



Predicting personalized pathogen engraftment with metabolic models

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from the **ISB Microbiome Course 2023**

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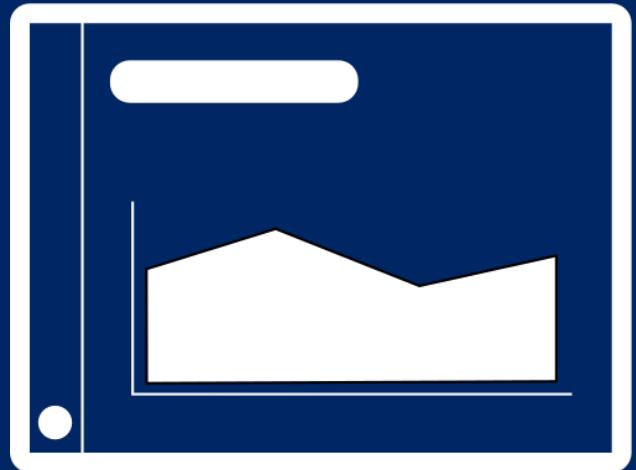
Let's get the slides first (use your computer, phone, TV, fridge)

https://gibbons-lab.github.io/isb_course_2023/micom



Quick reminder 

Presentation



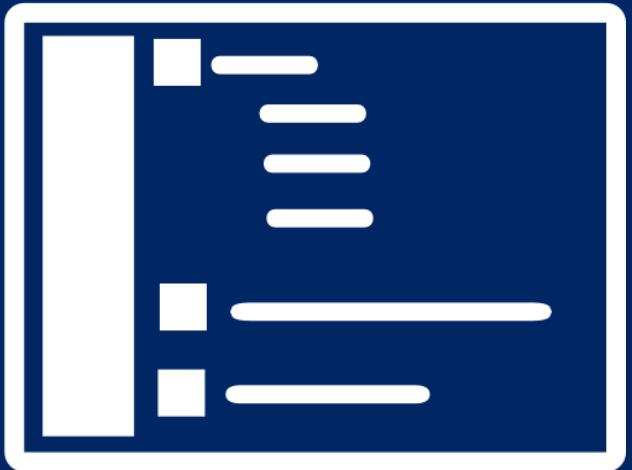
logic
explanations
links

Notebook



technical aspects
materials
visualizations

Chat

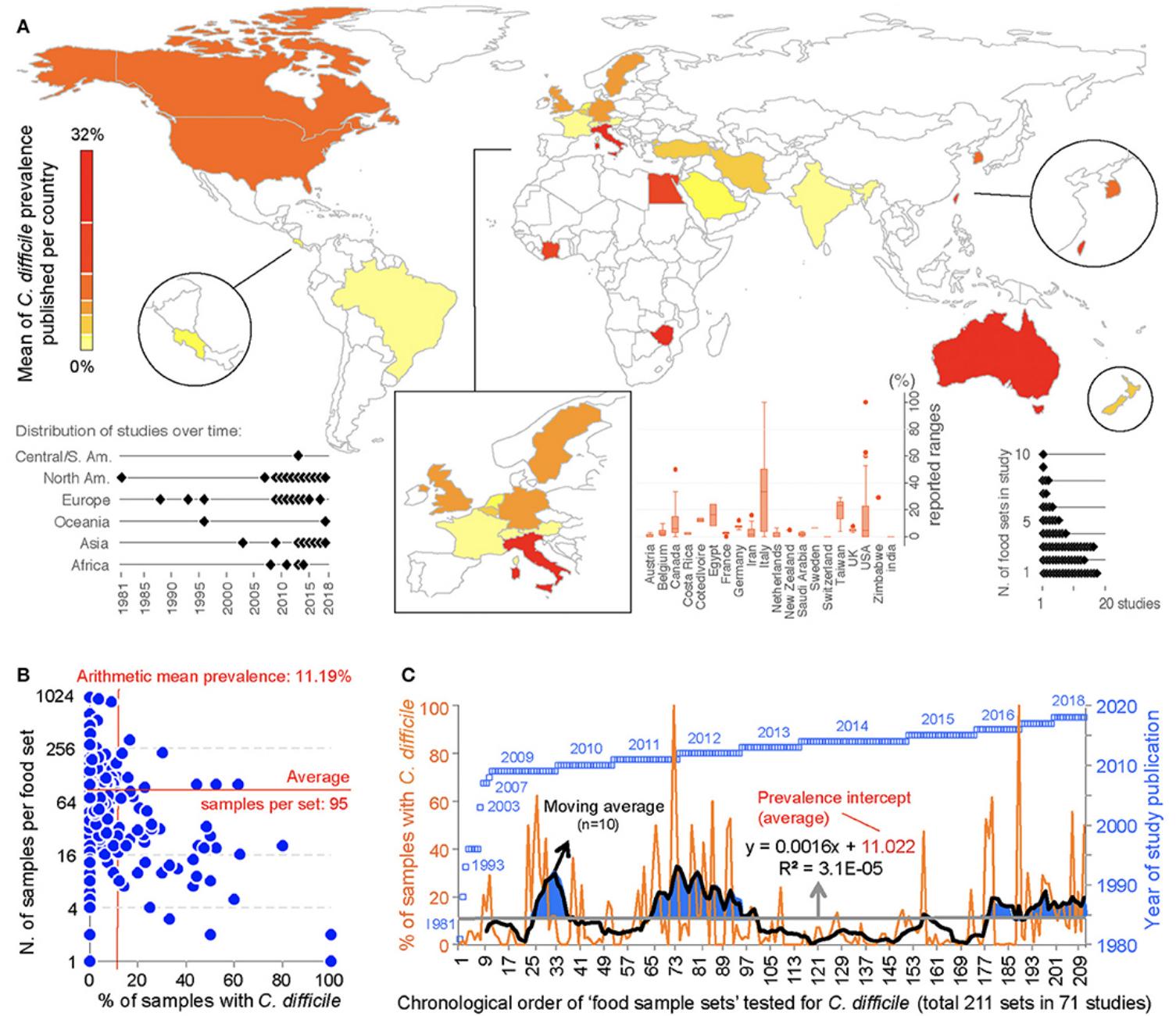


support
Q&A

Modeling pathogen engraftment: will it stick?

