

Characterizing microbial interactions in controlled and natural microbial communities

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

▶ **To cite this version:**

Maxime Lecomte, Simon Labarthe, David James Sherman, Hélène Falentin, Clémence Frioux. Characterizing microbial interactions in controlled and natural microbial communities. Workshop SimBioDiversity, 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)

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

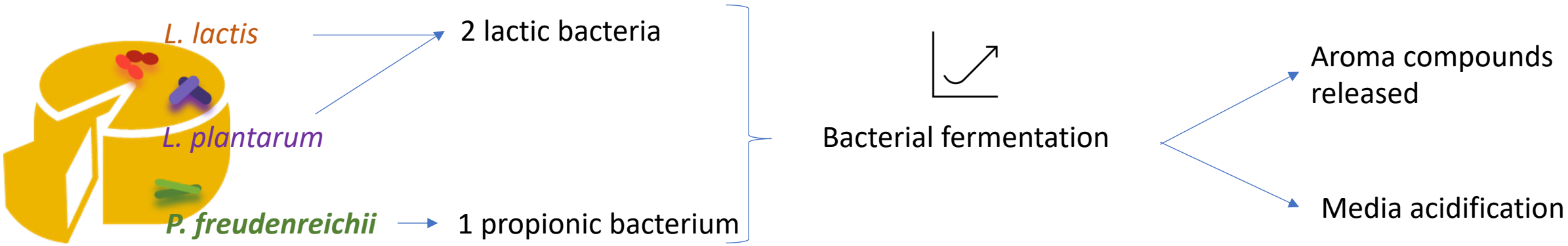
Characterizing microbial interactions in controlled and natural microbial communities

Maxime Lecomte, Simon Labarthe, David Sherman, Hélène Falentin, Clémence Frioux

Workshop SimBioDiversity 2021-2022

maxime.lecomte@inria.fr

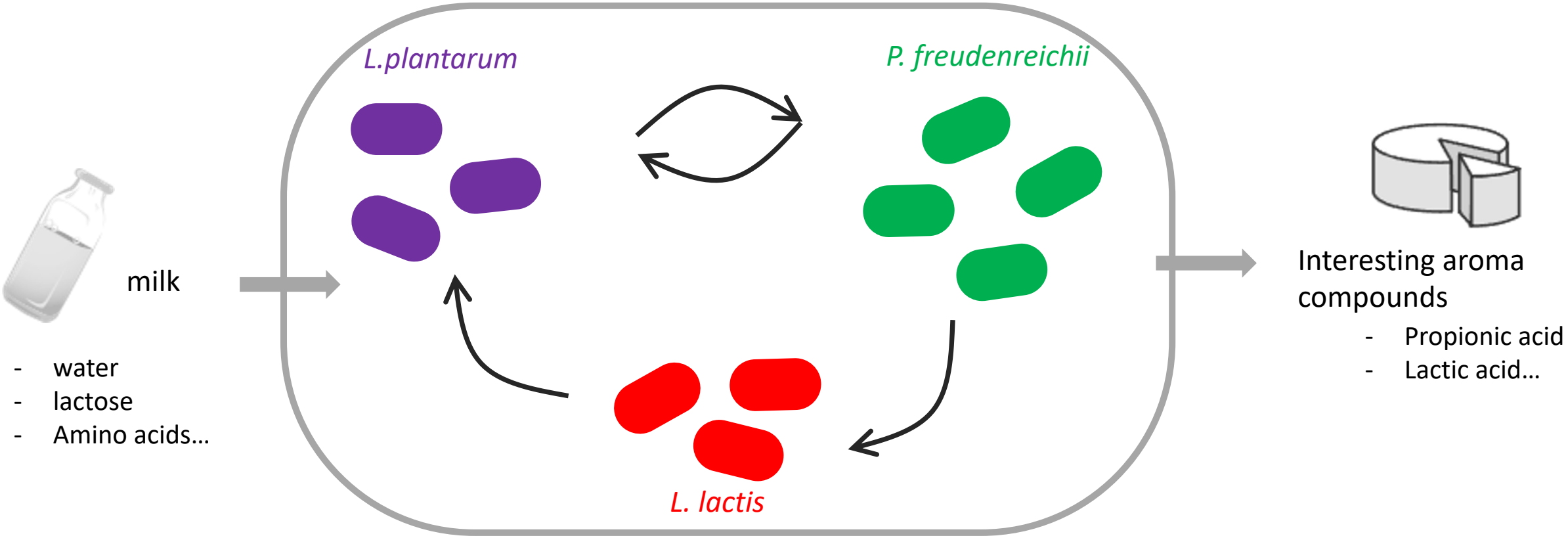
Industrial cheese starter bacterial community as a controlled ecosystem



Which biological phenomena rules aroma compounds production ?

Cao et al, 2021,*Journal of Agricultural and Food Chemistry*

Bacterial fermentation process in cheese



Model the metabolism enable us to monitor compounds

Cao et al, 2021,*Journal of Agricultural and Food Chemistry*

Multi-omics strategy



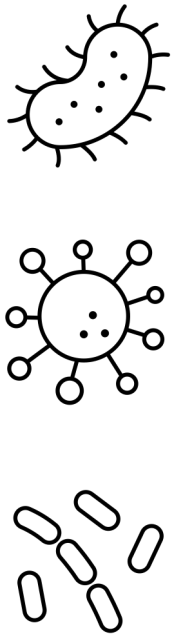
Annotated genomes



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

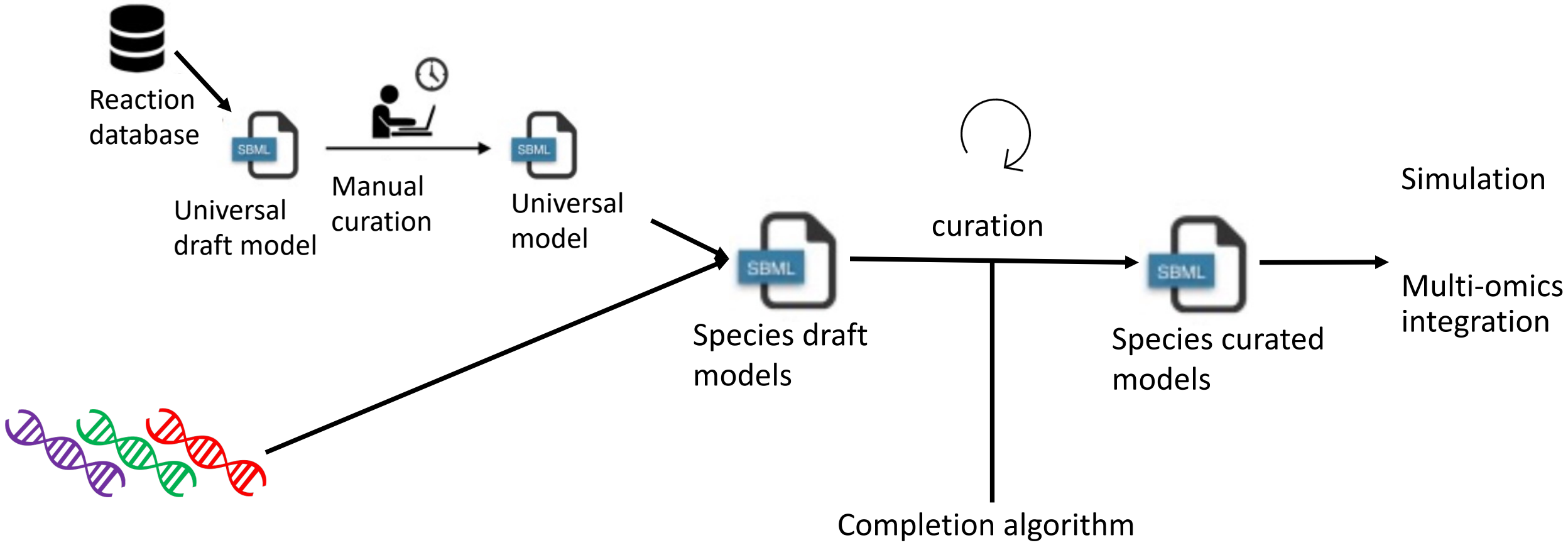


Growth and pH data in pure cultures

To integrate all this data, we first reconstruct the metabolism

Cao et al,2021,*Journal of Agricultural and Food Chemistry*

Inference of genome-scale metabolic networks



Machado, D. et al, 2018, *Nucleic Acids Research*

FBA as a numerical model of metabolism

Stoichiometric matrix =

$$\begin{array}{c} \text{metabolites} \\ \text{A} \\ \text{B} \\ \text{C} \end{array} \begin{array}{c} \begin{array}{ccc} r_1 & \dots & r_n \end{array} \\ \begin{pmatrix} -1 & \dots & 0 \\ 1 & \dots & -2 \\ 0 & \dots & 1 \end{pmatrix} \end{array}$$

