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

Maxime Lecomte, David James Sherman, Hélène Falentin, Clémence Frioux

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GT-BIOSS NANTES November, 17 2022

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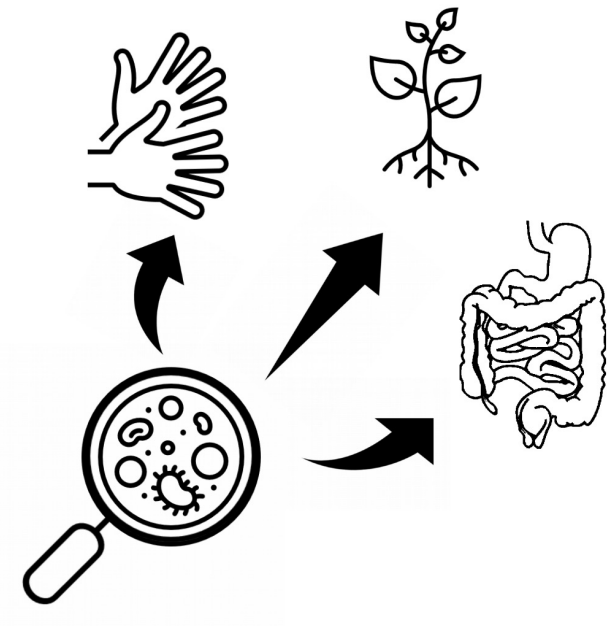
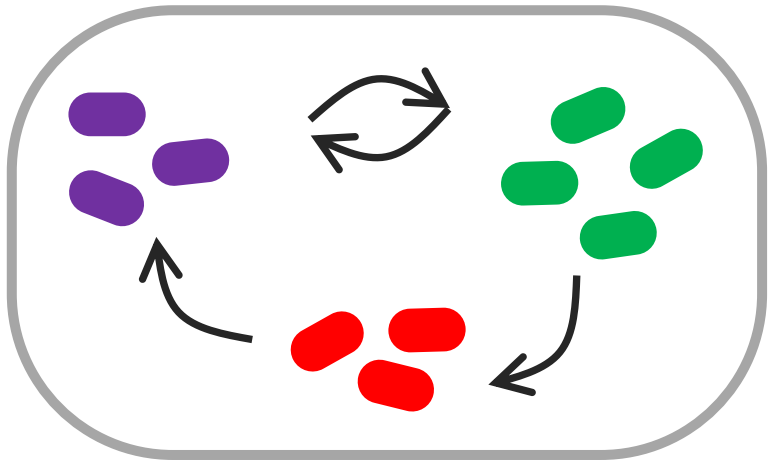
Motivation

Bacterial communities ?



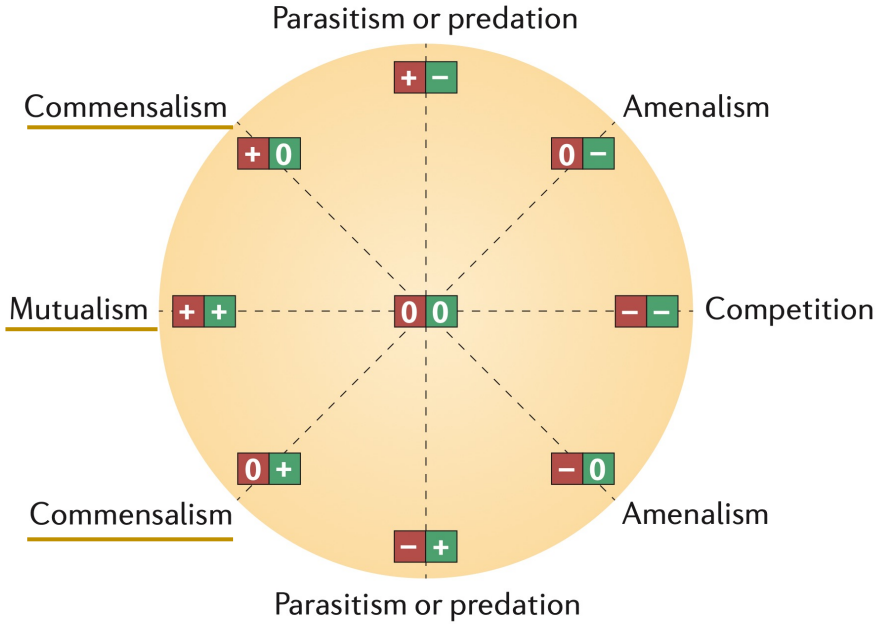
Microbes are essential in ecosystems

System biology



Bacterial interactions as a key mechanism

Interaction types



Cooperation and competition

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

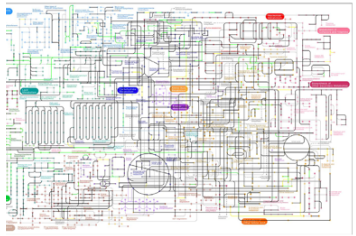
Faust, Karoline; Raes, Jeroen (2012). *Nature Reviews Microbiology*

State-of-the art for modeling bacterial communities

Reconstruction from annotated genomes

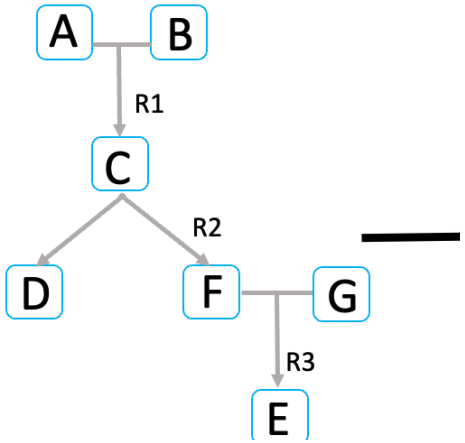
Stoichiometric matrix =

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



Metabolism

Genome-scale metabolic network



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
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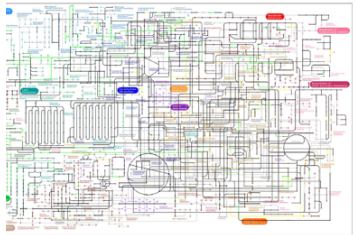
D	0	1	0
E	0	0	1
F	0	1	−1
G	0	0	−1

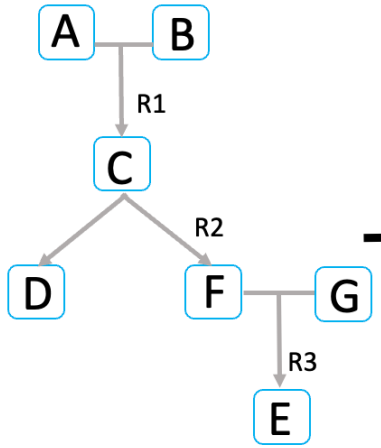
$$\max v_{growth}$$
$$\text{such that } \mathbf{S.v} = 0$$
$$\text{and } v_{min} \leq \mathbf{v} \leq v_{max}$$

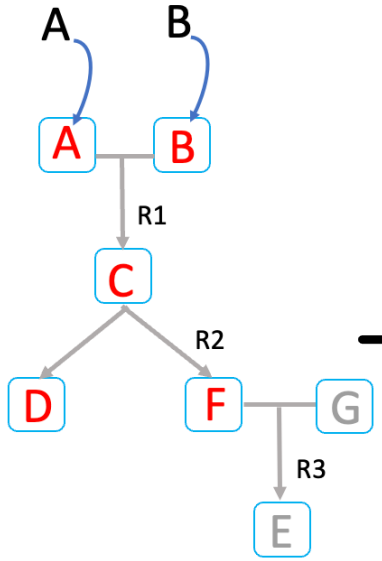
Numerical methods (e.g., FBA-like)



Metabolism

Genome-scale metabolic network





Discrete method

Metabolite scope from the A,B in the environnent

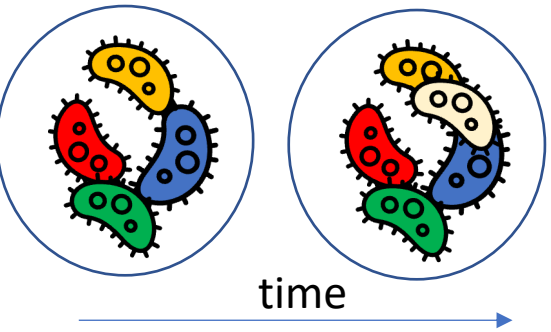
Two mathematical formalisms used for modeling the behavior of an organism in its environment

Ebenhöh, O et al, (2004) . *International Conference on Genome Informatics*.

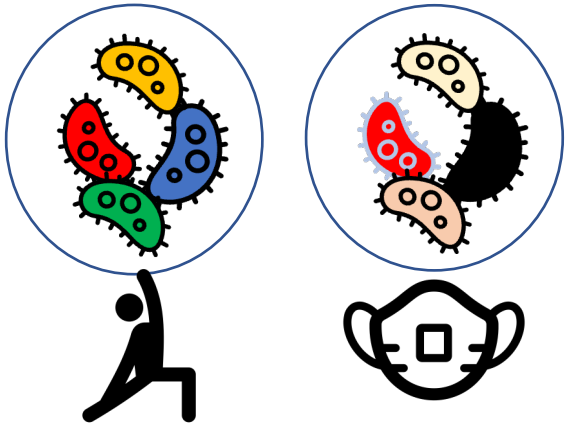
Goal : Identify cooperation and competition potential in large scale bacterial communities

Cooperation and competition potential

Longitudinal analysis



Cross sectional analysis



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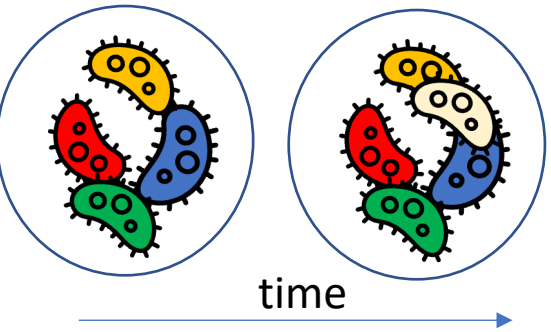

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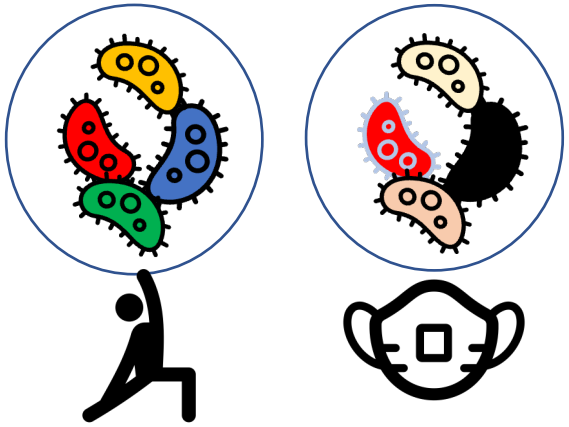
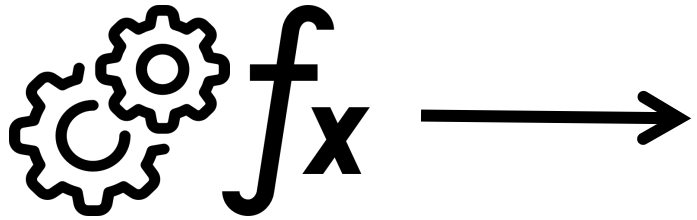
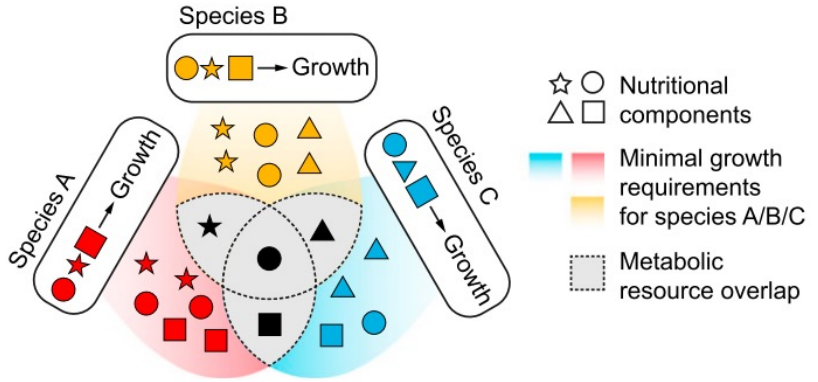




Nutrient point of view



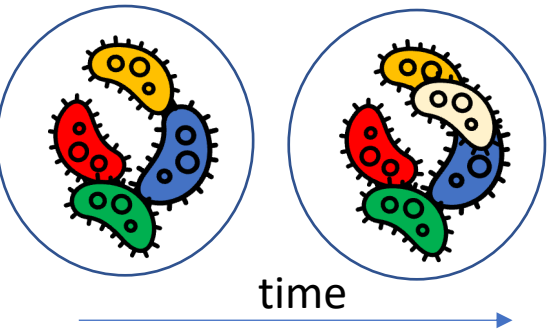
Competition potentials

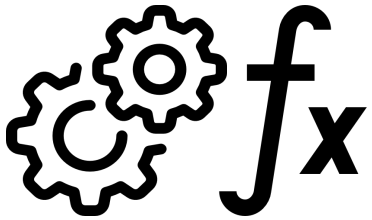
Freilich. S, et al,2011, *Nat. Coms.*
Zelezniak, A et al,2015,*PNAS*.

