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Characterizing microbial interactions in controlled and natural microbial communities

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Maxime Lecomte, Simon Labarthe, David James Sherman, H el ene Falentin, Cl emence Frioux. Characterizing microbial interactions in controlled and natural microbial communities. Workshop Sym-BioDiversity, May 2022, Santiago, Chile. hal-03857848v2

HAL Id: hal-03857848

<https://hal.inrae.fr/hal-03857848v2>

Submitted on 9 Dec 2022

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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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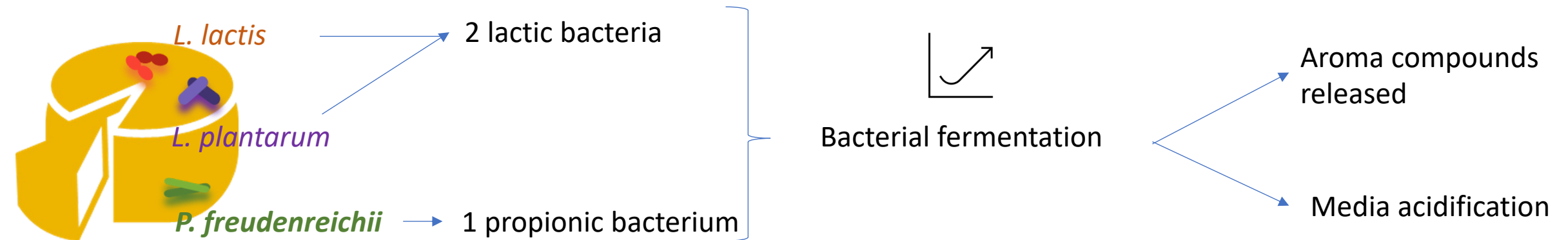
Workshop SymbioDiversity 2021-2022

INRAE

Inria

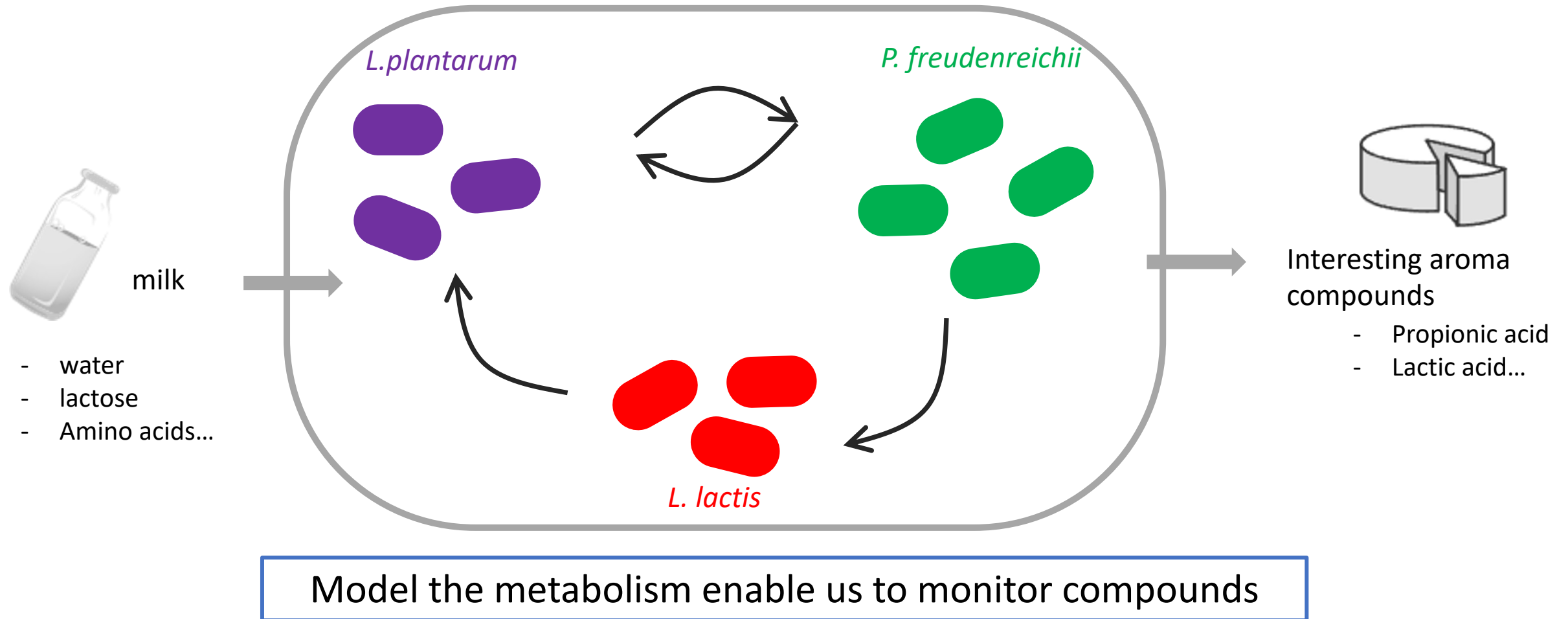
universit e
de **BORDEAUX**

Industrial cheese starter bacterial community as a controlled ecosystem



Which biological phenomena rules aroma compounds production ?

Bacterial fermentation process in cheese



Multi-omics strategy



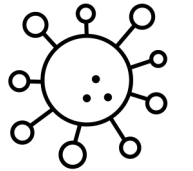
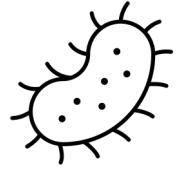
Annotated genomes



