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## Characterizing microbial interactions in controlled and natural microbial communities

Maxime Lecomte, Simon Labarthe, David James Sherman, H el ene Falentin,  
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# Characterizing microbial interactions in controlled and natural microbial communities

Maxime Lecomte, Simon Labarthe, David Sherman, H el ene Falentin,  
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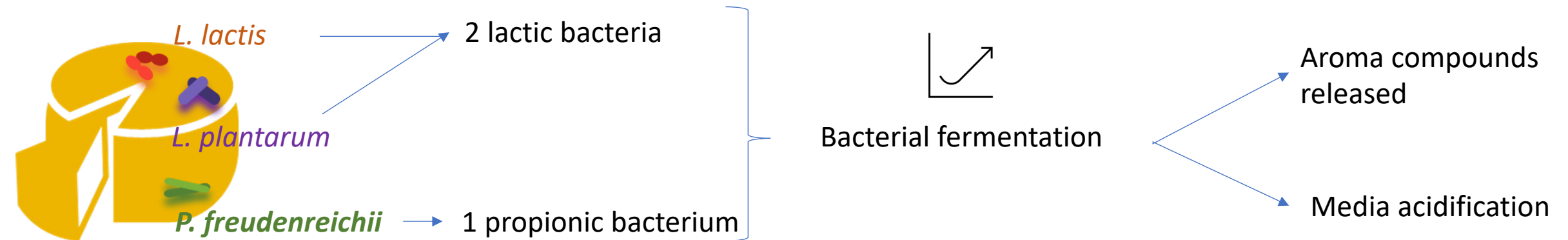
Workshop SymbioDiversity 2021-2022

**INRAE**

*Inria*

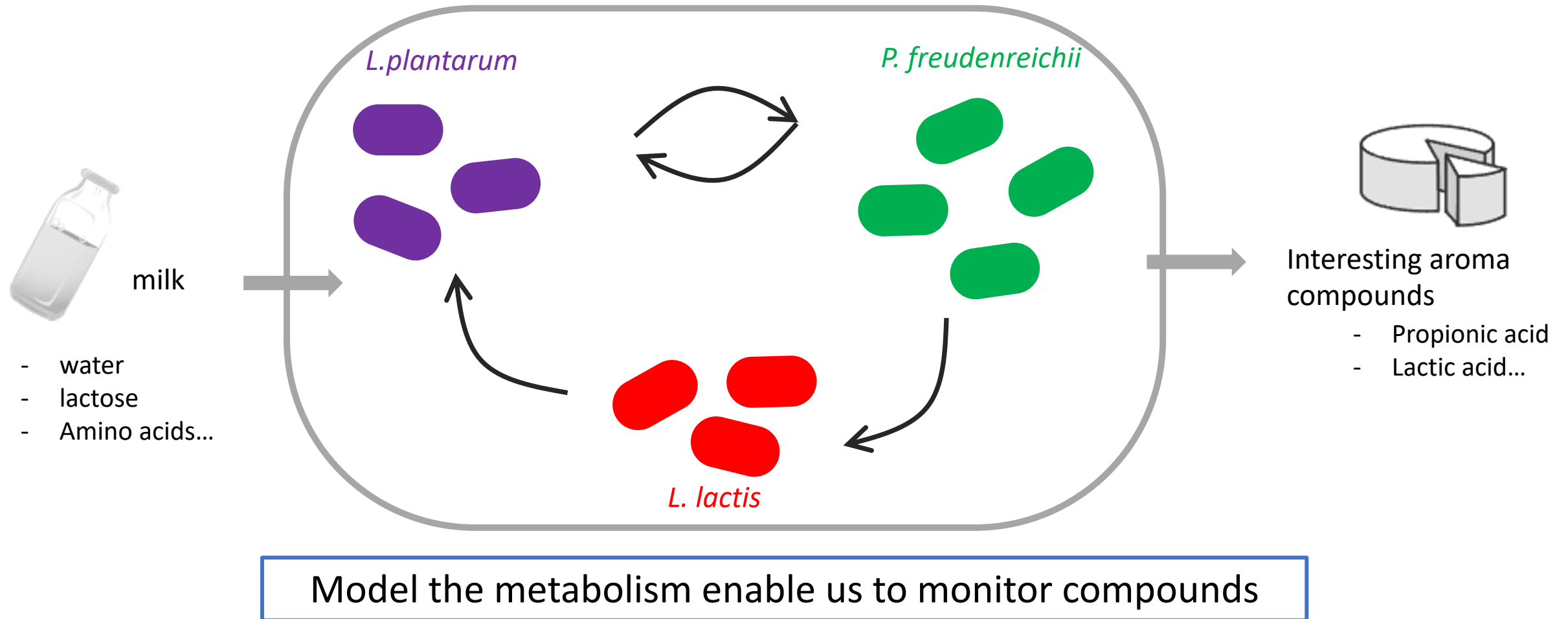
universit e  
de **BORDEAUX**

# Industrial cheese starter bacterial community as a controlled ecosystem



Which biological phenomena rules aroma compounds production ?

# Bacterial fermentation process in cheese



# Multi-omics strategy



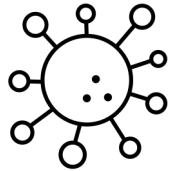
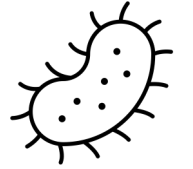
Annotated genomes



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

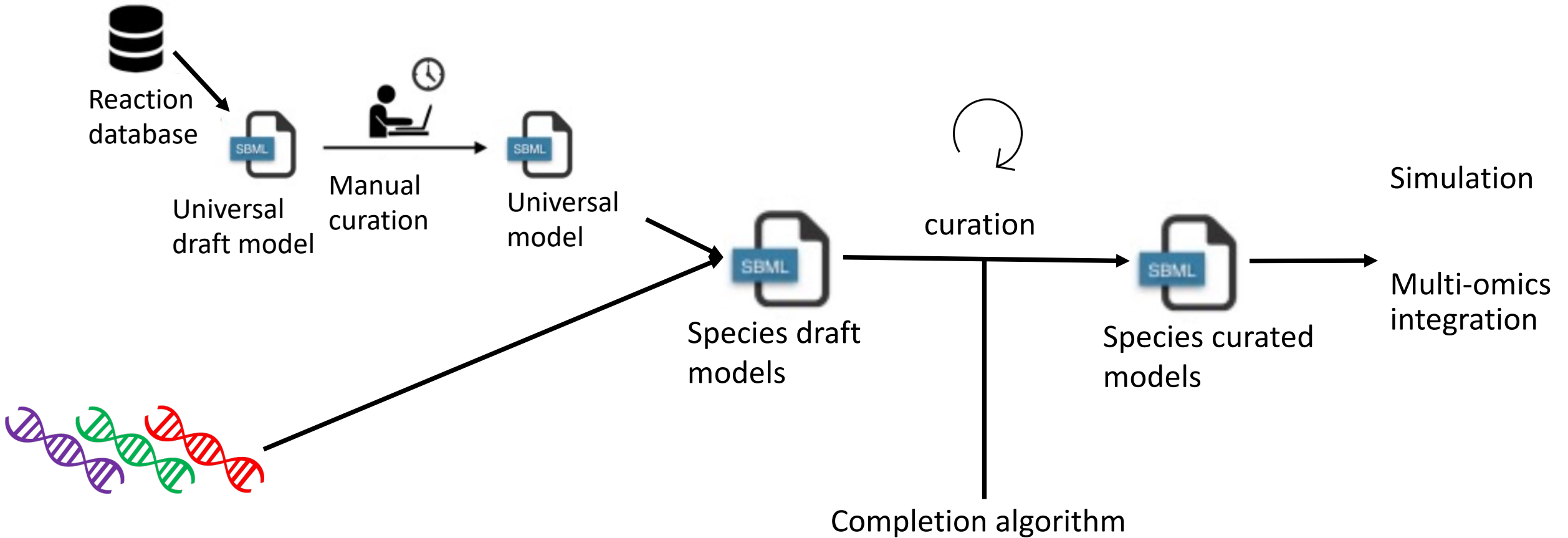
Metabolomics data



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

$$\max v_{growth}$$

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

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

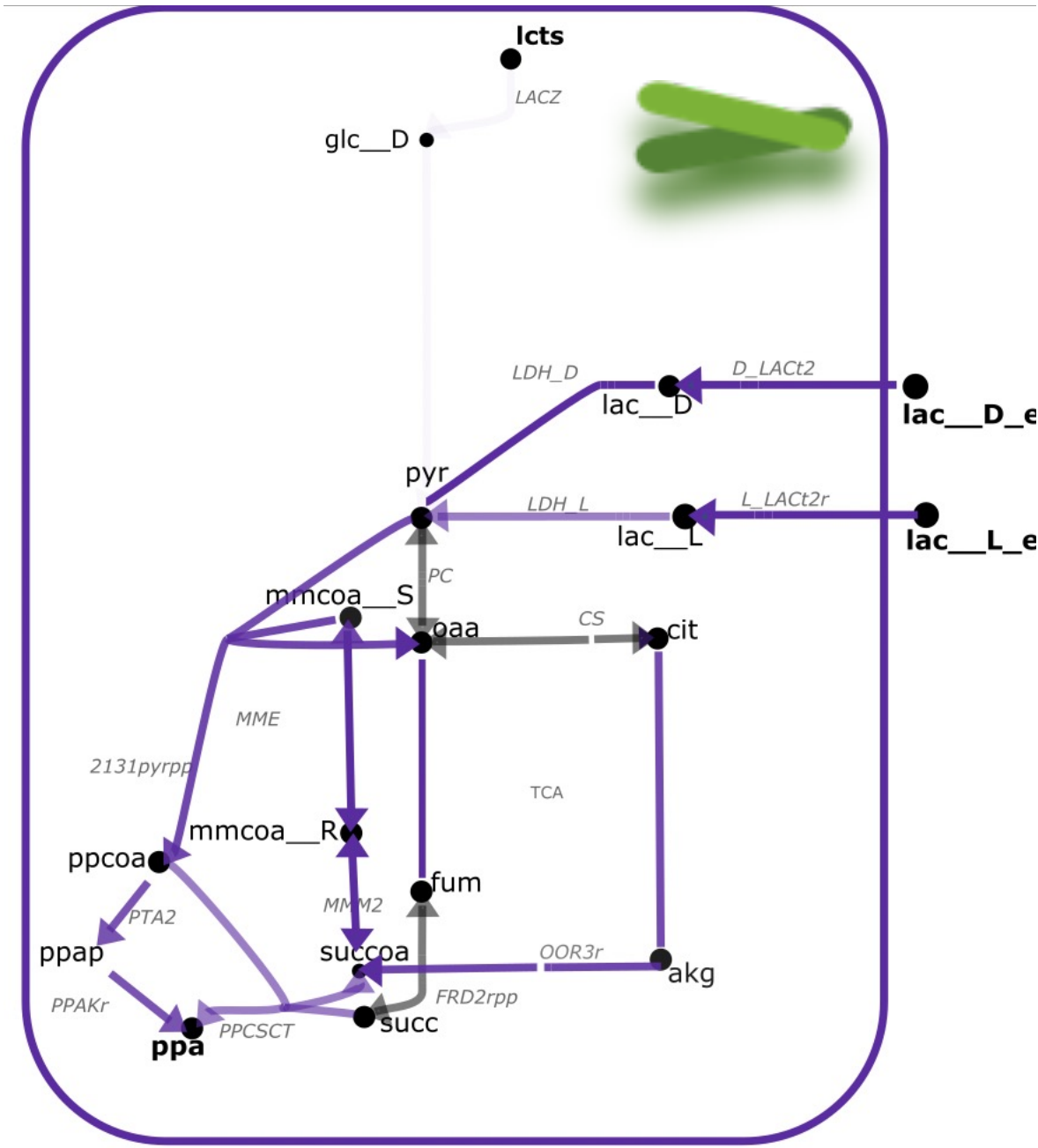
# FBA as a numerical model of metabolism

