Microbiome Bioinformatics

2017 Spring Lecture Series for High School Students

Bioinformatics and Research Computing
Whitehead Institute

http://jura.wi.mit.edu/bio/education/

What is microbiome bioinformatics?

- Microbiome
  - the microorganisms in a particular environment
  - can be in or on the body or somewhere else
- Bioinformatics
  - the application of computational methods to the field of molecular biology
  - also called *computational biology*
- Metagenome
  - the combined genetic material of the microorganisms in a particular environment

- Bioinformatics is essential for studying and interpreting the microbiome and its metagenome.

Bioinformatics & Research Computing

at Whitehead Institute

Consultation and collaboration, training and education, and software in the areas of Bioinformatics and Graphics.

BaRC
Bioinformatics and Research Computing

Missing from photo:
Kris Richardson

| George Bell | Bingbing Yuan | Prat Thiru | Inma Barrasa |

Why study the microbiome?

- Determine what microorganisms are living in an environment

- For the human microbiome, part of what we want to learn is
  - how the microbiome differs in and on healthy compared to sick people
  - if the microbiome can be used to diagnose disease
 - if changing one's microbiome can make him/her sick or healthy

Old-fashioned microbe identification

- Grow the microbes in culture dishes and run classification tests on what grows

- Problems
  - We can only identify major microbe groups
  - Most microbes don't grow in culture dishes

- This gave us interesting information, but we missed most microbes

Ribosomal RNA microbe identification
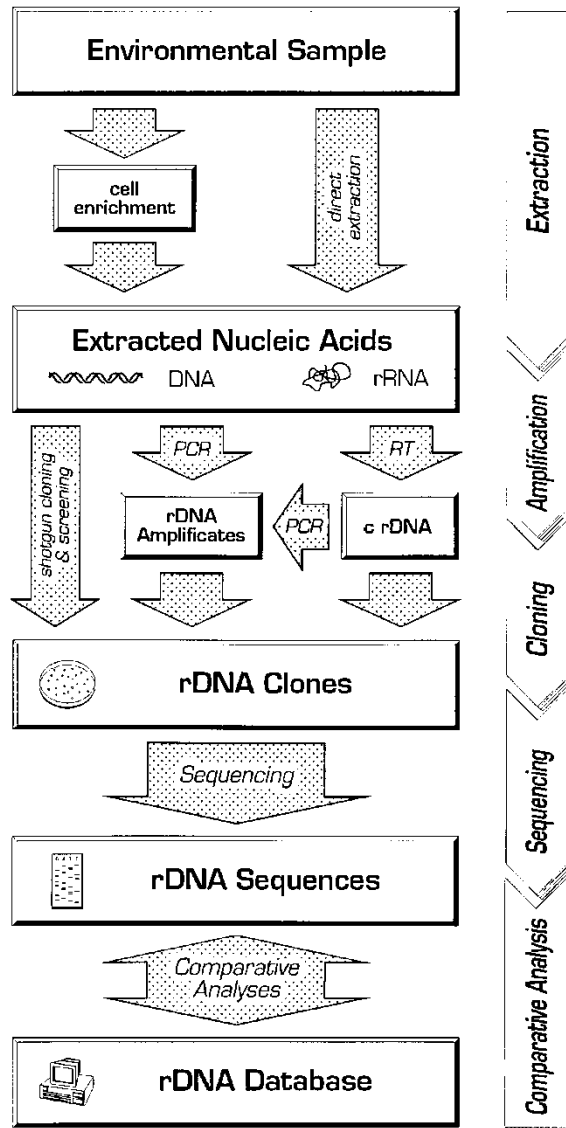
- Identify each microbe
  - by amplifying and sequencing its rRNA
  - Comparing the rRNA sequence to a database of many rRNA sequences

- 16S rRNA (~1500 nt) is most common

Amann et al., 1995

6

Sample 16S rRNA alignment

Metagenomic sequencing

- An attempt to sequence all the DNA in a sample

- Requires a reference database of microbe genomes for comparison and identification

- Can be used to identify genes and type of organism (and predict what the genes do)

- The DNA will typically also contain DNA from the host (ex: the person)

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The Human Microbiome Project

- Goal: characterize the human microbiome and its role in human health and disease

- Assayed 300 people at 15-18 body sites

- Used 16S rRNA gene sequencing

- Lots of interesting findings

- Q: Does the microbiome depend more on the person or on the body site?