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

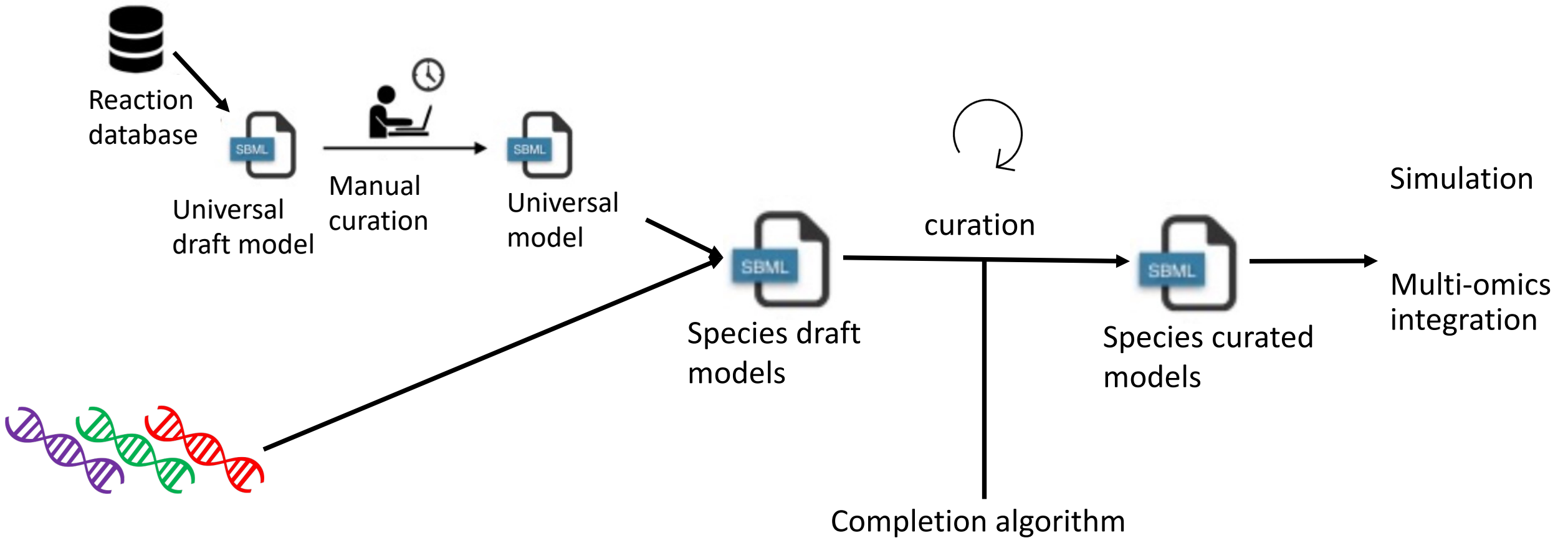
Metabolomics data



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

$$\max v_{growth}$$

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

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

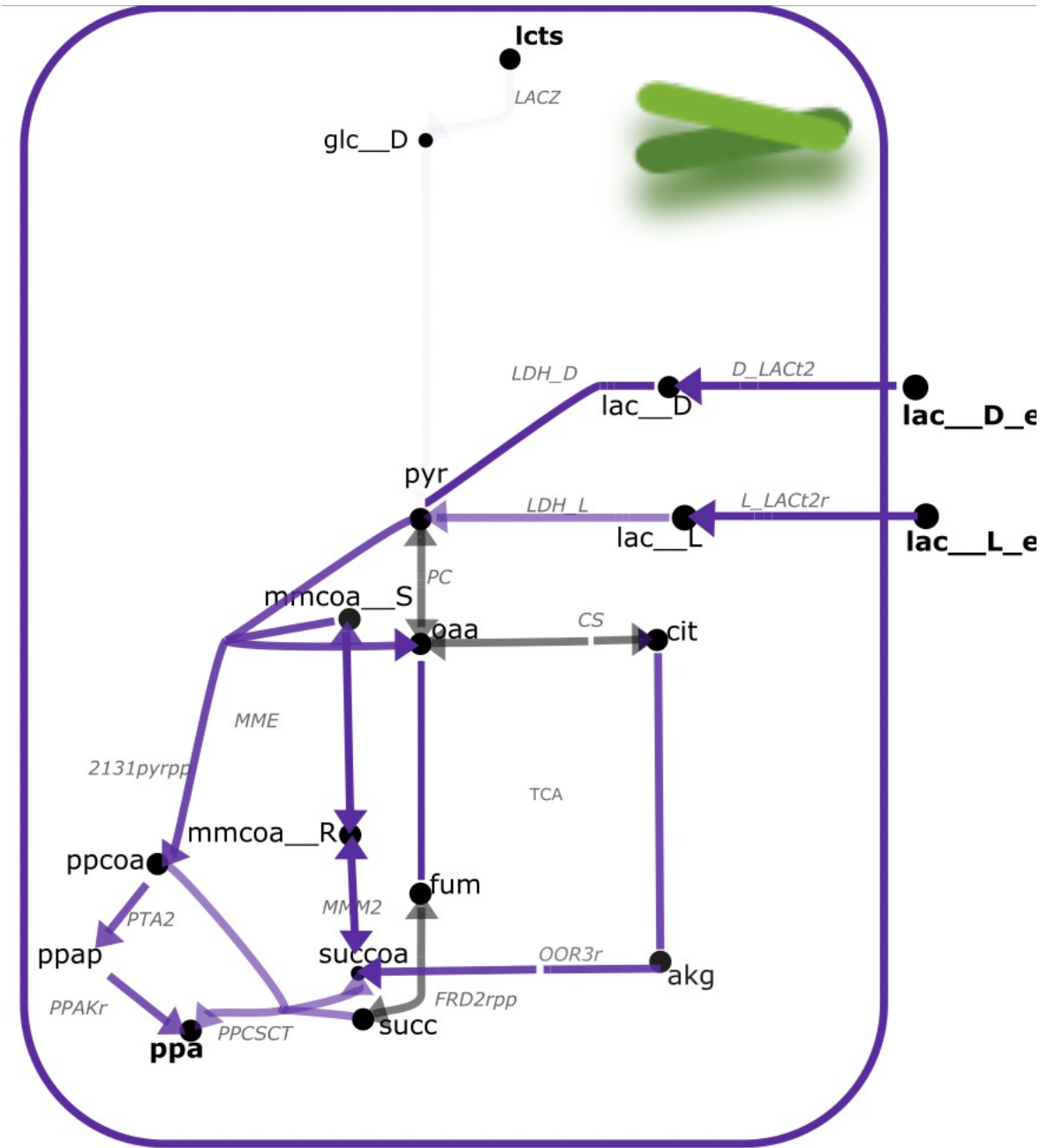
FBA as a numerical model of metabolism

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

Flux distribution that maximizes biomass production

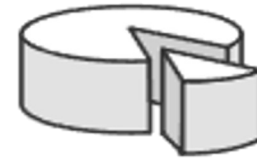


Cheese production: a dynamic and complex biological process

Liquid environment



solid environment



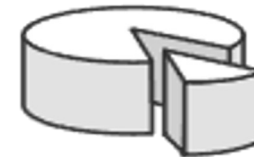
The consistency of the environment changes

Cheese production: a dynamic and complex biological process

Liquid environment

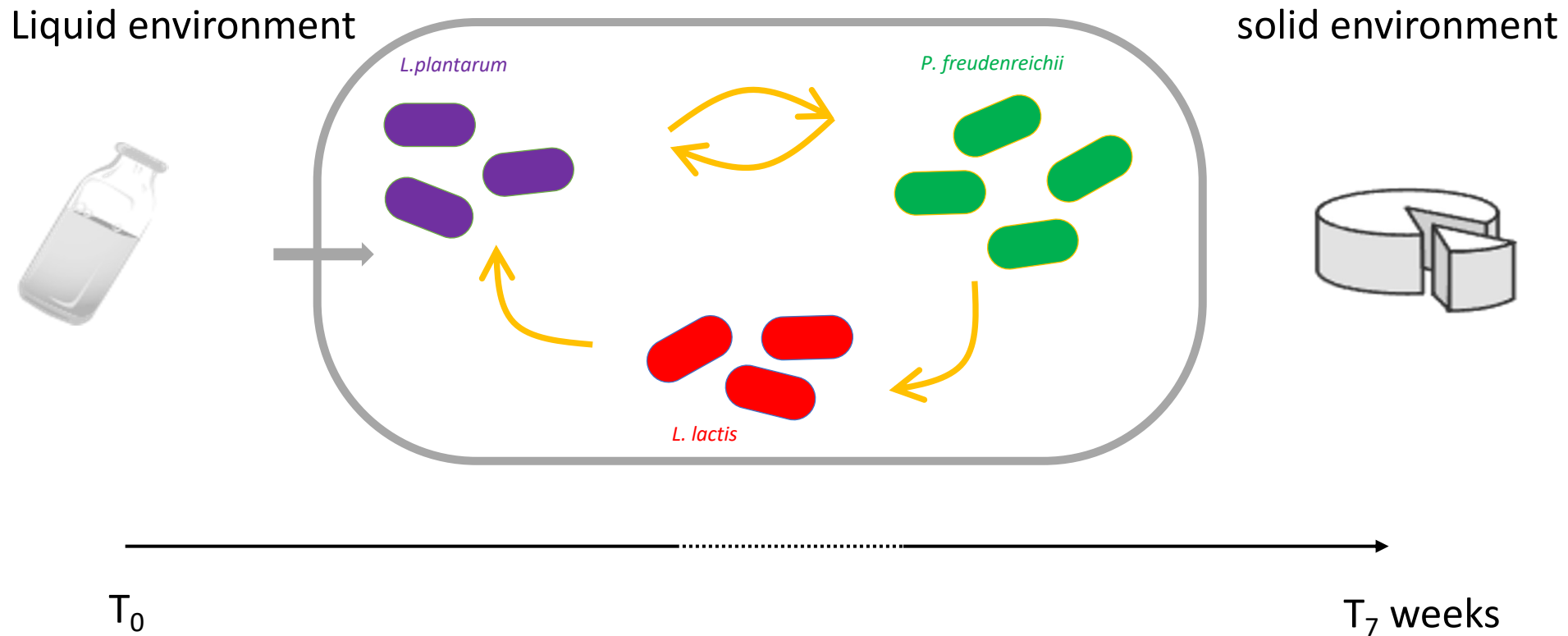


solid environment



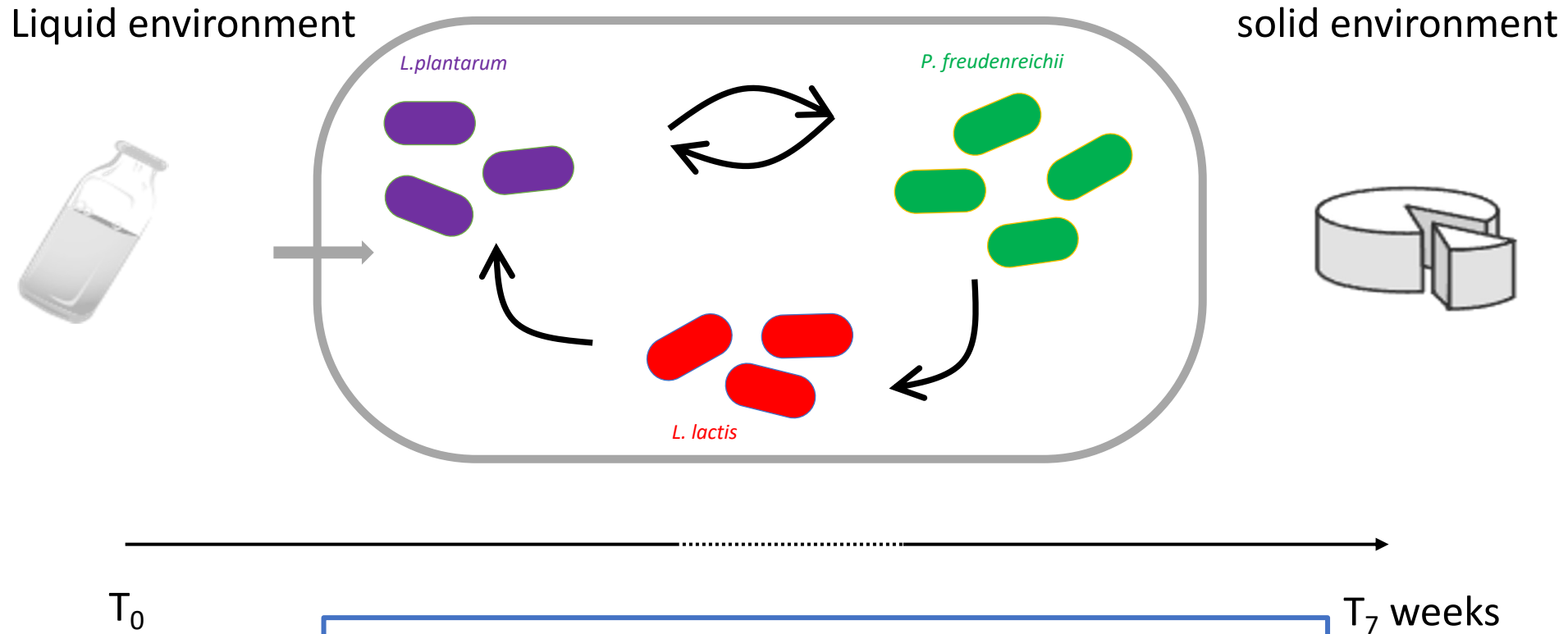
The consistency of the environment changes
A **dynamic** process

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 :

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

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 :

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

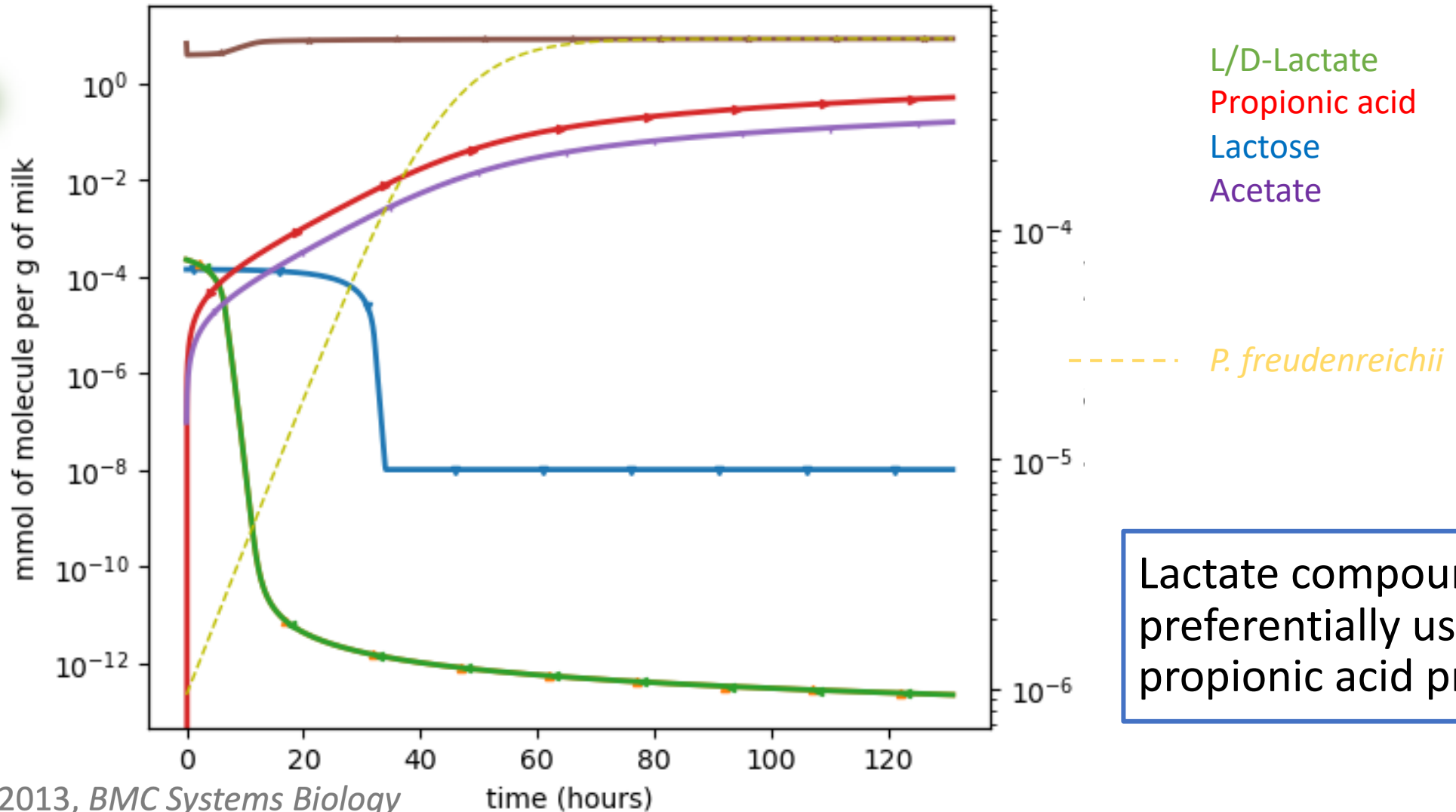
Bacterial concentration :

