Feb. 18, 2021

Engineering the Metabolism of the Gut Microbiome

→ Purposely manipulating production of metabolites by the gut microbiota

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Martin Oeggerli/Micronaut

Biome – collection of plants and animals formed in response to a shared physical environment

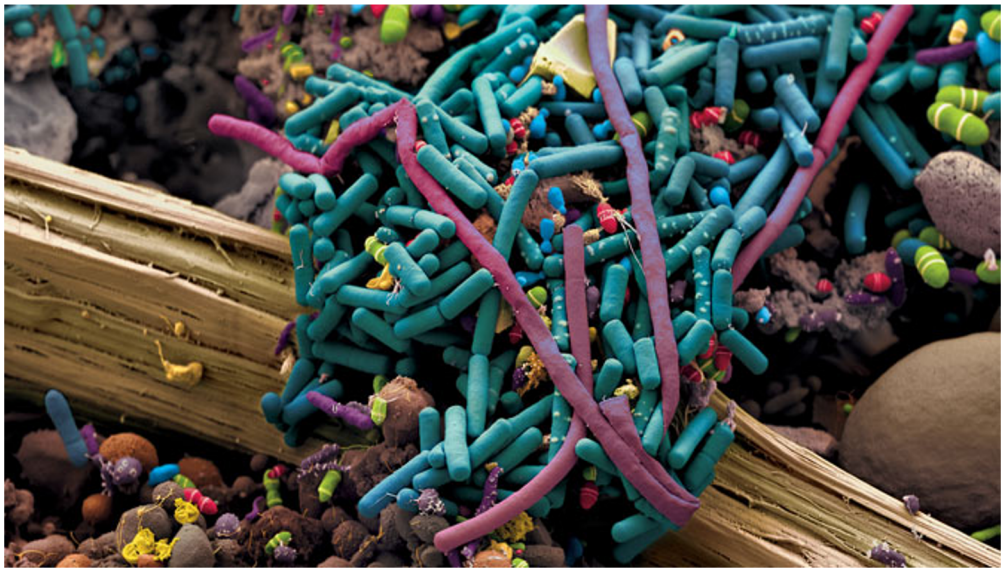
Shared physical environment of desert biome

- little rainfall (< 50 centimeters/yr)
- temperatures vary greatly between day/night
- high evaporation rates
- coarse-textured soils

Biota – the collection of organisms in a biome in a geographic region or time period

→ The biota varies between different deserts

The human gut – a microbiome



Shared physical characteristic of gut microbiome

- little or no O_2
- constant temperature, ca. 37C
- pH between 5.5 – 7.0
- daily flux of resources

Microbiota – the collection of microbes in a sample of a microbiome

→ The microbiota vary temporally within a person and between people

Where did the most abundant and metabolically active members of your gut microbiota come from?

A. Drinking water
B. Food
C. Family members and housemates
D. Soil
E. Pets

Outline for tutorial

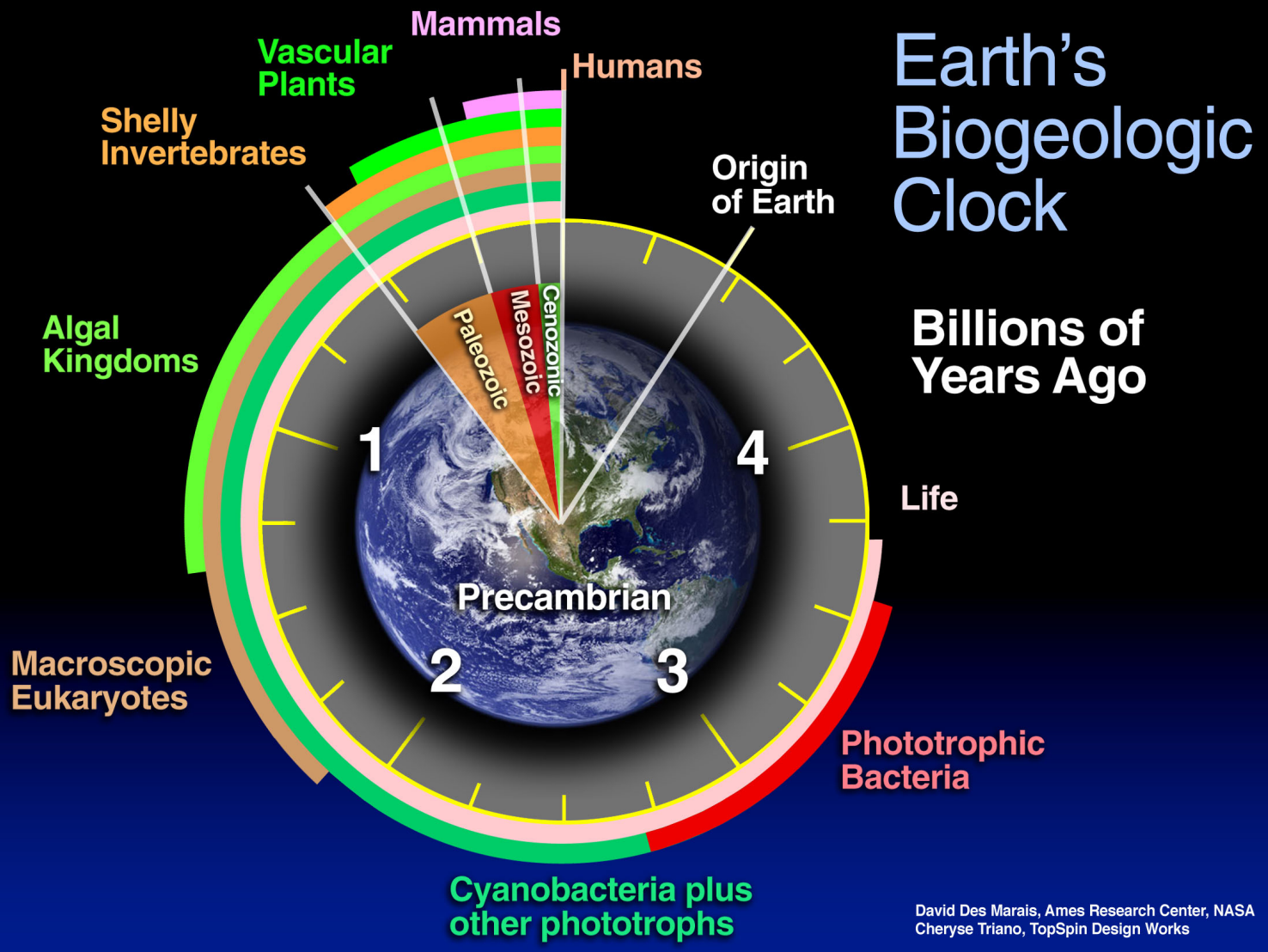
1. Overview of evolution of gut microbiome

2. Why might we want to engineer the gut microbiome?

3. What rates determine the composition of the biota in an ecosystem?

4. How is metabolism in the gut ecosystem influenced by the composition of the microbiota and the local environment? (H_2)

Plants and Animals Evolved in a Microbial World

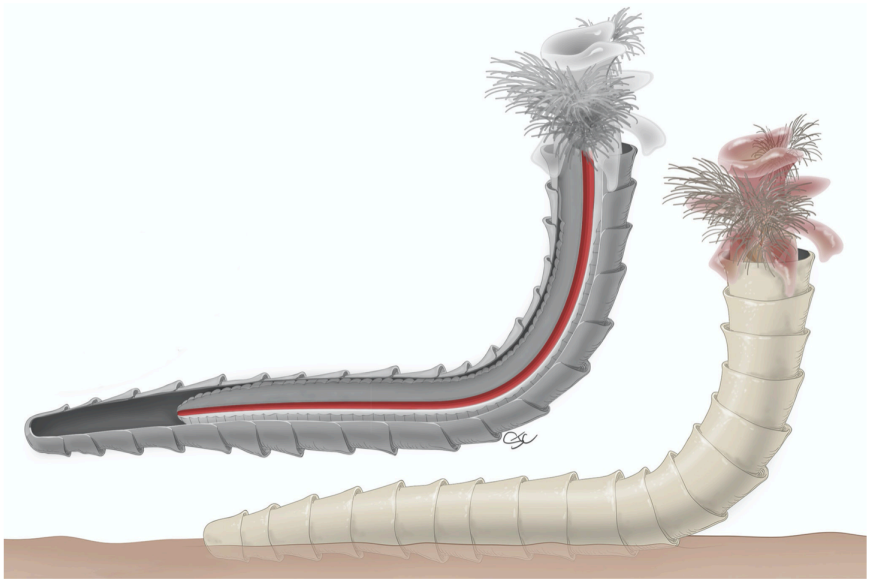


550 million year old fossil has a gut

New York Times (Jan. 10, 2020), [Nature Communications Article]

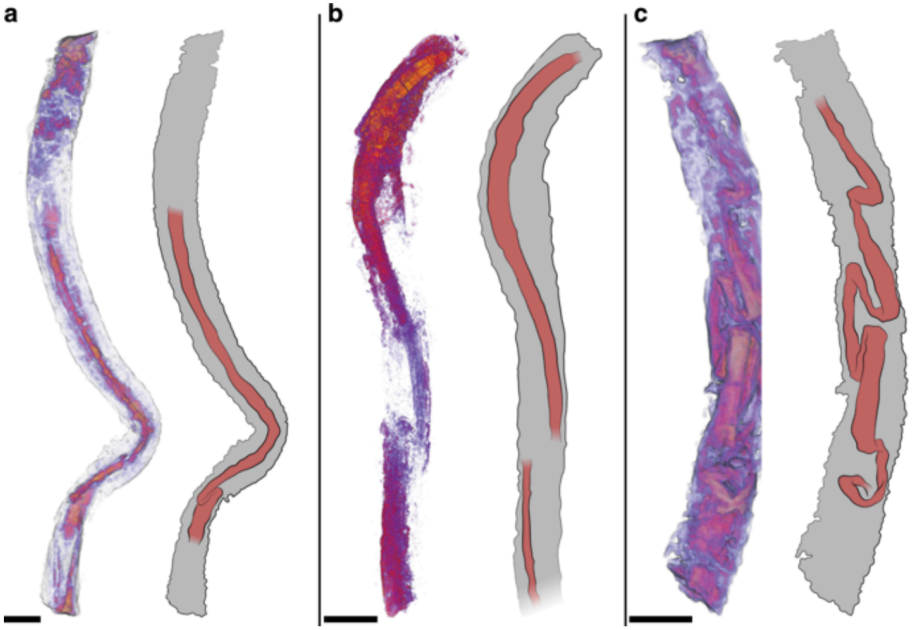
Fossil Reveals Earth's Oldest Known Animal Guts

The find in a Nevada desert revealed an intestine inside a creature that looks like a worm made of a stack of ice cream cones.



Illustrated views of Cloudina, a worm that lived about 550 million years ago. Stacy Turpin Cheavens, University of Missouri

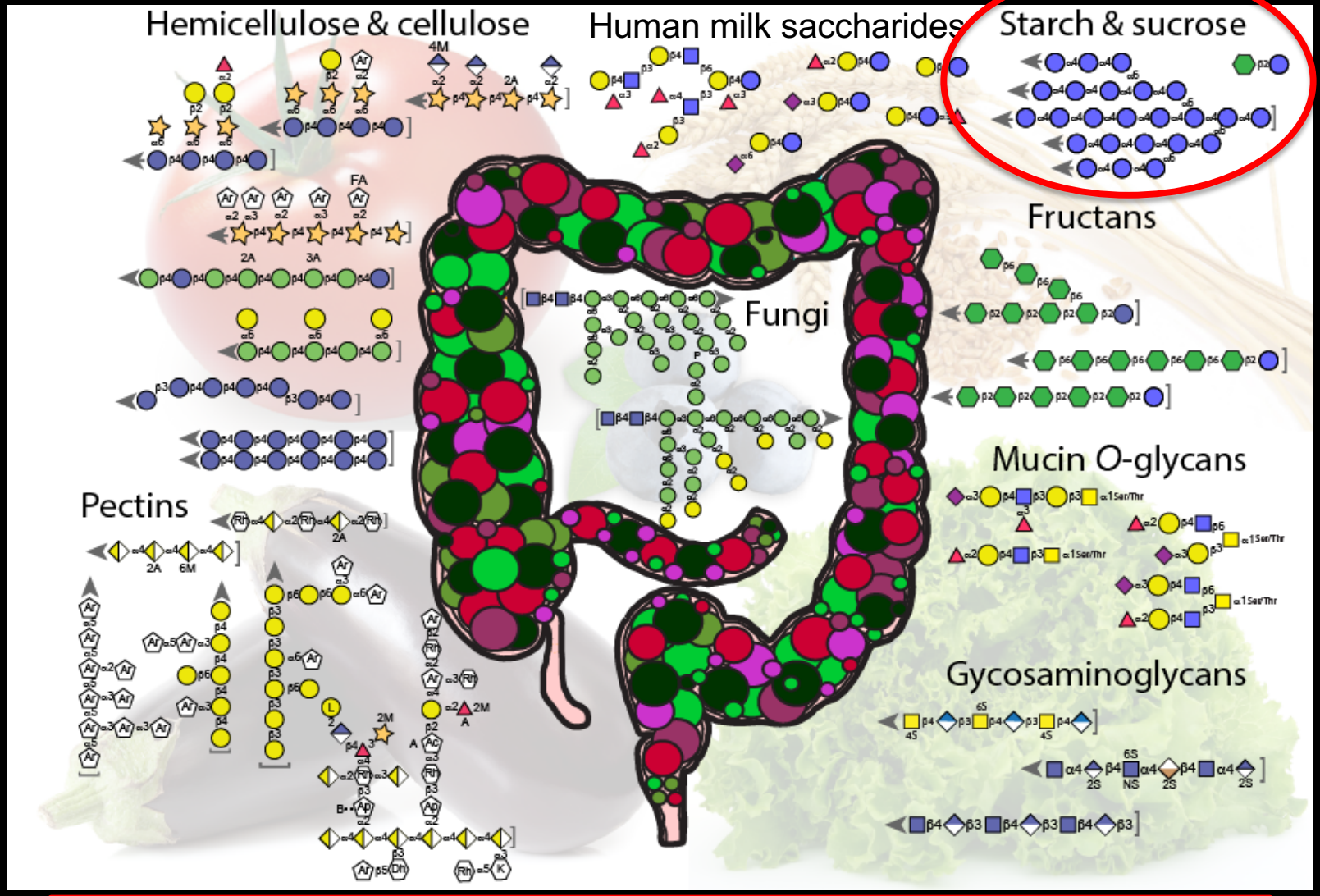
Fig. 3: Soft tissue-bearing cloudinomorphs with schematic interpretation.