Stoichiometric matrix =

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A	$-1$	...	$0$
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C	$0$	...	$1$

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

Flux distribution that maximizes biomass production





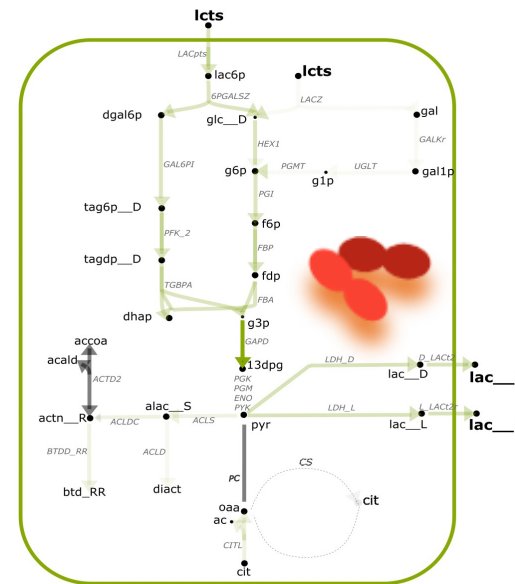
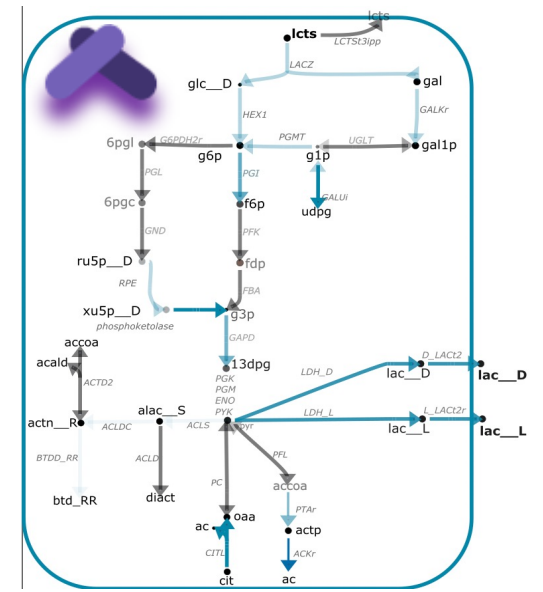
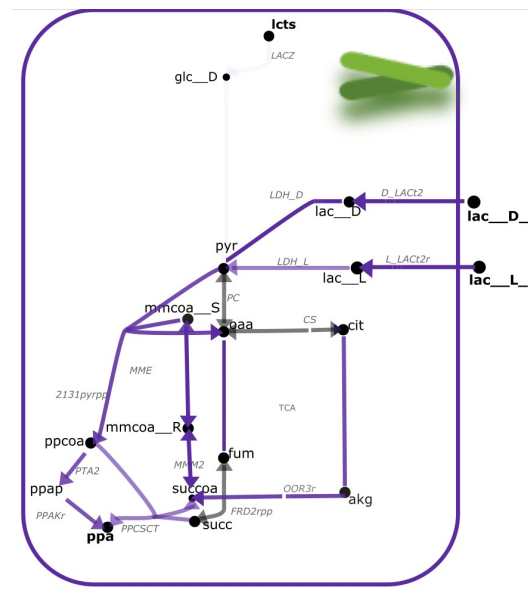
# FBA as a numerical model of metabolism

Stoichiometric matrix =

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 \end{matrix}$$

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Flux distribution that maximizes biomass production



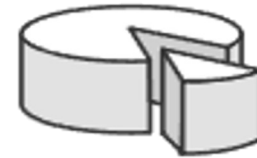
Individual models are in accordance with literature

# Cheese production: a dynamic and complex biological process

Liquid environment



solid environment



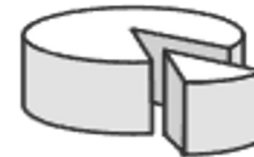
The consistency of the environment changes

# Cheese production: a dynamic and complex biological process

Liquid environment

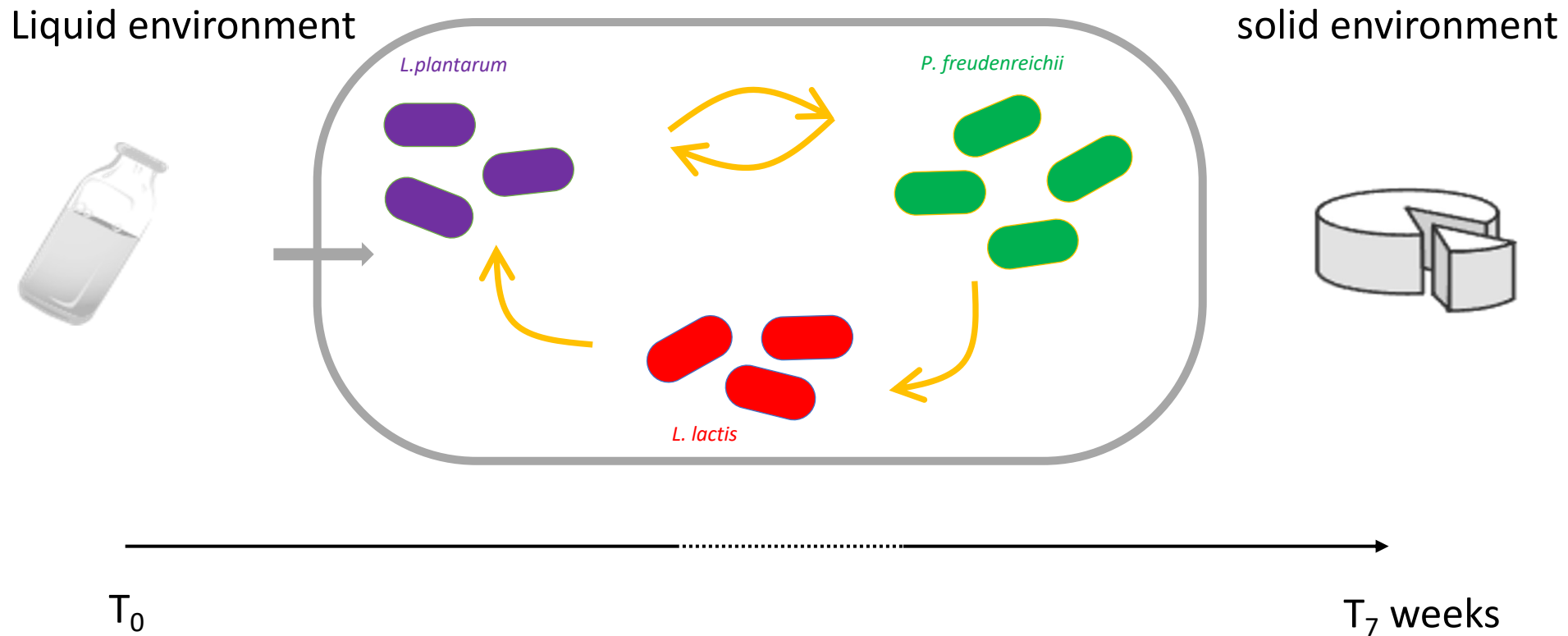


solid environment



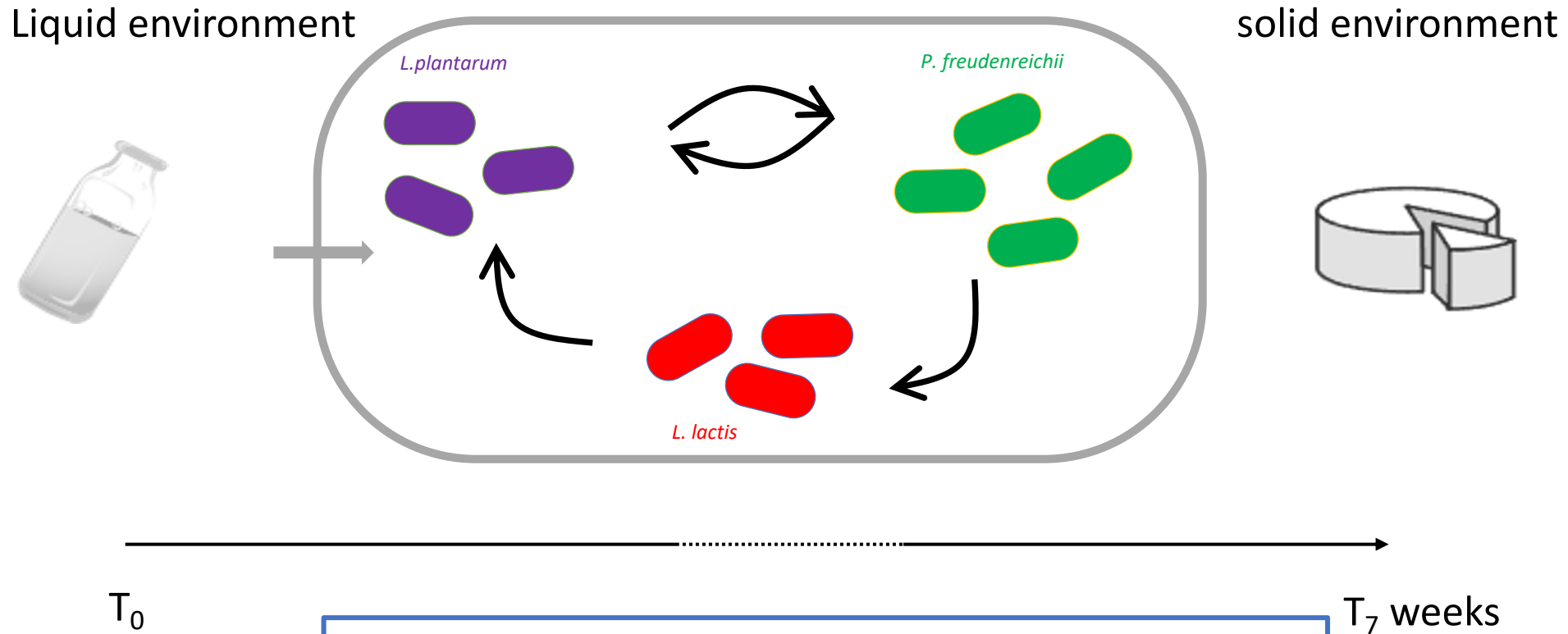
The consistency of the environment changes  
A **dynamic** process

# 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



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

# Dynamic modeling of metabolism (dFBA)

List of pre-defined interest compounds :

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

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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 :