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

Orth, J. D. et al,2010,*Nature Biotechnology*

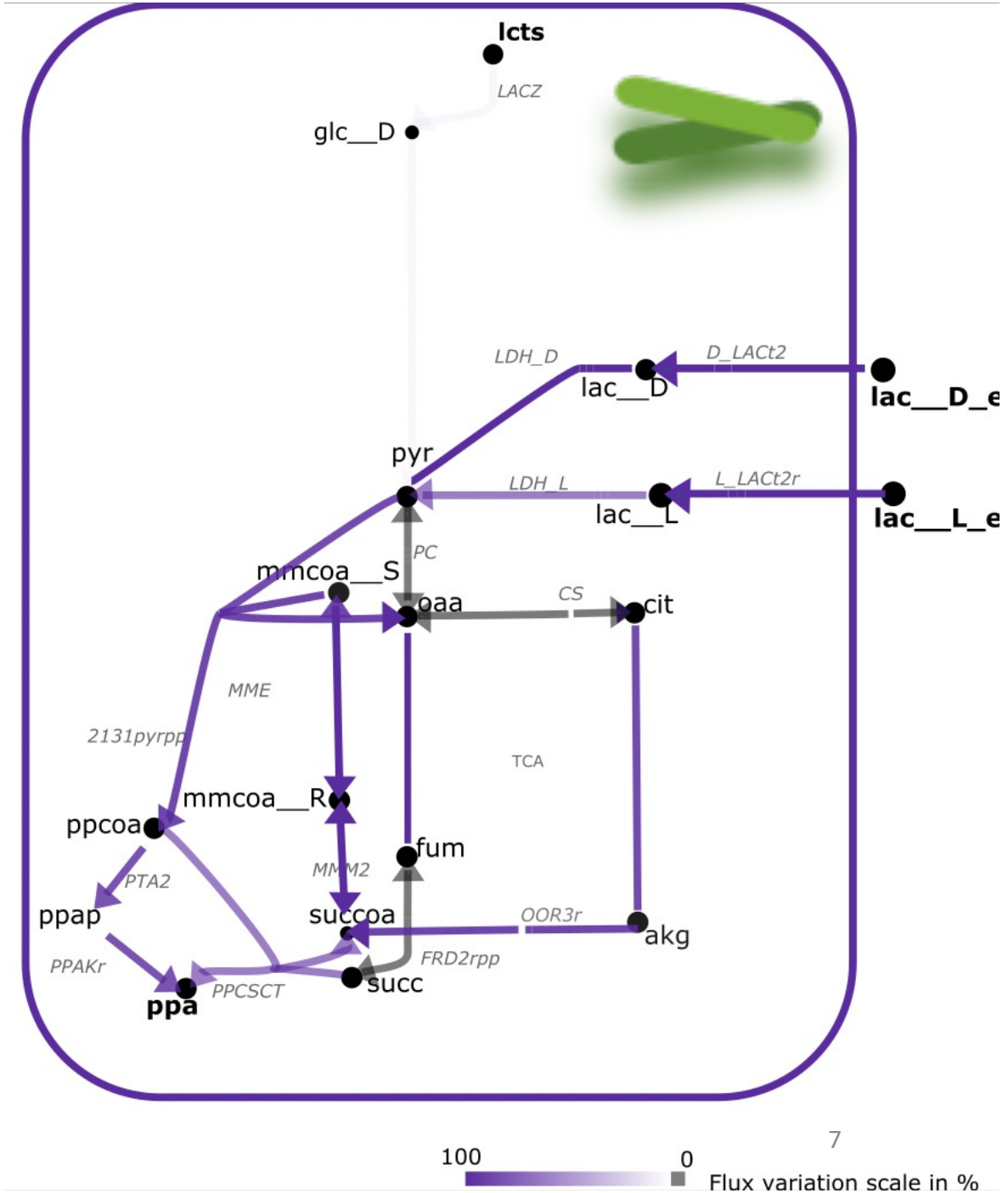
FBA as a numerical model of metabolism

Stoichiometric matrix =

$$\begin{array}{c} \text{metabolites} \\ \text{A} \\ \text{B} \\ \text{C} \end{array} \begin{array}{c} \begin{array}{ccc} r_1 & \dots & r_n \end{array} \\ \begin{pmatrix} -1 & \dots & 0 \\ 1 & \dots & -2 \\ 0 & \dots & 1 \end{pmatrix} \end{array}$$

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

Flux distribution that maximizes biomass production



Orth, J. D. et al,2010,*Nature Biotechnology*
King, Z. et al,2015. *PLoS Computational Biology*

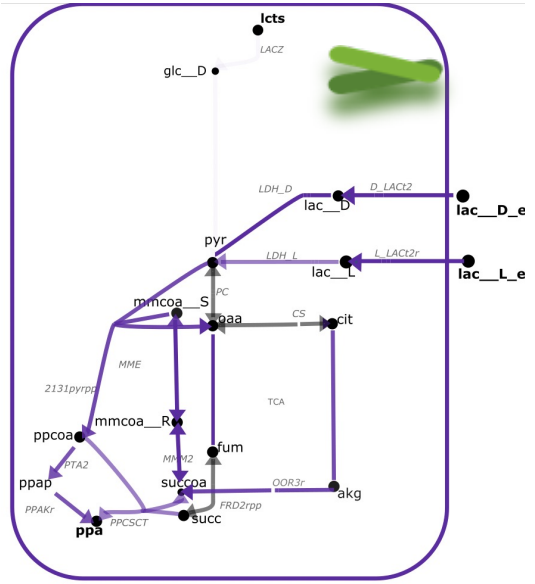
FBA as a numerical model of metabolism

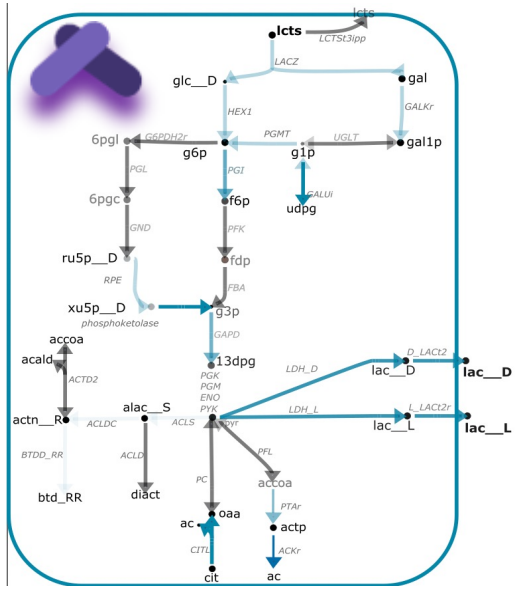
Stoichiometric matrix =

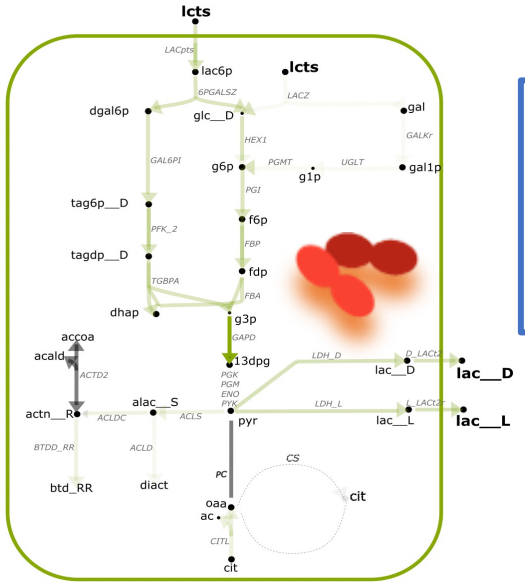
$$\begin{array}{c} \text{metabolites} \\ \text{A} \\ \text{B} \\ \text{C} \end{array} \begin{array}{c} \begin{array}{ccc} r_1 & \dots & r_n \end{array} \\ \begin{pmatrix} -1 & \dots & 0 \\ 1 & \dots & -2 \\ 0 & \dots & 1 \end{pmatrix} \end{array}$$

