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Reasoning approaches for the characterization of cooperation and competition in large-scale microbial communities

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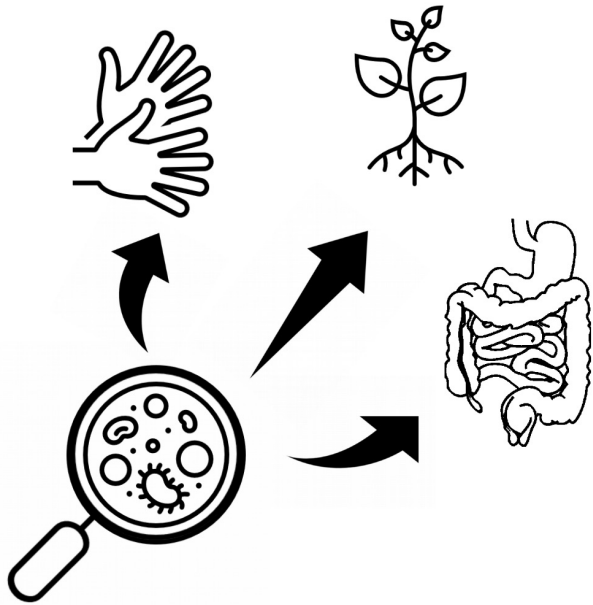
➤ Reasoning approaches for the characterization of cooperation and competition in large-scale microbial communities

Maxime Lecomte – David Sherman – Hélène Falentin – Clémence Frioux

GT-BIOSS NANTES November, 17 2022

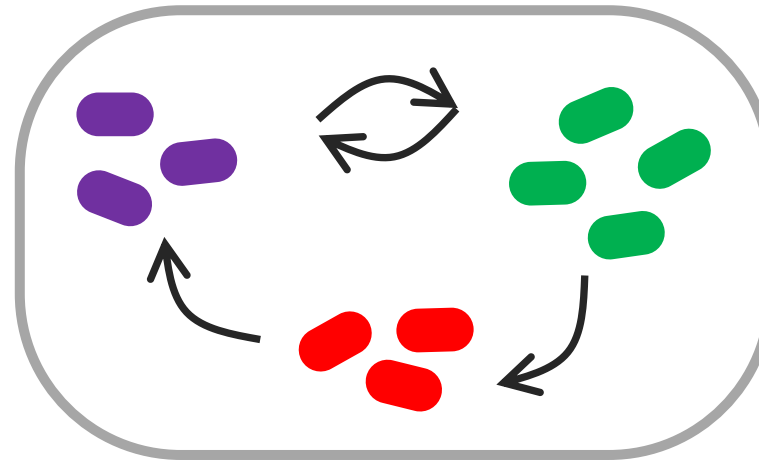
> Motivation

Bacterial communities ?



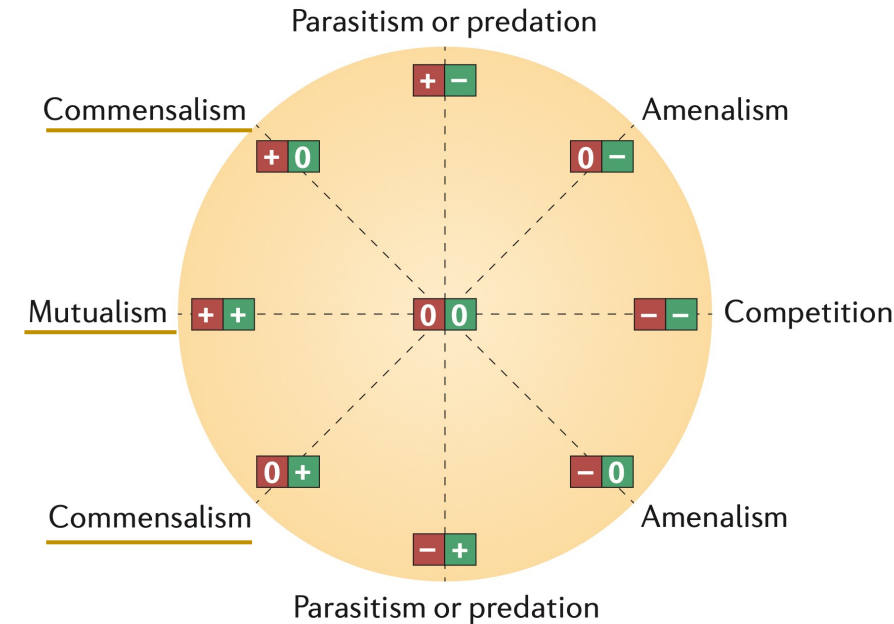
Microbes are essential in ecosystems

System biology



Bacterial interactions as a key mechanism

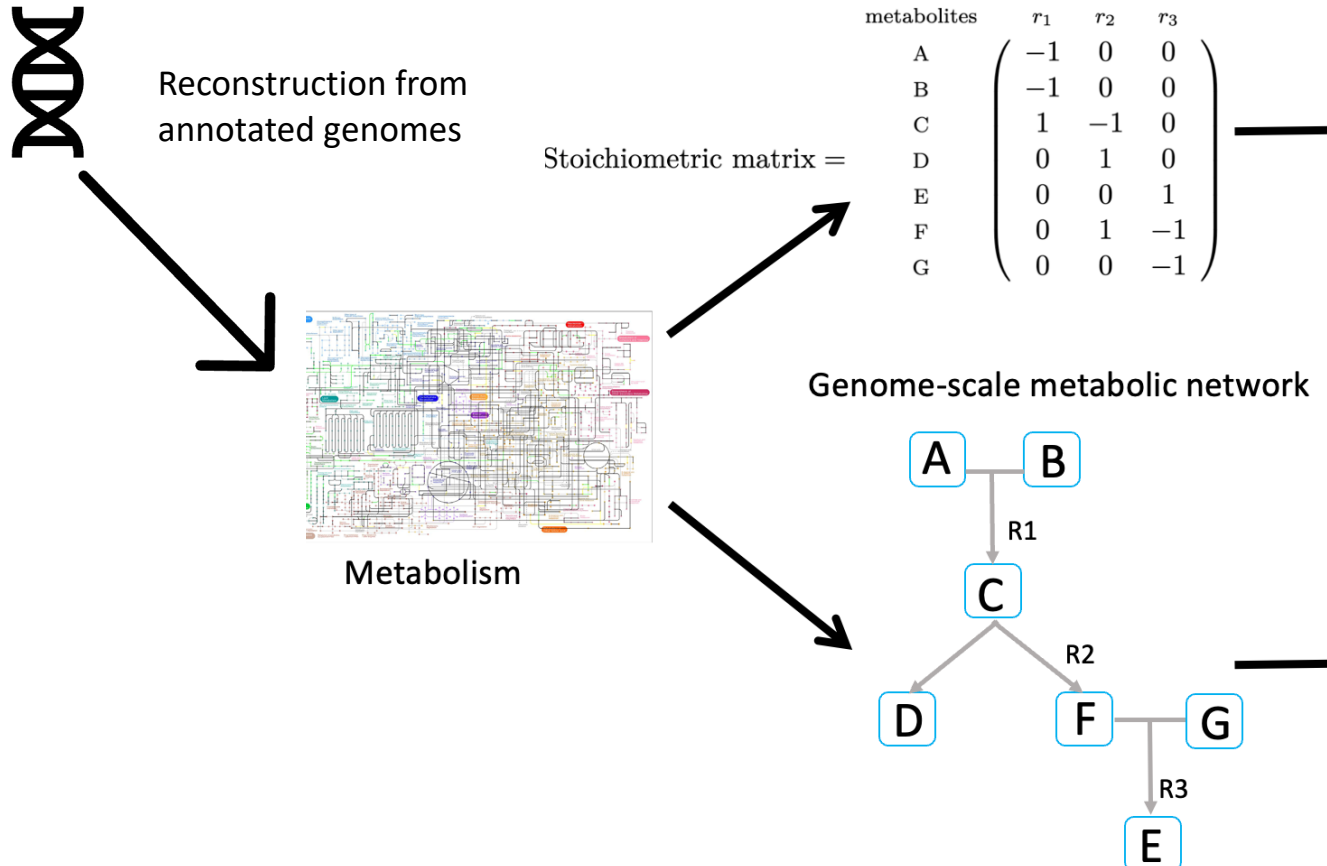
Interaction types



Cooperation and competition

Metabolism enable the understanding of interaction-based mechanisms in microbial communities

➤ State-of-the art for modeling bacterial communities



Genome-scale metabolic networks describe all functions associated to genomes

State-of-the art for modeling bacterial communities



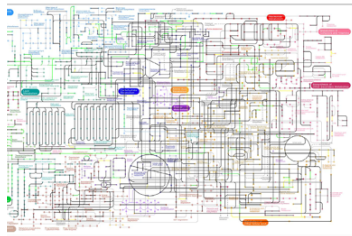
Reconstruction from annotated genomes

Stoichiometric matrix =

metabolites	r_1	r_2	r_3
A	-1	0	0
B	-1	0	0
C	1	-1	0
D	0	1	0
E	0	0	1
F	0	1	-1
G	0	0	-1

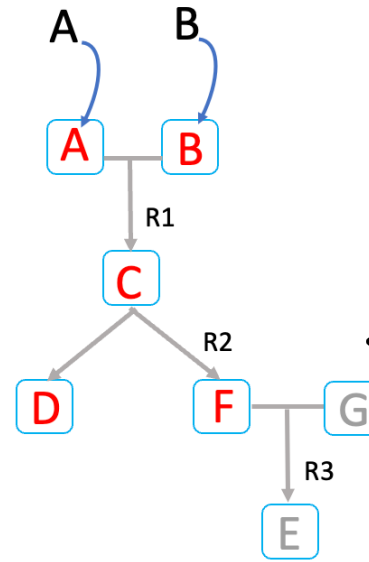
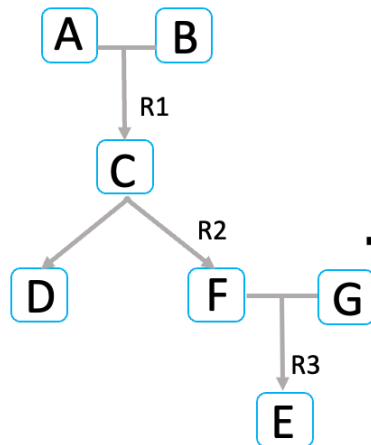
$$\begin{aligned} & \max v_{growth} \\ & \text{such that } S \cdot v = 0 \\ & \text{and } v_{min} \leq v \leq v_{max} \end{aligned}$$

Numerical methods (e.g., FBA-like)



Metabolism

Genome-scale metabolic network



Metabolite scope from the A,B in the environment

Discrete method

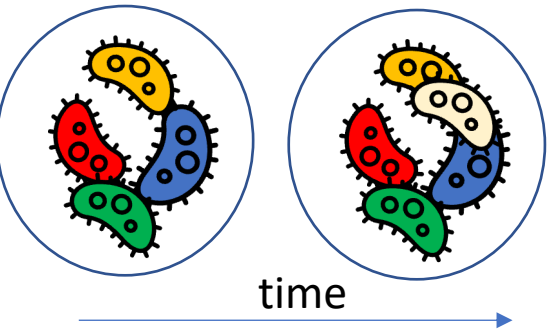
Two mathematical formalisms used for modeling the behavior of an organism in its environment



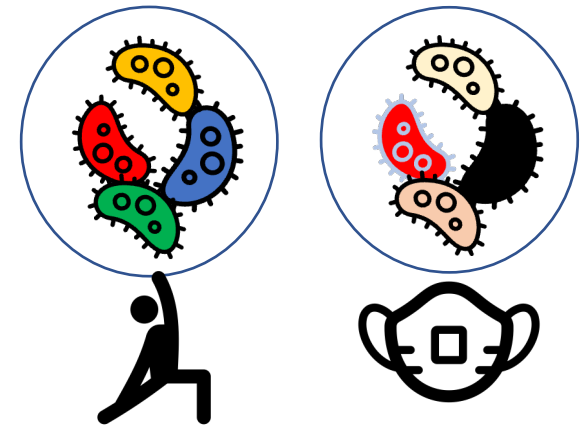
➤ Goal : Identify cooperation and competition potential in large scale bacterial communities

Cooperation and competition potential

Longitudinal analysis



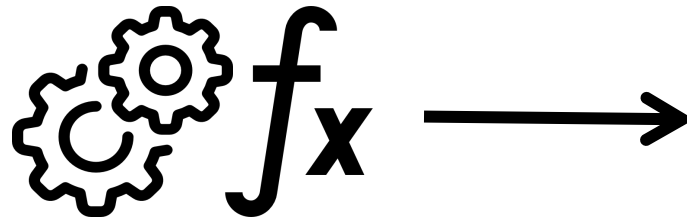
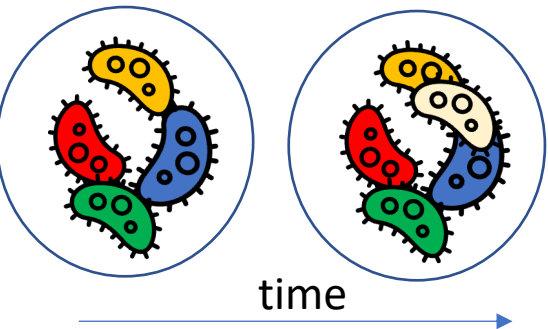
Cross sectional analysis



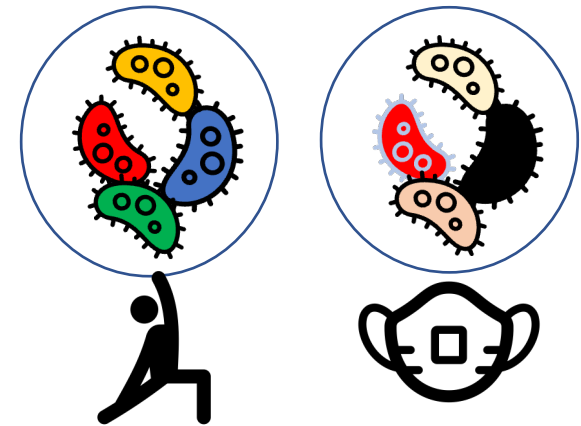
➤ Goal : Identify cooperation and competition potential in large scale bacterial communities

