Population Genetics in the Human Microbiome

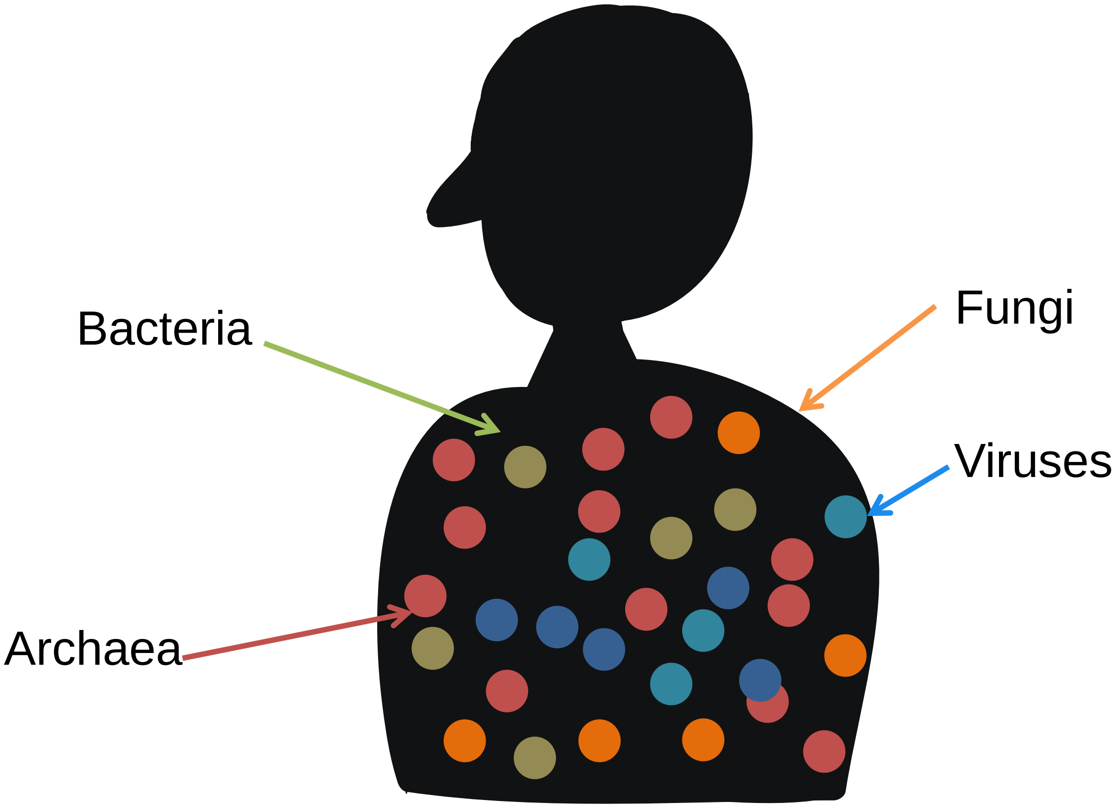
Nandita Garud

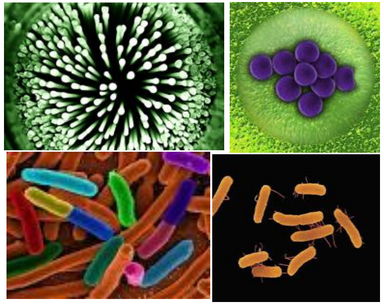
Department of Ecology and Evolutionary Biology, UCLA
ngarud@ucla.edu | http://garud.eeb.ucla.edu

@nanditagarud

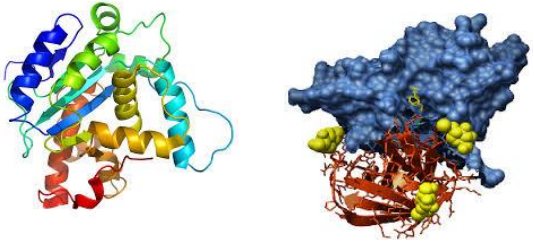
UCLA

The human microbiome is a complex community

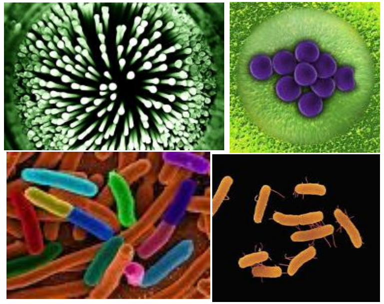




Who is there?



What are they doing?



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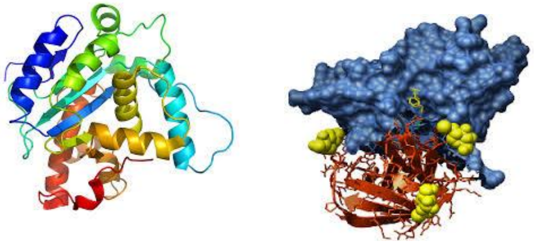

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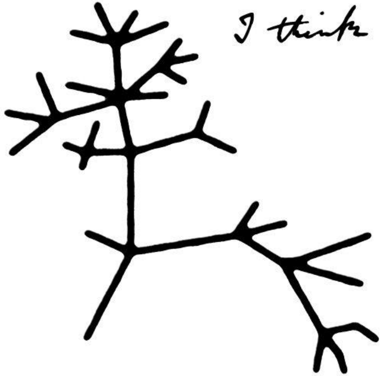
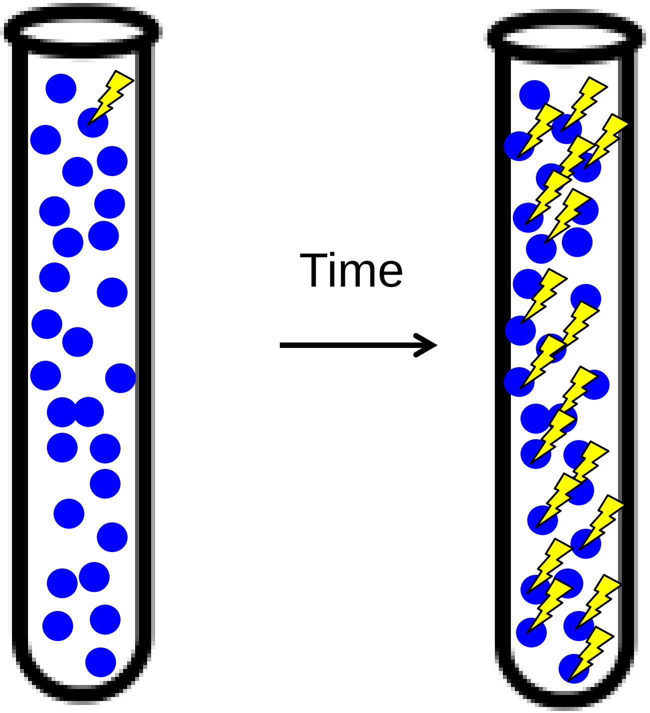


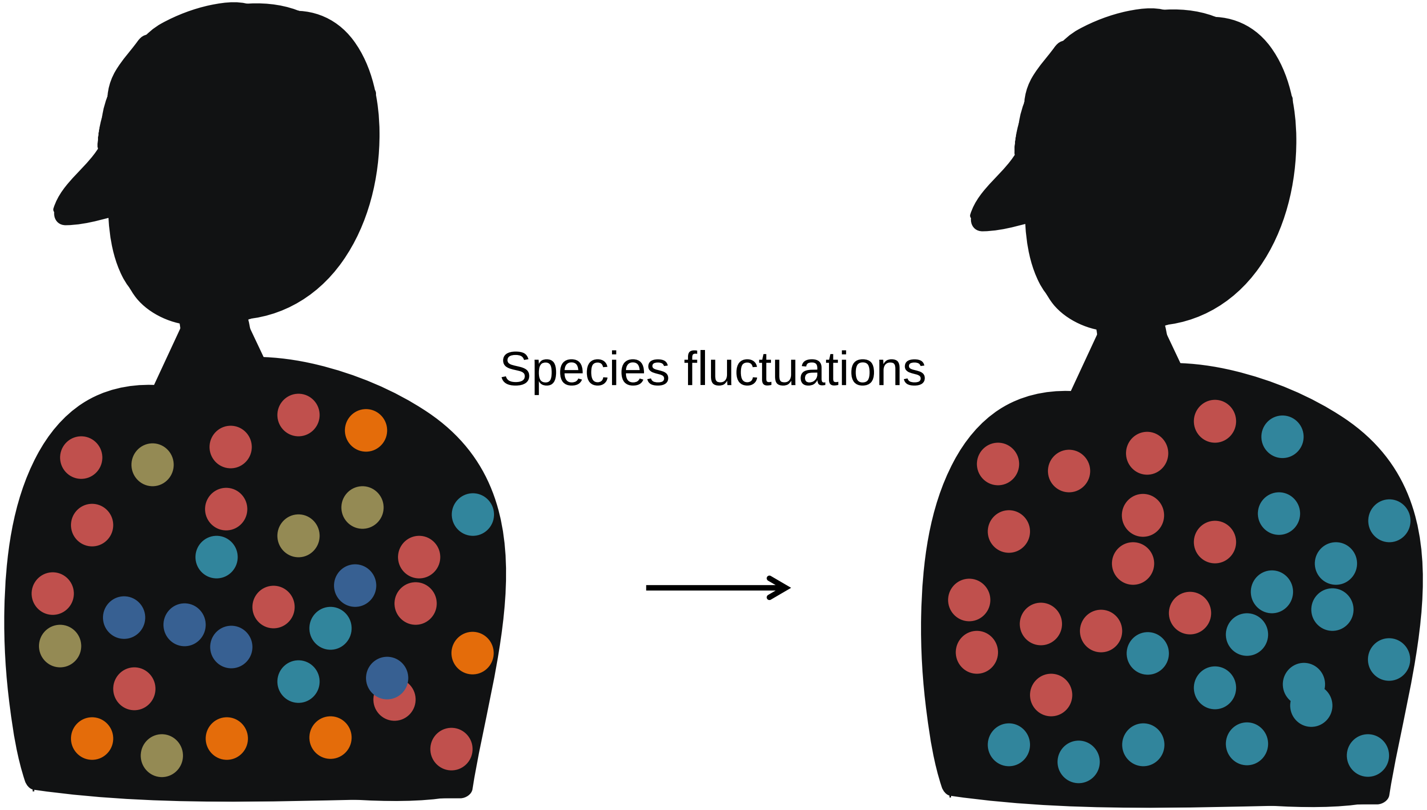
How are they evolving?

Rapid evolution in a simple community



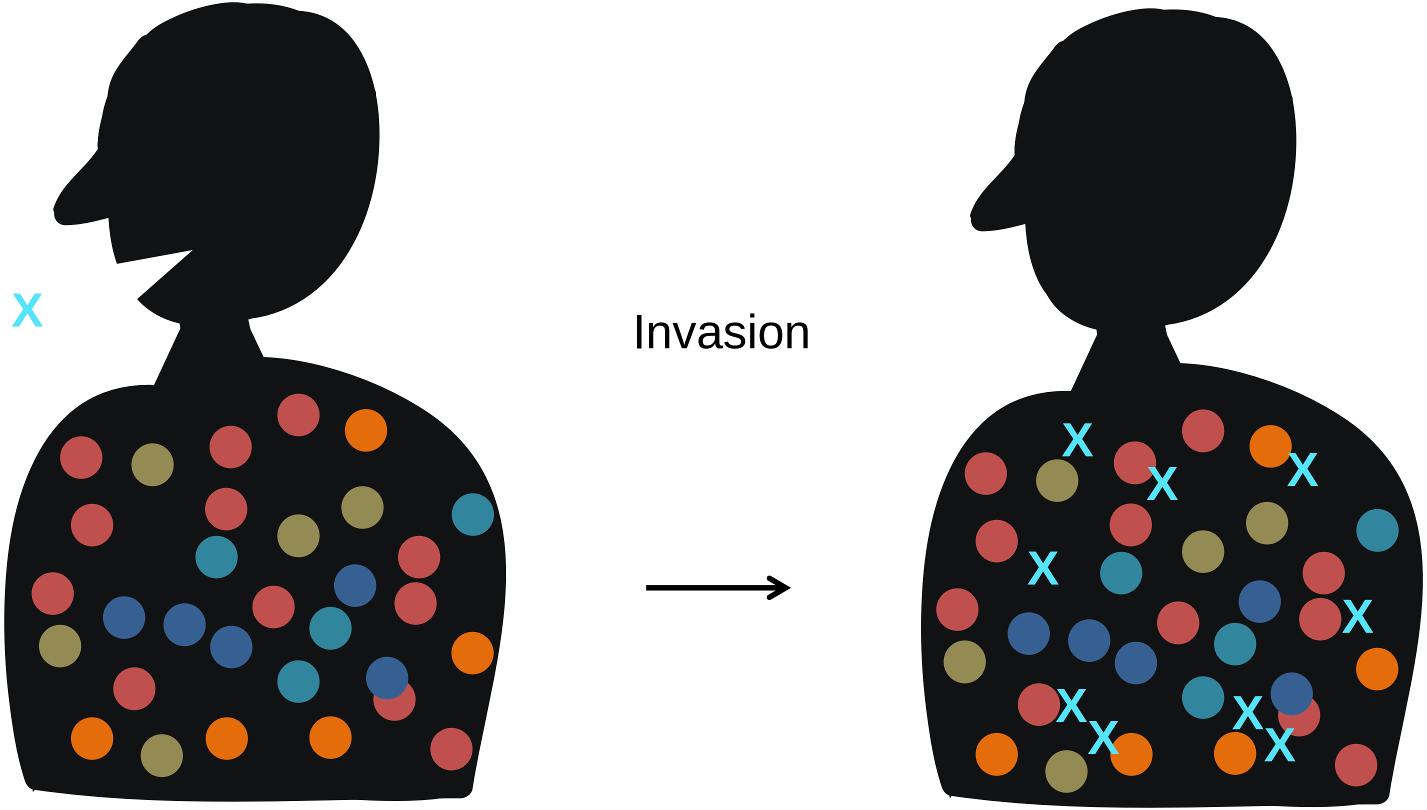
Richard Lenski and colleagues

Do microbiota respond to their environment by evolutionary or ecological processes?



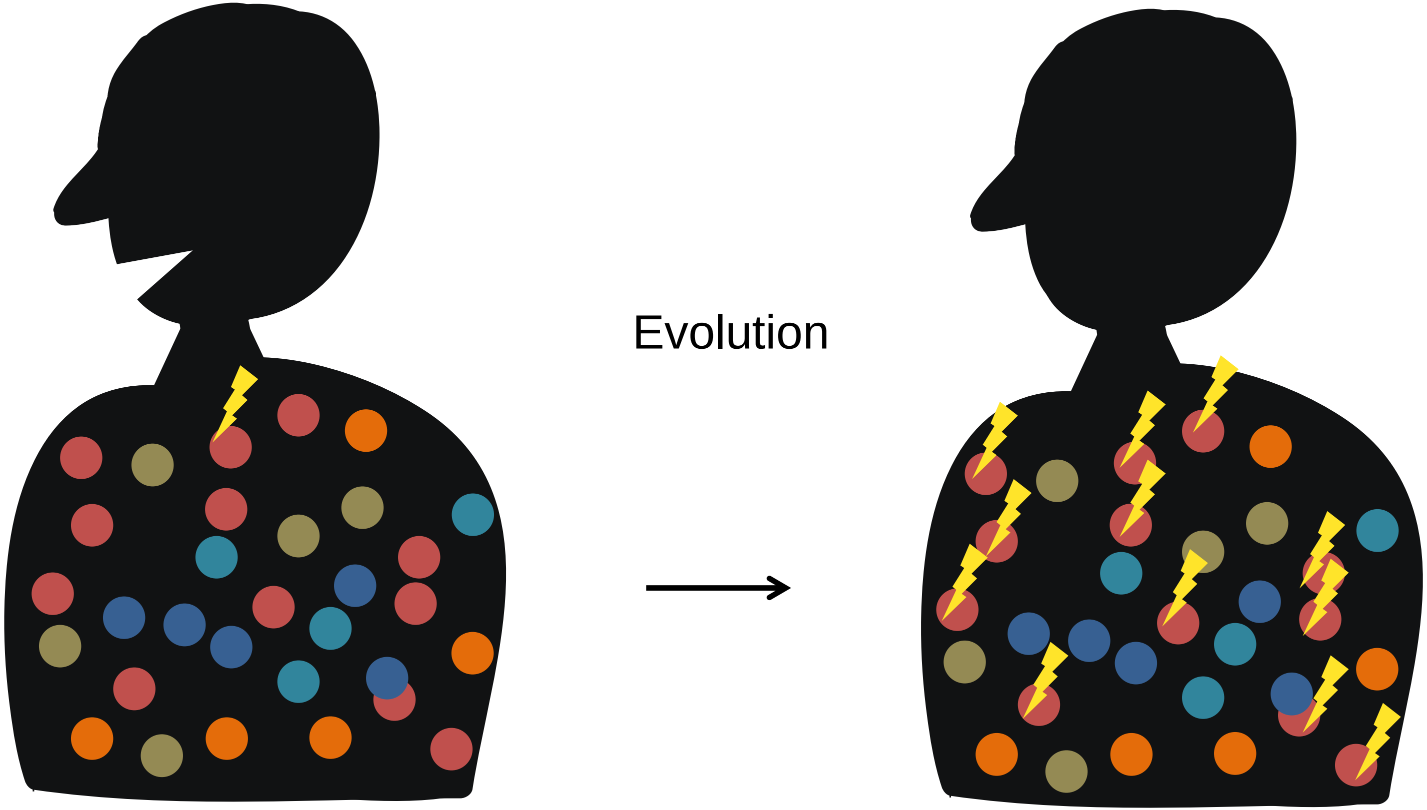
Species fluctuations

Do microbiota respond to their environment by evolutionary or ecological processes?



Invasion

Do microbiota respond to their environment by evolutionary or ecological processes?



Evolution

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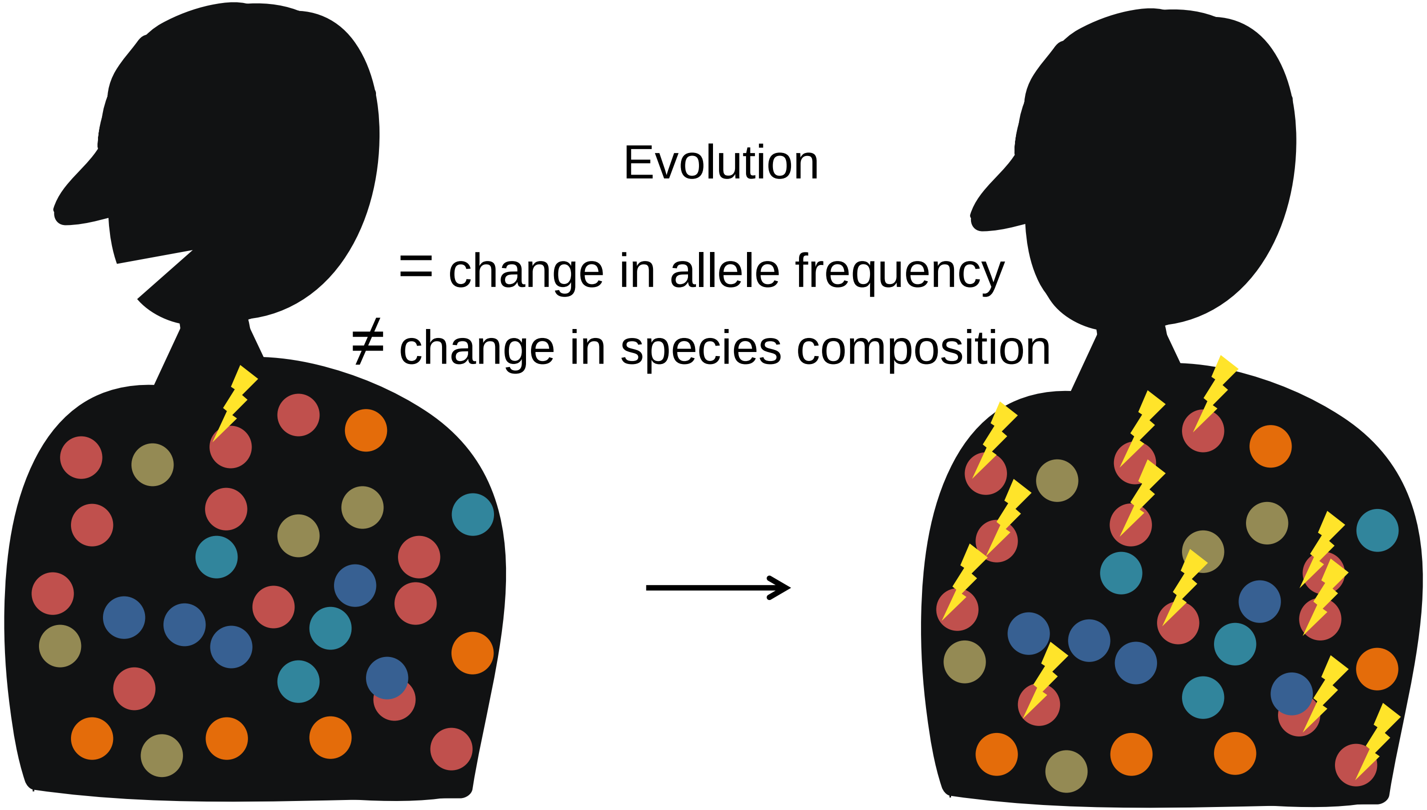


Evolution

= change in allele frequency

≠ change in species composition

Abundant opportunity for evolution in the human microbiome

~1:1 ratio of human to microbial cells!

Sender *et al.* 2016 PLoS Bio.

~1 billion mutations entering our microbiomes daily!

Zhao, Lieberman *et al.* 2019 Cell Host Microbe

Evolution

⟶

What determines the fate of a new mutation?

- Drift and migration
- Adaptation
- Recombination

Population genetic processes can give rise to a range of traits in the microbiome

Digestion of food

Hehemann *et al*. 2010 Nature

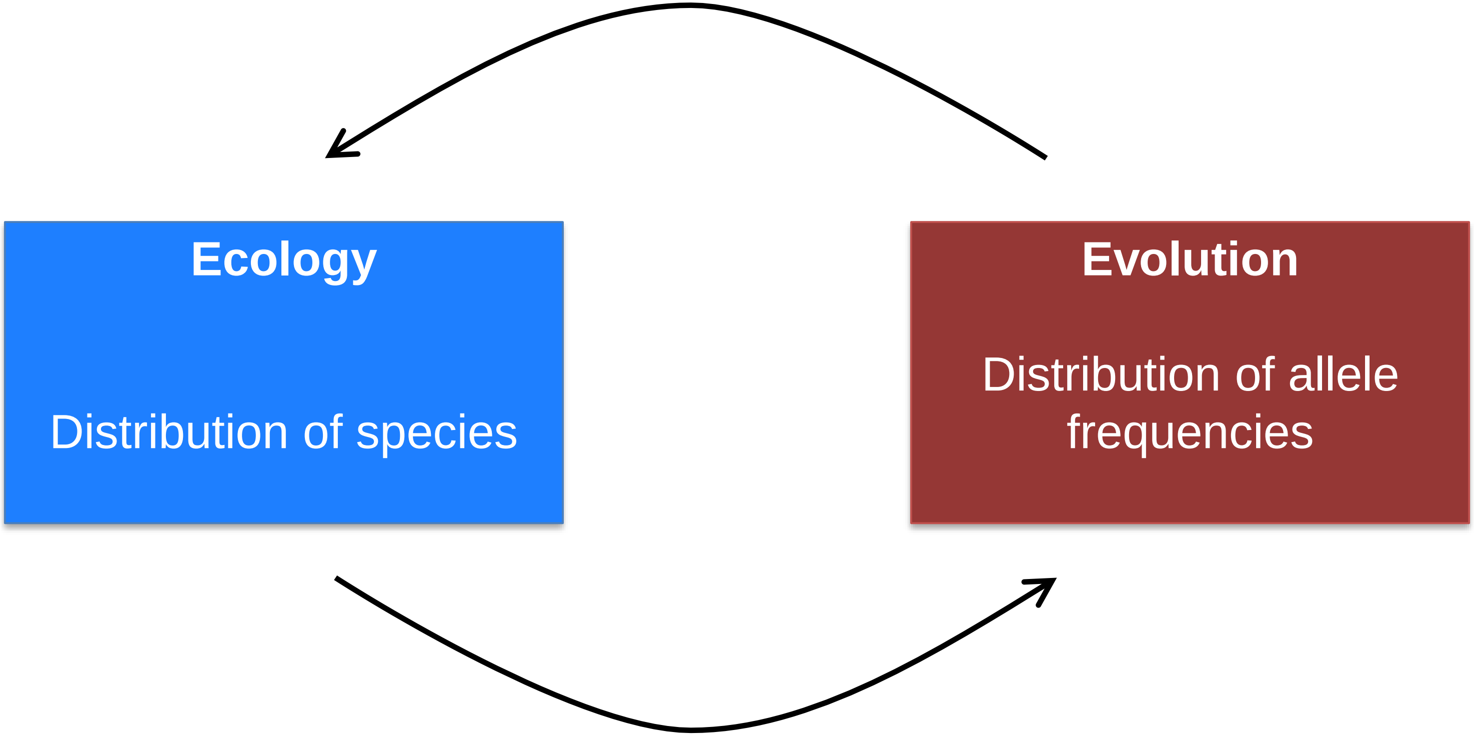
Antibiotic resistance

(e.g. Karami *et al*. 2007 J. Antimicrob. Chemother.)

Drug metabolism

(Haiser *et al.* 2013 Science)

Ecology AND Evolution



Ecology

Distribution of species

Evolution

Distribution of allele frequencies

Trends in Genetics

CellPress REVIEWS

Review

Population Genetics in the Human Microbiome

Nandita R. Garud[1,*] and Katherine S. Pollard[2,3,4,*]

While the human microbiome's structure and function have been extensively studied, its within-species genetic diversity is less well understood. However, genetic mutations in the microbiome can confer biomedically relevant traits, such as the ability to extract nutrients from food, metabolize drugs, evade antibiotics, and communicate with the host immune system. The population genetic processes by which these traits evolve are complex, in part due to interacting ecological and evolutionary forces in the microbiome. Advances in metagenomic sequencing, coupled with bioinformatics tools and population genetic models, facilitate quantification of microbiome genetic variation and inferences about how this diversity arises, evolves, and correlates with traits of both microbes and hosts. In this review, we explore the population genetic forces (mutation, recombination, drift, and selection) that shape microbiome genetic diversity within and between hosts, as well as efforts towards predictive models that leverage microbiome genetics.

Highlights

Genetic variation in host-associated microbiomes can be assayed in a high-throughput manner with a variety of technologies.

Many bacterial species recombine extensively, although they asexually reproduce.

The genetic diversity of many species within and across hosts is spatially structured.

Evidence for rapid adaptation within hosts is starting to emerge.

Modeling efforts are connecting microbiome genetic variants with host phenotypes, highlighting the biomedical importance of genetic variation in the microbiome.

A Population Genetic View of the Dynamic Microbiome

The human microbiome comprises bacteria, archaea, viruses, and microbial eukaryotes living in our bodies. The taxonomic composition of these communities has been extensively studied and is significantly associated with a variety of diseases and traits [1]. However, each species in the microbiome is genetically heterogeneous, comprising individual cells whose genomes contain different mutations [2]. Widespread deployment of sequencing technologies (Box 1) has revealed that most microbiota harbor extensive genetic variation between hosts, within a host over time, and even within a host at a given time [2,3]. As in other species, this variation comprises single-nucleotide variants (SNVs) [2], short insertions and deletions (indels) [4], and larger structural variants (SVs) [5], which include duplications, deletions, insertions, and inversions and can generate gene copy-number variants (CNVs) [6]. There has been substantial progress towards quantifying genetic diversity in the human microbiome [2,6–8].

By contrast, our knowledge of population genetic processes that shape the human microbiome is nascent. Population genetics is a discipline that makes statistical inferences about the evolutionary events that gave rise to patterns of genetic variation across individuals of the same species. The

Population genetic processes in the human microbiome

- Drift and migration
- Adaptation
- Recombination

Overview

- Data
- Drift and migration
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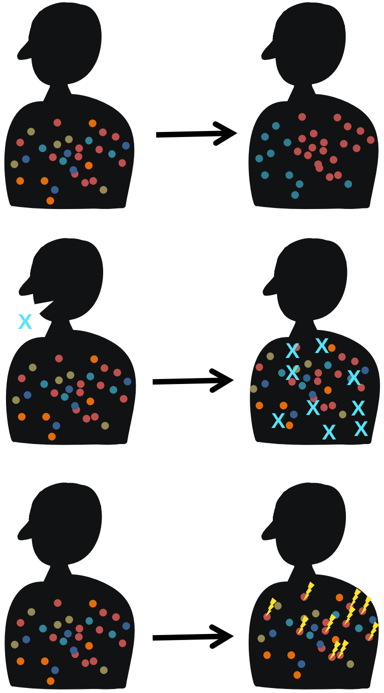
What kind of data do we need to study population genetics in the microbiome?