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

Flux distribution that maximizes biomass production







Individual models are in accordance with literature

Orth, J. D. et al,2010,*Nature Biotechnology*
King, Z. et al,2015. *PLoS Computational Biology*

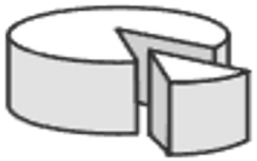
Thierry, A et al,2011, *International Journal of Food Microbiology*
Loux, V. et al, 2015, *BMC Genomics*

Cheese production: a dynamic and complex biological process

Liquid environment



solid environment



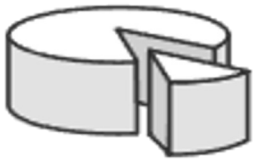
The consistency of the environment changes

Cheese production: a dynamic and complex biological process

Liquid environment



solid environment

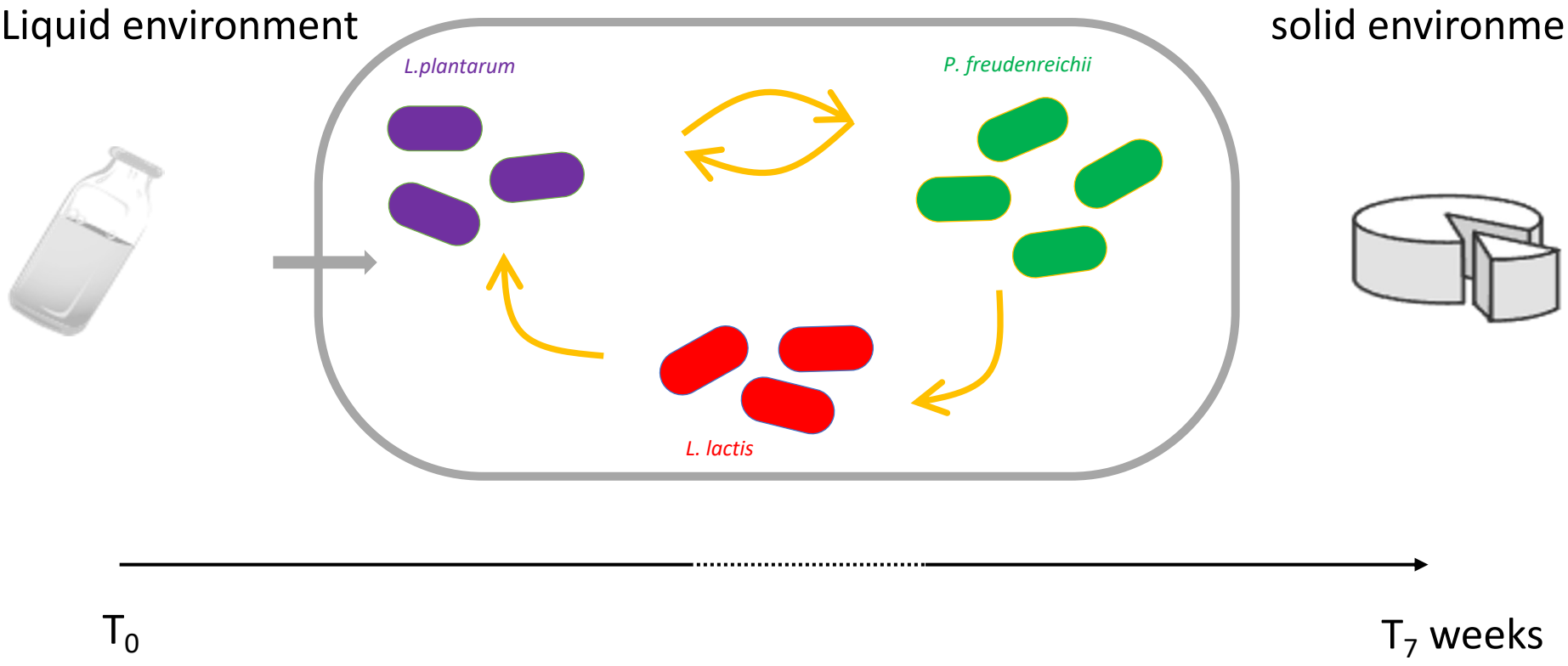


T_0

T_7 weeks

The consistency of the environment changes
A dynamic process

Cheese production: a dynamic and complex biological process

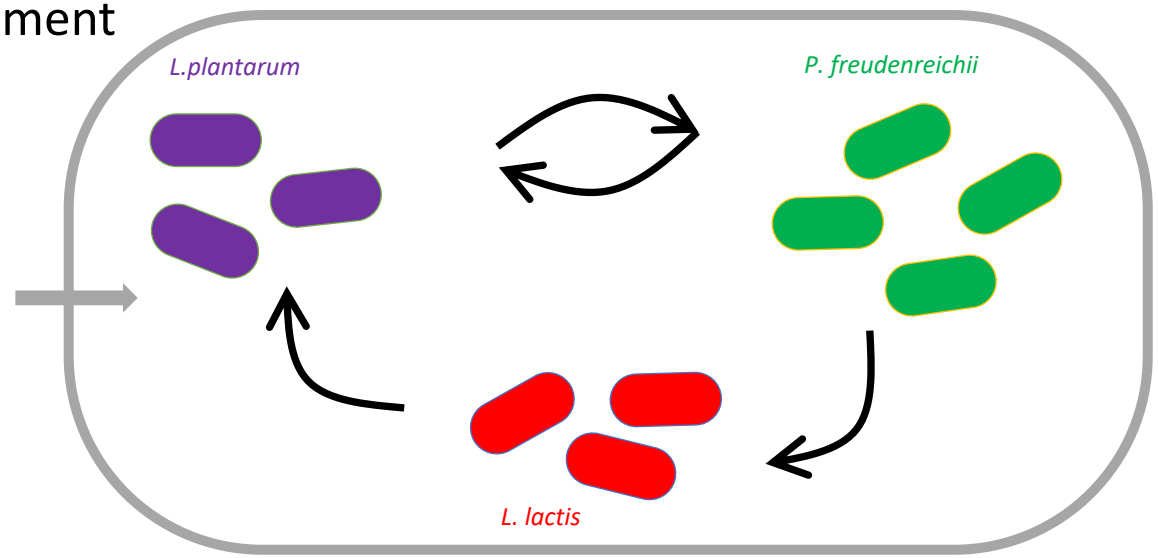


The consistency of the environment changes
A dynamic process
Interaction bacterium-bacterium

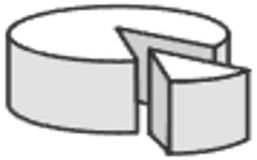
Cheese production: a dynamic and complex biological process

Liquid environment





solid environment



T_0

T_7 weeks

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

Dynamic modeling of metabolism (dFBA)

List of pre-defined interest compounds :

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

Mahadevan et al,2002, *Biophysical Journal*

Dynamic modeling of metabolism (dFBA)

List of pre-defined interest compounds :

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

Bacterial concentration :

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

Mahadevan et al,2002, *Biophysical Journal*

Dynamic modeling of metabolism (dFBA)

List of pre-defined interest compounds :

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

Bacterial concentration :

