



Characterizing microbial interactions in controlled and natural microbial communities

Maxime Lecomte, Simon Labarthe, David James Sherman, H  l  ne Falentin,
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Maxime Lecomte, Simon Labarthe, David James Sherman, H  l  ne Falentin, Cl  mence Frioux. Characterizing microbial interactions in controlled and natural microbial communities. Workshop SimBio-Diversity, May 2022, Santiago, Chile. hal-03857848v1

HAL Id: hal-03857848

<https://hal.inrae.fr/hal-03857848v1>

Submitted on 17 Nov 2022 (v1), last revised 9 Dec 2022 (v2)

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Characterizing microbial interactions in controlled and natural microbial communities

Maxime Lecomte, Simon Labarthe, David Sherman, H  l  ne Falentin,
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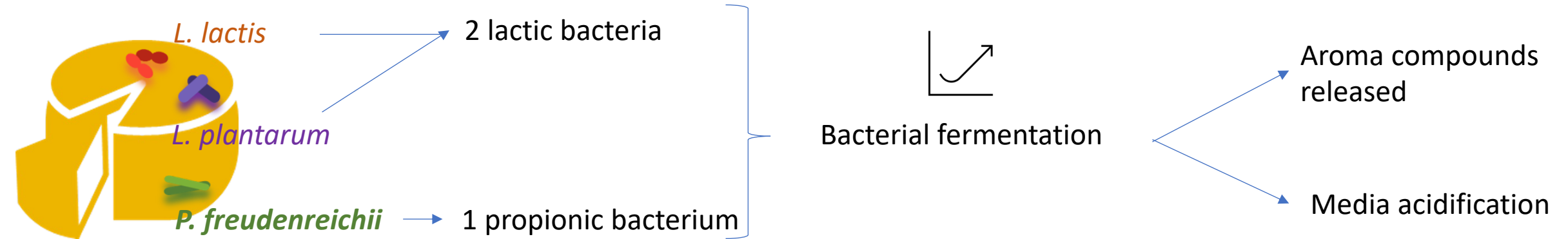
Workshop SimBioDiversity 2021-2022

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Inria

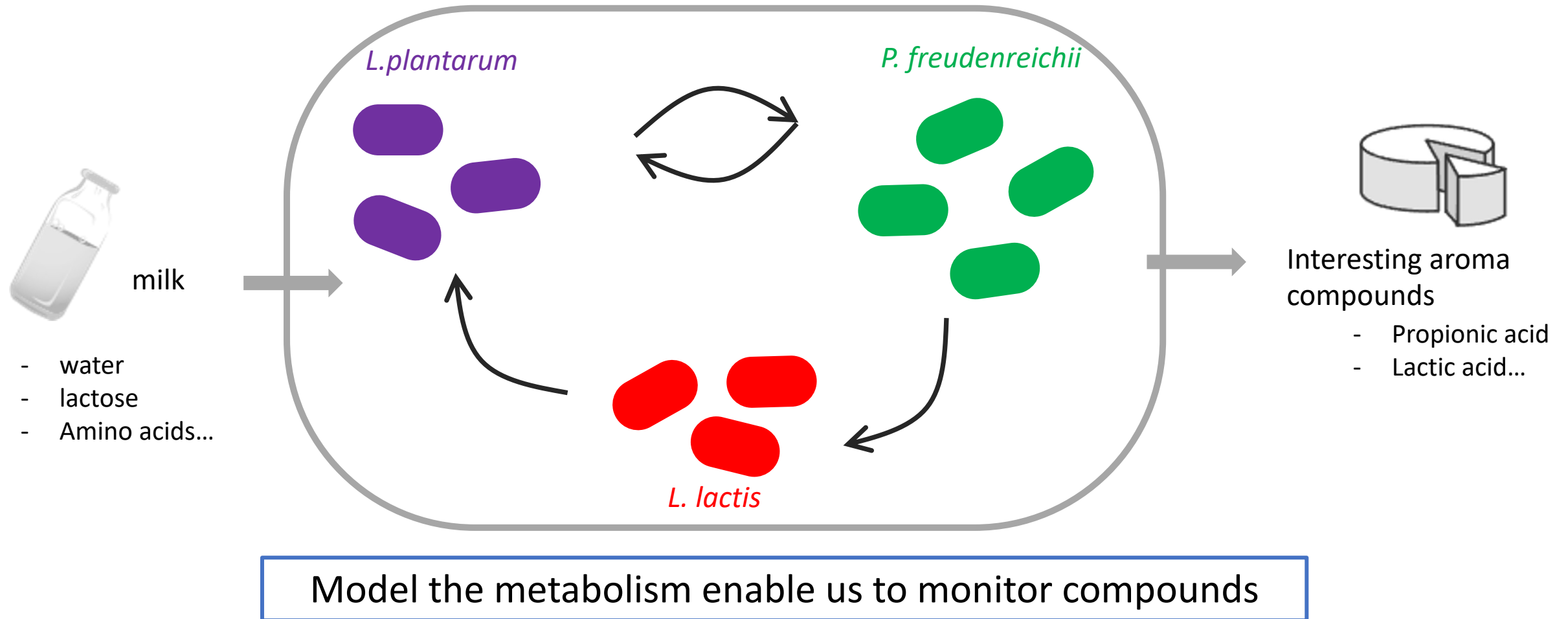
universit  
de **BORDEAUX**

Industrial cheese starter bacterial community as a controlled ecosystem



Which biological phenomena rules aroma compounds production ?

Bacterial fermentation process in cheese



Multi-omics strategy



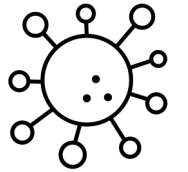
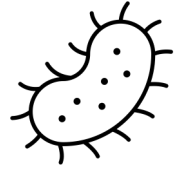
Annotated
genomes



Genes expression
(metatranscriptomics)

Acétate-HPLC-F1	Acétate-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

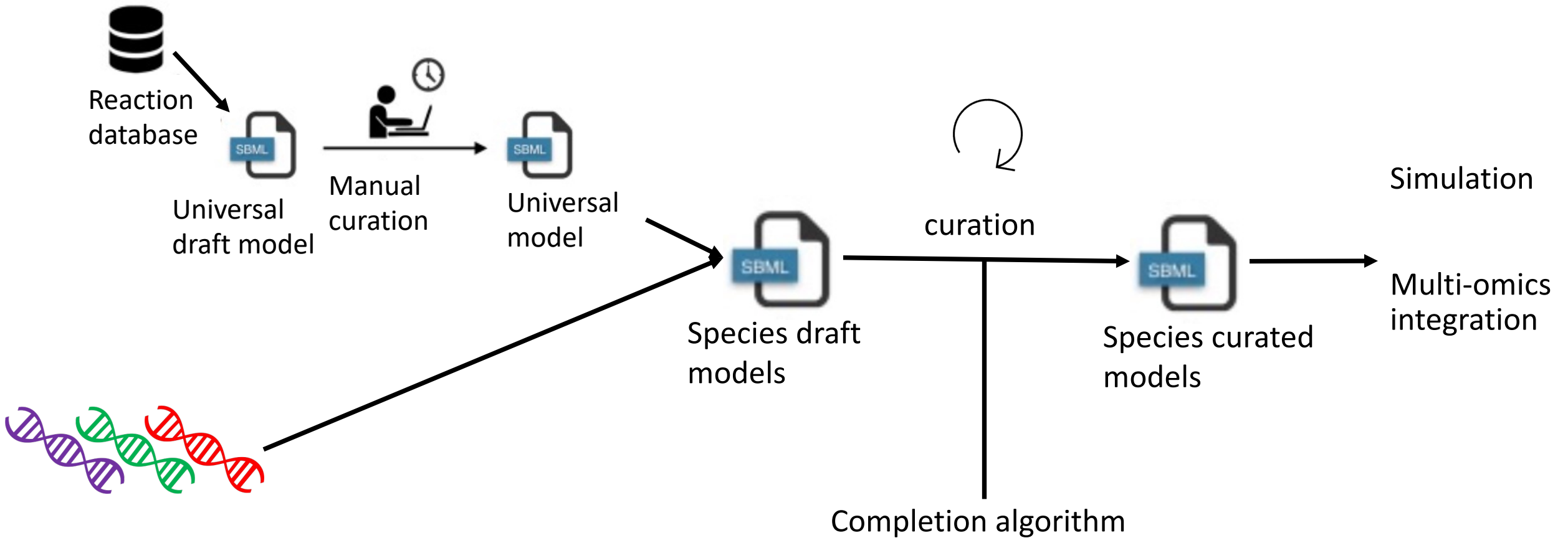
Metabolomics data



Growth and pH
data in pure
cultures

To integrate all this data, we first reconstruct the metabolism

Inference of genome-scale metabolic networks



FBA as a numerical model of metabolism

Stoichiometric matrix =

metabolites	r_1	...	r_n
A	-1	...	0
B	1	...	-2
C	0	...	1

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

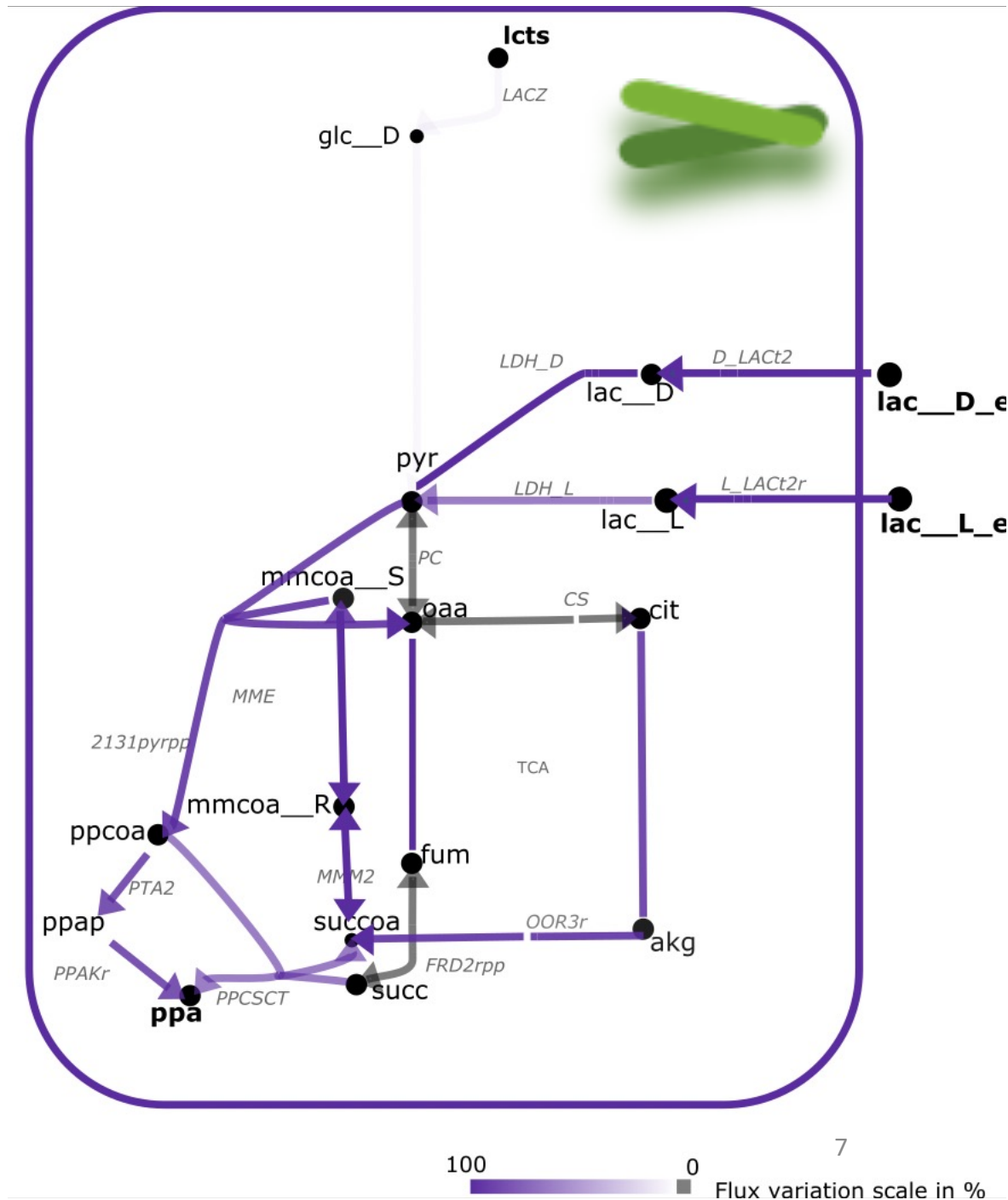
FBA as a numerical model of metabolism

Stoichiometric matrix =

metabolites	r_1	...	r_n
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$\max v_{growth}$
 such that $S.v = 0$
 and $v_{min} \leq v \leq v_{max}$

