

Approche hybride de modélisation explicable du métabolisme des écosystèmes microbiens

Hybrid approach for explainable metabolic modelling of microbial ecosystems'

Présenté par Maxime LECOMTE

November 28, 2023

Membres du jury

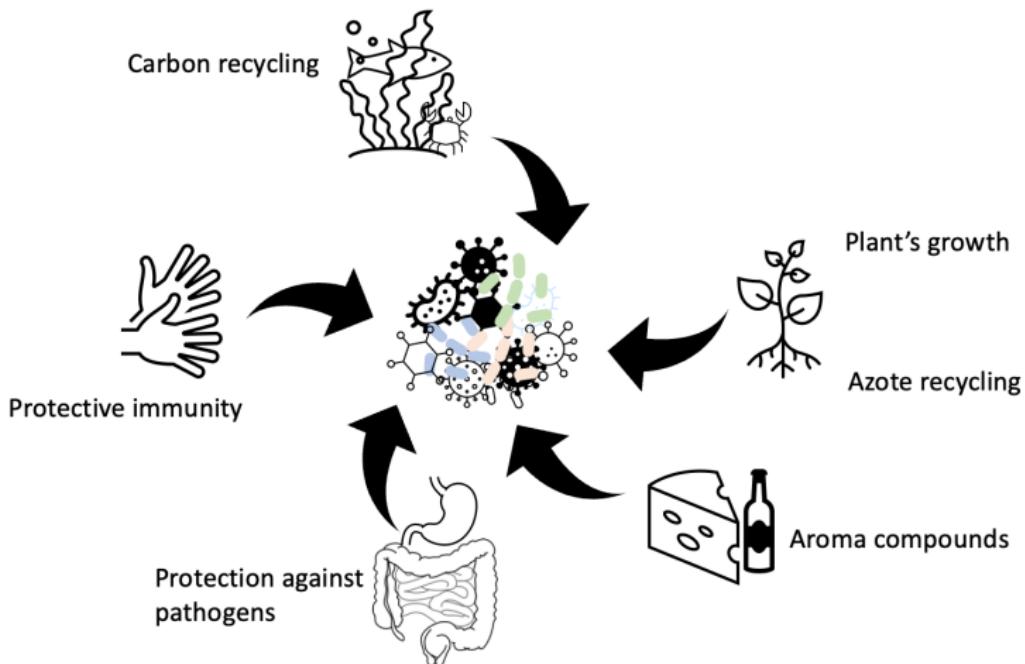
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Co-direction: David SHERMAN et Hélène FALENTIN
Encadrement: Clémence FRIOUX

Why study microorganisms ?



- High diversity of microorganisms in all ecosystems
- Microorganisms roles specific to the environment ([10.1093/chemse/bjh067](https://doi.org/10.1093/chemse/bjh067); BELKAID2014121; Zhang2015; Hoorman2011; McSweeney2000)

Bacterial interaction are responsible of the observed roles

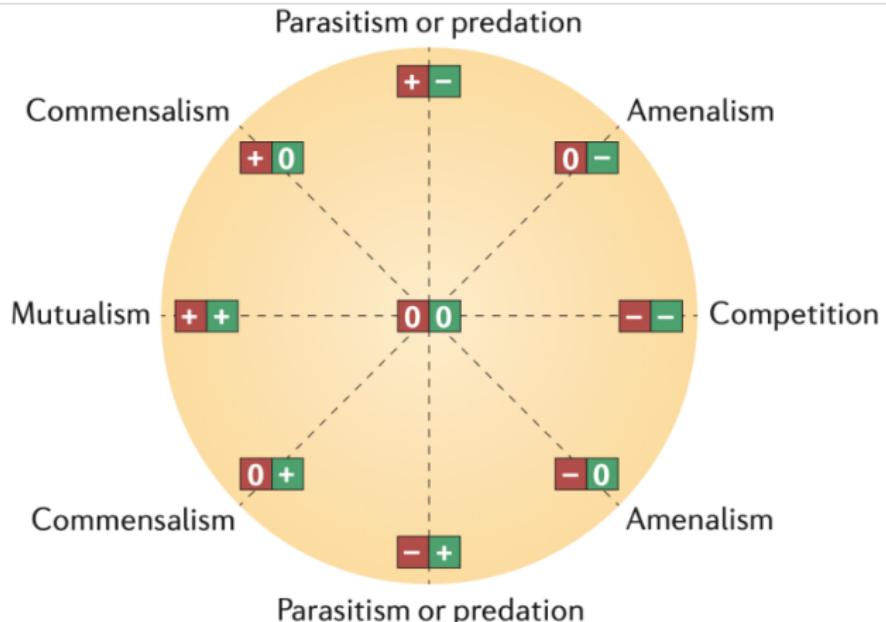


Figure 1: List of different types of bacterial interactions (Faust2012)

- Bacterial interactions are distinguishable within two species
- And within ecosystems composed of thousand of species ? → computational biology

How can we combine biological knowledge and infomatic program ?

Systems biology

System biology

Associate an organism to a system and study the all system (Kitano2002)

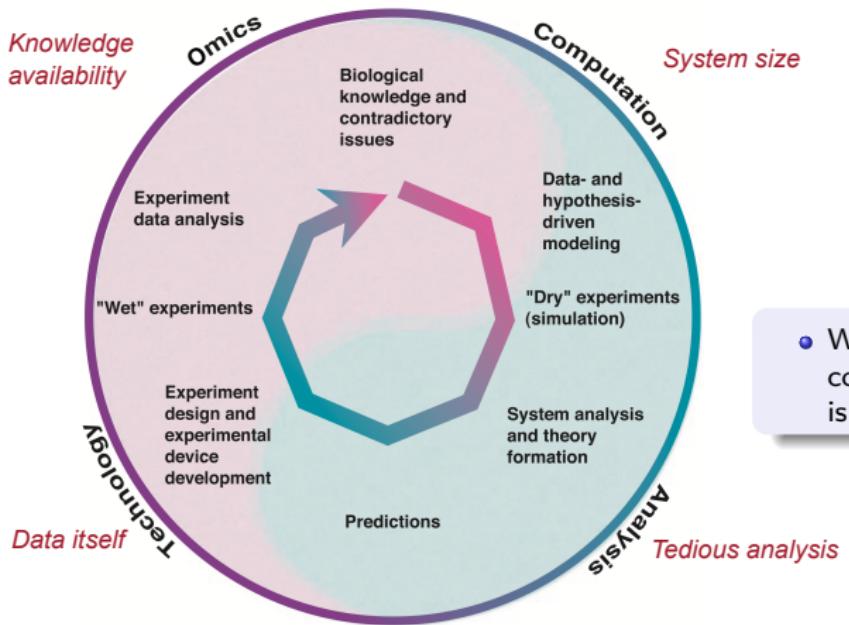


Figure 2: System biology modified from Kitano2002

Metabolism as a starter pack for analysing bacterial interactions

Metabolism

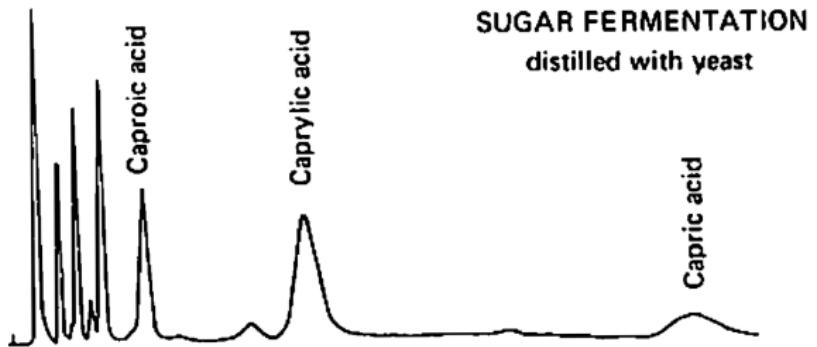


Figure 3: Gas chromatograms of the major aroma compounds isolated from rum (from Suomalainen 1978)

Metabolism as a starter pack for analysing bacterial interactions

Metabolism

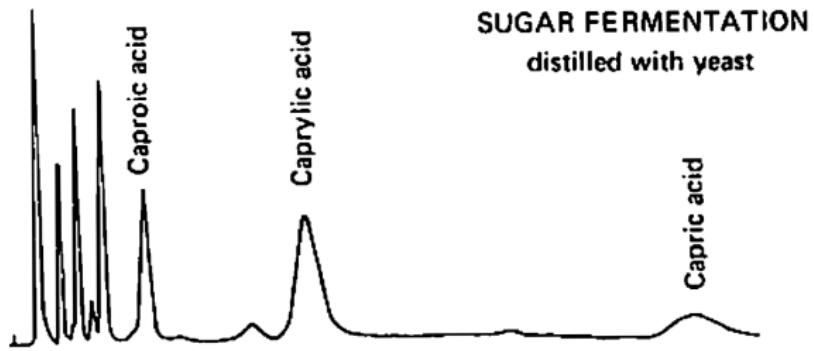


Figure 3: Gas chromatograms of the lower fatty acids produced by yeast in a nitrogen-free sugar fermentation (from Suomalainen 1978)

What is metabolism ?

Set of all biochemical reactions occurring in the cell of an organism that permit the production of energy and metabolic goods. (Nava 2023)

What underlying mechanisms are responsible of the observed activity ?