3D volume render from μCT data shown in left image per frame (red-to-orange coloration indicates high density internal regions within exterior tube), with interpretive diagram in right image per frame. Examples here

Complex Carbohydrates in the human diet

Chemical structures of complex carbohydrates in human diet



Only starch and sucrose degraded by human enzymes – others are food for gut microbiota!

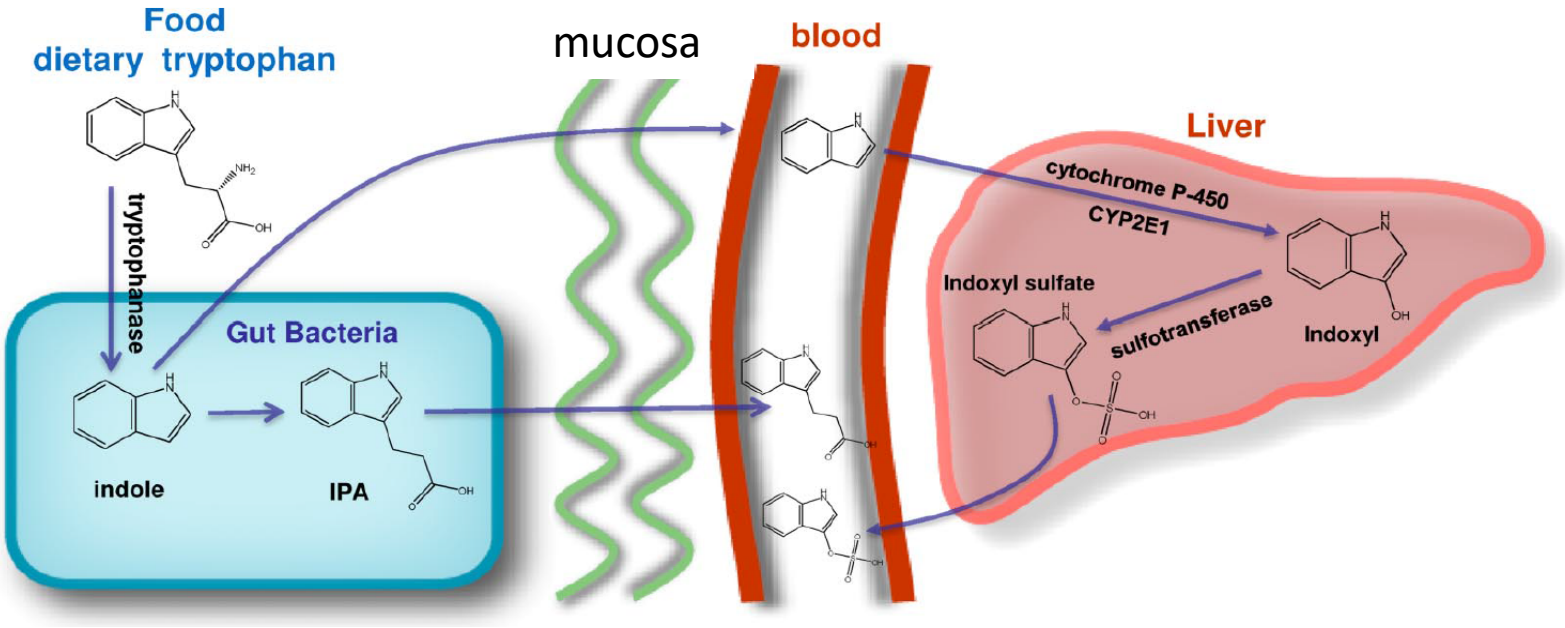
Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites

William R. Wikoff[a], Andrew T. Anfora[b], Jun Liu[b], Peter G. Schultz[b,1], Scott A. Lesley[b], Eric C. Peters[b], and Gary Siuzdak[a,1]

PNAS (2009) 106:3698

metabolite – a substance formed by metabolism

metabolomics – the large-scale study of metabolites



→ Hundreds of metabolites in blood attributed to gut microbiome

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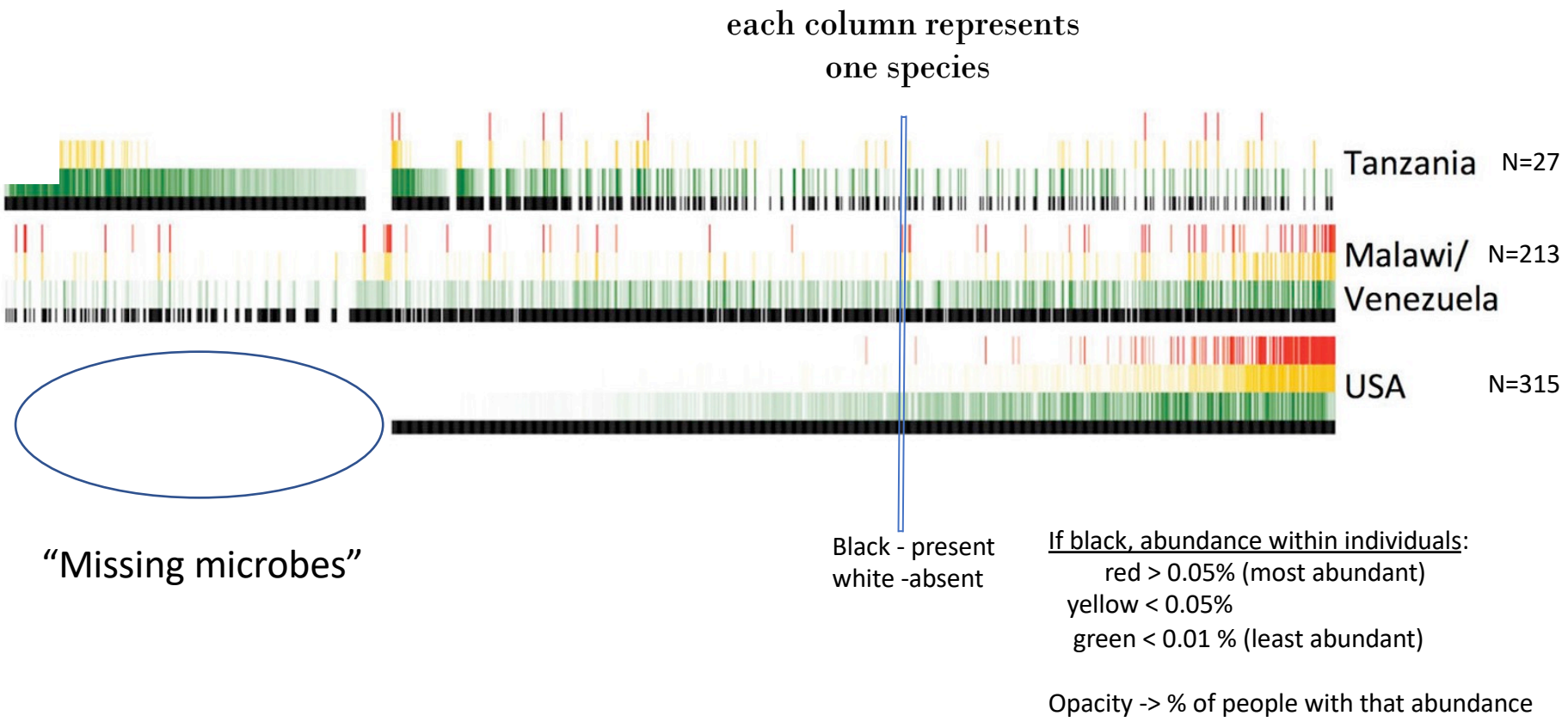
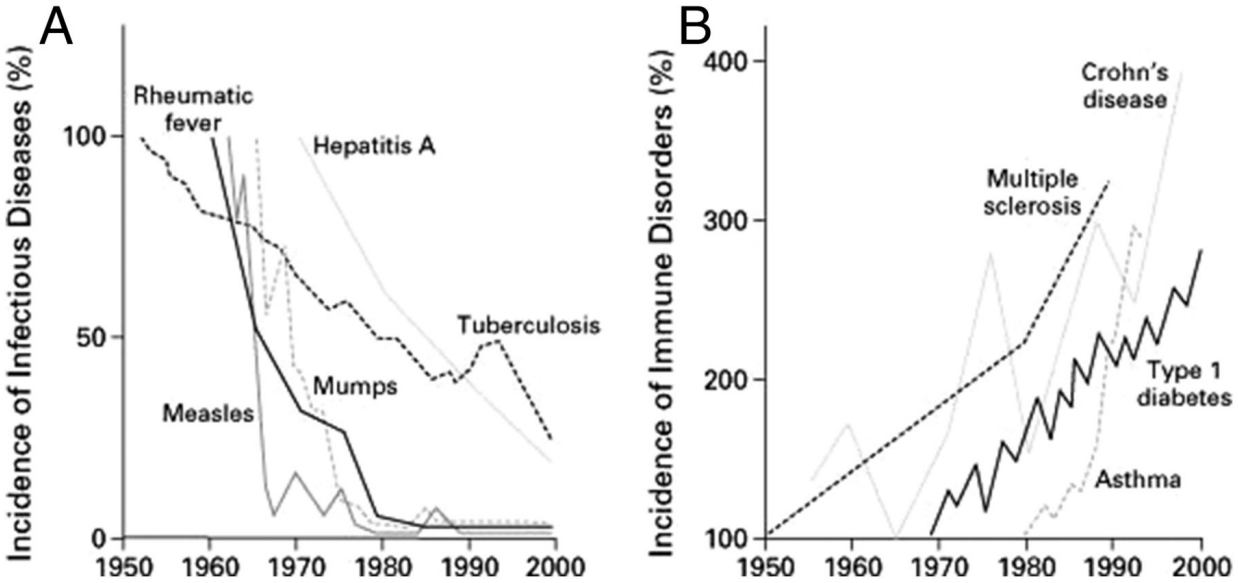
Circumstances that might warrant engineering of the gut microbiome:
1. Loss of species associated with Western diet



Diet-induced extinction in the gut microbiota compounds over generations.
Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL.
Nature. 2016;529(7585):212-215

Circumstances that might warrant engineering of the gut microbiome: 2. The Hygiene Hypothesis

→ Early exposure to a diverse range of microbes is necessary to train the human immune system to react appropriately to stimuli.



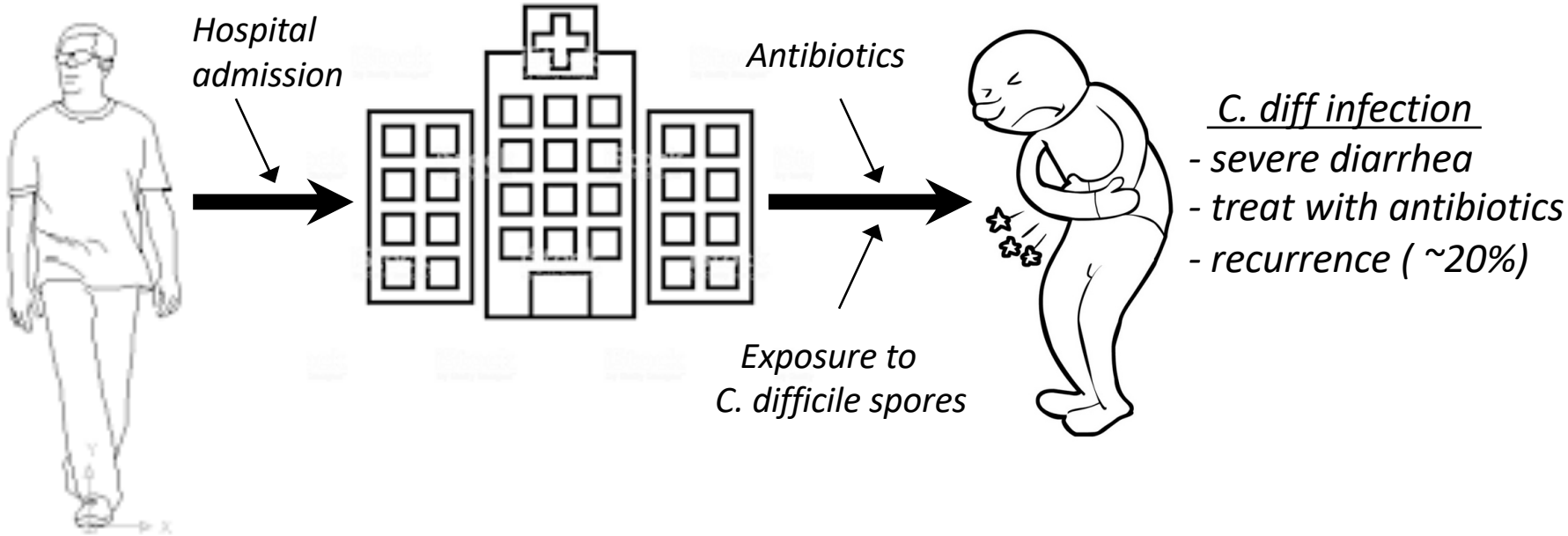
Observation: There is an inverse relationship between incidence of infectious disease (A) and the rates of immune disorders (B).

