

Modeling microbiota-wide metabolism with MICOM

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from the **ISB Microbiome Course 2020**

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 gibbons.isbscience.org

 [gibbons-lab](#)

 [@thaasophobia](#)



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

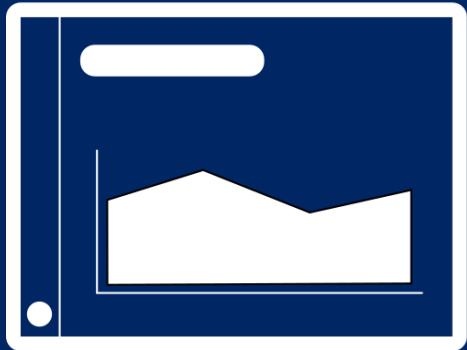
https://gibbons-lab.github.io/isb_course_2020/micom



Quick reminder

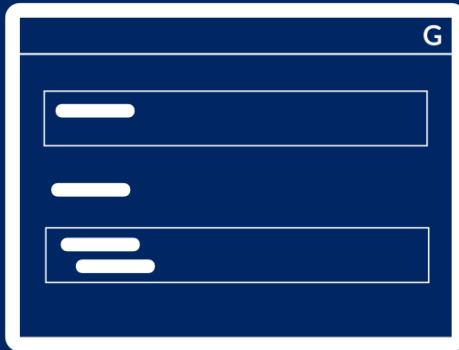


Presentation



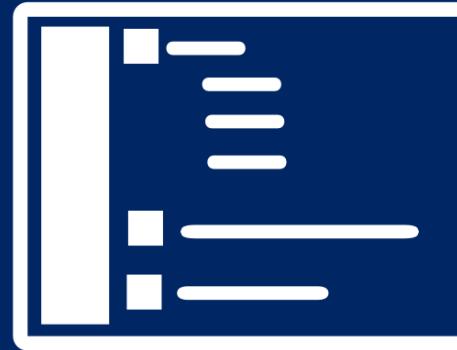
logic
explanations
links

Notebook



technical aspects
materials
visualizations

Chat



support
Q&A

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).

Yields metabolic **capacity** or **potential**.