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

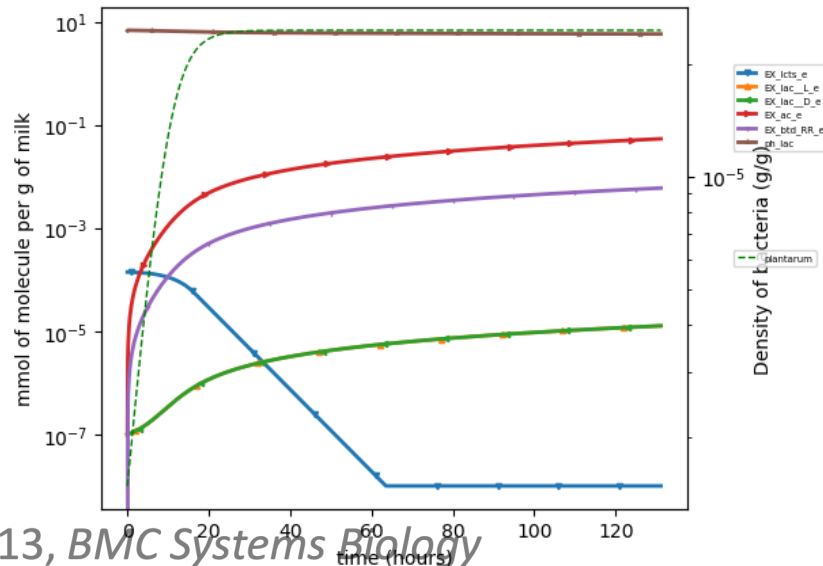
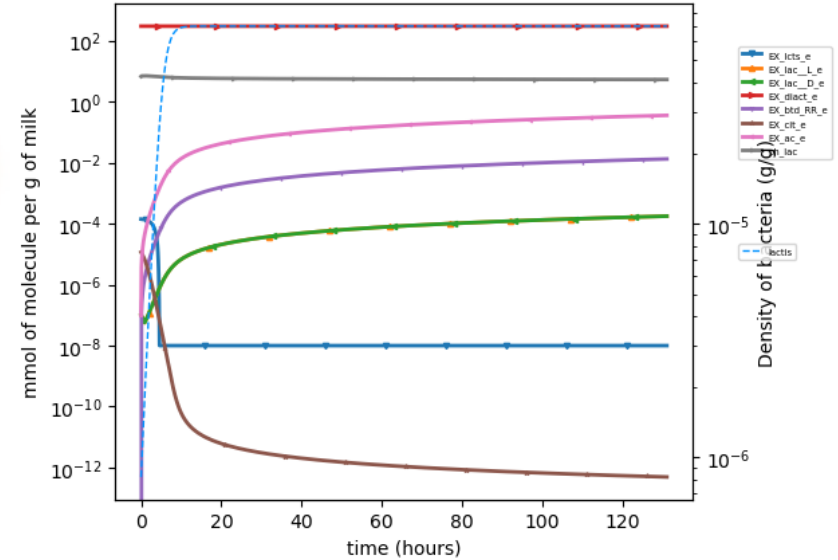
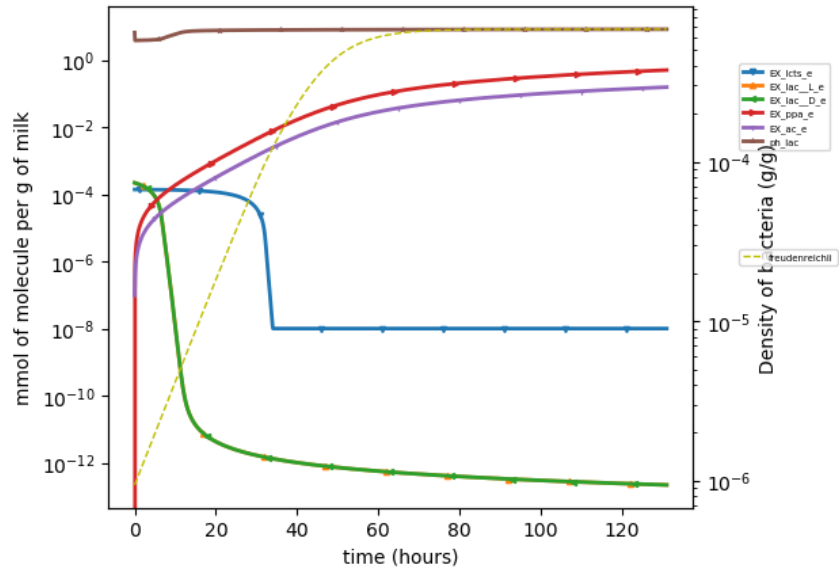
q_s = Quorum sensing

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

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

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

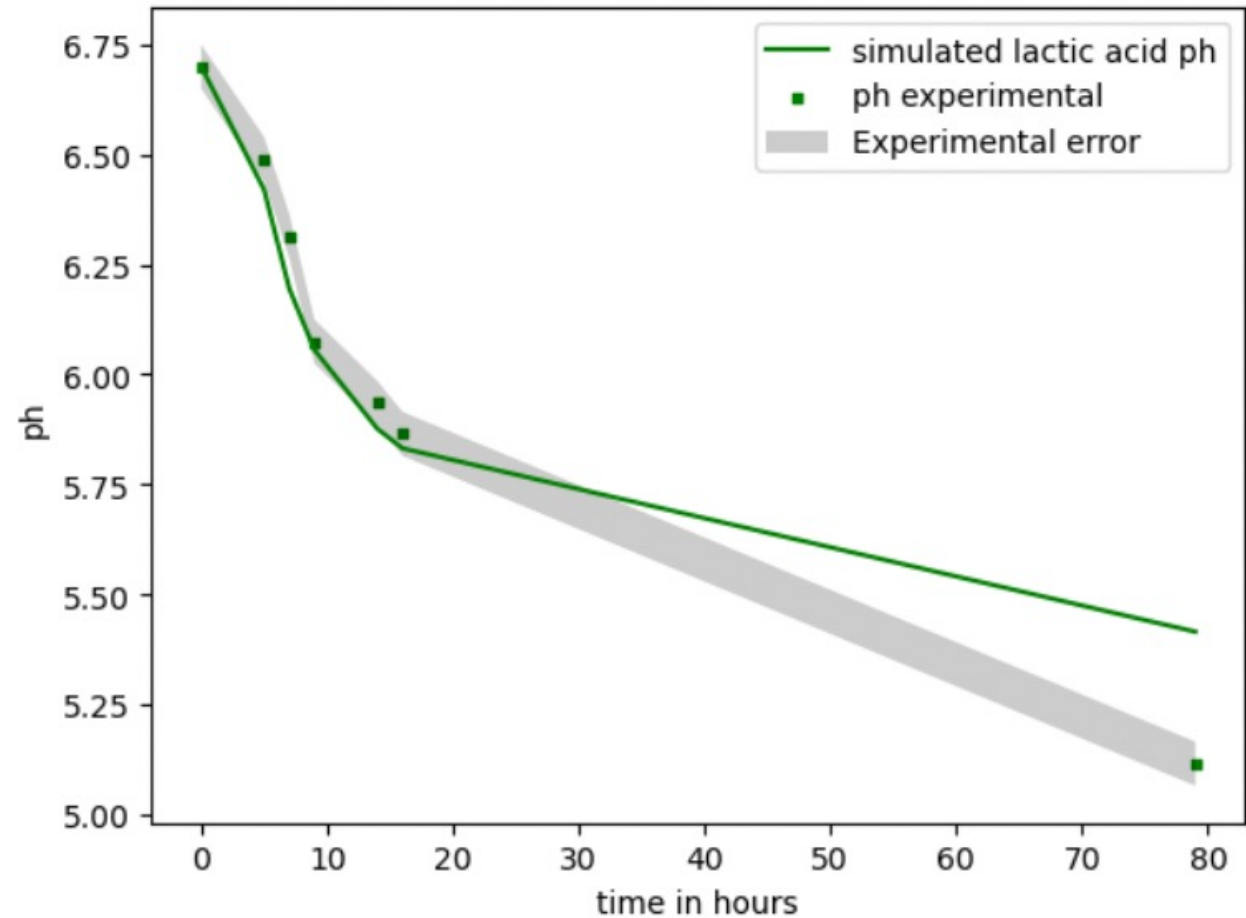
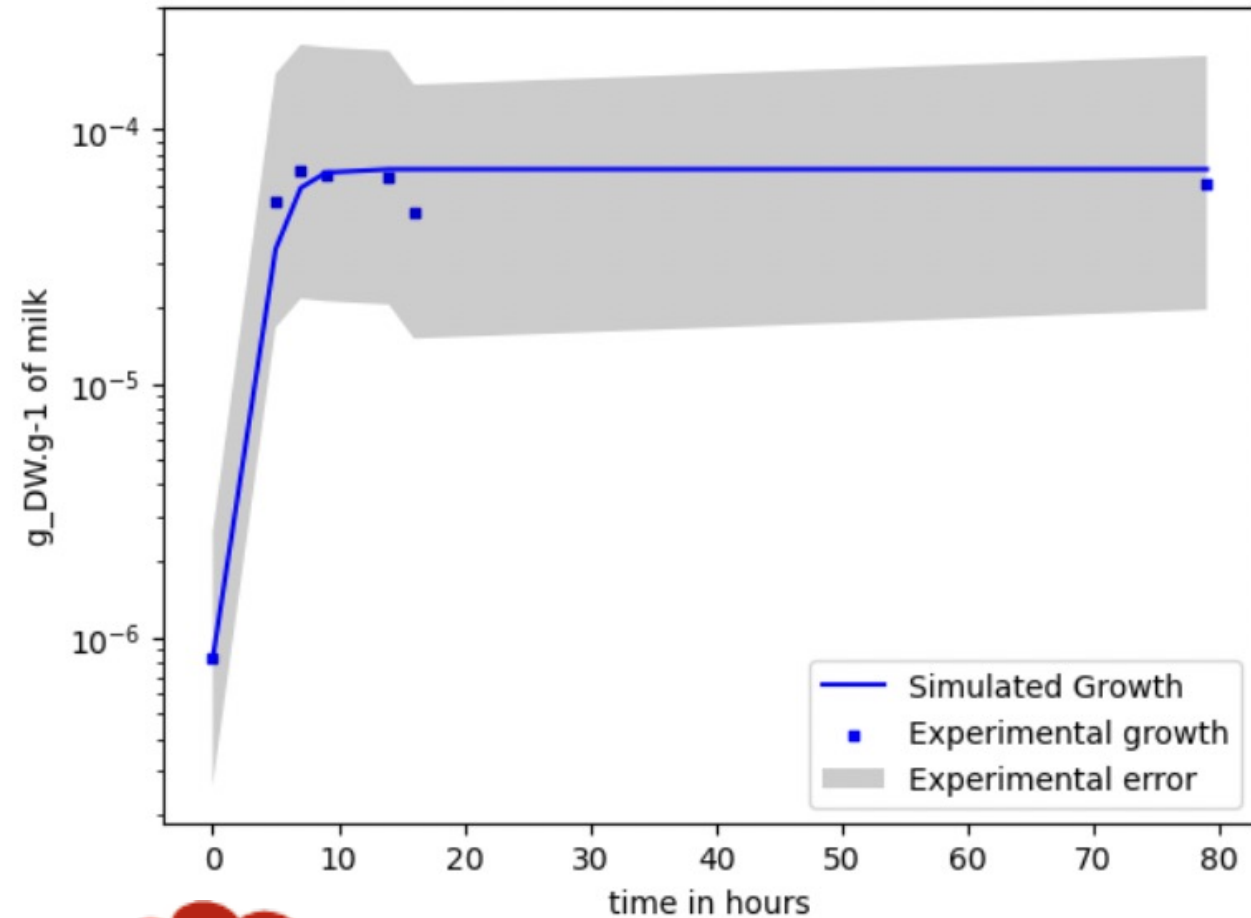
Optimizing dynamic models on pure cultures