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

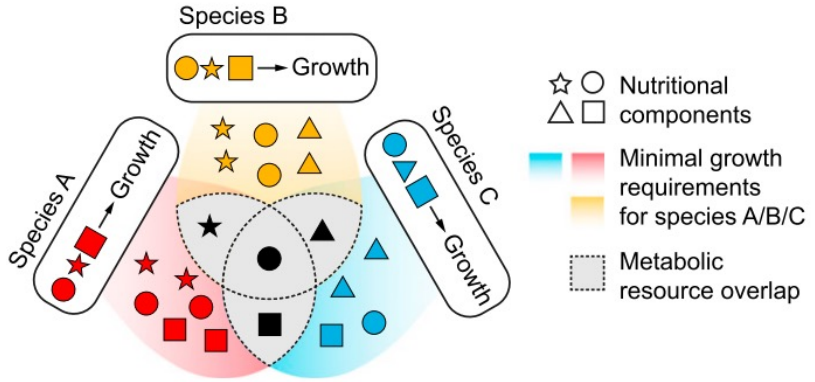
Cooperation and competition potential

Longitudinal analysis





Nutrient point of view



Competition potentials

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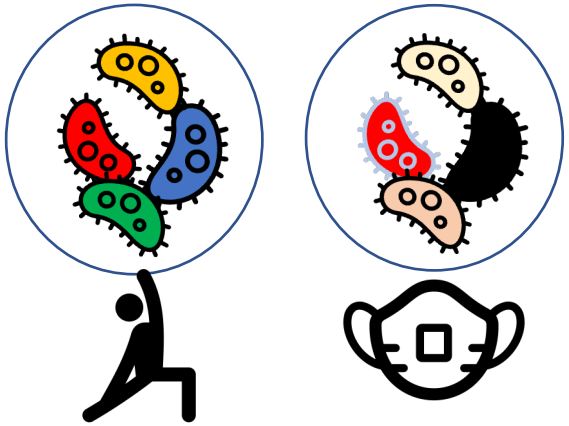
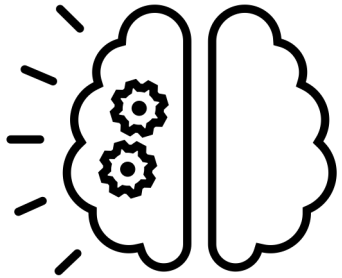
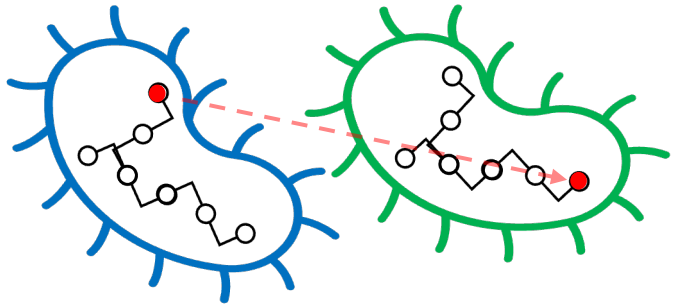






Cooperation potentials

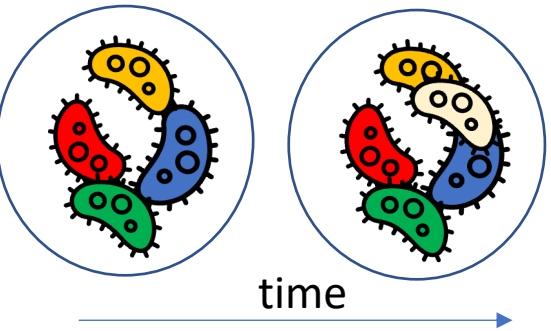
Either numerical or discrete methods highlight cooperation and competition potentials

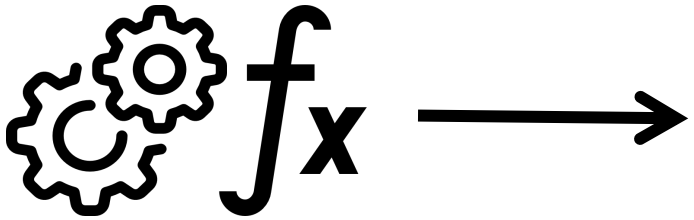
Freilich. S, et al,2011, *Nat. Coms.* Levy et al, 2015.,*BMC Bioinformatics.* Zelezniak, A et al,2015,*PNAS.* Kreimer, A et al, 2012 *Bioinformatics.*

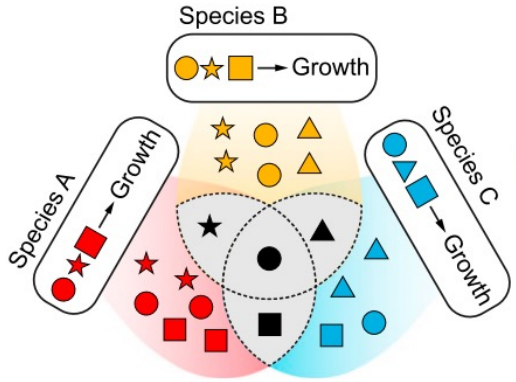
Goal : Identify cooperation and competition potential in large scale bacterial communities

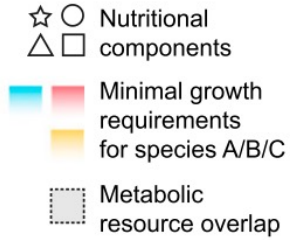
Scale-up to large scale bacterial communities

Longitudinal analysis



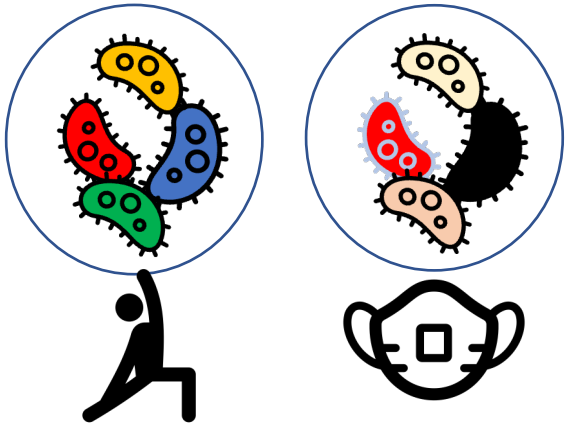






Community size up to 18

Cross sectional analysis



Cost in computational time

Freilich. S, et al,2011, *Nat. Coms.*
Zelezniak, A et al,2015,*PNAS*.

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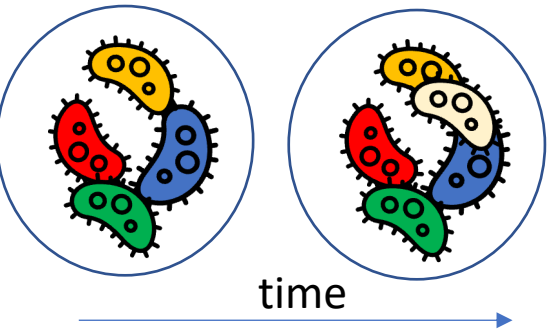
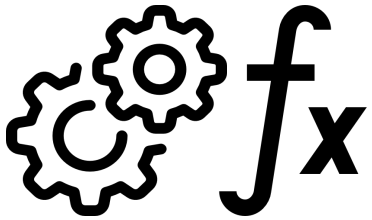
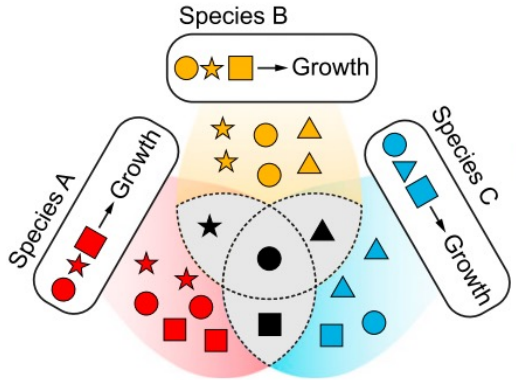
Scale-up to large scale bacterial communities

Longitudinal analysis







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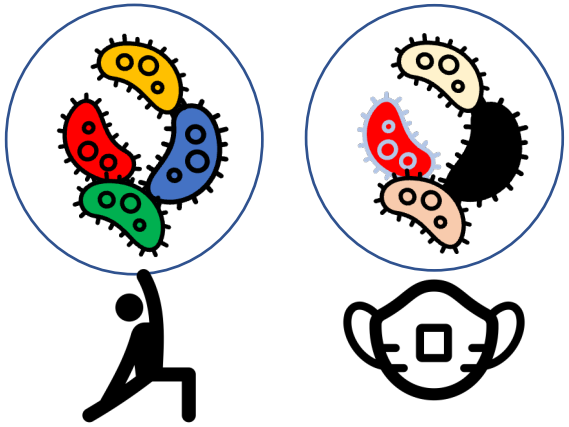
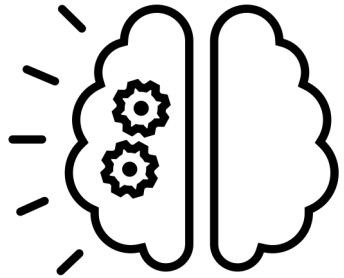




Cost in computational time

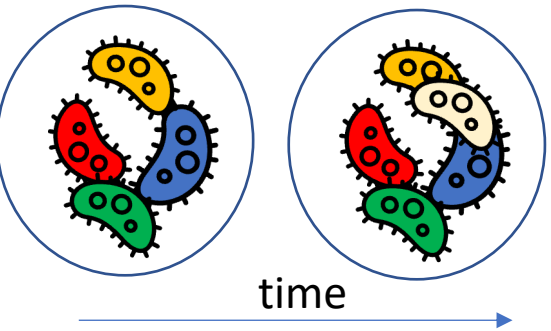
Pairwise

Not limited by the community size

Freilich. S, et al,2011, *Nat. Coms.*
Zelezniak, A et al,2015,*PNAS*.
Levy et al, 2015.,*BMC Bioinformatics*.
Kreimer, A et al, 2012 *Bioinformatics*.

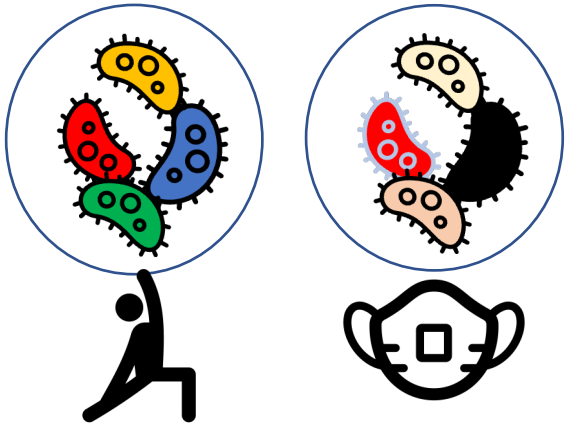
Avoid pairwise analysis for characterizing cooperation and competition in microbial communities