Cooperation and competition potential

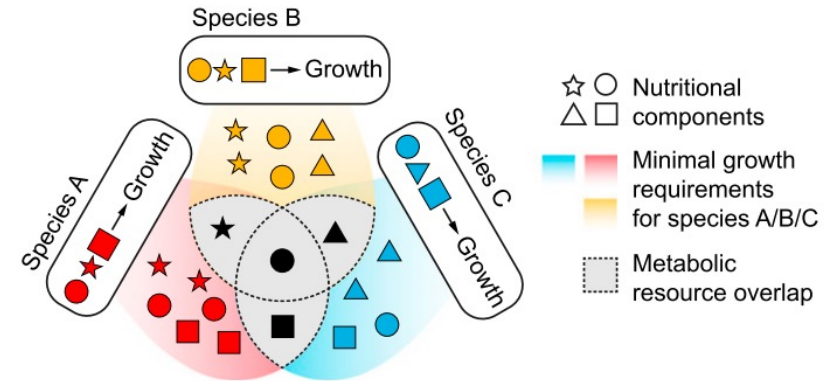
Longitudinal analysis



Cross sectional analysis



Nutrient point of view

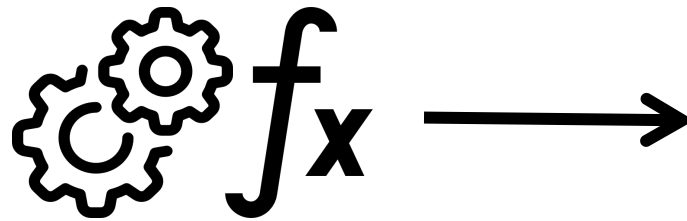
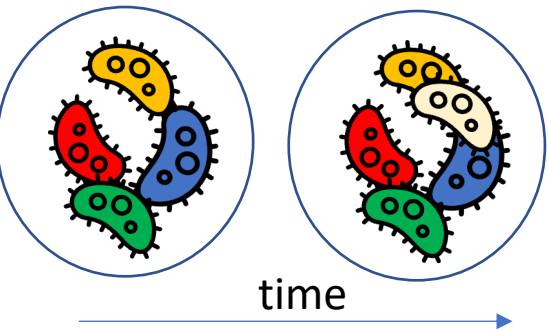


Competition potentials

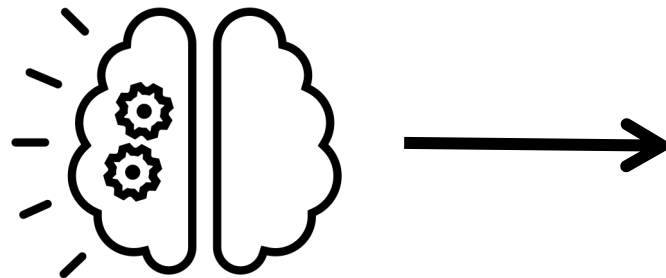
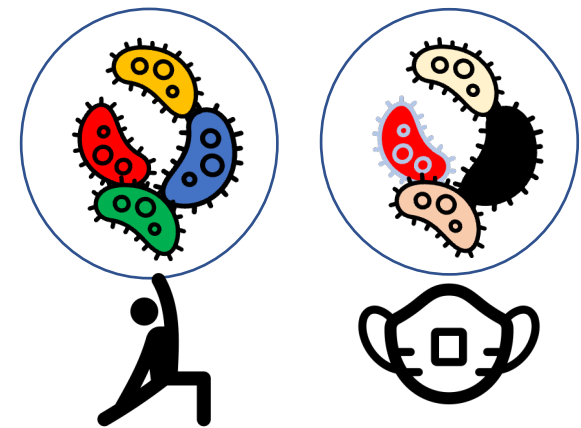
➤ Goal : Identify cooperation and competition potential in large scale bacterial communities

Cooperation and competition potential

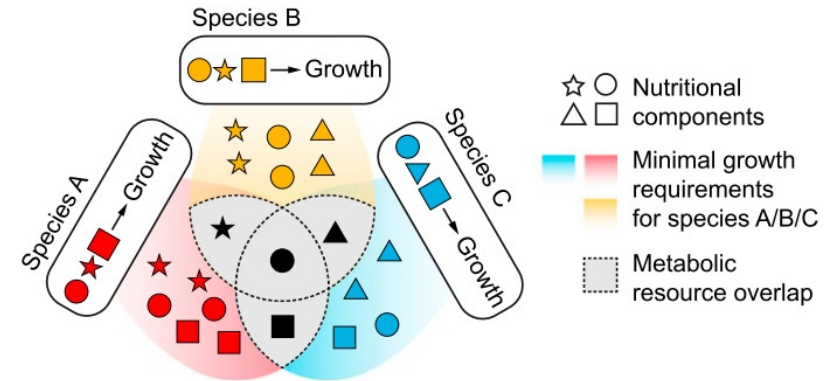
Longitudinal analysis



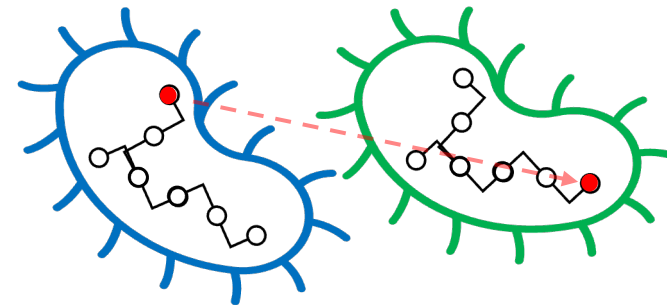
Cross sectional analysis



Nutrient point of view



Competition potentials



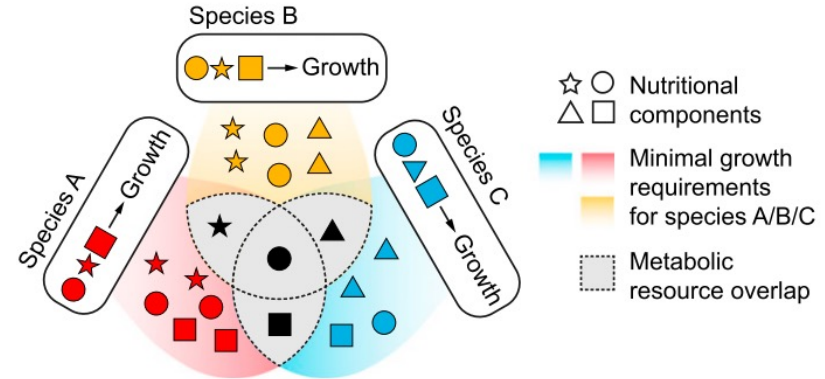
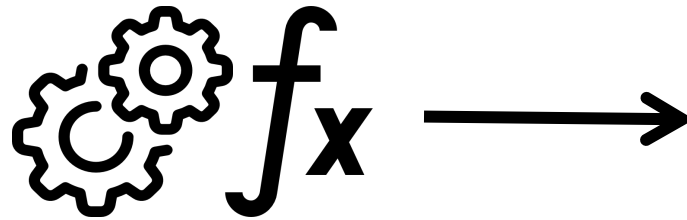
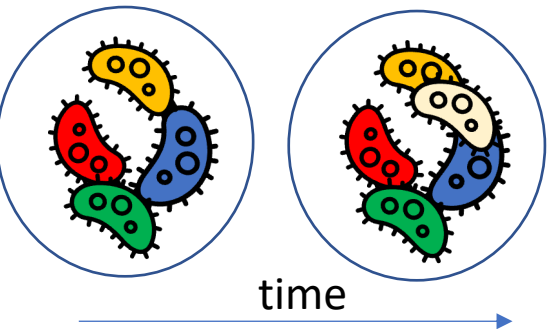
Cooperation potentials

Either numerical or discrete methods highlight cooperation and competition potentials

➤ Goal : Identify cooperation and competition potential in large scale bacterial communities

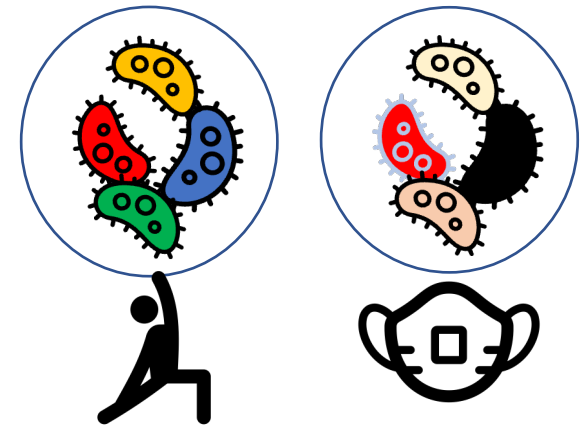
Scale-up to large scale bacterial communities

Longitudinal analysis



Community size up to 18

Cross sectional analysis

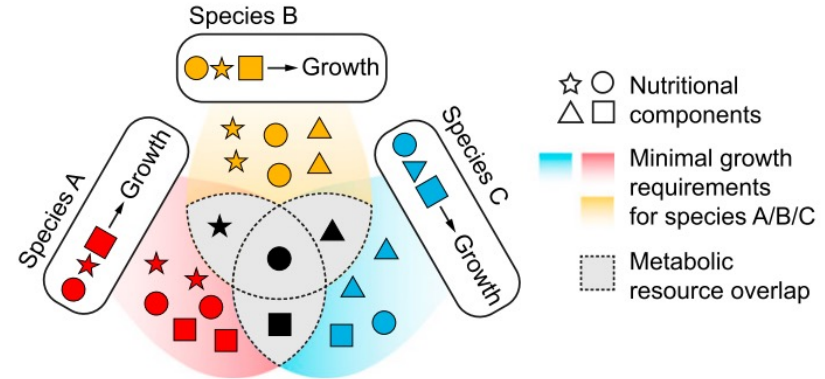
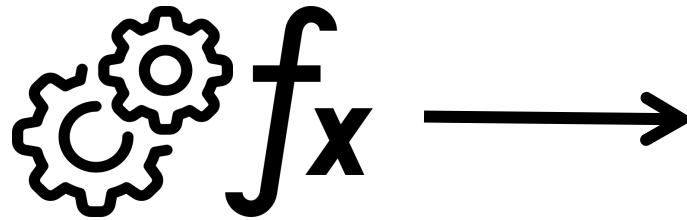
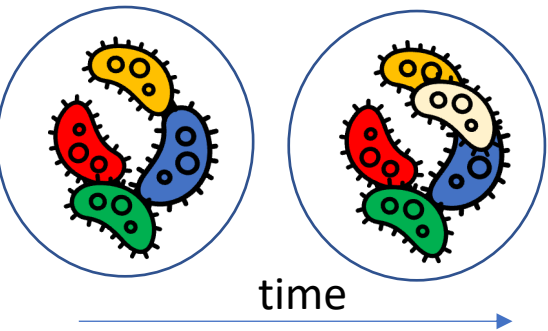


Cost in computational time

➤ Goal : Identify cooperation and competition potential in large scale bacterial communities

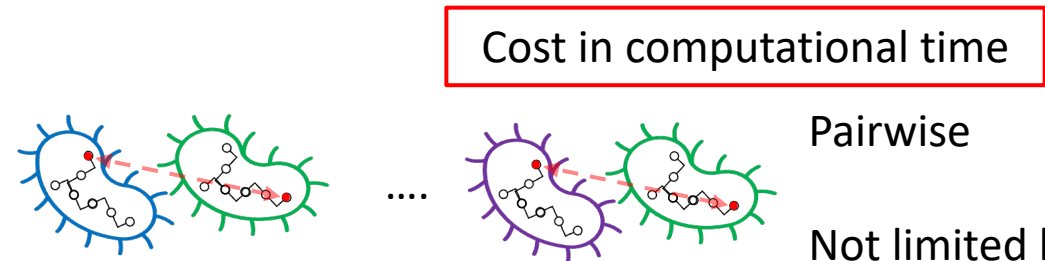
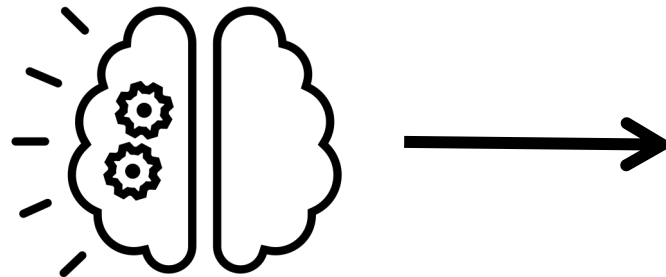
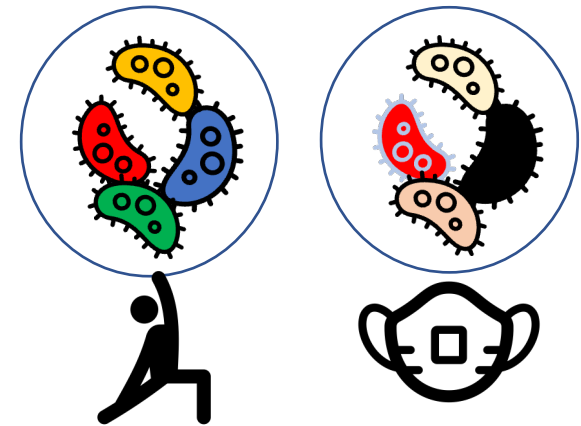
Scale-up to large scale bacterial communities

Longitudinal analysis



Community size up to 18

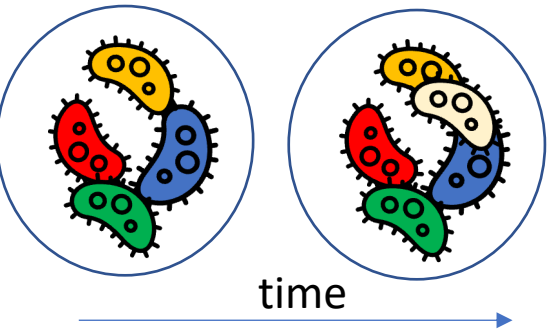
Cross sectional analysis



Pairwise
Not limited by the community size

➤ Avoid pairwise analysis for characterizing cooperation and competition in microbial communities