Human variation between 5 main body areas

Principal
components
plot

The Human Microbiome Project Consortium, 2012.

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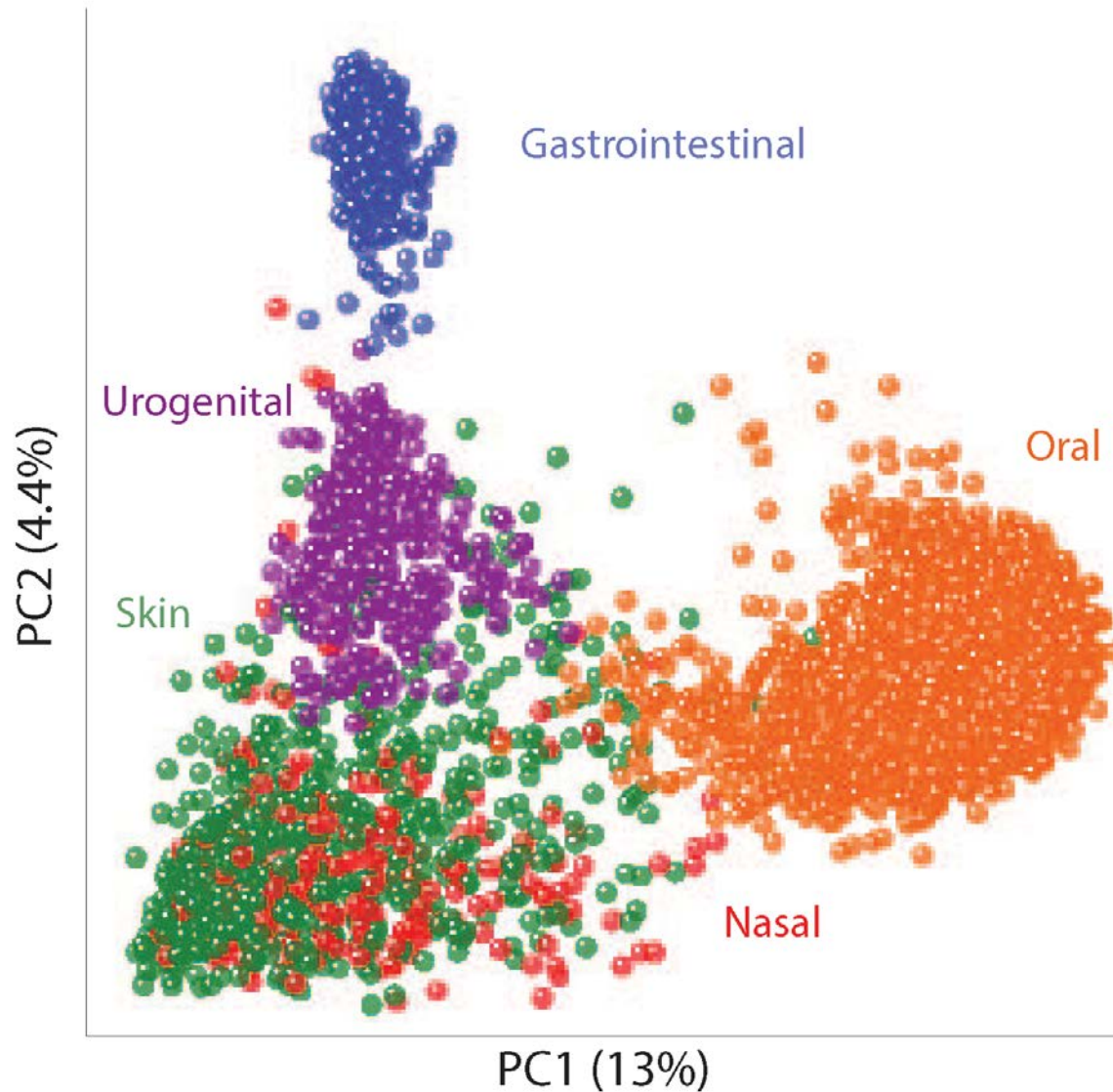