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

- Lambda   
- QS   
- K_{lactate} 
- C1 & C2  
- V_{min} & V_{max} lactose 
- Lactate_{upper} 

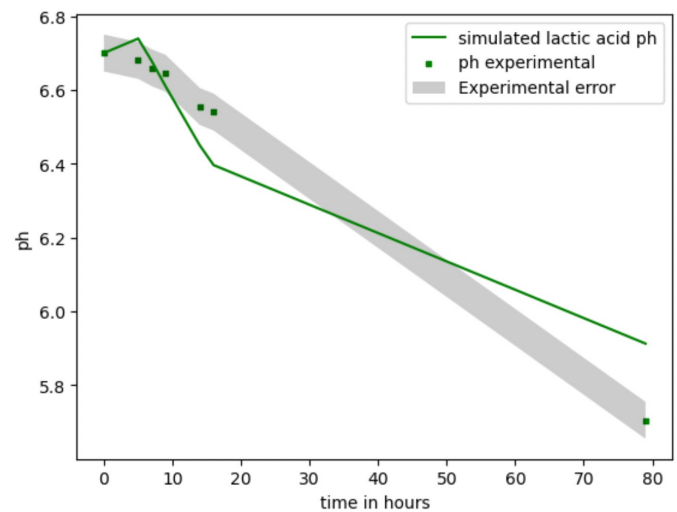
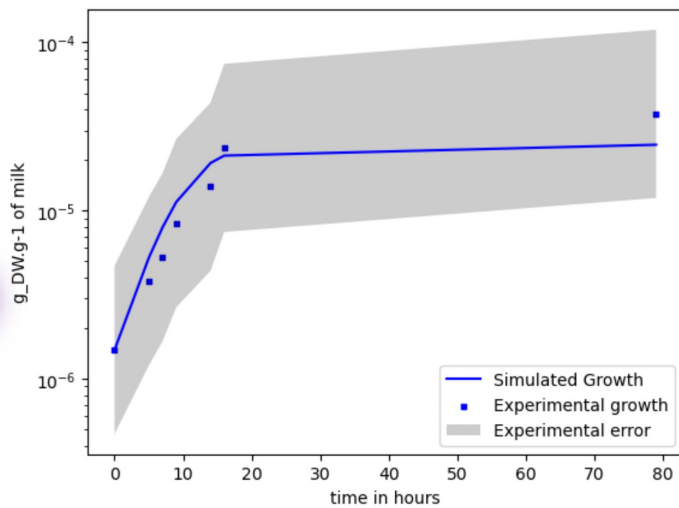
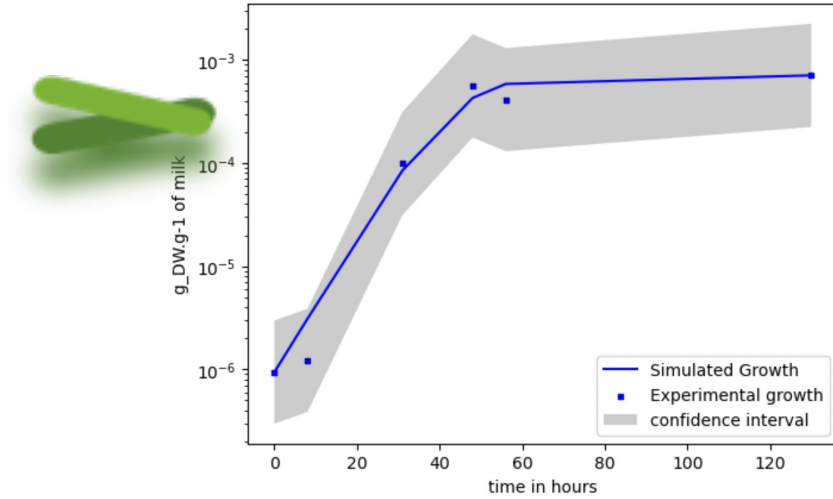
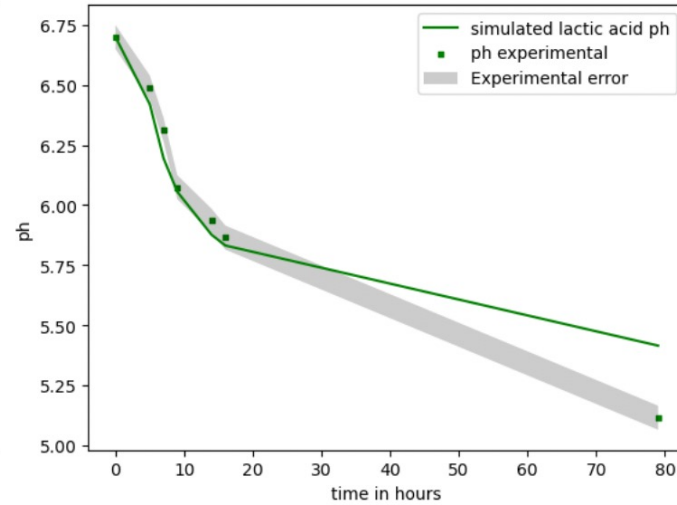
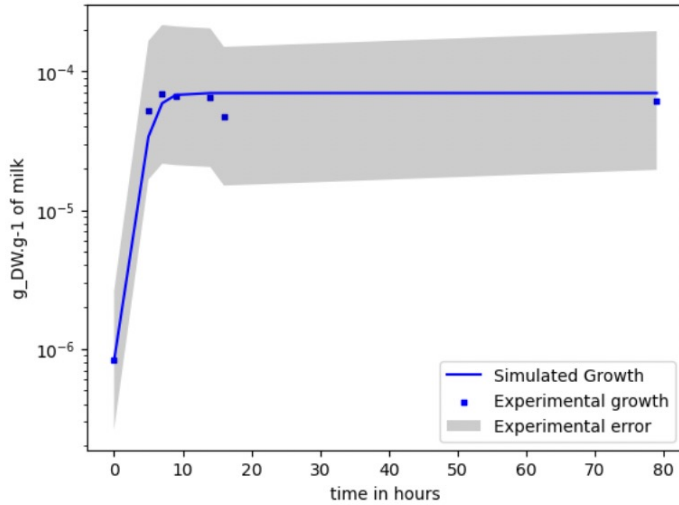
Identification of parameters to fit with experimental data

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



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

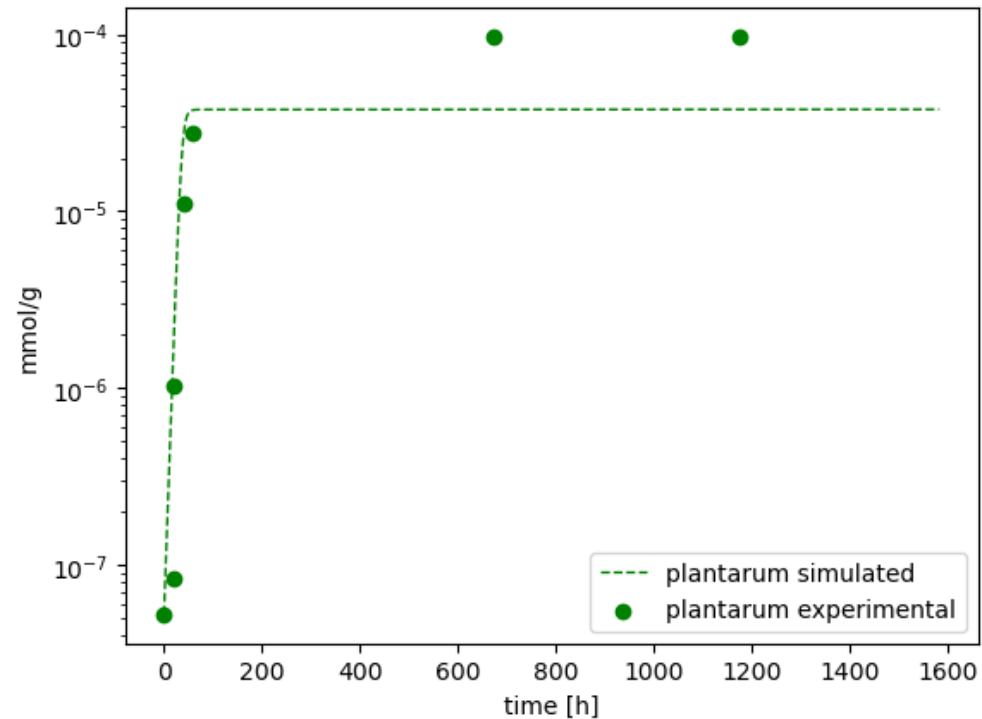
Optimised dFBA models for each bacterium

