ETH zürich

Model-based Analysis of Microbial Communities

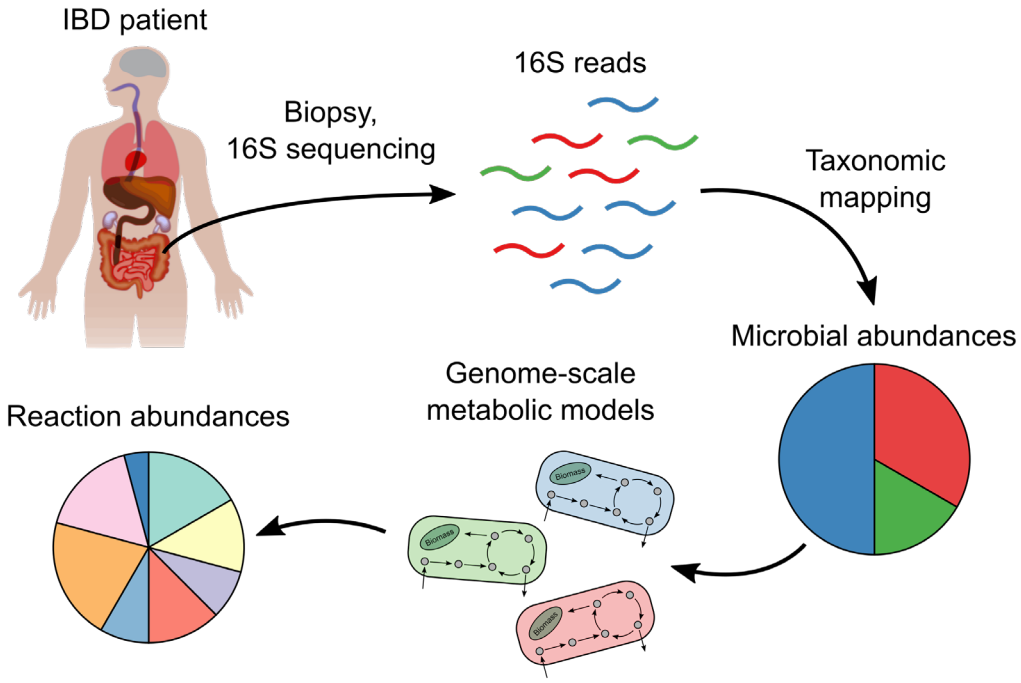
Jörg Stelling, D-BSSE, ETH Zurich

Metabolism and mathematical models, Oct. 2022

csb computational systems biology

SIB Swiss Institute of Bioinformatics

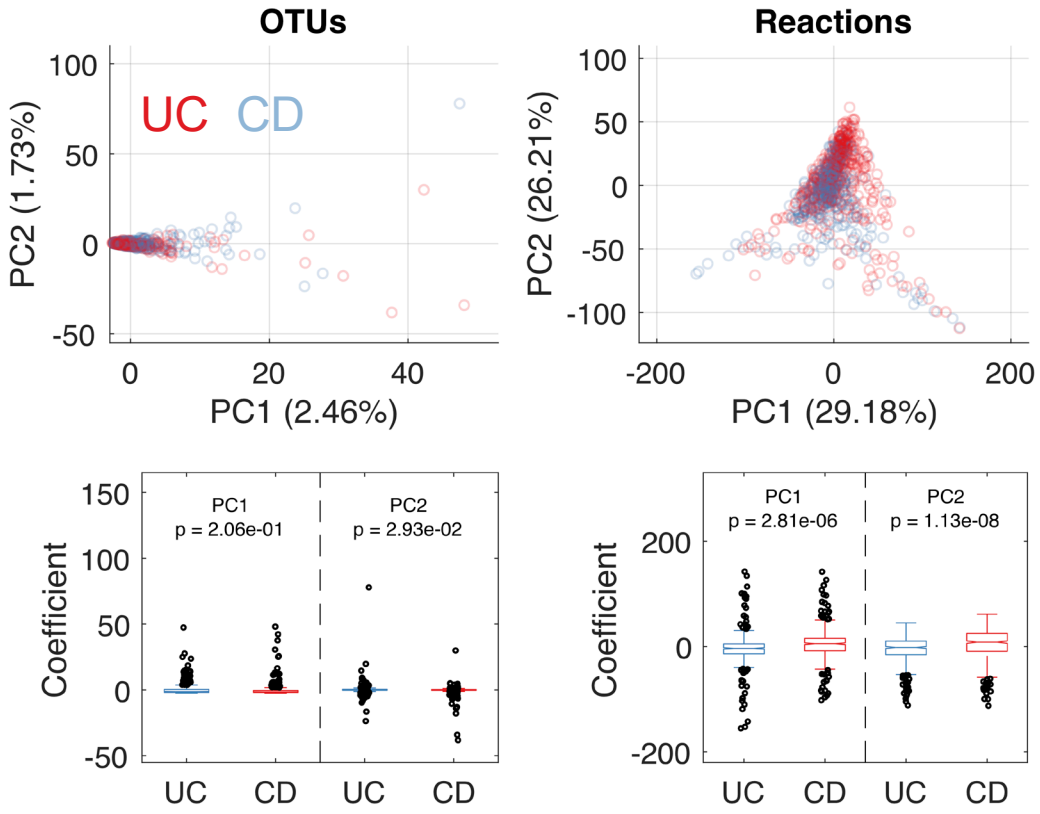
Example Communities: Analysis of Gut Microbiota From IBD Patients



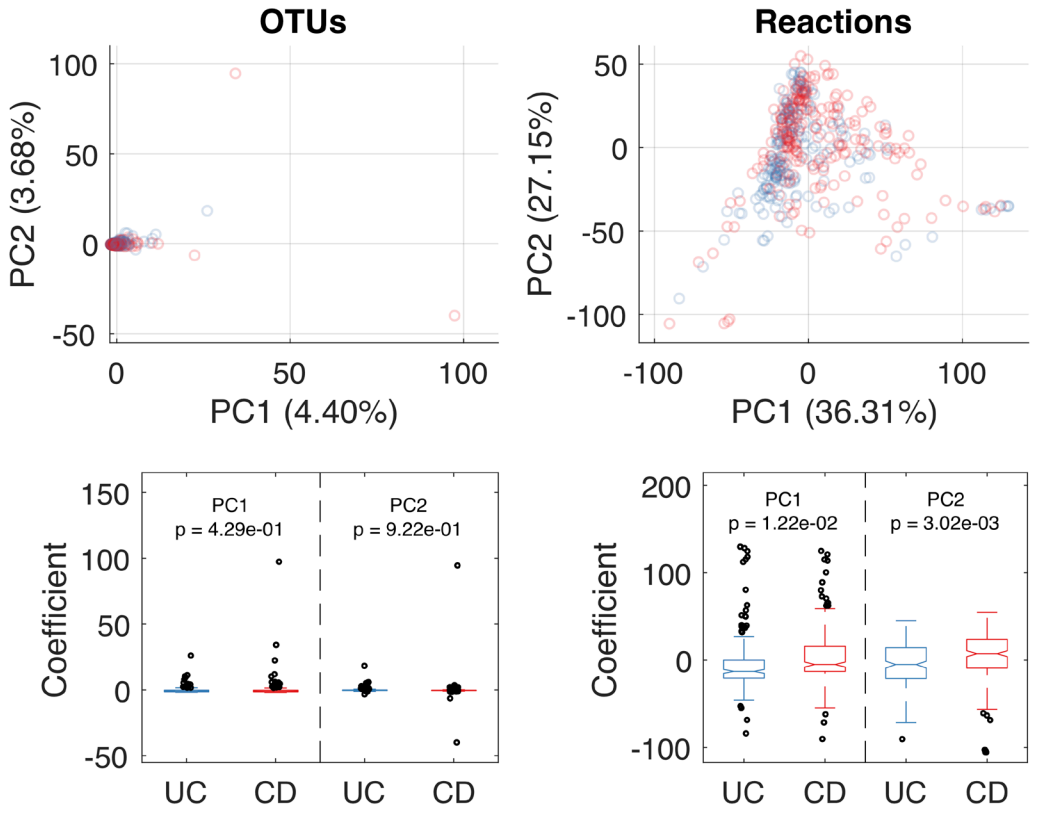
- Swiss inflammatory bowel disease (IBD) cohort data analysis:
  - Discrimination between ulcerative colitis (UC) and Crohn's disease (CD)?
  - Are microbial taxa or metabolic capabilities associated with diseases?

