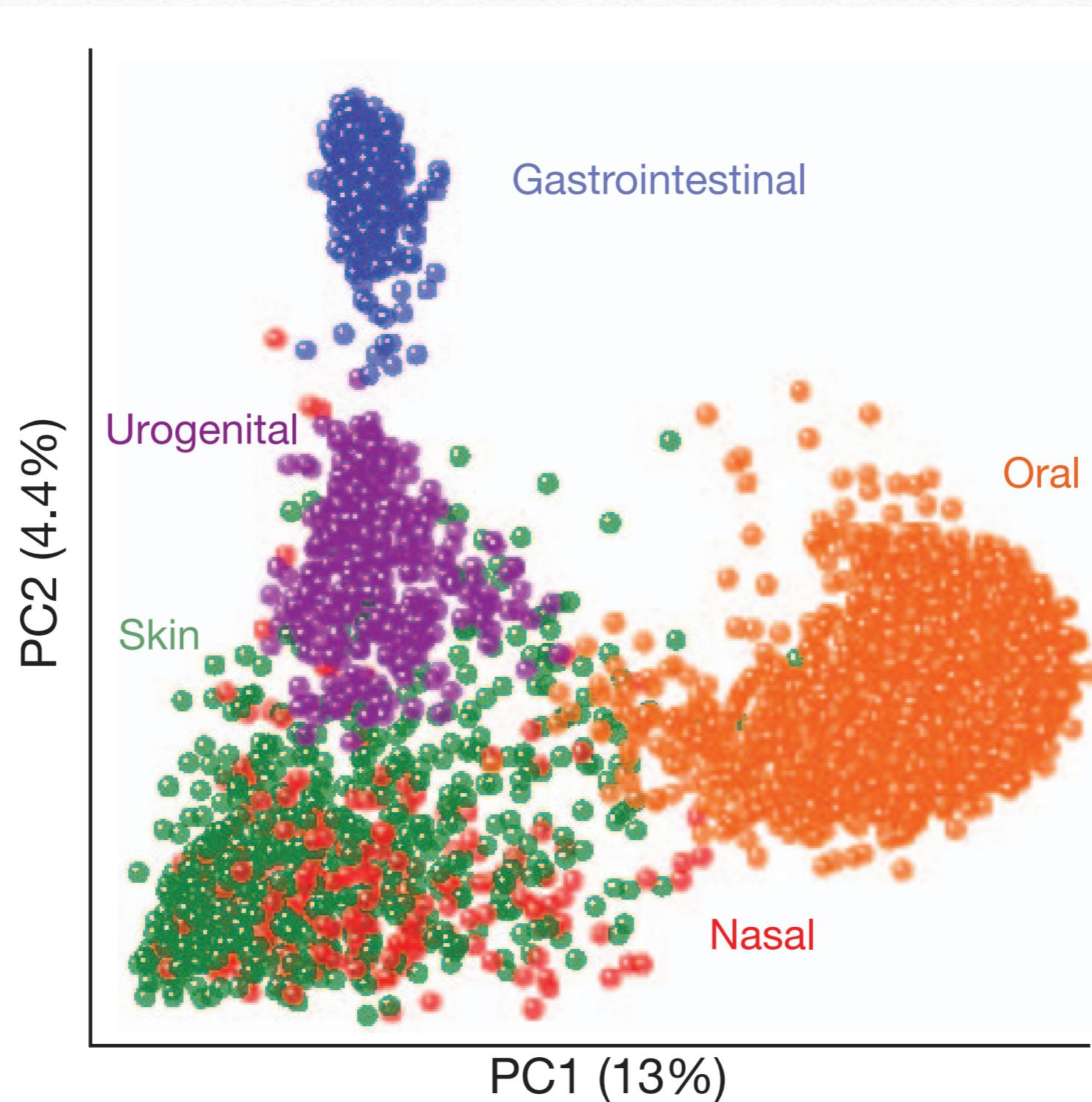


species

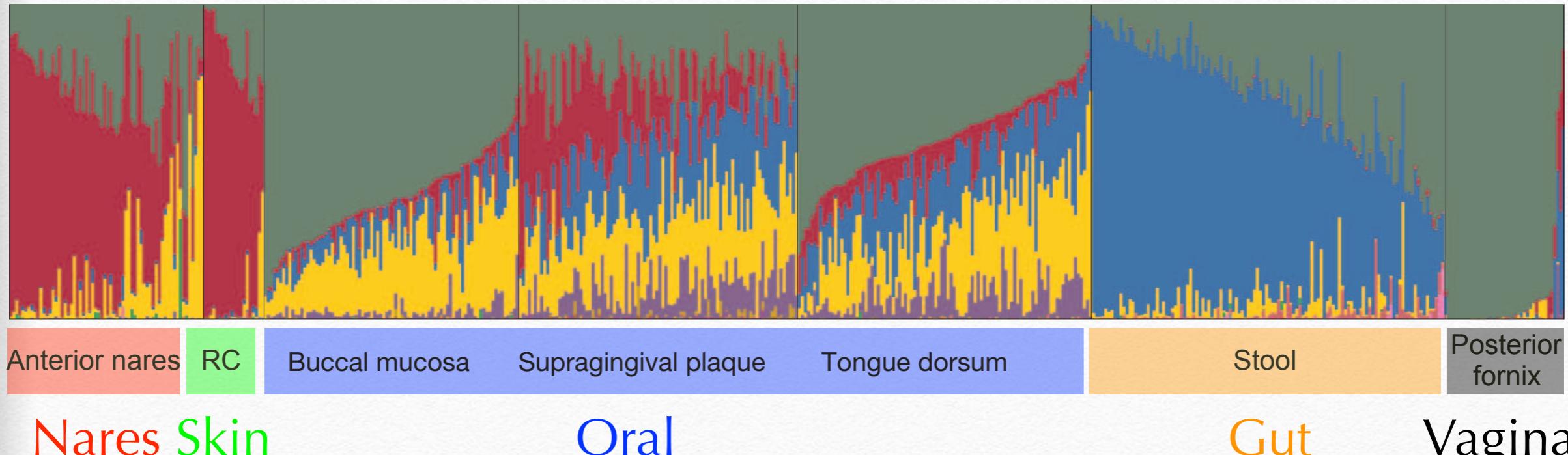
Days



Different body sites: different ecosystems



Our microbiota is highly personalized.



The Human Microbiome Project Consortium, *Nature* (2012)



Identifying personal microbiomes using metagenomic codes

Eric A. Franzosa^{a,b}, Katherine Huang^b, James F. Meadow^c, Dirk Gevers^b, Katherine P. Lemon^{d,e}, Brendan J. M. Bohannan^c, and Curtis Huttenhower^{a,b,1}

^aBiostatistics Department, Harvard School of Public Health, Boston, MA 02115; ^bMicrobial Systems and Communities, Genome Sequencing and Analysis Program, The Broad Institute, Cambridge, MA 02142; ^cInstitute of Ecology and Evolution, University of Oregon, Eugene, OR 97403; ^dDepartment of Microbiology, The Forsyth Institute, Cambridge, MA 02142; and ^eDivision of Infectious Diseases, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115

Edited by Ralph R. Isberg, Howard Hughes Medical Institute, Tufts University School of Medicine, Boston, MA, and approved April 6, 2015 (received for review December 15, 2014)



Our microbiota is highly personalized.



PNAS PLUS

Identifying personal microbiomes using metagenomic codes

Eric A. Franzosa^{a,b}, Katherine Huang^b, James F. Meadow^c, Dirk Gevers^b, Katherine P. Lemon^{d,e}, Brendan J. M. Bohannan^c, and Curtis Huttenhower^{a,b,1}

^aBiostatistics Department, Harvard School of Public Health, Boston, MA 02115; ^bMicrobial Systems and Communities, Genome Sequencing and Analysis Program, The Broad Institute, Cambridge, MA 02142; ^cInstitute of Ecology and Evolution, University of Oregon, Eugene, OR 97403; ^dDepartment of Microbiology, The Forsyth Institute, Cambridge, MA 02142; and ^eDivision of Infectious Diseases, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115

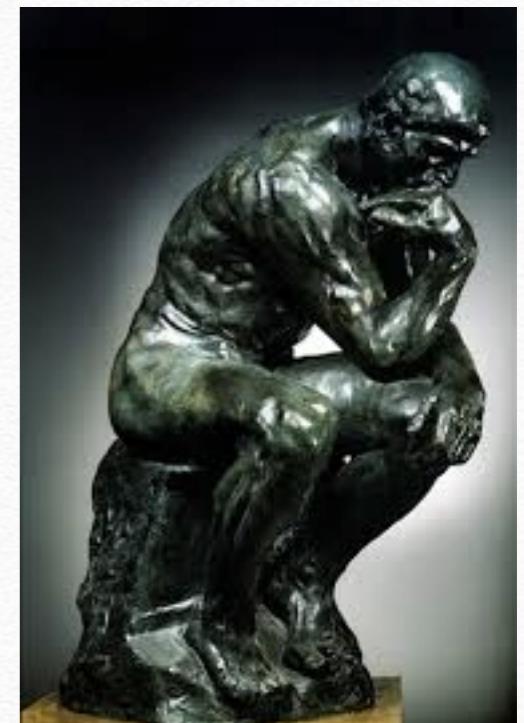
Edited by Ralph R. Isberg, Howard Hughes Medical Institute, Tufts University School of Medicine, Boston, MA, and approved April 6, 2015 (received for review December 15, 2014)

- Individuals can be uniquely identified among populations of 100s based on their microbiomes alone.
- In the case of the gut microbiome, >80% of individuals could still be uniquely identified up to a year later.

You are what you eat!



You are what you think!



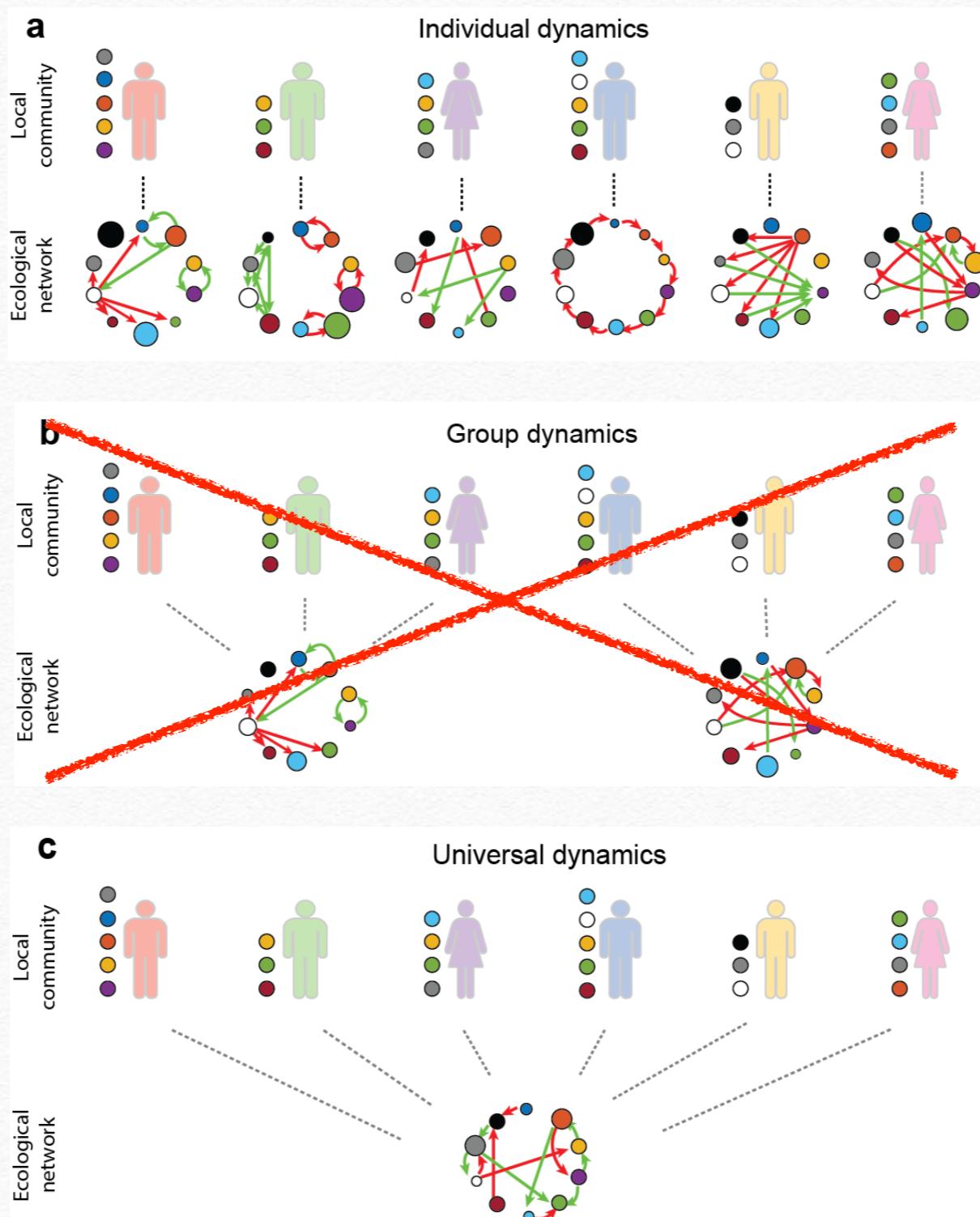
You are what you _____ !



Do we share similar microbial dynamics?

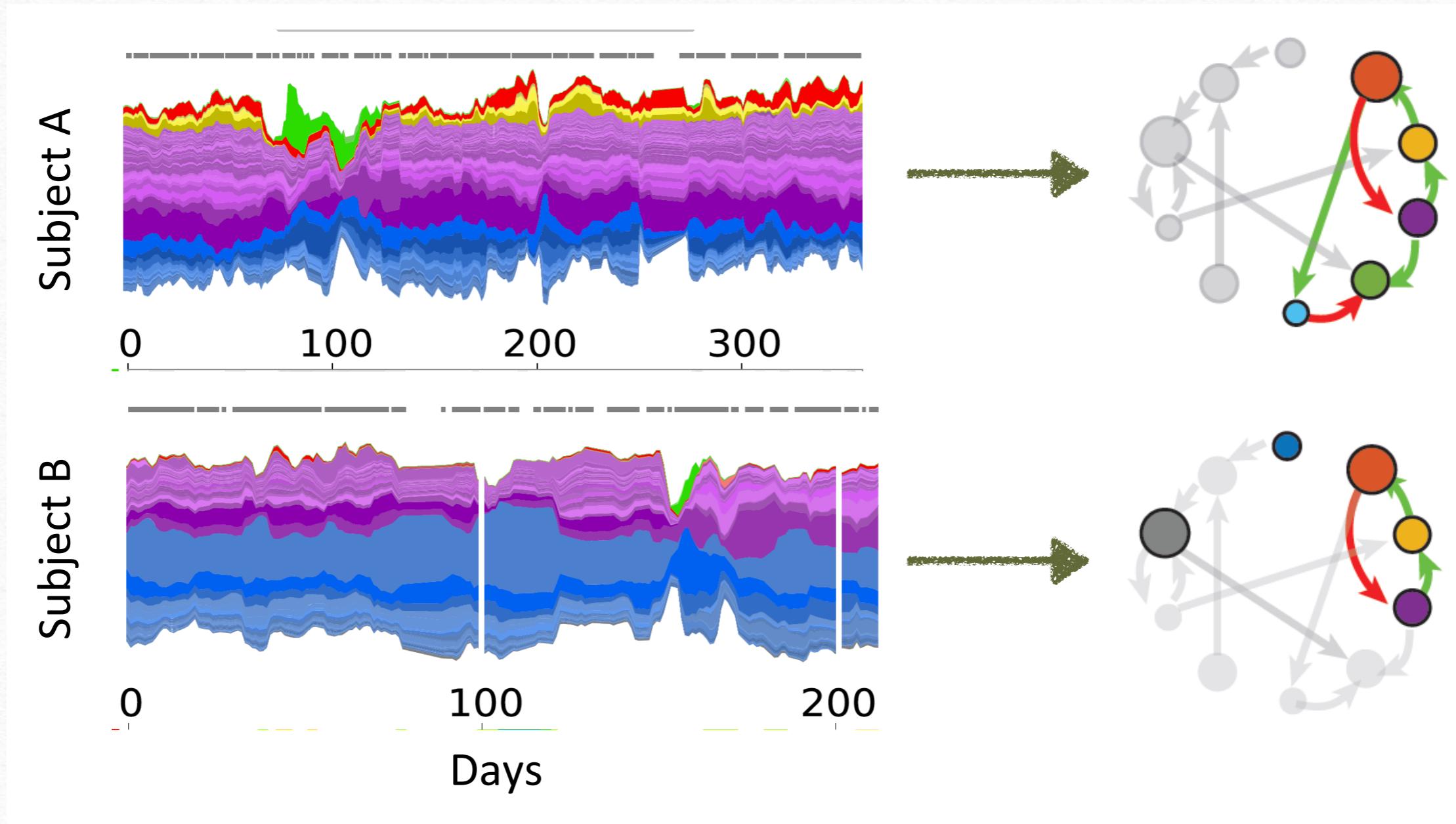
Do we share similar microbial dynamics?