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

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

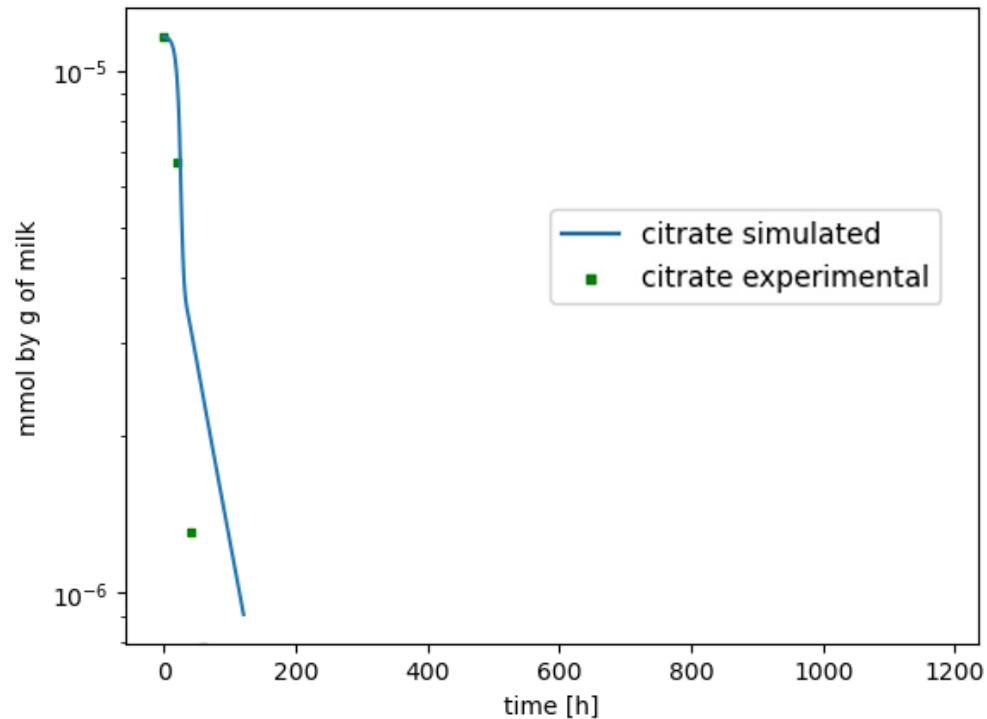
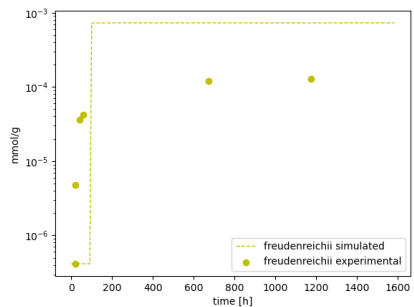
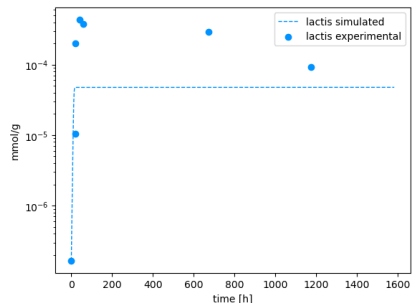
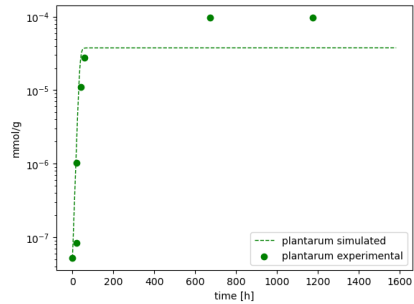
$$\text{where } v(t) = \begin{cases} V_M & \text{if } t \leq t_M \\ V_M + \frac{t-t_M}{t_D-t_M} V_D & \text{if } t_M \leq t \leq t_D \\ V_D & \text{if } t \geq t_D \end{cases}$$

Community dFBA results



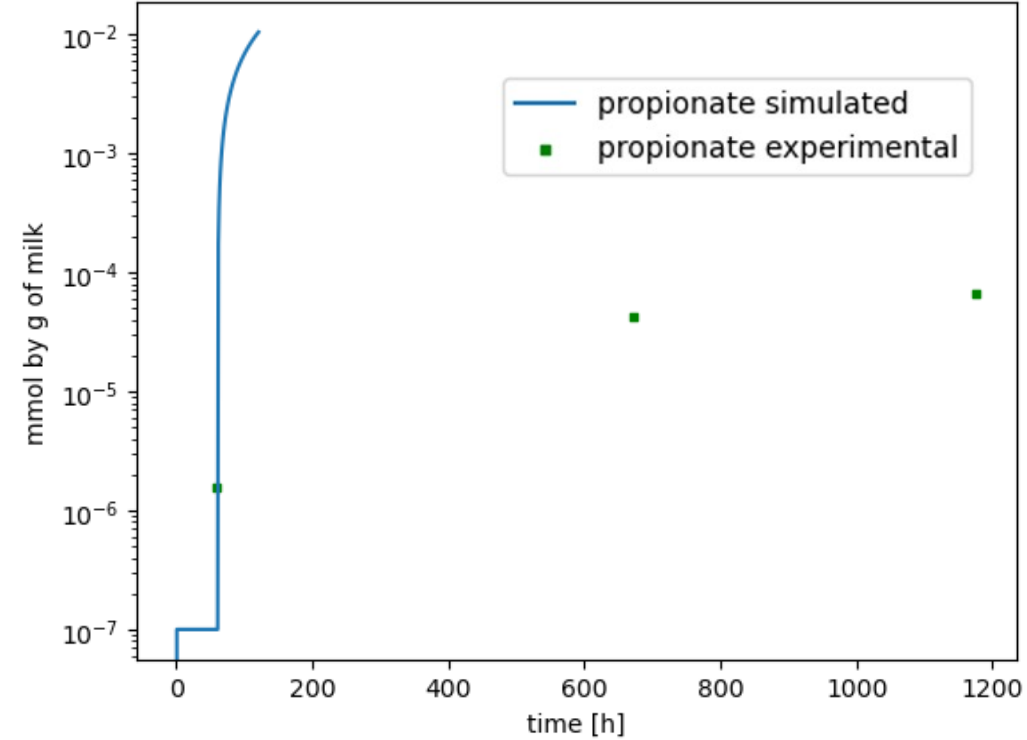
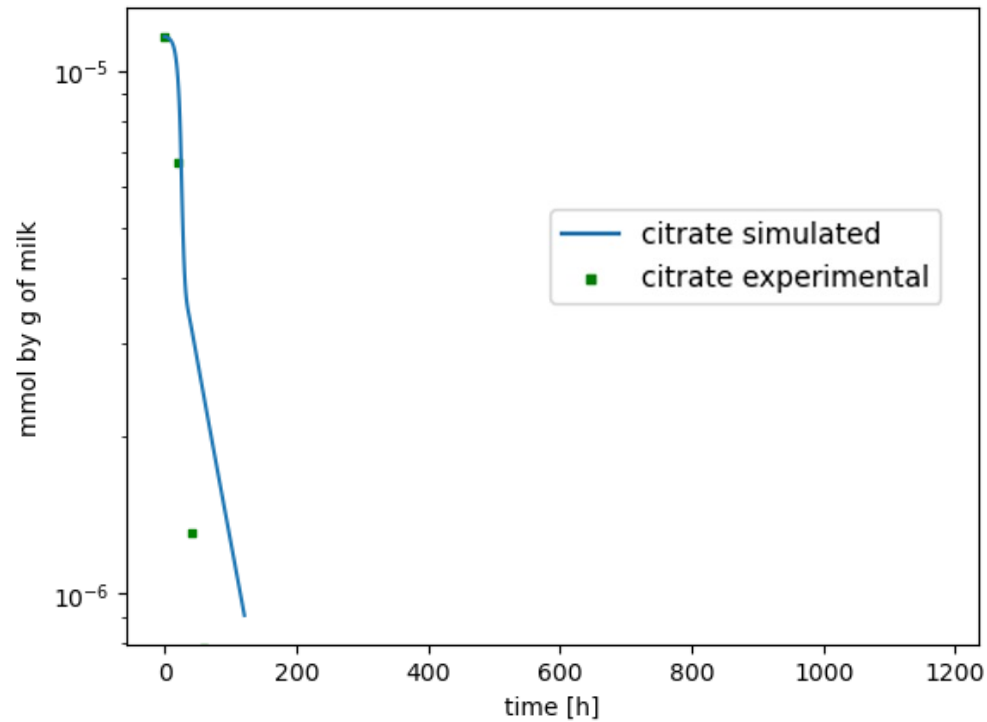
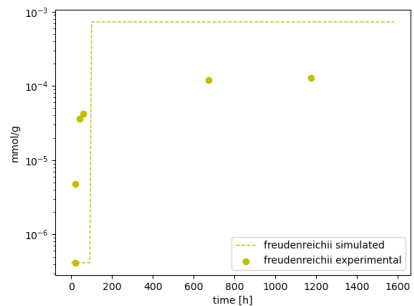
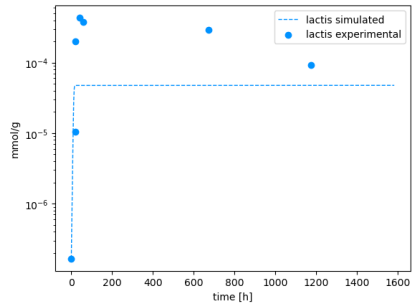
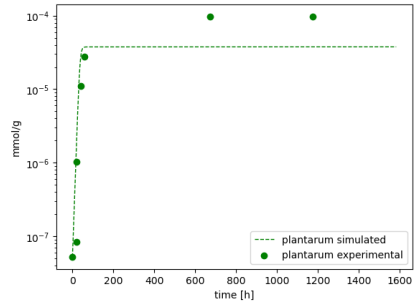
Bacterial growth computed with community dFBA fits with experimental data

