

A Deep-Dive into Microbe-Centric Metabolic Modeling

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Workshop B

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Outline



1. Flux Balance Analysis
2. Metabolic reconstruction
3. Break
4. Metagenome-scale metabolic modeling
5. Introduction to the hands-on setup
6. Hands-on exercise
7. Wrap-up

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**.

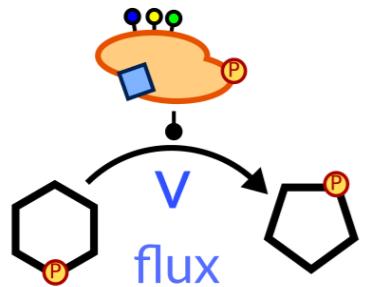


Genes and metabolite concentrations are cool but not
what you really care about*

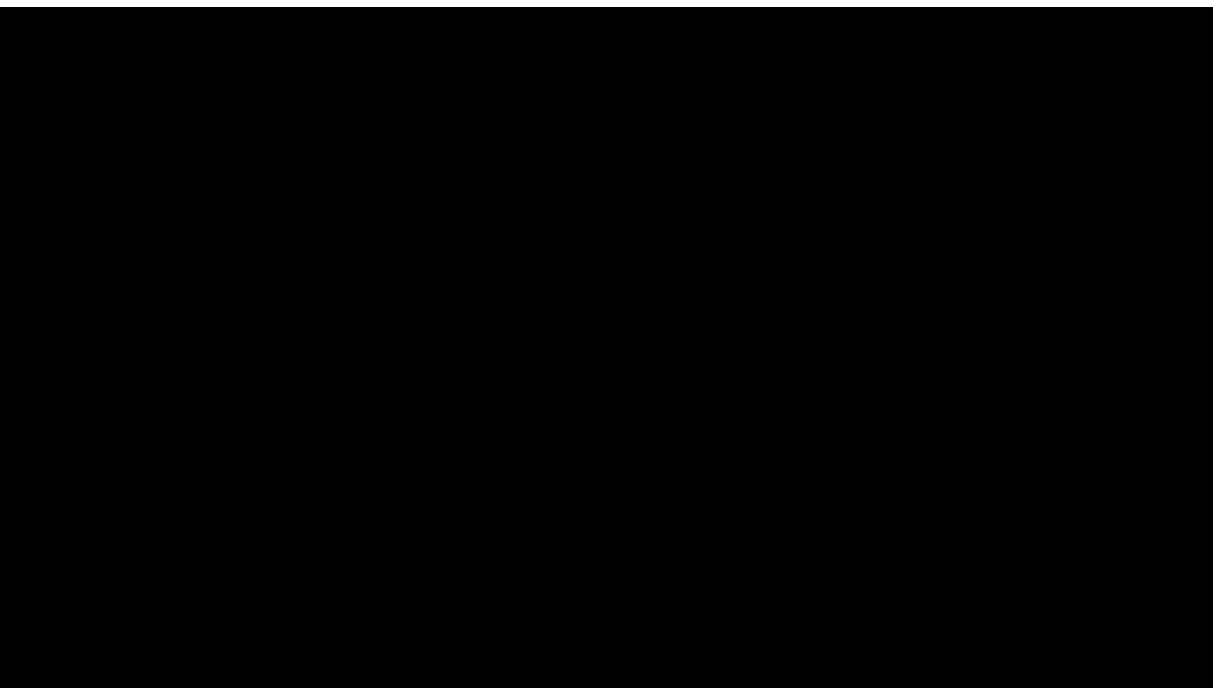
hot take 🔥



Fluxes



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



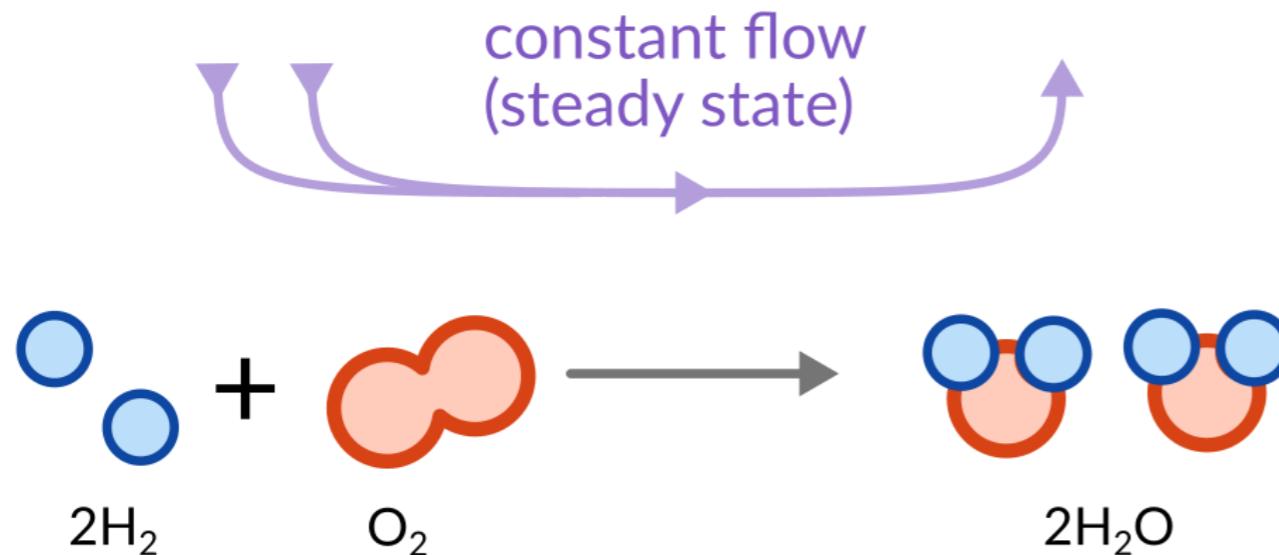
video courtesy of [S. Nayak](#) and [J. Iwasa](#)

Flux Balance Analysis(FBA)