Megan Scudellari PNAS 2017;114:7:1433-1436

PNAS

Circumstances that might warrant engineering of the gut microbiome:

3. Recurrent infections with *Clostridium difficile*



Engineering the gut microbiome

Poop in a Pill

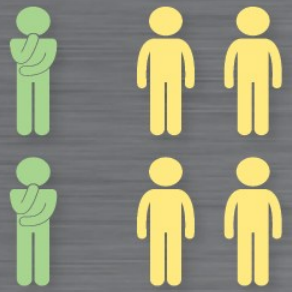
It's no joke. *Clostridium difficile*, or C-diff, causes debilitating diarrhea and is linked to 14,000 deaths in the U.S. every year.

Fecal transplantation—the delivery of pre-screened, healthy donor stool to a patient by colonoscopy or nasogastric tube—is typically prescribed as an effective alternative to long-term antibiotic use in treating this infectious disease. But new research co-authored by Boston Children's Pediatric Gastroenterologist Dr. George Russell, says there is a third, less invasive, less expensive option to treat C-diff: poop in a pill.

A group of physicians from Boston Children's, Massachusetts General Hospital, Harvard Medical School and Tel Aviv University conducted a clinical trial with 20 patients and found:

Initial treatment
Symptoms resolved in 14 of the 20 patients.

Second try
This time symptoms cleared up in 4 of the 6 patients who did not respond at first.



= **90% success**

Boston Children's Hospital
Until every child is well™

Learn more at **bostonchildrens.org/fecaltransplant**

“Correlations between the composition of the gut microbiome and human disease”

2019 mini-review

2. *Obesity*
3. *Hypertension*
4. *Cardiovascular disease*
5. *Diabetes*
6. *Cancer*
7. *Inflammatory Bowel Disease*
8. *Gout*
9. *Depression*
10. *Arthritis*
11. *Infant Health*
12. *Longevity*

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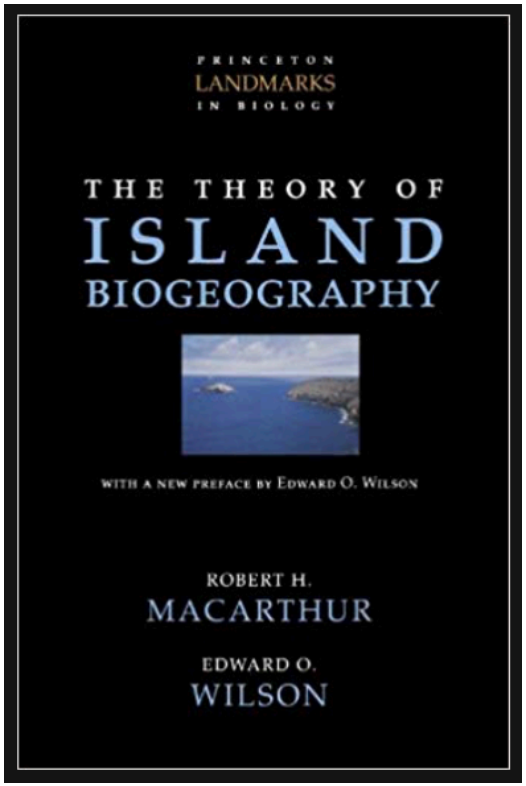
Like a new volcanic island, the GI tract of infant is sterile

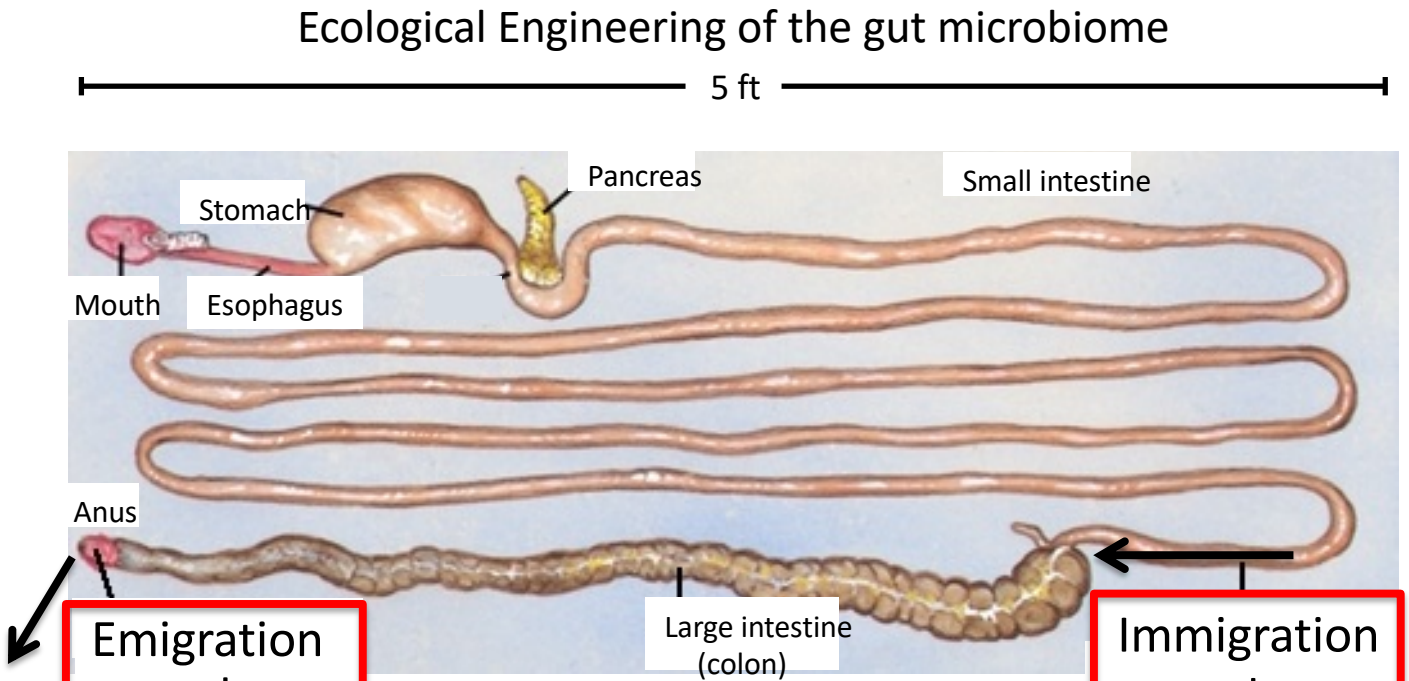


1967

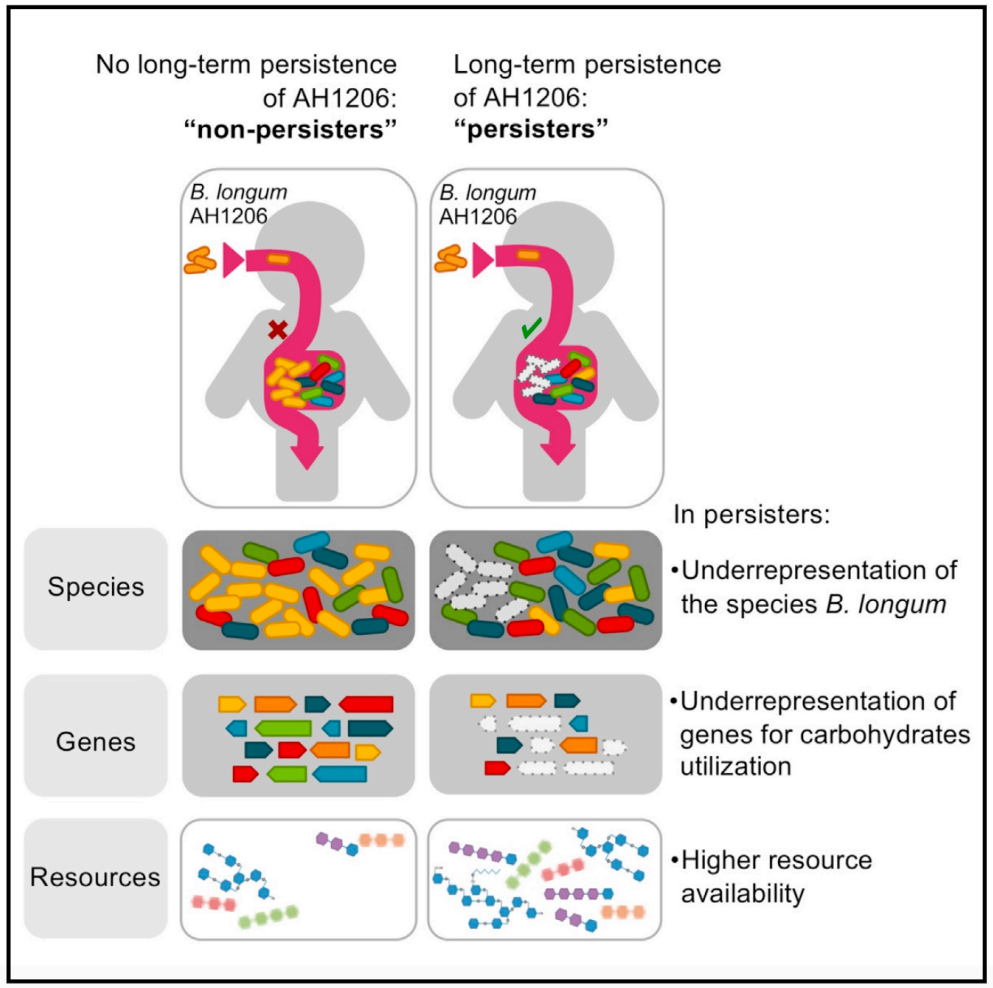
Island biogeography: species composition based on rates of immigration and extinction

Subsequently, expanded to four rates:
immigration, birth, death, emigration

Ecological engineering of the gut microbiome: Four rates dictate composition of gut microbiota



Engineering the gut microbiome: Immigration
Stable colonization of *Bifidobacterium longum* (persisters) depends on individualized features of the resident microbiome



Cell Host & Microbe (2016) http://dx.doi.org/10.1016/j.chom.2016.09.001

Probiotics + Prebiotics

Probiotic - live microorganisms that provide health benefits when consumed

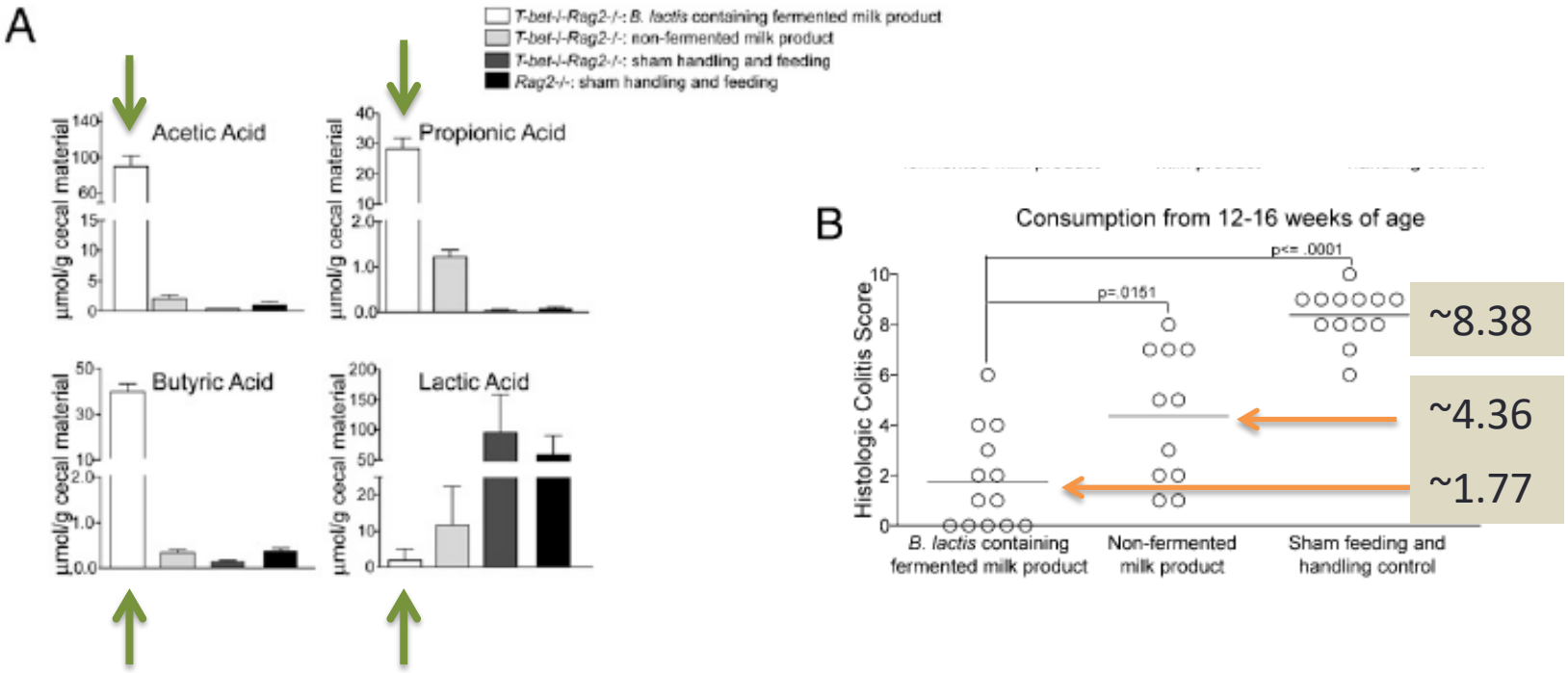
Prebiotic - a substance that induces growth or activity of microorganisms that contribute to well-being of their host

INGREDIENTS: STRAWBERRY BANANA:

Cultured Non Fat Milk, Strawberries, Water, Modified Food Starch, Less Than 1%: Banana Puree, Natural Flavors, Carmine (For Color), Kosher Gelatin, Acacia Gum, Pectin, Xanthan Gum, Inulin, Sucralose, Acesulfame Potassium, Calcium Lactate, Malic Acid, Live Cultures L. Bulgaricus (2), L. Lactis, S. Thermophilus, Live And Active Probiotic B. Lactis Dn 173-010/Cncm I-2494.