$$\dot{\boldsymbol{x}}^{(\nu)} = \boldsymbol{f}(\boldsymbol{x}^{(\nu)}; \boldsymbol{\Theta}^{(\nu)})$$

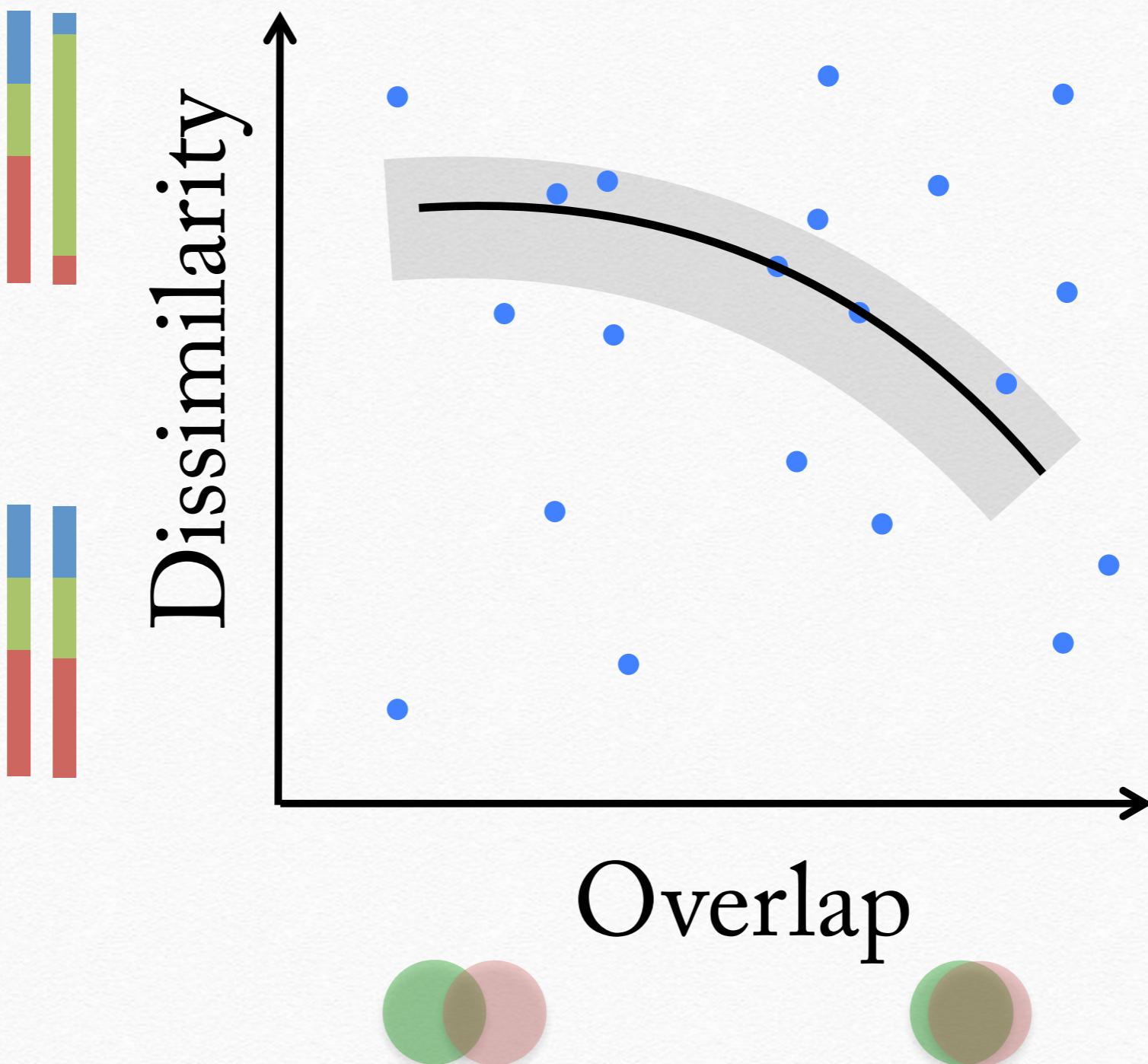


Naive Approach: System Identification using Longitudinal Data

$$\dot{\boldsymbol{x}}^{(\nu)} = \boldsymbol{f}(\boldsymbol{x}^{(\nu)}; \boldsymbol{\Theta}^{(\nu)})$$

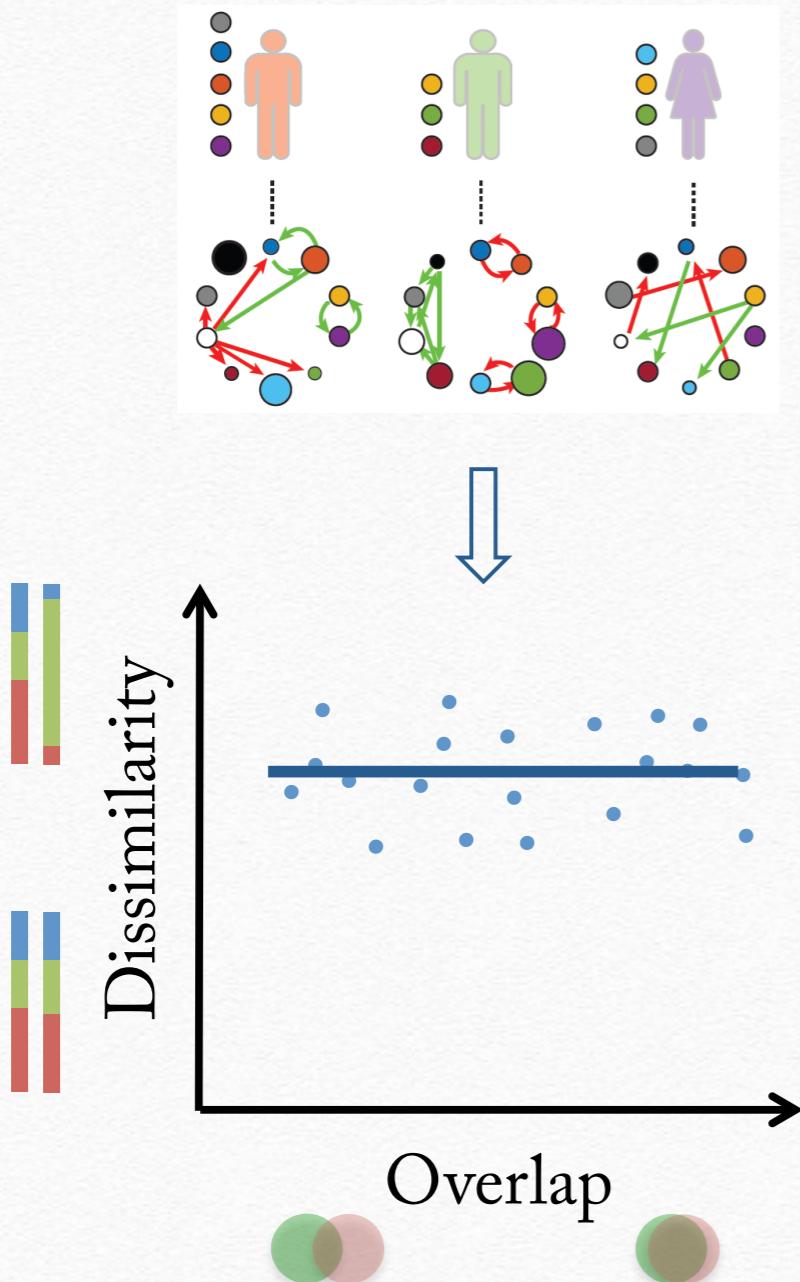


Dissimilarity-Overlap Curve (DOC) Analysis

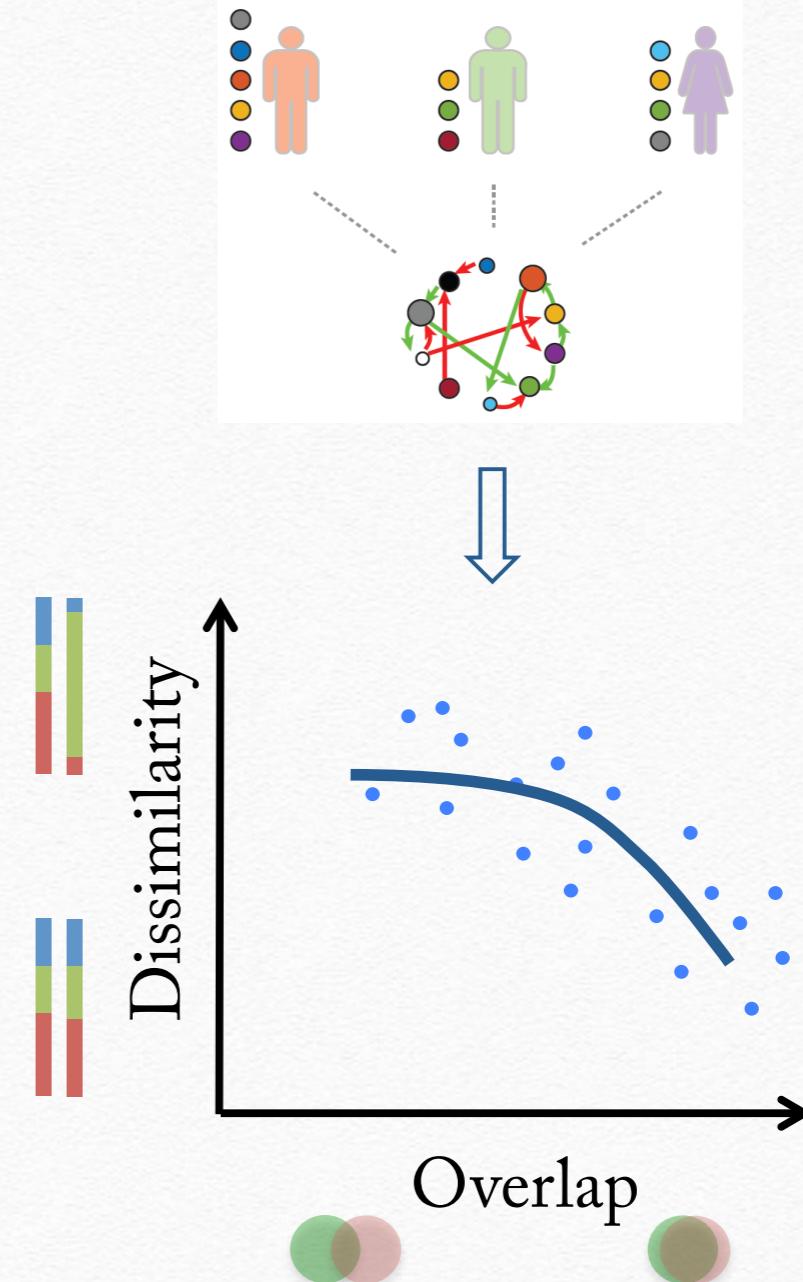


Dissimilarity-Overlap Curve (DOC) Analysis

individual dynamics



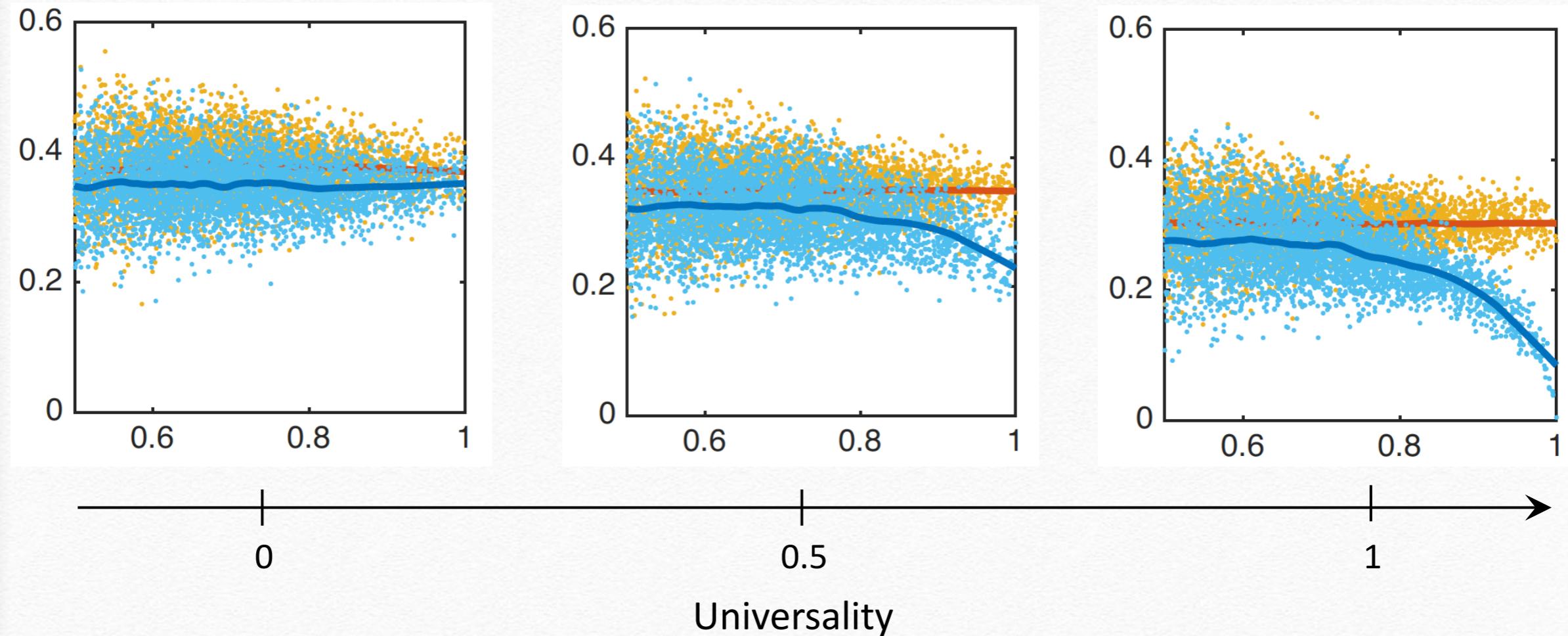
universal dynamics



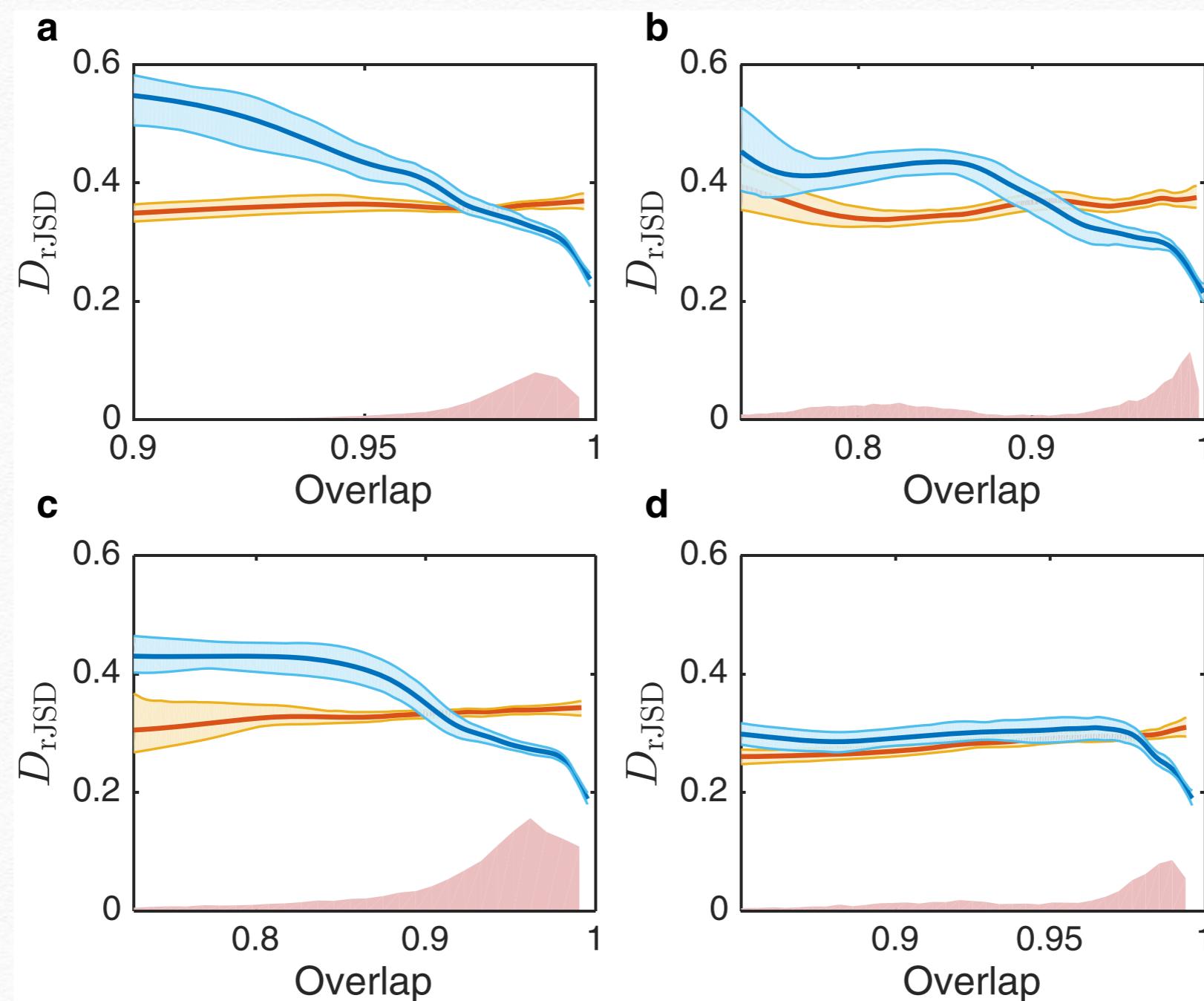
Assumption: True multi-stability does not exist for human microbiome.