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



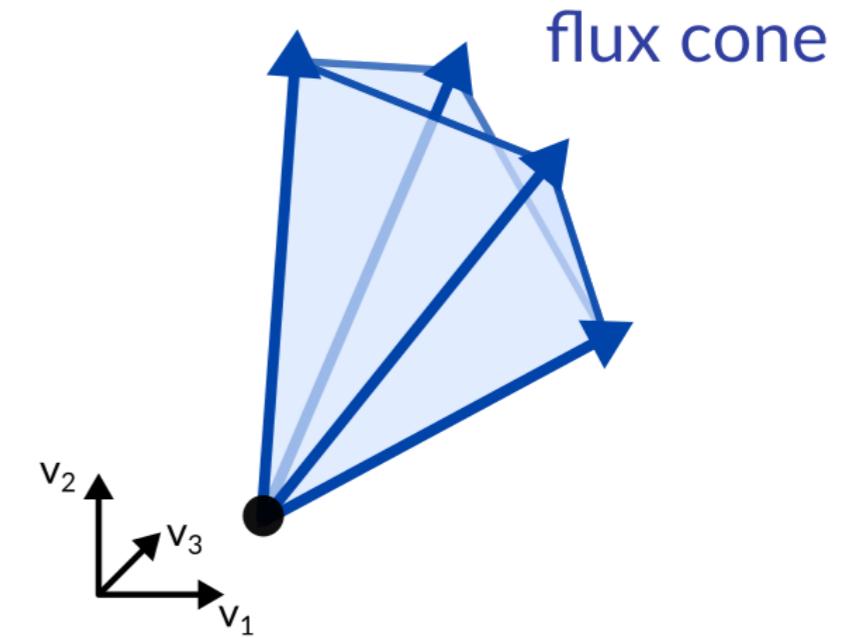
The flux cone



balance equations

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

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



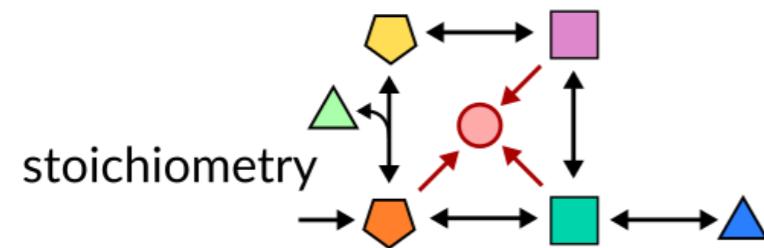
$$\mathbf{S} \cdot \mathbf{v} = 0$$

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

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



Genome-scale metabolic modeling

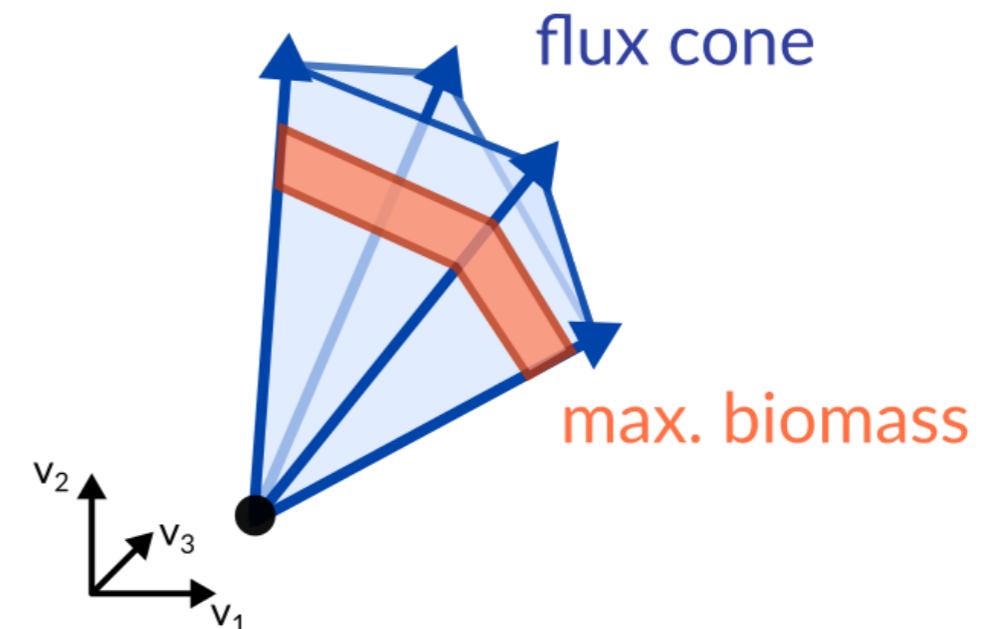
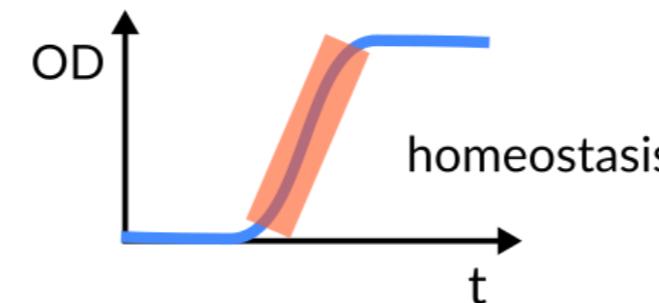