Community dFBA results



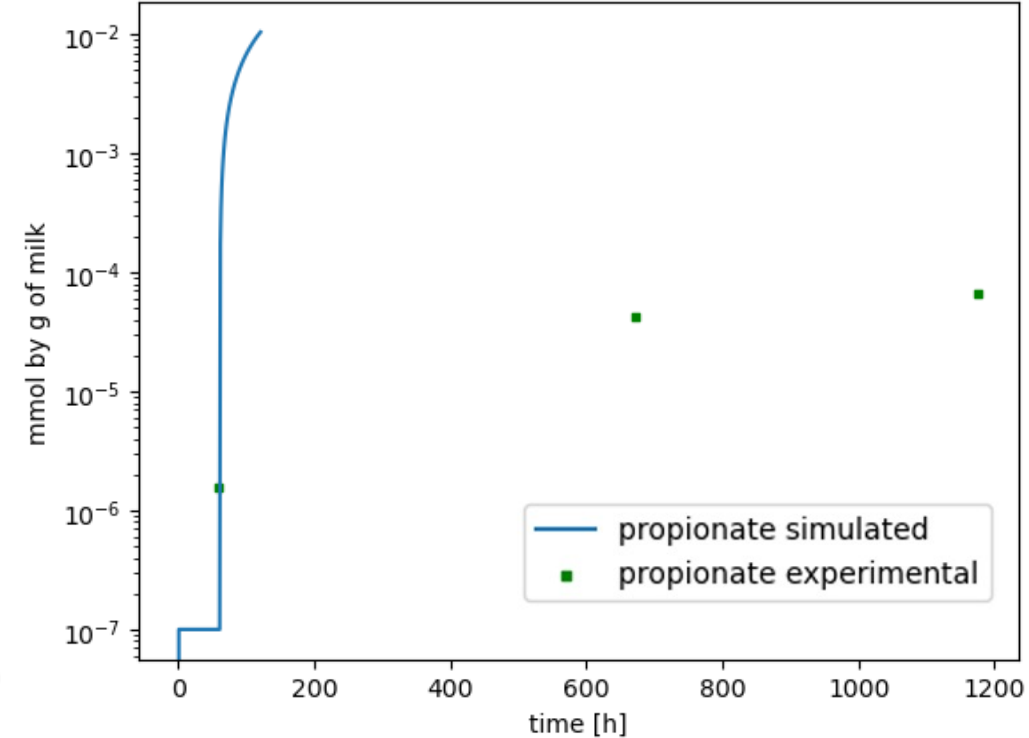
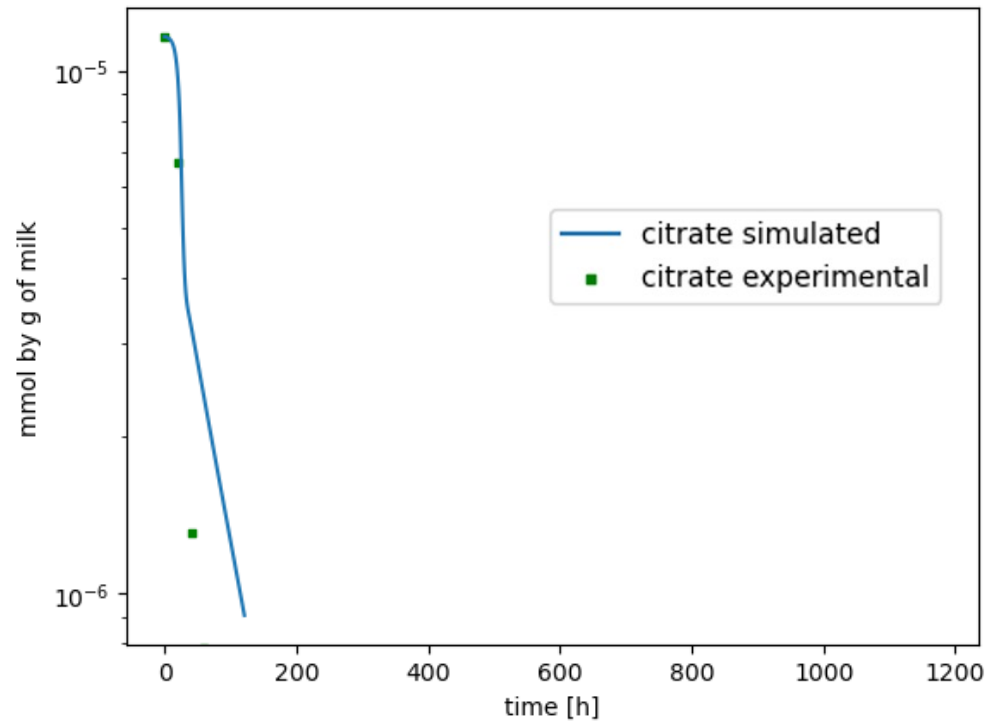
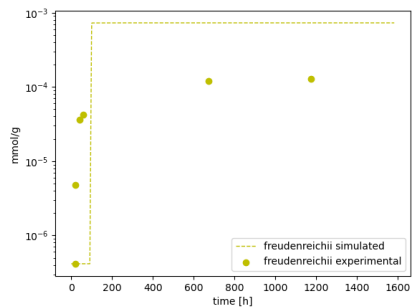
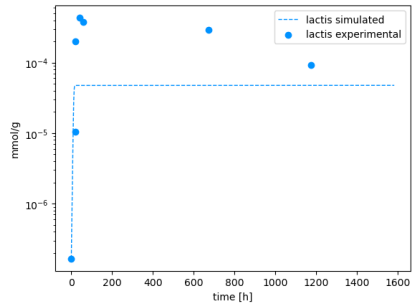
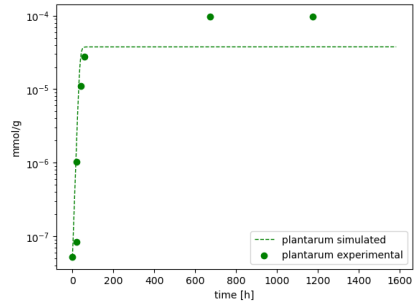
Some metabolites fit with metabolomics data ...

Community dFBA results



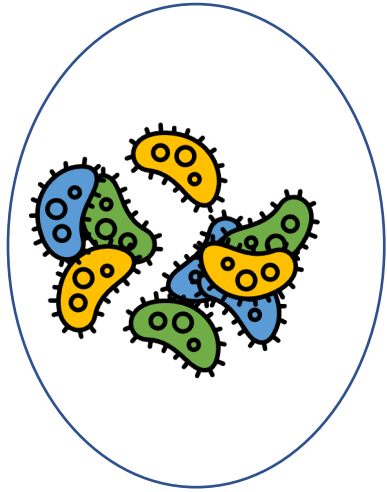
Not all of them

Community dFBA results

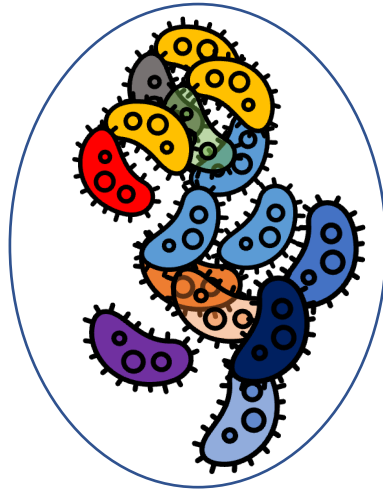


- The model do not capture all modifications brings by the community
- Integration of transcriptomic data is not significantly different
- Is qualitative result enough for characterizing communities ?

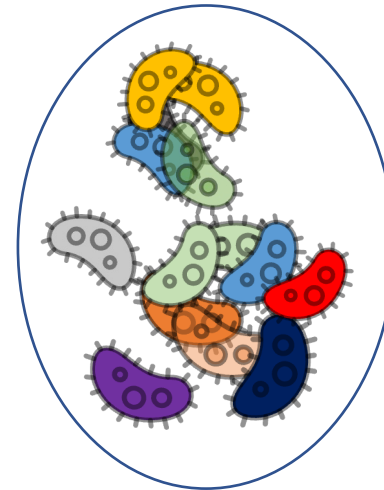
Characterizing natural communities (meta)genomics data



Community 1



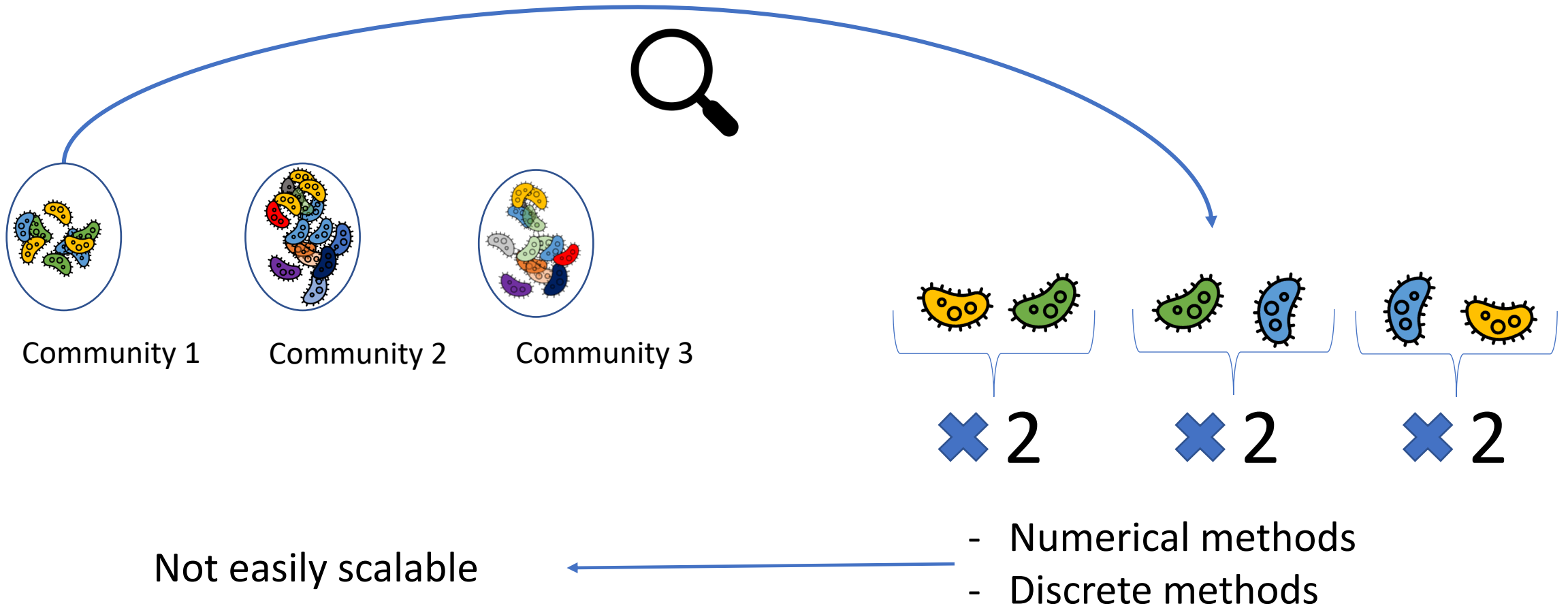
Community 2



Community 3

Calculating cooperation and competition potentials

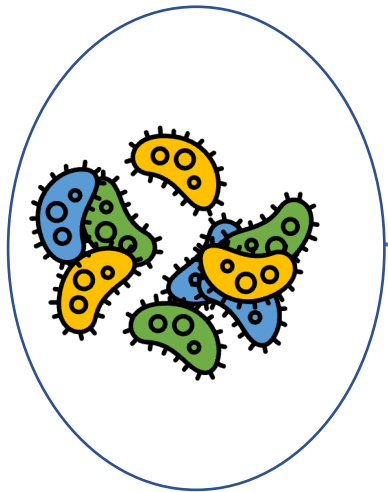
Characterizing natural communities with (meta)genomics data



