In Silico Optimization of Biochemical Pathways Using Elementary Conversion Modes in Microbial Community Models

Bachelor Thesis of Julia Jasovski

Course of studies: Computational Engineering Science

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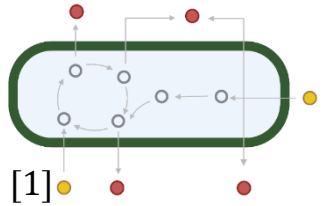
Background and Aim

Introduction to constraint-based metabolic modelling



- Metabolism can be understood as a network of reactions
- Reaction network are expressed in a stoichometric matrix S with n metabolites and m reactions [1]
- The concentration change for every metabolite is given by $\dot{c}_j$ for $j = 1, \dots, n$

$$\begin{pmatrix} \dot{c}_1 \\ \vdots \\ \dot{c}_n \end{pmatrix} = \underbrace{\begin{pmatrix} s_{1,1} & \cdots & s_{1,m} \\ \vdots & \ddots & \vdots \\ s_{n,1} & \cdots & s_{n,m} \end{pmatrix}}_{S} \cdot \underbrace{\begin{pmatrix} v_1 \\ \vdots \\ v_m \end{pmatrix}}_{\text{Flux vector } \boldsymbol{v}} = \begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix}$$

Possible objective:
$maximize\ v_{Biomass}$

- Flux Balance Analysis (FBA) is currently used to optimize such constraint-based metabolic models [2]
- **Problem**: It requires prior knowledge of metabolic uptake rates and only considers optimal pathways

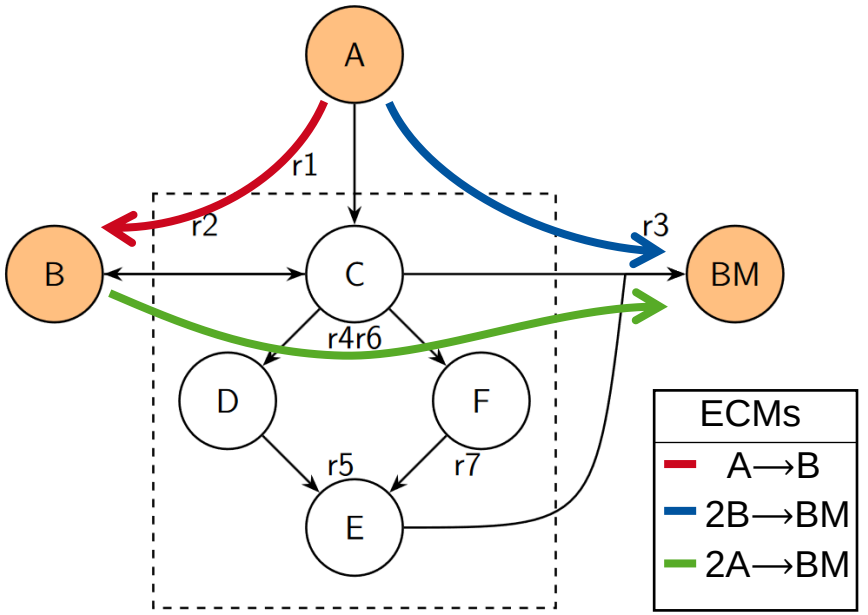
⇨ We are interested in all possible pathways

[1] Palsson, 2015, DOI: 10.1017/CBO9781139854610
[2] Orth, 2010, DOI:10.1038/nbt.1614

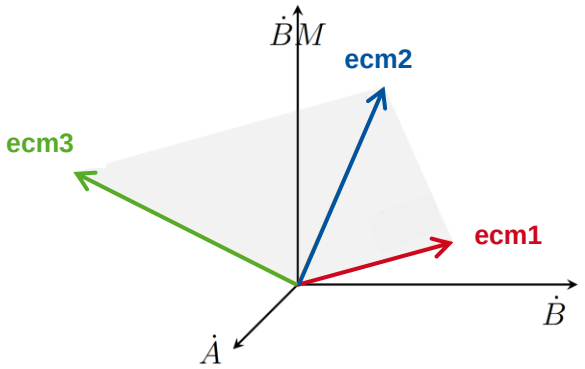
Motivation Elementary Conversion Mode

- Elementary Flux Mode (EFM) analysis enumerates all possible pathways in a network
- **Problem:** Huge number of EFMs and often infeasible with a lot of redundancy in the conversion
- Elementary Conversion Mode (ECM) analysis identifys all overall conversions from nutrients to products [1]
  ⇒ focuses only on external metabolites
- The internal metabolites $j \in Int$ are assumed to be steady state
  $\Rightarrow \ \dot{c}_j = 0$ for all $j \in Int$
- The conic combination of every ECM can be described as a steady-state conversion cone:

$$C = \{\dot{c}_{ext} \in \mathbb{R}^l : \dot{c}_{ext} = Ev, v \geq 0\}, \quad l = \#\ of\ external\ metabolites$$