Longitudinal analysis



time

Cross sectional analysis



Characterize community

150 bacteria

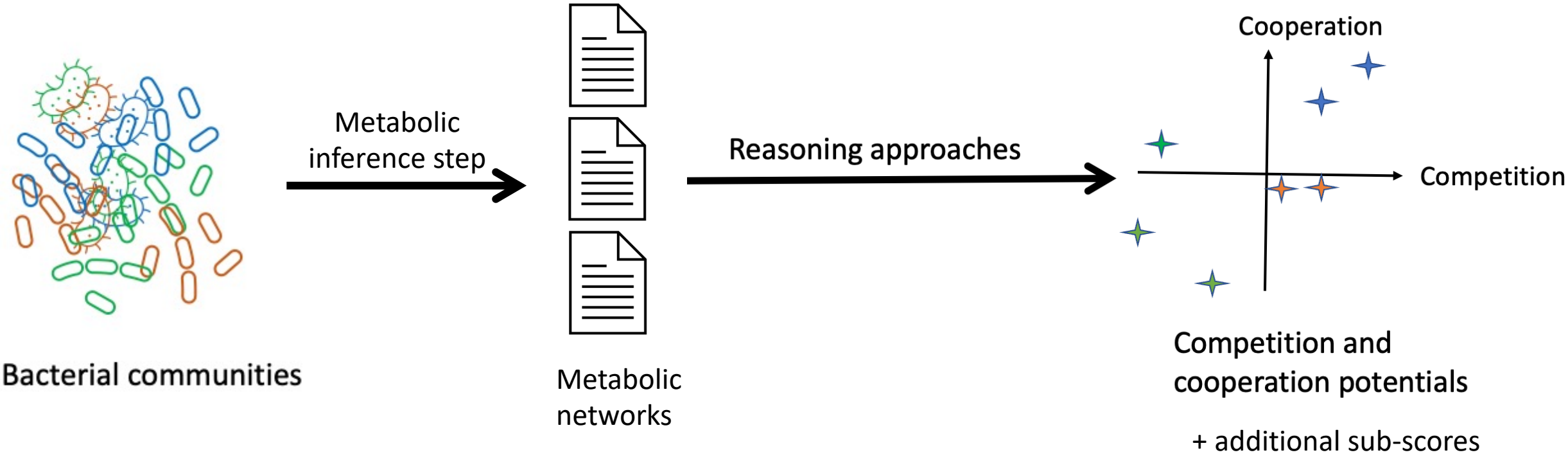
Pairwise analysis

(150 * (150-1))/2 = 11 375 combinations

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

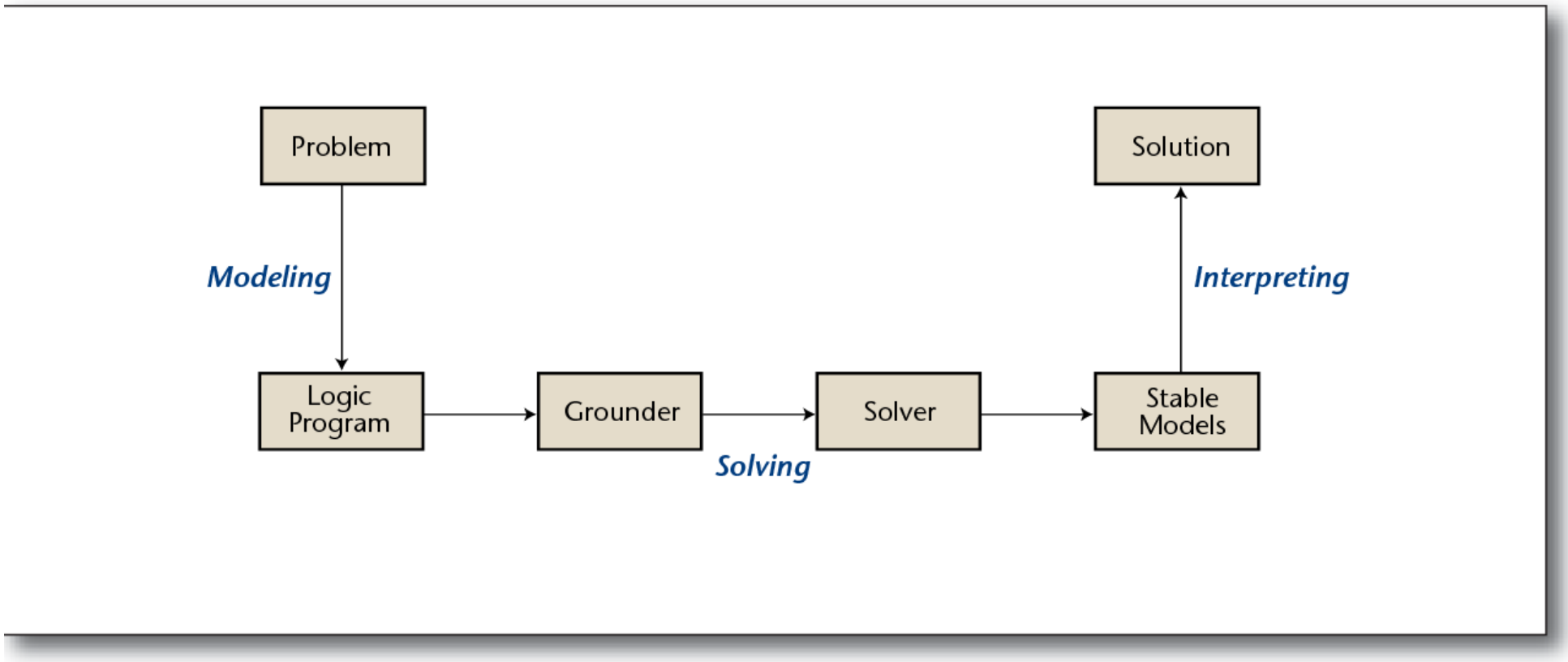
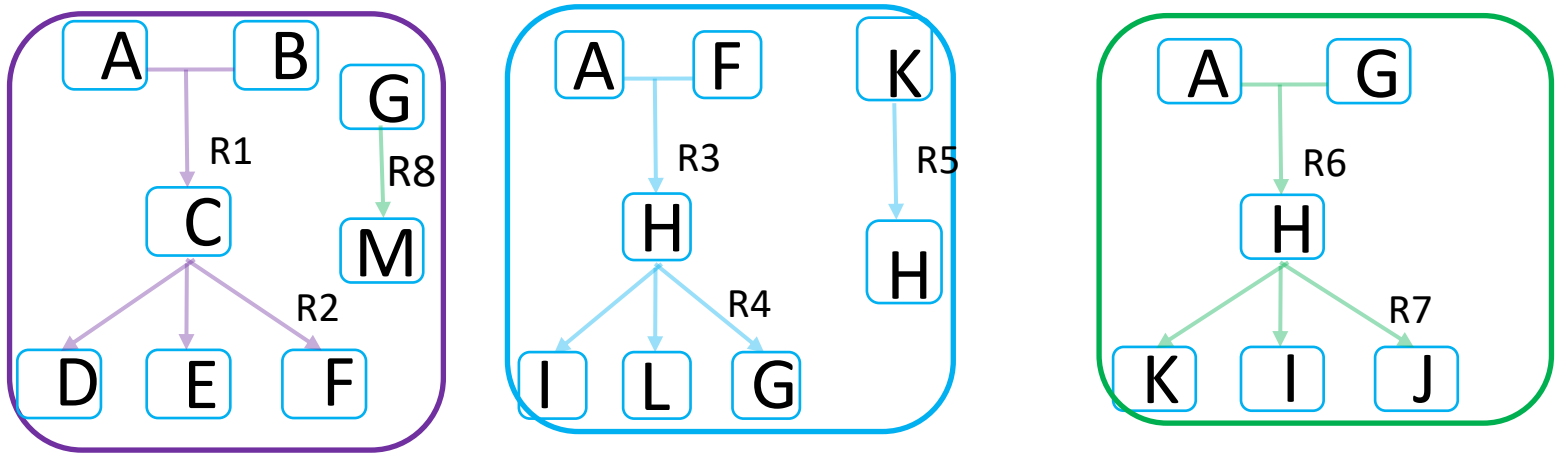


Figure 1. The Work Flow of Answer Set Programming.

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

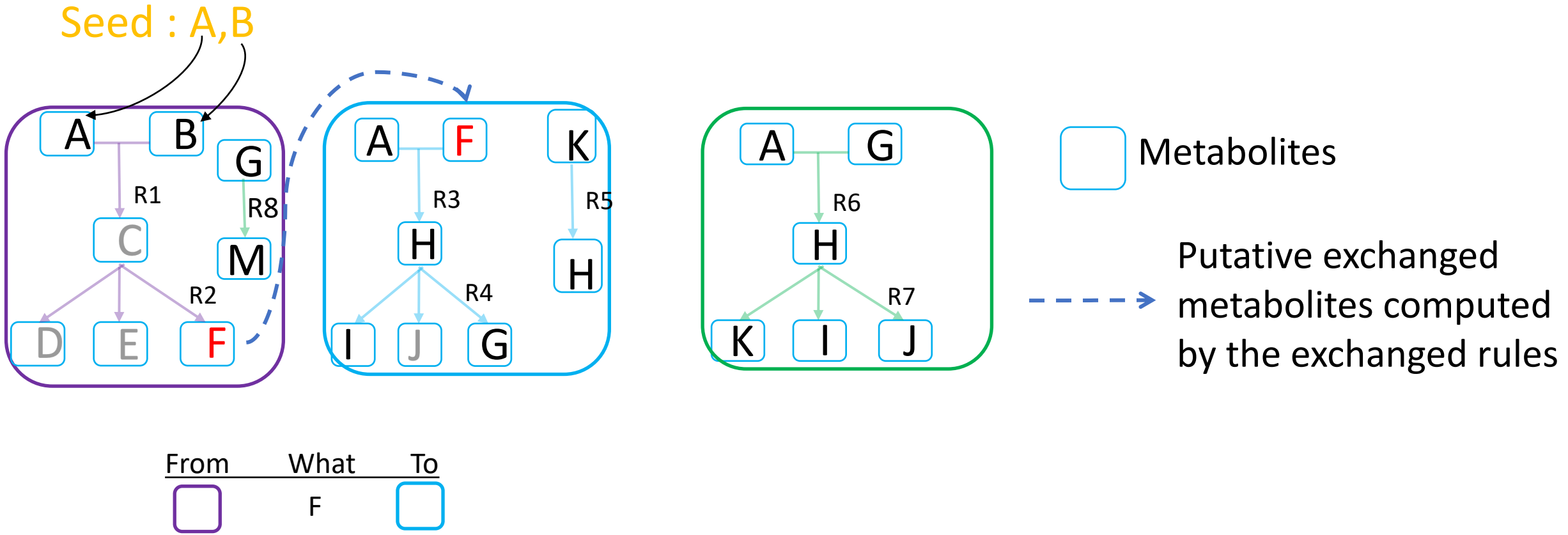
Cooperation potential based on exchanged metabolites using ASP

Seed : A,B

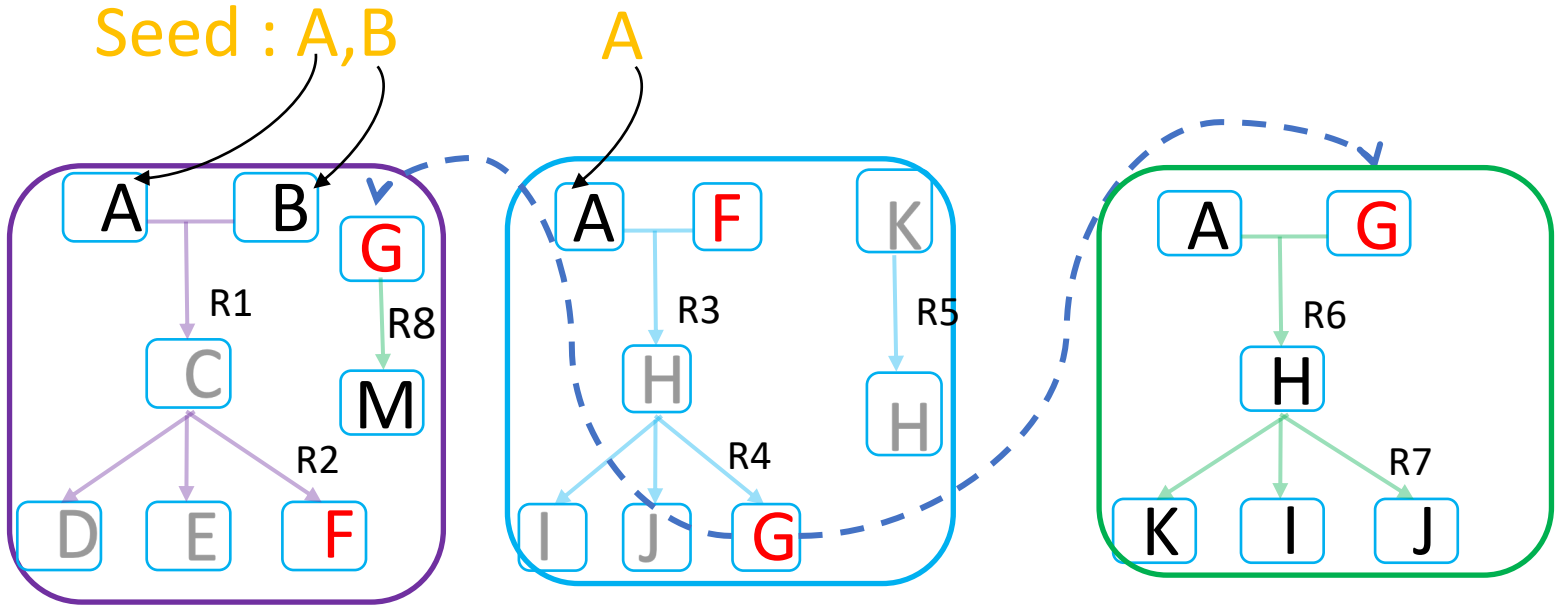


$exchanged_{metabolites} = scope(G_s, S), not\ indivProducible(S, G_t), products(S, G_s)$. Where S ∈ G and $T \in G, and\ S \neq T$.

