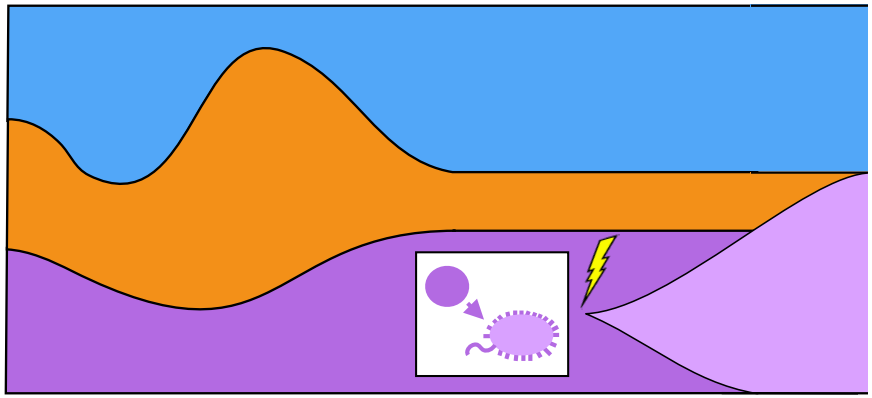
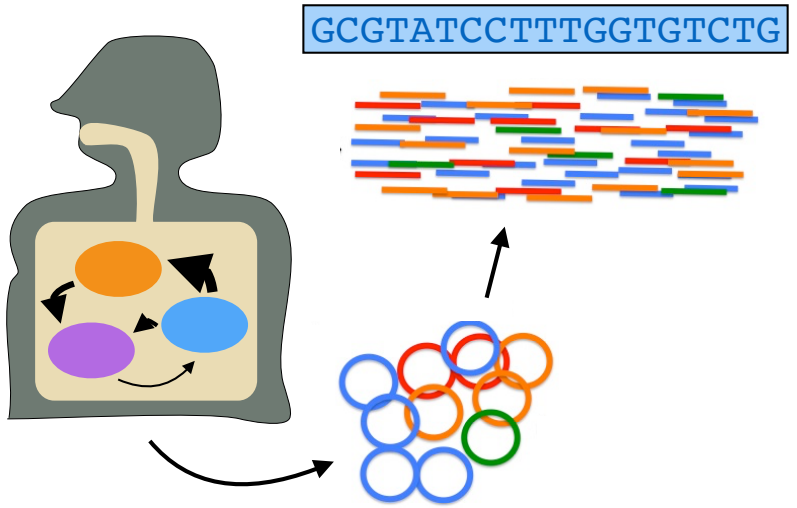
Eco-evolutionary feedbacks in the gut microbiome

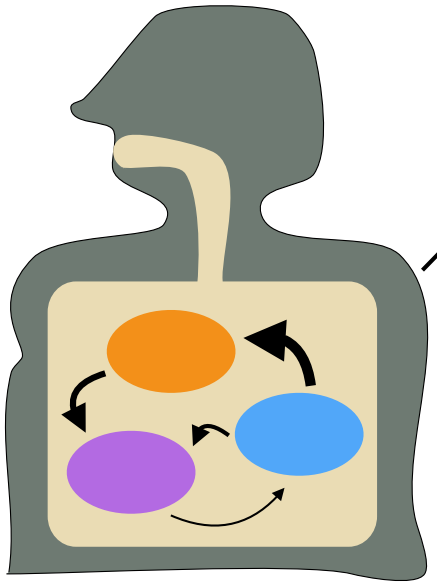




Benjamin Good
Assistant Professor of Applied Physics
Stanford University

The Ecology and Evolution of Microbial Communities 7/26/21
Kavli Institute for Theoretical Physics

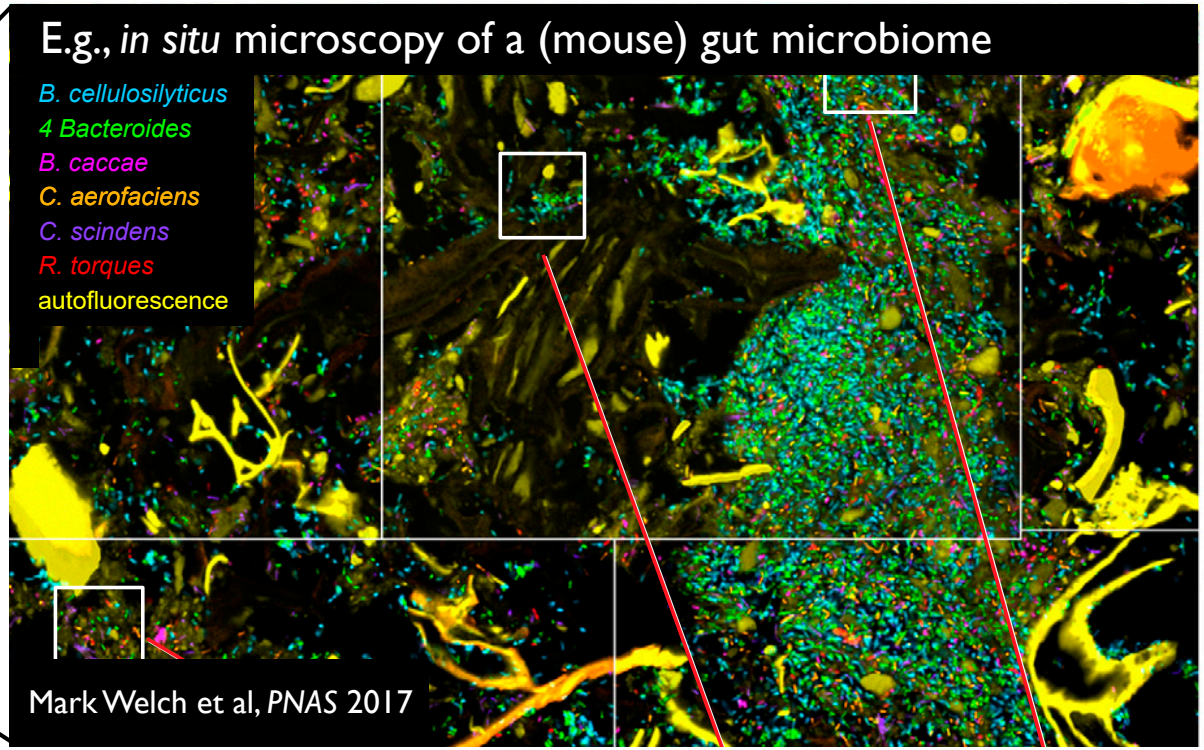
Understanding the *collective behavior* of microbial communities



Large intestine:

~10^{12} cells

~100 distinct species



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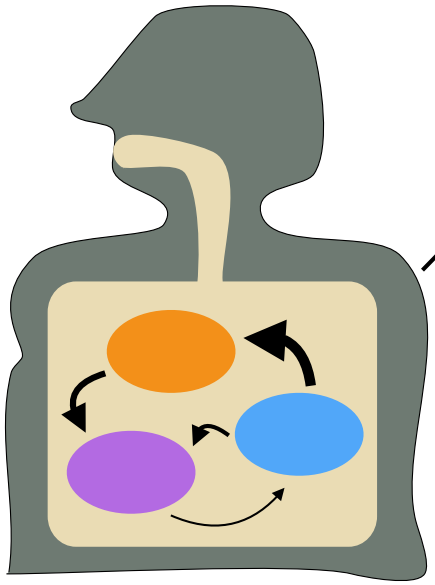

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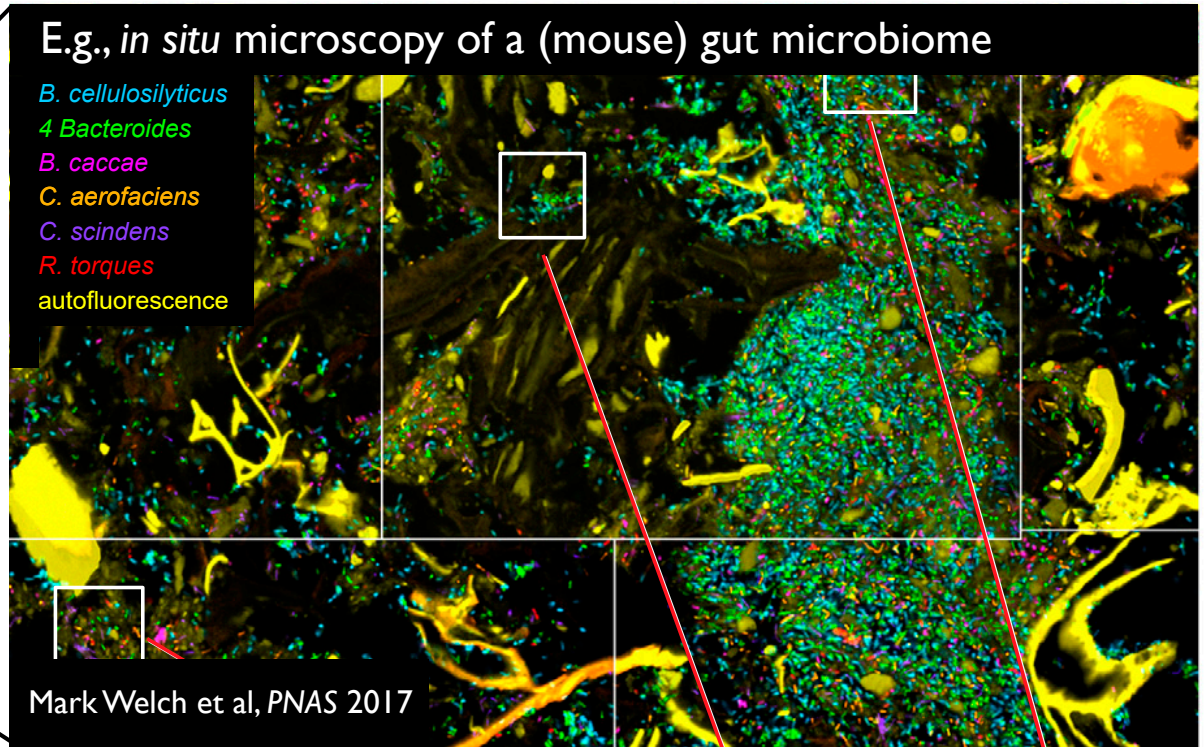

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1. Structure & function emerge from many interacting parts ***(ecology)***

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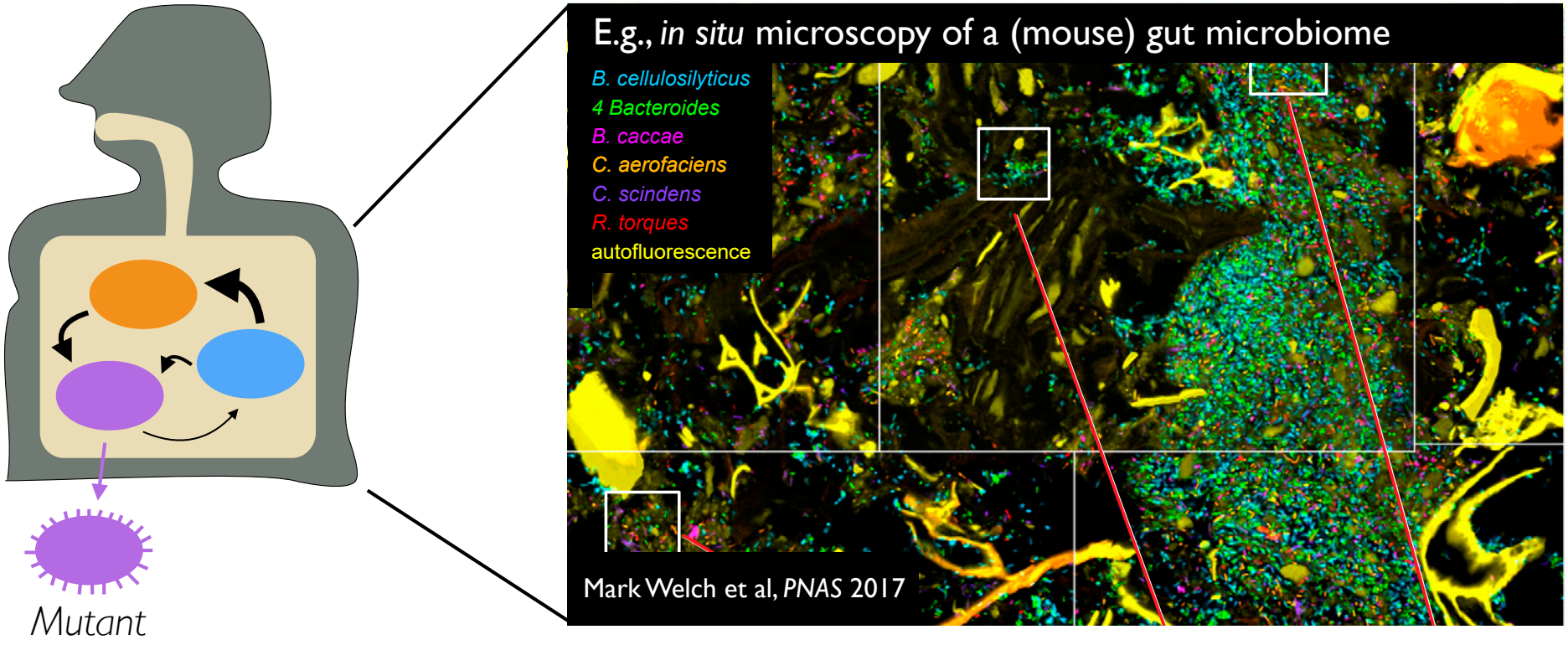

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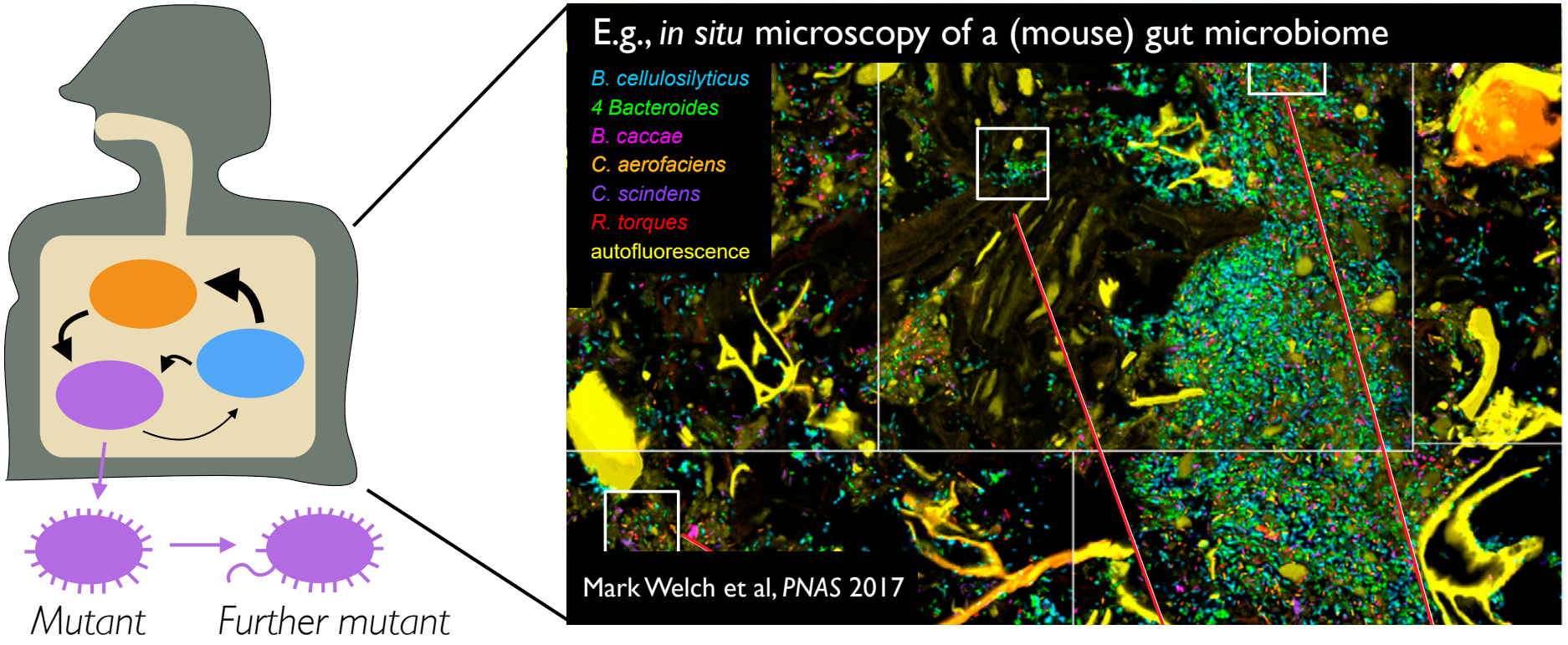

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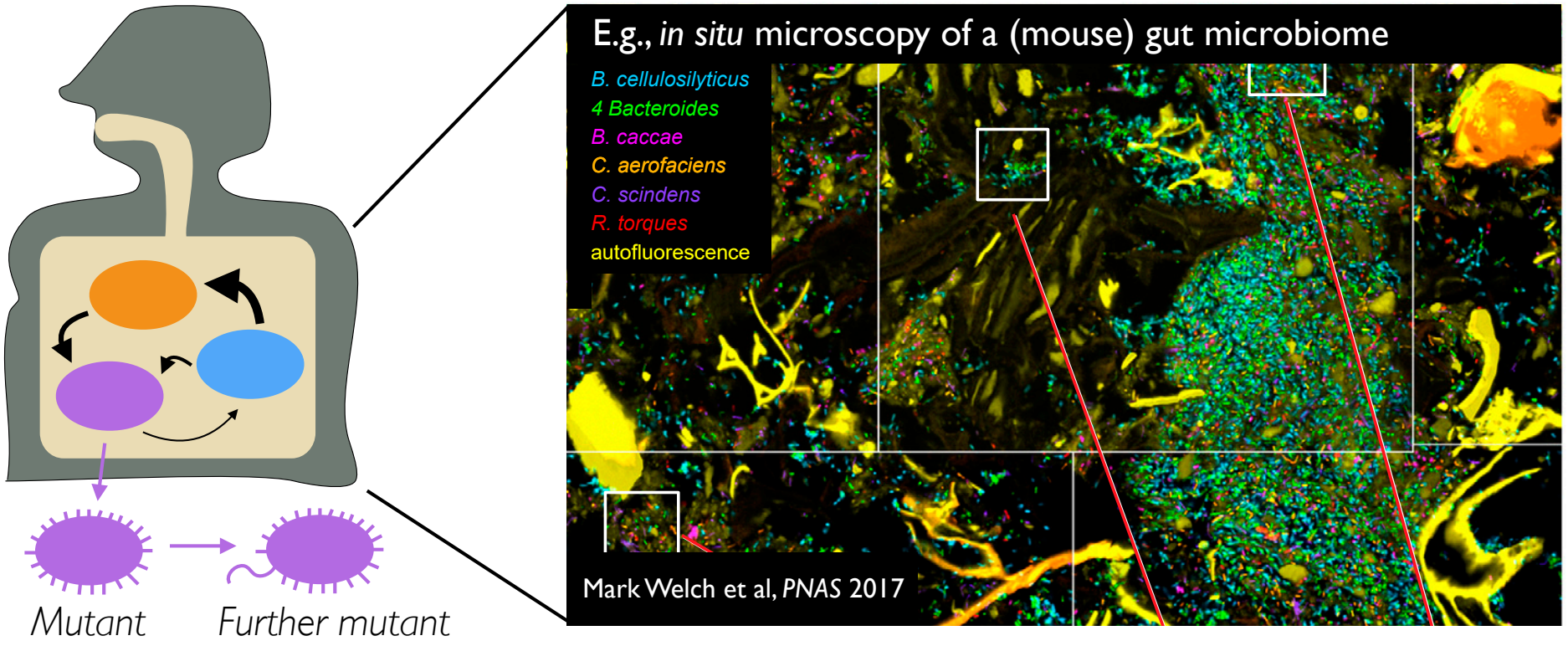

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(pathogens, lab expt's: Δt ~ years, months, days)

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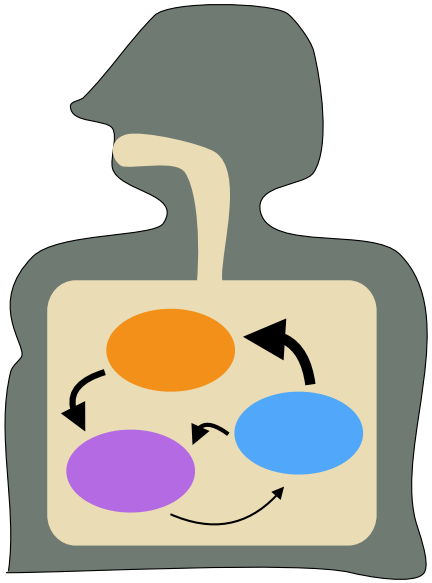

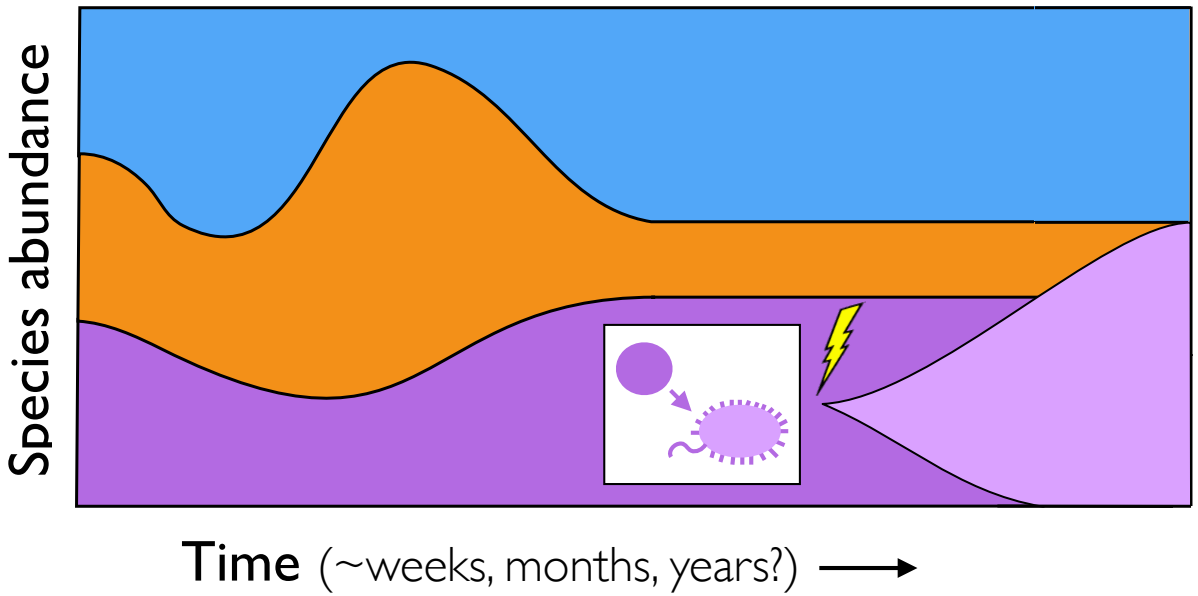

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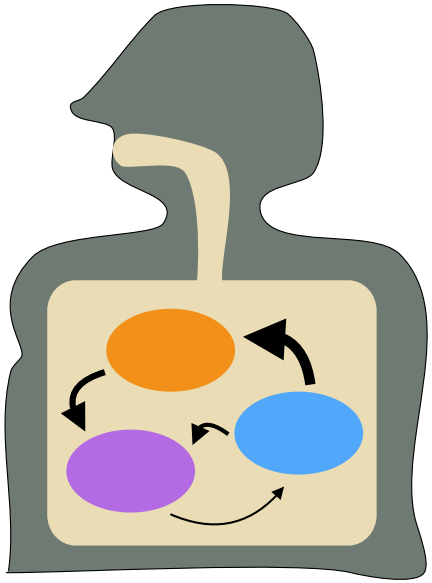

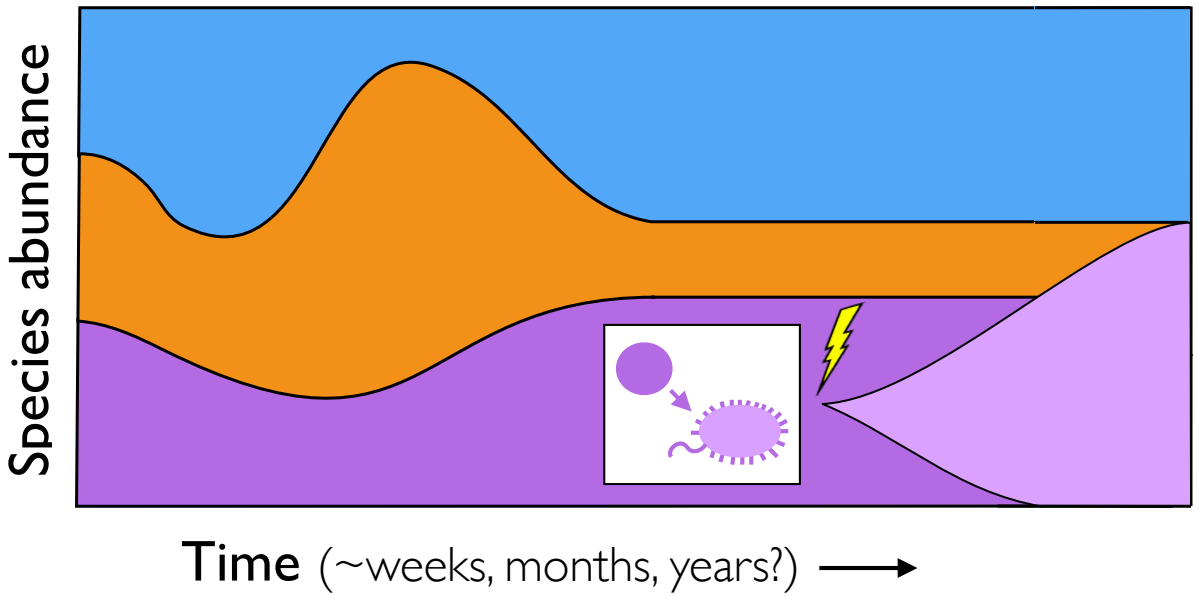

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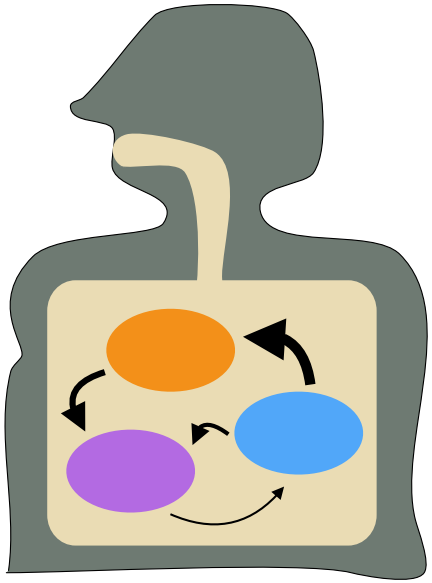

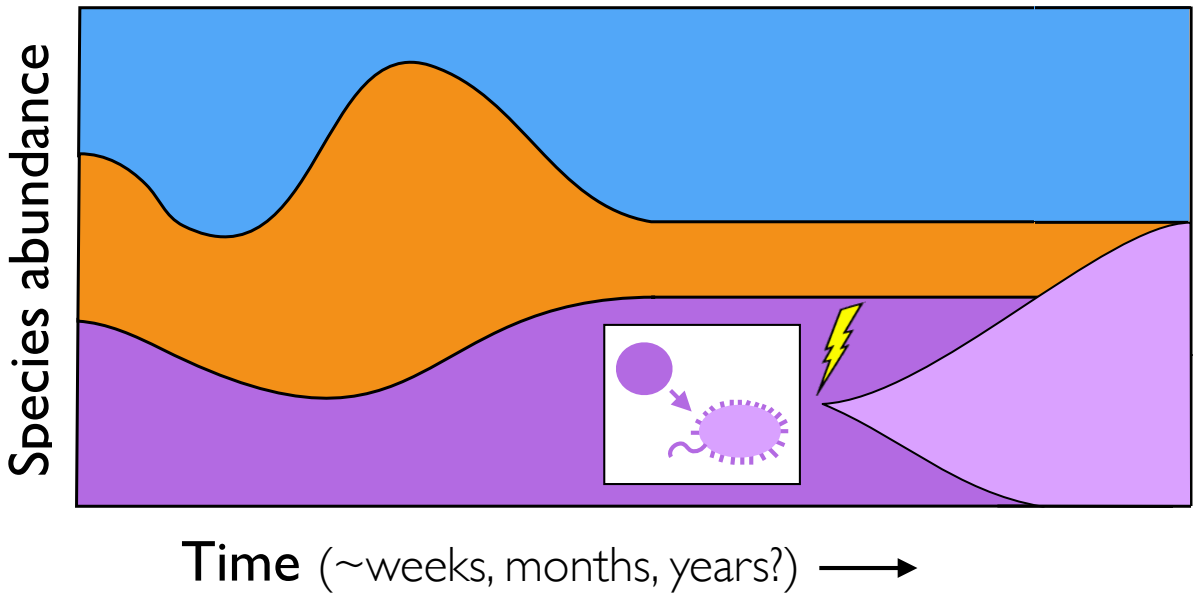

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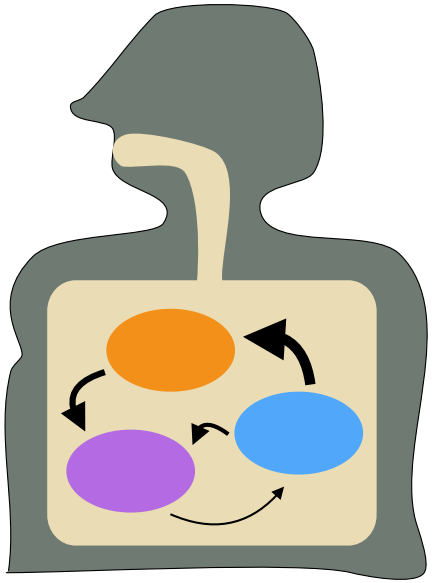

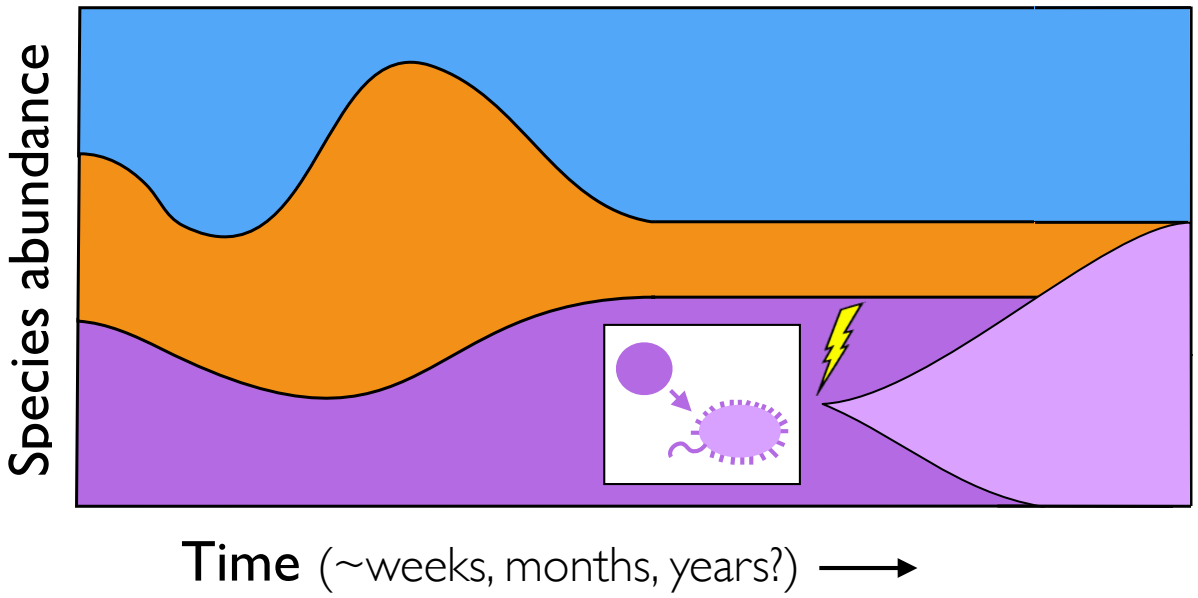

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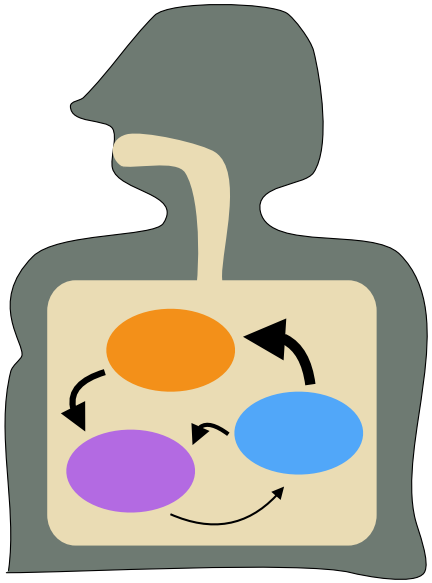

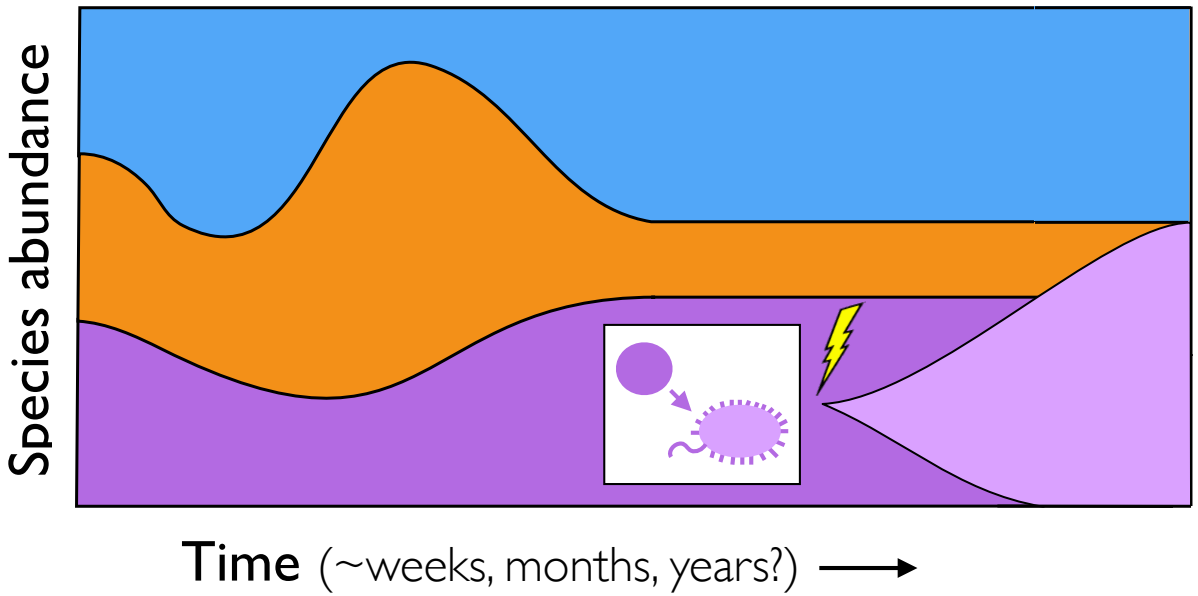

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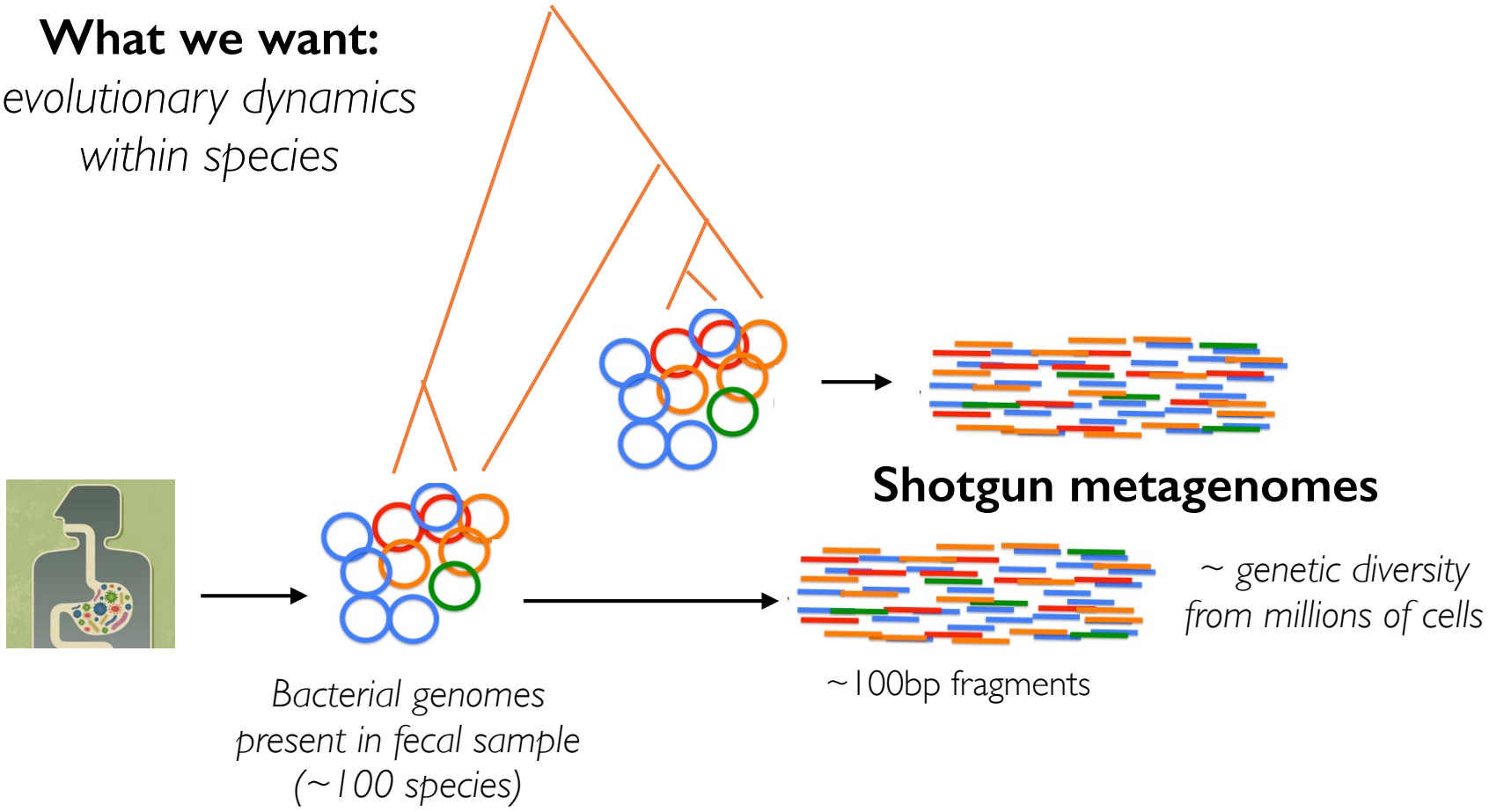
Measuring evolutionary dynamics in shotgun metagenomes

What we want:
evolutionary dynamics within species



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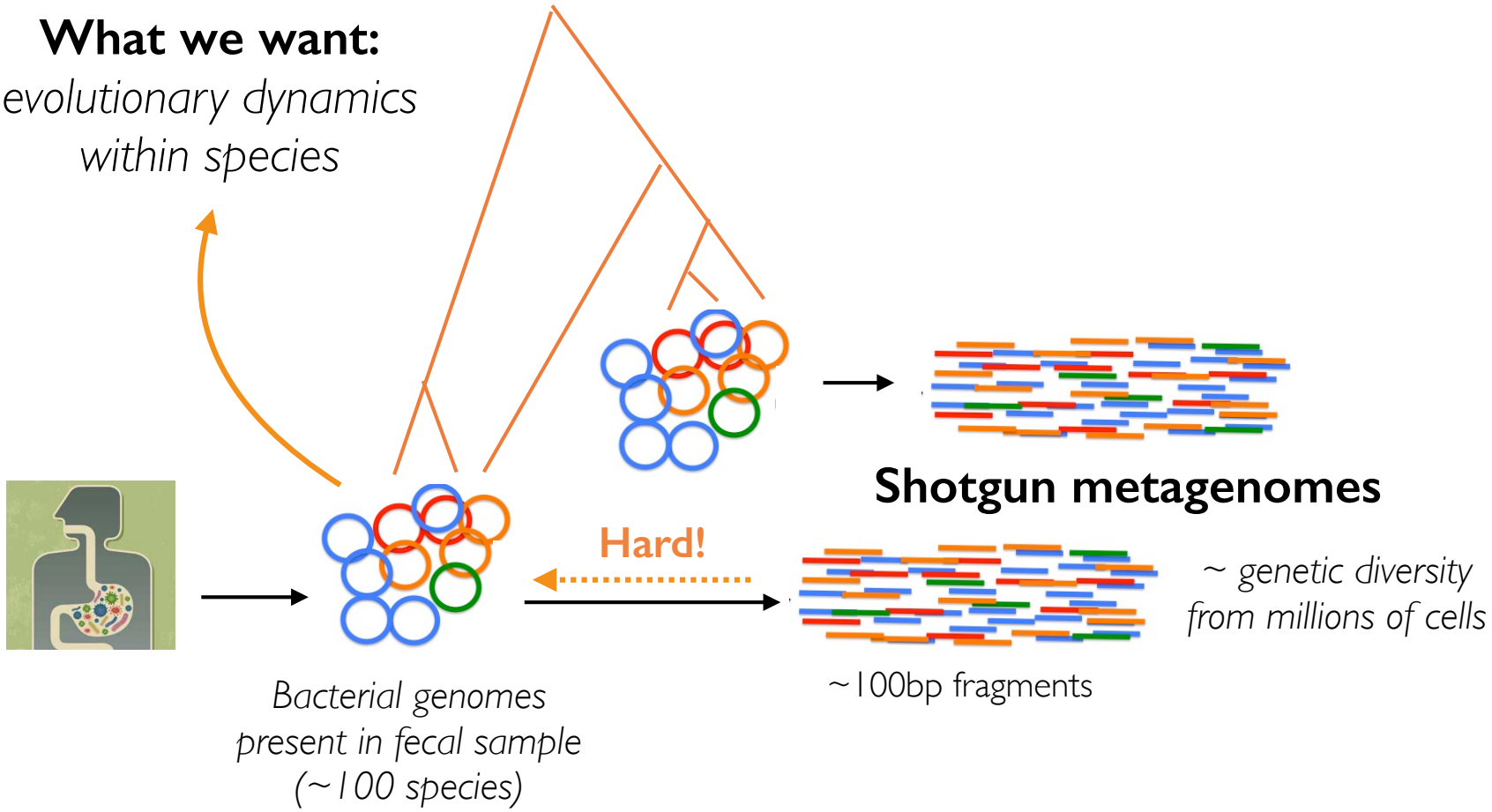

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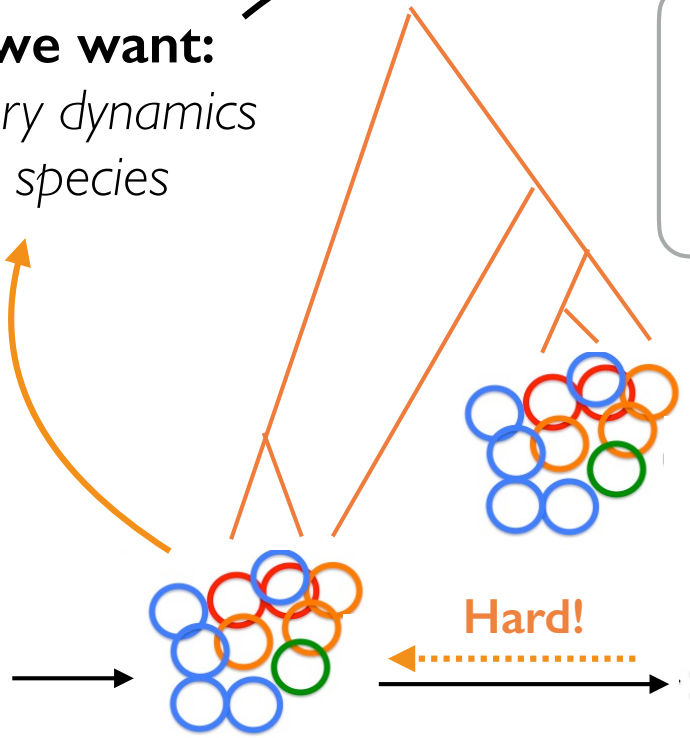

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Hard!

Shotgun metagenomes

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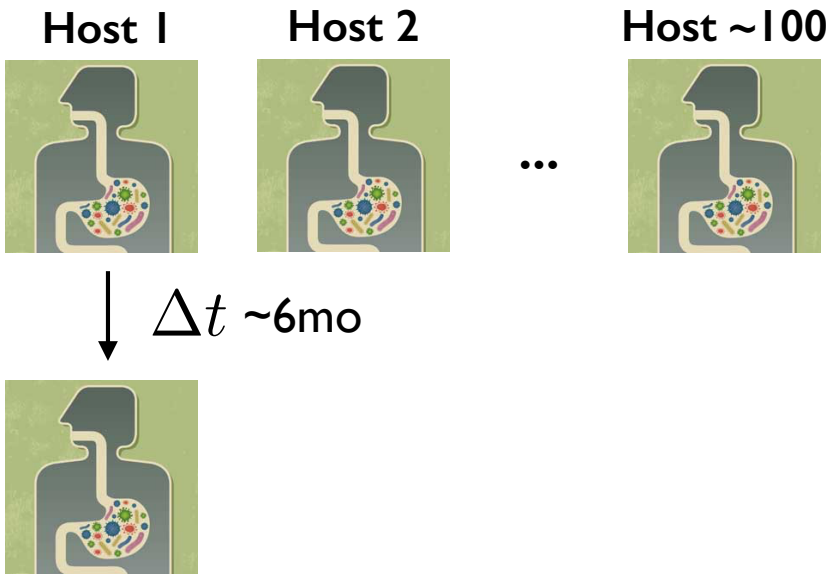
First pass: what can we learn from a large healthy cohort?