Longitudinal analysis



Characterize community

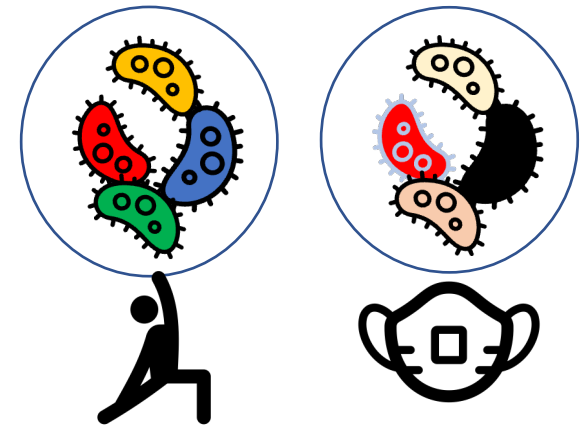


150 bacteria

Pairwise analysis

$$(150 * (150-1))/2 = 11\ 375 \text{ combinations}$$

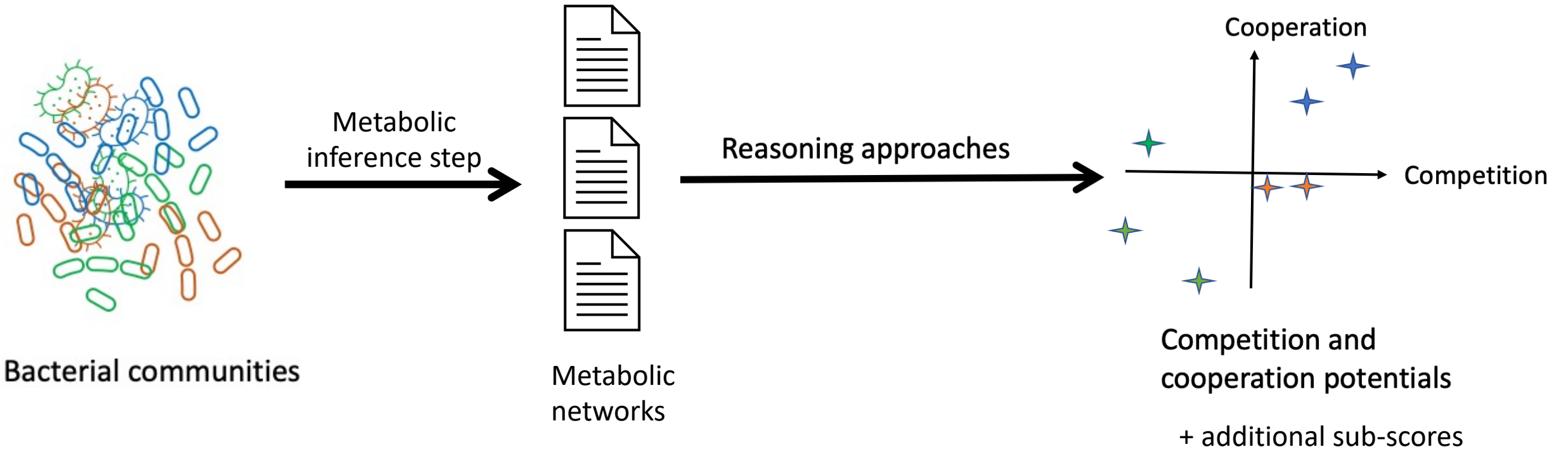
Cross sectional analysis



Cost in computational time + tedious analysis

How to characterize cooperation and competition potentials? → trade-off between scalability and accuracy

➤ Avoid pairwise analysis for characterizing cooperation and competition in microbial communities



Calculation of scores for characterizing the whole community with Answer Set Programming

➤ Answer Set Programming

Logic paradigm and Knowledge representation & reasoning

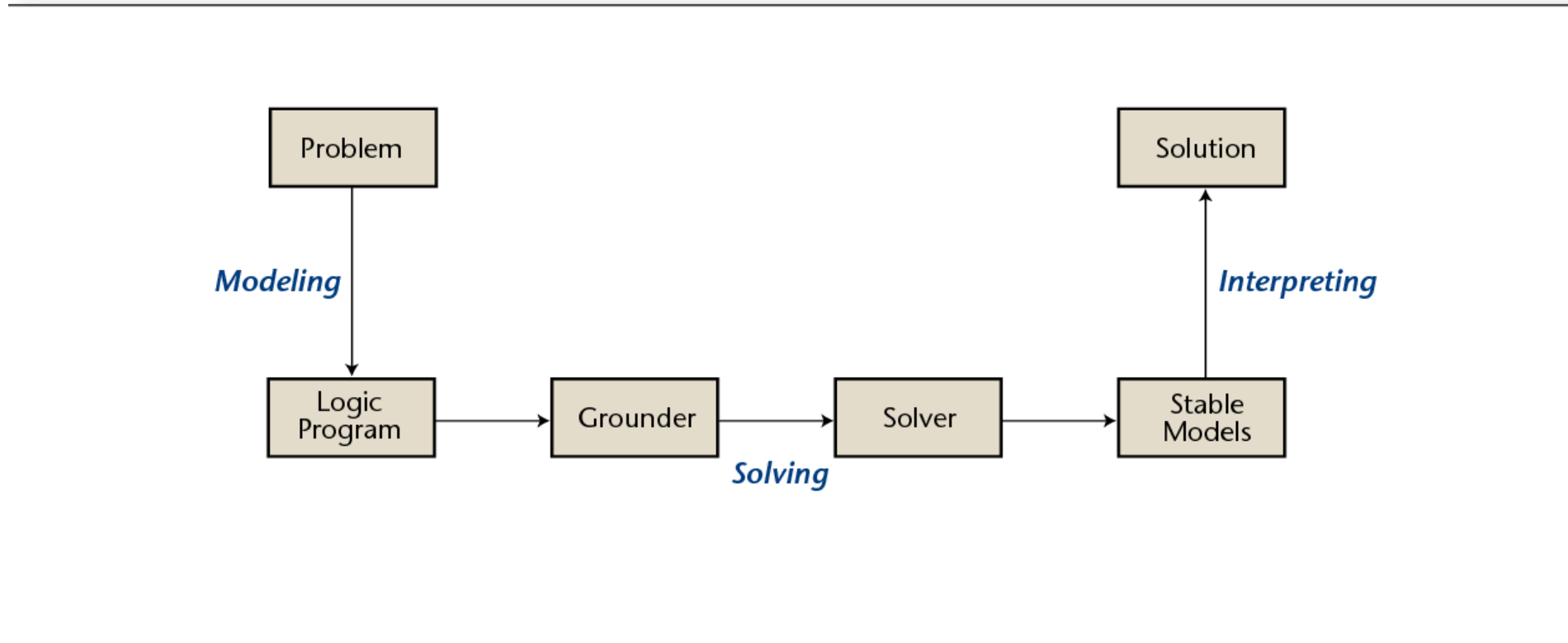
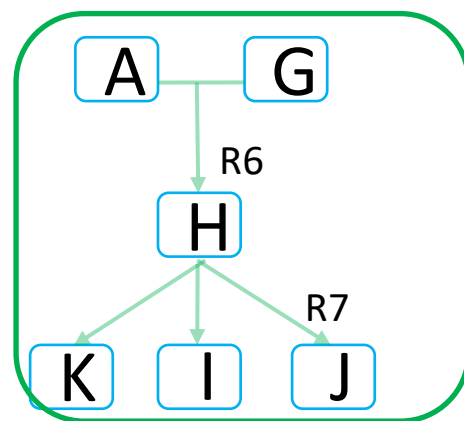
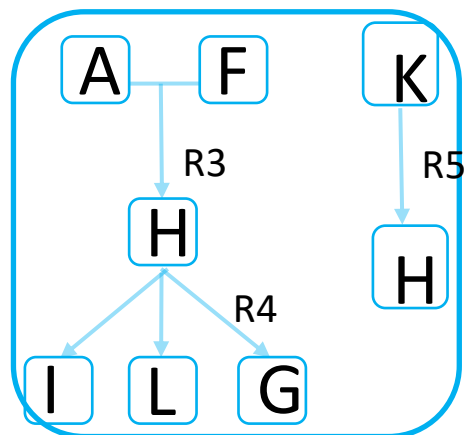
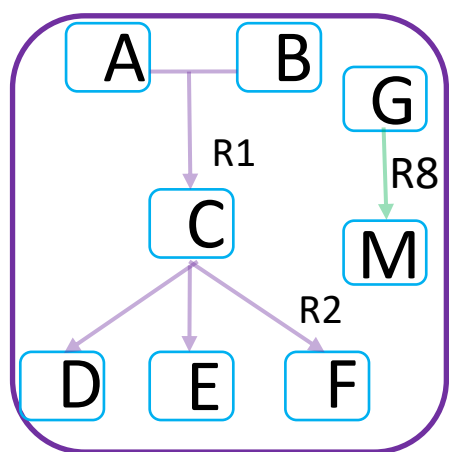


Figure 1. The Work Flow of Answer Set Programming.

Kaufmann, Benjamin et al. "Grounding and Solving in Answer Set Programming." *AI Mag.* 37 (2016): 25-32.

➤ Cooperation potential based on exchanged metabolites using ASP

Seed : A,B

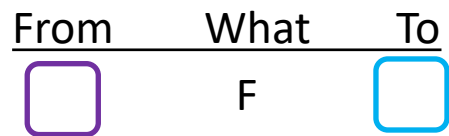
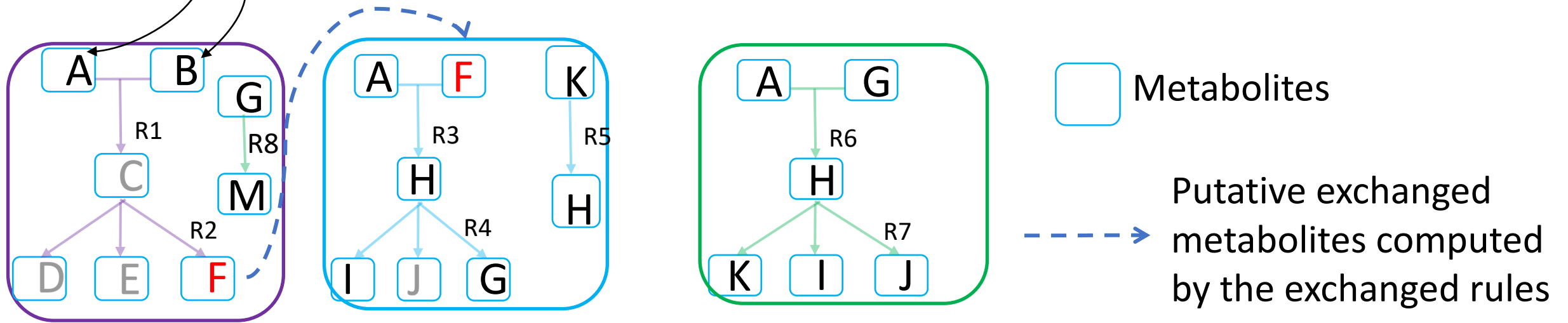


 Metabolites

$exchanged_{metabolites} = scope(G_s, S), not indivProducible(S, G_t), products(S, G_s)$. Where $S \in G$ and $T \in G$, and $S \neq T$.

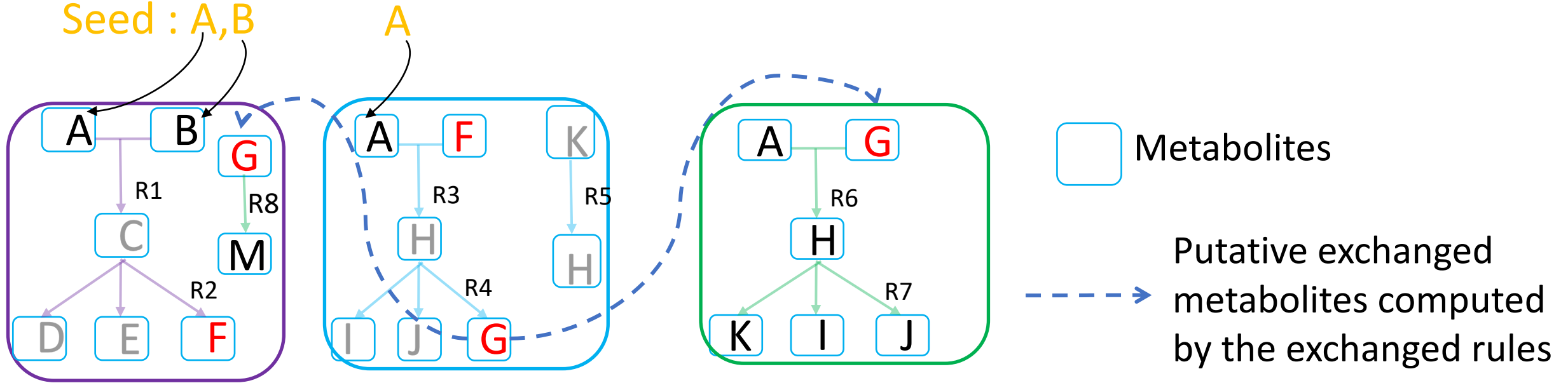
➤ Cooperation potential based on exchanged metabolites using ASP

Seed : A,B



➤ Cooperation potential based on exchanged metabolites using ASP

Seed : A,B

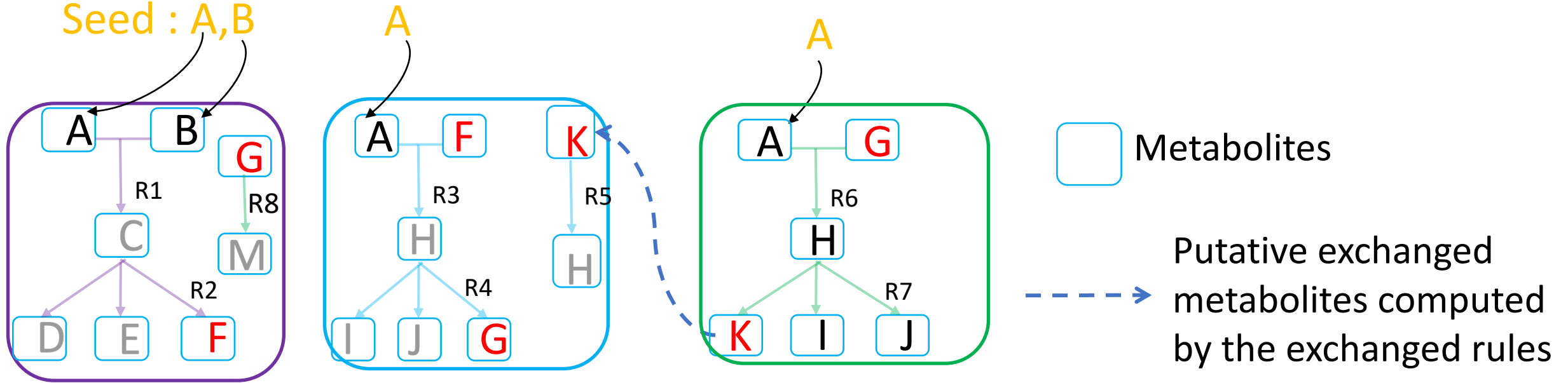


From	What	To
<input type="checkbox"/>	F	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>