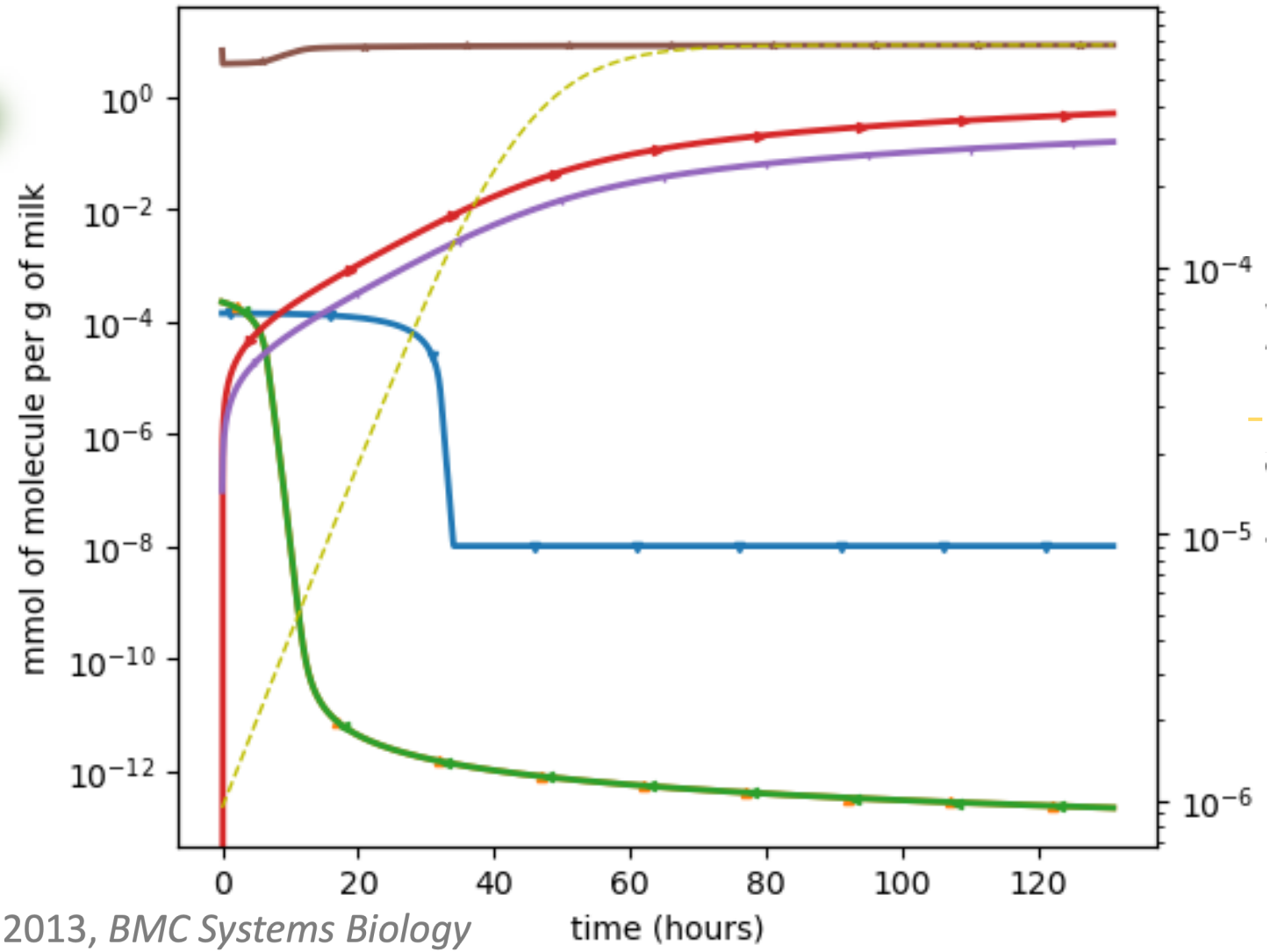
$$\partial_t b_i = q_s(b_i)\mu_{FBA_i}(c)_i b_i$$

q_S = Quorum sensing

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

Mahadevan et al,2002, *Biophysical Journal*

dFBA results of pure cultures



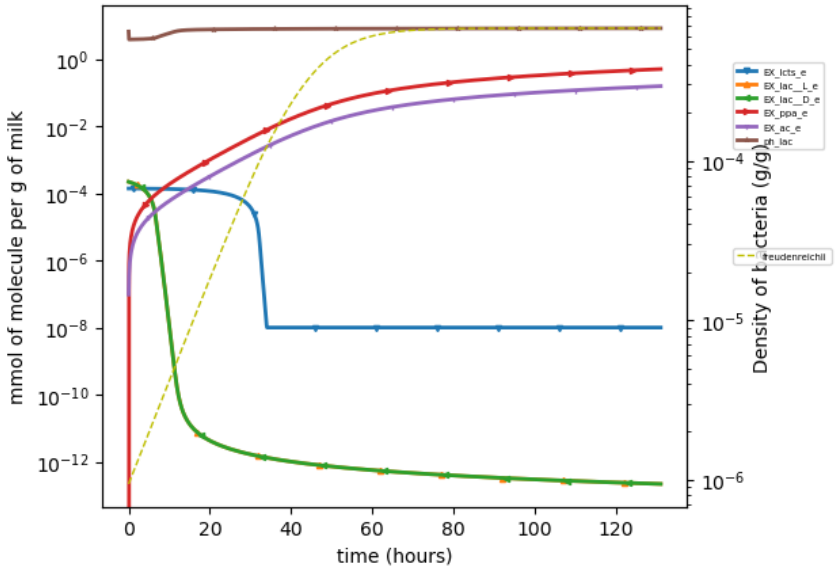
L/D-Lactate
Propionic acid
Lactose
Acetate

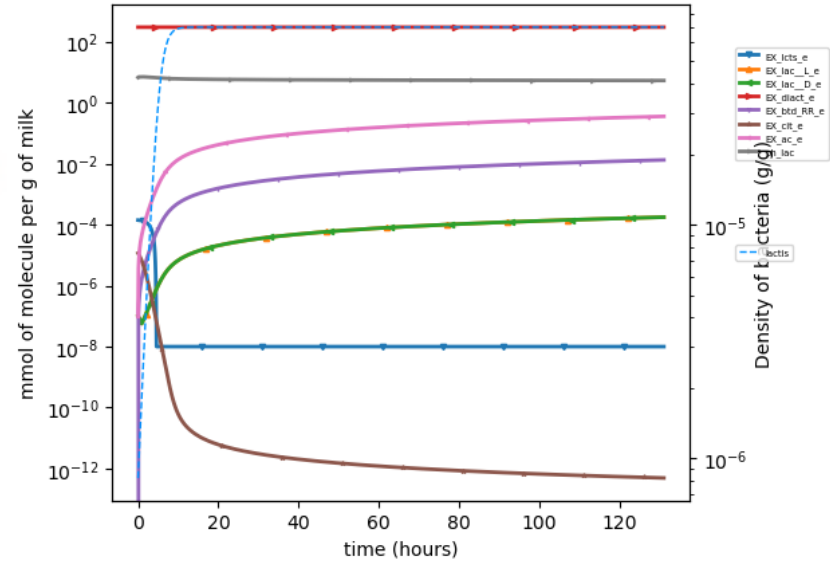
P. freudenreichii

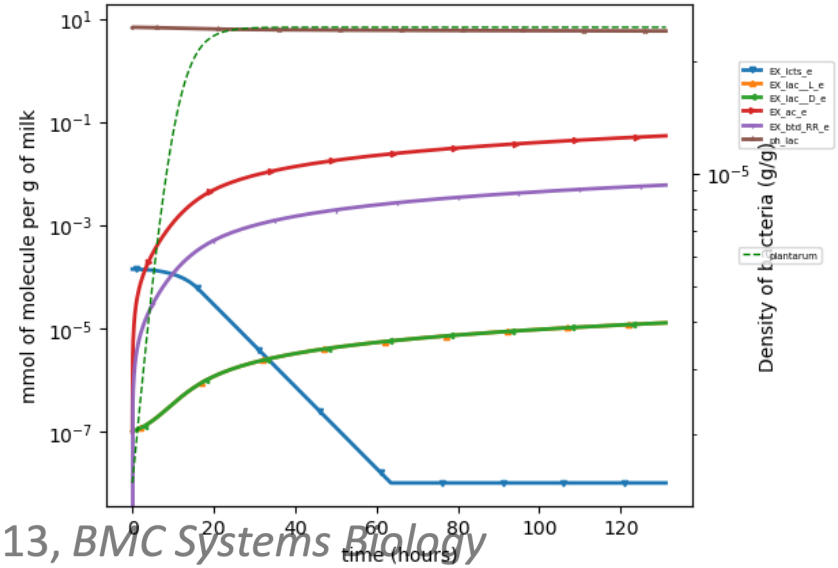
Lactate compounds preferentially used for propionic acid production