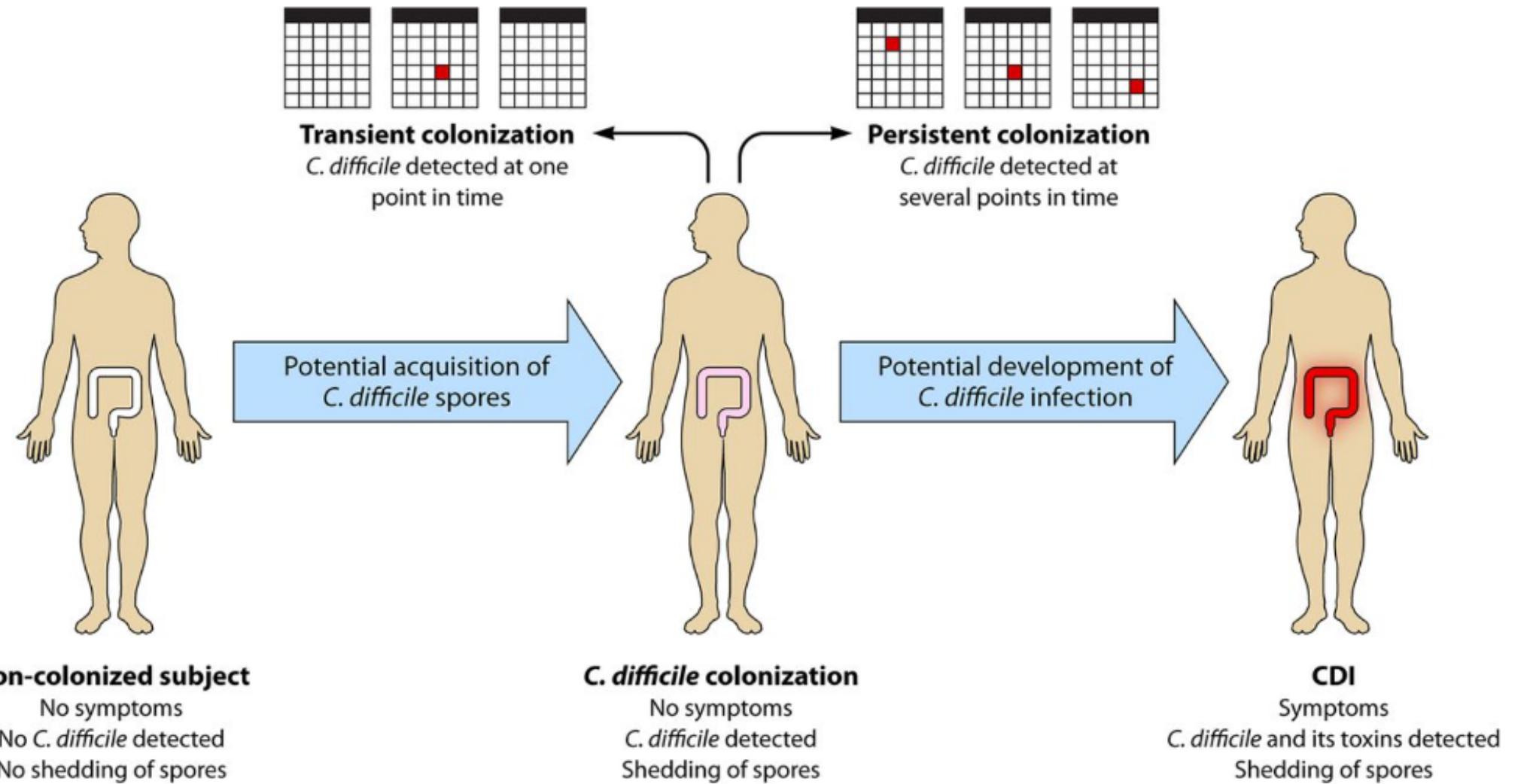


Clostridioides difficile (*C. diff*) is a leading cause of GI track infections

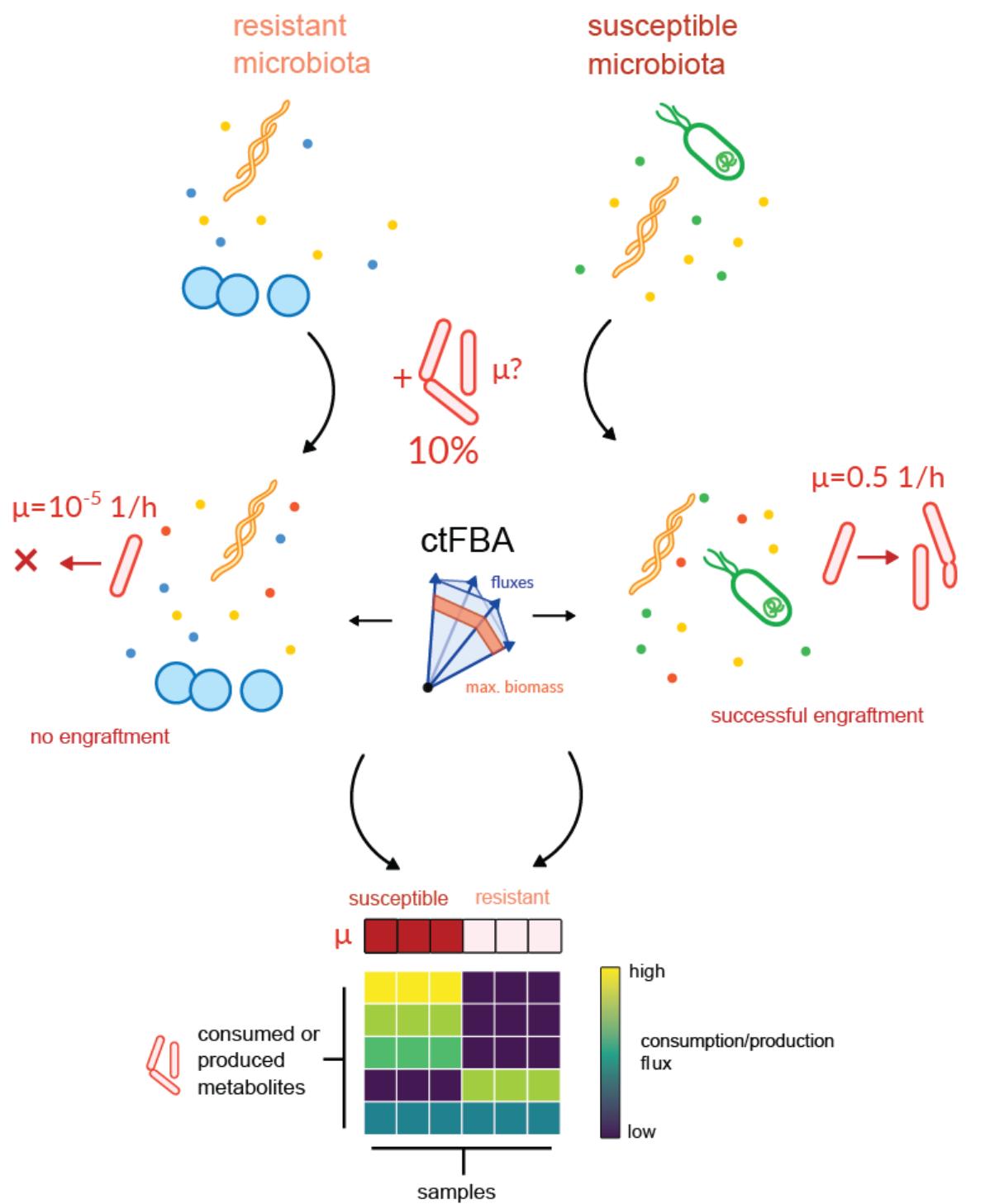


C. diff colonization and the transition to infection

More of us have more *C. diff* in the gut than you might expect



Predicting *C. diff* colonization with MICOM



Let's set up our Notebook!

 Let's switch to the notebook

Click me to open the notebook!



Functional analyses

Tries to predict what the microbiome **does** from sequencing data.

Uses gene/transcript/protein/metabolite abundances (metagenomics, metatranscriptomics, proteomics or metabolomics).

Gene content yields metabolic **capacity** or **potential**.

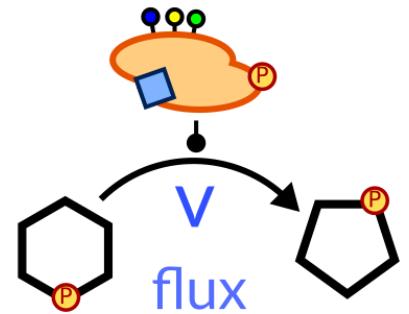


Genes abundances are cool but not what you really care about*

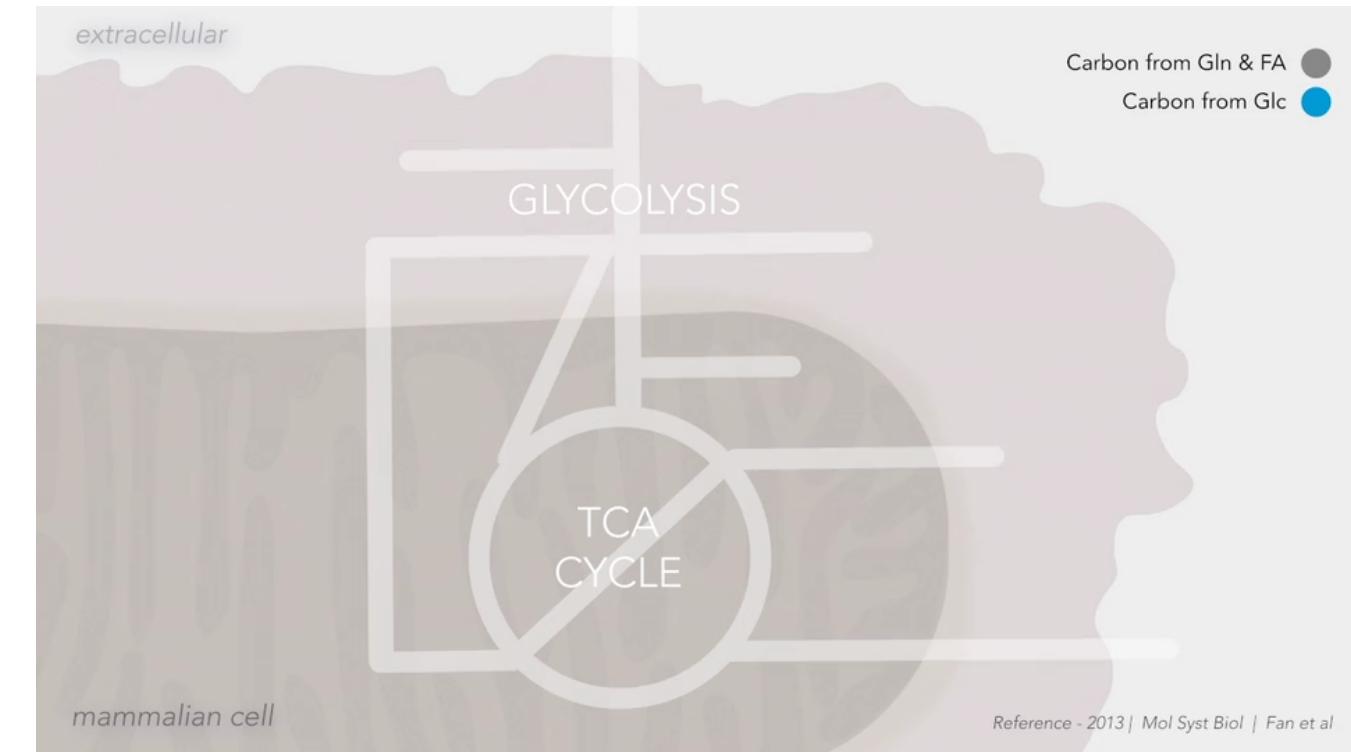
hot take 🔥



Fluxes



- rate of mass conversion
- unit is mmol/(gDW·h)
- costly to measure
 - longitudinal metabolomics
 - targeted temporal ^{13}C or ^{15}N