➤ Cooperation potential based on exchanged metabolites using ASP

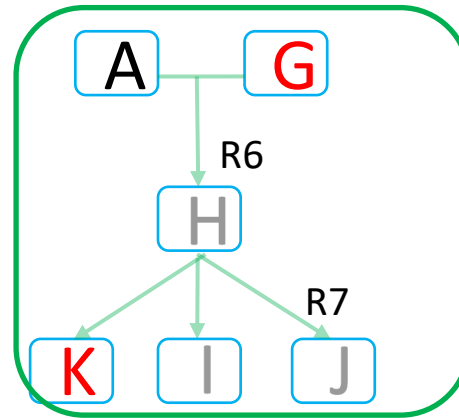
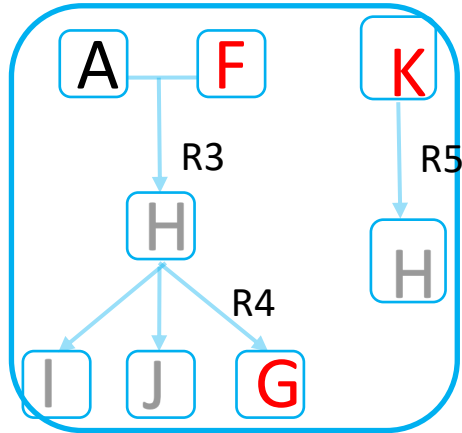
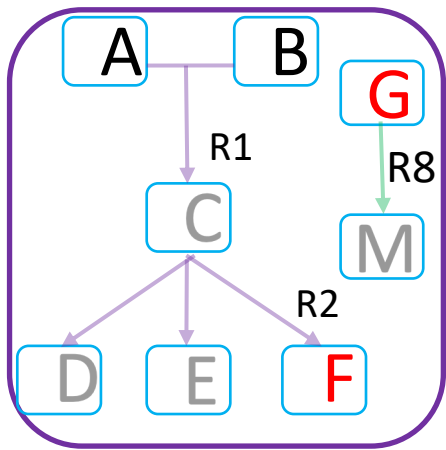
Seed : A,B



From	What	To
<input type="checkbox"/>	F	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	K	<input type="checkbox"/>

➤ Exponential bonus (python)

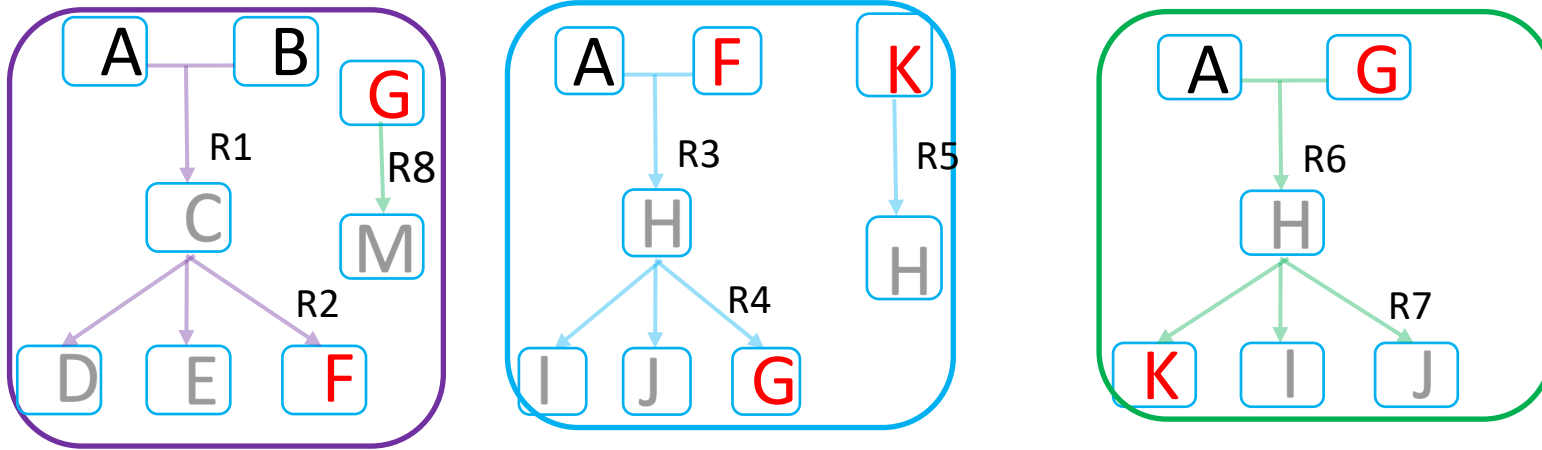
hypothesis : each species contributes differently



From	What	To
<input type="checkbox"/>	F	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	K	<input type="checkbox"/>

Exponential bonus (python)

hypothesis : each species contributes differently



From	What	To
<input type="checkbox"/>	F	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	K	<input type="checkbox"/>



$$cooperation = \sum_{i=1}^m \sum_{k=2}^n 1 + 2^{-(k-1)}$$

Number of metabolites

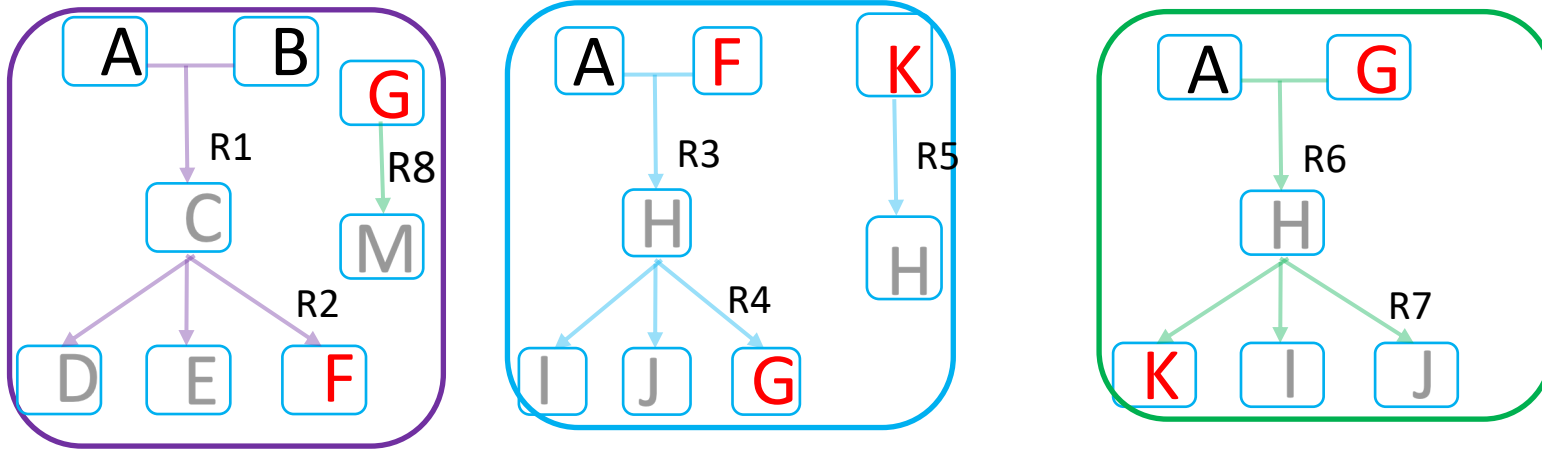
Number of different producers / consumers



INRAE

Exponential bonus (python)

hypothesis : each species contributes differently



Metabolites	Producers	consumers
F	1	1

From	What	To
<input type="checkbox"/>	F	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	K	<input type="checkbox"/>



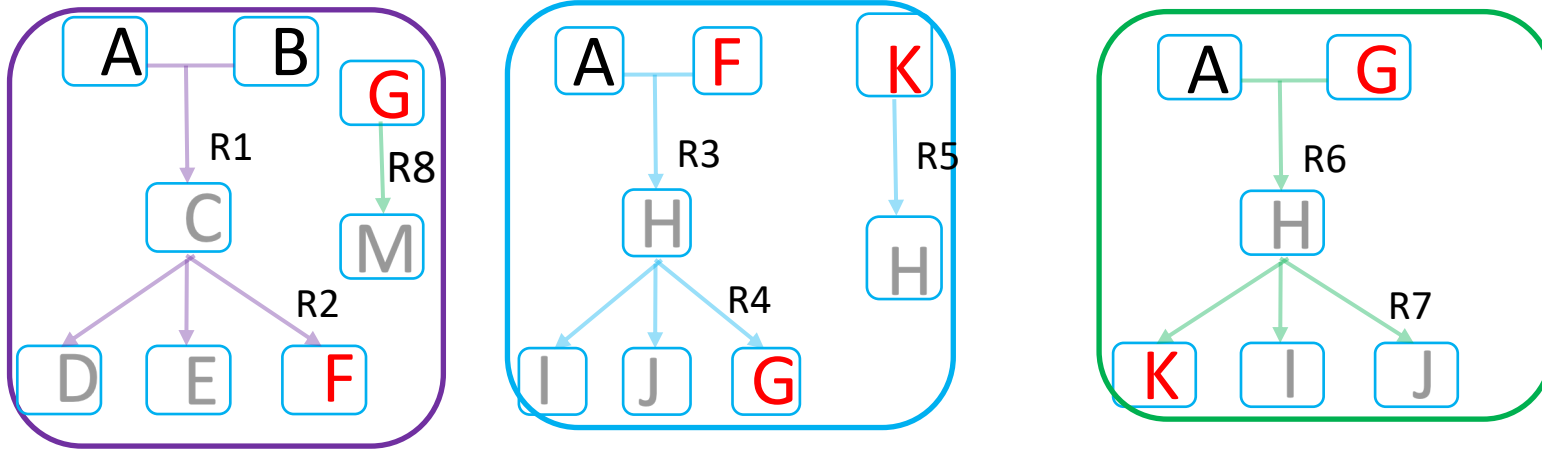
$$cooperation = \sum_{i=1}^m \sum_{k=2}^n 1 + 2^{-(k-1)}$$

Number of metabolites

Number of different producers / consumers

Exponential bonus (python)

hypothesis : each species contributes differently



Metabolites	Producers	consumers
F	1	1
G	1	1 + 2 ¹ =1.5

From	What	To
<input type="checkbox"/>	F	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	K	<input type="checkbox"/>



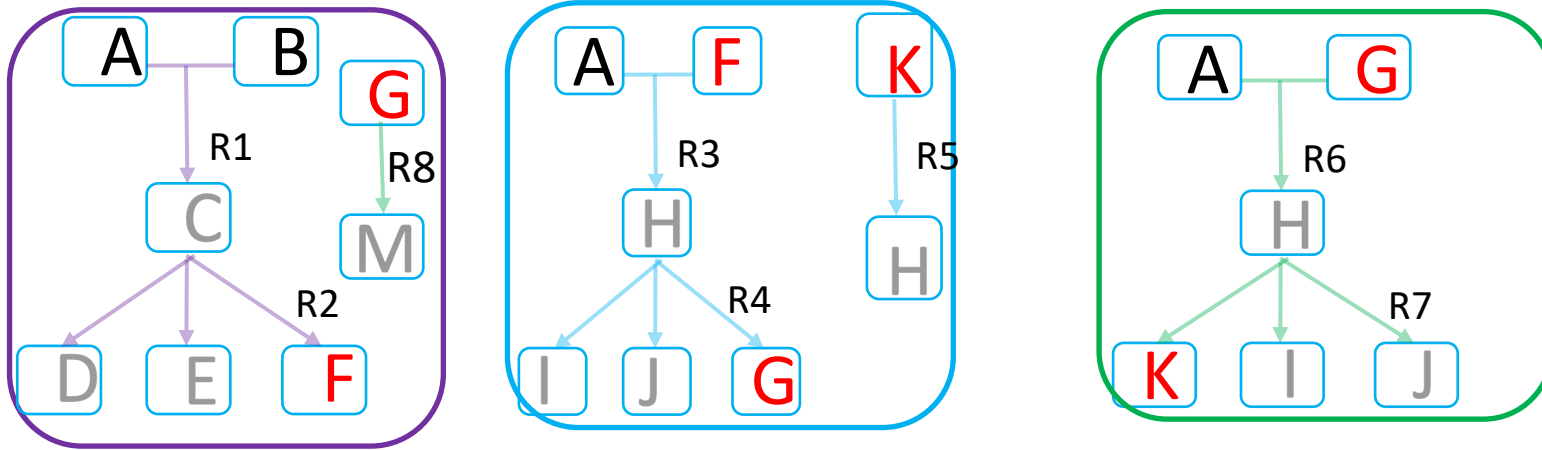
$$cooperation = \sum_{i=1}^m \sum_{k=2}^n 1 + 2^{-(k-1)}$$