Ebrahim et al,2013, *BMC Systems Biology*

dFBA results of pure cultures







Individual dFBA simulations are performed

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

Ebrahim et al,2013, *BMC Systems Biology*

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

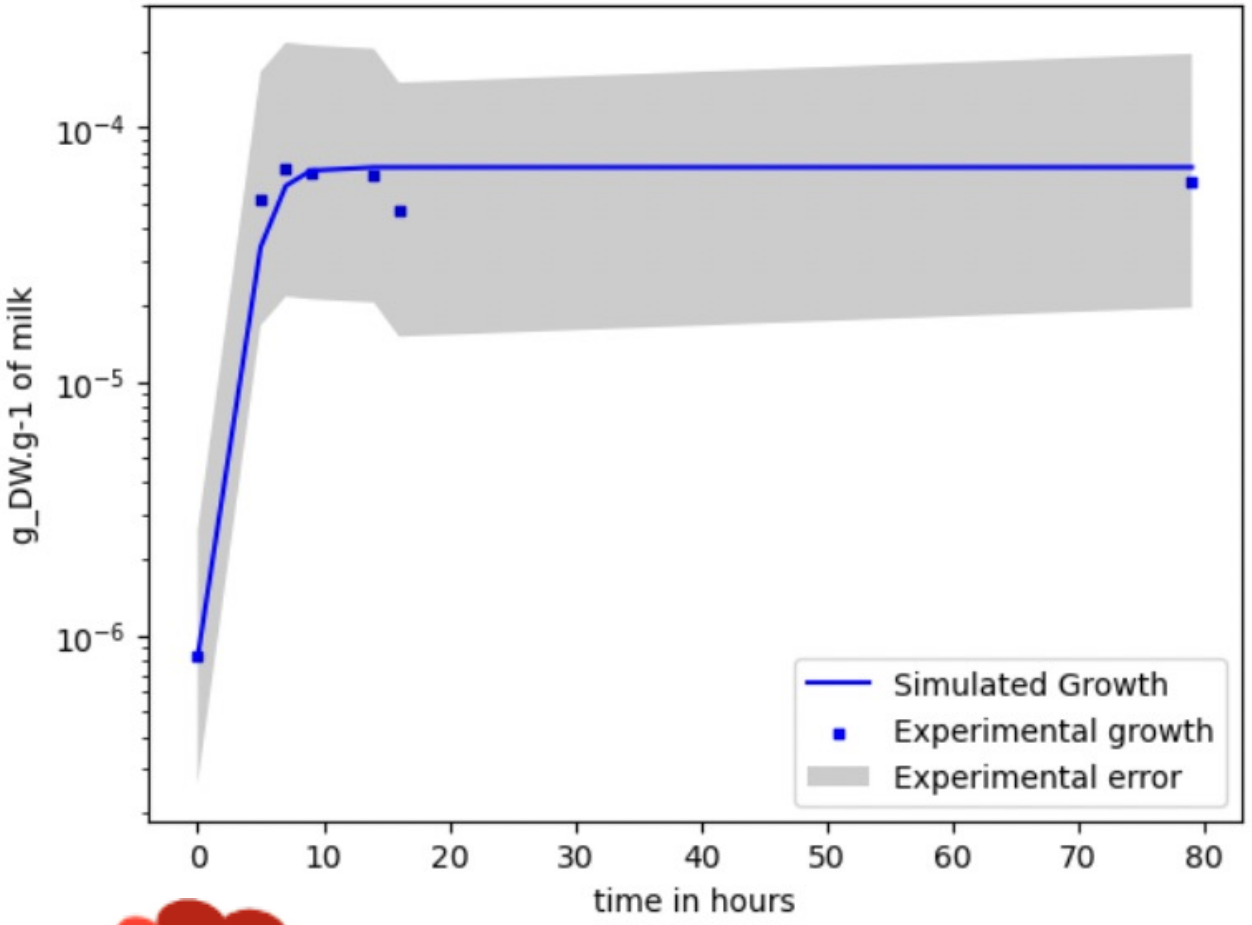
$$J(b, pH | b_{exp}, pH_{exp}) = \|b - b_{exp}\|^2 + \alpha \|pH - pH_{exp}\|^2$$

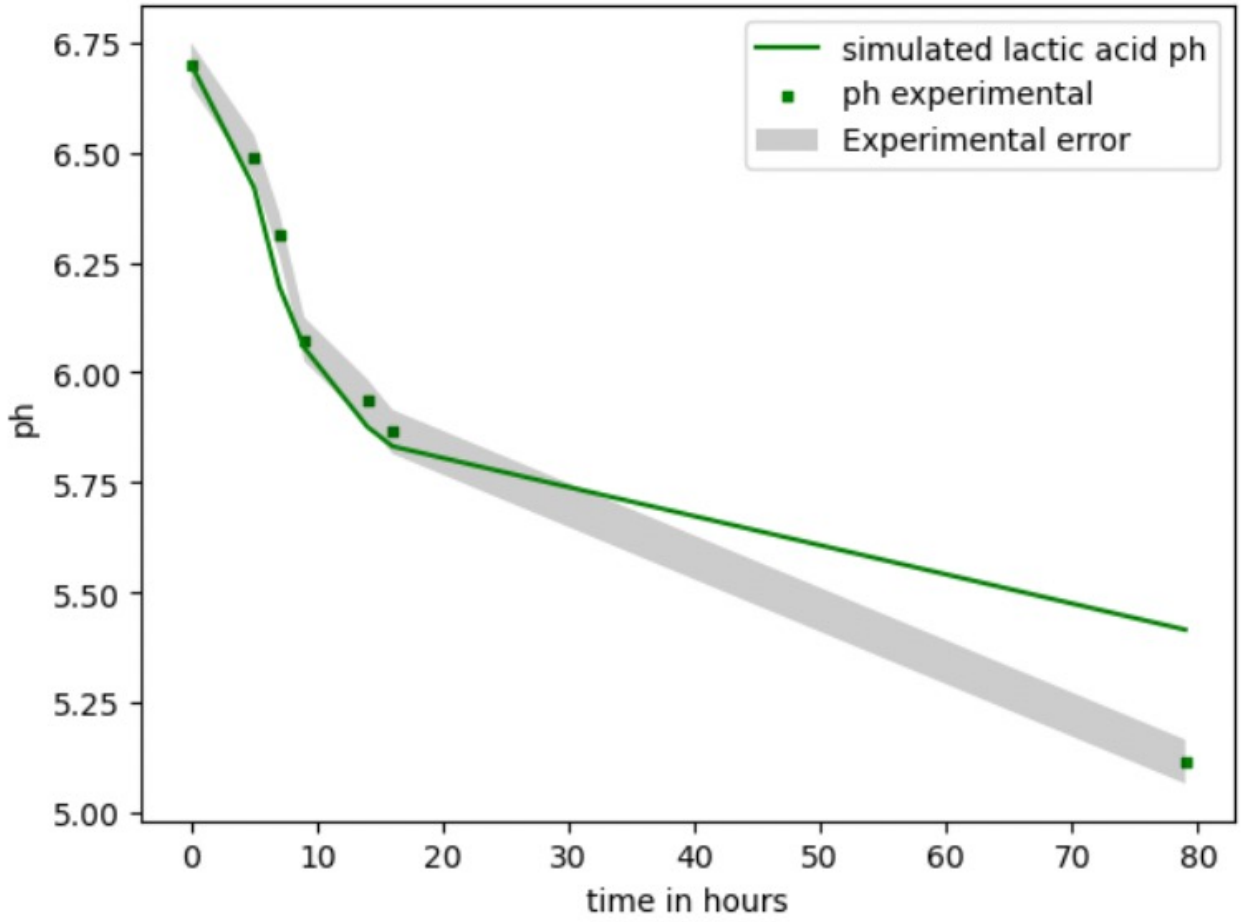
- Lambda 
- QS 
- K_lactate 
- C1 & C2 
- Vmin & Vmax lactose 
- Lactate_upper 