Cooperation potential based on exchanged metabolites using ASP



Cooperation potential based on exchanged metabolites using ASP

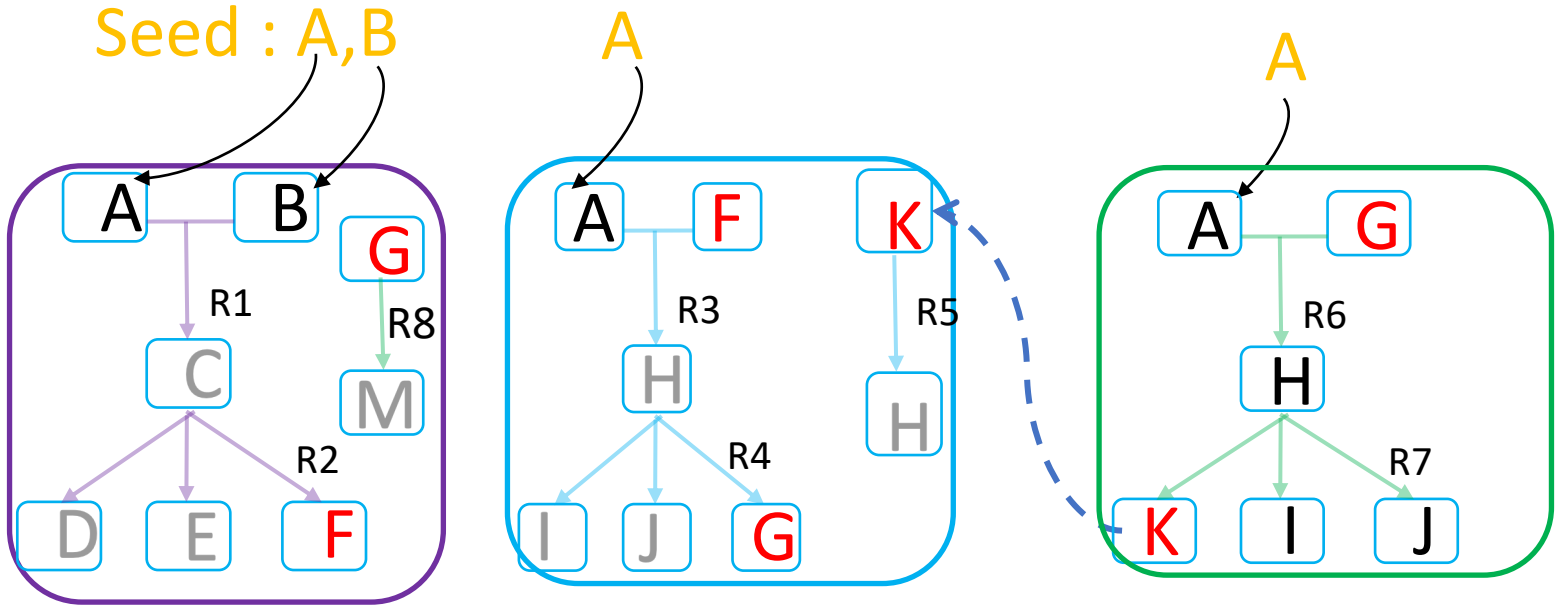


Metabolites

Putative exchanged metabolites computed by the exchanged rules

From	What	To
	F	
	G	
	G	

Cooperation potential based on exchanged metabolites using ASP



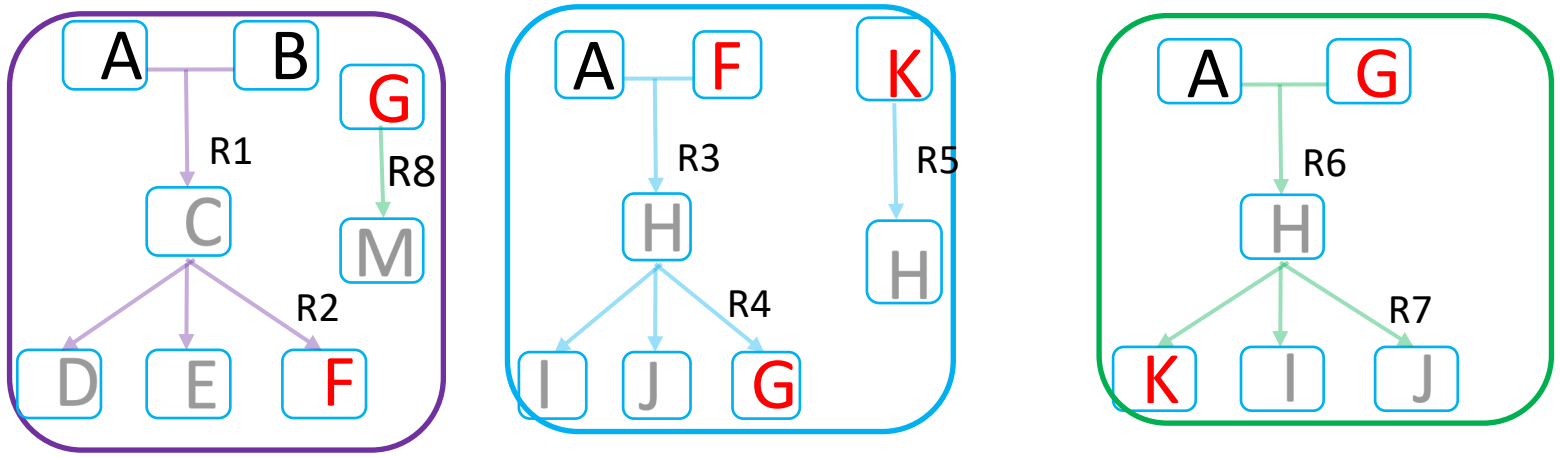
Metabolites

Putative exchanged metabolites computed by the exchanged rules

From	What	To
	F	
	G	
	G	
	K	

Exponential bonus (python)

hypothesis : each species contributes differently



From	What	To
	F	
	G	
	G	
	K	

Exponential bonus (python)

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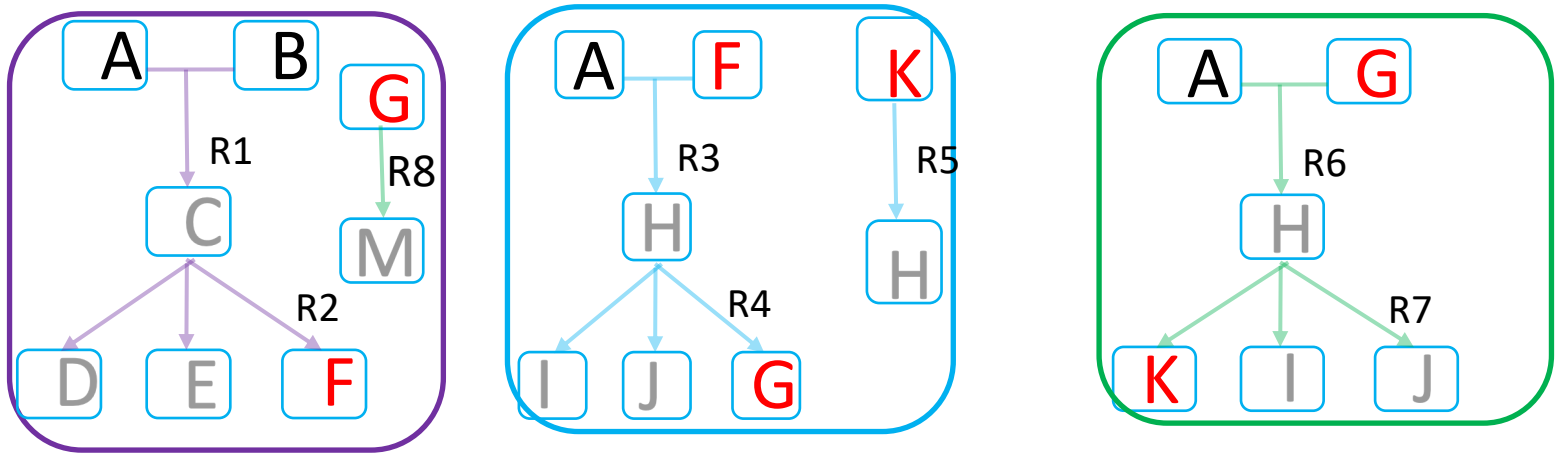


From	What	To
	F	
	G	
	G	
	K	

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

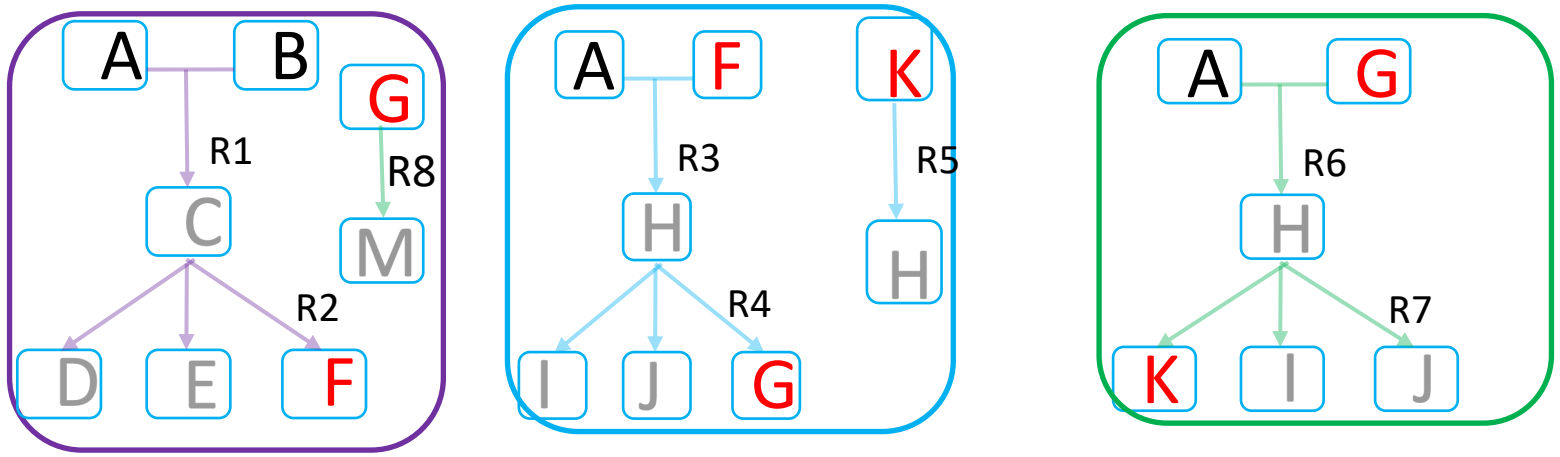
Number of metabolites

Number of different producers / consumers

Exponential bonus (python)

hypothesis : each species contributes differently

Metabolites	Producers	consumers
F	1	1



From	What	To
	F	
	G	
	G	
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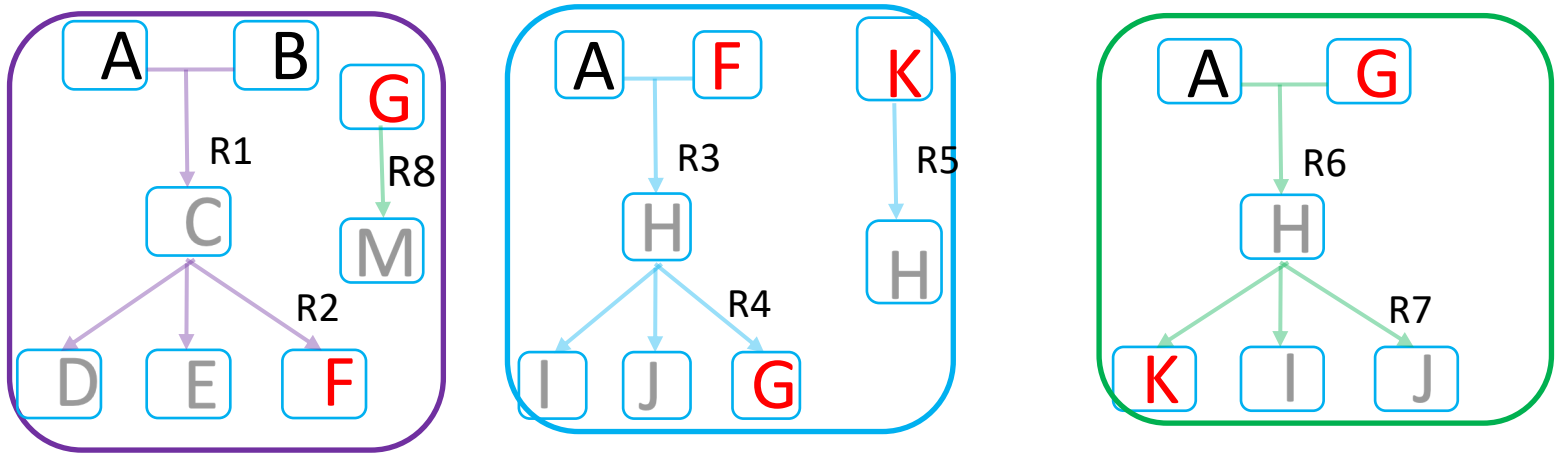


Metabolites	Producers	consumers
F	1	1
G	1	$1 + 2^{1}=1.5$

From	What	To
	F	
	G	
	G	
	K	

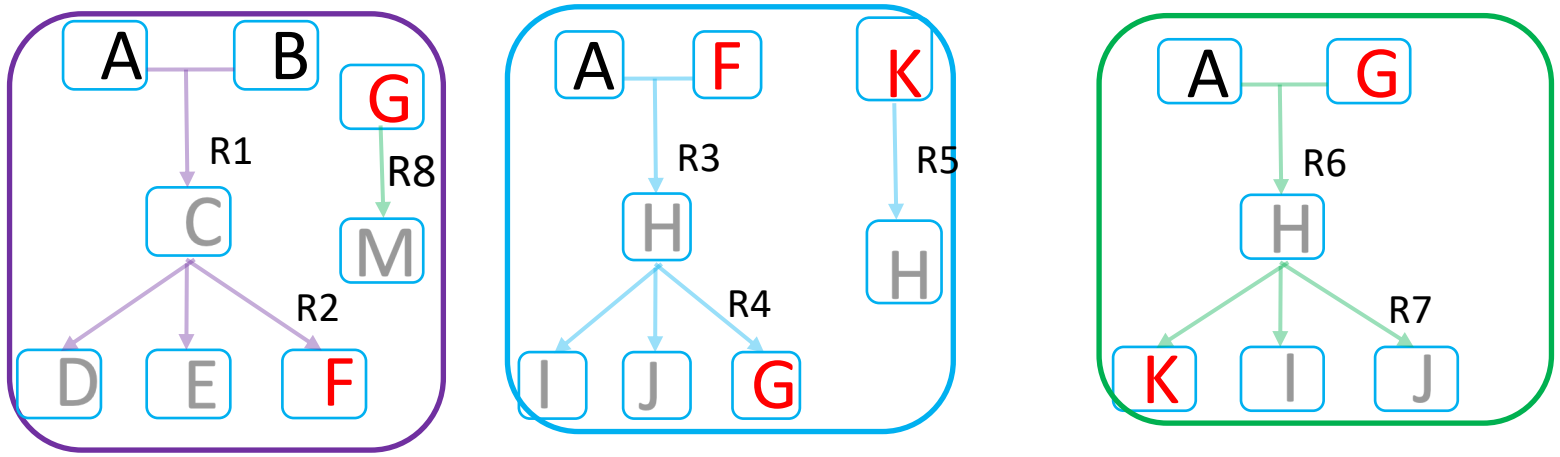
$$cooperation = \sum_{i=1}^{m} \sum_{k=2}^{n} 1 + 2^{-(k-1)}$$