Toy Network



[1] Clement *et. al*, 2021, DOI: 10.1016/j.patter.2020.100177

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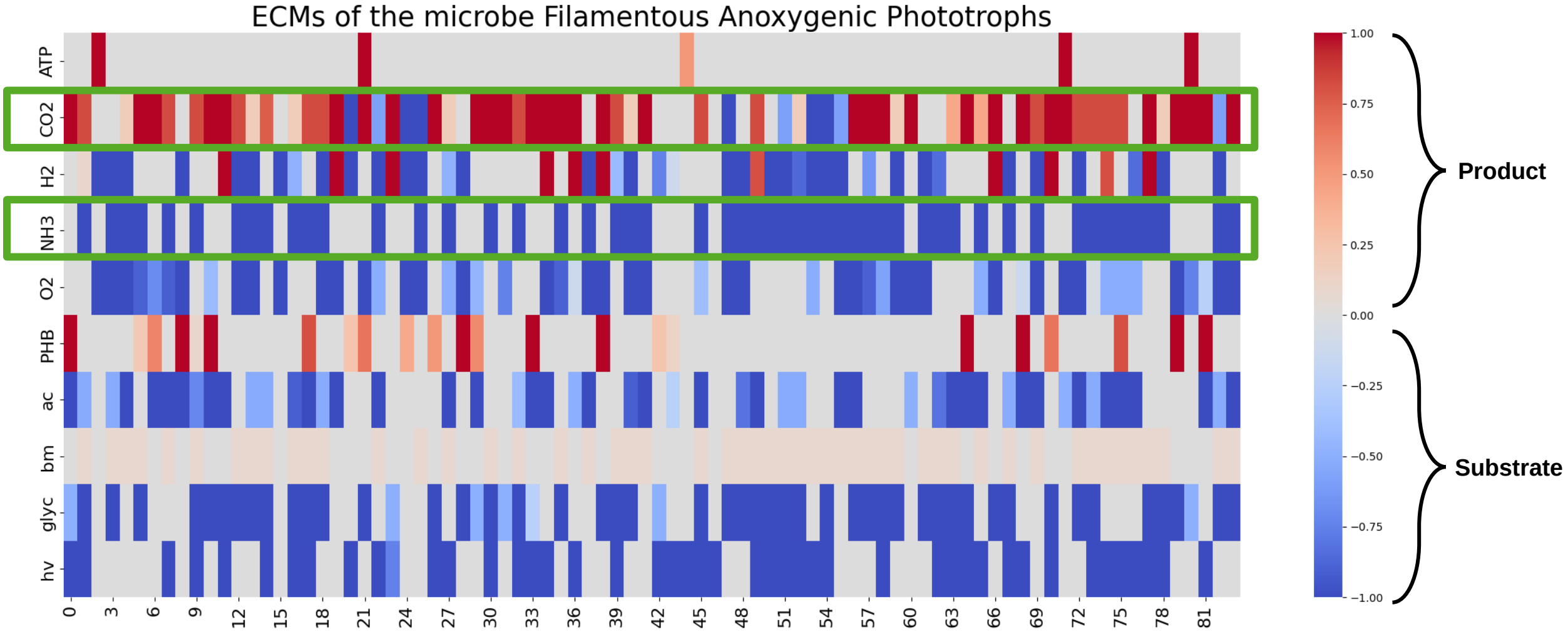
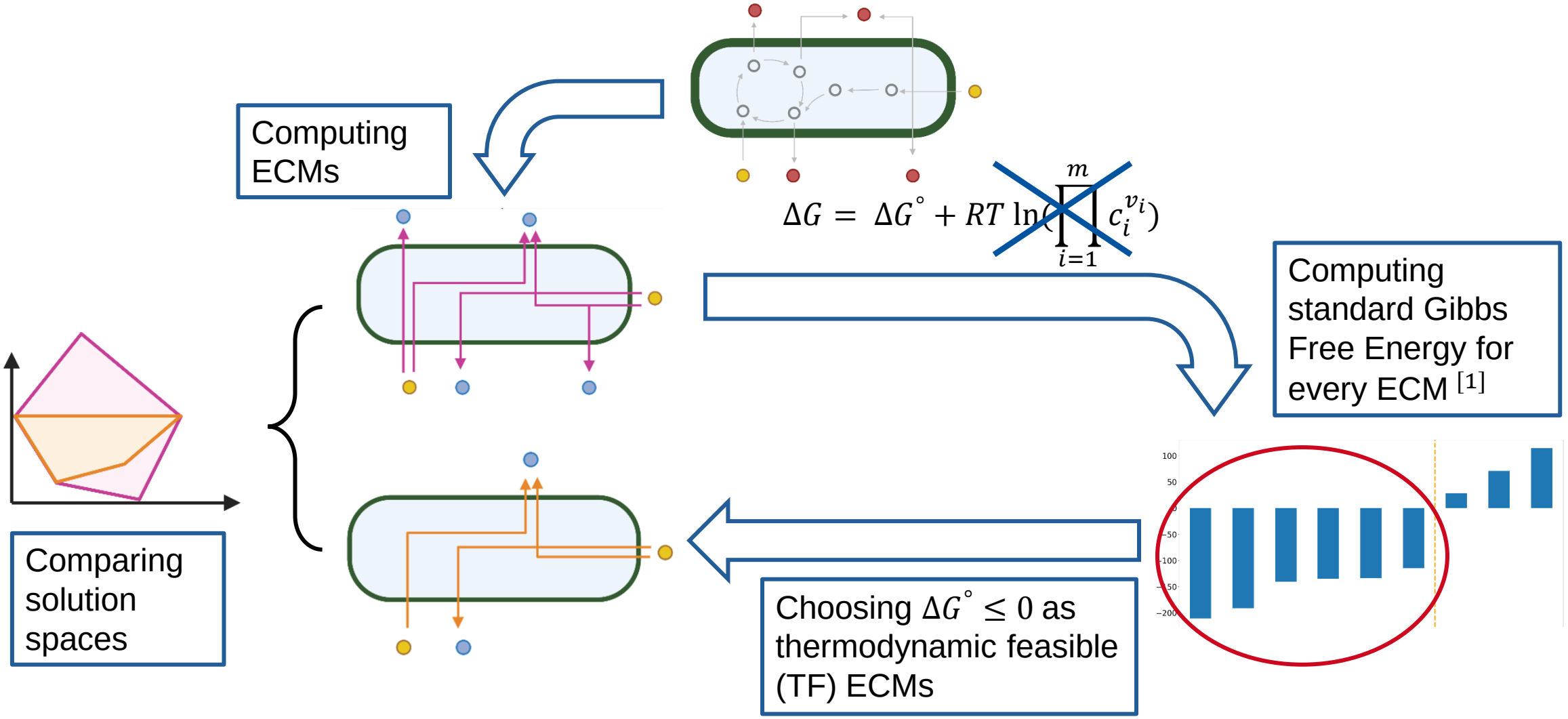
Visualization of an ECM-Matrix