$$S \cdot v = 0$$

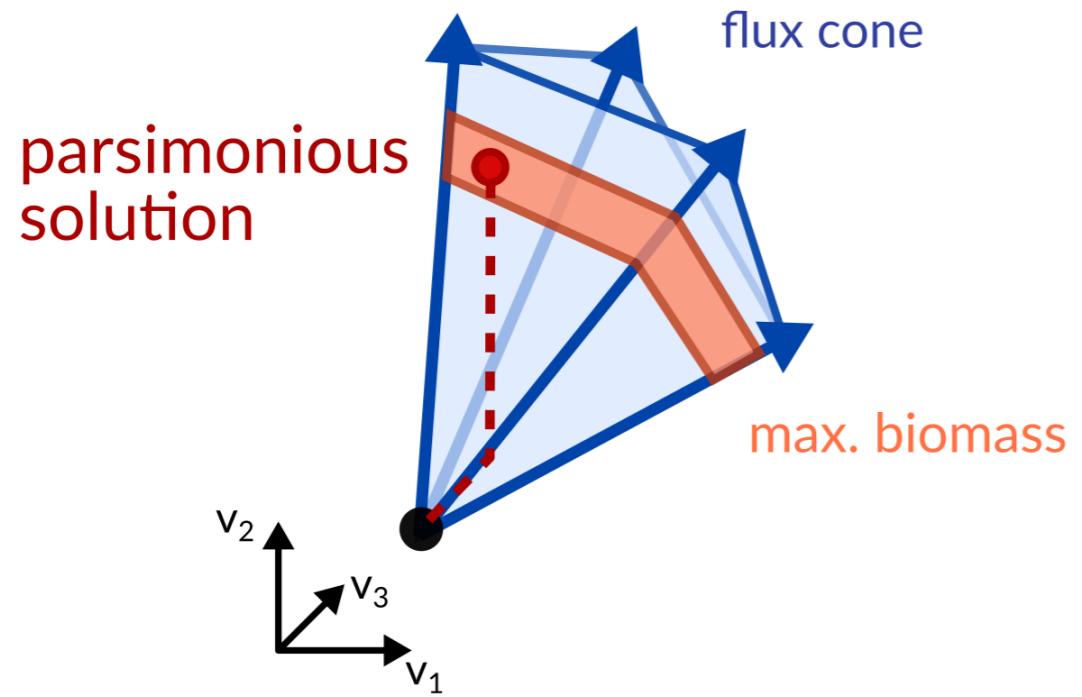
$$-1000 \leq v_i \leq 1000$$



thermodynamics



Selecting biologically relevant fluxes via parsimony



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

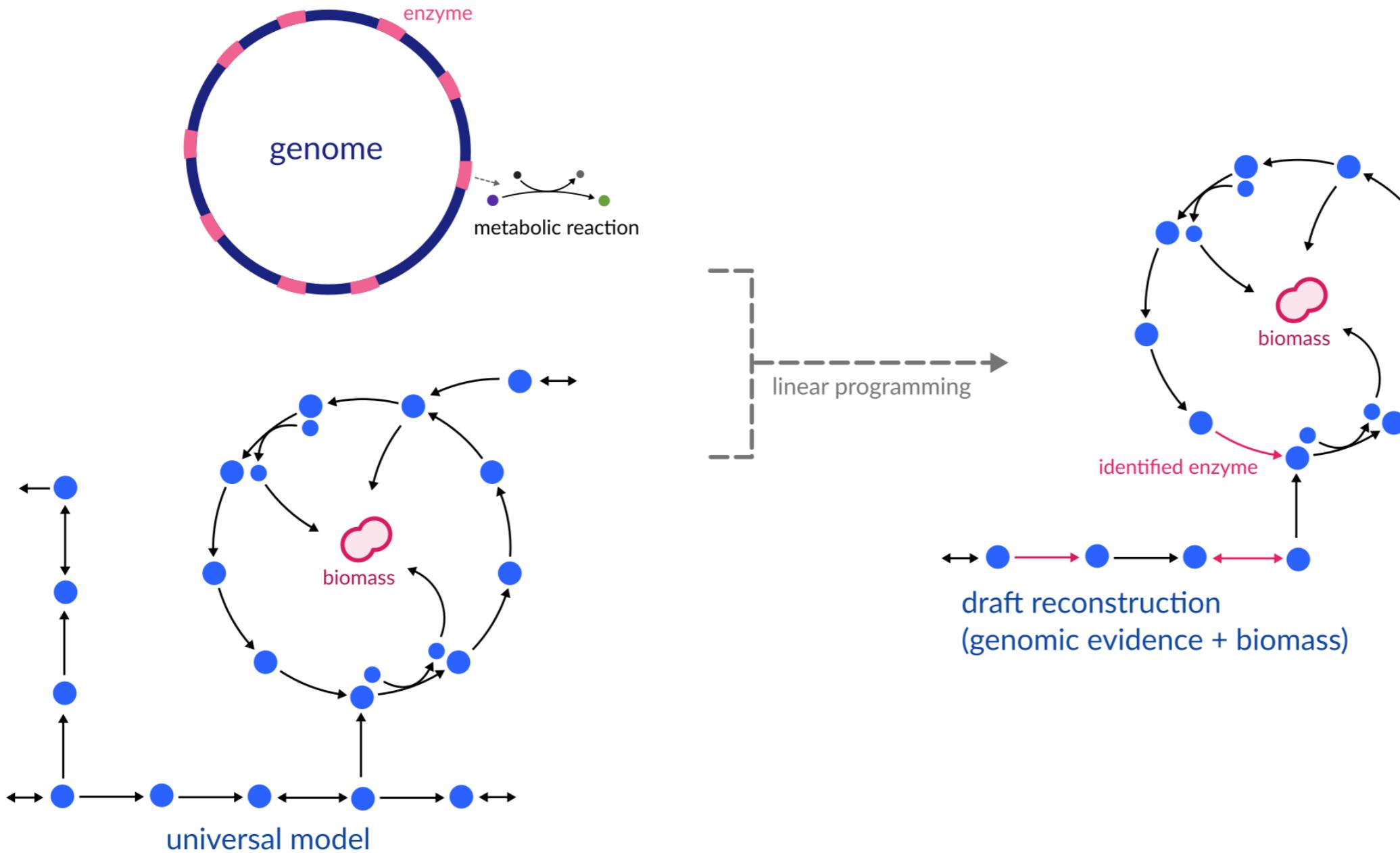
Bacteria do not like to produce more enzymes than necessary.

Metabolic reconstruction

How do we get a genome-scale metabolic model in the first place?