Number of metabolites

Number of different producers / consumers

Exponential bonus (python)

hypothesis : each species contributes differently



Metabolites	Producers	consumers
F	1	1
G	1	1 + 2 ¹ =1.5
K	1	1

Cooperation = F + G + K = 6.5

From	What	To
<input type="checkbox"/>	F	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	G	<input type="checkbox"/>
<input type="checkbox"/>	K	<input type="checkbox"/>



$$cooperation = \sum_{i=1}^m \sum_{k=2}^n 1 + 2^{-(k-1)}$$

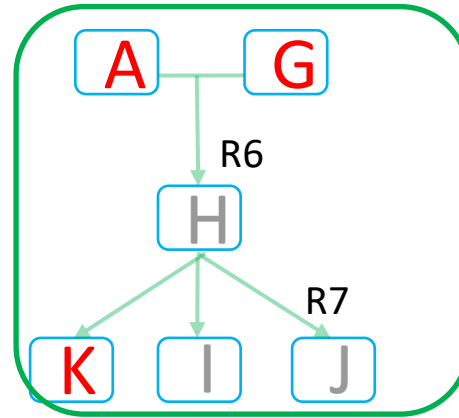
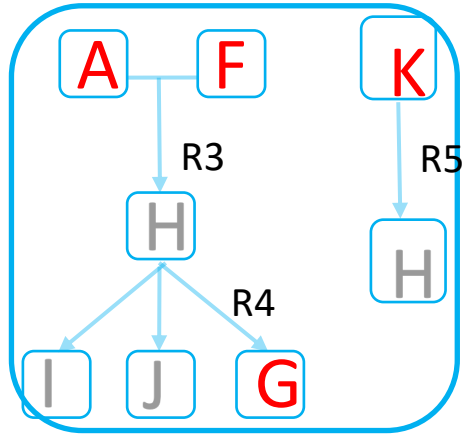
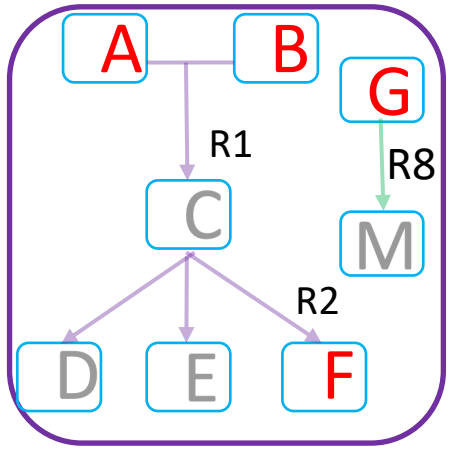
Number of metabolites

Number of different producers / consumers






Competition potential based on limiting substrate using ASP

Seed : A,B



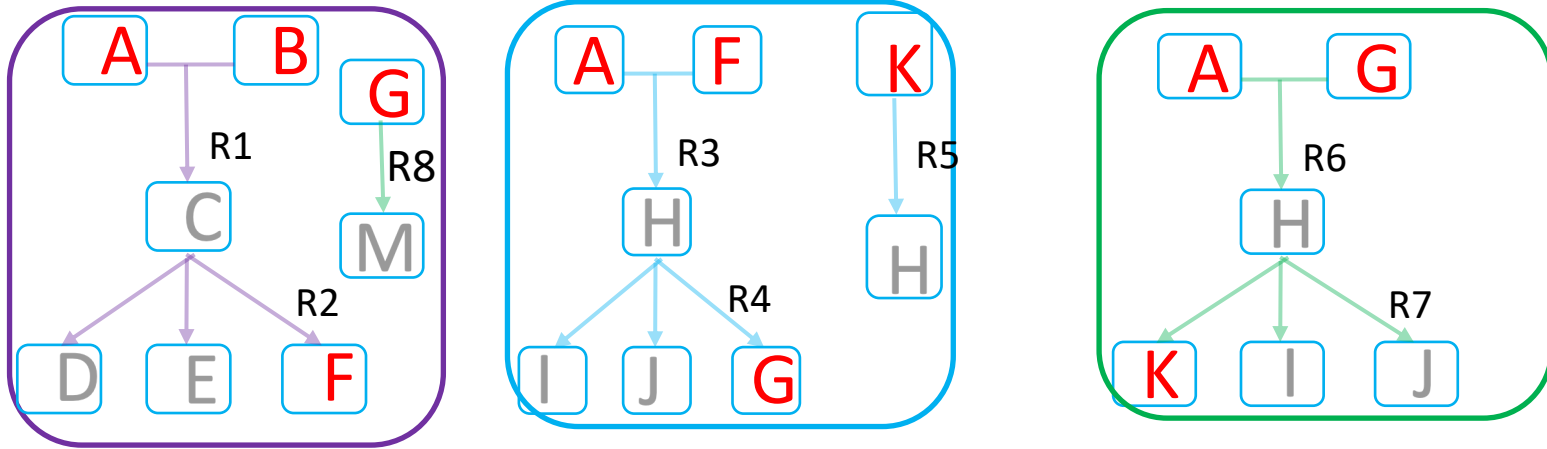
G Limiting substrates

-  A,B,F
-  A,B,G,K
-  A,G,K



➤ Calculation of the competition potential (python)

Seed : A,B



- A,B,F
- A,B,G,K
- A,G,K

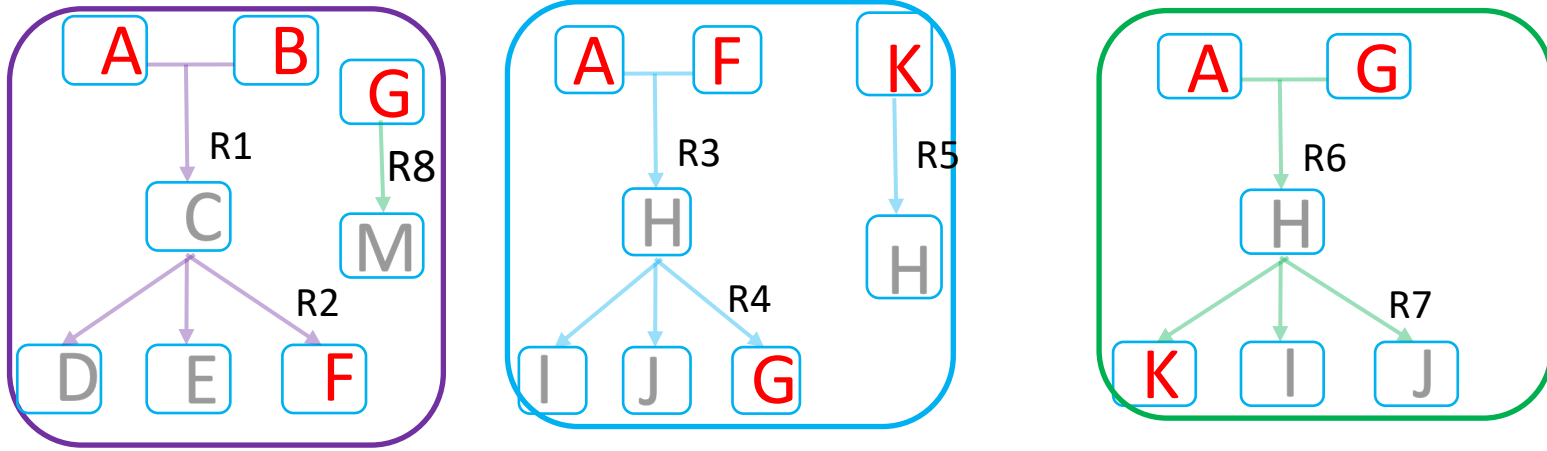


$$competition = \sum_{i=1}^m \frac{count(i)}{size_community}$$



➤ Calculation of the competition potential (python)

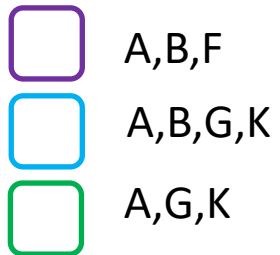
Seed : A,B



A : 3
B : 2
G : 2
K : 2
F : 1

Metabolites

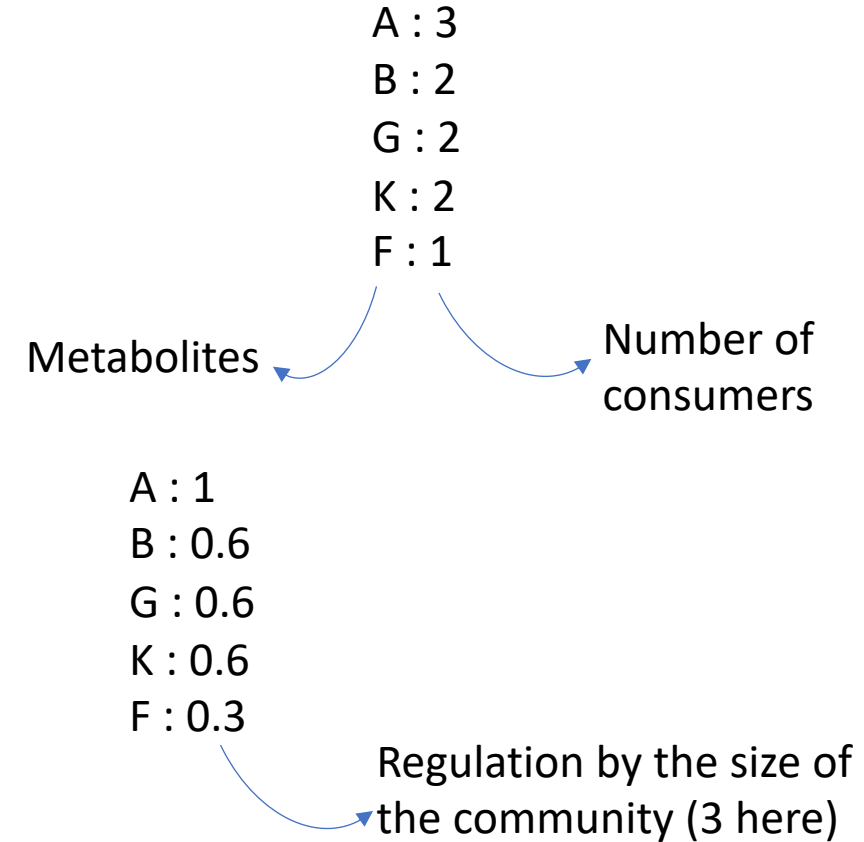
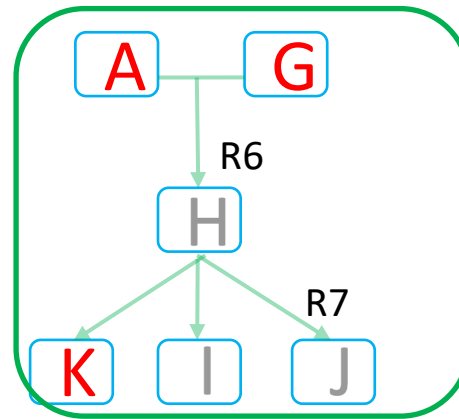
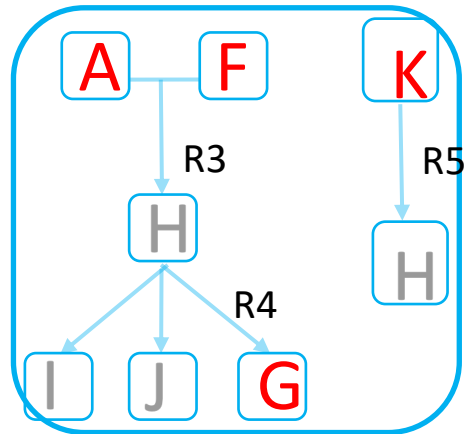
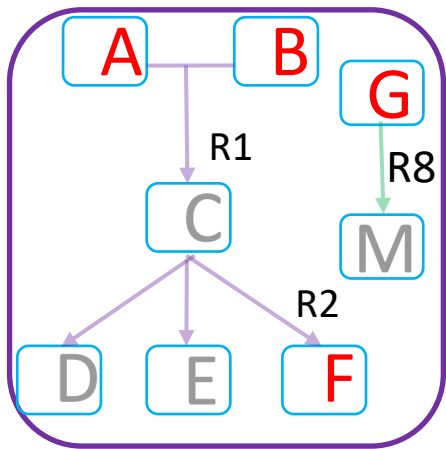
Number of consumers



$$competition = \sum_{i=1}^m \frac{count(i)}{size_community}$$

➤ Calculation of the competition potential (python)

Seed : A,B



- A,B,F
- A,B,G,K
- A,G,K

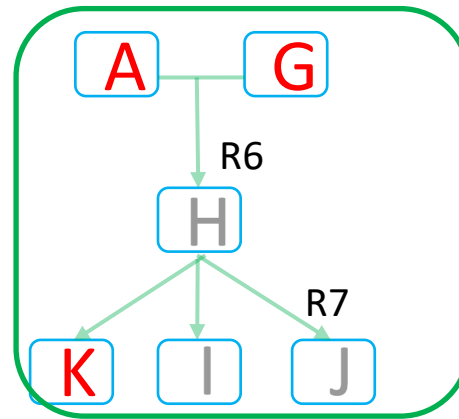
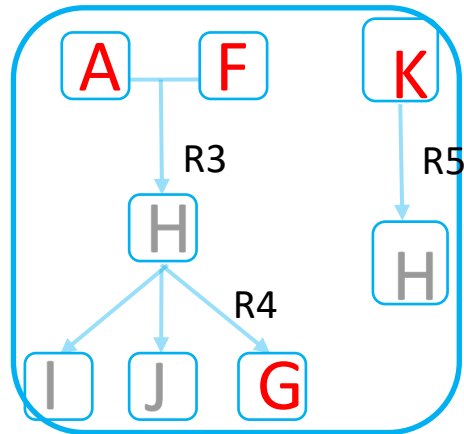
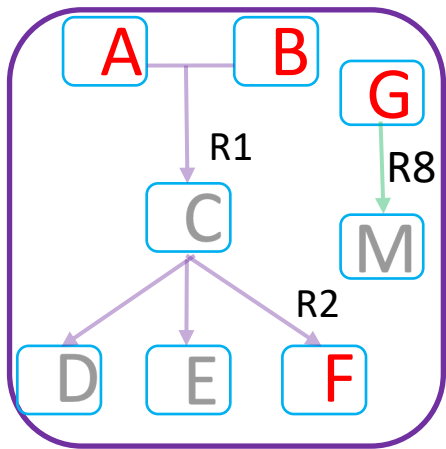


$$competition = \sum_{i=1}^m \frac{count(i)}{size_community}$$



➤ Calculation of the competition potential (python)

Seed : A,B



A : 3
B : 2
G : 2
K : 2
F : 1

Metabolites

Number of consumers

A : 1
B : 0.6
G : 0.6
K : 0.6
F : 0.3

Regulation by the size of the community (3 here)

- A,B,F
- A,B,G,K
- A,G,K



$$competition = \sum_{i=1}^m \frac{count(i)}{size_community}$$

Competition = 1 + 0.6 + 0.6 + 0.6 + 0.3 = **3.1**



INRAE

Reasoning approaches for the characterization of cooperation and competition in large-scale microbial communities