Species fluctuations

Invasion

Evolution

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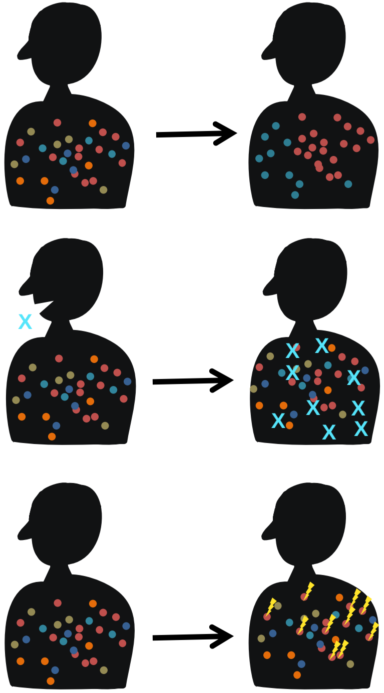

16S data

Species fluctuations

Invasion

Evolution

Species-level diversity has been extensively studied

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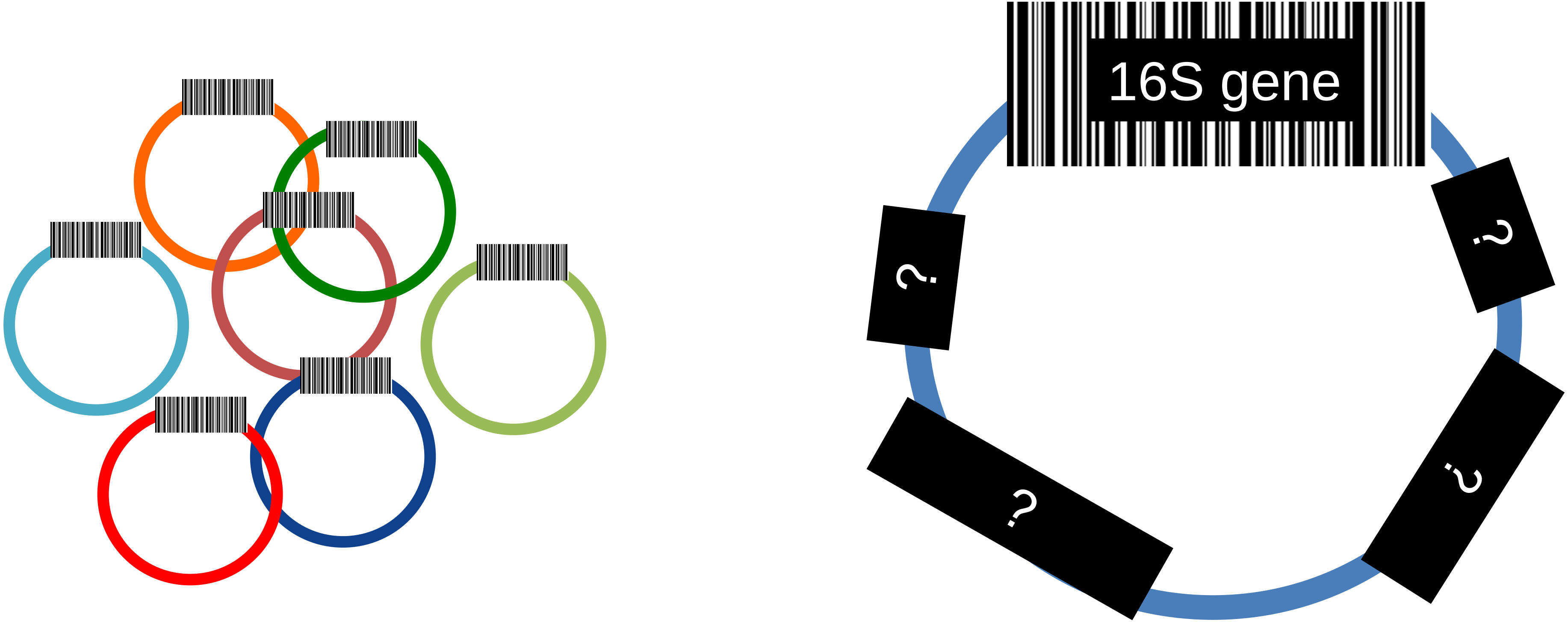
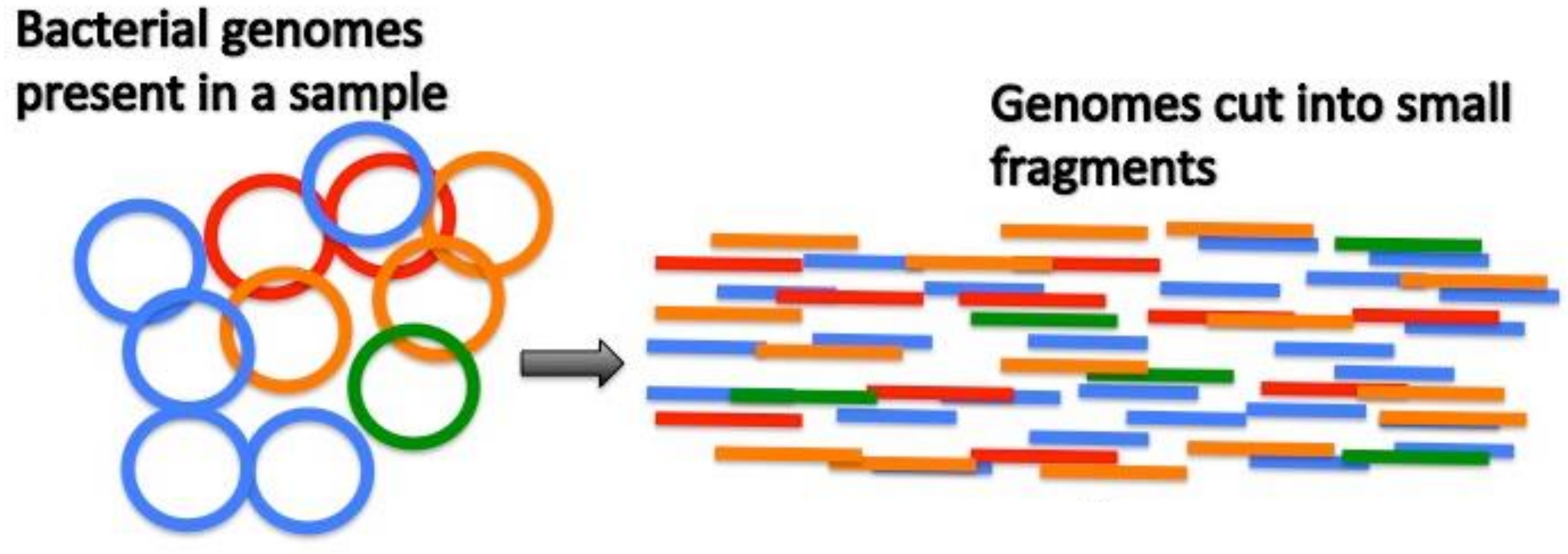


Whole genome shotgun sequencing allows us to sample the rest of the genome



Linkage on longer length scales

- Cultured isolate sequencing

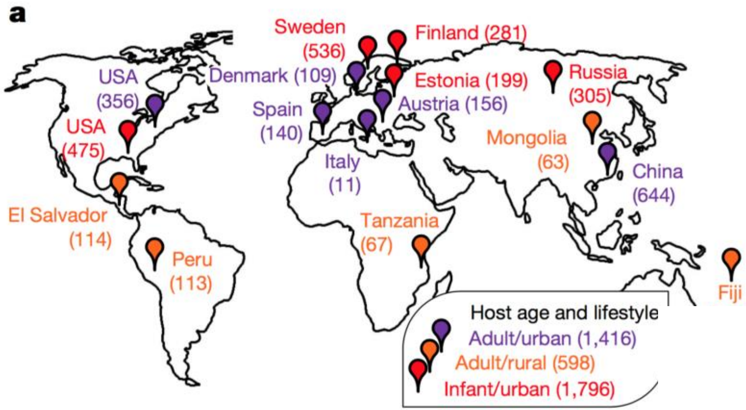
- Single cell and read-cloud sequencing

  (e.g., Bishara et al. 2018, Lan et al. 2017, Ma et al. 2017)

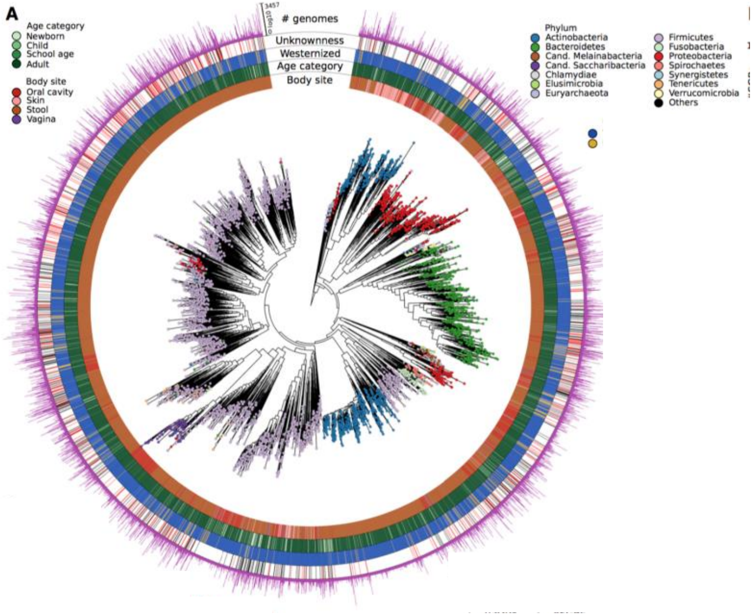
- Metagenome-assembled genomes

  (e.g., Pasolli et al. 2019, Nayfach et al. 2019, and Almeida et al. 2019)

Tree of life greatly expanded!

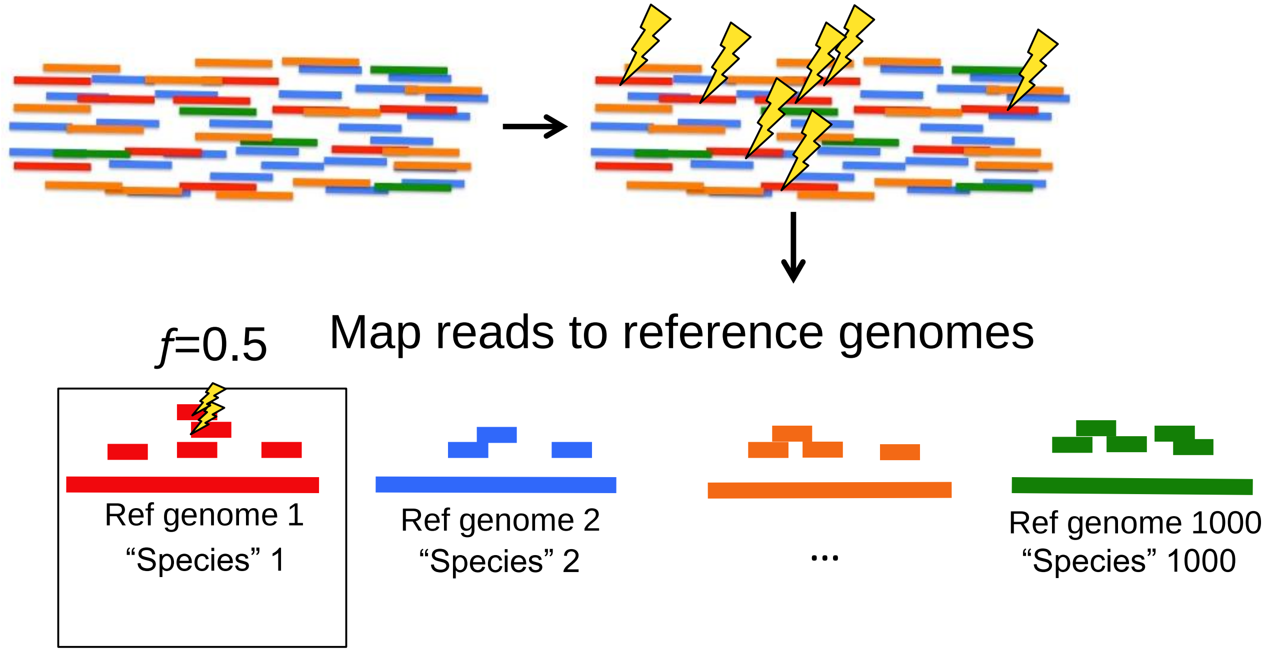


Nayfach et al. 2019



Pasolli et al. 2019

How can we detect genetic variation within species?



Map reads to reference genomes

$f=0.5$

Ref genome 1
“Species” 1

Ref genome 2
“Species” 2

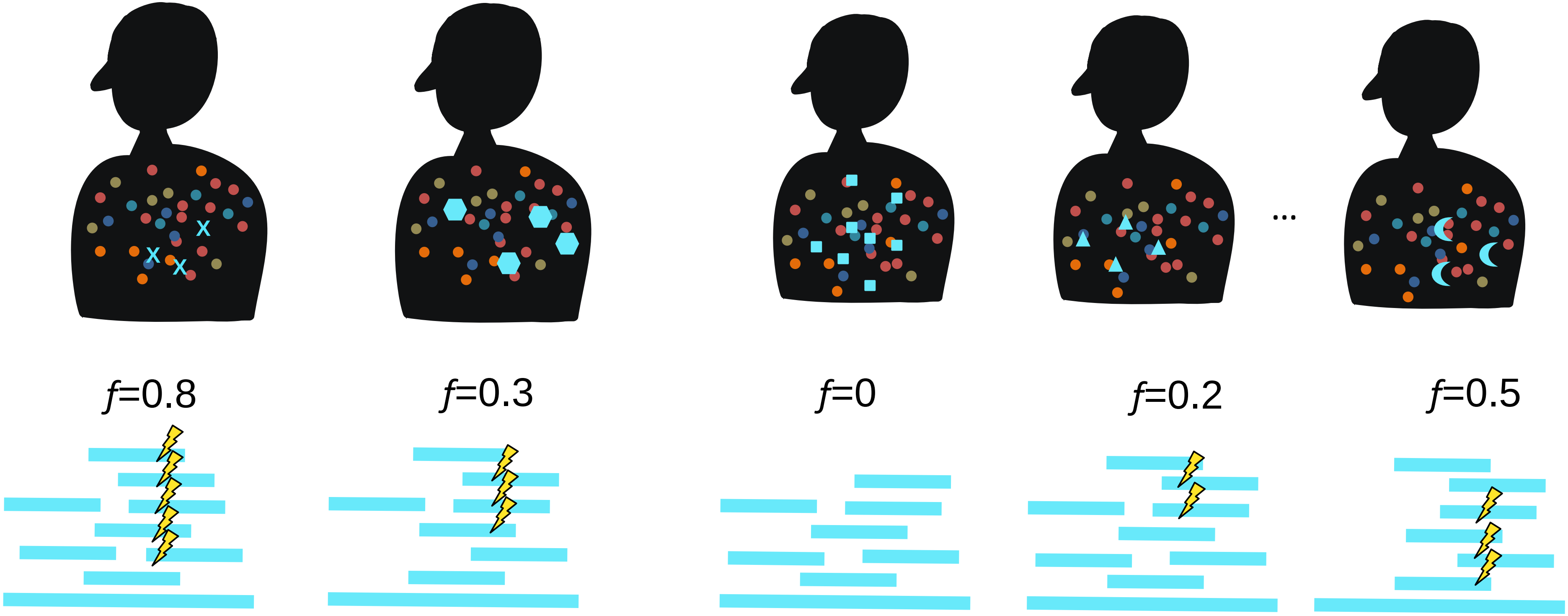
…

Ref genome 1000
“Species” 1000

Can analyze each species one by one

Nayfach, Rodriguez-Mueller, Garud, and Pollard, *Genome Research,* 2016

Genetic differences between samples



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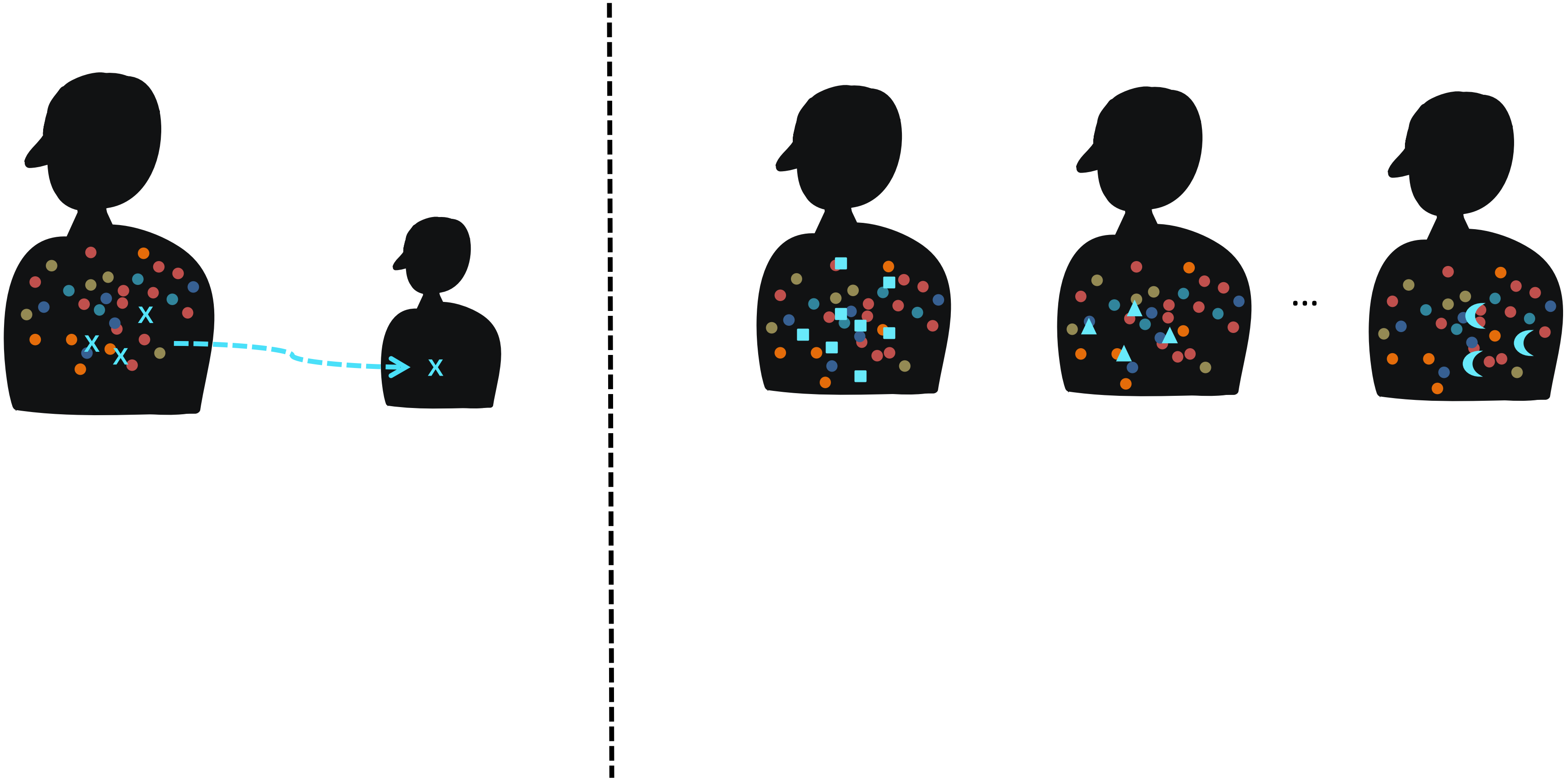
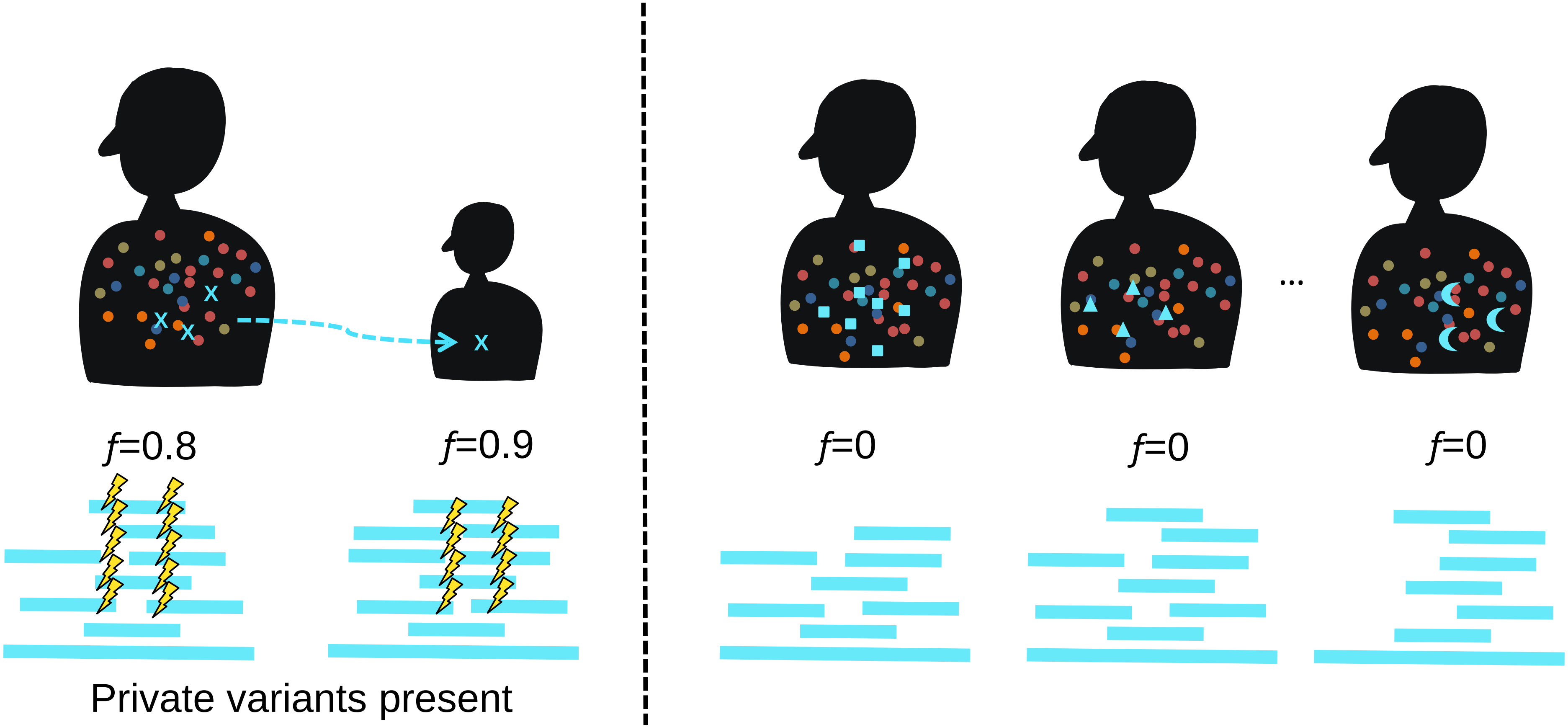


Ferretti et al. 2018, Yassour et al. 2018, Nayfach et al. 2016, Korpela et al. 2016

Genetic differences between samples



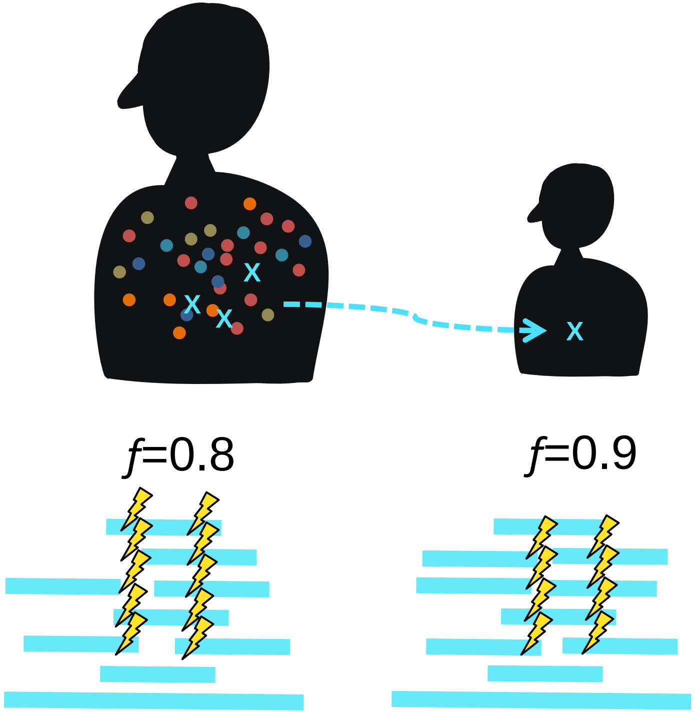
$f=0.8$ $f=0.9$

$f=0$ $f=0$ … $f=0$

Private variants present
in mother and infant only

Ferretti et al. 2018, Yassour et al. 2018, Nayfach et al. 2016, Korpela et al. 2016

Genetic differences between samples



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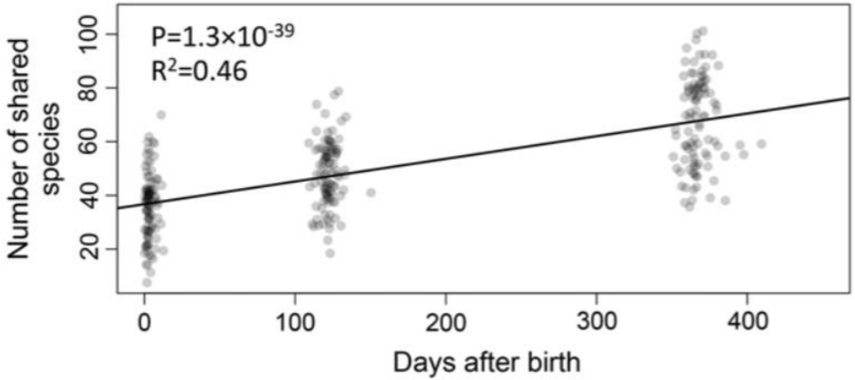
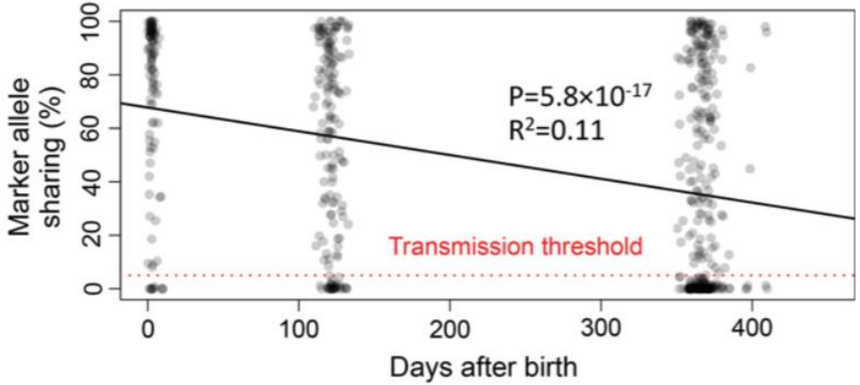




Nayfach, Rodriguez-Mueller, Garud, and Pollard, *Genome Research,* 2016

Overview

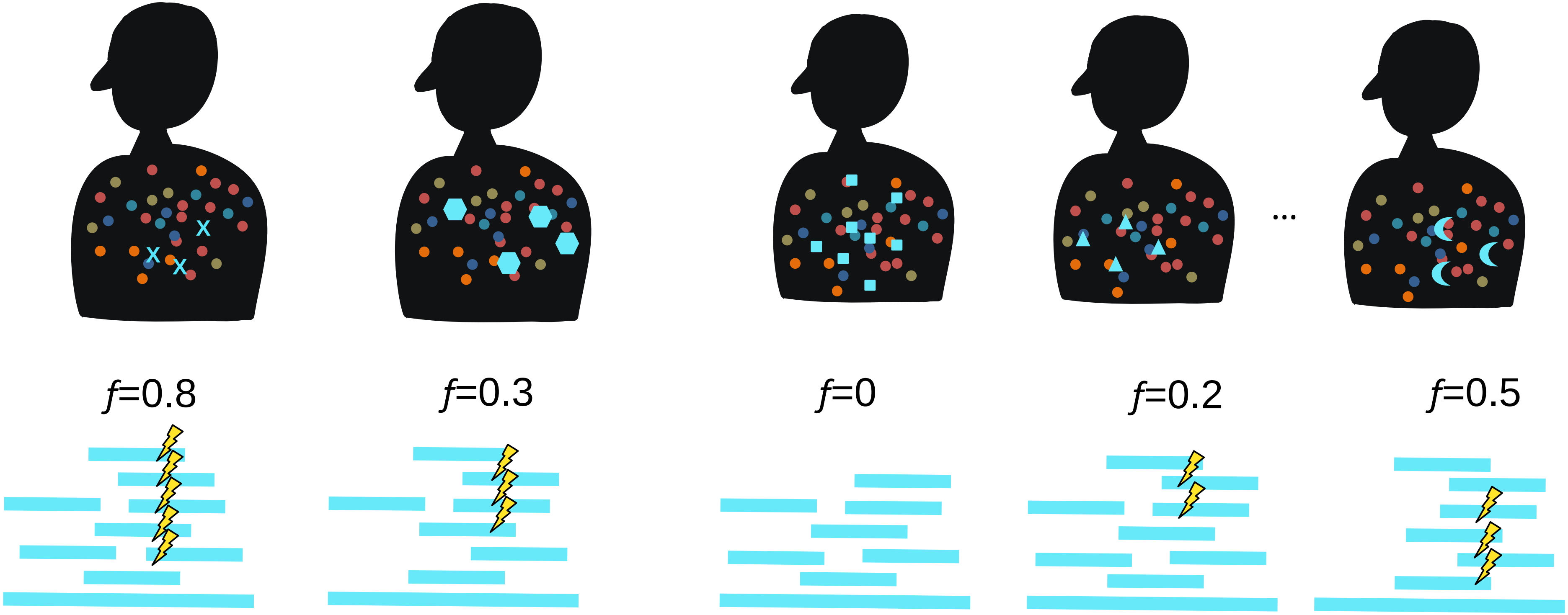
- Data
- Drift and migration
- Adaptation
- Recombination

Is everything everywhere?