Probiotics + Prebiotics

- Positive effects in **mice** consuming Activia yogurt
  - restoring levels of short-chain fatty acids to those found in healthy mice (A)
  - improving colitis score (B)



Viega et al. *Proc Natl Acad Sci* USA. 2010

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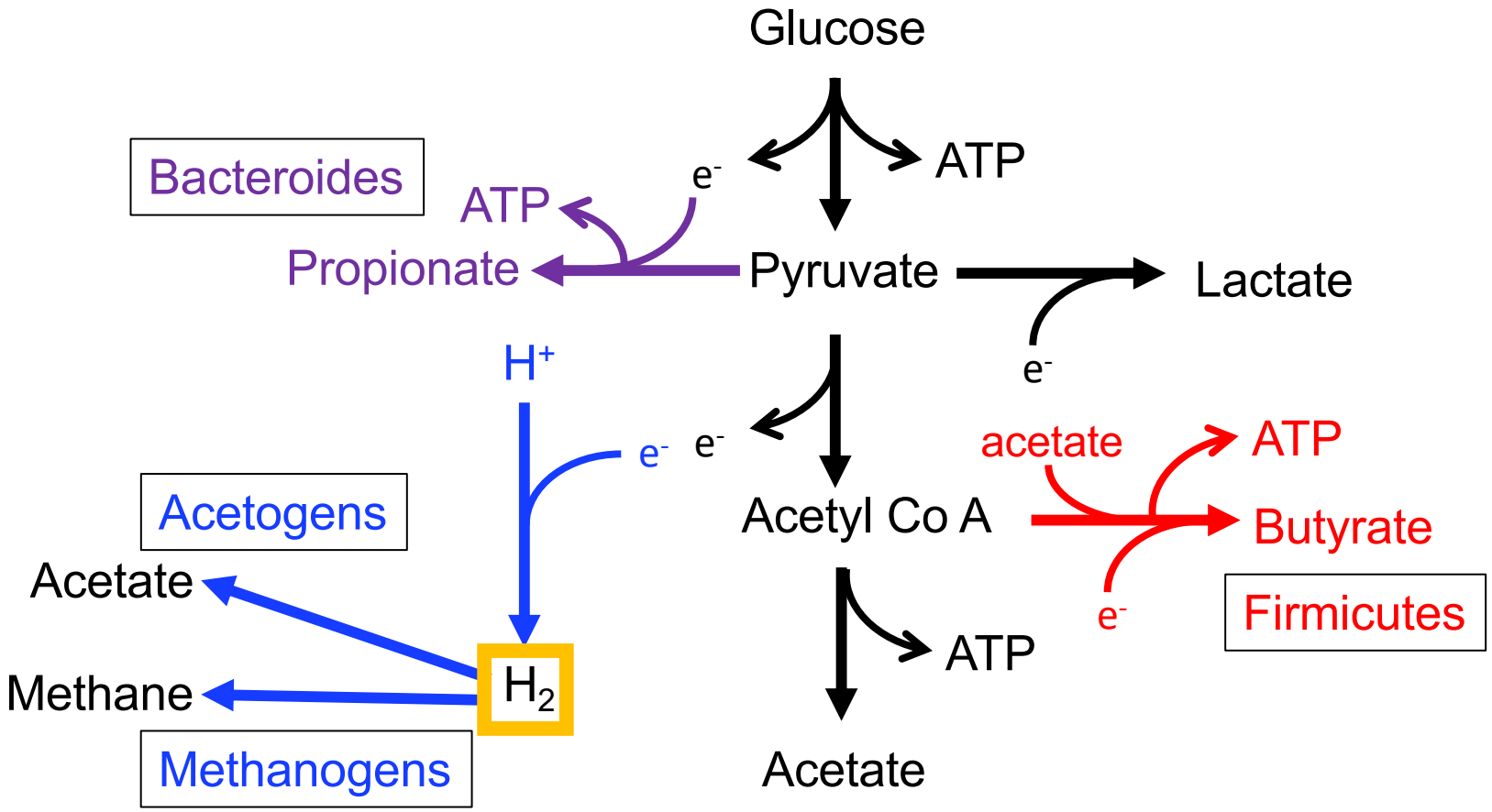
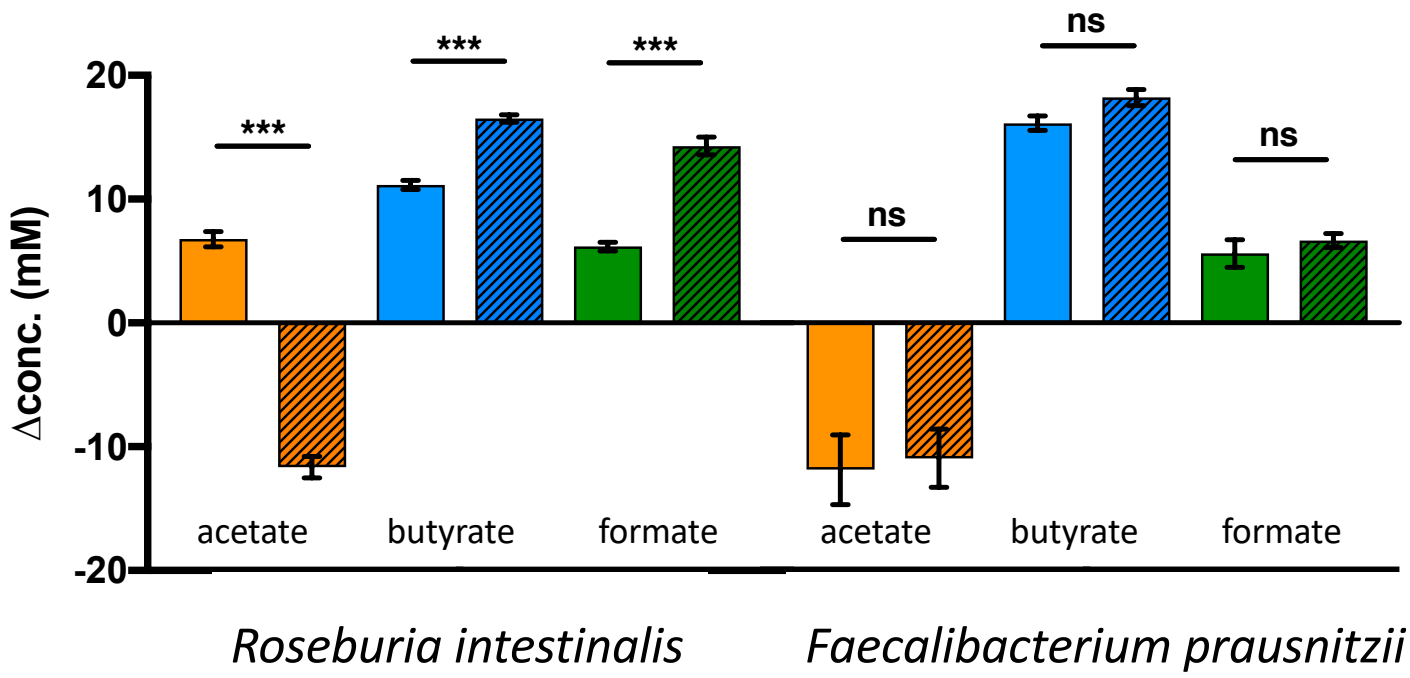
Carbon flow in anaerobic ecosystems:
Major challenge → sinks for reducing power (e^-)

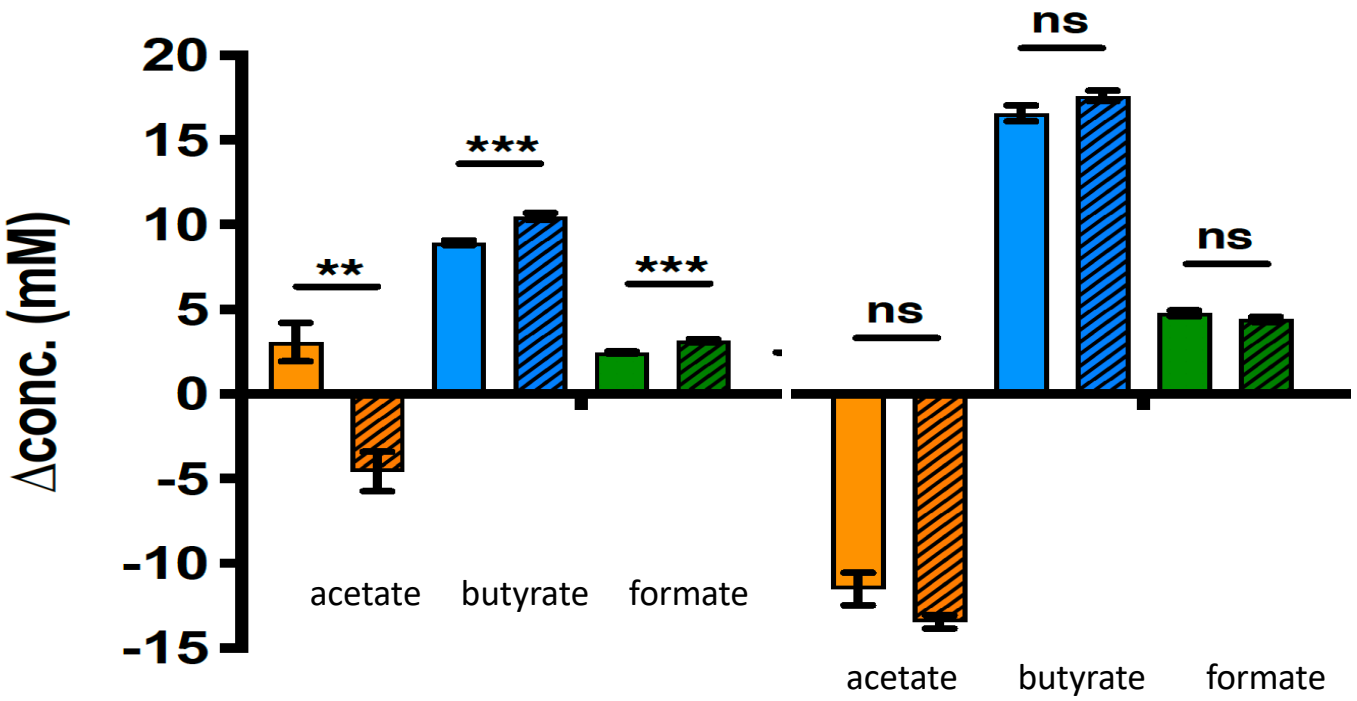


Hypothesis: More H_2 → more butyrate
Less H_2 → less butyrate

Effect of H_2 (striped bars) on fermentation products from two prominent butyrate-producing bacteria



Effect of carbon monoxide (hydrogenase inhibitor, striped bars) on fermentation products from butyrate-producing bacteria



Roseburia intestinalis *Faecalibacterium prausnitzii*

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Engineering the microbiome for better health

"To the extent that we are bearers of genetic information, more than 99 percent of it is microbial.

And it appears increasingly likely that this "second genome," as it is sometimes called, exerts an influence on our health as great and possibly even greater than the genes we inherit from our parents.

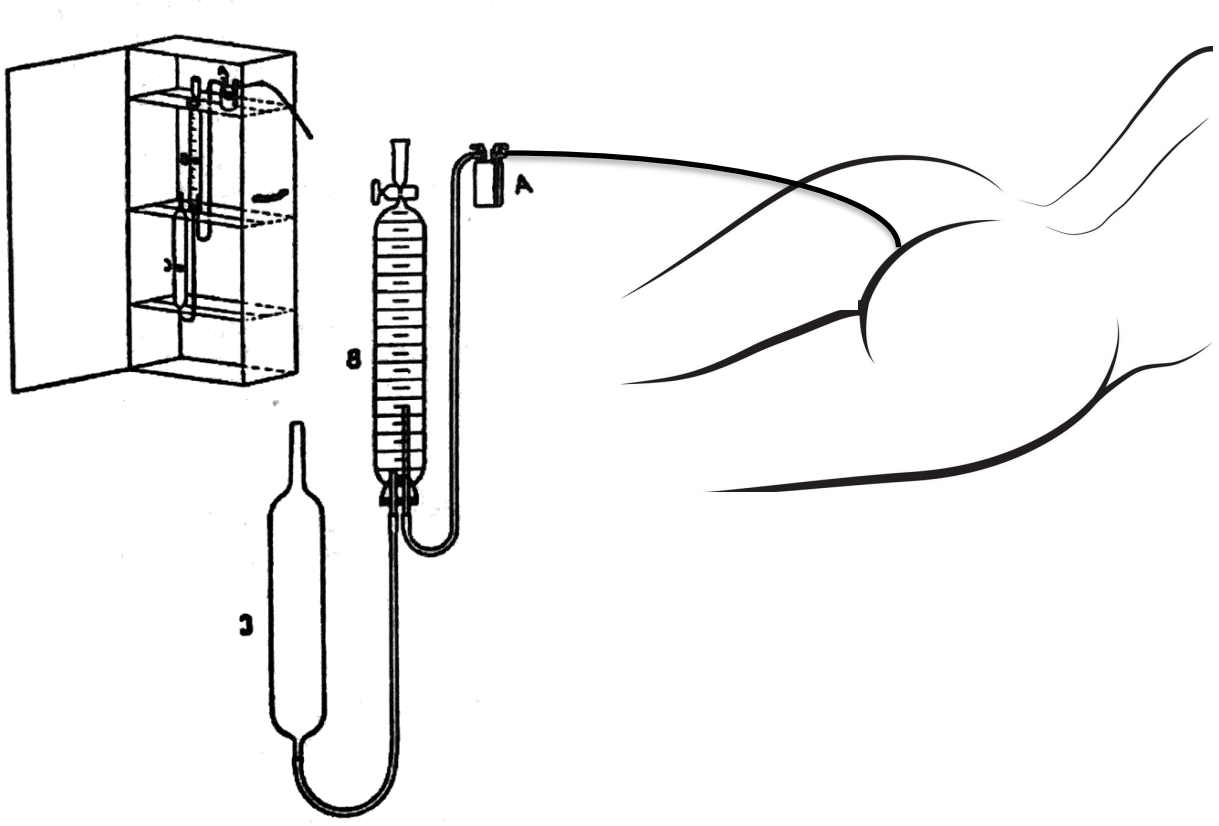
But while your inherited genes are more or less fixed, it may be possible to reshape, even cultivate, your second genome."