Metabolism and Bacterial interactions

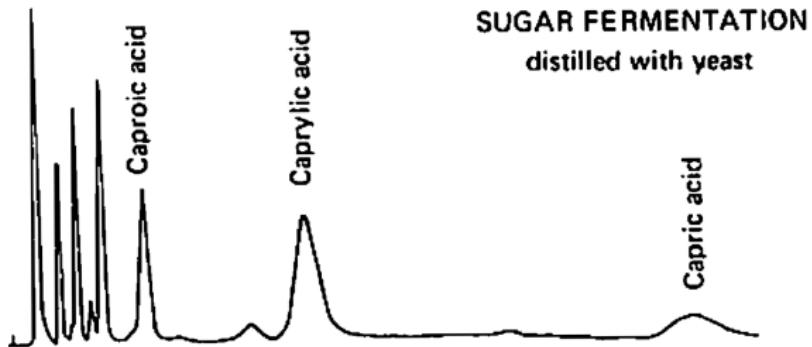
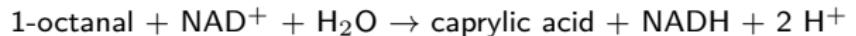


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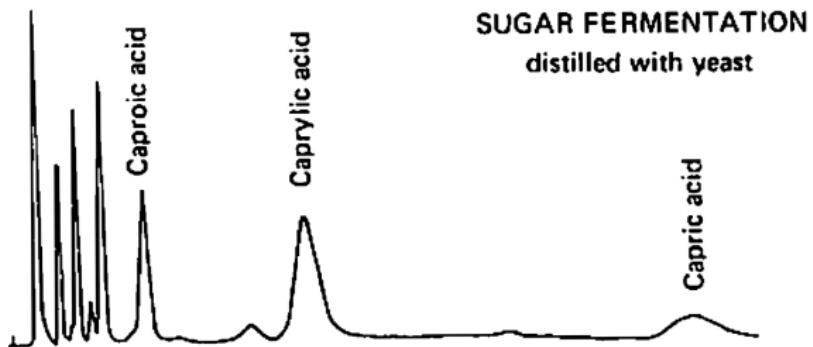
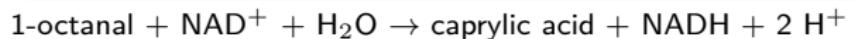


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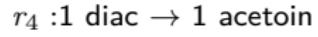
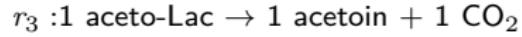
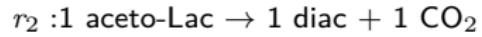
What is metabolism ?

Set of all biochemical reactions occurring in the cell of an organism that permit the production of energy and metabolic goods. (Nava2023)



- Metabolism of an organism explain observable phenotype
- Is impacted by bacterial interactions

How is the metabolism represented?



How is the metabolism represented?

- $$\begin{aligned}r_1 &: 2 \text{ pyr} \rightarrow 1 \text{ aceto-Lac} + 1 \text{ CO}_2 \\r_2 &: 1 \text{ aceto-Lac} \rightarrow 1 \text{ diac} + 1 \text{ CO}_2 \\r_3 &: 1 \text{ aceto-Lac} \rightarrow 1 \text{ acetoin} + 1 \text{ CO}_2 \\r_4 &: 1 \text{ diac} \rightarrow 1 \text{ acetoin} \\r_5 &: 1 \text{ acetoin} \rightarrow 1 \text{ butanediol}\end{aligned}$$

Stoichiometry matrix

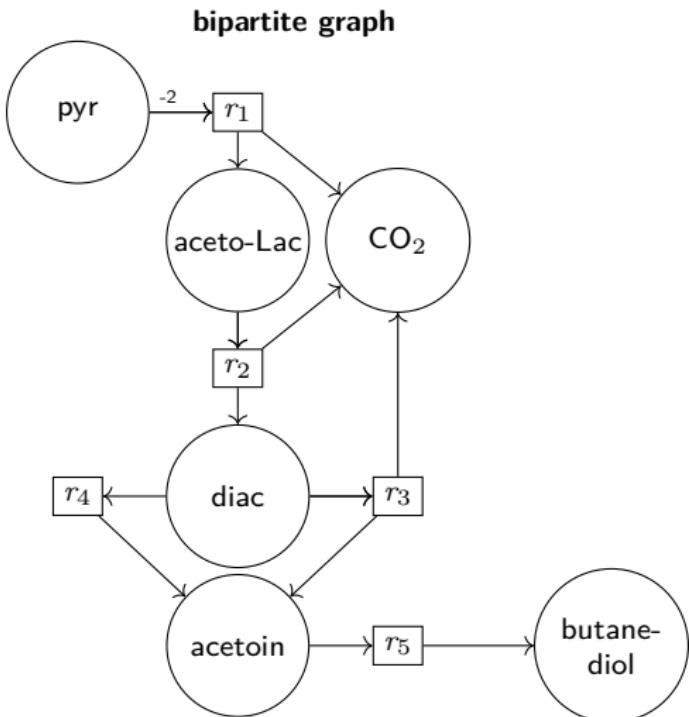
$$\begin{array}{c|ccccc} & r_1 & r_2 & r_3 & r_4 & r_5 \\ \text{pyr} & -2 & 0 & 0 & 0 & 0 \\ \text{aceto-Lac} & 1 & -1 & -1 & 0 & 0 \\ \text{diac} & 0 & 1 & 0 & -1 & 0 \\ \text{CO}_2 & 1 & 1 & 1 & 0 & 0 \\ \text{acetoin} & 0 & 0 & 1 & 1 & -1 \\ \text{butanediol} & 0 & 0 & 0 & 0 & 1 \end{array}$$

How is the metabolism represented?

$$\begin{aligned}
 r_1 & : 2 \text{ pyr} \rightarrow 1 \text{ aceto-Lac} + 1 \text{ CO}_2 \\
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 \end{aligned}$$

Stoichiometry matrix

$$\begin{array}{c|ccccc}
 & r_1 & r_2 & r_3 & r_4 & r_5 \\ \hline
 \text{pyr} & -2 & 0 & 0 & 0 & 0 \\
 \text{aceto-Lac} & 1 & -1 & -1 & 0 & 0 \\
 \text{diac} & 0 & 1 & 0 & -1 & 0 \\
 \text{CO}_2 & 1 & 1 & 1 & 0 & 0 \\
 \text{acetoin} & 0 & 0 & 1 & 1 & -1 \\
 \text{butanediol} & 0 & 0 & 0 & 0 & 1
 \end{array}$$



Stoichiometry matrix is commonly used for quantitative analysis instead of **graph**, more focused on topology analysis

How is the metabolism reconstructed?

Genome-scale metabolic network (GSMN) reconstruction

Genome-scale metabolic network (GSMNs)

Contain metabolic reactions predicted from the entire genomic content through gene-protein-reaction (GPR) relationships (Thiele.2010)

$$r1 : (g1 \wedge g2) \vee (g1 \wedge g3)$$

$$r2 : g1 \wedge (g2 \vee g3)$$

Example of trivial boolean GPR relationship

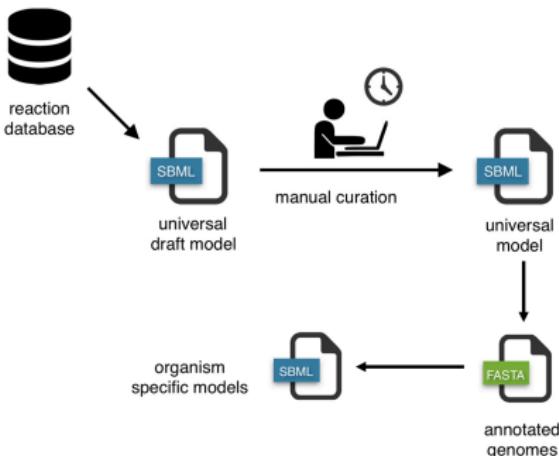


Figure 4: Top down genome-scale metabolic network reconstruction approach (modified from Machado2018)

- For bacteria: average of 2000 reactions, 1200 genes, 1000 metabolites
- In ecosystem, combinatorial problem occurs

Reasoning-based metabolic analysis

Definition

Reasoning-based

Allow us to infer qualitative models from logical rules based on biological knowledge

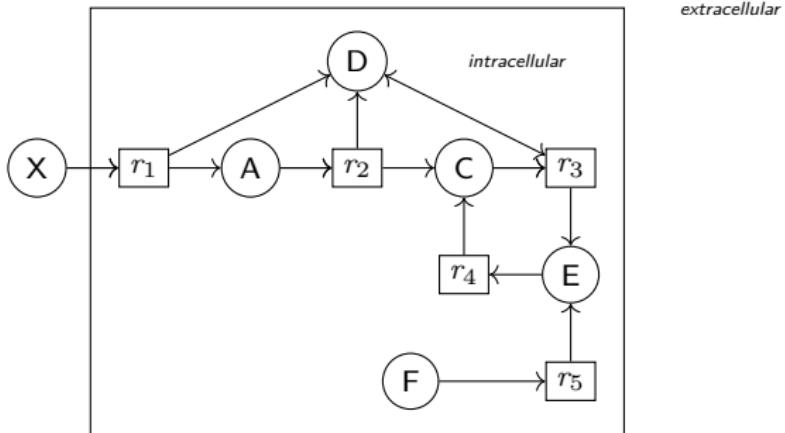
Reasoning-based metabolic analysis

Definition

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Allow us to infer qualitative models from logical rules based on biological knowledge

topological-based approaches



How to compute metabolic capability ?