Flux distribution that maximizes biomass production



FBA as a numerical model of metabolism

Stoichiometric matrix =

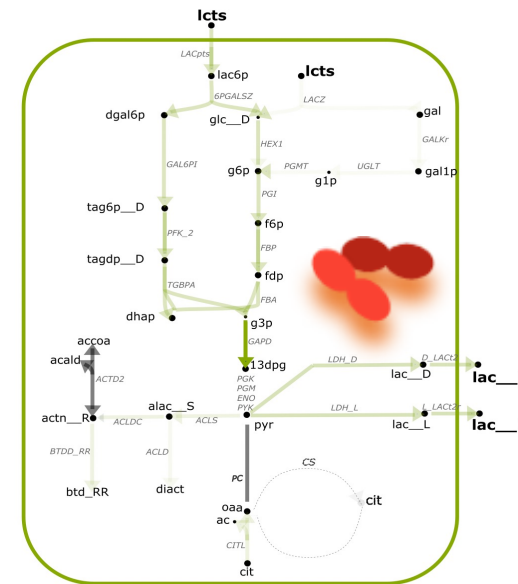
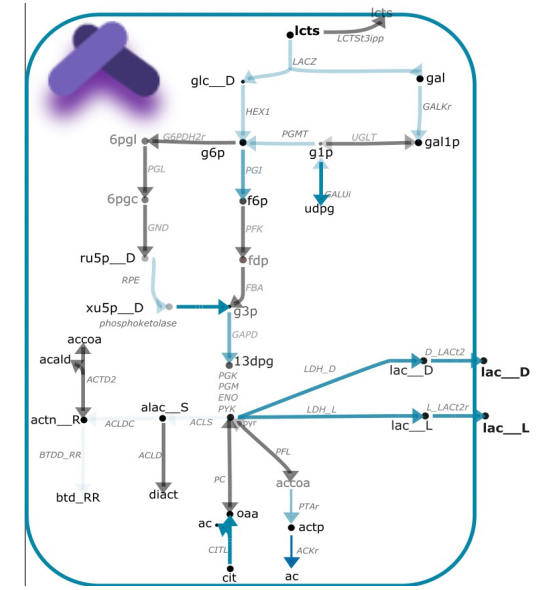
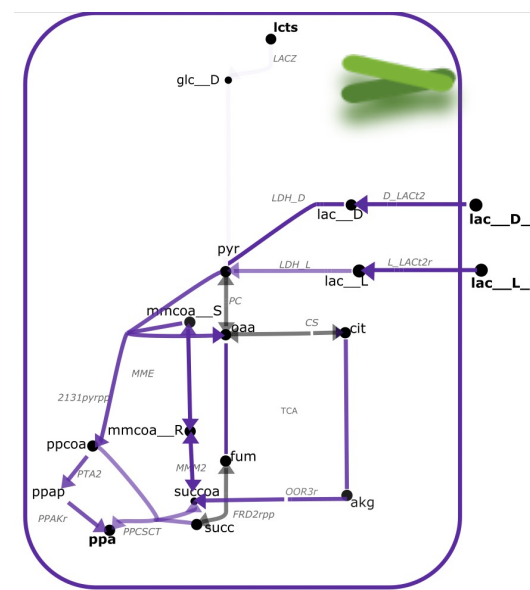
$$\begin{matrix} \text{metabolites} & r_1 & \dots & r_n \\ A & -1 & \dots & 0 \\ B & 1 & \dots & -2 \\ C & 0 & \dots & 1 \end{matrix}$$

$$\max v_{growth}$$

$$\text{such that } S.v = 0$$

$$\text{and } v_{min} \leq v \leq v_{max}$$

Flux distribution that maximizes biomass production



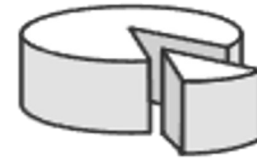
Individual models are in accordance with literature

Cheese production: a dynamic and complex biological process

Liquid environment



solid environment



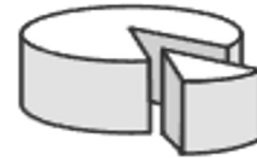
The consistency of the environment changes

Cheese production: a dynamic and complex biological process

Liquid environment

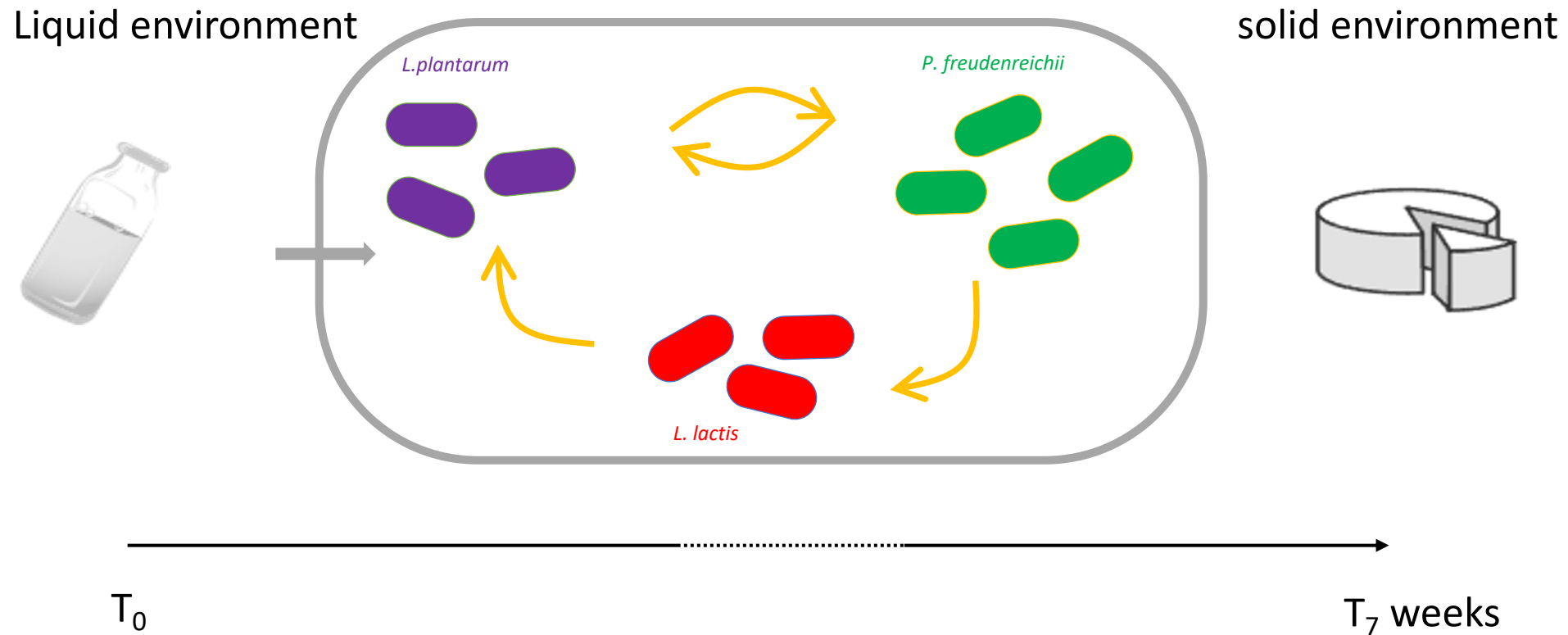


solid environment



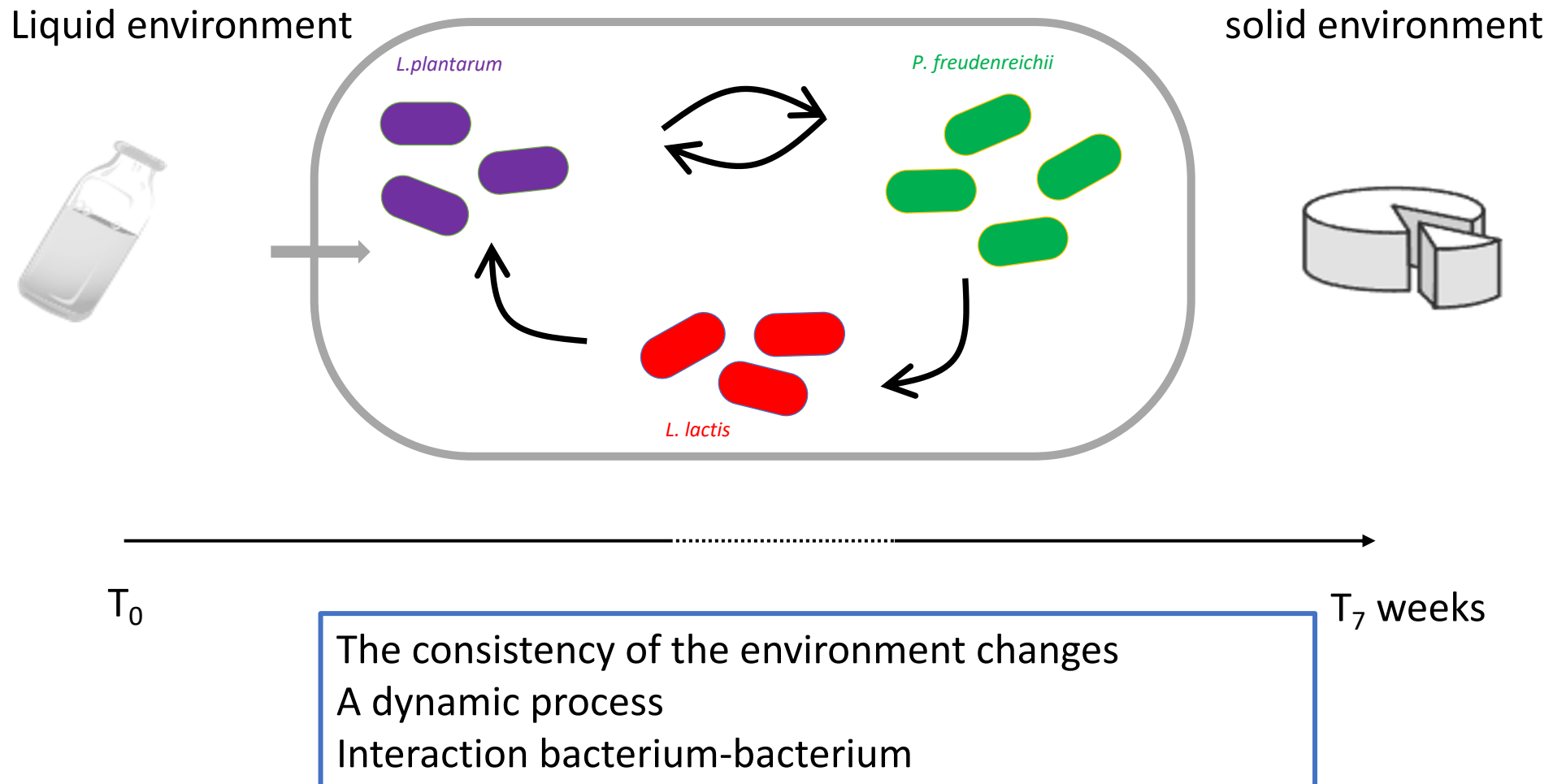
The consistency of the environment changes
A **dynamic** process