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
K	1	$1 + 2^{1}=1.5$

Cooperation = F + G + K = 6.5

From	What	To
	F	
	G	
	G	
	K	

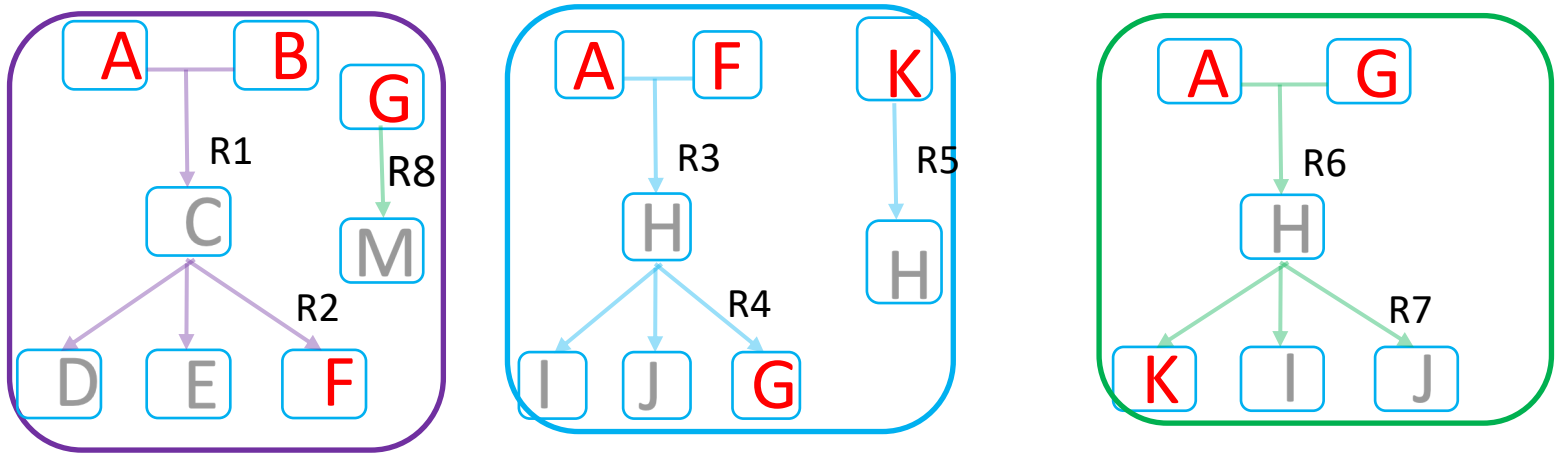
$$cooperation = \sum_{i=1}^{m} \sum_{k=2}^{n} 1 + 2^{-(k-1)}$$

Number of metabolites

Number of different producers / consumers

Competition potential based on limiting substrate using ASP

Seed : A,B



G Limiting substrates

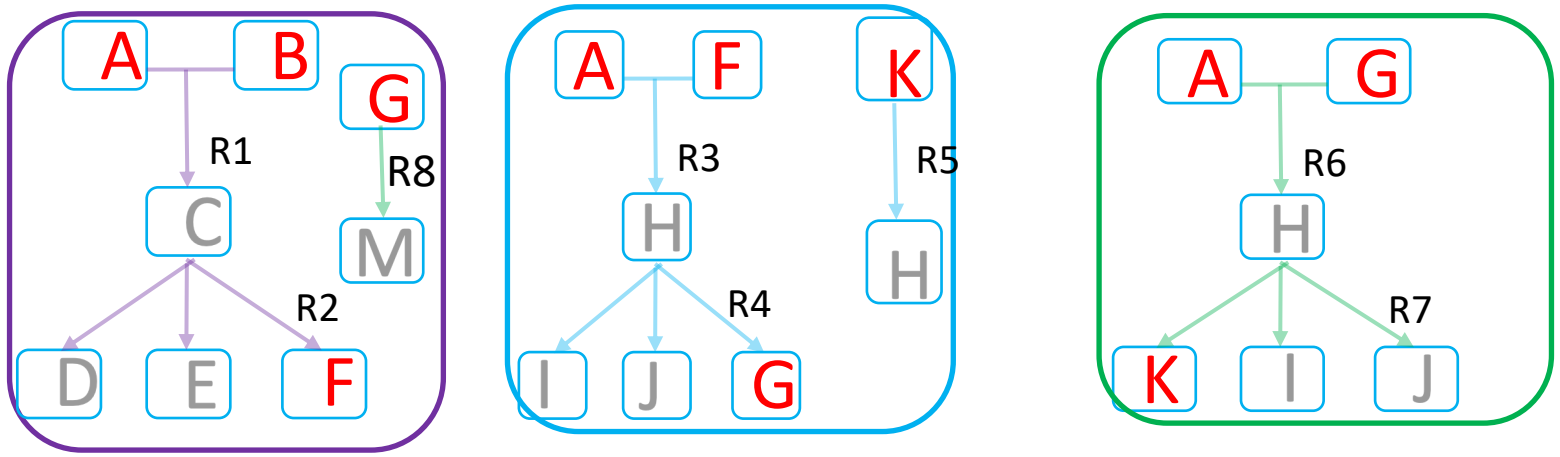
A,B,F

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

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

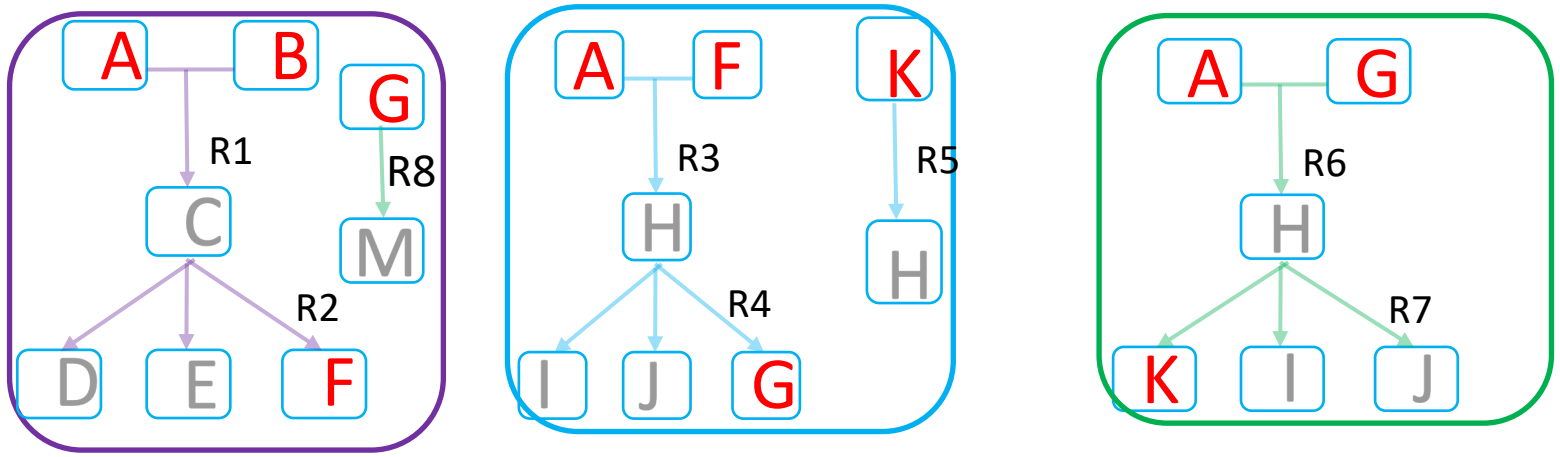
Calculation of the competition potential (python)

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

Metabolites

Number of consumers

Seed : A,B



A,B,F

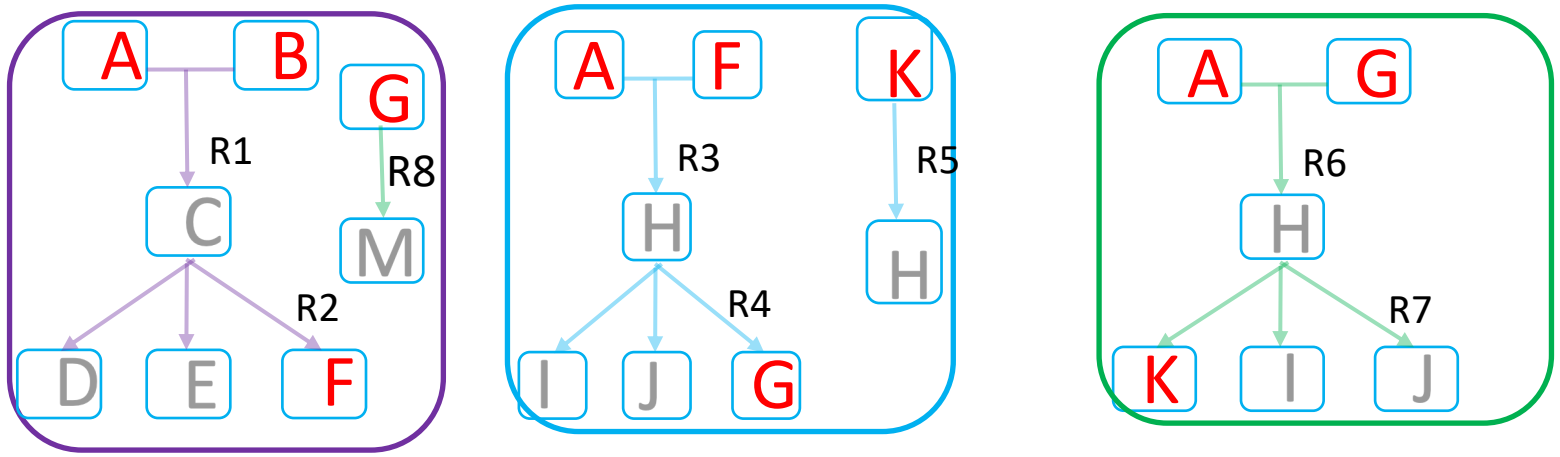
A,B,G,K

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

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

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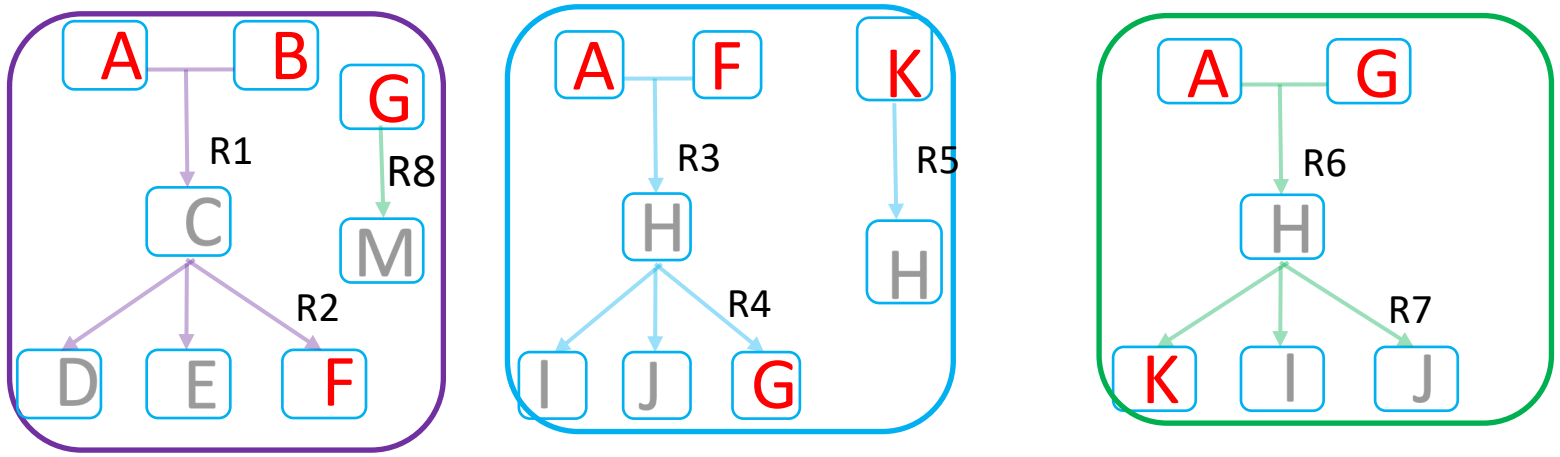

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A,B,G,K
A,G,K

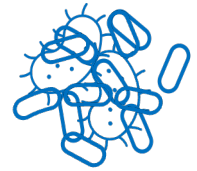
$$competition = \sum_{i=1}^{m} \frac{count(i)}{size\_community}$$

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

Benchmarks for testing scores

Scores in function of the ecosystem

gut

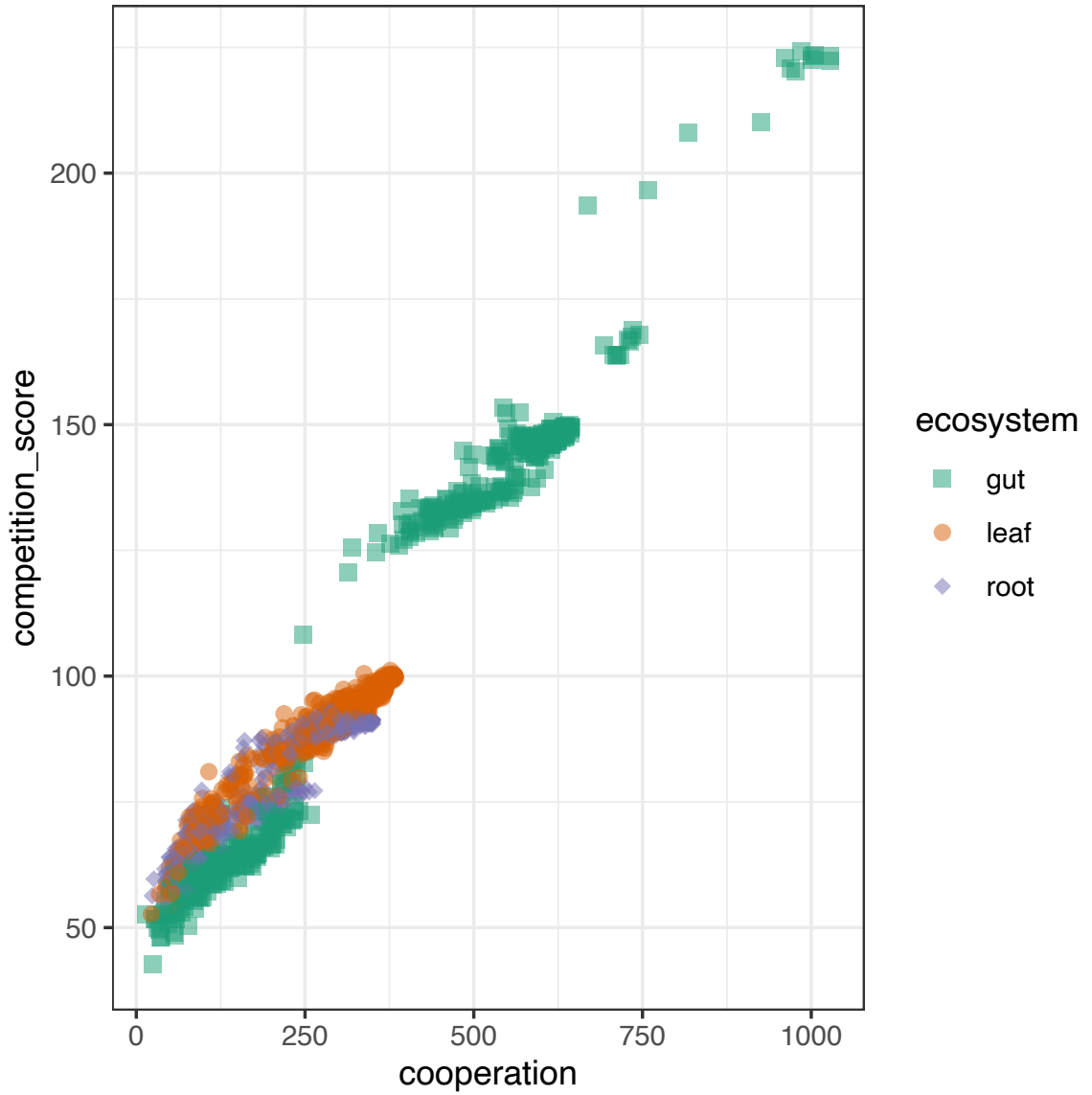


Leaf

root

50 communities of size X

Reference genomes of cultivable species from 3 ecosystems

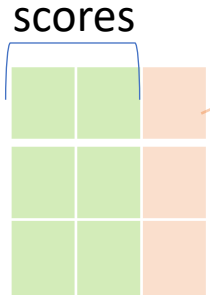


Different scores in function of the ecosystems

Zou, Y., et al, 2019,*Nature Biotechnology*
Bai, Y. et al. 2015

Ecosystem prediction from scores

Prediction of gut ecosystem (SVM)