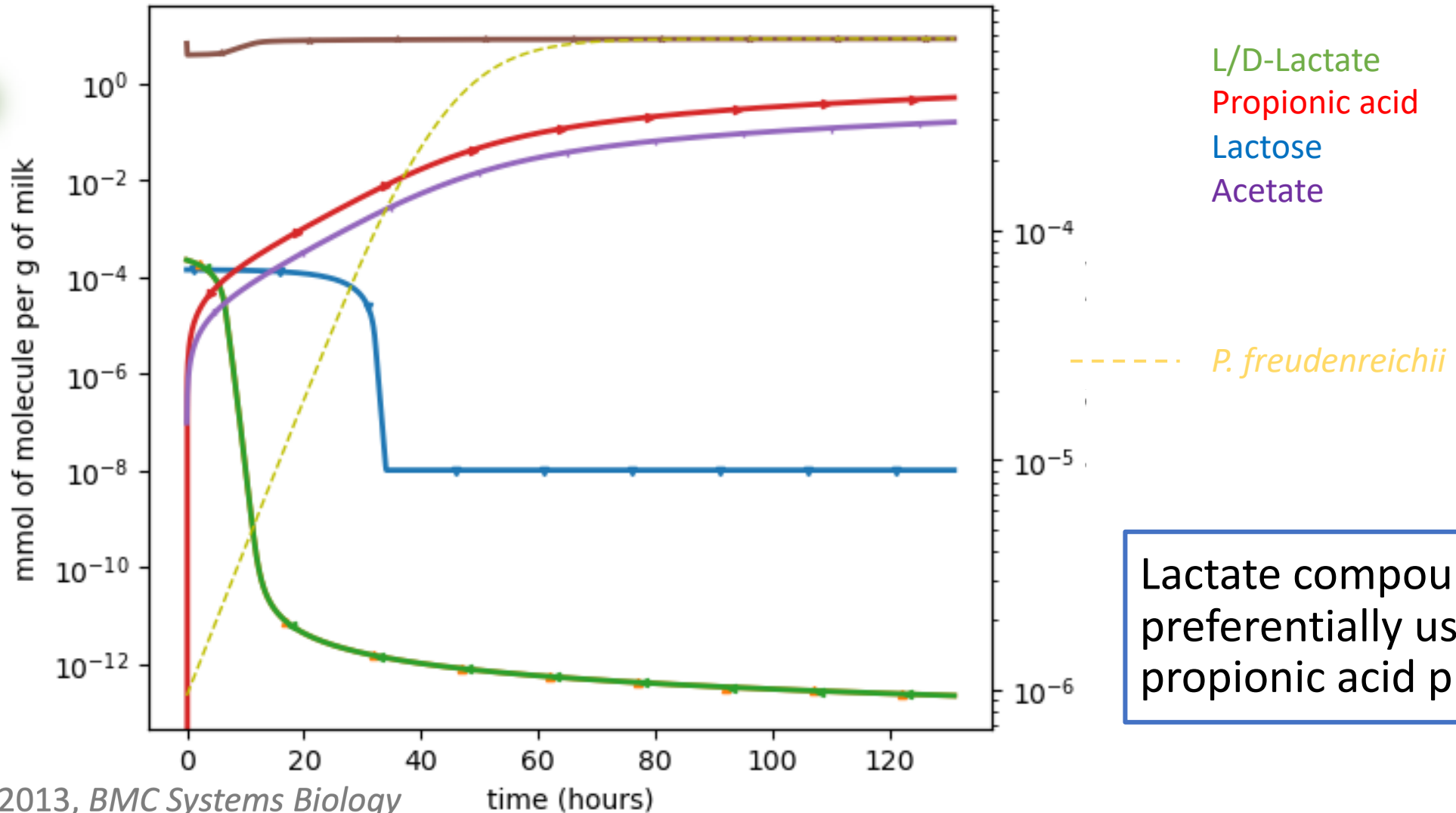
$$\partial_t b_i = q_s(b_i) \mu_{FBA_i}(c)_i b_i$$

$q_s$  = Quorum sensing

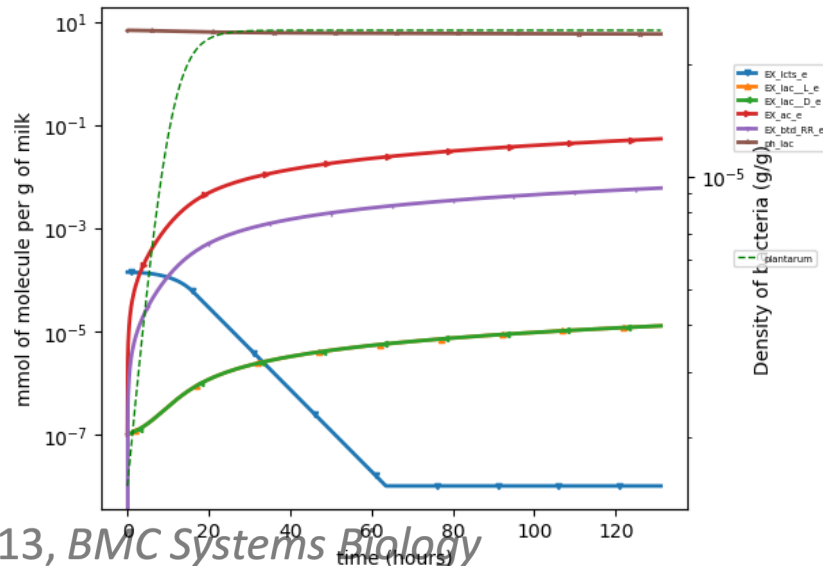
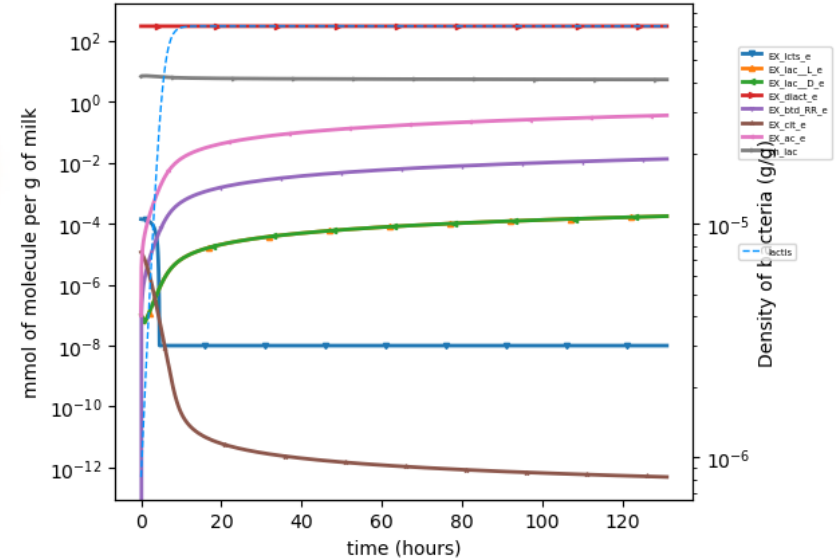
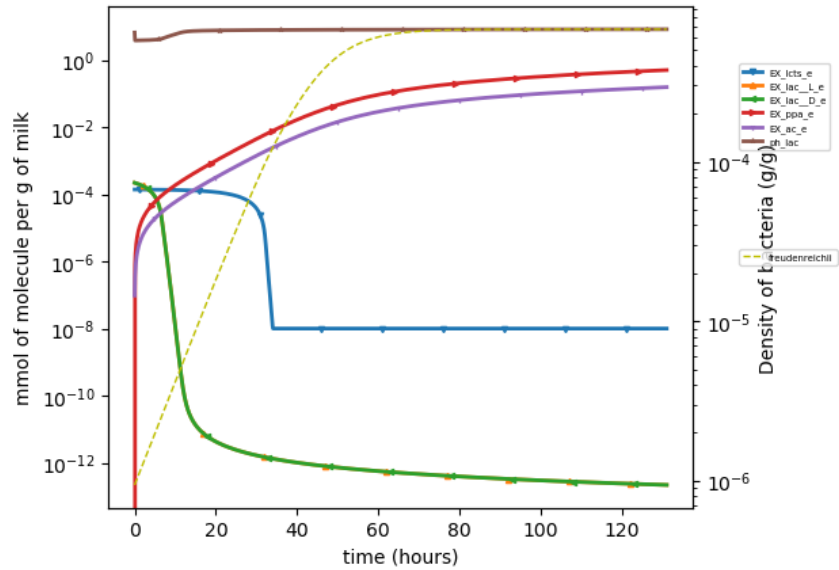
$$q_s(b_i) = 1 - \frac{b_i}{\beta_i}$$