Samples: Human Microbiome Project



joint work with

*** Nandita Garud**
(UCLA)

K. Pollard
(UCSF)

O. Hallatschek
(UC Berkeley)

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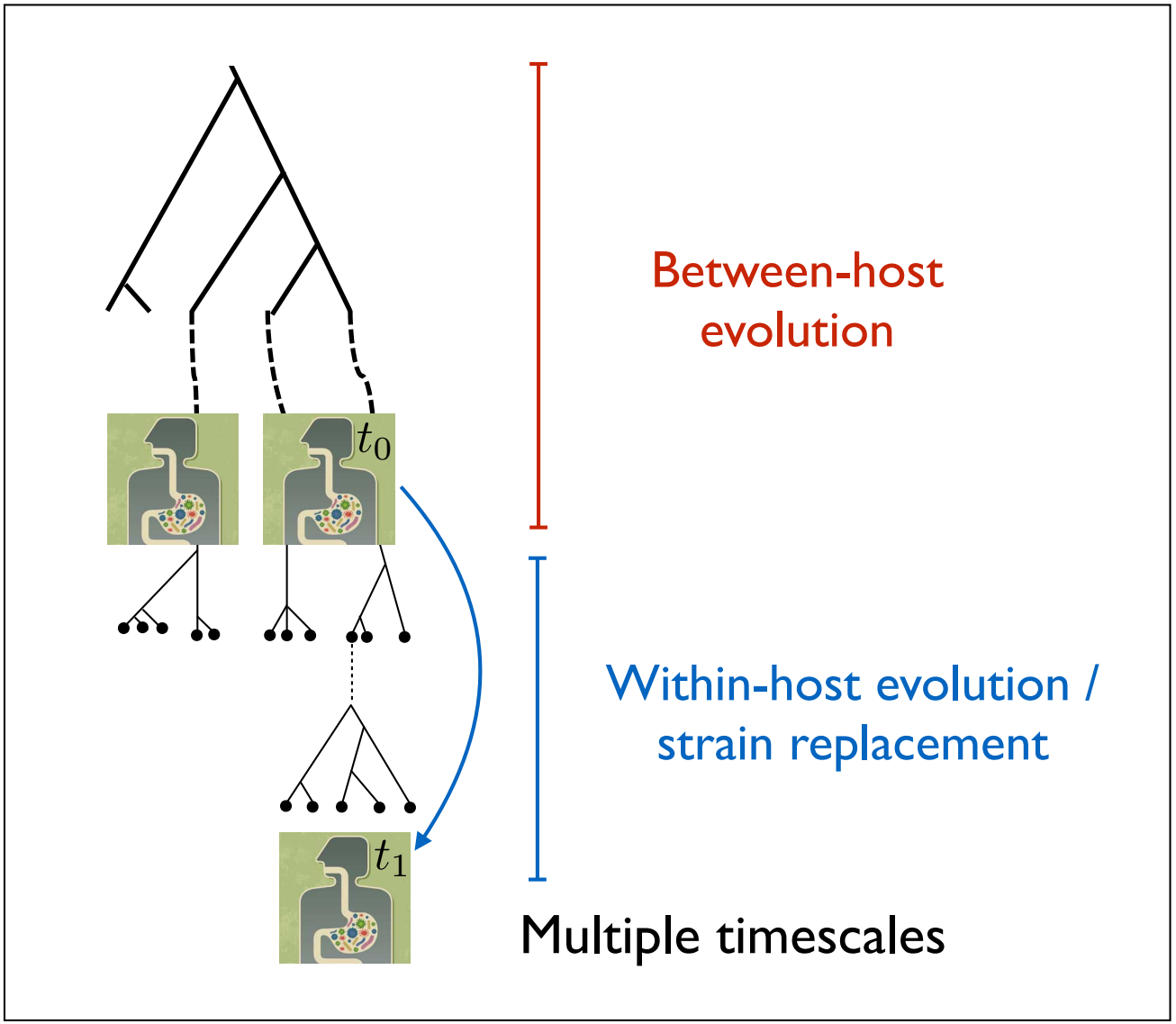
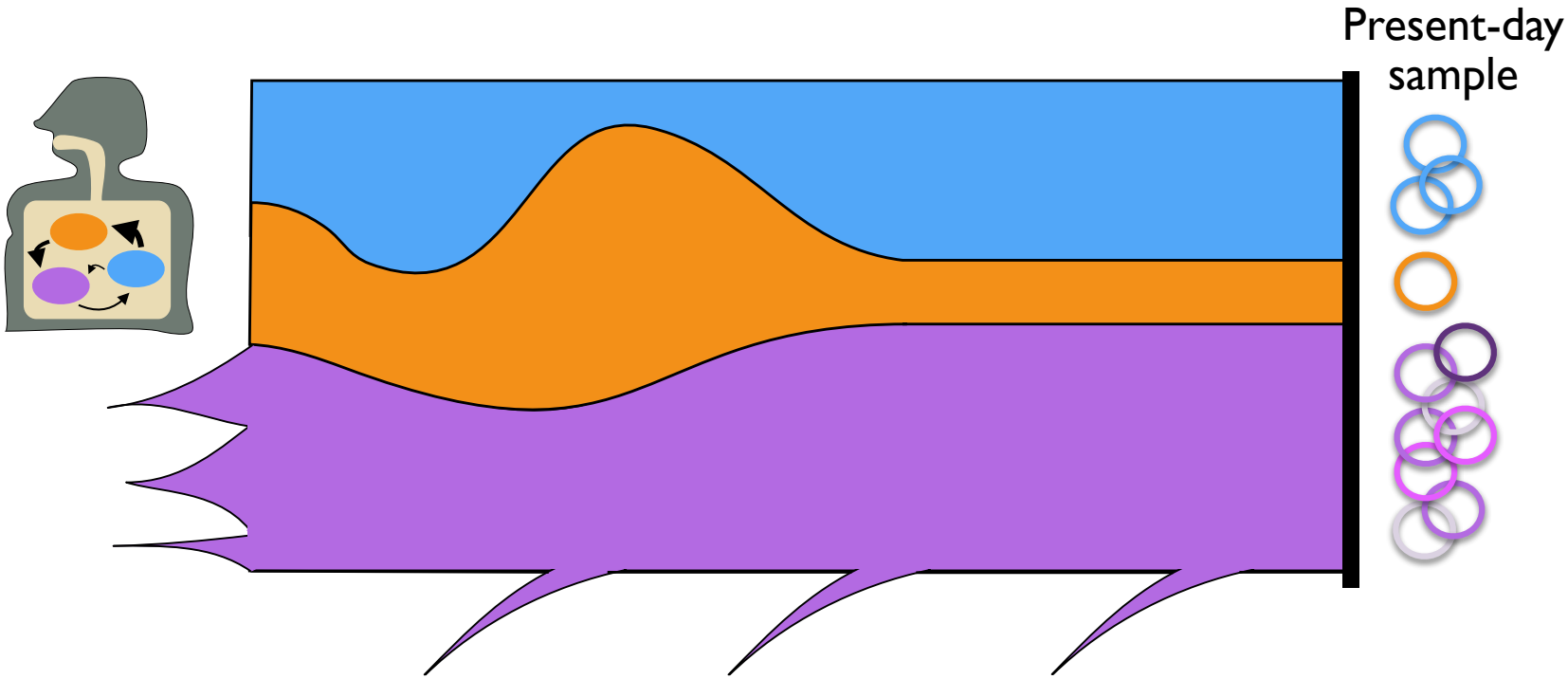


Parsing the genetic structure of a single resident population



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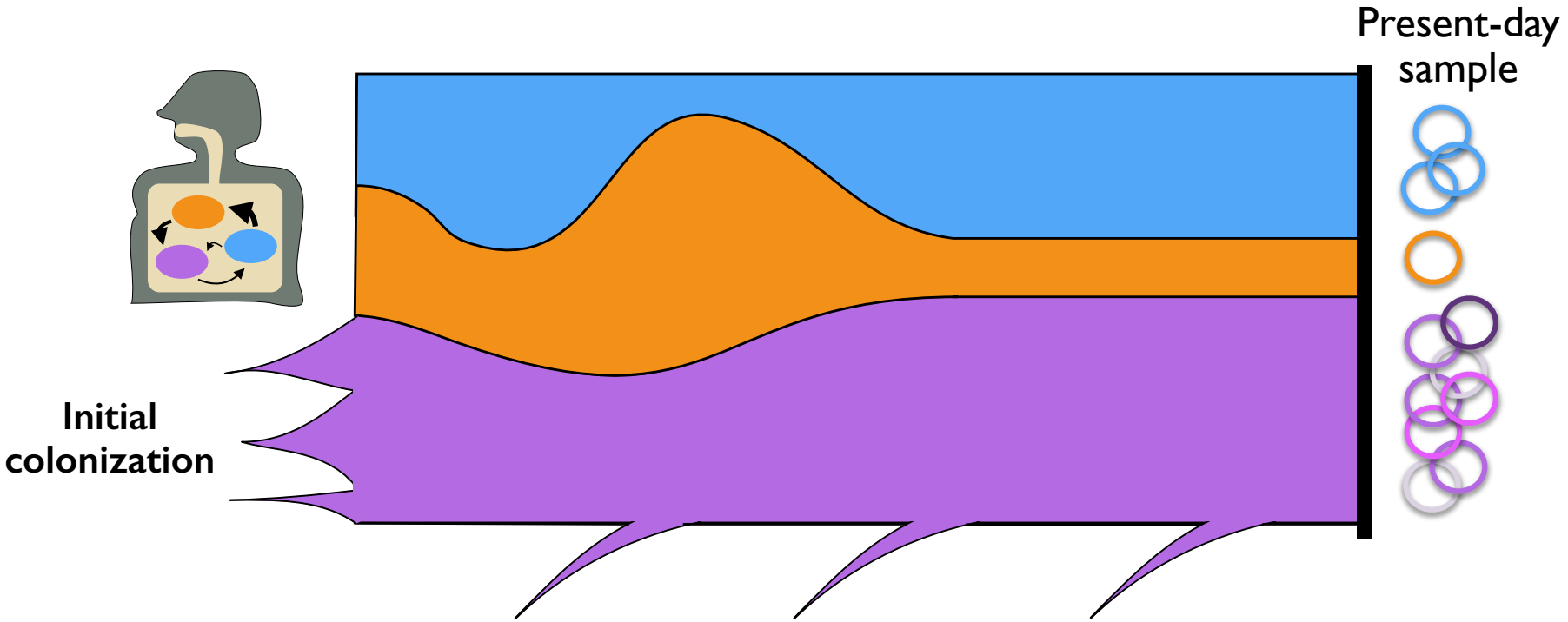

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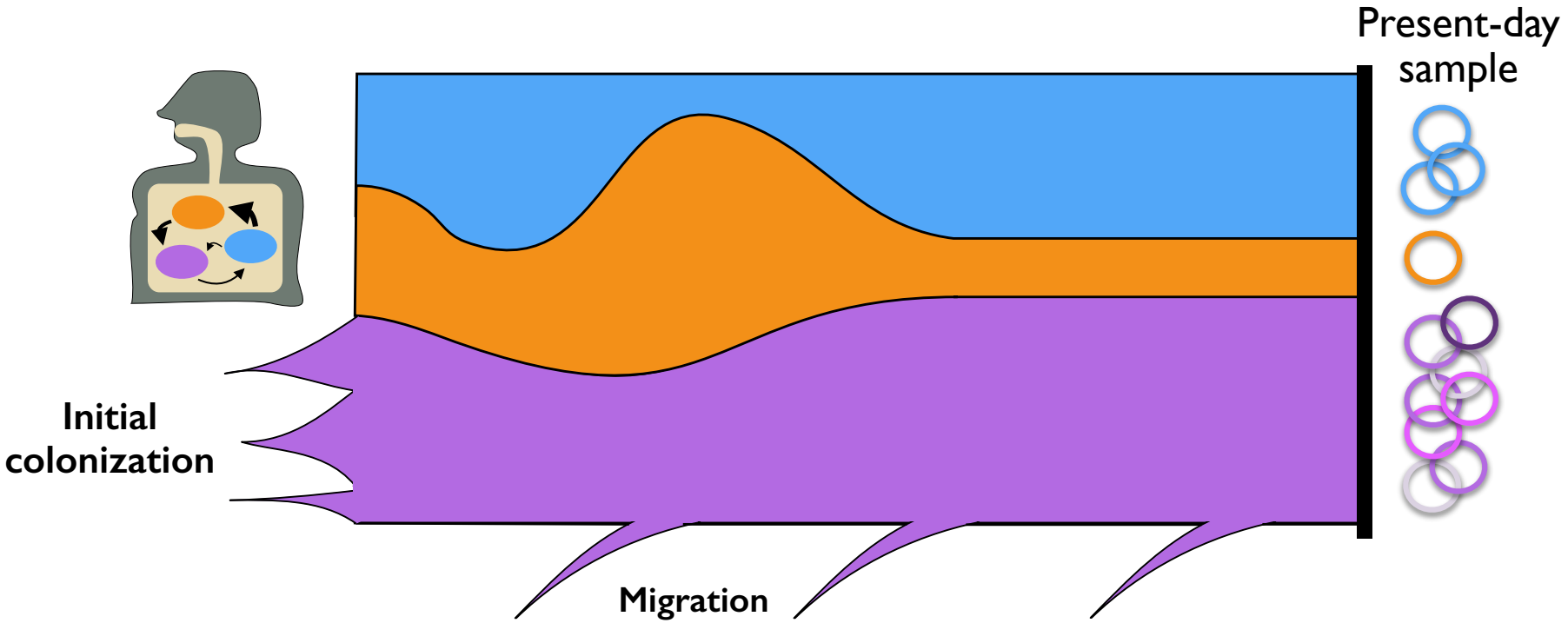

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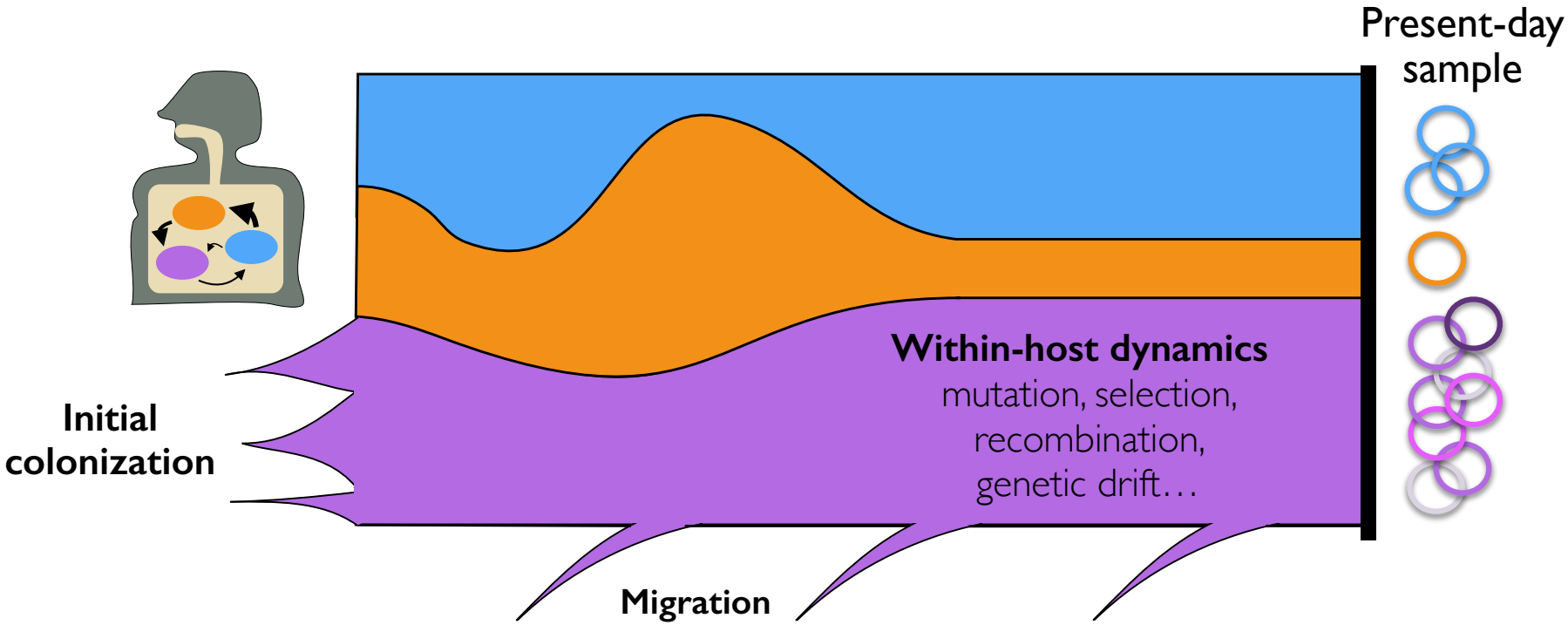

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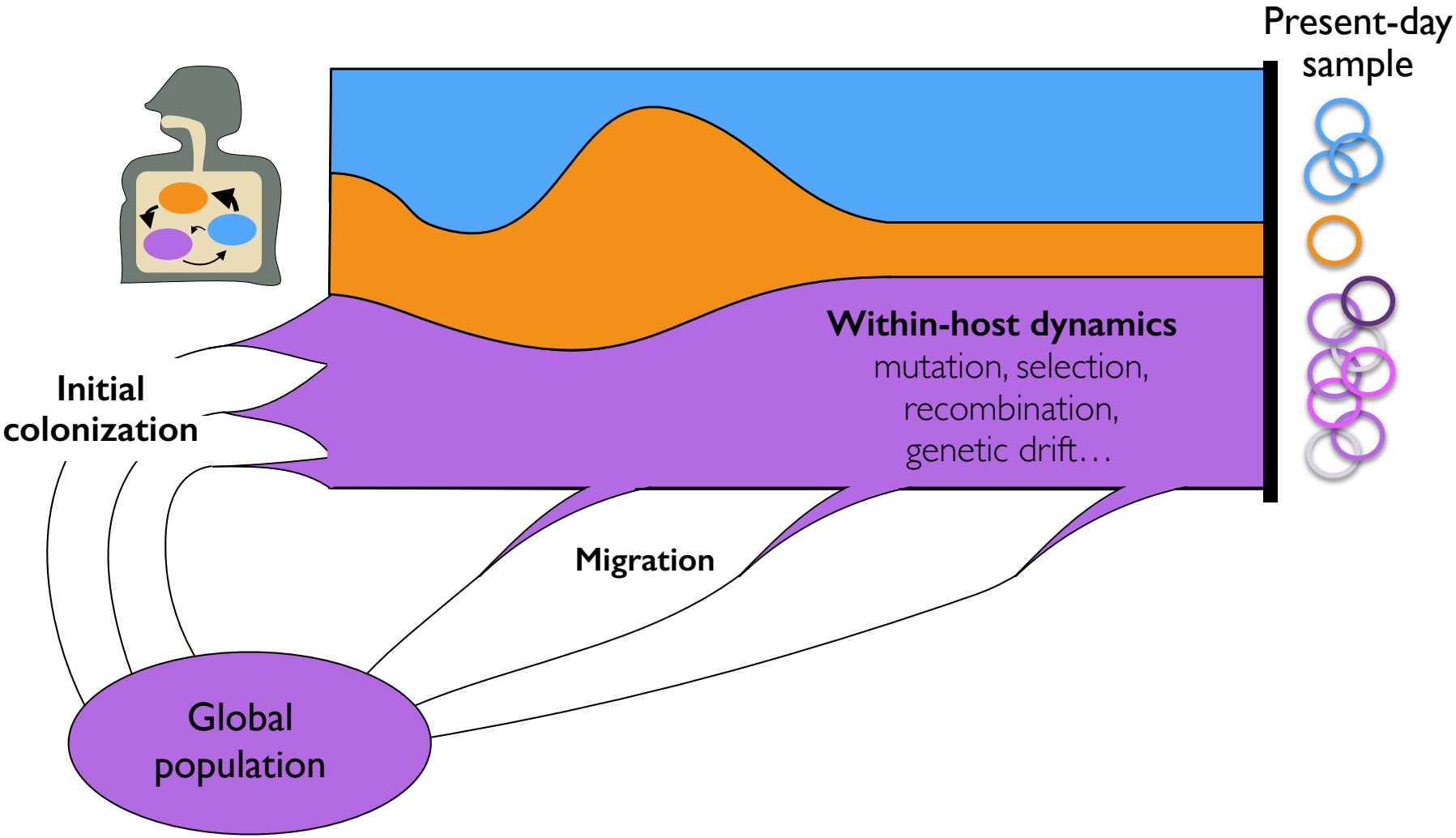

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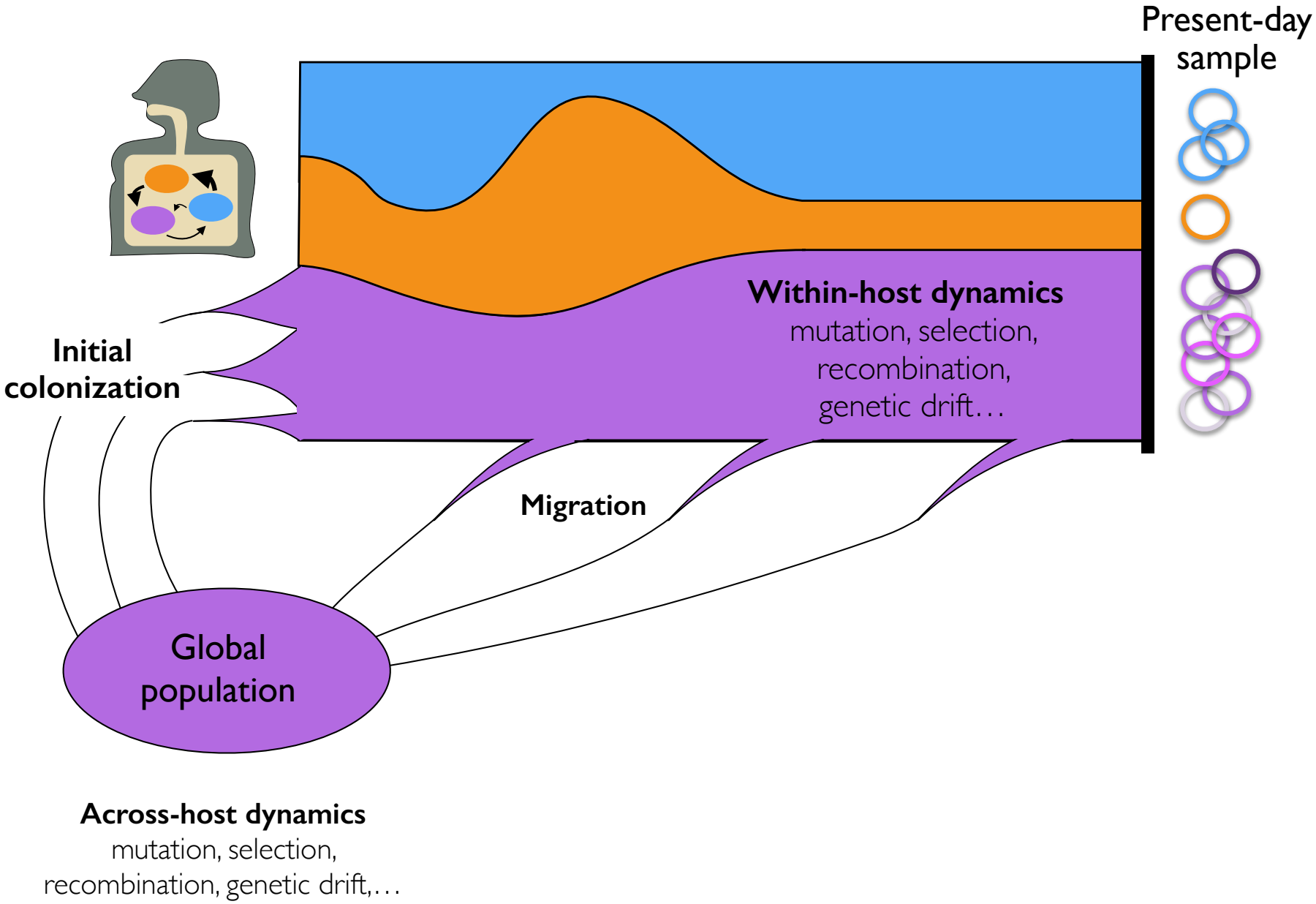

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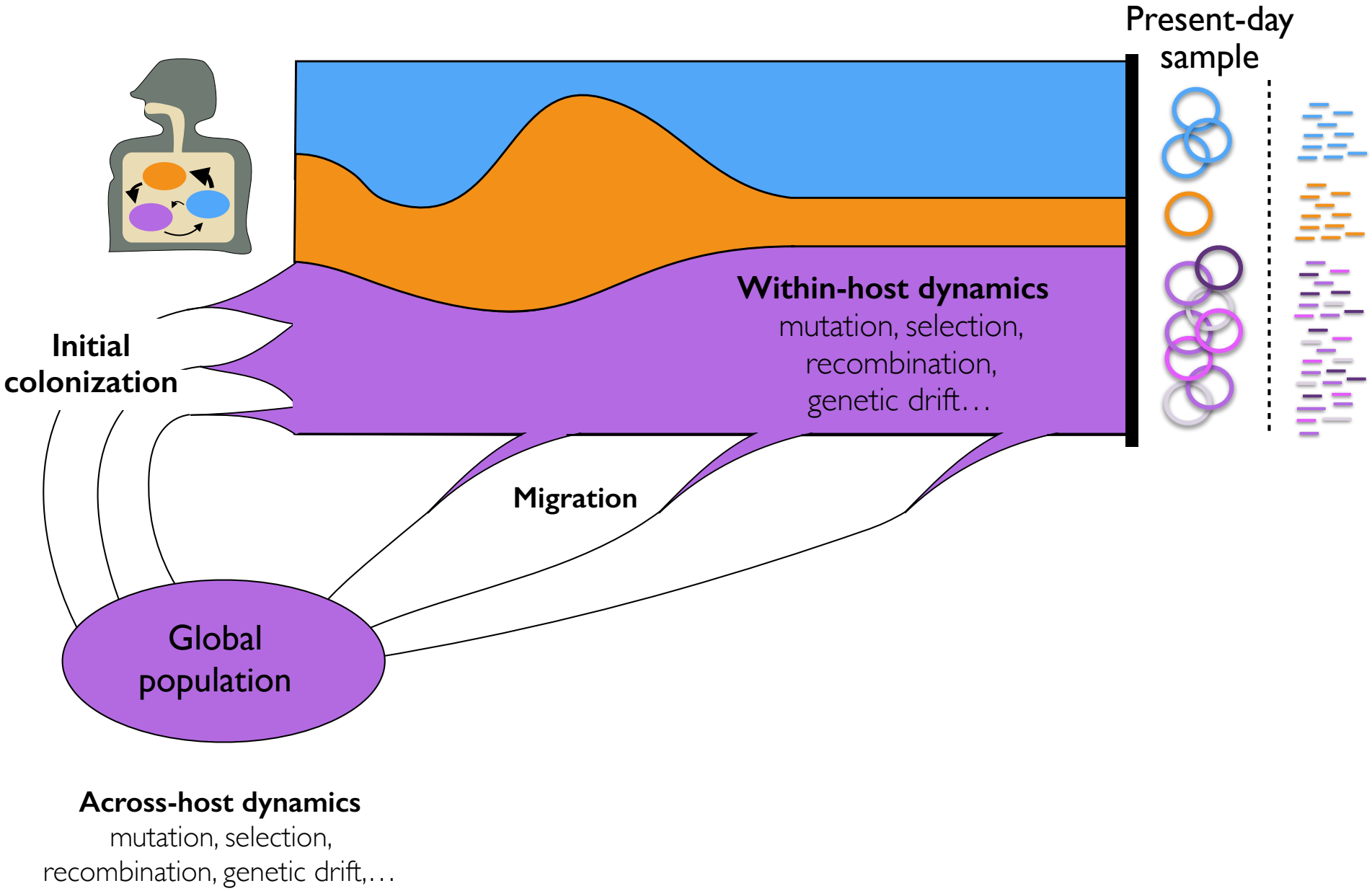

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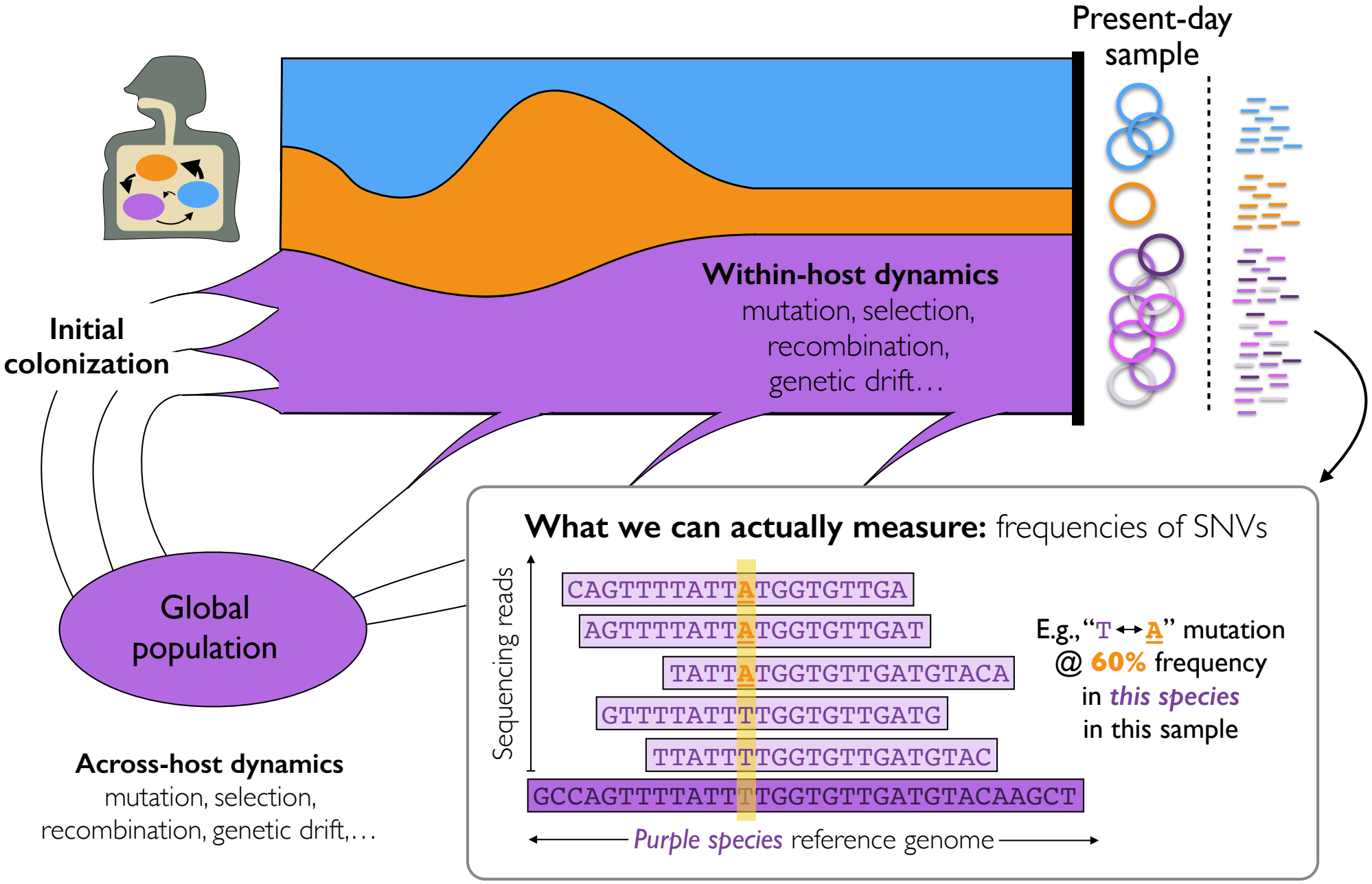
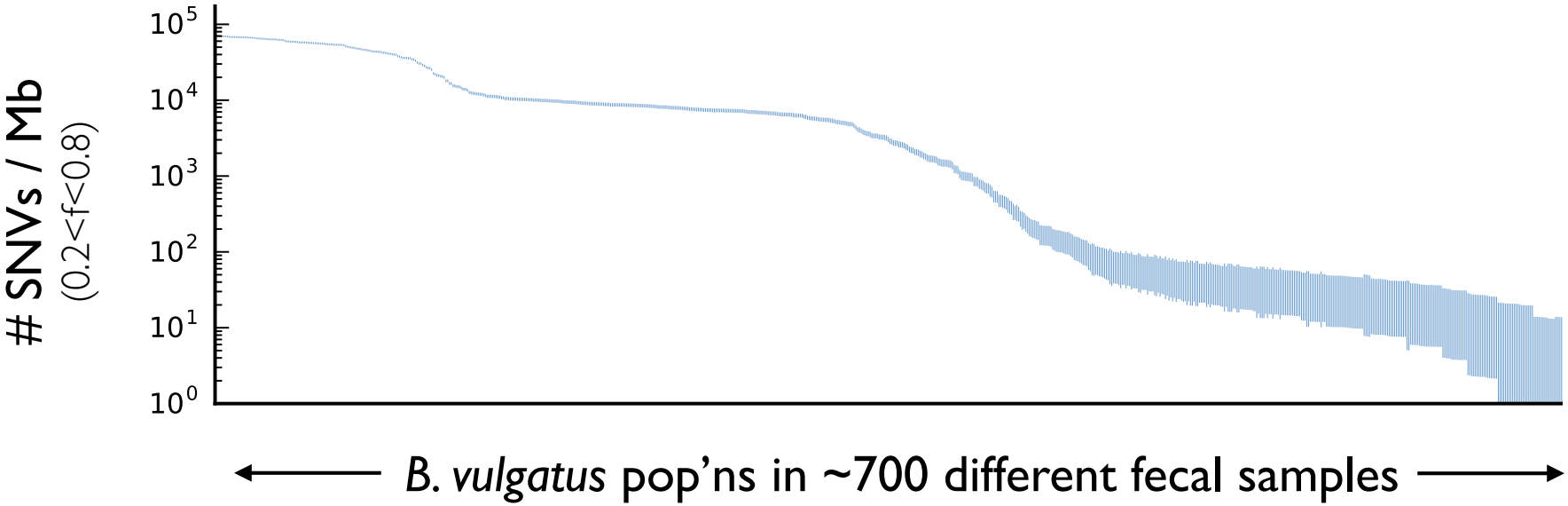


Genetic structure of resident pop'ns is highly variable across hosts



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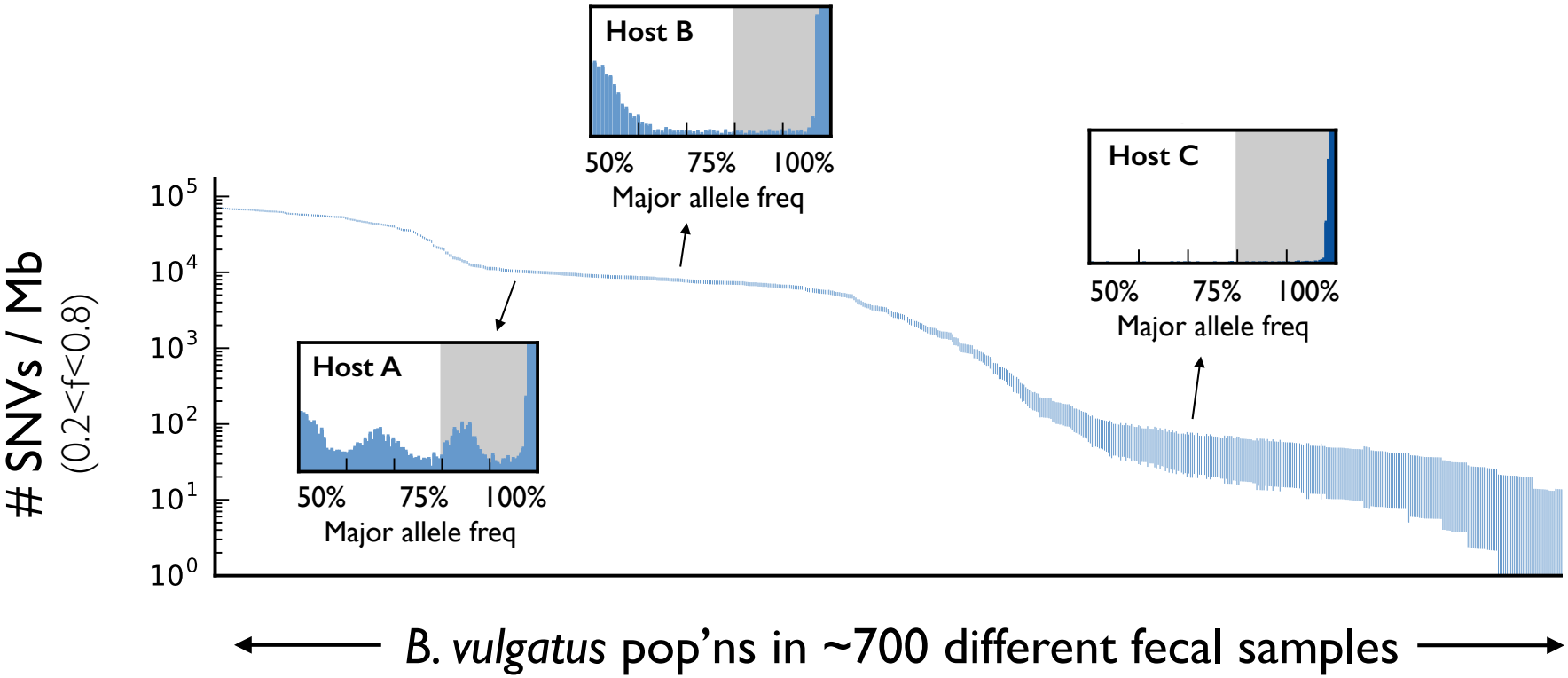

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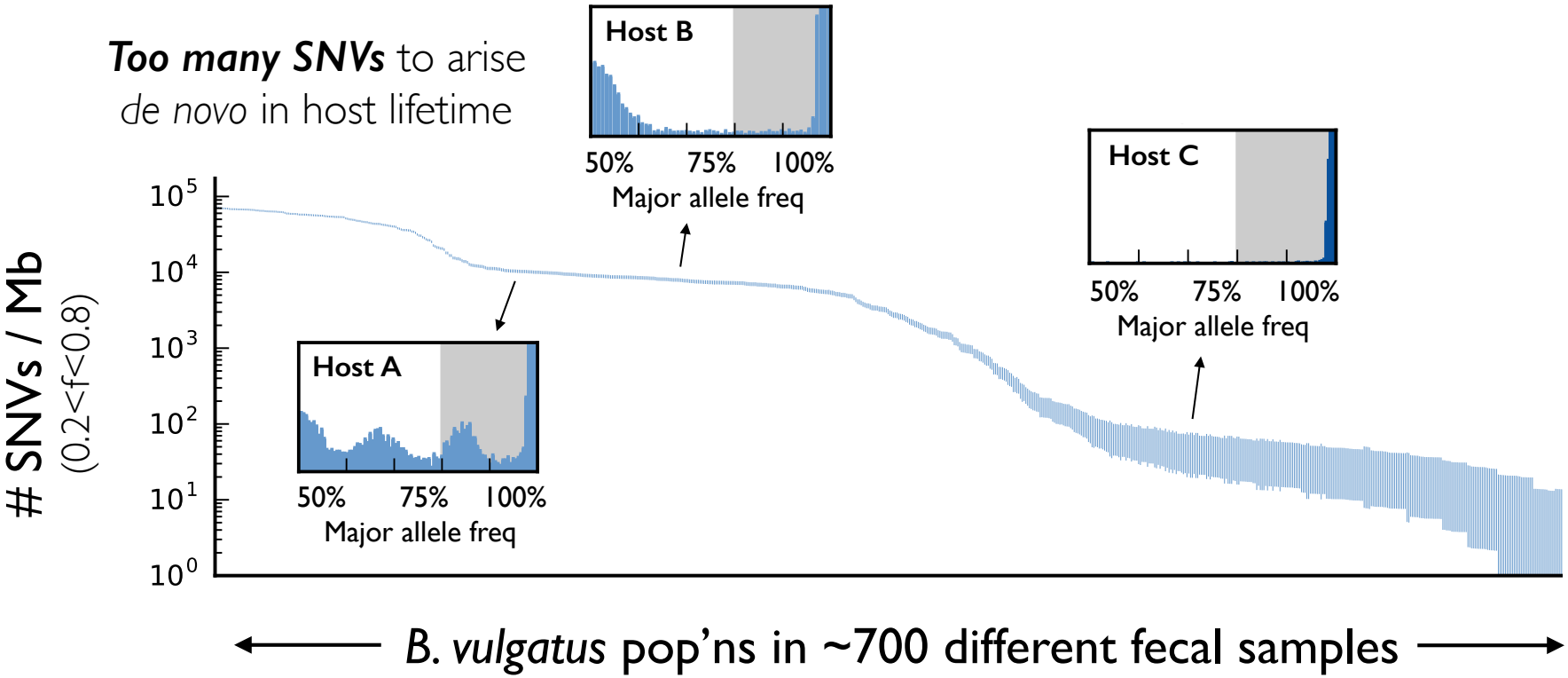

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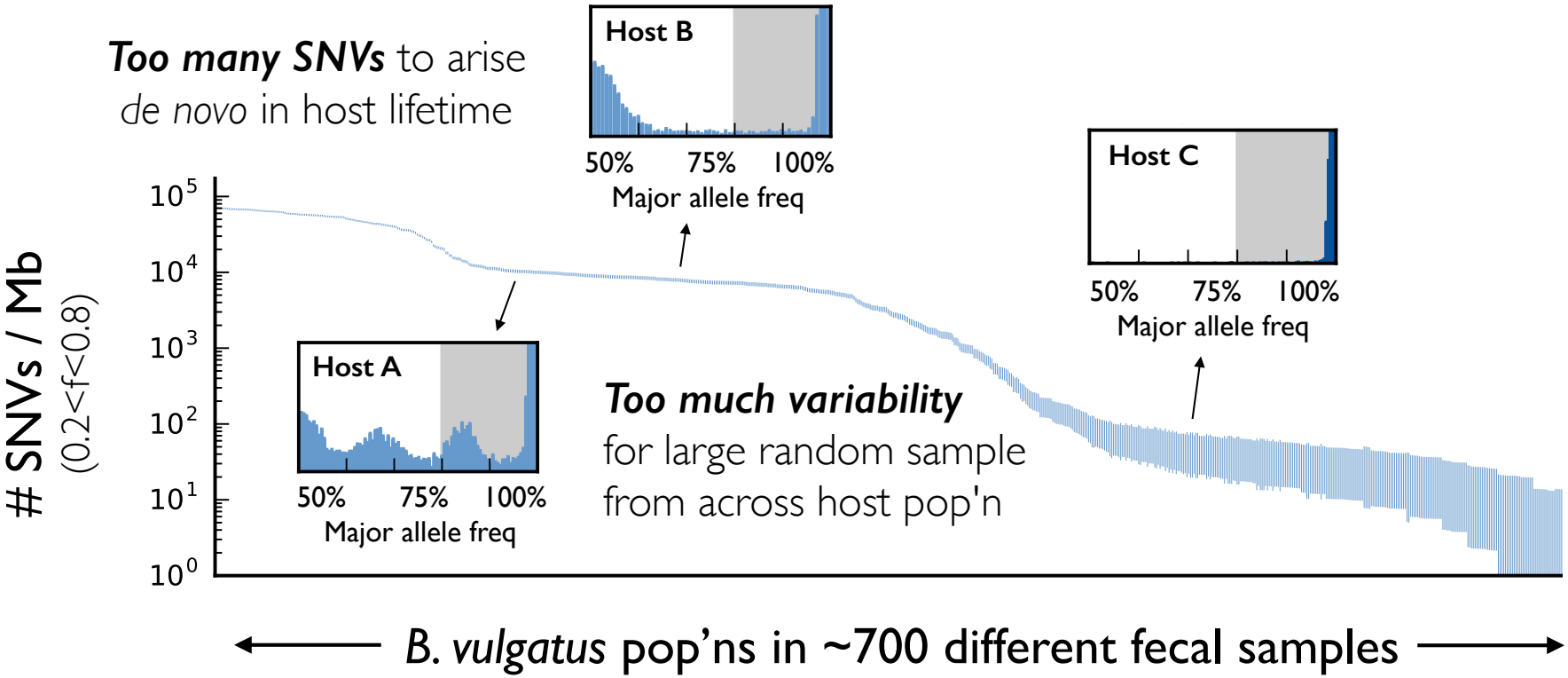

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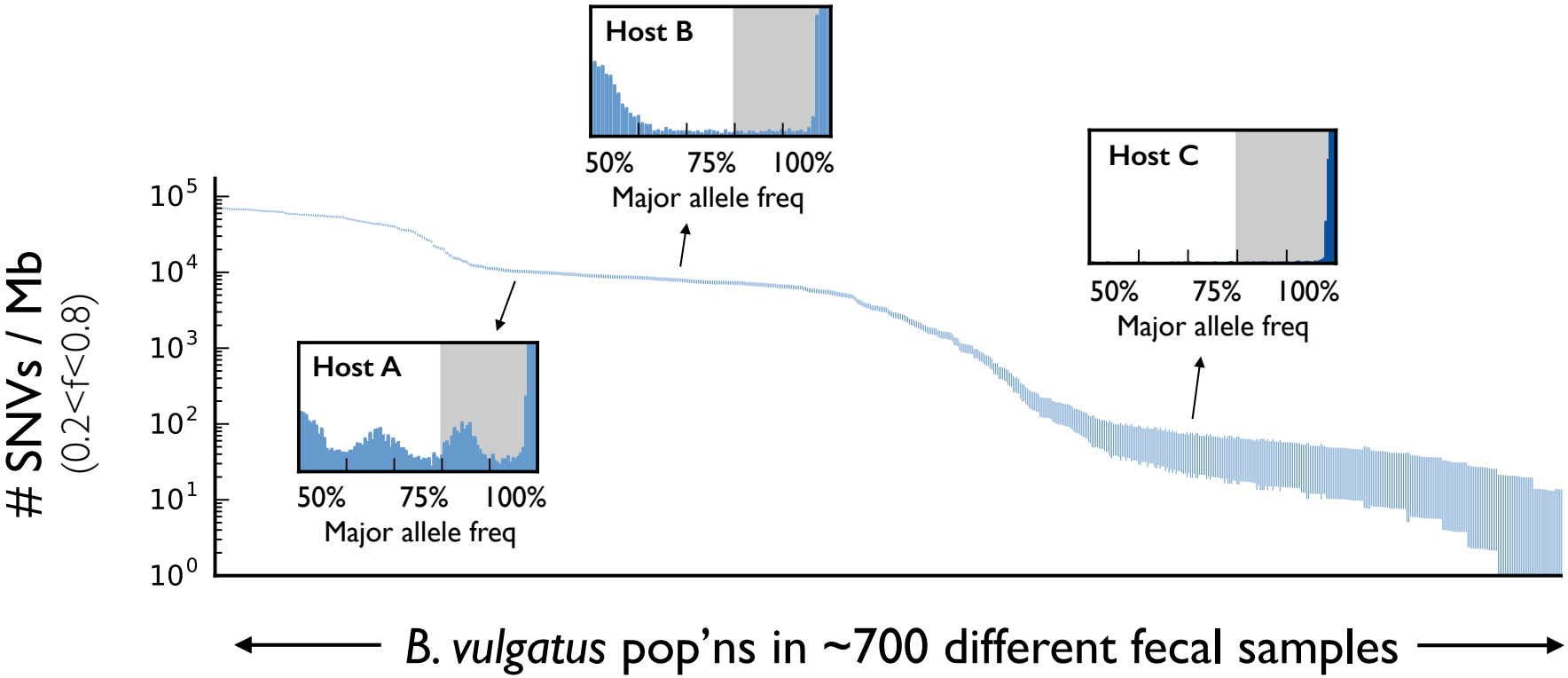
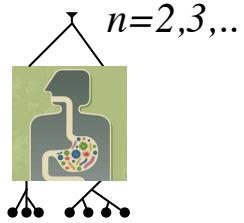