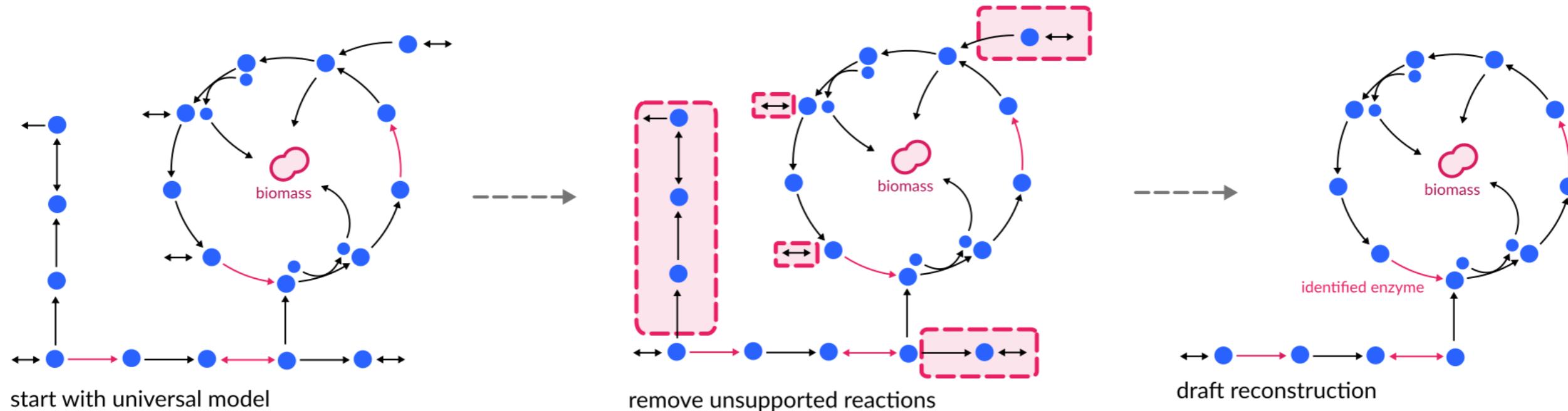


General strategy



top-down approach

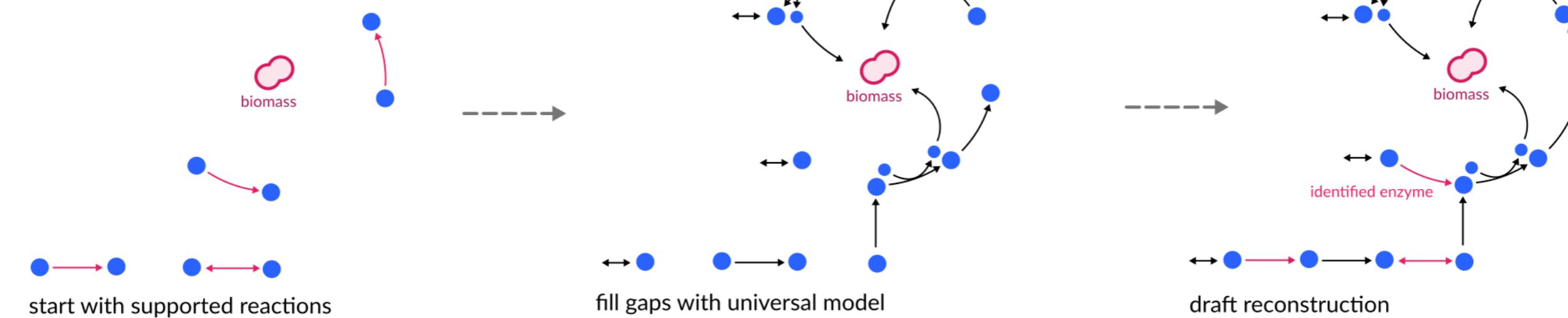
carveME (BIGG)



bottom-up approach

ModelSEED/Kbase (ModelSEED)

gapseq (ModelSEED + others)



Curated reconstructions

Curation is the process of adding or removing reactions to the model based on experimental evidence.

Basic

- structural quality ([MEMOTE](#))
- gap-filling for a standard growth medium (LB, M9, ...)
- example: [carveME EMBL GEMs](#) - 5587 strains

Stringent

- growth on various carbon sources ("likes maltose but not glucose")
- known metabolic conversion ("produces indole from tryptophan")
- strain-specific biomass composition
- example: [AGORA](#) - 818 strains from human gut



	carveME	ModelSEED/Kbase	gapseq
speed	😊	😔	😢
sensitivity	😔	😢	😊
model quality	😊	😔	😊
free solver	😢	😔	😊
easy to use	😔	😊	😢
many media	😔	😊	😔*
SBML standard	😊	😊	😊

Limitations

- unknown enzymes/pathways are never captured
- dependency on universal model
- hard to formulate growth media
- growth objective may not always apply (toxicity, human tissues)



Metagenome-scale metabolic modeling



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

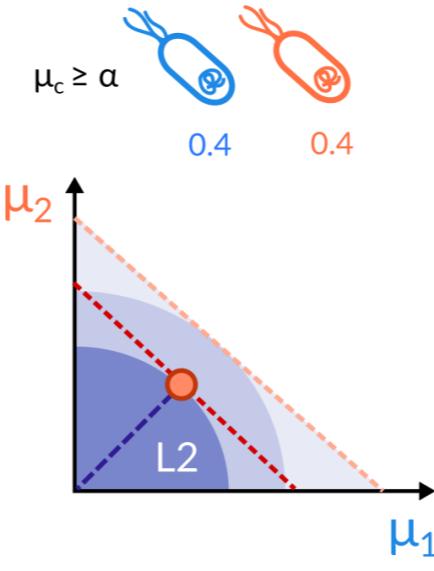
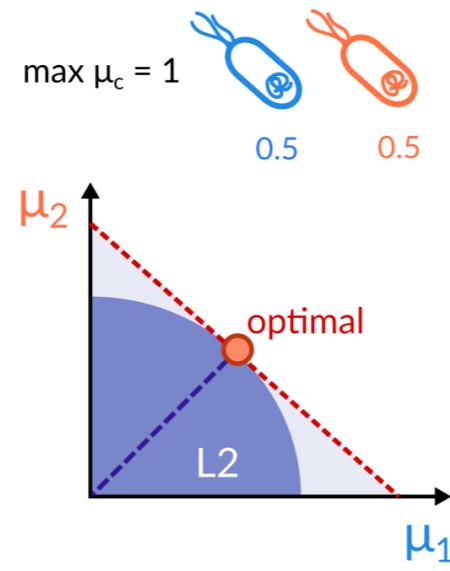
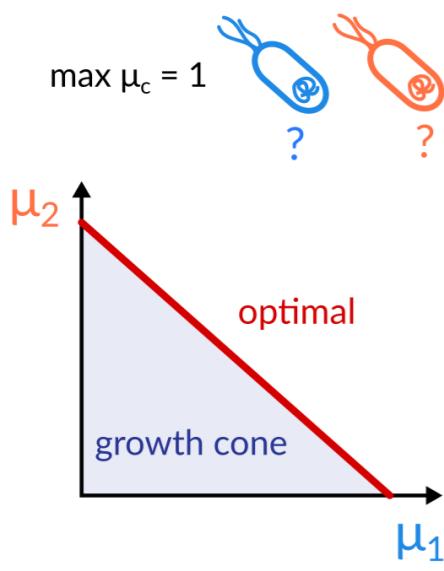
$$\mu_c = \sum_i a_i \cdot \mu_i$$