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)



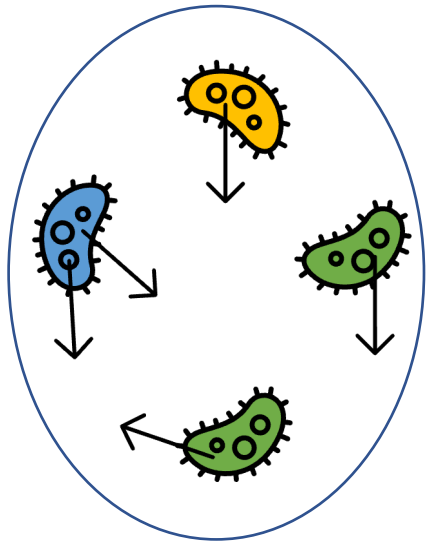
Descriptive

vocabular
using ASP

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

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

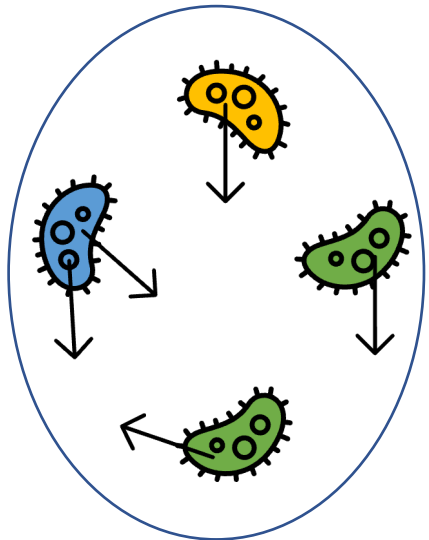
Cooperation and competition metrics



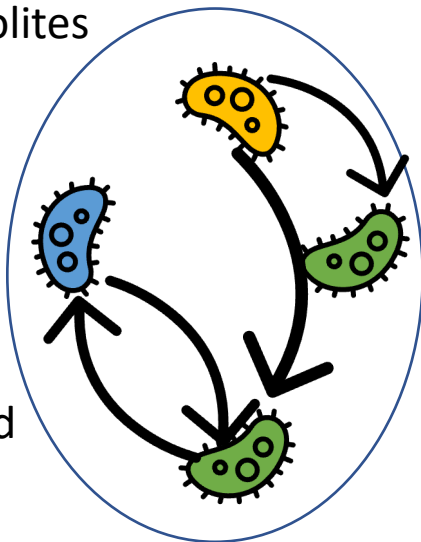
Number of metabolites
produced



Cooperation and competition metrics



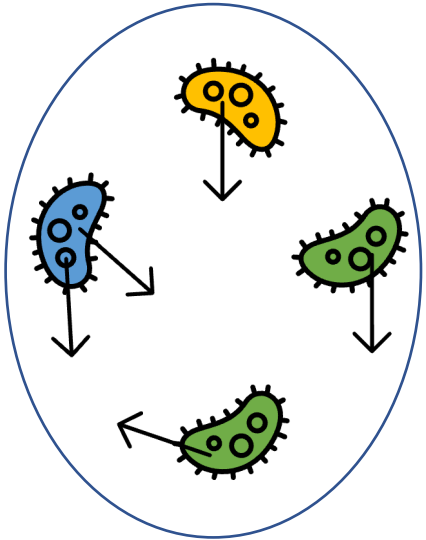
Number of metabolites produced



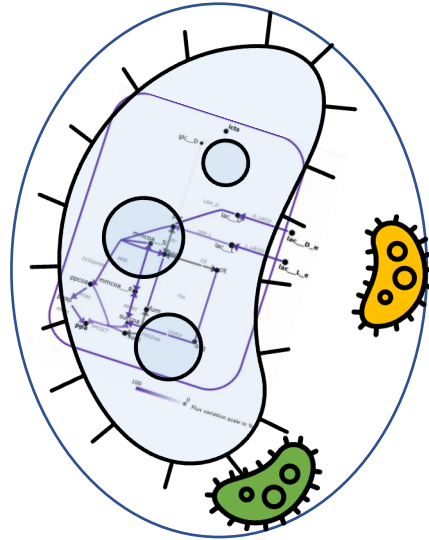
Number of exchanged metabolites



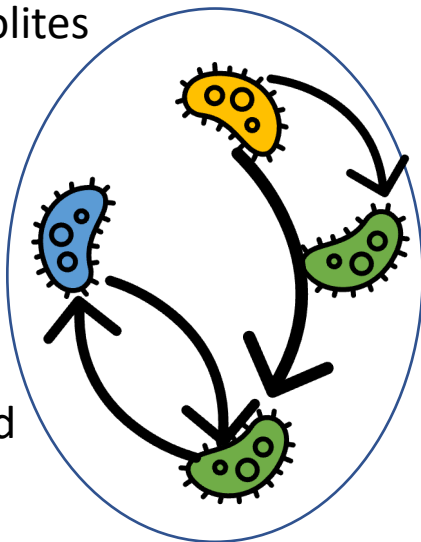
Cooperation and competition metrics



Number of metabolites produced



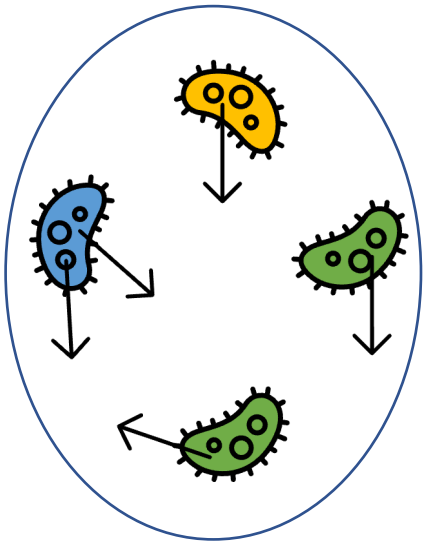
Number of activated reactions



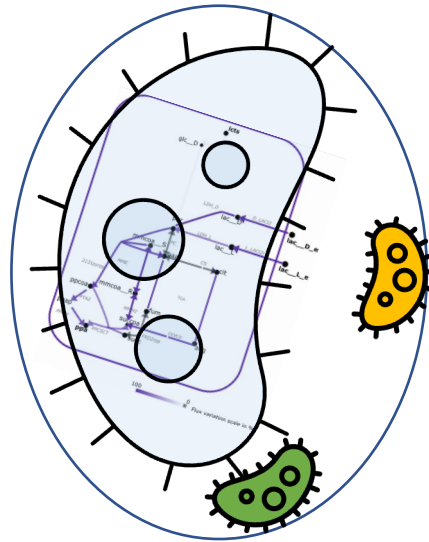
Number of exchanged metabolites



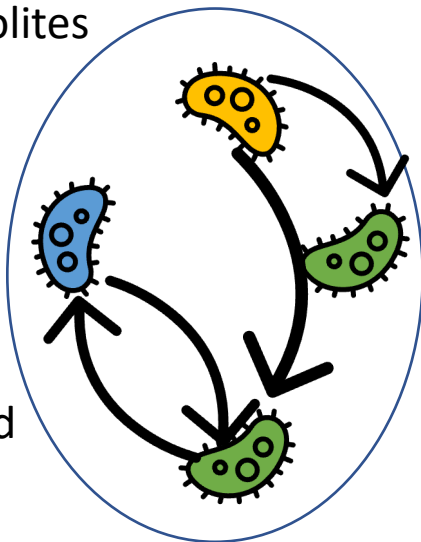