video courtesy of S. Nayak and J. Iwasa

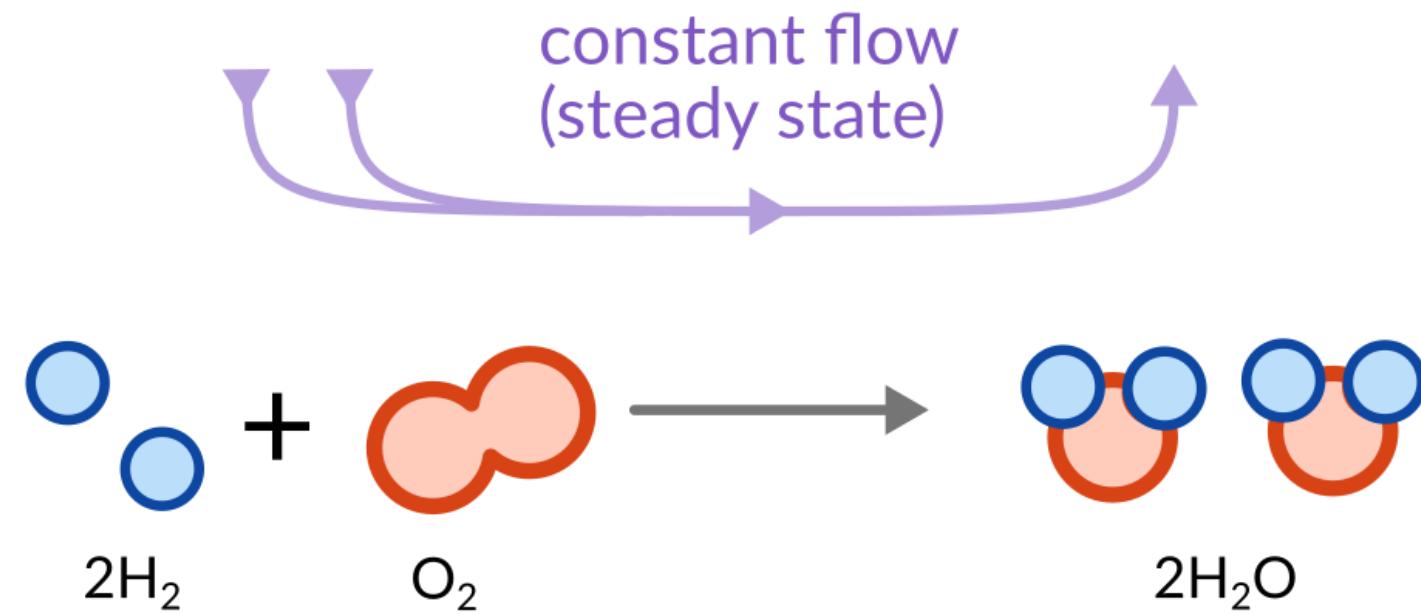


Flux Balance Analysis (FBA)

Can we infer the most likely fluxes in a biological system?



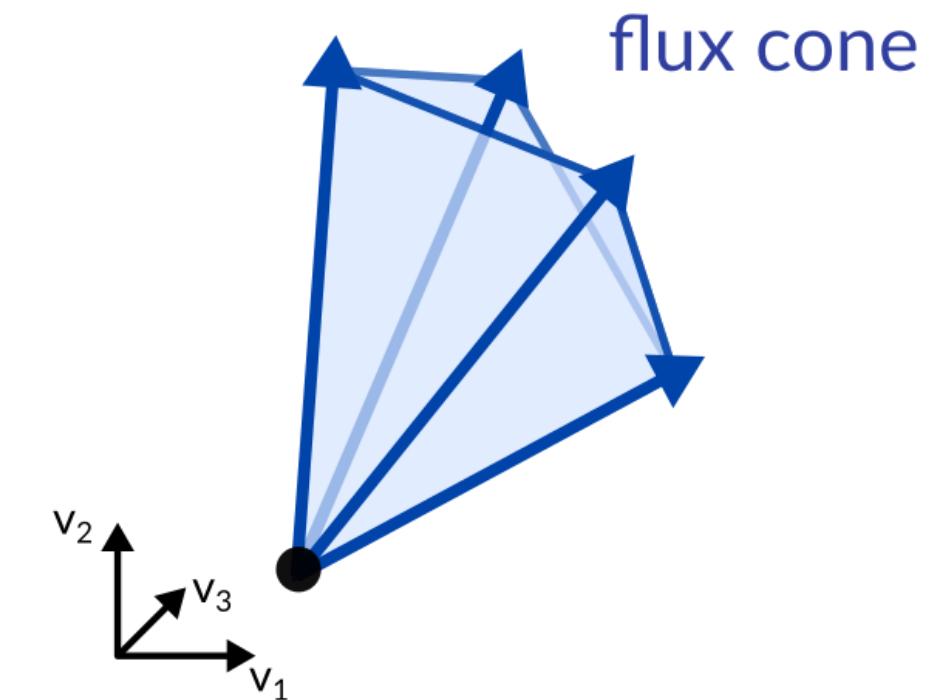
The flux cone



balance equations

$$2 \cdot v_{\text{H}_2\text{O}} - 2 \cdot v_{\text{H}_2} - v_{\text{O}_2} = 0$$

$$v_{\text{H}_2\text{O}} \geq 0$$



$$\mathbf{S} \cdot \mathbf{v} = 0$$

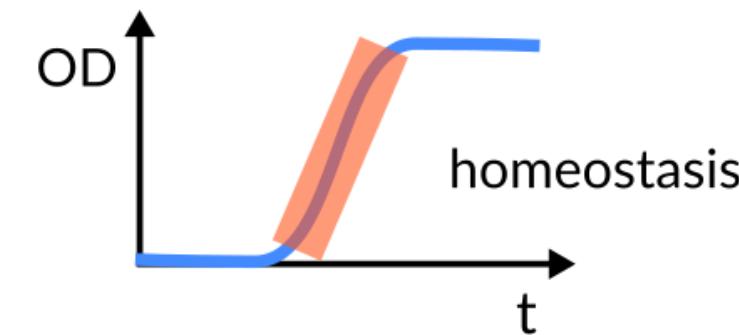
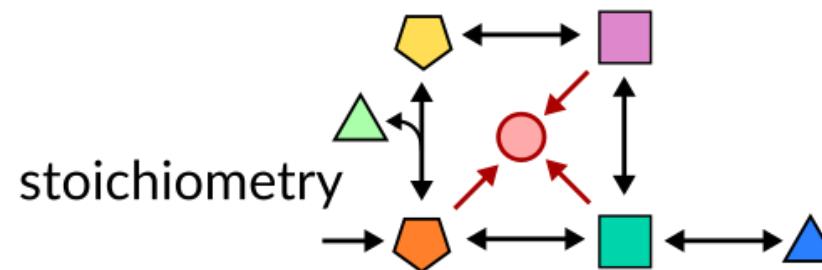
$$0 \leq v_i \leq 1000$$

for irreversible reactions

The goal of FBA is to **reduce** the flux space to a **biologically relevant** one.