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

Cooperative Tradeoff FBA combines flux balance analysis with an ecological model constraining the growth rates.



When 2 leads to infinity...

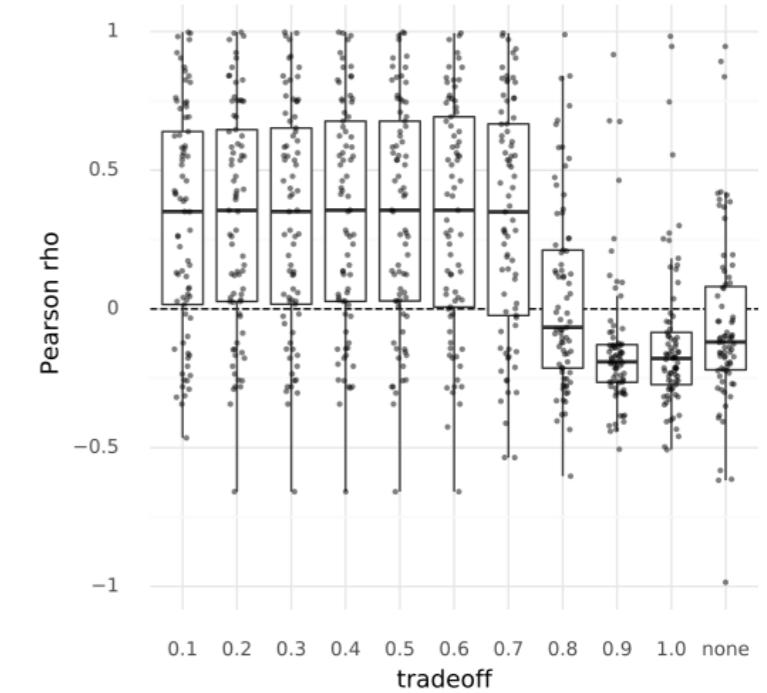
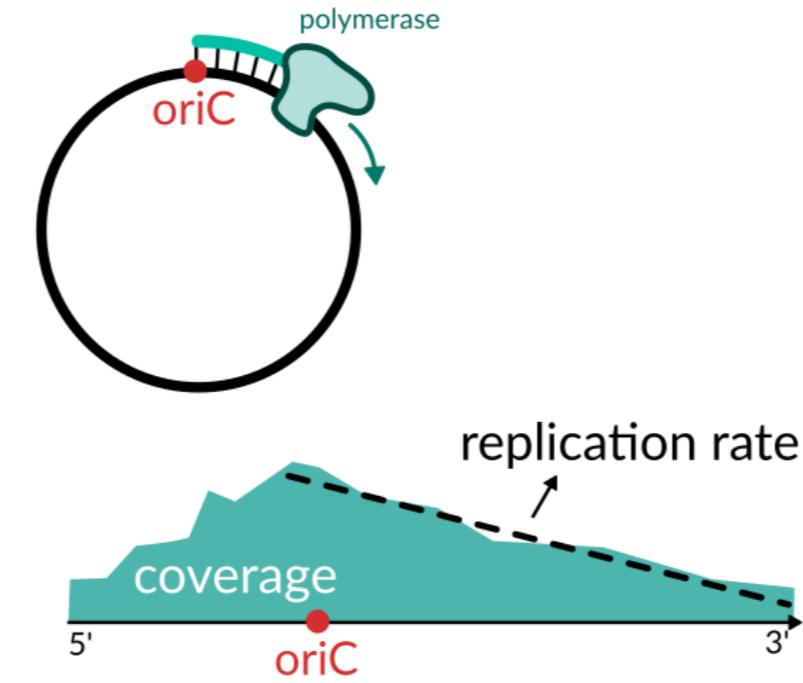
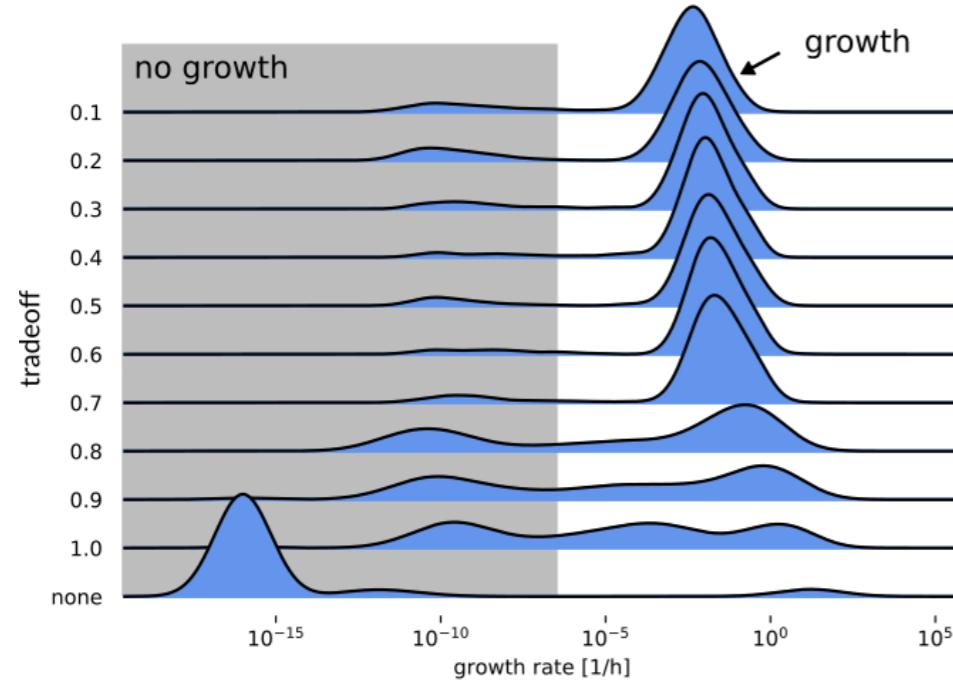


maximize μ_c

minimize $\sum \mu_i^2$
s.t. $\mu_c = \max \mu_c$

minimize $\sum \mu_i^2$
s.t. $\geq \alpha \cdot \max \mu_c$

But does it work?