Cheese production: a dynamic and complex biological process



The consistency of the environment changes
A dynamic process
Interaction bacterium-bacterium

Cheese production: a dynamic and complex biological process



Dynamic modeling of metabolism (dFBA)

List of pre-defined interest compounds :

$$\partial_t m_j = \mu_{FBA_i}(c)_j b_i$$

Dynamic modeling of metabolism (dFBA)

List of pre-defined interest compounds :

$$\partial_t m_j = \mu_{FBA_i}(c)_j b_i$$

Bacterial concentration :

$$\partial_t b_i = q_s(b_i) \mu_{FBA_i}(c)_i b_i$$

Dynamic modeling of metabolism (dFBA)

List of pre-defined interest compounds :

$$\partial_t m_j = \mu_{FBA_i}(c)_j b_i$$

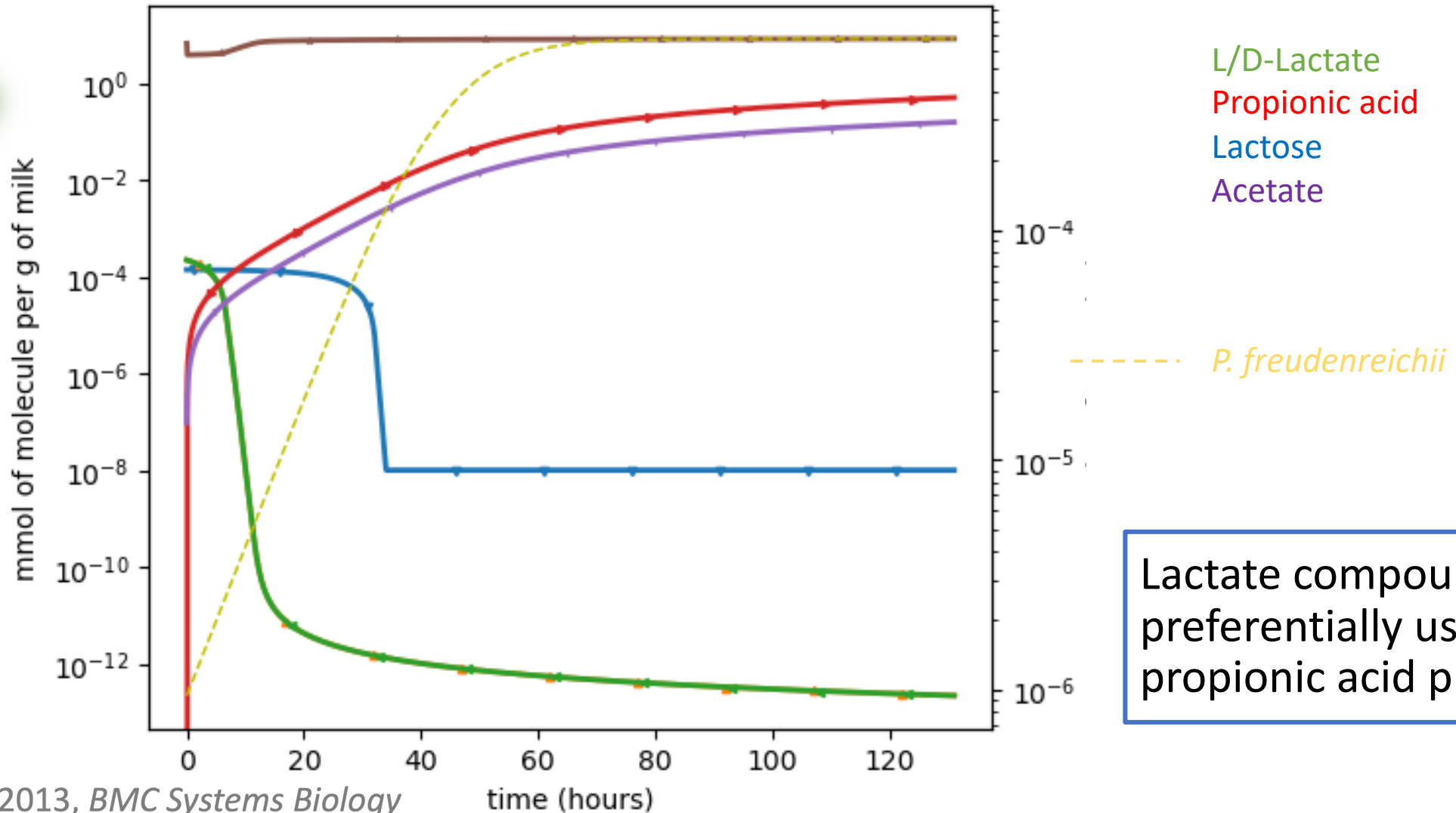
Bacterial concentration :

$$\partial_t b_i = q_s(b_i) \mu_{FBA_i}(c)_i b_i$$

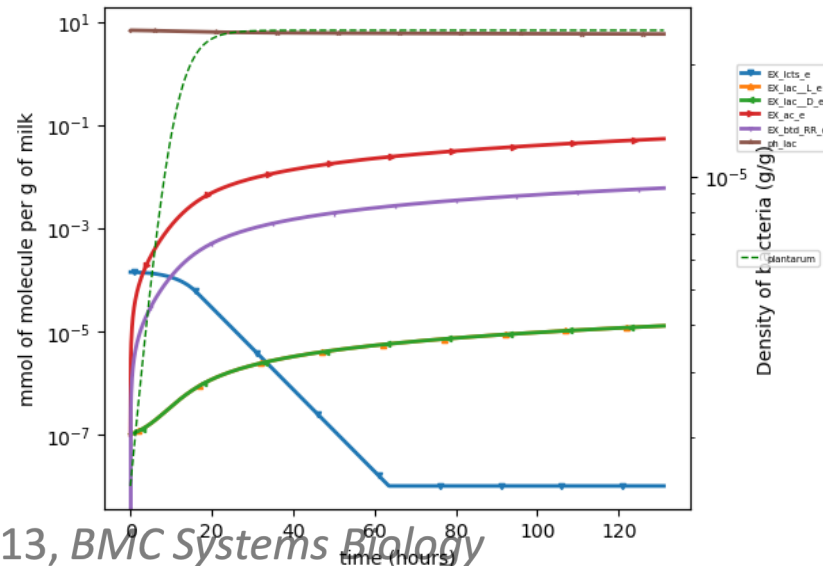
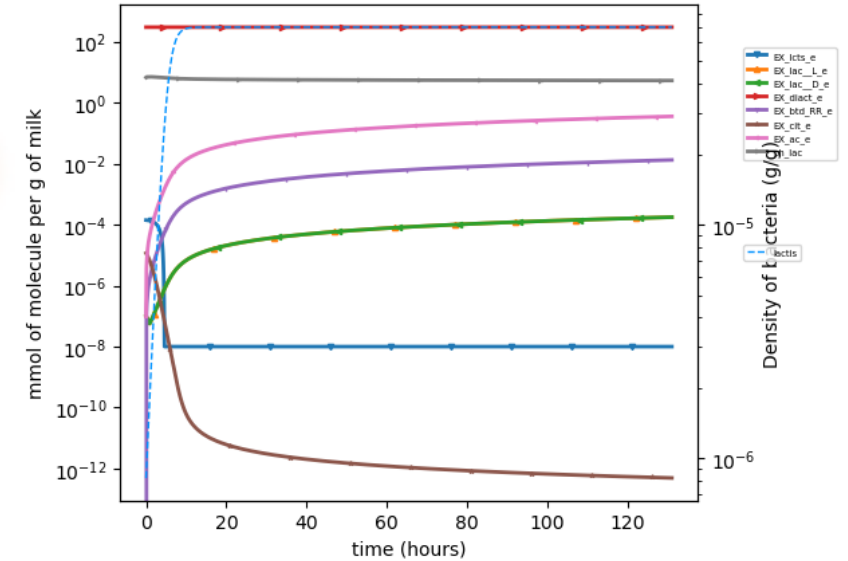
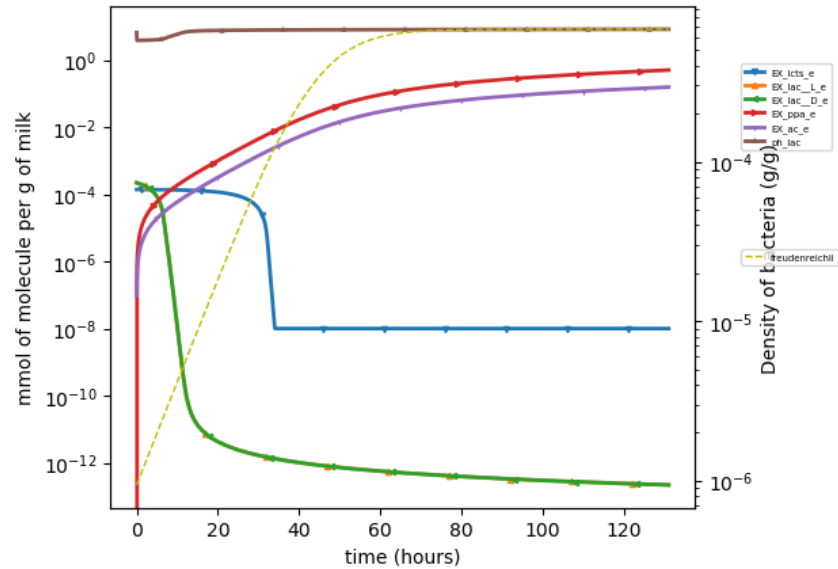
q_s = Quorum sensing

$$q_s(b_i) = 1 - \frac{b_i}{\beta_i}$$

dFBA results of pure cultures



dFBA results of pure cultures



Individual dFBA simulations are performed

Fit with experimental data ? → growth and pH curves and metabolomics data

Optimizing dynamic models on pure cultures

$$J(b, pH | b_{exp}, pH_{exp}) = \|b - b_{exp}\|^2 + \alpha \|pH - pH_{exp}\|^2$$