Genome-scale metabolic modeling



$$S \cdot v = 0$$

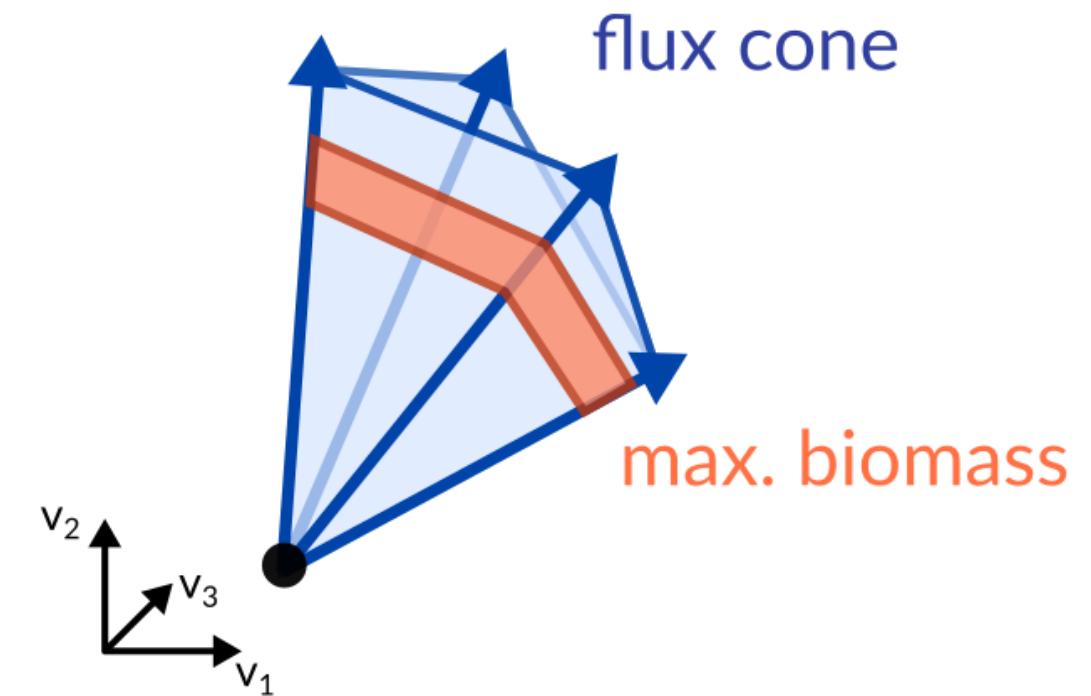
$$-1000 \leq v_i \leq 1000$$



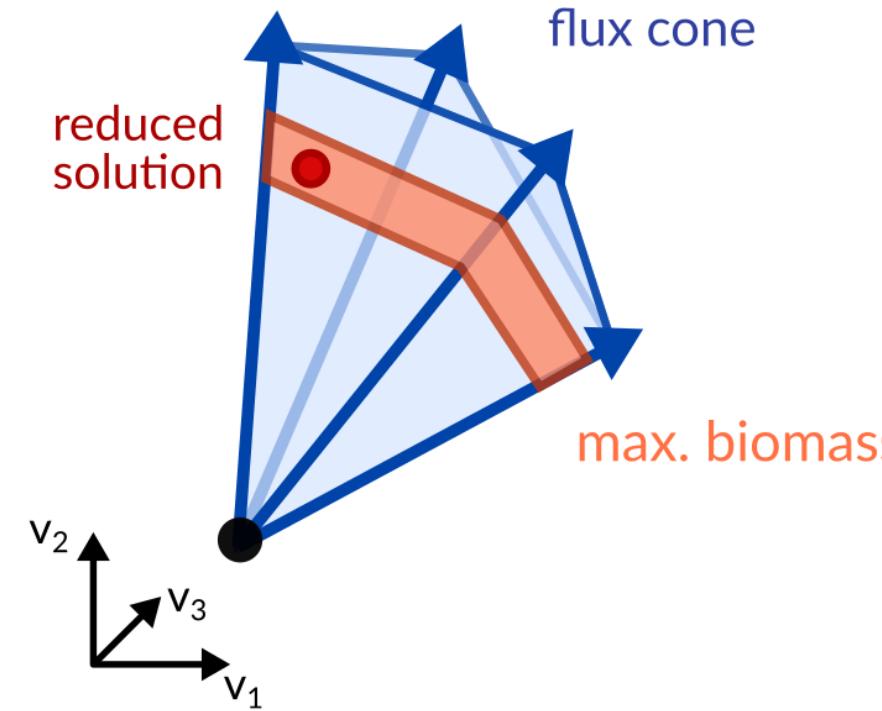
thermodynamics



environment



Selecting biologically relevant fluxes



Minimization of Metabolic Adjustment (MOMA)

closest flux distribution to a reference state
often used in gene deletions (closest to WT)

method

interpretation

Thermodynamic FBA

constrain fluxes based on free energy
apply second law of thermodynamics

minimum imports o

consume the least amount of nutrients
most competitive/smallest niche

parsimonious FBA o

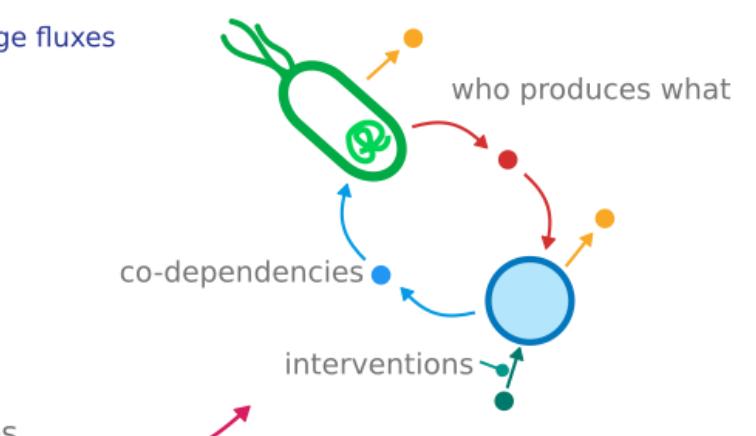
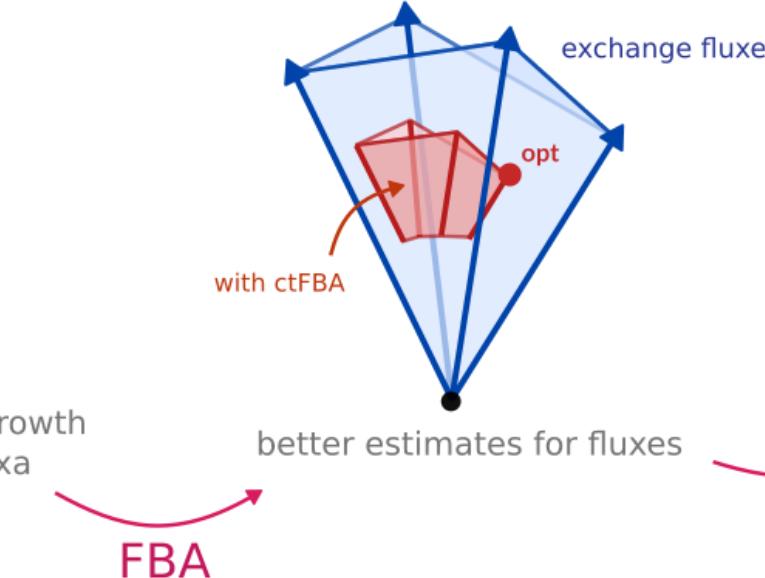
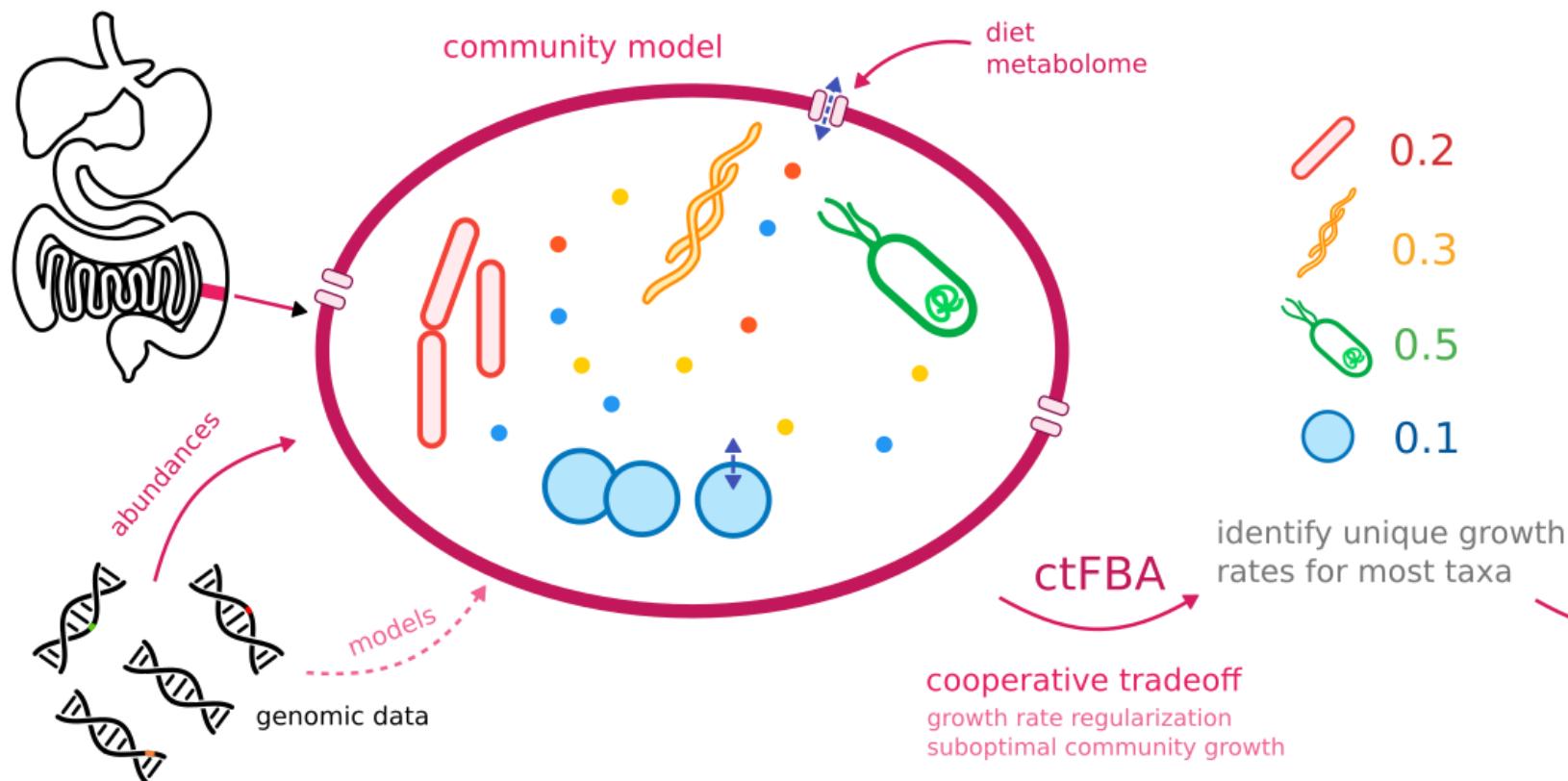
use the least amount of enzymes