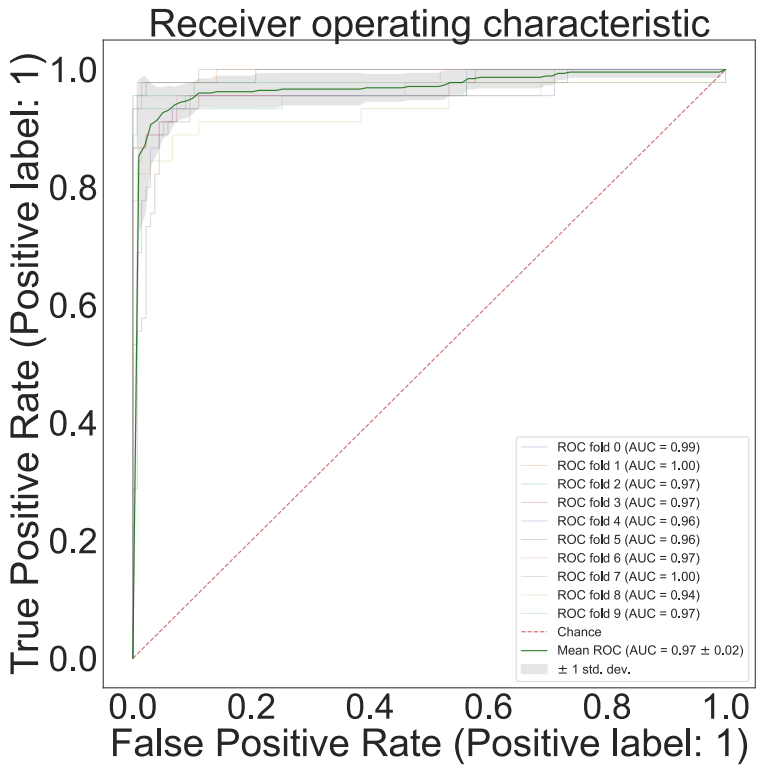


Up to 3 features = training

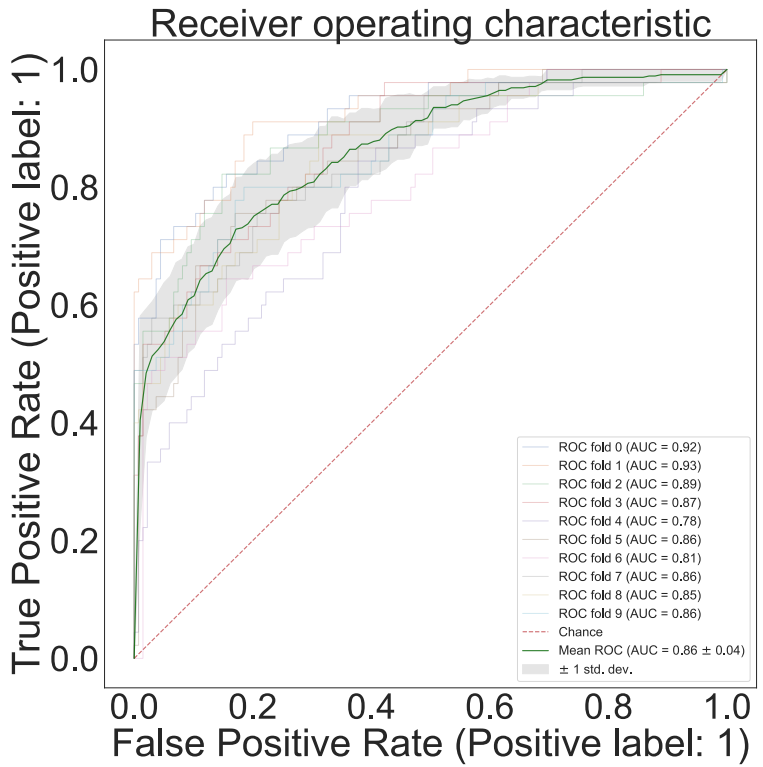
- Noise
- Cross validation

Ecosystem?

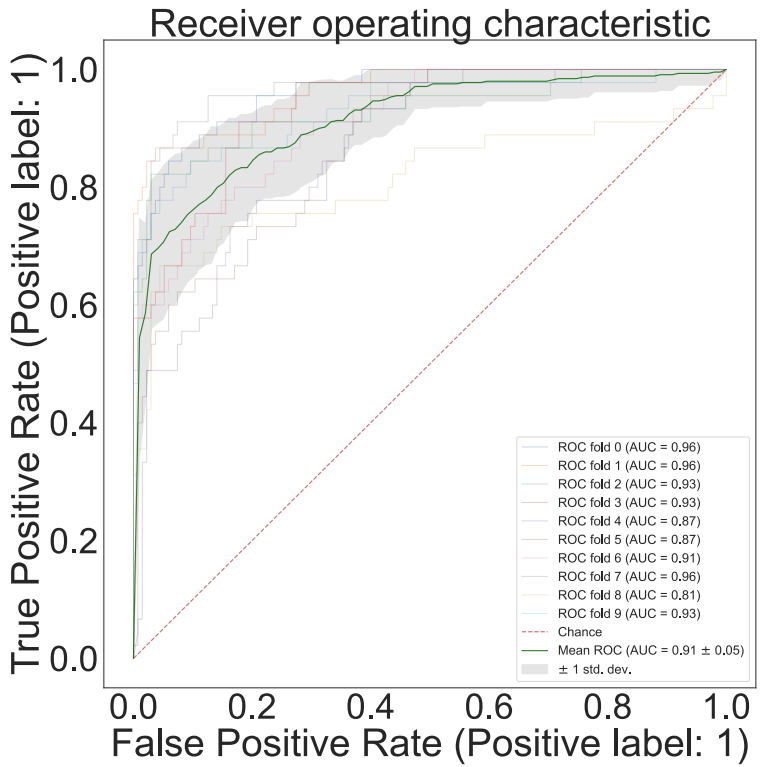
Up to 4



Only competition



Only cooperation

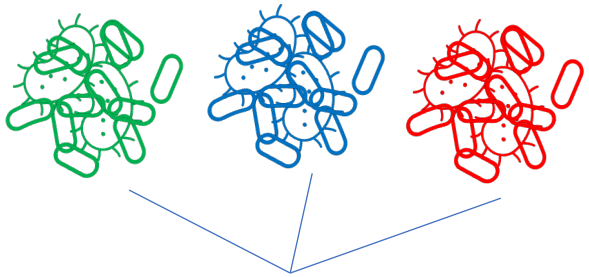


Both

Competition score seems to be enough for predicting ecosystem

Benchmarks for testing scores

Do scores differ between ecosystems ?



33% of each ecosystem

mix

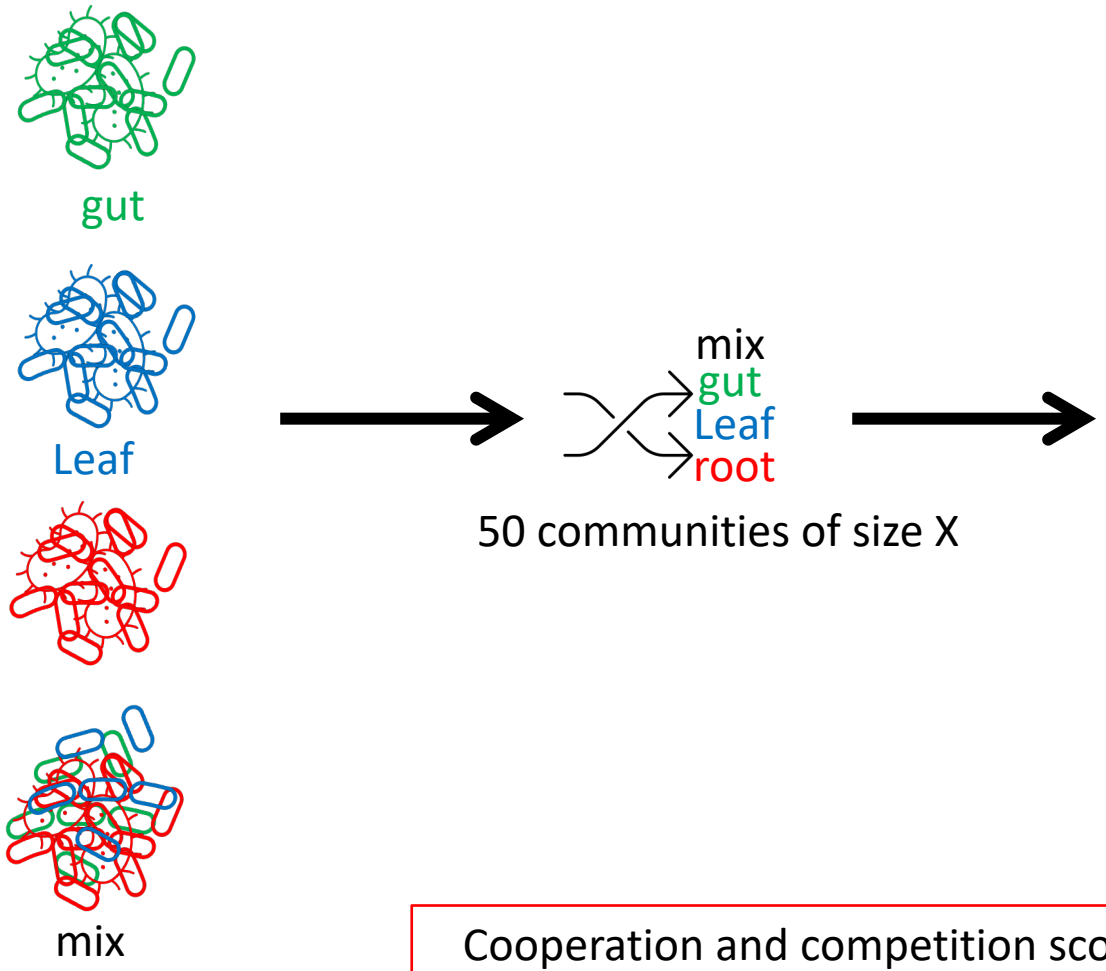
Cooperation and competition scores significantly differ between non-realistic and *ecosystem-consistent* communities