How many strains of each species colonize a host?

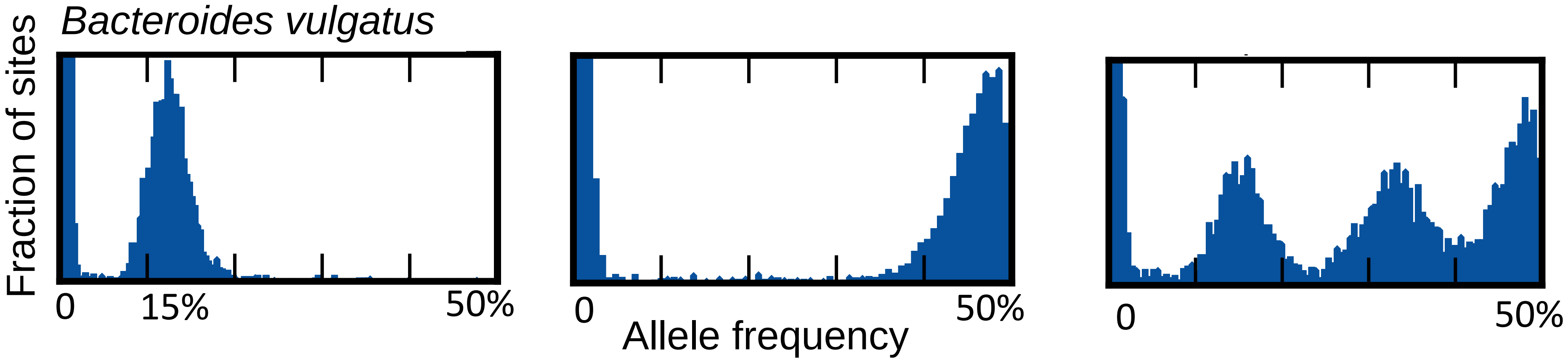
- Exactly 1
- A few
- Hundreds

Genetic variation within hosts

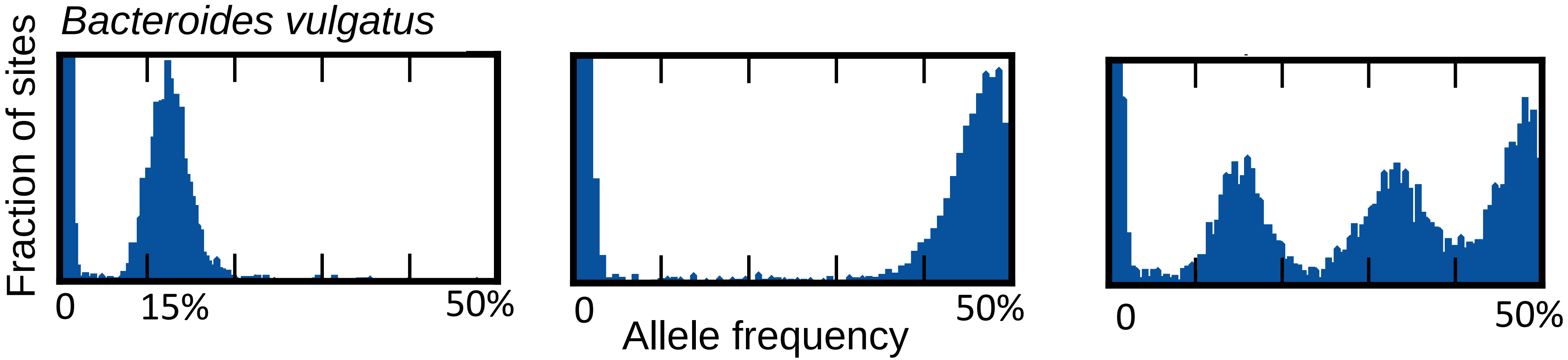


Nayfach, Rodriguez-Mueller, Garud, and Pollard, *Genome Research,* 2016

Resolving the lineage structure in the microbiome

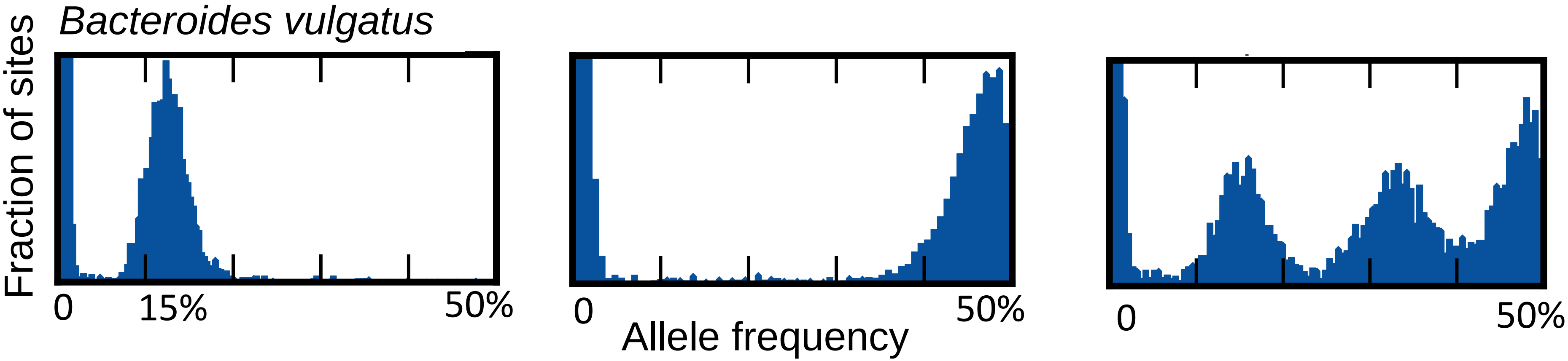


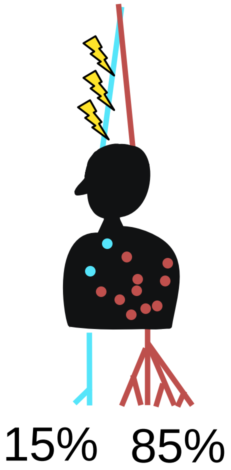
Resolving the lineage structure in the microbiome



A lot of variation across hosts!

Resolving the lineage structure in the microbiome


Bacteroides vulgatus



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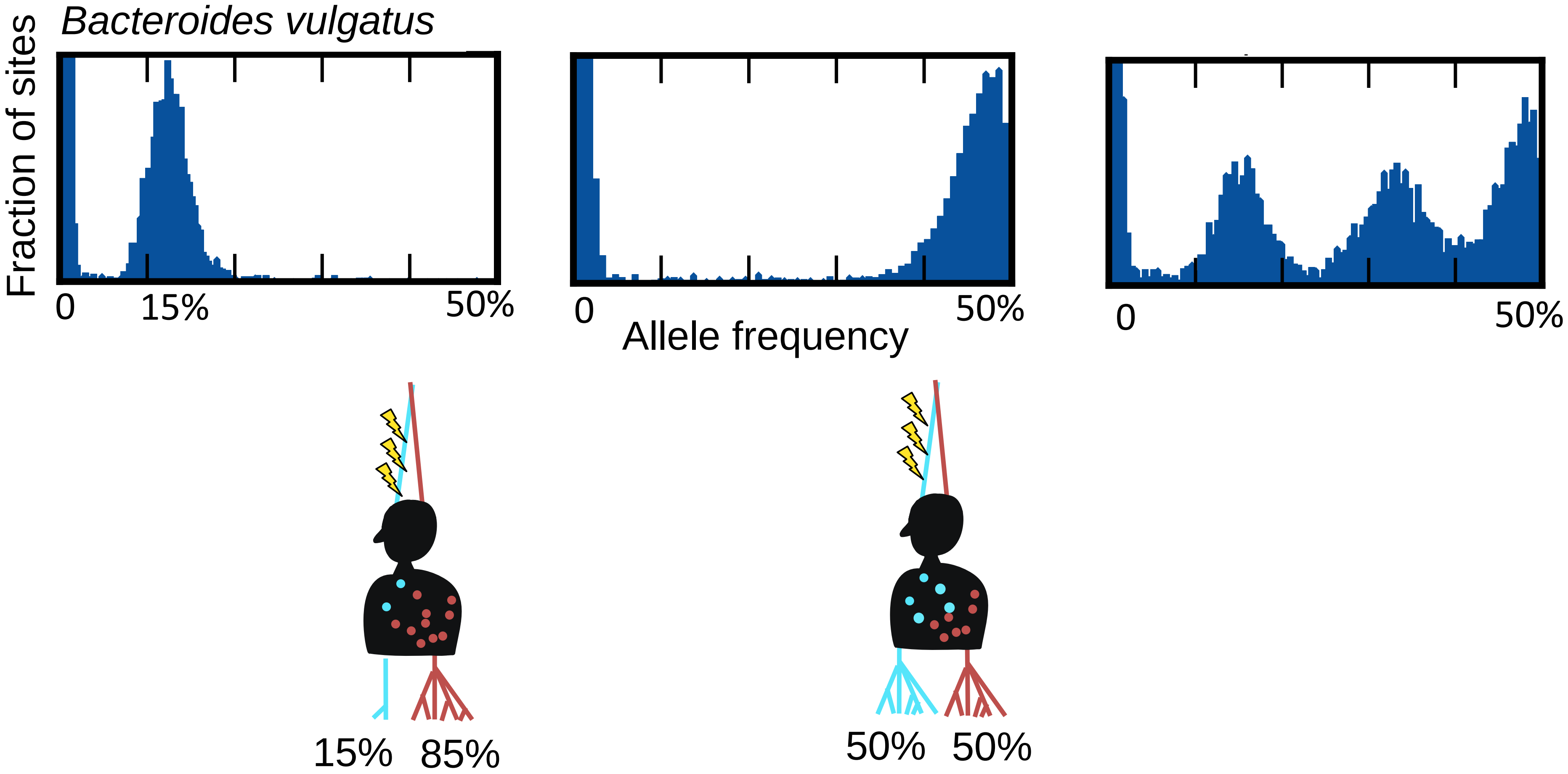

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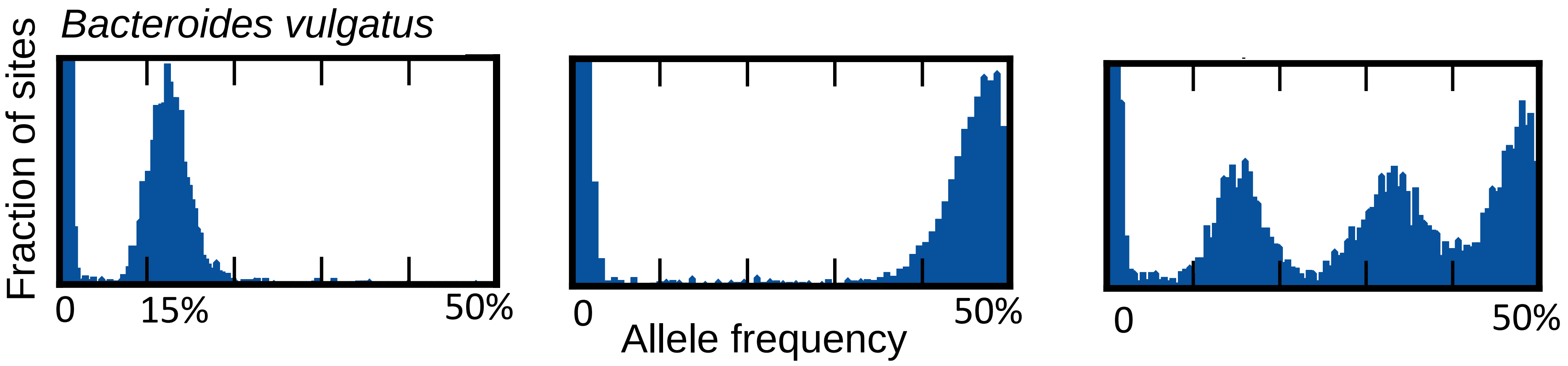

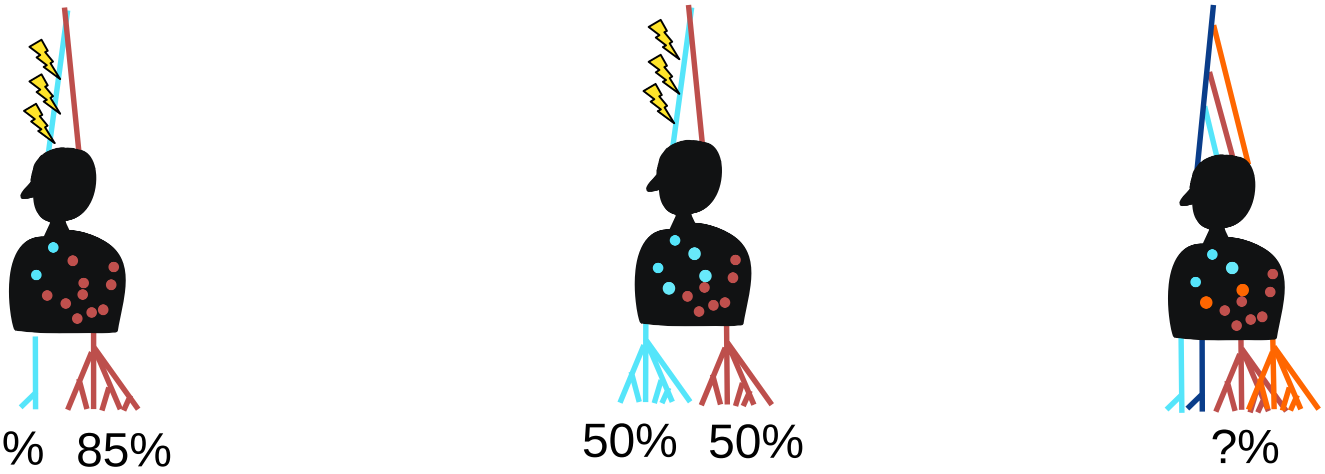

How many strains of each species colonize a host?

- Exactly 1
- [✓ A few]
- Hundreds

How many strains of each species colonize a host?

- ✓ Exactly 1 (*B. fragilis* Verster et al. 2017 Cell Host Microbe)
- ✓ A few
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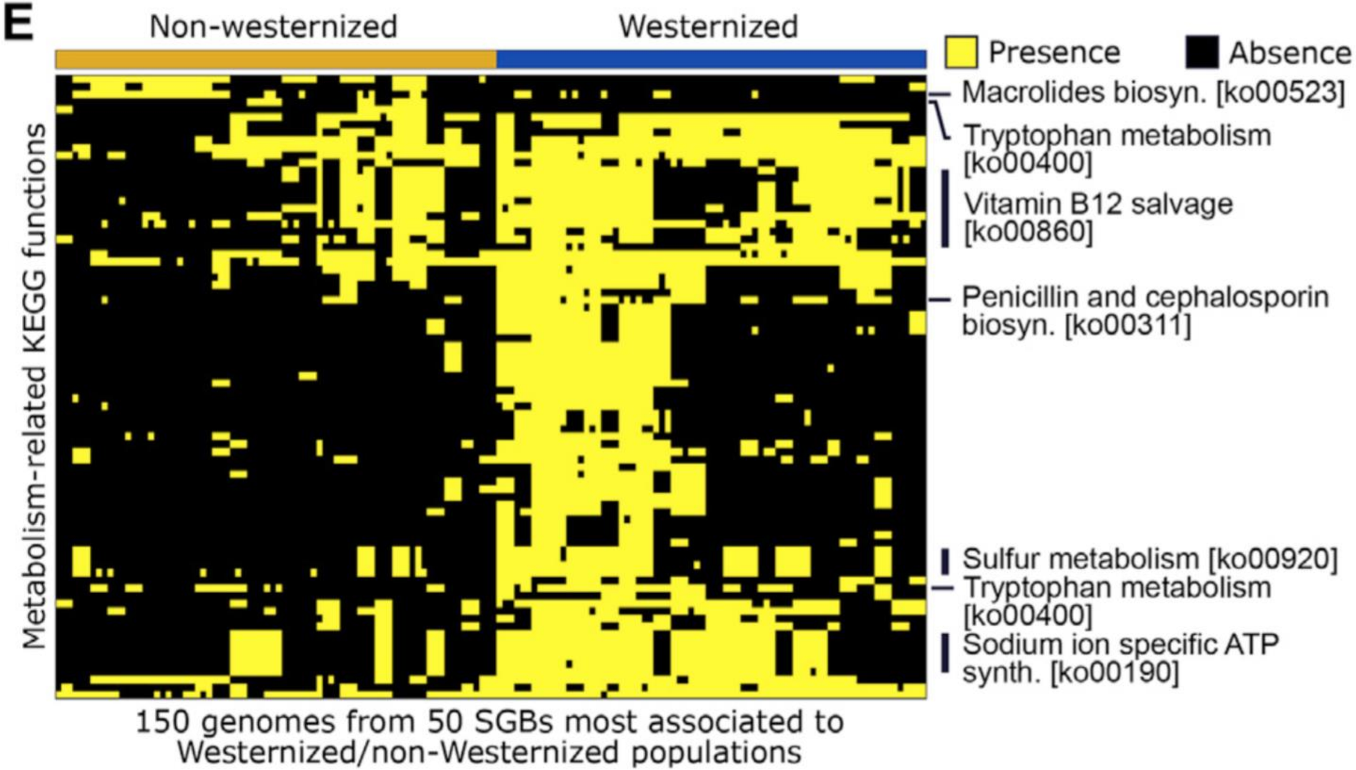
Is everything everywhere?

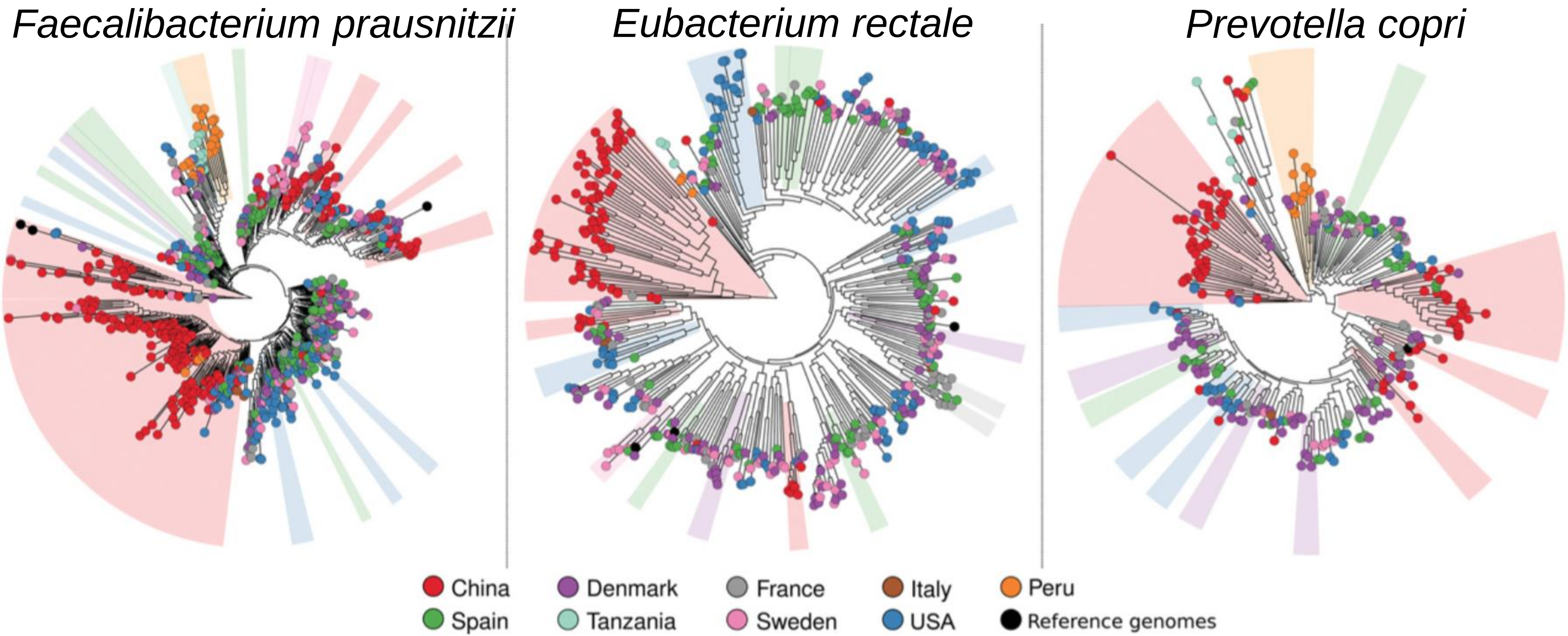
Structure within hosts
What about across hosts?

Different gene compositions in different environments



Pasolli et al. 2019

Biogeography of gut microbes



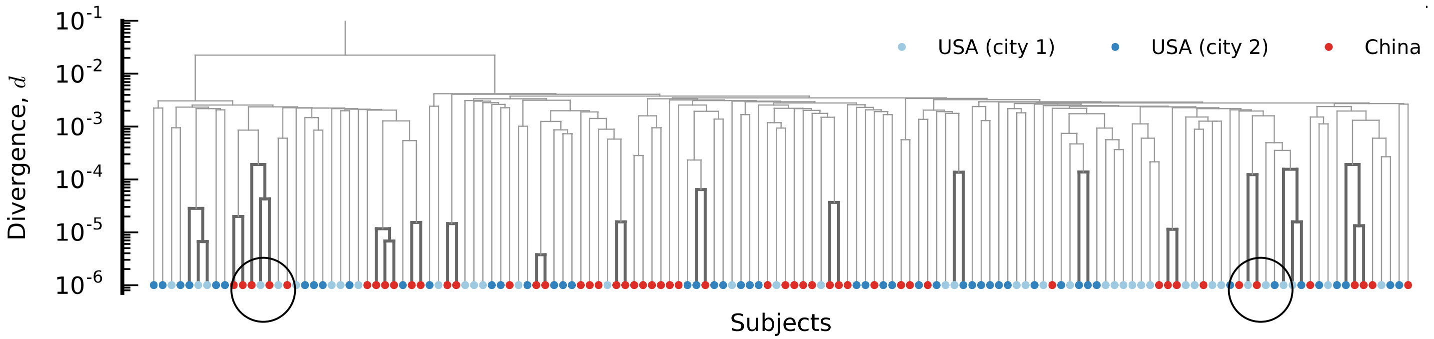
Faecalibacterium prausnitzii

Eubacterium rectale

Prevotella copri

Truong *et al.* 2017 Genome Research

Closely related strains on different continents



Closely related strains
found on two continents!

Garud, Good et al. 2019

Is everything everywhere?

No

Open Questions

- What ecological and evolutionary processes govern the ‘oligo colonization’ of individuals?

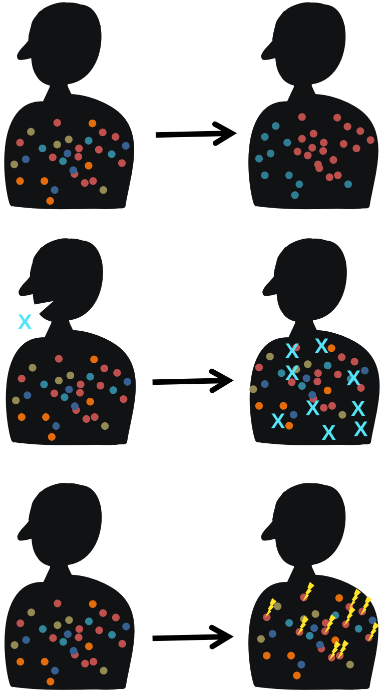
- Why do different species show different geographic distributions?

Overview

- Data
- Drift and migration
- **Adaptation**
- Recombination

See: Garud*, Good* *et al.* 2019, Ghalayini *et al*. 2018, Zhao*, Lieberman* *et al.* 2019, Poyet et al. 2019, and Yaffe and Relman 2020

Evolutionary dynamics within hosts



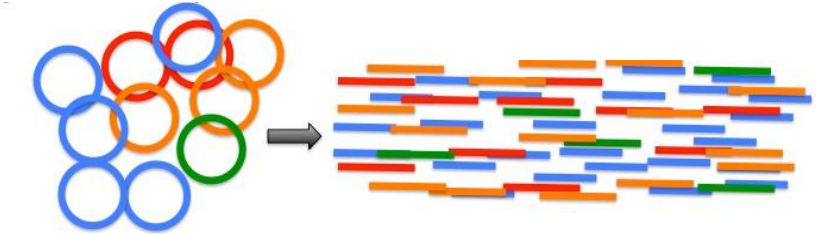
Species fluctuations

16S data

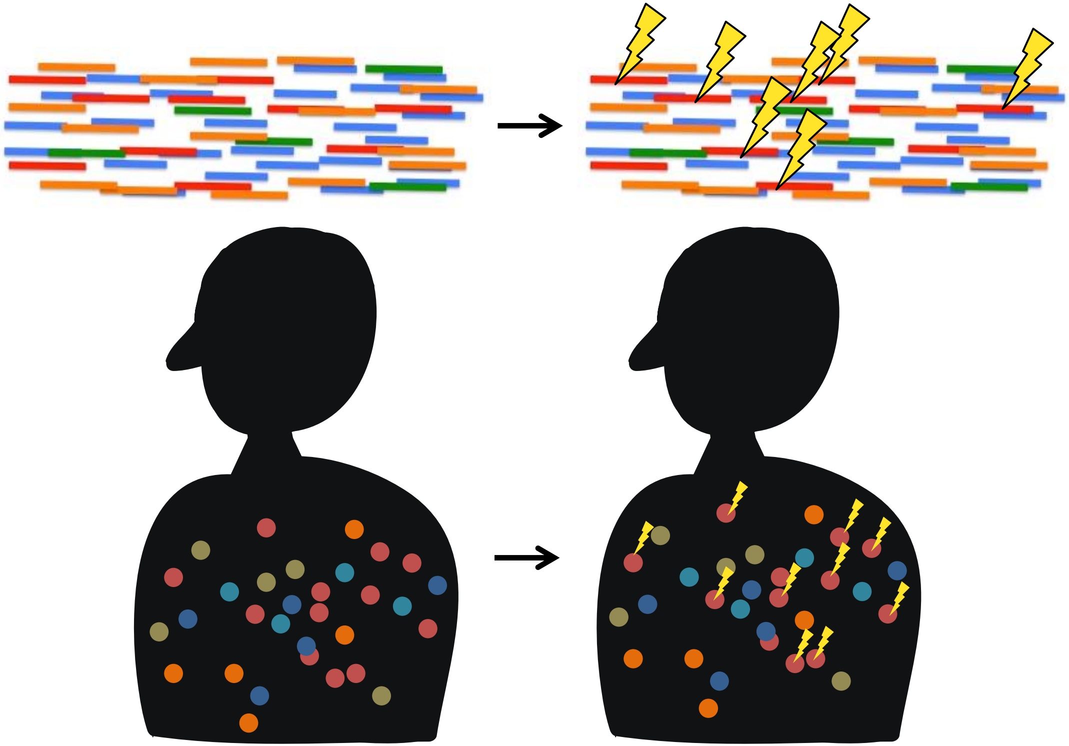
Invasion

Evolution

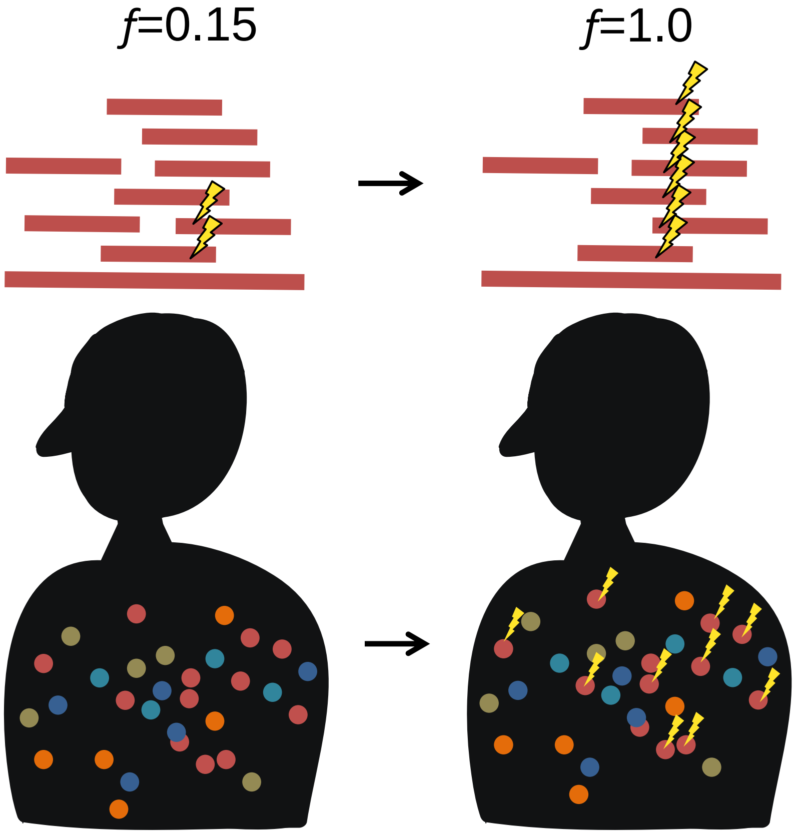
Whole genome
shotgun sequencing



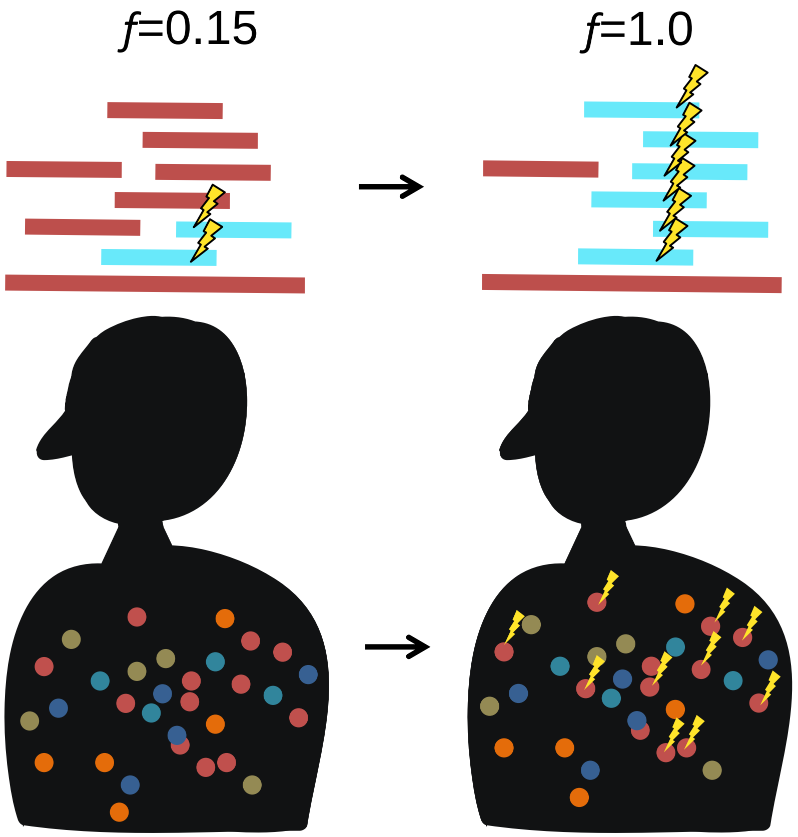
How can we detect evolution with shotgun reads?