November 17 2022 / maxime.lecomte@inrae.fr / Maxime Lecomte 3rd PhD student

➤ Benchmarks for testing scores

Scores in function of the ecosystem



gut



Leaf



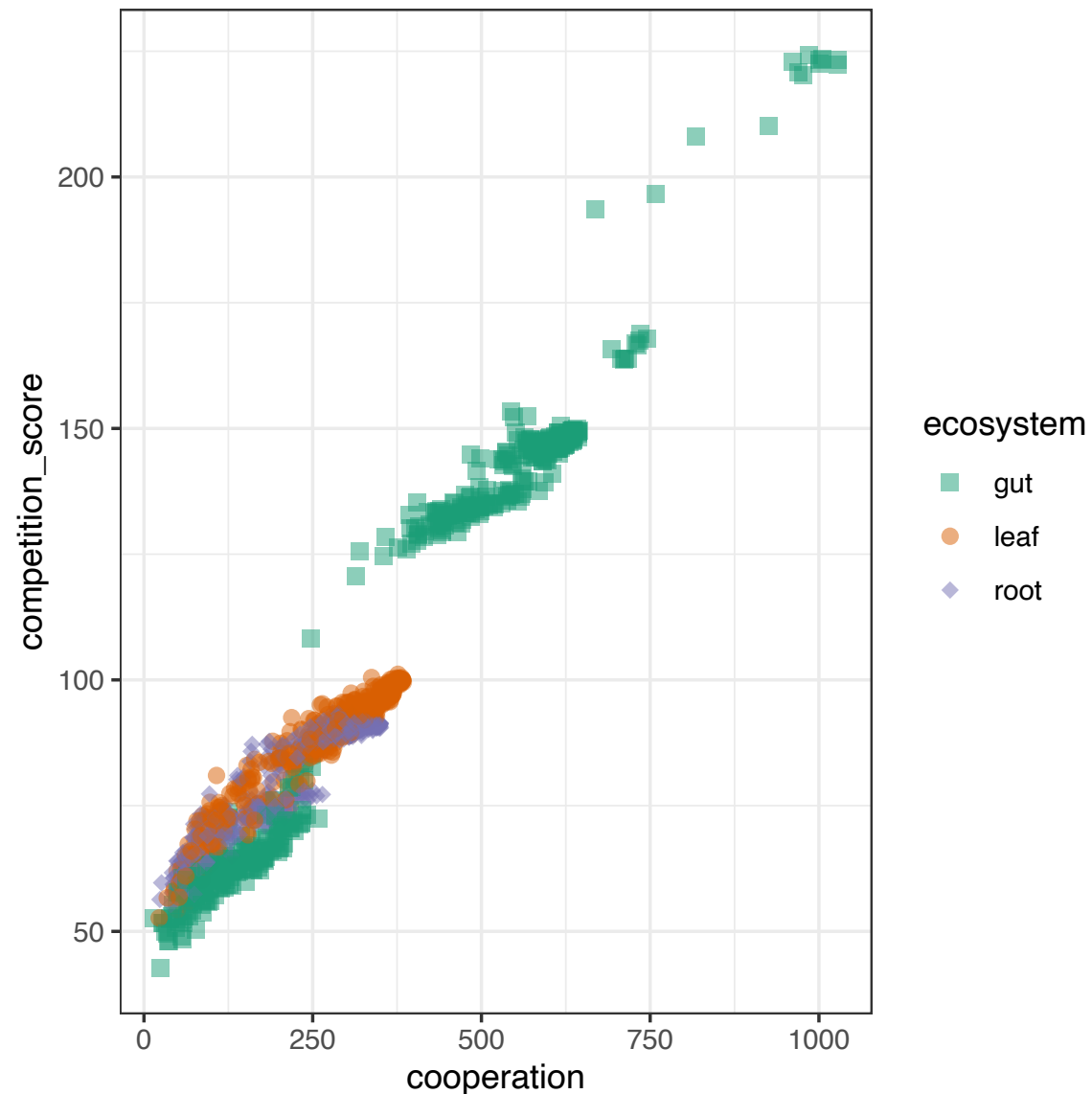
root



50 communities of size X

Reference
genomes of
cultivable species
from 3 ecosystems

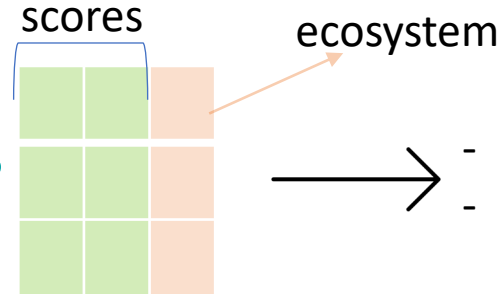
Different scores in function of the ecosystems



INRAE

➤ Ecosystem prediction from scores

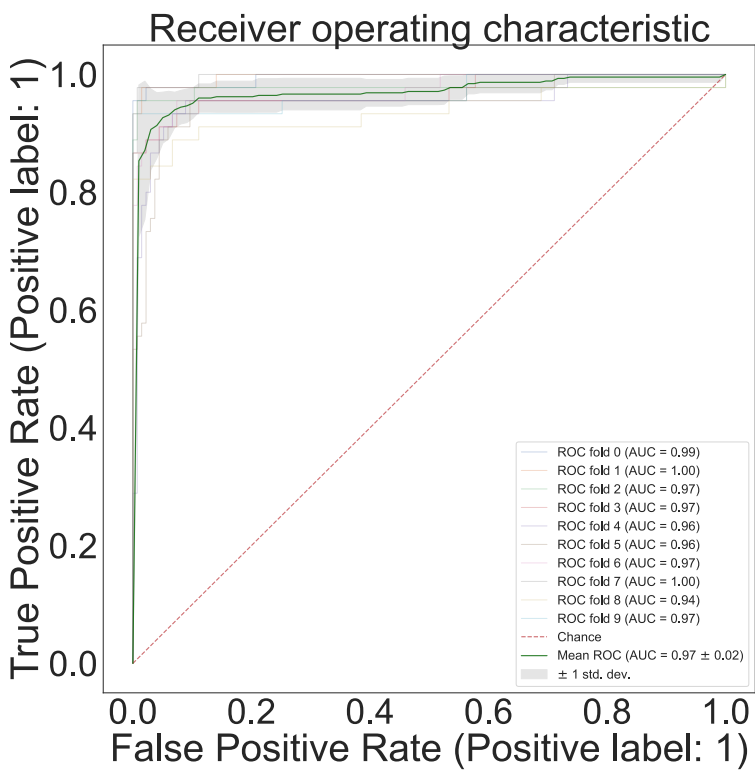
Prediction of gut ecosystem (SVM)



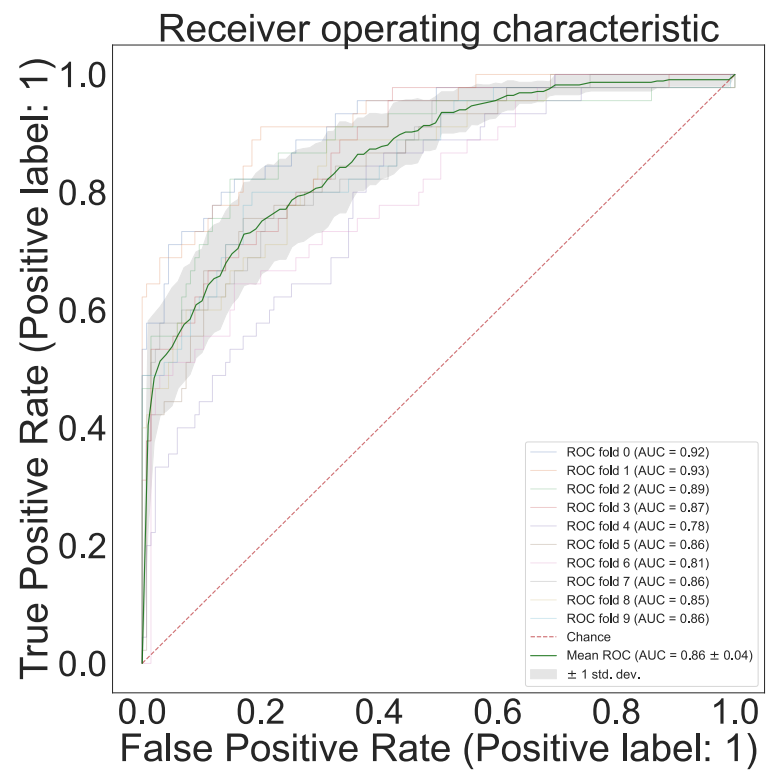
→ - Noise
- Cross validation → Ecosystem?

Up to 3 features = training

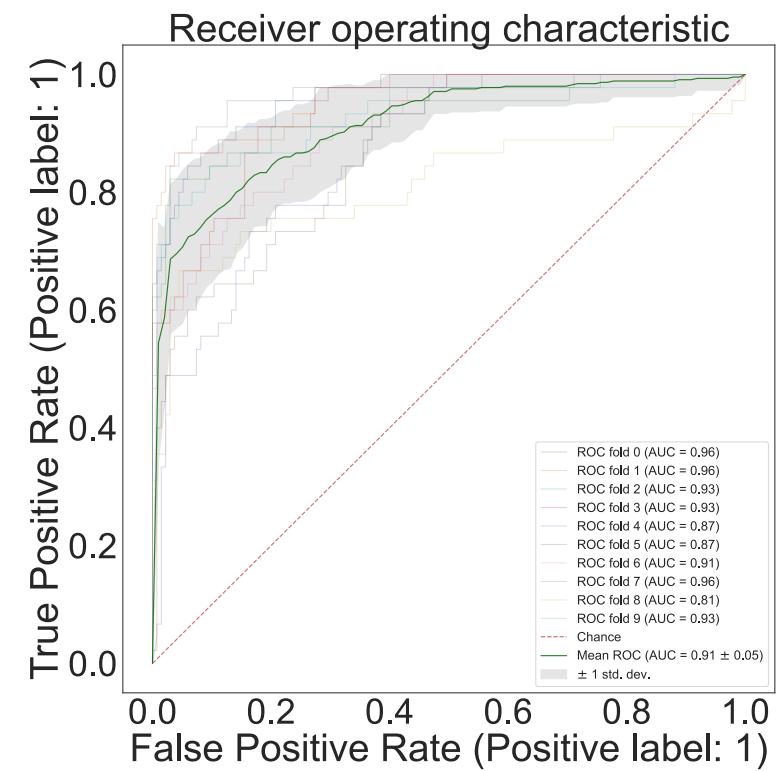
Up to 4



Only competition



Only cooperation



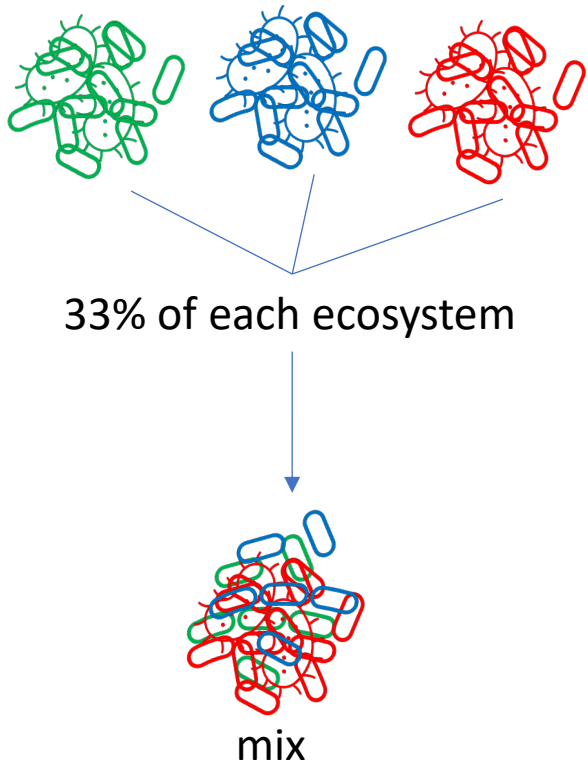
Both

Competition score seems to be enough for predicting ecosystem



➤ Benchmarks for testing scores

Do scores differ between ecosystems ?



Cooperation and competition scores significantly differ between non-realistic and *ecosystem-consistent* communities



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➤ Benchmarks for testing scores

Scores in function of the ecosystem



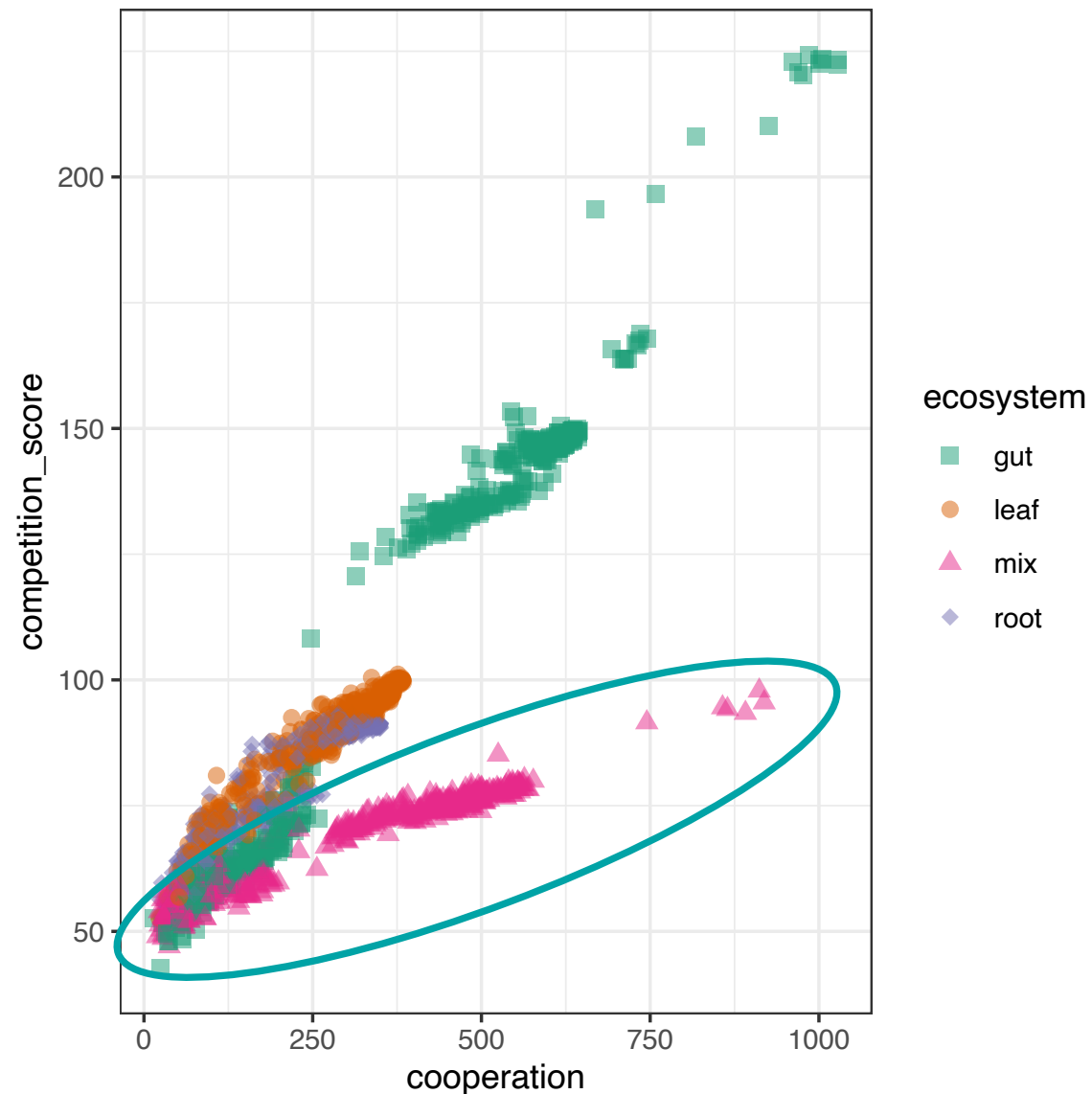
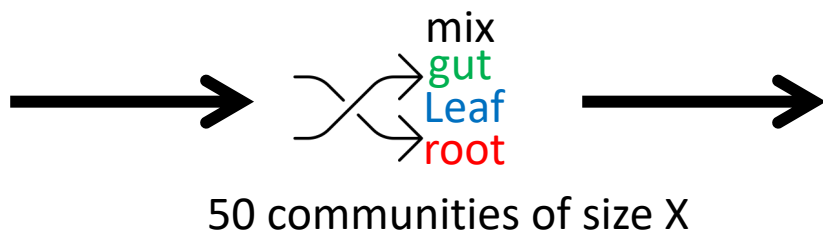
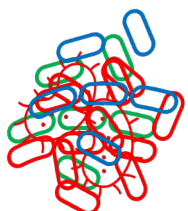
gut