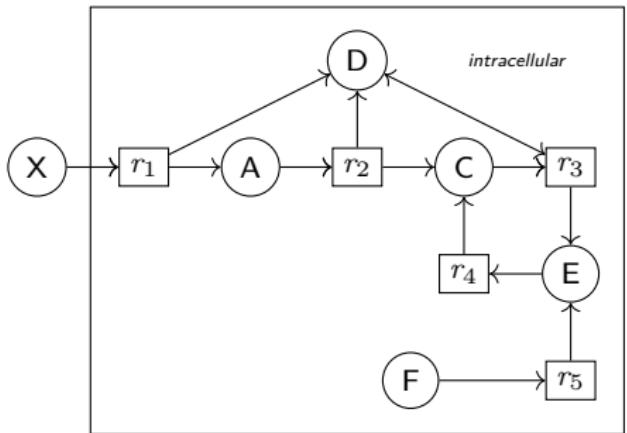
Reasoning-based metabolic analysis

Definition

Reasoning-based

Allow us to infer qualitative models from logical rules based on biological knowledge

topological-based approaches



extracellular

- Producibility is initiated by the presence of nutrients,
- The products of a reactions are producible if all reactants of this reaction are themselves producible

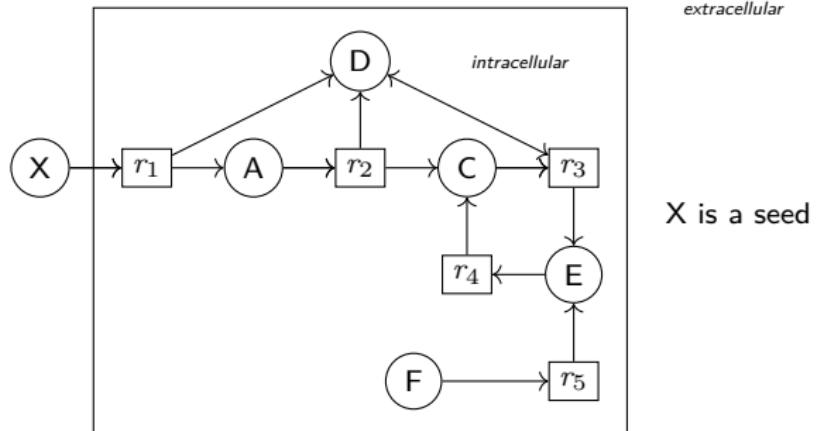
The scope, i.e. the metabolic capacity, a network is reached in 2 logical rules
(Ebenhoh2004)

Reasoning-based metabolic analysis

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Allow us to infer qualitative models from logical rules based on biological knowledge

topological-based approaches

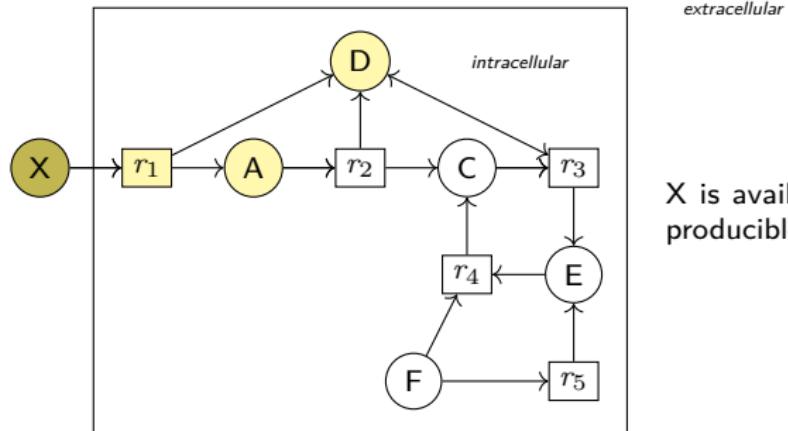


Reasoning-based metabolic analysis

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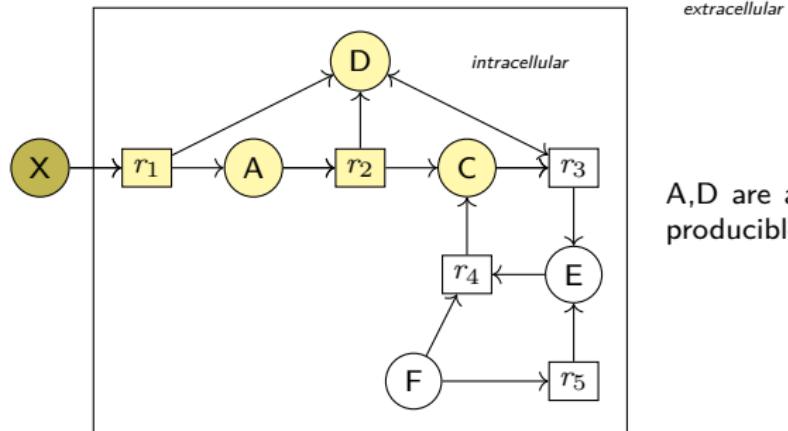
X is available; r_1 is activated and A,D are producible

Reasoning-based metabolic analysis

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Allow us to infer qualitative models from logical rules based on biological knowledge

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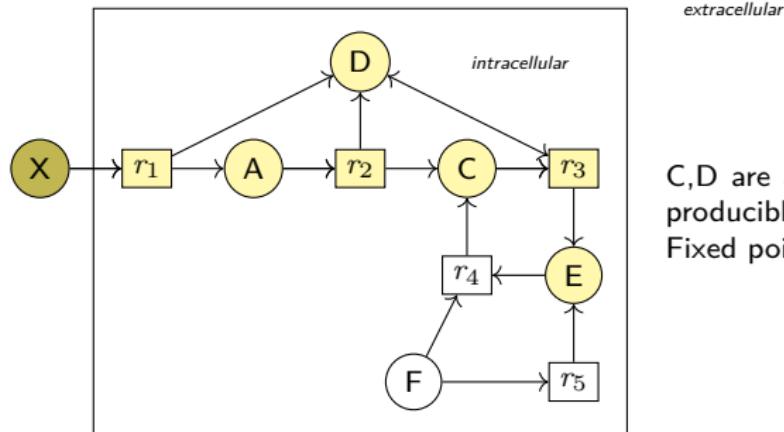
A,D are available; r₂ is activated and C is producible

Reasoning-based metabolic analysis

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Allow us to infer qualitative models from logical rules based on biological knowledge

topological-based approaches



C,D are available; r_3 is activated and E is producible
Fixed point : E

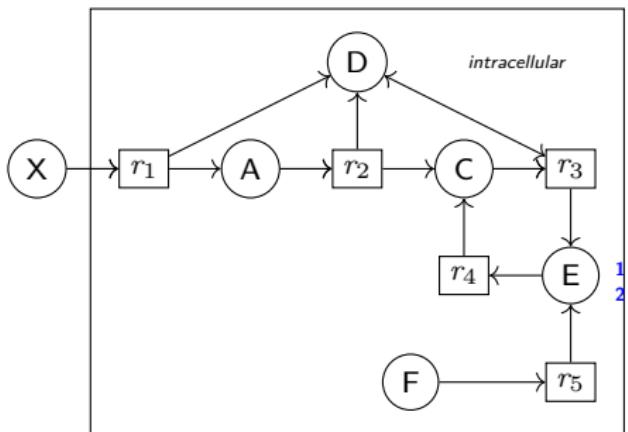
- The potential metabolic capability and topology dependant

Logical rules implementation

Reasoning-based

Allow us to infer qualitative models from logical rules based on biological knowledge

topological-based approaches



extracellular

- Producibility is initiated by the presence of nutrients,
- The products of a reactions are producible if all reactants of this reaction are themselves producible

```
scope(M) :- seed(M).  
scope(M) :- bacteria(B), product(M,R,B),  
          reaction(R,B), scope(M2) : reactant(M2,R,  
          B).
```

Logical rules are embedded using Answer Set Programming (Lifschitz2008)

Why using Answer Set Programming

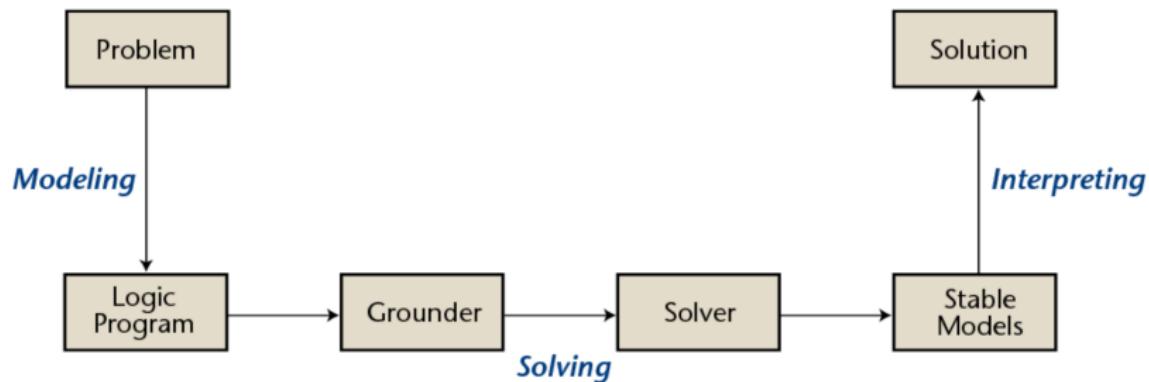


Figure 5: The workflow of Answer set programming (ASP) (Kaufmann2016GroundingAS)

- Close assumption
- Mechanistic model
- Solve combinatorial problems

Numerical metabolic model of the metabolism

definition

Metabolic model

From a GEM, a model metabolic has the capacity to simulate and to predict on the metabolic activity

Numerical metabolic model of the metabolism

Flux Balance Analysis (Orth2010)

Metabolic model

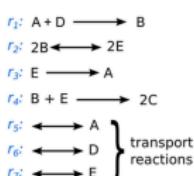
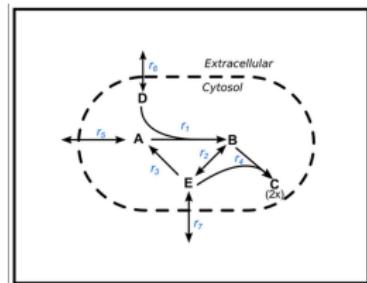
From a GEM, a model metabolic has the capacity to simulate and to predict on the metabolic activity

Constraint-based approaches

maximiser/minimiser f_{obj}

$$\text{tel que } (S.v)_{int} = 0$$

$$\text{et } v_{i_{min}} \leq v_i \leq v_{i_{max}}$$



	r_1	r_2	r_3	r_4	r_5	r_6	r_7
A	-1	0	1	0	1	0	0
B	1	-2	0	-1	0	0	0
C	0	0	0	2	0	0	0
D	-1	0	0	0	0	1	0
E	0	2	-1	-1	0	0	1

(Stoichiometric values)

$$\bar{v} = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \\ v_6 \\ v_7 \end{bmatrix}$$

(Metabolic flux values)