and many more...

o used in MICOM

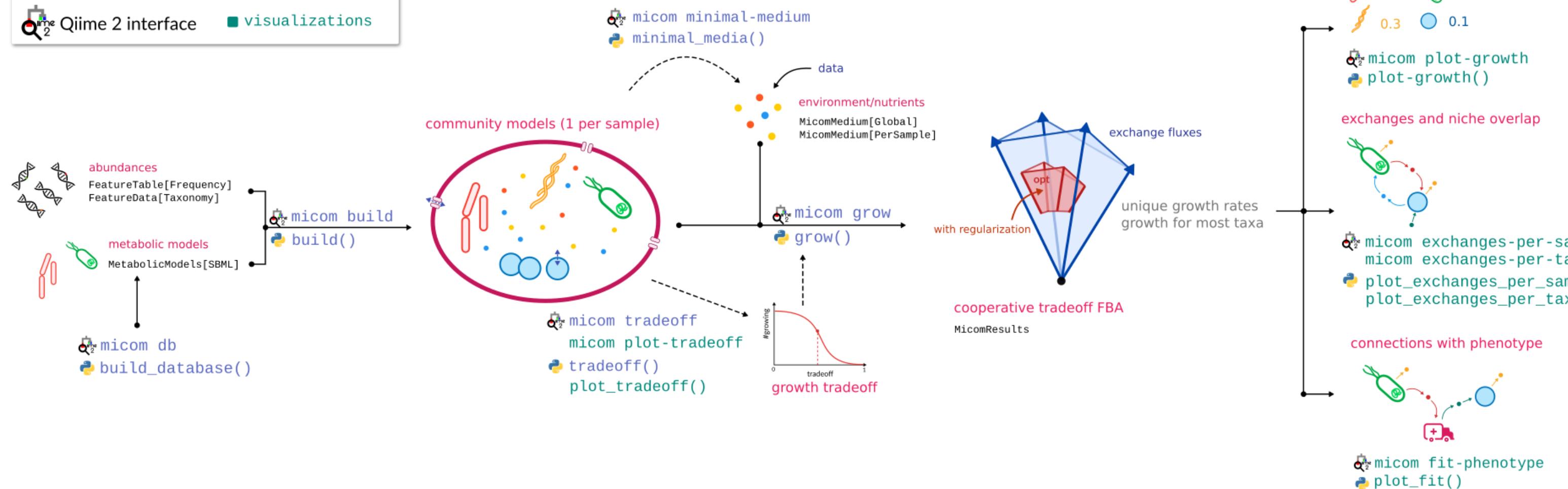
For instance, parsimonious FBA reproduces experimental fluxes in *E. coli* very well.

MICOM



<https://micom-dev.github.io/micom>





Let's continue with our data

- ▀ Let's switch to the notebook...



Community-wide growth is hard 😢

In a single genome-scale model we only have a single growth rate μ . In a microbial community we have several μ_i and a community growth rate

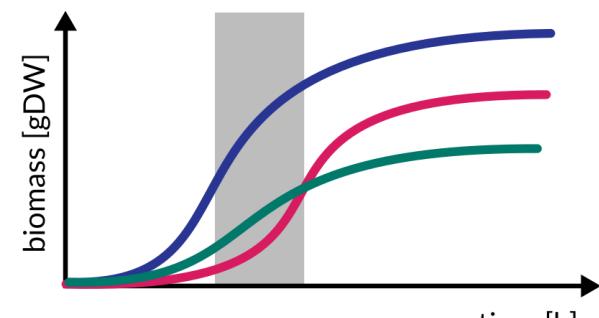
$$\mu_c = \sum_i a_i \cdot \mu_i$$

Why is this so hard? Can't we just maximize the community growth rate? Well...



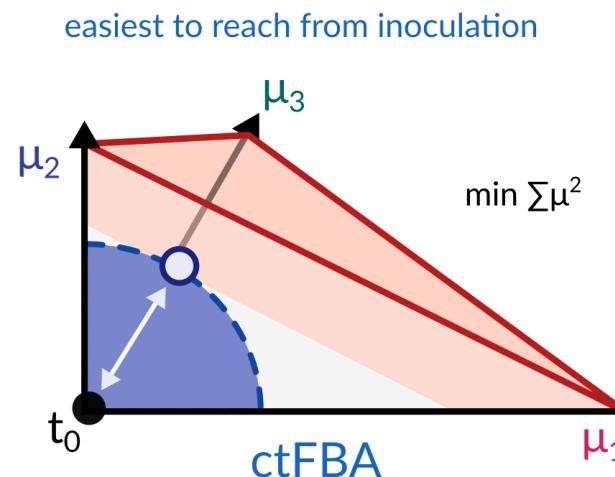
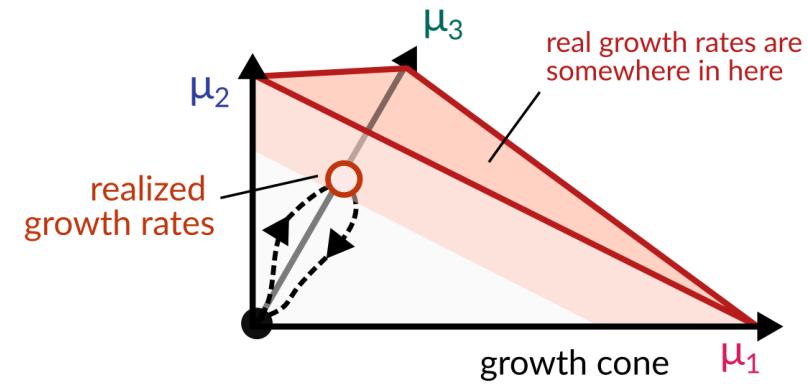
Estimating community wide growth rates with cooperative trade off flux balance analysis (ctFBA)