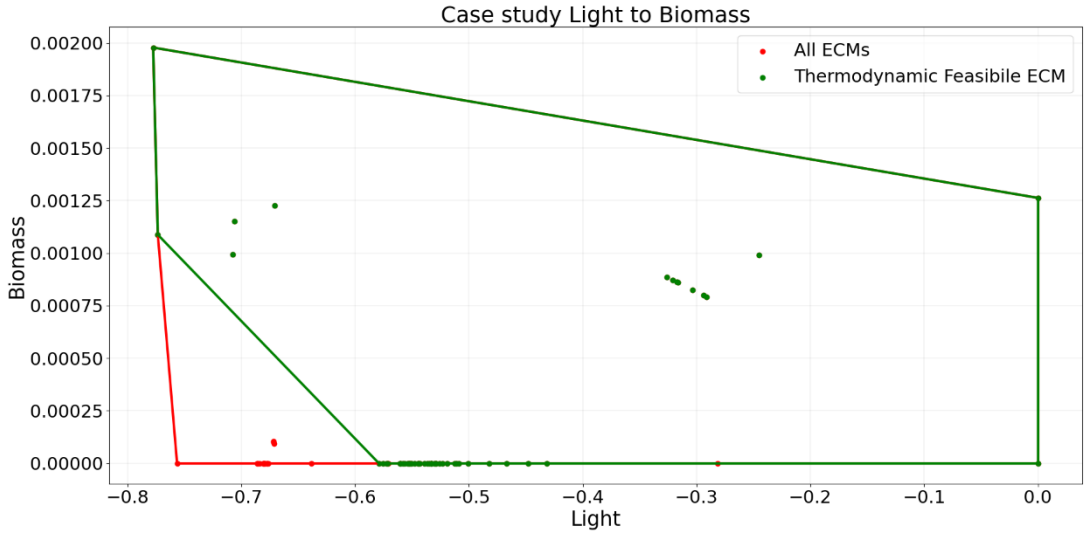


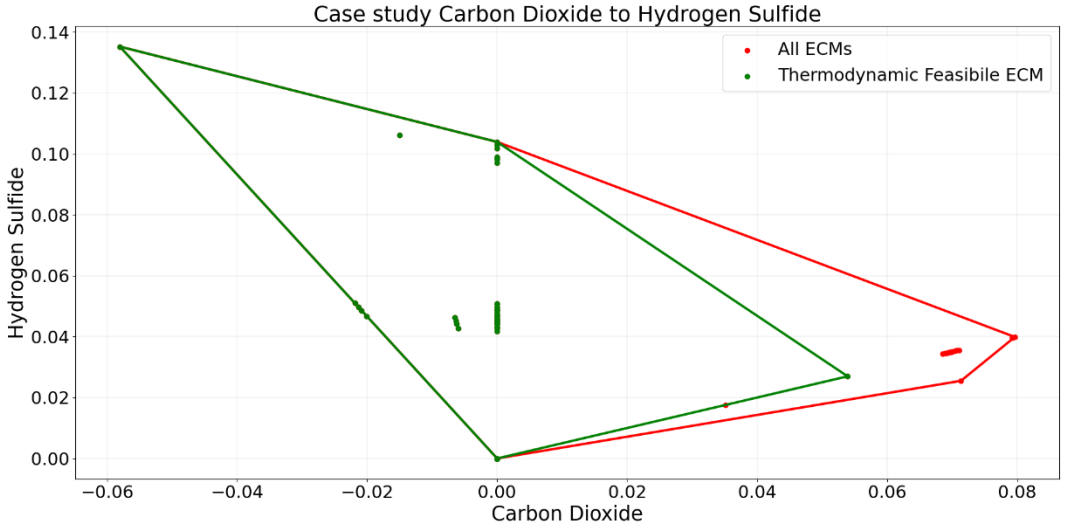
Thermodynamic Feasibilty

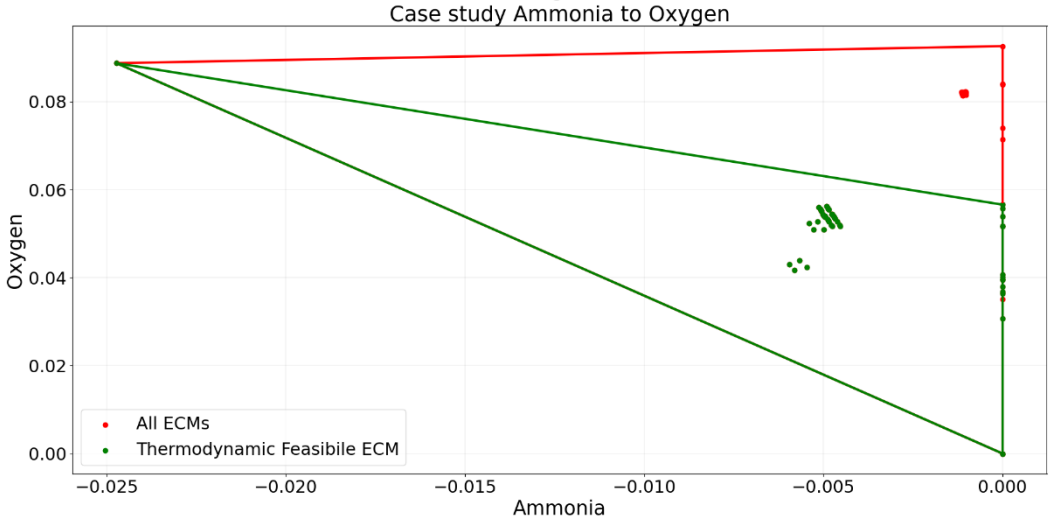


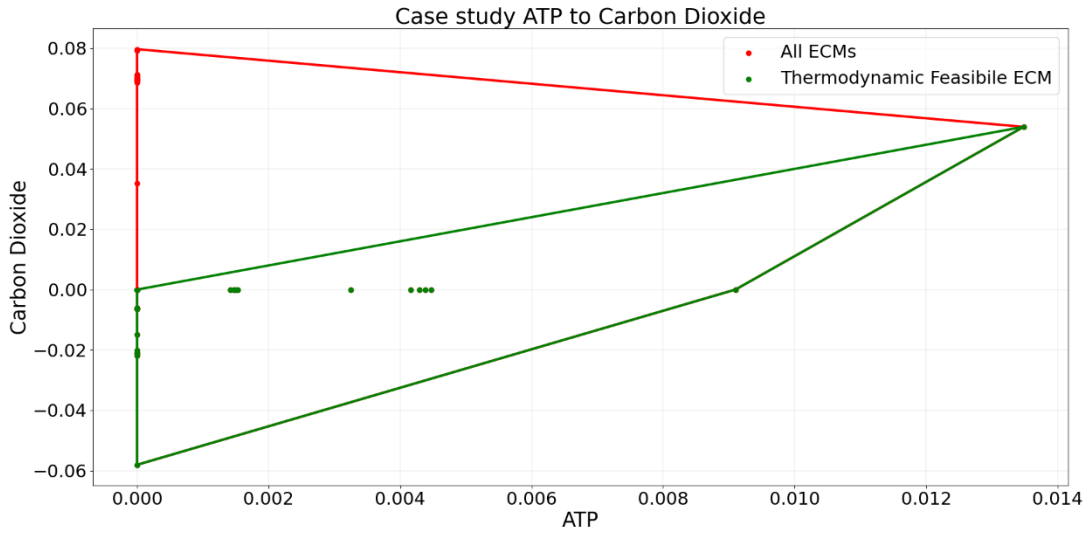