Reaction-Level Analysis Increases Explanatory & Discriminatory Power

Cohort 1



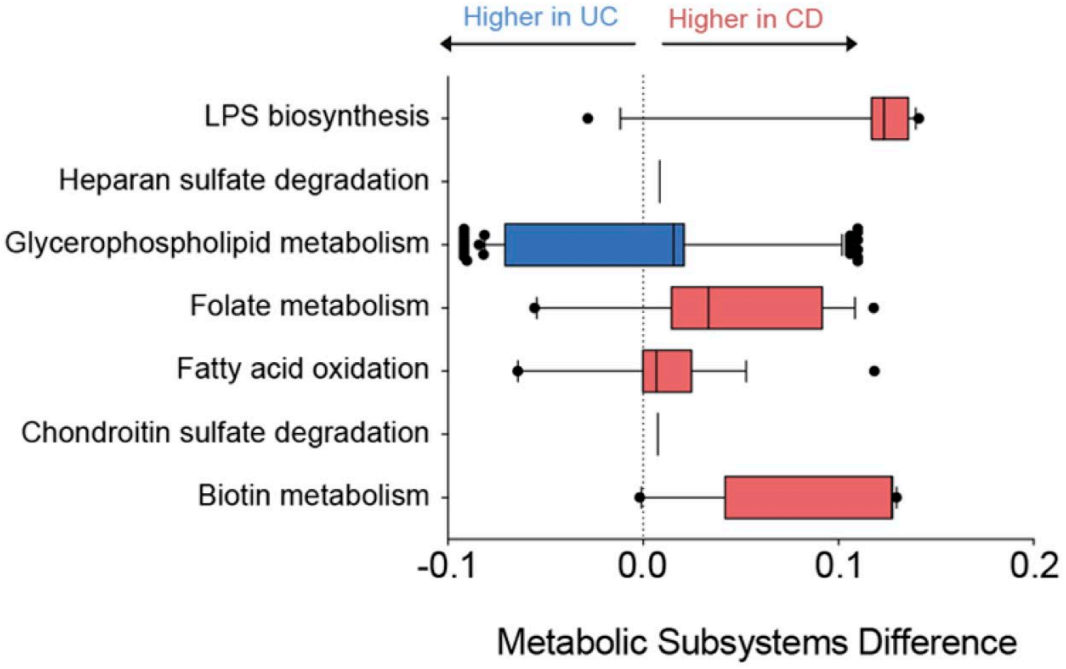
Cohort 2



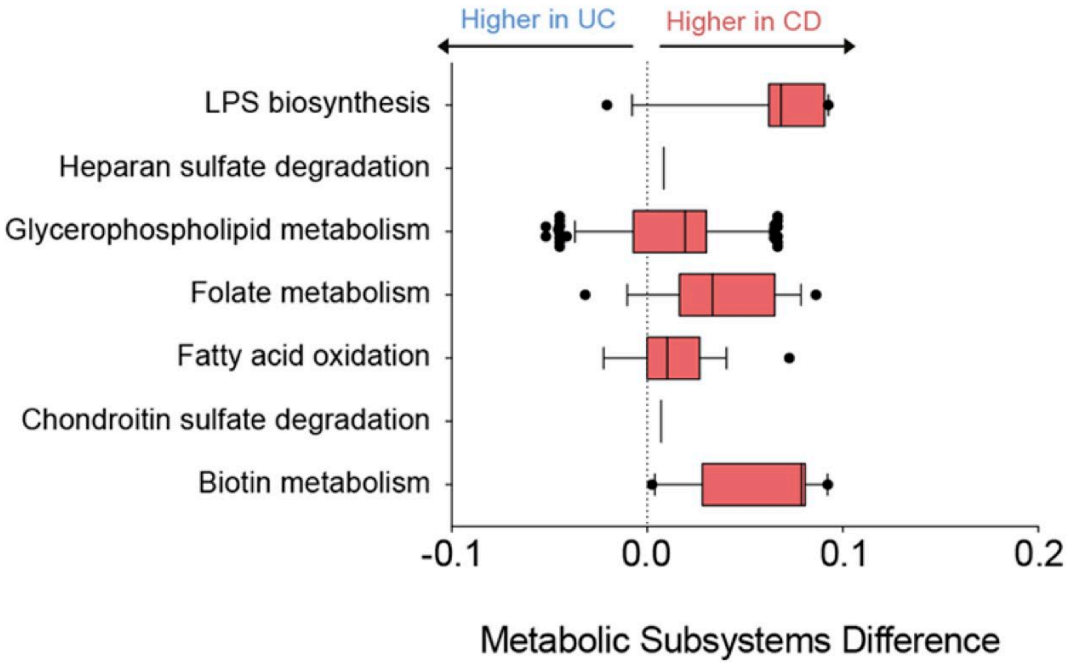
B. Yilmaz et al. (2019) *Nat. Medicine* 25: 323.

Reaction-Level Analysis Identifies Subsystem Enrichments in CD

Cohort 1



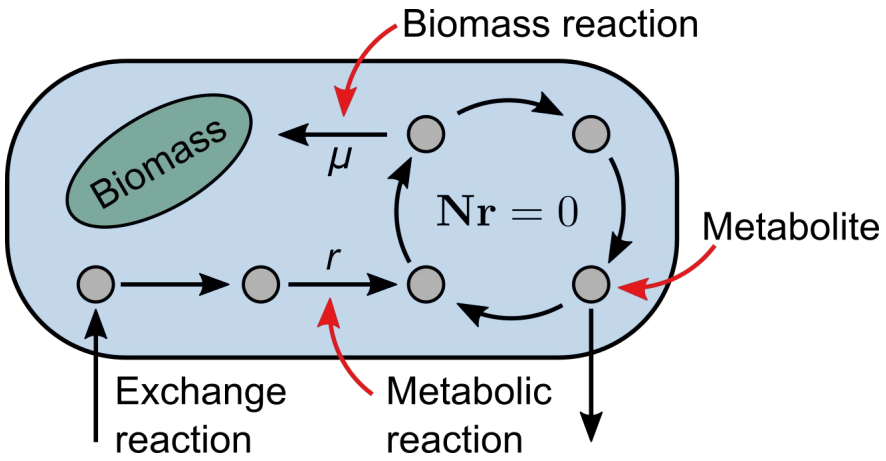
Cohort 2



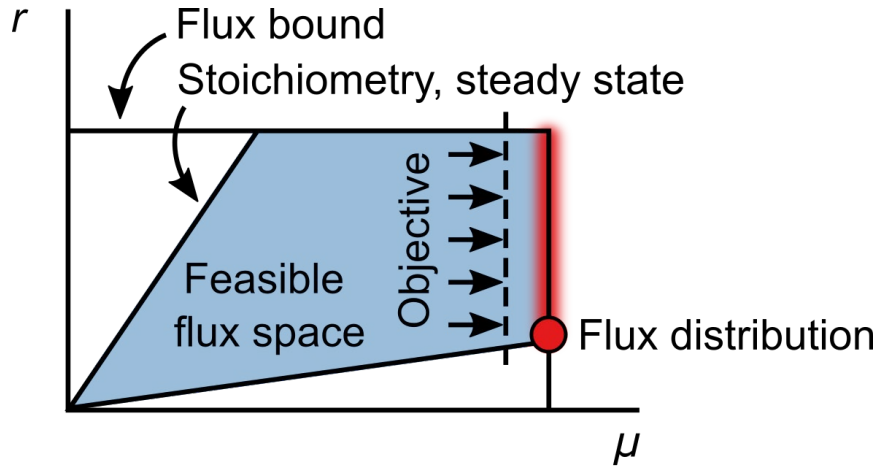
B. Yilmaz et al. (2019) *Nat. Medicine* 25: 323.