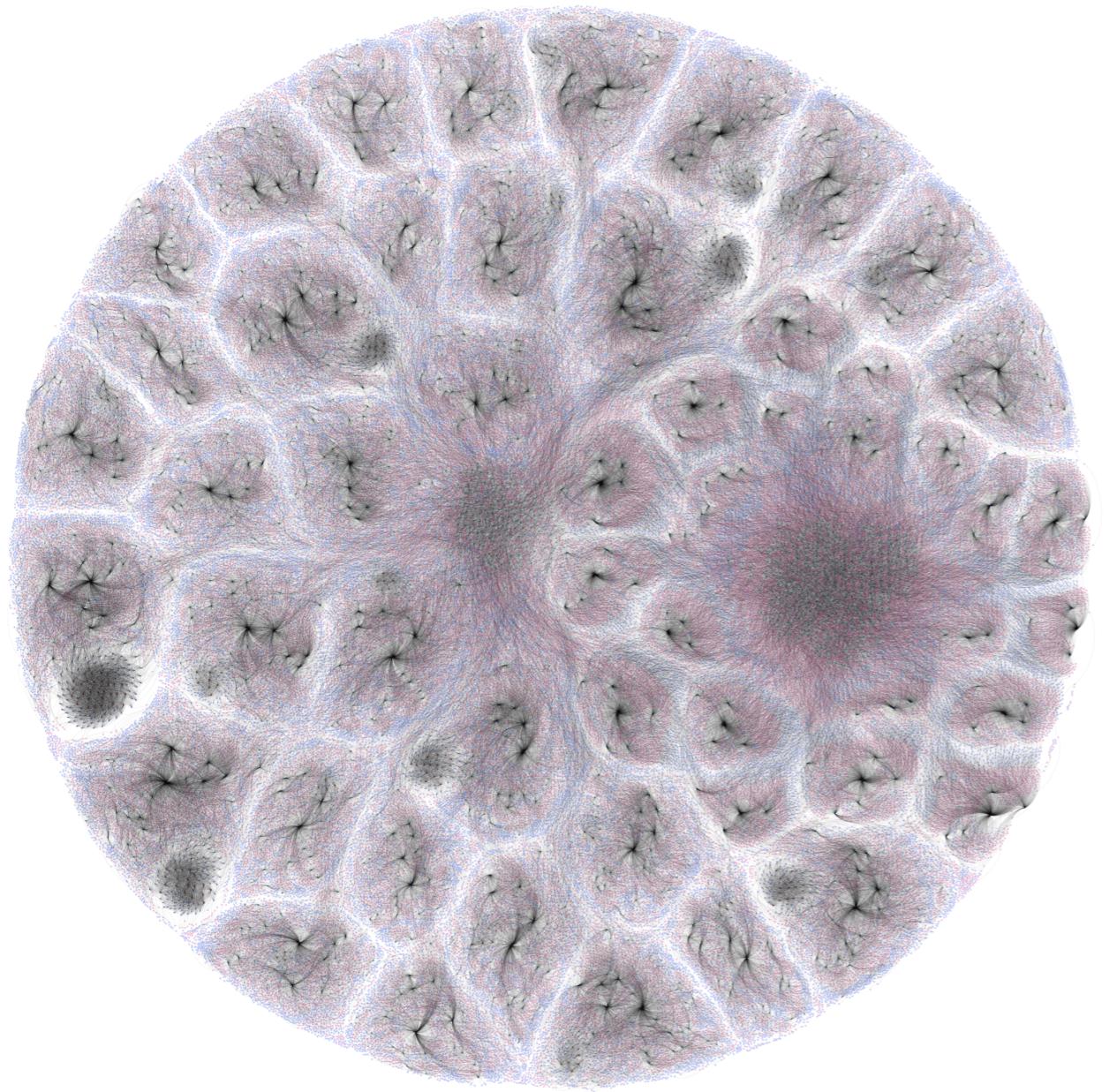
<https://doi.org/10.1128/mSystems.00606-19>



Easy peasy. What's taking so long then?

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





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



Your turn

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

[open the notebook](#)