[1] Ebenhöh *et. al*, 2024, DOI: 10.3390/life14020247

Solution Spaces Thermodynamic Feasibility









Case Study

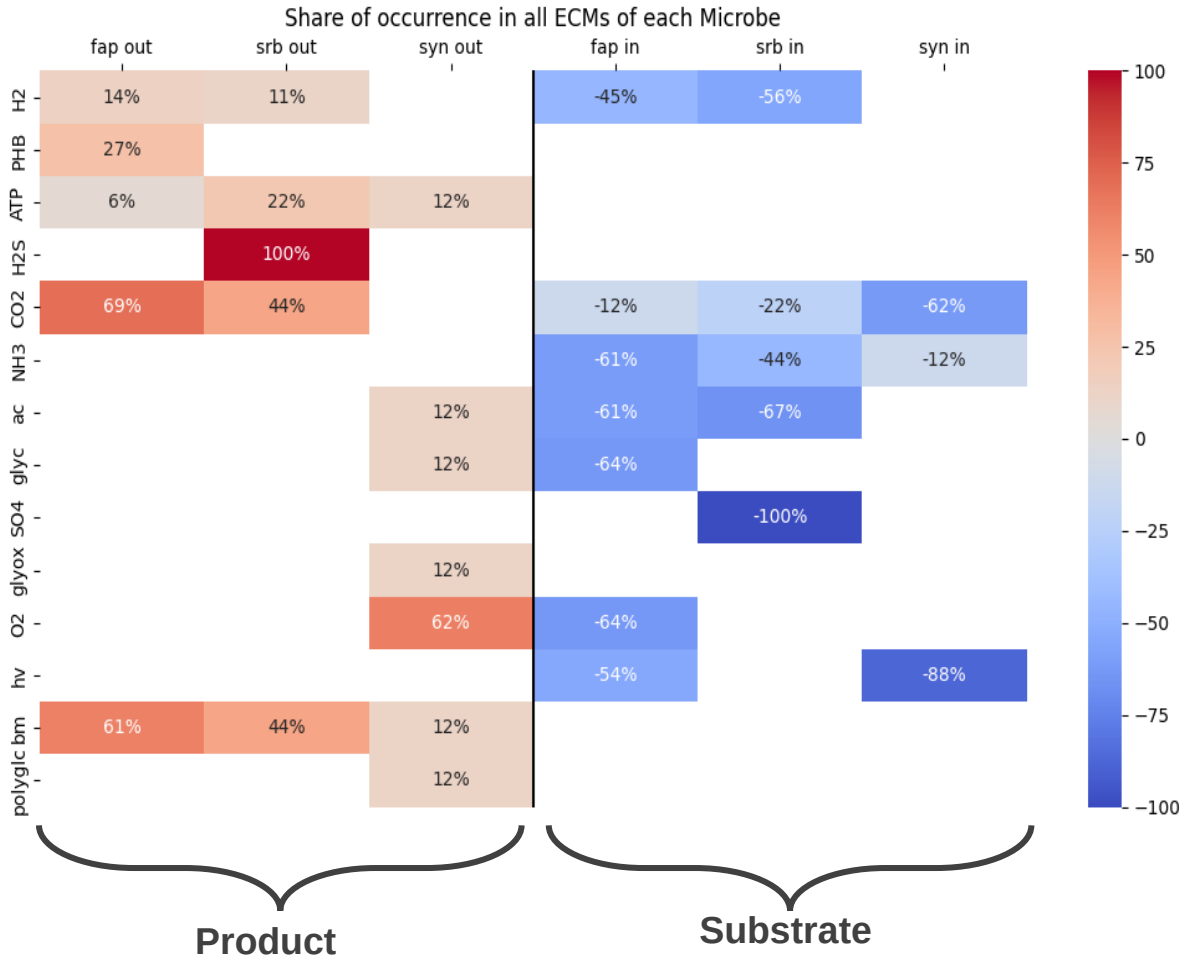
- Genome Scale Metabolic Models of OMM19 strain were not available yet