NYTimes – Michael Pollan
May 15, 2013

The Quantity and Composition of Human Colonic Flatus

(1949) Esben Kirk, Gastroenterology 12:782-794

- N = 44 (men and women)
- Collected flatus for 10 hrs. → two 5-hour periods



N_2	64.7
H_2	16.1
CO_2	9.4
O_2	4.7
CH_4	5.0
Total	100%

Engineering the Metabolism of the Gut Microbiome

→ Butyric Acid and Graft versus Host Disease

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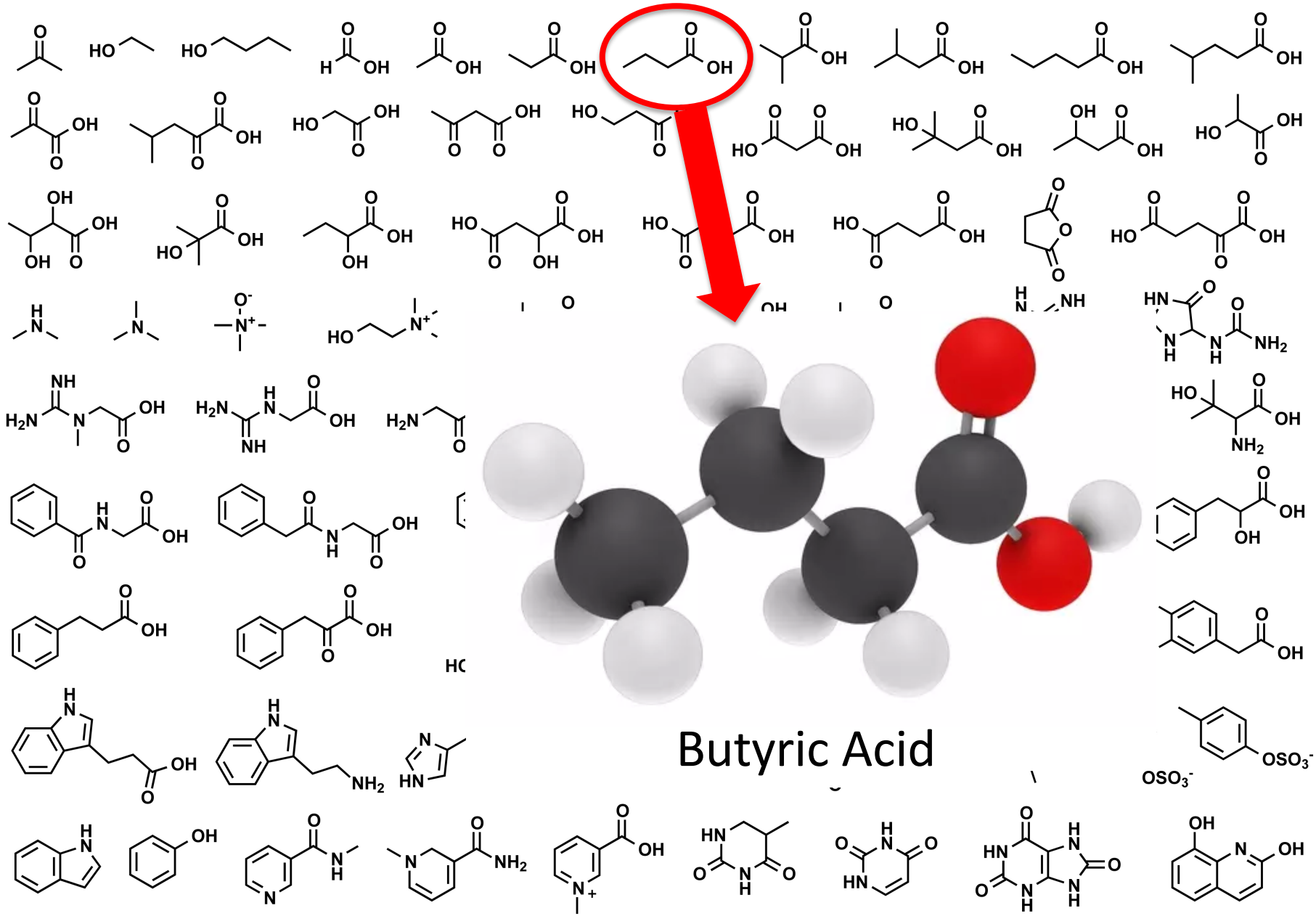
Martin Oeggerli/Micronaut

Some metabolites from the human microbiota

Donia and Fischbach (2015) Science 349:395



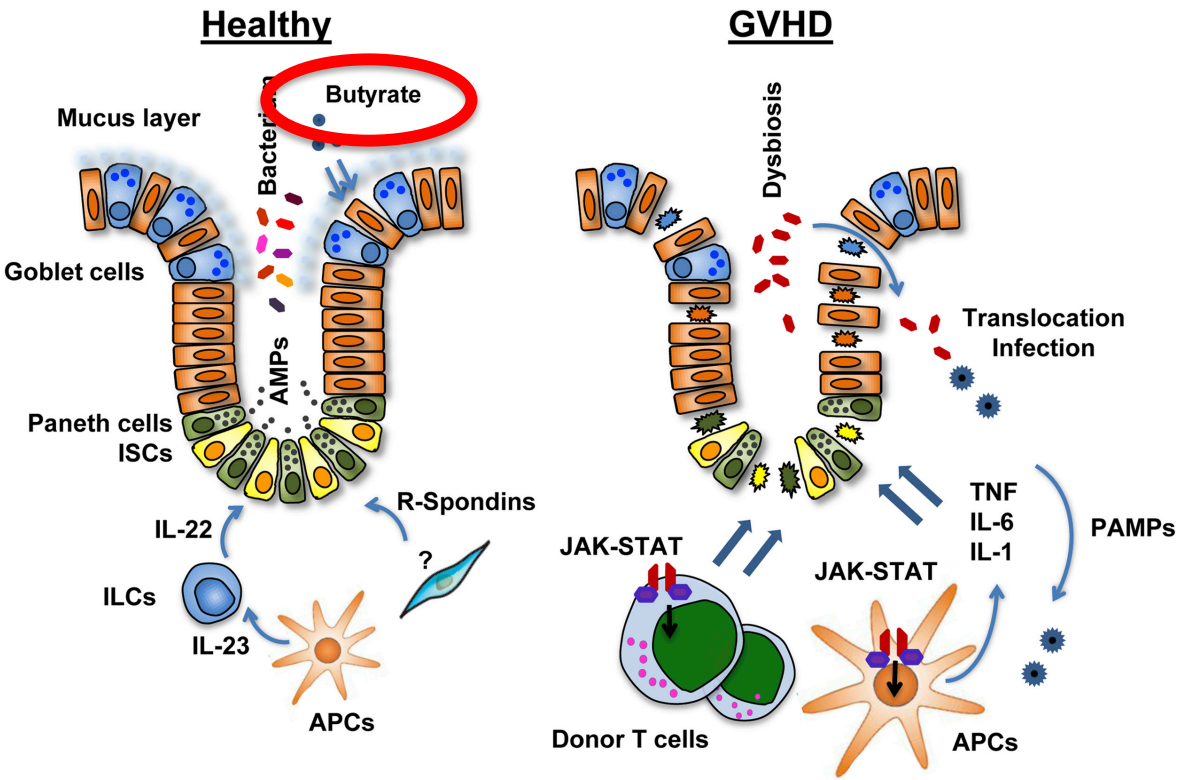
Graft Versus Host Disease (GVHD)

GVHD - a common, life-threatening complication following bone marrow transplant

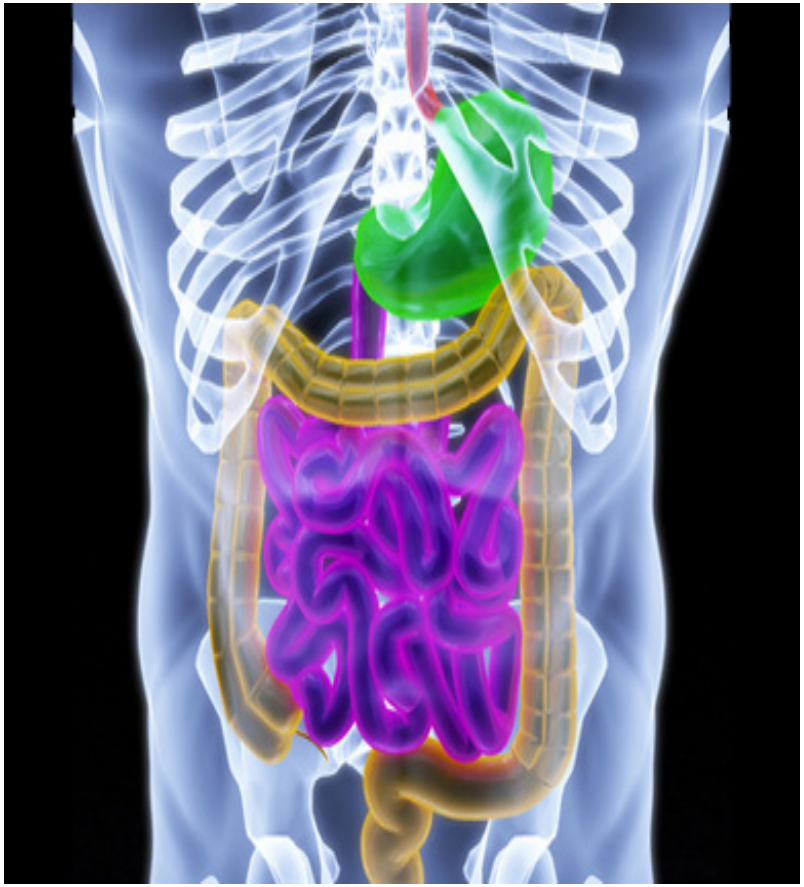
→ Treatment of some leukemias includes destruction of bone marrow

→ Bone marrow can be restored with transplant from a matched donor

→ Donor's bone marrow can attack recipient's body as foreign and attack → GVHD



One important ecosystem service of the gut microbiome – butyrate production



(Tremaroli & Backhed 2012 *Nature*; Lee & Hase 2014 *Nature Chemical Biology*)

<u>Some beneficial effects of butyrate:</u>

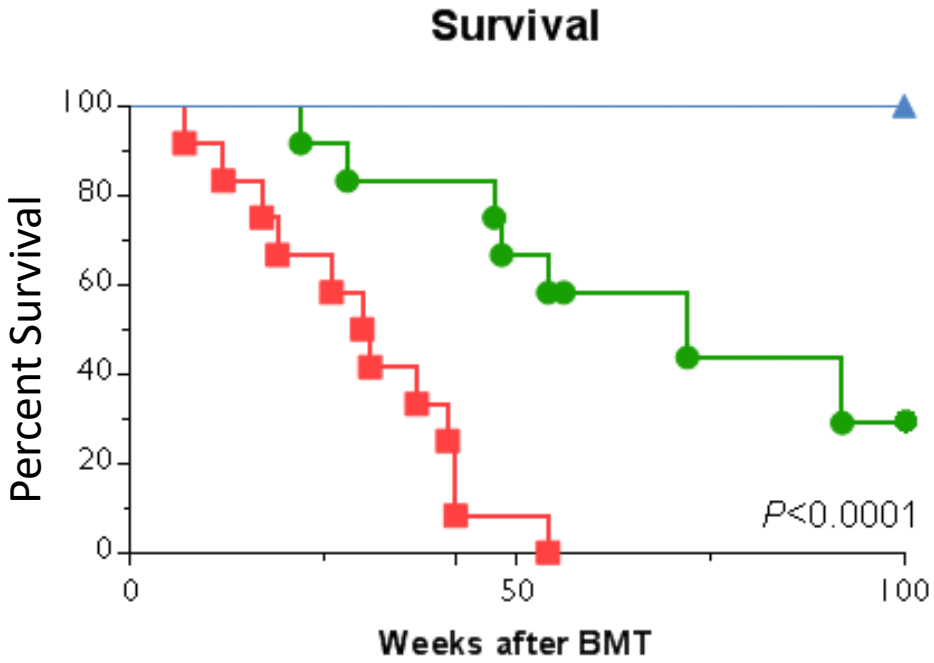
- Prefered energy source for mitochondria in cells lining the colon --> decreases inflammat

- Decreases likelihood of colon cancer

- Regulates satiety

- Reduces incidence and severity of graft vs. host disease (GVHD)

Impact of Butyrate Treatment on Survival from Bone Marrow Transplant (mouse model)