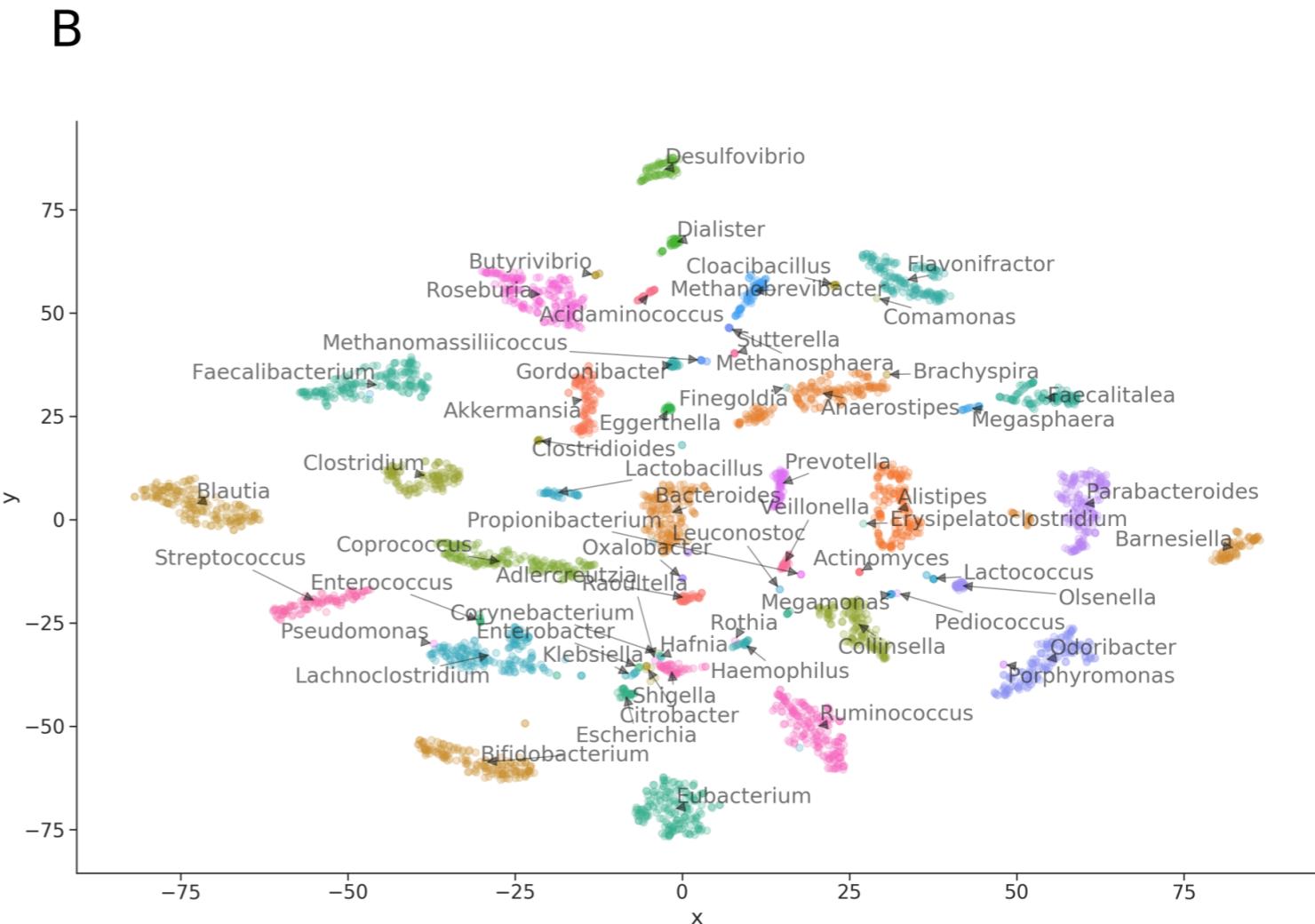
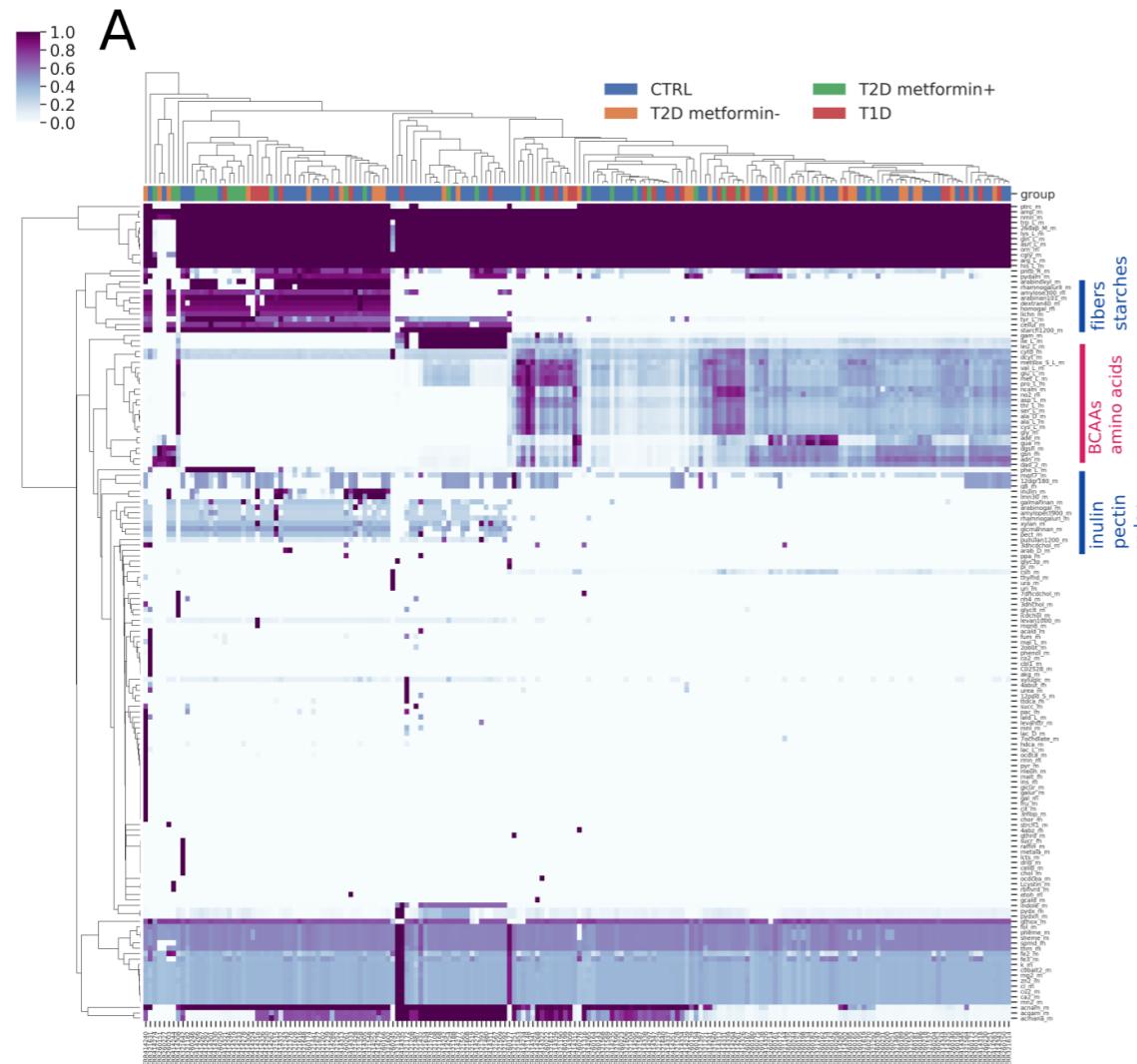