- Data from three microbes of an community in a phototrophic microbial mats were used [1]
  - Filamentous anoxygenic phototrophs (FAP)
  - Synechococcus (SYN)
  - Sulfate reducing bacteria (SRB)

- Unicellular models were already build [2]

- ECMs were computed with the software ecmtool [3] and analyzed in this heatmap

- These models and all further models were build with the python library COBRApy



[1] Taffs *et. al*, 2009, DOI: 10.1186/1752-0509-3-114
[2] Wedmark *et. al*, 2023, DOI:10.1101/2023.09.05.556413
[3] Clement *et. al*, 2021, DOI: 10.1016/j.patter.2020.100177

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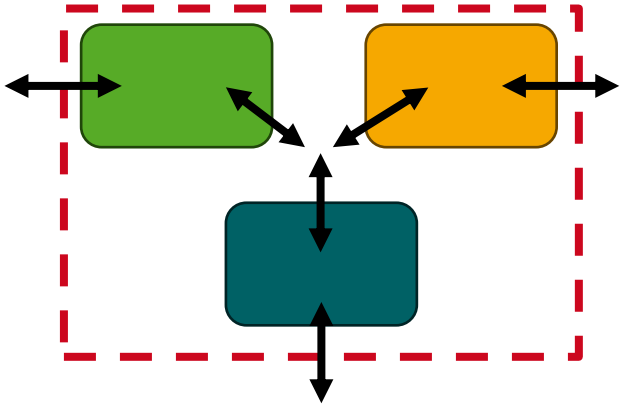
Community Model

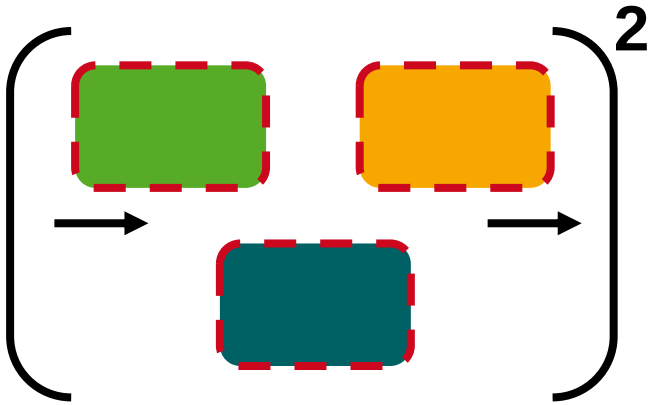


Compartmentalized Model

- All community members share a common internal space to exchange metabolites
- Every metabolite is keyed to its microbe

Pooled Model

- Every reaction and every metabolite is merged to one pooled organism
- Metabolites are unkeyed



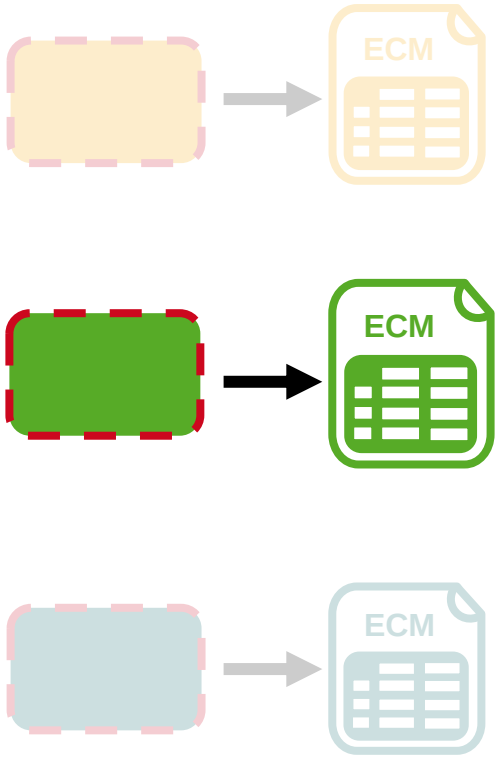
Nested Model

?