"Oligo-colonization" ~ a few external strains at intermediate freqs

see also Truong et al 2017



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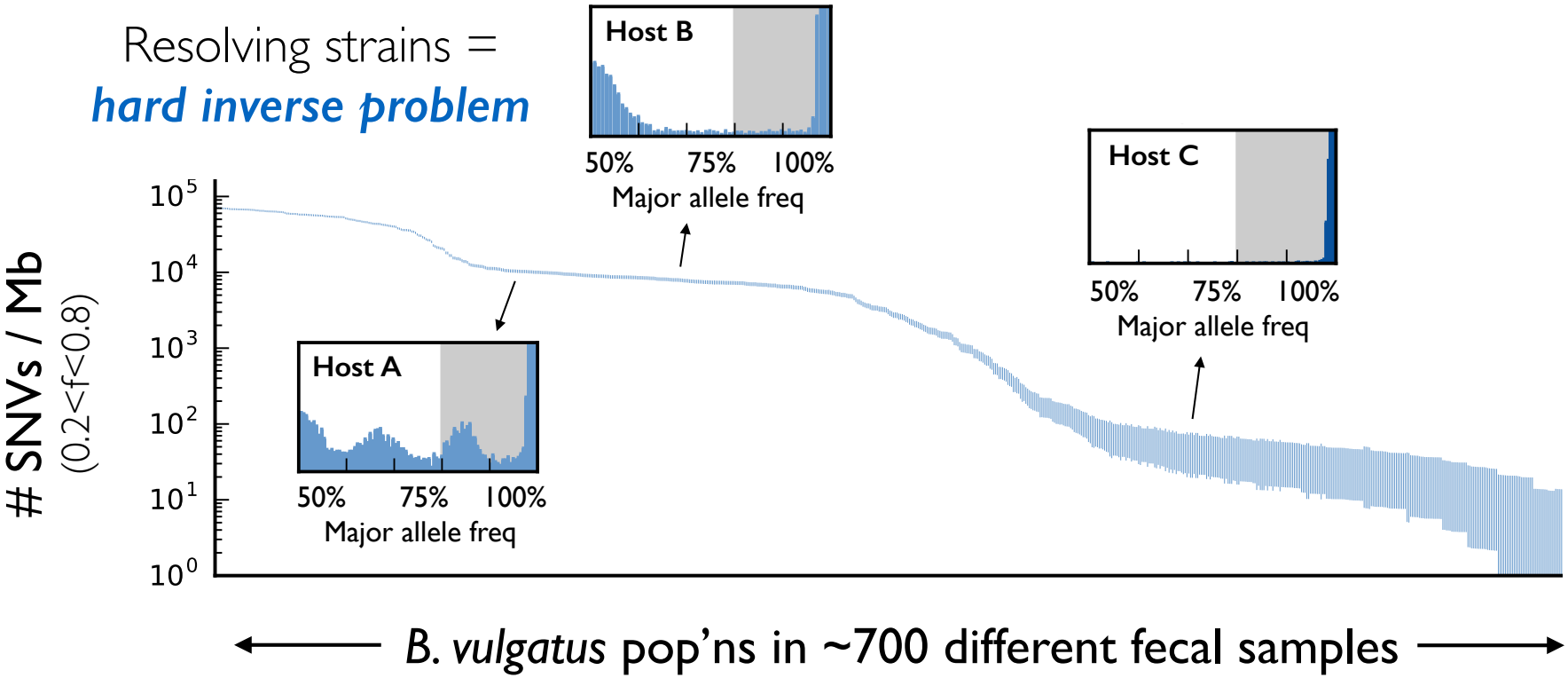

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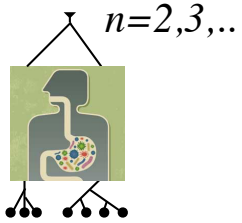

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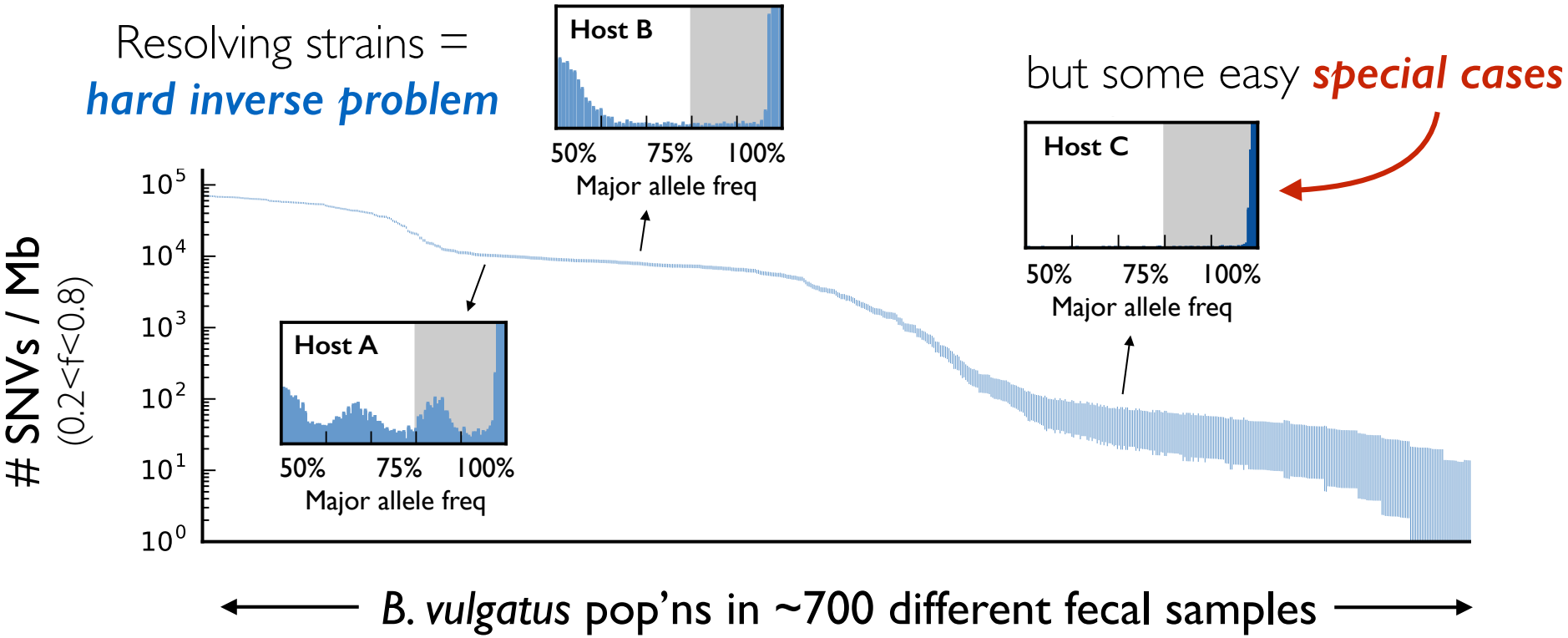

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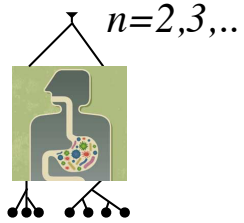

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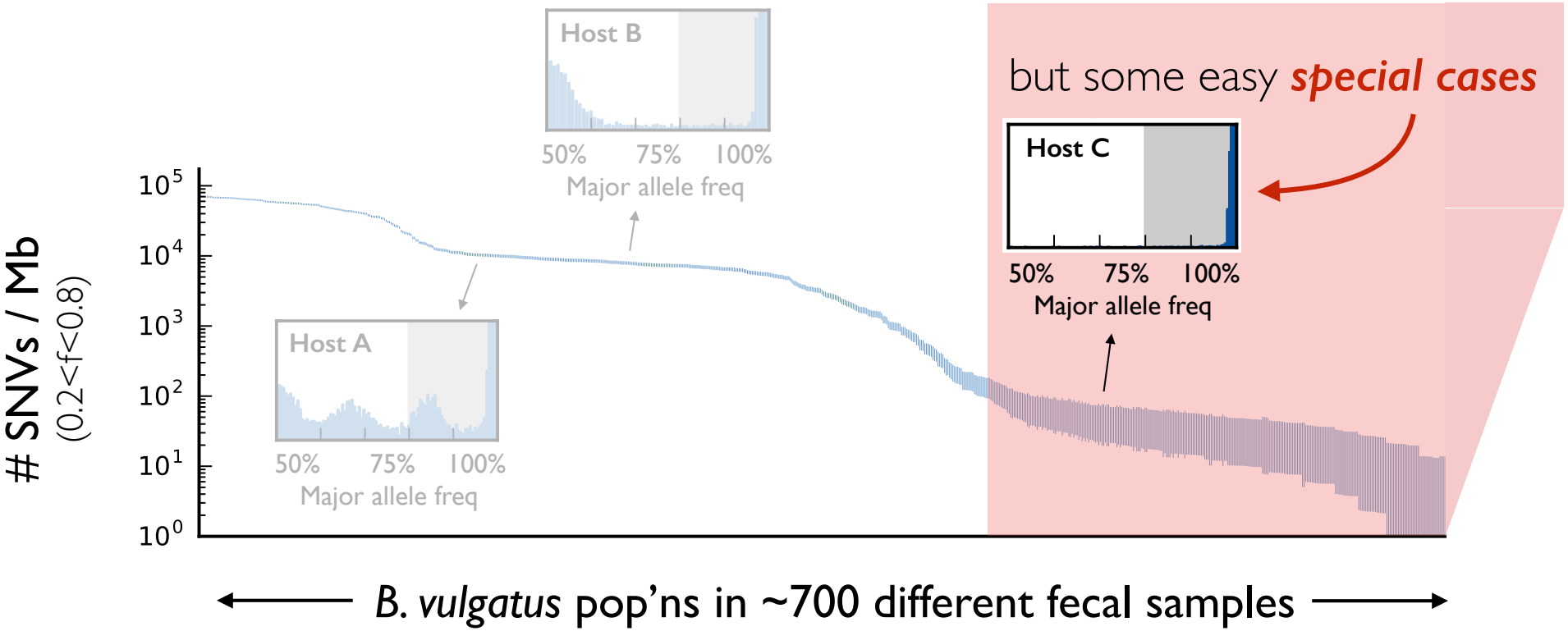
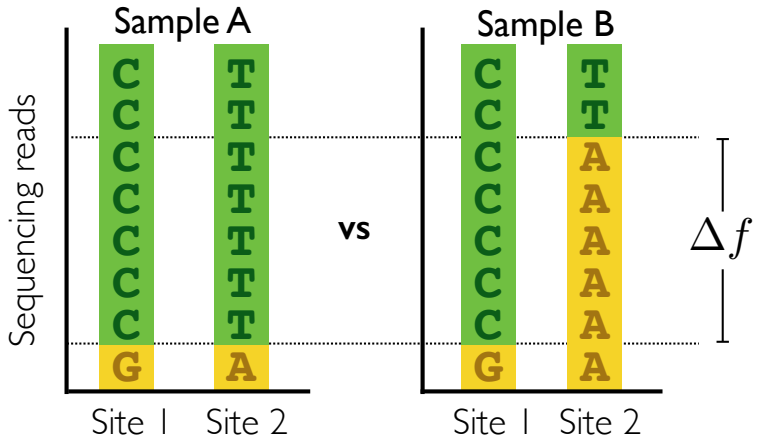


Approach: Focus on ***"easy" samples*** where we can infer the ***dominant lineage*** w/ high confidence

Detecting genetic differences between strains in "easy" samples



Approach: model ***sampling noise***
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Choose thresholds & discard samples
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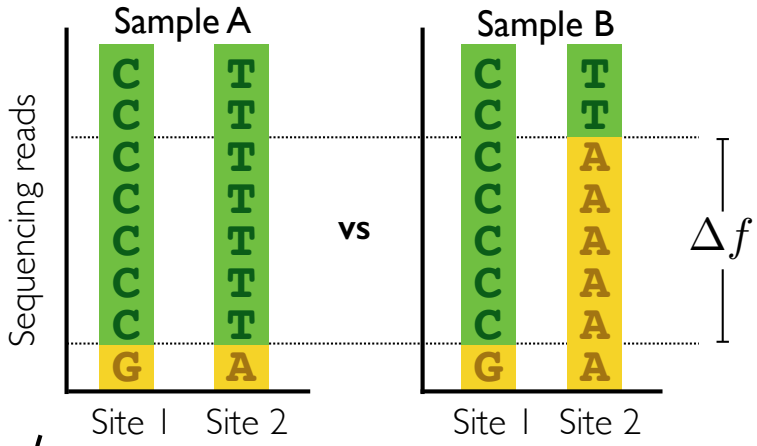

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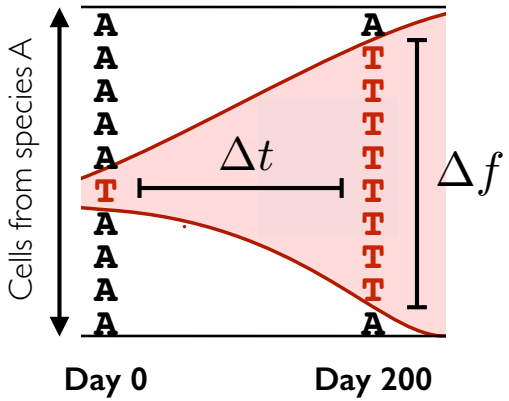
E.g., host-wide "sweep" w/in species



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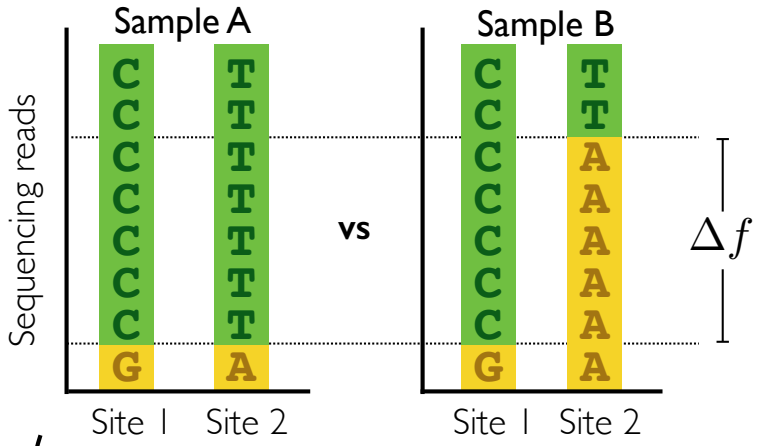

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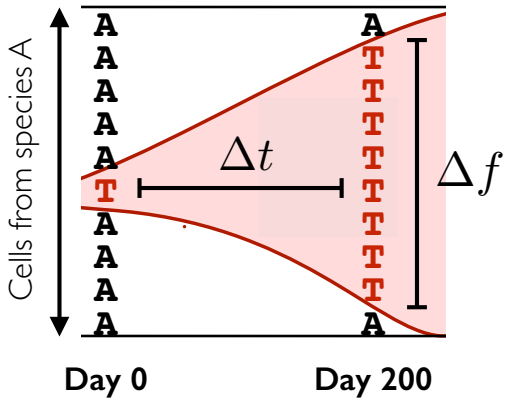

Upshot: must discard lots of data…

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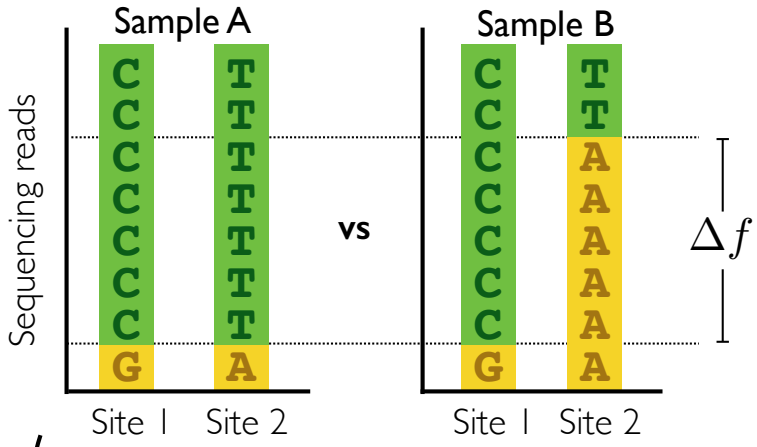

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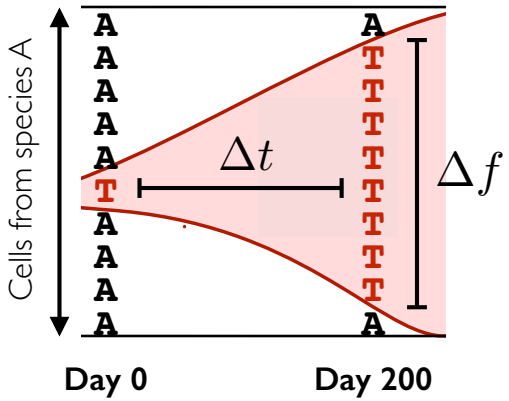
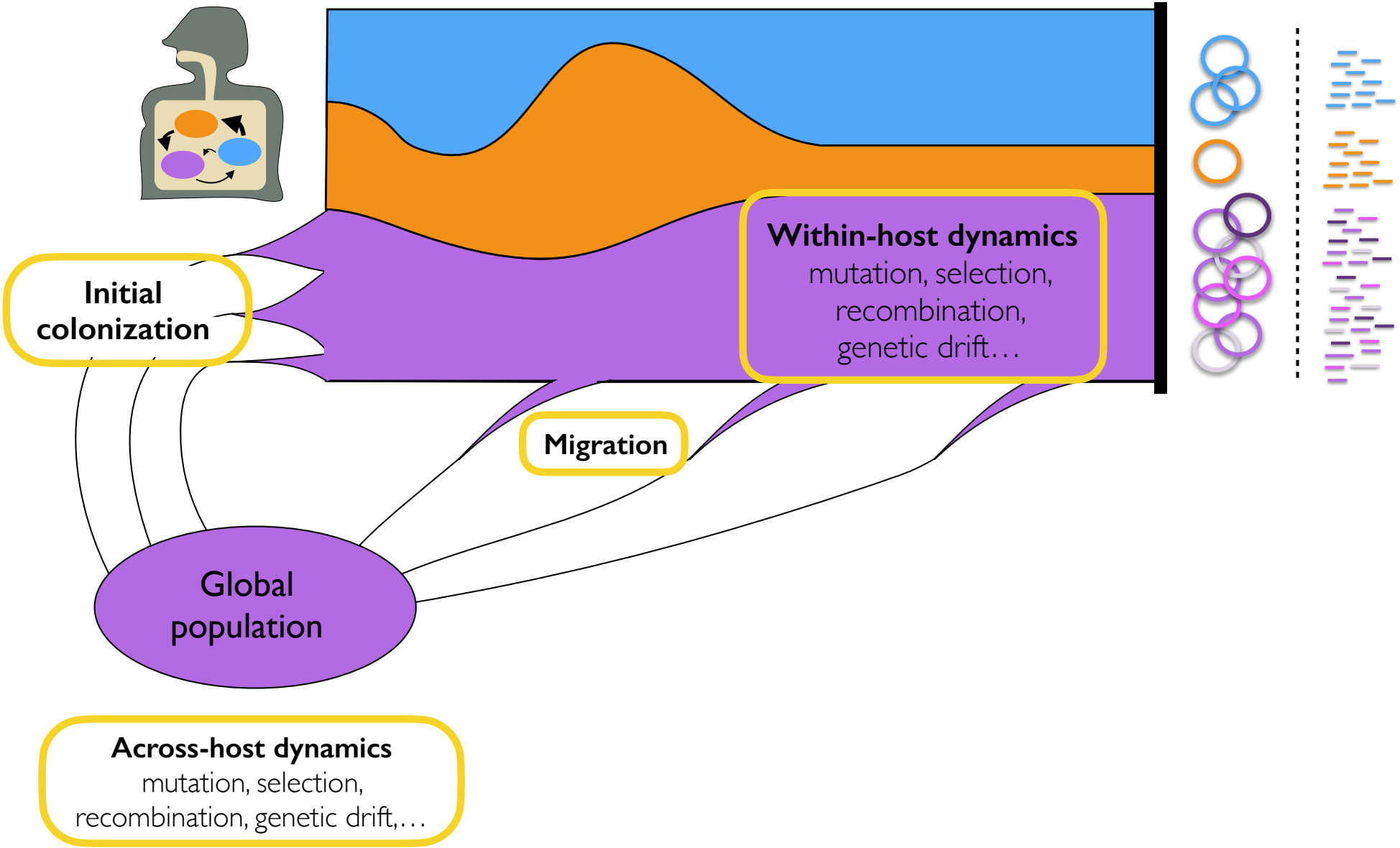
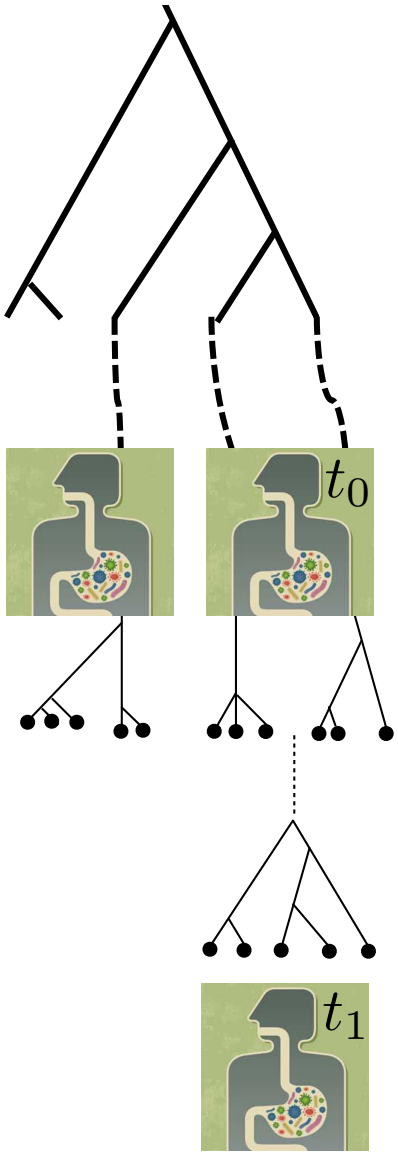


Upshot: must discard lots of data…

but w/ ***~100's of hosts***, can resolve genetic diffs btw ***~1000's of strains*** across ***~40 prevalent species***


Initial colonization
Within-host dynamics
mutation, selection, recombination, genetic drift…
Migration
Global population
Across-host dynamics
mutation, selection, recombination, genetic drift,…

Applications to HMP cohort: general trends across ~40 species



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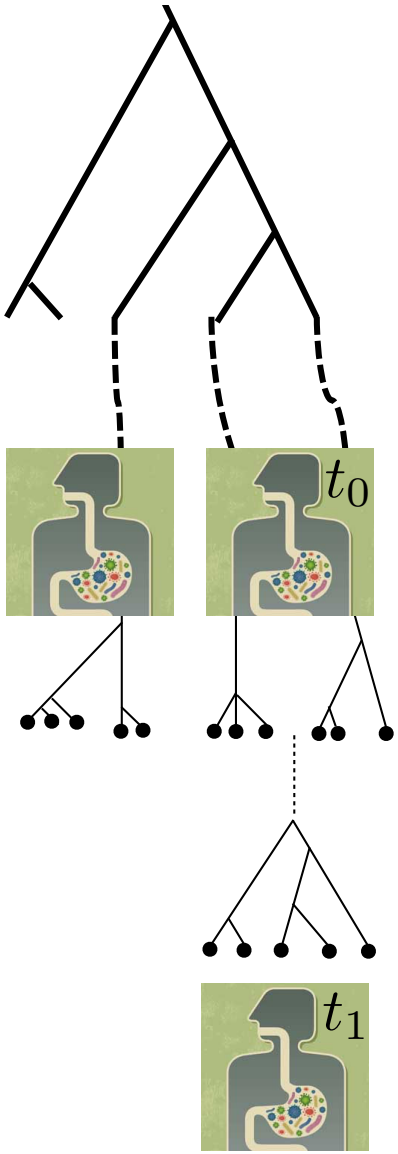

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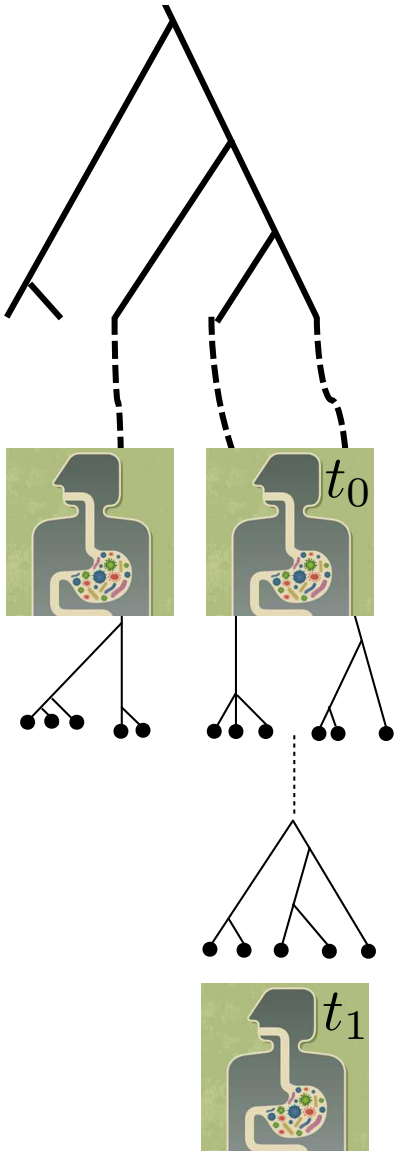

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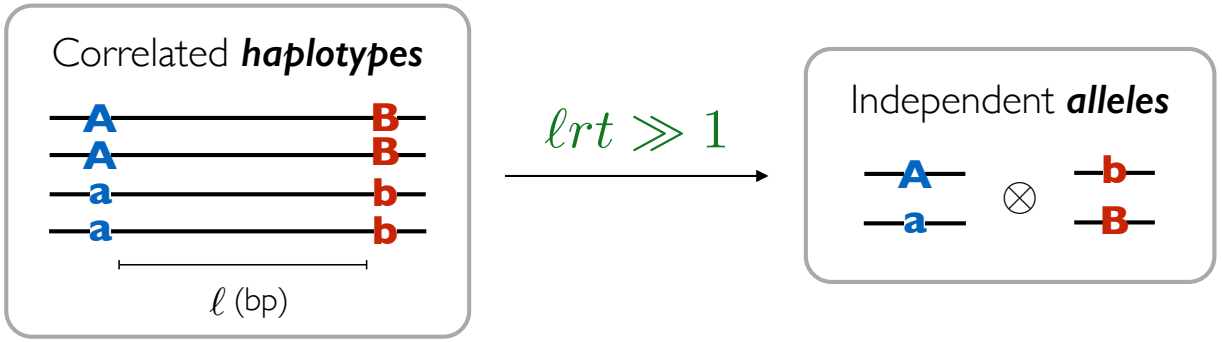

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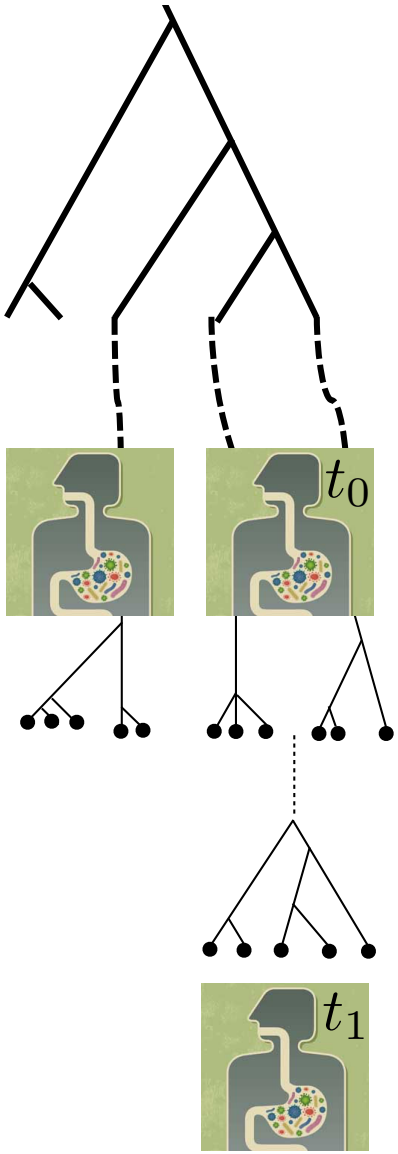

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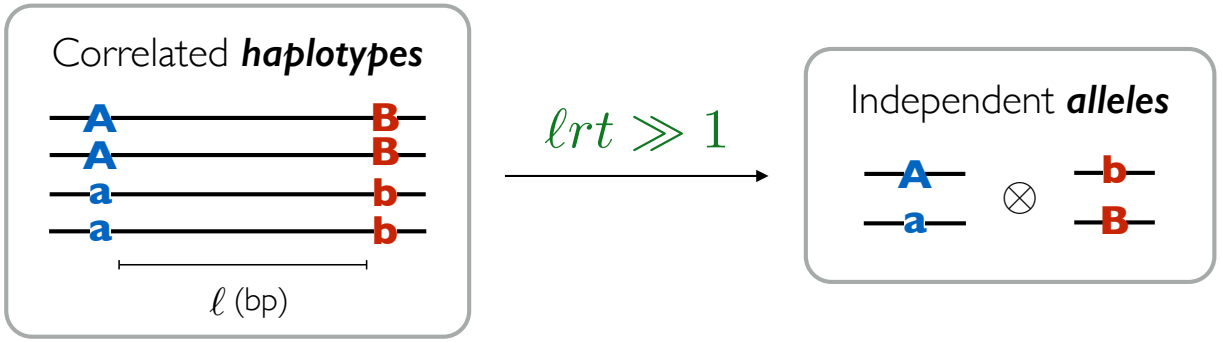

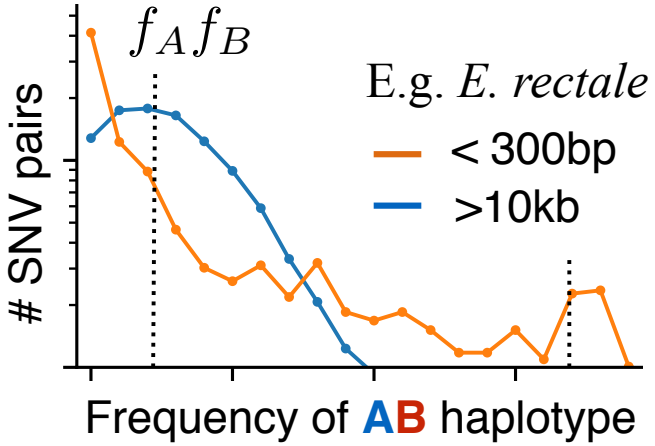

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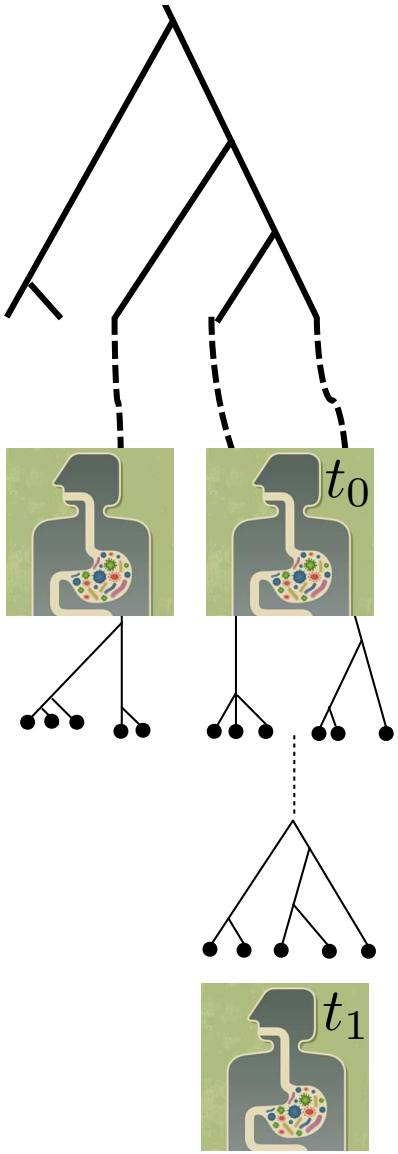

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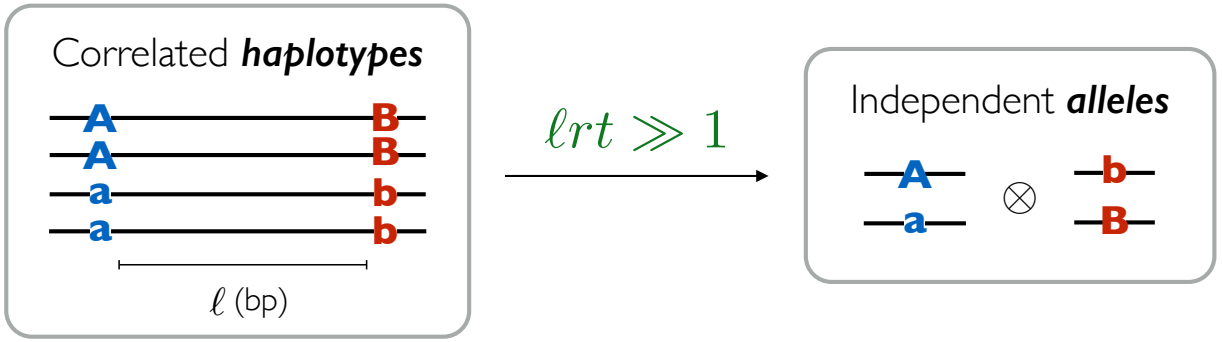
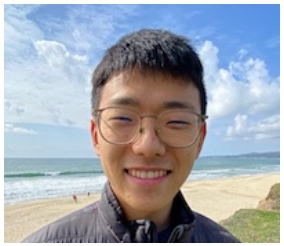
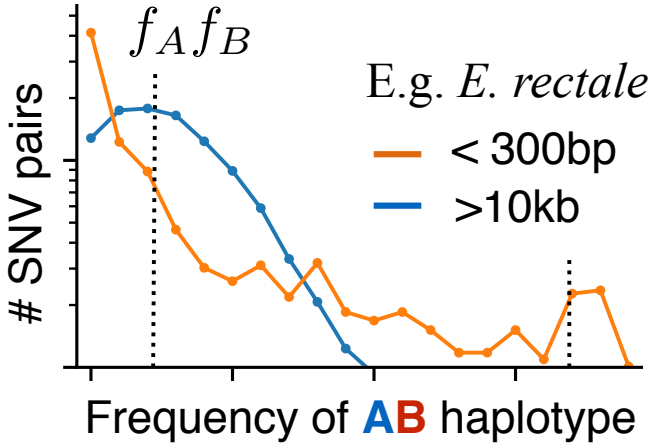




Zhiru Liu
(here @ KITP!)



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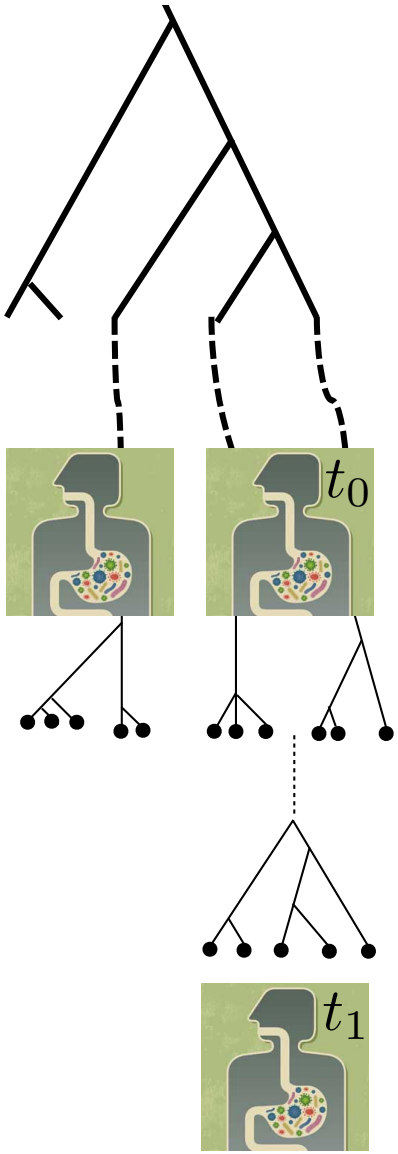

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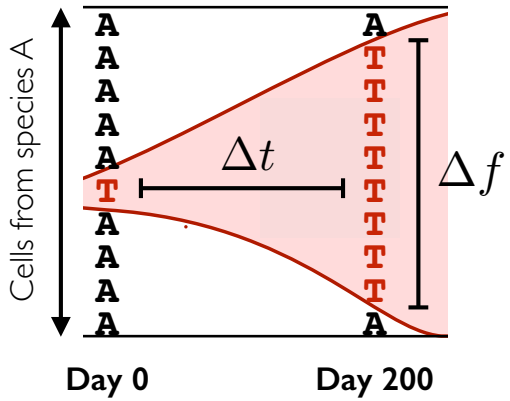
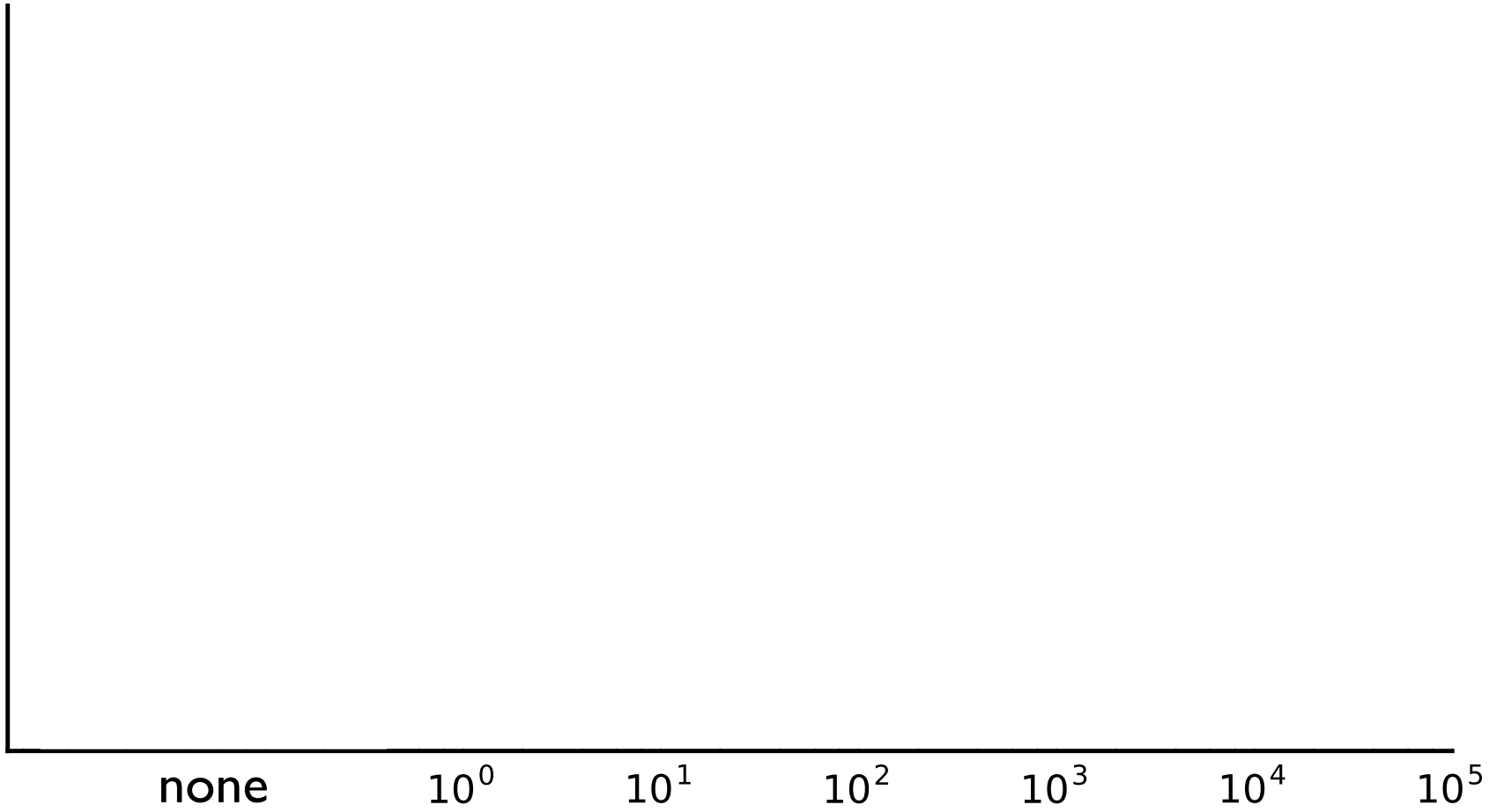
Within-host timescales (~6mo)

Scan for host-wide sweeps…



Within-host dynamics over ~6 month timescales



Garud* & Good* et al (*PLoS Bio*, 2019)

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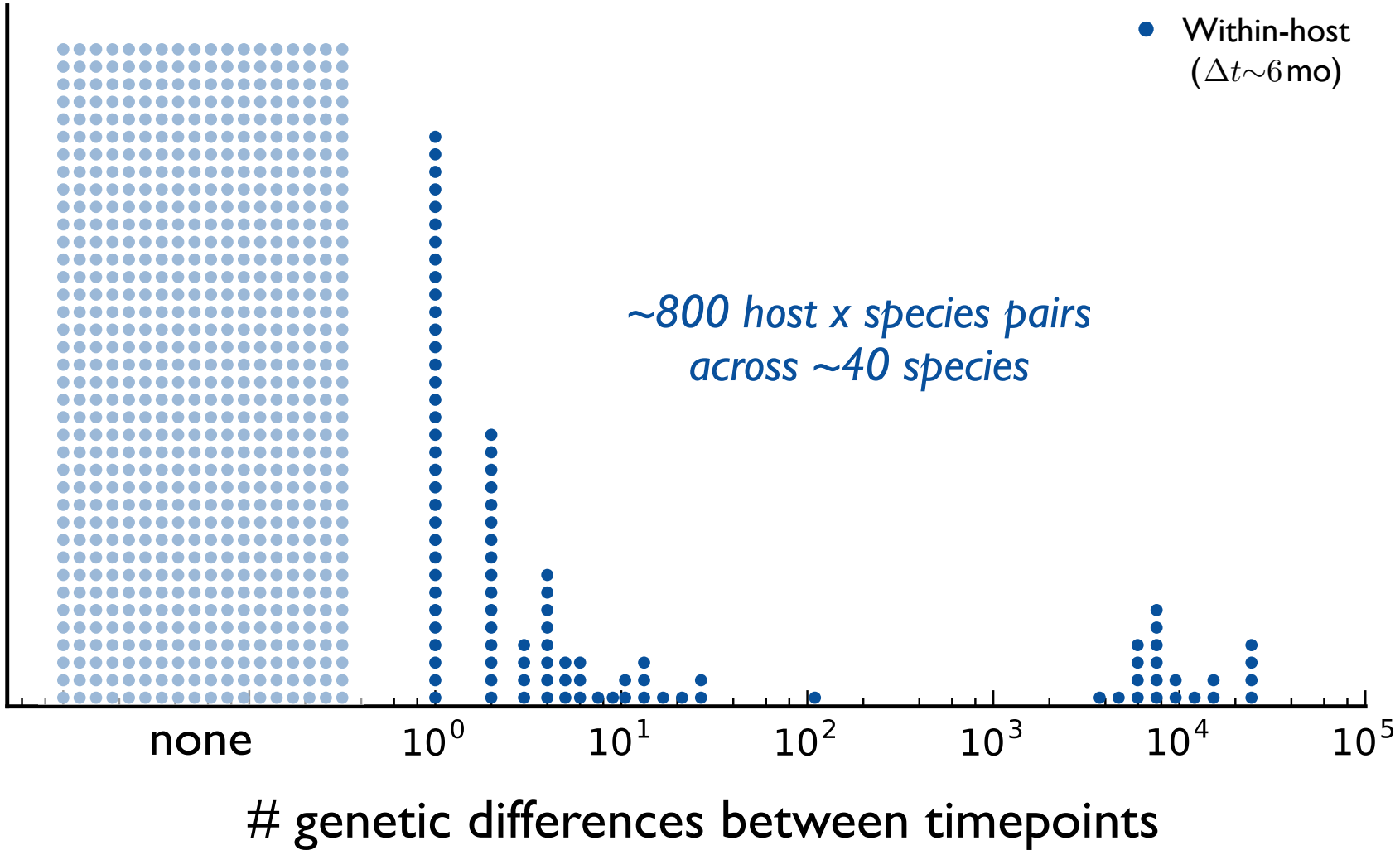

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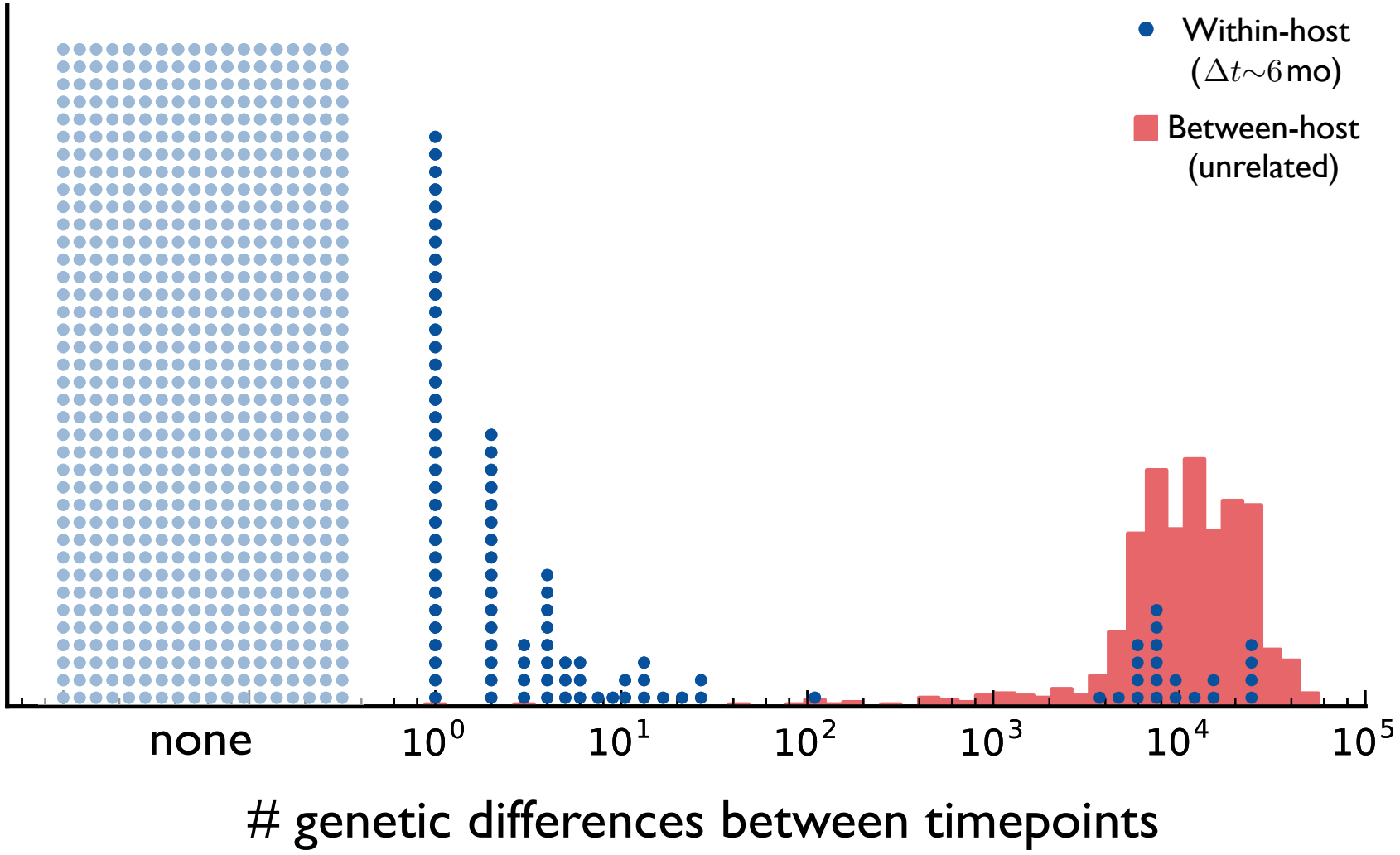