Bacterial phyla at different body sites
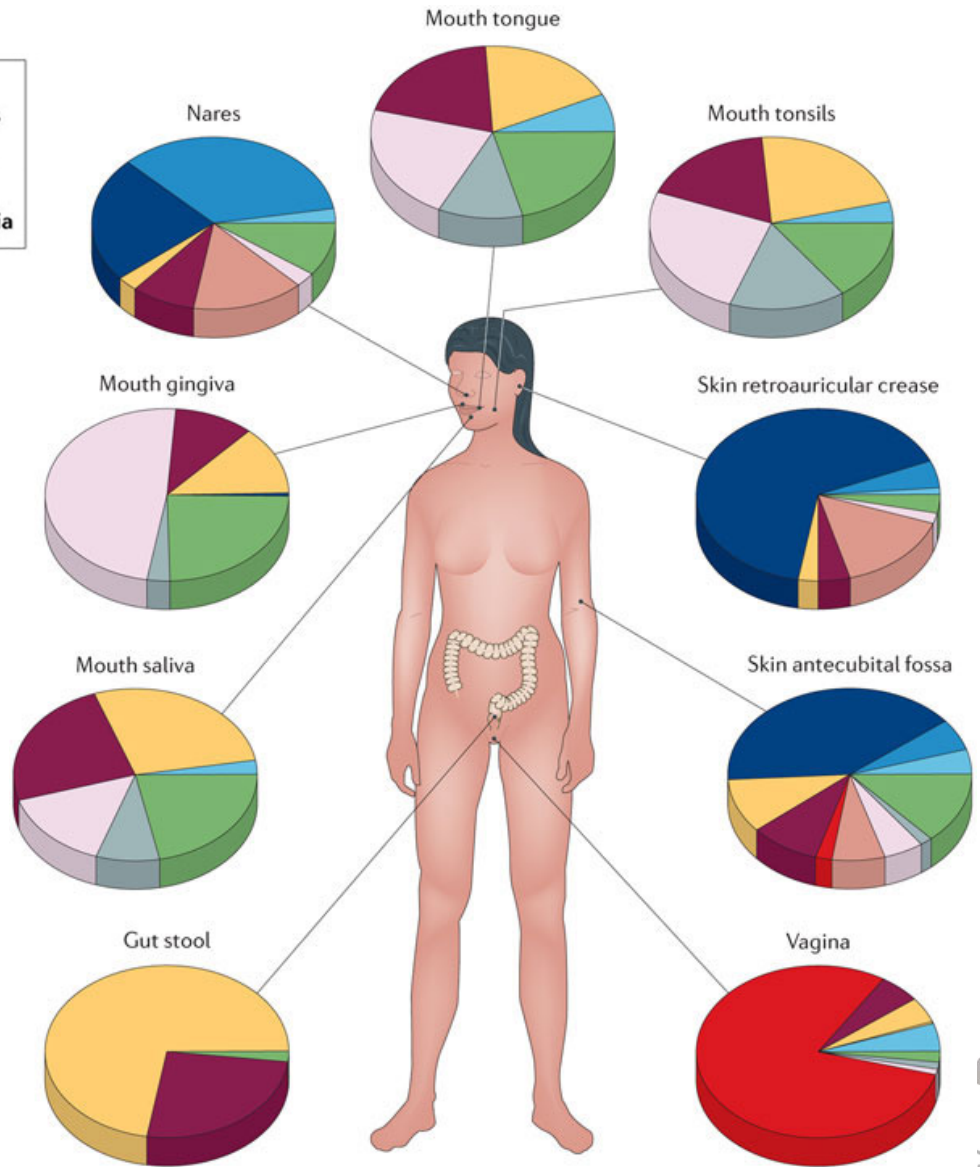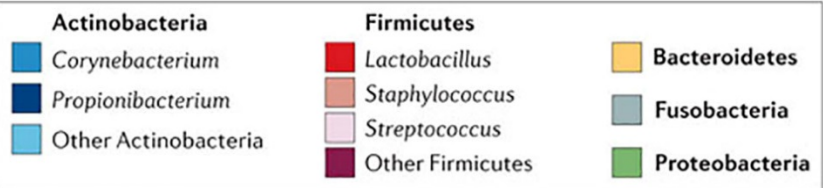
Summary from the
Human Microbiome Project