Taffs et al. [1] applied these community model types on EFM

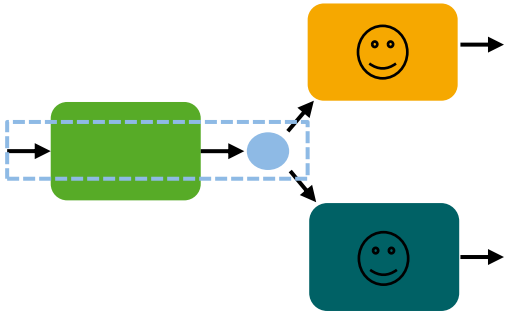
[1] Taffs *et. al*, 2009, DOI: 10.1186/1752-0509-3-114

Community Model: Nested Model



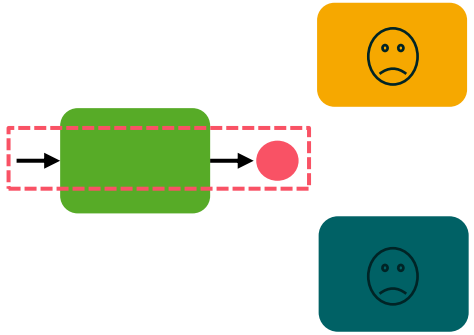
Altruistic ECM

max - efficiency

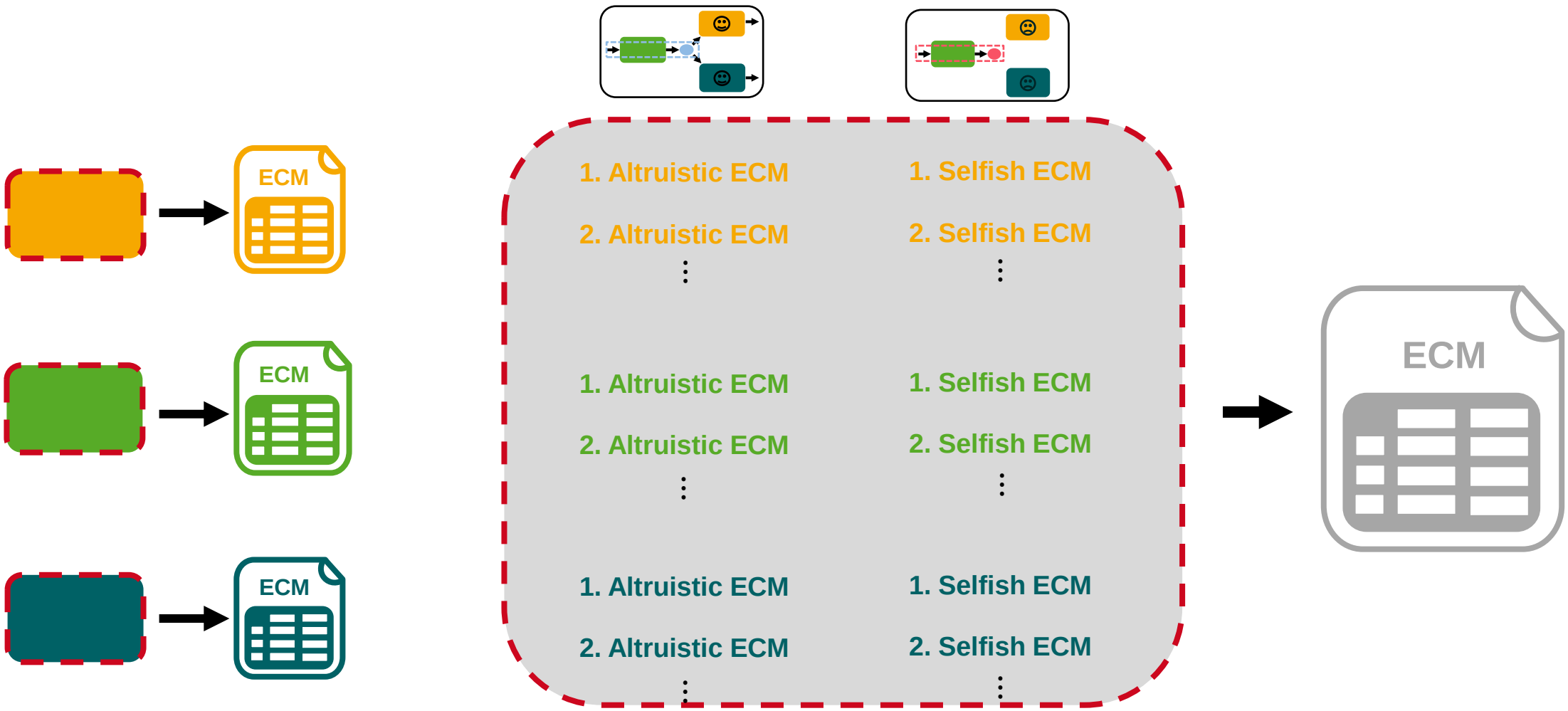


Selfish ECM

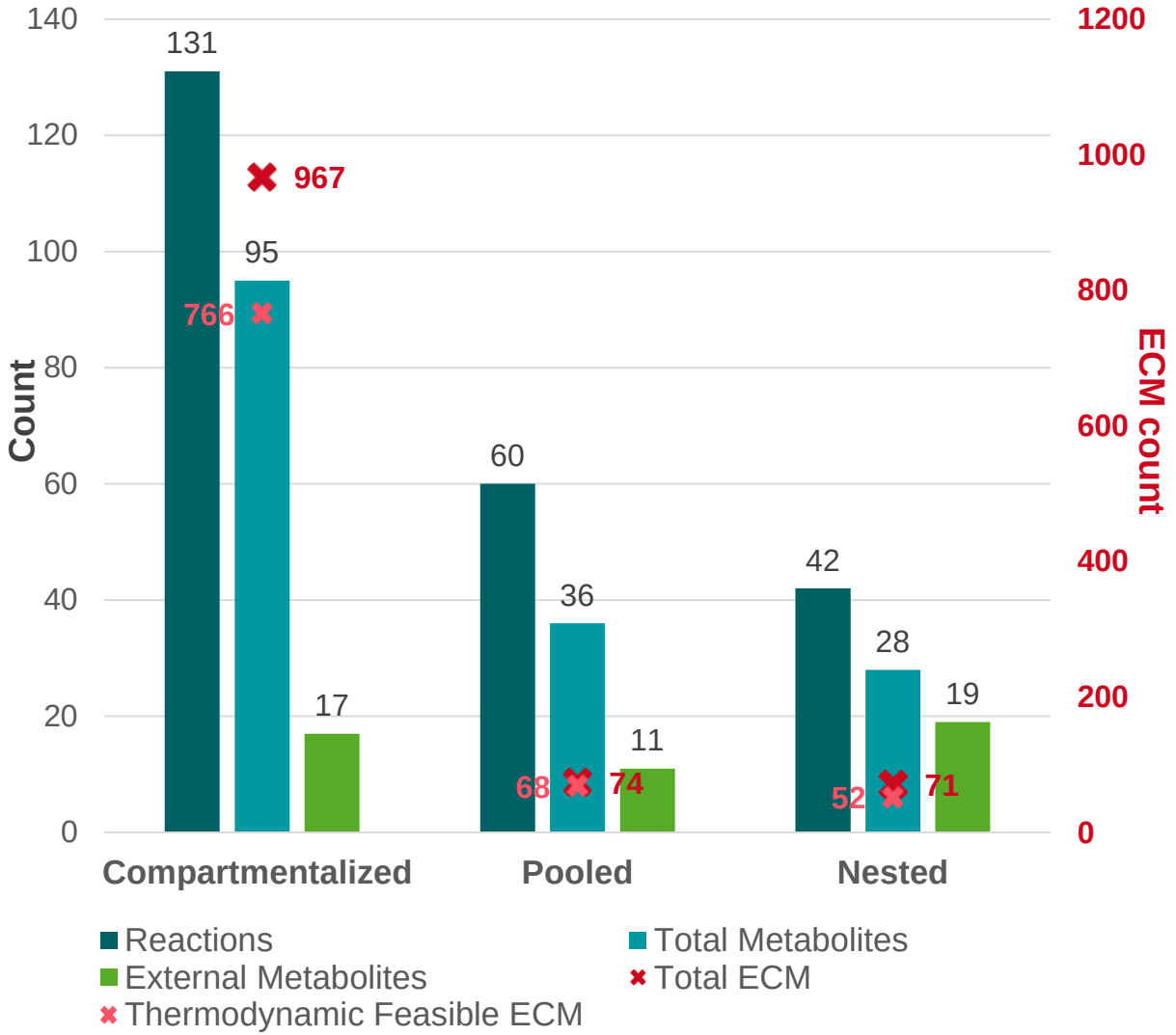
max - efficiency



Community Model: Nested Model

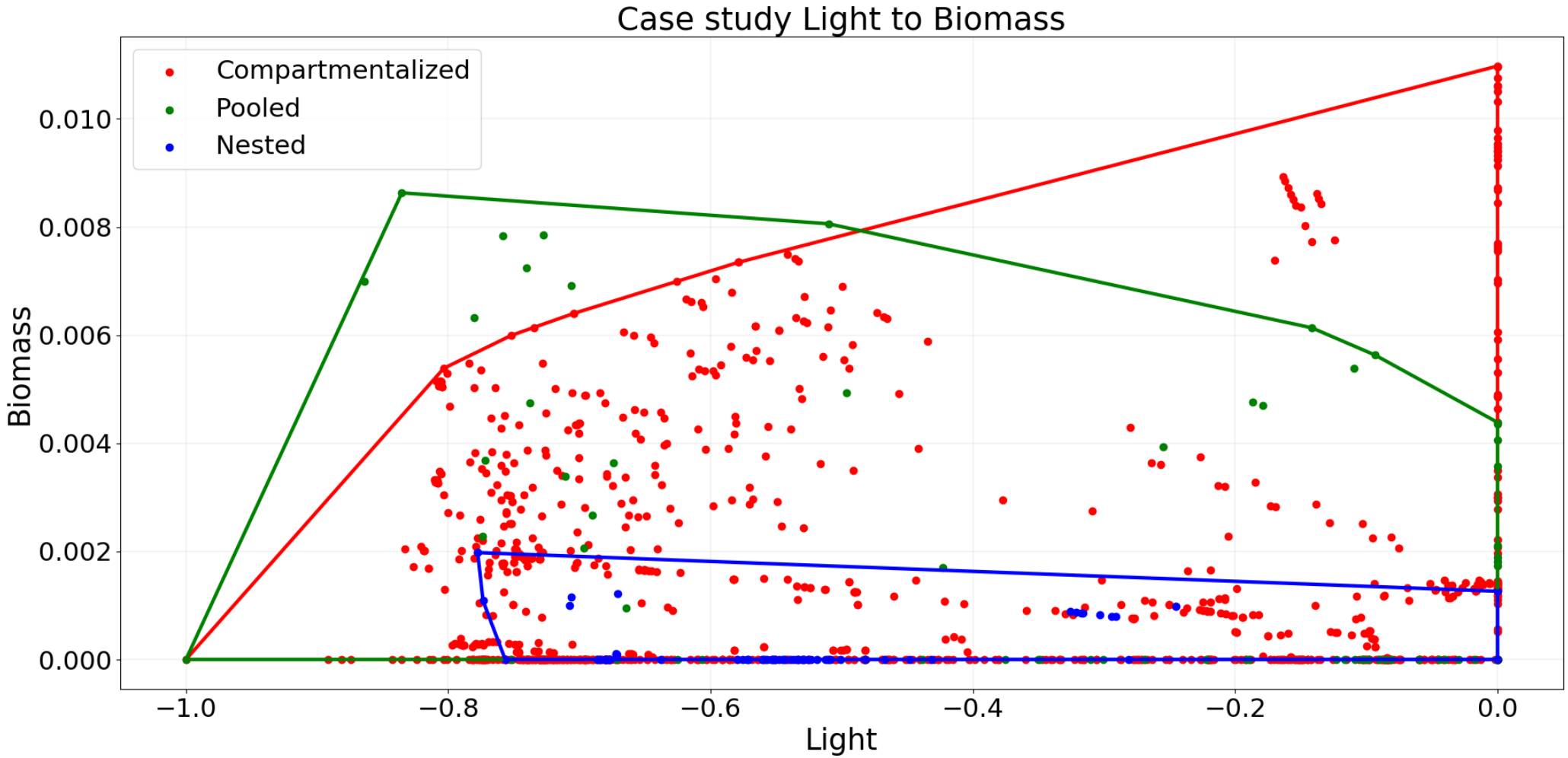