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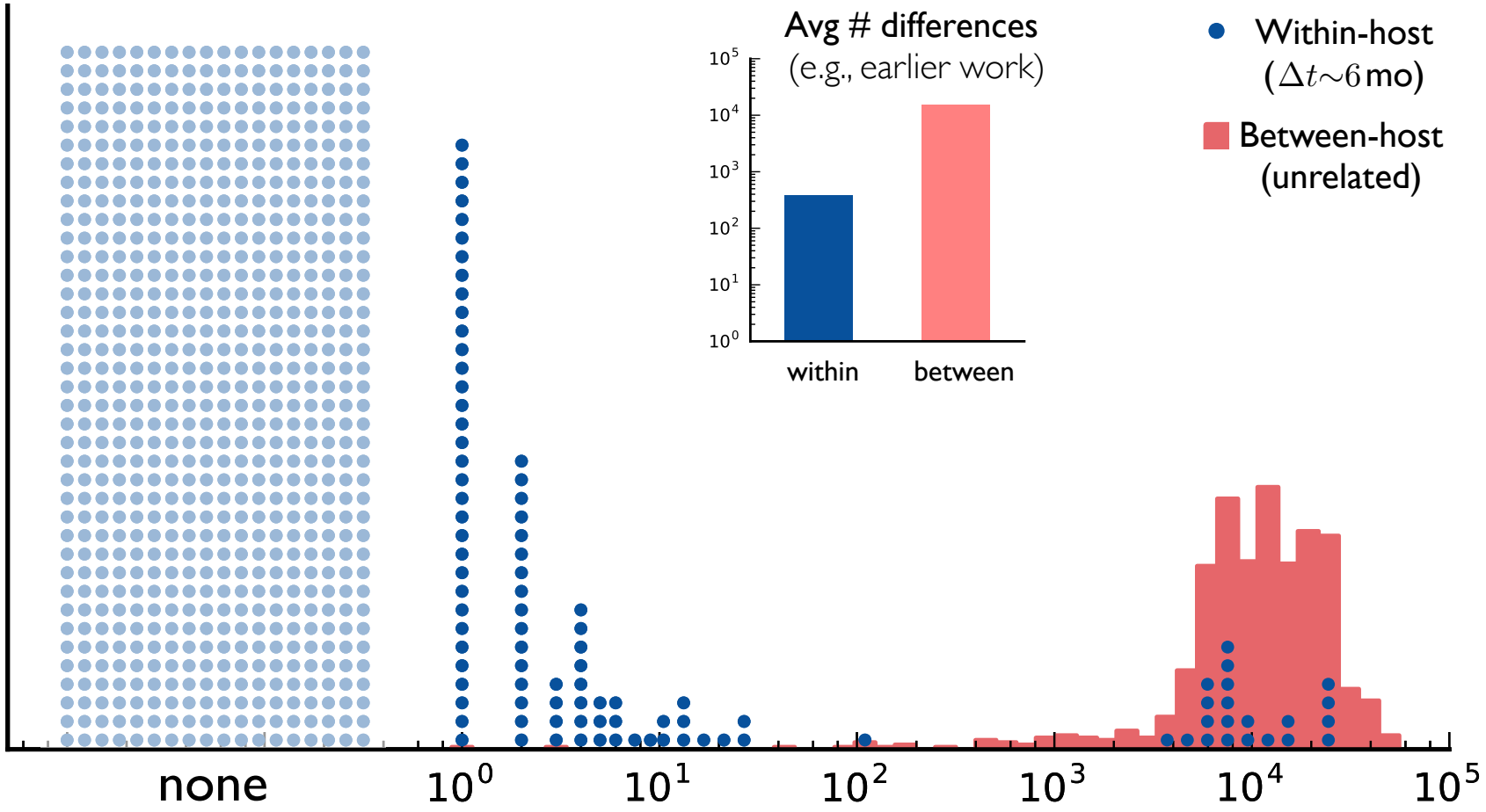

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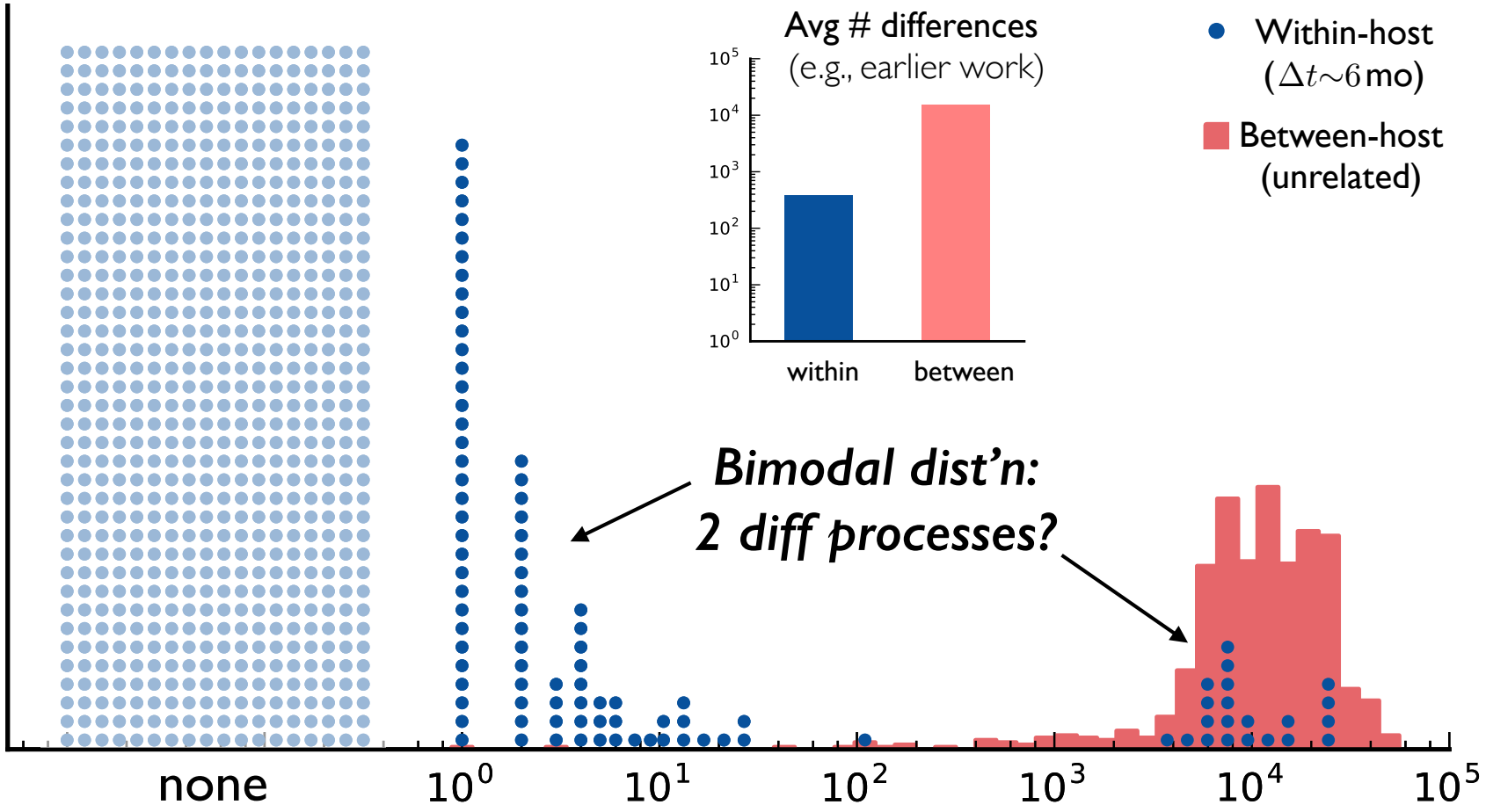

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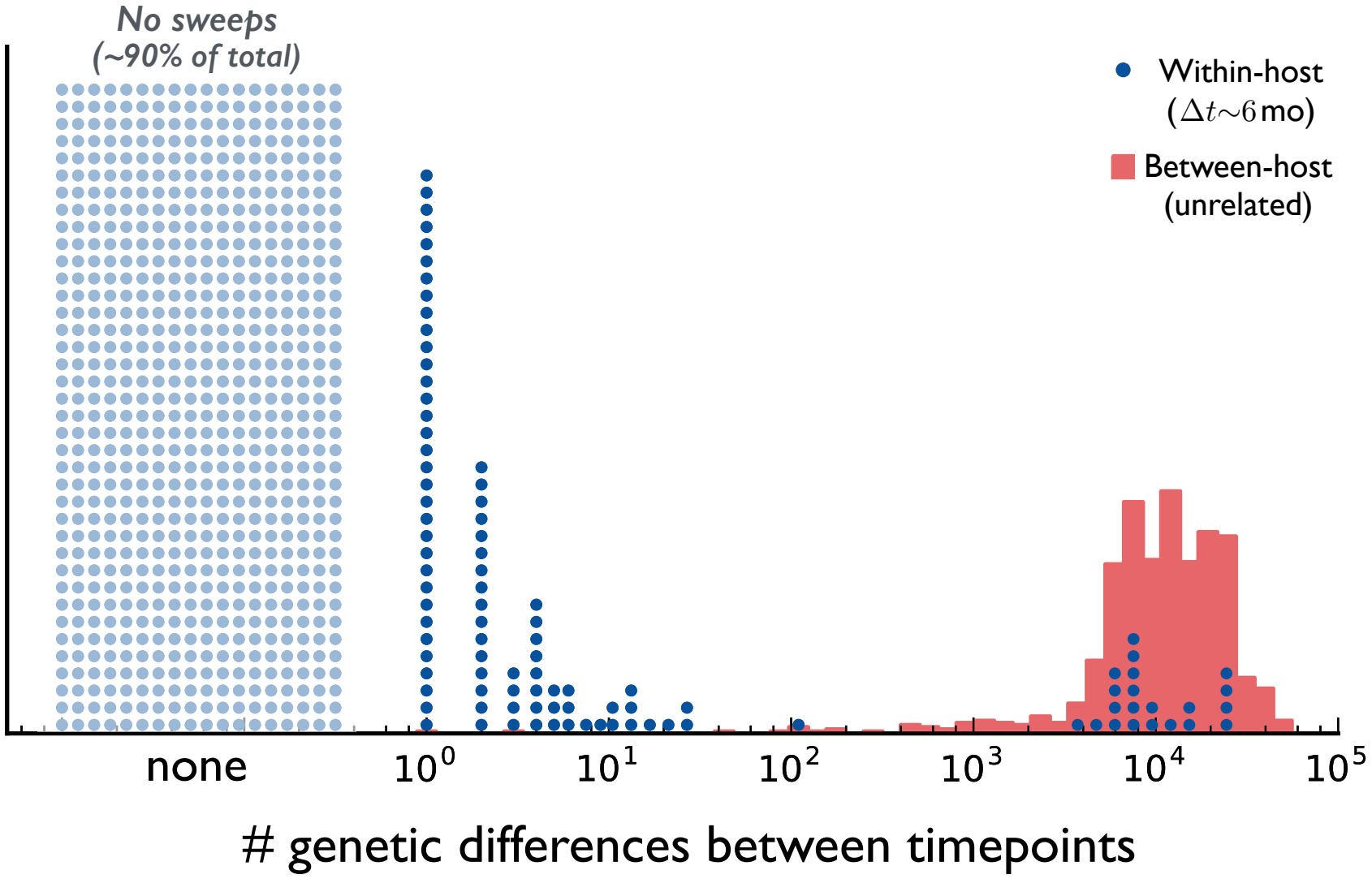

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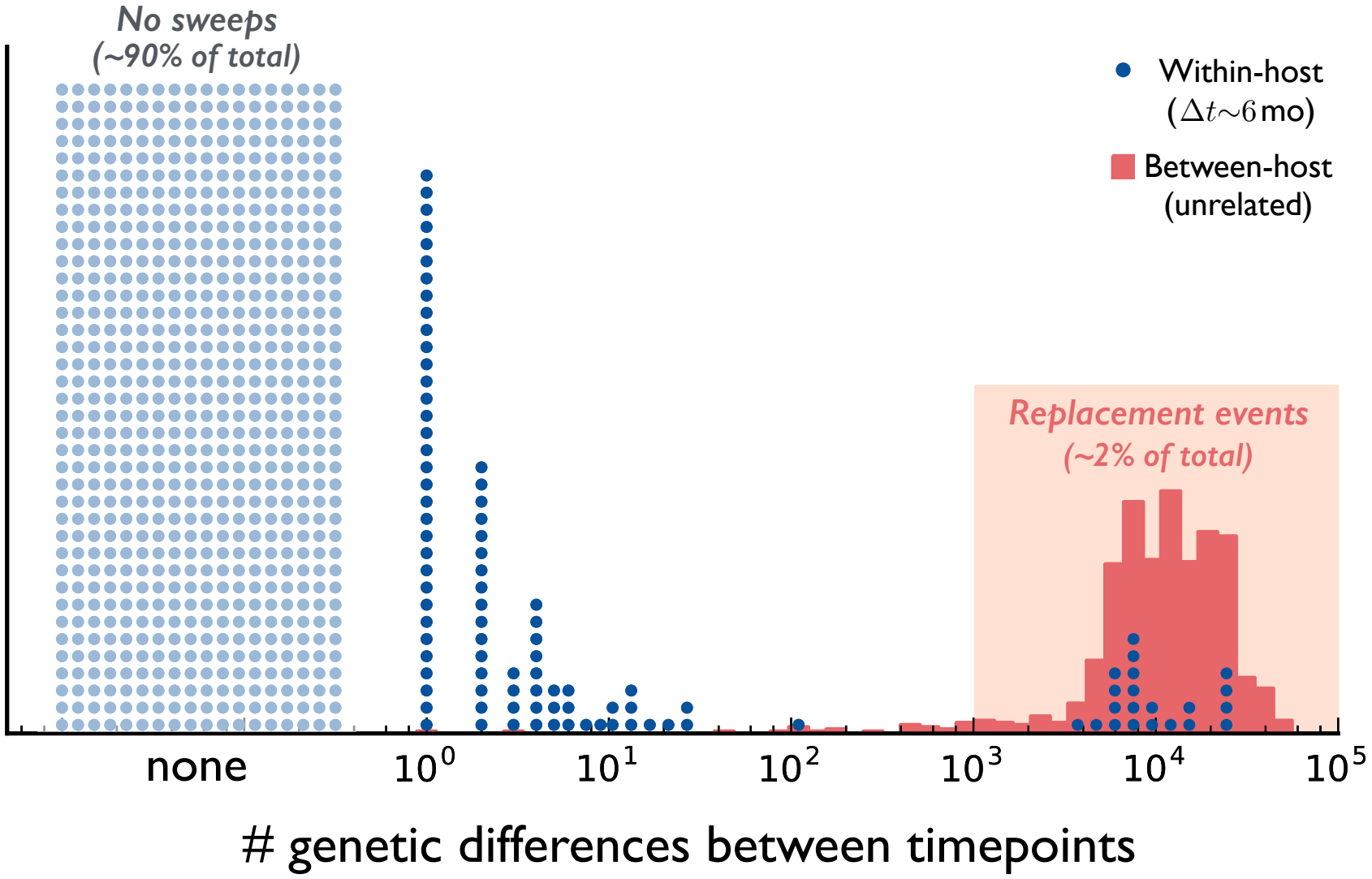

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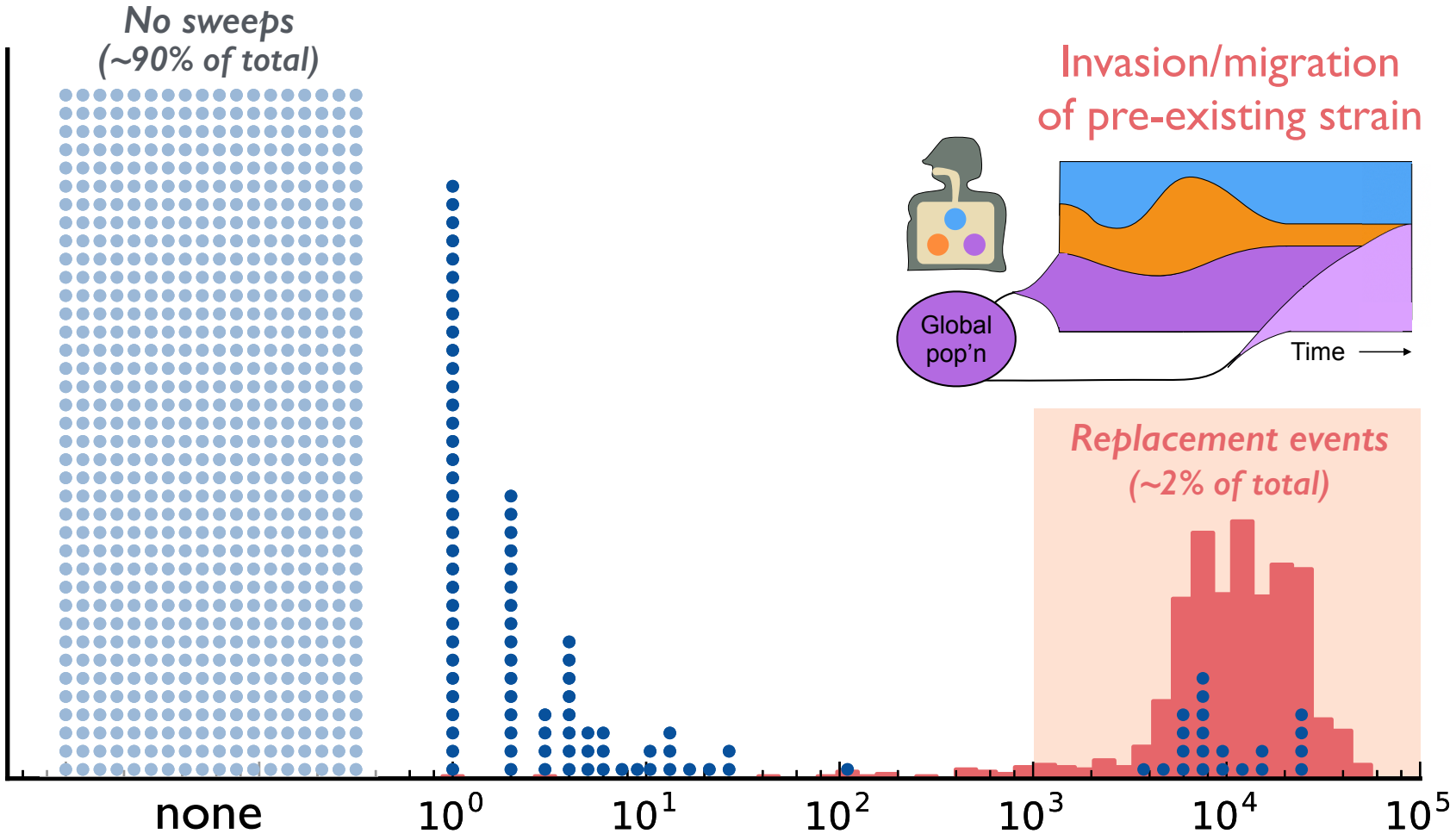

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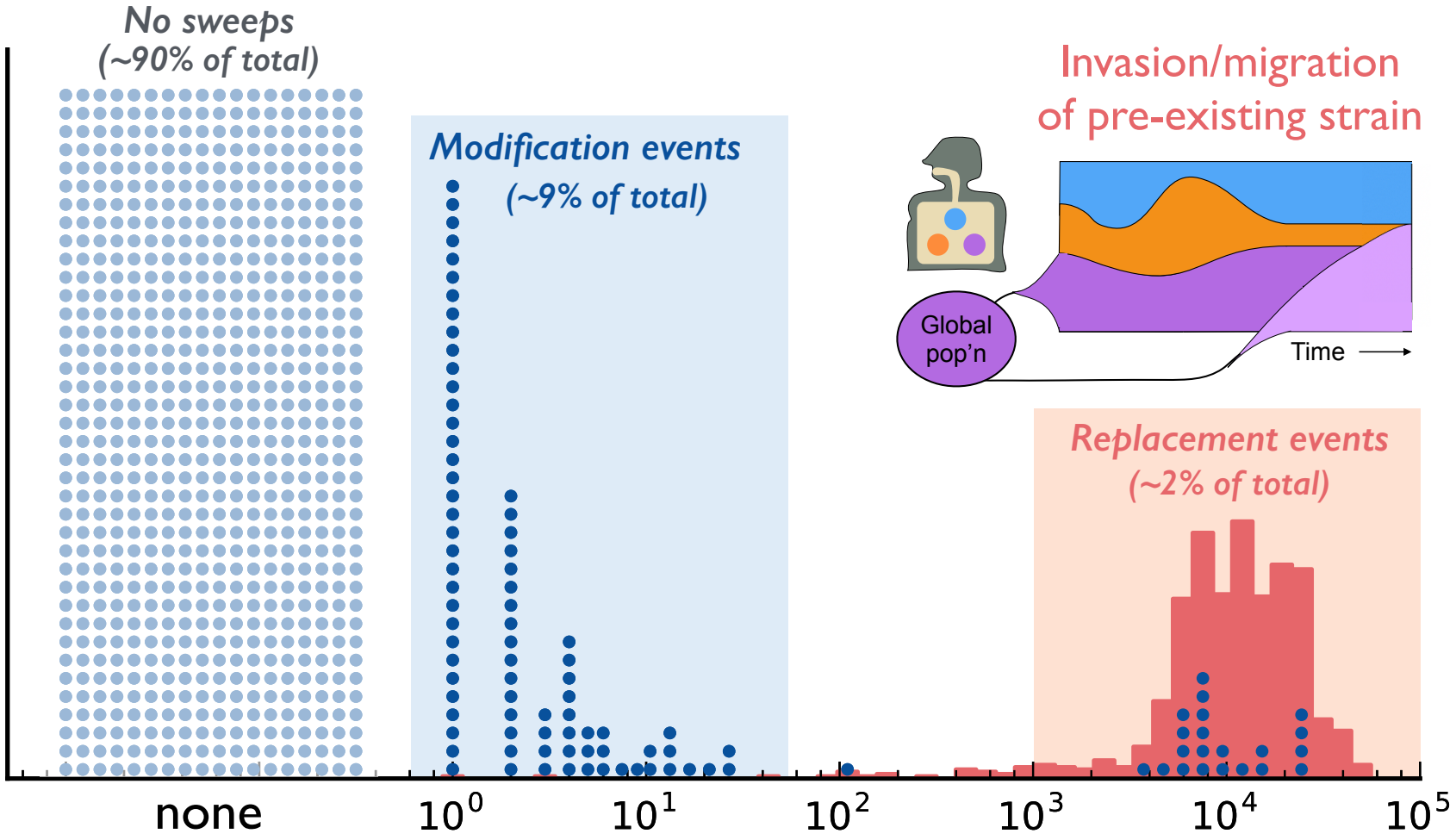

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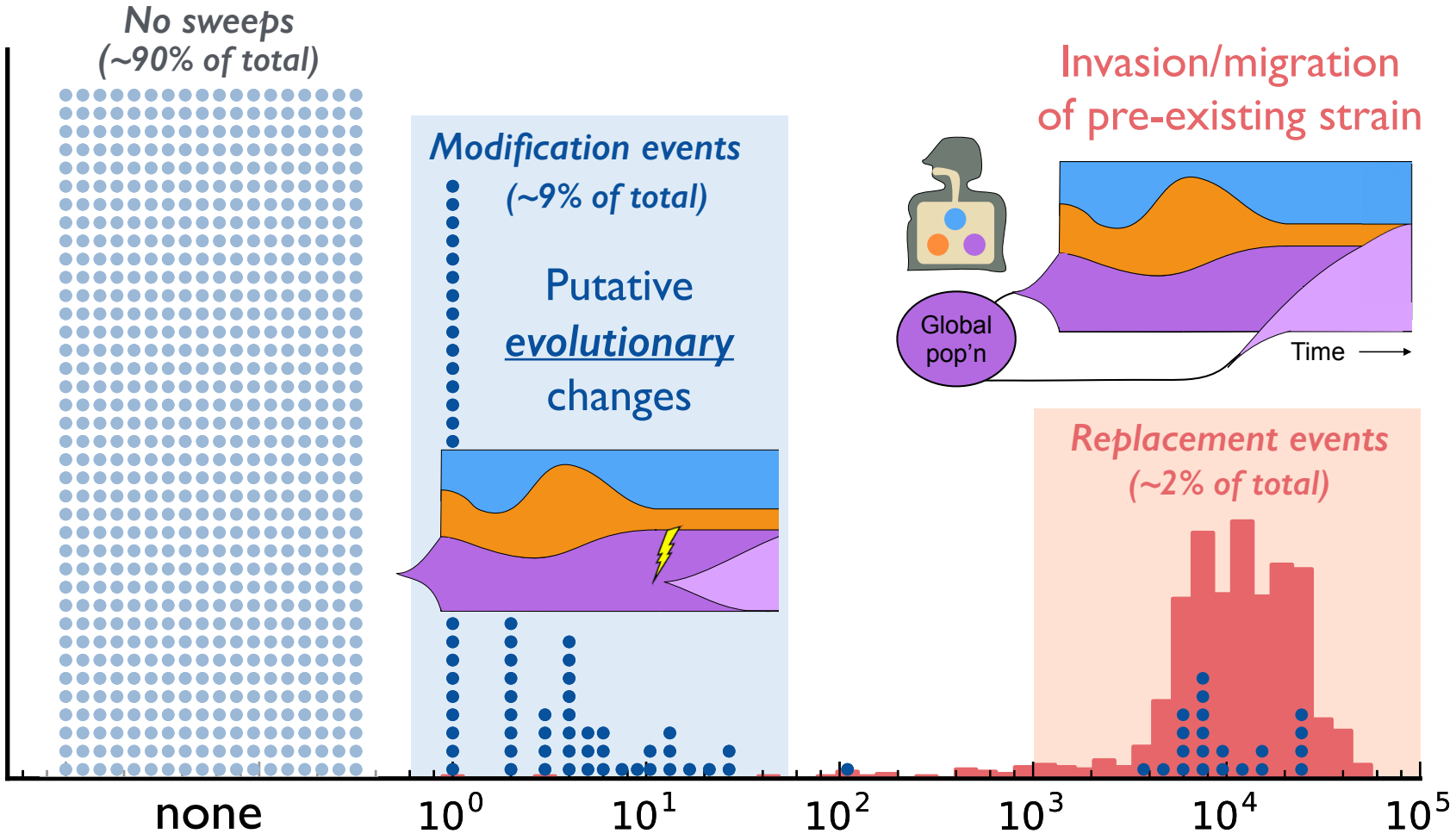

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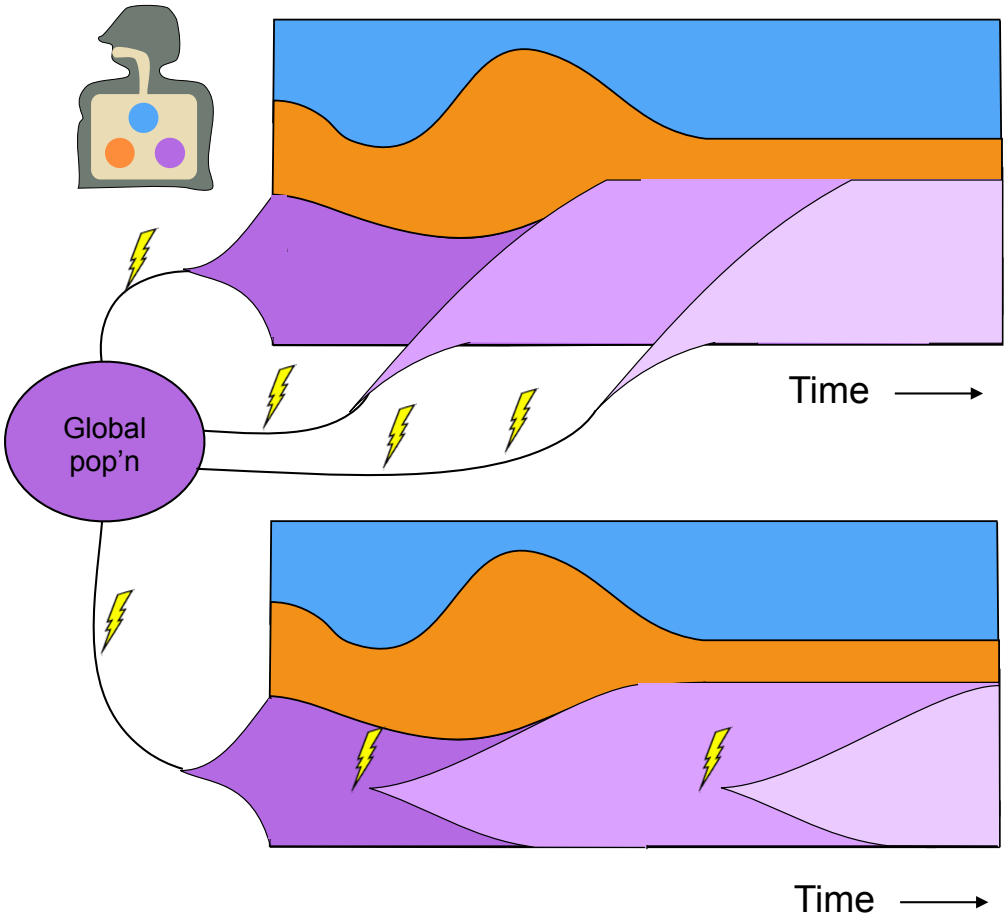
Distinguishing local evolution & strain replacement using time-reversal symmetry



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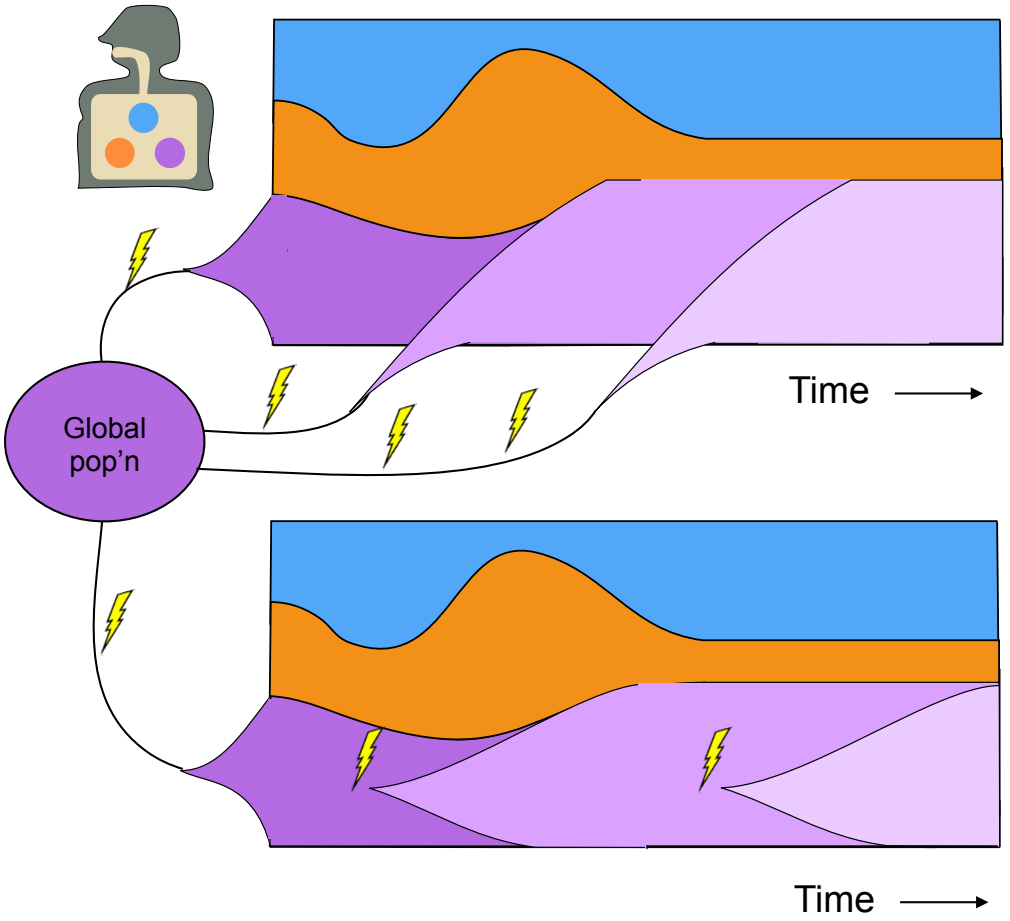

Global strain replacement:

population genetic quantities should be ***locally symmetric*** under time-reversal ($t \mapsto -t$)

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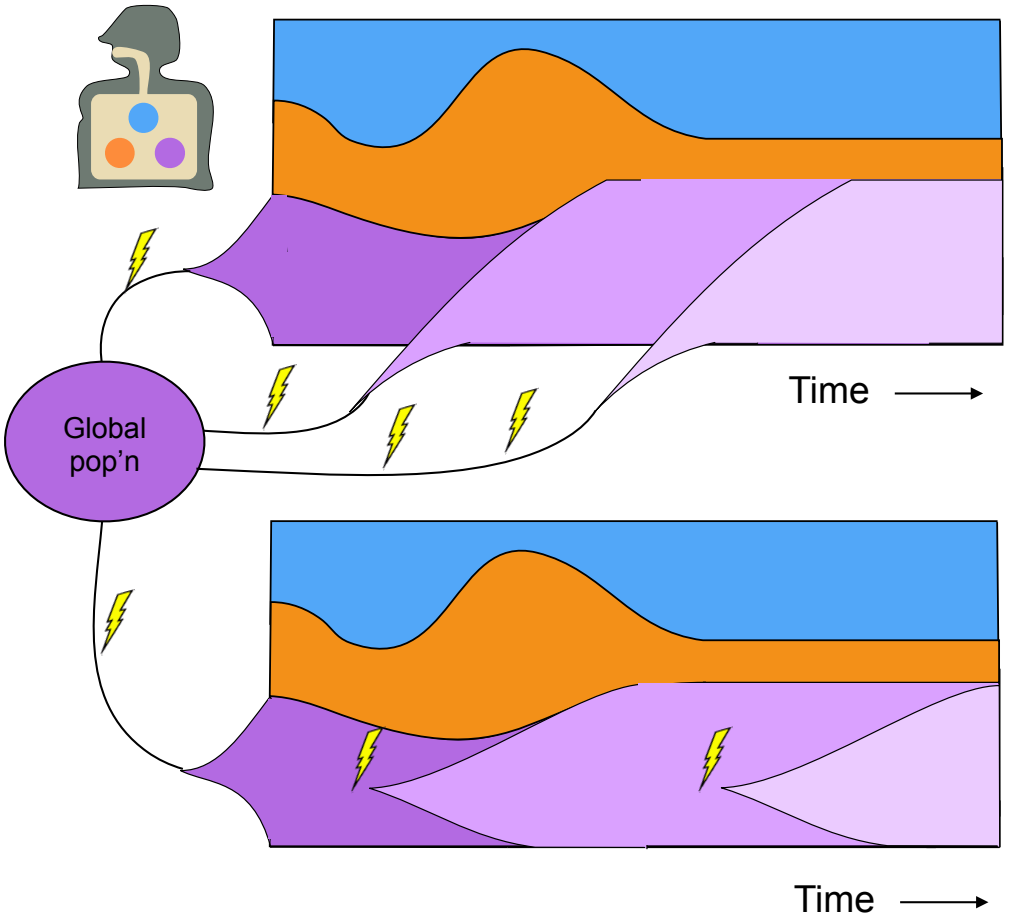

Global strain replacement:

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Local evolution: *asymmetric*

(most new mutations biased ***away from*** global consensus)

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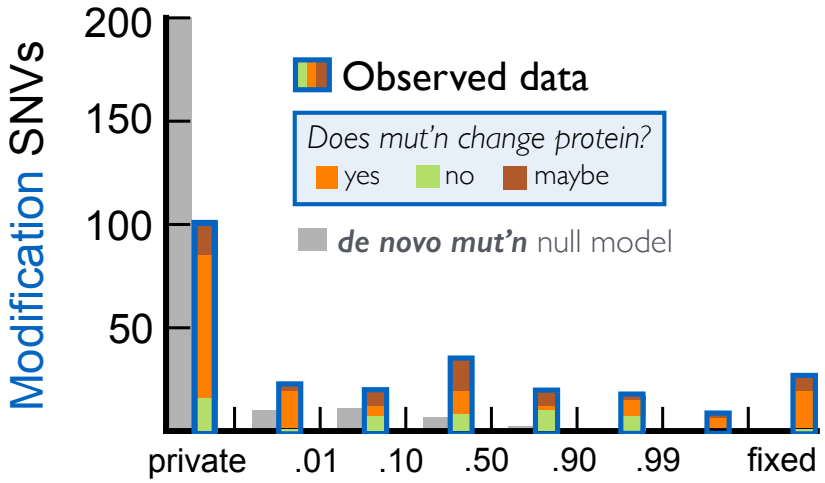
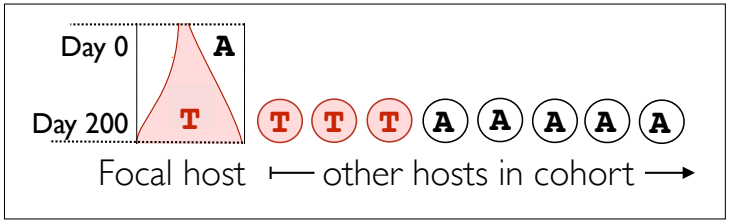


Prevalence of ***sweeping*** variant across other hosts



Do we see same variant in other hosts?

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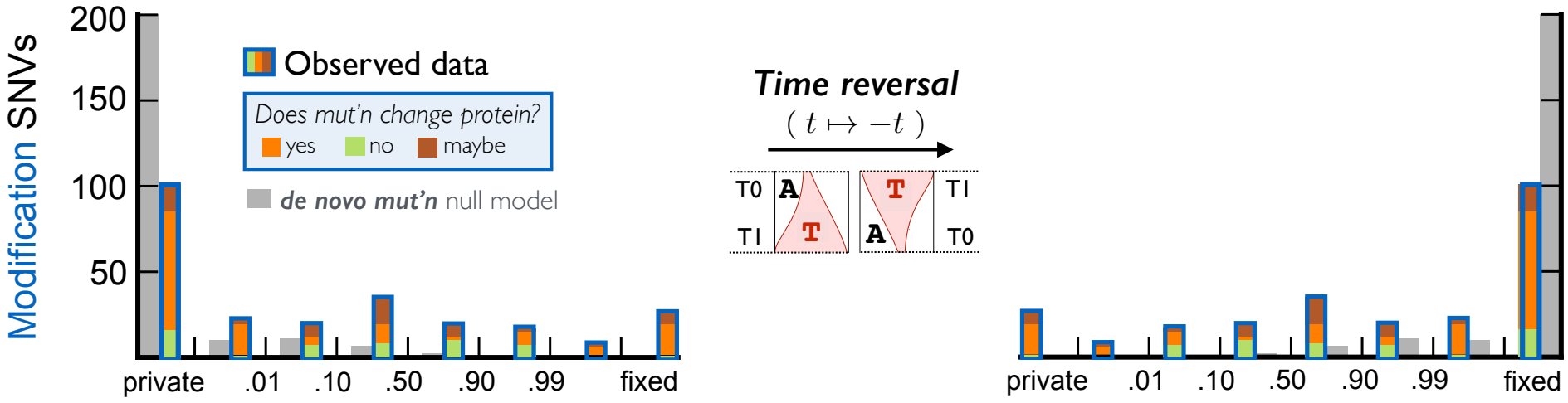

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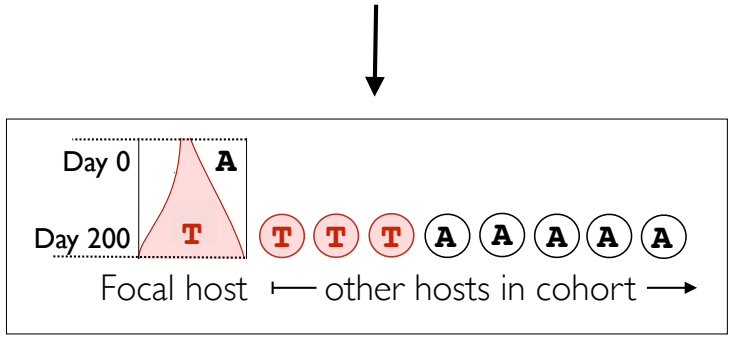


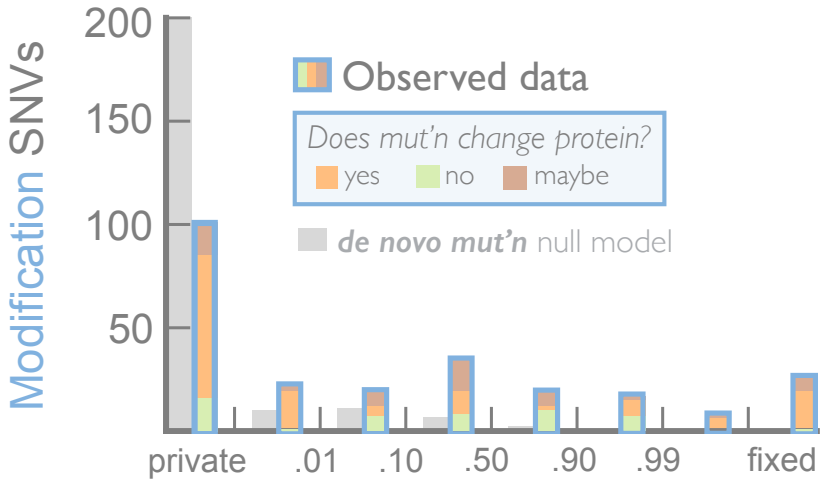
Do we see same variant in other hosts?