Figure 7: A. Stoichiometry matrix representation and the flux vector v

Figure 6: Example of metabolic network

Numerical metabolic model of the metabolism

Flux Balance Analysis (Orth2010)

Metabolic model

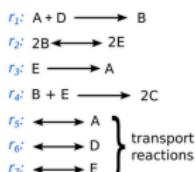
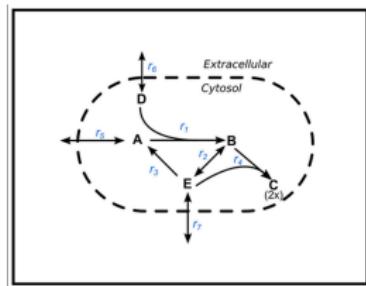
From a GEM, a model metabolic has the capacity to simulate and to predict on the metabolic content

Constraint-based approaches

maximiser/minimiser f_{obj}

$$\text{tel que } (S.v)_{int} = 0$$

$$\text{et } v_{i_{min}} \leq v_i \leq v_{i_{max}}$$



Subject to

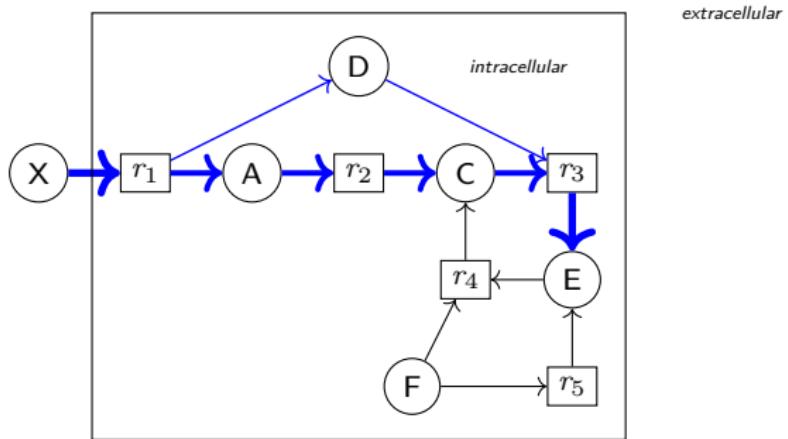
$$S\vec{v} = \vec{0} = \begin{cases} \frac{dA}{dt} = -v_1 + v_3 + v_5 & 0 \leq v_1 < \infty \\ \frac{dB}{dt} = v_1 - 2v_2 - v_4 & -\infty < v_2 < \infty \\ \frac{dC}{dt} = 2v_4 & 0 \leq v_3 < \infty \\ \frac{dD}{dt} = -v_1 + v_6 & 0 \leq v_5 \leq \infty \\ \frac{dE}{dt} = 2v_2 - v_3 - v_4 + v_7 & -\infty < v_6 < \infty \\ \end{cases}$$

(Steady state system) (Reaction bounds)

Figure 7: B. Linear programming problem.

Figure 6: Example of metabolic network

Flux application



- Reaction flux depending of the stoichiometry coefficient
- Can explain metabolic observations through reaction fluxes
- difficult to apply to large-scale: computational cost, cultivated species

Contributions and objective

Objective

Contribute to analyzing metabolic interactions of bacterial communities associated to two use cases: controlled and uncontrolled environment

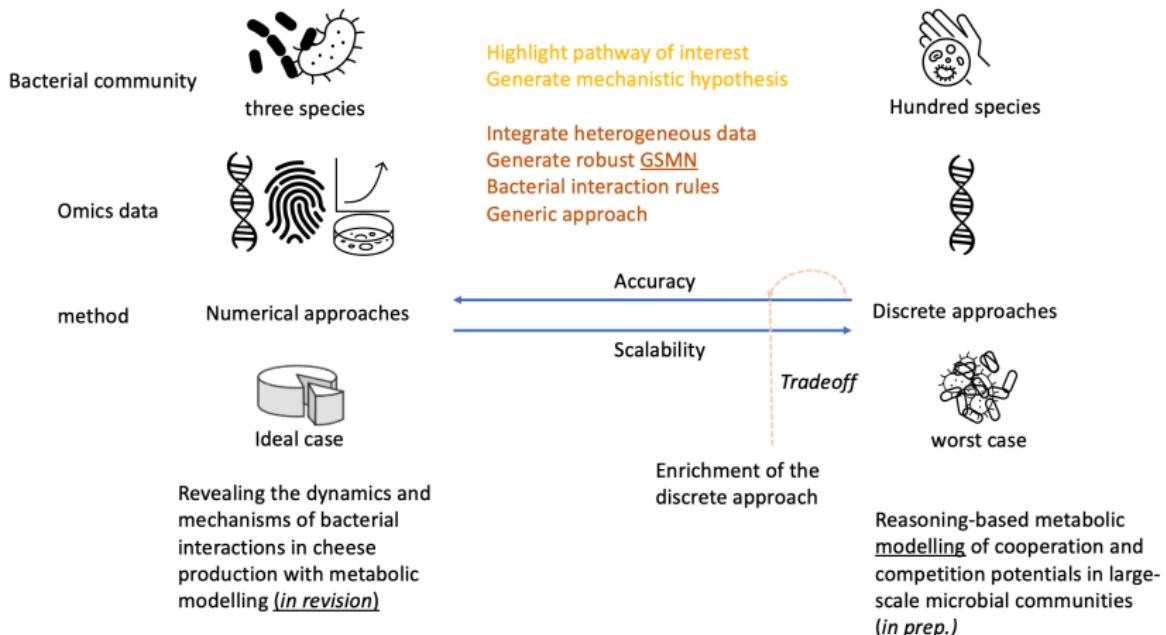
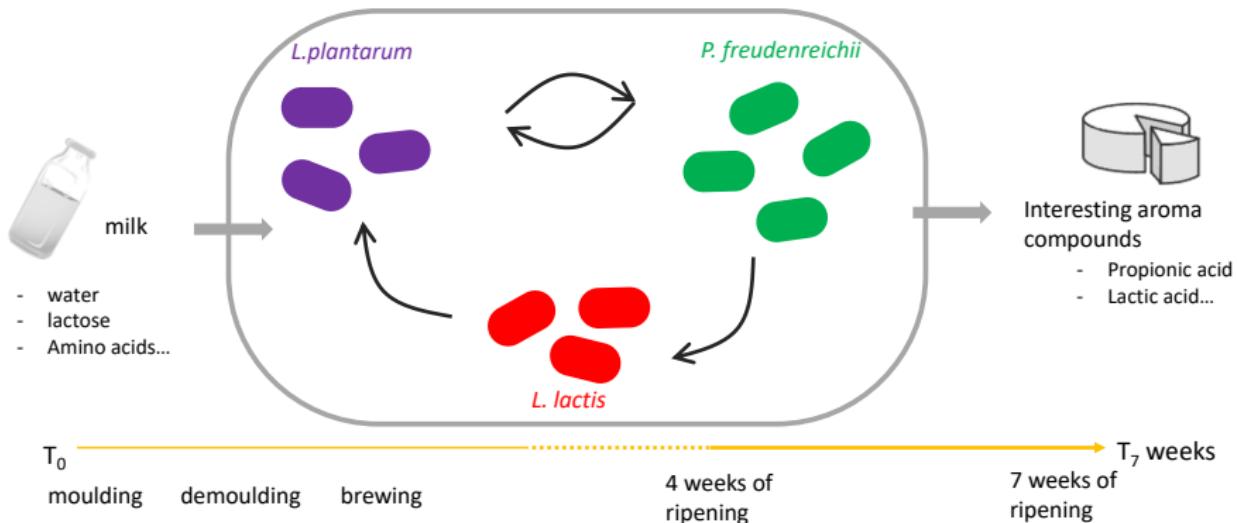


Figure 8: Contributions in my thesis. In yellow and brown-red are respectively biological and methodological contributions

Biological context: cheese bacterial fermentation



Heterogenous data are available for analysing bacterial fermentation

Multi-omics strategy



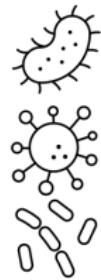
Annotated genomes



Genes expression
(metatranscriptomics)

Acétiate-HPLC-F1	Acétiate-HPLC-F3
0,01	0,01
0,04	0,05
0,44	0,36
0,92	0,81
1,05	0,97
2,00	1,77
2,59	2,52