Leaf



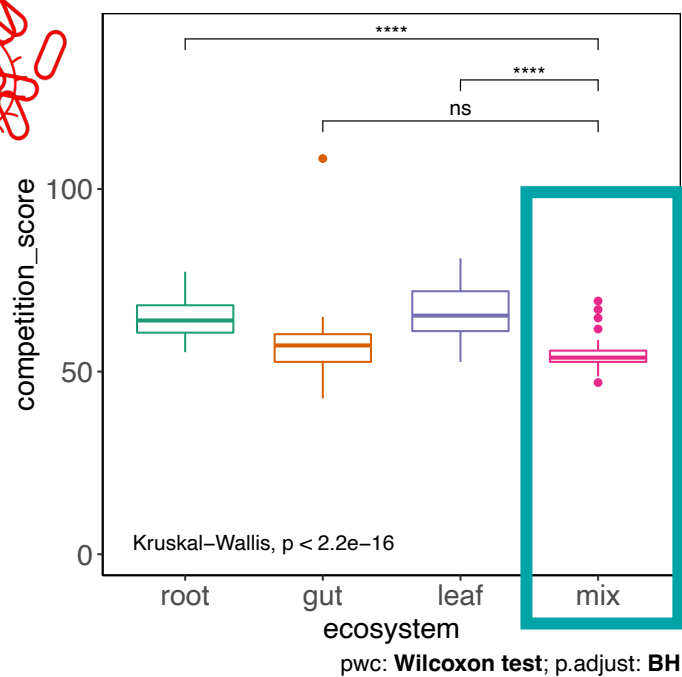
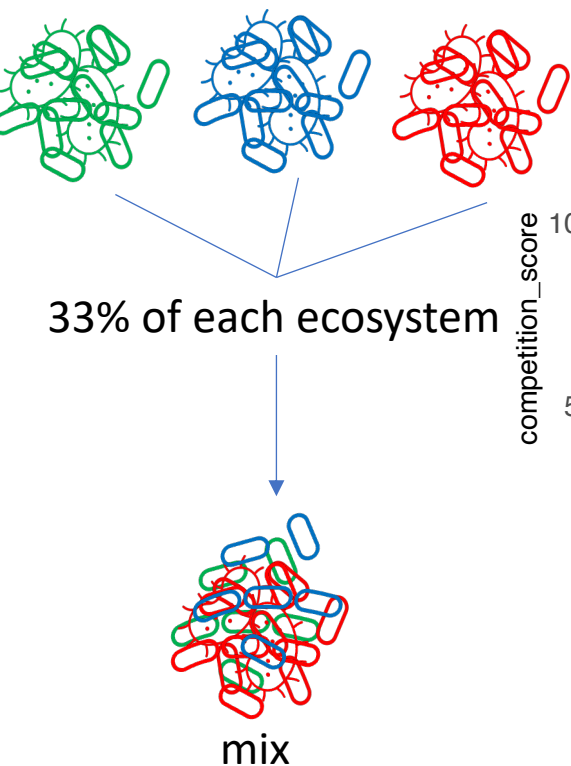
mix



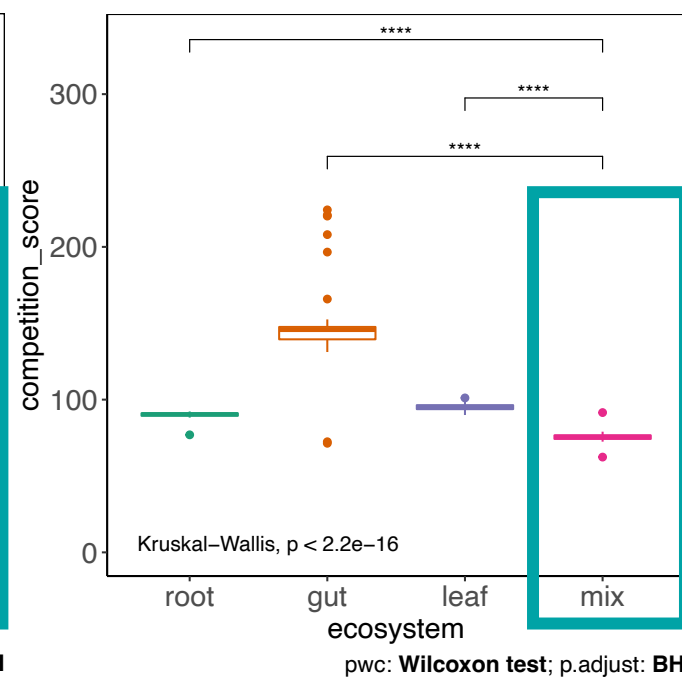
Cooperation and competition scores significantly differ between non-realistic and *ecosystem-consistent* communities

➤ Benchmarks for testing scores

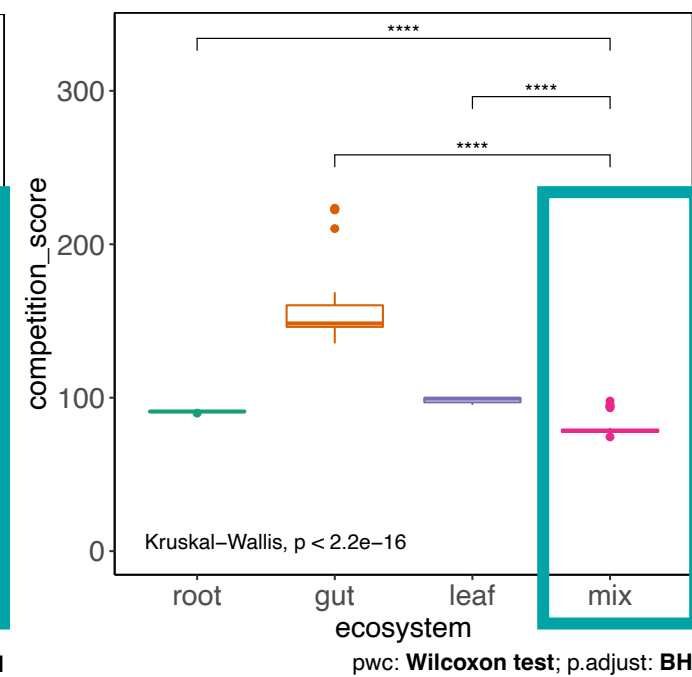
Do competition score differ between ecosystems ?



Size = 3



Size = 75

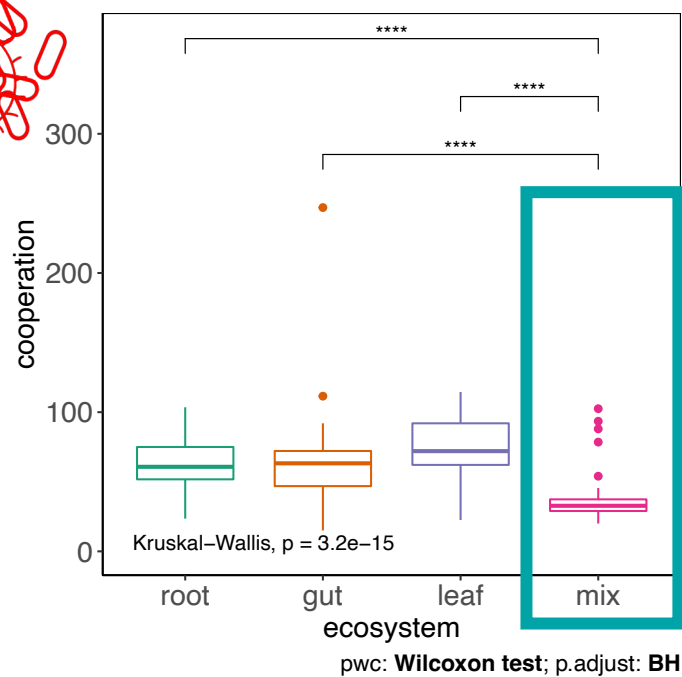
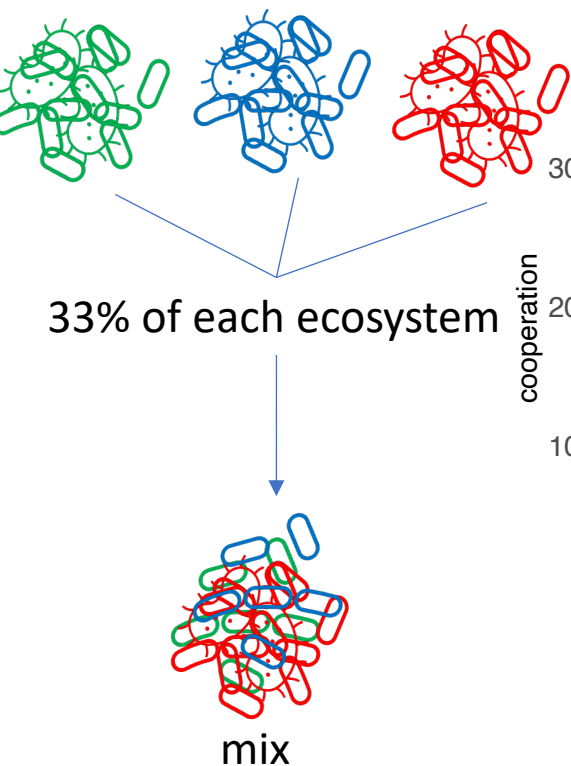


Size = 150

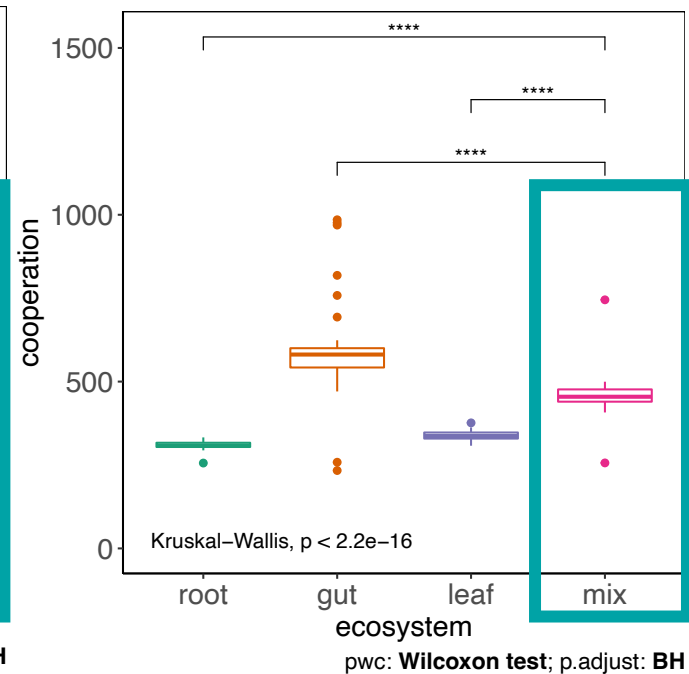
Cooperation and competition scores significantly differ between non-realistic and *ecosystem-consistent* communities

➤ Benchmarks for testing scores

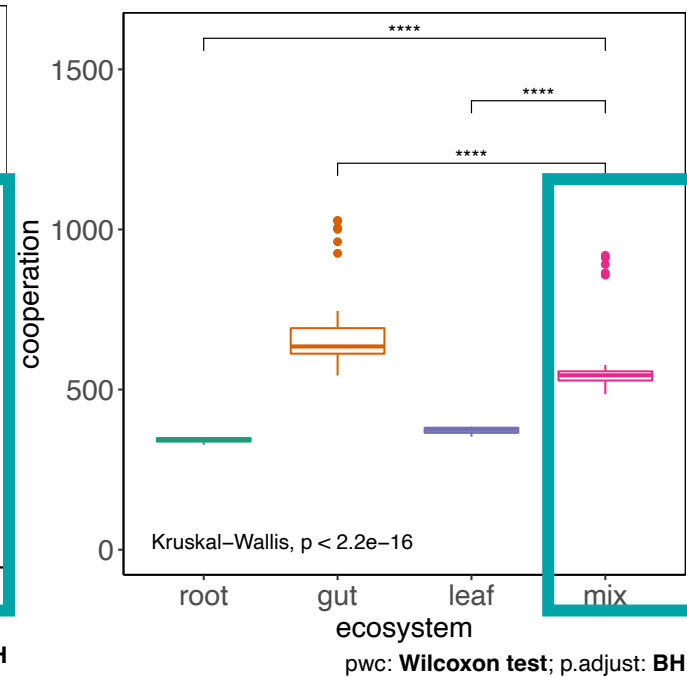
Do cooperation score differ between ecosystems ?