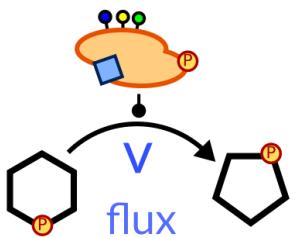


Genes and metabolite abundances are cool
but not what you really care about*

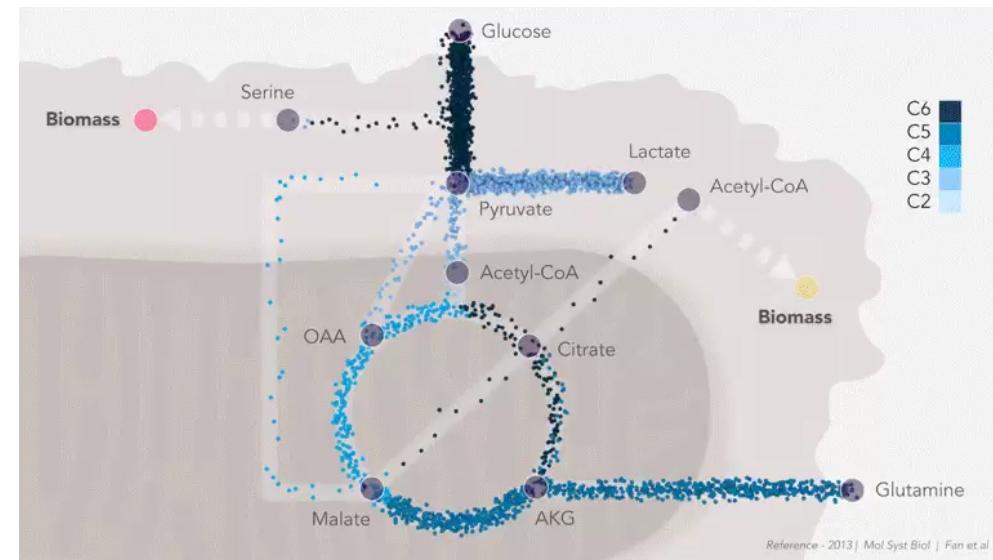
hot take 🔥



Fluxes



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



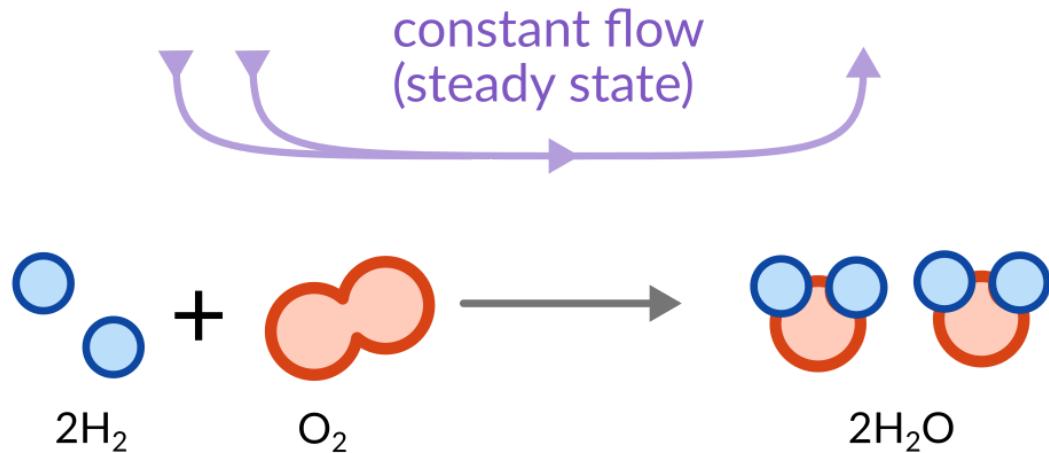
video courtesy of [S. Nayak](#) and [J. Iwasa](#)

Flux Balance Analysis (FBA)

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

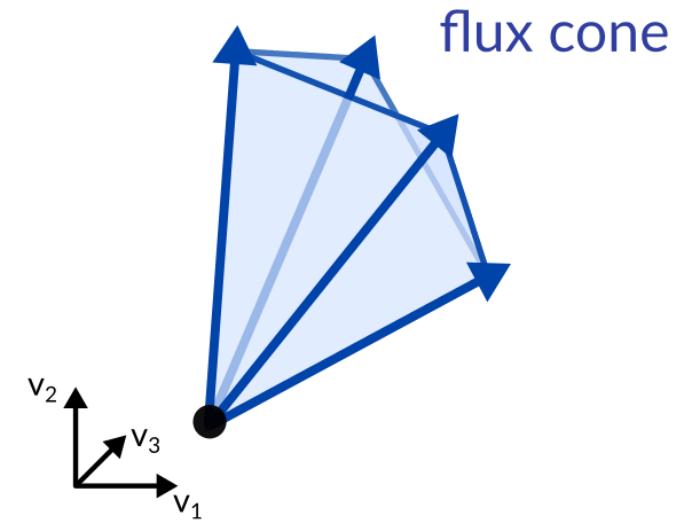


The flux cone



balance equations

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



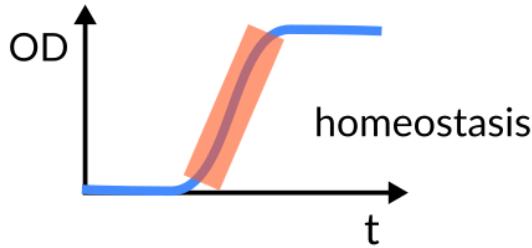
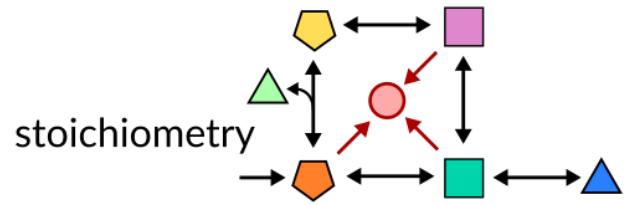
$$\mathbf{S} \cdot \mathbf{v} = 0$$