# 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

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

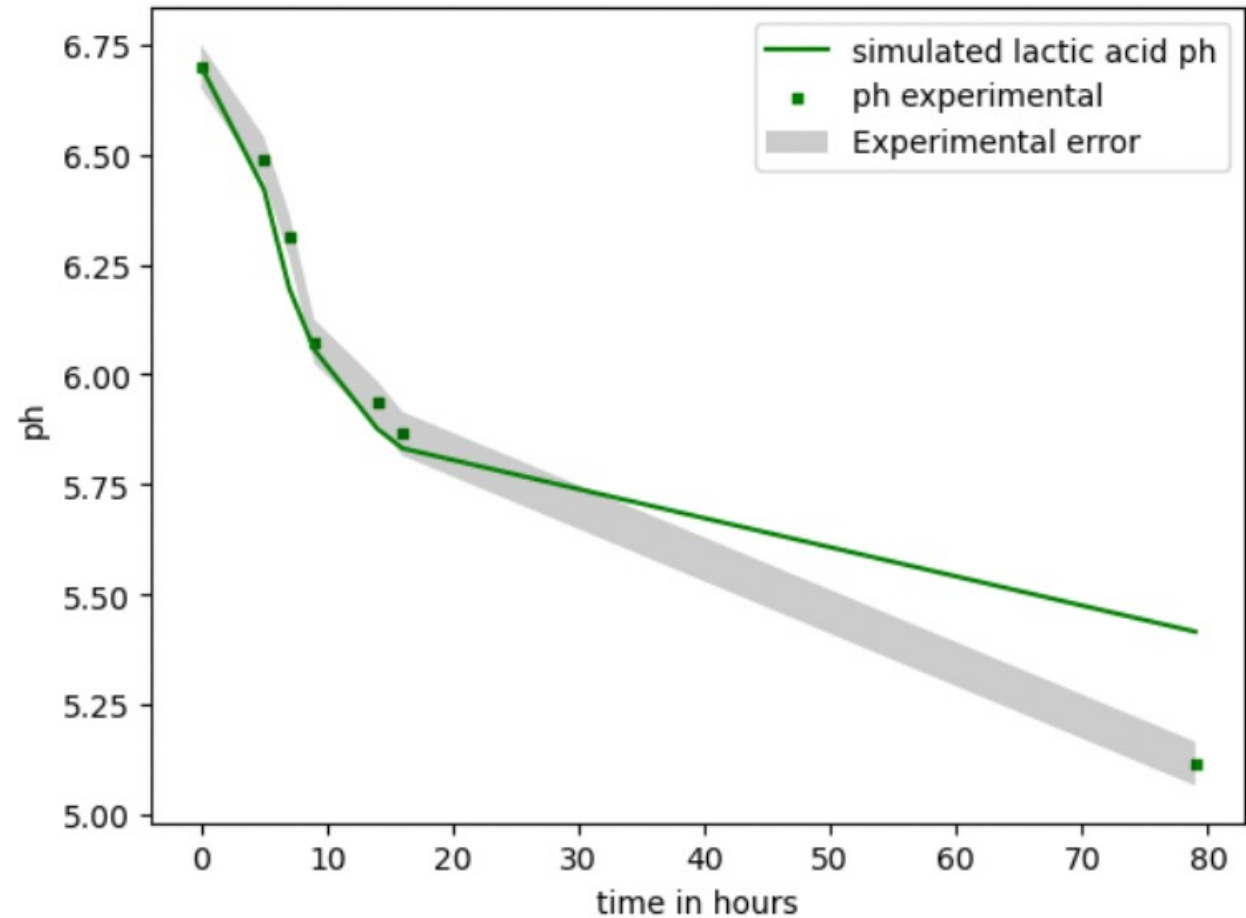
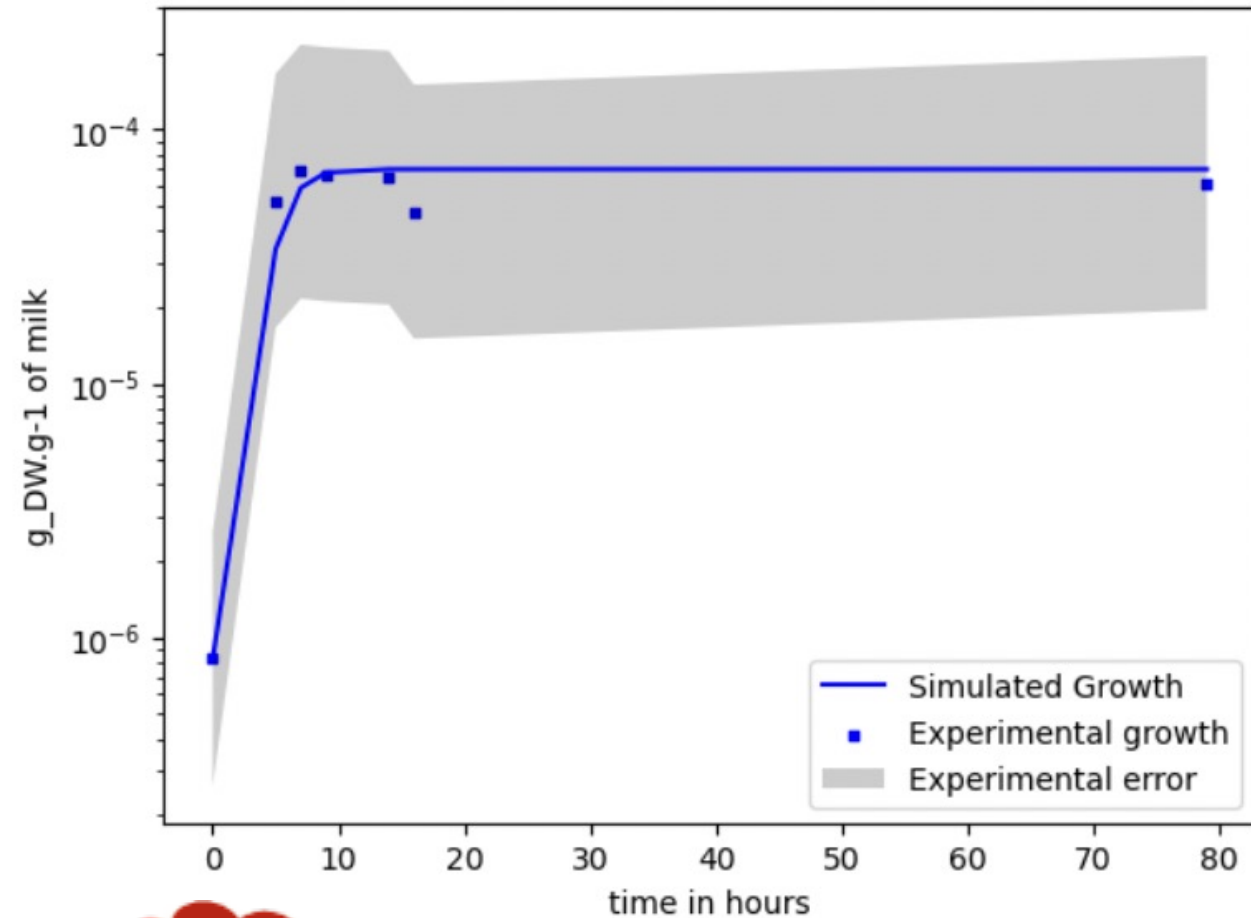
# Optimizing dynamic models on pure cultures

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

- Lambda   
- QS   
- K<sub>lactate</sub> 
- C1 & C2  
- V<sub>min</sub> & V<sub>max</sub> lactose 
- Lactate<sub>upper</sub> 

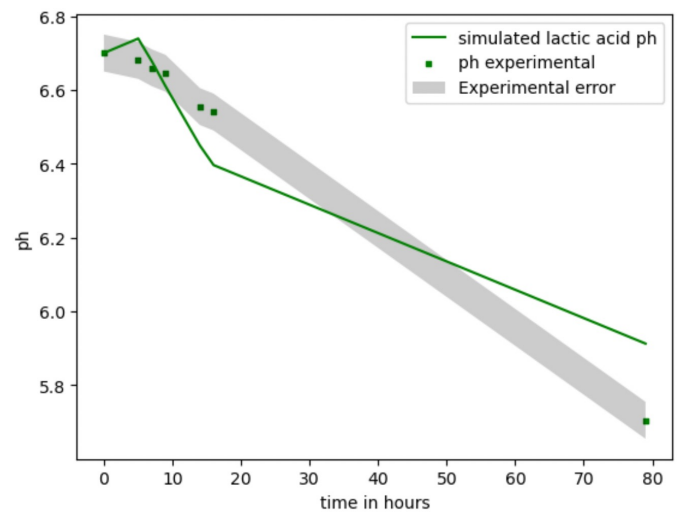
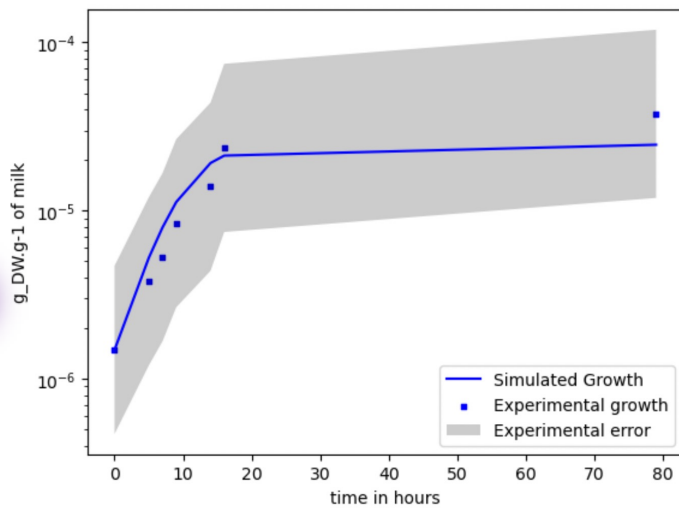
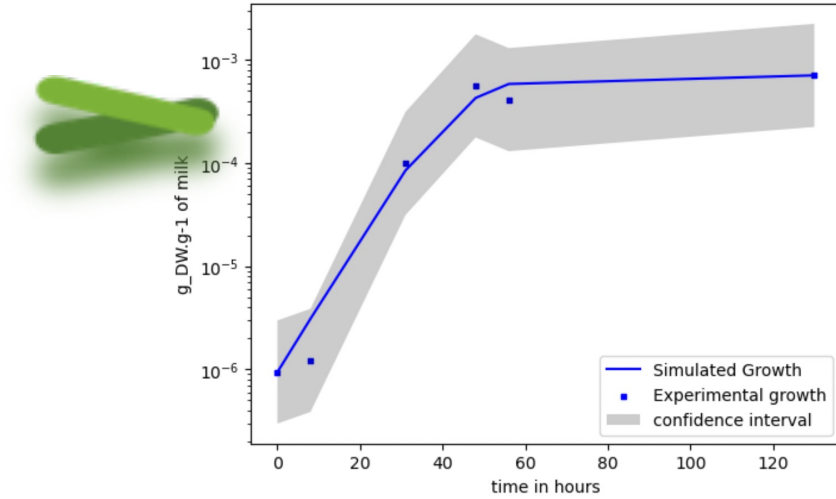
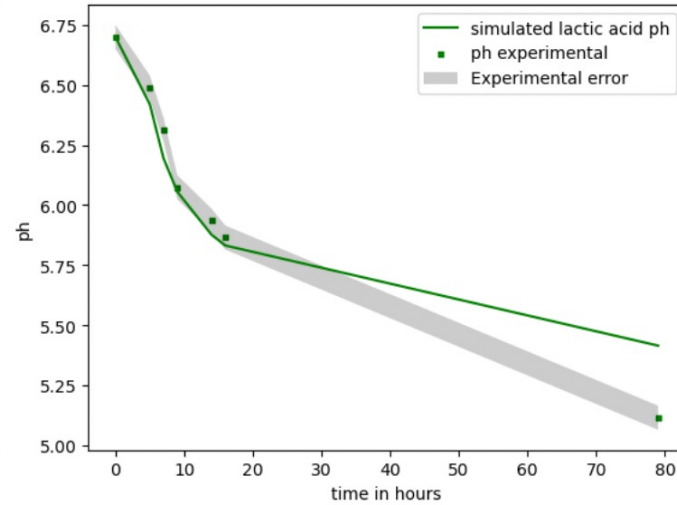
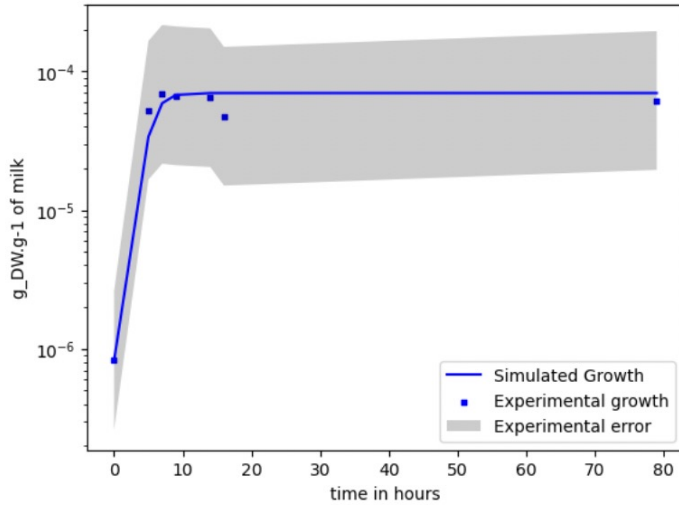
Identification of parameters to fit with experimental data

# 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



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

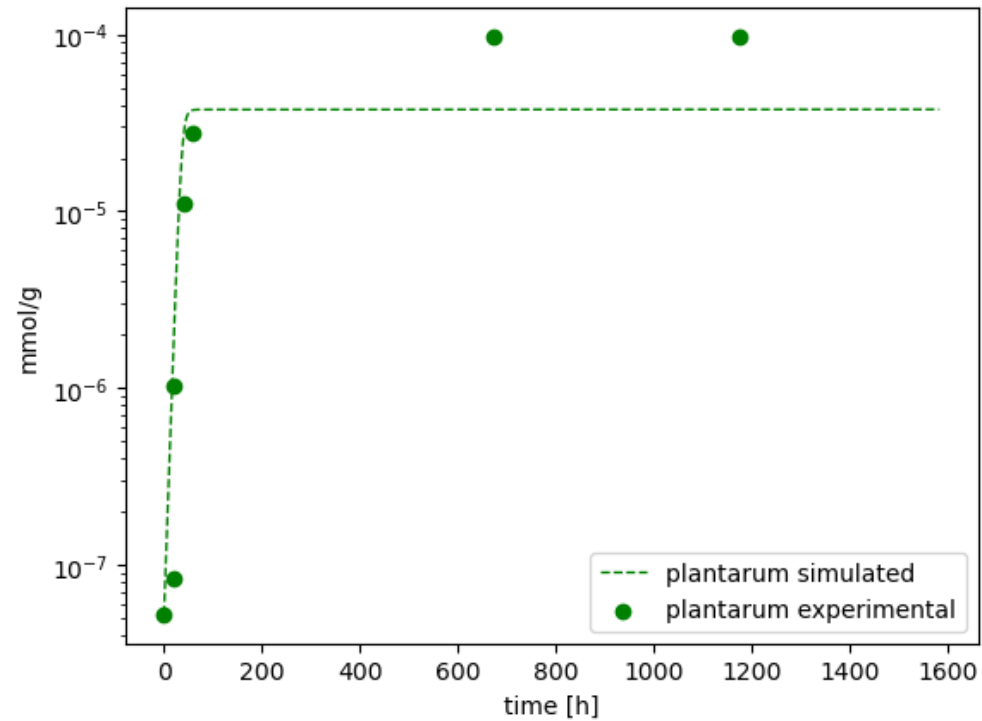
Optimised dFBA models for each bacterium