Time reversal

$(t \mapsto -t)$

Prevalence of *time-reversed sweep*

Distinguishing local evolution & strain replacement using time-reversal symmetry



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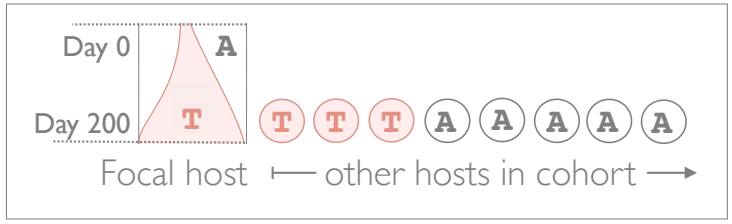

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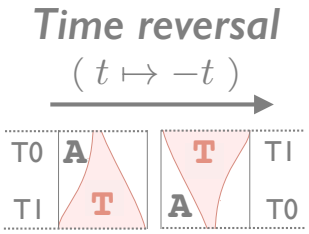
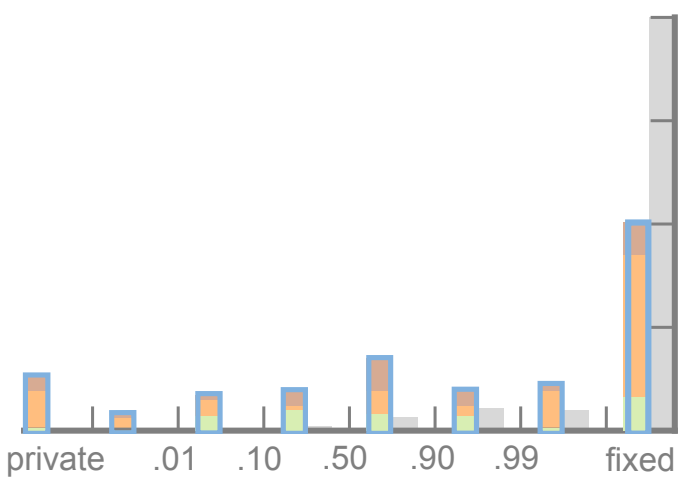
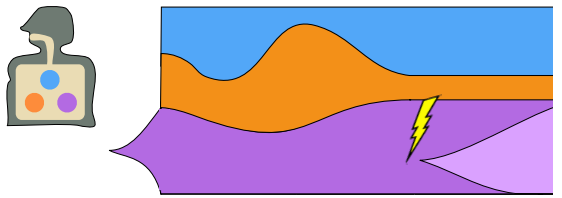




Prevalence of *time-reversed sweep*

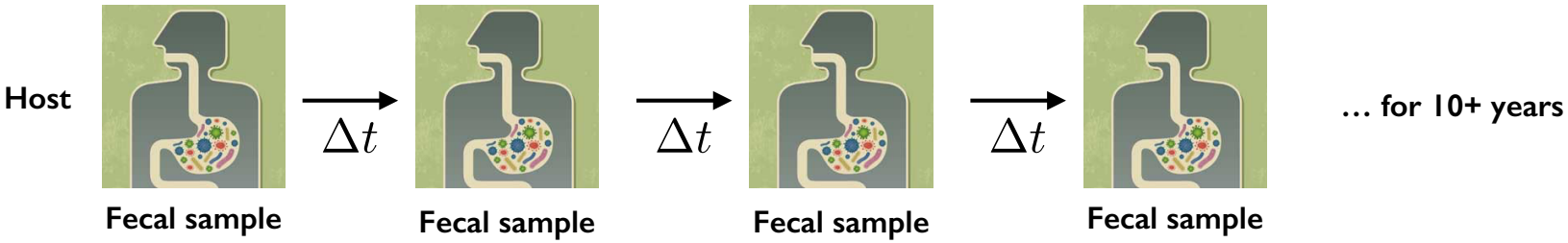
Modification events are ***asymmetric*** under local time reversal ($p<10^{-4}$)



~ local evolution

Probing *replacement* & *modification* on longer timescales

Ideal data: *track (many) individual hosts over 10+ years*



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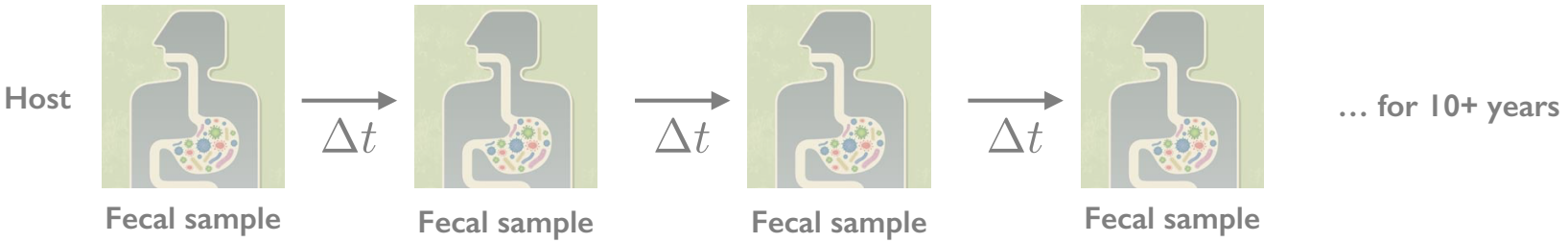
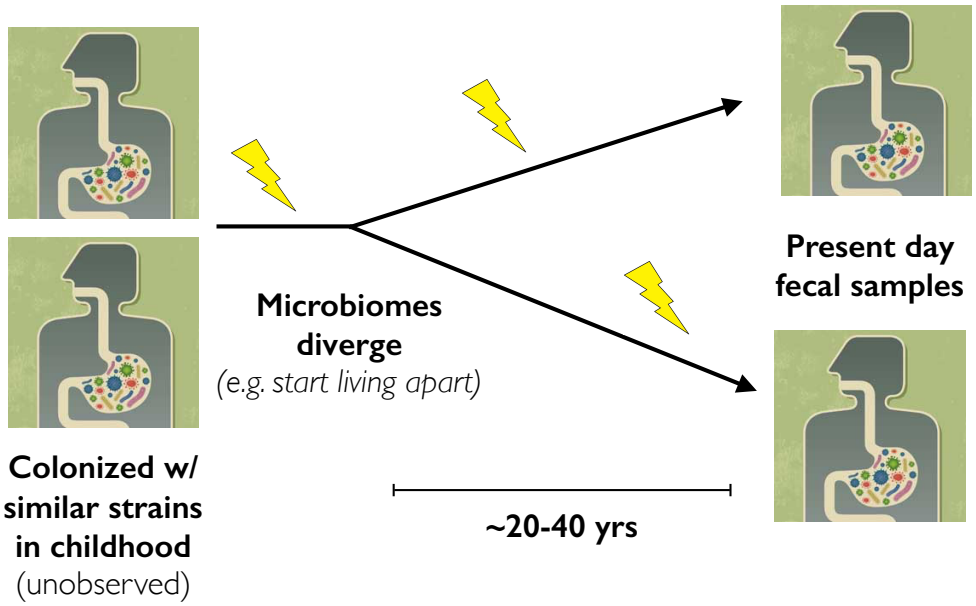


Proxy: *compare microbiomes of ~200 adult twins*



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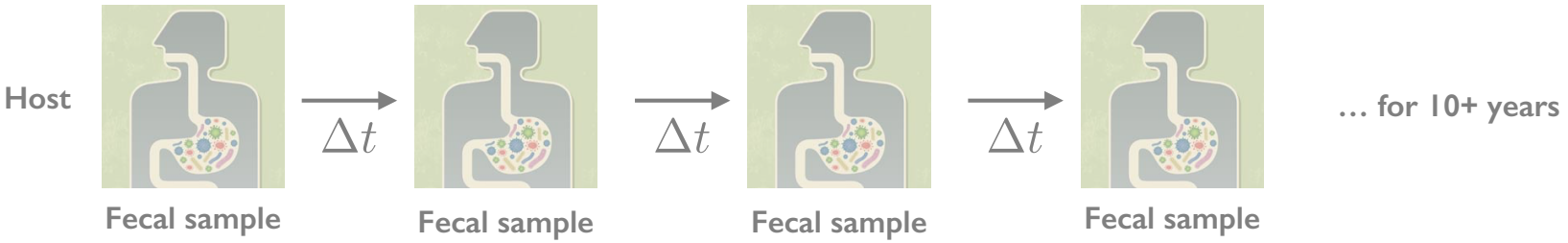

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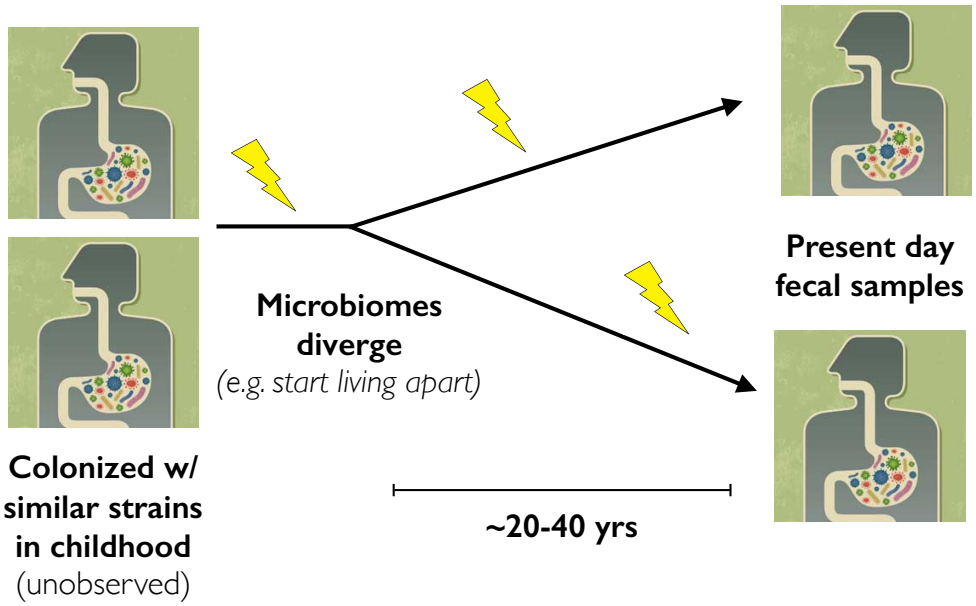

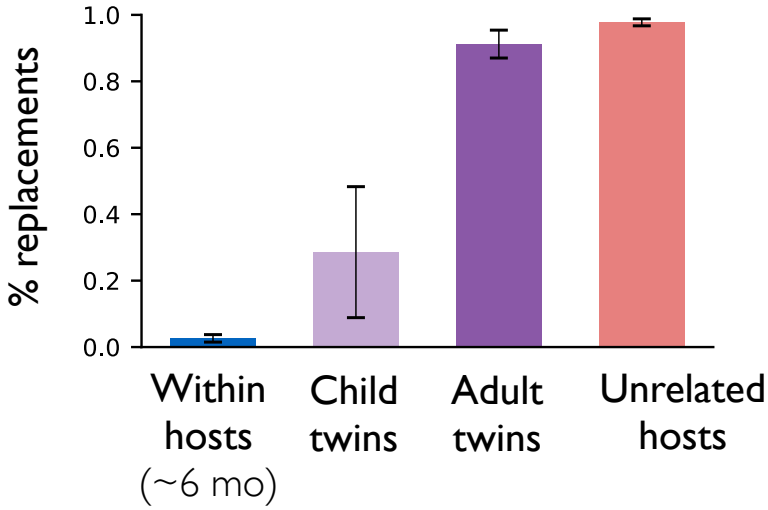

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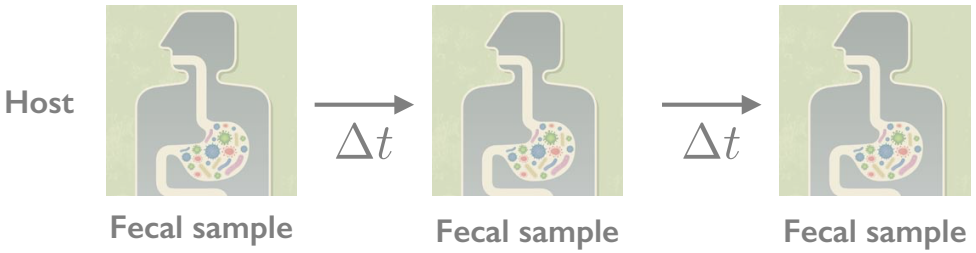
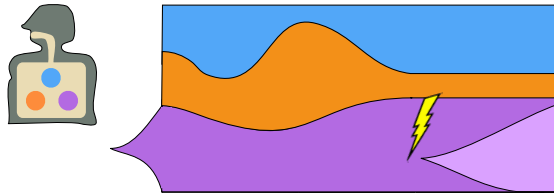


→ benefits of ***local evolution*** don't compound indefinitely



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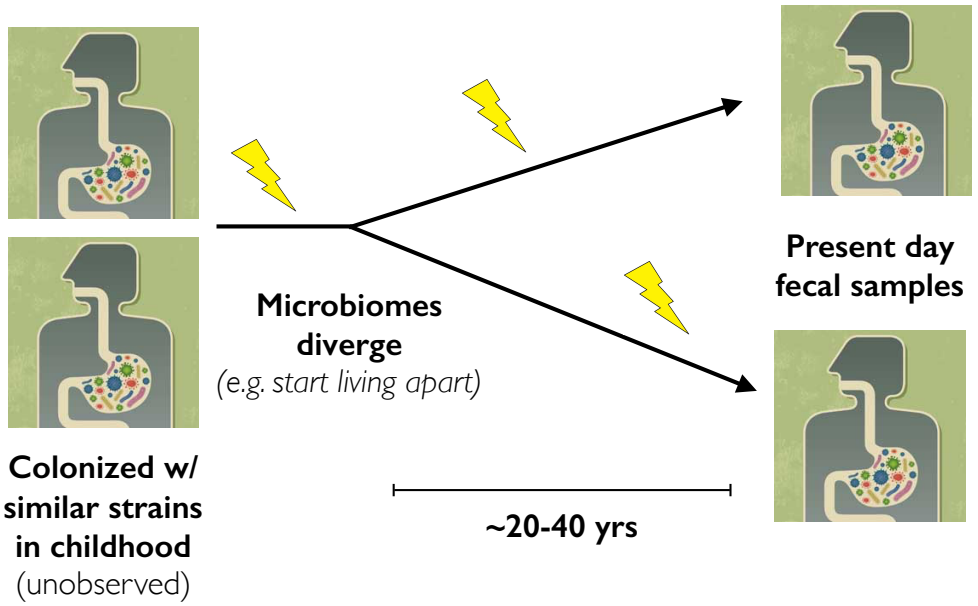
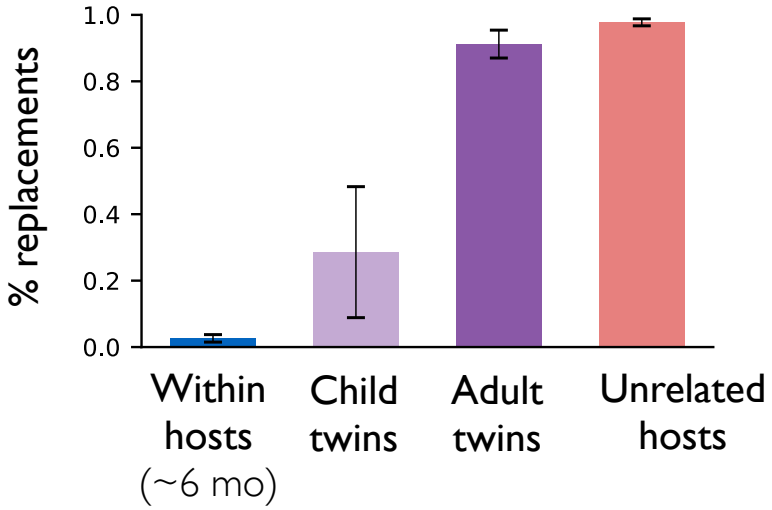
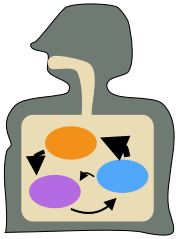


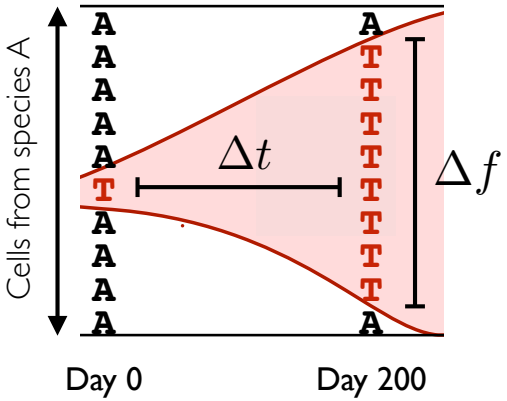


Key takeaways

- **Comparing 2 timepoints:** native microbiota ***can*** acquire genetic diffs on human-relevant timescales



→ ***mixture of "strain replacement" and "evolutionary modification"***



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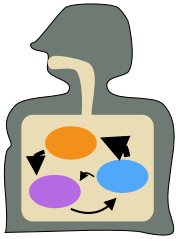

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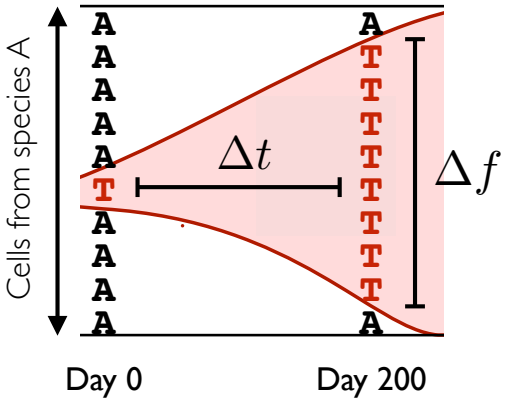

- **Next steps:** what do the ***population genetics*** of this process look like?

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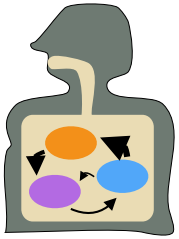

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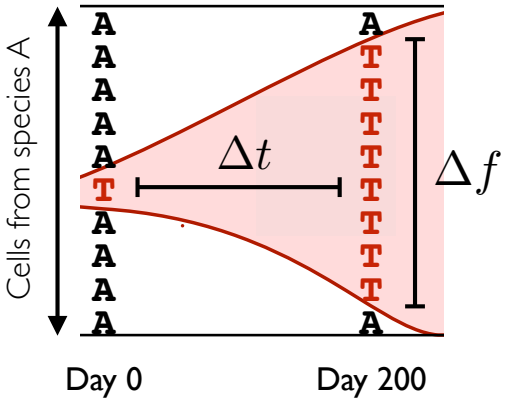

- **Next steps:** what do the ***population genetics*** of this process look like?
  - How important are natural selection, genetic drift, recombination w/in hosts?

Key takeaways

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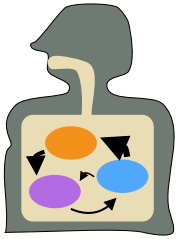

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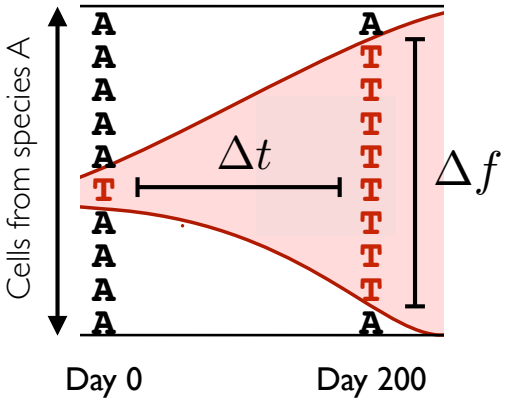

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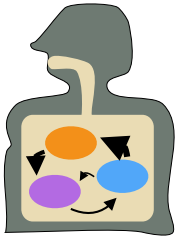
Key takeaways

- **Comparing 2 timepoints:** native microbiota ***can*** acquire genetic diffs on human-relevant timescales



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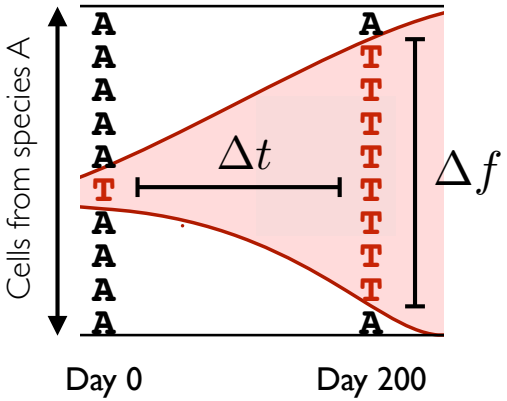

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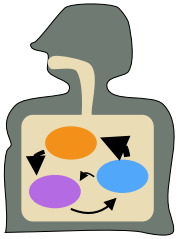

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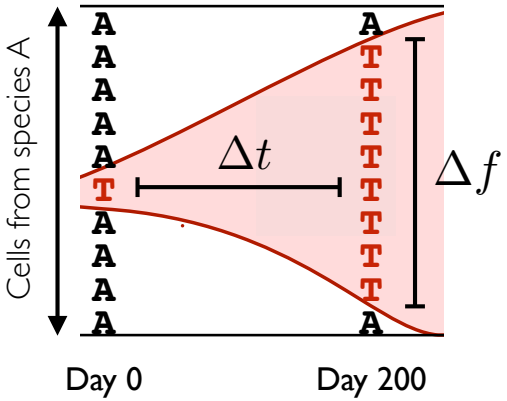

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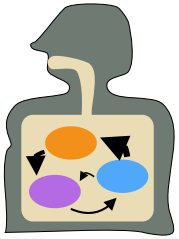

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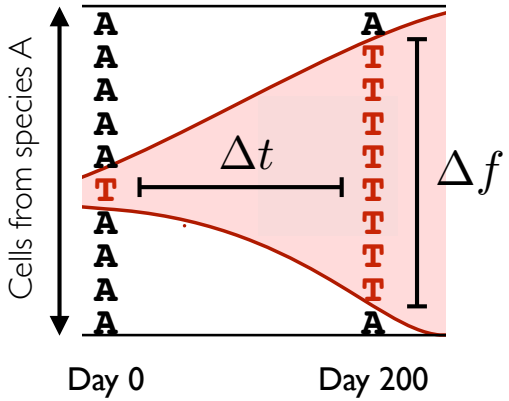

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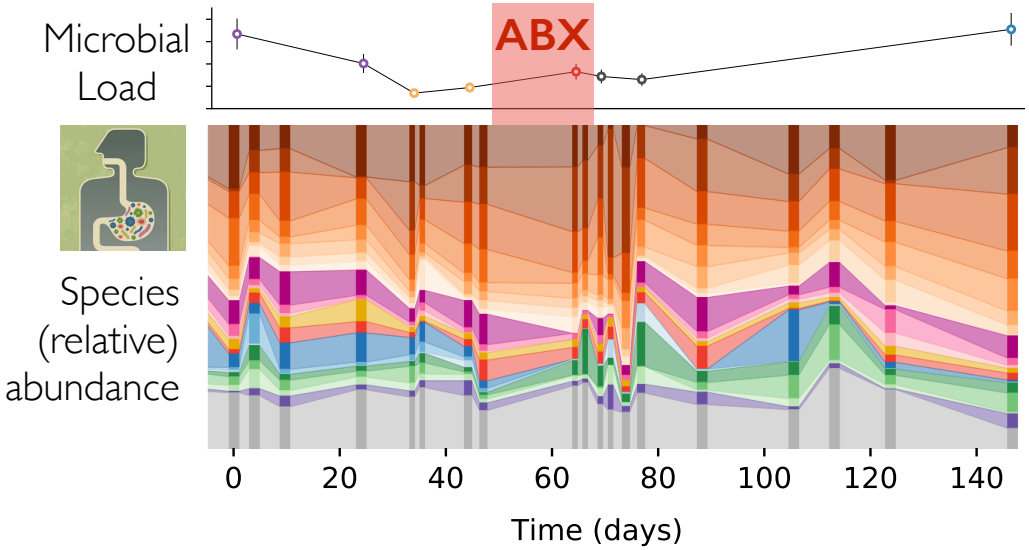
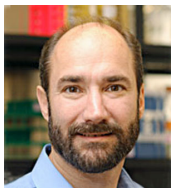
→ ***requires denser longitudinal sampling***

Next steps: dense time series data to infer *dynamics of this process*

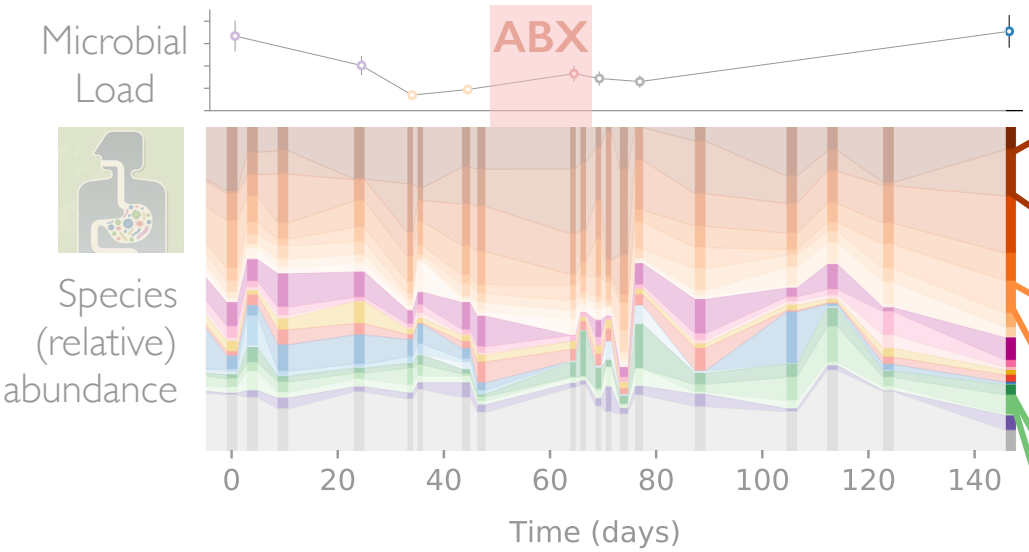


Morteza Roodgar



Mike Snyder (Stanford)

Next steps: dense time series data to infer *dynamics of this process*



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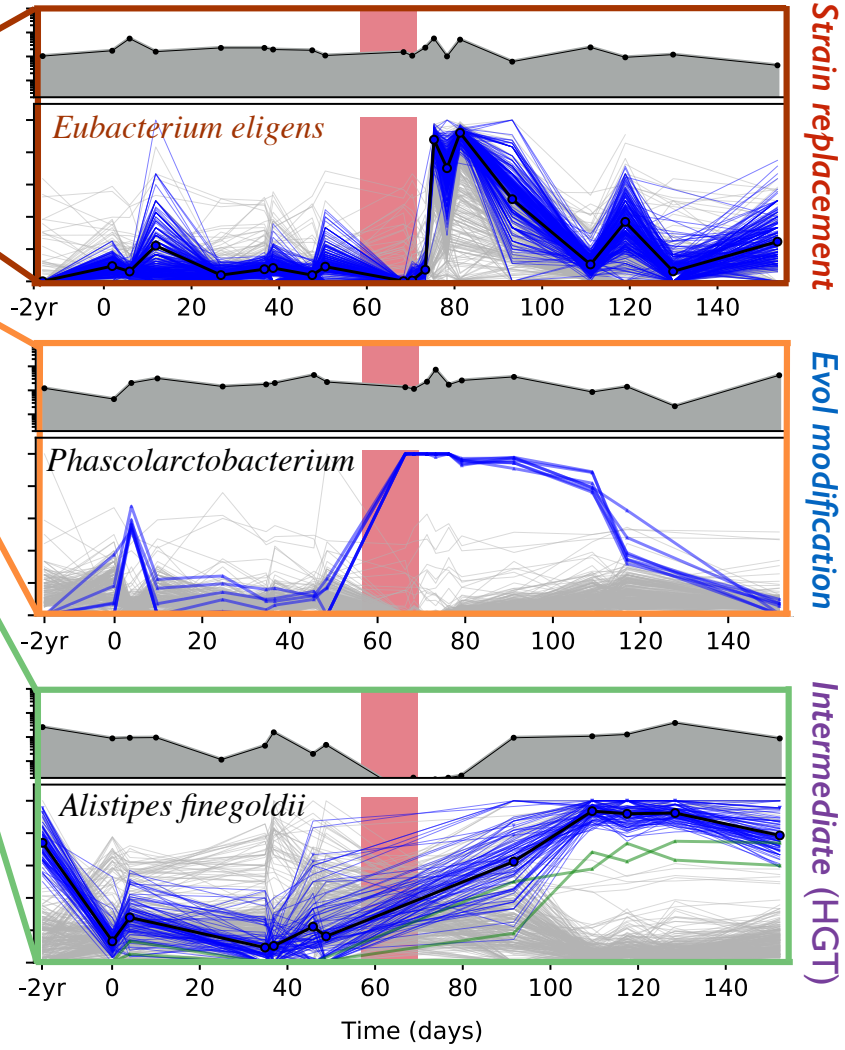

\+

33 other species

(18 w/ genetic changes)

Morteza Roodgar

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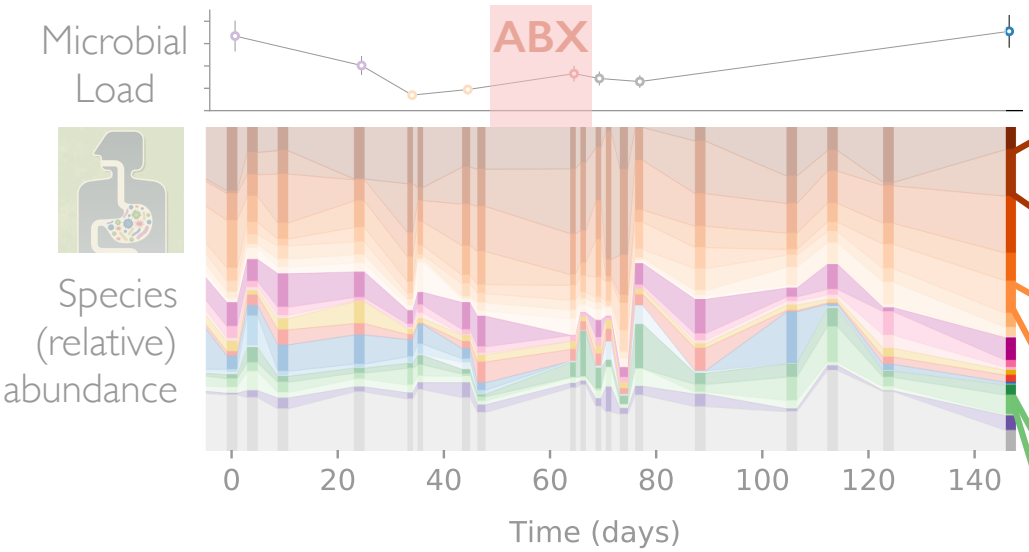
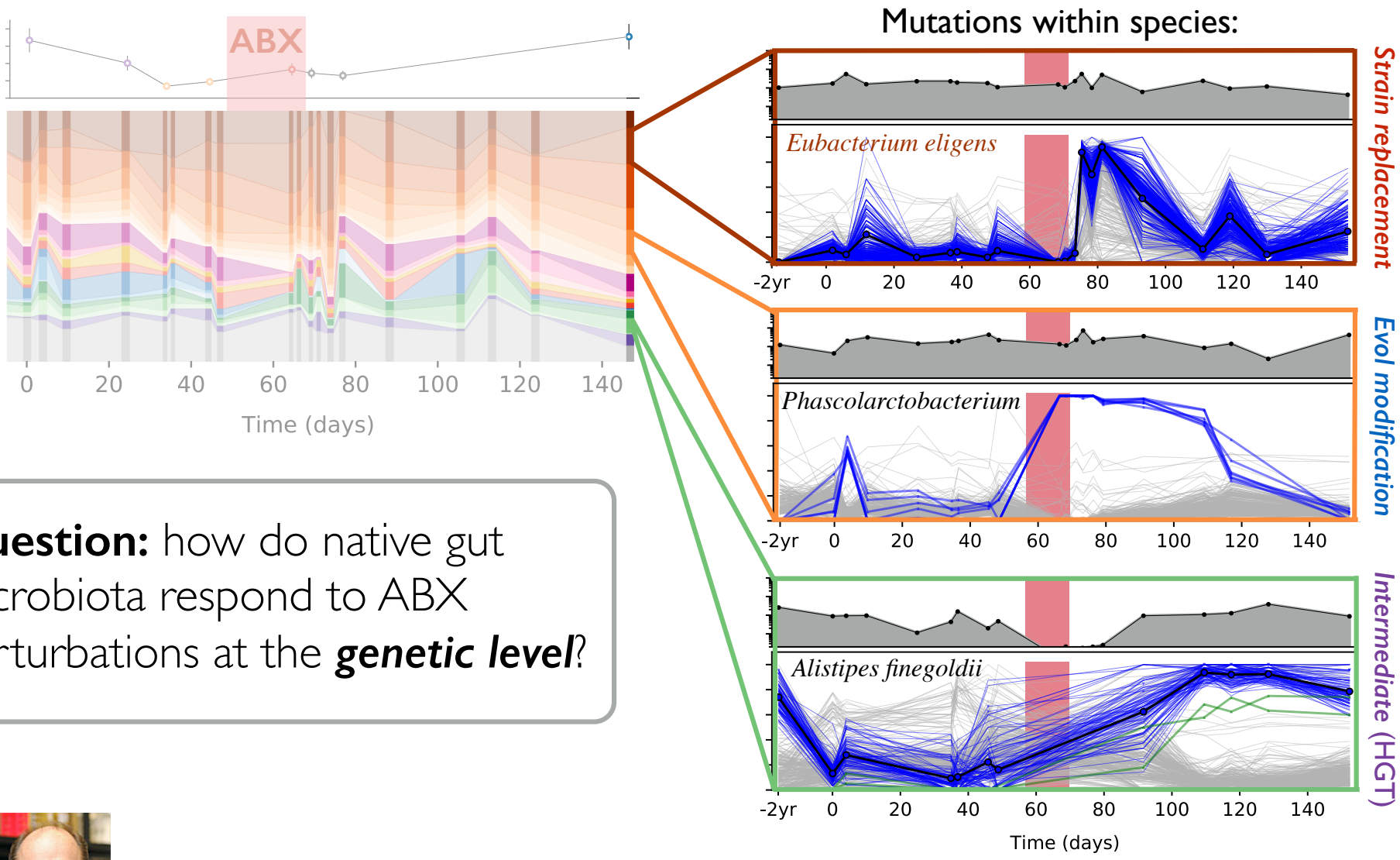


Question: how do native gut microbiota respond to ABX perturbations at the ***genetic level***?



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Morteza Roodgar

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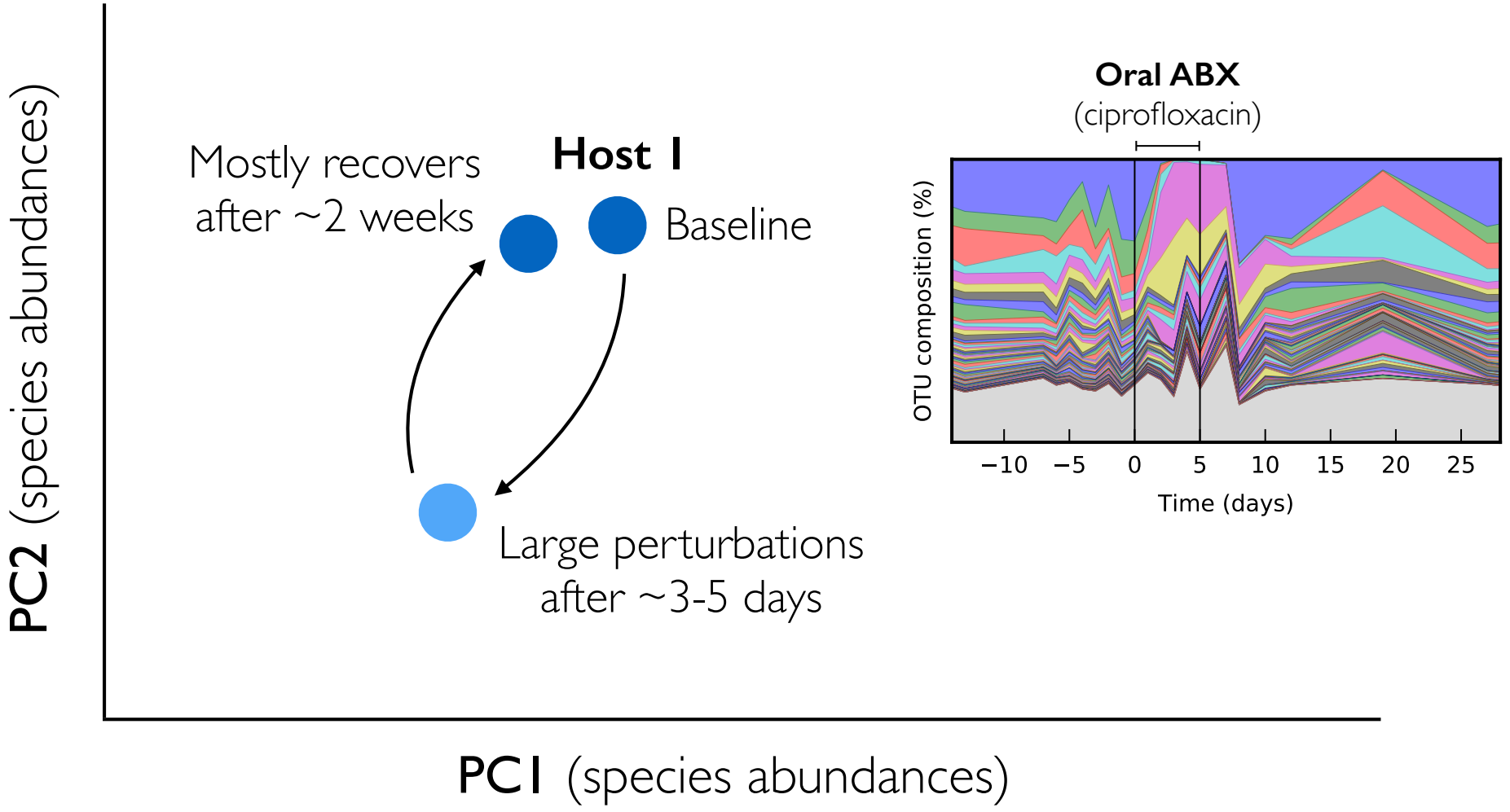
Previous work: effects of ABX treatment at species level

- Severe cases ⟶ purges native flora, allows for ***C. diff*** infection
- Typical oral dose produces more resilient response:



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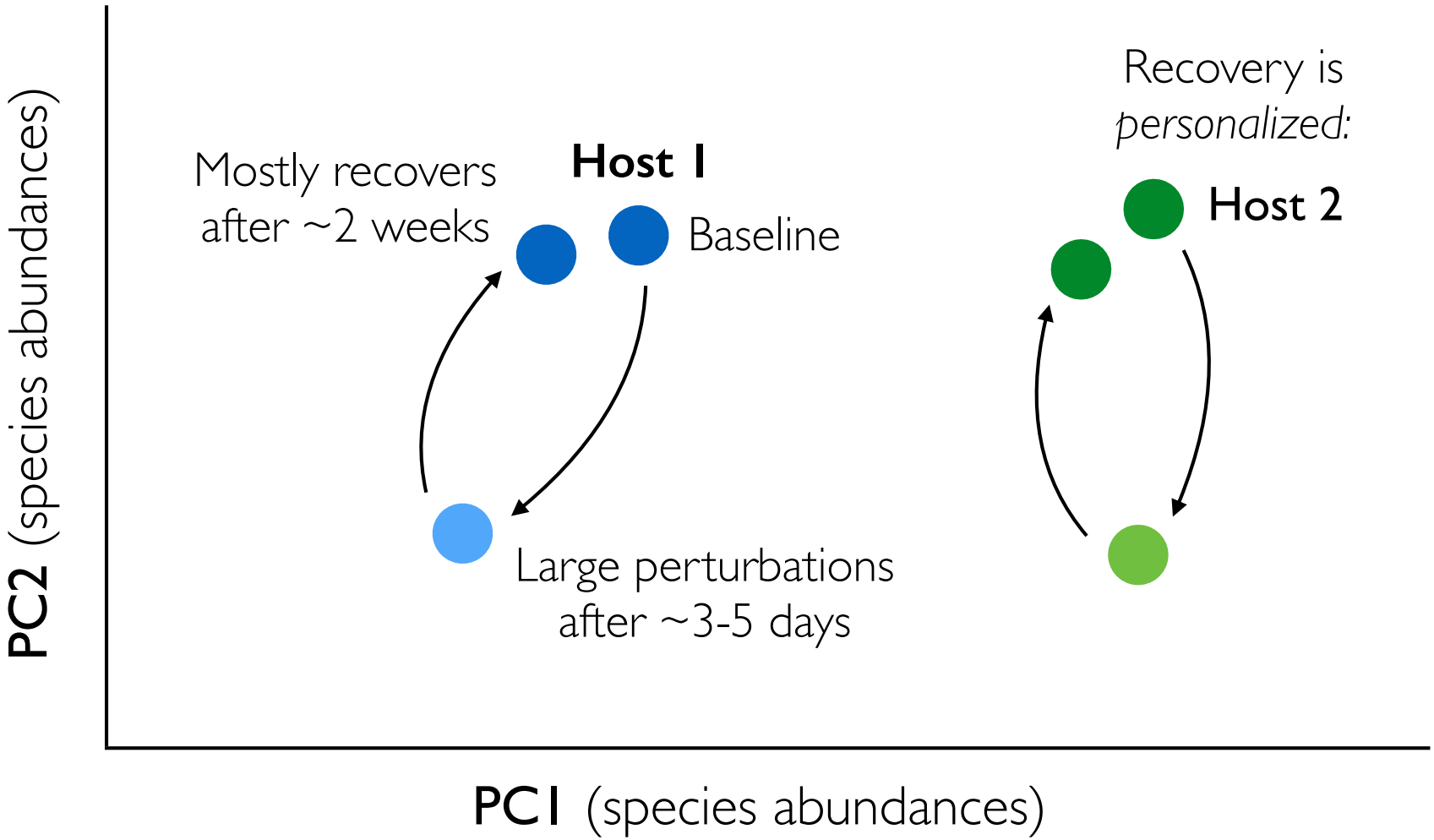

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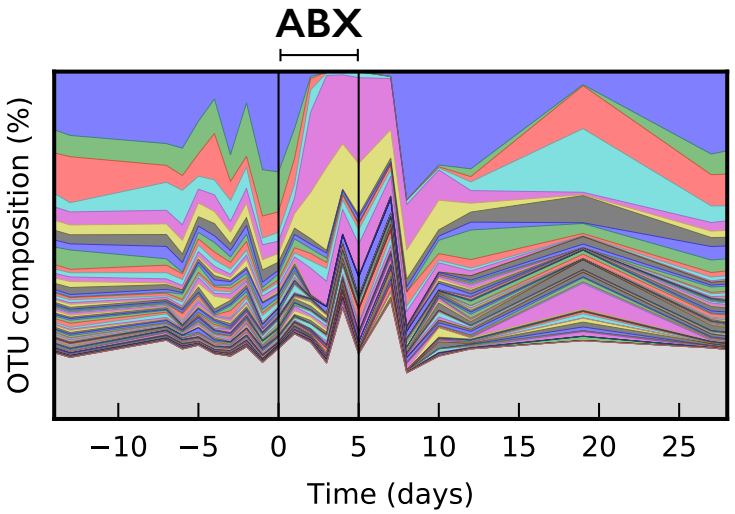
Question: How is this ***species level*** resilience implemented at the ***strain level*****?**



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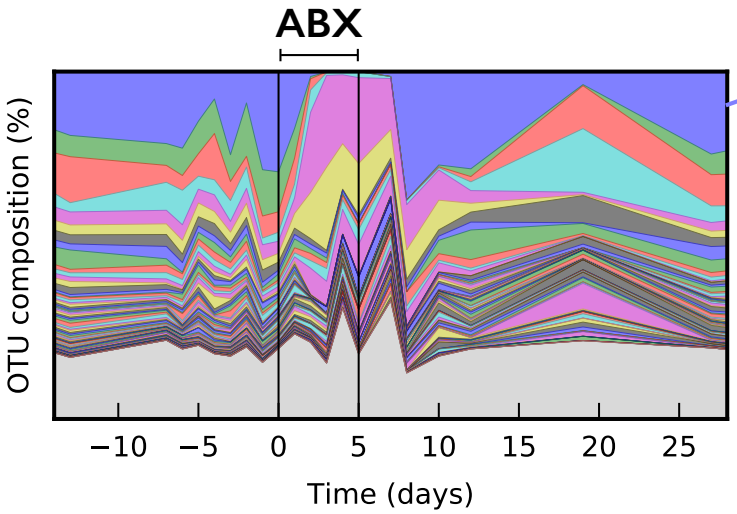

Re-colonization by new strain of same species?
or survivors of original strain?

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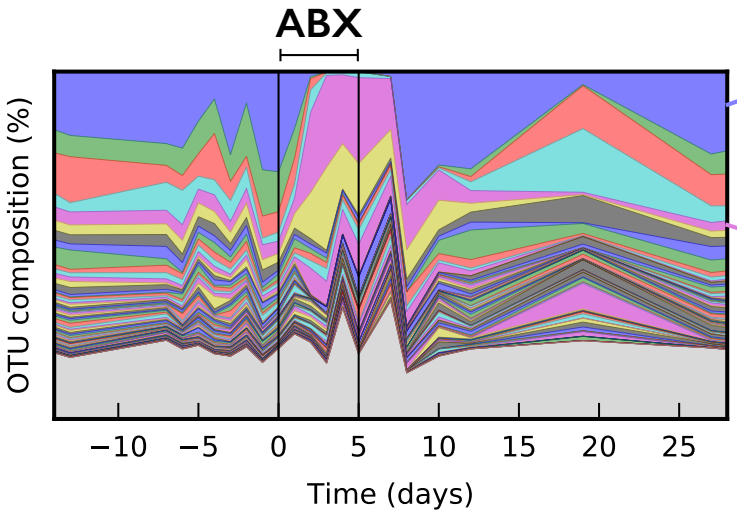

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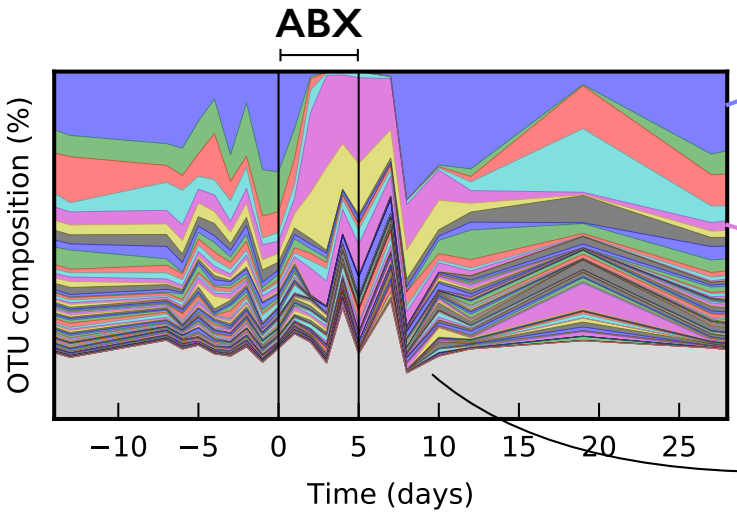

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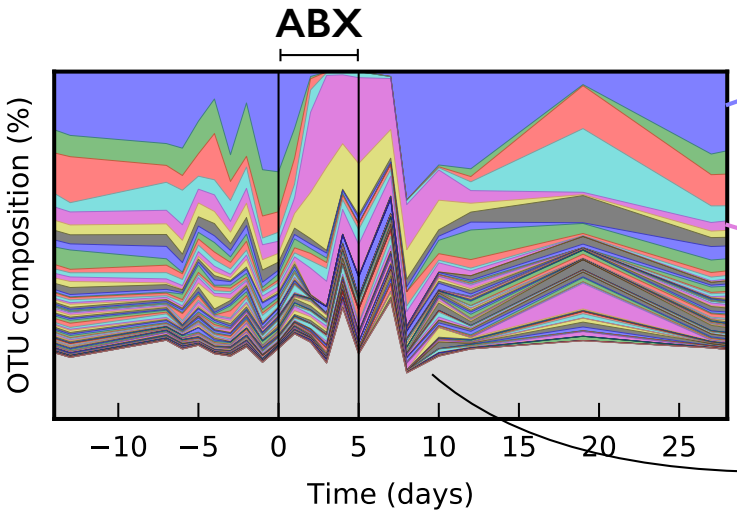

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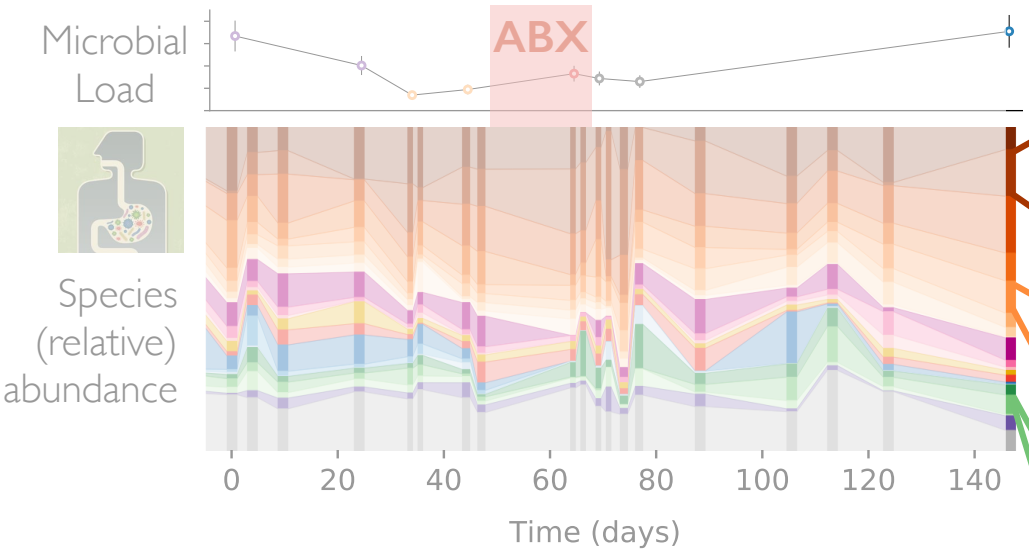
Can we look "under the hood" to find out?