Community Model Comparison



Modeltype	+	-
Compartmentalized	• Detailed interaction network	• High computation cost
Pooled	• Low computation cost	• Hardly any interaction information
Nested	• Low computation cost • Focussed on relevant information	• Dependent on efficiency factors • Dependent on number of choosen ECMs

Comparison of ECM Solution Spaces



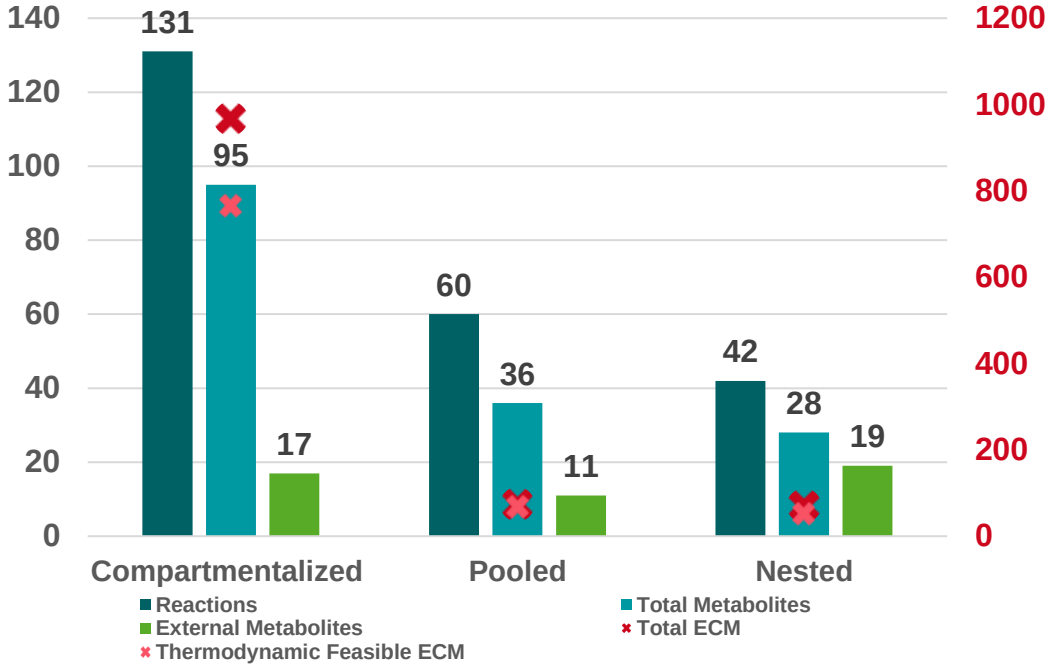
Conclusion and Outlook