Metabolomics data



Growth and pH
data in pure
cultures

Dynamic and numerical model of the metabolism can integrate all the data

Refinement of metabolic networks - 1

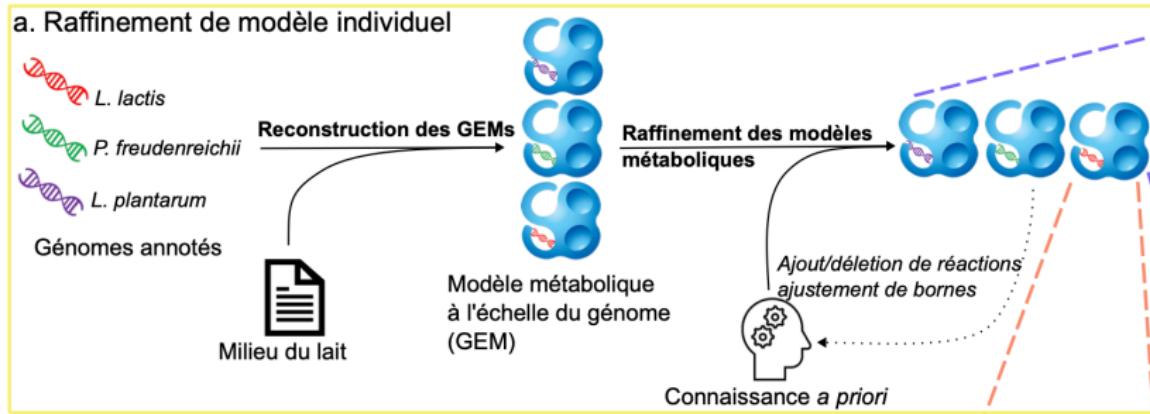
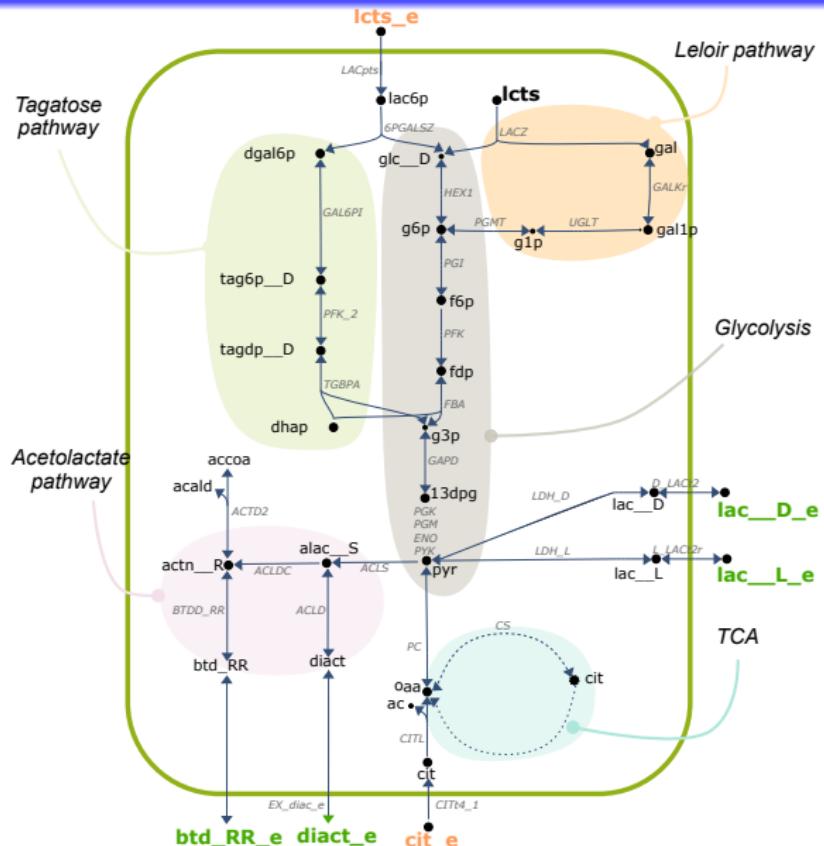


Figure 9: First part of the numerical workflow

- Adding/removing reactions
- Qualitative check of existing pathway and metabolic goods
- Tedious analysis

Refinement of metabolic networks - 2

L. lactis case

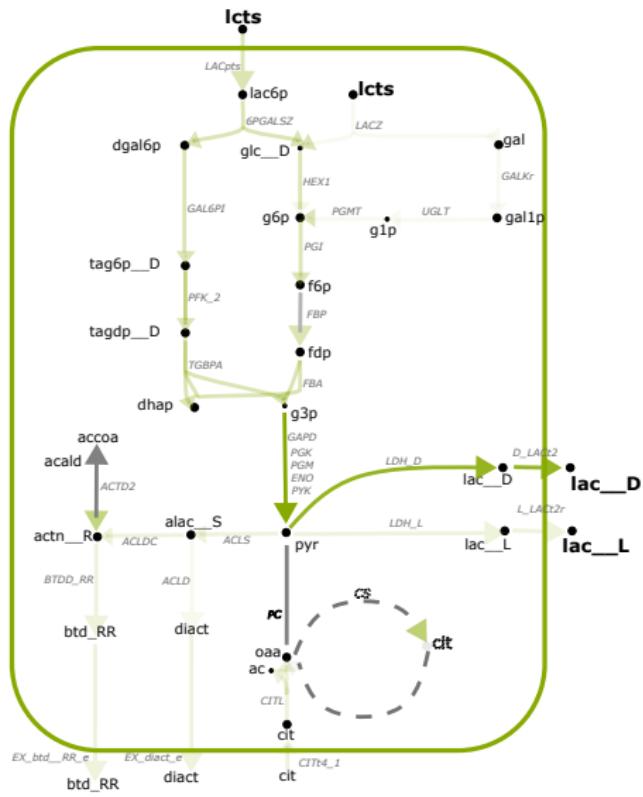


Objectif

- Production of butanediol
- activation of acetolactate pathway

Refinement of metabolic networks - 2

L. lactis case



Objectif

- Production of butanediol
- activation of acetolactate pathway

Refinement

- Acétoine-dehydrogenase was blocked (ACTD2)
- Modification of bounds: acétolactate decarboxylase (ACLDC) and acétolactate synthase (ACLS)

Dynamic individual calibration

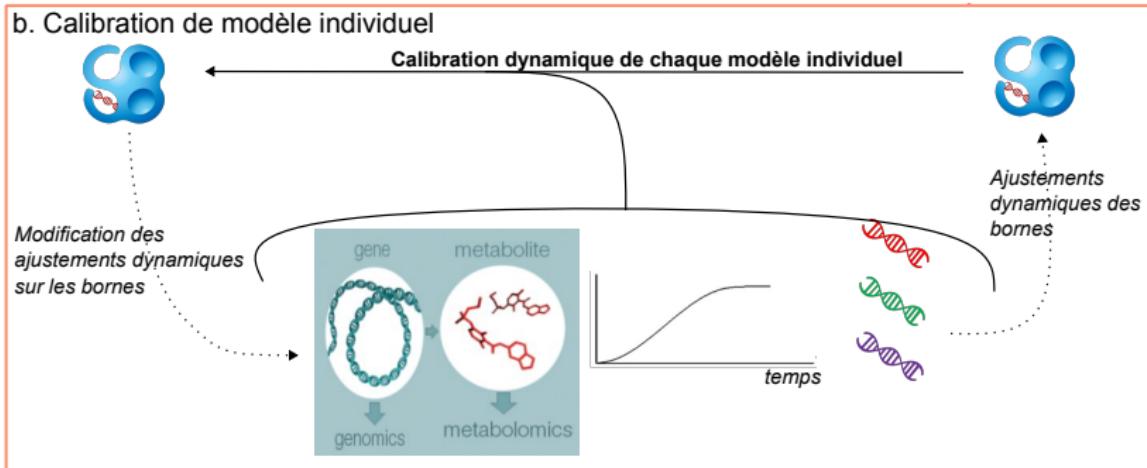


Figure 10: Second part of the numerical workflow

- Finding optimal parameters for explaining **individual** biological observations
- Quantitative check of metabolic goods and biomass density

Individual metabolic model calibration

Goal

Make individual GSMN accurate for inferring mechanistic bacterial behavior

LAB

$$J(b_i, pH | \theta_i, b_{i,exp}, pH_{exp}) = \left\| \frac{\log_{10}(b_i) - \log_{10}(b_{i,exp})}{\sigma_{log,i,exp}} \right\|^2 + \alpha \left\| \frac{pH - pH_{exp}}{\sigma_{pH,exp}} \right\|^2 \quad (1)$$

GEM	Temps	Densité bactériennes	pH
<i>L. plantarum</i>	0	1.485e-06	6.7
	5	3.795e-06	6.68
	7	5.28e-06	6.66
	9	8.415e-06	6.555
	14	1.386e-05	6.54
	16	2.3595e-05	6.51
	79	3.762e-05	5.705
	0	8.25e-07	6.7
<i>L. lactis</i>	5	5.230500e-05	6.49
	7	6.831e-05	6.315
	9	6.649500e-05	6.075
	14	6.468e-05	5.935
	16	4.735e-05	5.865
	79	6.171e-05	5.115

Individual metabolic model calibration

Goal

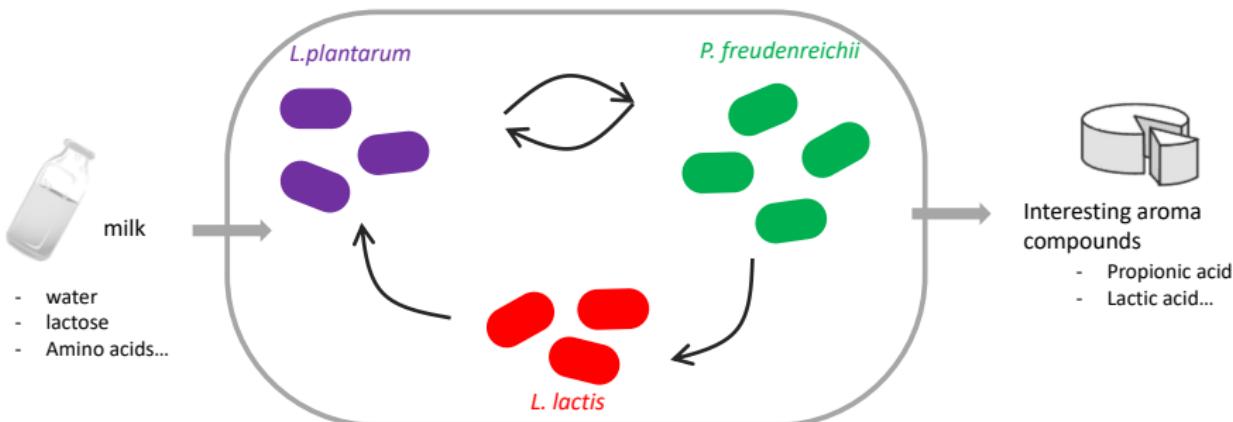
Make individual GSMN accurate for inferring mechanistic bacterial behavior

P. freudenreichii

$$J(b, m | \theta_i, b_{exp}, m_{exp}) = \left\| \frac{\log_{10}(b) - \log_{10}(b_{exp})}{\sigma_{log, b, exp}} \right\|^2 + \alpha \left\| \frac{m - m_{exp}}{\sigma_{m, exp}} \right\|^2 \quad (1)$$

GEM	Temps	Densité bactériennes	pH
<i>P. freudenreichii</i>	0	0.000001	∅
	23	0.000099	∅
	40	0.000561	∅
	48	0.000412	∅
	130	0.000710	∅

Bacterial fermentation: a dynamic process



Challenge

- Nutrient concentration over time
- The dynamic of bacterial density
- Resource sharing

Solution

- Compute dynamic model of the metabolism (dFBA) (Mahadevan.2002)

Dynamic modeling of the metabolism (dFBA)

Compute the total flux



$$F_j = \sum_{i \in \mathcal{B}} \mu_{i,j} ((c_{min,i}^{ex}, c_{max,i}^{ex})(b^n, m^n)) b_i \quad (2)$$

F_j total flux computed in $mmol.gDW^{-1}.h^{-1}$

$\mu_{i,j} ((c_{min,i}^{ex}, c_{max,i}^{ex})(b^n, m^n)) b_i$ is the correspondence between exchange reaction, bacterial and metabolite constraints in the system from a given environment.