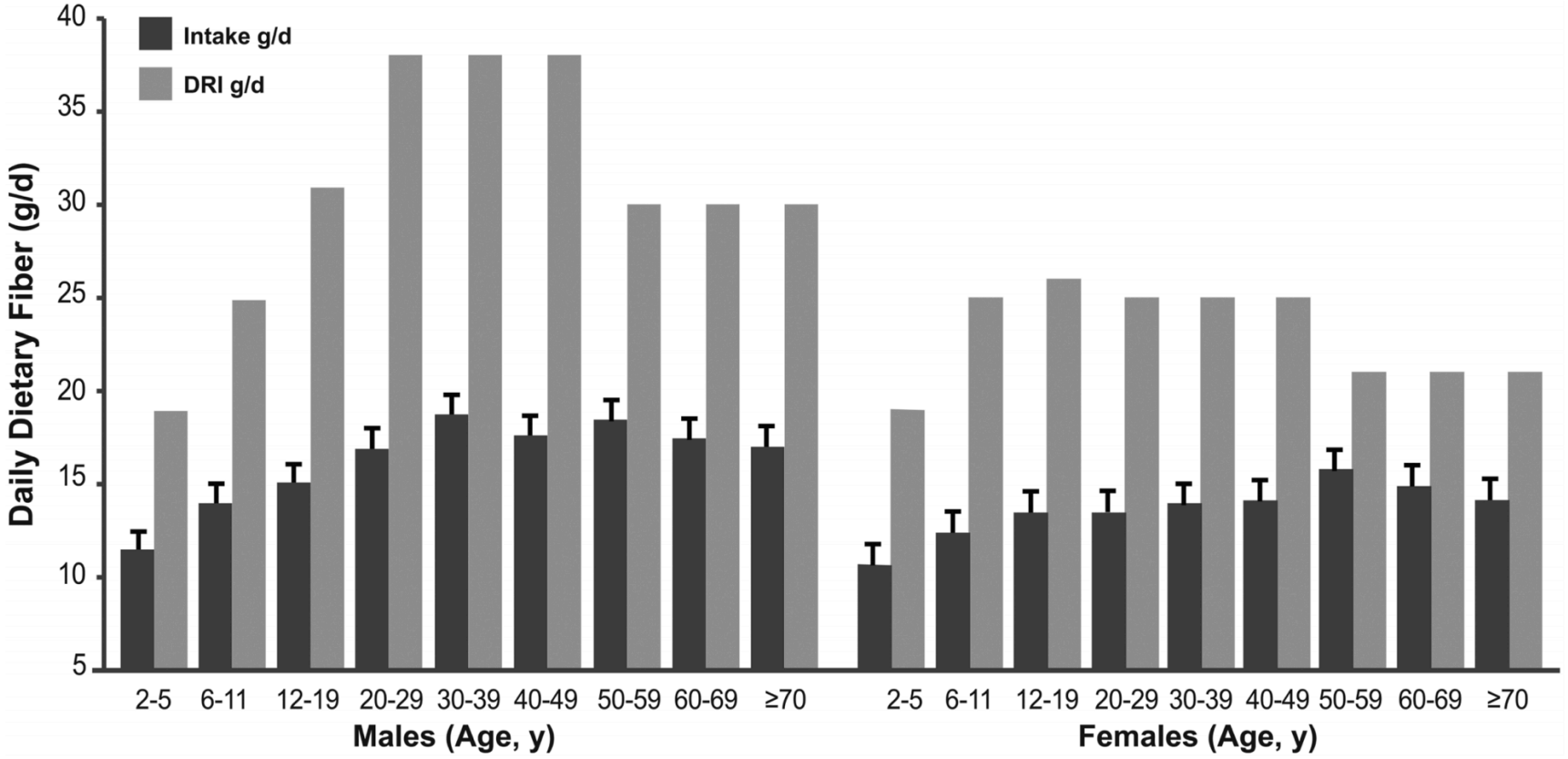
- Control (isogenic transplant)
- Saline treatment
- Butyrate treatment

Pavan Reddy and colleagues (2016) Nature Immunology

Can fermentation from gut microbiome be enhanced by supplementing dietary fibers?

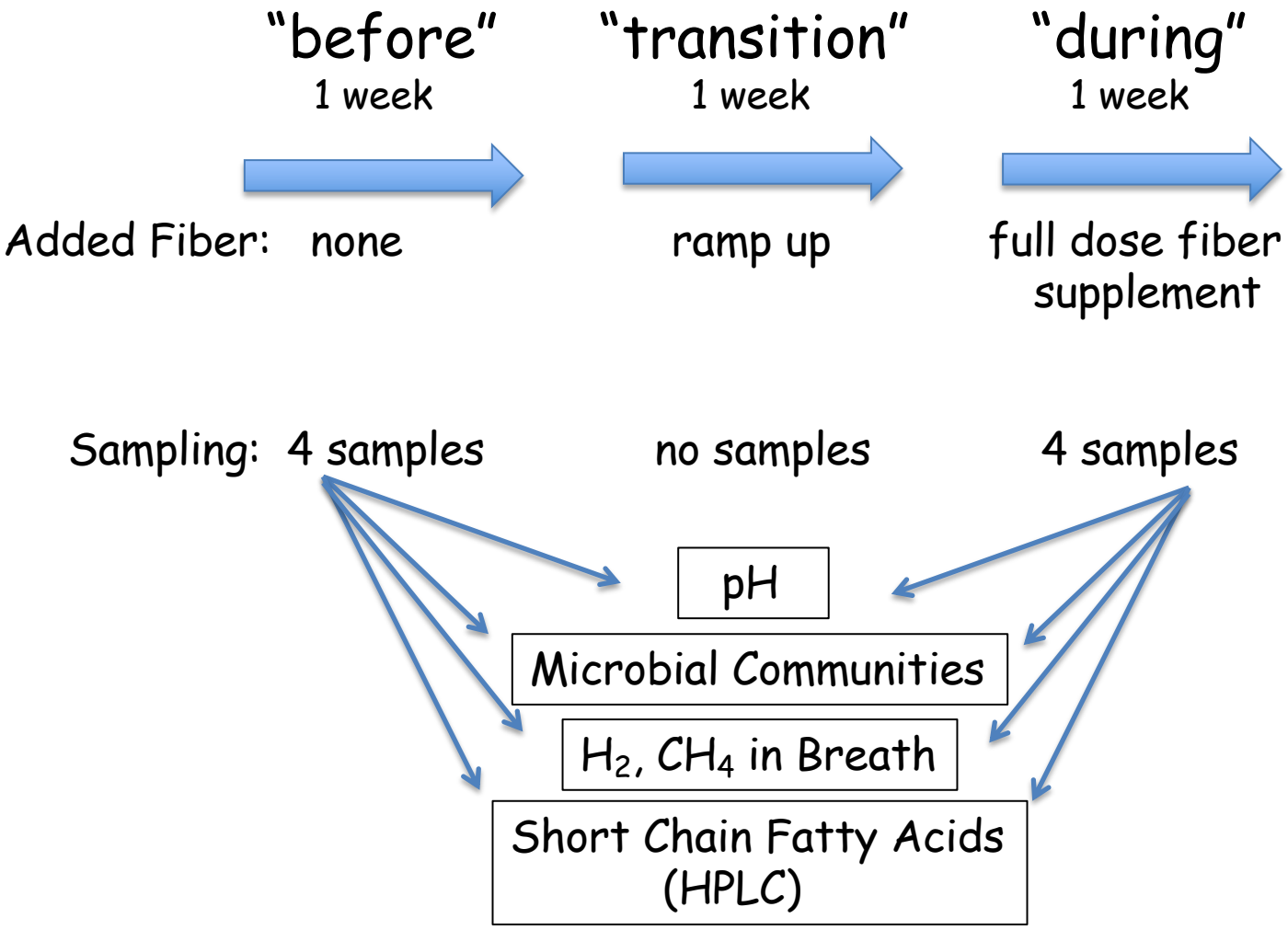
Healthy Human Cohort: students in an introductory biology course

Energy flow (fiber) to gut microbes is often less than recommended
→ limits their metabolism, including H_2 and butyrate production



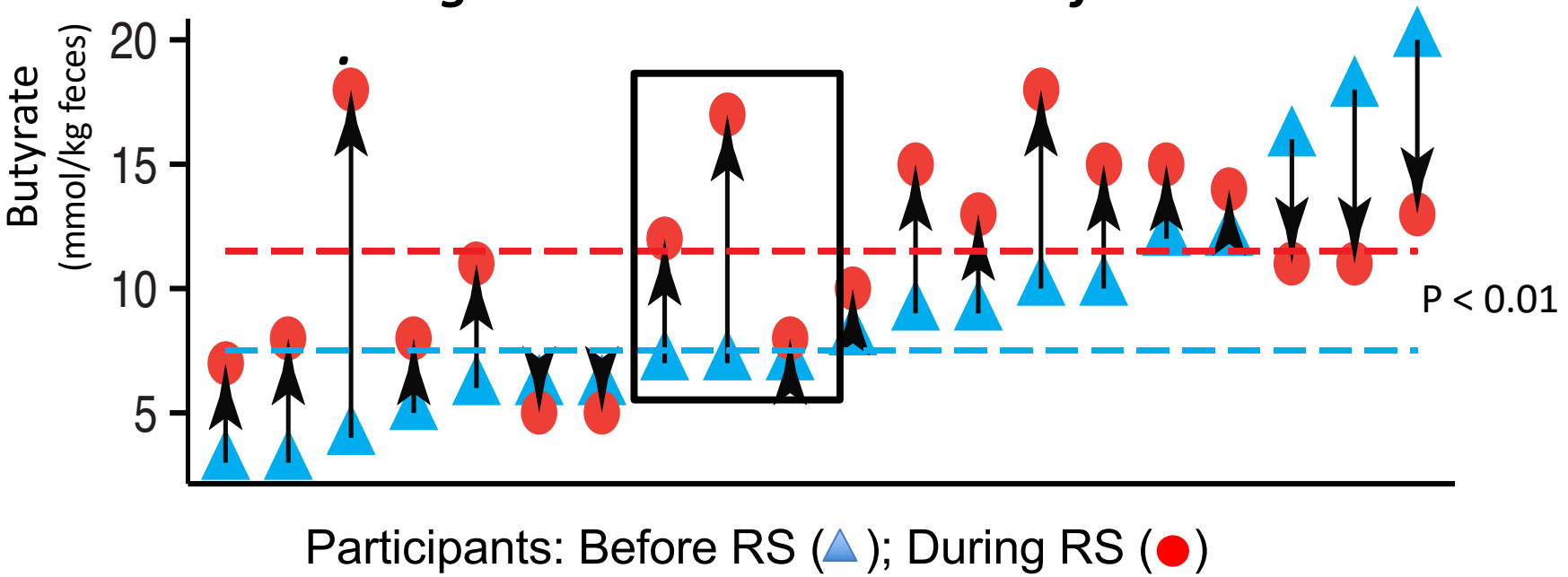
Clemens et al. 2012 *J Nutrion*

Experimental Design



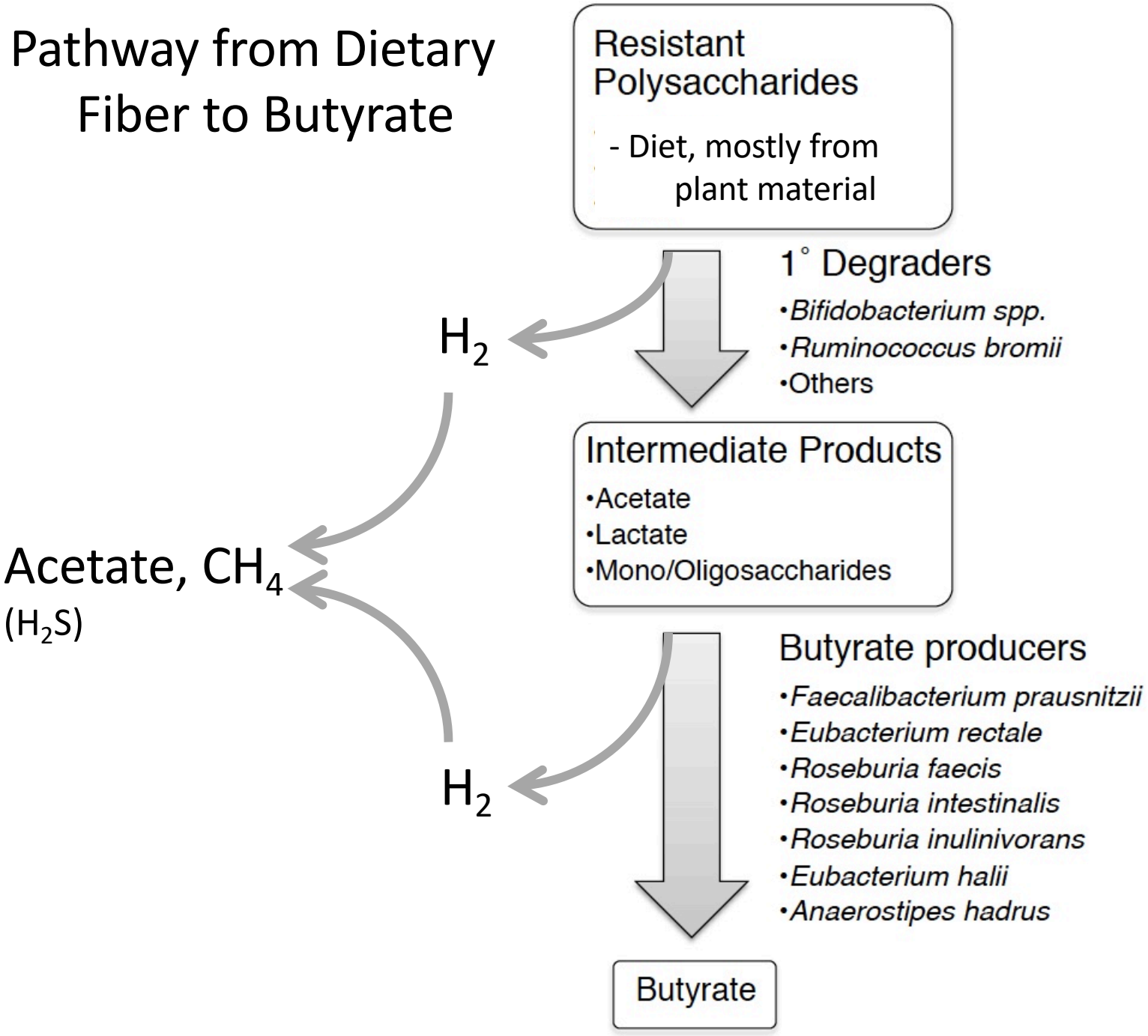
Dietary supplement of resistant starch (from potatoes) increases butyrate, inter-individual variation is striking