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

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



Genome-scale metabolic modeling



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

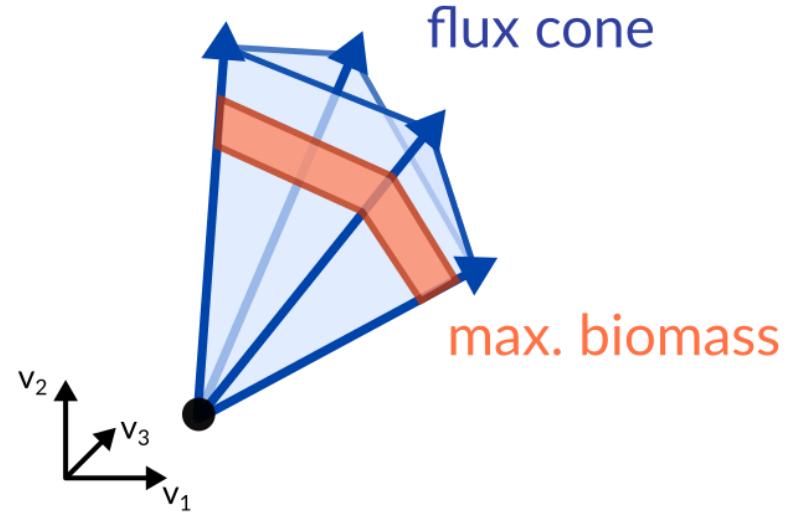
$$-1000 \leq v_i \leq 1000$$



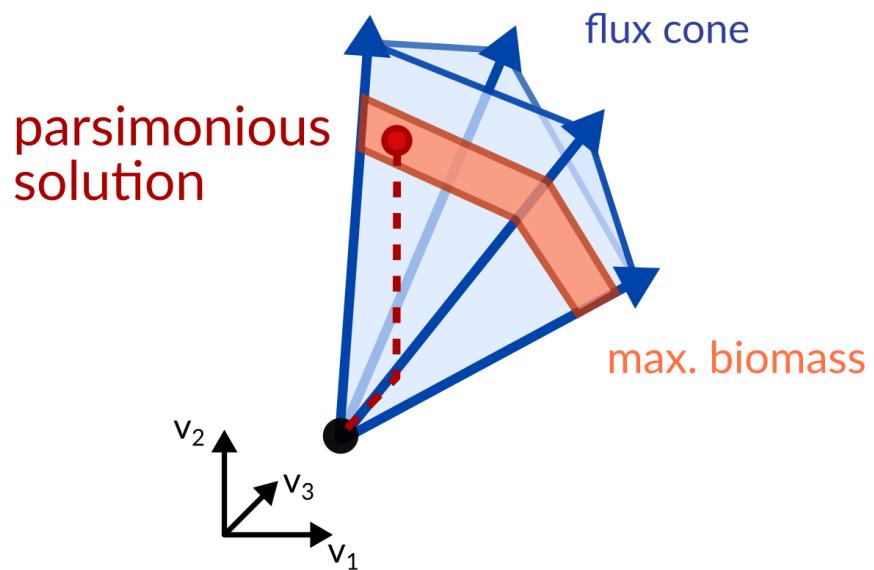
thermodynamics



environment



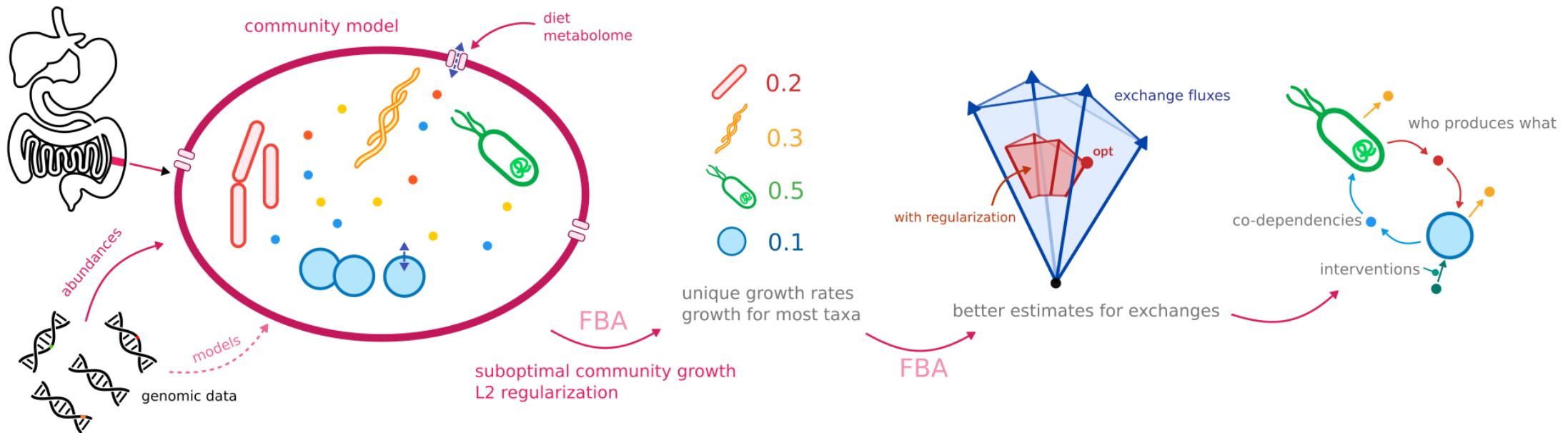
Selecting biologically relevant fluxes via parsimony



Reproduces experimental fluxes in *E. coli* very well.