Next steps: dense time series data to infer ***dynamics*** *of this process*



ABX can drive ***rapid genetic changes*** w/in species this complex community

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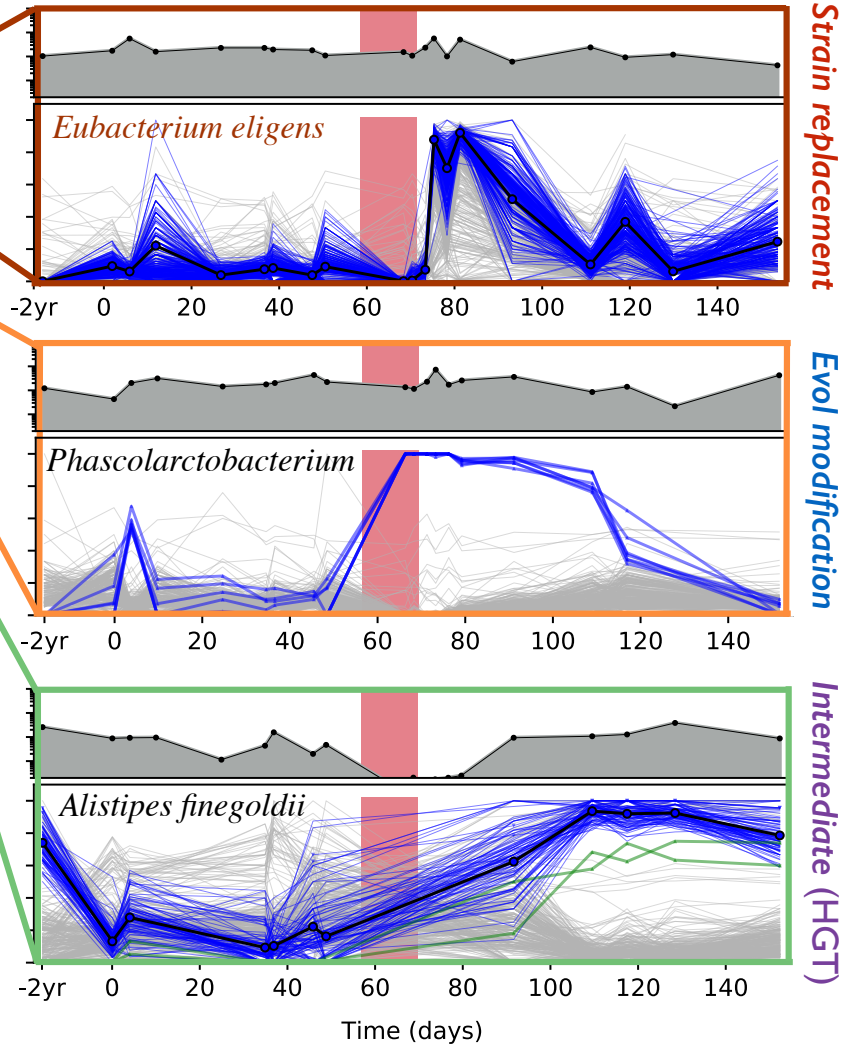

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33 other species

(18 w/ genetic changes)

Roodgar* & Good* et al (*Genome Research*, 2021)

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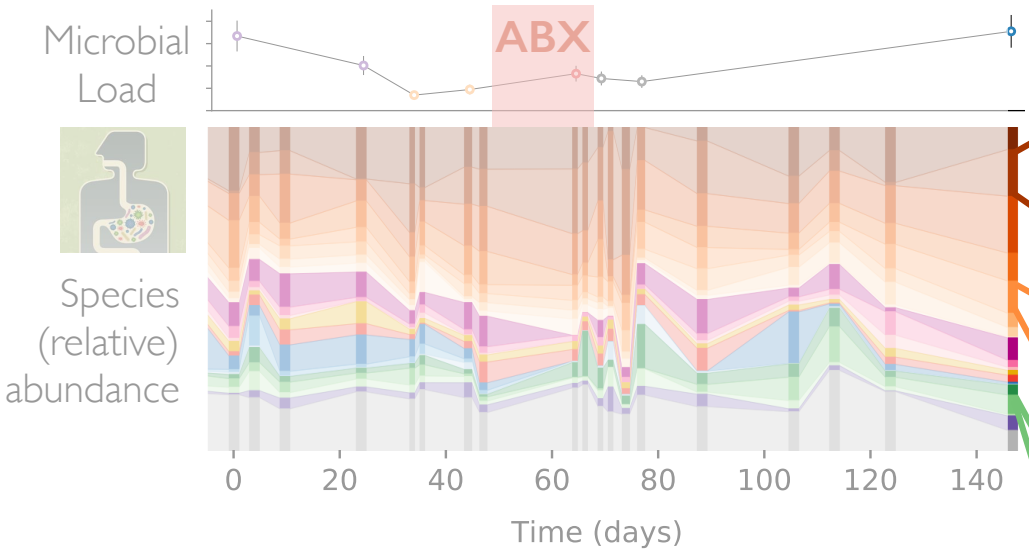

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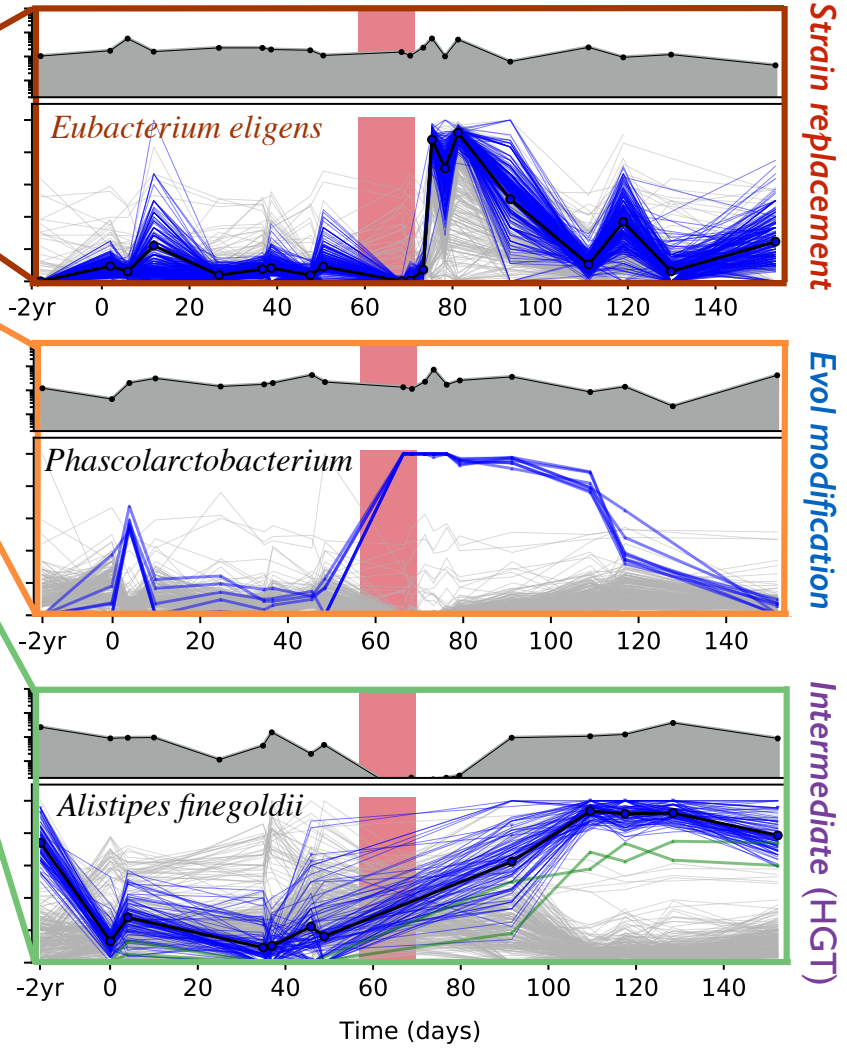

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↳ ***but not consistent with simple extinction & recolonization picture…***

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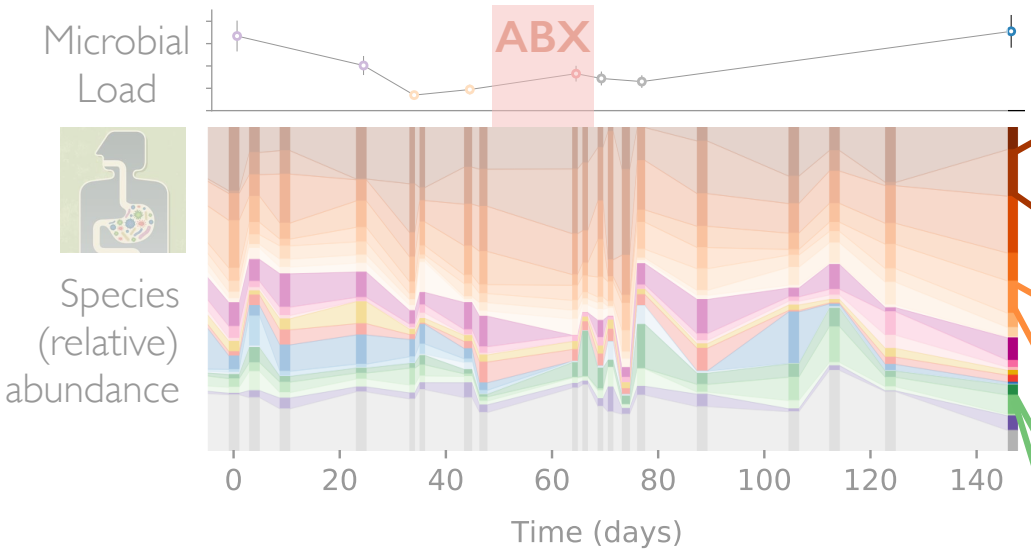
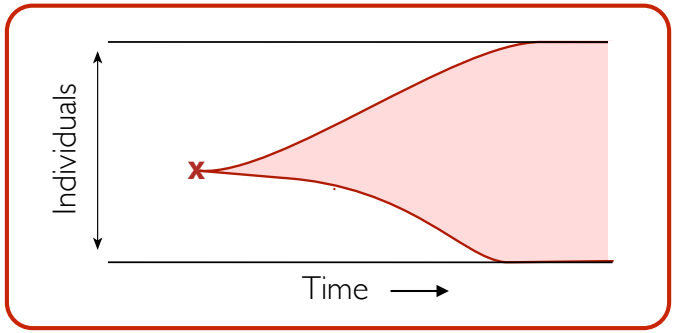


➔ ***but also inconsistent w/ simplest models of ABX resistance evolution***



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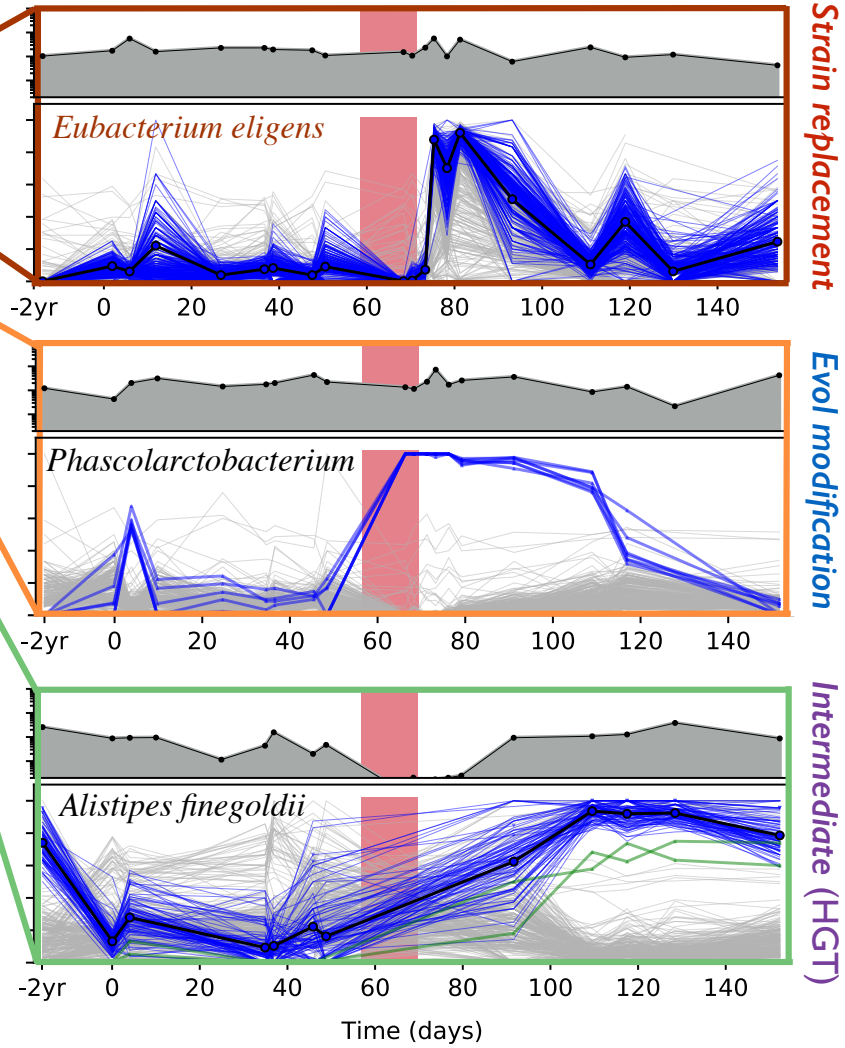

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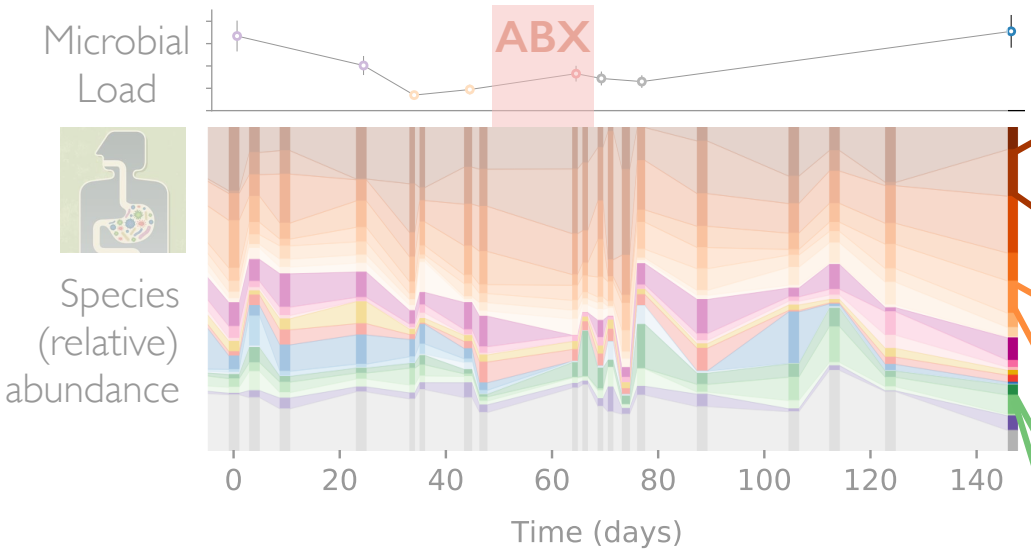

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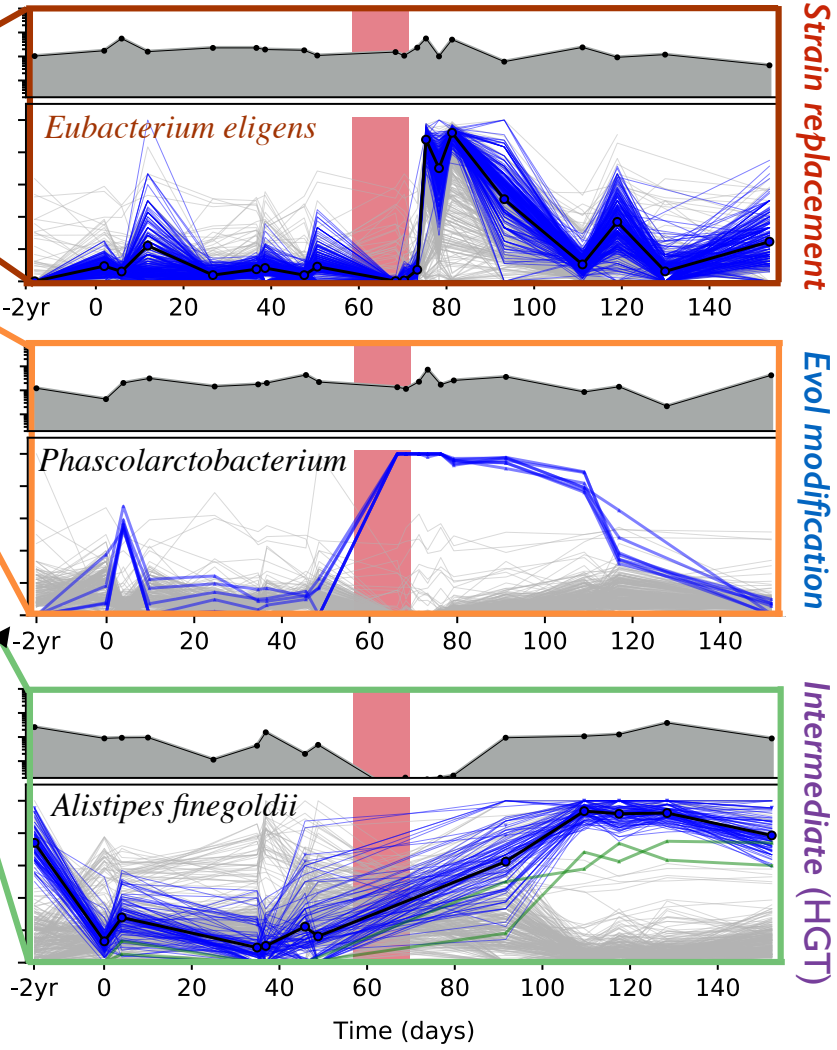

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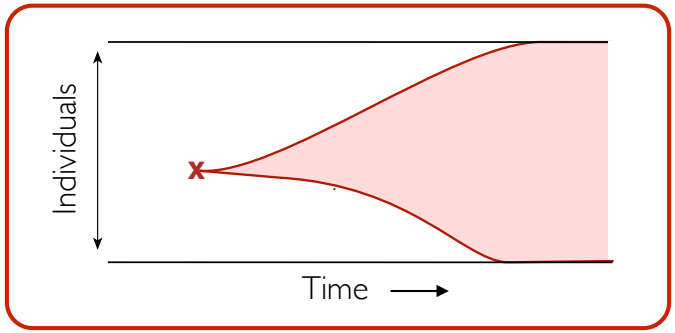

Very different from cartoon!

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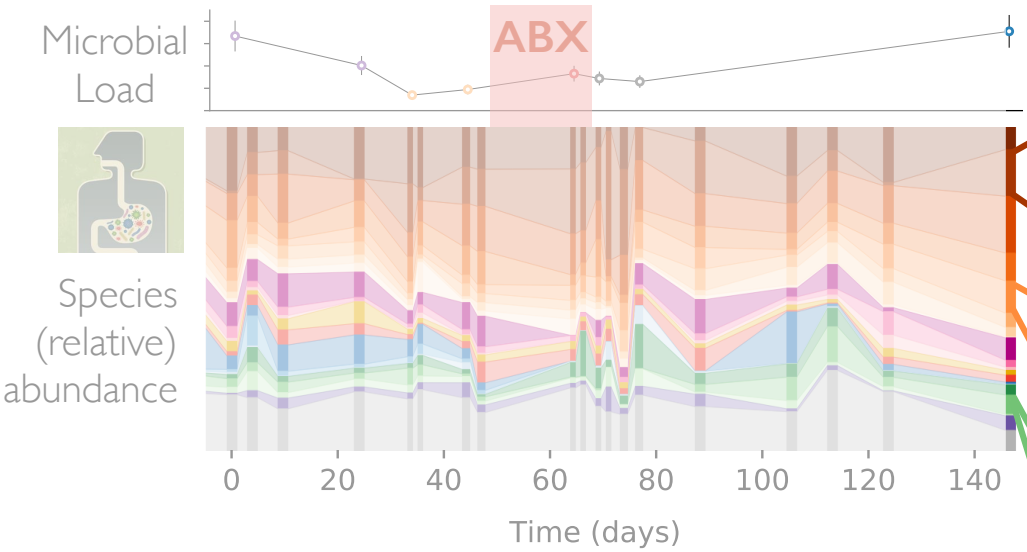

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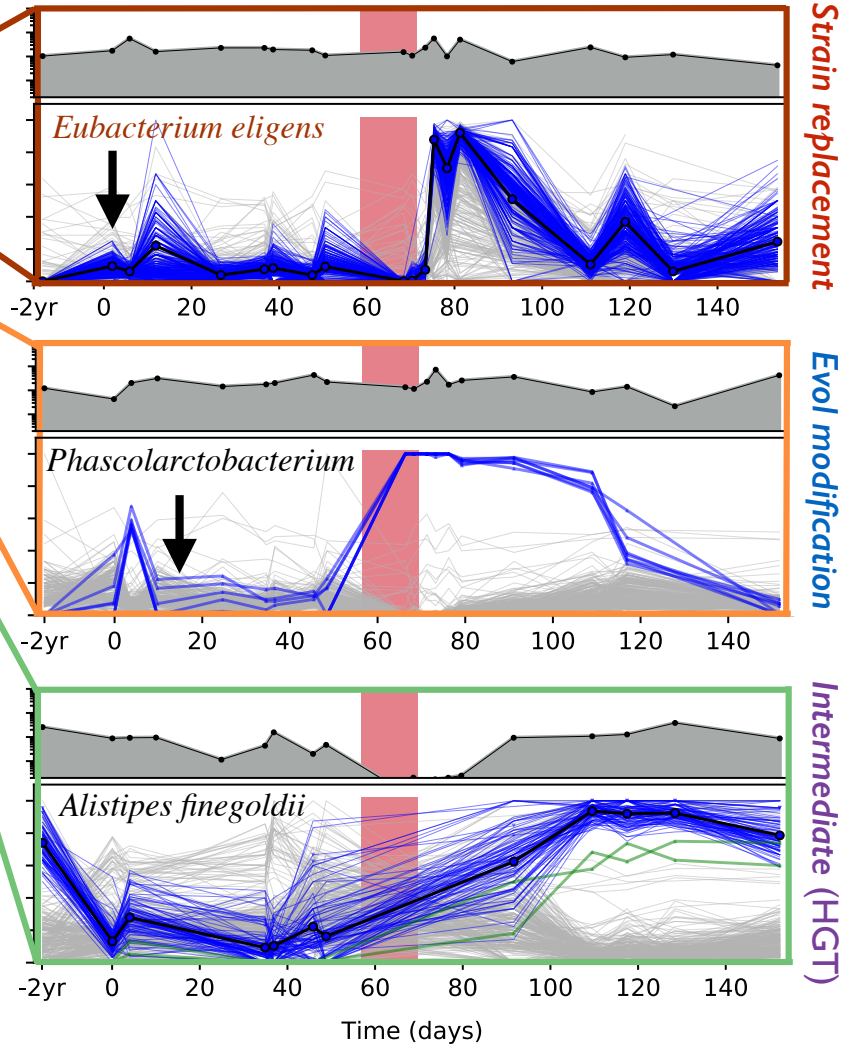

Instead, common trends:

- Sweeping variants often present at low freqs before ABX

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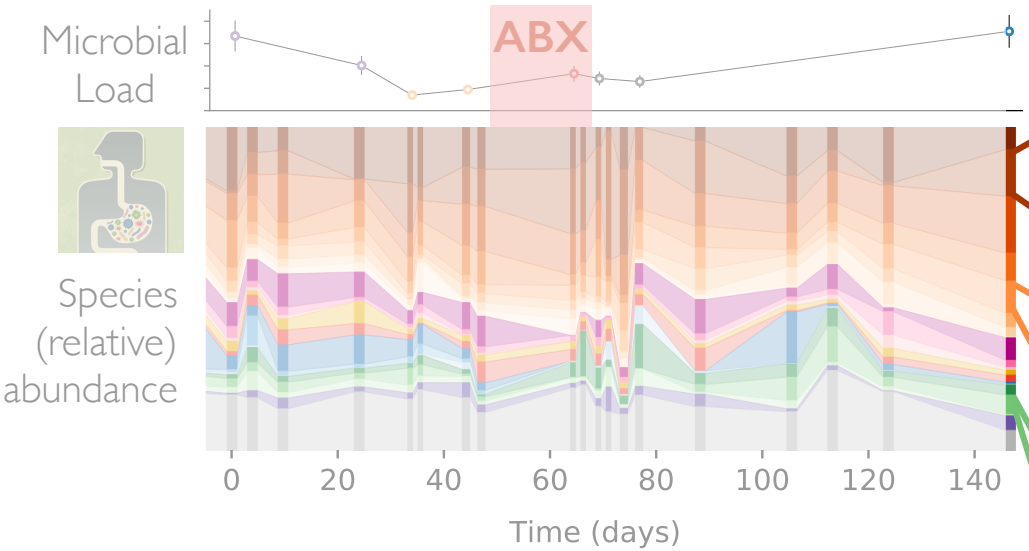

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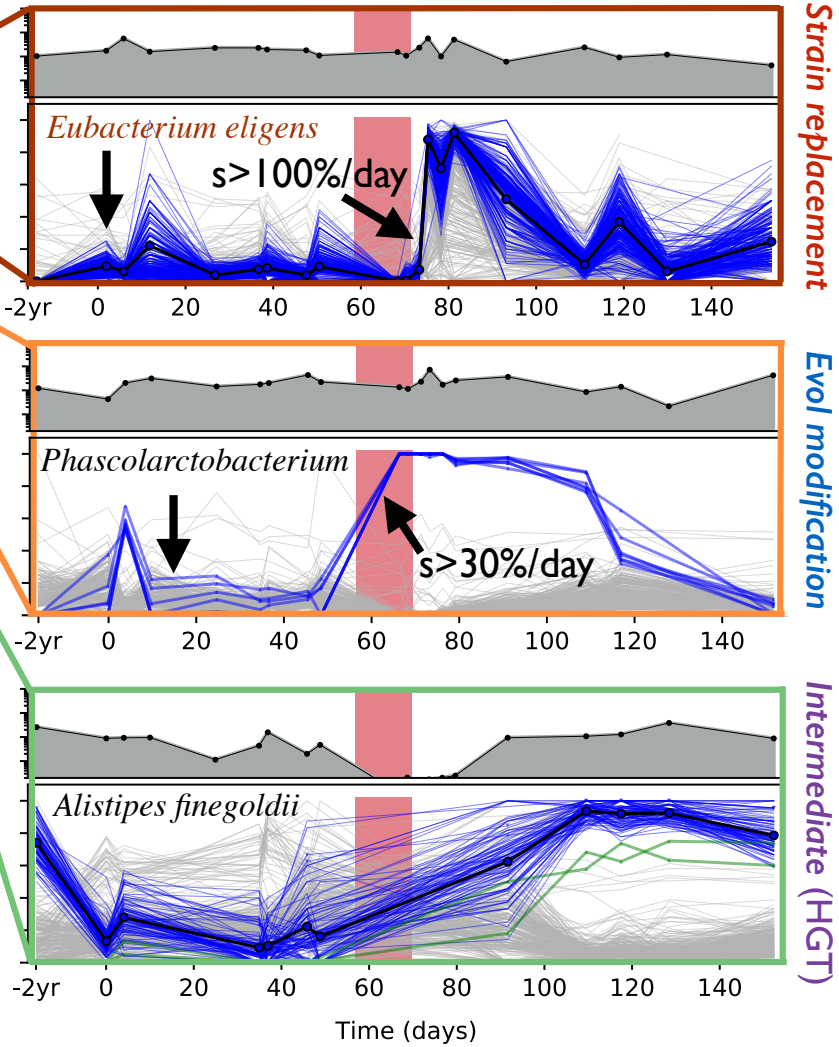

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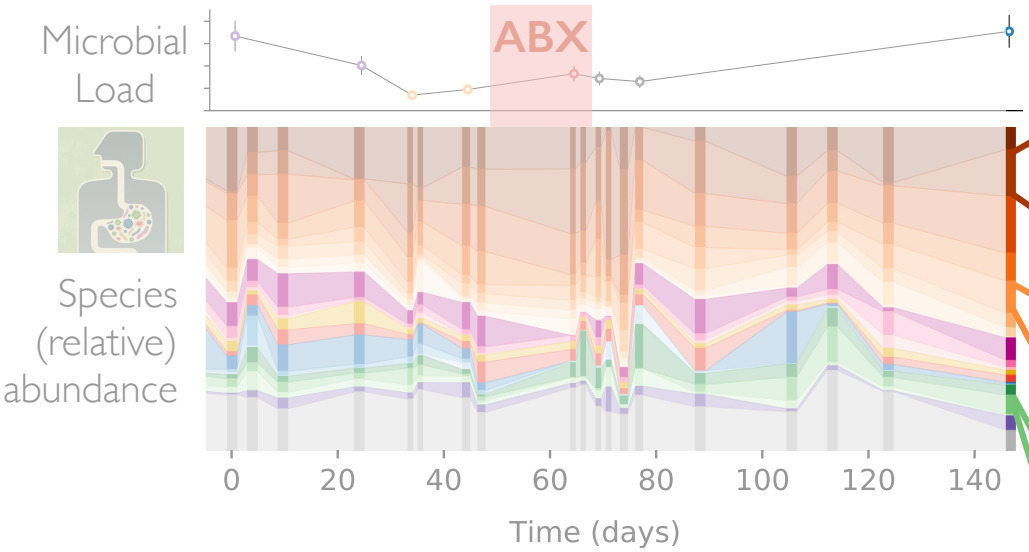

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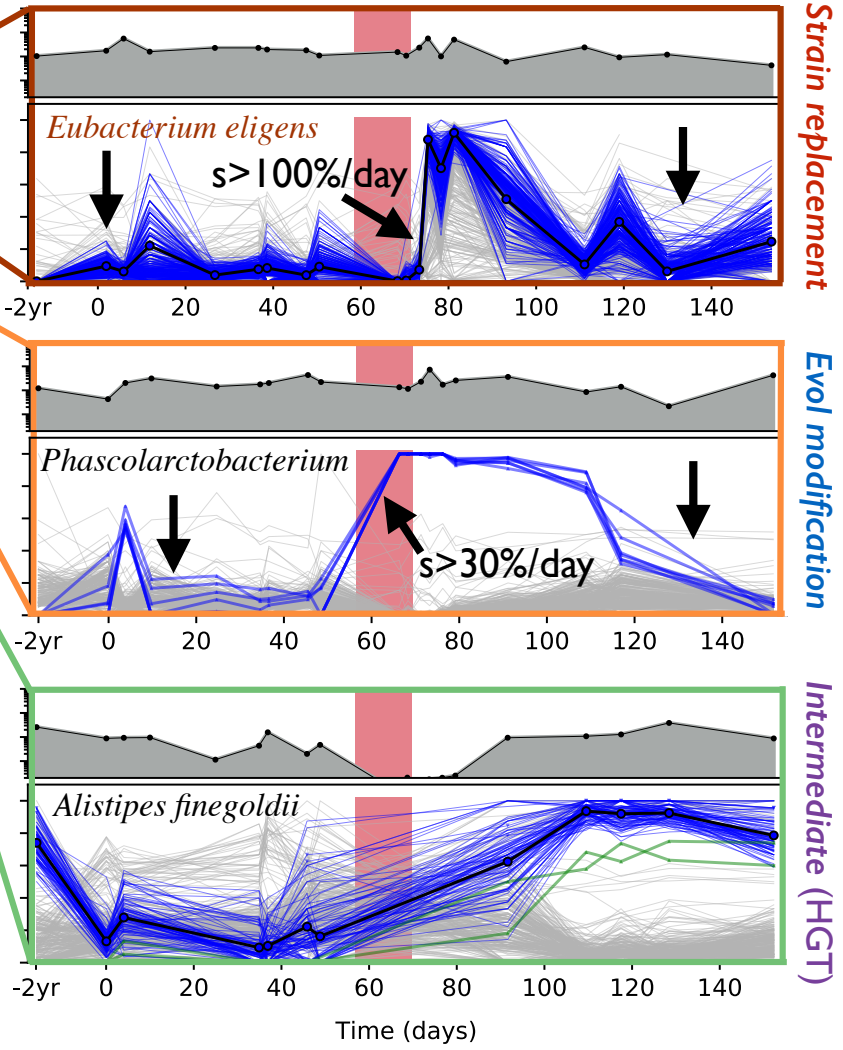

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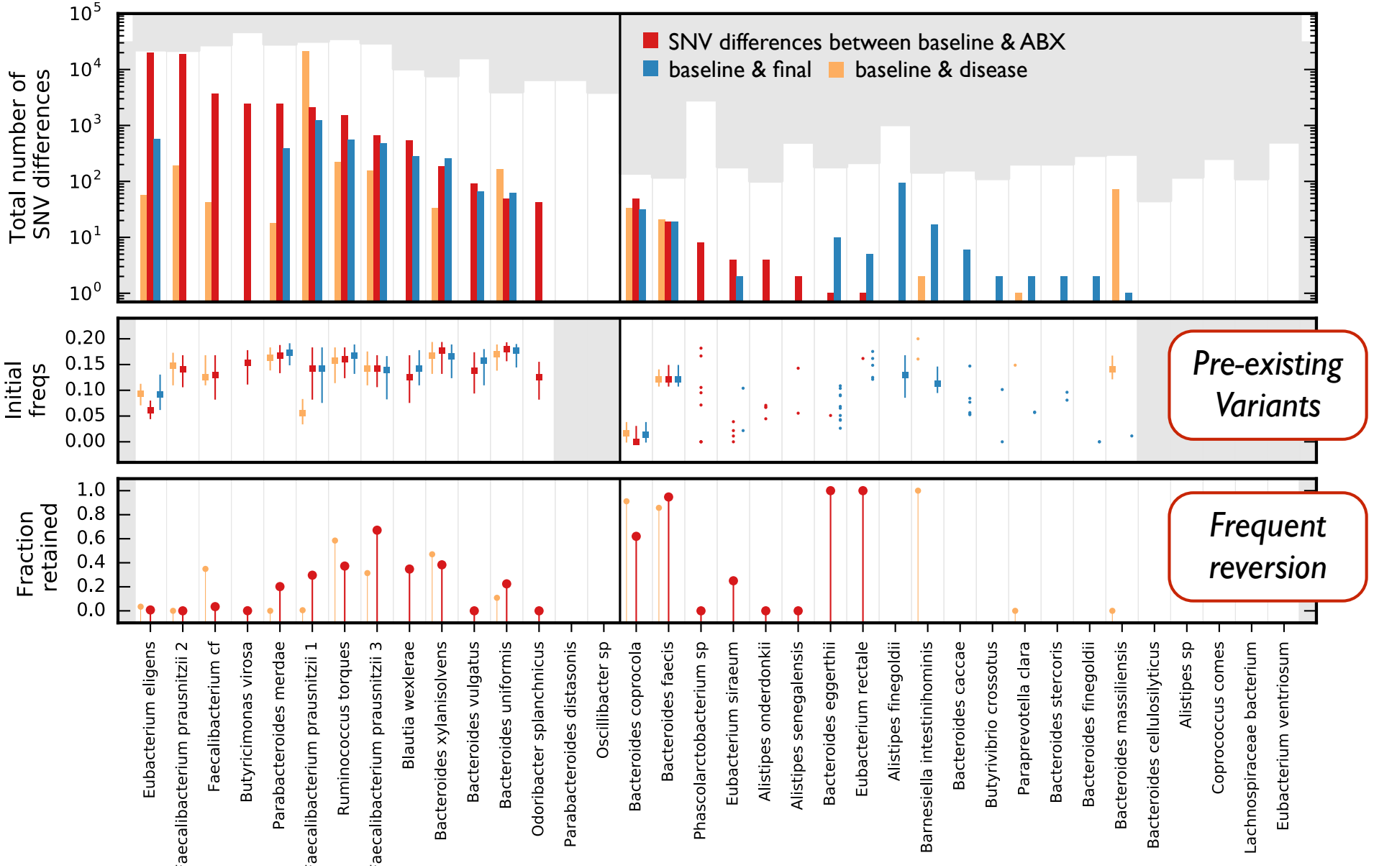
Roodgar* & Good* et al (*Genome Research*, 2021)

These trends are recapitulated across ~35 species in the community



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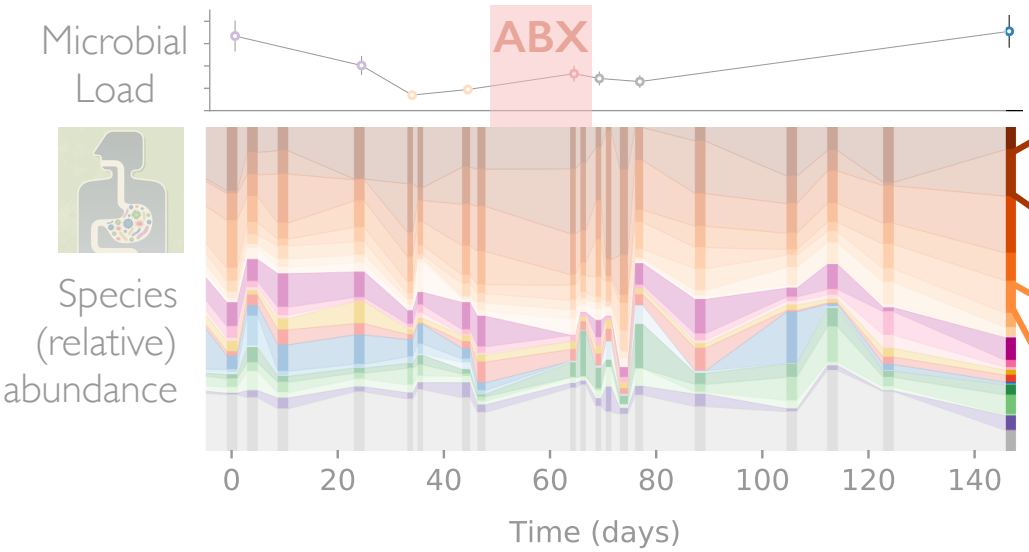

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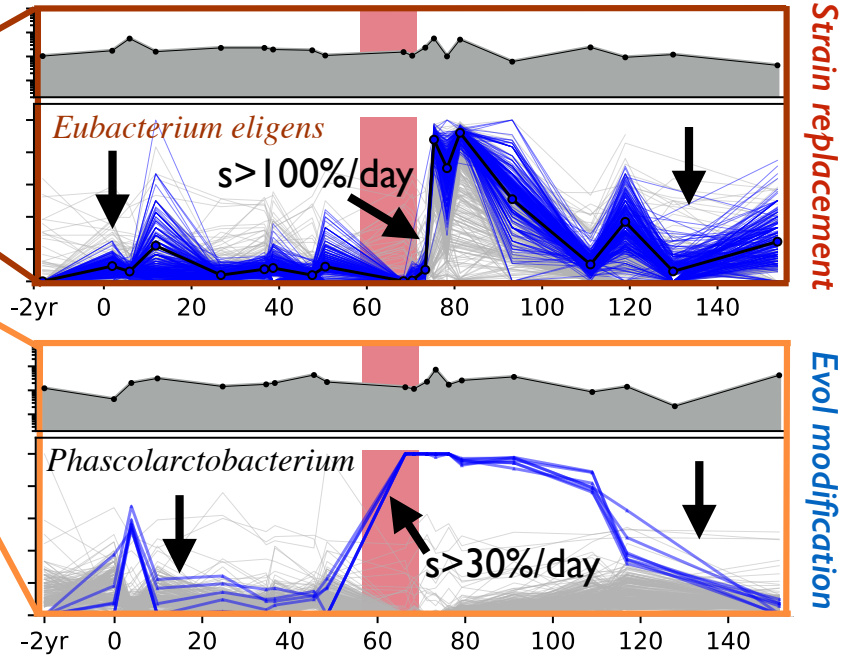

Instead, common trends:

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→

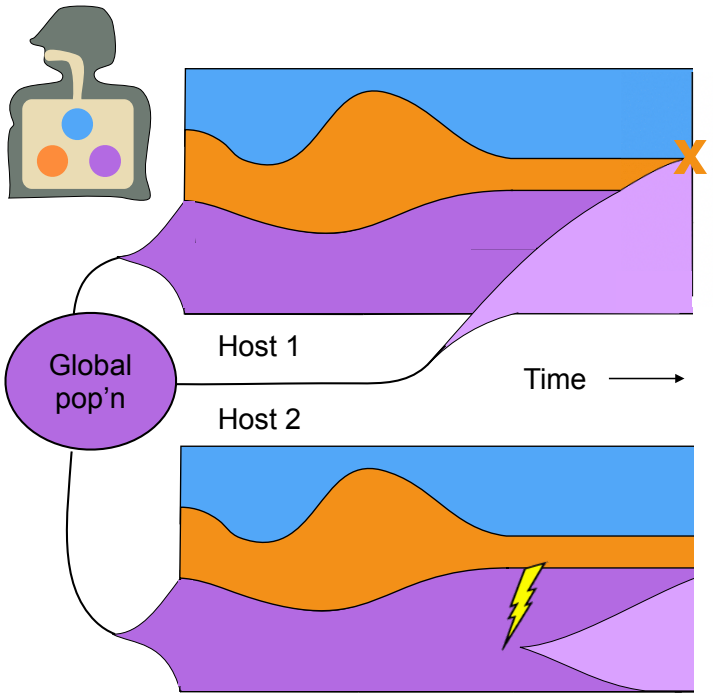
Evidence for add'l ecological structure within species in this complex community?

+ 34 other species (19 w/ genetic changes)

See also: Zhao* & Liberman* et al (*Cell Host & Microbe*, 2019)

Roodgar* & Good* et al (*Genome Research*, 2021)

Next steps: does *evolution* alter *ecological structure* of gut microbiota?



Layton Rosenfeld
Undergrad BioX Fellow

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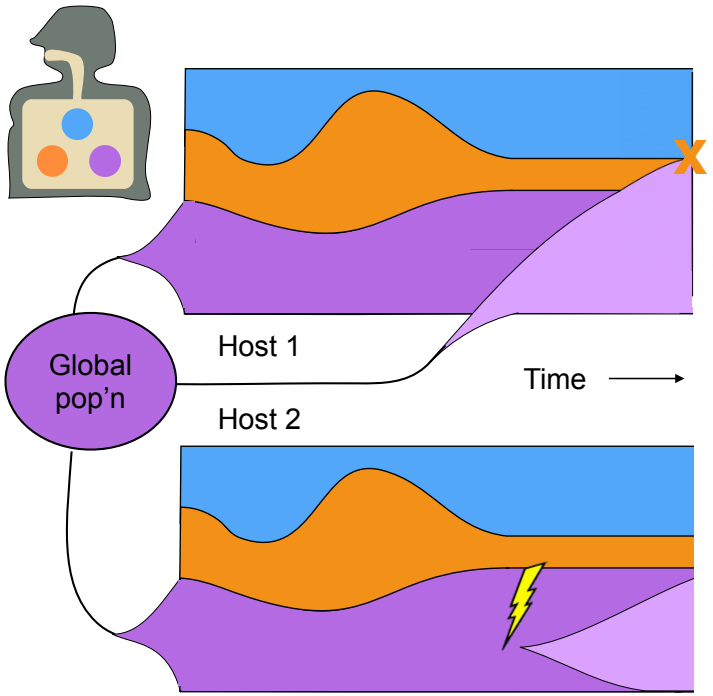

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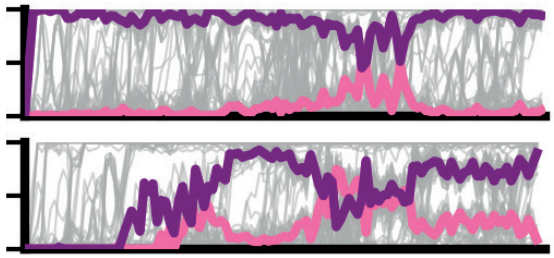
Good*, McDonald* et al (*Nature*, 2017)



Like Lenski's LTEE?

Layton Rosenfeld
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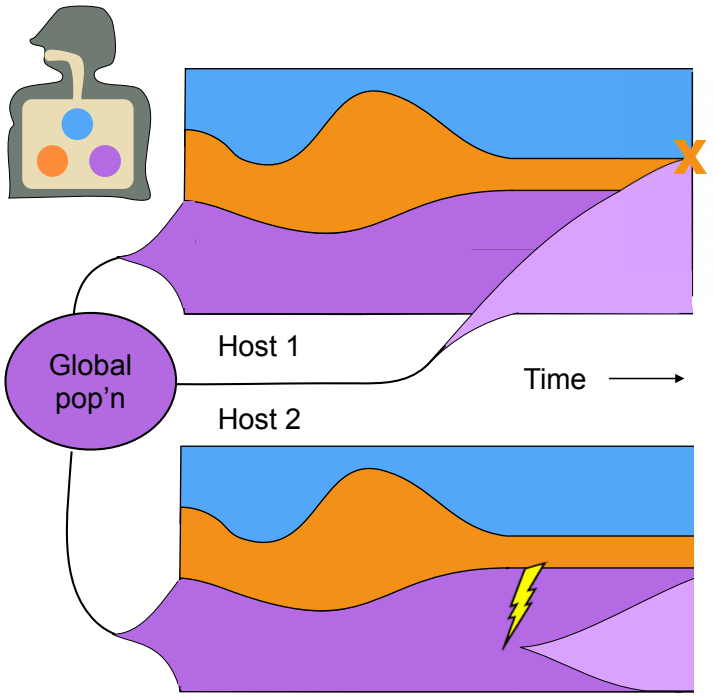

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vs

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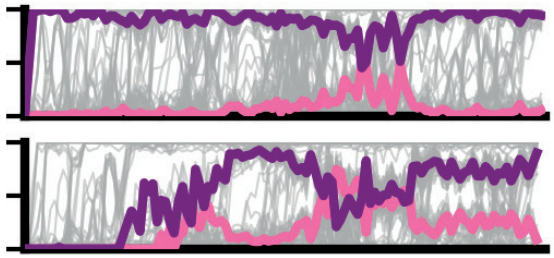

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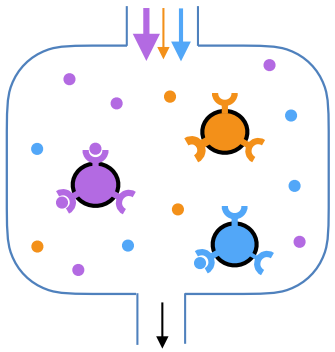
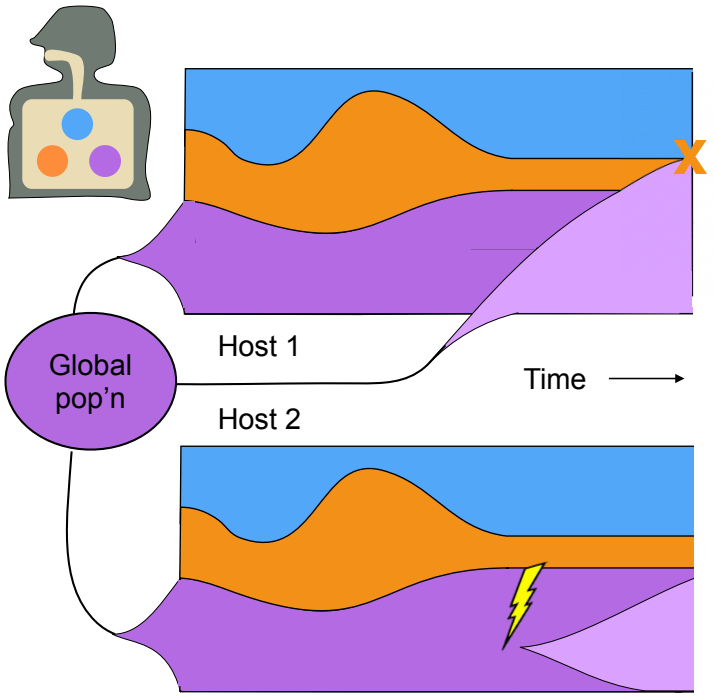


Separate ecological "niches"?

Layton Rosenfeld
Undergrad BioX Fellow

Next steps: does *evolution* alter *ecological structure* of gut microbiota?



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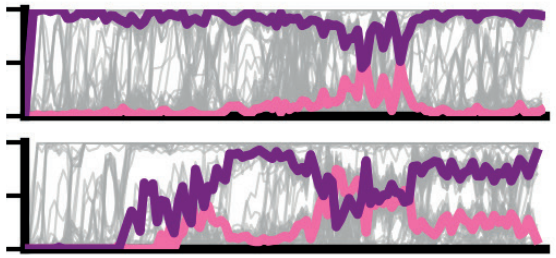

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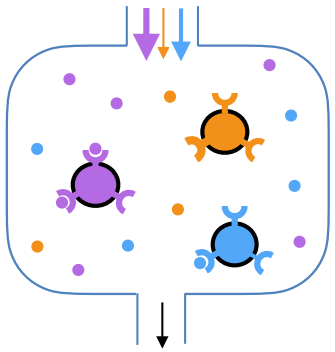

Separate ecological "niches"?