Size = 3



Size = 75

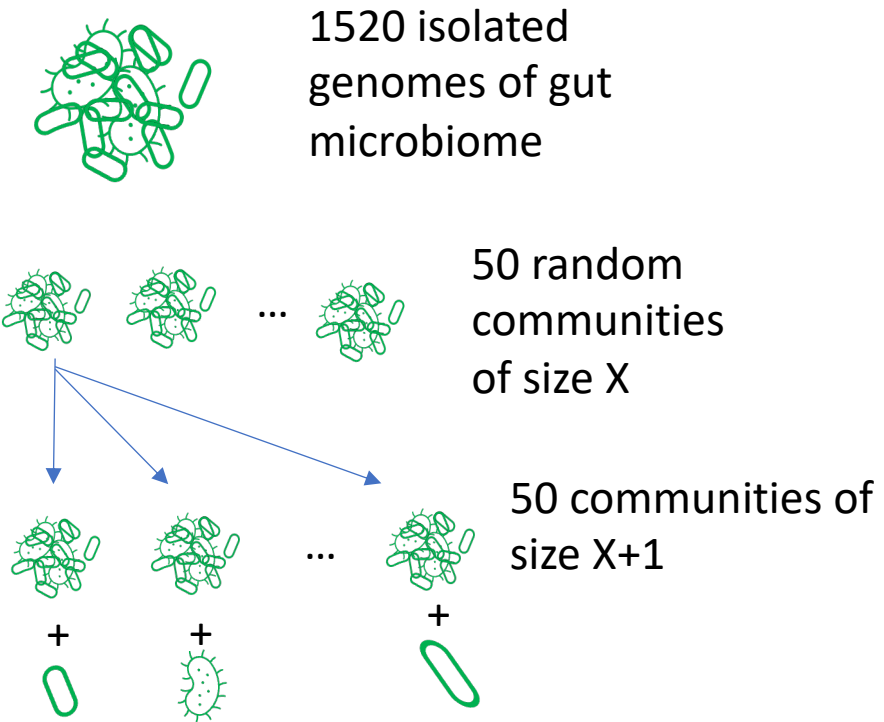


Size = 150

Cooperation and competition scores significantly differ between non-realistic and *ecosystem-consistent* communities

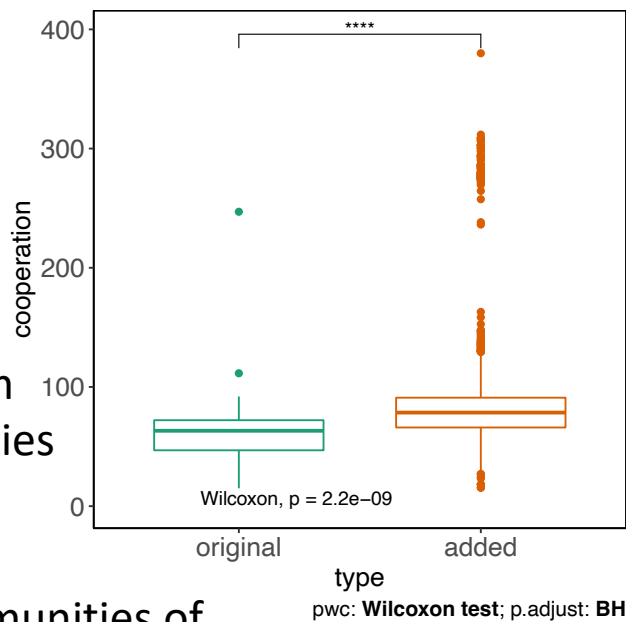
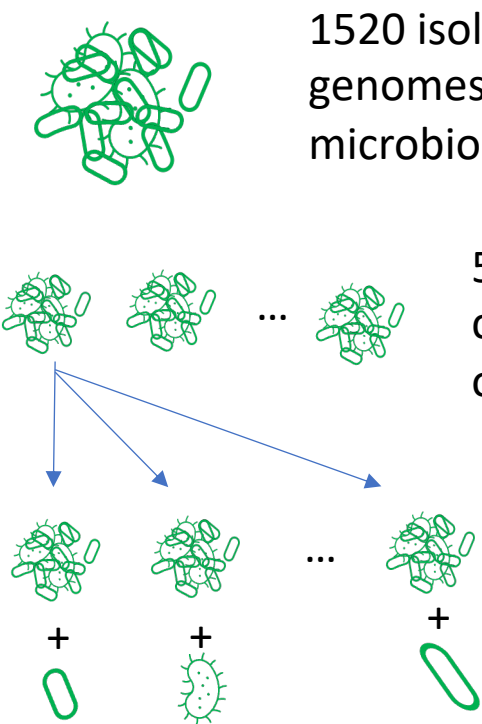
➤ Benchmarks for testing scores

Added-value of adding a bacteria in community

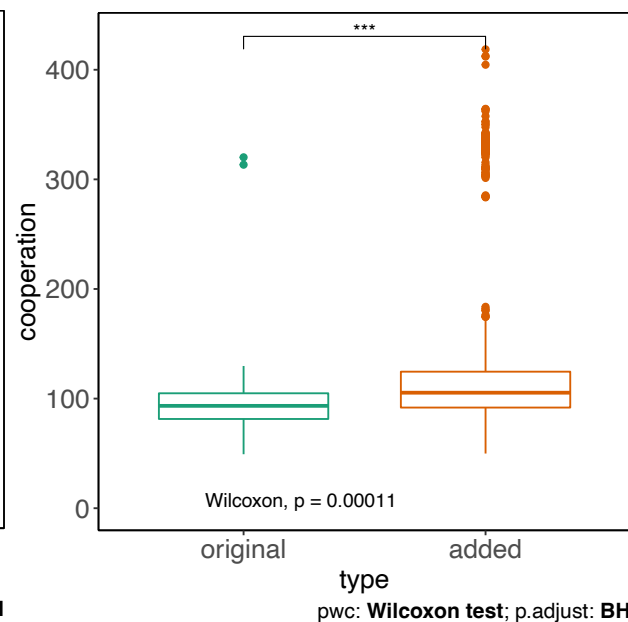


➤ Benchmarks for testing scores

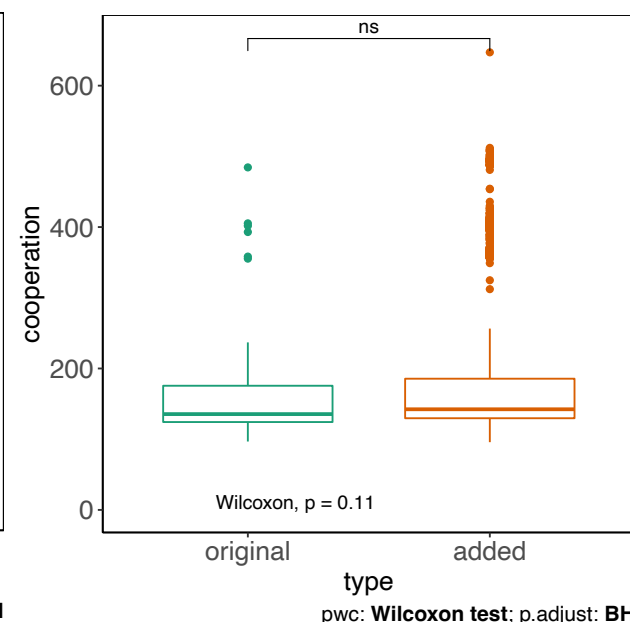
Added-value of adding a bacteria in community based on cooperation score



Size = 3



Size = 5



Size = 10

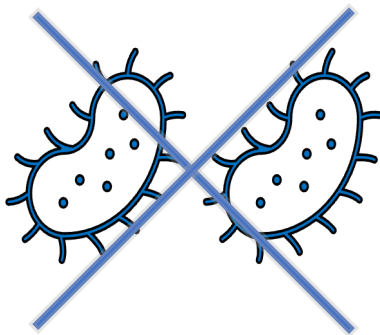
The larger is the community the less the community is disturbed by another species

➤ Conclusion

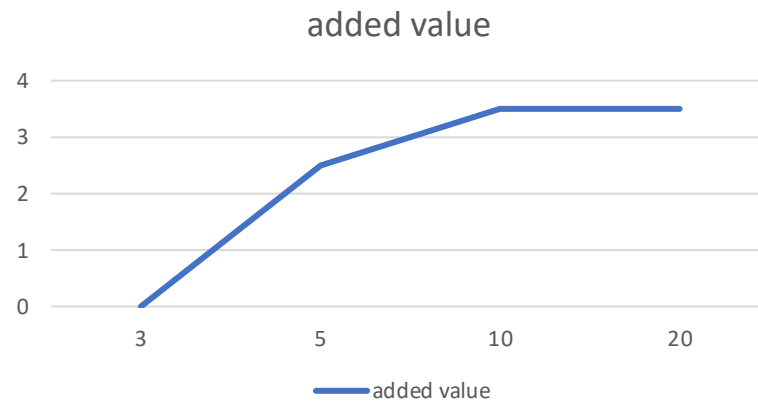
Tradeoff



Scalability



Pairwise



Resilience



Potentials



gut



Leaf



Root

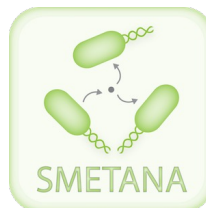


mix

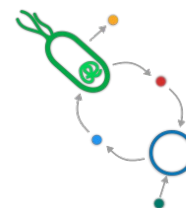
Perspective



Soil



SMETANA



micom

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Reasoning approaches for the characterization of cooperation and competition in large-scale microbial communities

November 17 2022 / maxime.lecomte@inrae.fr / Maxime Lecomte 3rd PhD student



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- David Sherman
- Clémence Frioux
- Simon Labarthe
- Coralie Muller

- Hélène Falentin

Thanks for your attention



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Reasoning approaches for the characterization of cooperation and competition in large-scale microbial communities

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➤ Benchmarks for testing scores

Scores in function the community size



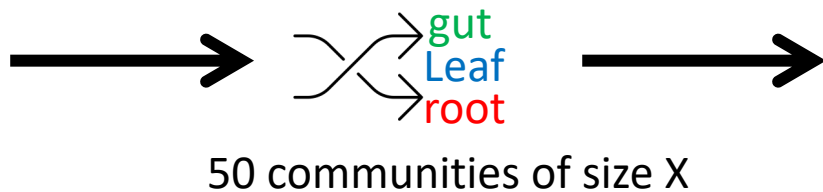
gut



Leaf

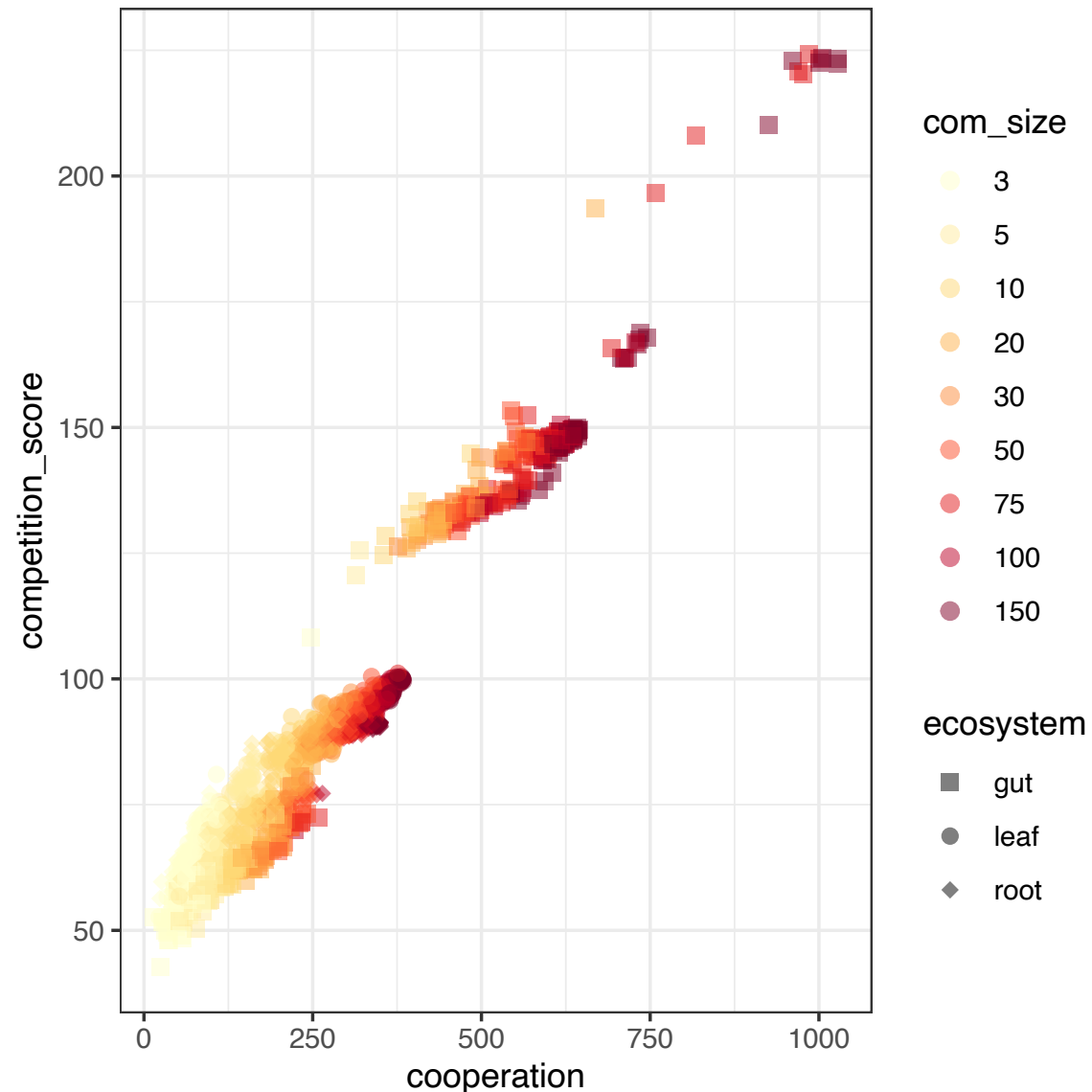


root



Reference genomes of cultivable species from 3 ecosystems

Community size is not the main actor in the score variations



Zou, Y., et al, 2019, *Nature Biotechnology*