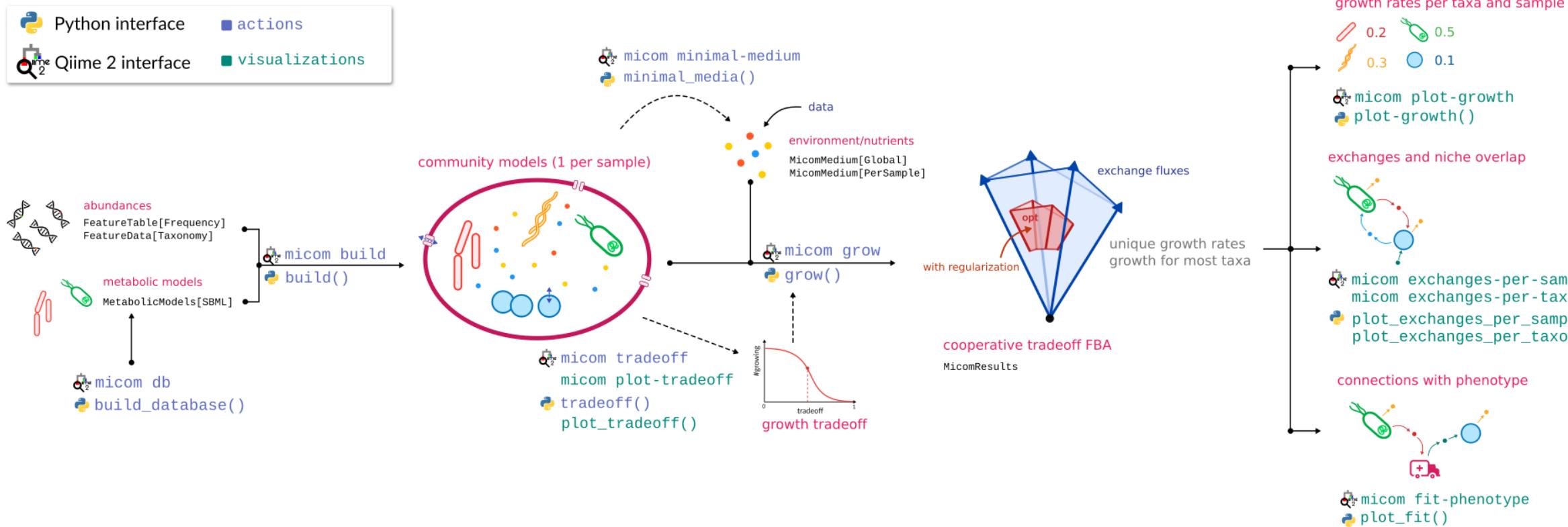
Bacteria do not like to produce more enzymes than necessary.

MICOM



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





Let's continue with our data



Let's switch to the notebook...



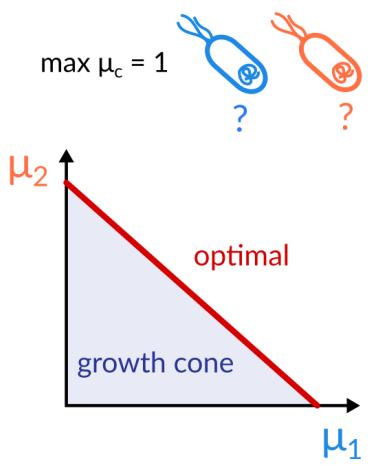
Community-wide growth is hard 😢

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

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

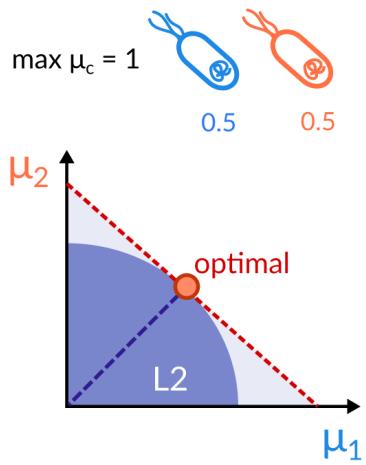
Why is this so hard? Can't we just maximize the community growth rate? Well...

When 2 leads to infinity...