Formalization: Metabolic Models and Constraint-Based Analysis

Model contents



Solution space



Flux balance analysis (FBA):

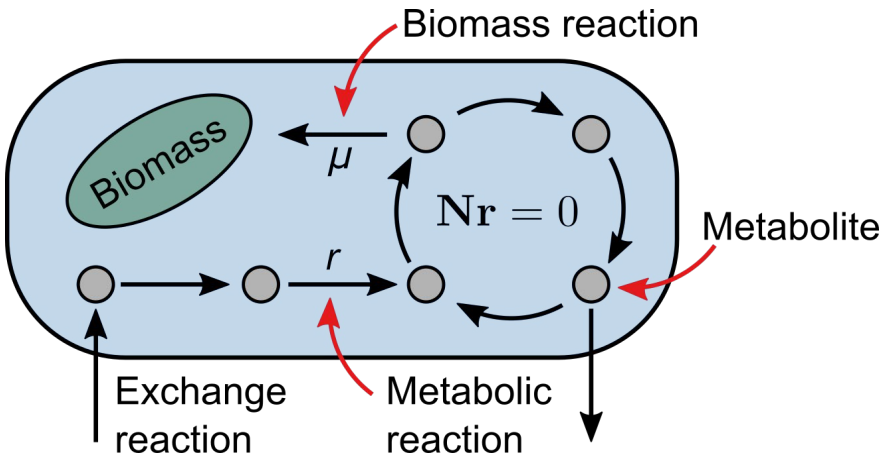
maximize μ

subject to $\mathbf{Nr} = 0$

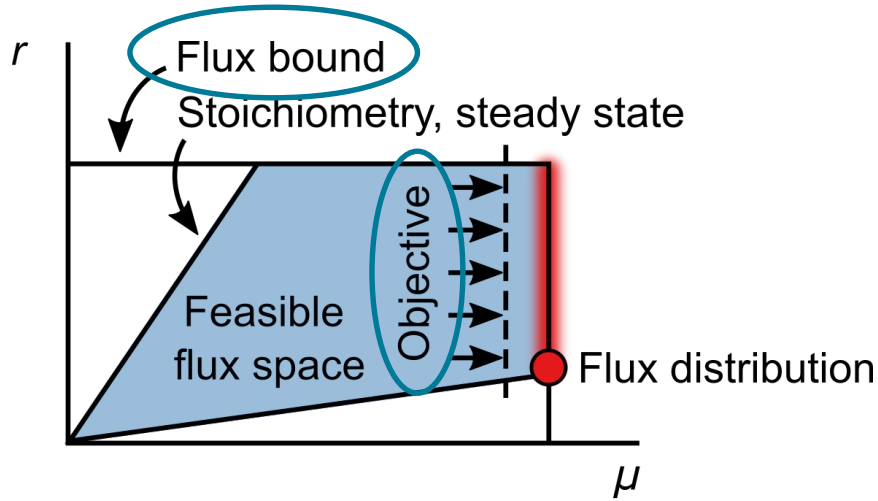
$\mathbf{r}_{\min} \leq \mathbf{r} \leq \mathbf{r}_{\max}$

Flux Bounds and Objectives Allow Problem-Specific Adaptations

Model contents



Solution space



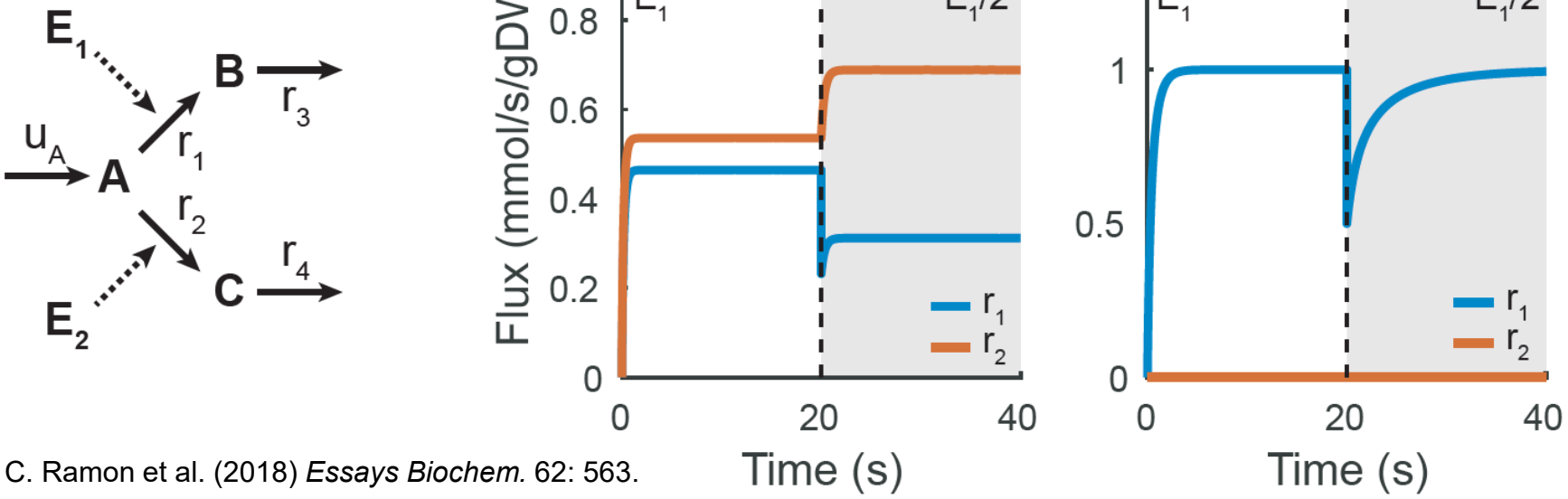
Flux balance analysis (FBA):

maximize μ

subject to $\mathbf{Nr} = 0$

$\mathbf{r}_{\min} \leq \mathbf{r} \leq \mathbf{r}_{\max}$

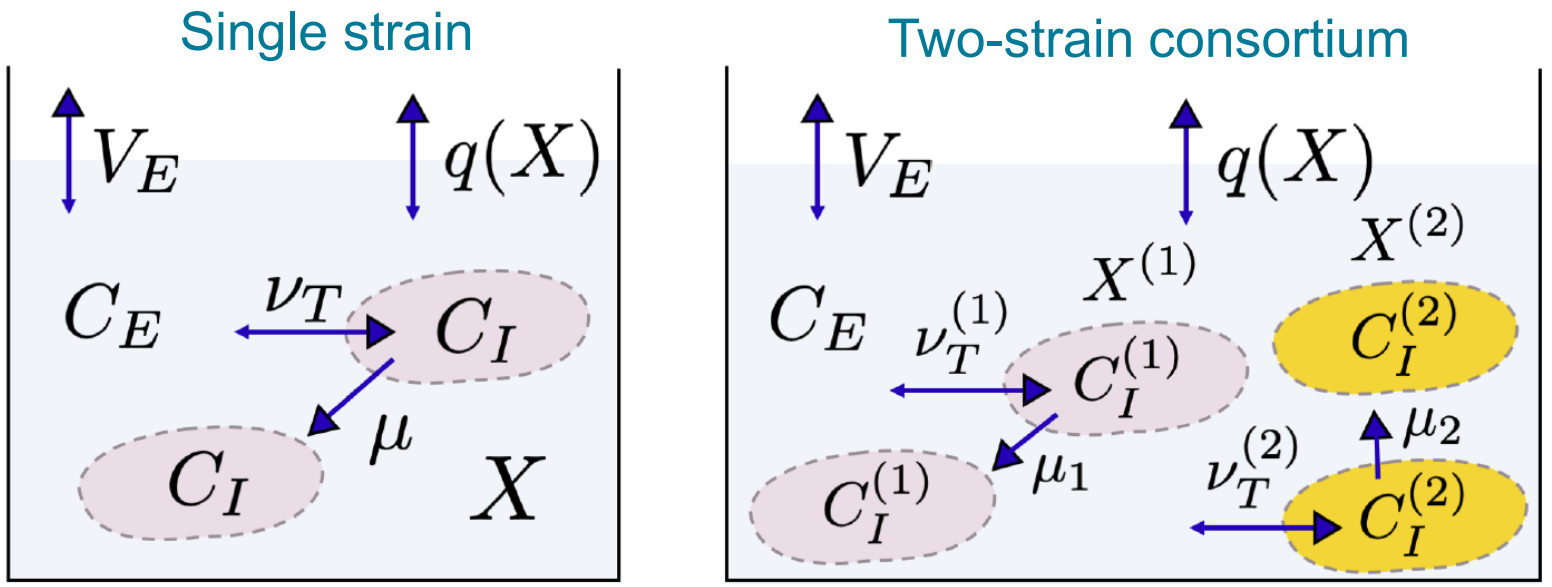
Reality: Flux Responses are Hard to Predict Because of Kinetics



C. Ramon et al. (2018) *Essays Biochem.* 62: 563.

- Difficulty of integrating genomics data (fluxes are not proportional to enzyme levels) and metabolomics data (metabolite concentrations are not represented).