Lasken and McLean, 2014

Each person has a unique gut microbiome
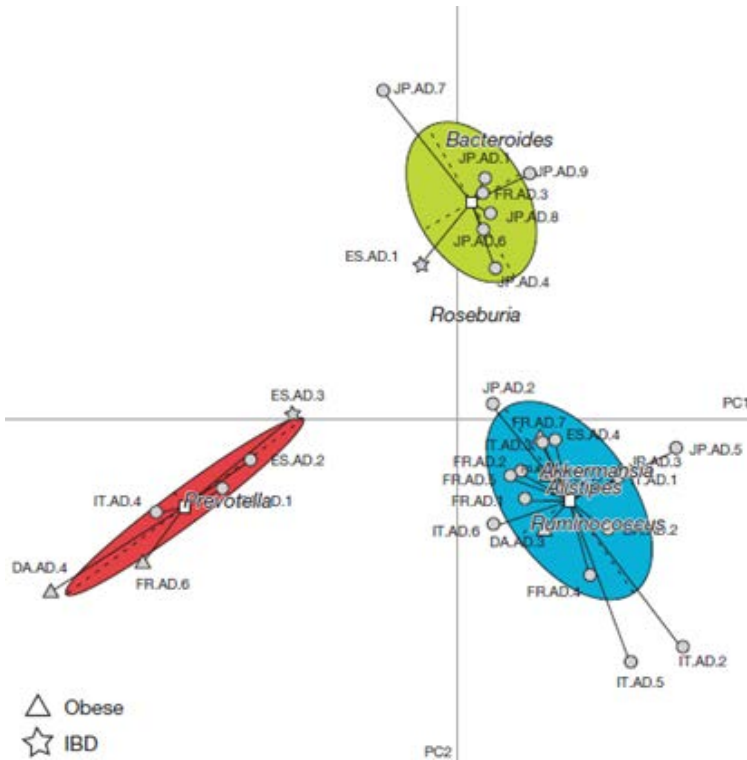
Arumugam, M. et al. Nature (2011)

Ley, R.E., et al. Nature (2006)

Differences within the same enterotypes between individuals
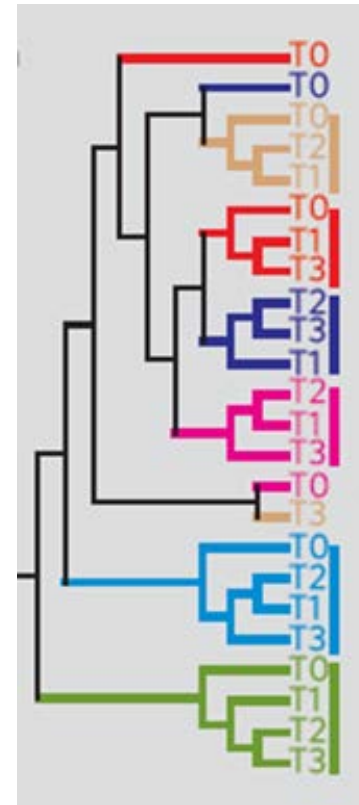
Clustering of gut flora is by individual (same color bars) over time (approx 3, 6, and 12 months)

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Medical conditions associated with microbiome changes

- Dental cavities
- Diabetes
- Obesity
- Inflammatory bowel disease (Crohn's disease, etc.)
- Acute gastroenteritis
- Some skin diseases
- Some food allergies

What influences what?

- Observation: obese people tend to have a different gut microbiome than healthy people
- Why? Many possible explanations
  1. Obesity influences the microbiome
  2. The microbiome influences one's chance of becoming obese
  3. One's diet leads to obesity <u>and</u> a change in the microbiome
  4. Others?
- How could you figure out which explanation(s) are correct?

- To remember: "Correlation does not imply causation"

Fecal transplantation (part 1)

- Can a "good" microbiome cure a disease?
- Experiment:
  - Take stool from a healthy person
  - Put it into a sick person's gut
  - Does the sick person get better?
- Example studies (at right):
  - diarrhea caused by *Clostridium difficile*
- Stool source: OpenBiome project ($40 per deposit)