Ideally, look for within-species allele frequency changes

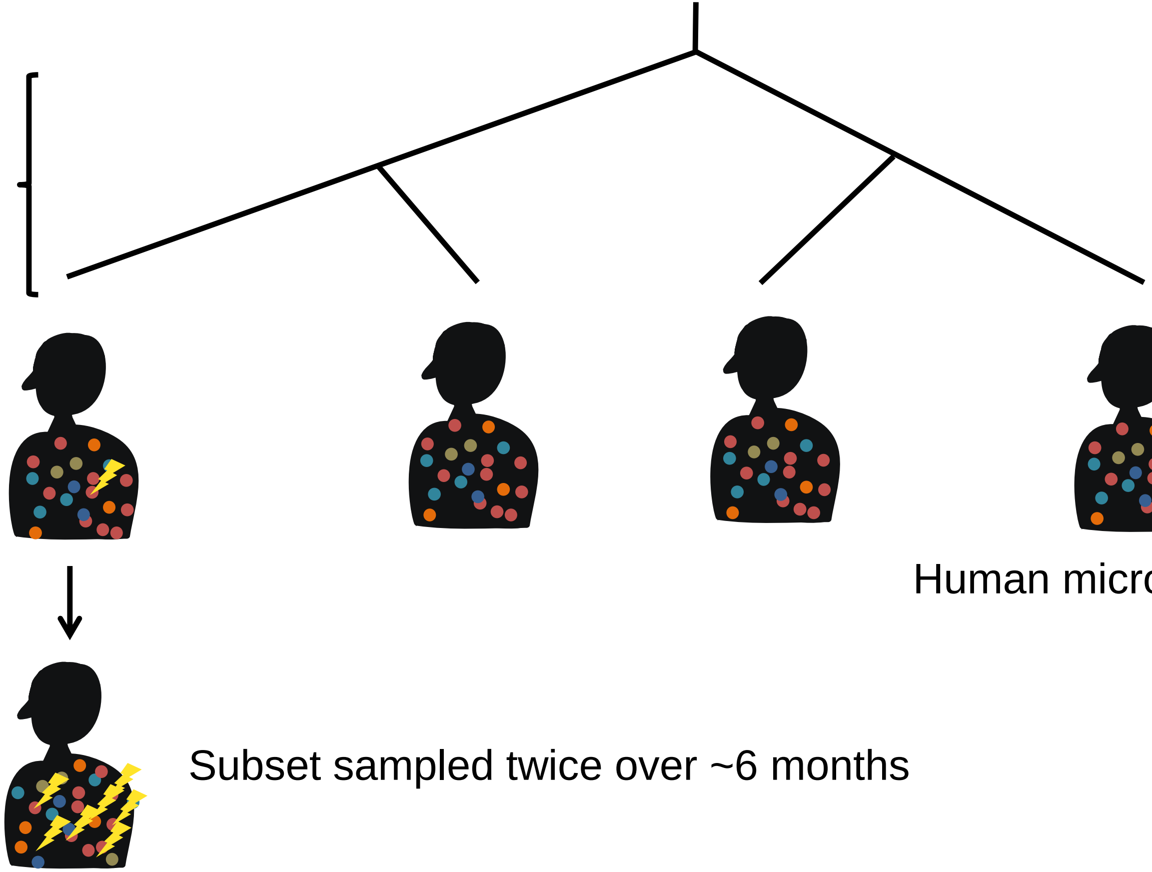


But! Detecting evolutionary events is not so simple…



Complication!
Multiple strains may be colonizing a host at high frequency.

Distinguishing evolution from strain fluctuations



1% diverged

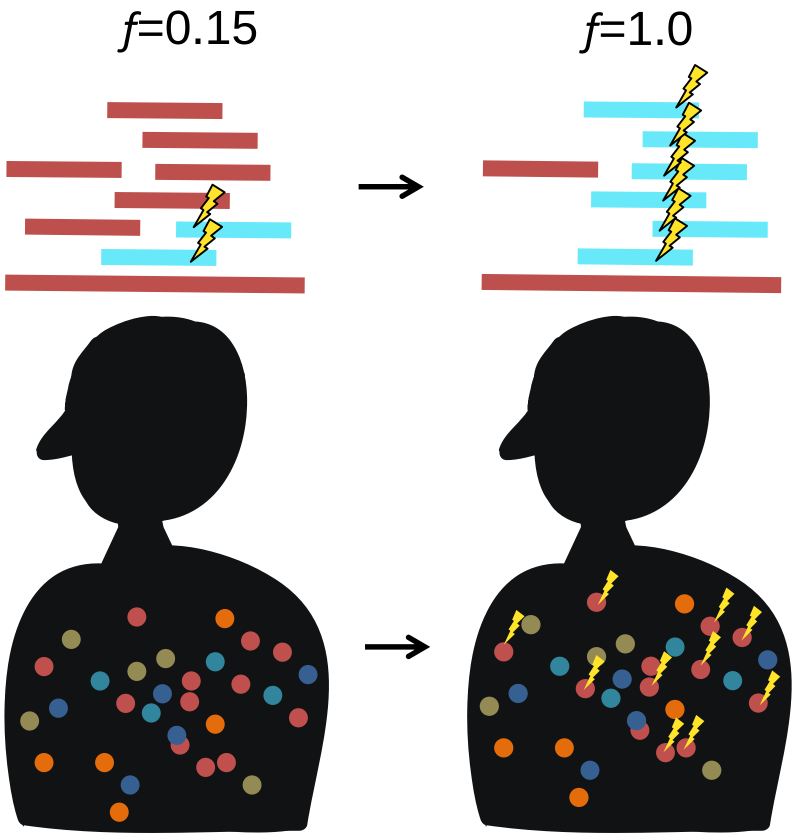
X 250 hosts

Human microbiome project

Handful of differences

Subset sampled twice over ~6 months

But! Detecting evolutionary events is not so simple…



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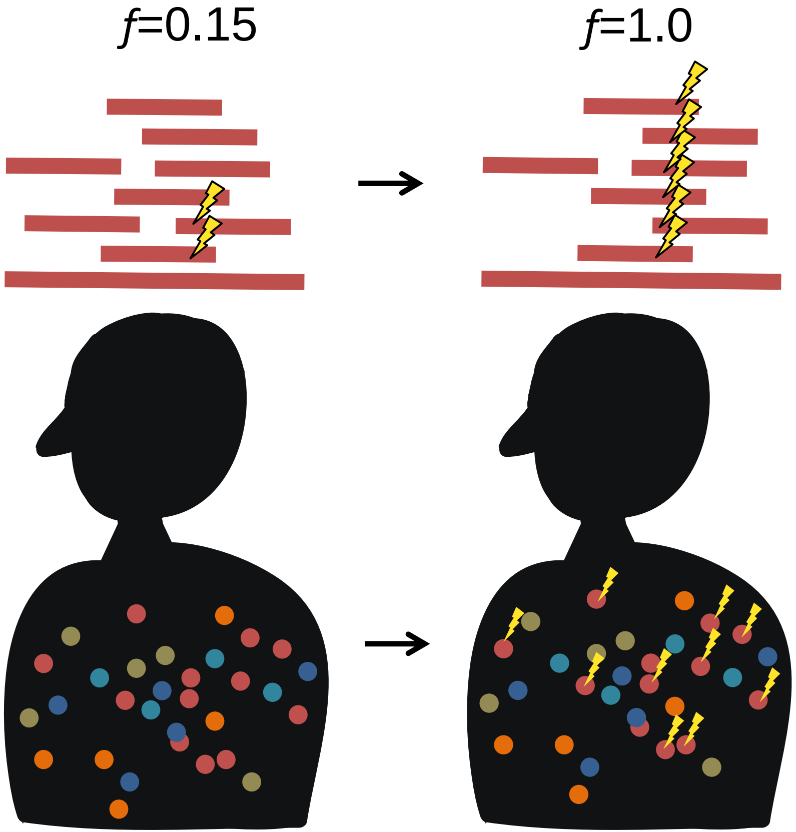

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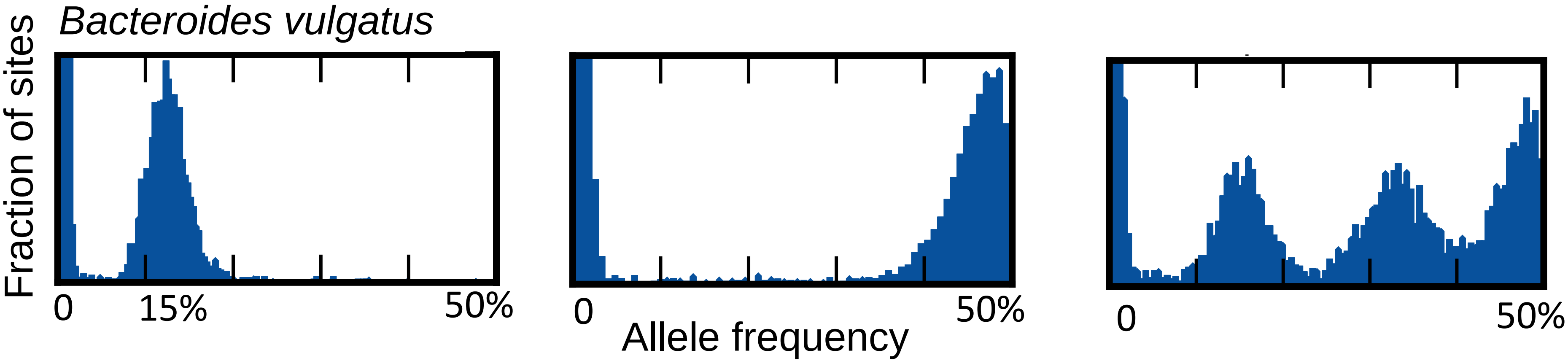
Resolving the lineage structure in the microbiome



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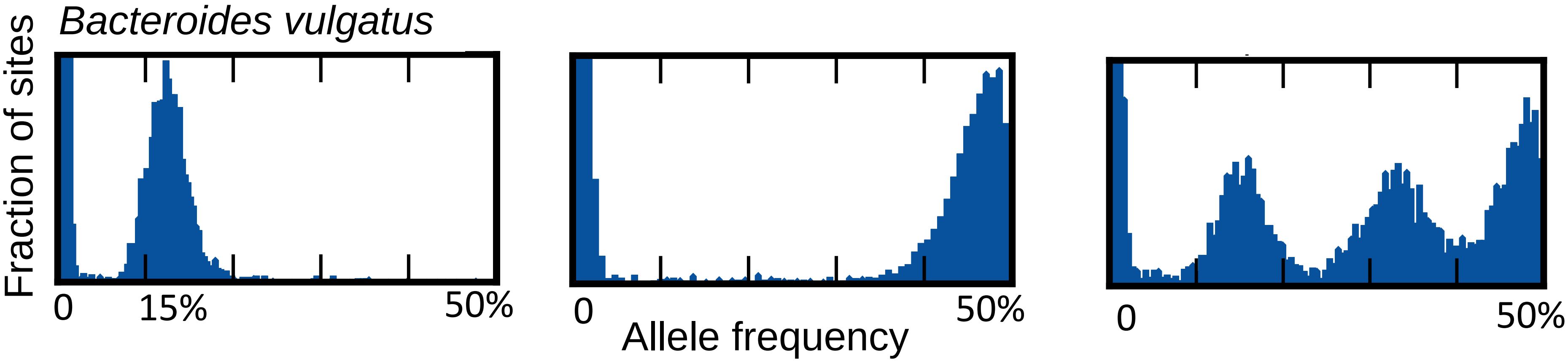

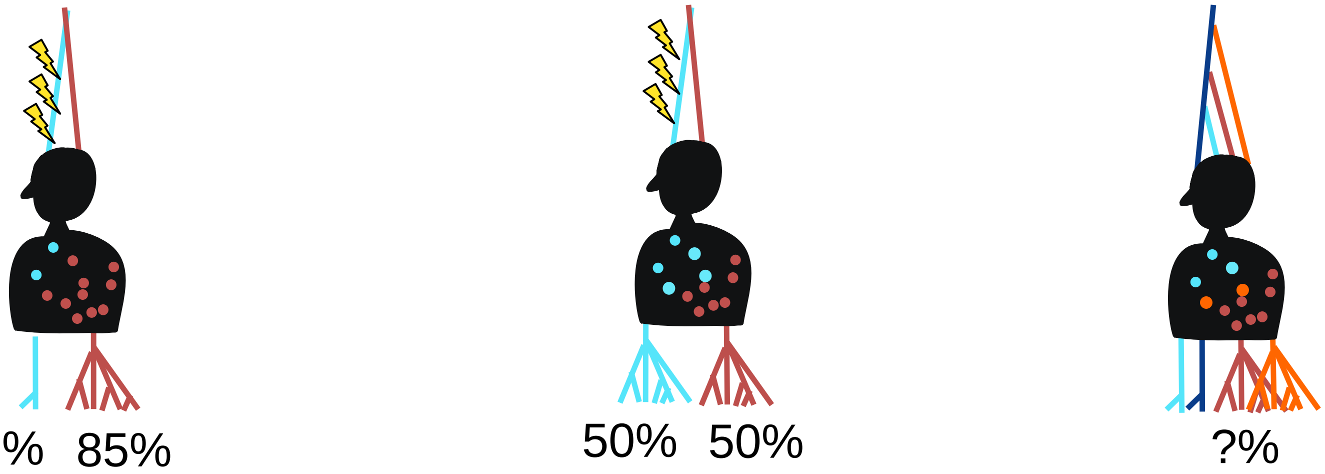

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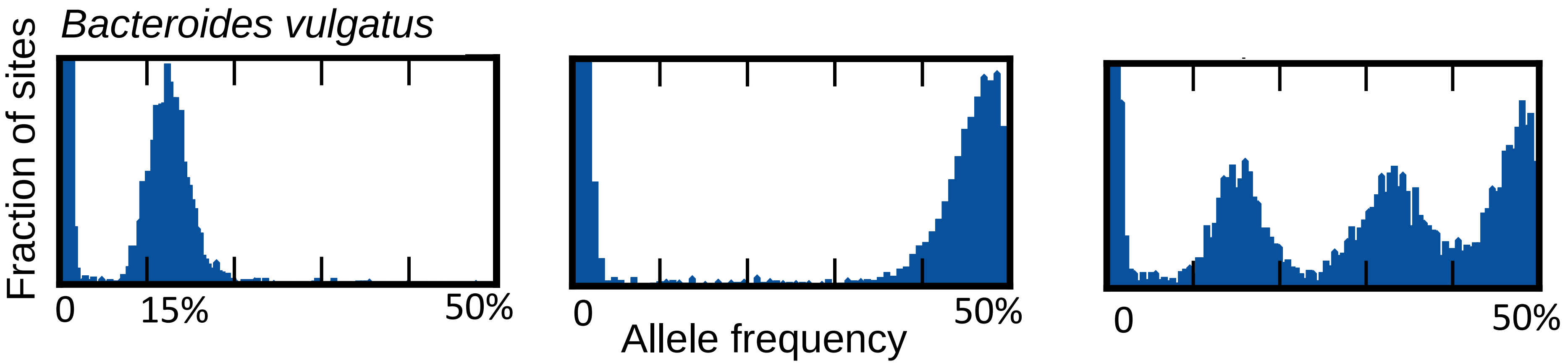

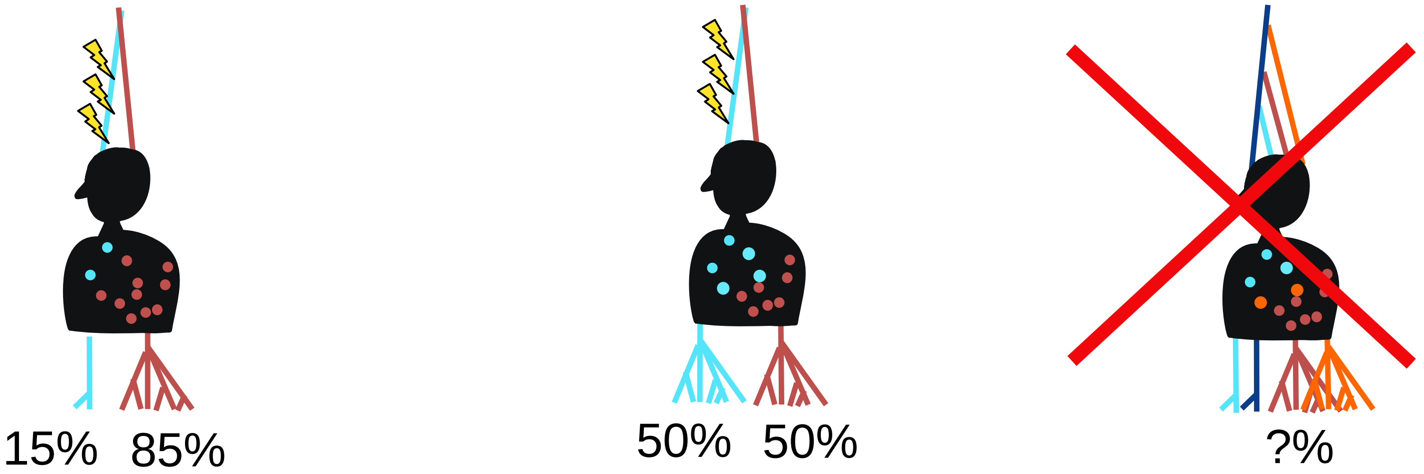

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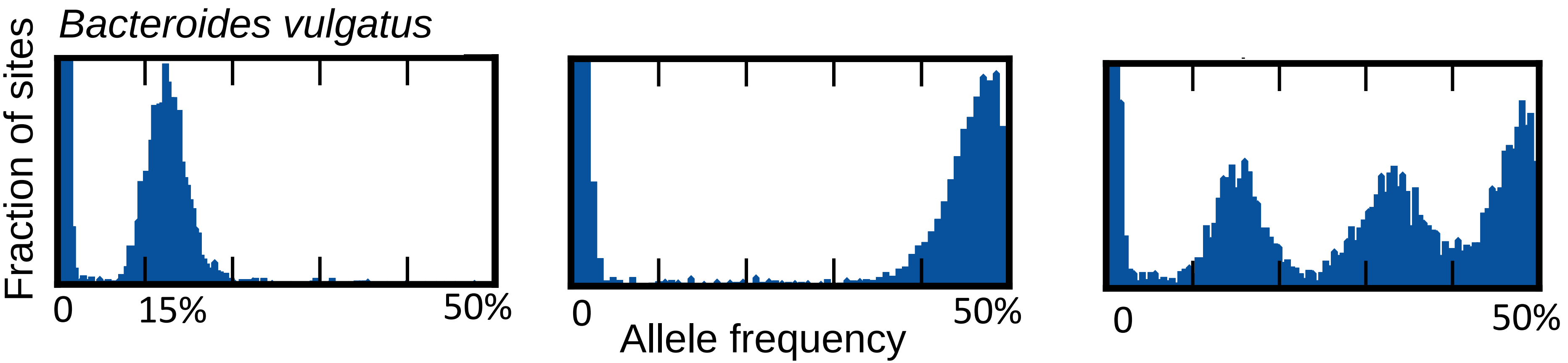

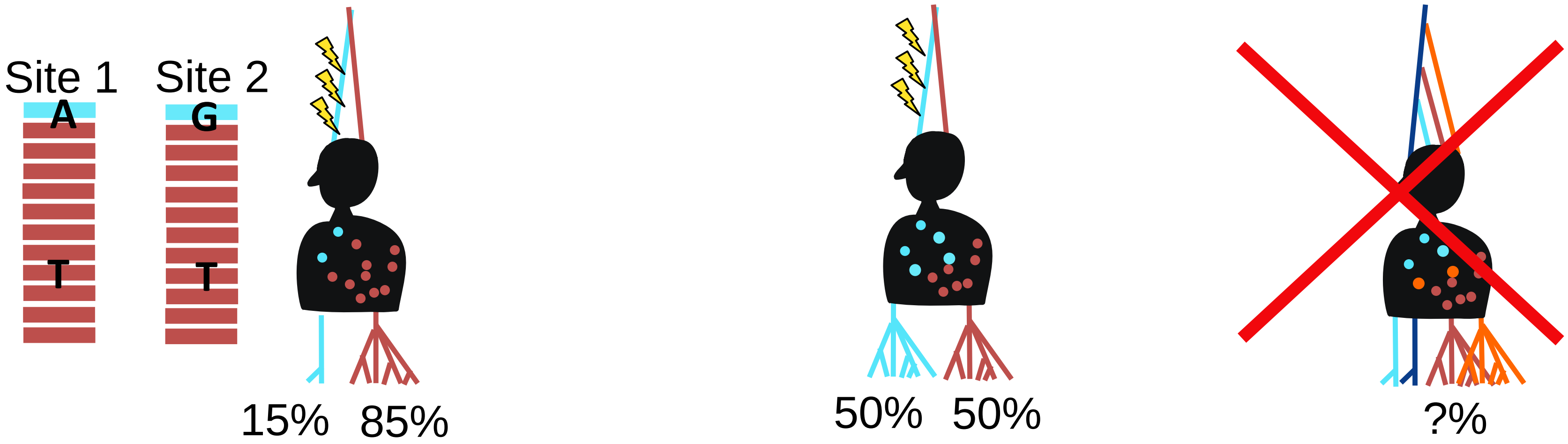

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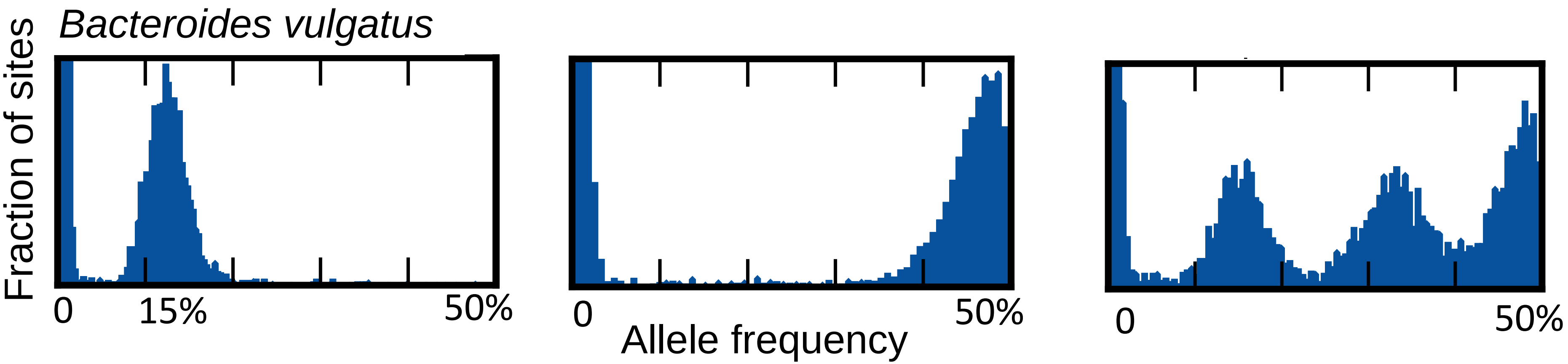