Validation-1: using synthetic data generated from the Generalized Lotka-Volterra (GLV) model

$$\dot{x}(t) = \text{diag}(x(t)) (r + Ax(t))$$

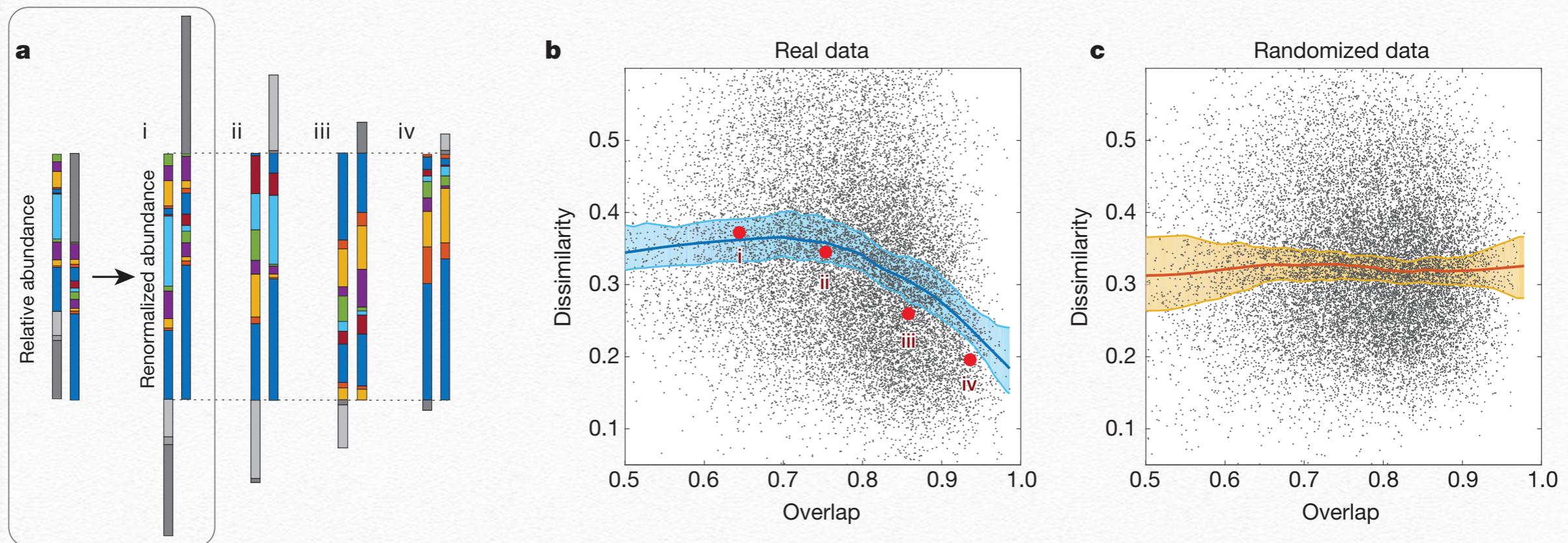


Validation-2: using real longitudinal gut microbiome data from 4 subjects



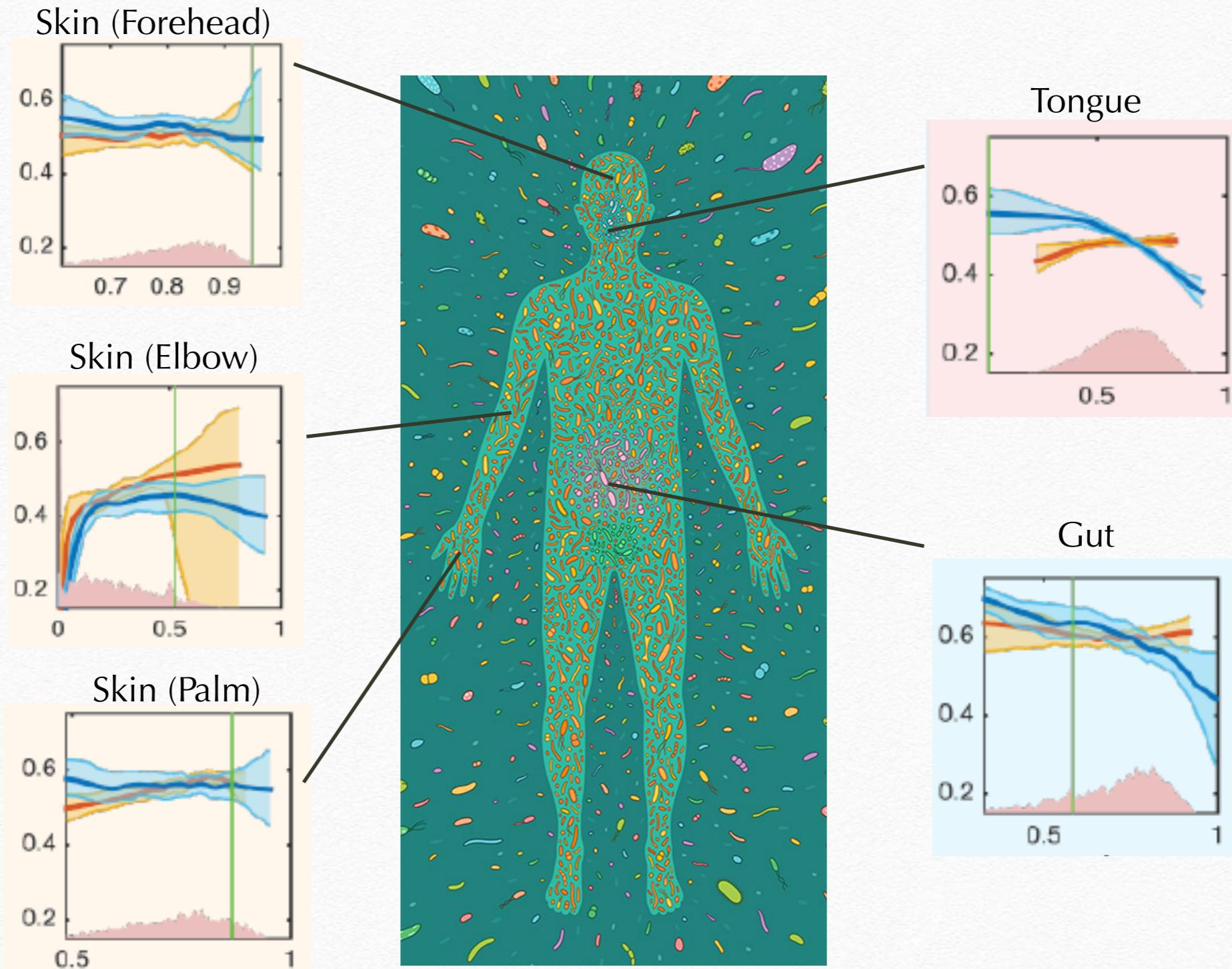
DOC analysis: cross-sectional **gut** microbiome data

$M = 195$ healthy subjects (Human Microbiome Project)



For healthy individuals, their gut microbiota display strong universal microbial dynamics.

DOC analysis: Different body sites



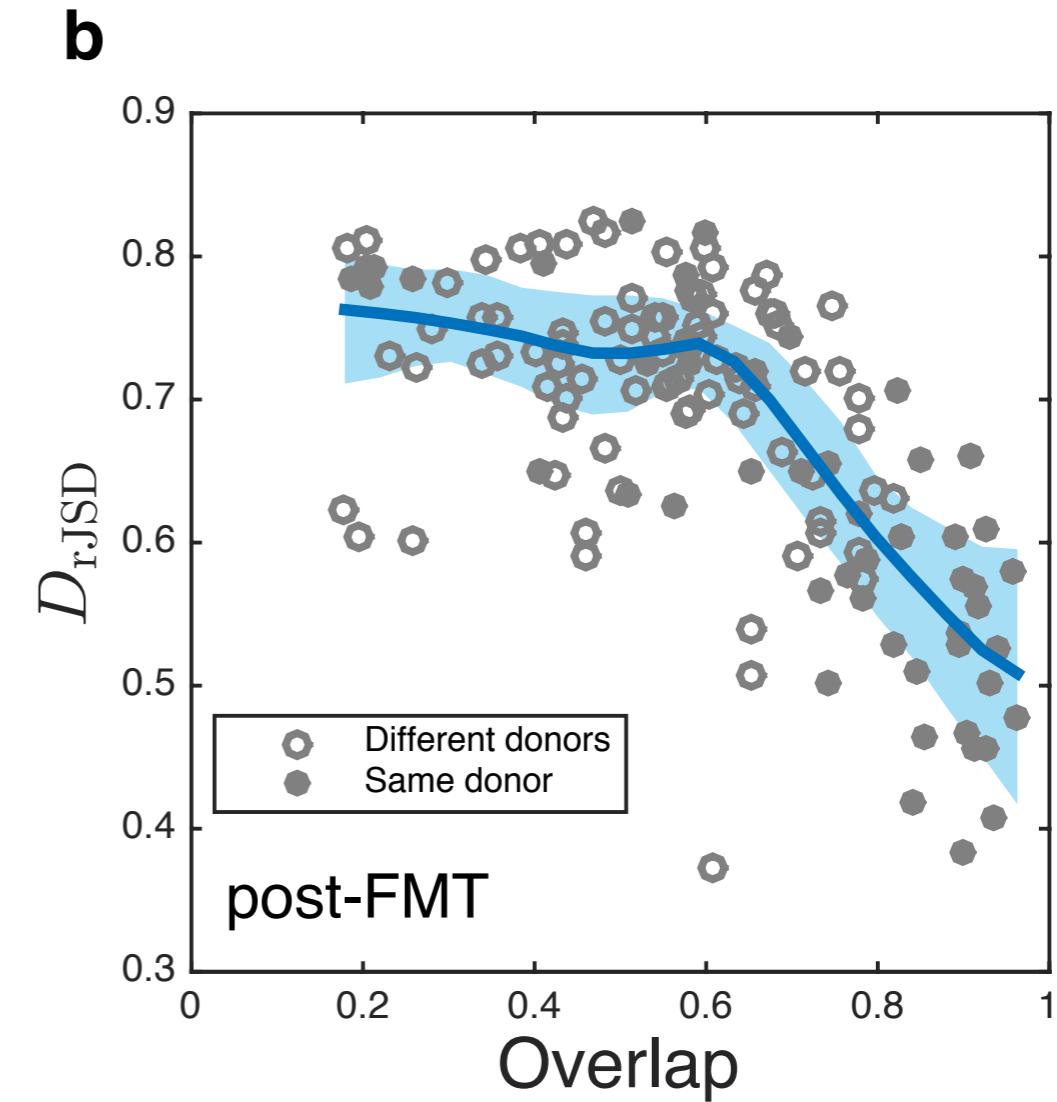
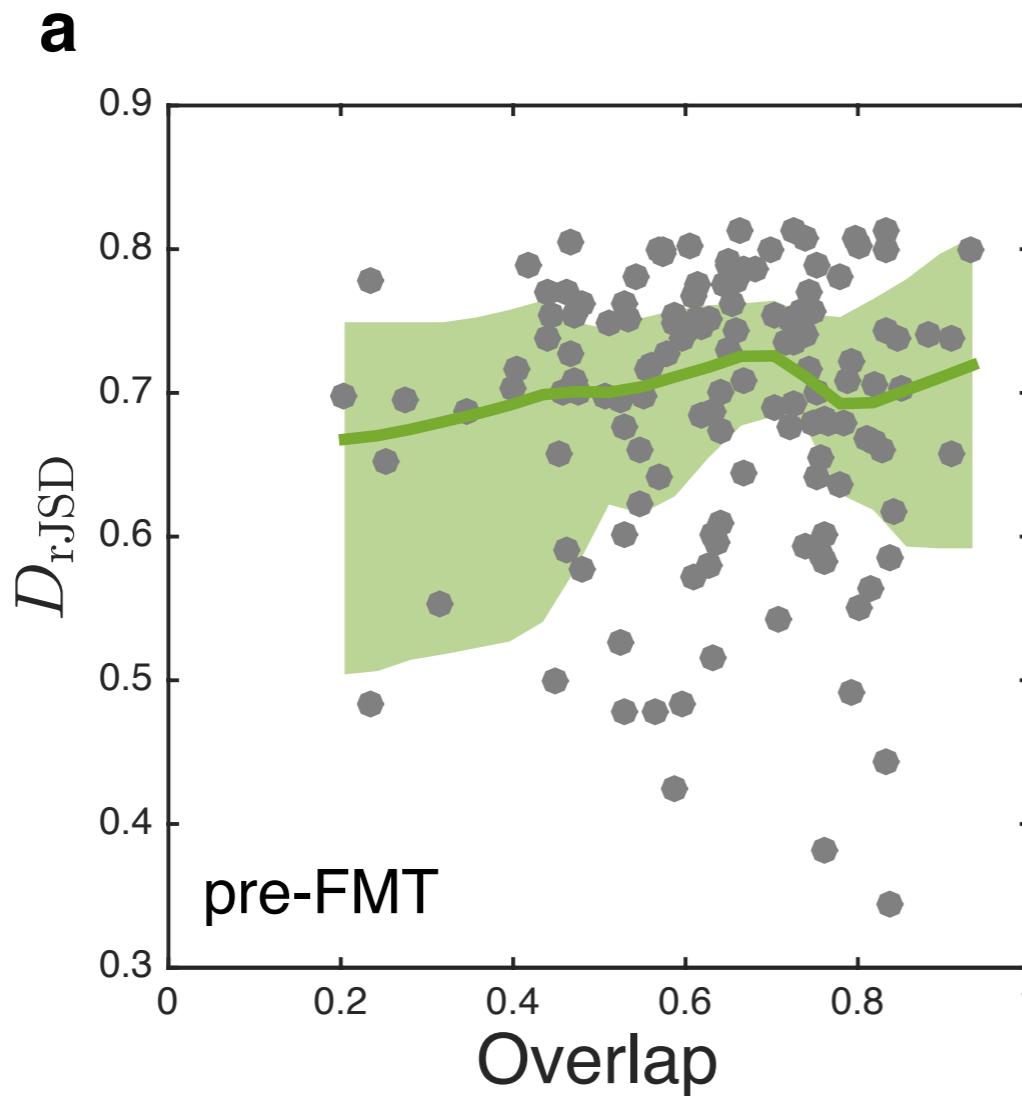
The negative slope of DOC is most significantly observed in samples from gut and mouth and least observed in samples from skin.