Identification of parameters to fit with experimental data

Virtanen. P, et al,2020, *Nature Methods*

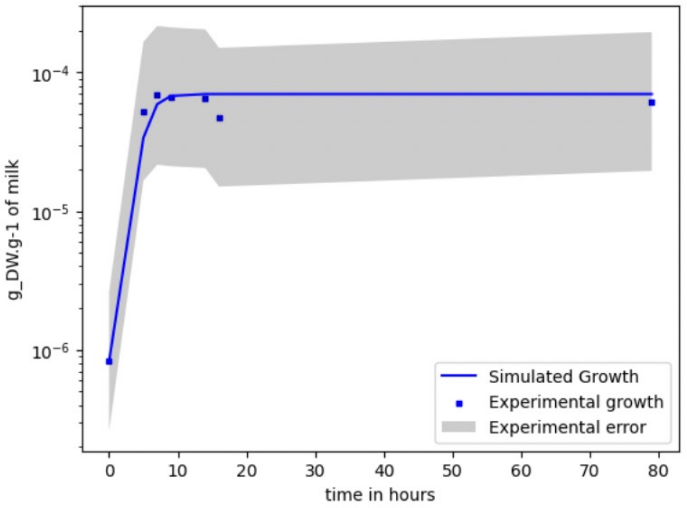
dFBA results after optimization

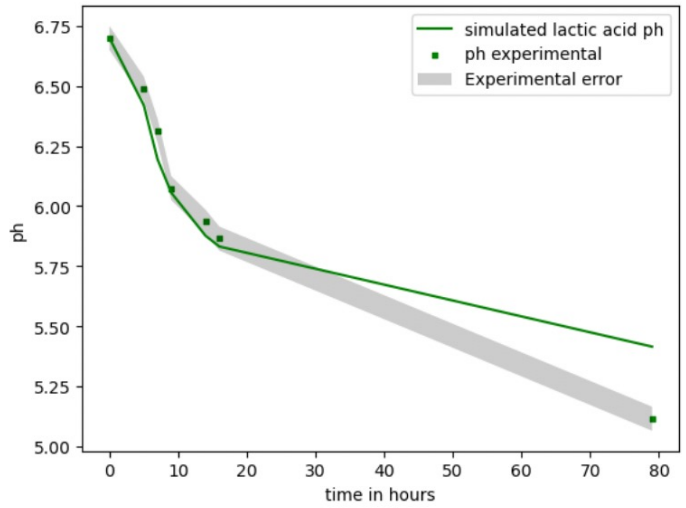


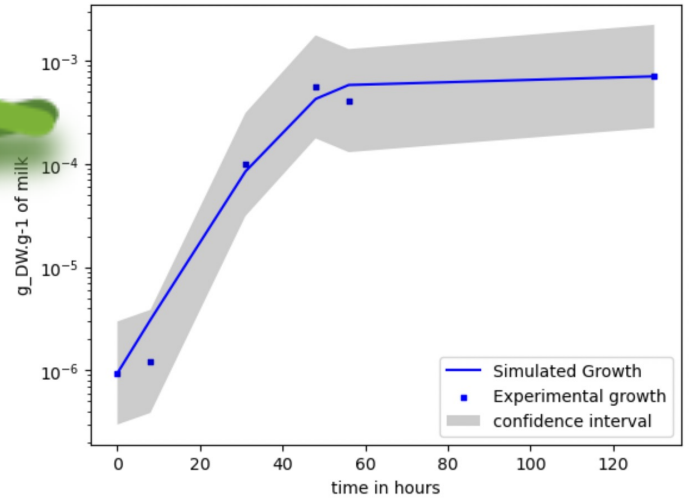


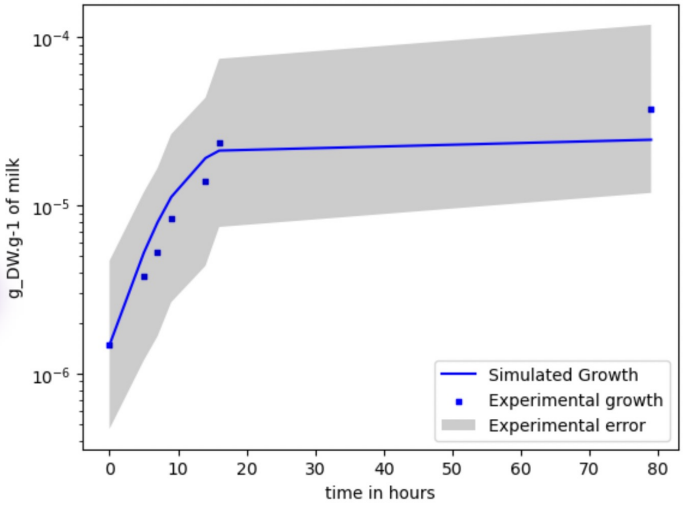
Virtanen. P, et al,2020, *Nature Methods*
Ebrahim et al,2013, *BMC Systems Biology*

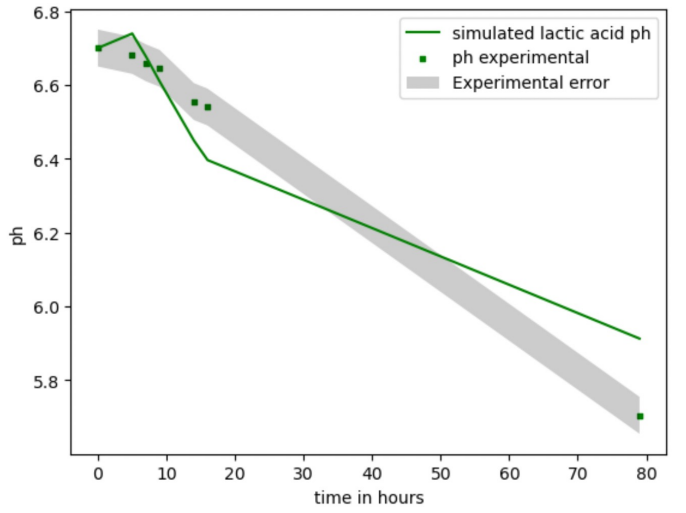
dFBA results after optimization







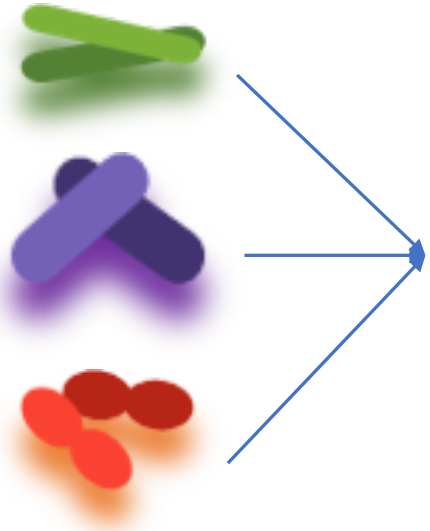




The small number of parameters is sufficient to explain the experimental data

What about metabolomics ?

Community dFBA



Community dFBA model

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

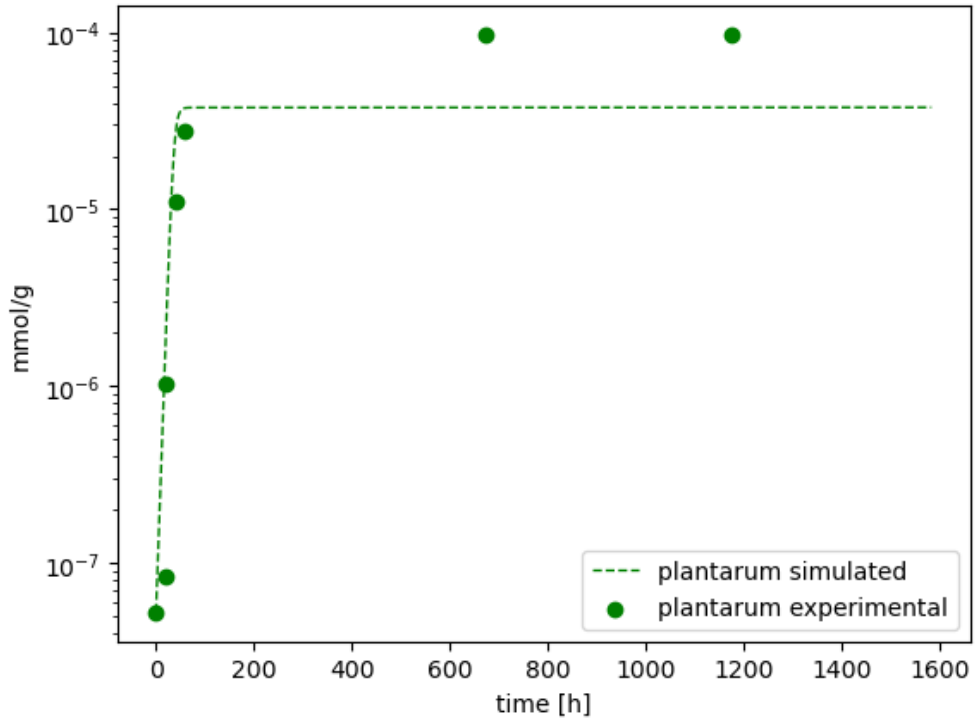
Optimised dFBA models for each bacterium

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

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

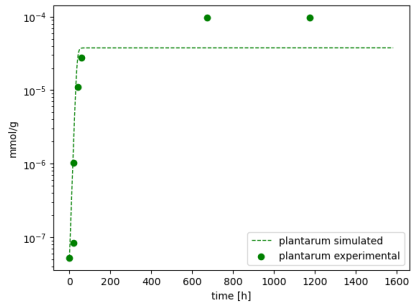
$$\text{where } v(t) = \begin{cases} V_M & \text{if } t \leq t_M \\ V_M + \frac{t - t_M}{t_D - t_M} V_D & \text{if } t_M \leq t \leq t_D \\ V_D & \text{if } t \geq t_D \end{cases}$$