Study

Satokari et al.,2014
Emanuelsson et al.,2014
Ray et al.,2014
Dutta et al.,2014
Brandt et al.,2012
Mattila et al.,2012
Kelly et al.,2012
Youngster et al.,2014
Zainah et al.,2014
Macconnachie et al.,2009
Aas et al.,2003
Pathak et al.,2014
Russell et al.,2014
Lee et al.,2014
Hirsch et al.,2015
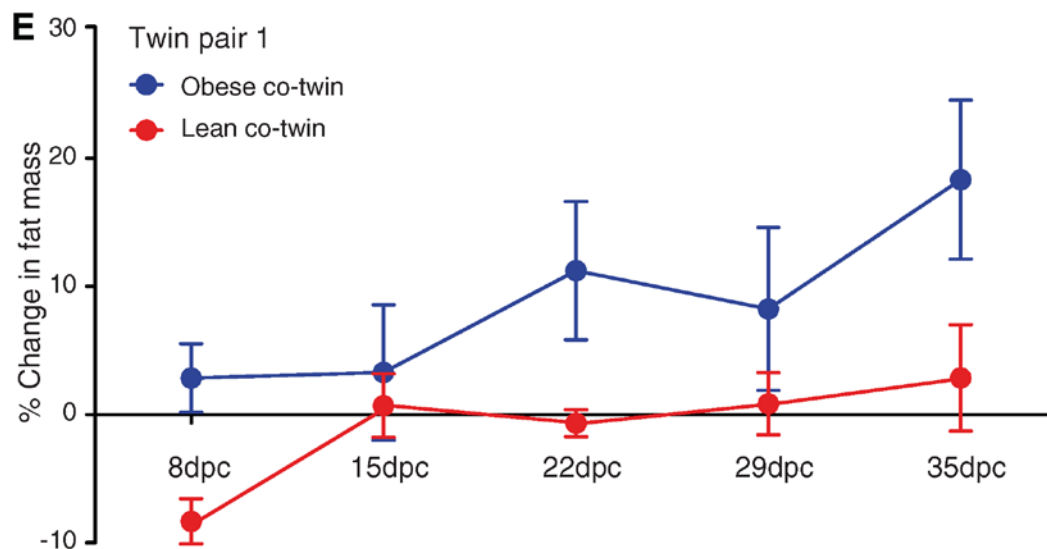Aroniadis et al.,2015
Khan et al.,2014

Random effects model

0.5   0.6   0.7   0.8   0.9   1
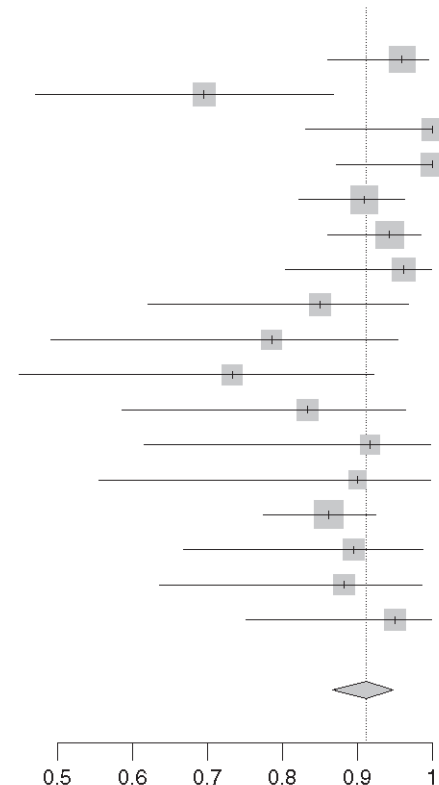
Fraction of patients cured
(average = 91%)

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Fecal transplantation (part 2)

- Does the gut microbiome influence body fat?
- Experiment:
  - Raise germ-free baby mice
  - Do fecal transplantation from lean and obese human twin donors
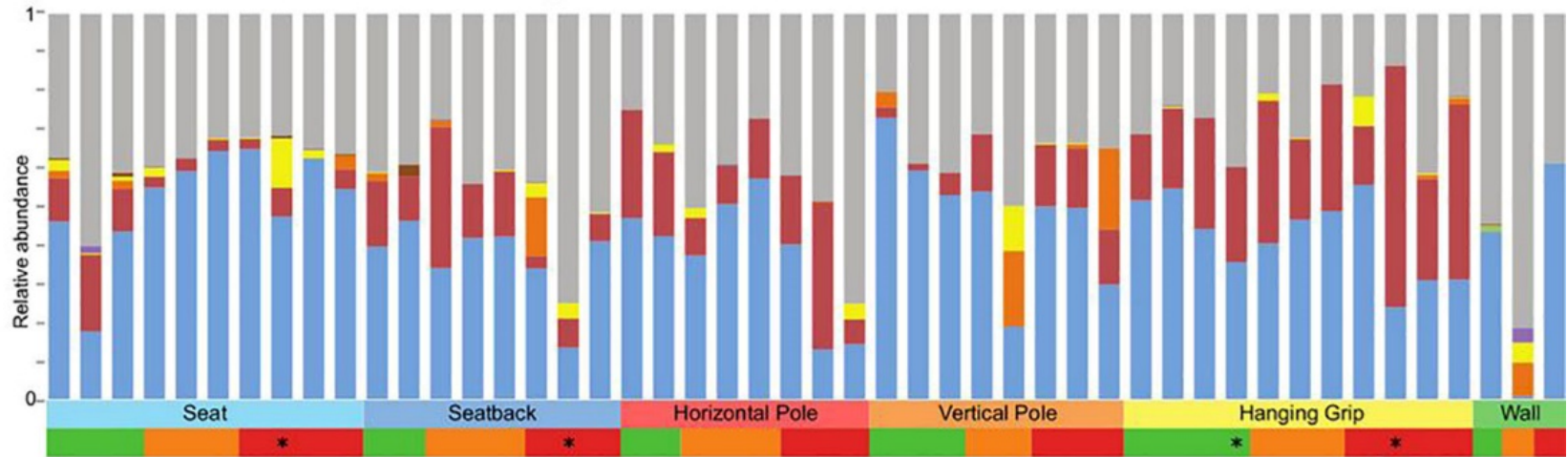 - Does this influence the mice as they grow? Yes!