Optimizing dynamic models on pure cultures

$$J(b, pH | b_{exp}, pH_{exp}) = \|b - b_{exp}\|^2 + \alpha \|pH - pH_{exp}\|^2$$

- Lambda



- QS



- K_{lactate}



- C1 & C2



- V_{min} & V_{max} lactose

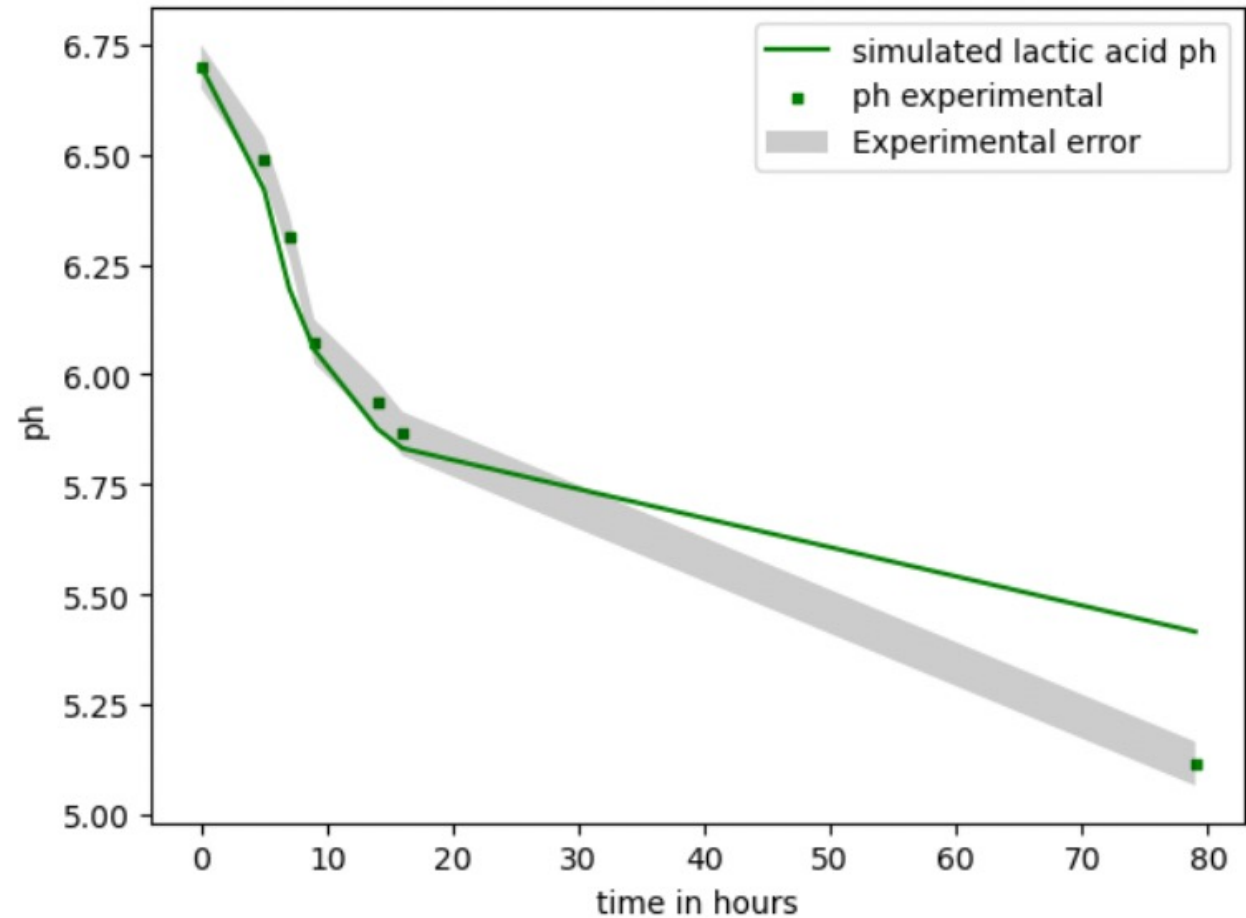
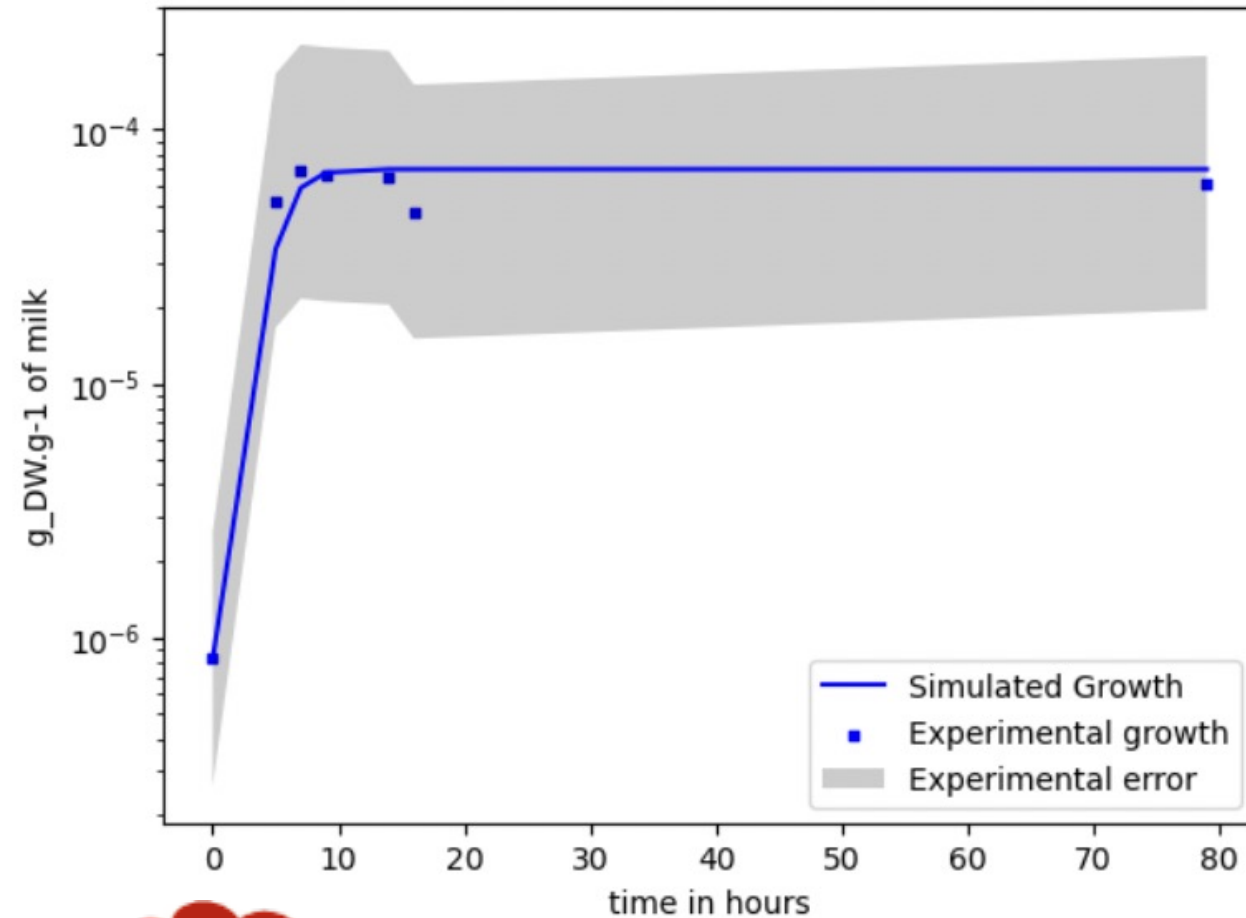


- Lactate_{upper}



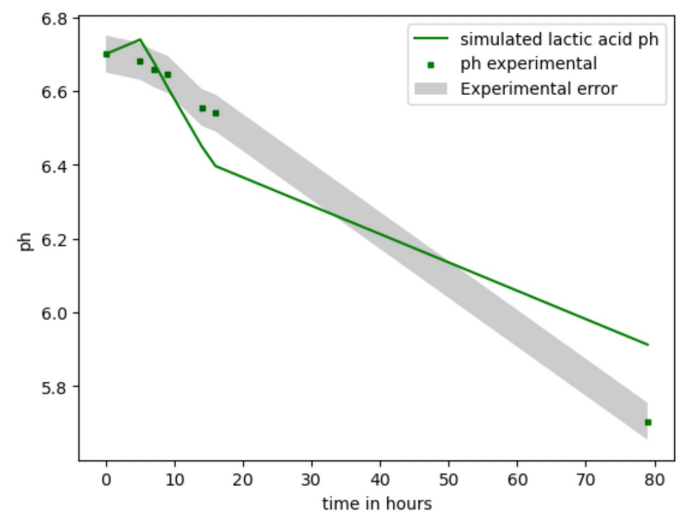
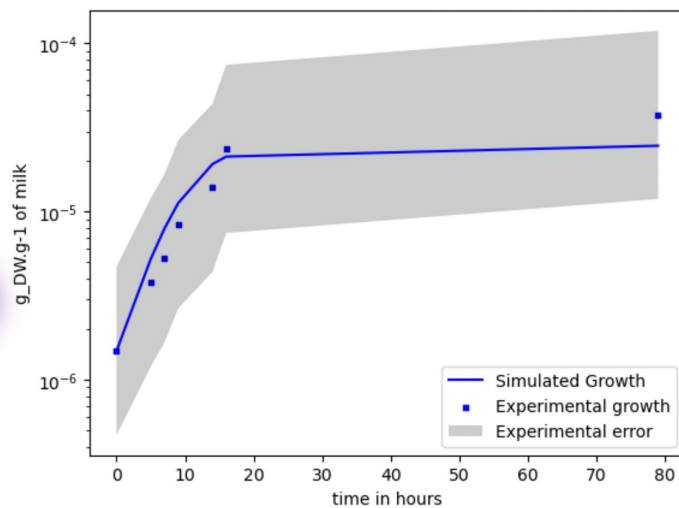
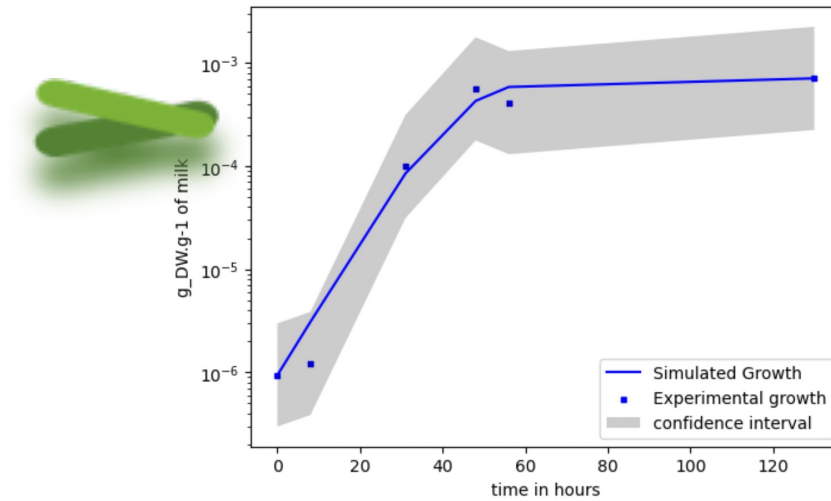
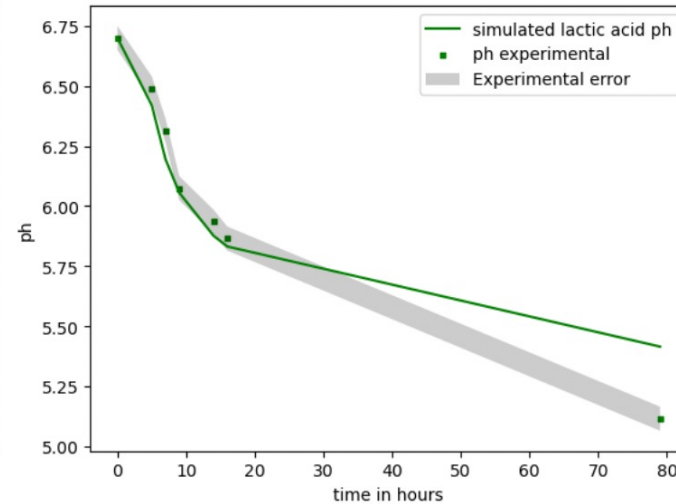
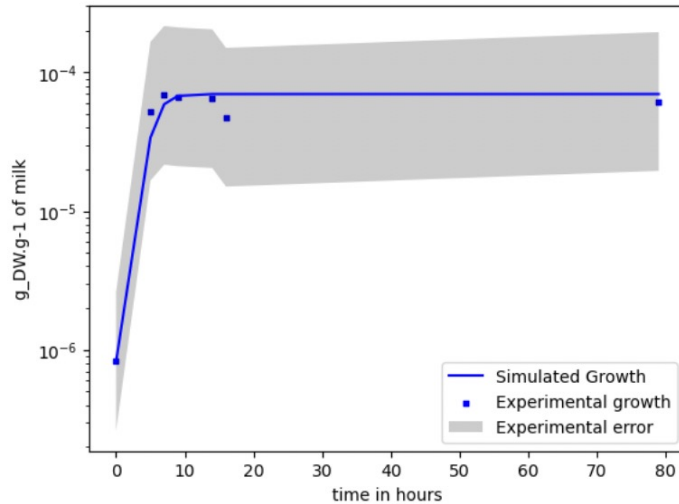
Identification of parameters to fit with experimental data