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

$$\mathcal{V}(t) = \frac{\partial_t v(t)}{V(t)}$$

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

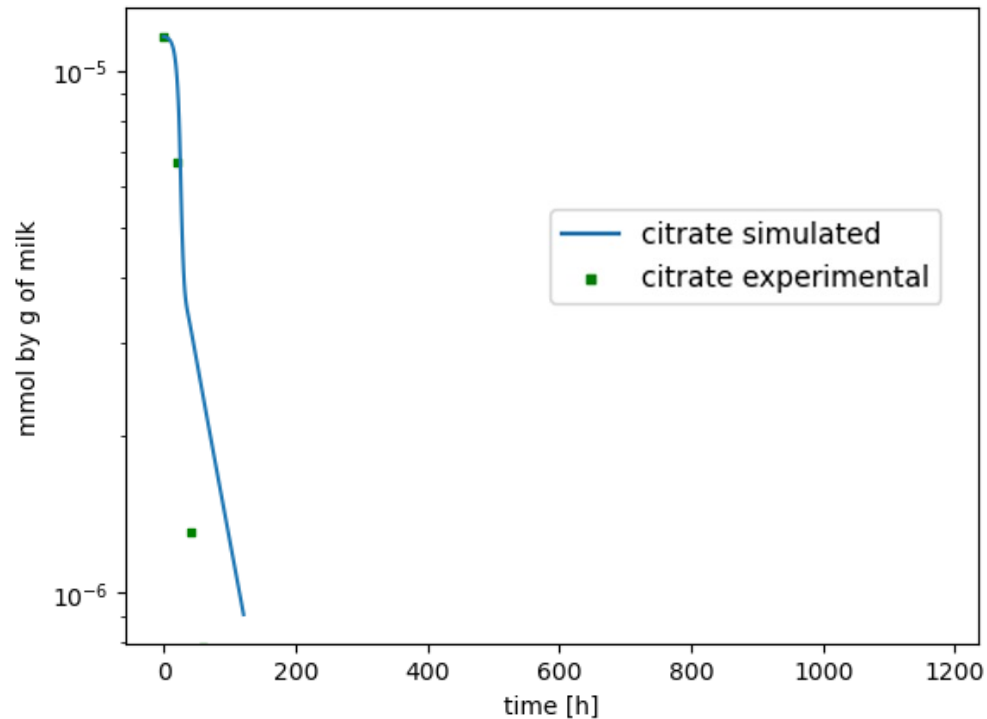
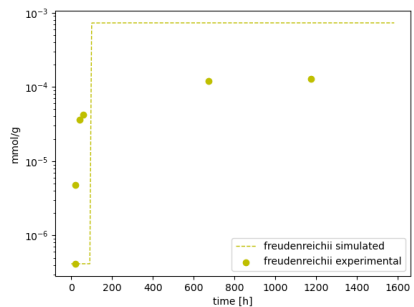
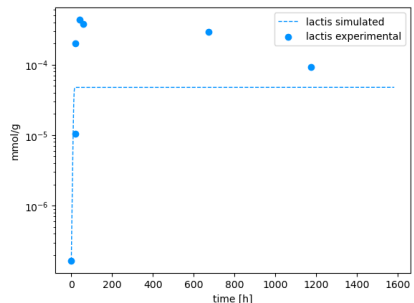
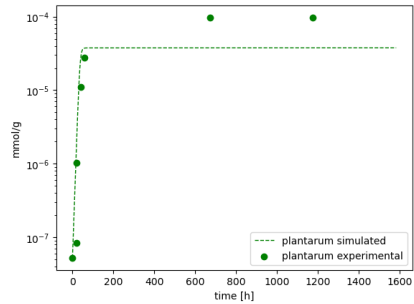
# Community dFBA results



Bacterial growth computed with community dFBA fits with experimental data

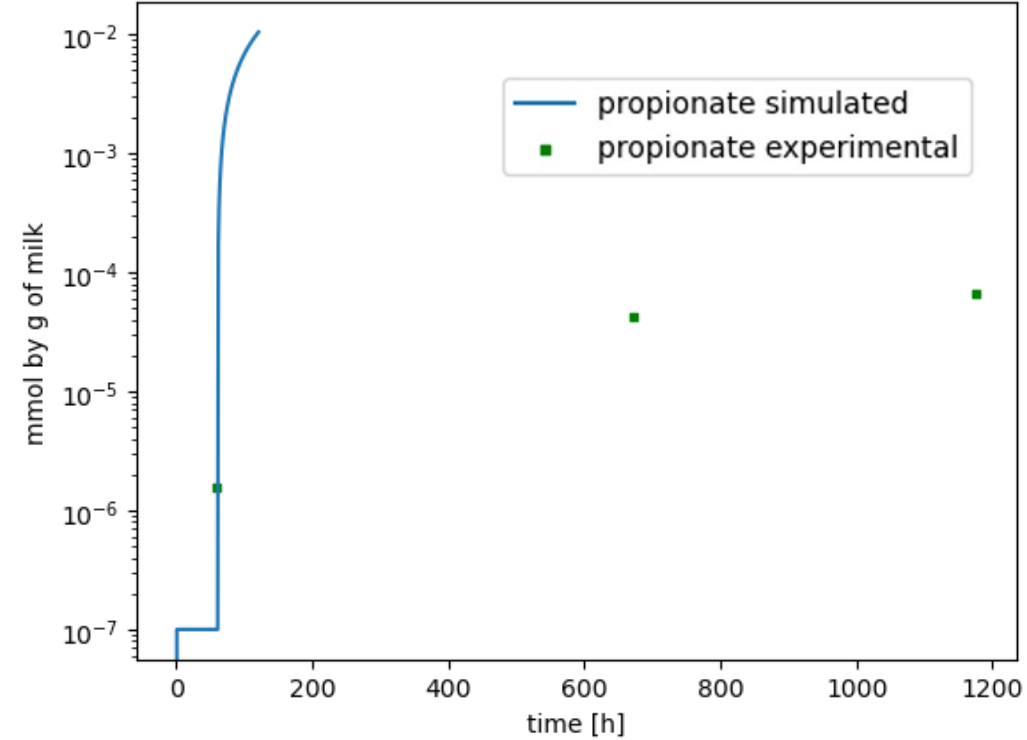
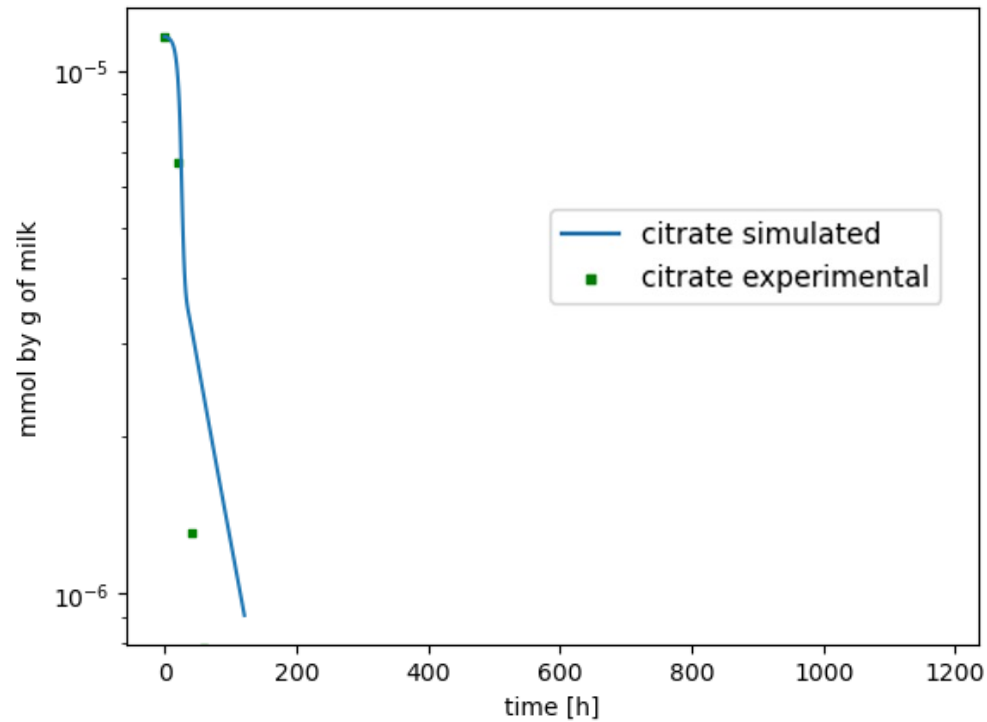
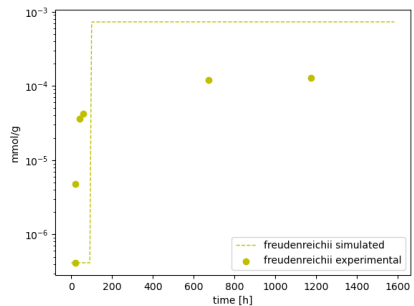
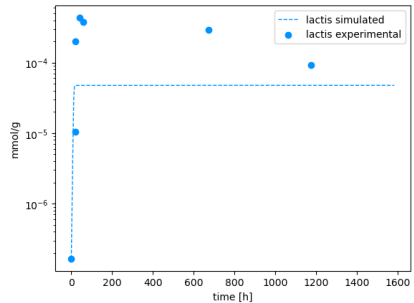
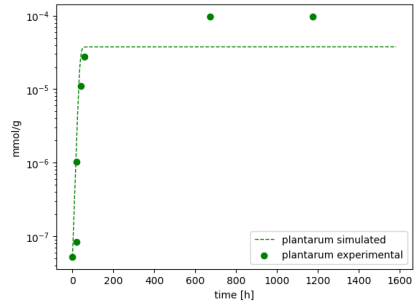