growth curves



real trajectories

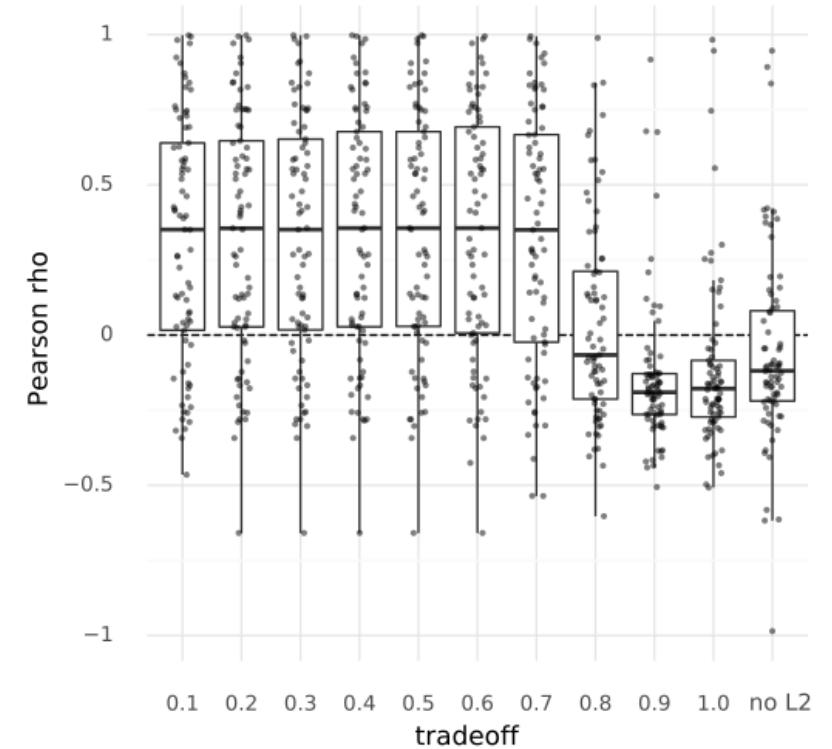
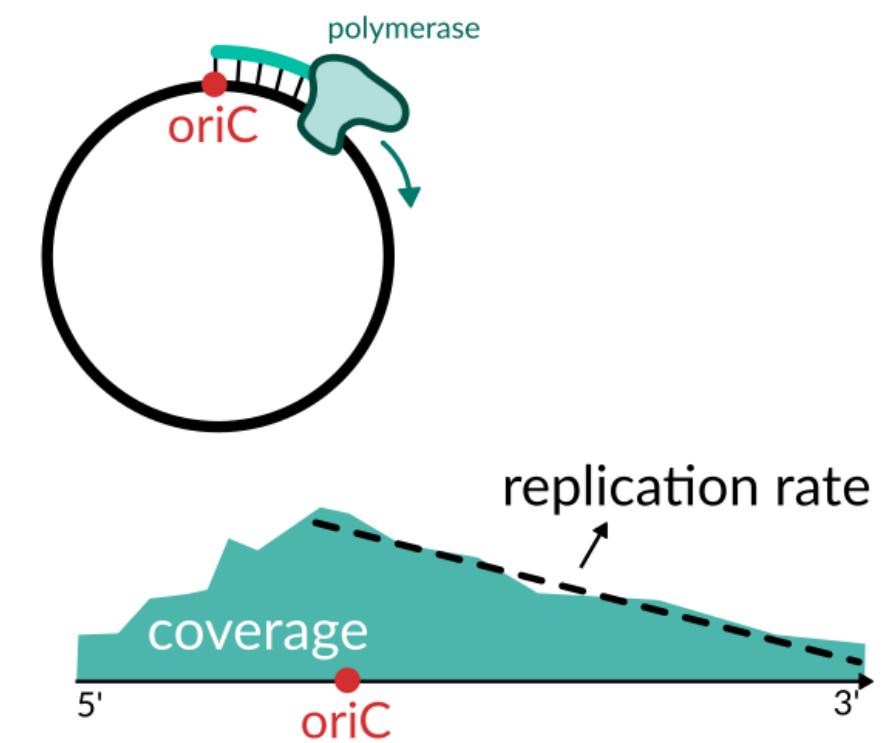
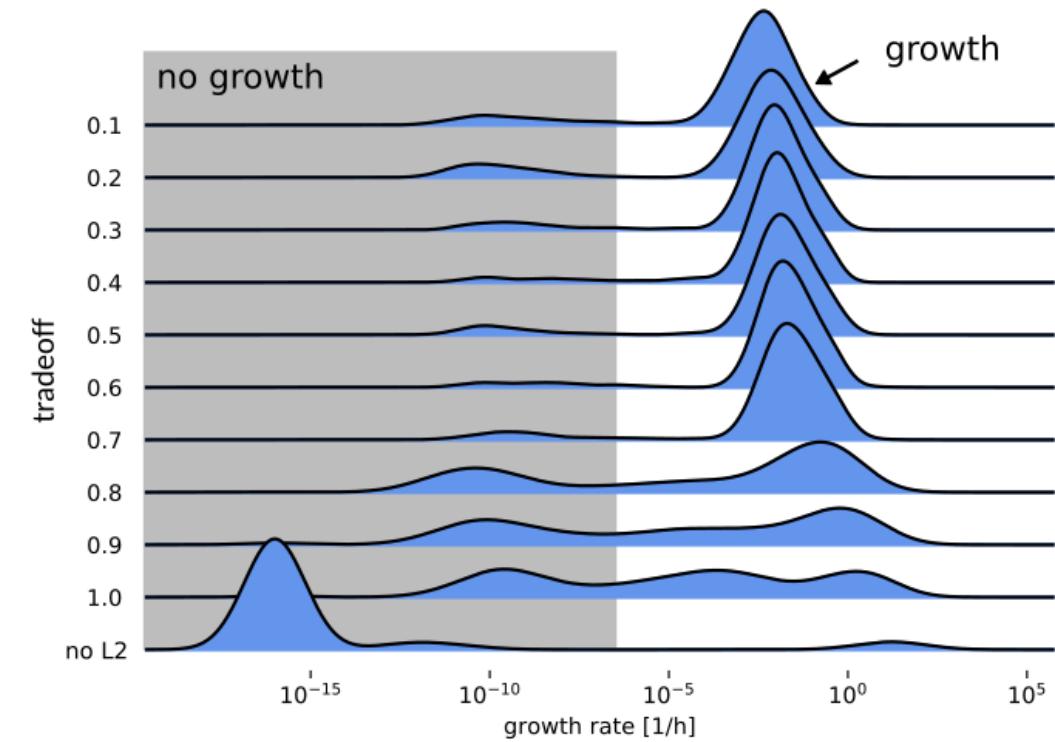
growth cone
(all possible growth rates)



Cooperative Tradeoff FBA allows us to treat metagenome-scale models with the **same** methods as genome-scale metabolic models (pFBA, minimal media, etc).



But does it work?



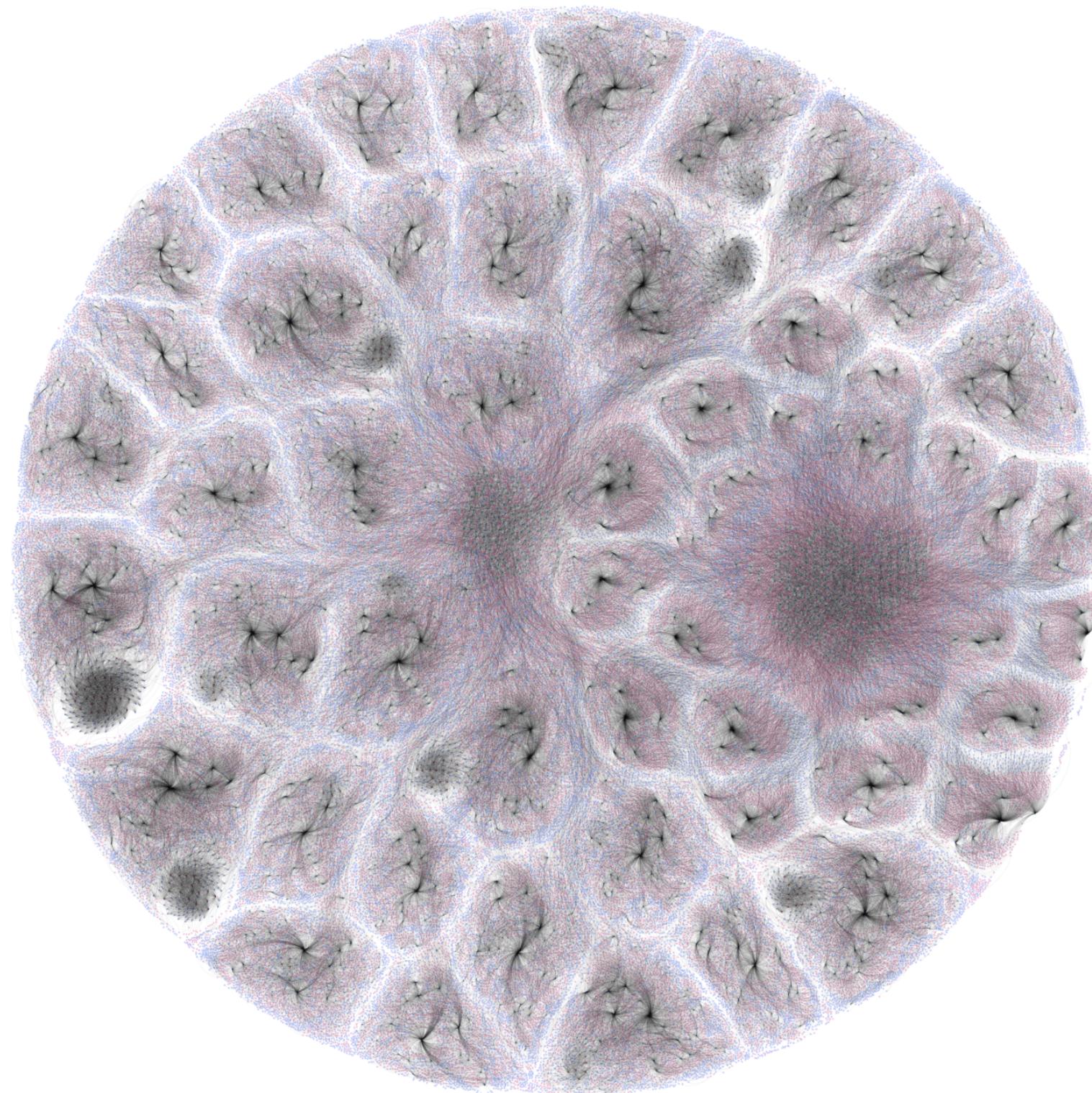
<https://doi.org/10.1128/mSystems.00606-19>



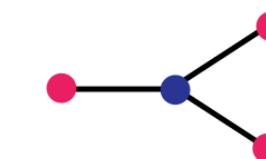
Easy peasy. What's taking so long then?