Challenge: a few known examples, but ***global impact*** difficult to quantify due to extensive ***heterogeneity*** (hosts, species, mut's)

Layton Rosenfeld
Undergrad BioX Fellow

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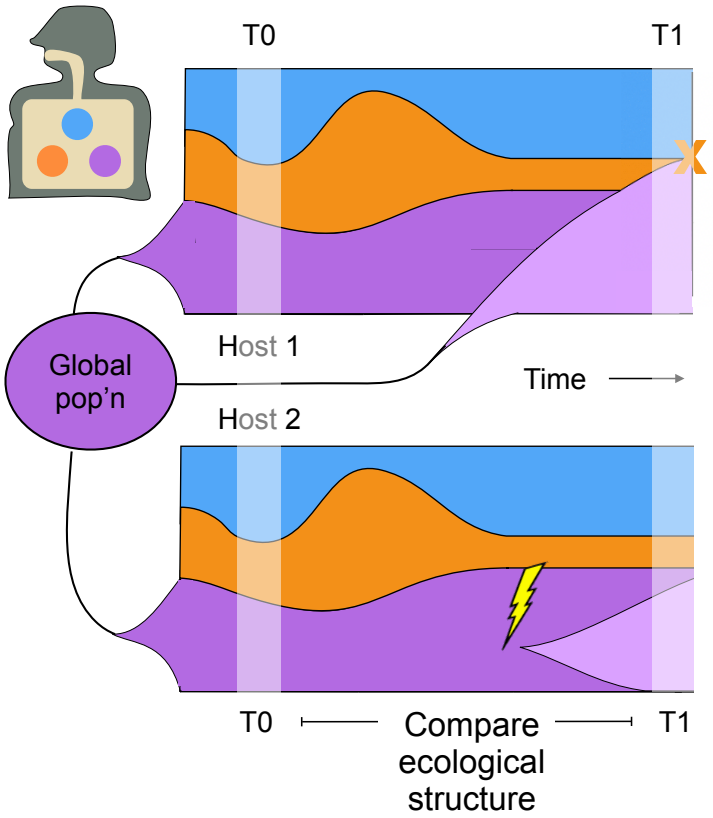
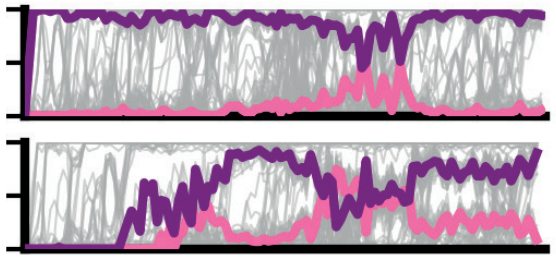


?

vs

?

Good*, McDonald* et al (*Nature*, 2017)



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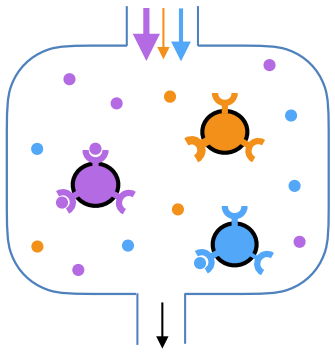

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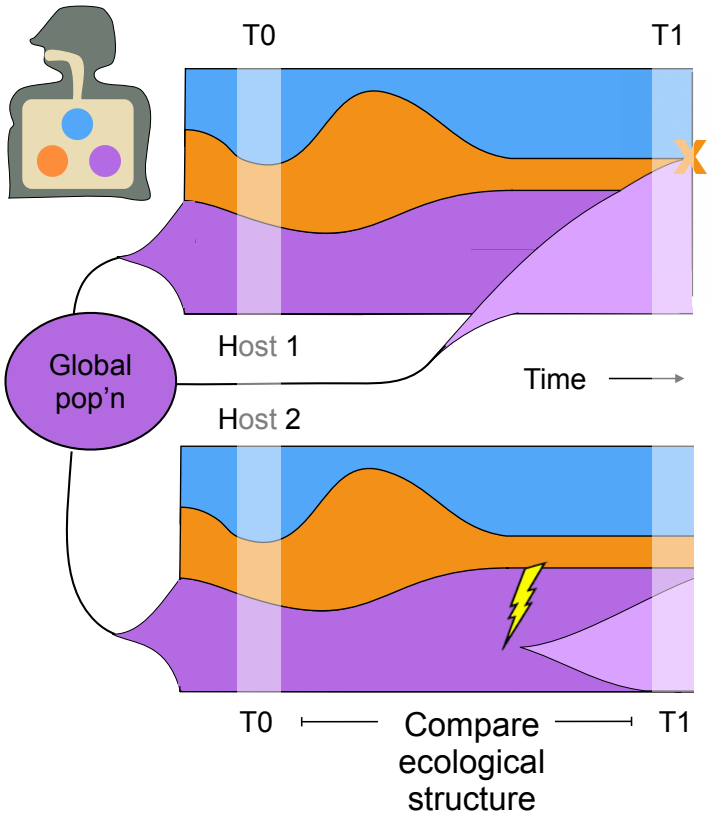
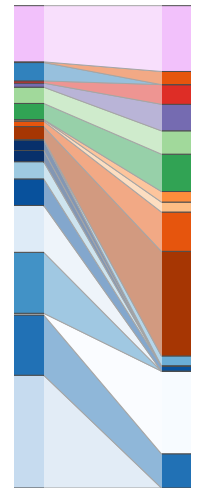


Example Host 1:
2 ***replacement events*** w/in species



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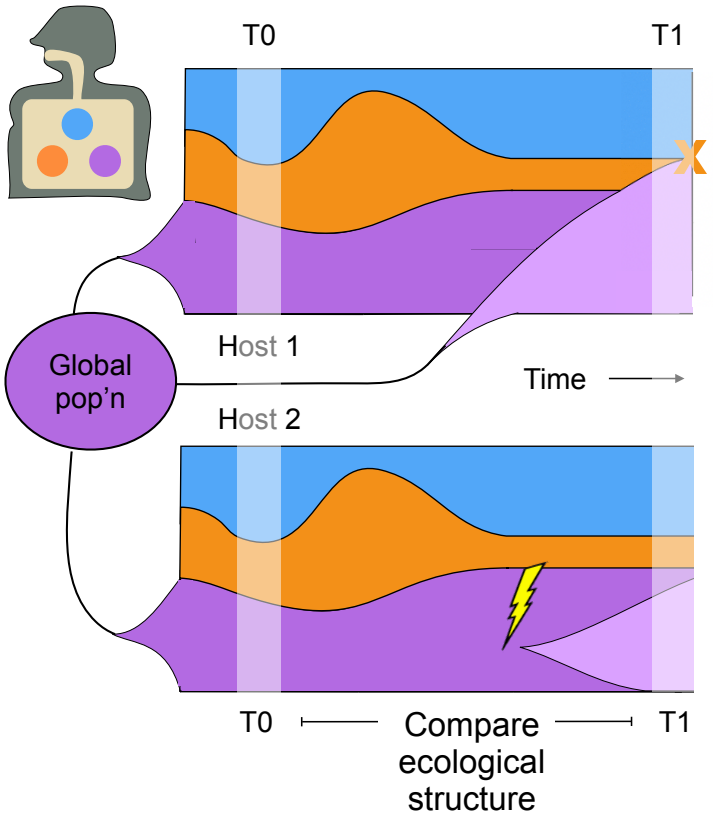

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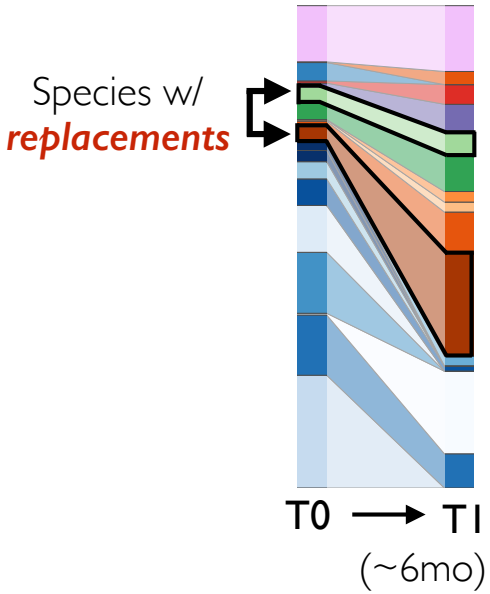

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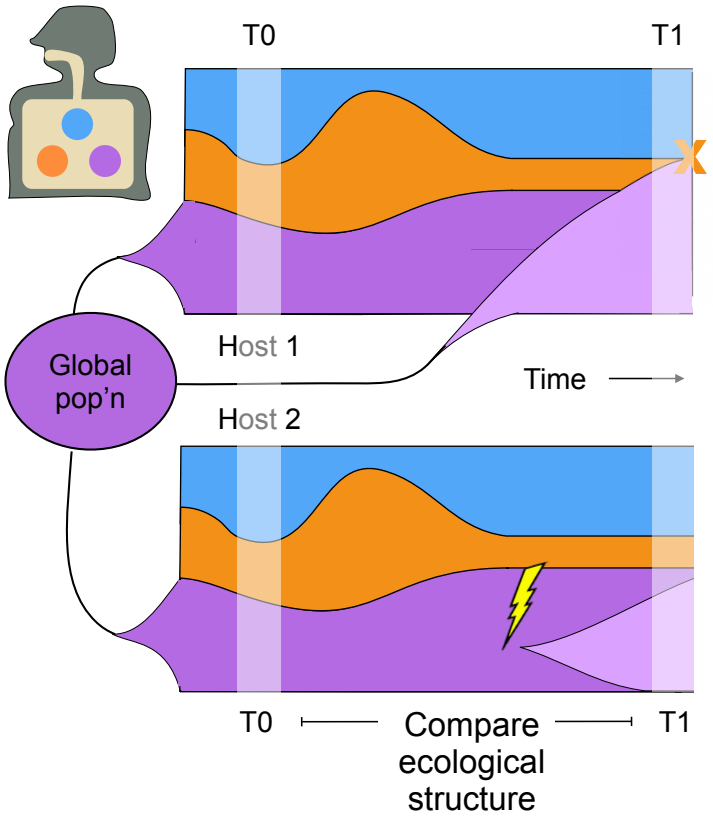

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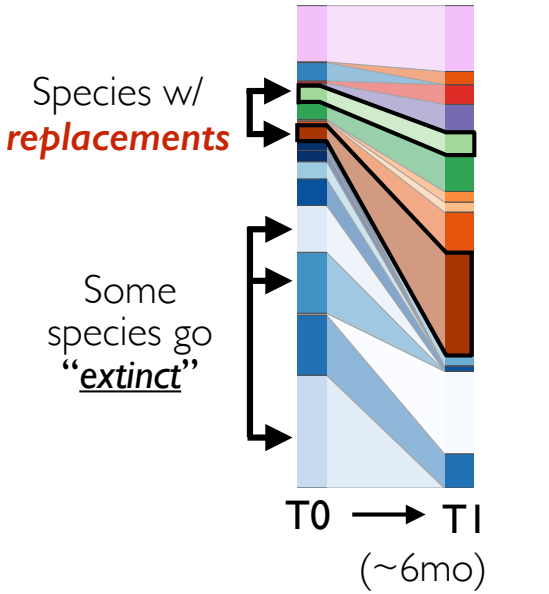

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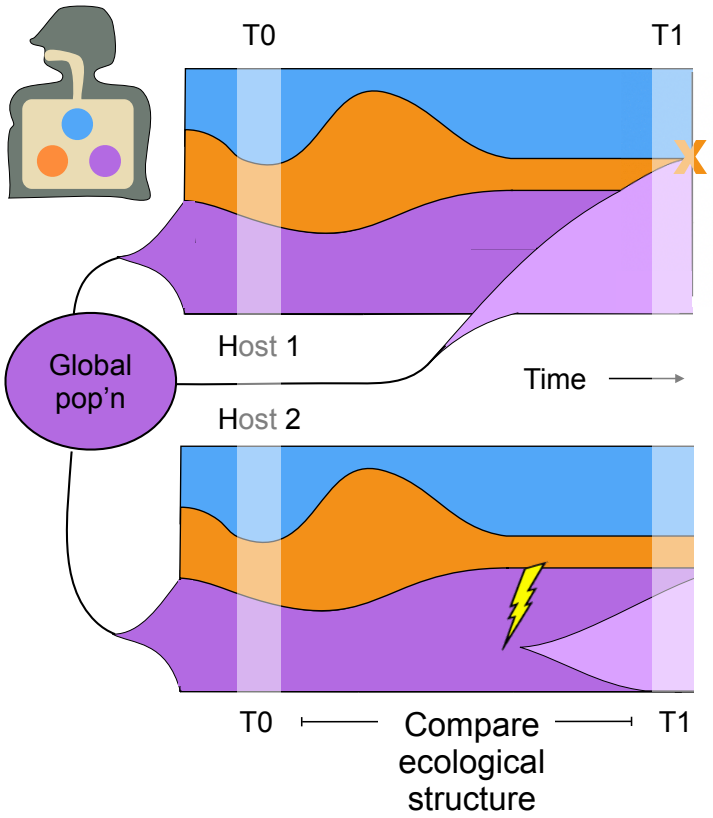

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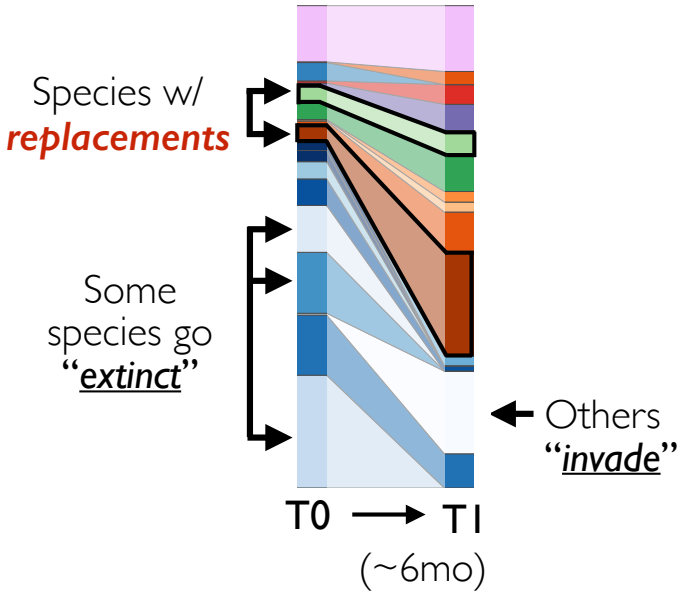

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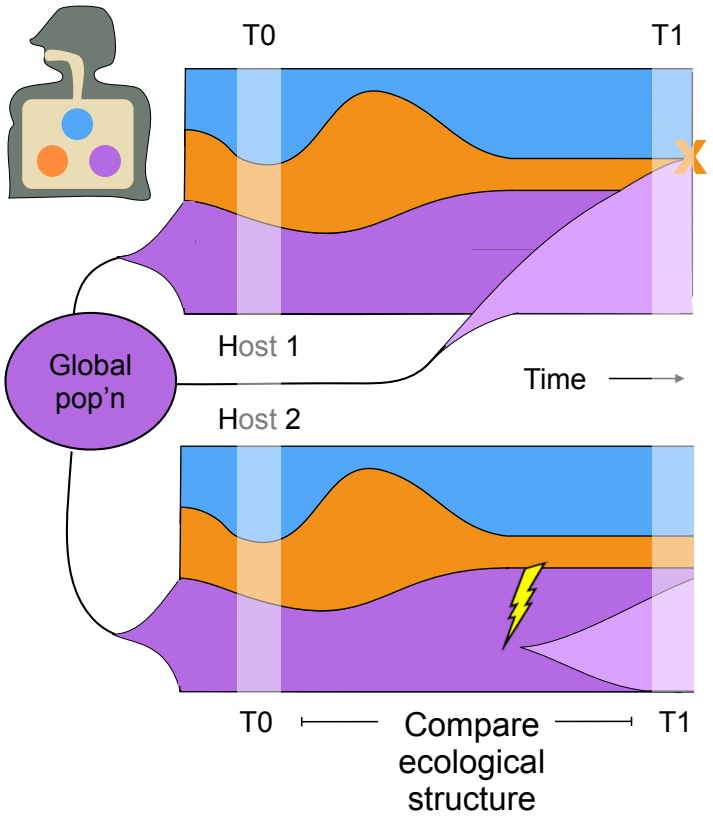

Example Host 1:
2 ***replacement events*** w/in species

Species w/ ***replacements***

Some species go "***extinct***"

Others "***invade***"

T0 → T1
(~6mo)

Example Host 2:
No genetic changes w/in species

T0 → T1
(~6mo)

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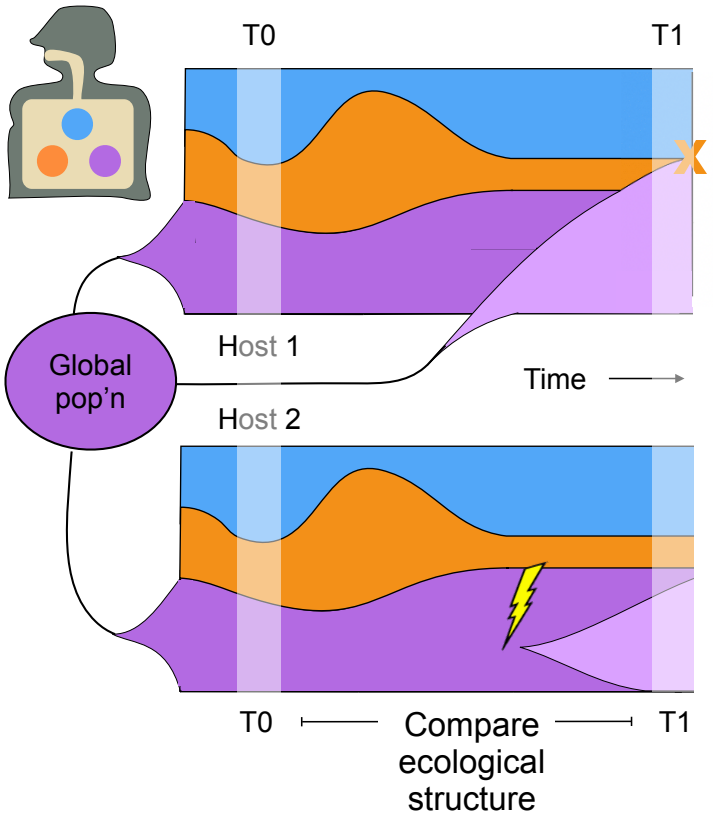

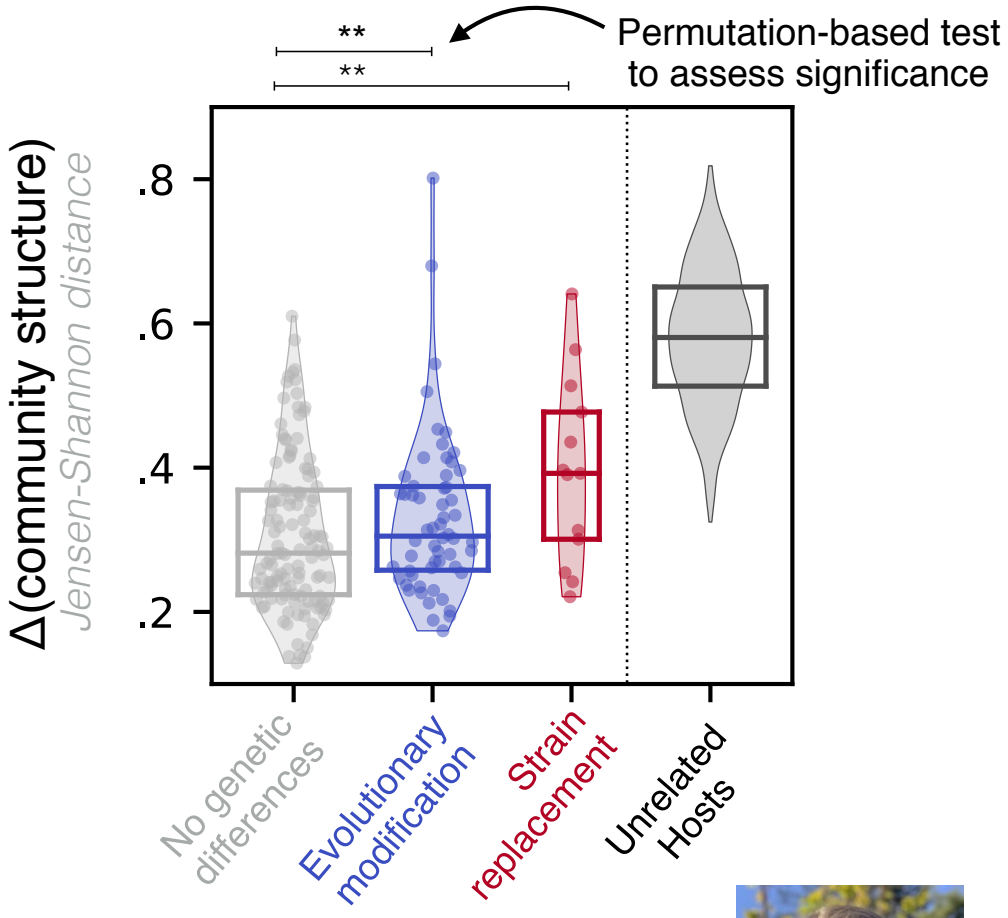

Preliminary evidence that ***genetic changes w/in species*** are ***statistically associated*** w/ larger ***shifts in species composition***

Layton Rosenfeld
Undergrad BioX Fellow

Permutation tests to quantify eco-evolutionary correlations

Observed data

Species w/ ***genetic changes***

Host 1: **Host 2:** **Host n:**

T0 → T1 T0 → T1 T0 → T1

Shuffle genetic events across (eligible) hosts

Fake data (null model)

Host 1: **Host 2:** **Host n:**

T0 → T1 T0 → T1 T0 → T1

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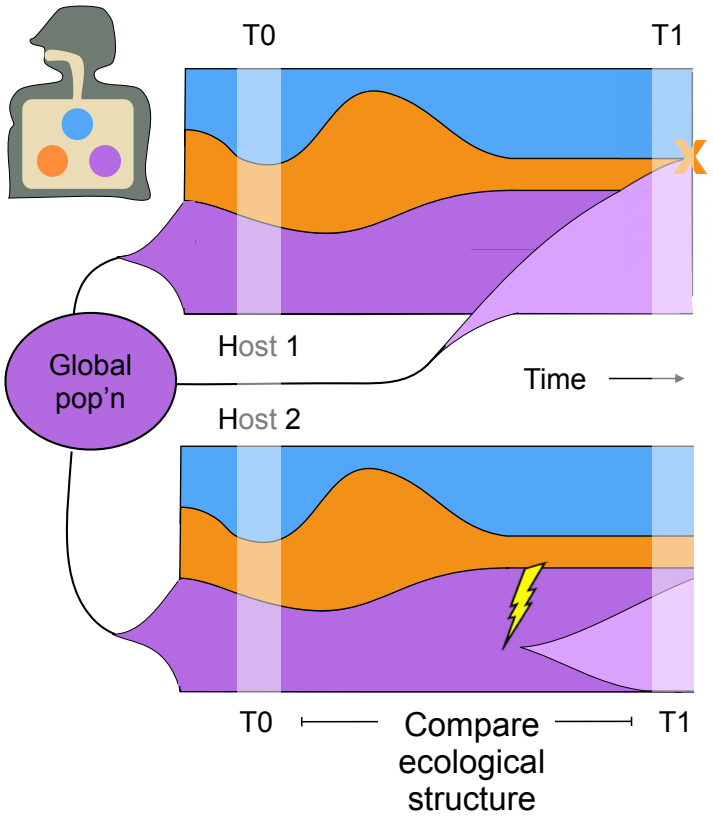
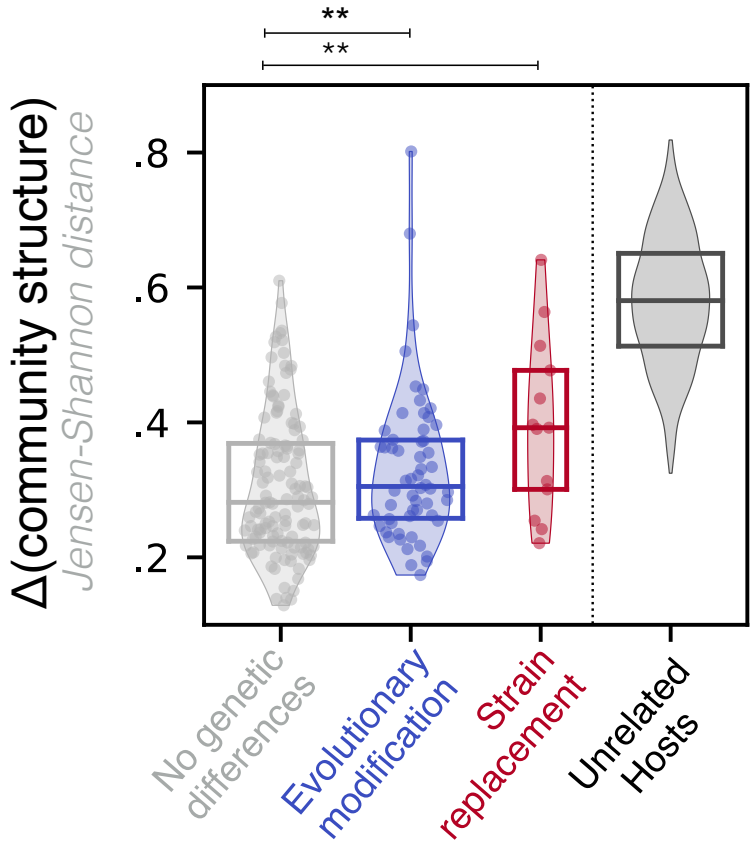
Undergrad BioX Fellow

Genetic turnover w/in species is associated with larger shifts in the species-level composition of the gut microbiota





But, changes in ***community structure*** not solely driven by frequency increases in ***focal species***

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Undergrad BioX Fellow

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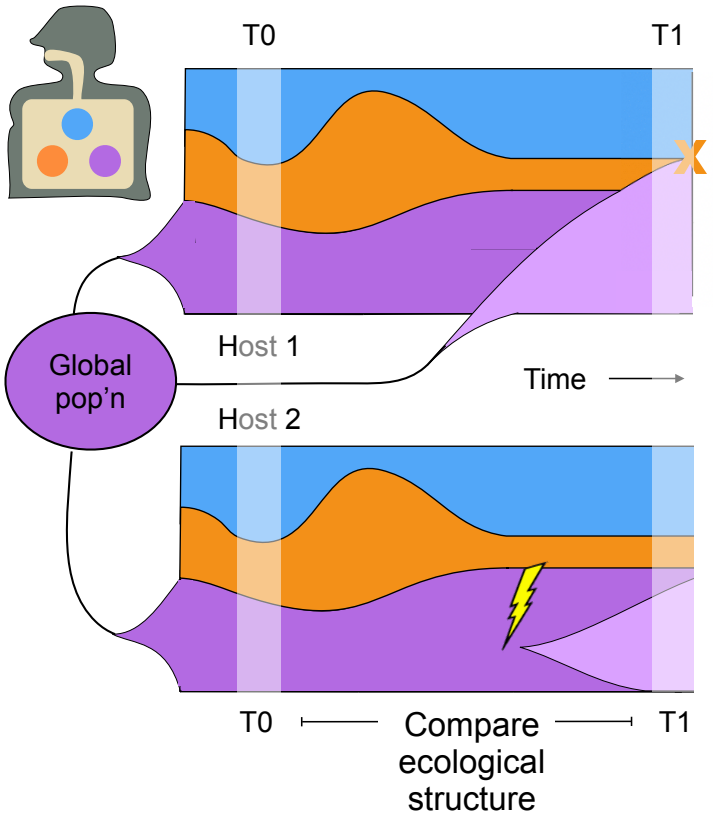

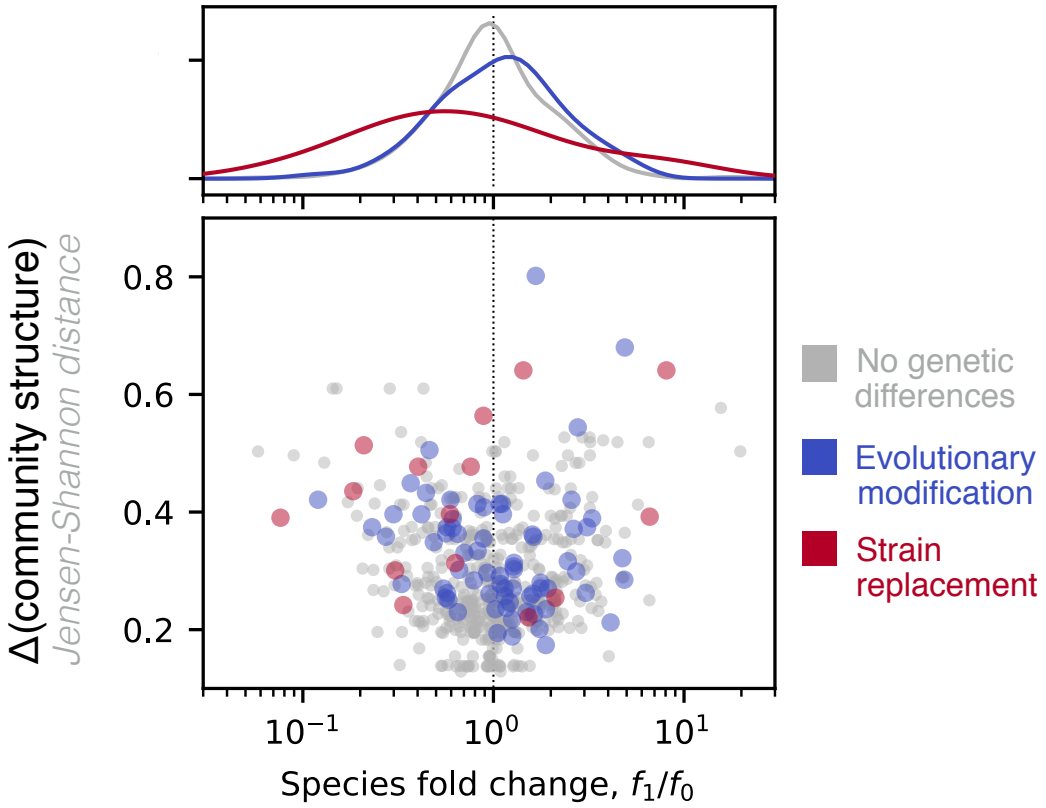

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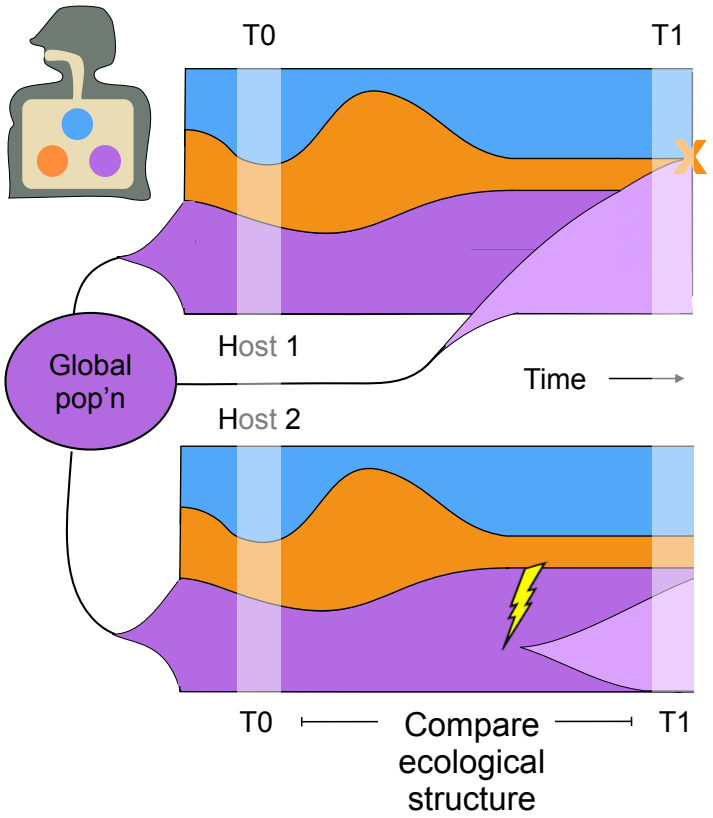

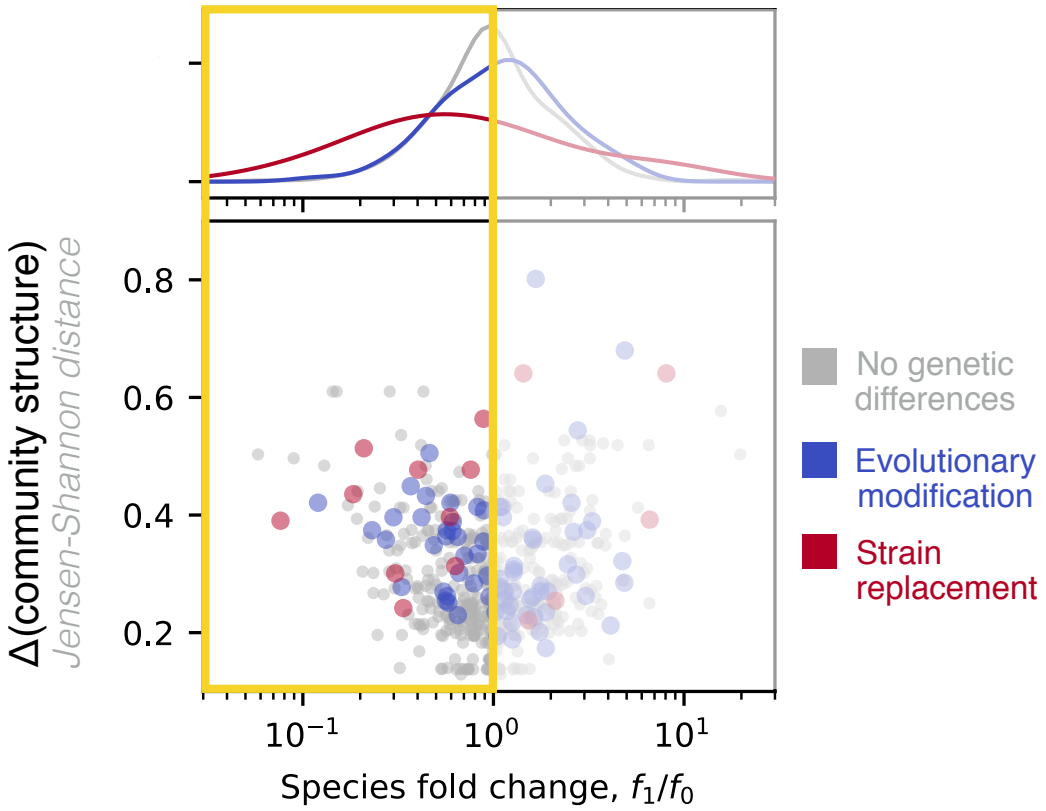

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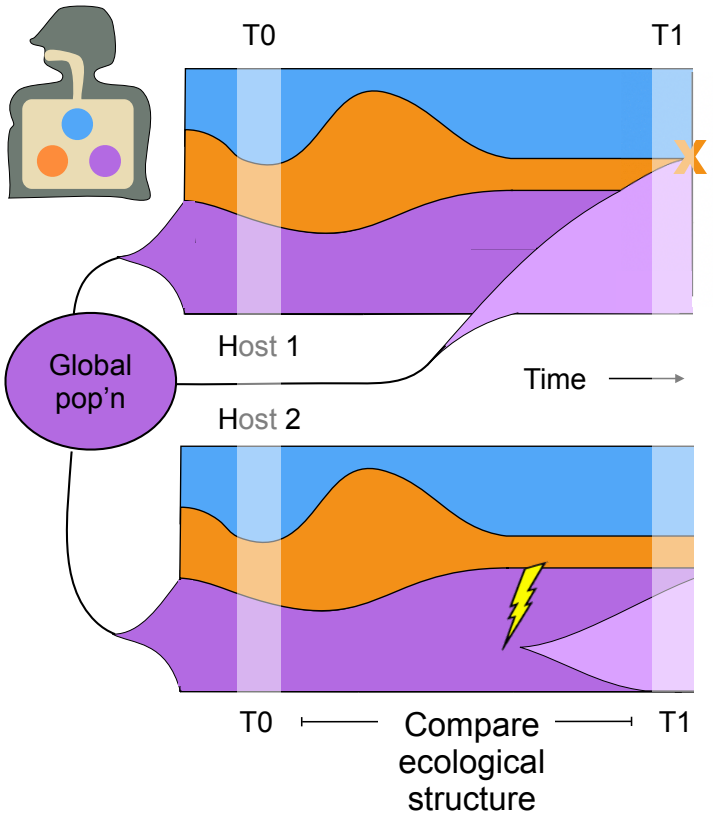

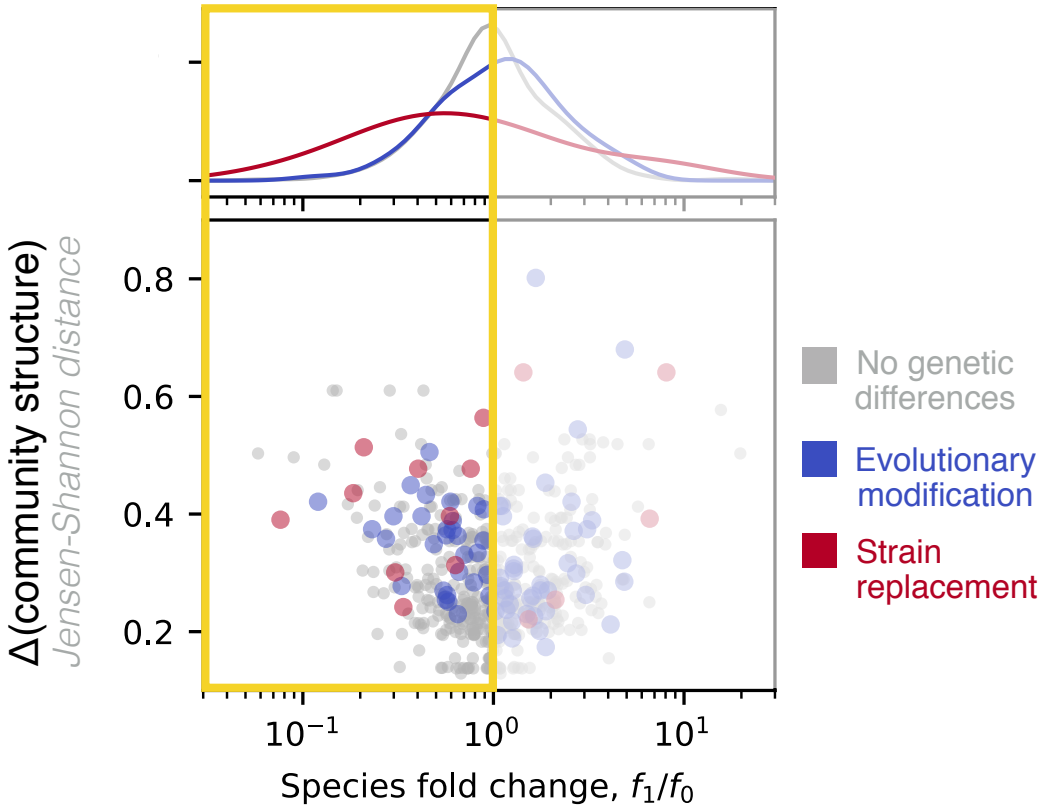

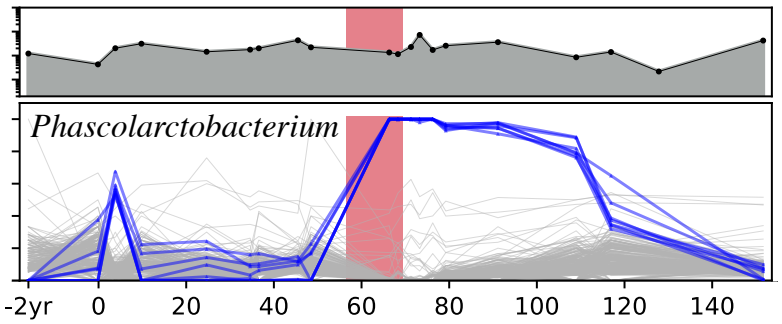

Similar to ABX timecourse

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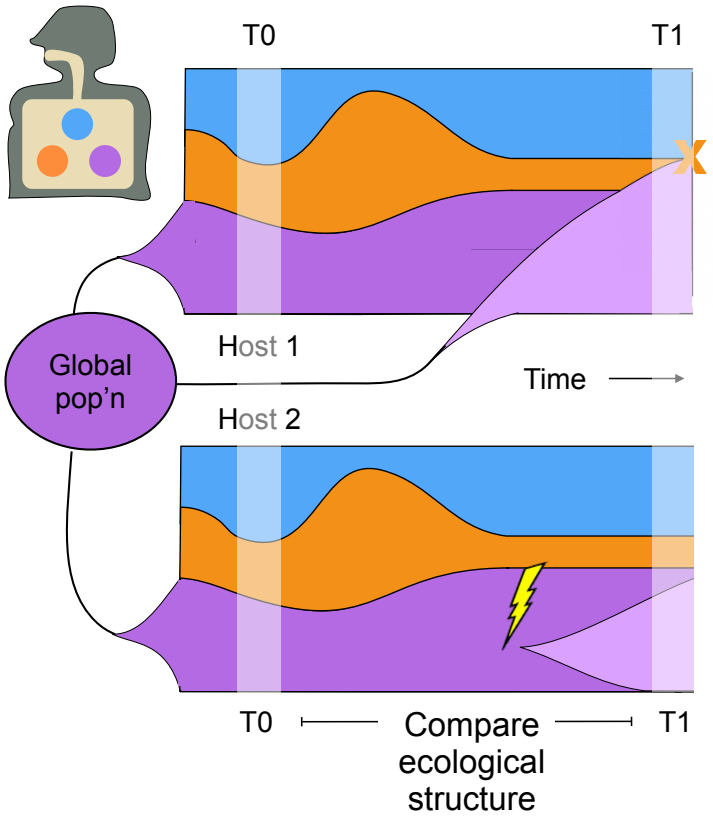
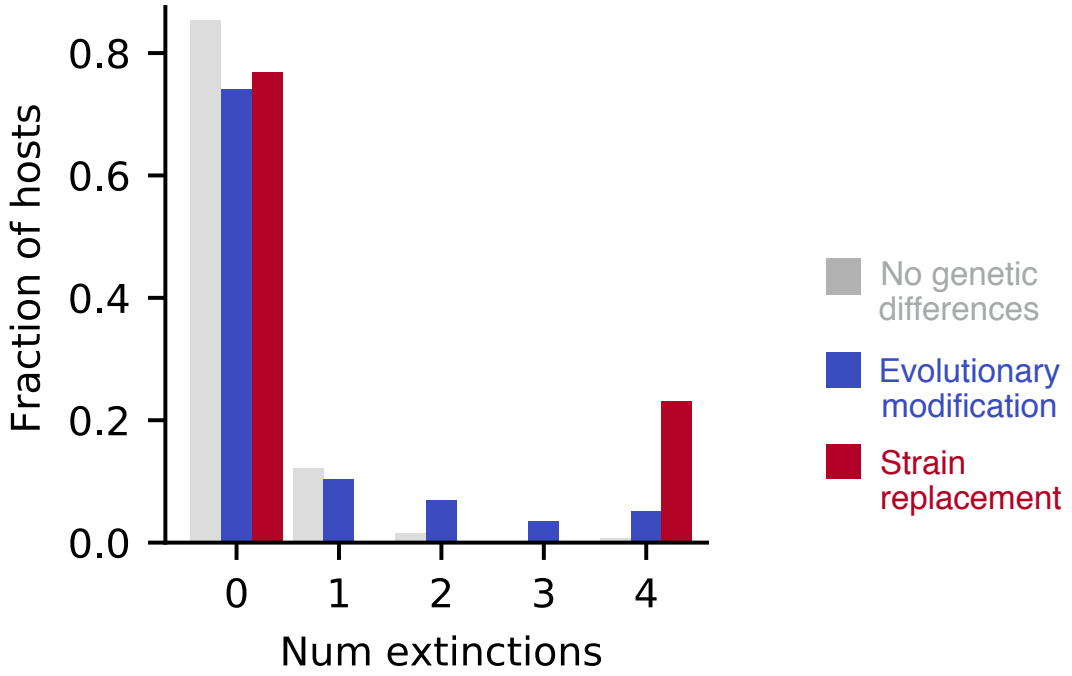
Genetic turnover w/in species is associated with larger shifts in the species-level composition of the gut microbiota





Genetic turnover w/in species is associated with more frequent ***extinction events in other species*** (even if ***focal species*** declines)

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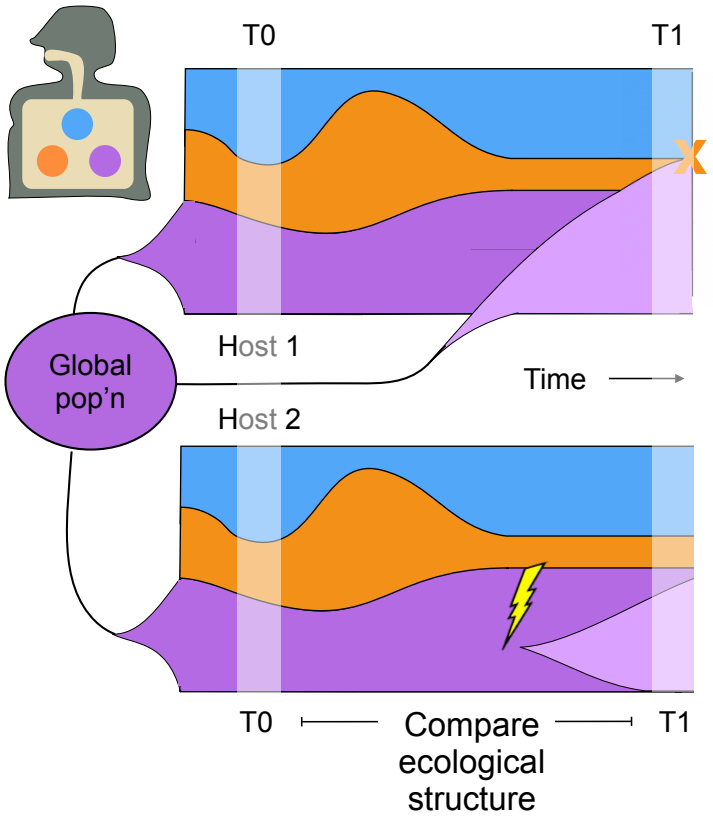

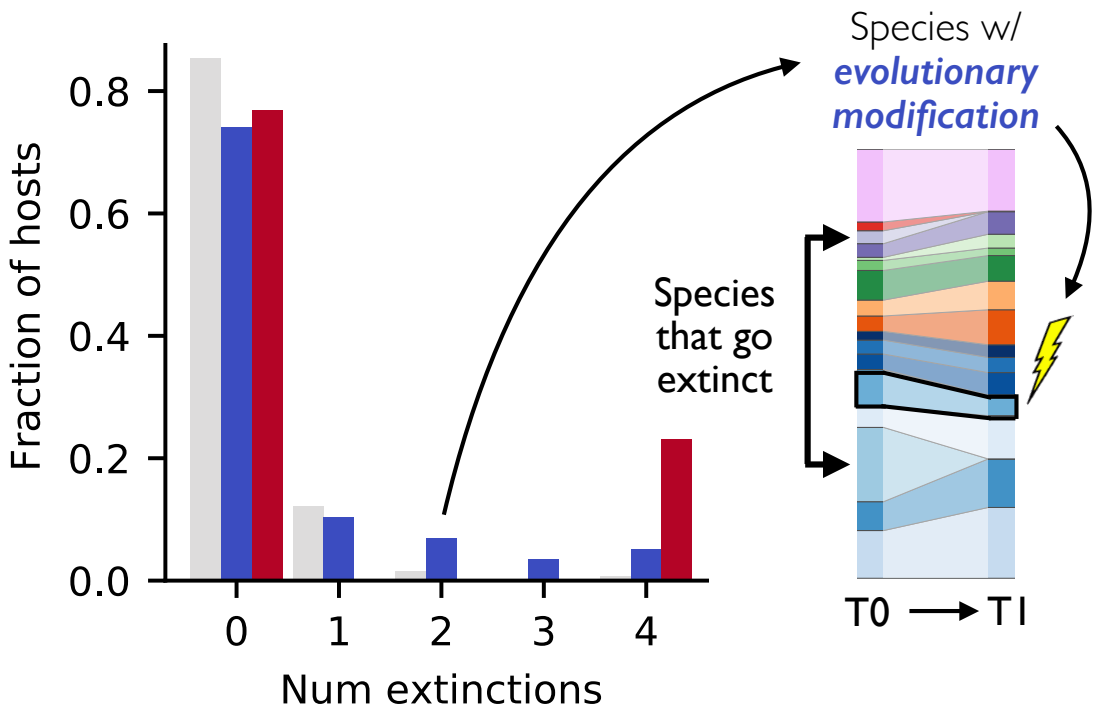

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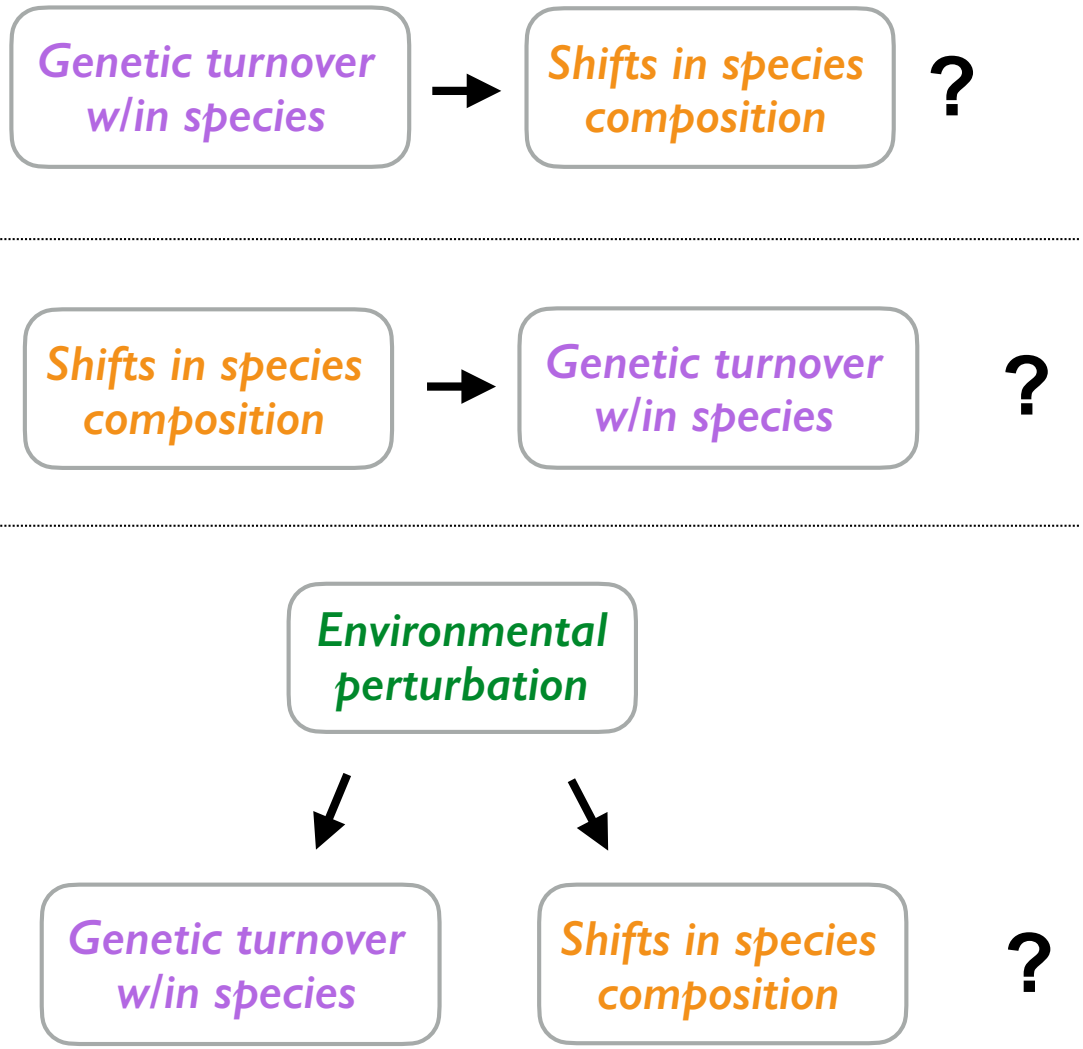
Next steps: does *evolution* alter *ecological structure* of gut microbiota?