# Community dFBA results



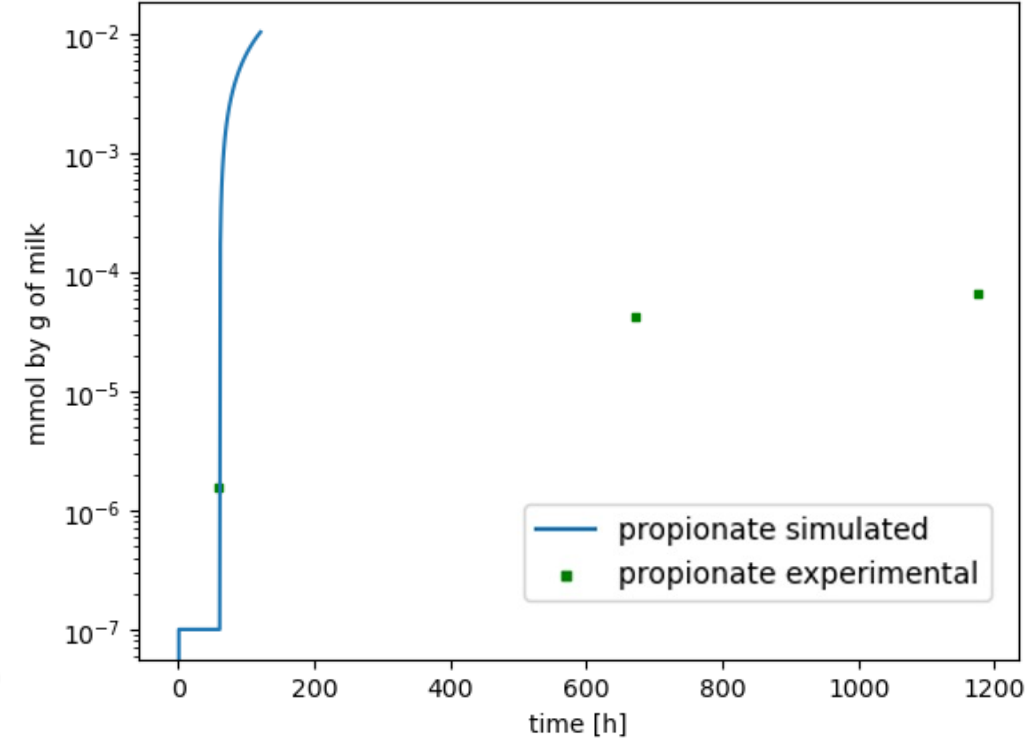
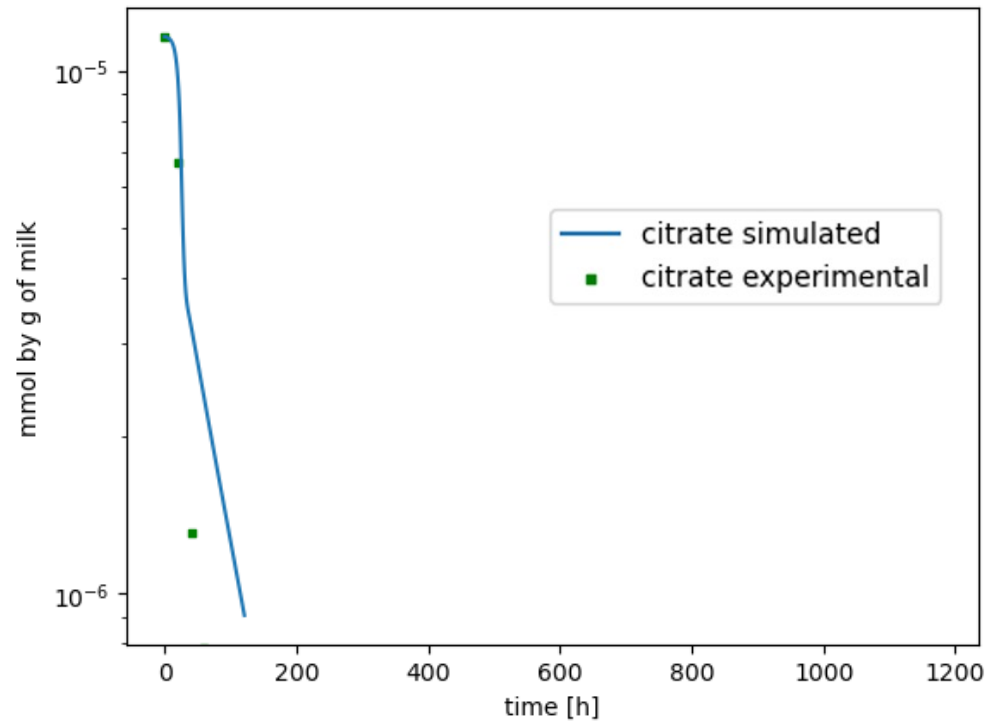
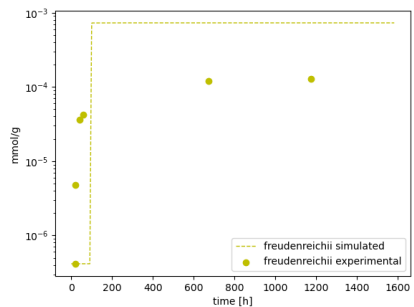
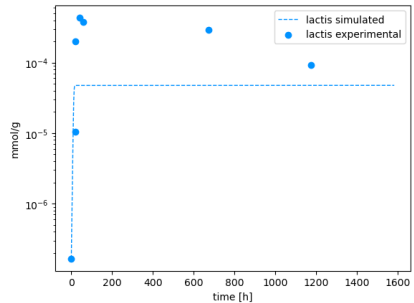
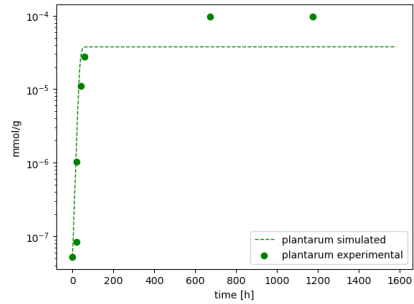
Some metabolites fit with metabolomics data ...

# Community dFBA results



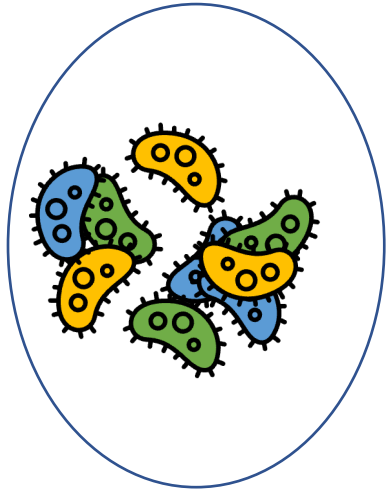
Not all of them

# Community dFBA results

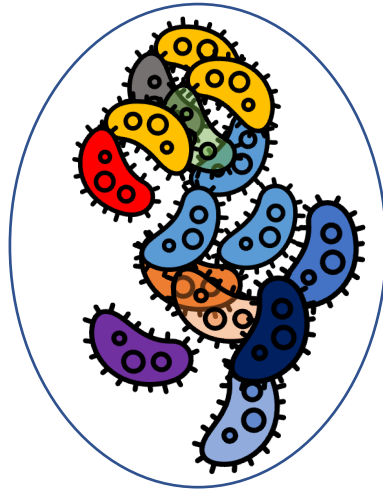


- The model do not capture all modifications brings by the community
- Integration of transcriptomic data is not significantly different
- Is qualitative result enough for characterizing communities ?

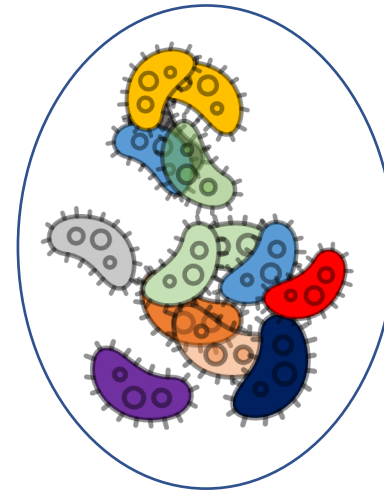
# Characterizing natural communities (meta)genomics data



Community 1



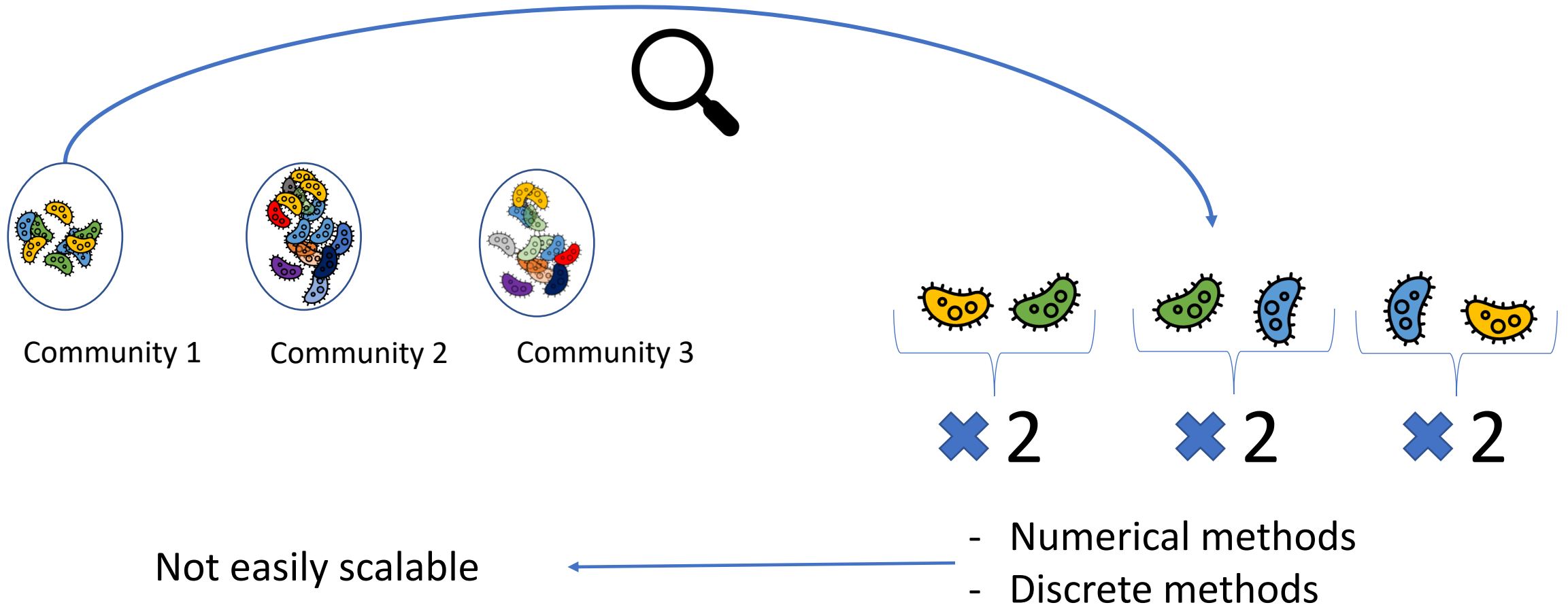
Community 2



Community 3

Calculating cooperation and competition potentials

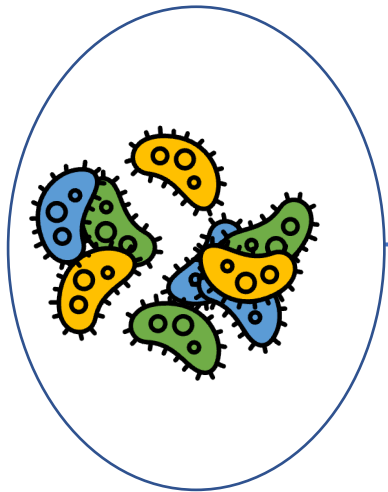
# Characterizing natural communities with (meta)genomics data



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)