<u>Hypothesis</u>: variable response is due to differences in composition of microbiome and gases in the environment of microbiome



Venkatarraman…Schmidt (2016) Microbiome

Pathway from Dietary Fiber to Butyrate



University Student Cohort

801 participants consented to share data

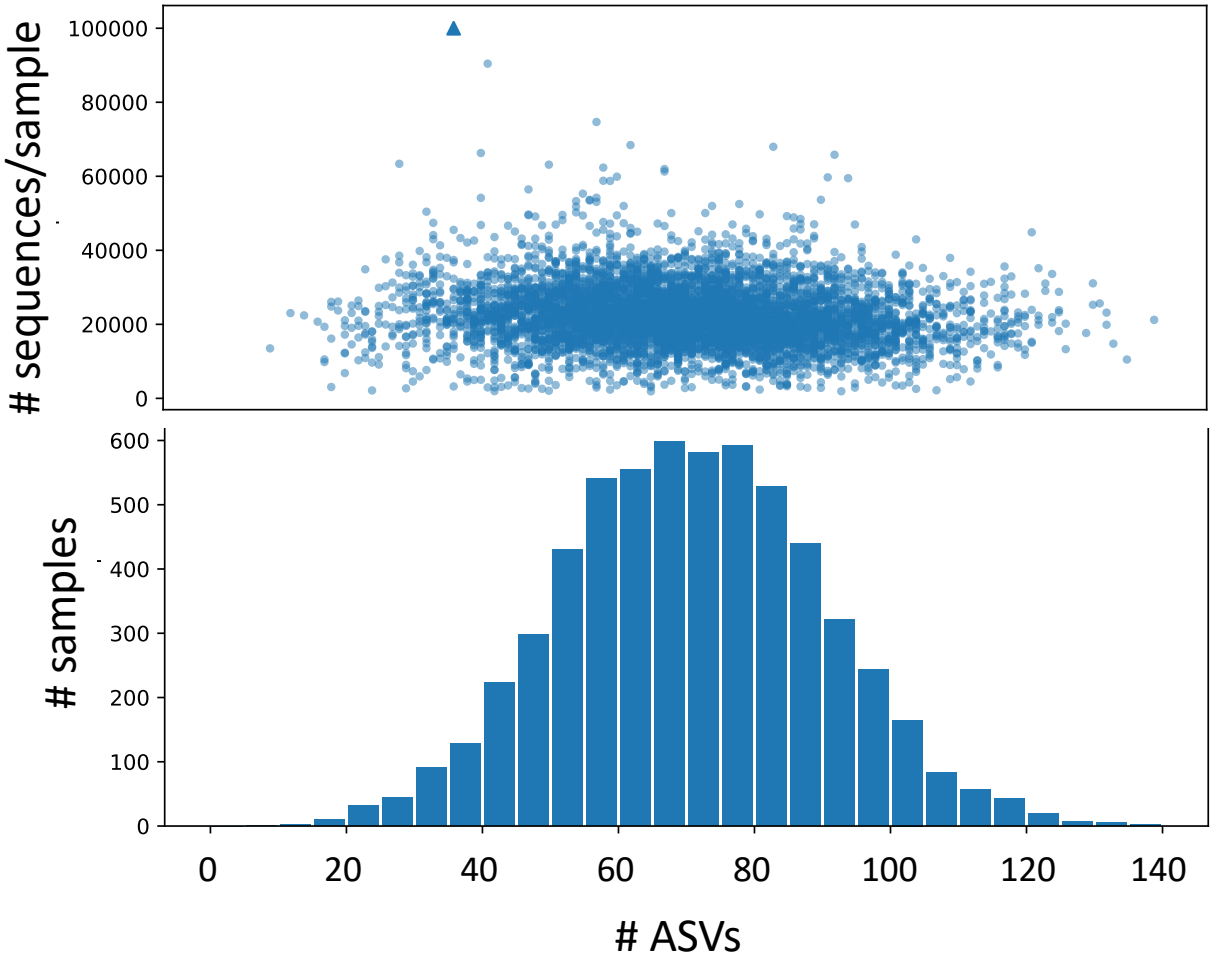
732 consented to consume supplement
- 75% compliance among those

67% female, 33% male

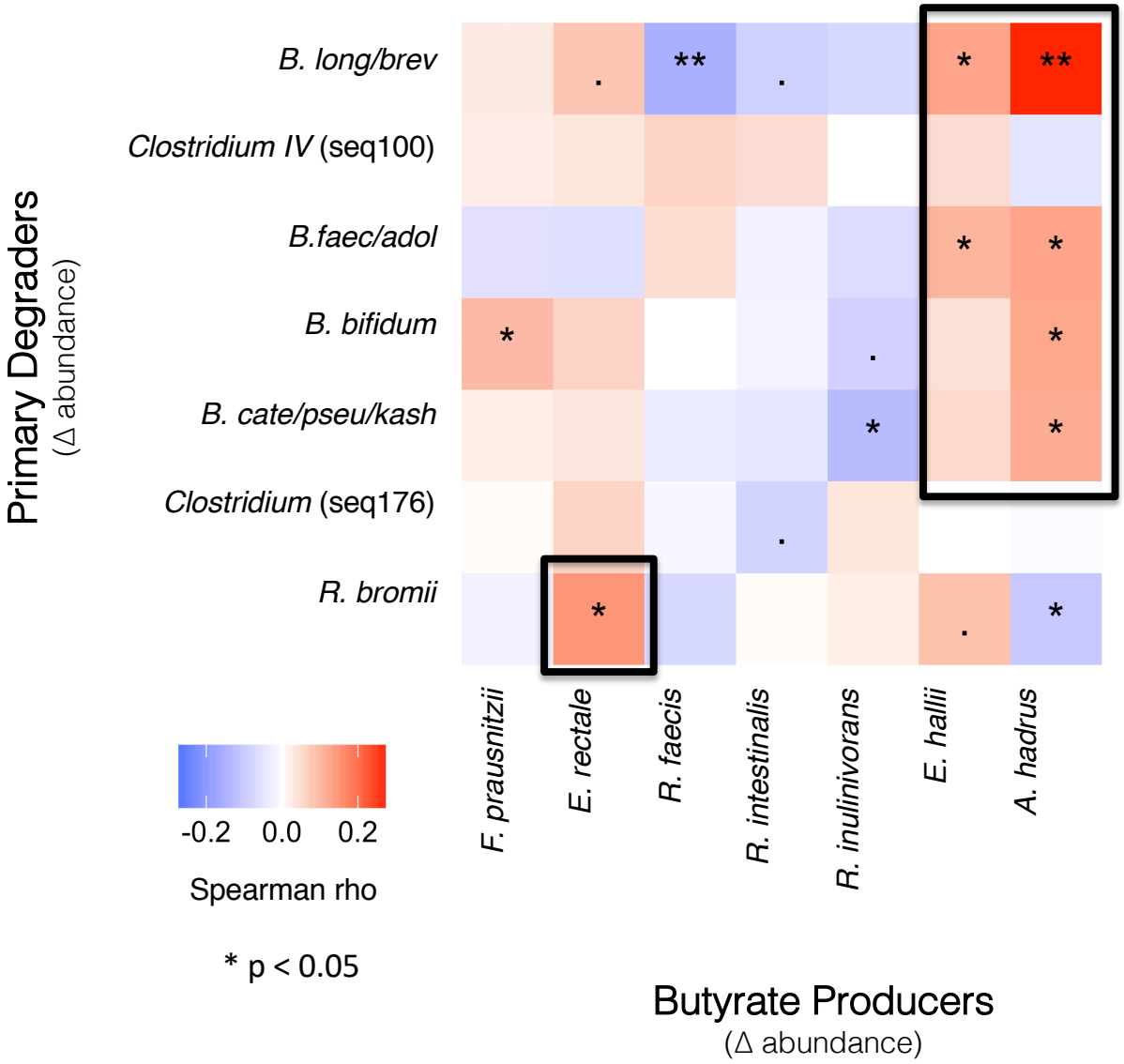
Age range: 17 – 22 (six between 22 & 29)

How many kinds of bacteria are in a fecal sample?

- Kind = Amplicon Sequence Variants (ASVs) – no clustering
- 6,047 samples from a total of 783 participants
- Global singletons and ASVs below 1/1,000 removed