dFBA results after optimization



Virtanen. P, et al,2020, *Nature Methods*
Ebrahim et al,2013, *BMC Systems Biology*

dFBA results after optimization



The small number of parameters is sufficient to explain the experimental data

What about metabolomics ?

Community dFBA



Community dFBA model

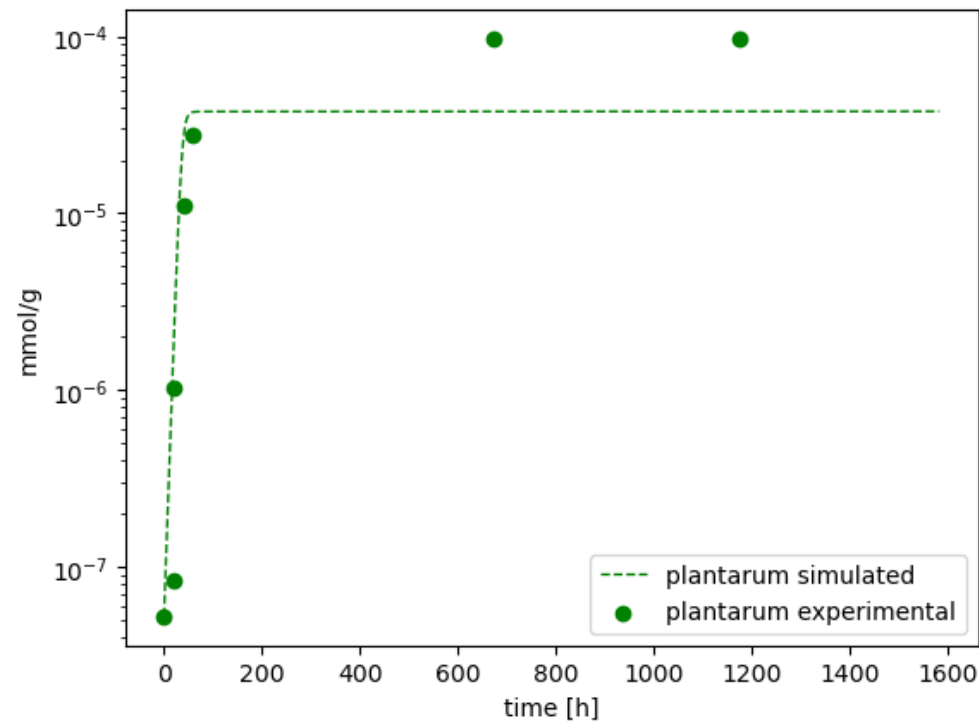
- Consider the change in medium volume
- Each bacterium optimizes its own biomass

Optimised dFBA models for each bacterium

$$\partial_t b_i = q_s(b_i) \mu_{FBA_i}(c)_i b_i + \mathcal{V}(t) b_i$$

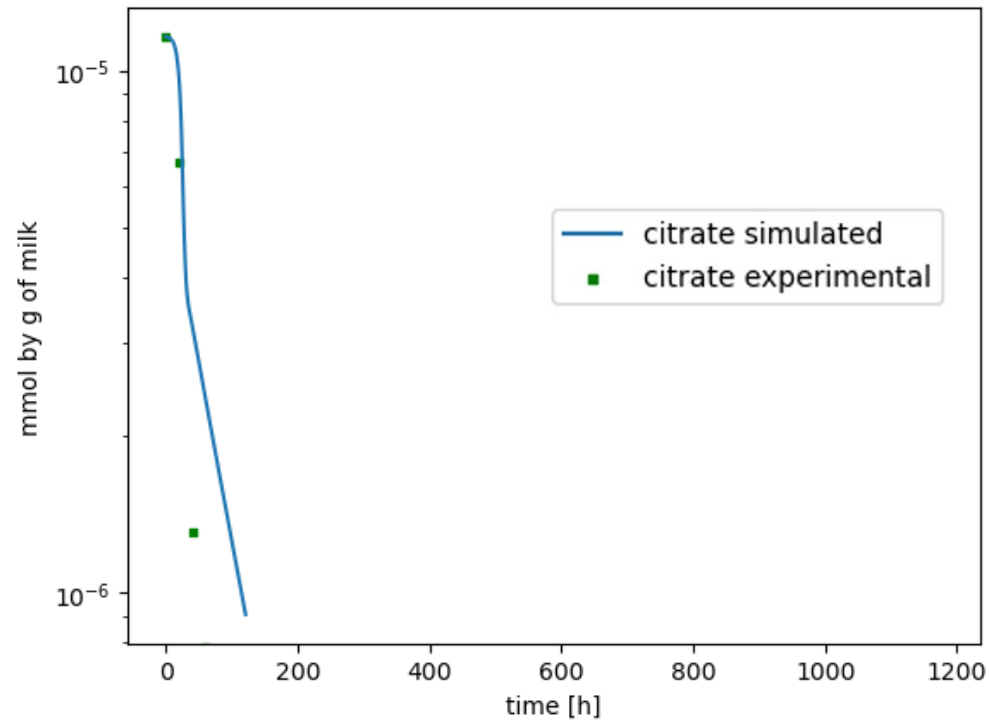
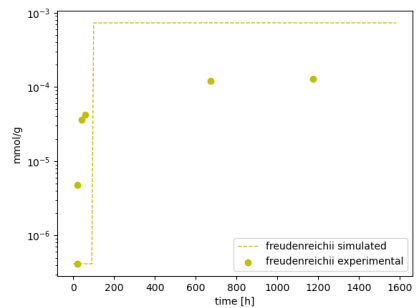
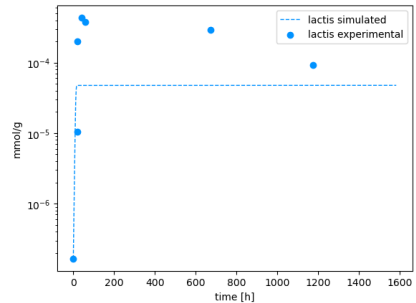
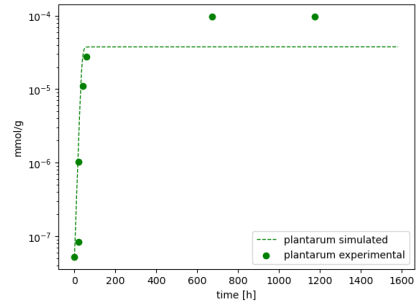
$$\mathcal{V}(t) = \frac{\partial_t v(t)}{V(t)} \quad \text{where } v(t) = \begin{cases} V_M & \text{if } t \leq t_M \\ V_M + \frac{t-t_M}{t_D-t_M} V_D & \text{if } t_M \leq t \leq t_D \\ V_D & \text{if } t \geq t_D \end{cases}$$