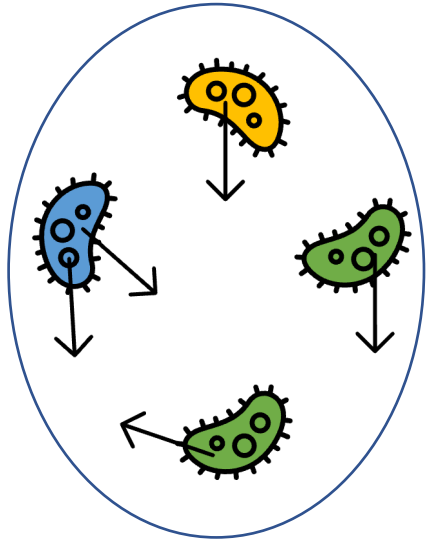
Descriptive

vocabular  
using ASP

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

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

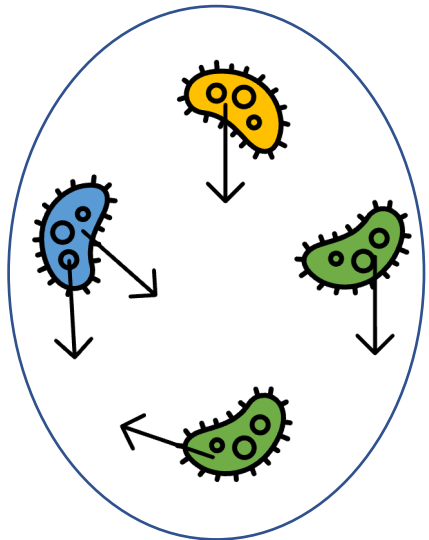
# Cooperation and competition metrics



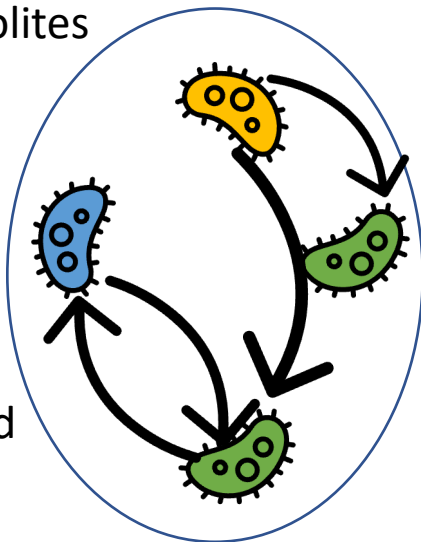
Number of metabolites  
produced



# Cooperation and competition metrics



Number of metabolites produced

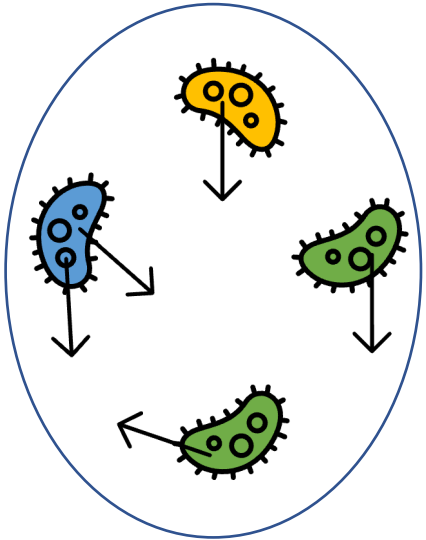


Number of exchanged metabolites

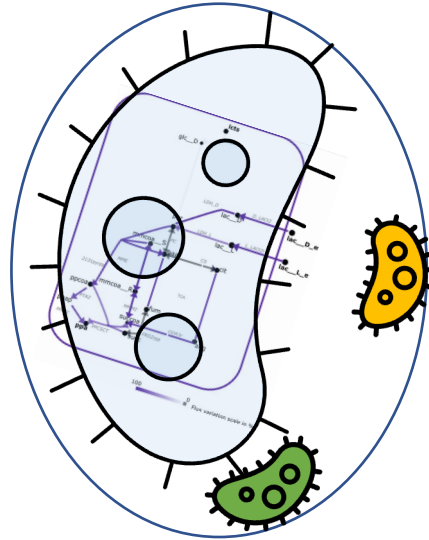




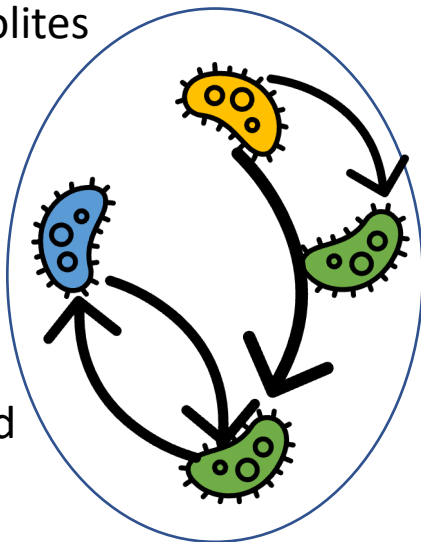
# Cooperation and competition metrics



Number of metabolites produced

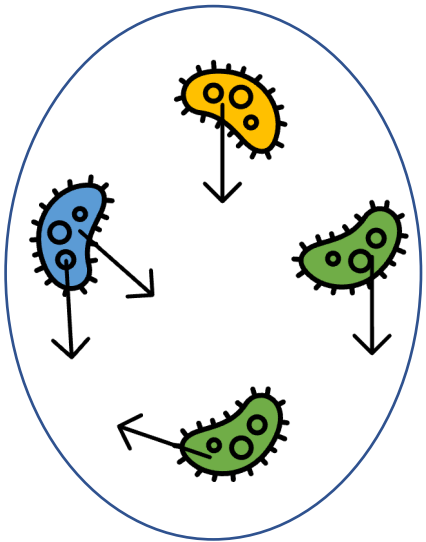


Number of activated reactions

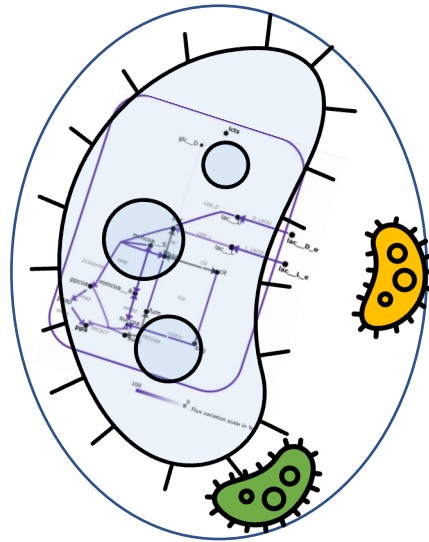


Number of exchanged metabolites

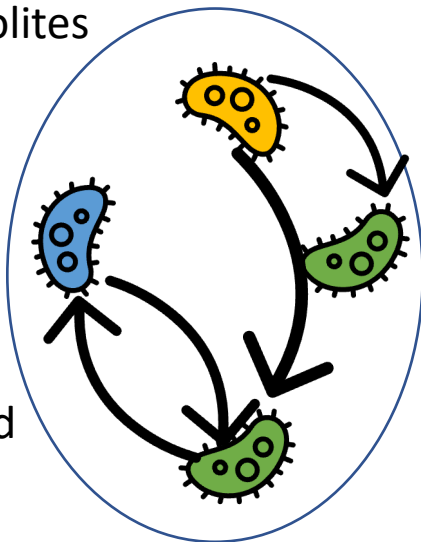
# Cooperation and competition metrics



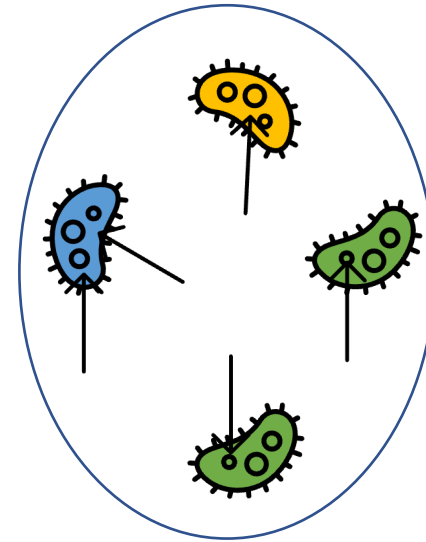