Reality: Metabolic Communication Makes Consortia More Challenging

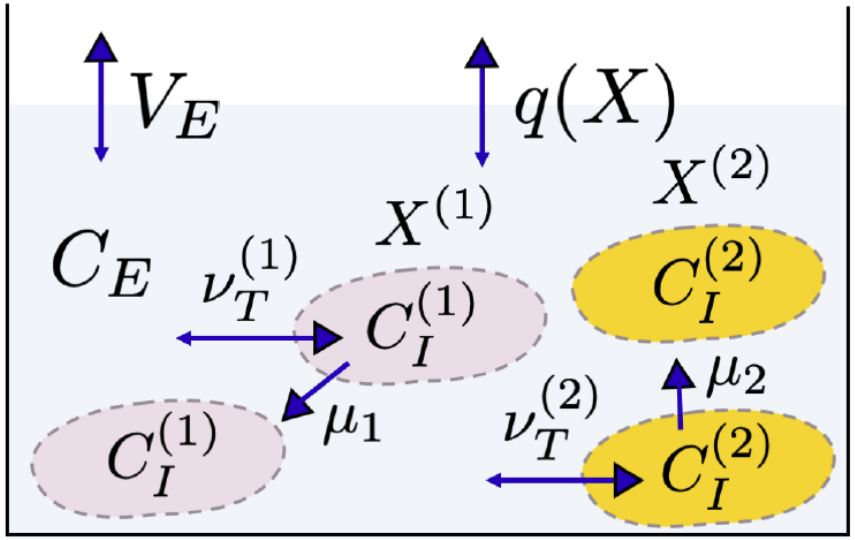


A. Theorell & J. Stelling (2022) *Proc. IEEE* 110:541.

- Metabolic communication via the external medium (e.g., cross-feeding) makes the prediction of metabolic activities and composition of consortia even harder.

Reality: Multiple Objectives (May) Exist for Consortia

Two-strain consortium



$$\max_{\nu,X,V_E} f(\nu, X)$$ Community objective

$$V_E + \sum_i X^{(i)} T^{(i)} \nu_T^{(i)} = 0, \text{ s.t.}$$ External mass balance

$$V_{E,min} \leq V_E \leq V_{E,max}$$ External flux constraints

$$\left[\begin{array}{c} \nu^{(i)} = \arg\max_{\nu^{(i)\prime}} g^{(i)}(\nu^{(i)\prime}) \\ S^{(i)}\nu^{(i)\prime} = 0 \\ B^{(i)}\nu^{(i)\prime} \leq b^{(i)} \\ \nu_T^{(i)\prime} = \nu_T^{(i)} \end{array}\right], \ \forall i\,.$$

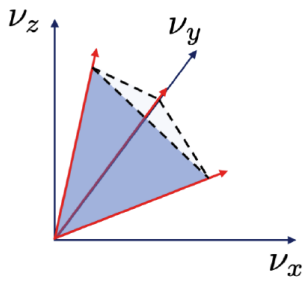
Individual objective
Internal mass balances
Internal flux constraints
Constraints 'dictated' by the community

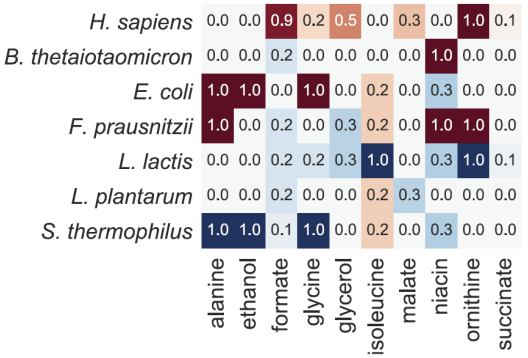
A. Theorell & J. Stelling (2022) *Proc. IEEE* 110:541.

- Example for the constraint-based analysis of consortia with a hierarchy of objectives: OptCom (Zomorrodi & Maranas, PLoS Comp. Biol. (2012)).

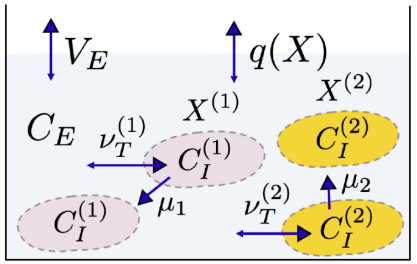
Proposals for the Analysis of Microbial Consortia

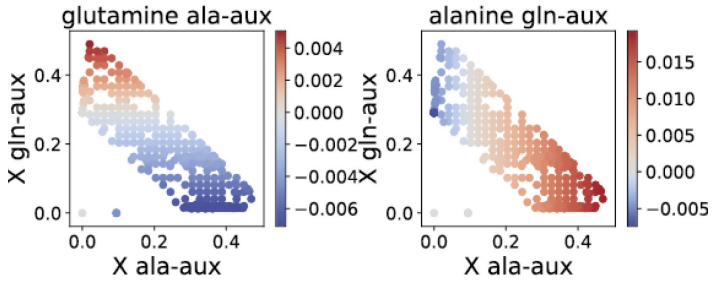
- Metabolic pathway analysis (enumerating all possible interactions in a consortium)





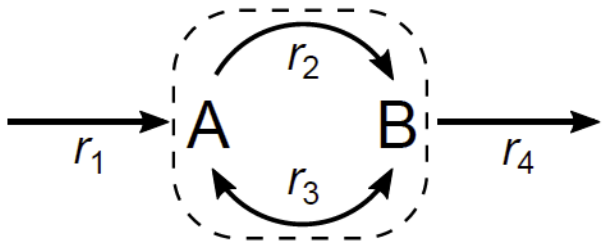
- Explicit models for consortia, objectives, and environment (without extensive simulations and need for kinetic parameters)





Metabolic Pathway Analysis: Minimal Pathways (MPs)

Metabolic (sub)network:



Bounds:

$0 \le r_1 \le 1000$

$0 \le r_2 \le 1000$

$-1000 \le r_3 \le 1000$

$1 \le r_4 \le 1$

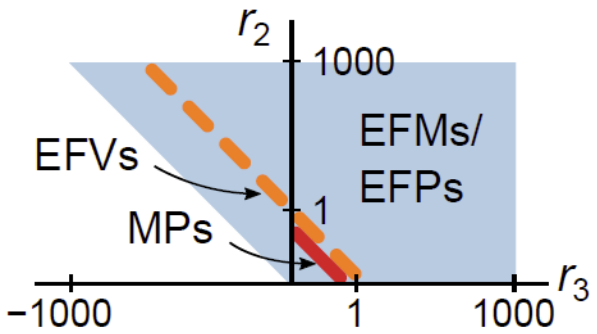
MCSs:

$\{r_1\}$

$\{r_4\}$

$\{r_2, r_3\}$

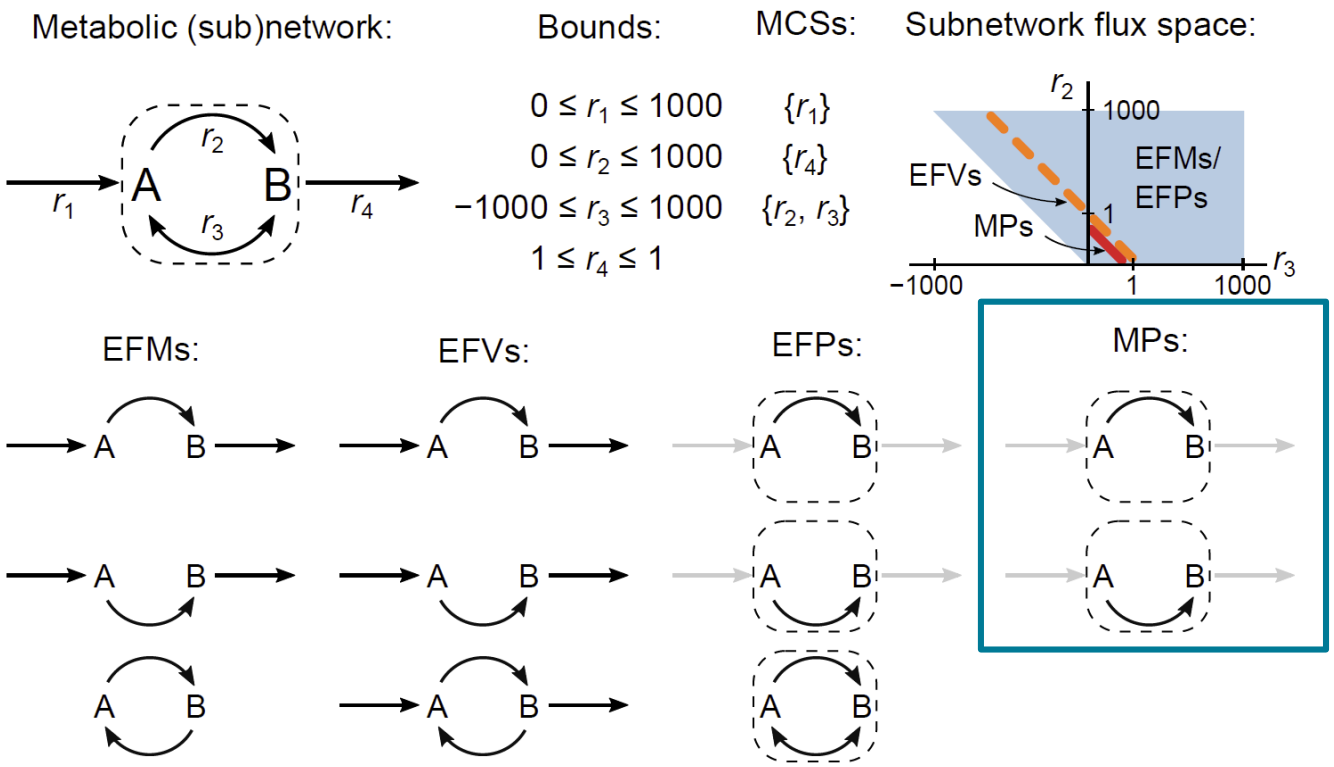
Subnetwork flux space:



O. Oyas & J. Stelling (2020) https://www.biorxiv.org/content/10.1101/2020.07.31.230177v2.abstract.

- Concept: Minimal pathways without loops that span the bounded flux space.