Possible causal scenarios:



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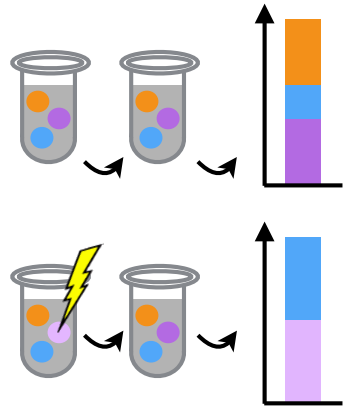
Genetic turnover w/in species → *Shifts in species composition* ?

Shifts in species composition → *Genetic turnover w/in species* ?

Environmental perturbation → *Genetic turnover w/in species*, *Shifts in species composition* ?

1. Replay experiments
w/ synthetic communities



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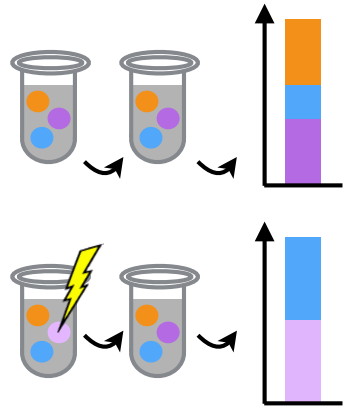
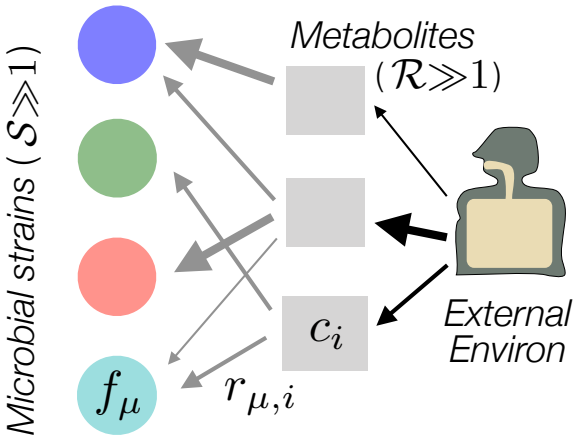


2. Theory: do similar behaviors emerge in simple models where interactions are known?

Some qualitative features can be recapitulated by simple resource competition models evolving in the high diversity limit



$$\partial_t \log f_\mu = \vec{r}_\mu \cdot \vec{c} - \delta_\mu$$

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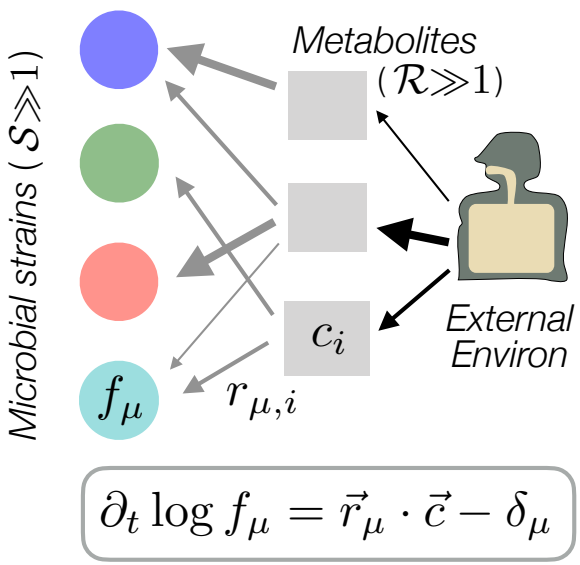

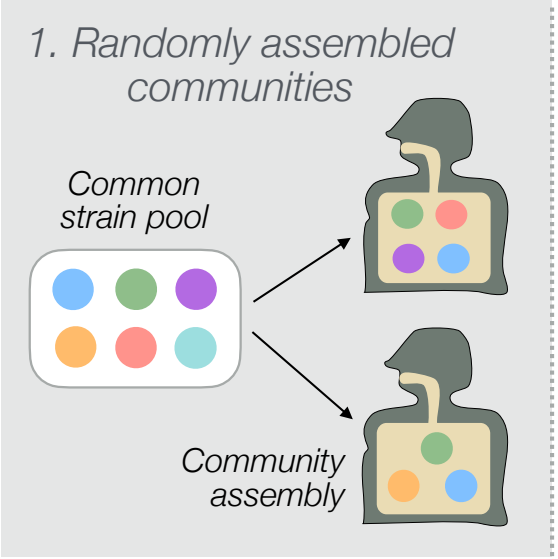

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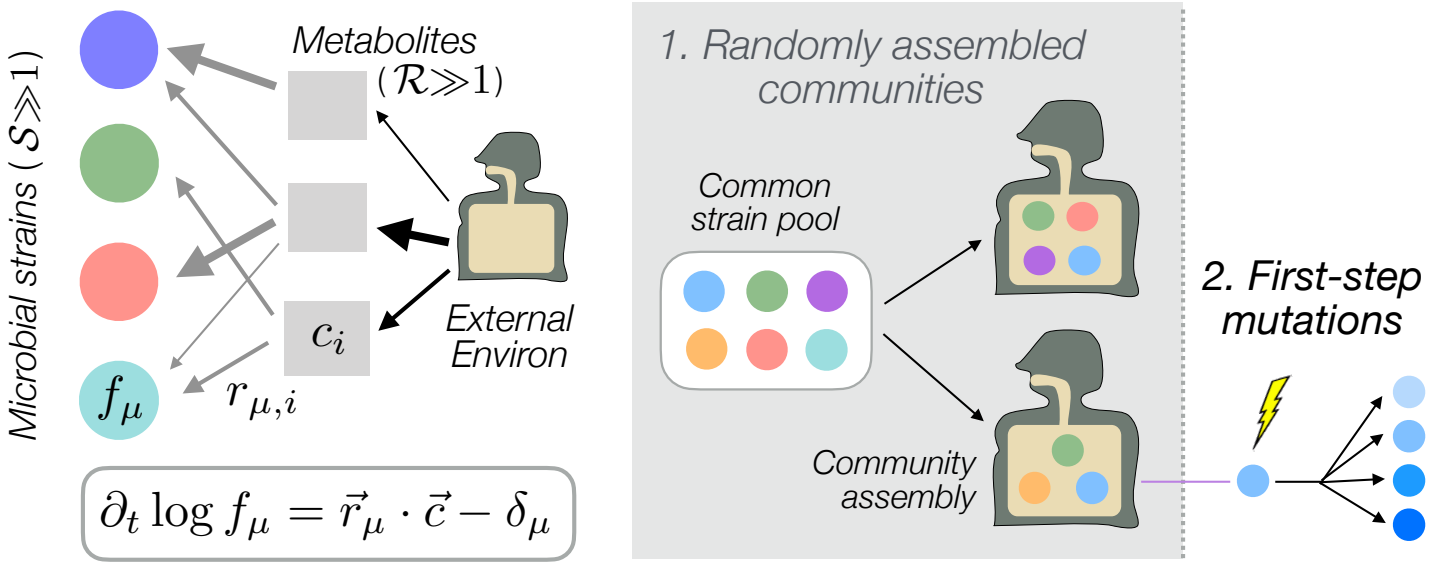

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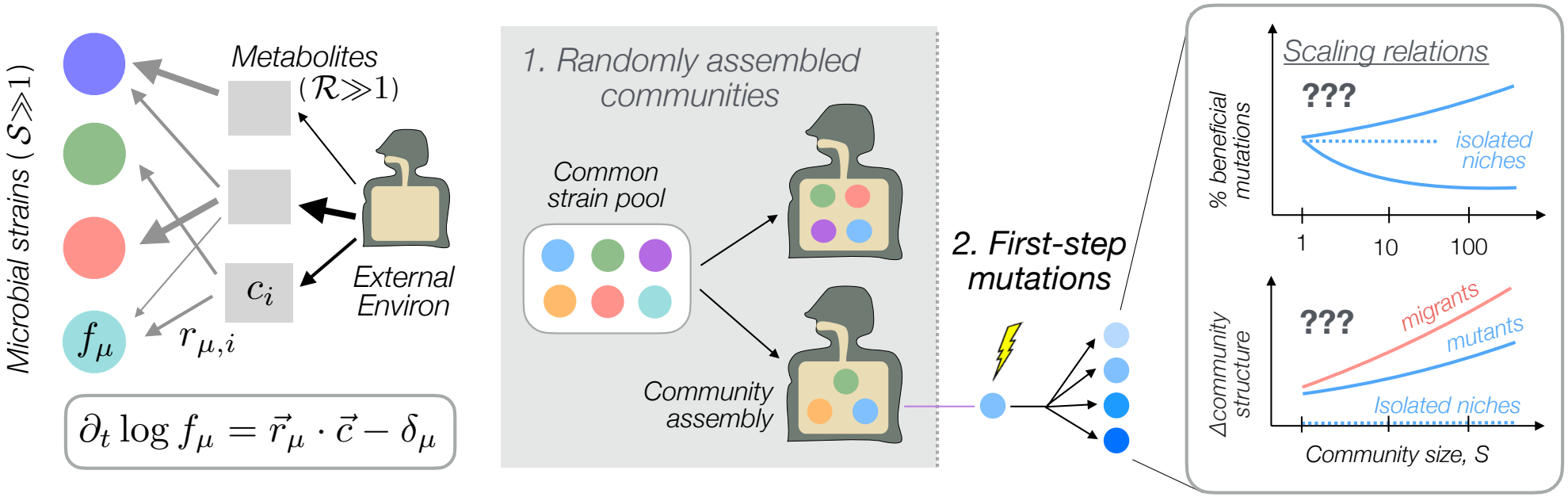

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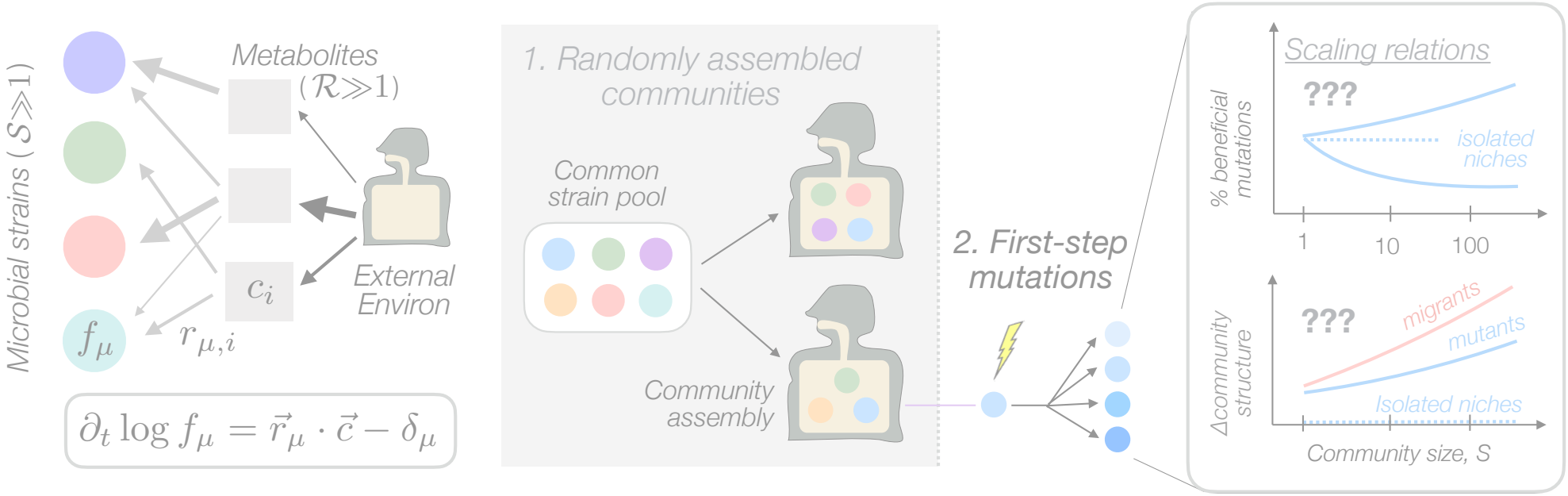

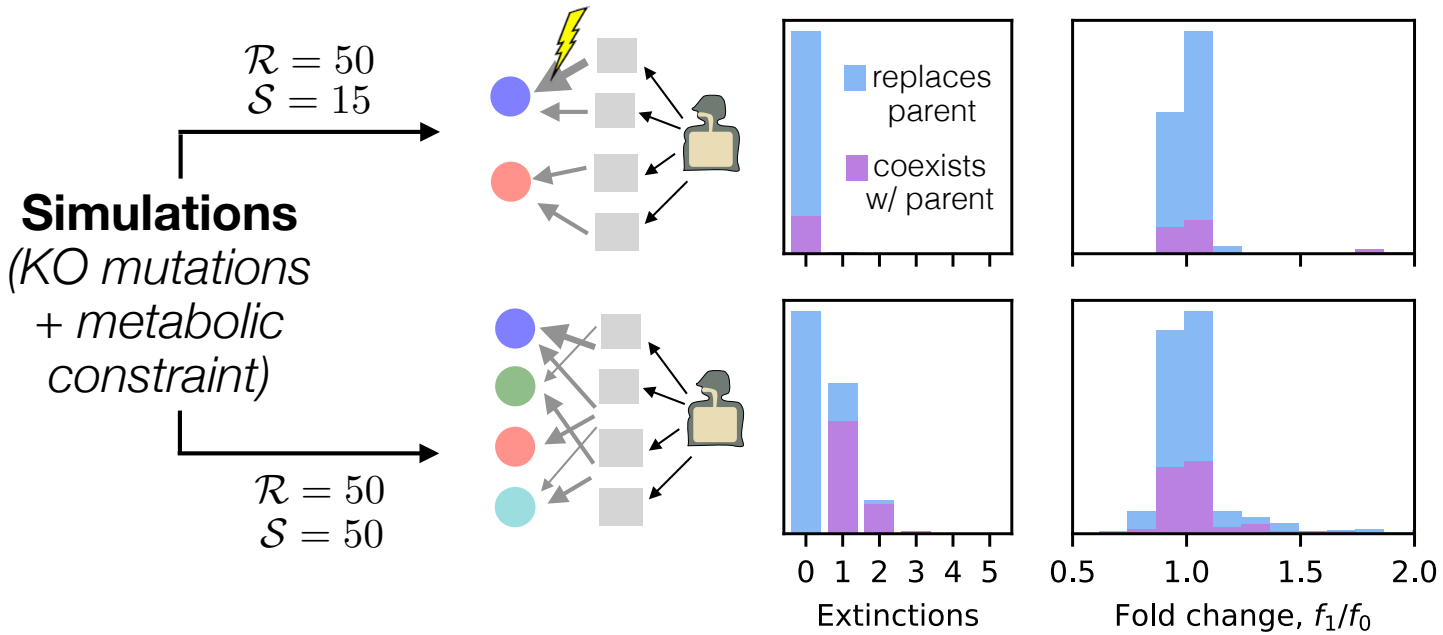

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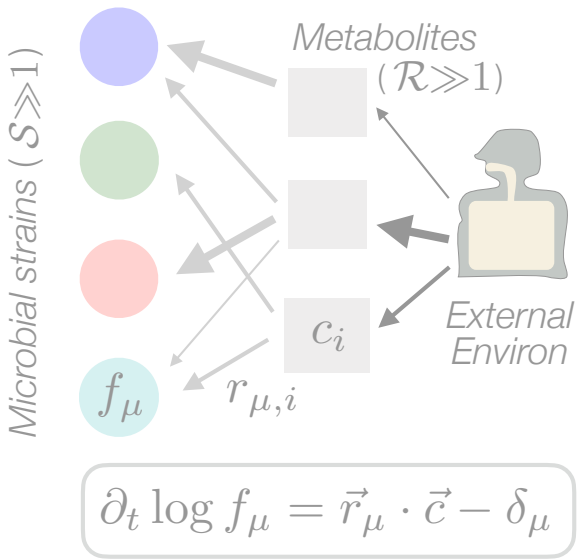

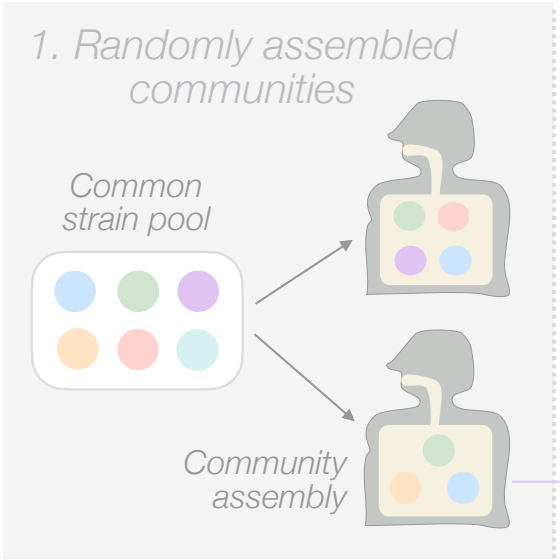

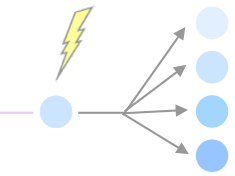

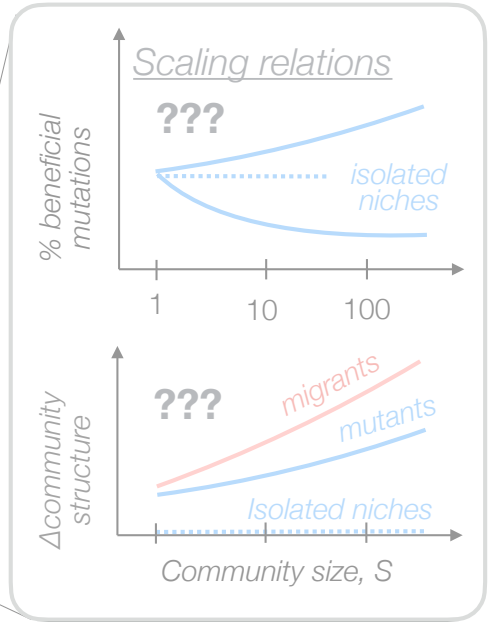

Simulations
(KO mutations + metabolic constraint)

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$\mathcal{S} = 15$

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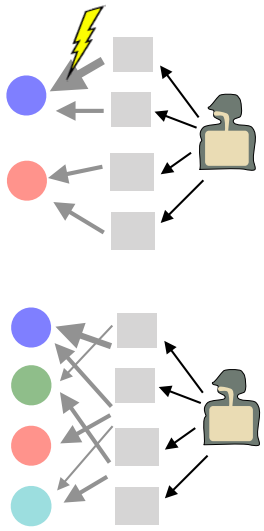

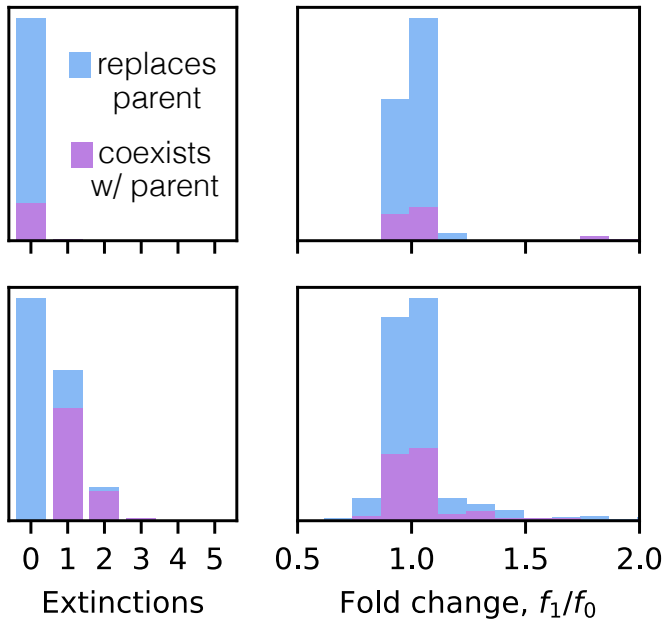

Many successful KOs can ***coexist with parent strain***, even in 'saturated' comm's where ***other species are driven to extinction***.

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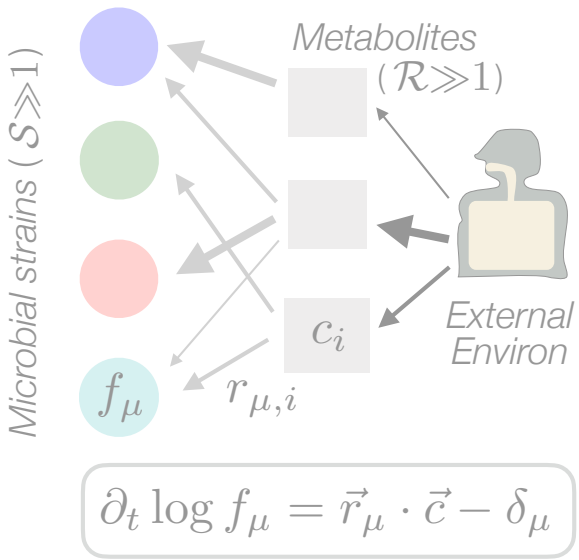

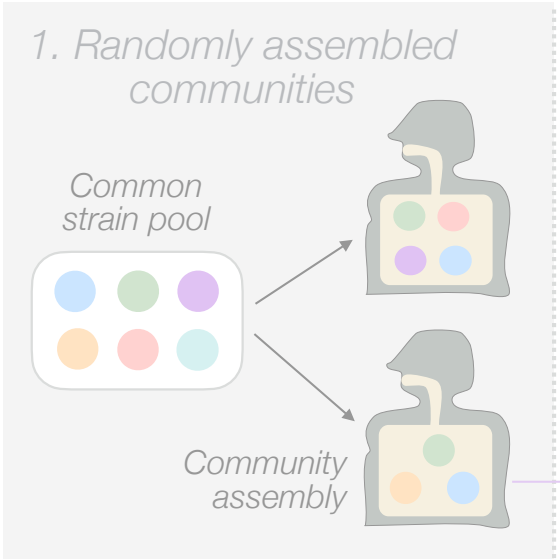

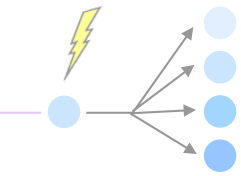

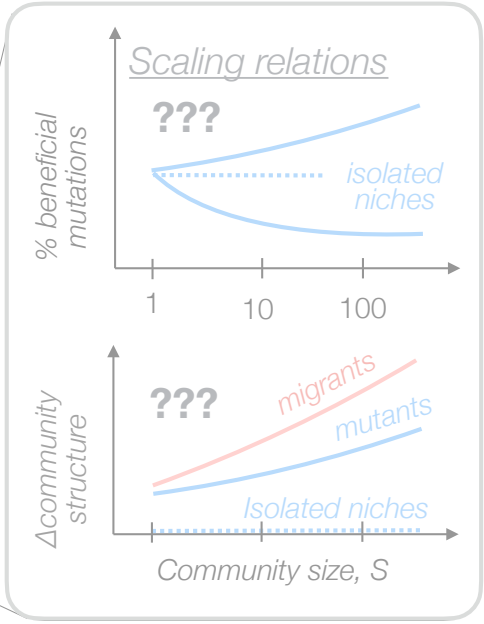

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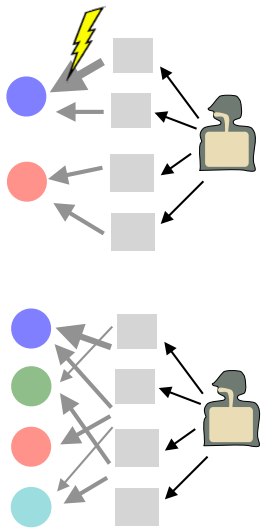
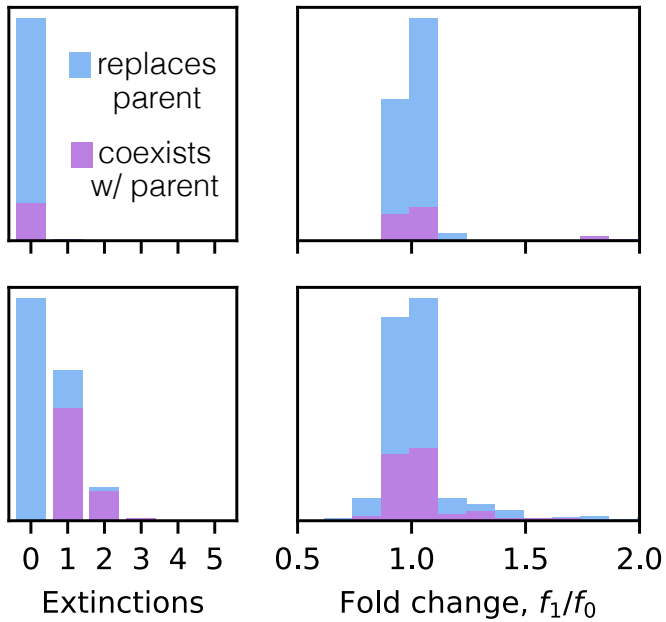
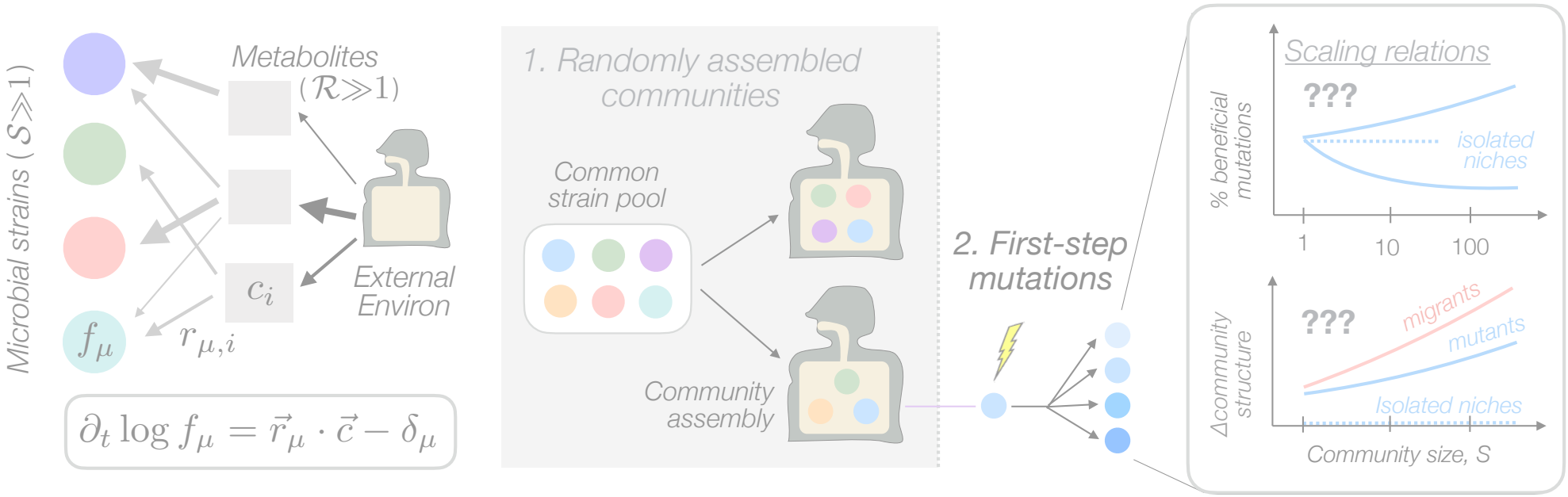




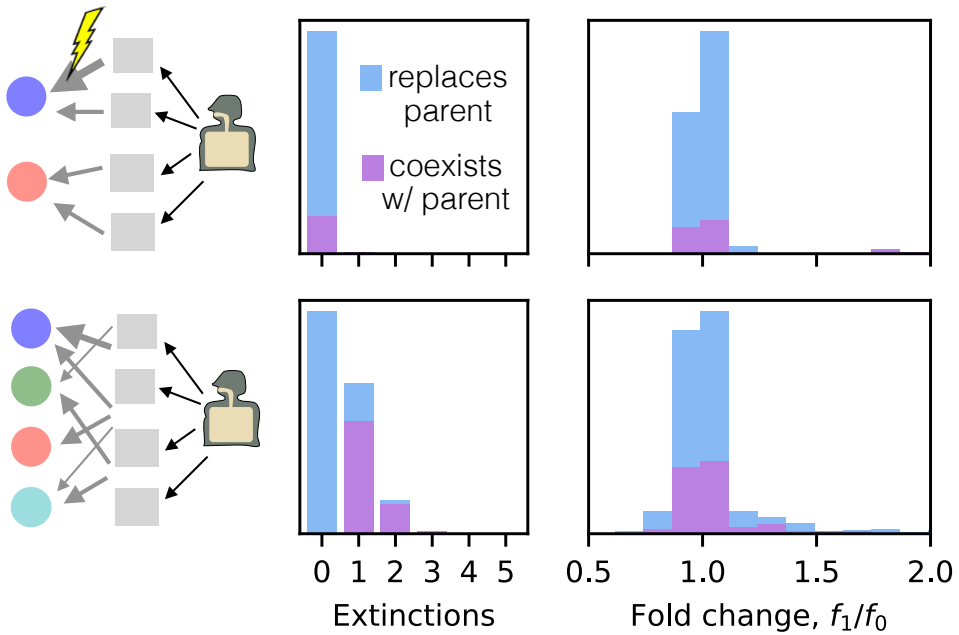
Many successful KOs can ***coexist with parent strain***, even in 'saturated' comm's where ***other species are driven to extinction***.

\+ small / negative changes in freq of ***focal species***

Some qualitative features can be recapitulated by simple resource competition models evolving in the high diversity limit



\+
analytical calc'ns
(replica theory)



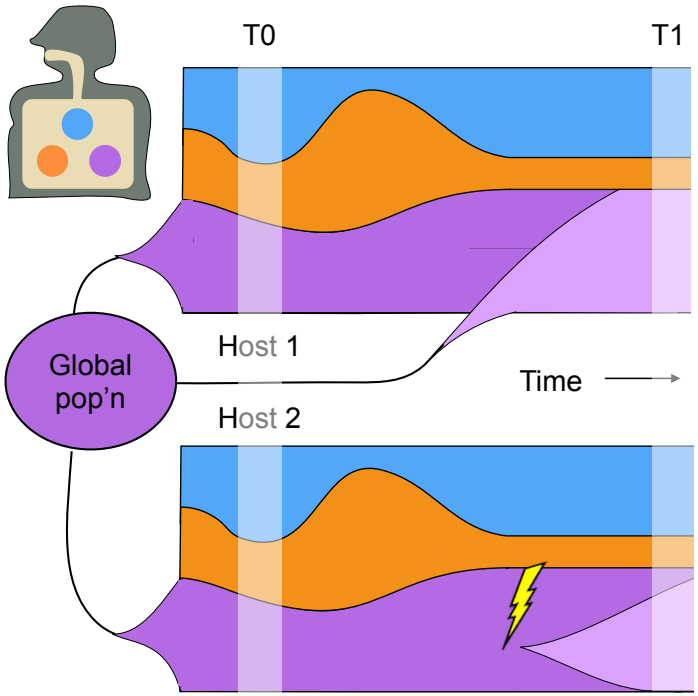
Many successful KOs can ***coexist with parent strain***, even in 'saturated' comm's where ***other species are driven to extinction***.

\+ small / negative changes in freq of ***focal species***

Conclusions

- Native gut bacteria ***can*** evolve within healthy human hosts on clinically relevant timescales

  → ***mixture of "strain replacement" and "evolutionary modification"***



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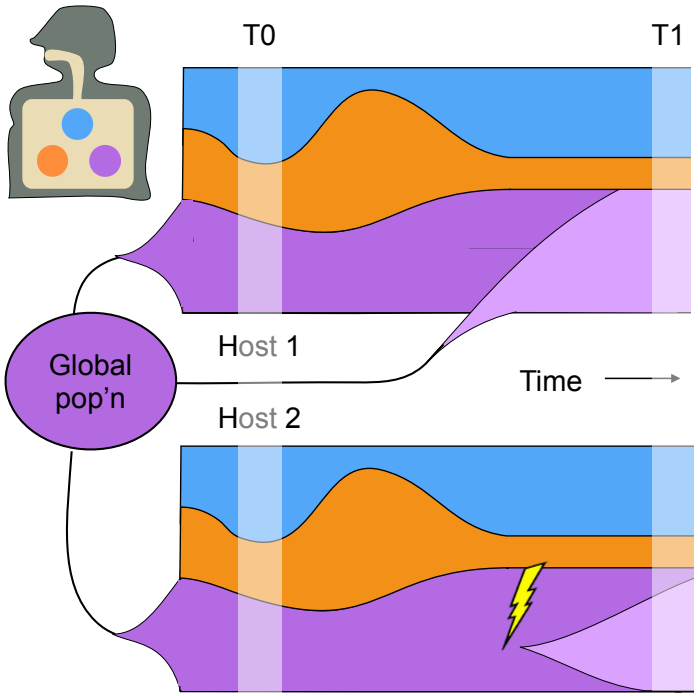

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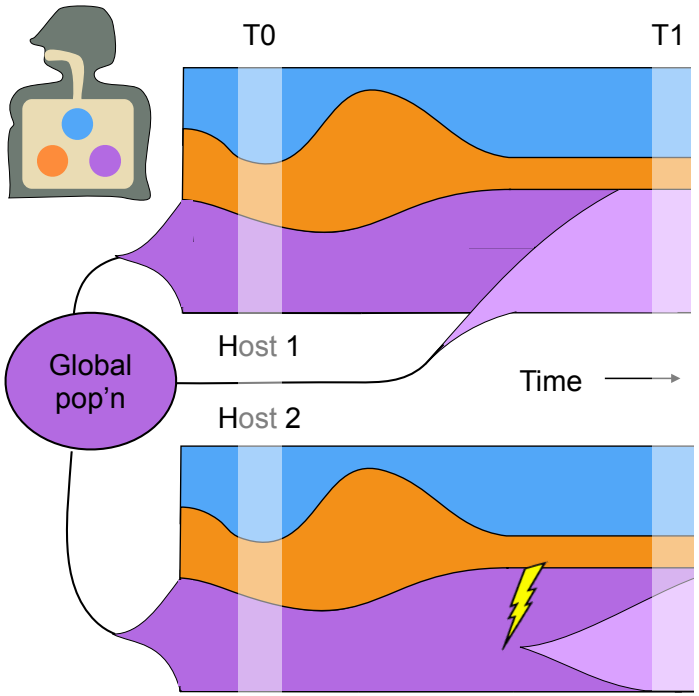

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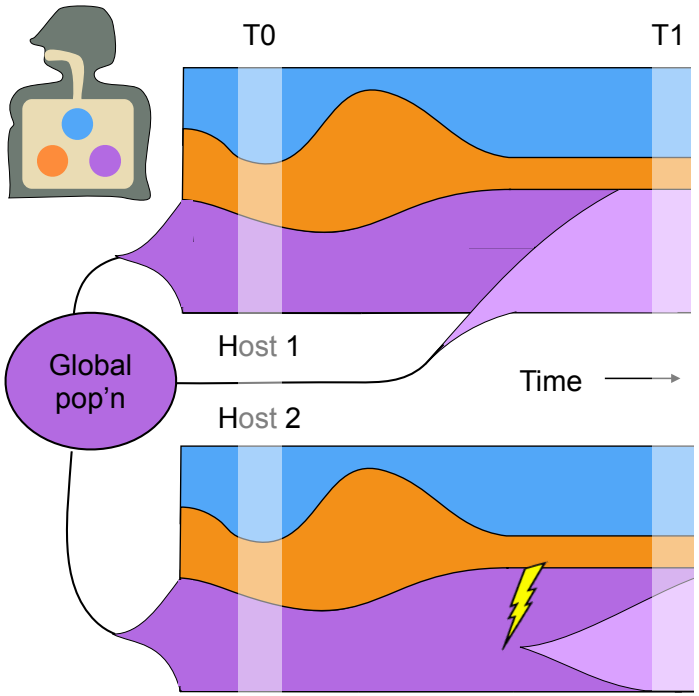

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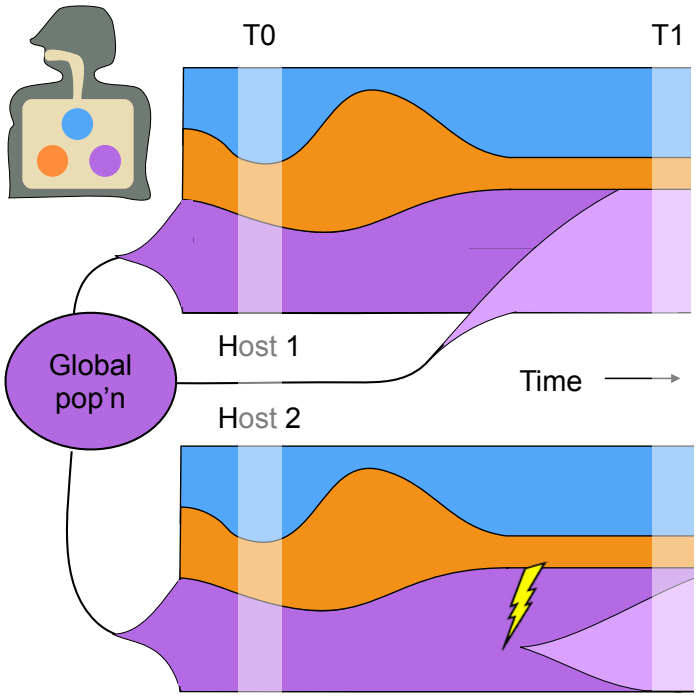

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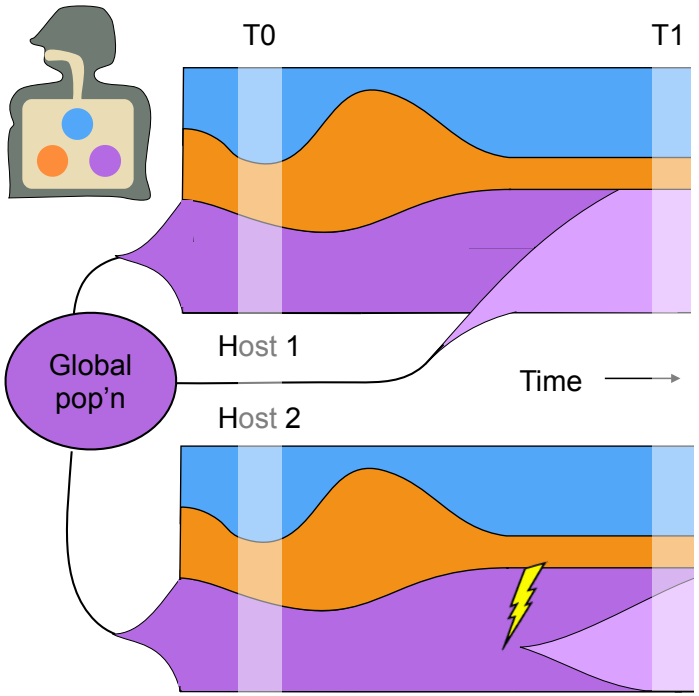

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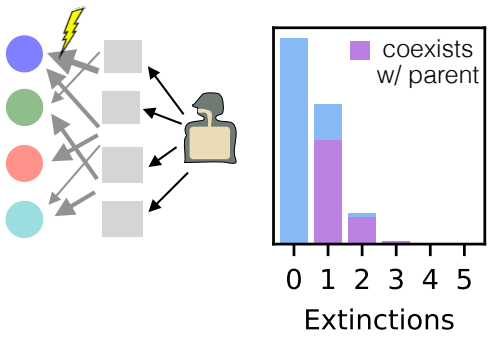


Thanks!

Evolutionary dynamics in the human gut microbiome:

Garud*, **BHG***, et al, *PLoS Bio* 2019

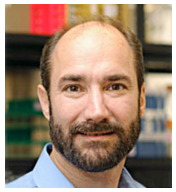
Nandita Garud
(UCLA)

Katie Pollard
(UCSF)

Oskar Hallatschek
(UC Berkeley)

Longitudinal ABX study
Roodgar*, **BHG*** biorxiv 2020

Morteza
Roodgar



Mike Snyder
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Good Lab @ Stanford Bio-X

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Caroline Van
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Serena Debesai
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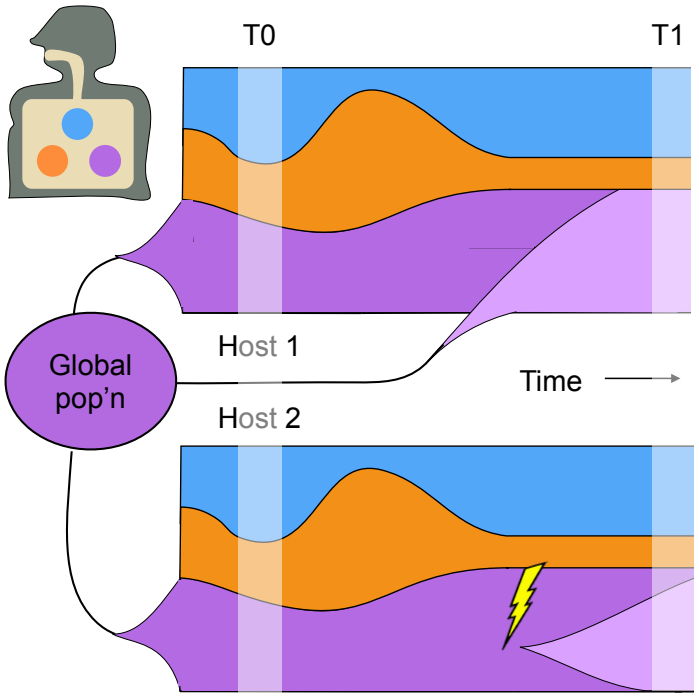
Conclusions



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