Number of metabolites produced



Number of activated reactions

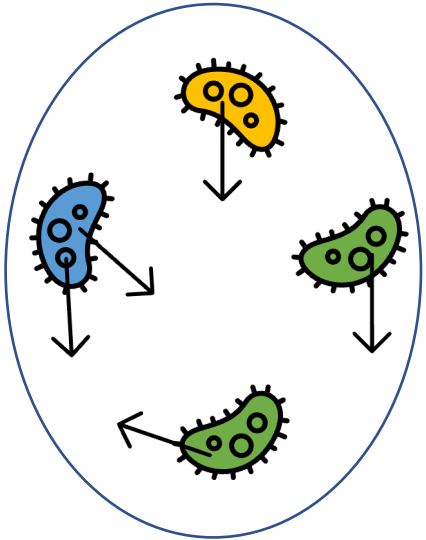


Number of exchanged metabolites

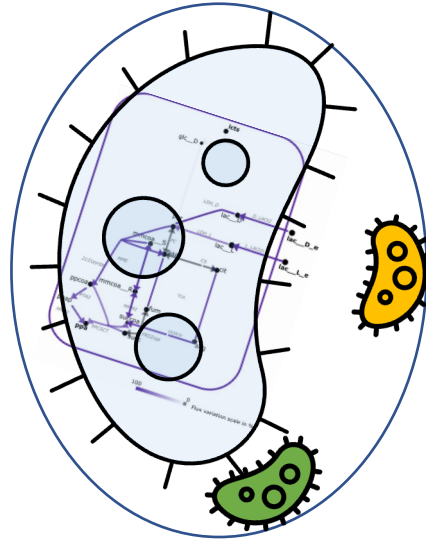


Related to limiting substrates consumed

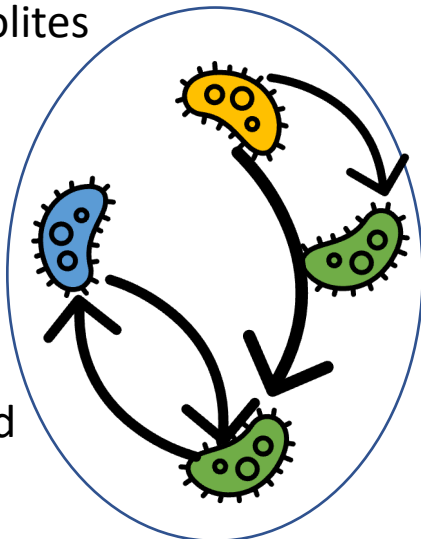
# Cooperation and competition metrics



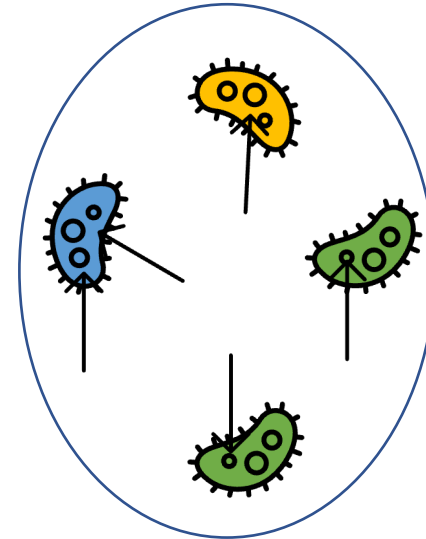
Number of metabolites produced



Number of activated reactions



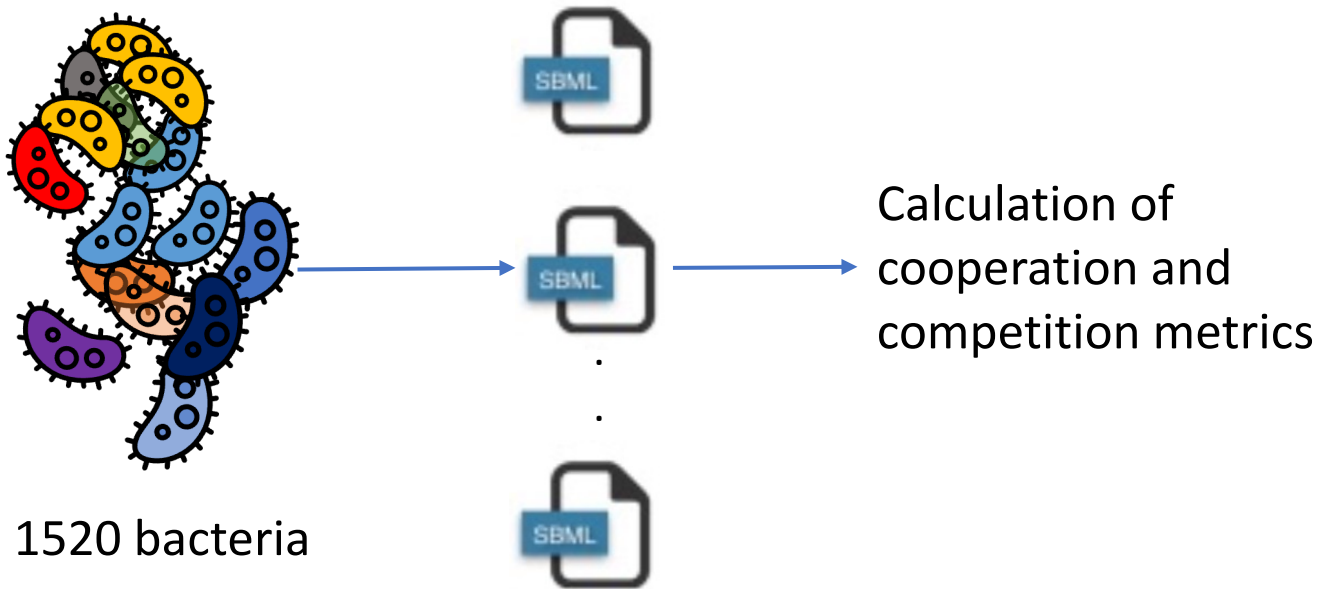
Number of exchanged metabolites



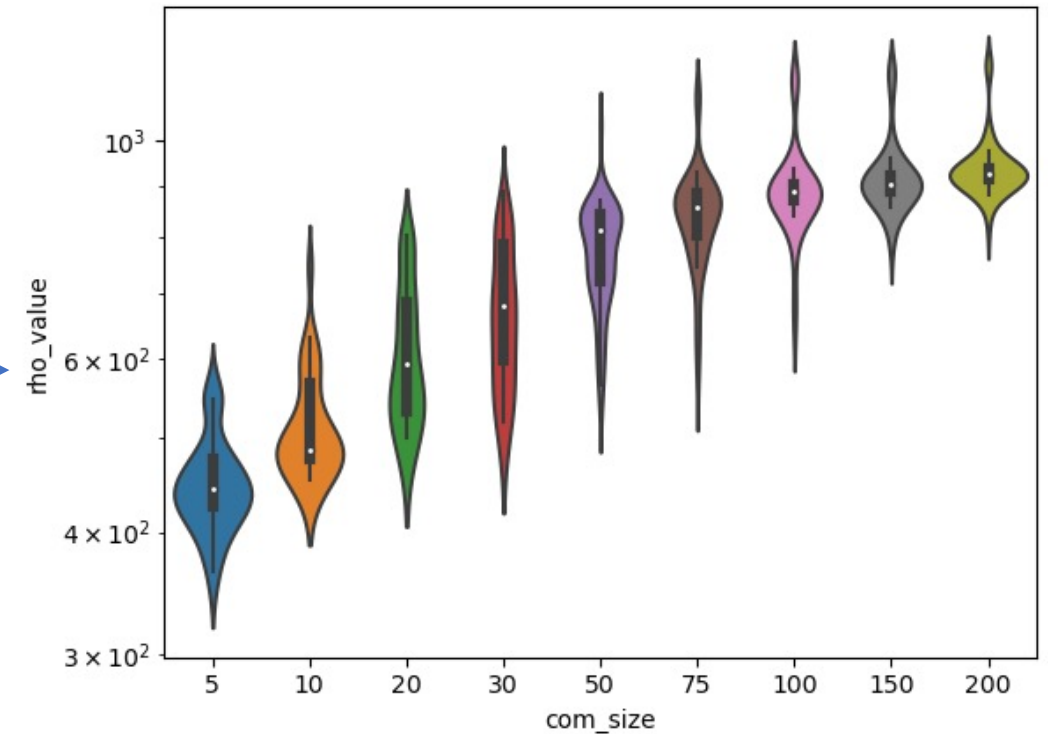
Related to limiting substrates consumed

Unify cooperation metrics to one unique score

# Model test on designed communities

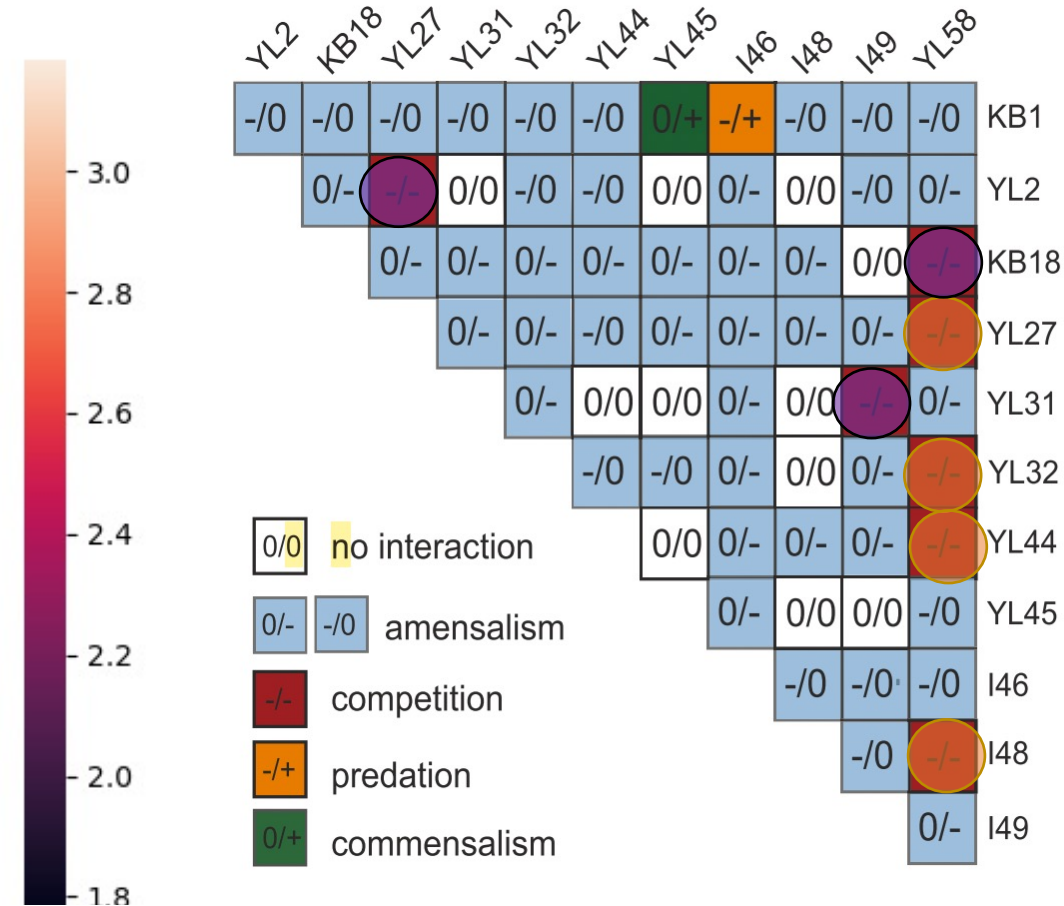
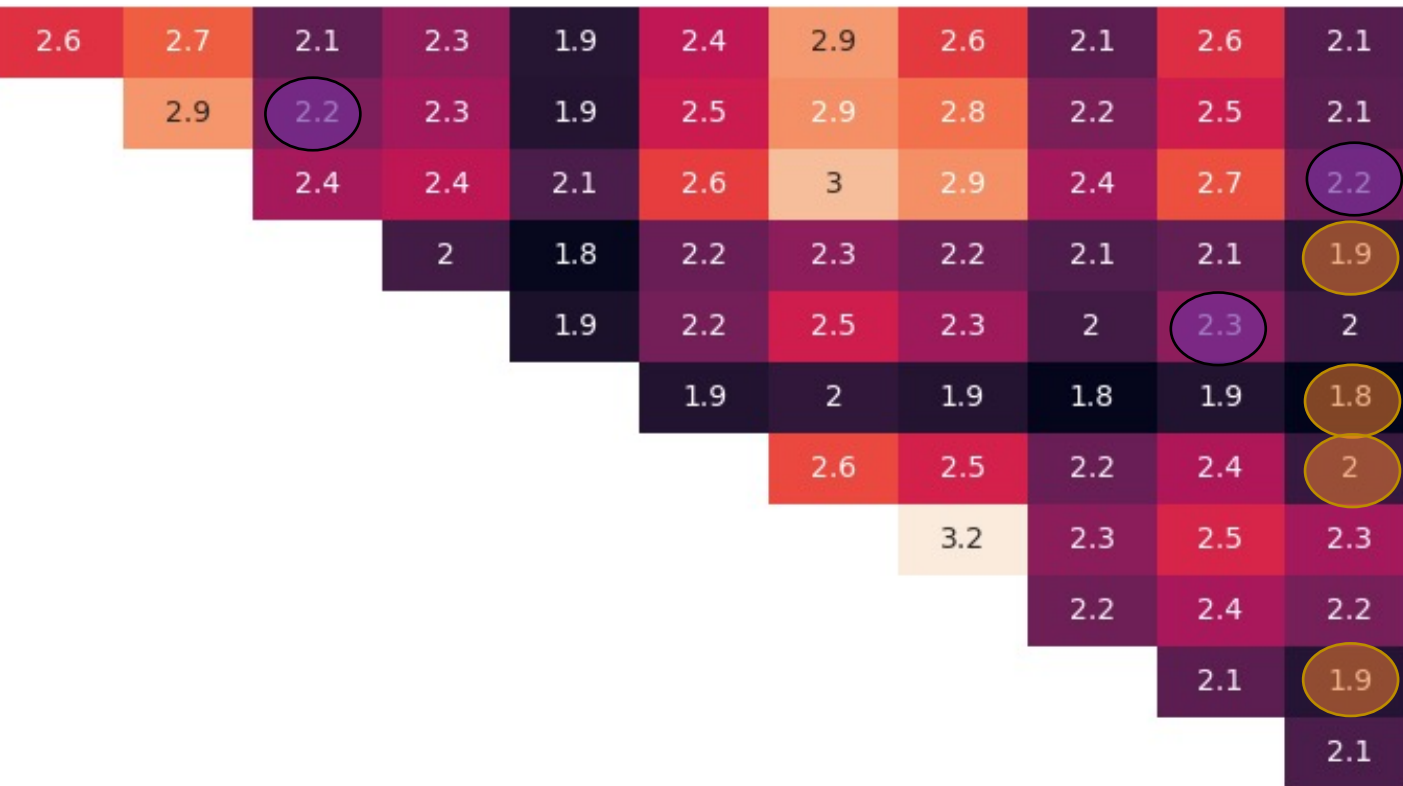


50 random communities  
of size 5 to 200



Metrics are not linearly correlate with  
the community size

# 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