Cooperation and competition metrics



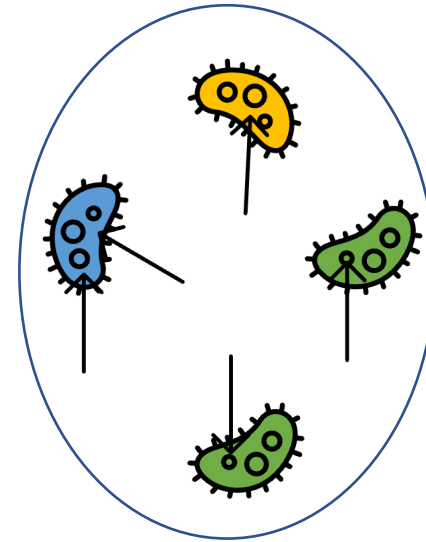
Number of metabolites produced



Number of activated reactions

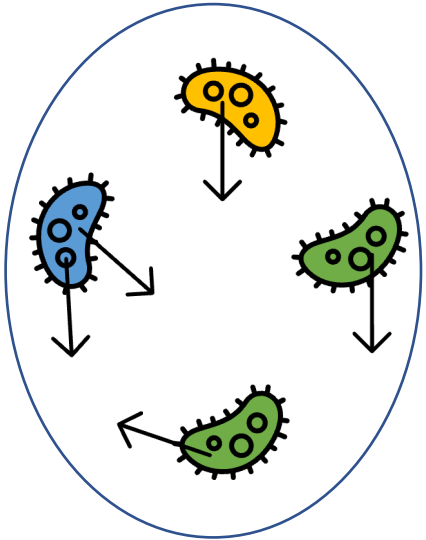


Number of exchanged metabolites

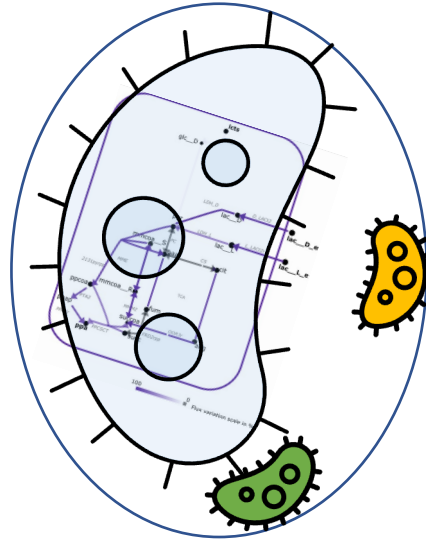


Related to limiting substrates consumed

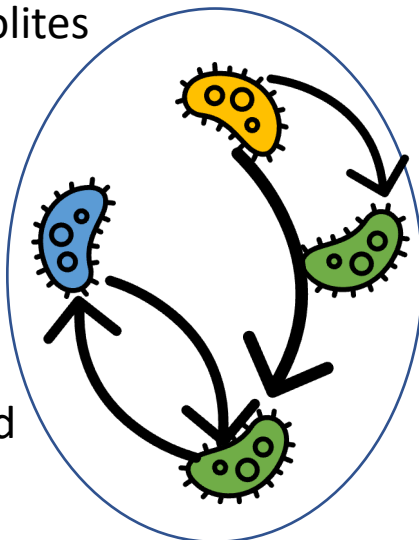
Cooperation and competition metrics



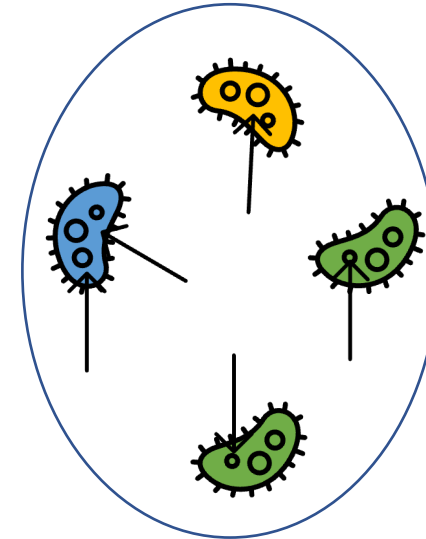
Number of metabolites produced



Number of activated reactions



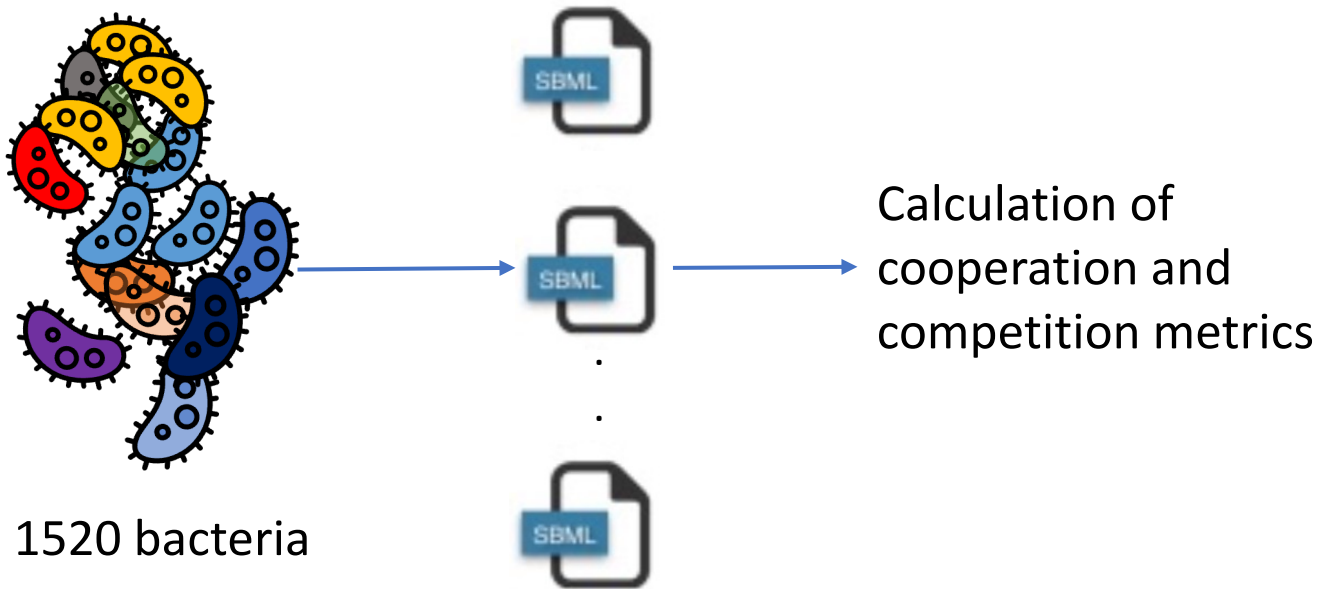
Number of exchanged metabolites



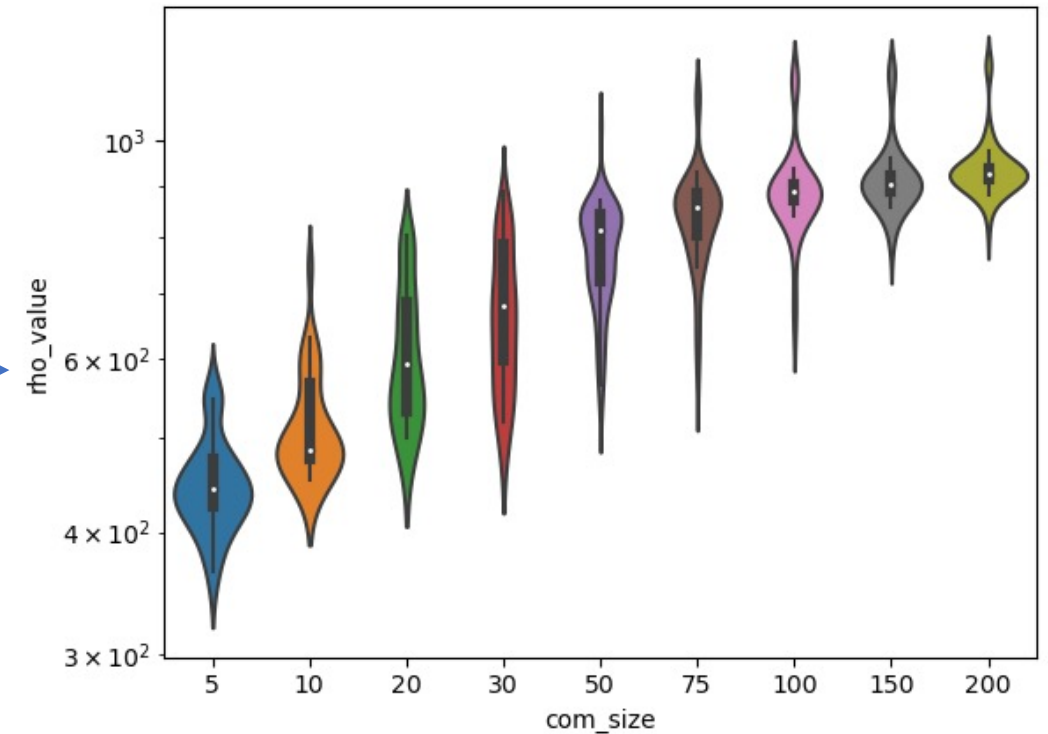
Related to limiting substrates consumed

Unify cooperation metrics to one unique score

Model test on designed communities

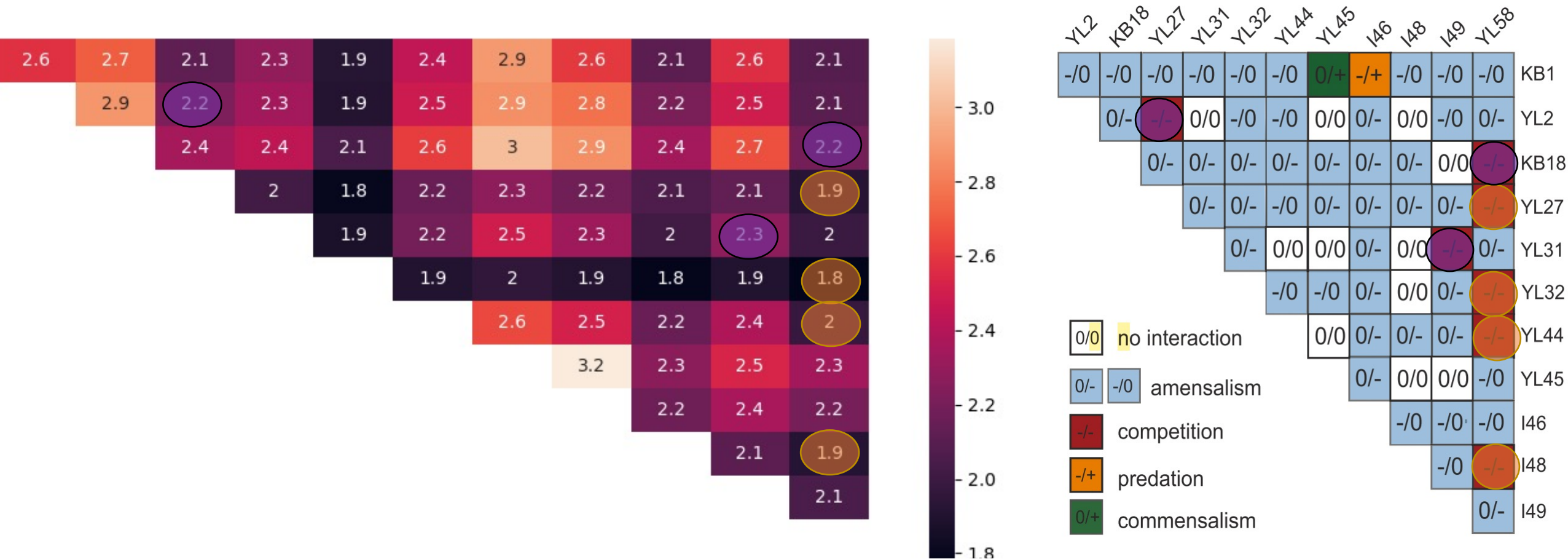


50 random communities
of size 5 to 200



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