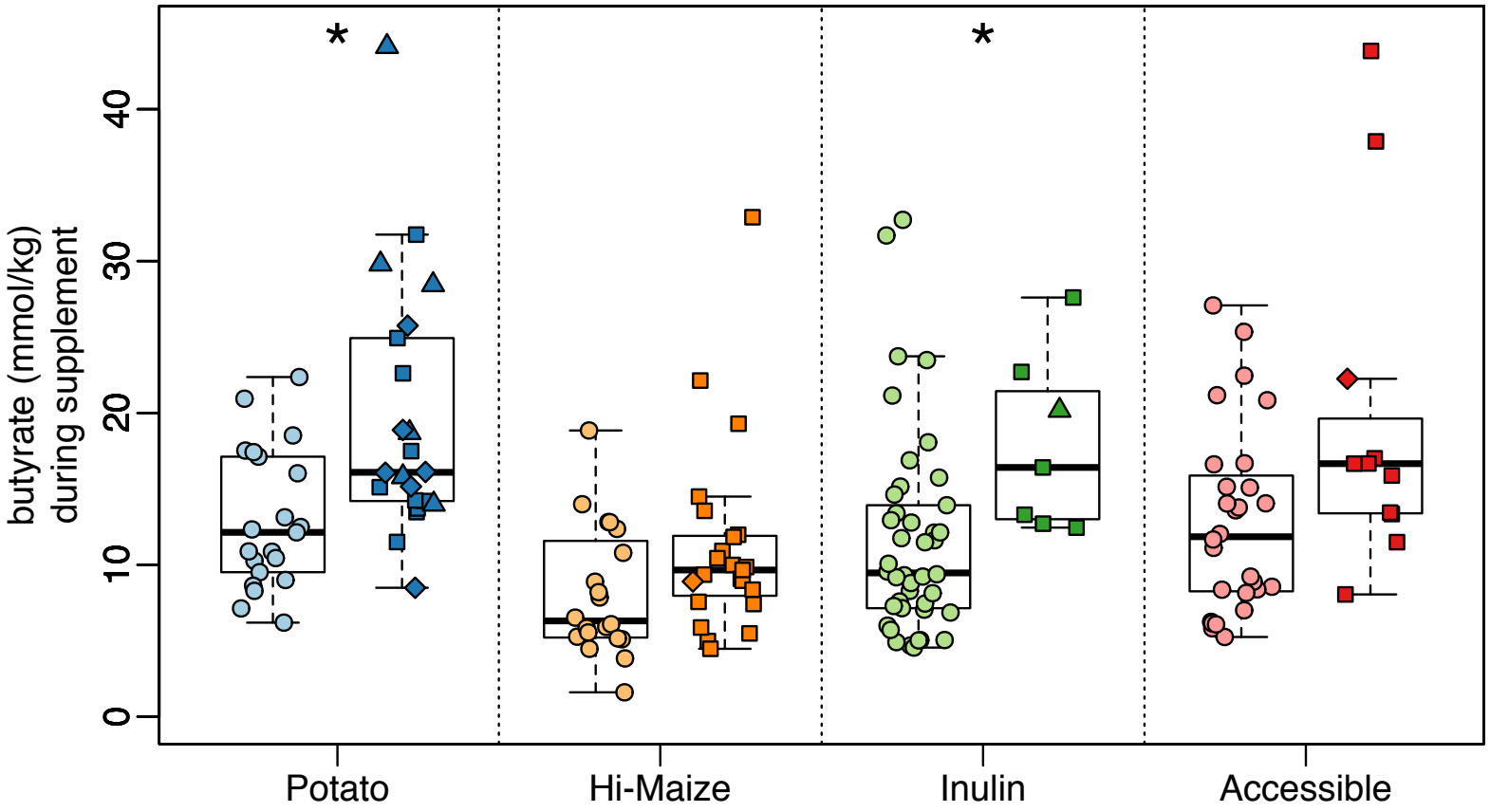


Correlations between primary degraders and butyrate producers

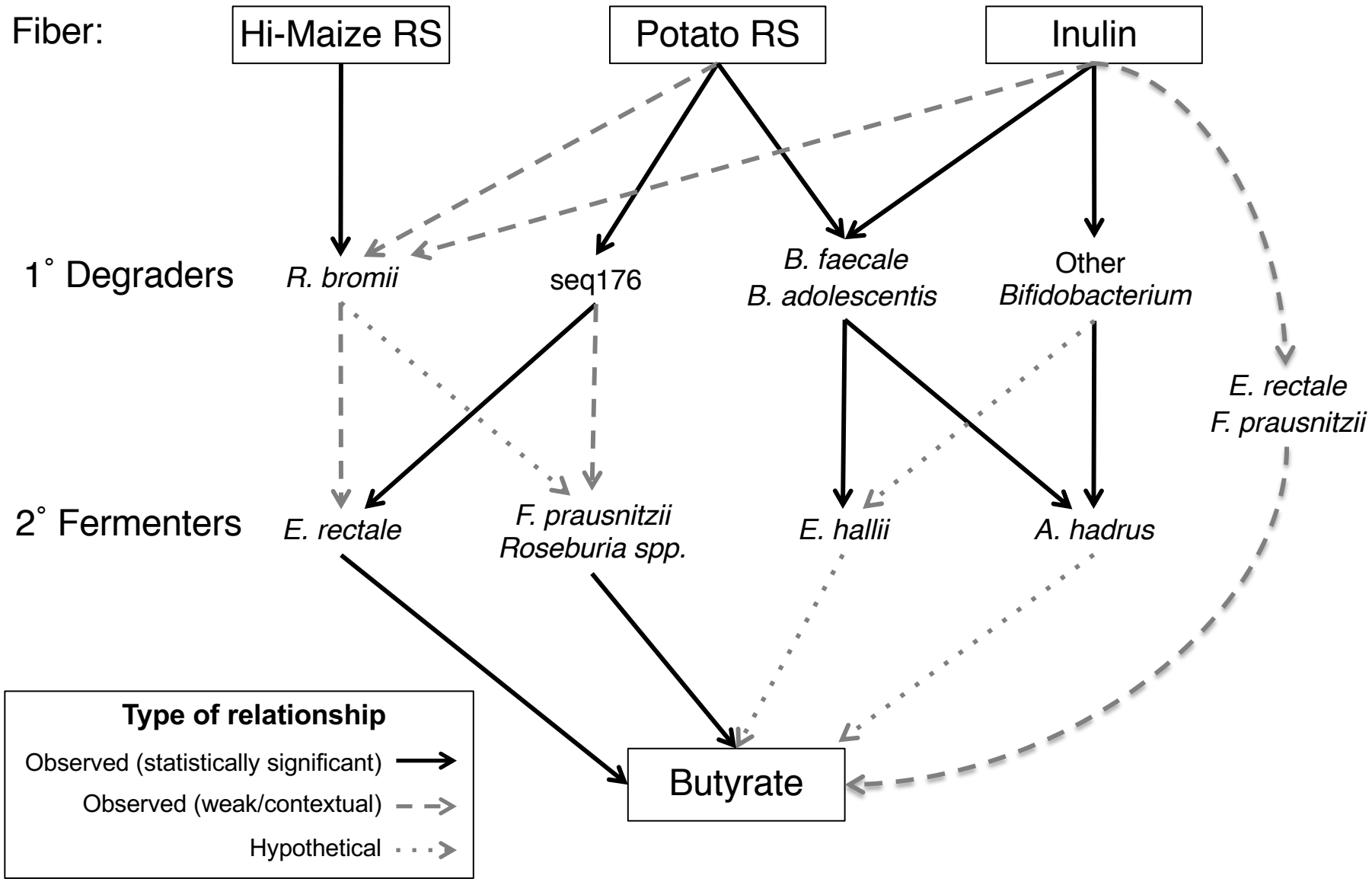


Ruminococcus bromii is a keystone species

Increases in abundance of *R. bromii* (darker symbols on right of each panel) are associated with higher [butyrate] with all fibers tested

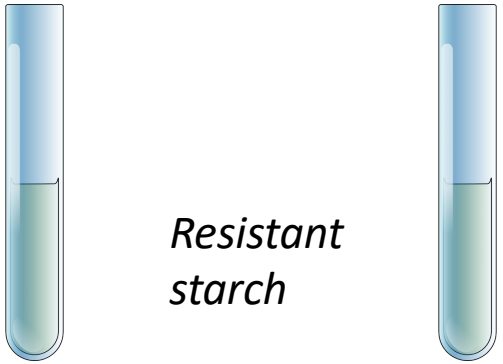


Anaerobic food web from fiber to butyrate



Preferential relationships between primary degraders and butyrate producers

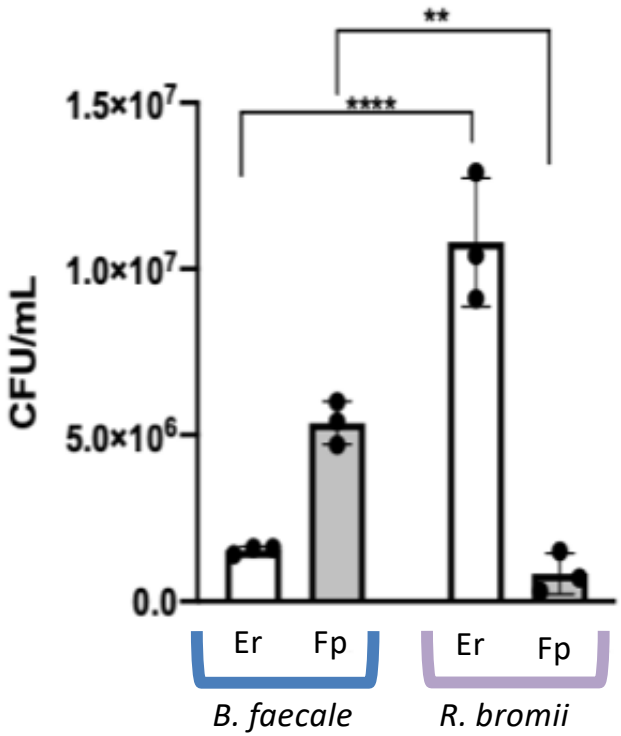
Competition experiment between *E. rectale* (Er) and *F. prausnitzii* (Fp) when resistant starch is degraded by either *B. faecale or R. bromii*



Resistant starch

B. faecale
F. prausnitzii
E. rectale

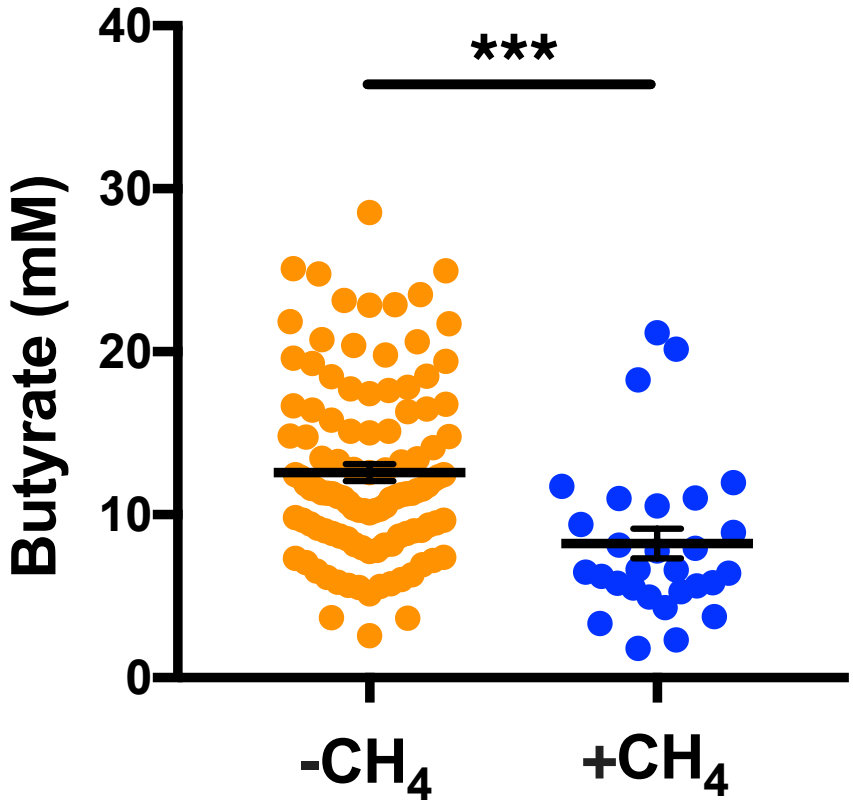
R. bromii
F. prausnitzii
E. rectale



Evidence for role of H_2 in butyrate production

→ Less butyrate in individuals who exhale methane

$$4H_2 + CO_2 \longrightarrow CH_4 + 2H_2O$$



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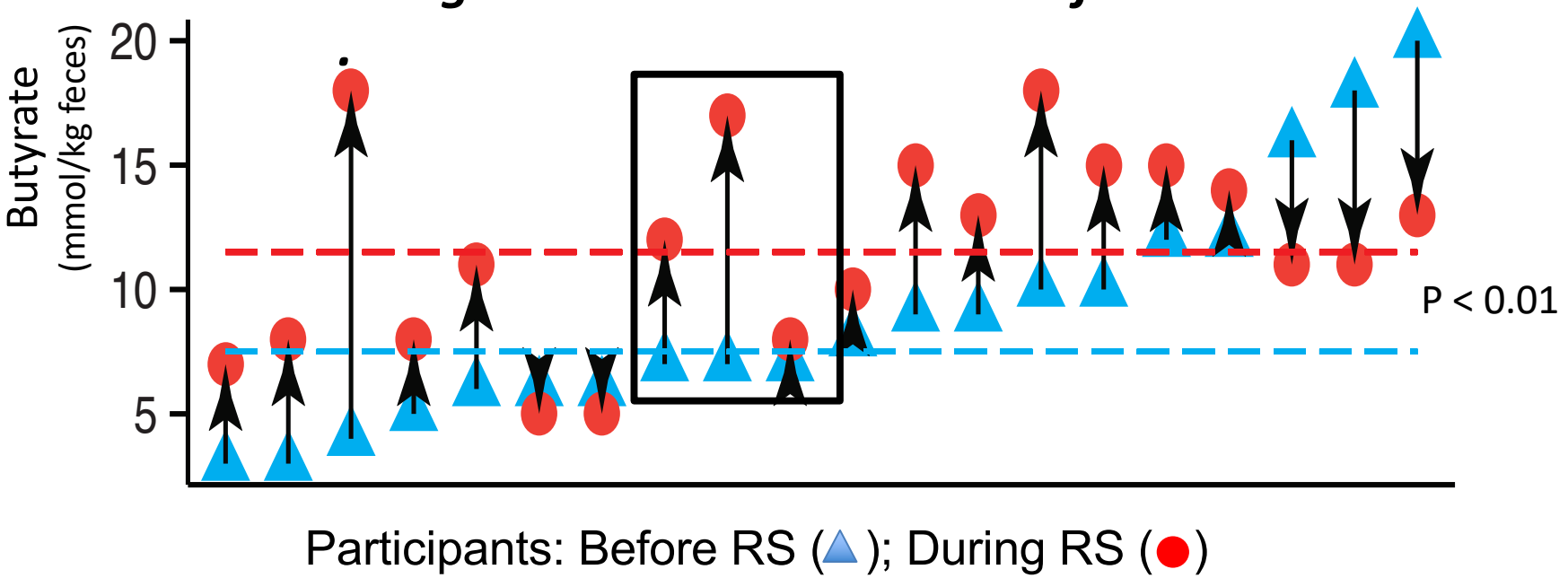


Schmidt and colleagues (2016) Microbiome; (2018) mBIO

Summary

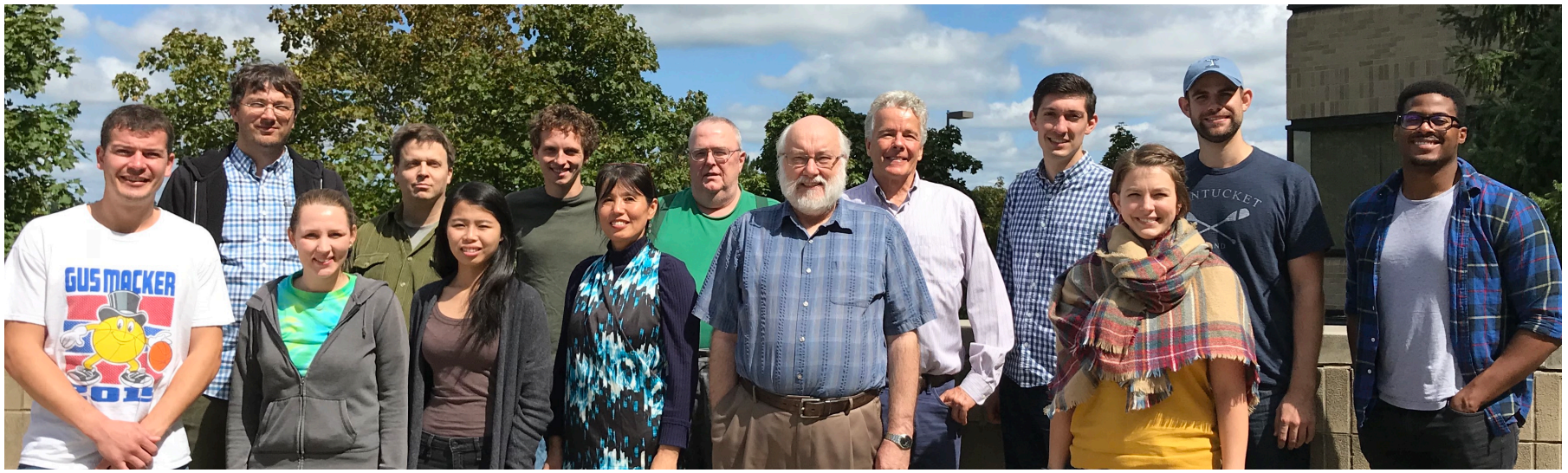
1. Supplementing diet with fibers (30 g/day) increases fecal [butyrate] in > 60% of individuals

2. *Ruminococcus bromii* is a keystone species

3. [H_2] impacts fermentation products of butyrogens

4. Methanogens impact butyrate production

Schmidt Lab



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MEDICAL SCHOOL
HOST MICROBIOME INITIATIVE
UNIVERSITY OF MICHIGAN

Take care of your
microbial garden,
Eat more fiber!

Tom Schmidt
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