C. diff Infection (CDI) and Fecal Microbiota Transplantation (FMT)



DOC analysis: cross-sectional data (Diseased vs. Healthy)

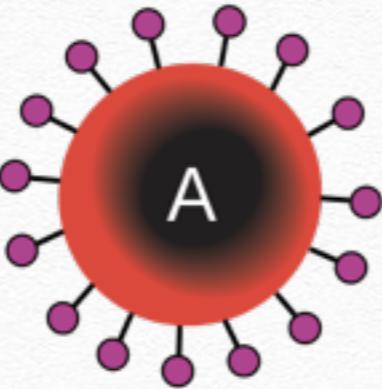
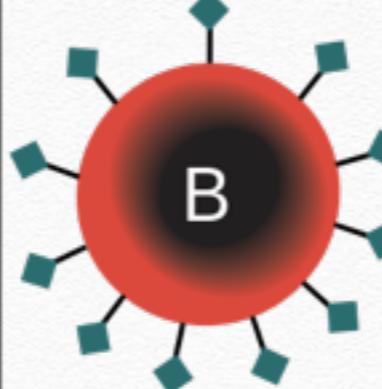
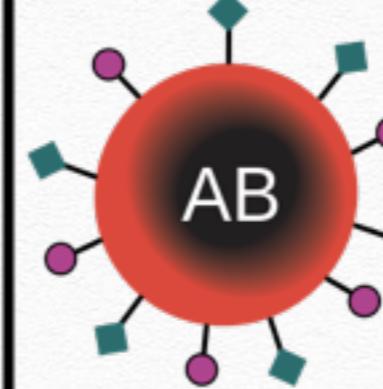
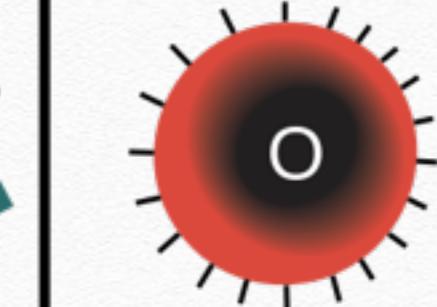
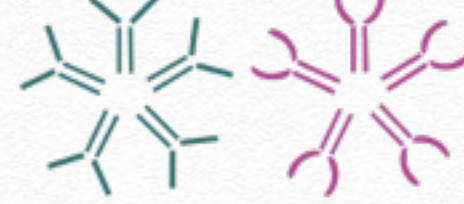
$M=17$ subjects in a clinical trial



All healthy microbiota are alike;
each unhealthy microbiota is unhealthy in its own way.

II. Origins and Control of Enterotypes

Blood type

	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in Plasma			None	
Antigens in Red Blood Cell				None

Enterotype

ARTICLE

doi:10.1038/nature09944

Enterotypes of the human gut microbiome

Manimozhiyan Arumugam^{1*}, Jeroen Raes^{1,2*}, Eric Pelletier^{3,4,5}, Denis Le Paslier^{3,4,5}, Takuji Yamada¹, Daniel R. Mende¹, Gabriel R. Fernandes^{1,6}, Julien Tap^{1,7}, Thomas Bruls^{3,4,5}, Jean-Michel Batto⁷, Marcelo Bertalan⁸, Natalia Borruel⁹, Francesc Casellas⁹, Leyden Fernandez¹⁰, Laurent Gautier⁸, Torben Hansen^{11,12}, Masahira Hattori¹³, Tetsuya Hayashi¹⁴, Michiel Kleerebezem¹⁵, Ken Kurokawa¹⁶, Marion Leclerc⁷, Florence Levenez⁷, Chaysavanh Manichanh⁹, H. Bjørn Nielsen⁸, Trine Nielsen¹¹, Nicolas Pons⁷, Julie Poulain³, Junjie Qin¹⁷, Thomas Sicheritz-Ponten^{8,18}, Sebastian Tims¹⁵, David Torrents^{10,19}, Edgardo Ugarte³, Erwin G. Zoetendal¹⁵, Jun Wang^{17,20}, Francisco Guarner⁹, Oluf Pedersen^{11,21,22,23}, Willem M. de Vos^{15,24}, Søren Brunak⁸, Joel Doré⁷, MetaHIT Consortium†, Jean Weissenbach^{3,4,5}, S. Dusko Ehrlich⁷ & Peer Bork^{1,25}

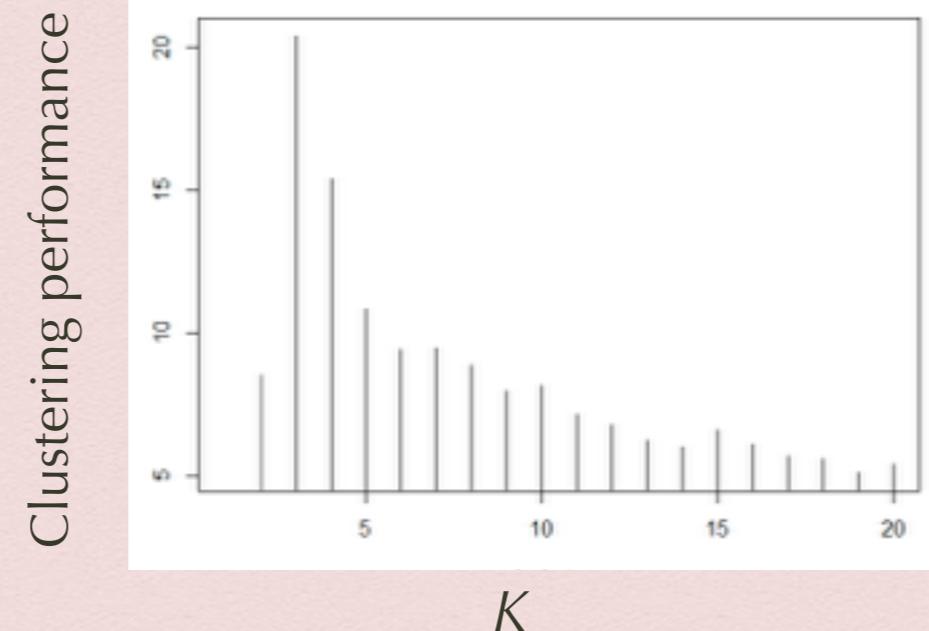
Our knowledge of species and functional composition of the human gut microbiome is rapidly increasing, but it is still based on very few cohorts and little is known about variation across the world. By combining 22 newly sequenced faecal metagenomes of individuals from four countries with previously published data sets, here we identify three robust clusters (referred to as enterotypes hereafter) that are not nation or continent specific. We also confirmed the enterotypes in two published, larger cohorts, indicating that intestinal microbiota variation is generally stratified, not continuous. This indicates further the existence of a limited number of well-balanced host-microbial symbiotic states that might respond differently to diet and drug intake. The enterotypes are mostly driven by species composition, but abundant molecular functions are not necessarily provided by abundant species, highlighting the importance of a functional analysis to understand microbial communities. Although individual host properties such as body mass index, age, or gender cannot explain the observed enterotypes, data-driven marker genes or functional modules can be identified for each of these host properties. For example, twelve genes significantly correlate with age and three functional modules with the body mass index, hinting at a diagnostic potential of microbial markers.

Enterotype

Data



Cluster analysis

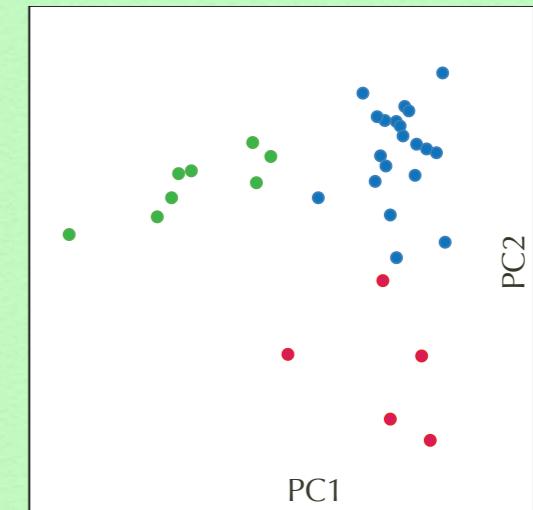


We chose the number of clusters by maximizing

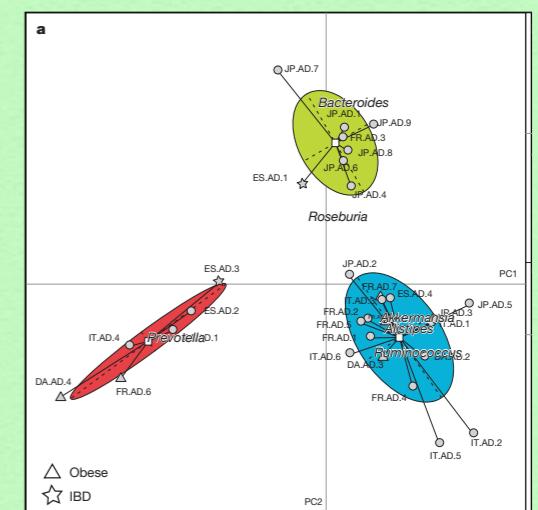
- * Calinski-Harabasz (CH) Index
- * Prediction Strength (PS)
- * Silhouette Index (SI)