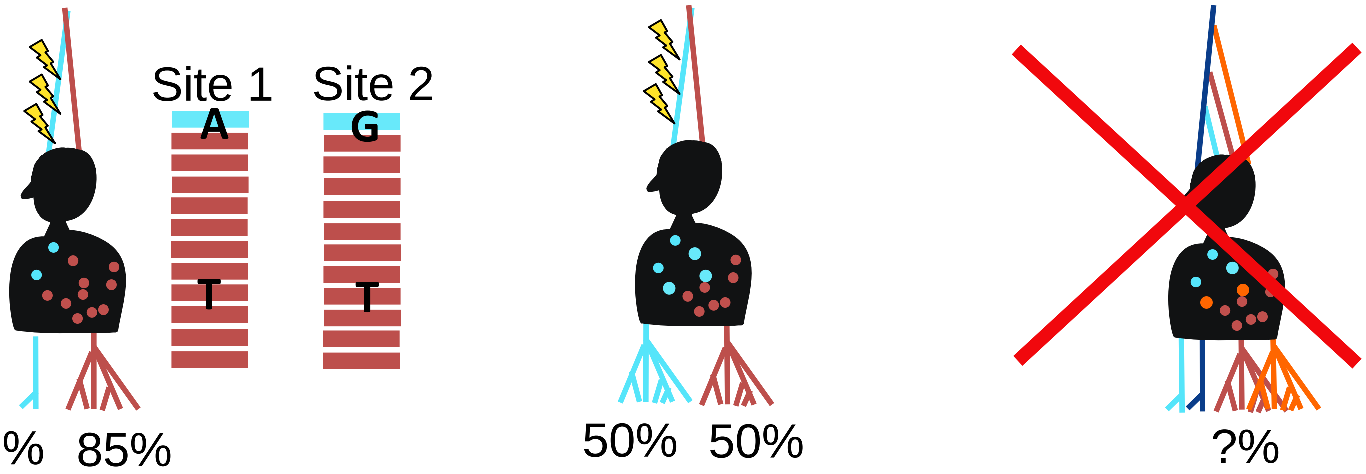

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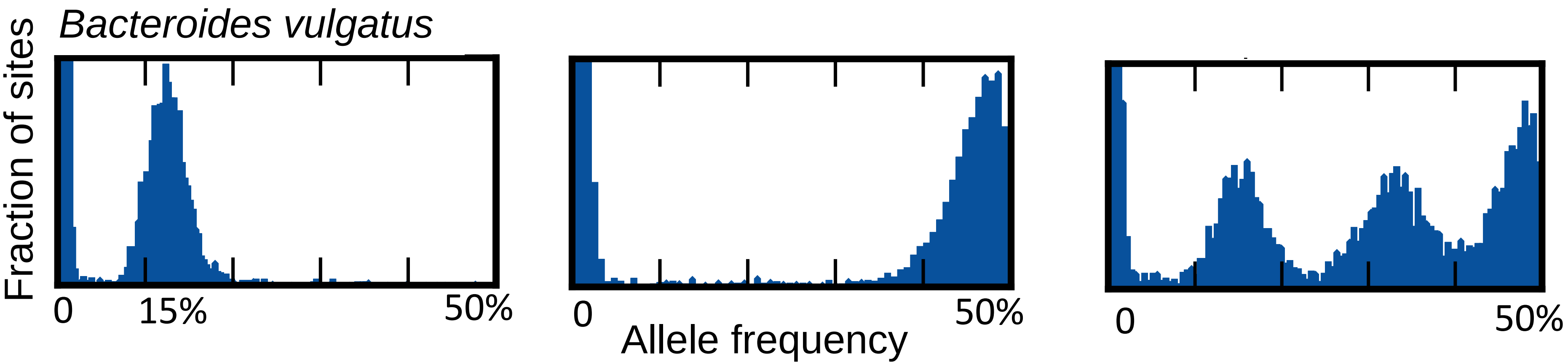
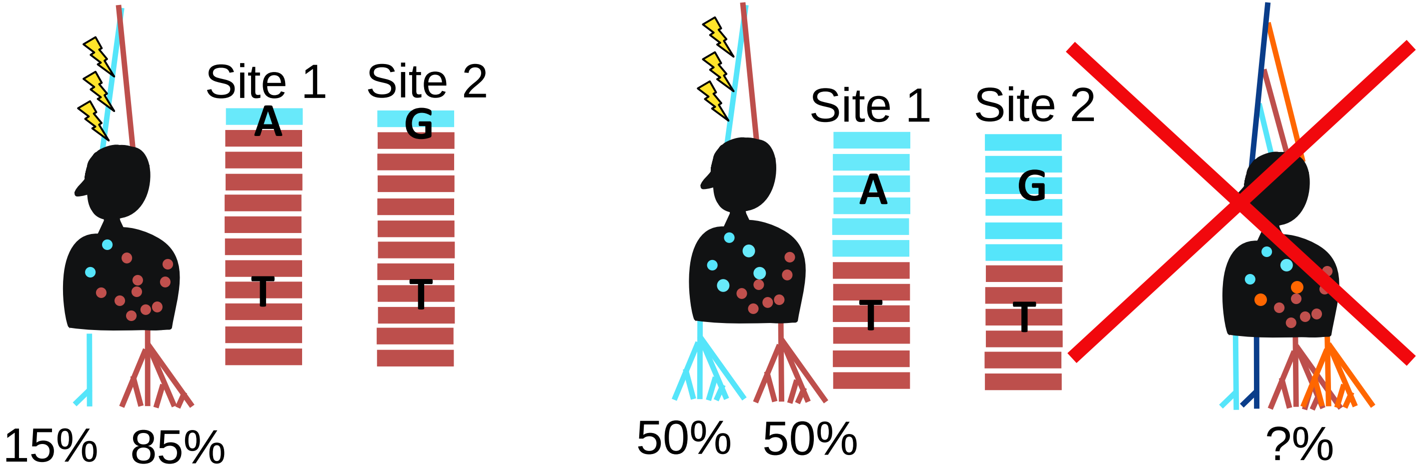
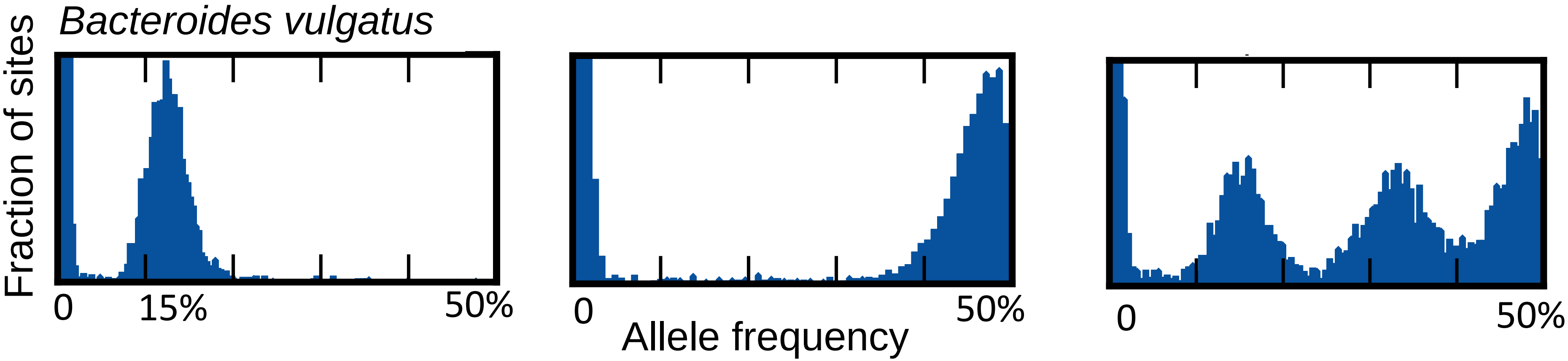
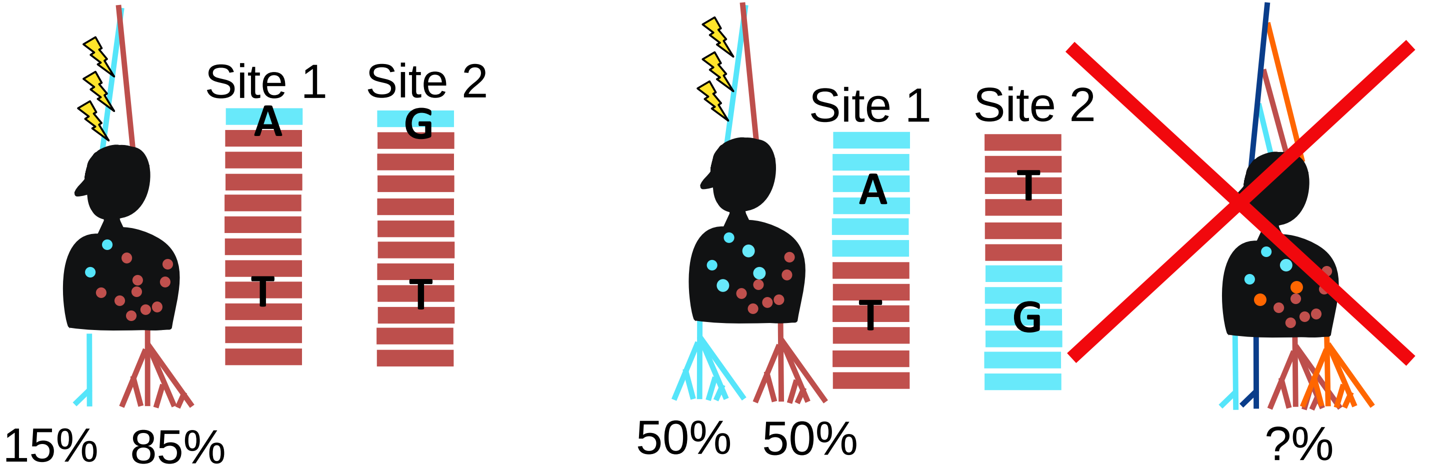




Resolving the lineage structure in the microbiome





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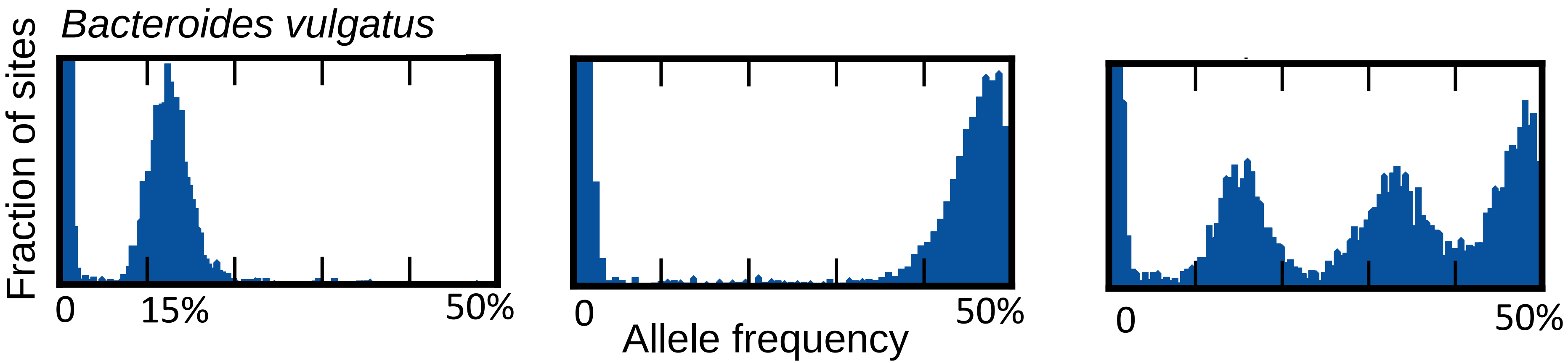

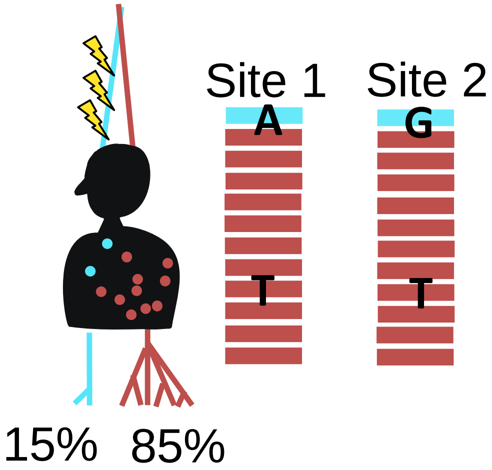

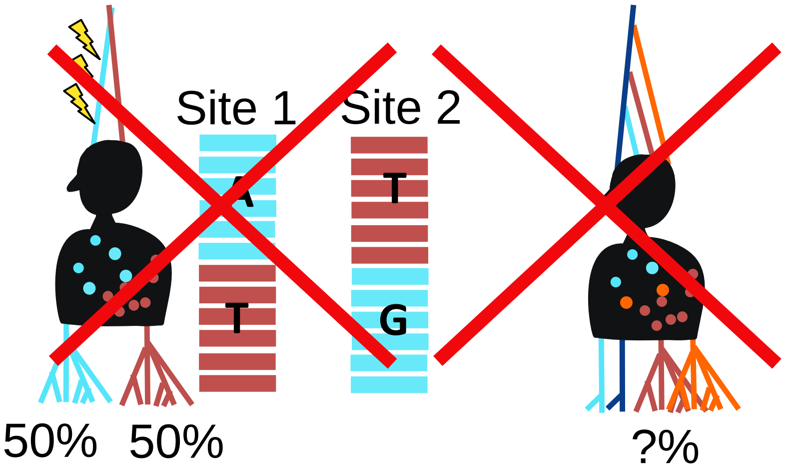

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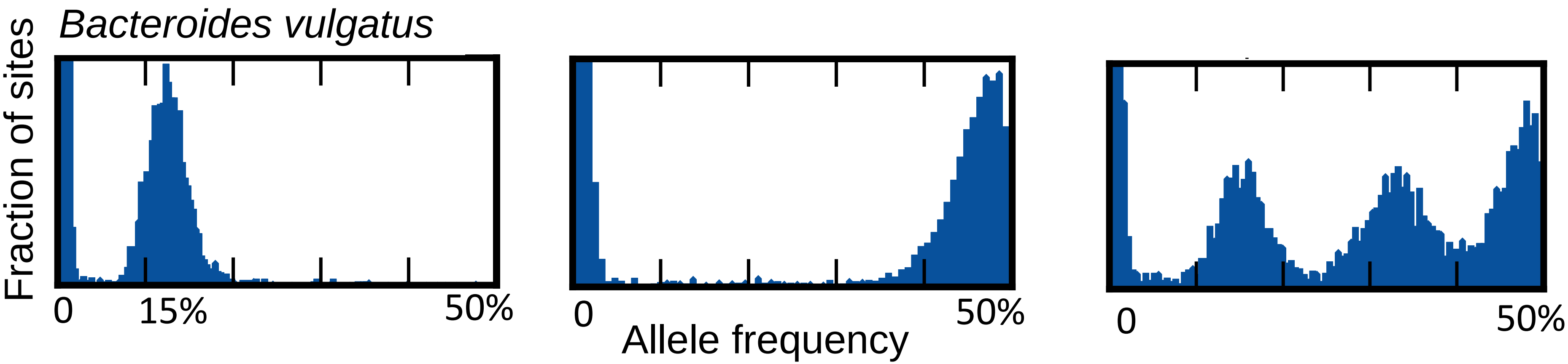

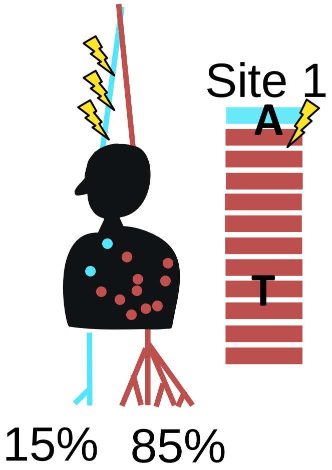

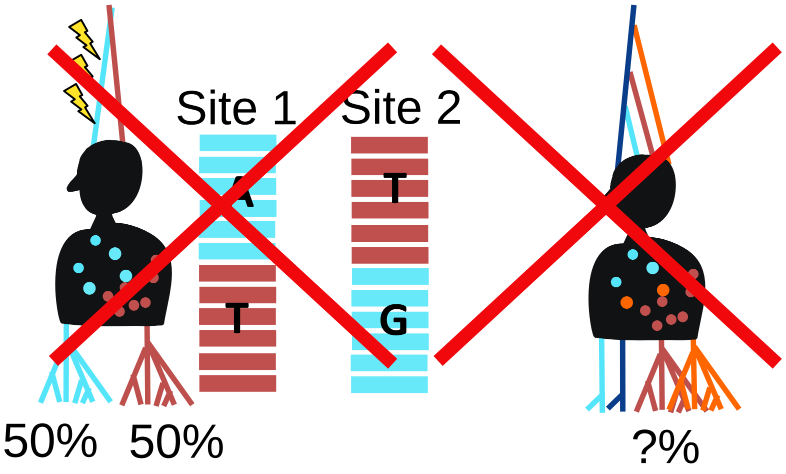

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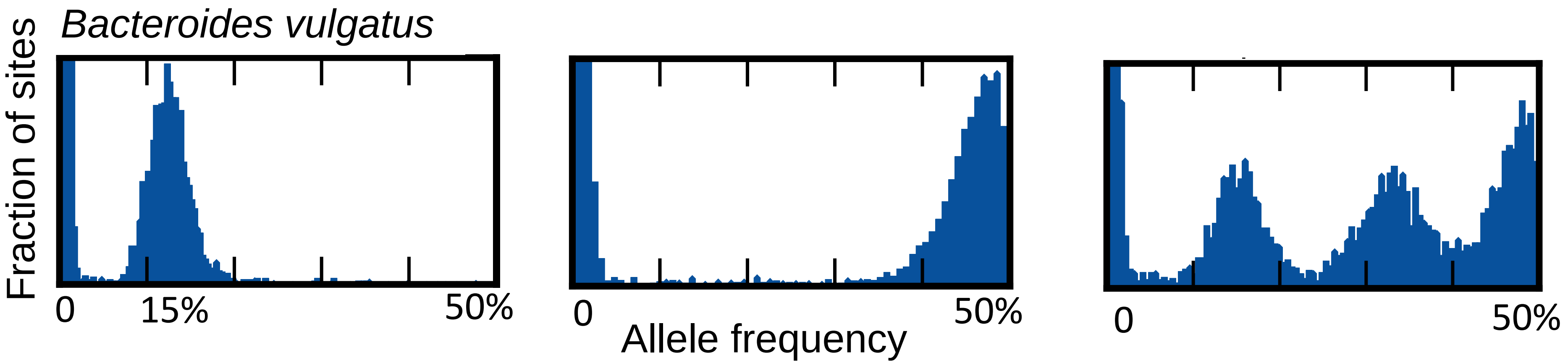

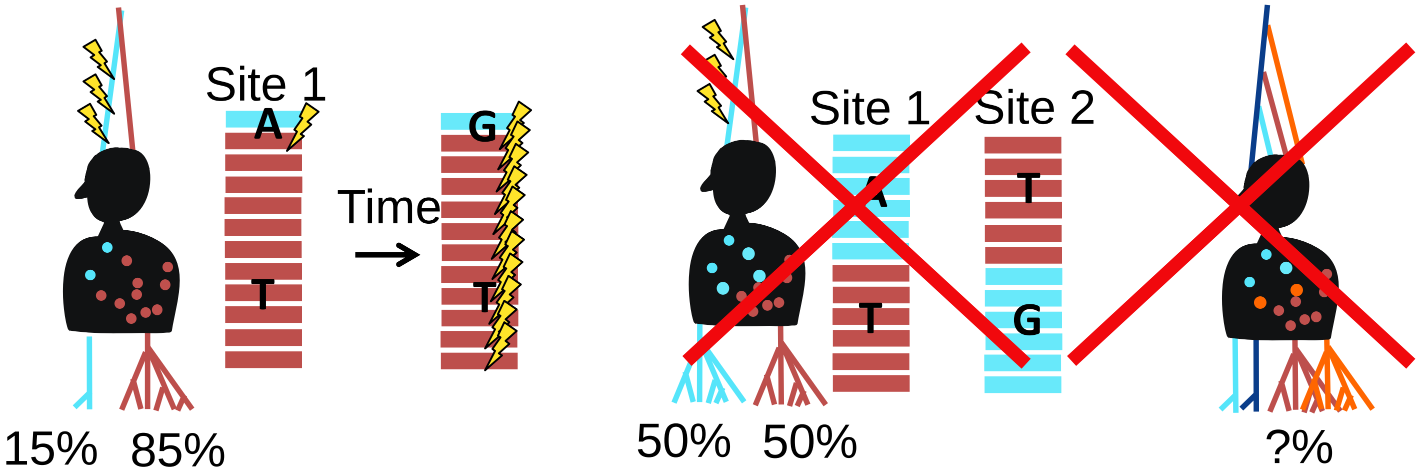

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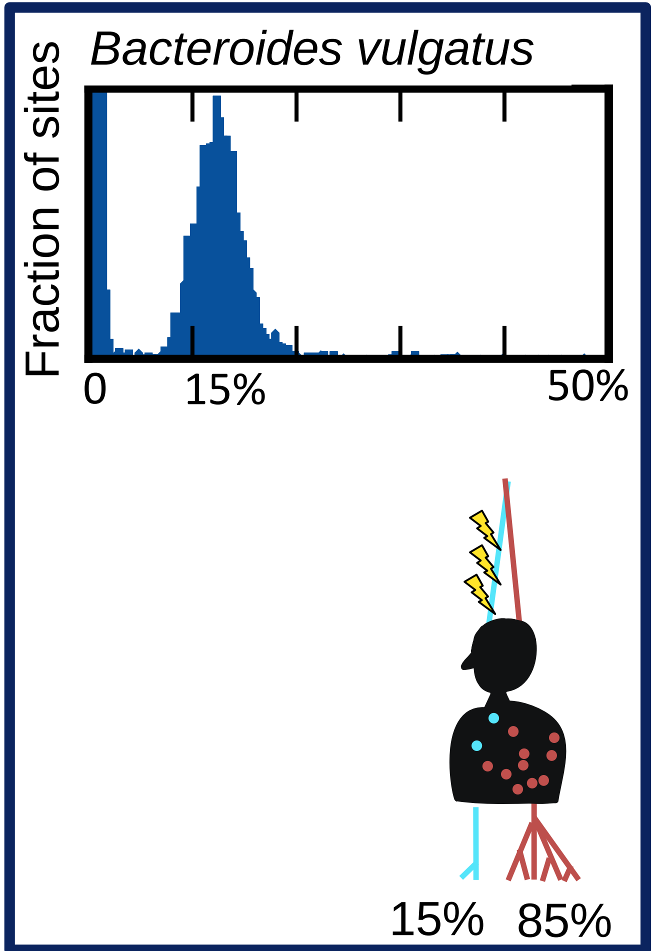
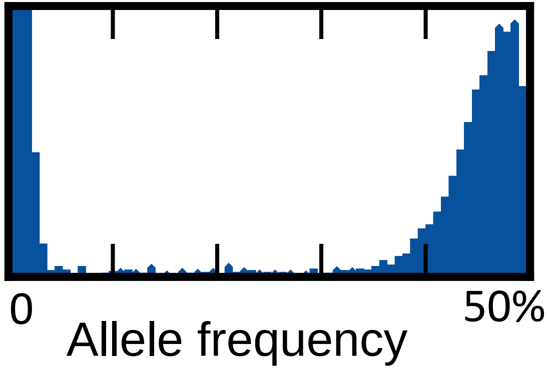
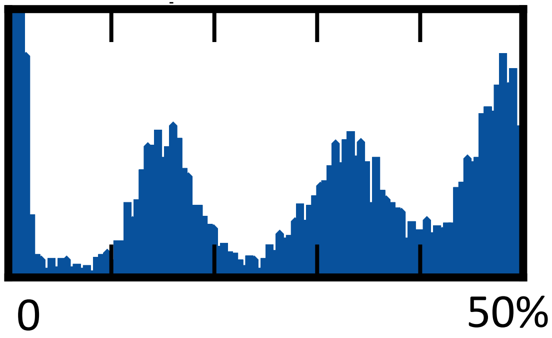
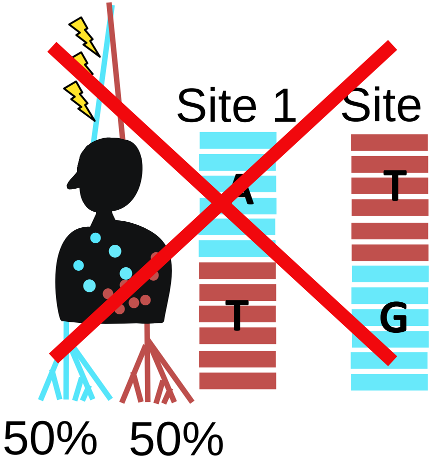
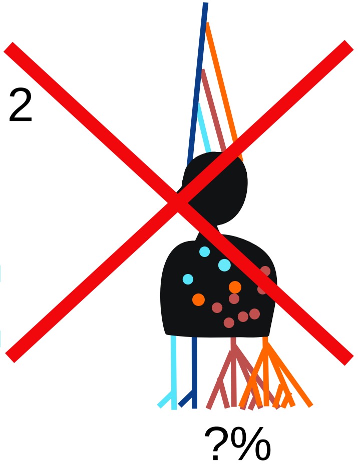


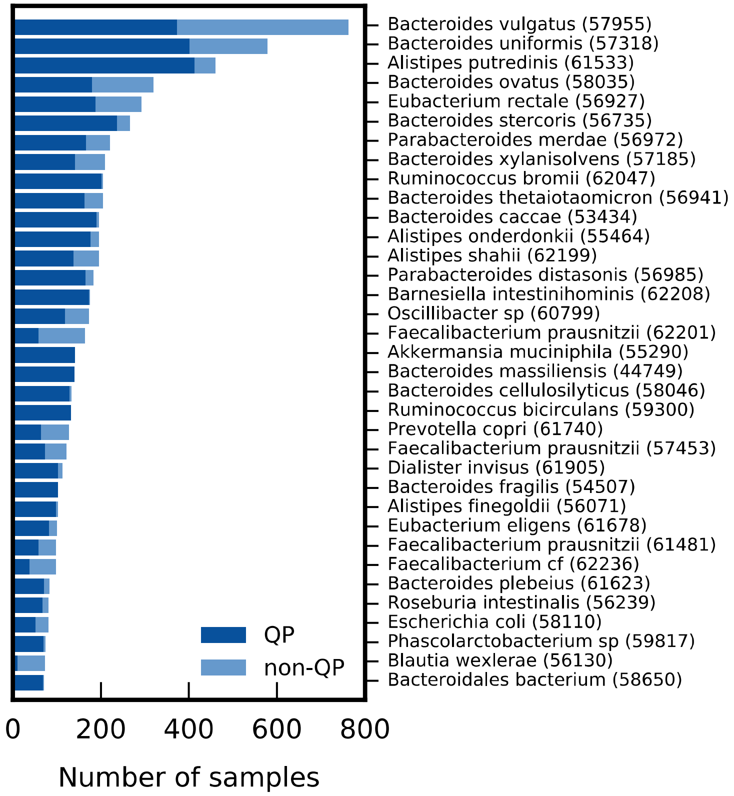








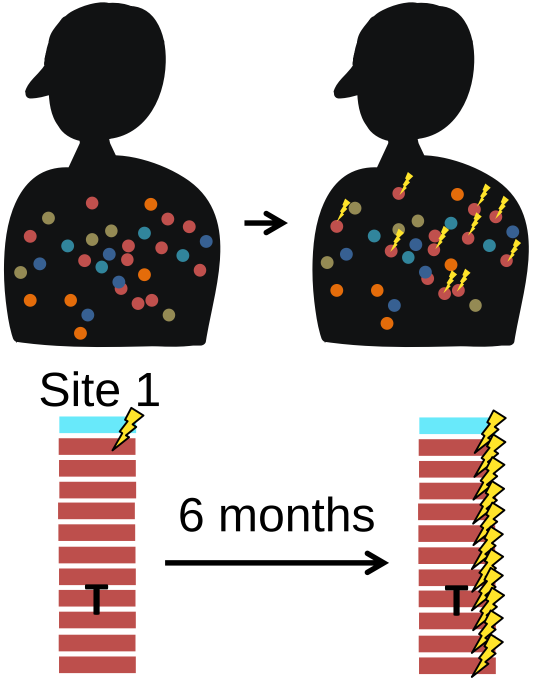
Population genetics in >30 species simultaneously!



801 resident populations
across hosts x species

Data from the Human Microbiome Project

Do bacteria evolve in the host gut?



Human
Microbiome
Project

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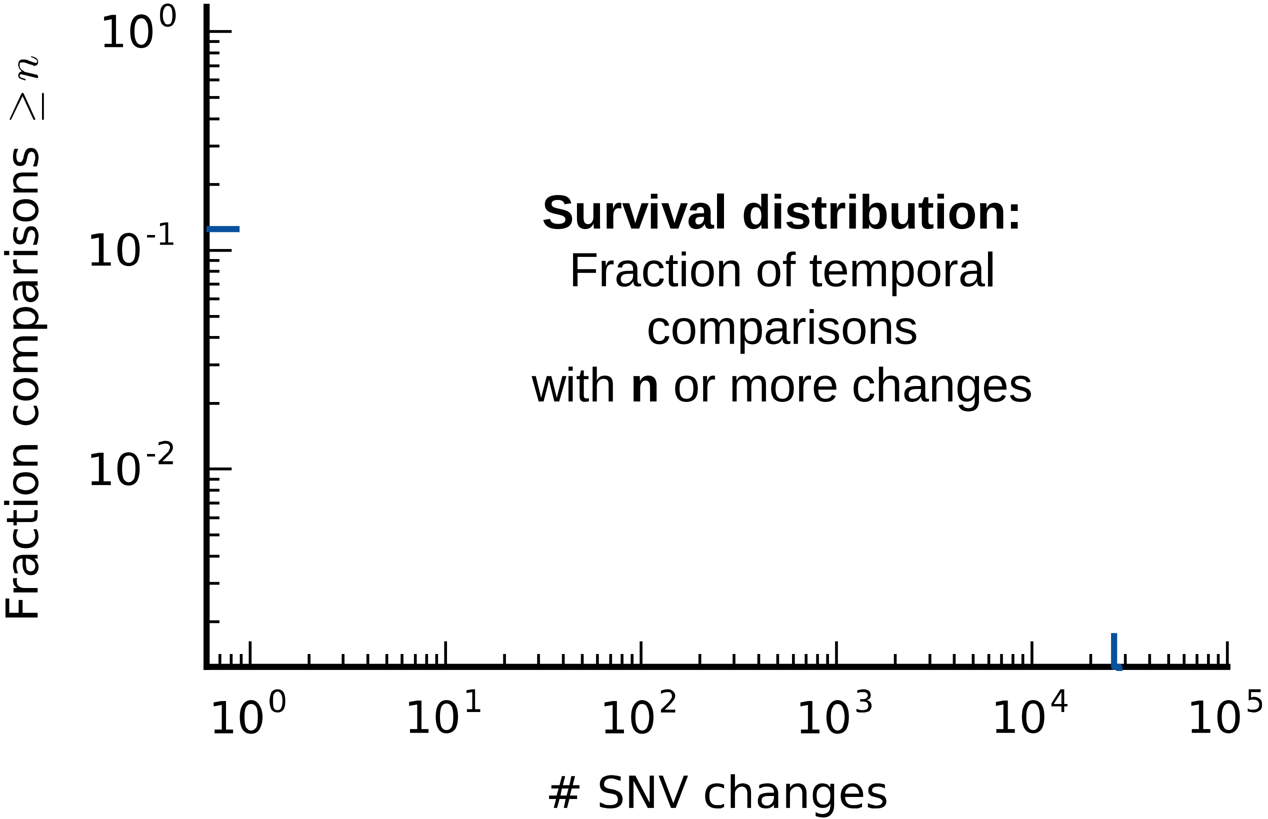
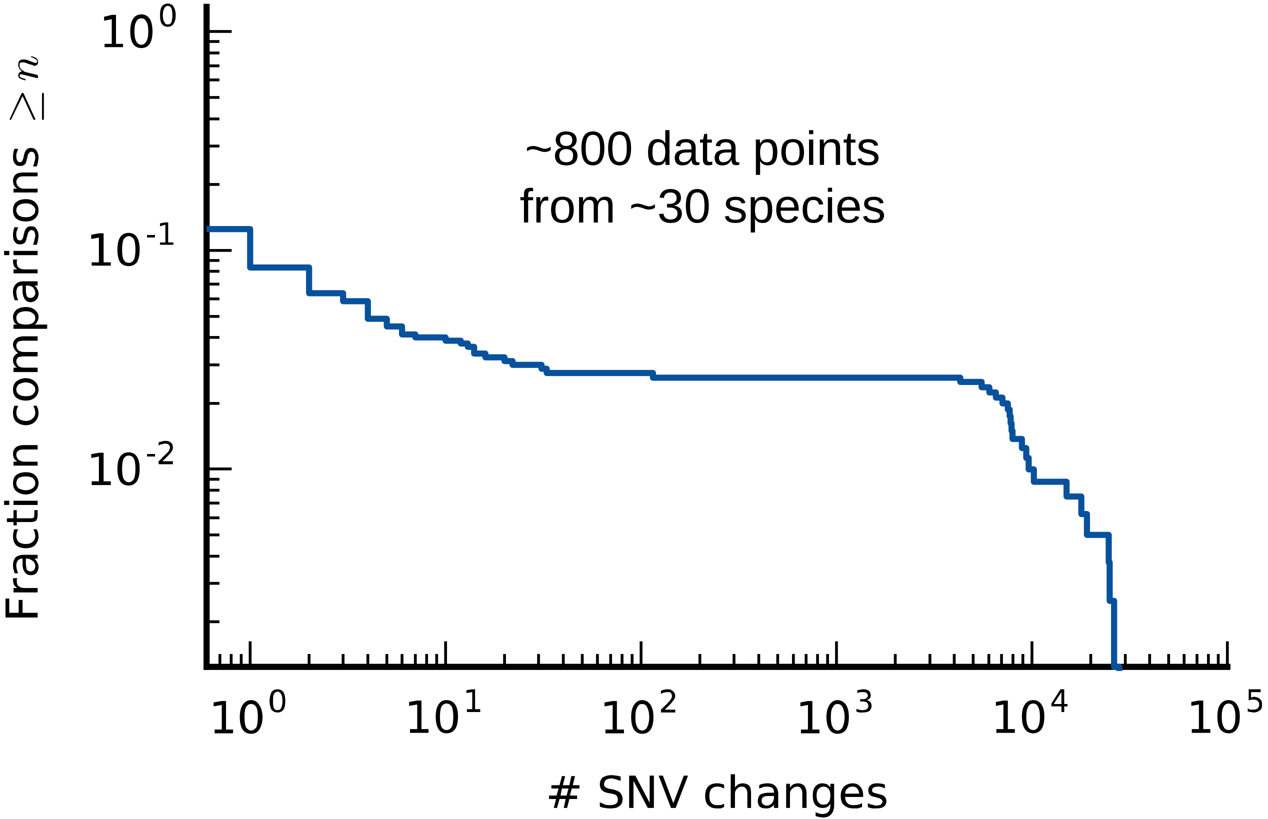