Community dFBA results



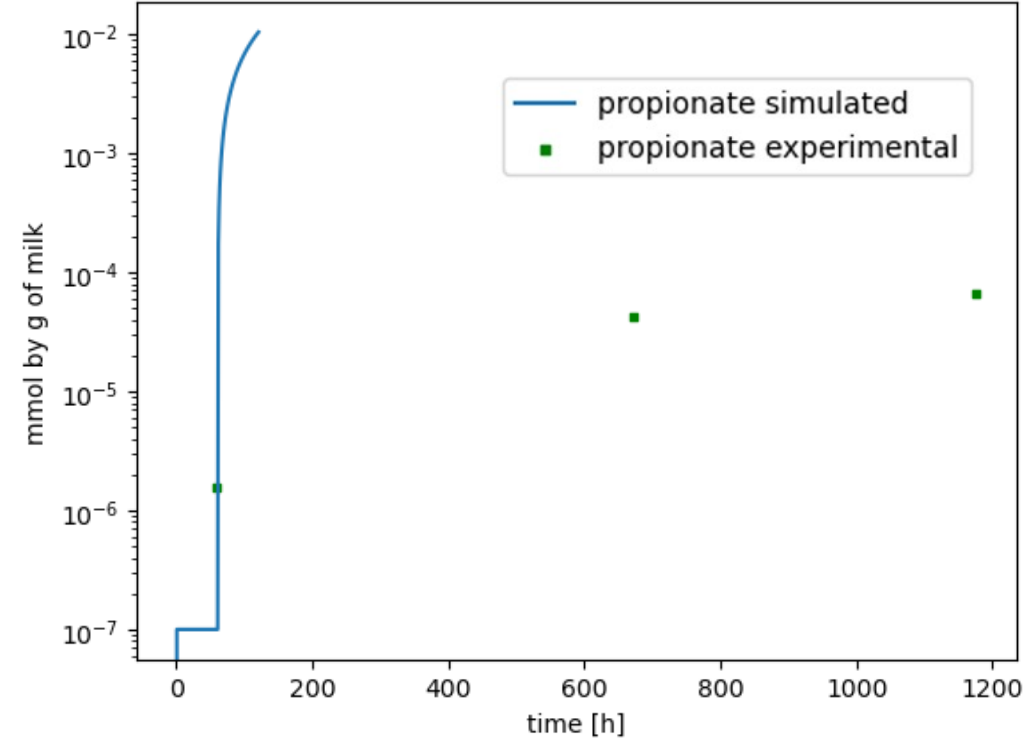
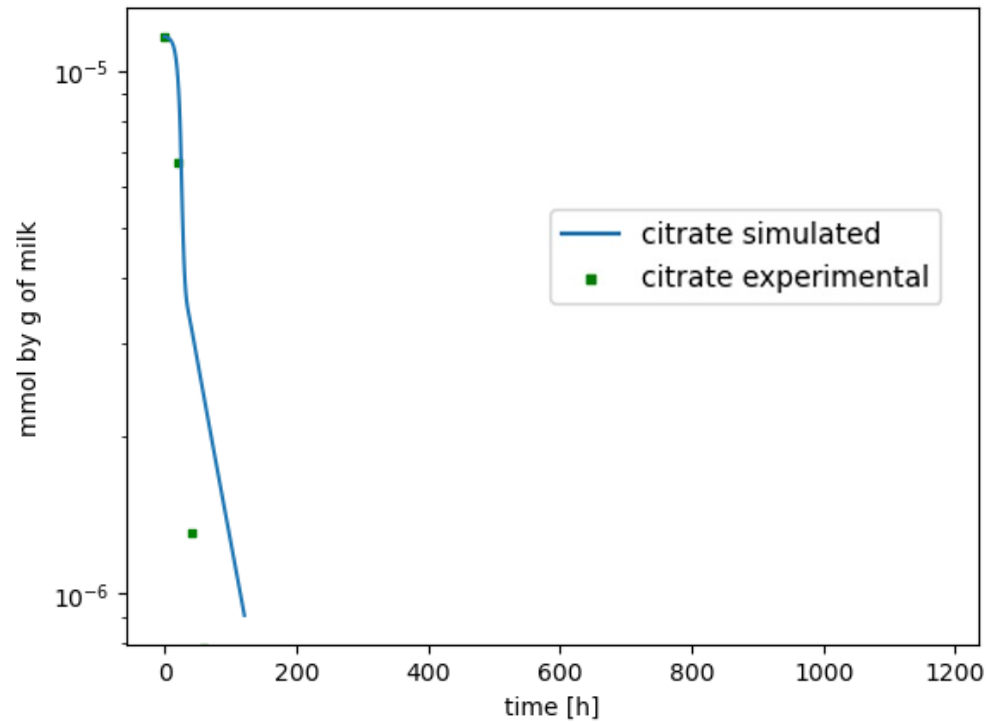
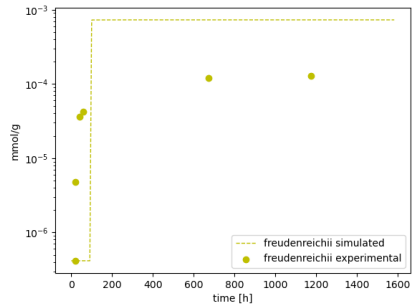
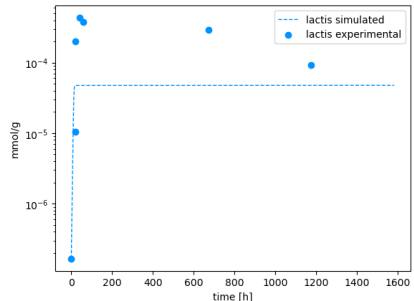
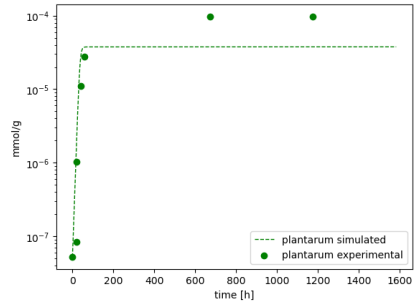
Bacterial growth computed with community dFBA fits with experimental data

Community dFBA results



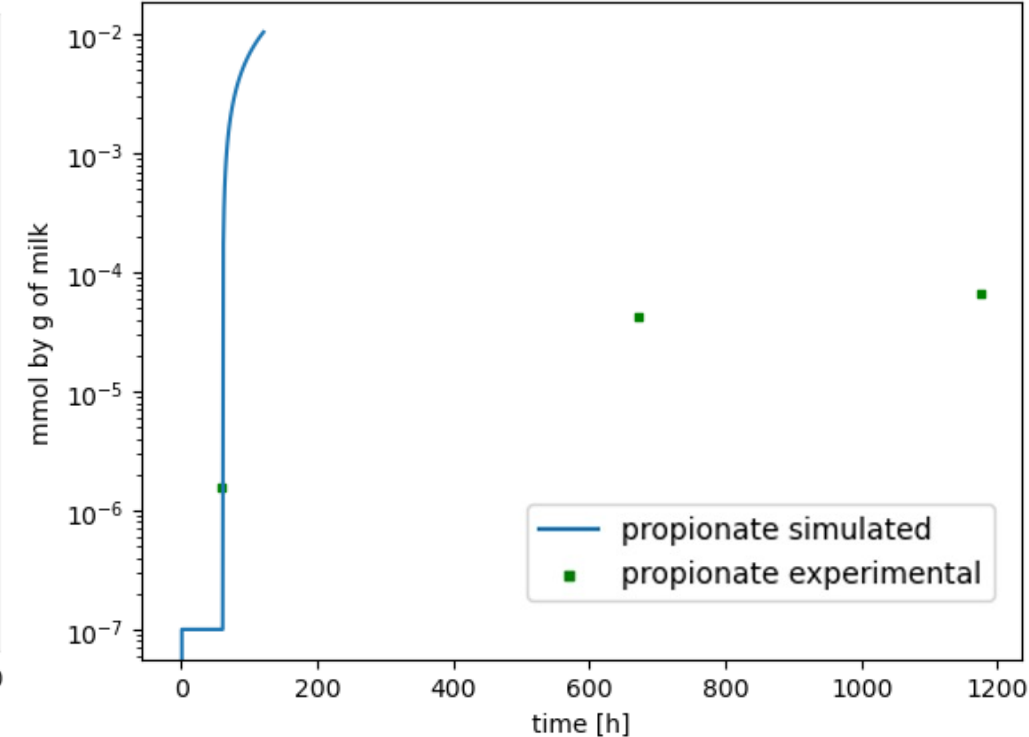
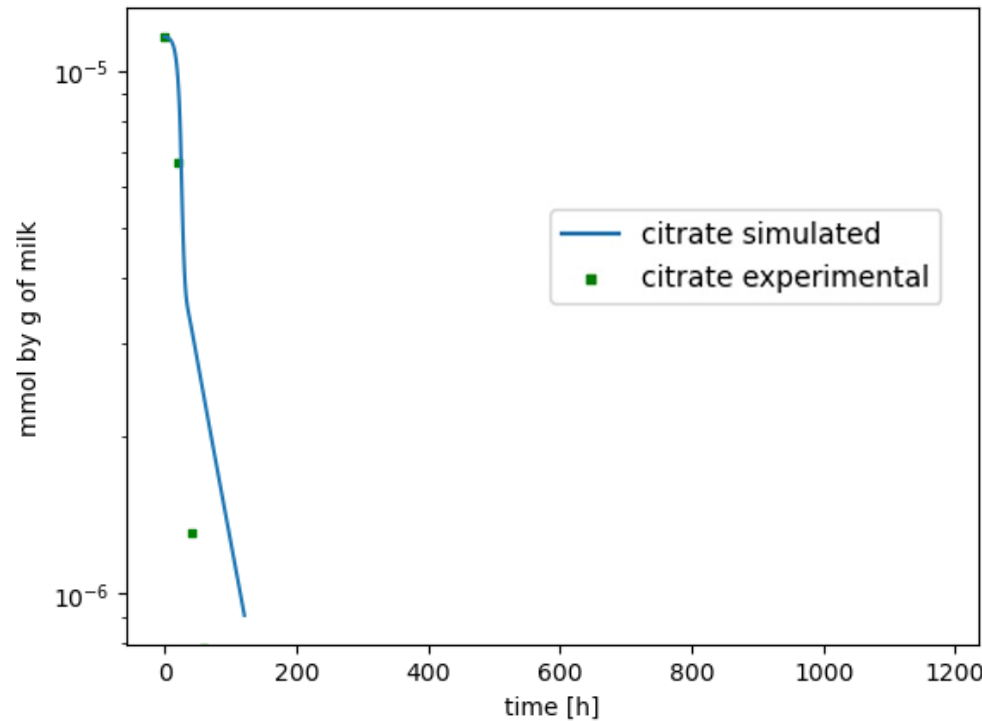
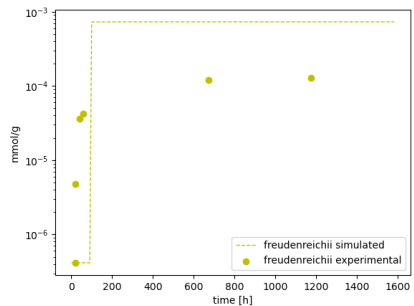
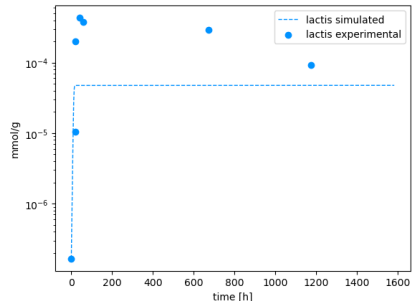
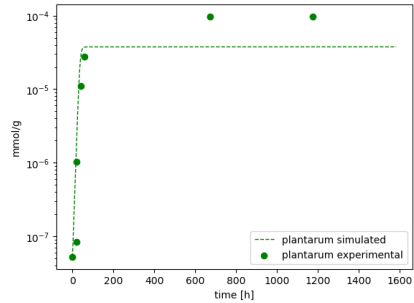
Some metabolites fit with metabolomics data ...

Community dFBA results



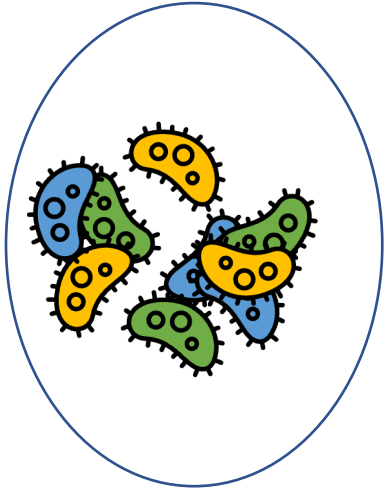
Not all of them

Community dFBA results

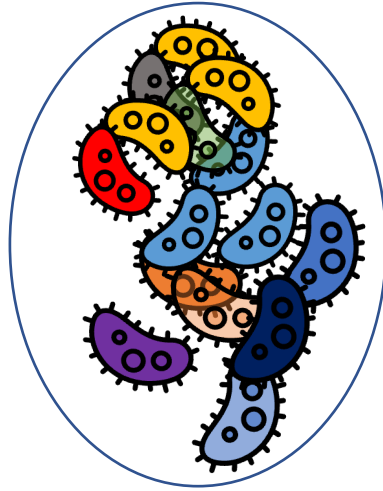


- The model do not capture all modifications brings by the community
- Integration of transcriptomic data is not significantly different
- Is qualitative result enough for characterizing communities ?