Metabolic Pathway Analysis: Minimal Pathways (MPs)



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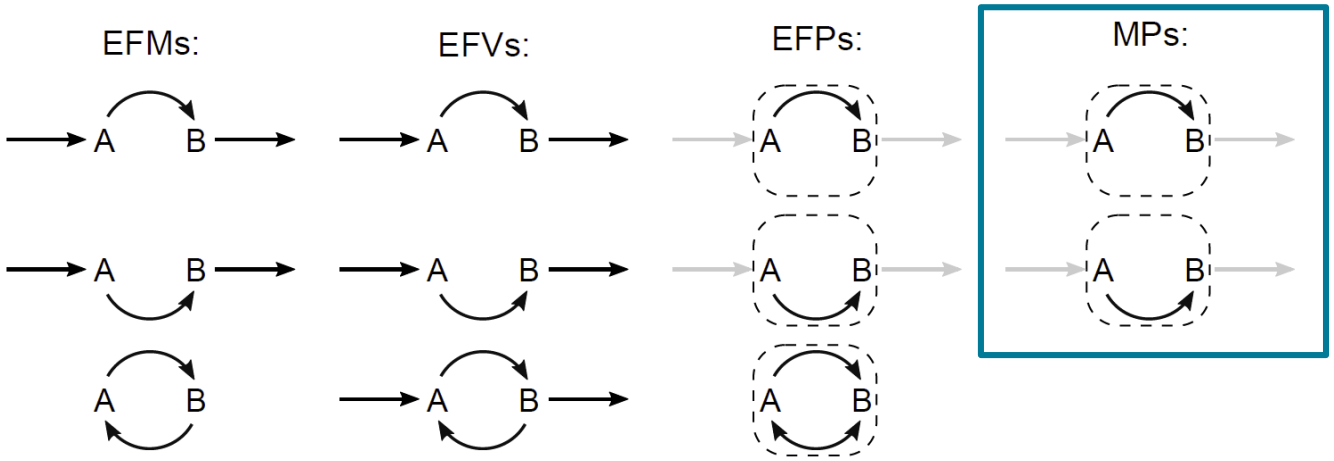
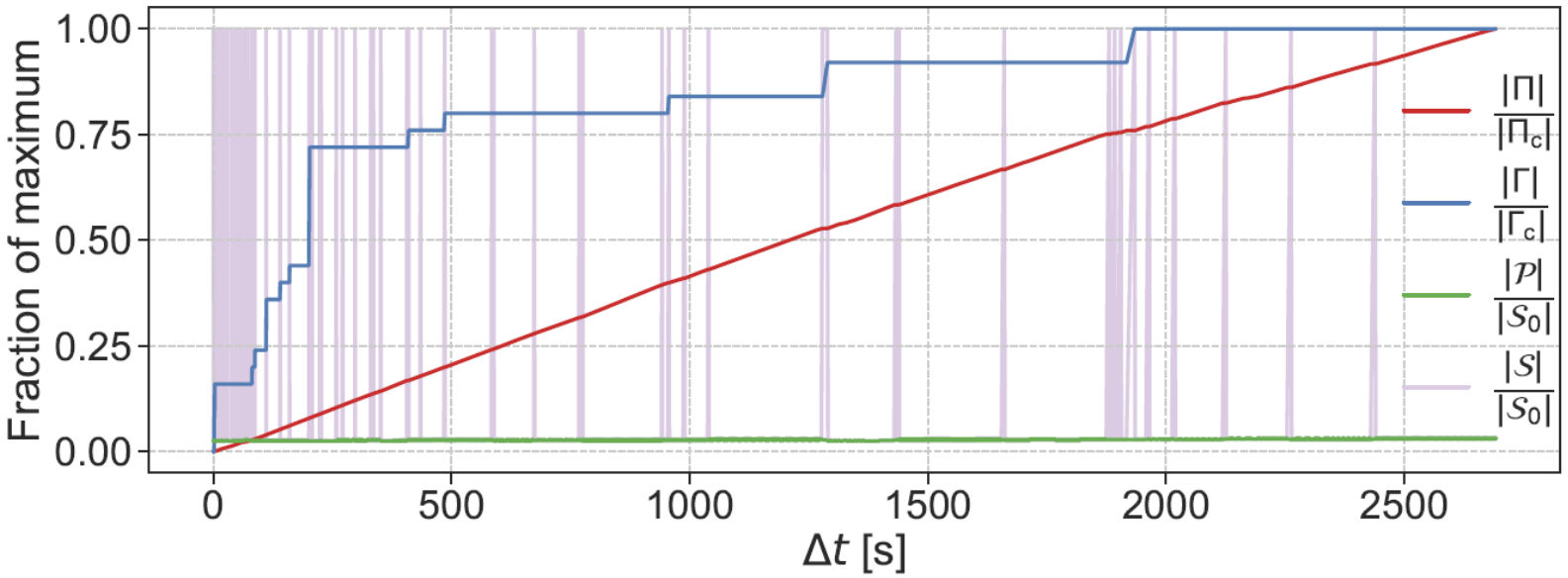
Metabolic Pathway Analysis: Minimal Pathways (MPs)



- MPs are defined for arbitrary subnetworks (↔ elementary conversion modes).
- MPs fulfill constraints on the entire network including bounds (↔ EFMs).
- MPs are support-minimal subsets of EFVs w.r.t. the subnetwork and network.

MPs Can be Determined Efficiently at Large Scale



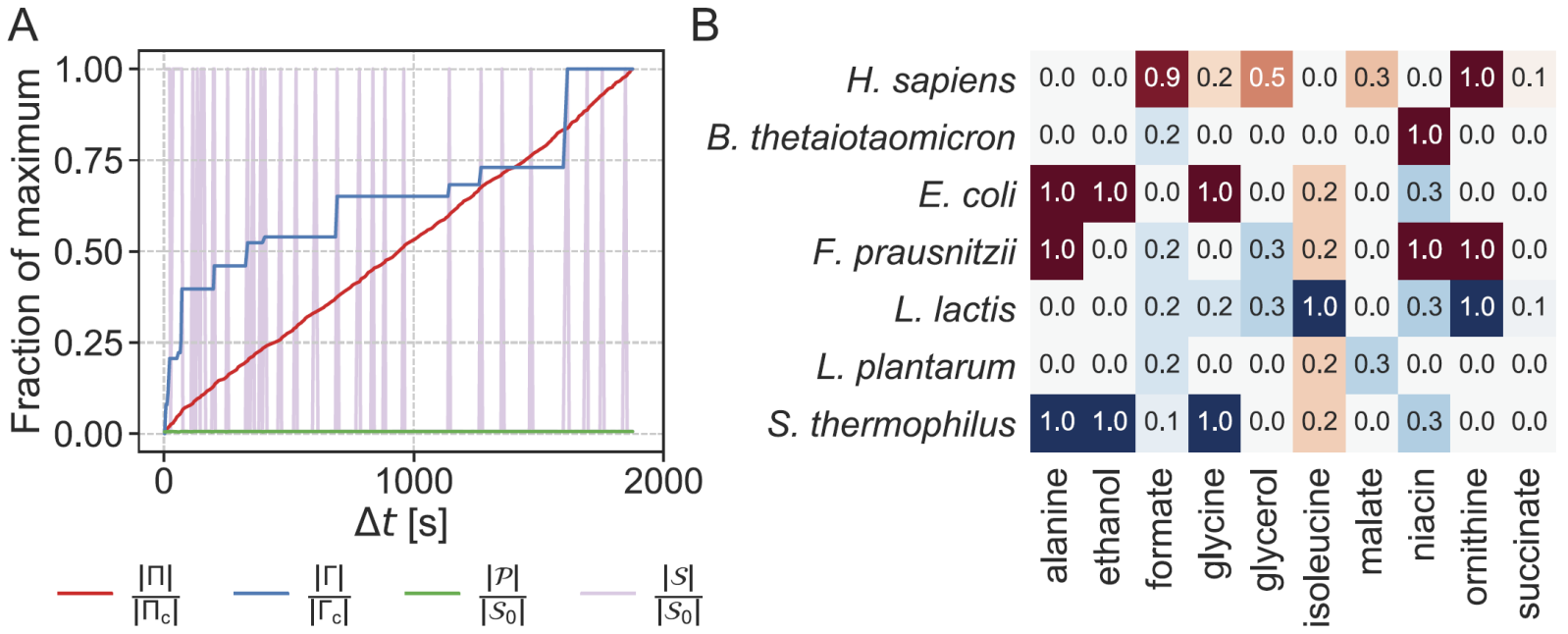
Fraction of 27,468 MPs

Relative MP size

Effective subnetwork size

- Algorithms based on iterative solution of linear programs for enumeration and sampling: Example of random subnetwork with 562 reactions in *E. coli* network.