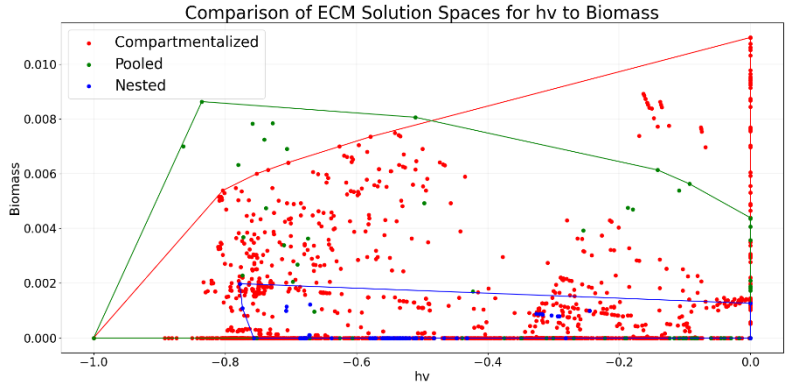
Conclusion

- Analyzed ECMs
- Reduced solution space by thermodynamic feasibility
- Solved optimization with thermodynamic feasible ECM
- Built and compared 3 types of community models
- Data vizualisation

Outlook

- Validation of thermodynamic feasibility with concentration data
- Verify ECM models with BIOLOG data
- Application on Genome Scale Metabolic Models of the OMM19 strain





Thank you for your attention