Ordination

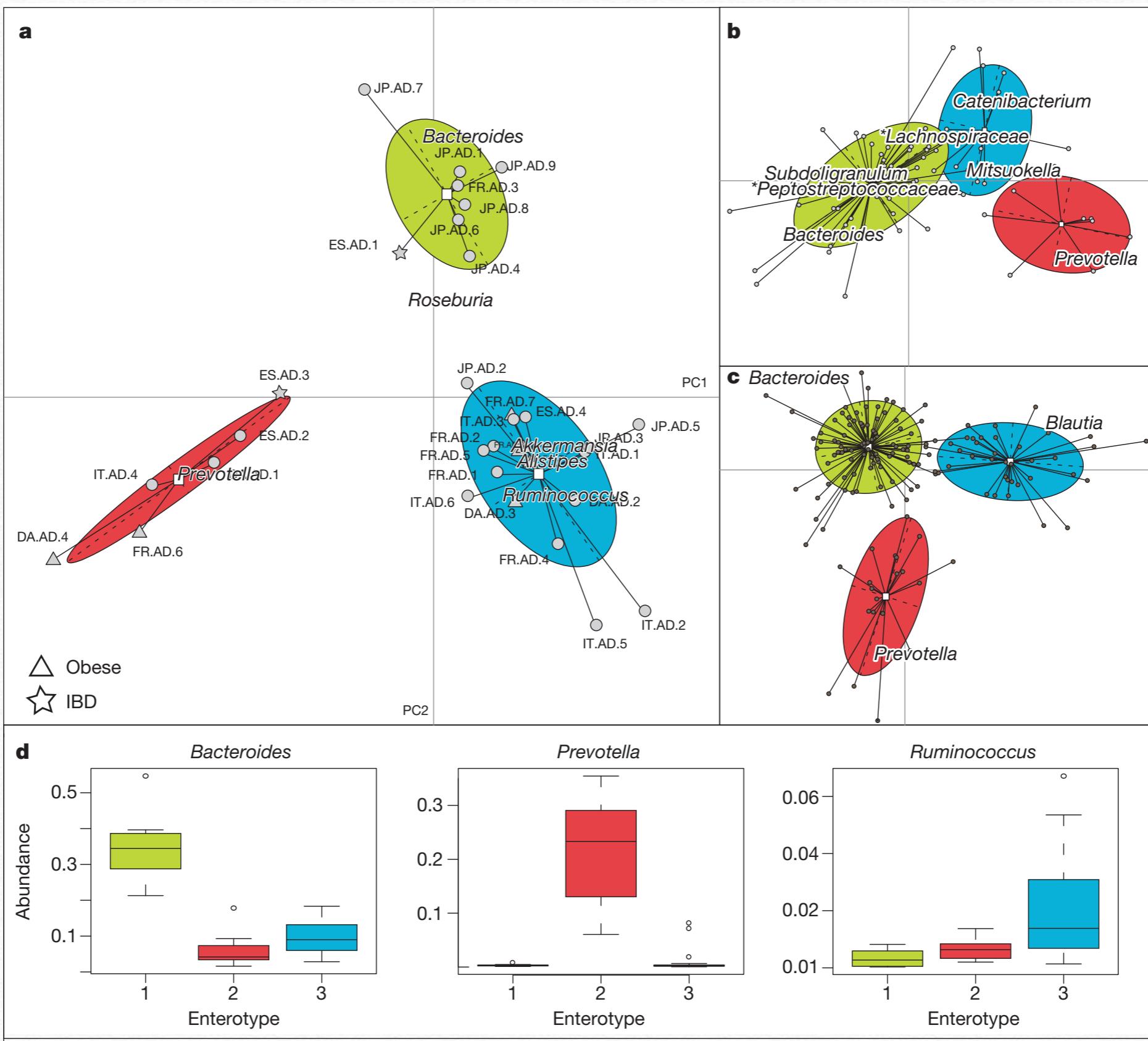
Principle Coordinate Analysis



Between Class Analysis



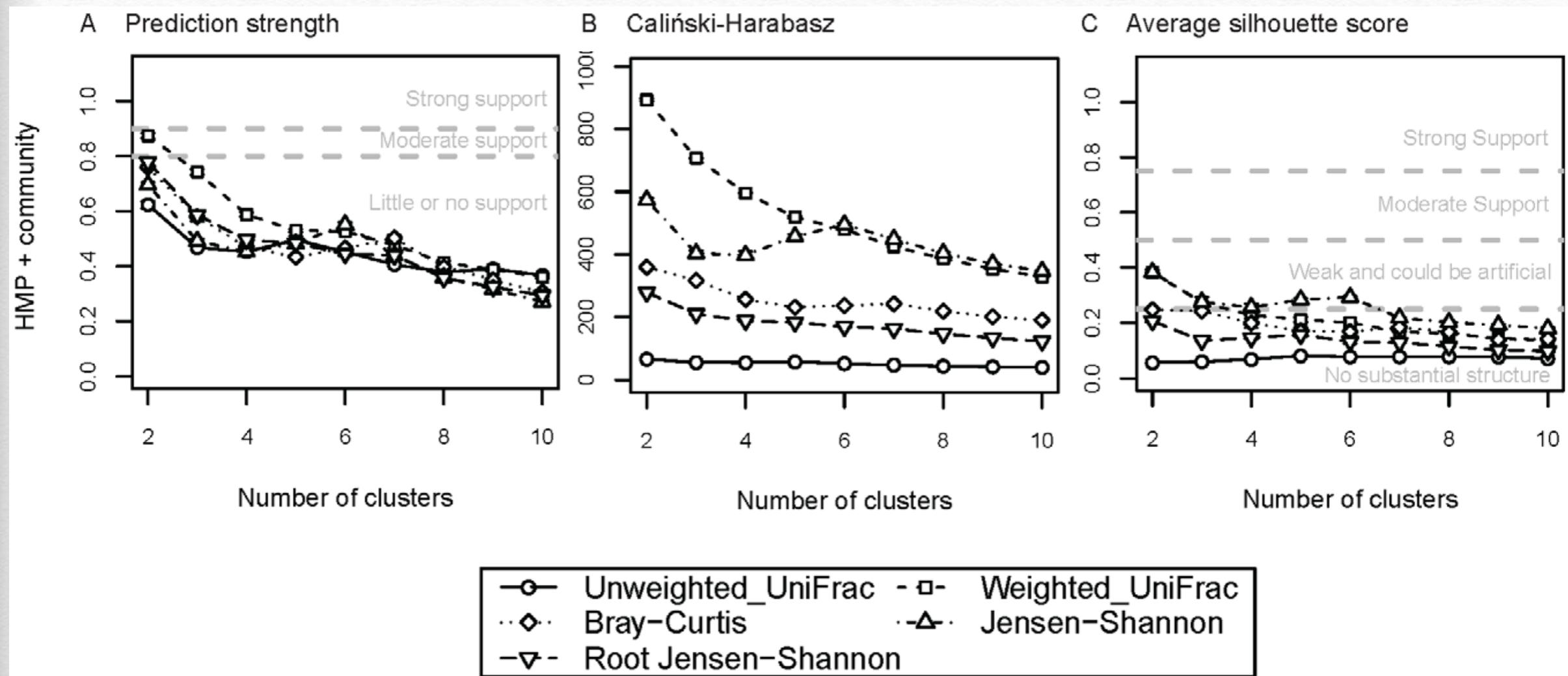
M=33



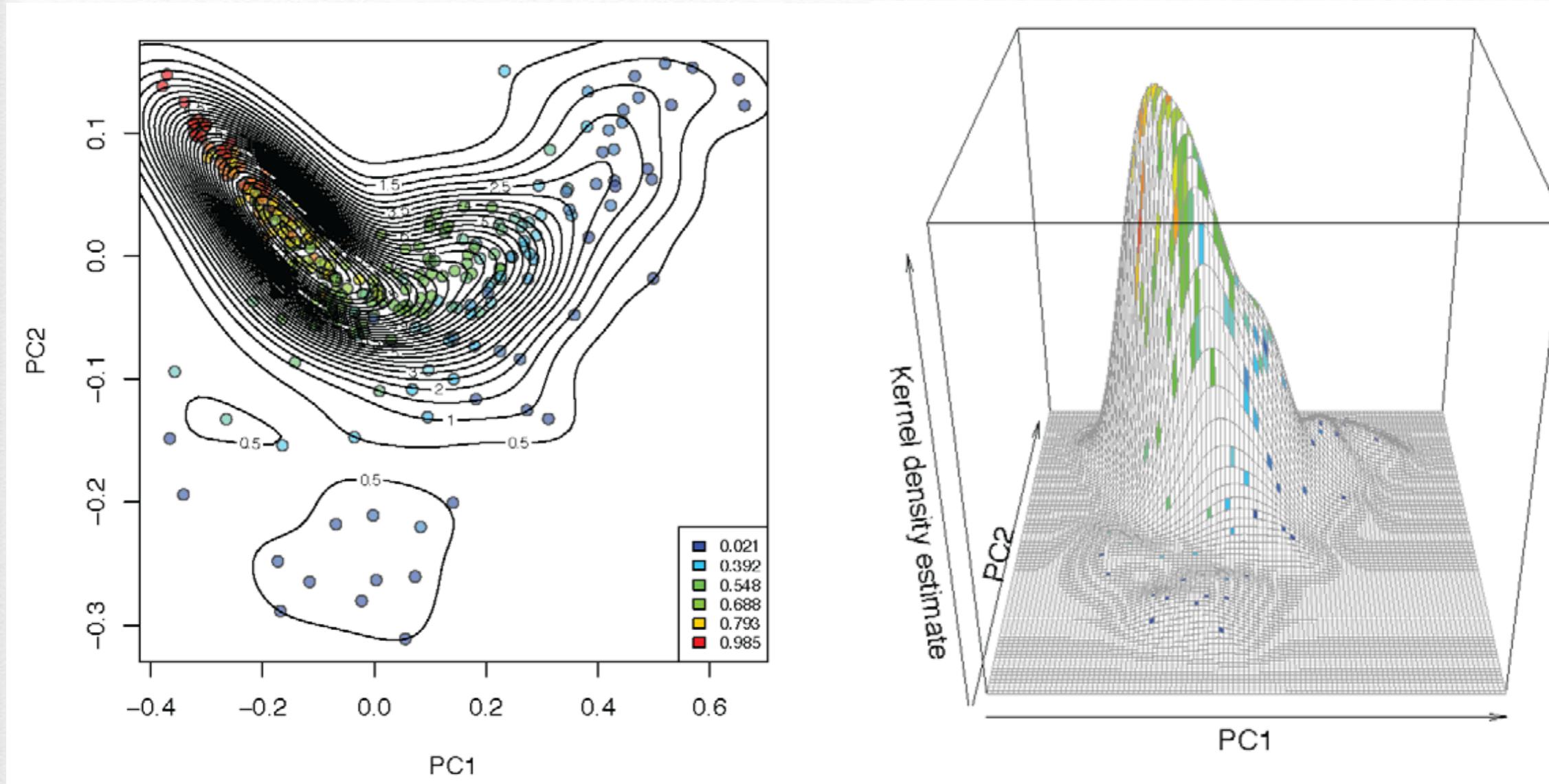
M=85

M=154

Categorization of the Gut Microbiota: Distinct clusters or Continuous gradients?



Categorization of the Gut Microbiota: Distinct clusters or Continuous gradients?



Human Microbiome Project **M=190**

Categorization of the Gut Microbiota: Distinct clusters or Continuous gradients?

Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes

Gary D. Wu,^{1*} Jun Chen,^{2,3} Christian Hoffmann,^{4,5} Kyle Bittinger,⁴ Ying-Yu Chen,¹ Sue A. Keilbaugh,¹ Meenakshi Bewtra,^{1,2} Dan Knights,⁶ William A. Walters,⁷ Rob Knight,^{8,9} Rohini Sinha,⁴ Erin Gilroy,² Kernika Gupta,¹⁰ Robert Baldassano,¹⁰ Lisa Nessel,² Hongzhe Li,^{2,3} Frederic D. Bushman,^{4*} James D. Lewis^{1,2,3*}

LETTER

doi:10.1038/nature13178

Dynamics and associations of microbial community types across the human body

Tao Ding¹ & Patrick D. Schloss¹

Zhou et al. *Genome Biology* 2014, **15**:R66
http://genomebiology.com/2014/15/5/R66



RESEARCH

Open Access

Exploration of bacterial community classes in major human habitats

Yanjiao Zhou^{1,4}, Kathie A Mihindukulasuriya¹, Hongyu Gao², Patricio S La Rosa³, Kristine M Wylie^{1,4}, John C Martin¹, Karthik Kota¹, William D Shannon³, Makedonka Mitreva¹, Erica Sodergren^{1,5} and George M Weinstock^{1,5*}

OPEN ACCESS Freely available online

PLOS COMPUTATIONAL BIOLOGY

A Guide to Enterotypes across the Human Body: Meta-Analysis of Microbial Community Structures in Human Microbiome Datasets

Omry Koren^{1,9}, Dan Knights^{2,9}, Antonio Gonzalez^{2,9}, Levi Waldron^{3,4}, Nicola Segata³, Rob Knight^{5,6}, Curtis Huttenhower³, Ruth E. Ley^{1*}

COMMENT

Categorization of the gut microbiota: enterotypes or gradients?

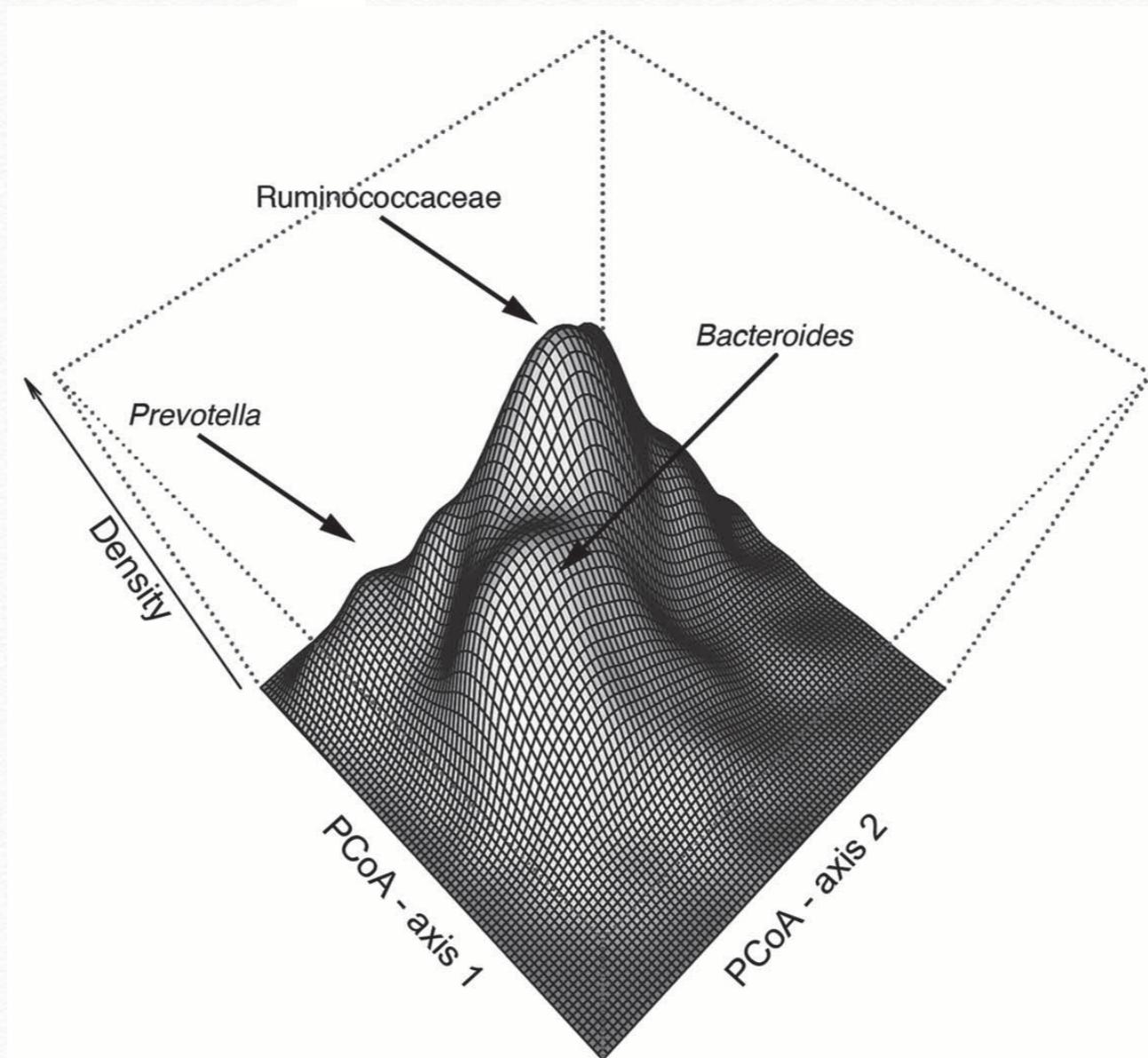
Grouping the microbiota of individual subjects into compositional categories, or enterotypes, based on the dominance of certain genera may have oversimplified a complex situation.

Cell Host & Microbe
Forum

Rethinking “Enterotypes”

Dan Knights,^{1,2} Tonya L. Ward,² Christopher E. McKinlay,^{1,2} Hannah Miller,¹ Antonio Gonzalez,³ Daniel McDonald,³ and Rob Knight^{3,4,5,6,*}

Categorization of the Gut Microbiota: Distinct clusters or Continuous gradients?



Belgian Flemish Gut Flora Project (FGFP)

M=1,106

Falony et al., Science (2016)

Categorization of the Gut Microbiota: Distinct clusters or Continuous gradients?

Enterotypes:

- should NOT be seen as discrete clusters
- densely populated areas in a multi-dimensional space of community composition

Questions:

- What's the origin of enterotypes?
- How to control enterotypes?

Generalized Lotka-Volterra (GLV) model

$$\dot{x}_i(t) = r_i x_i(t) + x_i(t) \sum_{j=1}^n a_{ij} x_j(t) \quad i = 1, \dots, n$$

$$\dot{x}(t) = \text{diag}(x(t)) (r + Ax(t))$$

$\mathbf{r} = [r_1, \dots, r_n]^\top$ is a column vector of the growth rates

$\mathbf{A} = (a_{ij})$ is the inter-species interaction matrix

diag generates a diagonal matrix from a vector.

Generalized Lotka-Volterra (GLV) model

$$\dot{x}(t) = \text{diag}(x(t)) (r + Ax(t))$$

$$x = \begin{bmatrix} x_1 \\ \vdots \\ x_n \end{bmatrix}$$

↓ add a new species

$$\dot{z}(t) = \text{diag}(z(t)) (g + Fz(t))$$

$$z = \begin{bmatrix} z_1 \\ \vdots \\ z_n \\ \hline z_{n+1} \end{bmatrix}$$

$$g = \begin{bmatrix} r_1 \\ \vdots \\ r_n \\ \hline s \end{bmatrix}$$

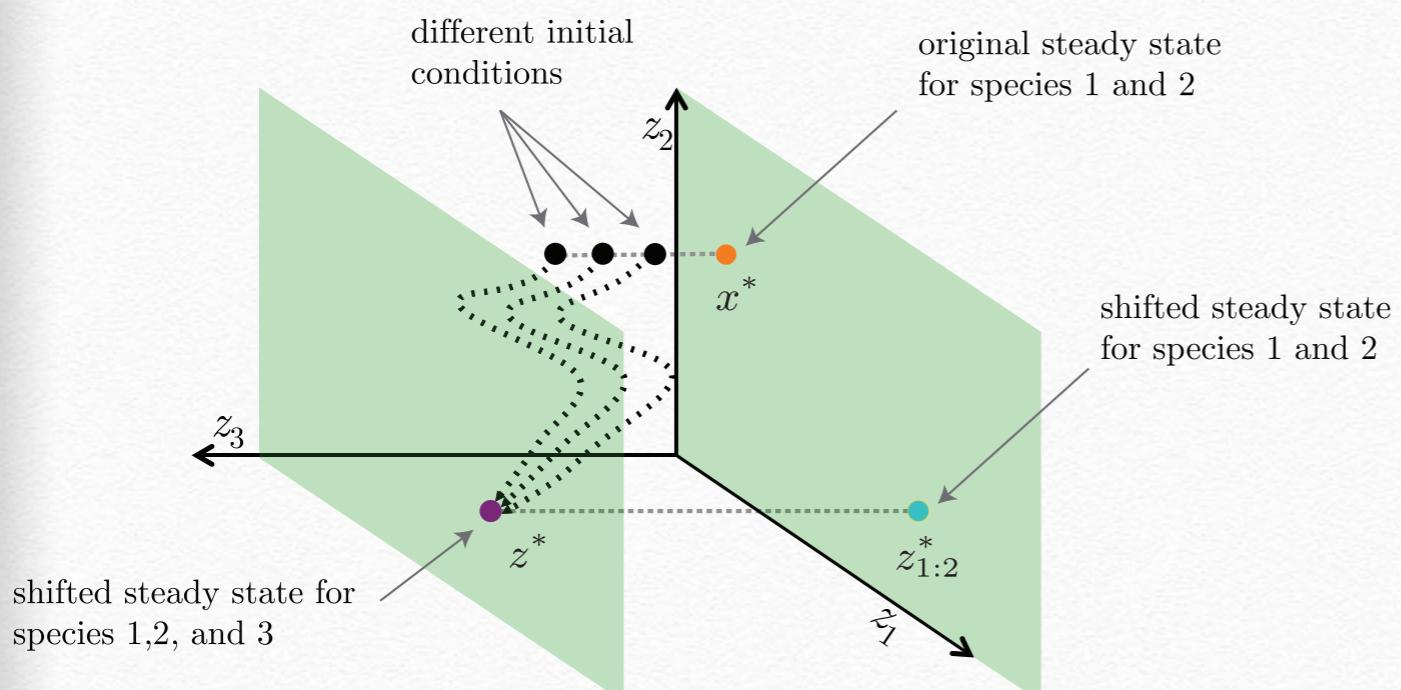
$$F = \left[\begin{array}{c|c} A & \begin{matrix} b_1 \\ \vdots \\ b_n \end{matrix} \\ \hline c_1 & \cdots & c_n & d \end{array} \right]$$

Steady-state shift in GLV model

$$\dot{z}(t) = \text{diag}(z(t)) (g + F z(t))$$

$$g = \begin{bmatrix} r_1 \\ \vdots \\ r_n \\ \hline s \end{bmatrix}$$

$$F = \left[\begin{array}{c|c} A & b_1 \\ \hline c_1 & \cdots & c_n & d \end{array} \right]$$



$$z_{1:n}^* - x^* = -z_{n+1}^* A^{-1} b$$

The shift of the steady state is proportional to the interaction strengths between the newly introduced species and the previously existing ones.