Well, metagenome-scale models are slightly larger... 





● reaction
● metabolite



reaction with
substrates and products

69,441 reactions
46,883 metabolites
292,699 connections

Let's return to the models we've built

 Let's switch to the notebook!

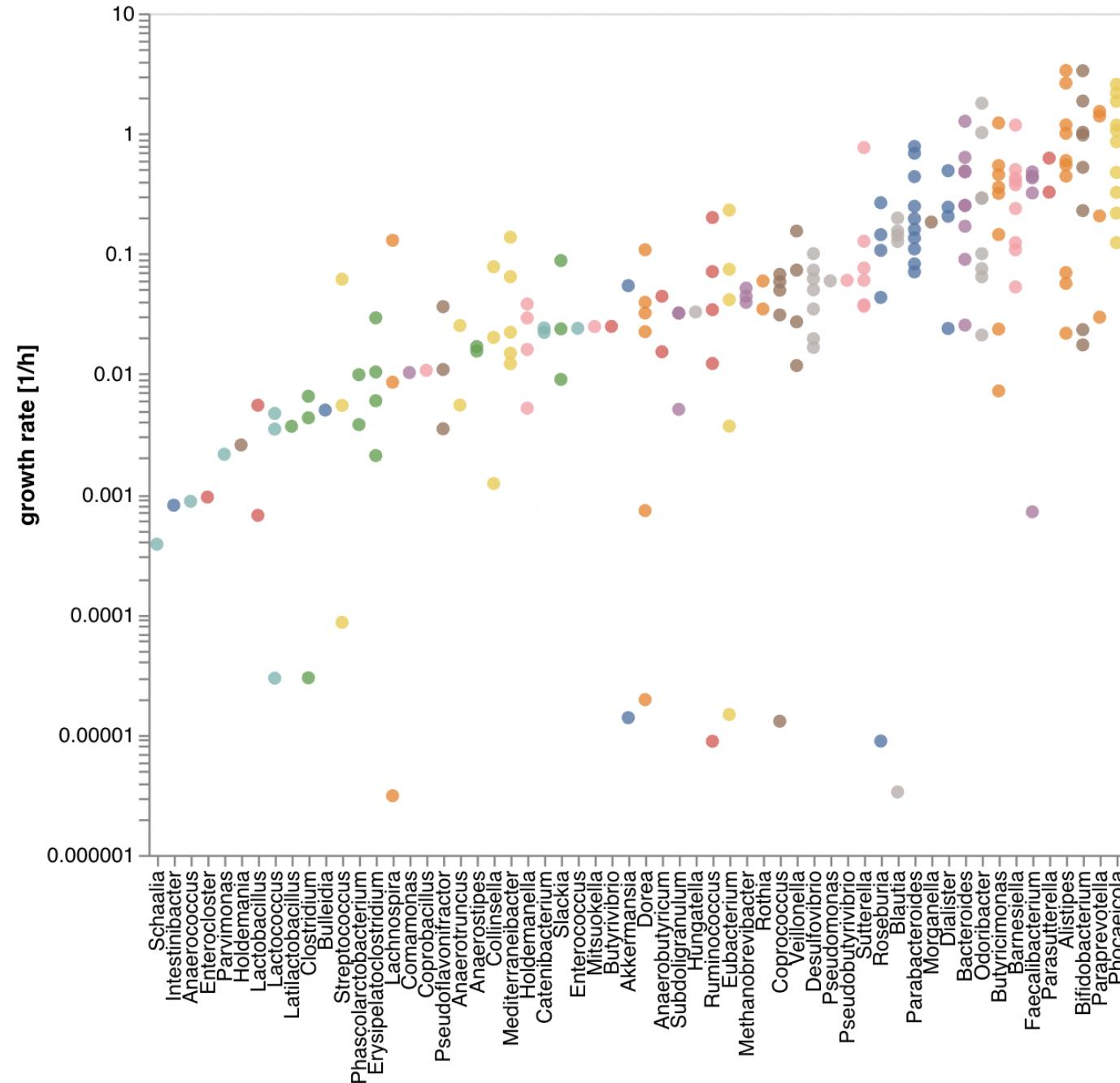


Before we look at our results...