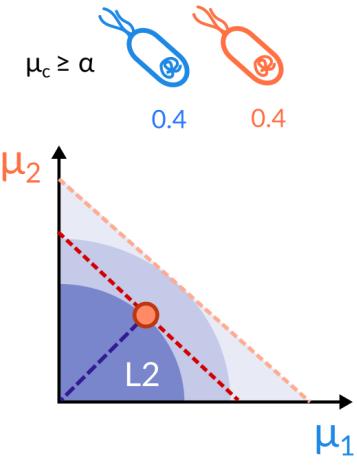
FBA

$$\text{maximize } \mu_c$$



cooperative

$$\begin{aligned} &\text{minimize } \sum \mu_i^2 \\ &\text{s.t. } \mu_c = \max \mu_c \end{aligned}$$



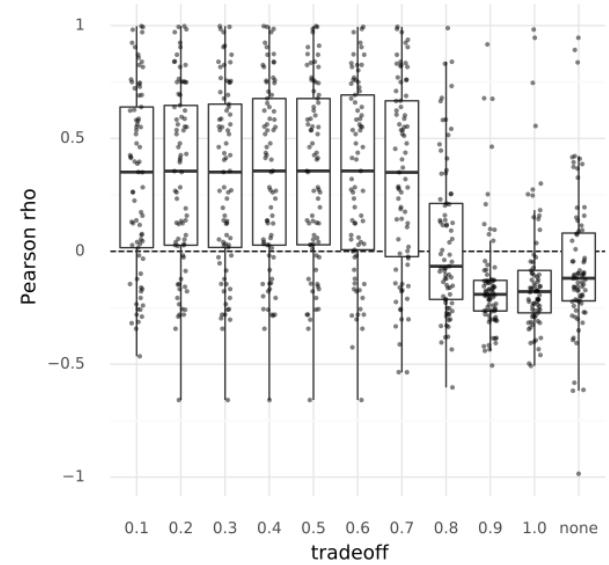
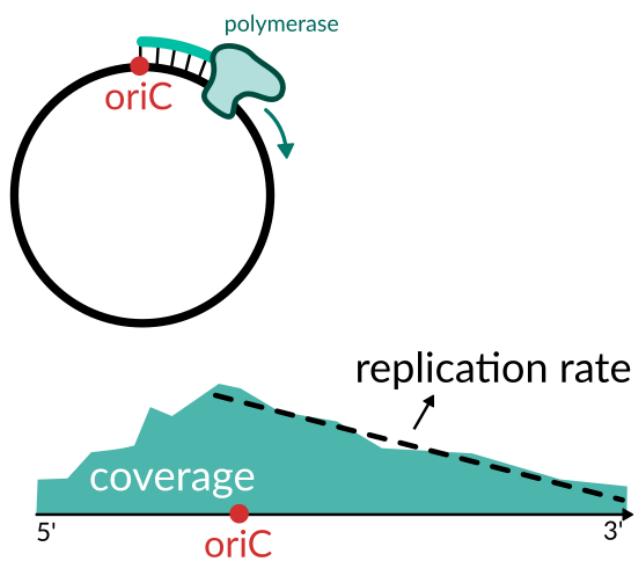
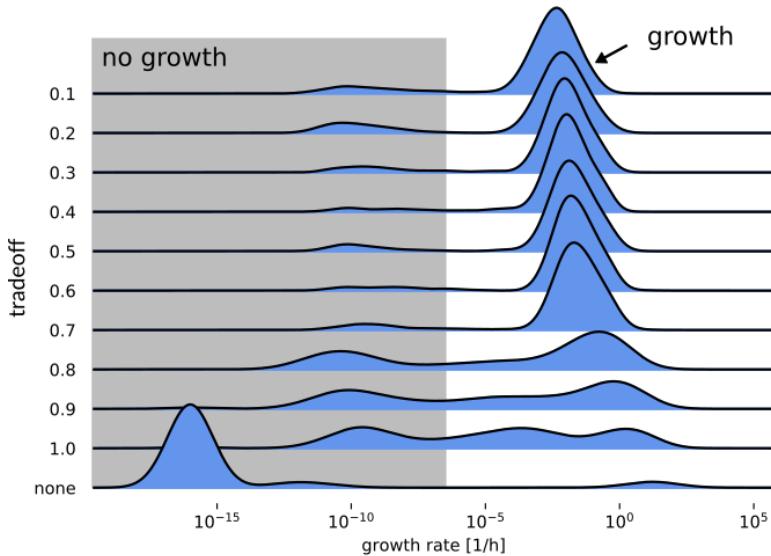
cooperative
tradeoff

$$\begin{aligned} &\text{minimize } \sum \mu_i^2 \\ &\text{s.t. } \geq \alpha \cdot \max \mu_c \end{aligned}$$

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?