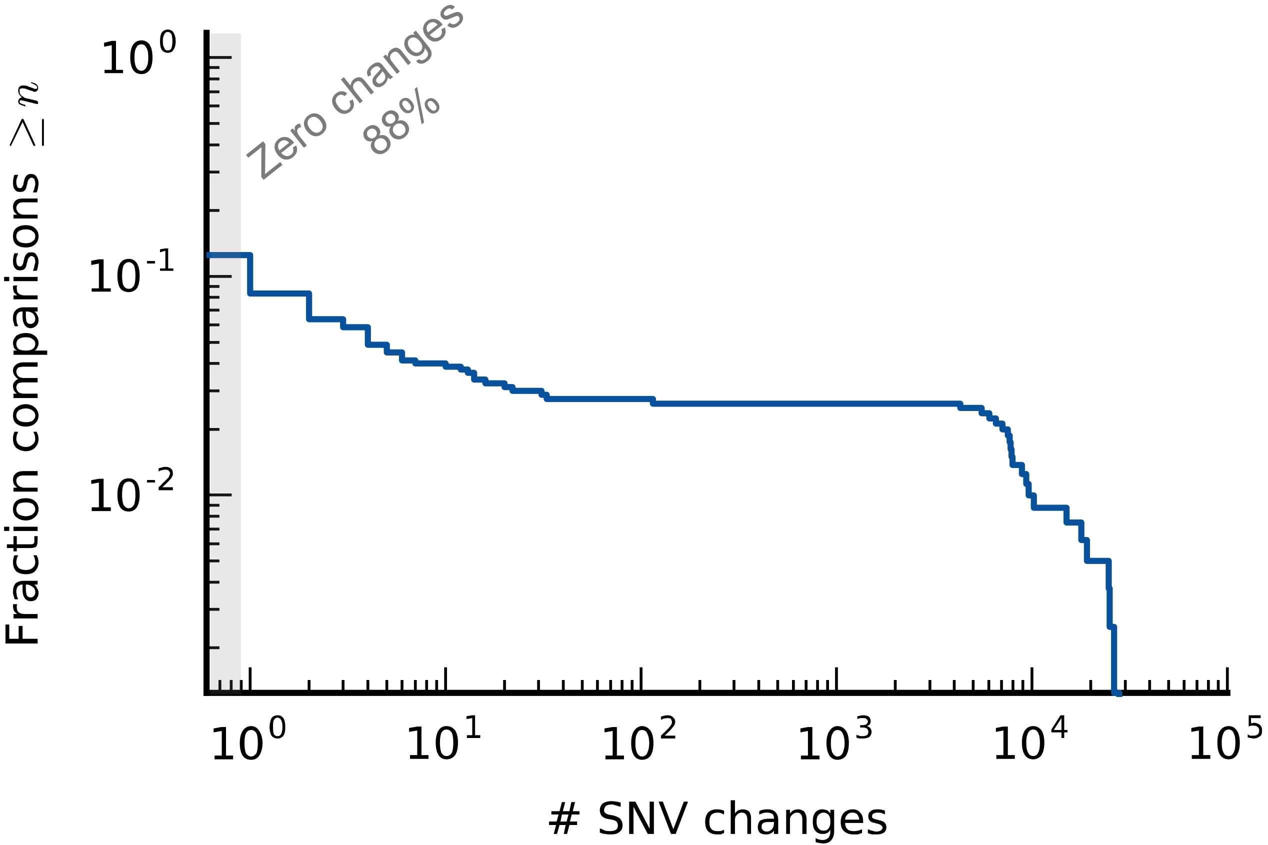
Survival distribution:
Fraction of temporal
comparisons
with **n** or more changes

Do bacteria evolve in the host gut?



~800 data points
from ~30 species

Do bacteria evolve in the host gut?



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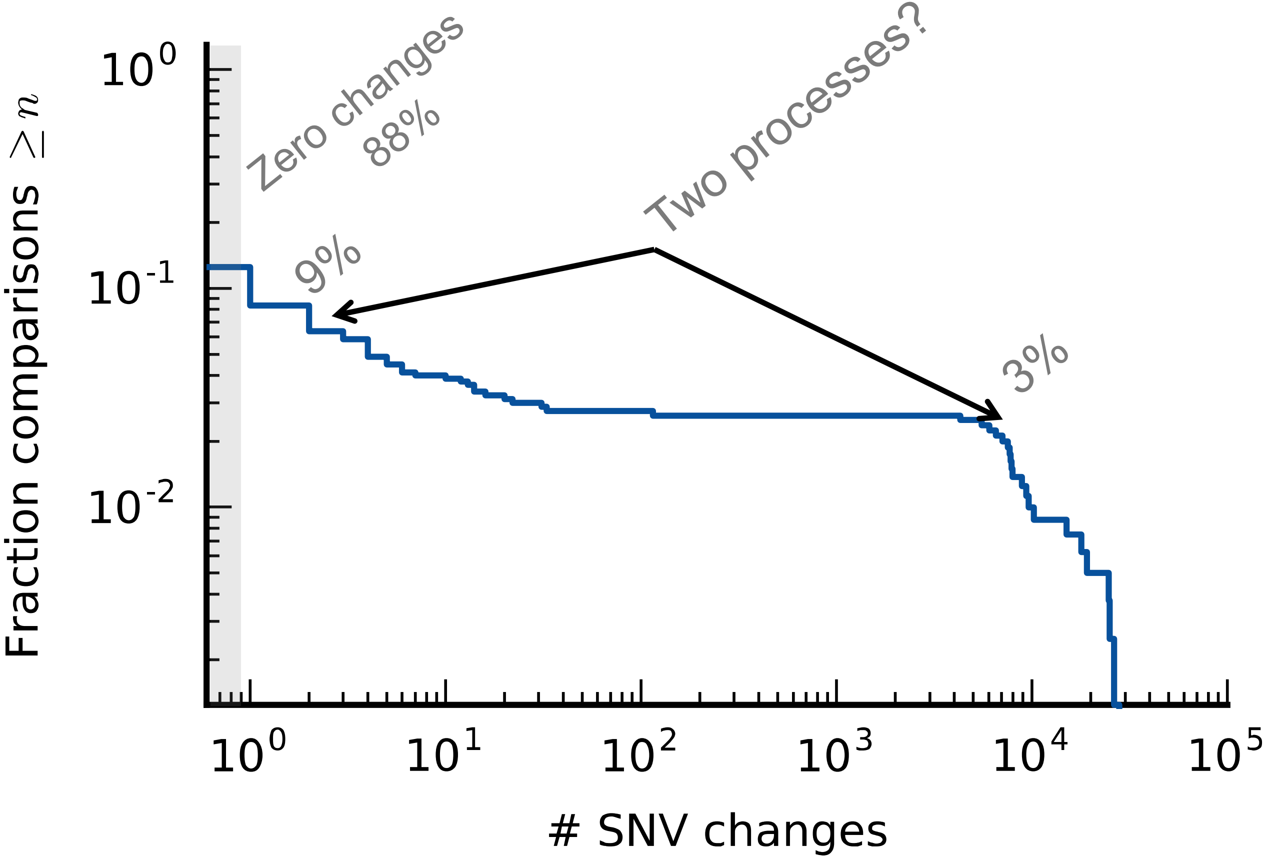
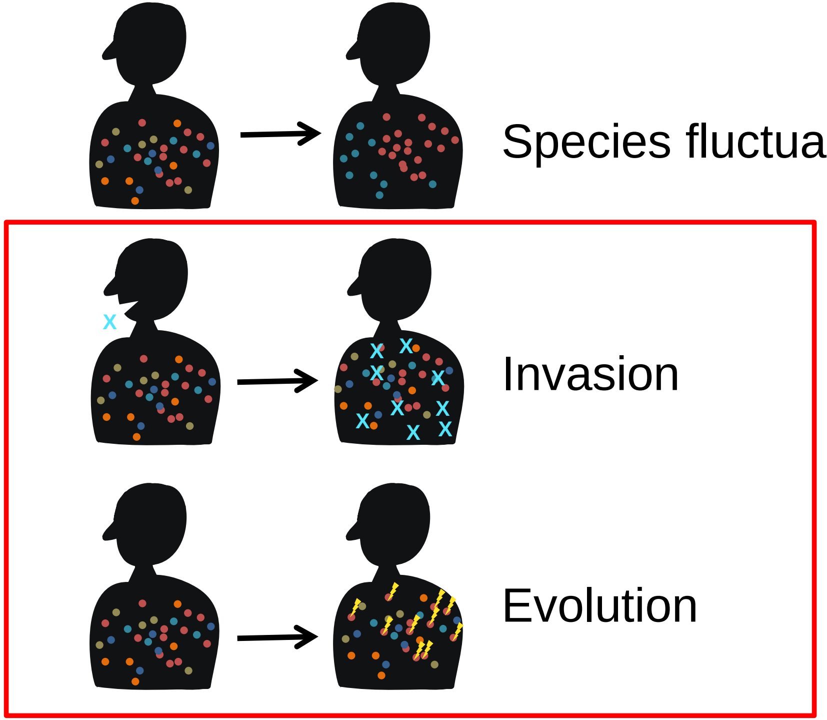


Distinguishing evolution from invasions in HMP data

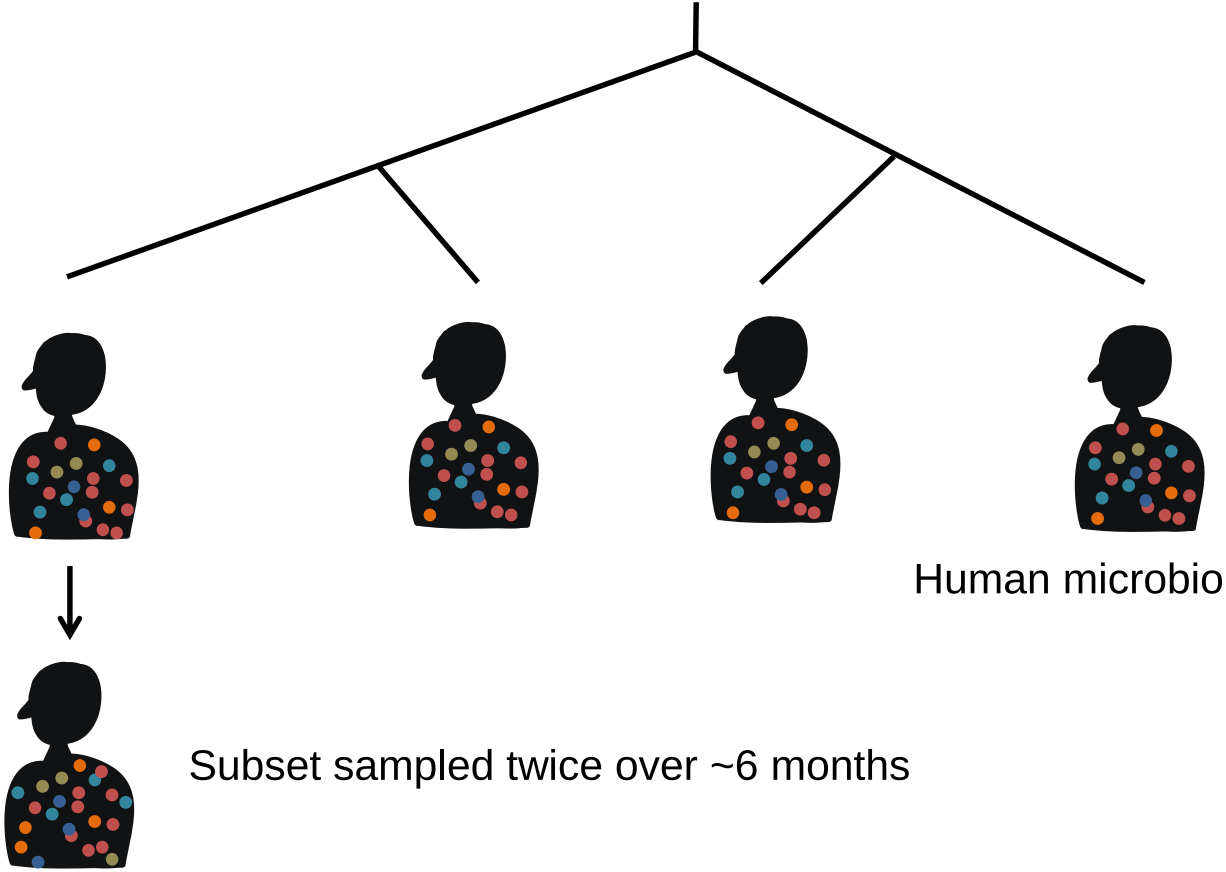


Species fluctuations

Invasion

Evolution

Distinguishing evolution from invasions

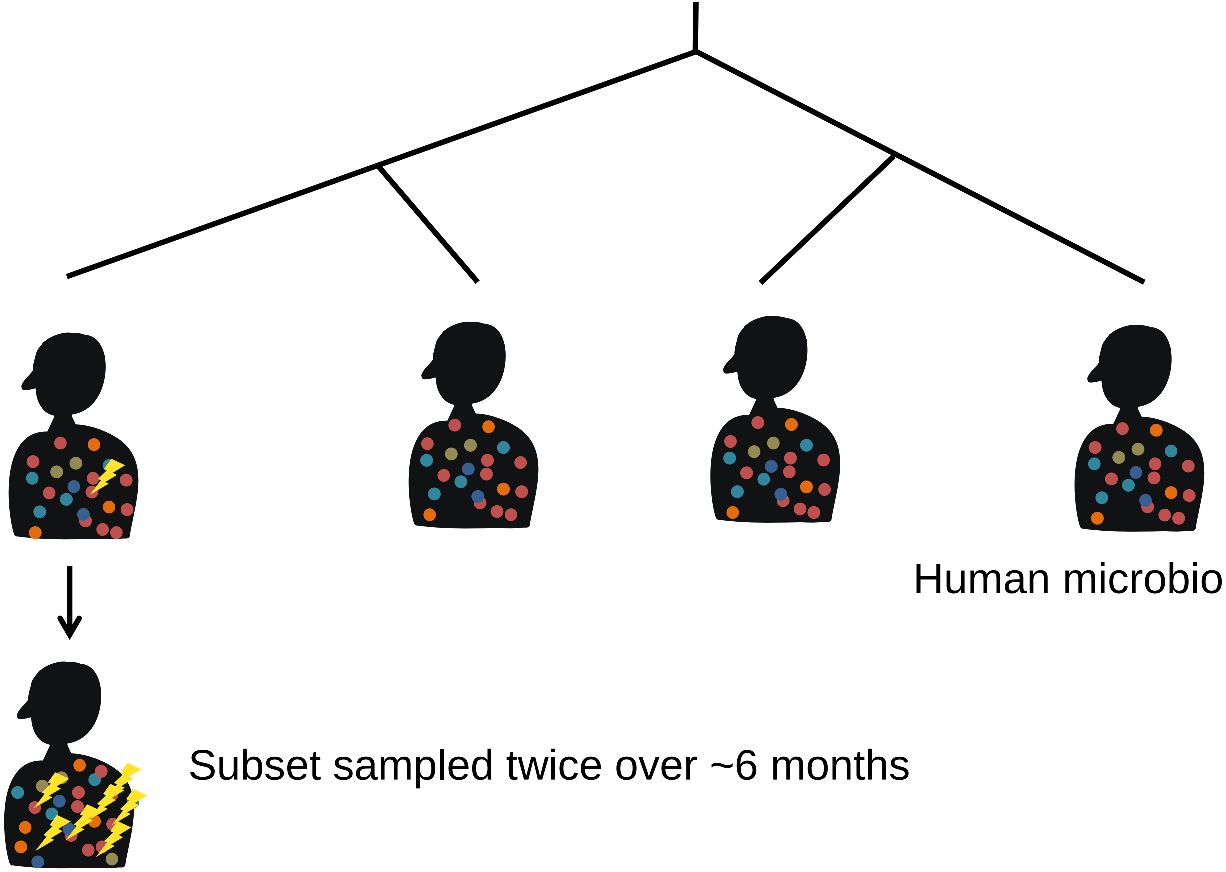


X 250 hosts

Human microbiome project

Subset sampled twice over ~6 months

Distinguishing evolution from invasions



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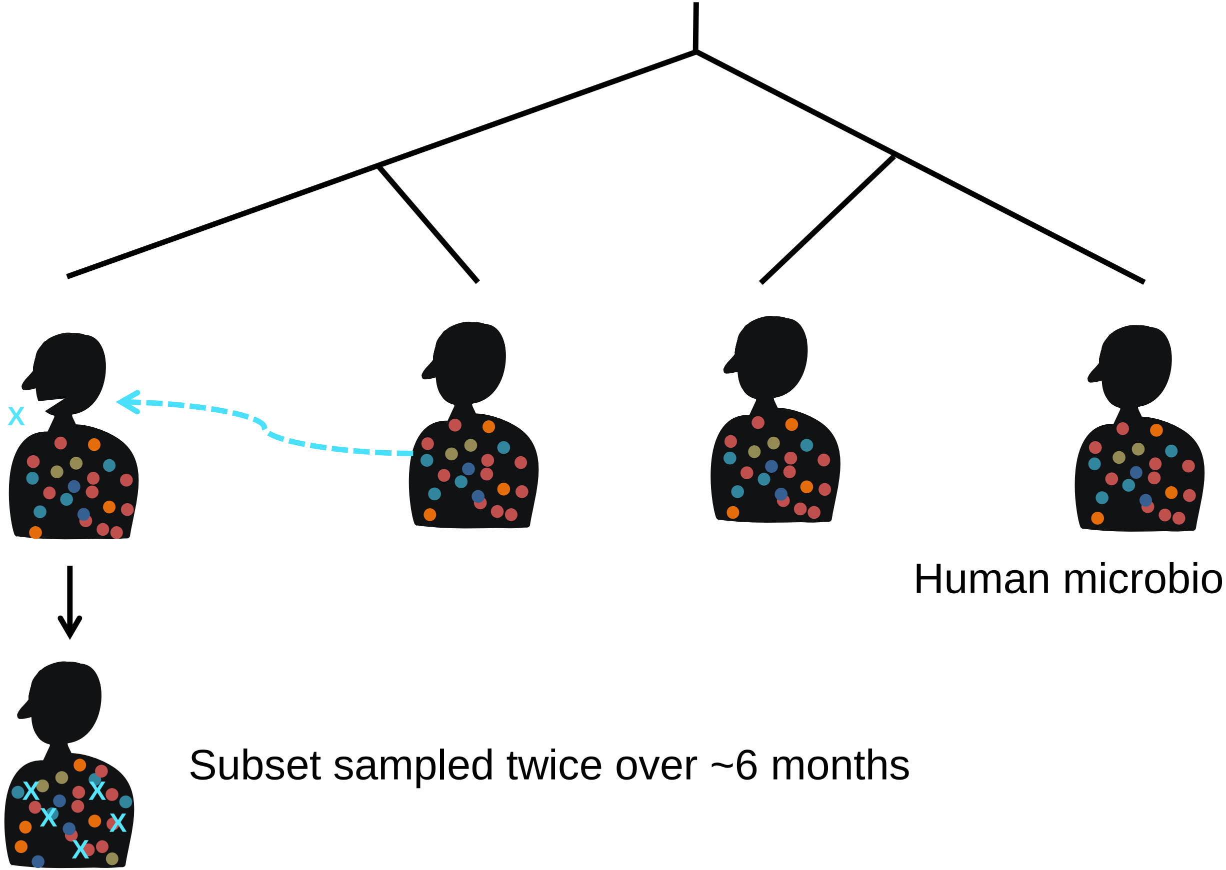

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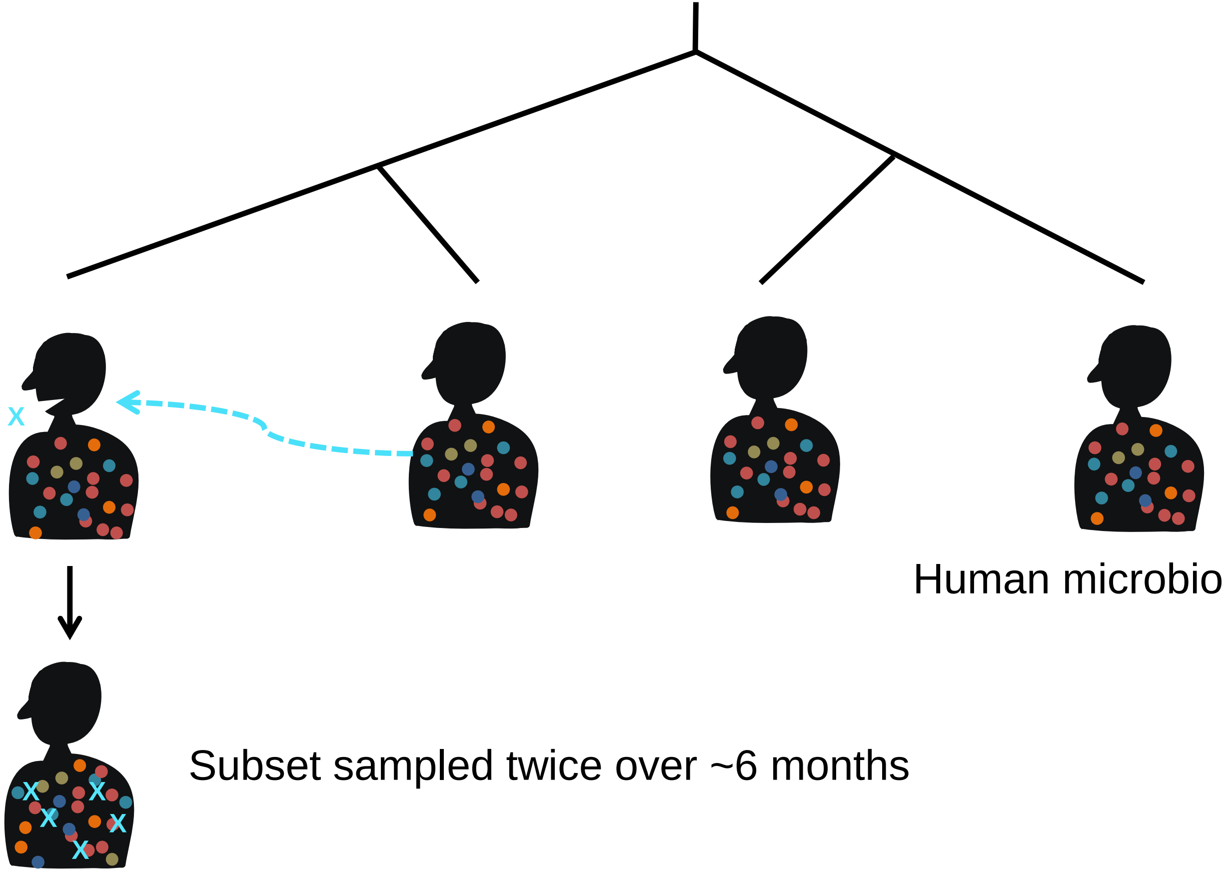

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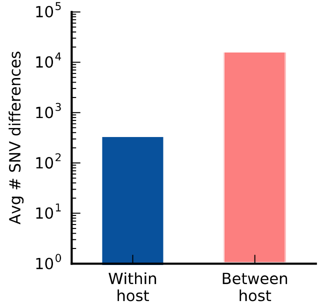

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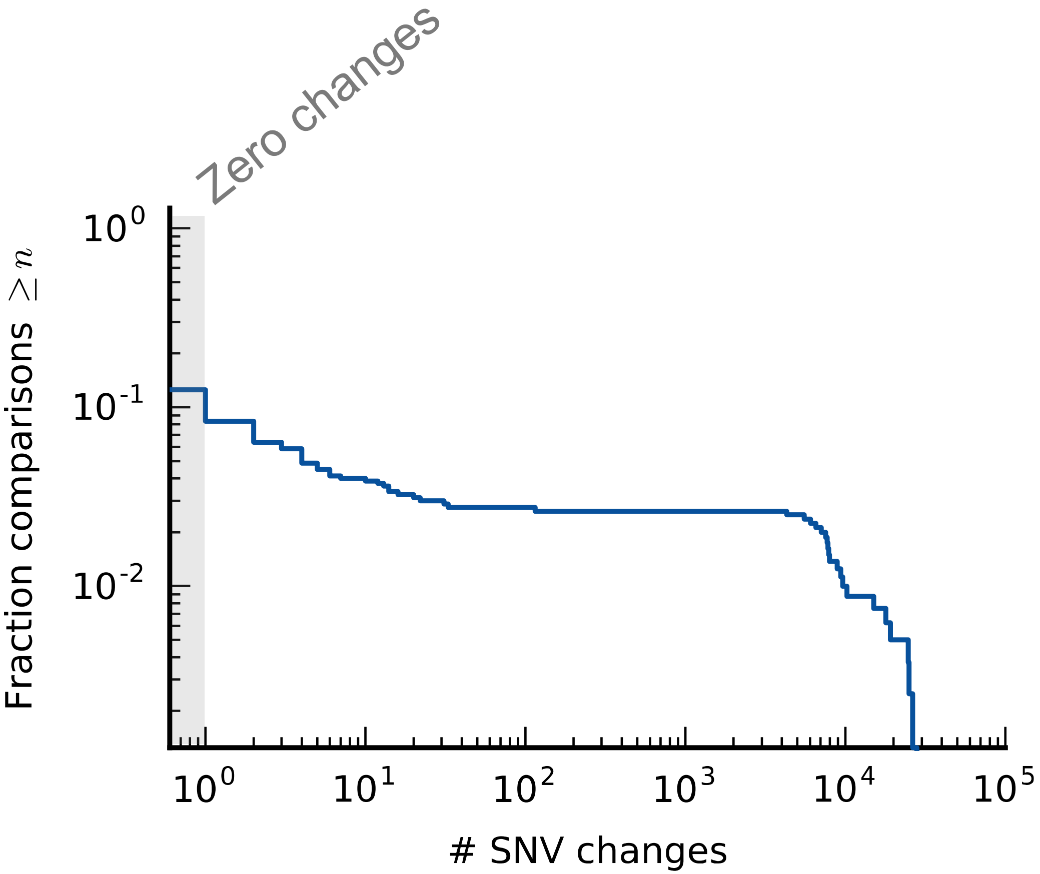