And we are done 🙌

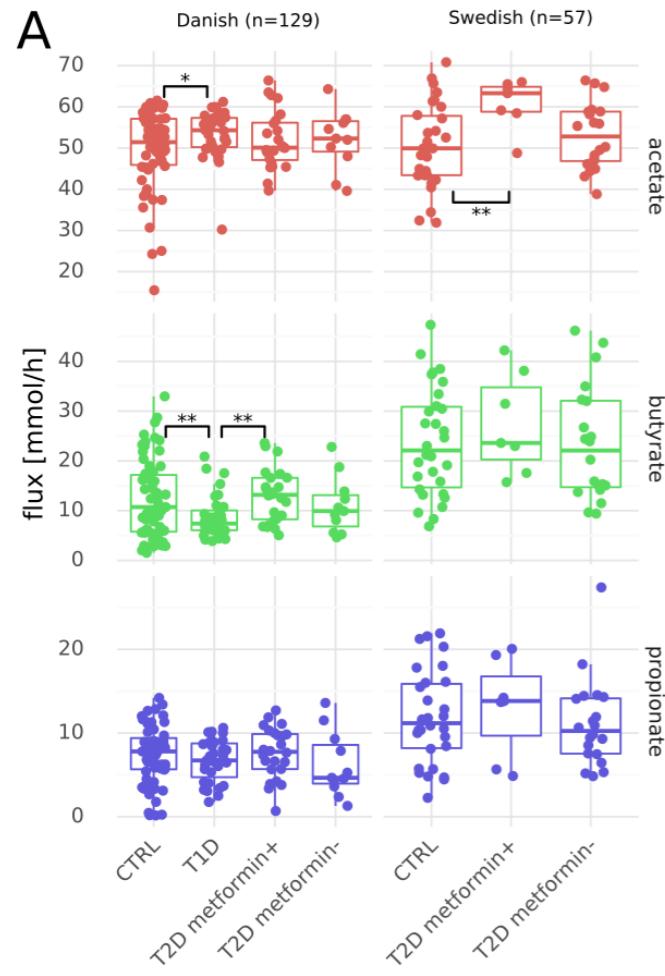
Thanks!



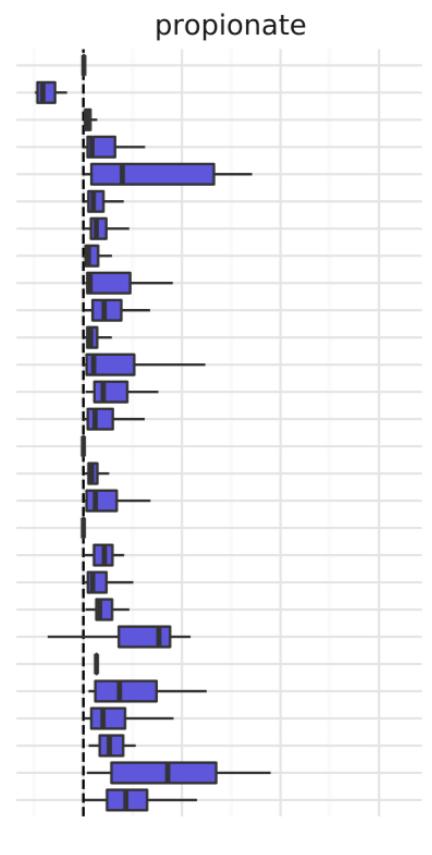
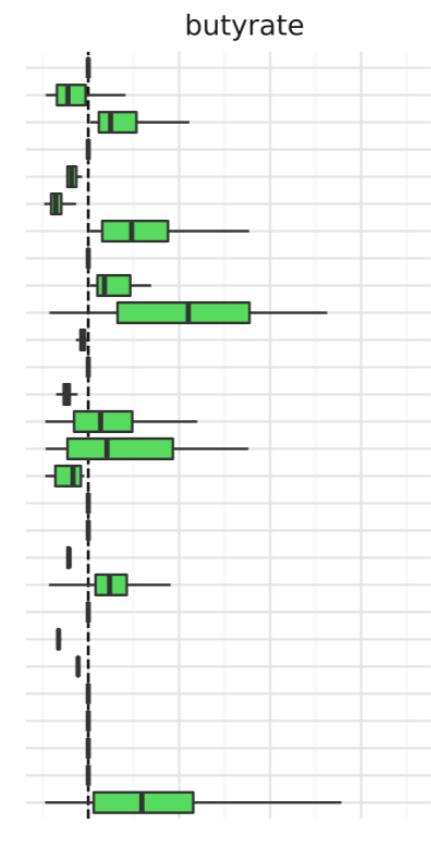
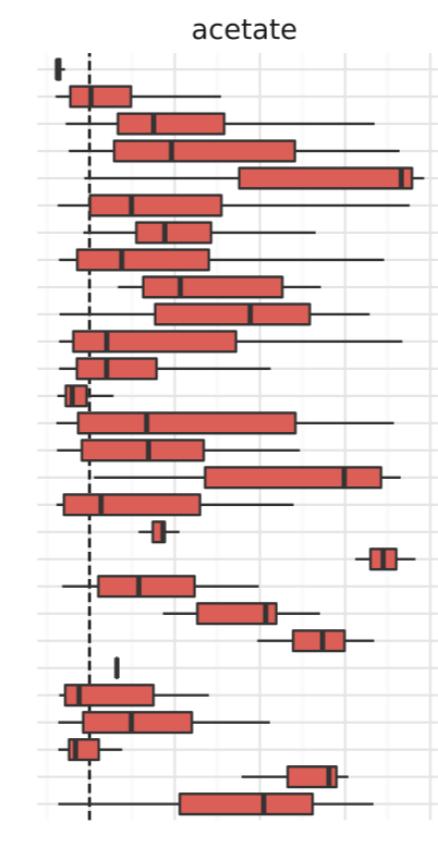
The niche space



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.