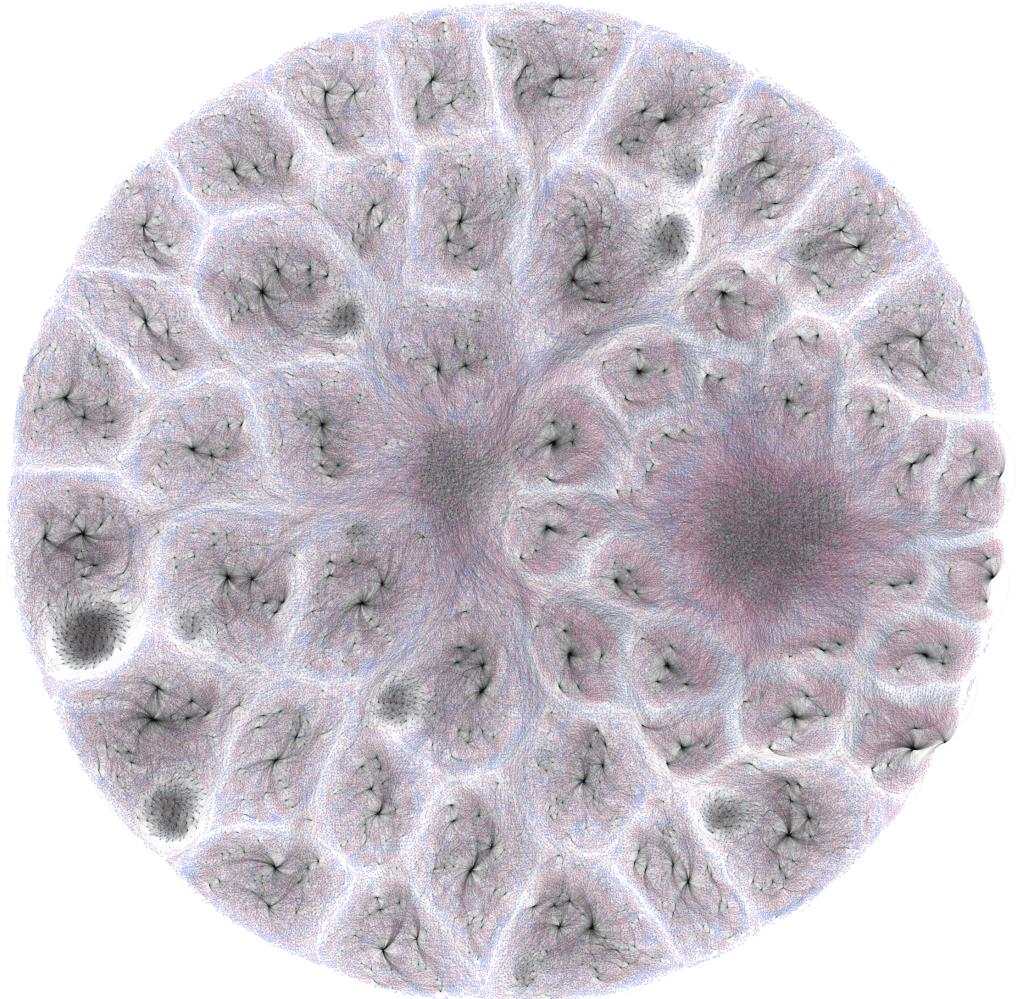
<https://doi.org/10.1128/mSystems.00606-19>



Easy peasy. What's taking so long then?