Random Inter-species Interaction Matrix

$$A = N H \circ G s$$

$$a_{ii} = -1$$

N: Nominal Component

H: Interaction Heterogeneity (diagonal)

G: Topology (takes values in {0,1})

s: Scaling Factor (a constant)

$$A = \begin{bmatrix} -1 & 0.04 & 0.08 & -0.04 \\ 7 & -1 & 0.06 & 0 \\ -1 & 0 & -1 & 0 \\ 0 & 0 & 0.08 & -1 \end{bmatrix}$$

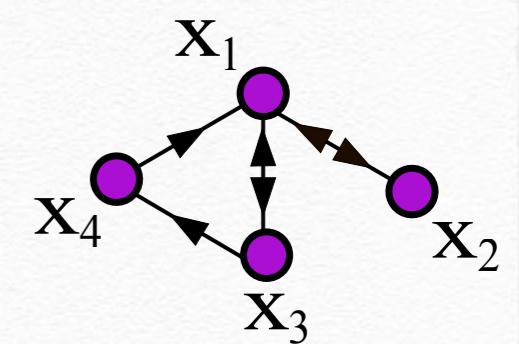
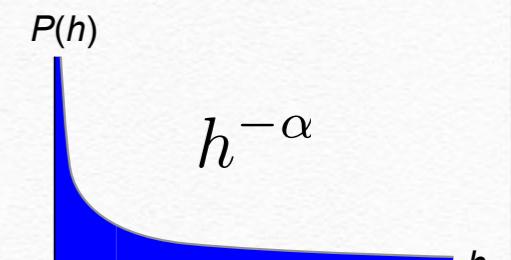
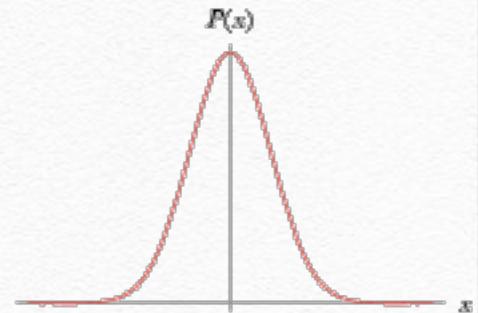
↓
strongly
interacting
species (SIS)

$$N = \begin{bmatrix} 0 & 0.2 & 0.4 & -0.1 \\ 0.7 & 0 & 0.3 & 0.4 \\ -0.1 & 0.7 & 0 & 0.1 \\ -0.3 & -0.2 & 0.4 & 0 \end{bmatrix}$$

$$H = \begin{bmatrix} 10 & 0 & 0 & 0 \\ 0 & 0.1 & 0 & 0 \\ 0 & 0 & 0.1 & 0 \\ 0 & 0 & 0 & 0.4 \end{bmatrix}$$

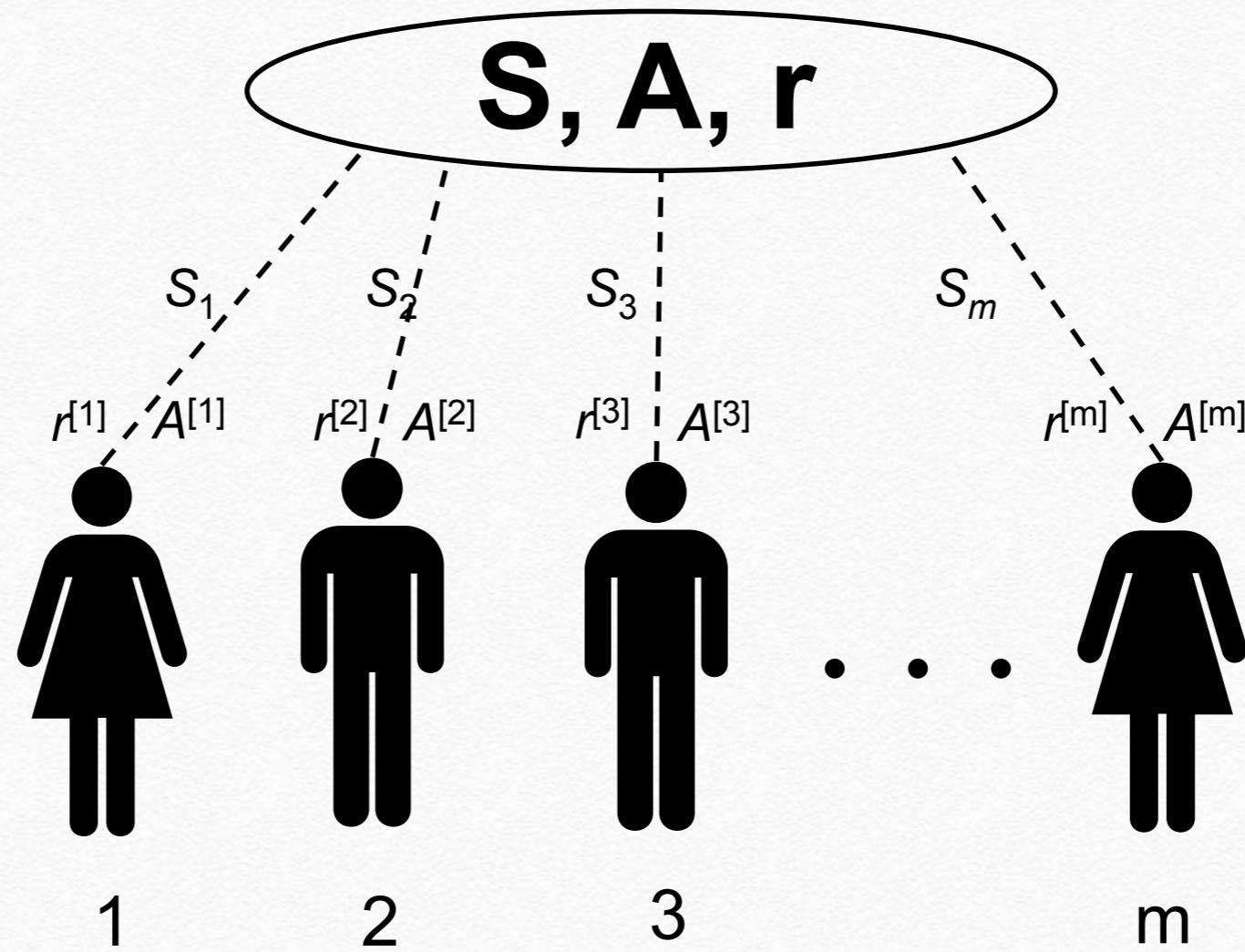
$$G = \begin{bmatrix} 0 & 1 & 1 & 1 \\ 1 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix}$$

$$s = 1$$



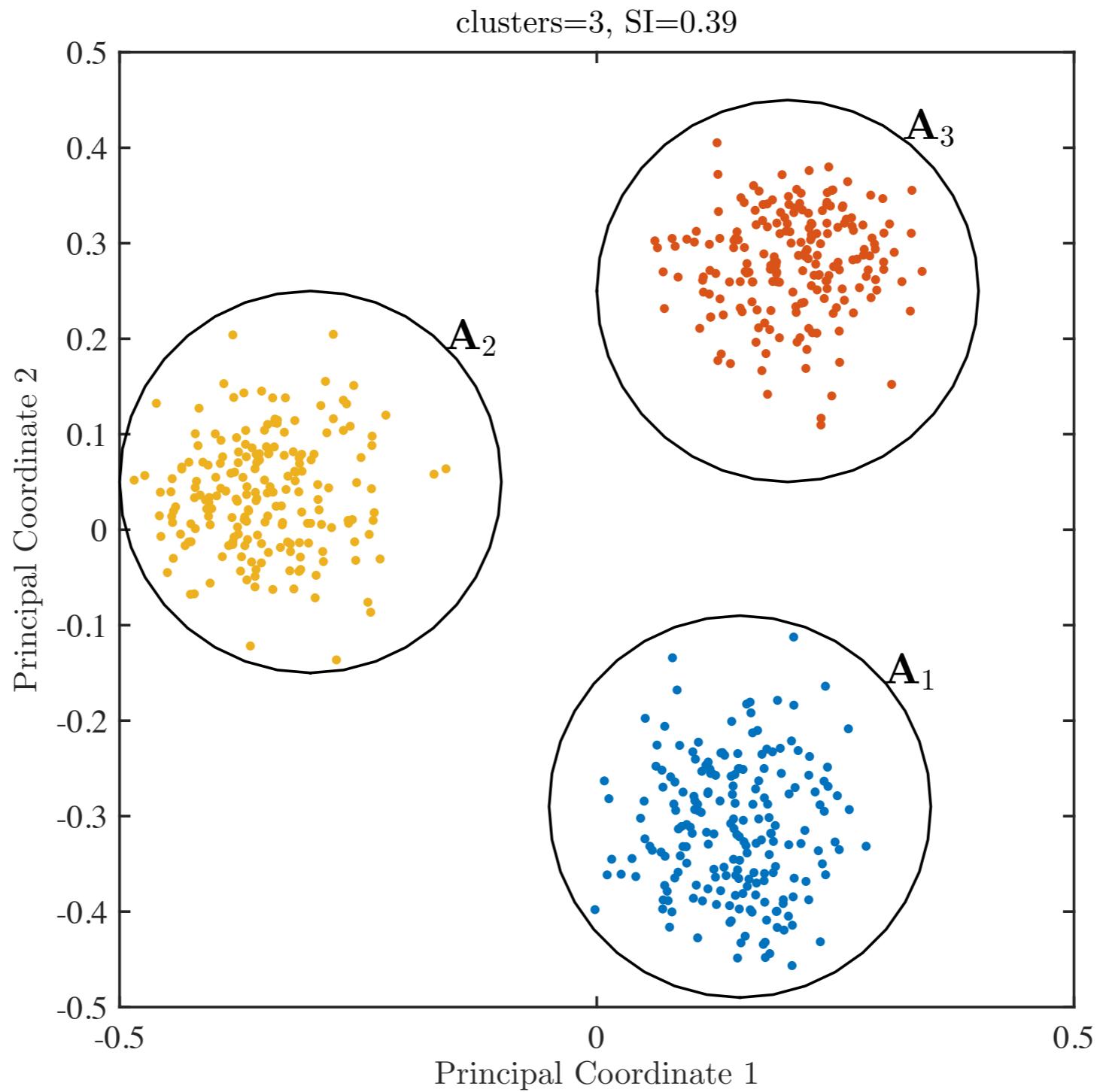
species pool: $S = \{1, 2, \dots, n\}$

universal dynamics: $\dot{x}(t) = \text{diag}(x(t)) (r + Ax(t))$



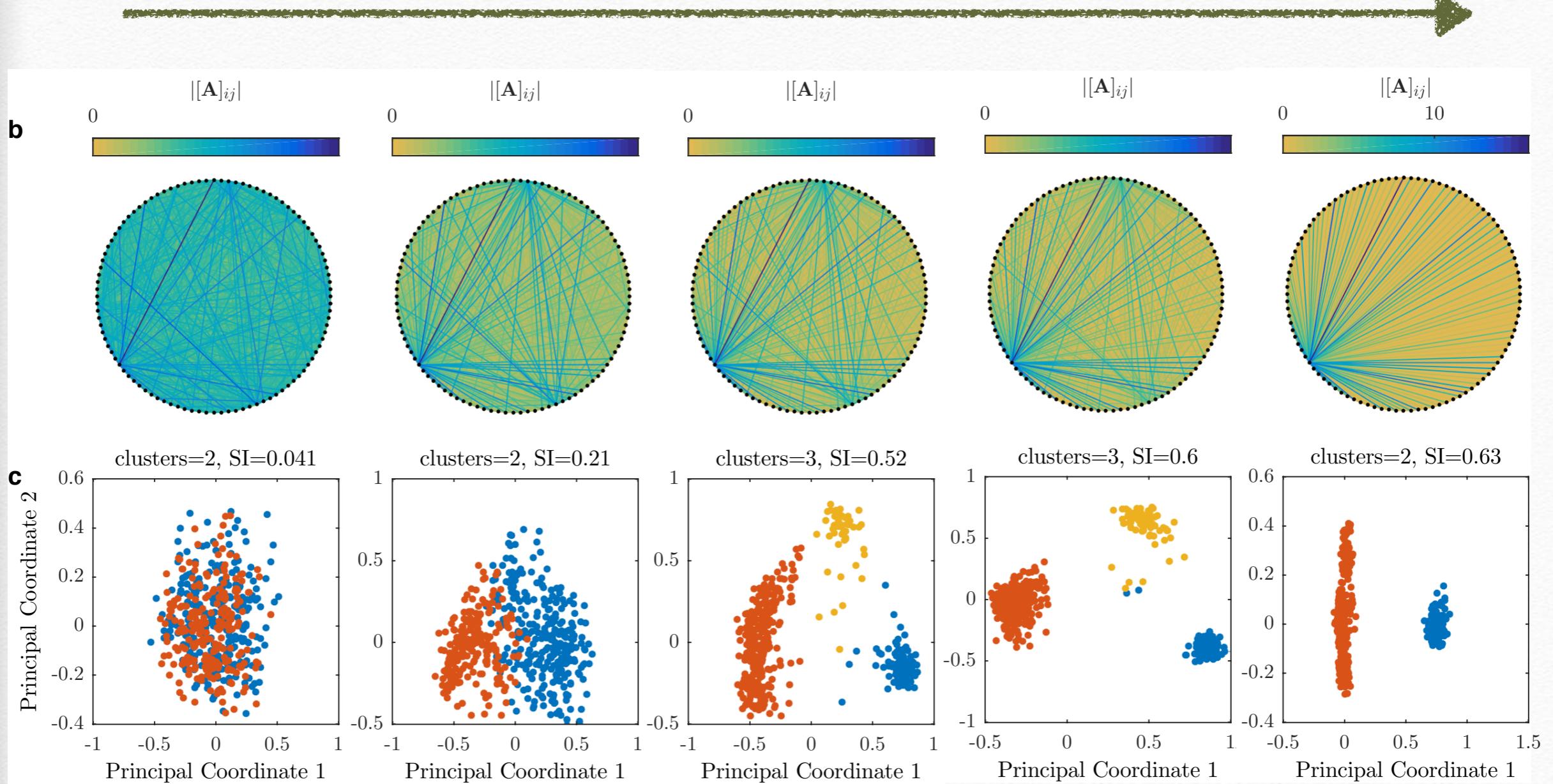
local communities (subjects)

$$\dot{x}^{[\nu]}(t) = \text{diag}(x^{[\nu]}(t)) (r^{[\nu]} + A^{[\nu]} x^{[\nu]}(t)) \quad \nu = 1, \dots, m$$