Dynamic modeling of the metabolism (dFBA)

Compute bacteria densities and metabolites concentrations



$$F_j = \sum_{i \in \mathcal{B}} \mu_{i,j} ((c_{min,i}^{ex}, c_{max,i}^{ex})(b^n, m^n)) b_i \quad (2)$$

$$b_i^{n+1} = b_i^n + \Delta t * F_{b_i} \quad (3)$$

$$m_j^{n+1} = \begin{cases} m_j^n + \Delta t * F_j & \text{si } F_j > 0 \text{ (cas explicite)} \\ m_j^n / (1 - \Delta t * F_j / m_j^n) & \text{sinon (cas implicite)} \end{cases} \quad (4)$$

Euler semi implicit schema guarantees the positivity of the solution

Dynamic modeling of the metabolism (dFBA)

General dynamic model



$$F_j = \sum_{i \in \mathcal{B}} \mu_{i,j} ((c_{min,i}^{ex}, c_{max,i}^{ex})(b^n, m^n)) b_i \quad (2)$$

$$b_i^{n+1} = b_i^n + \Delta t * F_{b_i} \quad (3)$$

$$m_j^{n+1} = \begin{cases} m_j^n + \Delta t * F_j & \text{si } F_j > 0 \text{ (cas explicite)} \\ m_j^n / (1 - \Delta t * F_j / m_j^n) & \text{sinon (cas implicite)} \end{cases} \quad (4)$$

$$\partial_t b_i = \mathcal{R}_i(b_i) \mu_{i,i} ((c_{min,i}^{ex}, c_{max,i}^{ex})(b, m)) b_i \quad (5)$$

$$\partial_t m_j = \sum_{i \in \mathcal{B}} \mu_{i,j} ((c_{min,i}^{ex}, c_{max,i}^{ex})(b, m)) b_i \quad (6)$$

Bacterial densities and metabolites concentrations are therefore computed in $g.L^{-1}$ and $mmol.L^{-1}$

Individual metabolic model calibration

Goal

Make individual GSMN accurate for inferring mechanistic bacterial behavior

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$$J(b_i, pH | \theta_i, b_{i,exp}, pH_{exp}) = \left\| \frac{\log_{10}(b_i) - \log_{10}(b_{i,exp})}{\sigma_{log,i,exp}} \right\|^2 + \alpha \left\| \frac{pH - pH_{exp}}{\sigma_{pH,exp}} \right\|^2 \quad (7)$$

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	23	0.000099	∅
	40	0.000561	∅
	48	0.000412	∅
	130	0.000710	∅

Dynamic modulations

Usual consumption limitation

$$c_{min,i,j}^{ex} = \max\left(-\frac{m_{lcts_e}}{\Delta t * \sum_{i \in \mathcal{M}_l} b_i}, v_{i,j}^{int}\right) \quad (8)$$

- \mathcal{M}_l Bacteria subset can metabolize j
- Balanced resource sharing

Lactose consumption

$$c_{min,i,j}^{ex} = \max\left(-\frac{m_{lcts_e}}{\Delta t * \sum_{i \in \mathcal{M}(lcts_e)} b_i}, -\mu_{max,lcts} * 10^{(-k_{lac} * \phi_{undiss})} - \mu_{min,lcts}\right) \quad (9)$$

- Lactose consumption negatively regulated by the non dissociated form of acid lactic

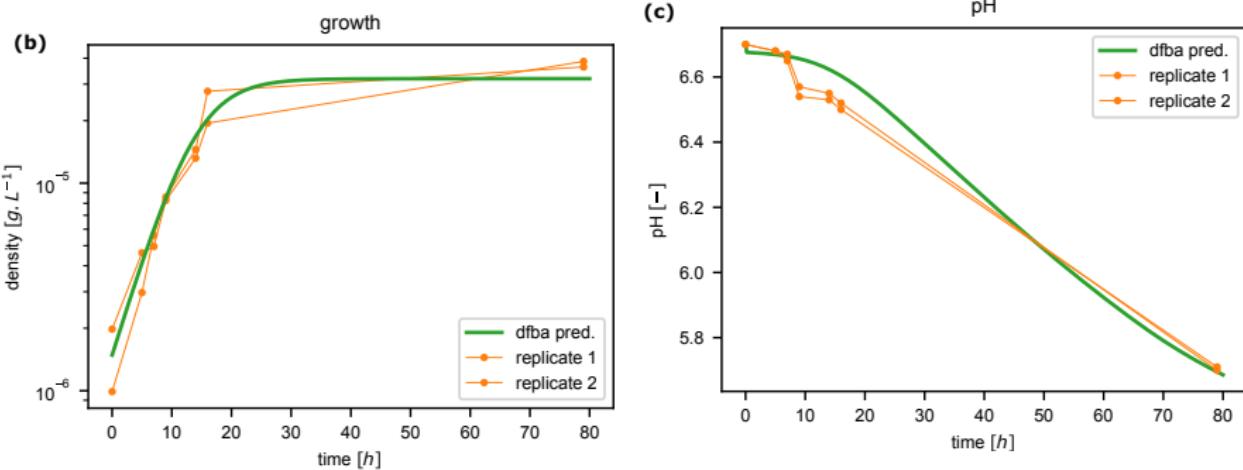
pH regulation

$$\phi_{undiss}(m_{lac_L_e}, m_{lac_D_e}) = \frac{m_{lac_L_e} + m_{lac_D_e}}{1 + 10^{c_1 * (m_{lac_L_e} + m_{lac_D_e}) + c_2}}. \quad (10)$$

- approximation of pH - pKa

Model validation

L. plantarum



Dynamic model of *L. plantarum* explains its experimental growth and pH

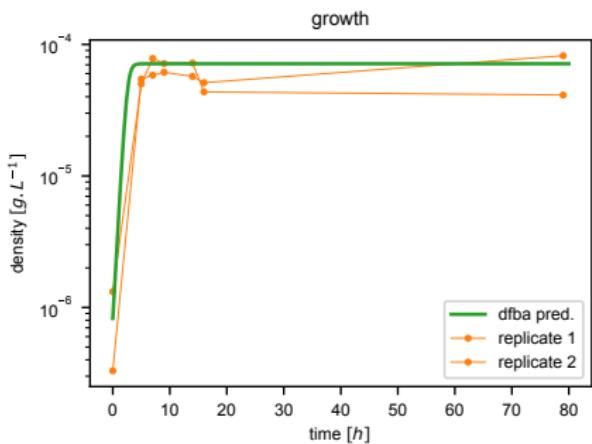
home message

Individual metabolic model well calibrated → retrieve experimental data

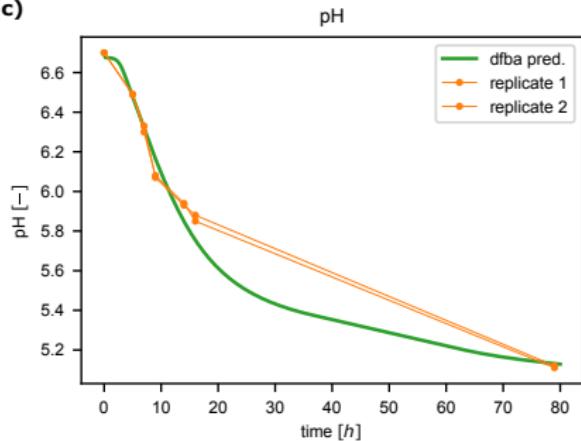
Model validation

L. lactis

(b)



(c)



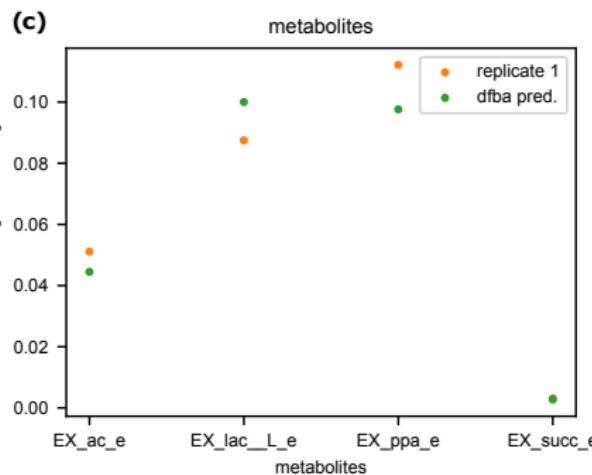
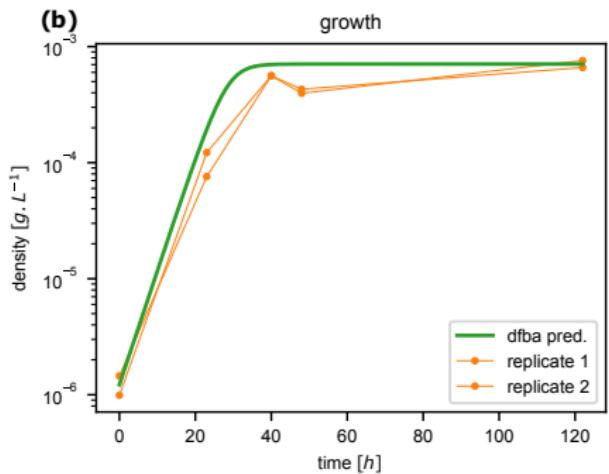
Dynamic model of *L. lactis* explains its experimental growth and pH