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

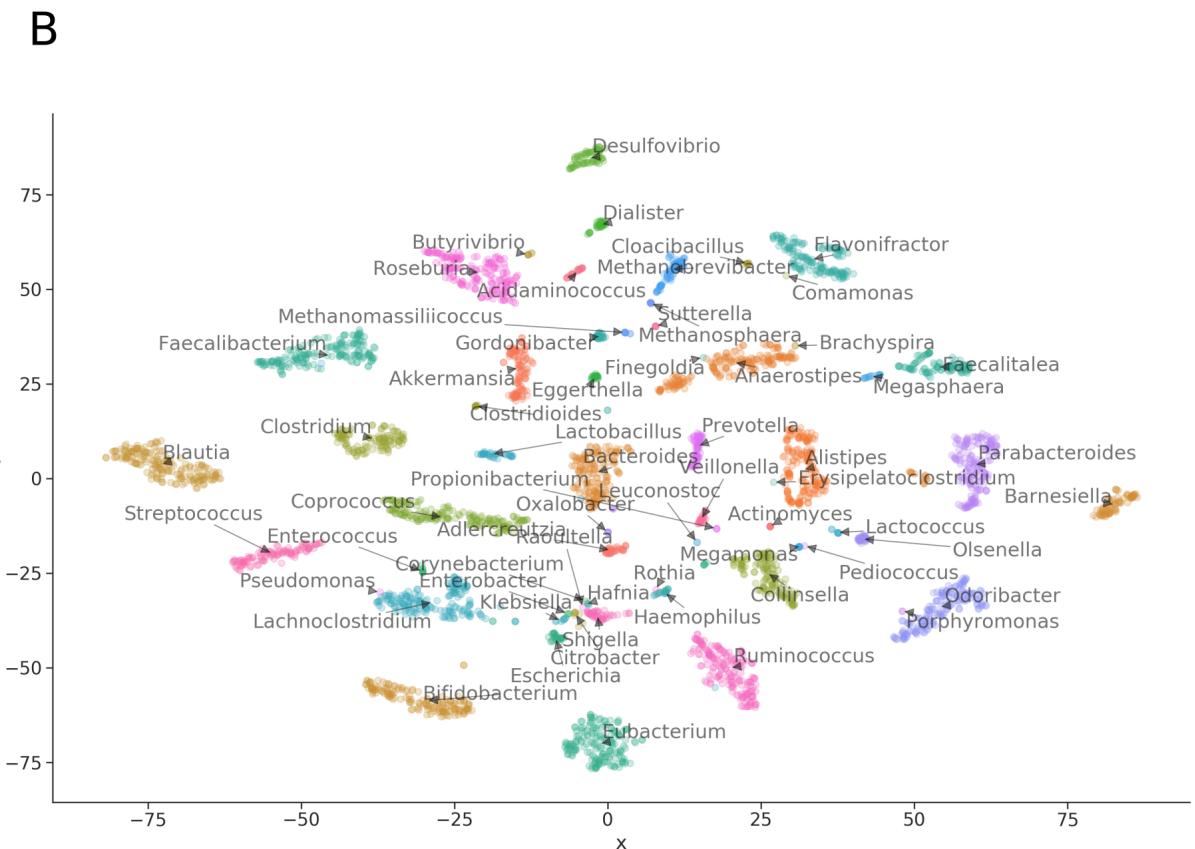
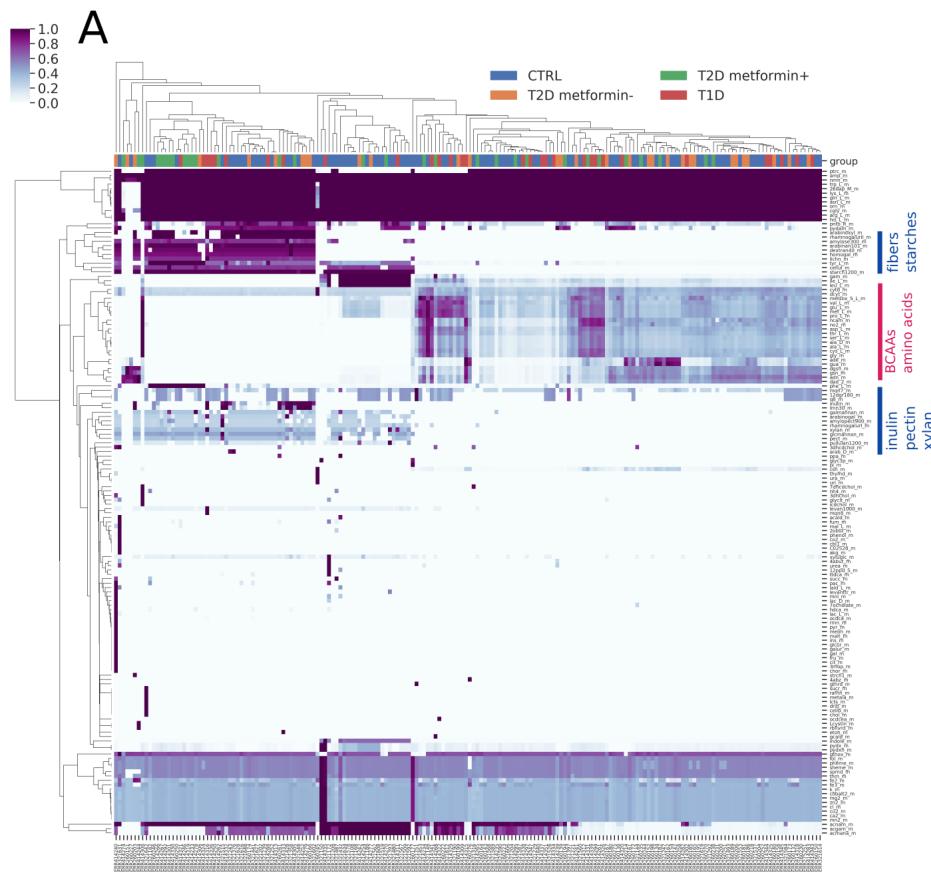