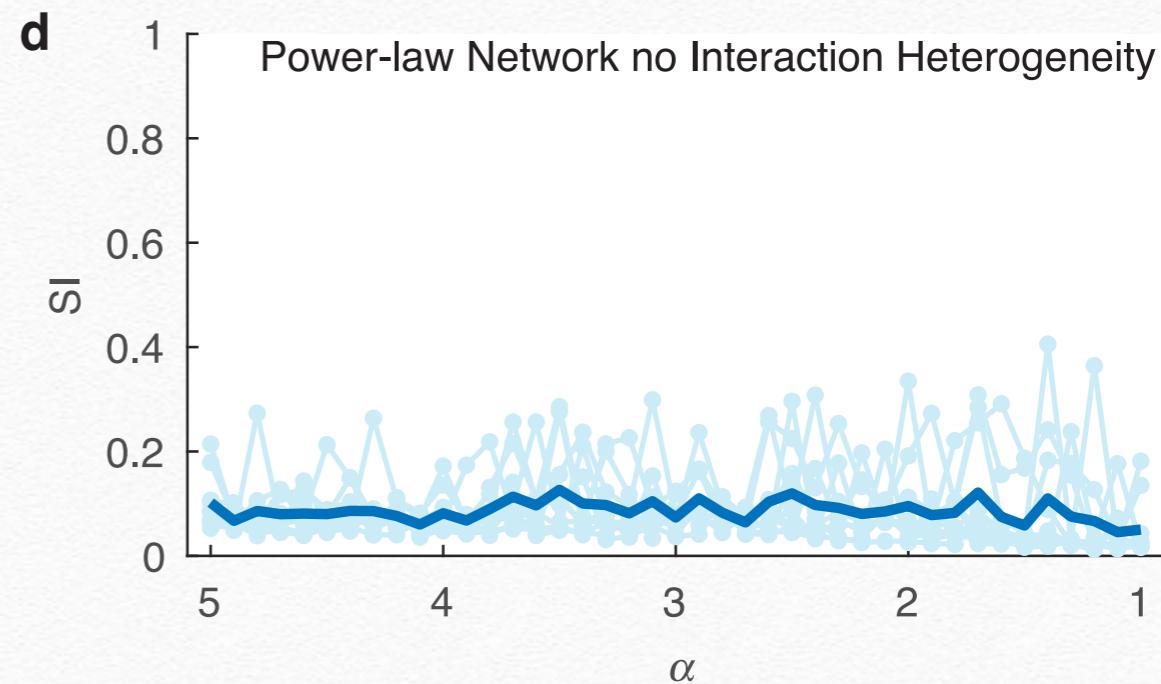
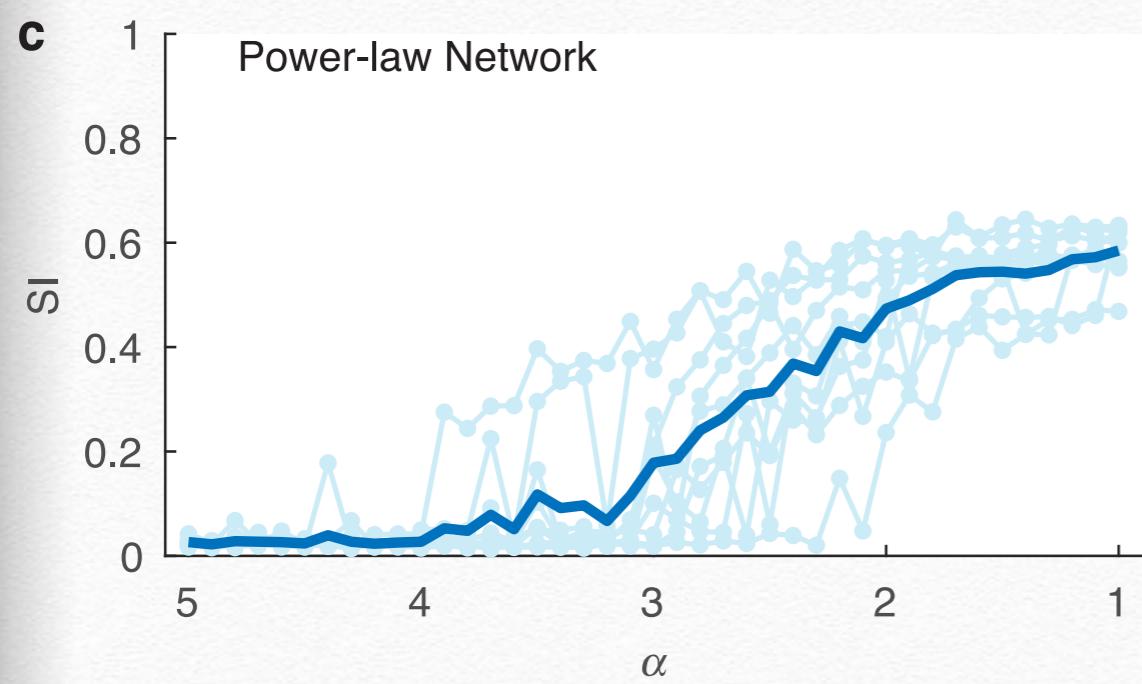
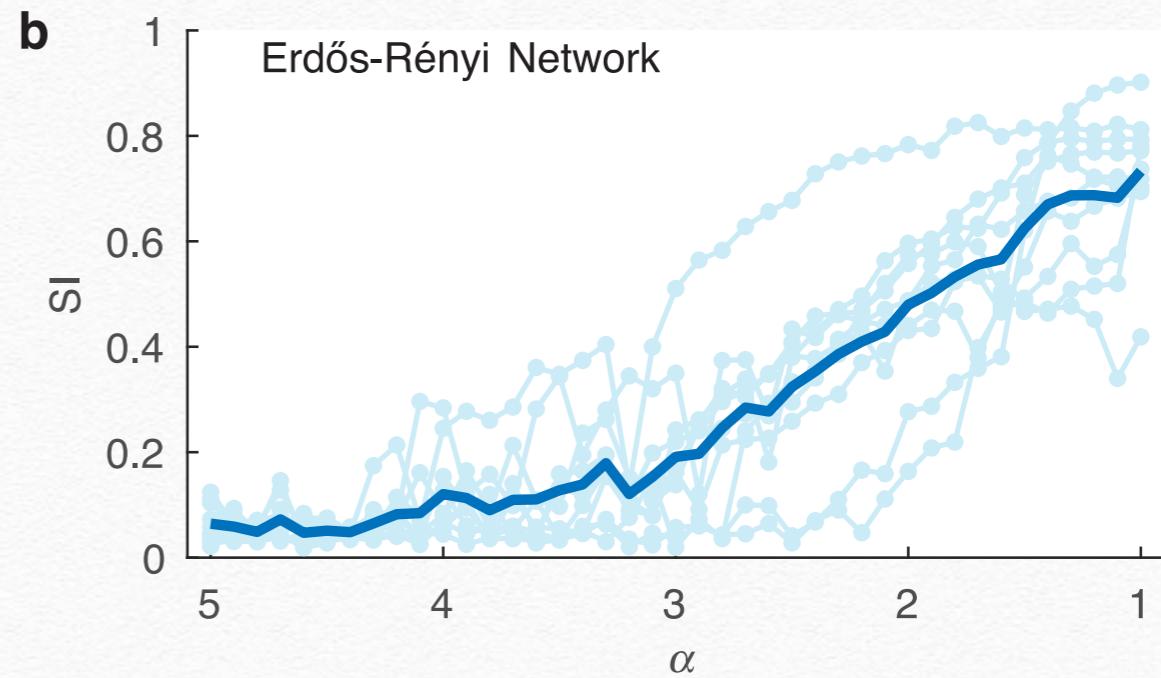
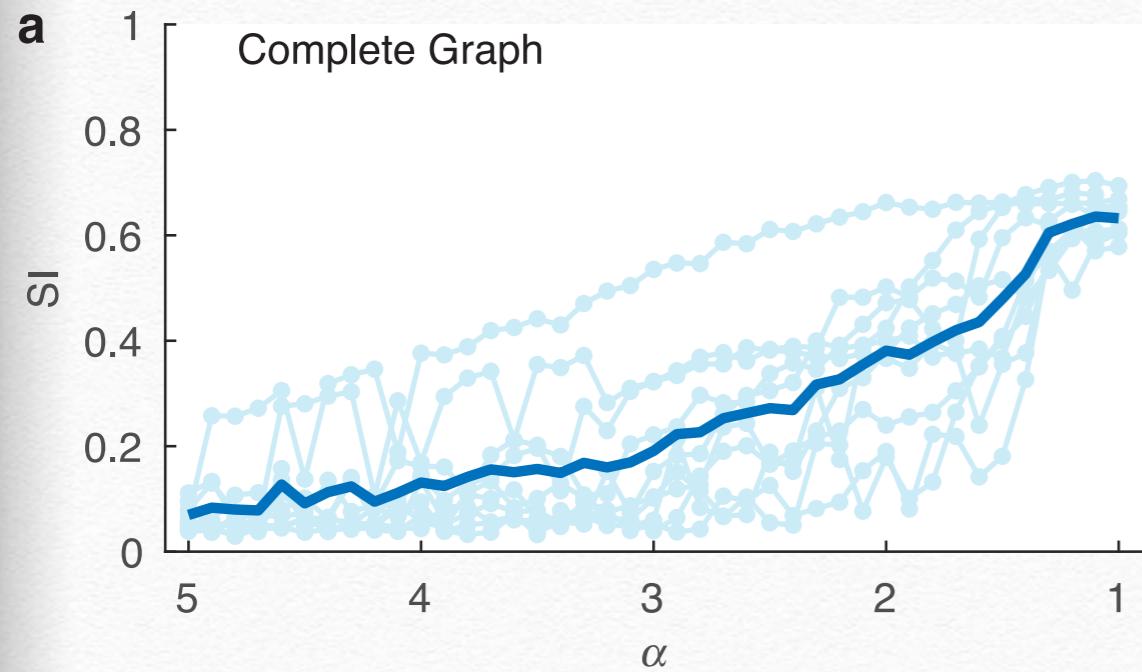


**Group Dynamics will cause strong clustering of
steady states —> distinct clusters!**

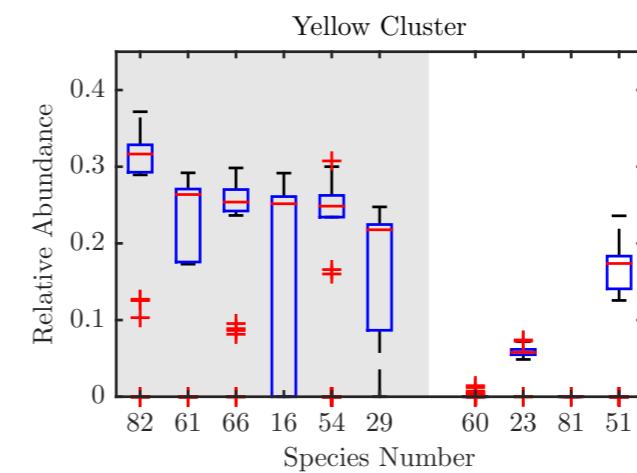
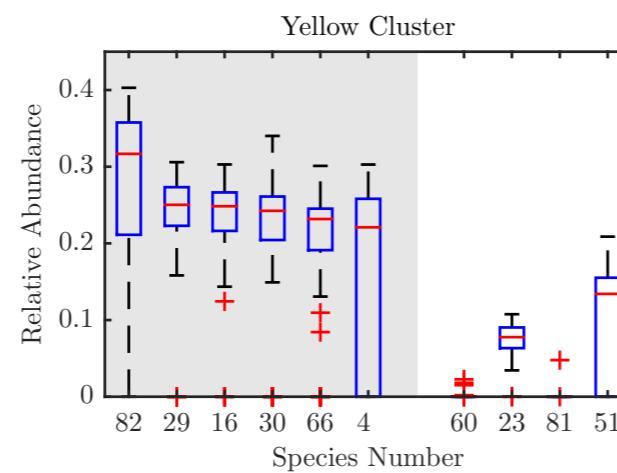
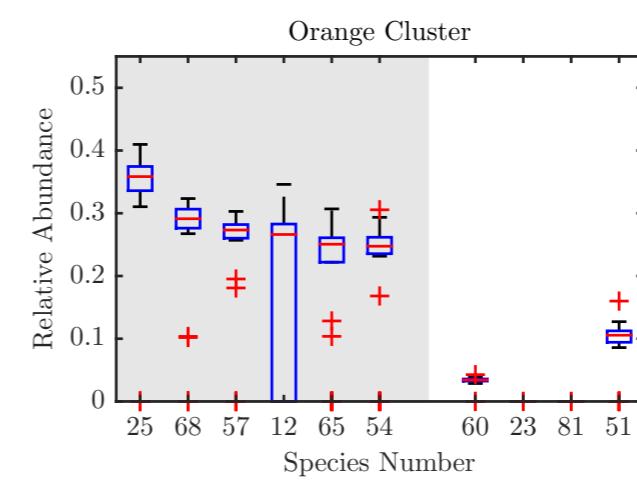
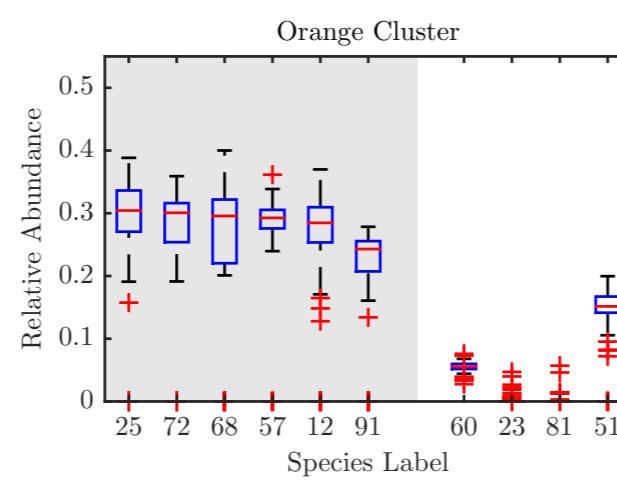
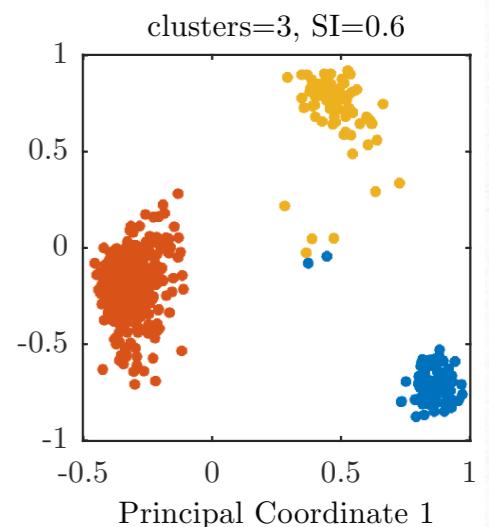
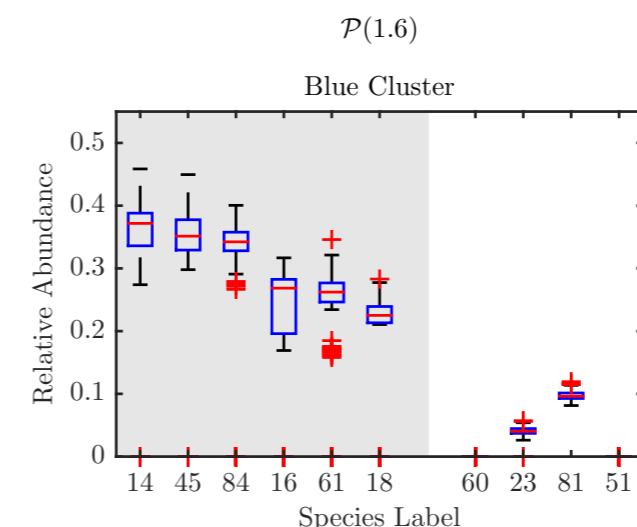
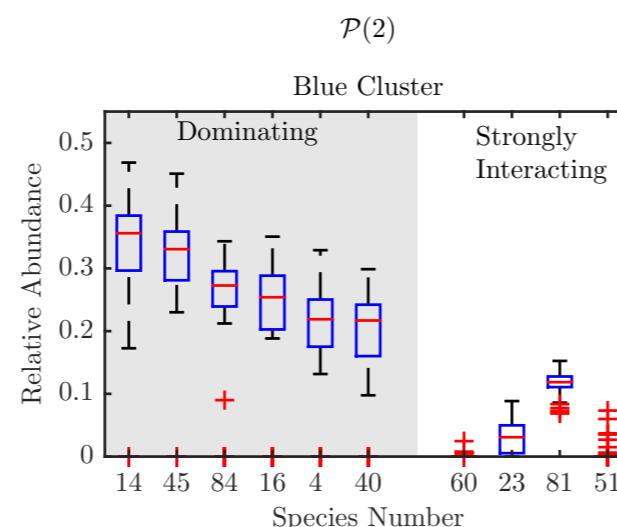
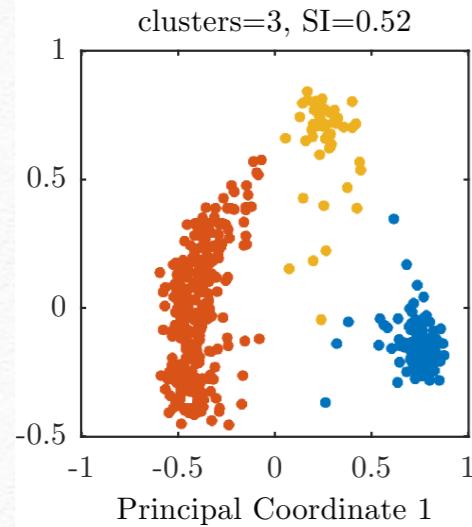
increase the interaction strength heterogeneity



Enterotypes can naturally emerge due to the presence of SIs!