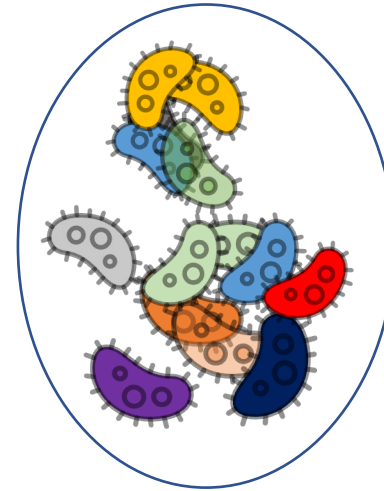
Characterizing natural communities (meta)genomics data



Community 1



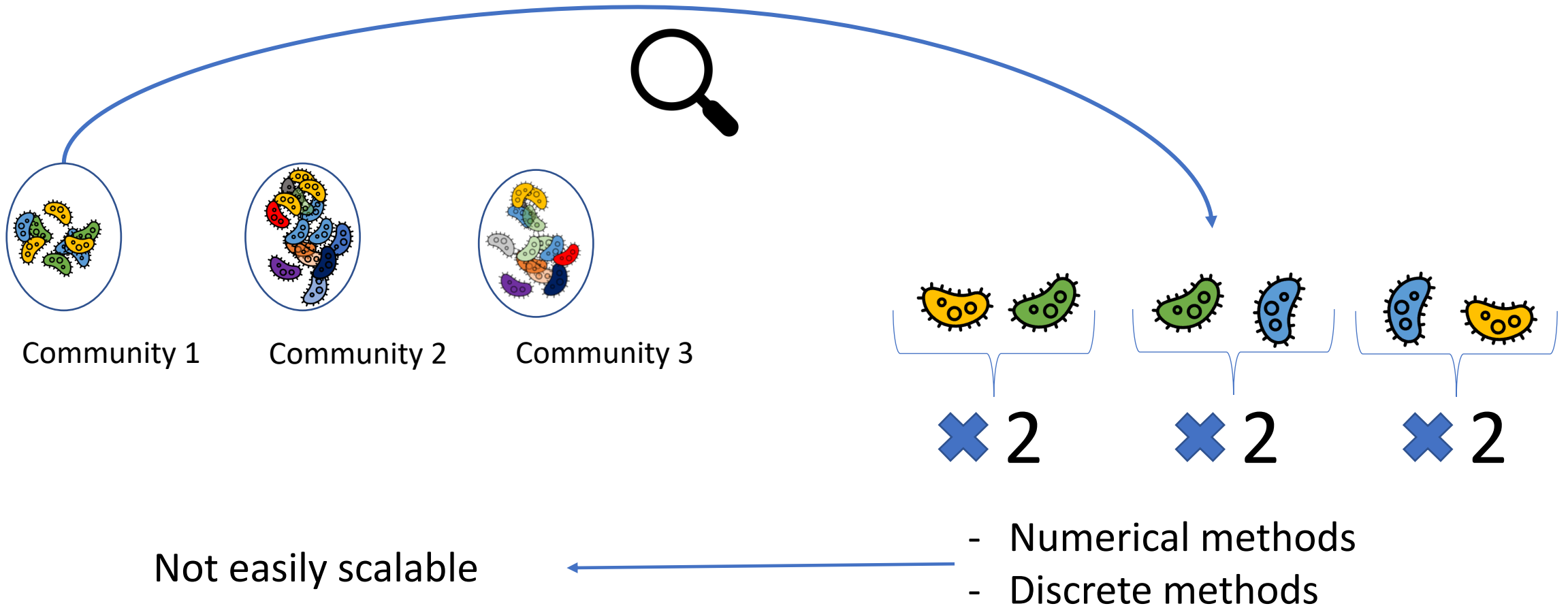
Community 2



Community 3

Calculating cooperation and competition potentials

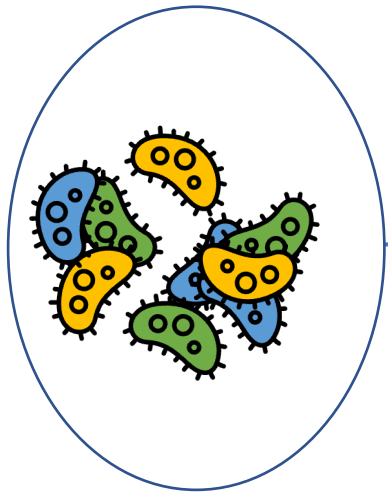
Characterizing natural communities with (meta)genomics data



Freilich. S, et al,2011, *Nature Communications*
Zelezniak, A et al,2015,*Proceedings of the National Academy of Sciences of the United States of America*.

Levy et al, 2015.,*BMC Bioinformatics*.
Kreimer, A et al, 2012 *Bioinformatics*.

Discrete modelling of metabolism using metabolic potentials (work in progress)



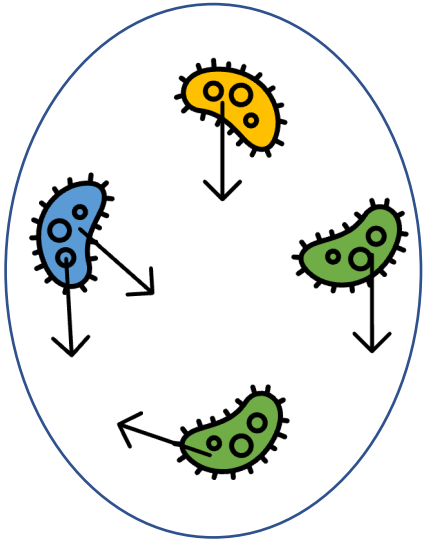
Descriptive

vocabular
using ASP

```
%%%%%%%% putative exchanged metabolites :  
cooperation metric
```

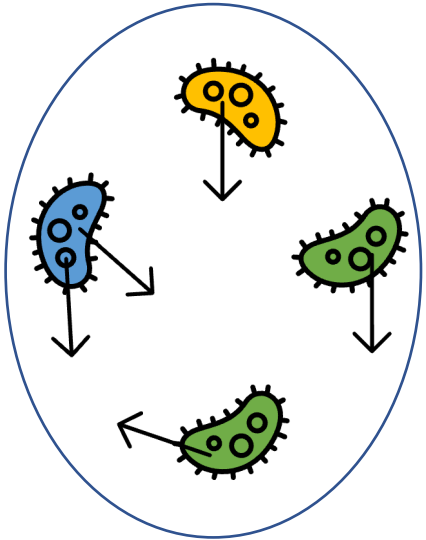
```
escope(M,T,S) :- pscope(M,S),  
reactant(M,_,T), not product(M,_,T), S!=T.
```