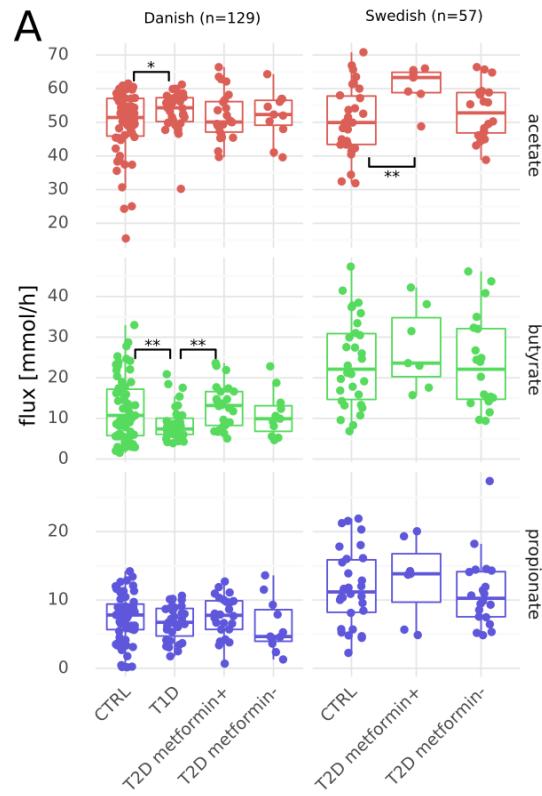
69,441 reactions / 46,883 metabolites / 292,699 connections



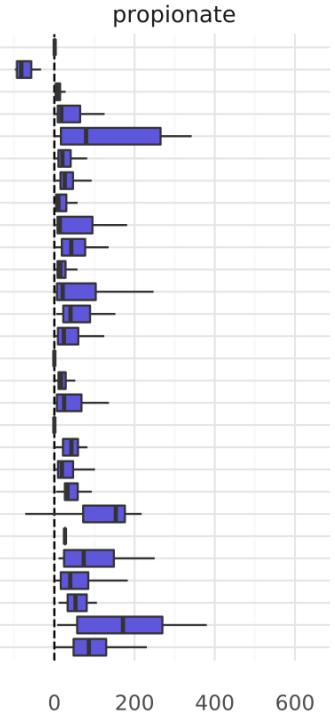
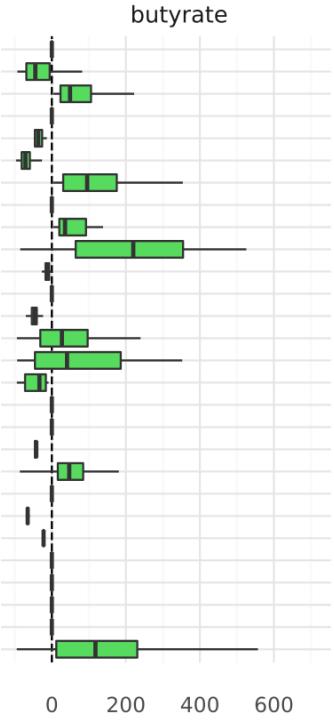
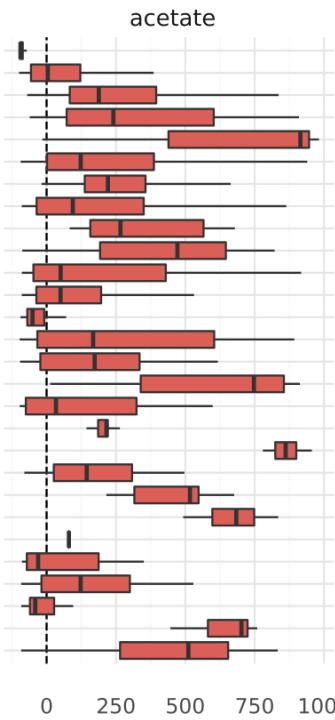
The niche space



Metabolic connections with disease



Bacteroides
Eubacterium
Faecalibacterium
Akkermansia
Klebsiella
Ruminococcus
Roseburia
Parabacteroides
Megasphaera
Coproccus
Blautia
Alistipes
Streptococcus
Bifidobacterium
Anaerostipes
Acidaminococcus
Prevotella
Methanobrevibacter
Shigella
Odoribacter
Lactococcus
Escherichia
Erysipelatoclostridium
Lactobacillus
Collinsella
Enterococcus
Dialister
Lachnoclostridium



We observed that the **overall production flux** $v_p = \sum a_i \cdot v_i^{ex}$ is most directly related to the phenotype.

This is the flux the **intestinal cells** can interact with.



Your turn

Check out how to use MICOM for a “n-of-1” analysis.



And we are done 🙌

Thanks!