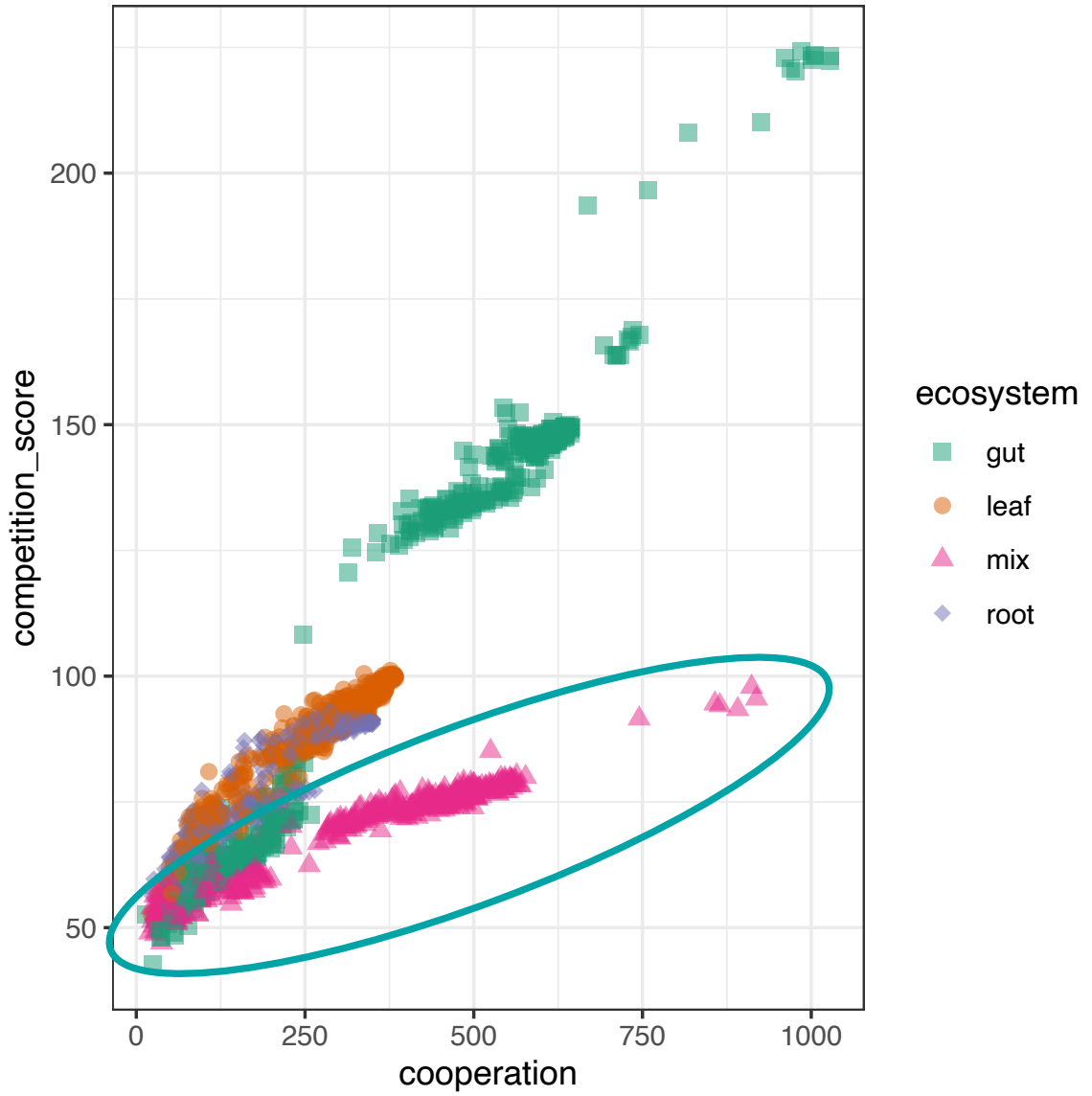
Zou, Y., et al, 2019,*Nature Biotechnology*

Bai, Y. et al. 2015

Benchmarks for testing scores

Scores in function of the ecosystem





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

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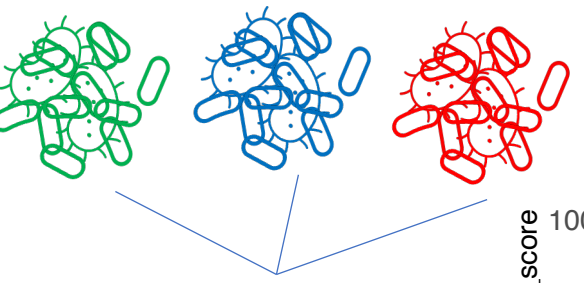
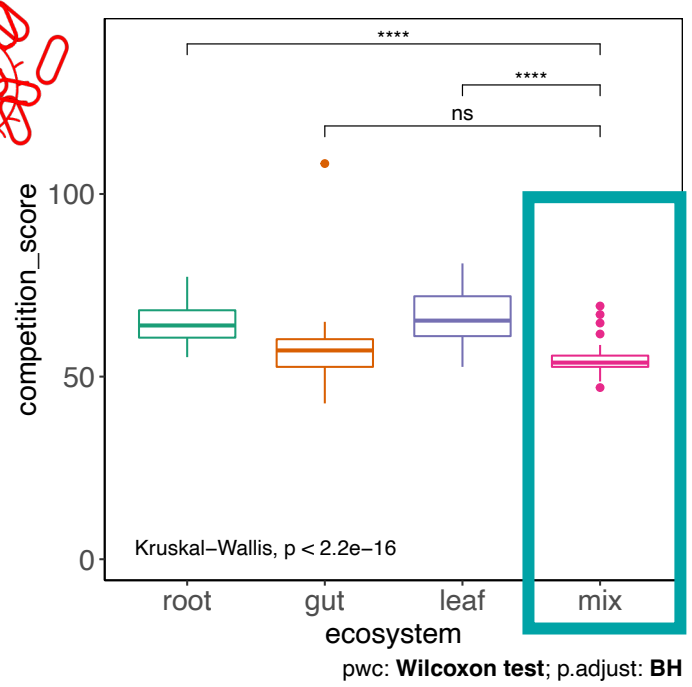
Benchmarks for testing scores

Do competition score differ between ecosystems ?

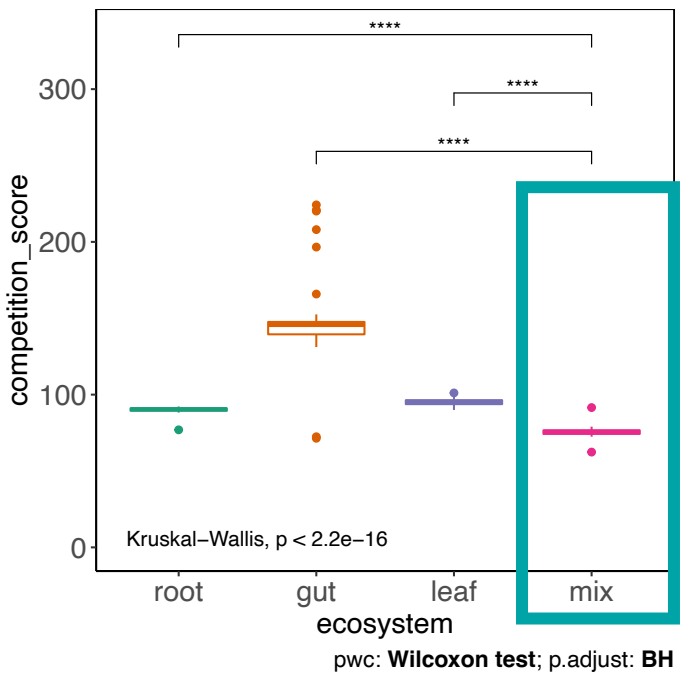


33% of each ecosystem

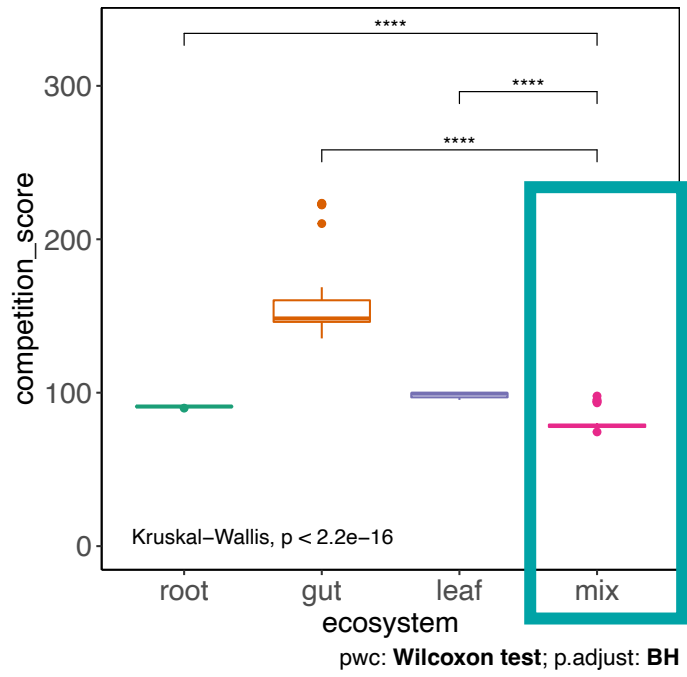
mix



Size = 3



Size = 75

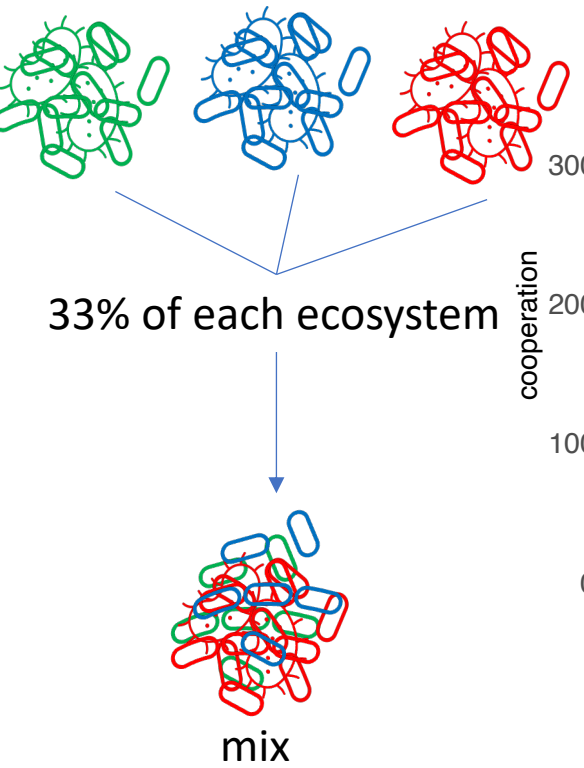


Size = 150

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

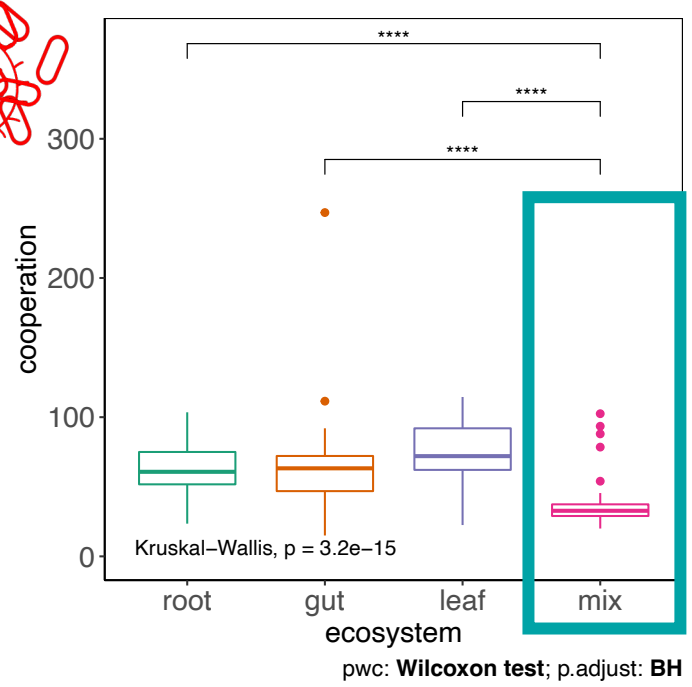
Benchmarks for testing scores

Do cooperation score differ between ecosystems ?