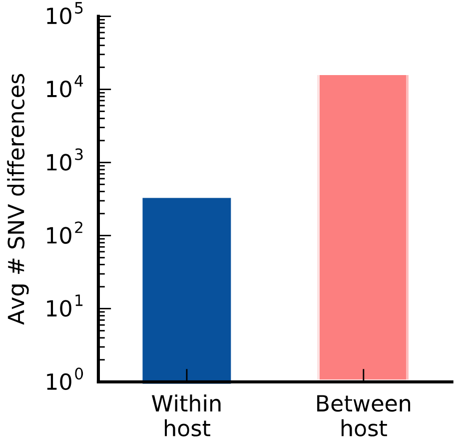

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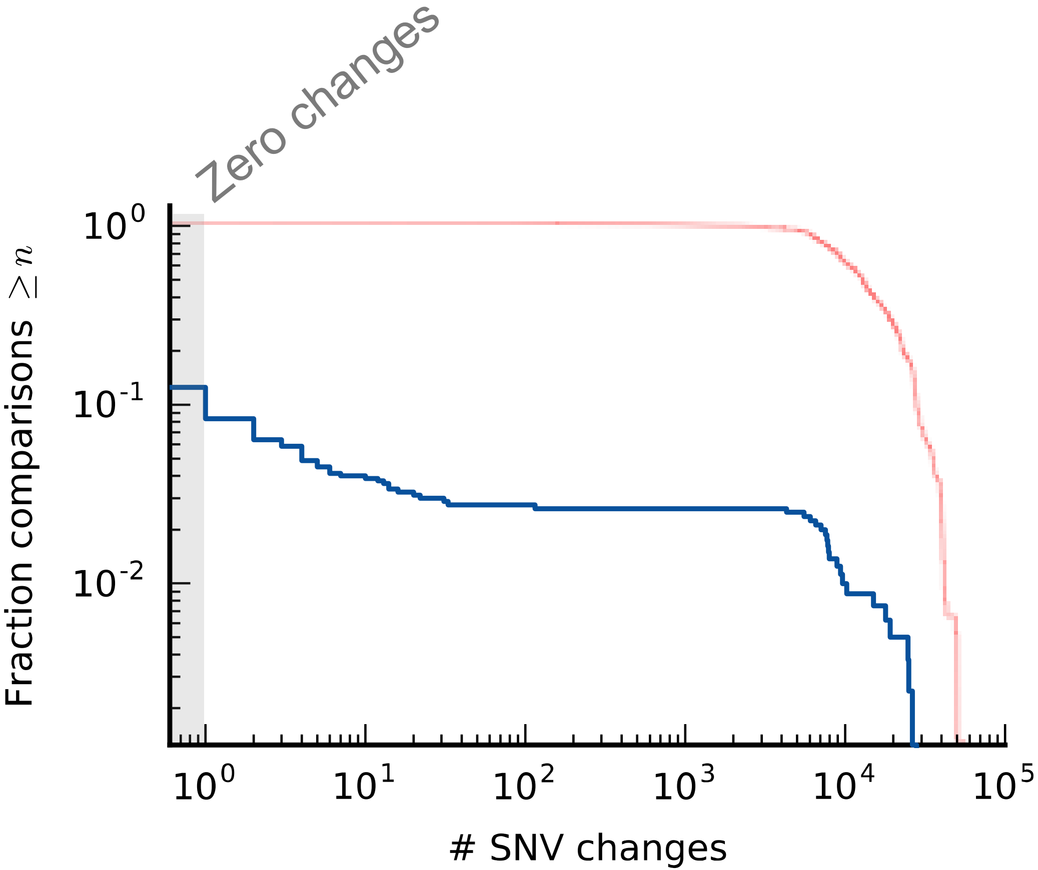

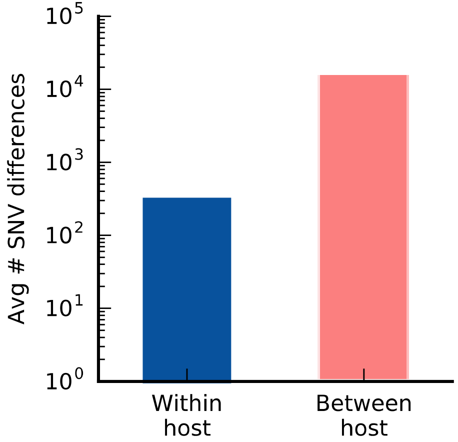

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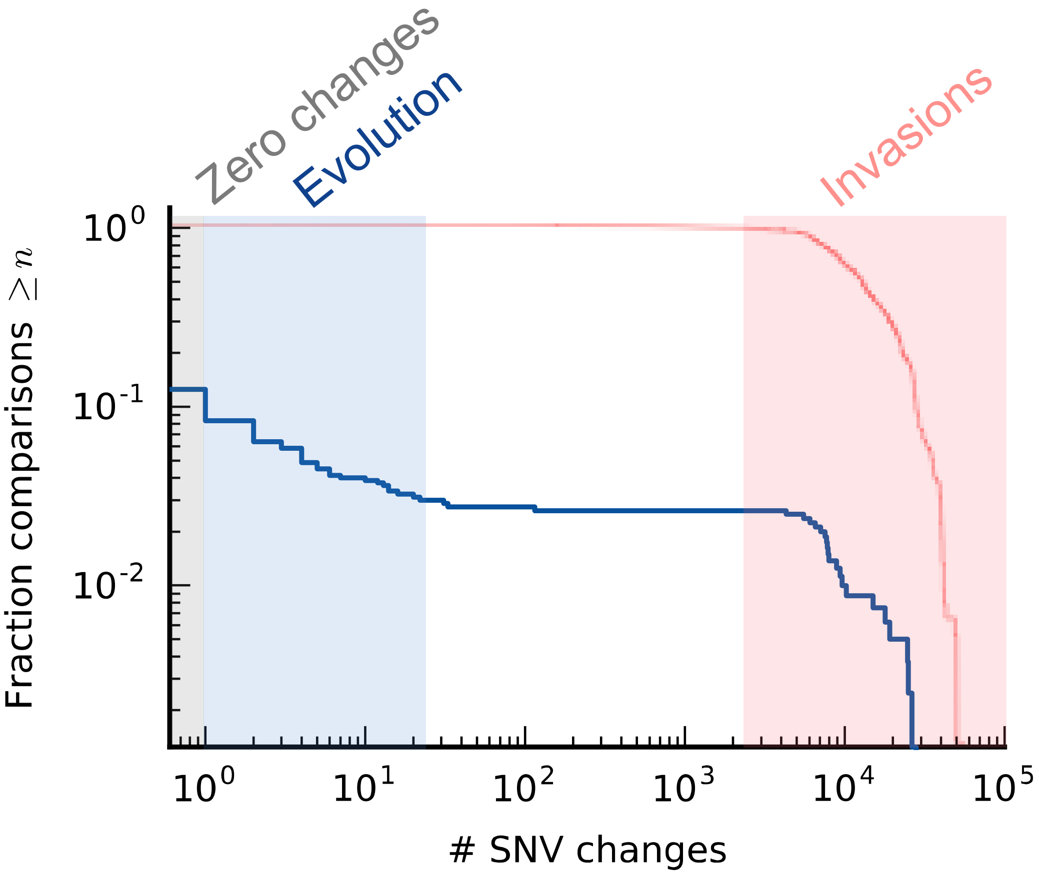

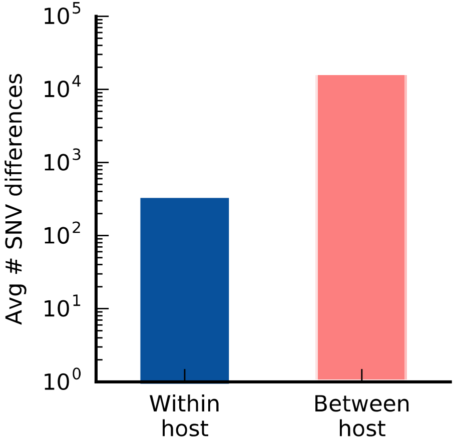

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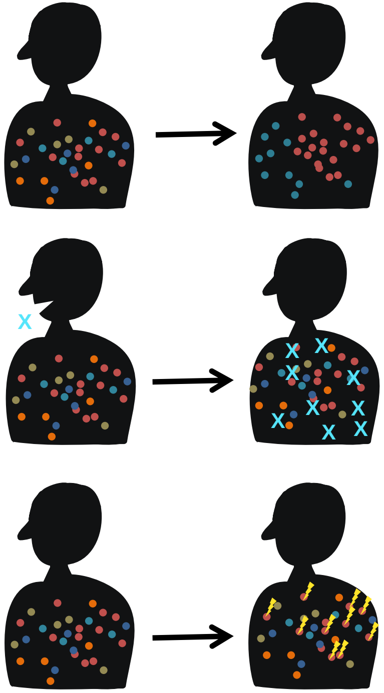


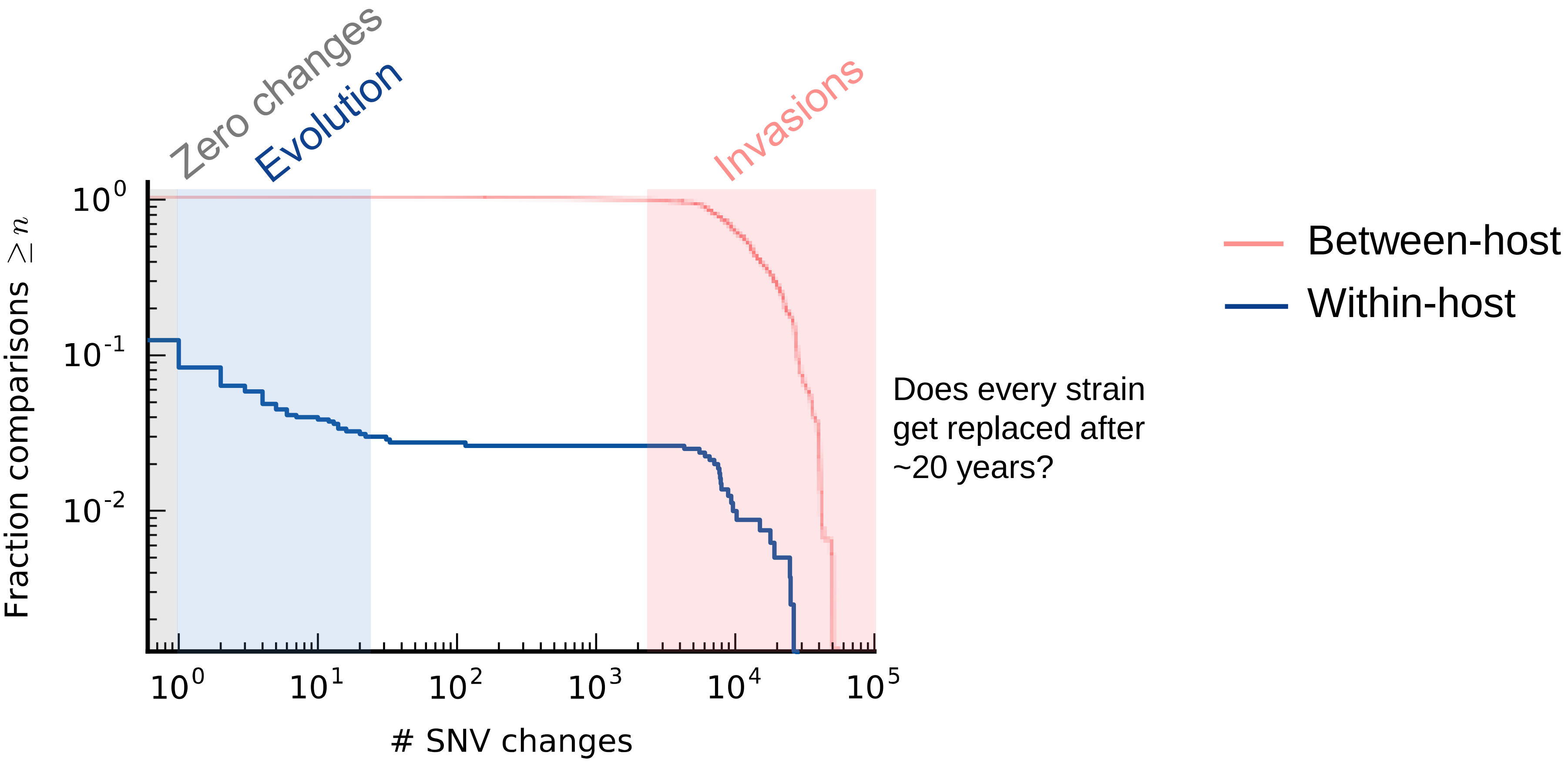
Species fluctuations

Invasion

Evolution ✓

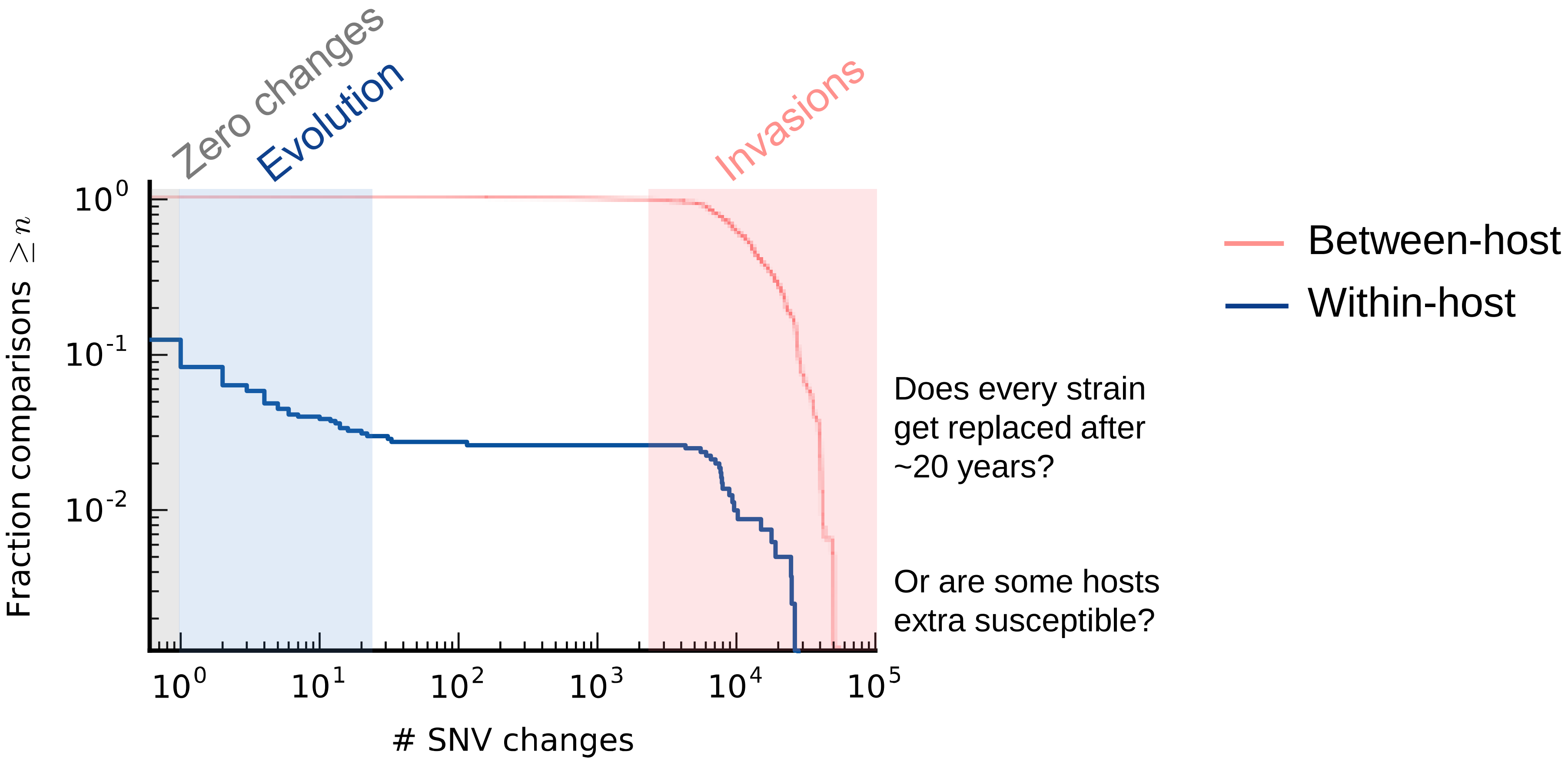
What about over our lifetime?

Evolutionary dynamics over our lifetime



Does every strain
get replaced after
~20 years?

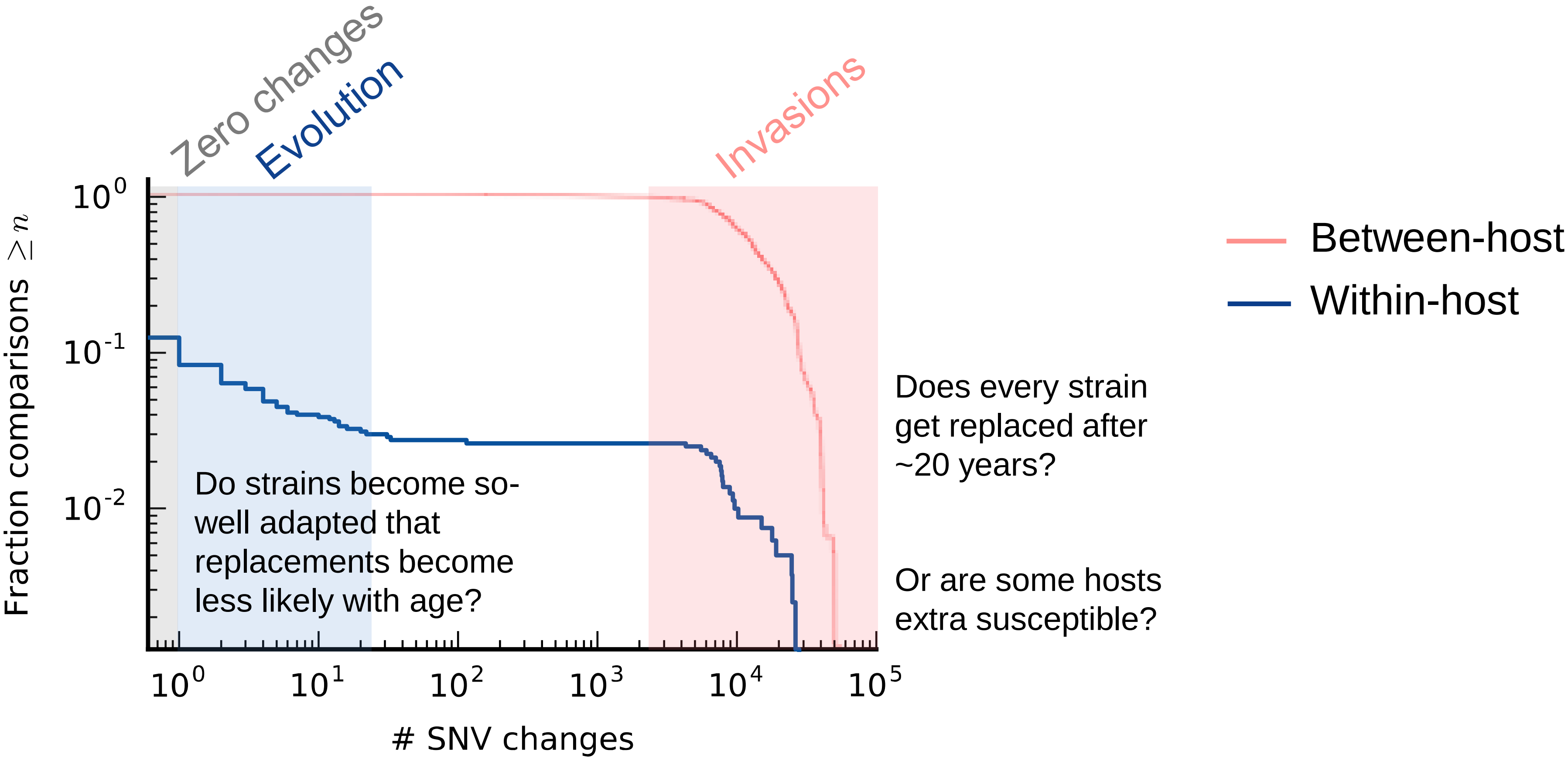
Evolutionary dynamics over our lifetime



Does every strain get replaced after ~20 years?

Or are some hosts extra susceptible?

Evolutionary dynamics over our lifetime

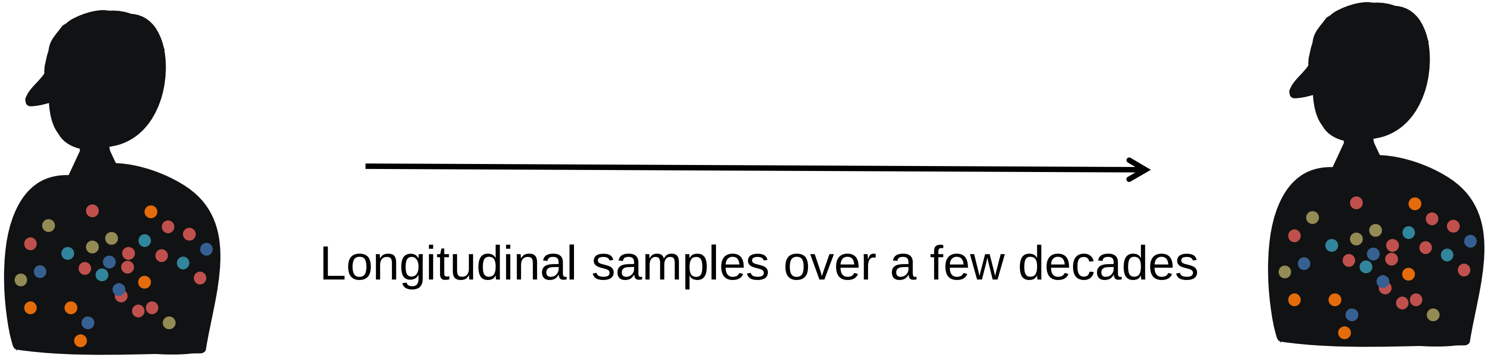


Do strains become so-well adapted that replacements become less likely with age?

Does every strain get replaced after ~20 years?

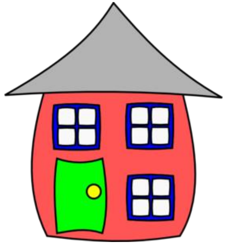
Or are some hosts extra susceptible?

Ideal data



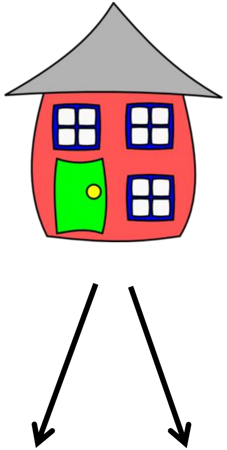
Longitudinal samples over a few decades

Leveraging adult twins to test for long-term dynamics



Korpela et al.: Cohabiting teenage twins and siblings share many strains

Leveraging adult twins to test for long-term dynamics

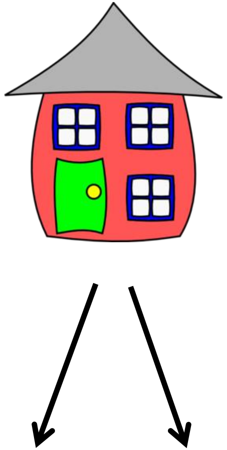


Korpela et al.: Cohabiting teenage twins and siblings share many strains

~40 years apart

125 Adult twin pairs
(Xie et al. 2016)

Leveraging adult twins to test for long-term dynamics



Korpela et al.: Cohabiting teenage twins and siblings share many strains

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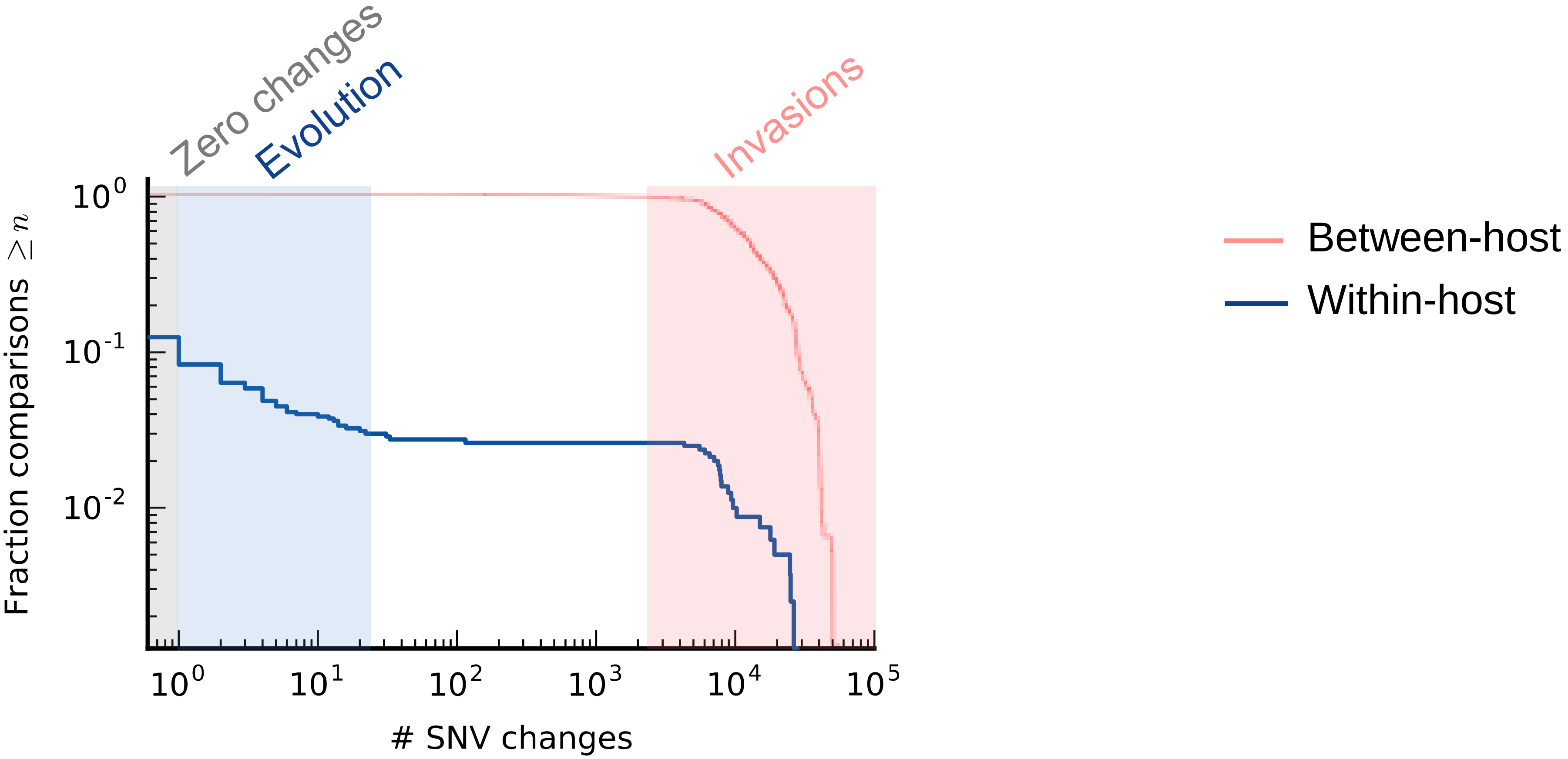
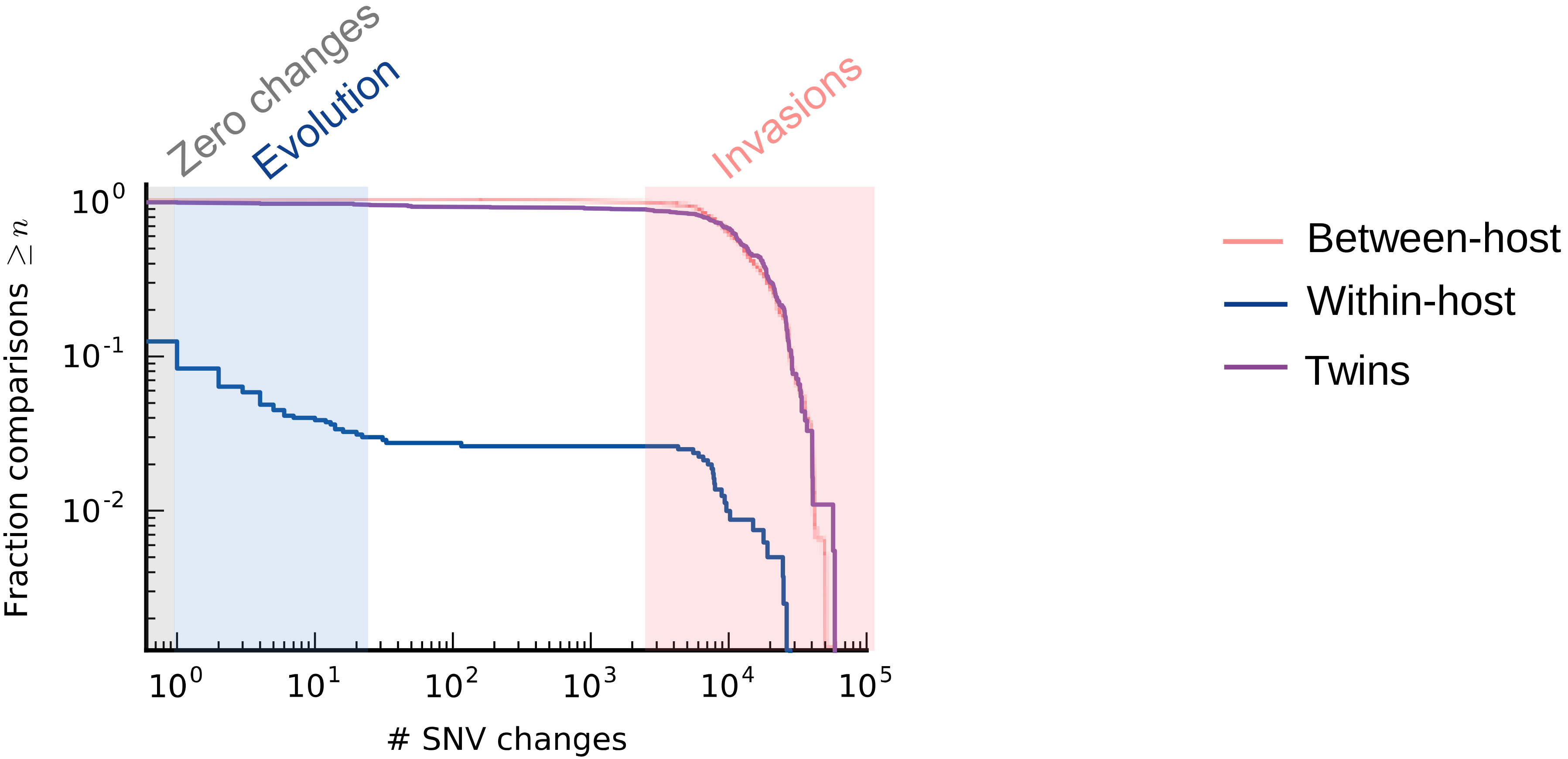
125 Adult twin pairs
(Xie et al. 2016)

Do adult twins share the same strains?