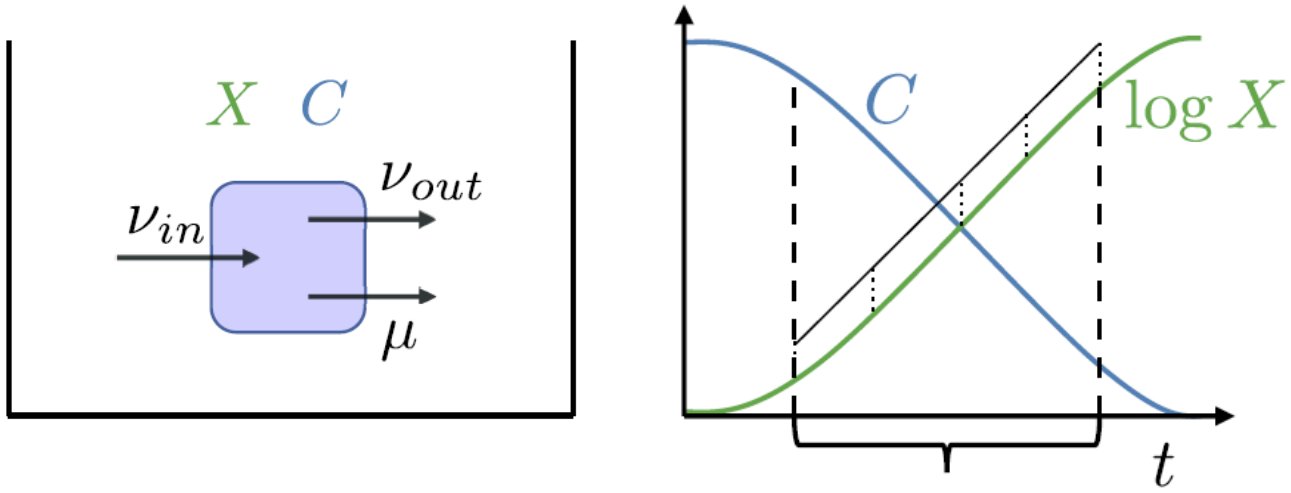
MPs Predict Essential Metabolite Exchanges in the Gut Microbiome



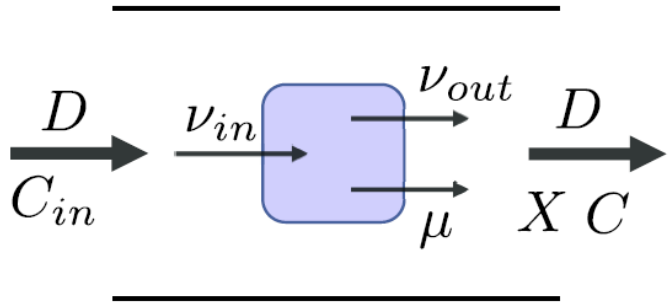
- Scalable: Human + 6 microbes, ~33’000 reactions, ~3’200 possible exchanges.
- Essential exchanges: Sequential minimization for given growth conditions.

Explicit Models for Consortia: Environment

Batch process



Chemostat



A. Theorell & J. Stelling (2021) *Proc. CMSB 2021*, 141-58.

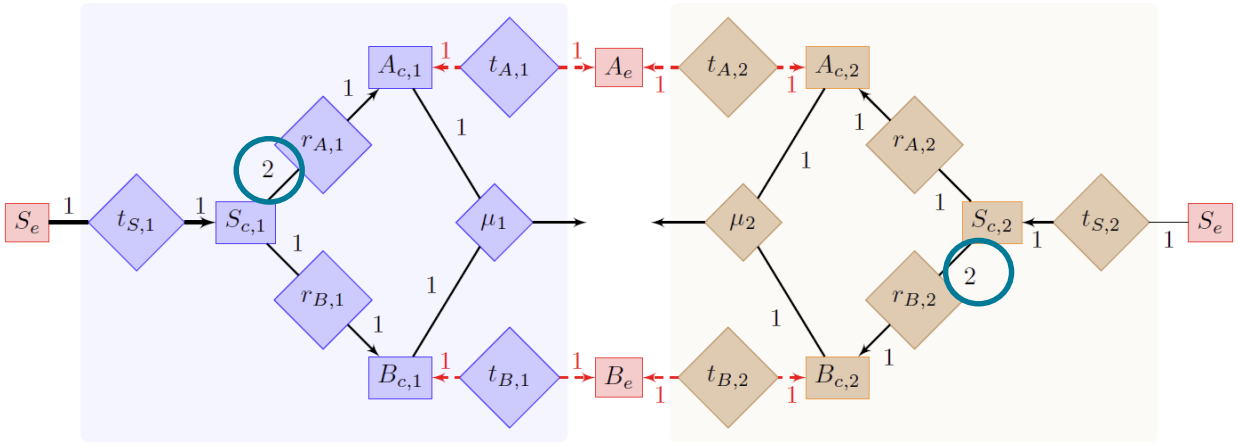
- Environment: Steady-state concepts differ between batch and chemostat.

Explicit Models for Consortia: Decision-Making

Generic prisoner's dilemma

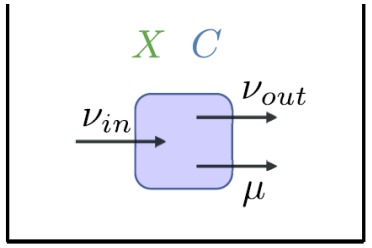
Player 1 \ Player 2	cooperate	defect
cooperate	(3, 3)	(1, 4)
defect	(4, 1)	(2, 2)

Metabolic PD 'game'



- Decision-making: Individual (agent) decisions vs. community decisions.

Batch / Chemostat with Agent / Community Objective: Four Models



CC model

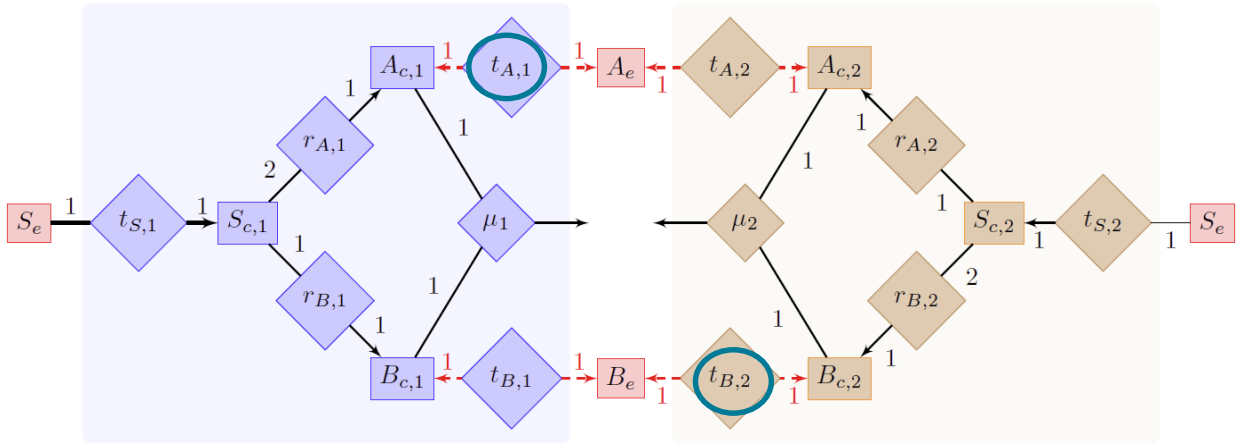
$$X_i(D - \hat{\nu}_{\mu,i}(X)) = 0, \forall i$$
$$X \geq 0$$
$$\hat{\nu}(X) = \underset{\nu \in \mathcal{R}^{n_\nu}, C \in \mathcal{R}^{n_C}}{\operatorname{argmax}} \sum_i \nu_{\mu,i} X_i$$
$$s.t.\ D(C_{in} - C) - \sum_i T_i \nu_i X_i = 0$$
$$S_i \nu_i = 0,\ \forall i$$
$$A_i \nu_i \leq b_i(C),\ \forall i$$
$$C \geq 0\ .$$

CA model

$$D(C_{in} - C) - \sum_i T_i \hat{\nu}_i(C) X_i = 0$$
$$X_i(D - \hat{\nu}_{\mu,i}(C)) = 0,\ \forall i$$
$$C, X \geq 0$$
$$\hat{\nu}_i(C) = \underset{\nu_i \in \mathcal{R}^{n_{\nu_i}}}{\operatorname{argmax}} \nu_{\mu,i}, \forall i$$
$$s.t.\ S_i \nu_i = 0,\ \forall i$$
$$A_i \nu_i \leq b_i(C),\ \forall i\ .$$

- Prototypes of decision-making formulated with dependence on environment.
- Steady-state solution: Analytical (KKT reformulation) or via optimization (MILP).