home message

Individual metabolic model well calibrated → retrieve experimental data

Model validation

P. freudenreichii



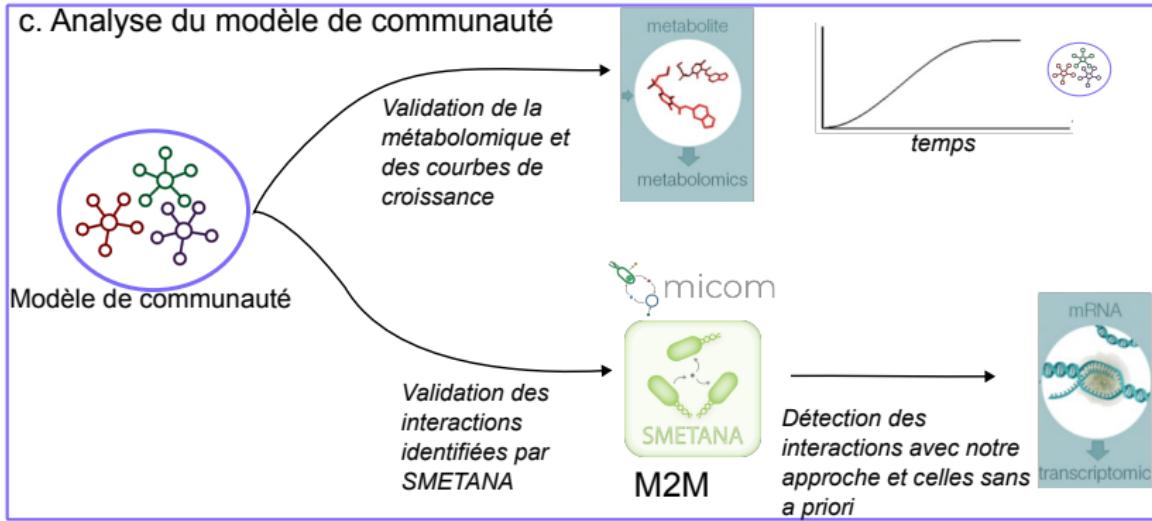
Dynamic model of *P. freudenreichii* explains its experimental growth and acid dosages

home message

Individual metabolic model well calibrated → retrieve experimental data

Community validation

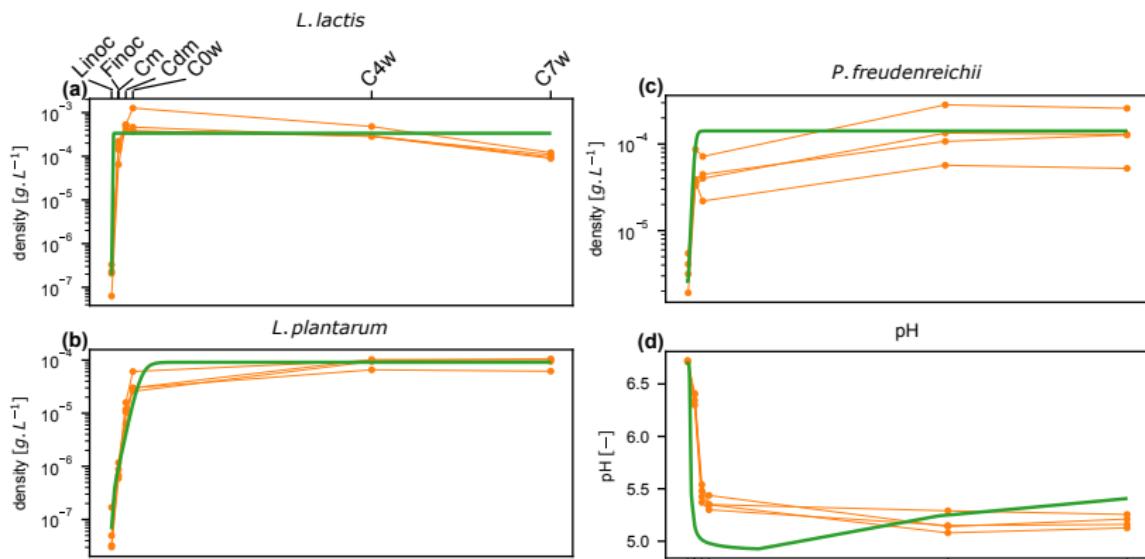
c. Analyse du modèle de communauté



- Bacterial interaction prediction
- Metabolic explanation of biological observations
- **No community calibration**

Community prediction

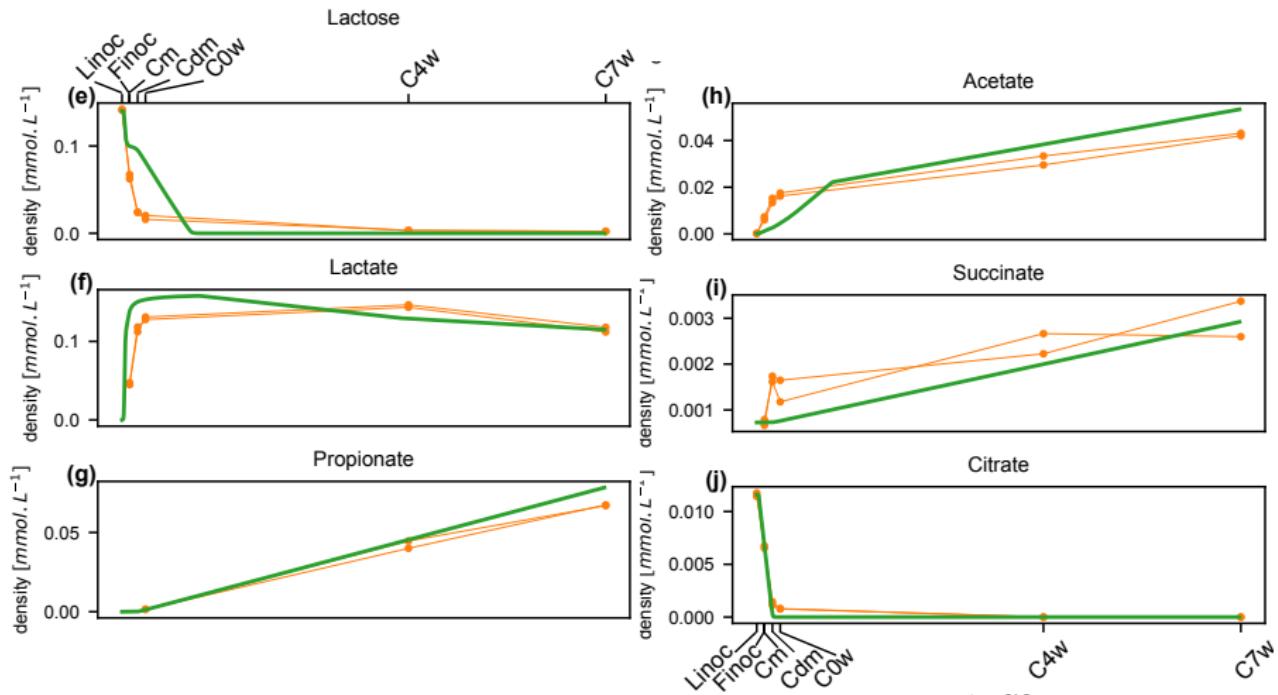
Growth and pH



- Growth well predicted for all bacteria
- Lactate proxy production can explain the observed pH

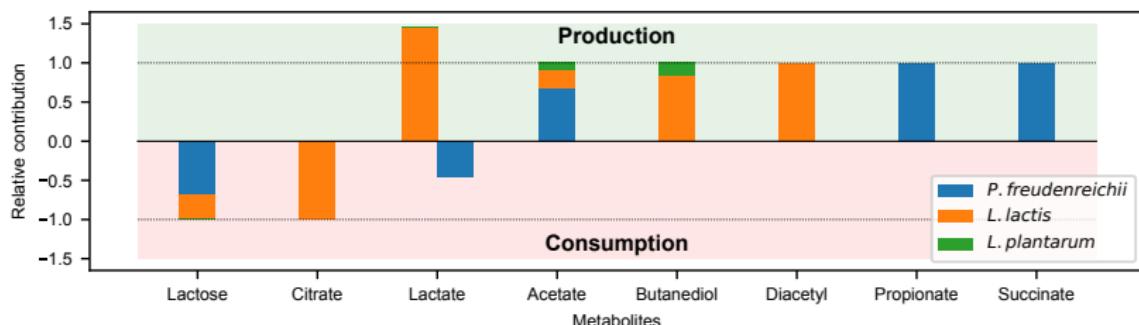
Community prediction

Metabolomics

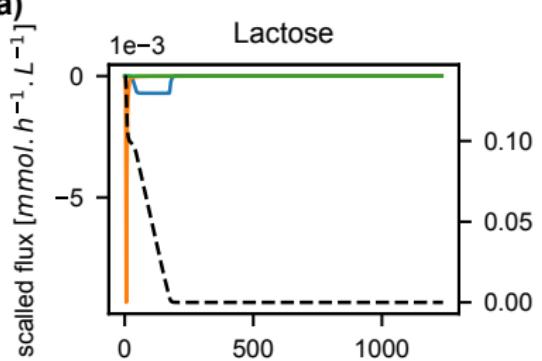


- Metabolomic is well predicted

So what....