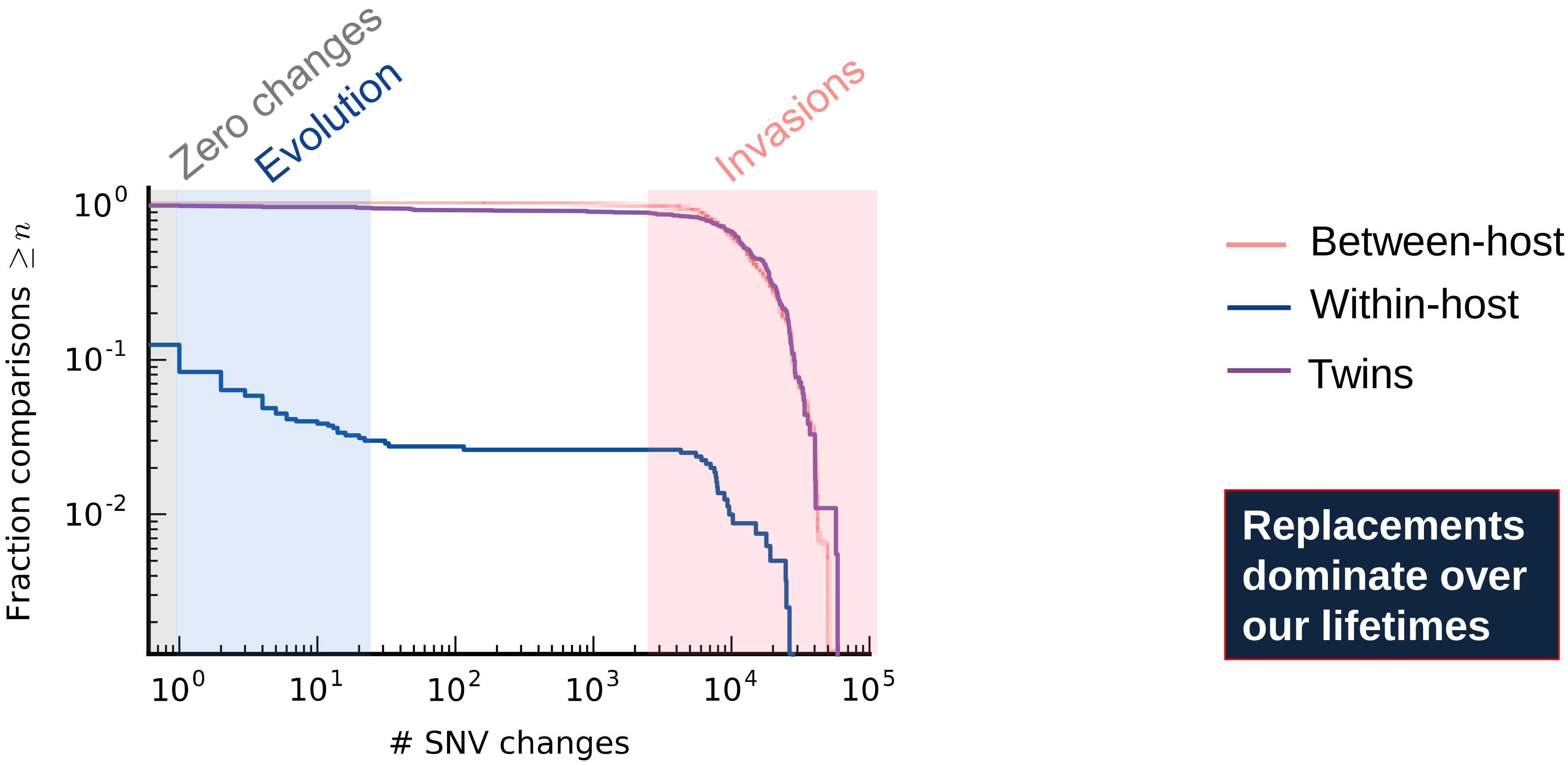
Evolutionary dynamics over our lifetime



Evolutionary dynamics over our lifetime

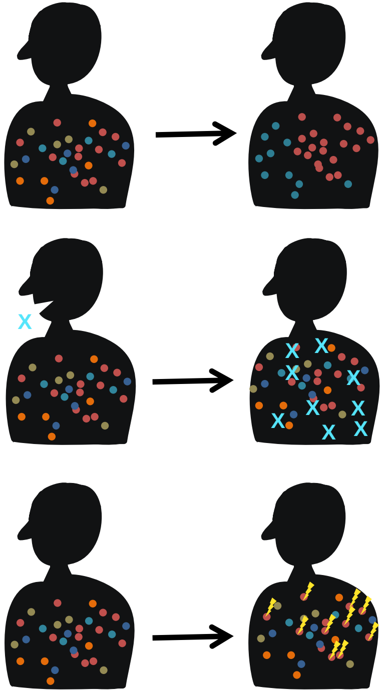


Evolutionary dynamics over our lifetime



Replacements dominate over our lifetimes

Do bacteria evolve in the host gut?



Species fluctuations

Invasion

Evolution ✓

Open Questions

- Does rapid evolution impact the ecology of the microbiome?

- How does adaptation of microbiota impact host health?

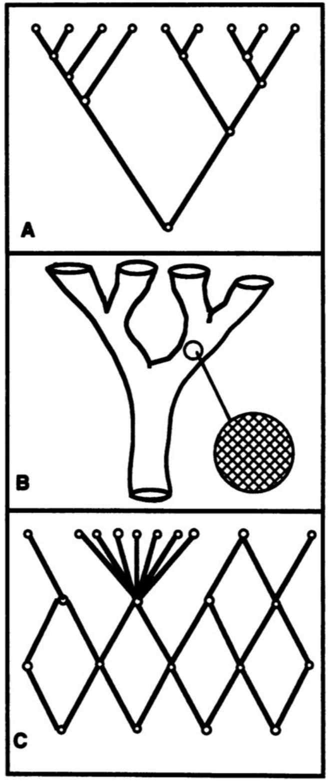
- How much adaptation is there?

- What are the targets of selection?

Overview

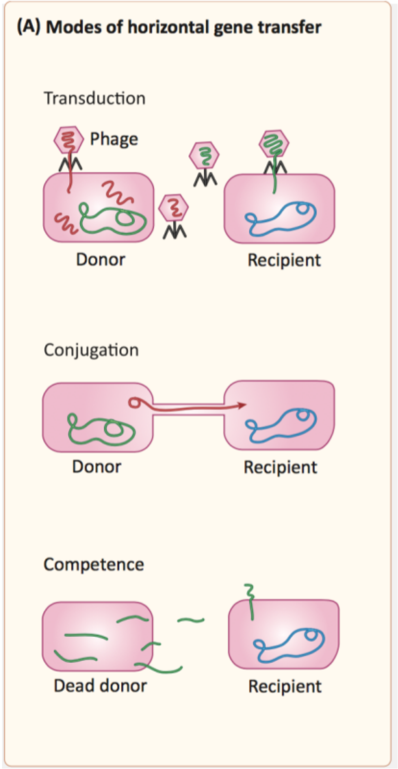
- Data
- Drift and migration
- Adaptation
- Recombination

How Clonal are Bacteria?



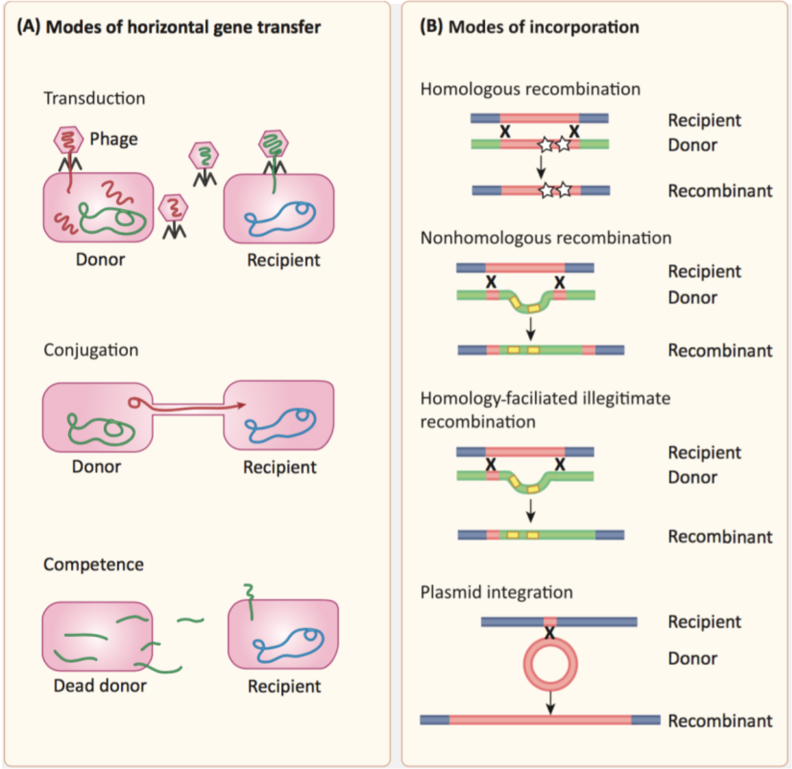
John Maynard Smith 1993

Do gut microbes recombine frequently?



Garud & Pollard 2019 Trends in Genetics

Do gut microbes recombine frequently?



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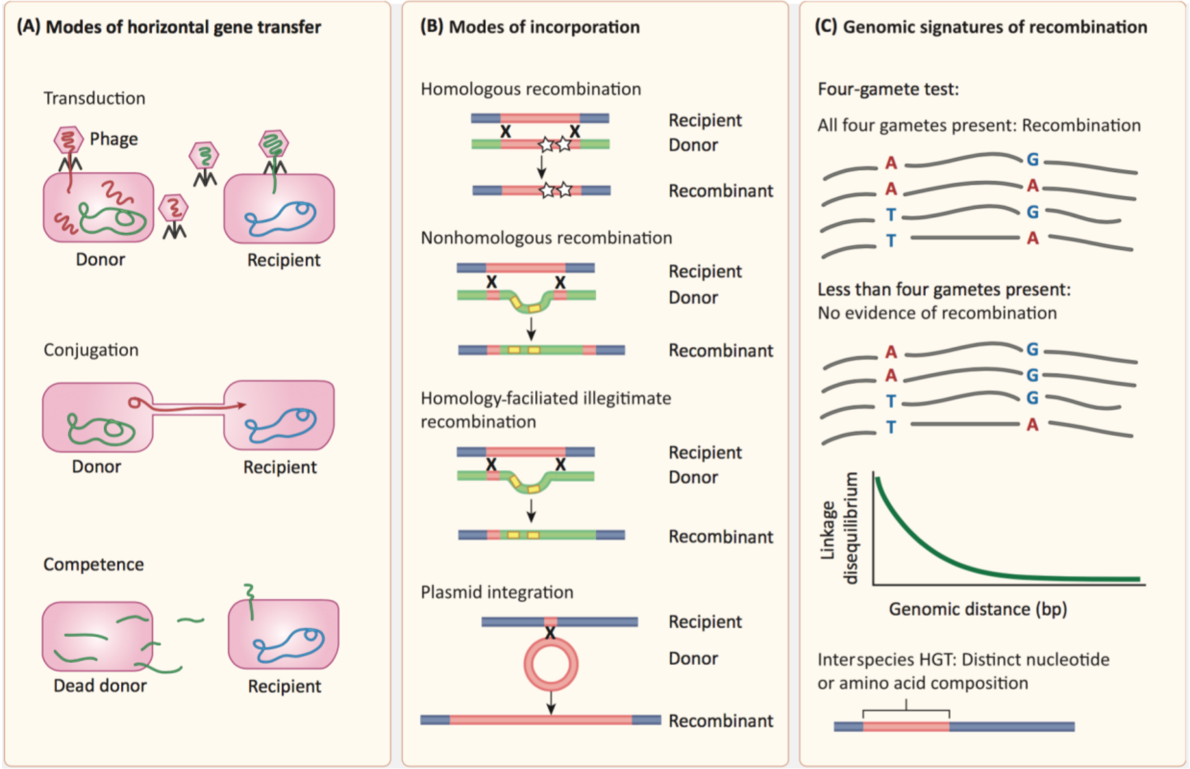
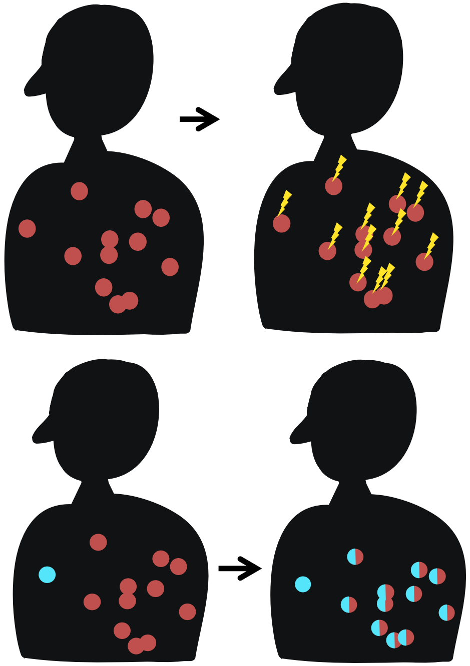


Garud and Good *et al.* 2019
Zhao and Lieberman *et al.* 2019
Yaffe and Relman 2019
Lin and Kussell 2019,
Sakoparnig *et al.* 2019,
Rosen *et al.* 2015

Garud & Pollard 2019 Trends in Genetics

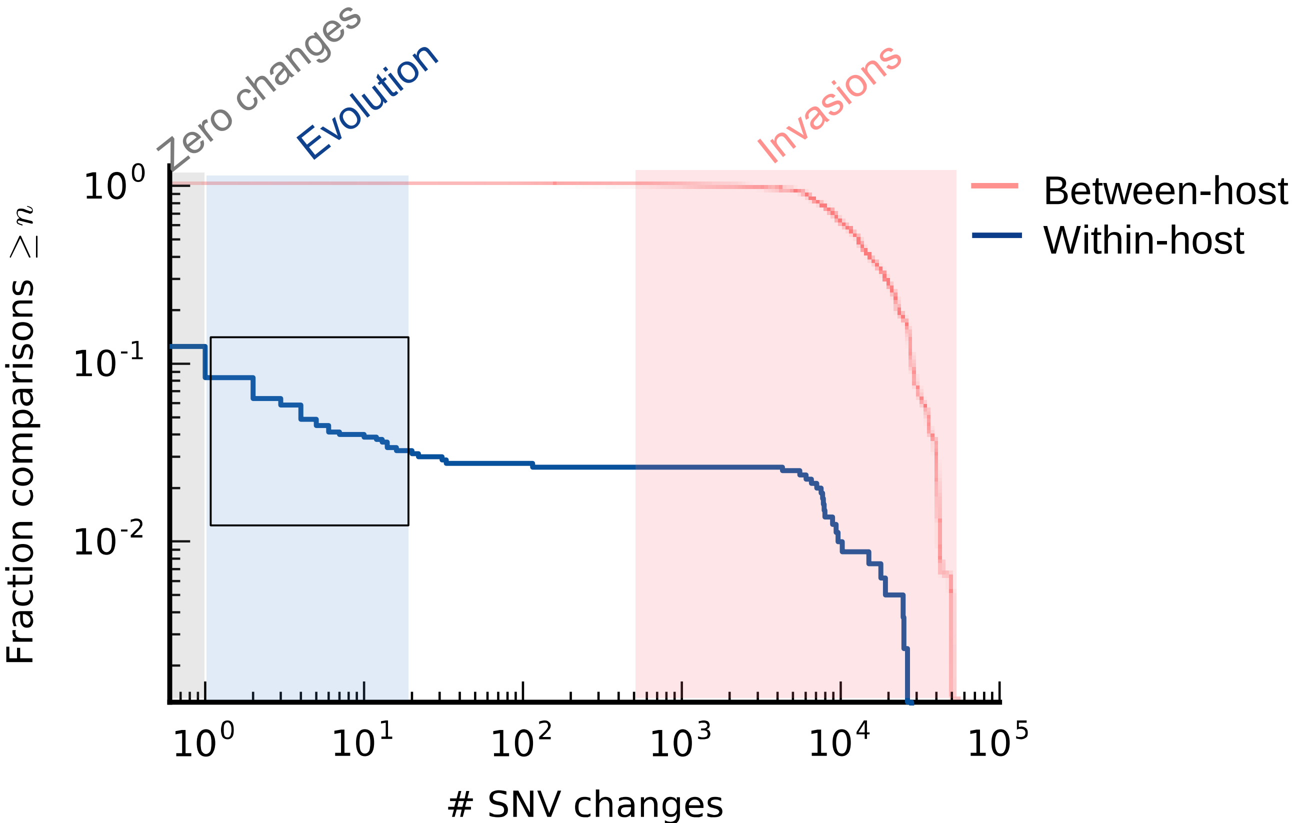
Are adaptive events seeded by ***de novo* mutations** or **recombination events**?



De novo
mutations

Recombination-
seeded sweeps

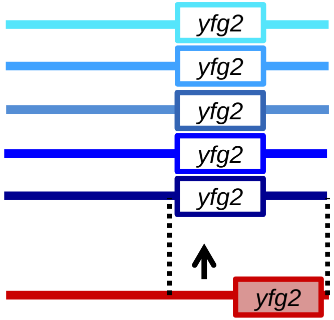
Are sweeps seeded by ***de novo* mutations** or **recombination events**?



Are sweeps seeded by ***de novo*** **mutations** or **recombination events**?

🟦 Within-host observed data

⬛ *De novo* expectation



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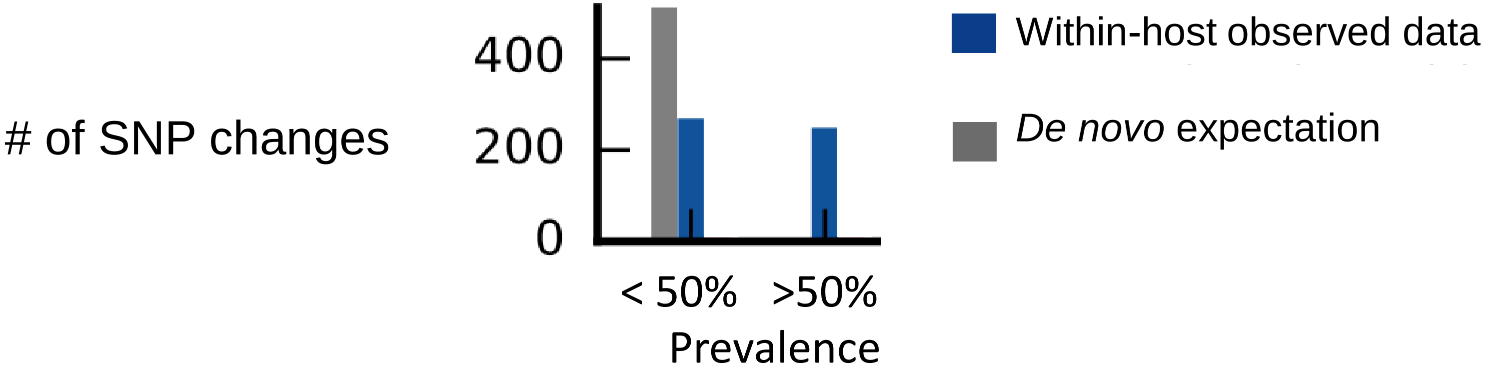

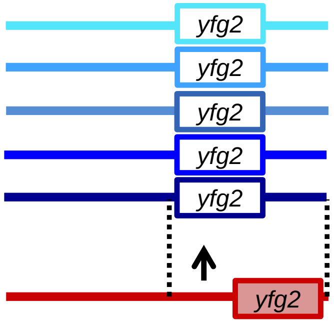

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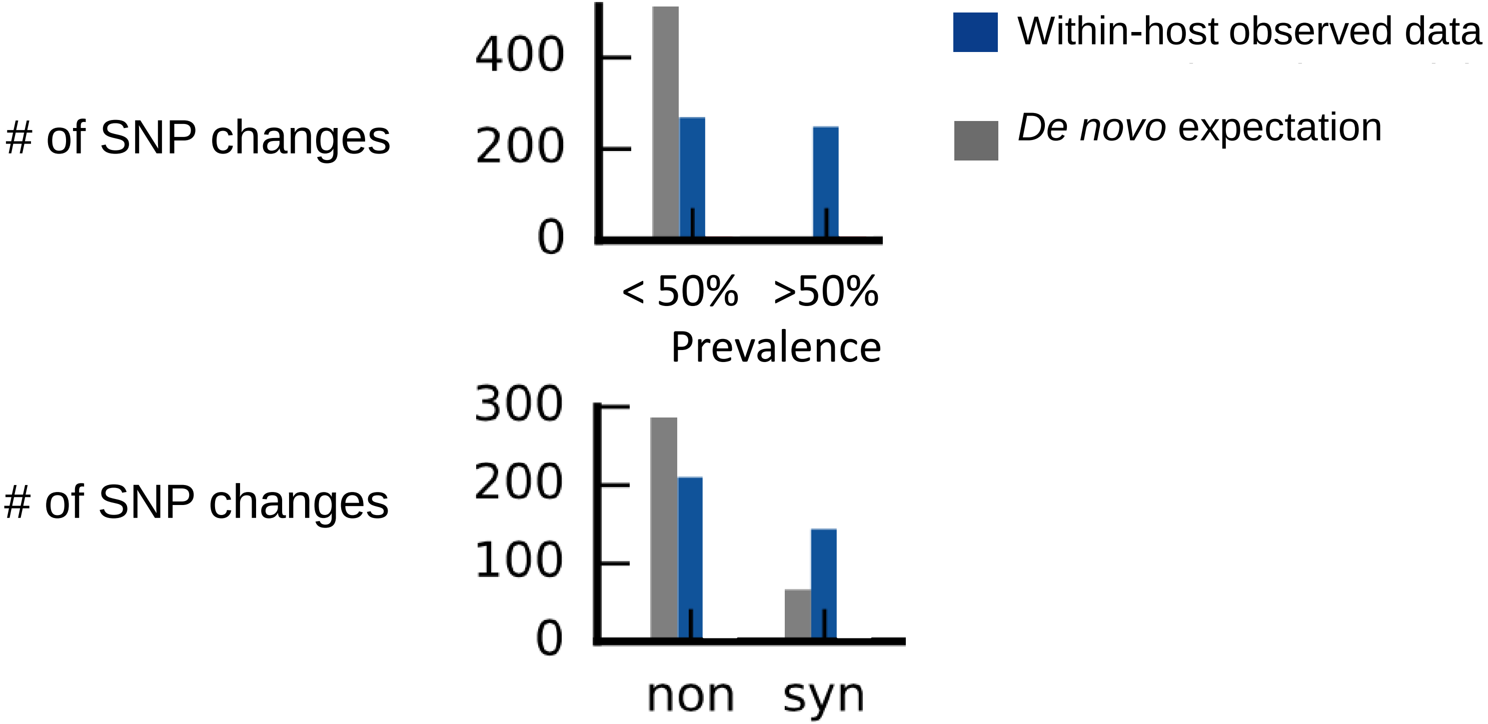
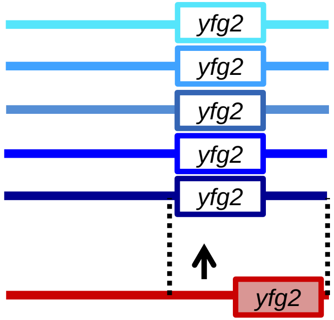
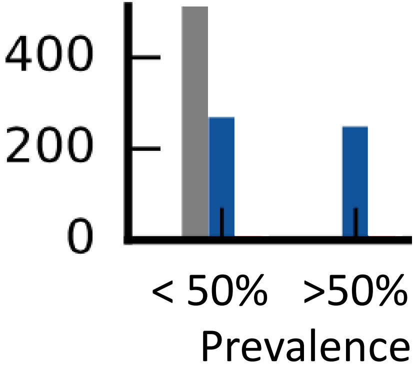




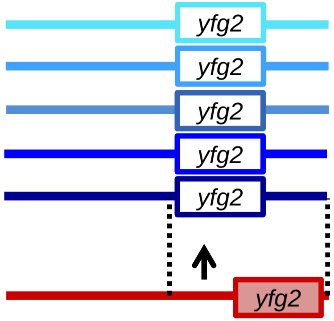
Are sweeps seeded by ***de novo* mutations** or **recombination events**?

of SNP changes

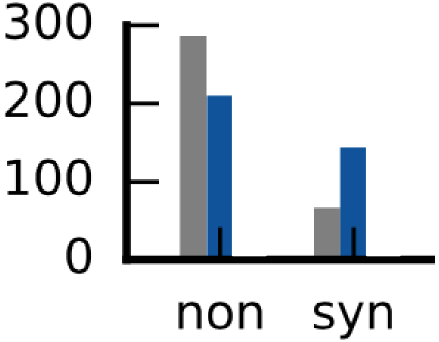


🟦 Within-host observed data

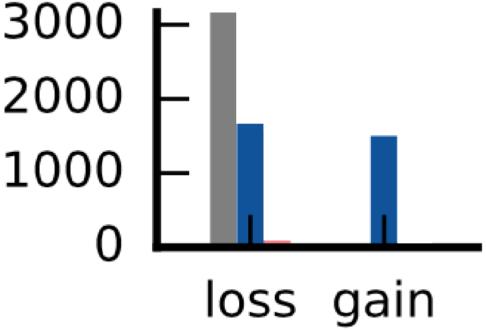
⬛ *De novo* expectation



# of SNP changes



# of gene changes



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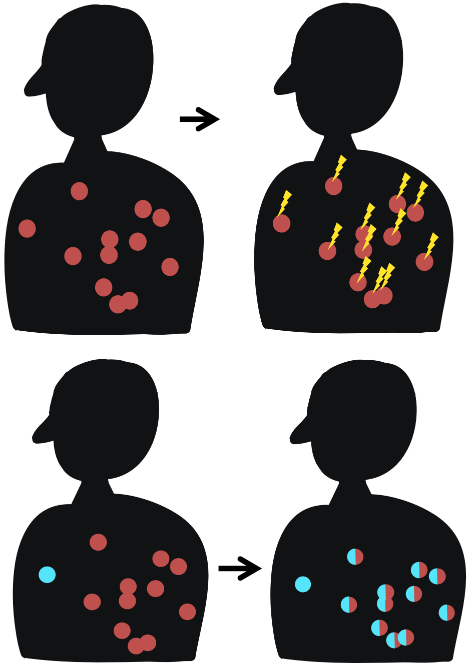


De novo mutations

Recombination-seeded sweeps ✓

Open Questions

- Do bacteria recombine randomly with each other?

- When do bacteria have the opportunity to recombine if hosts are ‘oligo colonized’?

- How does recombination impact the mode of adaptation?

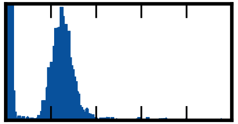
Conclusions:

Population genetics in the microbiome

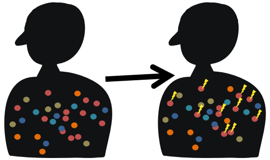
- Genetic variation in the microbiome impacts our **health**

- Lots of **data**!

- Inter and intra-host **population structure**

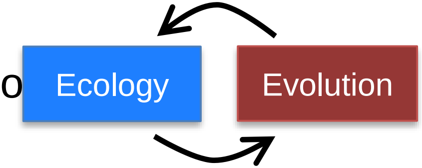


- **Bacteria can evolve** in the human microbiome on short time scales



- Extensive **recombination**

- Rapid evolution in a complex community affords us the opportunity to study **eco-evo** relationships



Ecology

Evolution

Nandita Garud
ngarud@ucla.edu

Recruiting postdocs and graduate students!

Join my lab in the Ecology and Evolutionary Biology department at **UCLA**!

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ngarud@ucla.edu

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Benjamin Good

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Garud*, Good* *et al.* 2019, *PLoS Biology*
Garud and Pollard 2019, *Trends in Genetics*

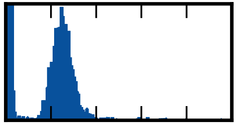
Conclusions:

Population genetics in the microbiome

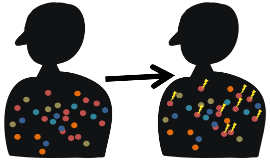
- Genetic variation in the microbiome impacts our **health**

- Lots of **data**!

- Inter and intra-host **population structure**

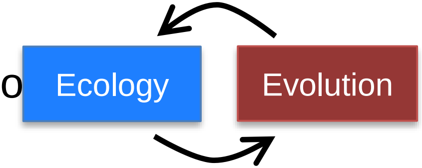


- **Bacteria can evolve** in the human microbiome on short time scales



- Extensive **recombination**

- Rapid evolution in a complex community affords us the opportunity to study **eco-evo** relationships



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