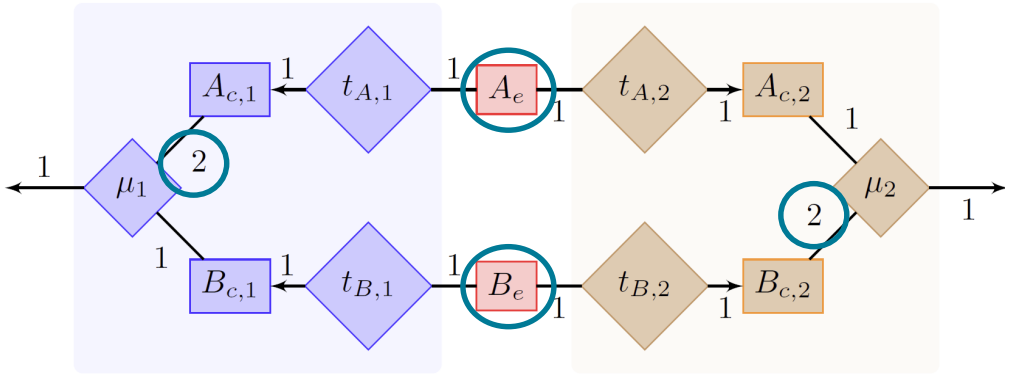
Proof-of-Concept: Metabolic Prisoner's Dilemma

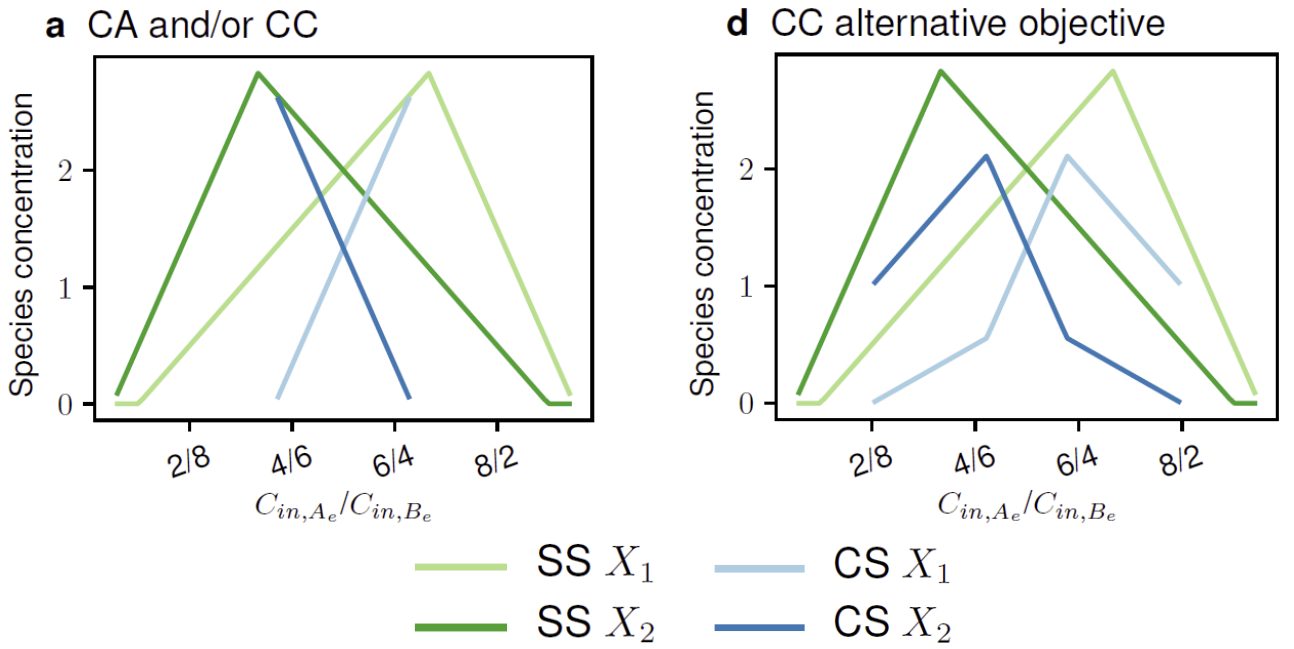


Variable	CA	CC	BC	CC $D = 1.2$
C_{A_e}	0	0.5		0
C_{B_e}	0	0.5		0
C_{S_e}	1.5	1.13		3.6
X_1	1.42	1.97	0.5	1.07
X_2	1.42	1.97	0.5	1.07
$\nu_{t_S,1}$	1.5	1.13	10	3.6
$\nu_{t_A,1}$	0	0.5	5	0
$\nu_{t_B,1}$	0	-0.627	-5	0
$\nu_{r_A,1}$	0.5	0	0	1.2
$\nu_{r_B,1}$	0.5	1.13	10	1.2
$\nu_{\mu,1}$	0.5	0.5	5	1.2
$\nu_{t_S,2}$	1.5	1.13	10	3.6
$\nu_{t_A,2}$	0	-0.627	-5	0
$\nu_{t_B,2}$	0	0.5	5	0
$\nu_{r_A,2}$	0.5	1.13	10	1.2
$\nu_{r_B,2}$	0.5	0	0	1.2
$\nu_{\mu,2}$	0.5	0.5	5	1.2

- Cross-feeding (cooperation) only for models with community objectives.
- Quantitative solutions for cooperation depend on the assumed environment.

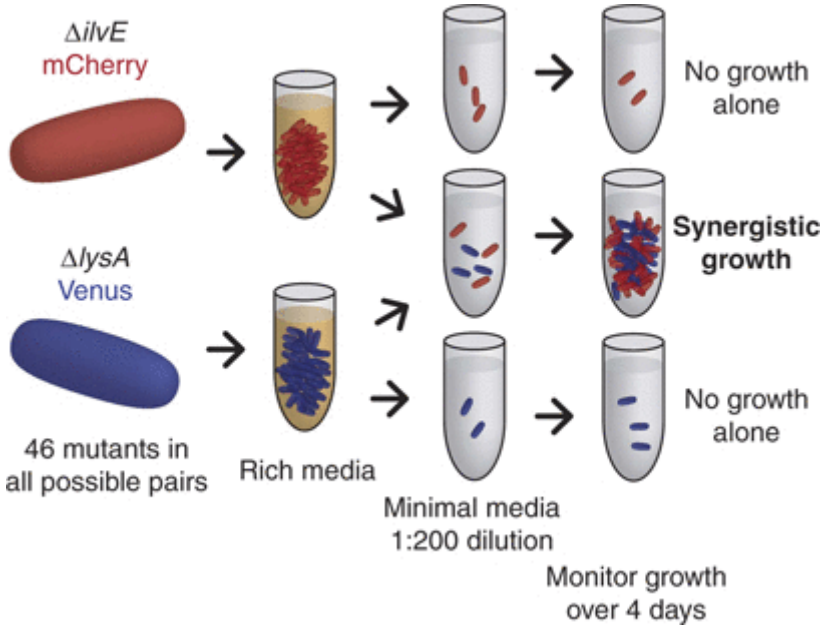
Proof-of-Concept: Coexistence Microbial Consortium





- Coexistence on different substrates without communication (cross-feeding).
- Community objectives impact on quantitative solutions (maximal growth rates).