Cooperation and competition metrics

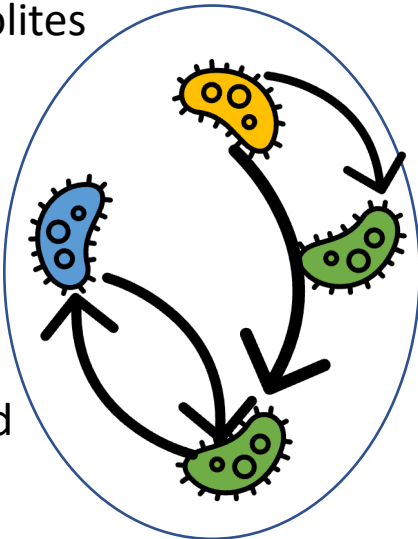


Number of metabolites
produced

Cooperation and competition metrics

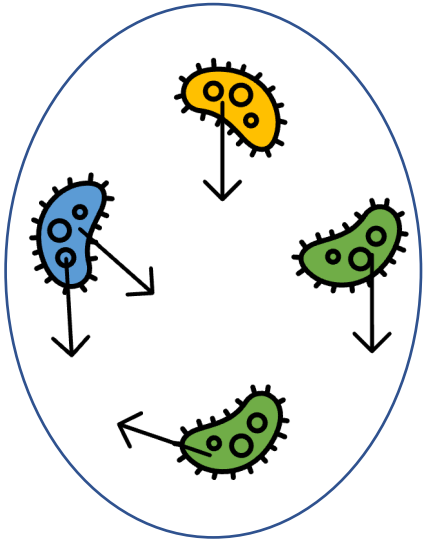


Number of metabolites
produced

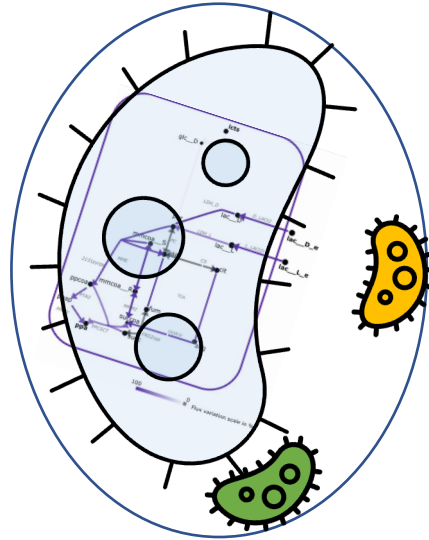


Number of exchanged
metabolites

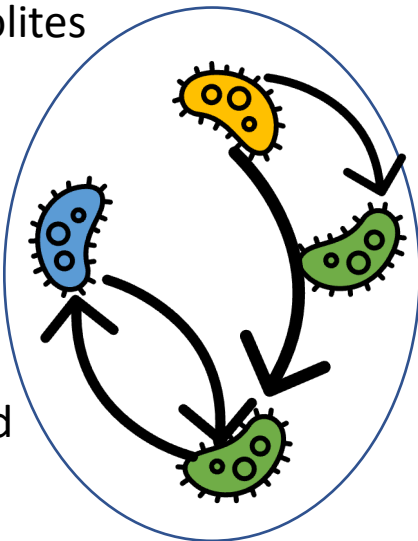
Cooperation and competition metrics



Number of metabolites produced

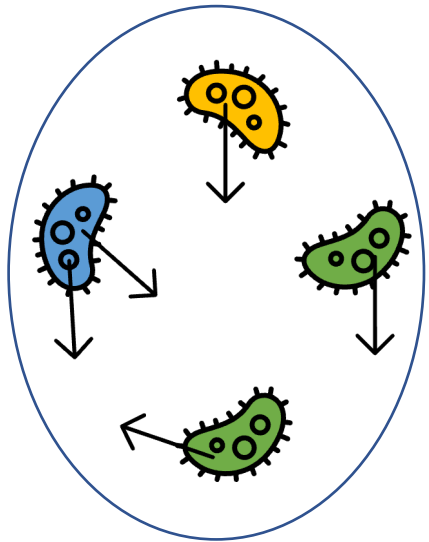


Number of activated reactions

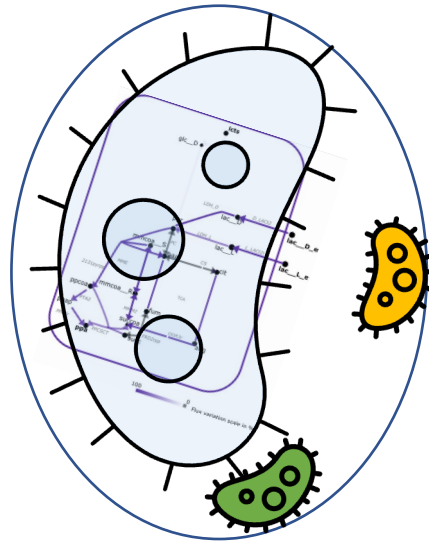


Number of exchanged metabolites

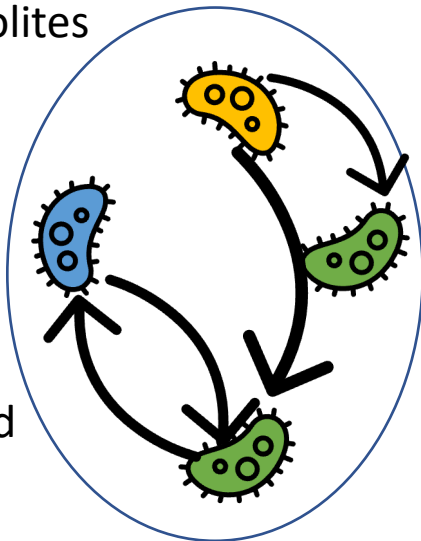
Cooperation and competition metrics



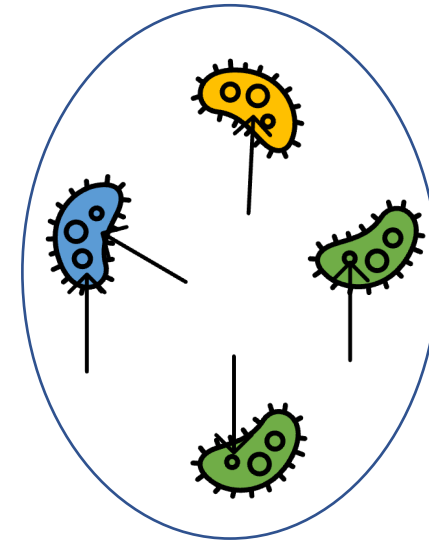
Number of metabolites produced



Number of activated reactions

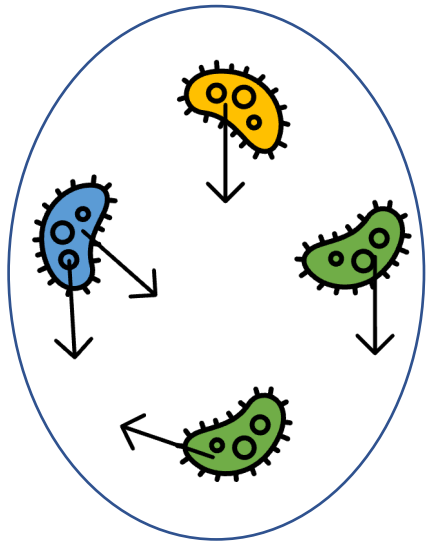


Number of exchanged metabolites

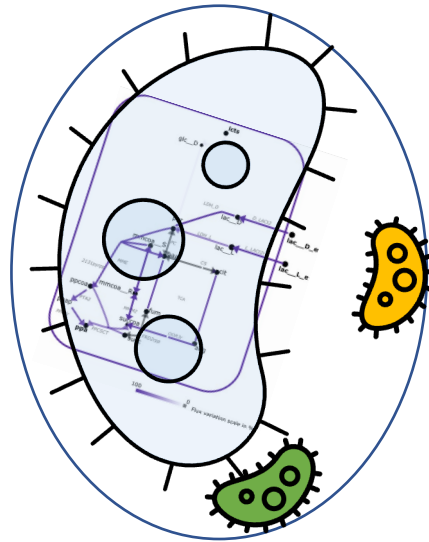


Related to limiting substrates consumed

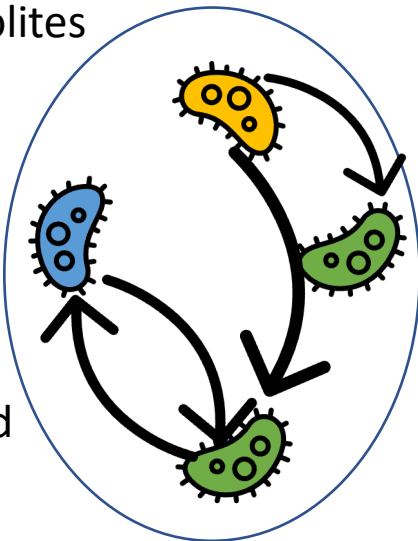
Cooperation and competition metrics



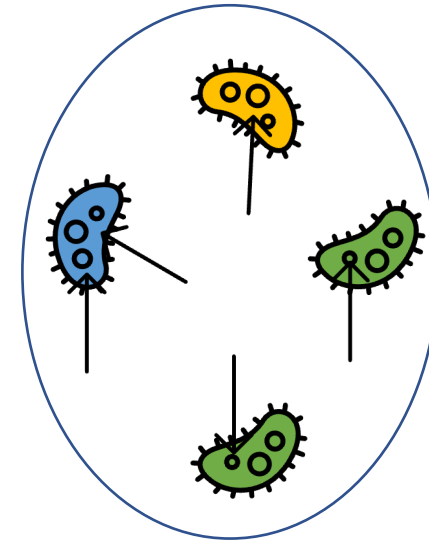
Number of metabolites produced



Number of activated reactions



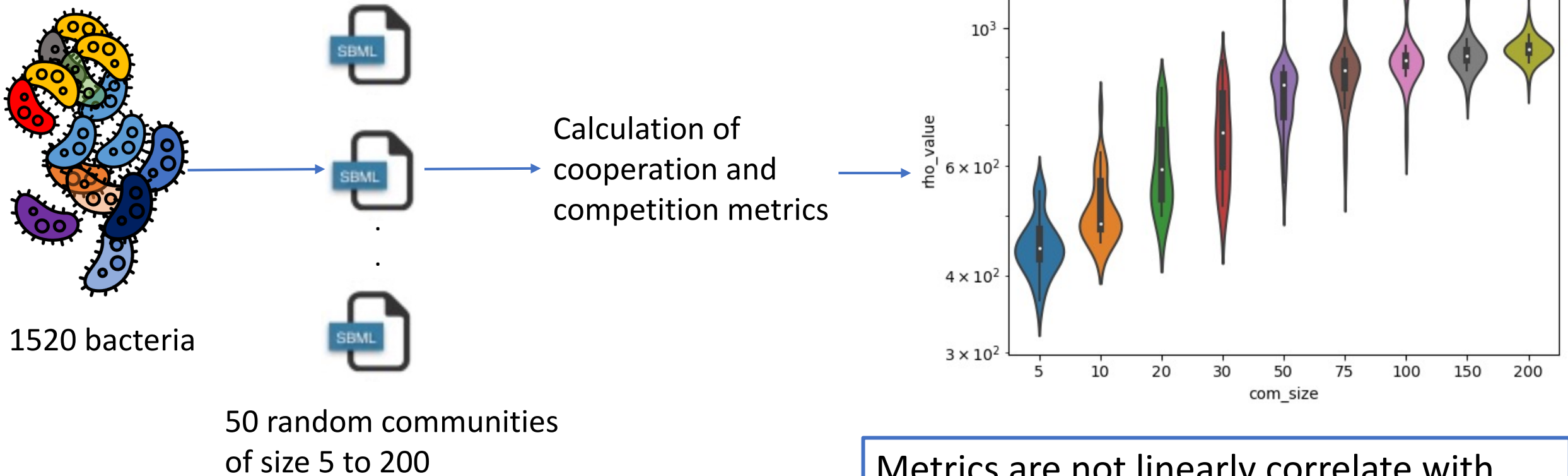
Number of exchanged metabolites



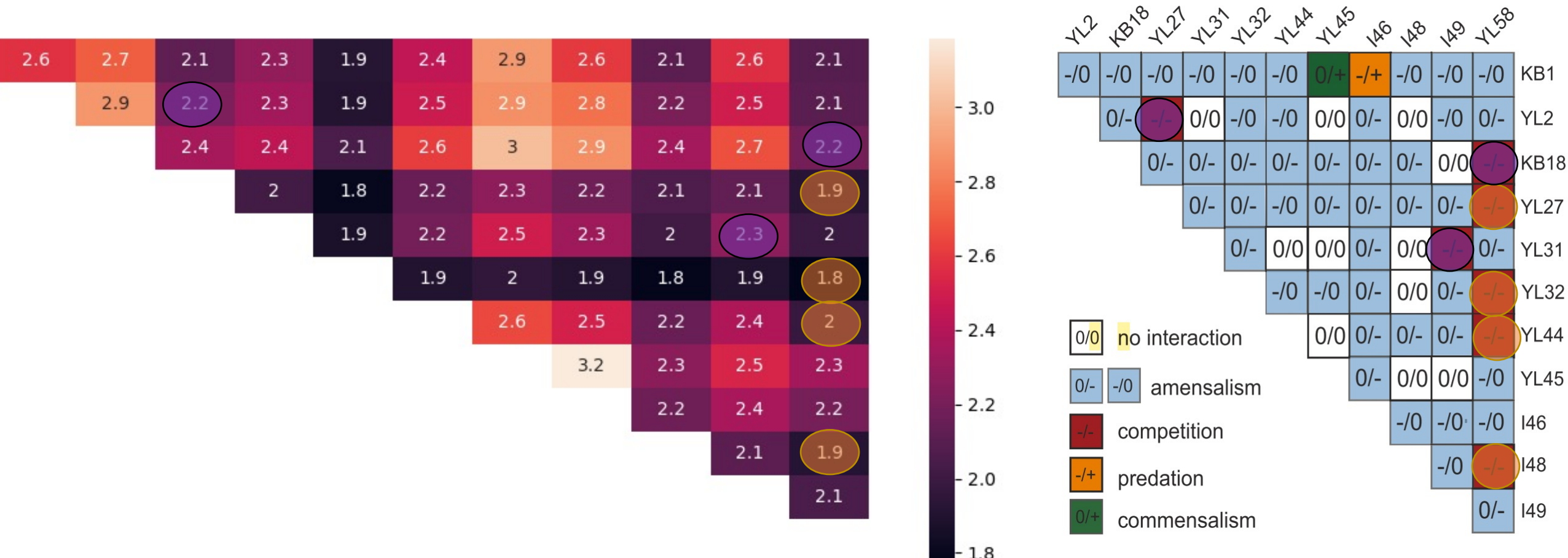
Related to limiting substrates consumed

Unify cooperation metrics
to one unique score

Model test on designed communities



Competition score test on real data



Identify some correlation between our score and the experimental data

Conclusion

- Numerical accuracy not mandatory to characterize community

- Our method based on discrete modeling seems to characterize natural community → improve cooperation and competition scores
- Test on different communities → Hiring data (genomic data)



INRAE



- David Sherman
- Clémence Frioux
- Simon labarthe

- Hélène Falentin

Thanks for your attention

Dynamic modeling of metabolism (dFBA)

List of pre-defined interest compounds :

$$\partial_t m_j = \mu_{FBA_i}(c)_j b_i$$

$$c_k = \begin{cases} \lambda_i \max(-m_k / (\Delta_t \sum_{i \in \mathcal{B}} b_i), c_k) & \text{if } 1 \neq k \neq N_m \\ = e_k & \text{if } N_m + 1 \leq k \leq N_c \end{cases}$$

Summary of the interactions in the cheese ecosystem