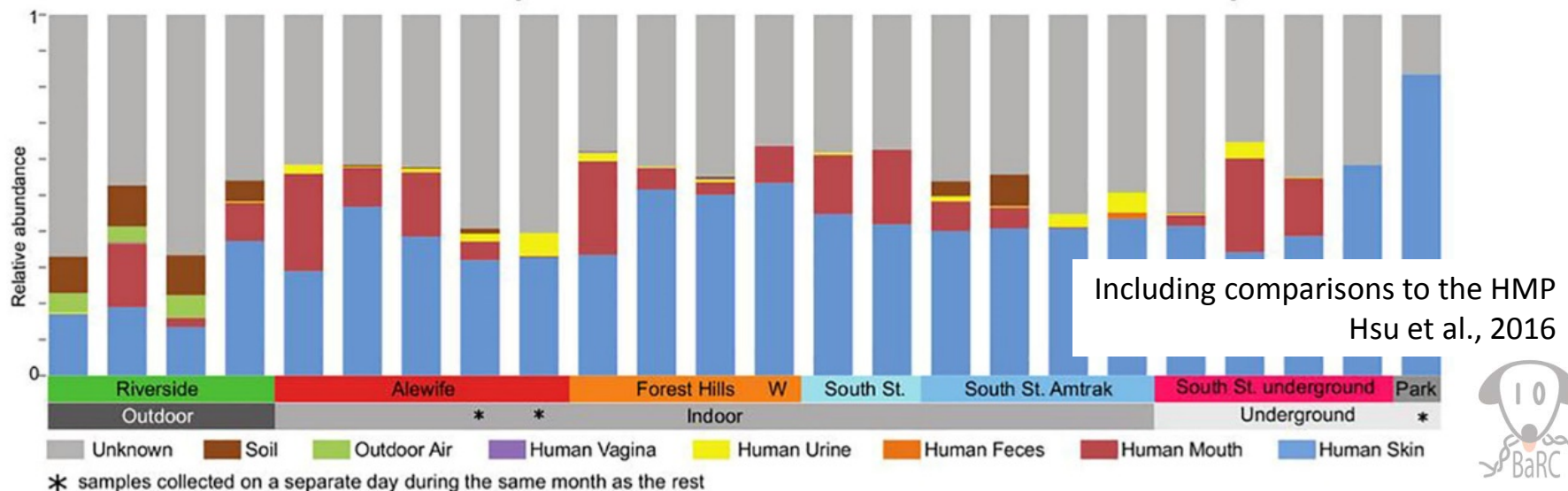dpc = days post colonization
Ridaura et al., 2013

The MBTA microbiome

B Predicted sources of subway surface microbial communities on train cars

C Predicted sources of subway surface microbial communities in subway stations

Including comparisons to the HMP
Hsu et al., 2016

Microbiome Bioinformatics: exercises

- How can gut microbiome rRNA help diagnose gastrointestinal problems?

- How do bacterial groups differ between the microbiomes of different body sites?

- [How] does the gut microbiome change after fecal transplantation?

- etc.

Microbial taxa varies while metabolic pathways remain stable within a healthy population

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