Application: Synthetic Microbial Communities

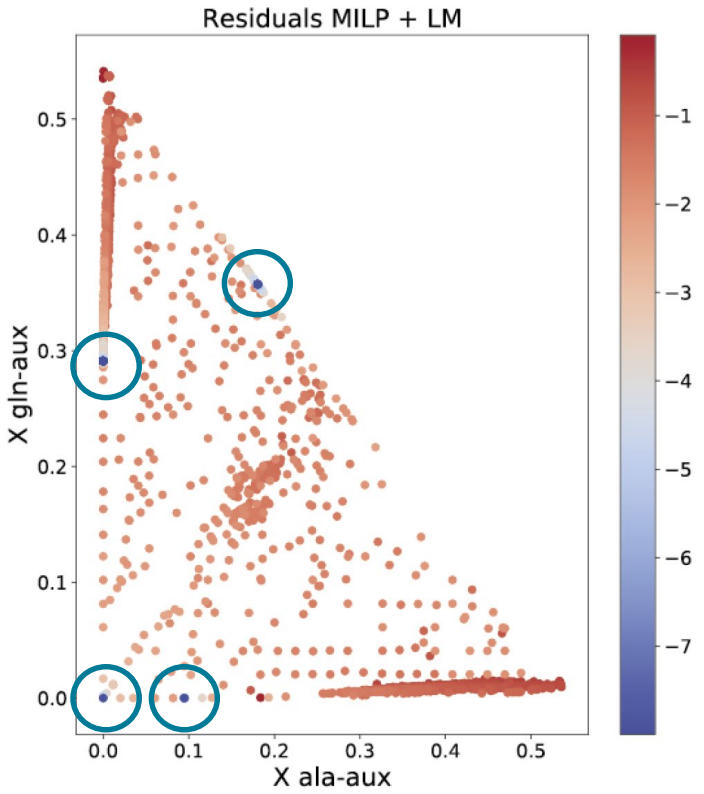


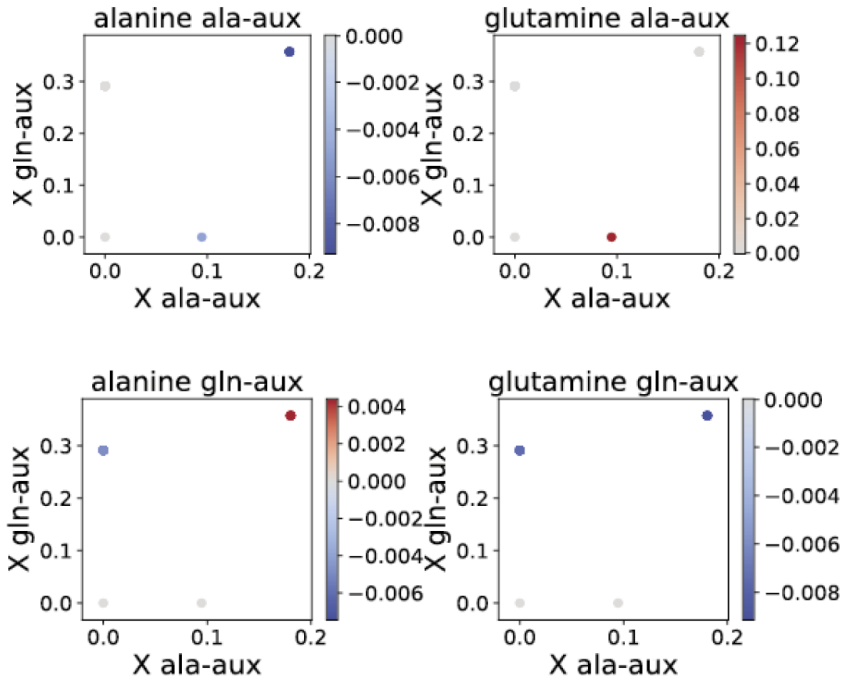
E. Wintermute & P. Silver (2010) *Molec. Syst. Biol.*, 6: 407.

- *E. coli* strains with amino acid auxotrophies → Synergistic growth possible.
- Core models for analyzing pairwise consortia (72 metabolites, 95 reactions).

Synthetic Microbial Consortium: Chemostat + Community Objective

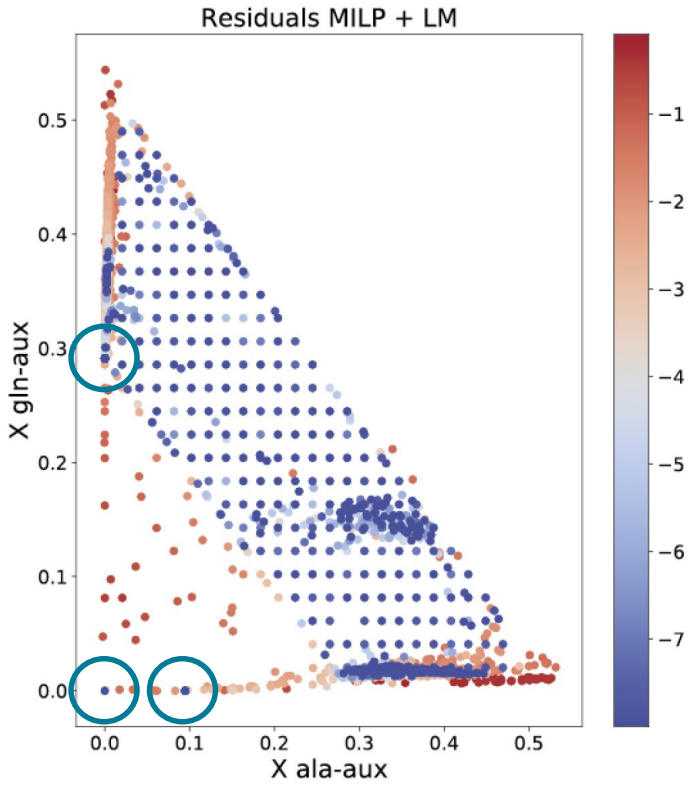
A. Theorell & J. Stelling (2022)
BMC Bioinf., under revision.

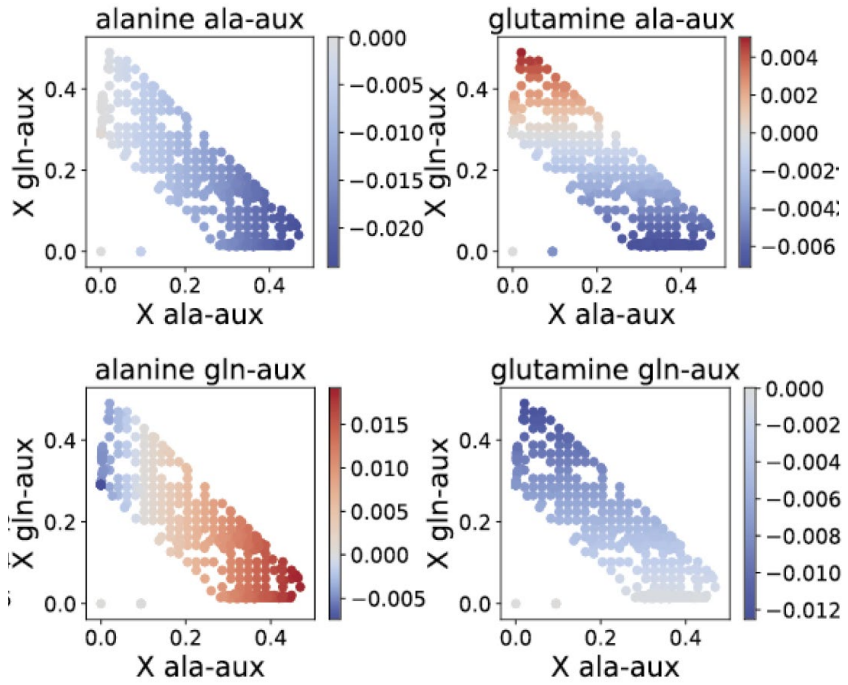




- Numerical solution for steady-states, validity characterized by residuals.
- Four solutions: 1 trivial, 2 single-species, and 1 coexistence solution.

Synthetic Microbial Consortium: Chemostat + Agent Objective



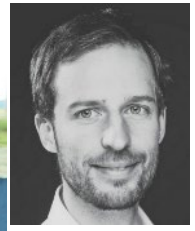


- Solutions: 1 trivial, 2 single-species, and band of coexistence solutions.
- Solution band cannot be characterized by alternative methods (dFBA).

Summary

- Model-based microbiome analysis does not always require complicated computational methods (IBD), but it can imply challenging problems.
- Minimal pathways may help in exploring and predicting metabolic crosstalk in real-world settings (regarding their complexity).
- Explicit models highlight influences of environment and decision-making, enabling interesting predictions without the need for (many) model parameters.
- Many important challenges remain: scaling of methods and algorithms, systematic uncertainty quantification, ….

Acknowledgements



Charlotte Ramon, Ove Oyas, Axel Theorell

Microbiome collaborations:

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Swiss National Science Foundation

Disclaimer

Science may be described as the art of systematic over-simplification.

K. Popper