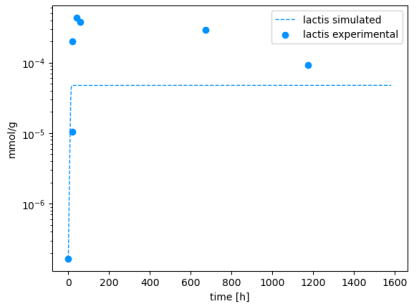
Community dFBA results

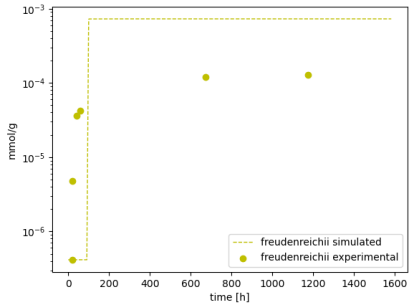


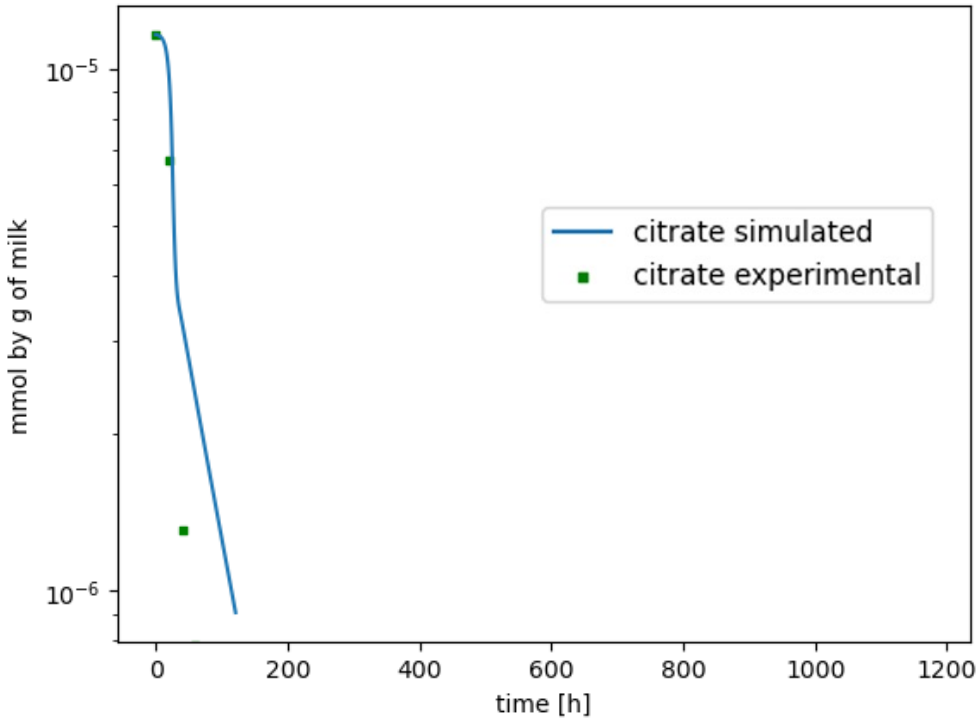
Bacterial growth computed with community dFBA fits with experimental data

Community dFBA results



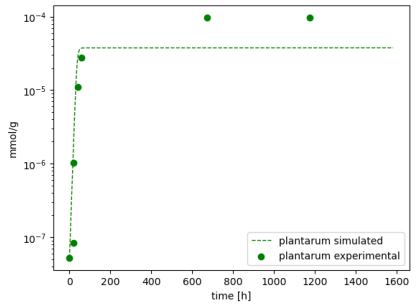


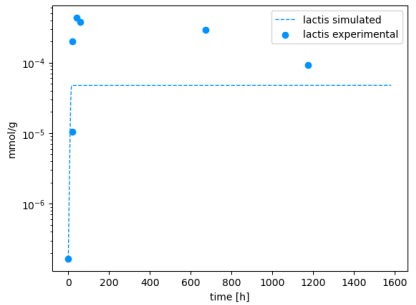


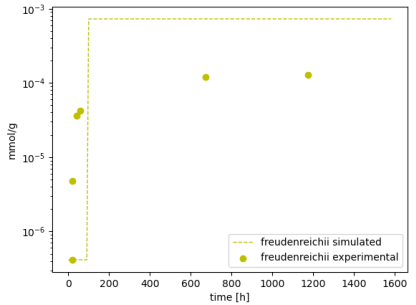


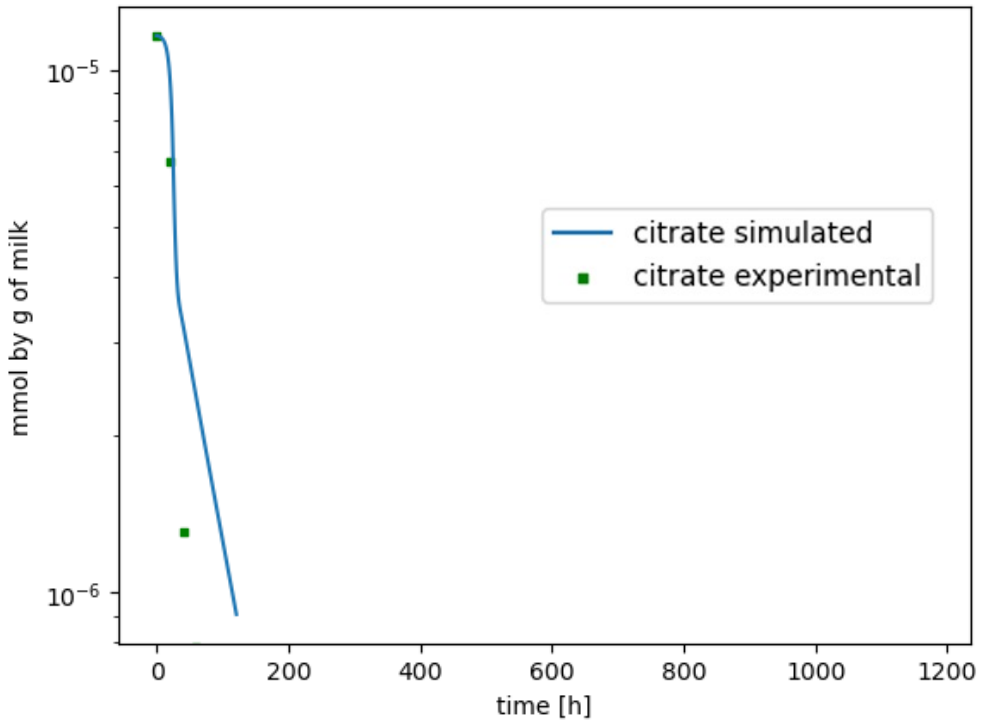
Some metabolites fit with metabolomics data …