(a)



- No competition for lactose
- *L. lactis* main lactate producer
- *P. freudenreichii* main producer of Acetate

- 11 shared metabolites predicted with SMETANA, MiCOM (phénylalanine, succinate, xanthine..)
- H_2S , ribose and glycerol seams to be relevant

Added-value and limitations

Take home message

Originality

- High quality of refinement and well calibrated individual GSMN from cheese
- Accurate dynamic model with few optimized parameters
- No need of community calibration to predict community behavior

Scalability issue

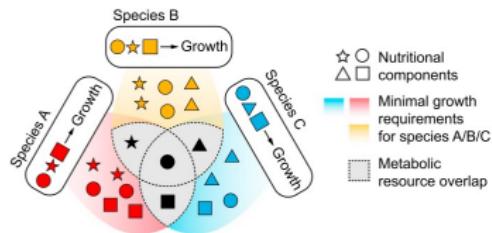
- Refinement process is time consuming
- The iterative methodology assume well documented GSMNs in literature
- Based on *a priori* knowledge for screening compounds

Solution

For screening large community, use of different formalism is required

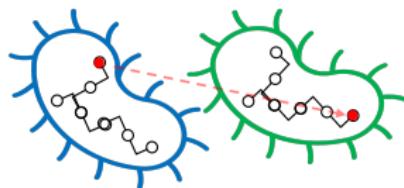
Discrete modelling able to screen large community

Numerical methods →



Competition potentials

Graph based methods →

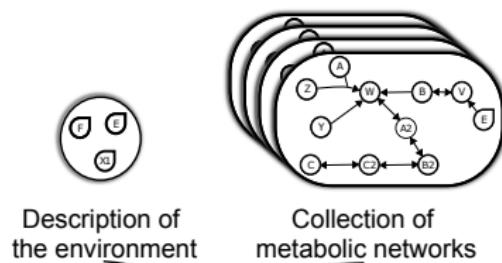


Cooperation potentials

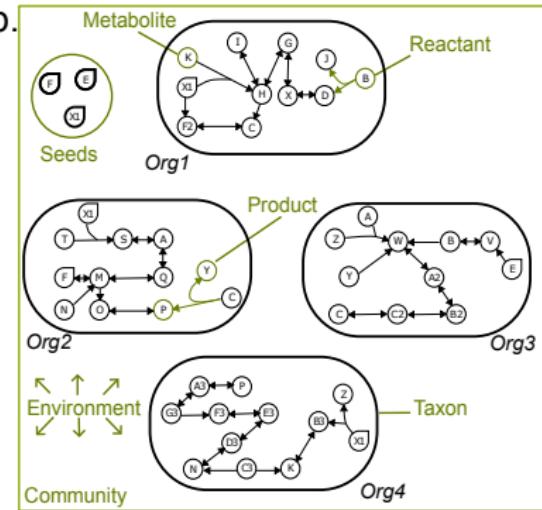
- Competition and cooperation potential are used for describing ecosystems
- Community size analysis up to 18 (Zeleznak 2015) in a reasonable time
- tedious pairwise analysis for graph base methods
- Discrete-based methods not limited by the size of community

Contributions 2: Discrete approach for characterizing large-scale bacterial

a.



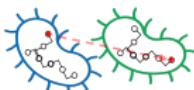
b.



- Combination of the extension of network expansion algorithm and answer set programming for the calculation of cooperation and competition potentials
- How to define cooperation and competition potentials ?

Cooperation & competition properties

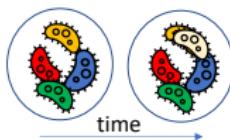
Exchanged metabolites



Cooperation at the community-scale vs
between individual



Compare community score with the
same size



Longitudinal analysis



Cross sectional analysis

Not over(under) estimate contributors
involved in the exchange

Polyopsonistic substrate

- Inference of polyopsonistic substrate and exchanged compounds in logical rules (ASP)
- Index of cooperation and competition in python

Potential interactions rules

Competition rules

```

1 exchange(M,P,C) :- taxon(P),
2   taxon(C),
3   P != C,
4   reactant(M,_,C),
5   product(M,_,P),
6   scope(metabolite(M,P), all),
7   not scope(metabolite(M,C), self(C)).

```

ligne 1: un métabolite M est échangeable entre un producteur P et un consommateur C si P est un taxon et

ligne 2: que C est un taxon et

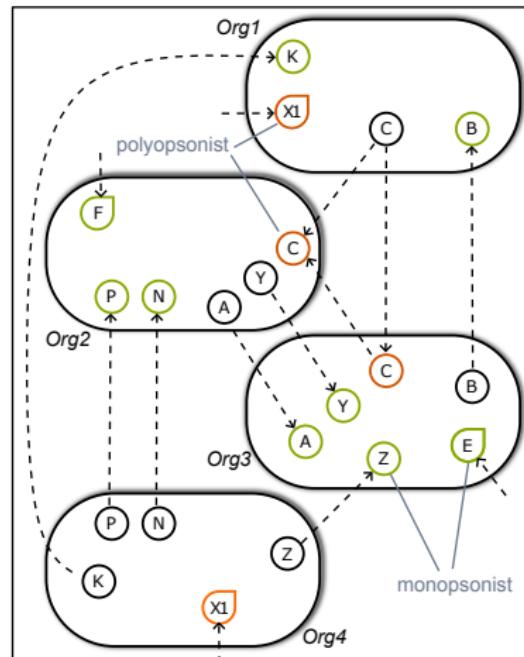
ligne 3: P est différent de C et

ligne 4: que M est un réactant de n'importe quelle réaction de C et

ligne 5: que M est un produit de n'importe quelle réaction de P et

ligne 6: que M est dans le scope communautaire produit par P et

ligne 7: que M n'est pas dans le scope de C



Potential interactions rules

Competition rules

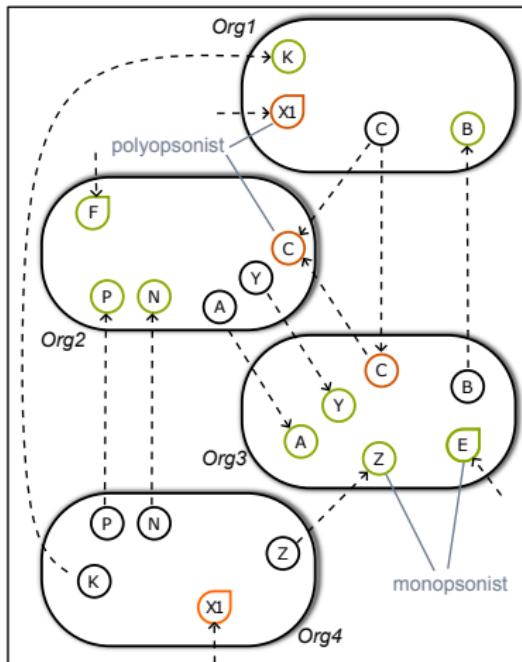
```

1 % cas pour les metabolites
2   echangeables
3 polyopsonist(M,N) :- N =# count{C,
4     M : exchange(M,_,C)},
5   exchange(M,_,_), N > 1.
6
7 % cas pour les graines
8 polyopsonist(S,N) :- N =# count{B:
9   seed_consumed_by_taxon(S,B)
10  },
11    N > 1, seed(S).

```

ligne 2-3: Un composé échangé M est limitant si lorsque le nombre de consommateurs C impliqués dans l'échange de ce métabolite M est strictement supérieur à 1.

ligne 6-7: Une graine M est considérée limitante lorsque le nombre de consommateurs C de cette graine M est strictement supérieur à 1.



Scores

Polyopsonistic, ρ and δ

Goal

Distinguish community with a difference in the number of consumers (resp. producers)

Exchangeable metabolites

$$2 - C - 2$$

$$1 - A - 1$$

$$1 - B - 1$$

$$1 - Y - 1$$

$$w(k) = 2 - 0.5^{k-1}$$

$$1.5 - C - 1.5$$

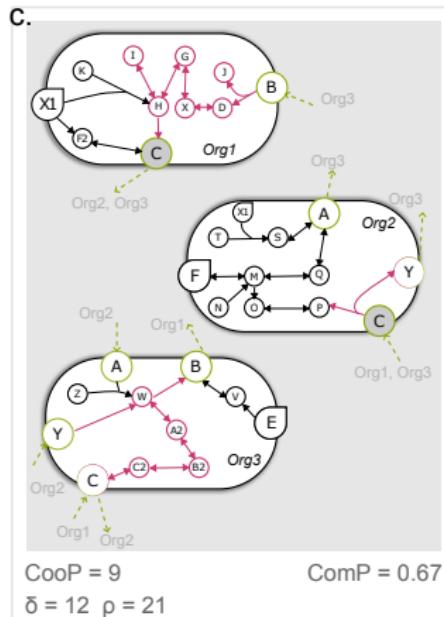
$$1 - A - 1$$

$$1 - B - 1$$

$$1 - Y - 1$$

$$\text{CooP} = \sum_{m \in M} w(|P_m|) + \sum_{m \in M} w(|C_m|)$$

$$\text{CooP} = 9$$



Scores

Polyopsonistic, ρ and δ

Polyopsonistic

Number of consumers involve in exchangeable metabolites and seed > 1

C — 2

```

1 Comp = sum(polyopsonist.values
    () / len(community.taxon)
2 Comp = 0.67

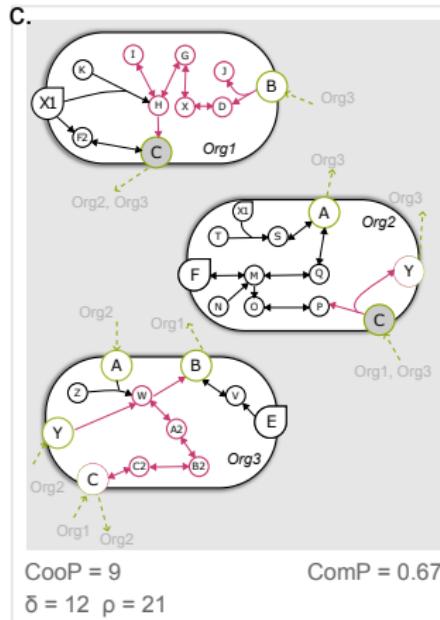
```

ρ

Identify the reactionary added-value between the reaction scope in community and individually

δ

Identify the producible compounds added-value between the metabolite scope in community and individually



(X) → Org4 Exchanged metabolite to

Org4 → (X) Exchanged metabolite from

(X) Newly produced metabolite

(X) ↔ (Z) Newly activated reaction