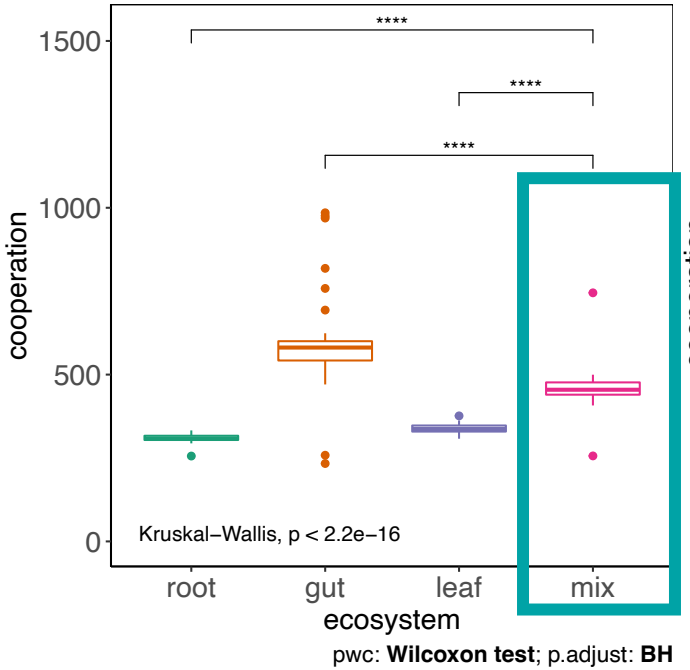


33% of each ecosystem

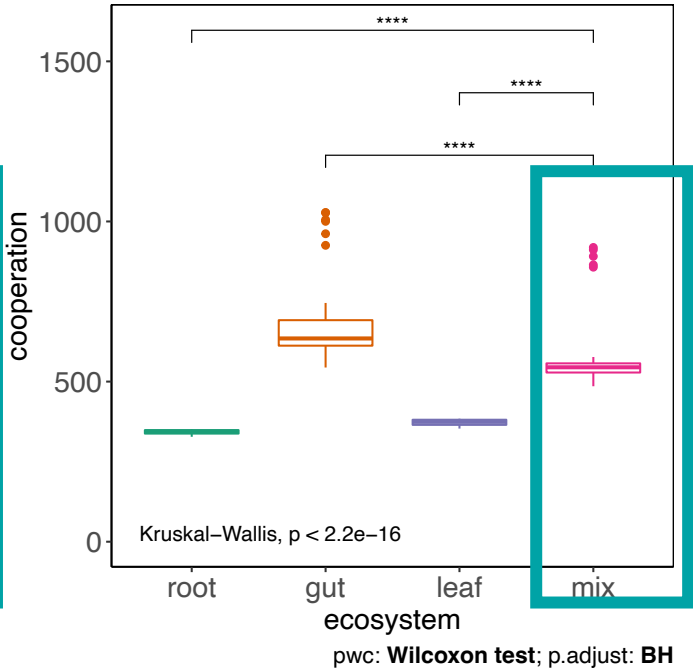
mix



Size = 3



Size = 75



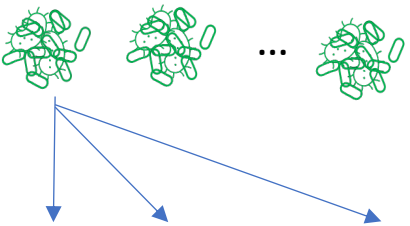
Size = 150

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

1520 isolated genomes of gut microbiome



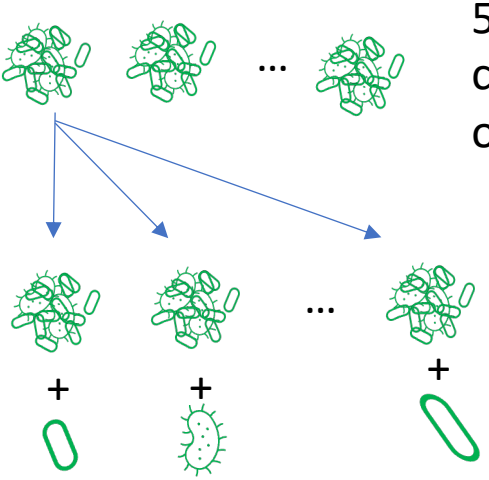
50 random communities of size X

50 communities of size X+1

Benchmarks for testing scores

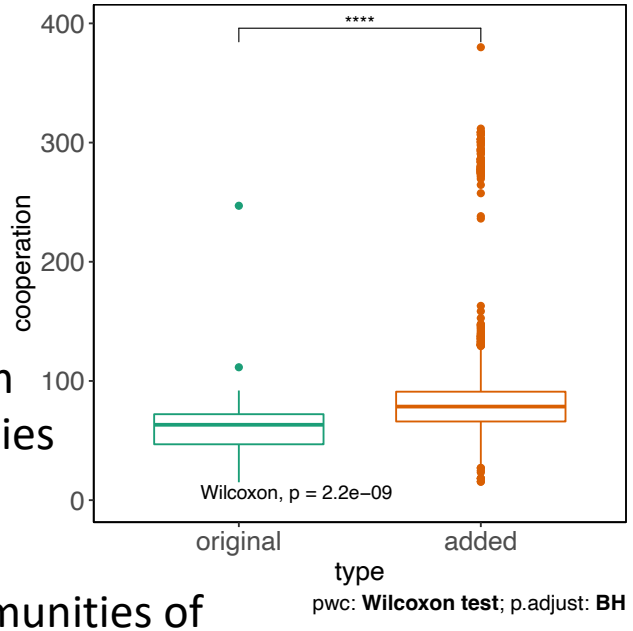
Added-value of adding a bacteria in community based on cooperation score

1520 isolated genomes of gut microbiome

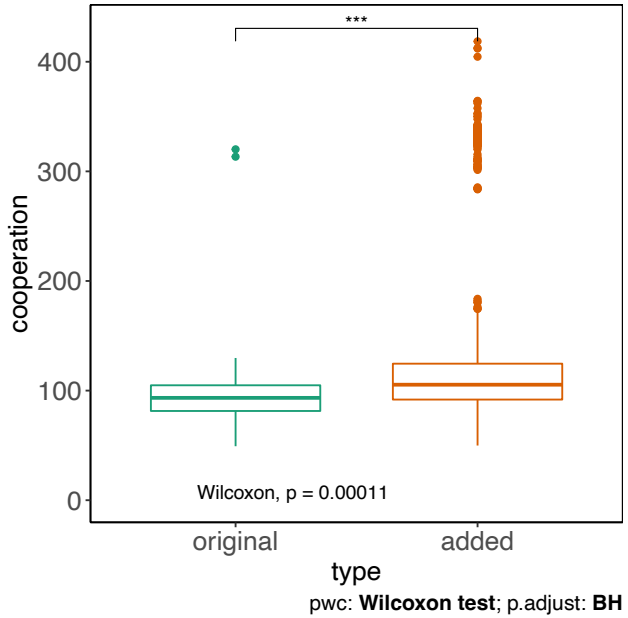


50 random communities of size X

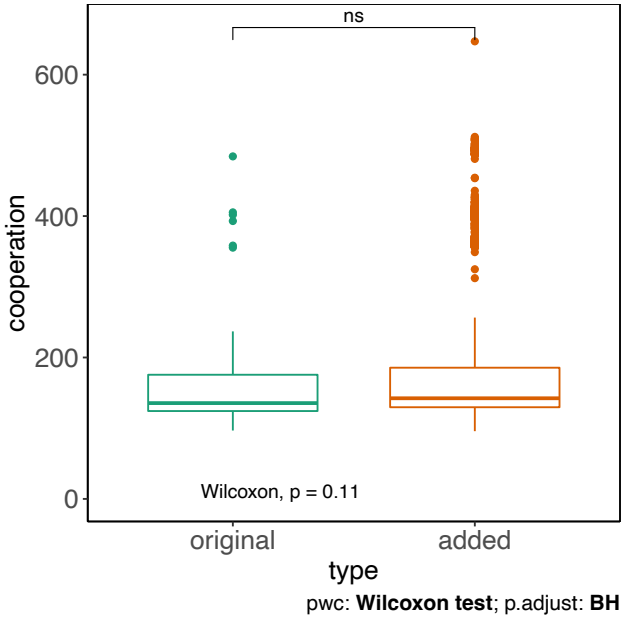
50 communities of size X+1



Size = 3



Size = 5



Size = 10

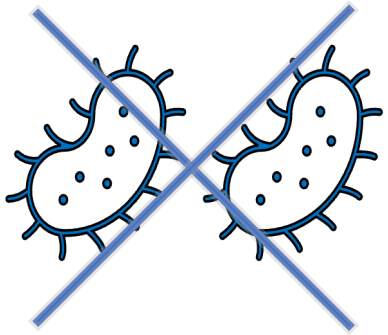
The larger is the community the less the community is disturbed by another species

Coyte KZ, et al (2021) Ecological rules for the assembly of microbiome communitie

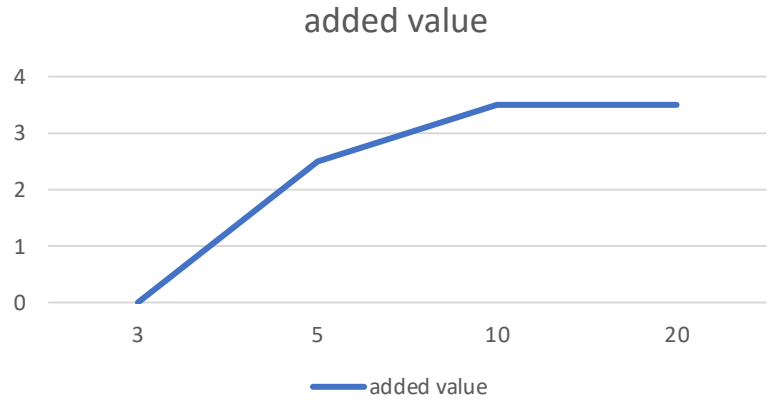
Conclusion

Tradeoff

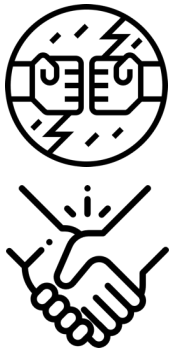
Scalability



Pairwise



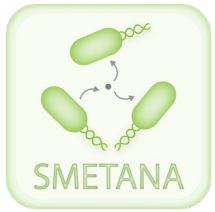
Resilience

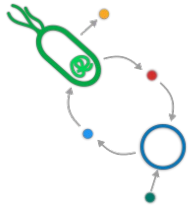


Potentials

Perspective

Soil





micom

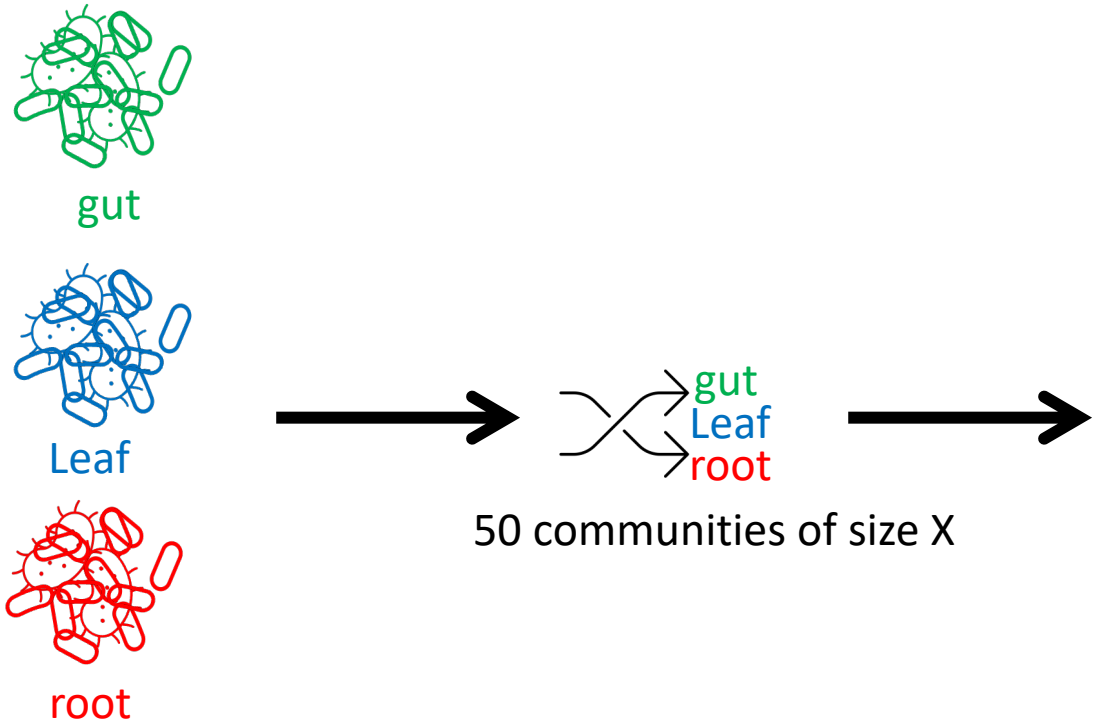
- David Sherman
- Clémence Frioux
- Simon Labarthe
- Coralie Muller

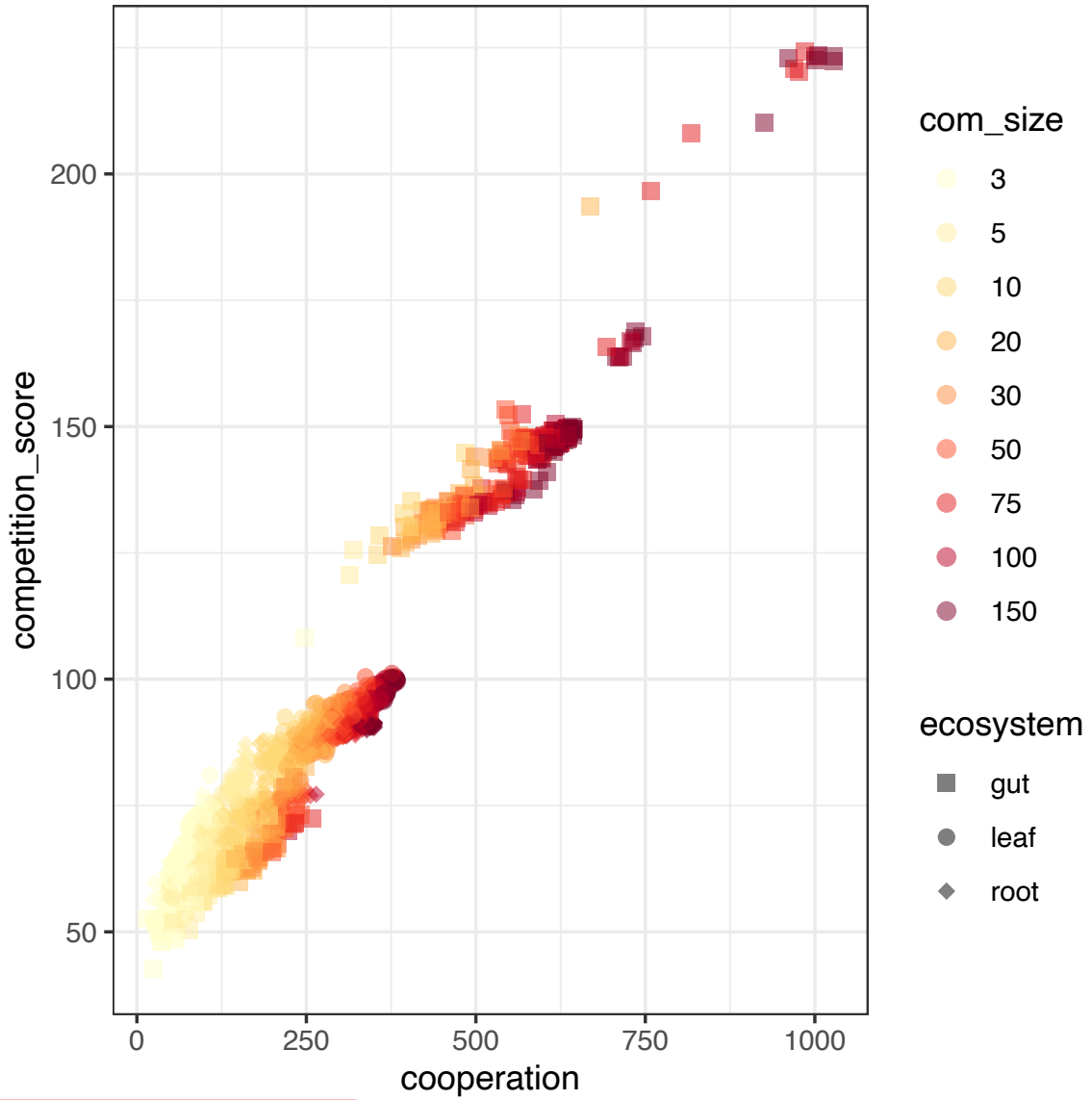
- Hélène Falentin

Thanks for your attention

Benchmarks for testing scores

Scores in function the community size





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*