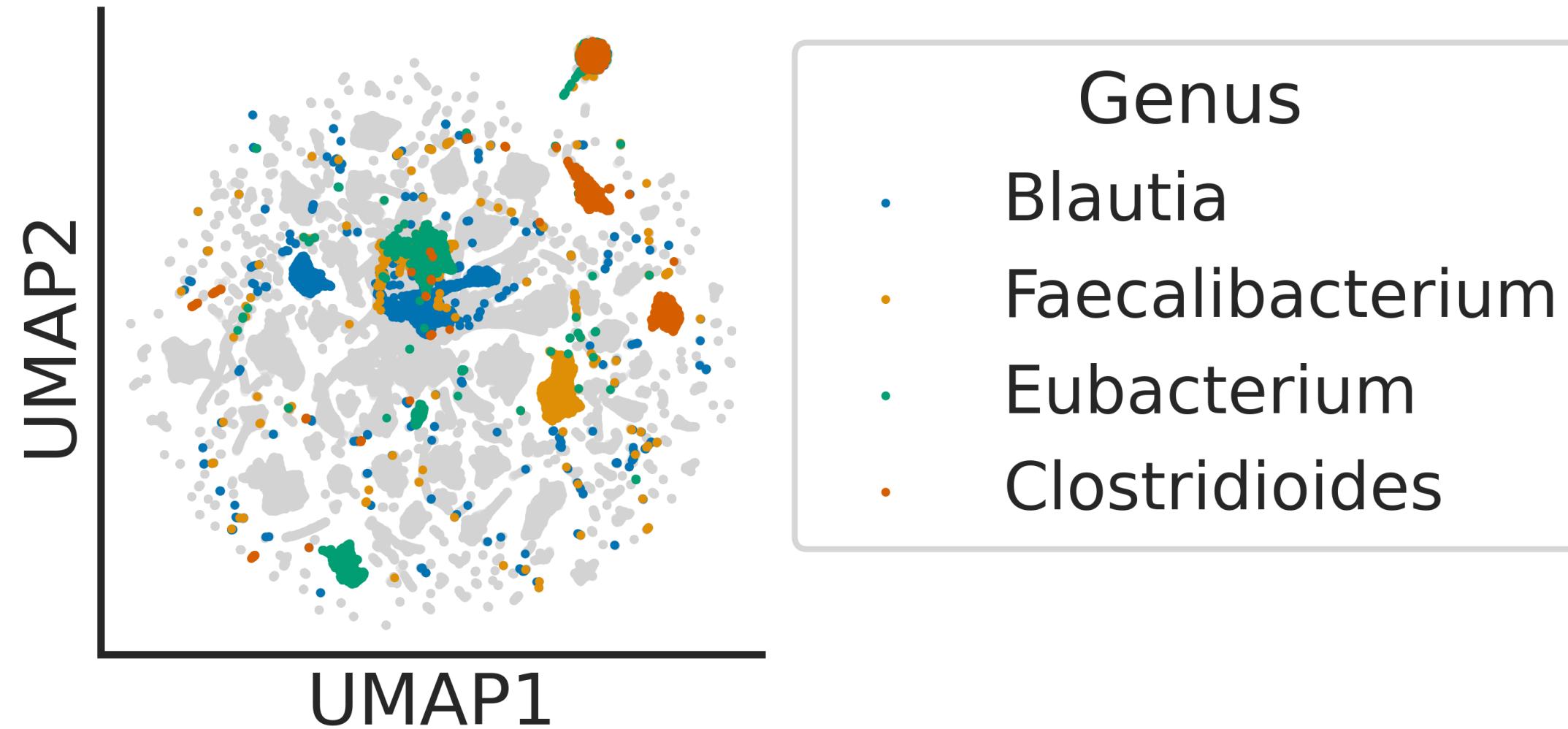
Growth Rates

Visualize growth rates of individual taxa per sample



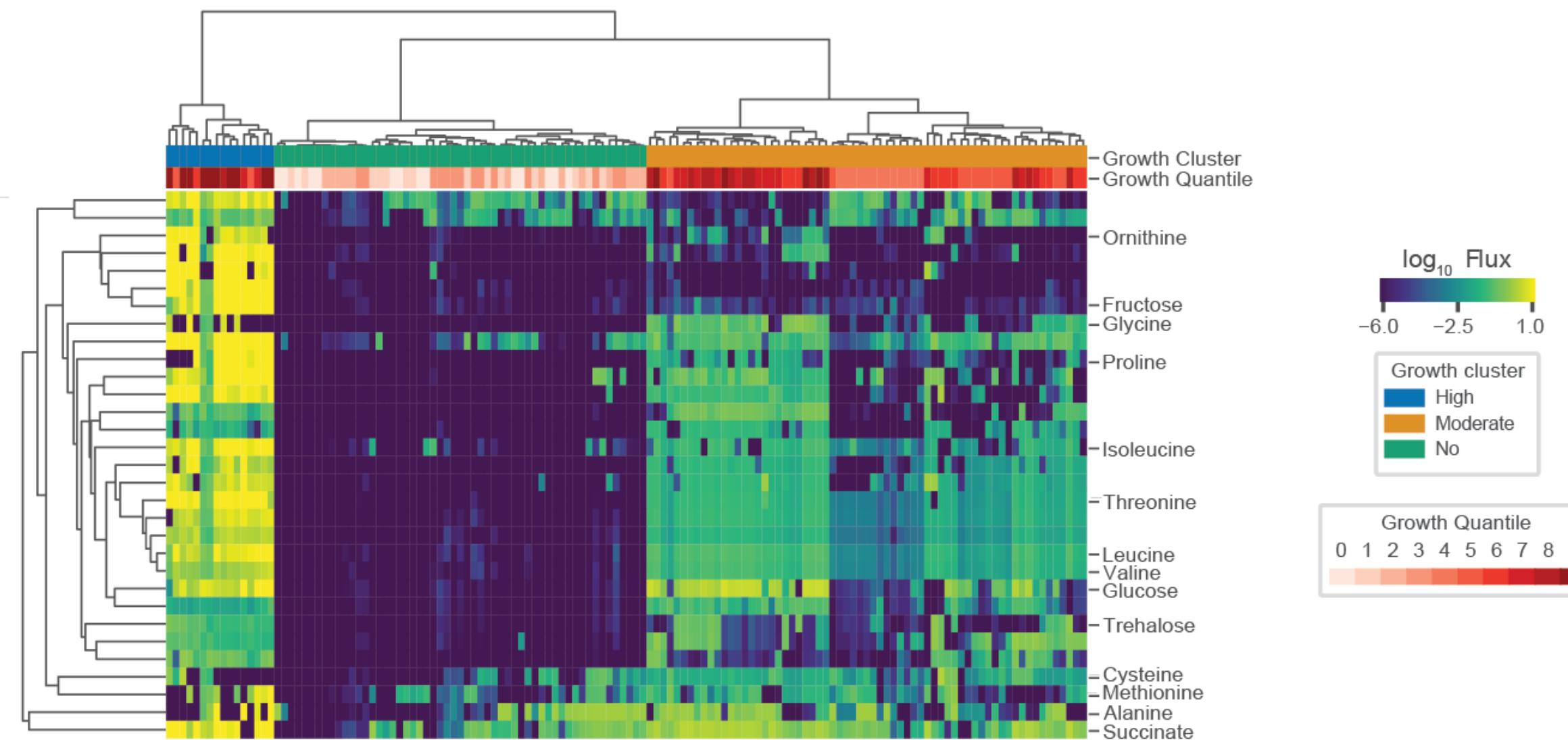
The niche space

The context-dependent way in which a microbial taxon uses its environment



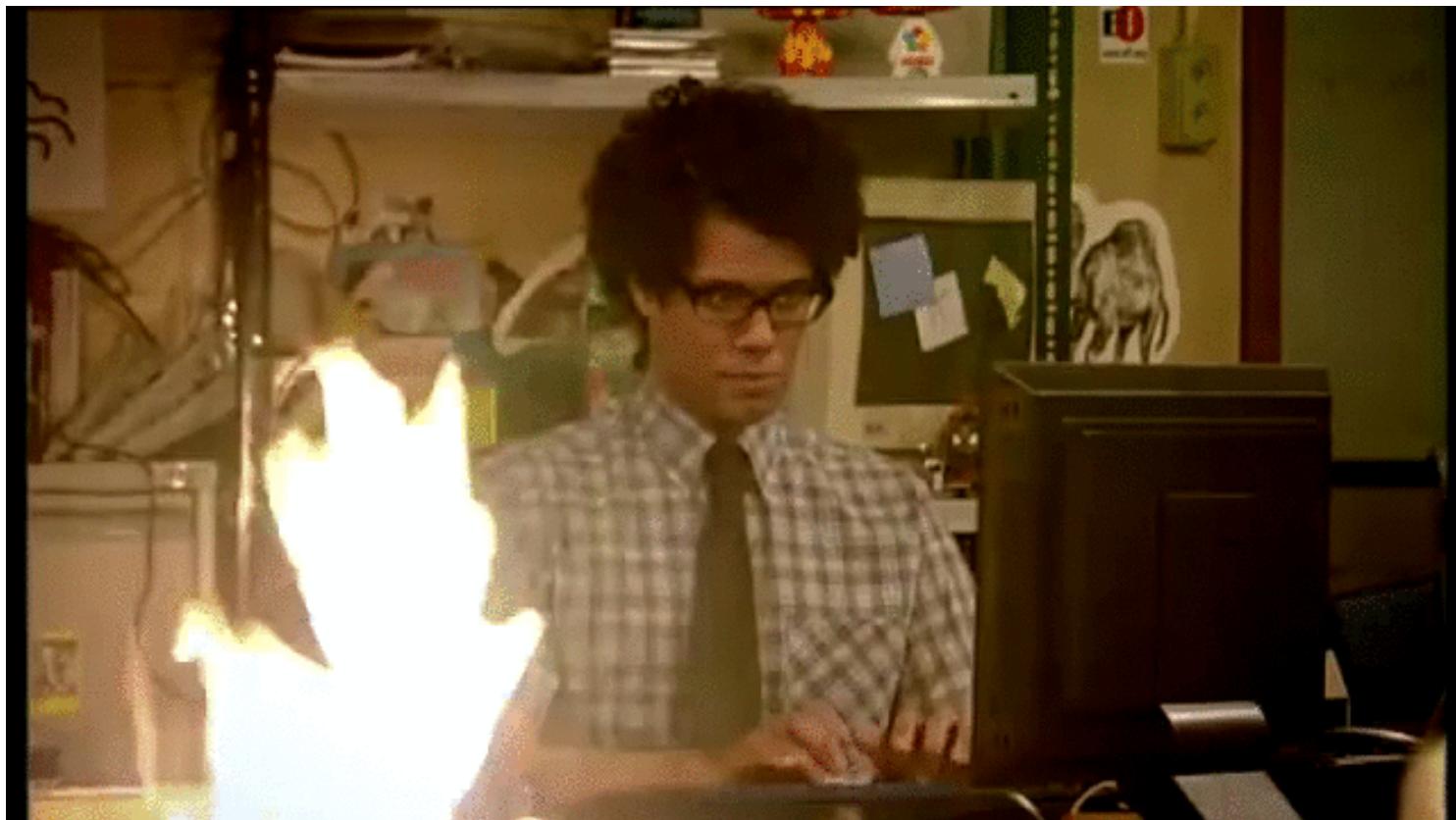
Comparative fluxomics

Metabolite exchanges are highly dependent on environmental context and can provide insights into the realized niche of organisms and communities



Your turn

Check out how to use MICOM for analysis of a single microbial community.



Let's check out our results and build some visualizations



Let's switch to the notebook!



And we are done 🙌

Nick Bohmann
Sean Gibbons
Alyssa Easton
Katherine Ramos Sarmiento
Noa Rappaport
Karl Gaisser
Chloe Herman
Greg Caporaso
Christian Diener

Dominic Lewis
Allison Kudla
Audri Hubbard
Joe Myxter
Thea Swanson
Victoria Uhl
Connor Kelly
Shanna Braga
ISB Facilities Team

Thanks! ❤️