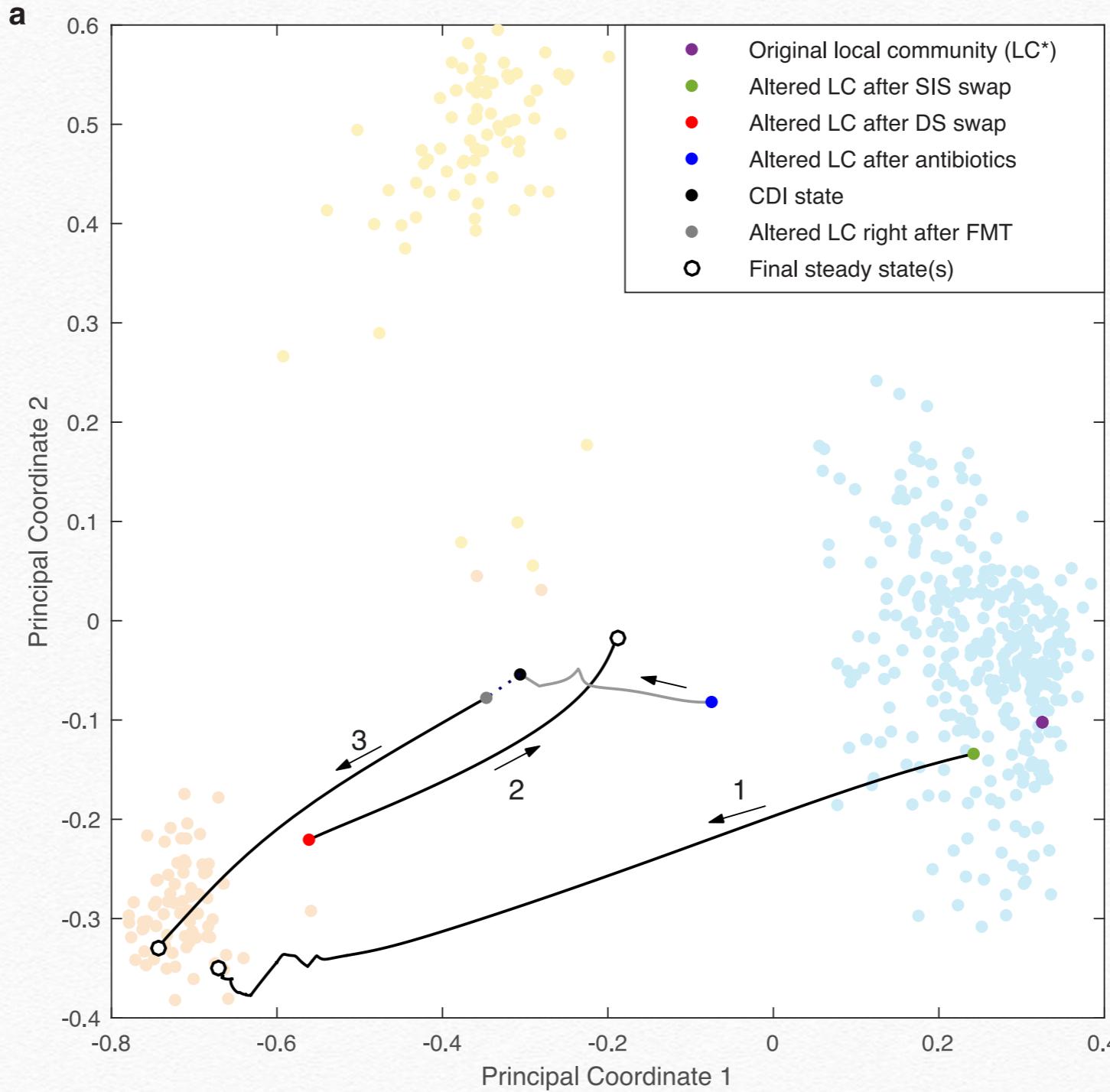


**Enterotypes can naturally emerge due to the presence of SISs,
regardless of the network topology!**



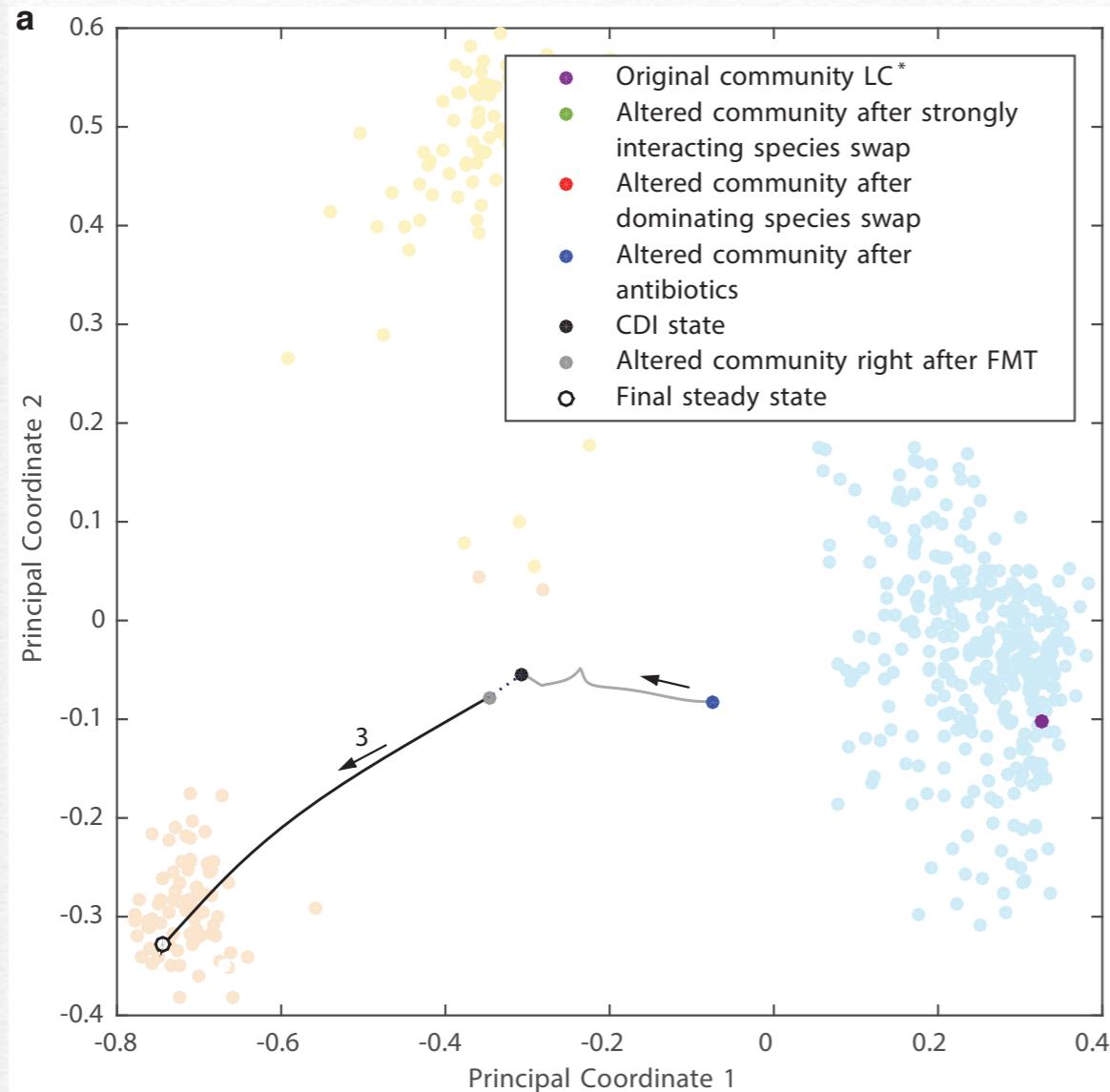
Each enterotype is associated with a unique set of SIs, which are not necessarily most abundant species!

Controlling Enterotypes

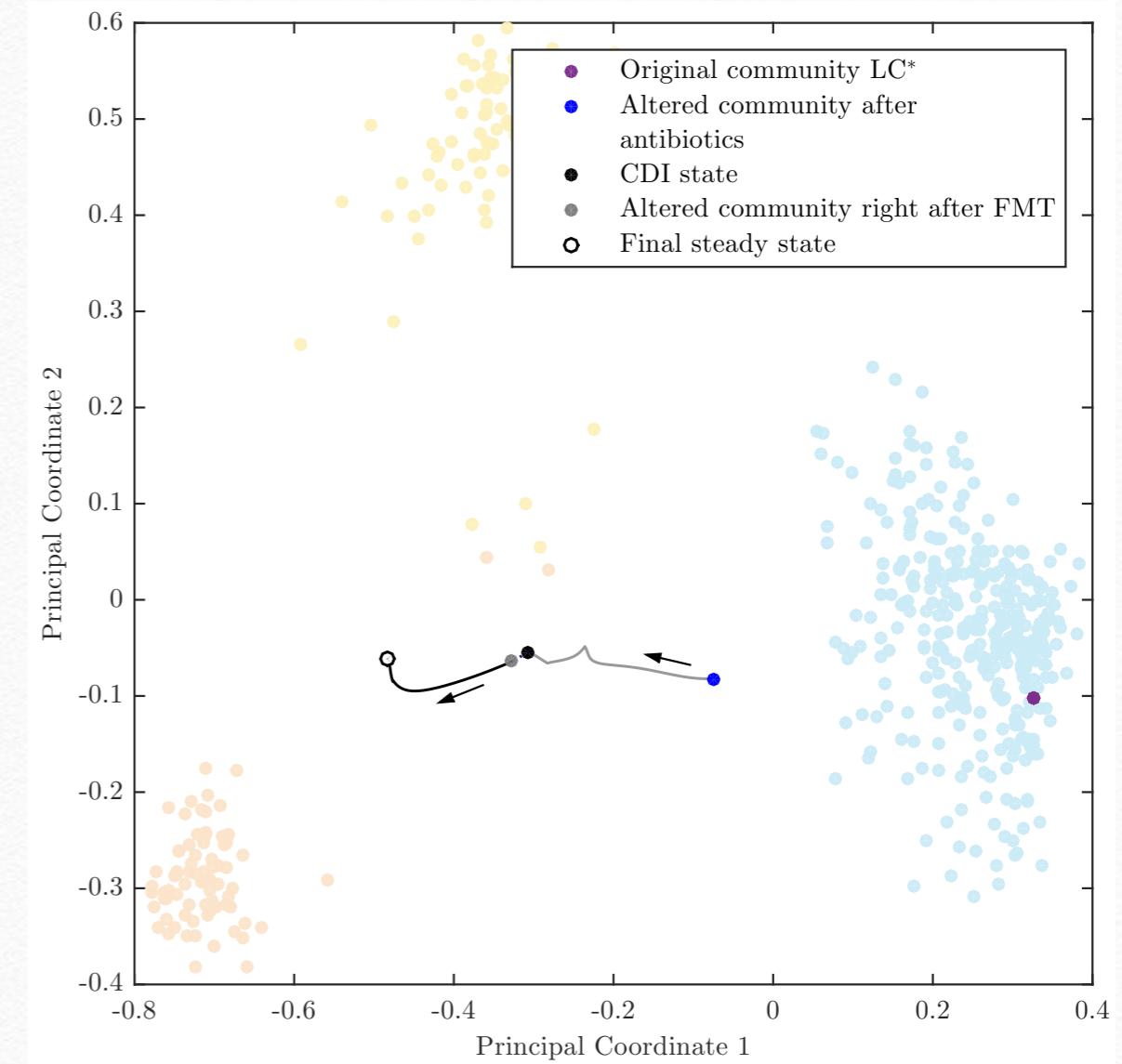


Strongly interacting species, rather than the most abundant species, drive the microbiota to desired enterotype!

Theoretical Justification of FMT



full transplantation



without transplanting SISs

Strongly interacting species are crucial for the success of FMT!

RESEARCH ARTICLE

On the Origins and Control of Community Types in the Human Microbiome

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Data Availability Statement: The data used in this study is publicly available from the metagenomics analysis server MG-RAST4457768.3-4459735.3 and can also be accessed from Qita (<http://qita.ucsd.edu>) under study ID 550. The processed data was downloaded as biom file "67_oto_table.biom" (2014-11-17 13:18:50.591389).

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Abstract

Microbiome-based stratification of healthy individuals into compositional categories, referred to as “enterotypes” or “community types”, holds promise for drastically improving personalized medicine. Despite this potential, the existence of community types and the degree of their distinctness have been highly debated. Here we adopted a dynamic systems approach and found that heterogeneity in the interspecific interactions or the presence of strongly interacting species is sufficient to explain community types, independent of the topology of the underlying ecological network. By controlling the presence or absence of these strongly interacting species we can steer the microbial ecosystem to any desired community type. This open-loop control strategy still holds even when the community types are not distinct but appear as dense regions within a continuous gradient. This finding can be used to develop viable therapeutic strategies for shifting the microbial composition to a healthy configuration.

Author Summary

We coexist with a vast number of microbes that live in and on our bodies, and play important roles in physiology and disease. Two interesting phenomena have been observed in the human microbiome. The first is the stratification of healthy individuals based on the relative abundances of their microbes, which holds promise for drastically improving personalized medicine. The second is the astounding success of fecal microbial transplantation in treating certain diseases related to disordered microbiomes. Surprisingly, both phenomena have not been analytically or quantitatively understood, despite a few early qualitative attempts. This work shows that through a dynamic systems and control theoretical approach the success of fecal microbial transplantation can be explained and that the microbiome-based stratification can be as simple as the existence of strongly interacting species.

LETTER

doi:10.1038/nature18301

Universality of human microbial dynamics

Amir Bashan¹, Travis E. Gibson¹, Jonathan Friedman², Vincent J. Carey¹, Scott T. Weiss¹, Elizabeth L. Hohmann³ & Yang-Yu Liu^{1,4*}

Human-associated microbial communities have a crucial role in determining our health and well-being^{1,2}, and this has led to the continuing development of microbiome-based therapies³ such as faecal microbiota transplantation^{4,5}. These microbial communities are very complex, dynamic⁶ and highly personalized ecosystems^{3,7}, exhibiting a high degree of inter-individual variability in both species assemblages⁸ and abundance profiles⁹. It is not known whether the underlying ecological dynamics of these communities, which can be parameterized by growth rates, and intra- and inter-species interactions in population dynamics models¹⁰, are largely host-independent (that is, universal) or host-specific. If the inter-individual variability reflects host-specific dynamics due to differences in host lifestyle¹¹, physiology¹² or genetics¹³, then generic microbiome manipulations may have unintended consequences, rendering them ineffective or even detrimental. Alternatively, microbial ecosystems of different subjects may exhibit universal dynamics, with the inter-individual variability mainly originating from differences in the sets of colonizing species^{7,14}. Here we develop a new computational method to characterize human microbial dynamics. By applying this method to cross-sectional data from two large-scale metagenomic studies—the Human Microbiome Project^{9,15} and the Student Microbiome Project¹⁶—we show that gut and mouth microbiomes display pronounced universal dynamics, whereas communities associated with certain skin sites are probably shaped by differences in the host environment. Notably, the universality of gut microbial dynamics is not observed in subjects with recurrent *Clostridium difficile* infection¹⁷ but is observed in the same set of subjects after faecal microbiota transplantation. These results fundamentally improve our understanding of the processes that shape human microbial ecosystems, and pave the way to designing general microbiome-based therapies¹⁸.

The underlying dynamics of a microbial ecosystem, that is, the ecological interactions that govern its change, equilibrium and stability, can be represented by a population dynamic model

$$\dot{\mathbf{x}}^{(\nu)} = f(\mathbf{x}^{(\nu)}; \Theta^{(\nu)}) \quad (1)$$

which describes the time-dependent abundance profile $\mathbf{x}^{(\nu)}(t) = (x_1^{(\nu)}(t), \dots, x_N^{(\nu)}(t))$ of N microbial species present in a particular body site of subject ν . Here, $f(\mathbf{x}^{(\nu)}; \Theta^{(\nu)})$ is typically a nonlinear function and $\Theta^{(\nu)}$ captures all the ecological parameters, that is, growth rates, and intra- and inter-species interactions. Those parameters may generally depend on host-independent factors, such as biochemical processes and microbial metabolic pathways¹⁹; and on host-specific ones, such as nutrient intake²⁰ and host genetic make-up¹³.

Three fundamental cases could represent the dynamics of M healthy subjects: (1) individual dynamics, in which the ecological parameters are different in different subjects, that is, $\Theta^{(1)} \neq \dots \neq \Theta^{(M)}$; (2) group dynamics, in which subjects can be classified into K groups ($K \ll M$) on the basis of certain host factors and subjects in the same group share the same set of parameters, that is, $\Theta^{(\nu)} = \Theta^P$ for all subjects in

group P ($P = 1, \dots, K$); and (3) universal dynamics, in which all the subjects share the same set of parameters, that is, $\Theta^{(\nu)} = \Theta$ for all subjects. If we represent the ecological parameters, such as the inter-species interactions, in a directed, weighted ecological network, the above three cases can be easily visualized (see Fig. 1).

Despite its crucial consequences, we do not know which case best represents the microbial ecosystems of healthy individuals. Addressing this question is vital for developing microbiome-based therapies^{3,18}. Indeed, if the dynamics are universal, the inter-personal variability stems solely from the different assemblages of colonizing species in different individuals. We can then design

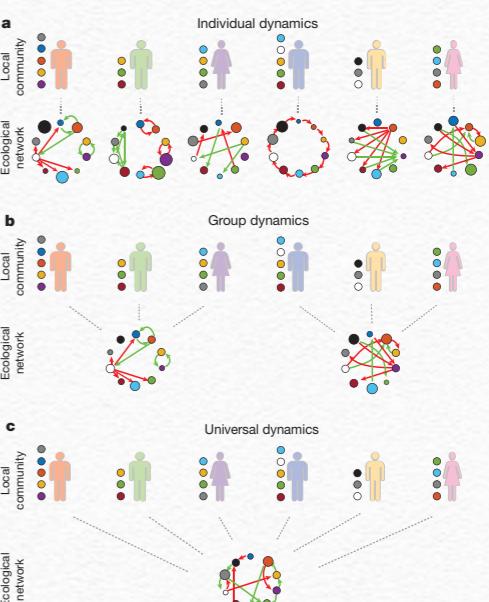


Figure 1 | Alternative scenarios of microbial dynamics across different healthy subjects. Microbial dynamics captured by equation (1) is simply represented by an ecological network, in which nodes represent species (with node sizes proportional to growth rates) and edges represent inter-species interactions (with green and red arrows representing excitatory and inhibitory interactions, respectively). Different subjects typically have different species assemblages, represented by coloured circles near each subject. **a**, The underlying dynamics/network is unique for each subject. **b**, Subjects within the same group share the same dynamics/network that is significantly different from that of other groups. **c**, Different subjects have the same underlying dynamics/network.

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Thank you!