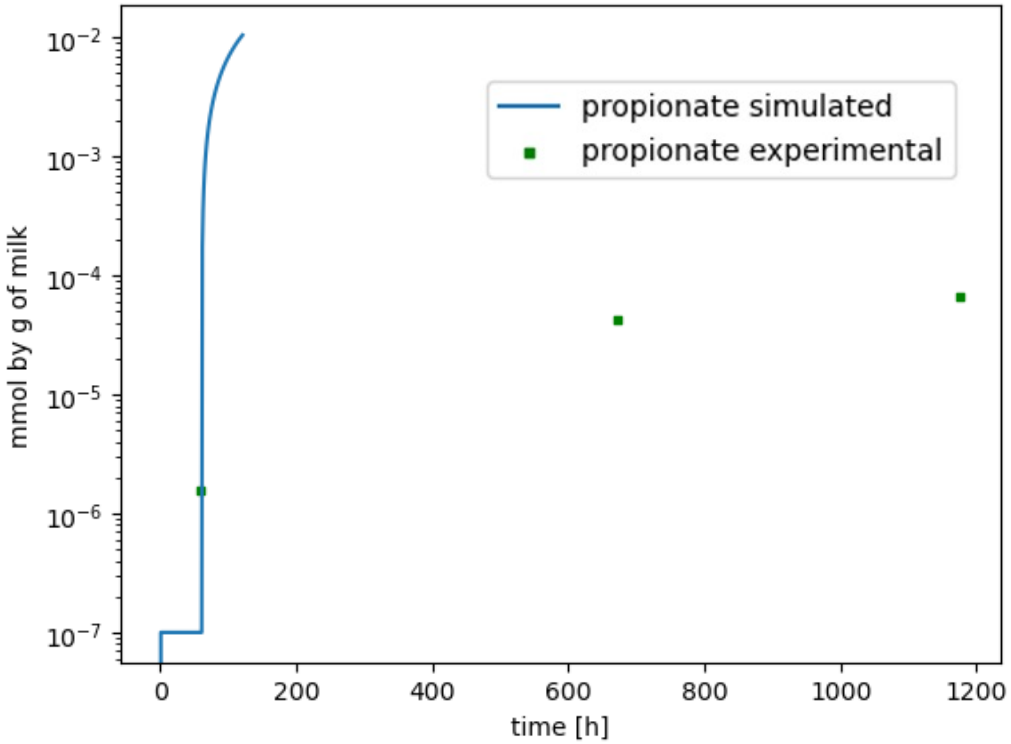
Community dFBA results





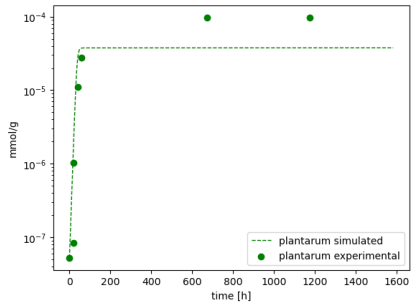


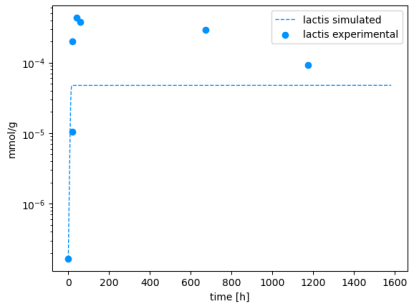


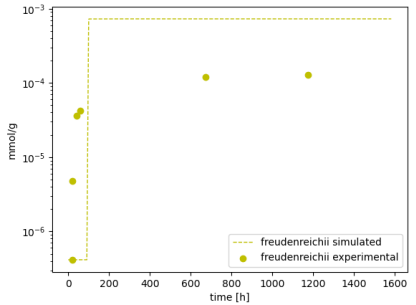


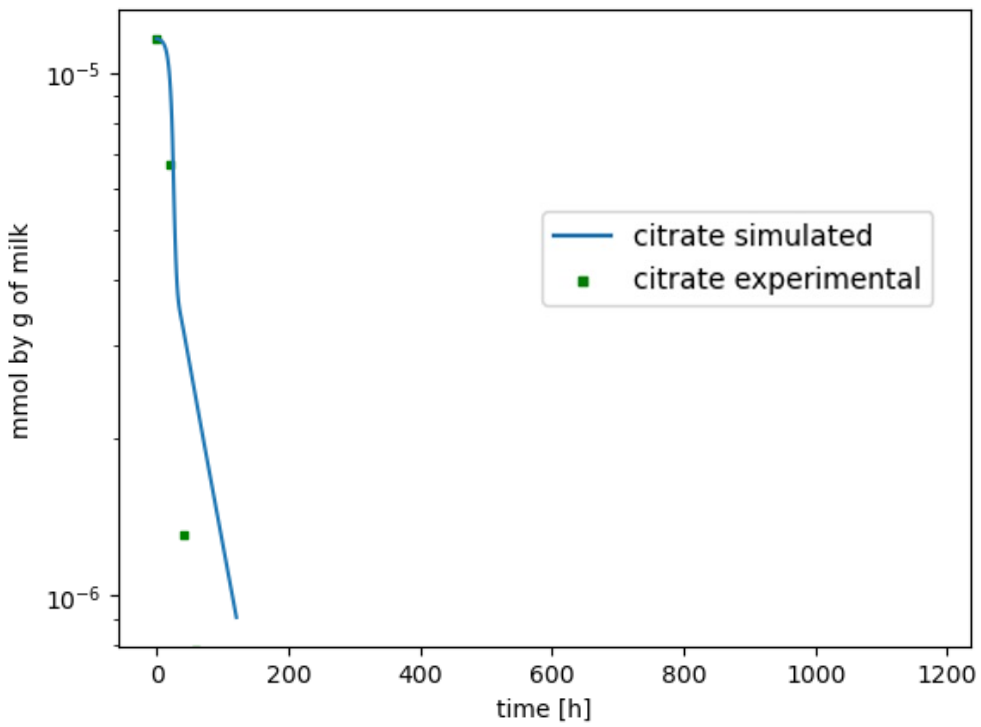
Not all of them

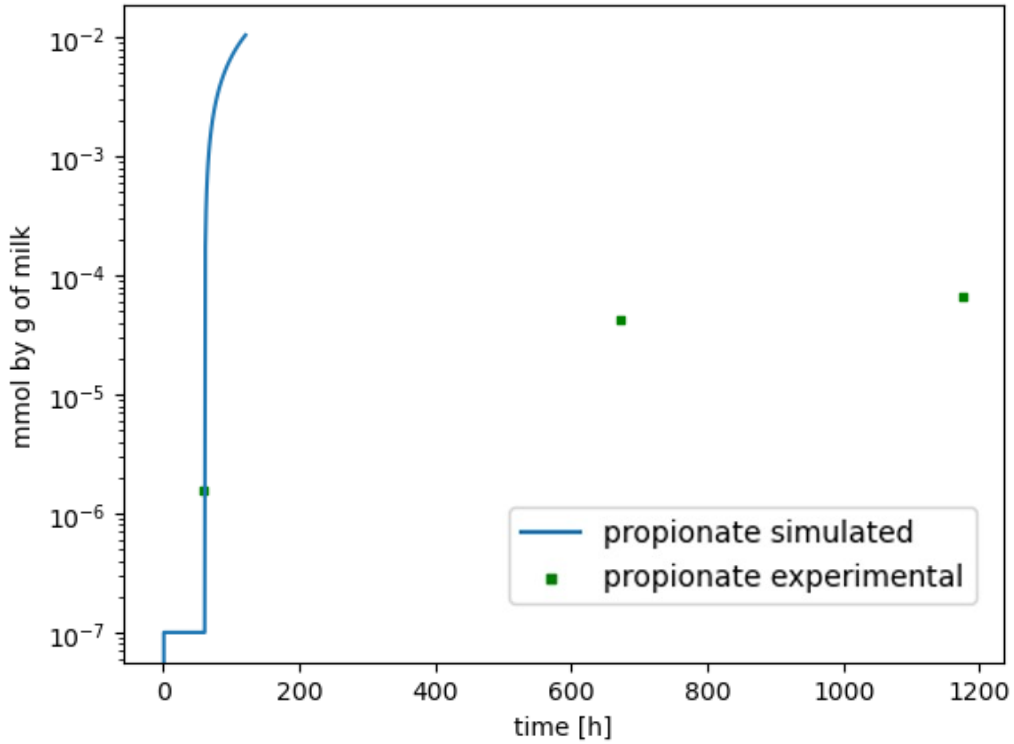
Community dFBA results





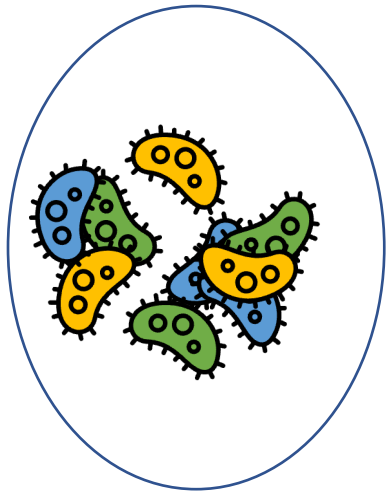




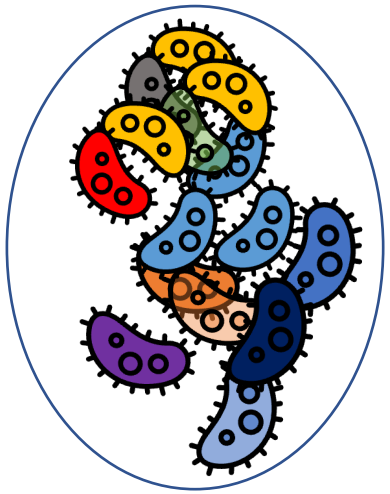


- The model do not capture all modifications brings by the community
- Integration of transcriptomic data is not significantly different
- Is qualitative result enough for characterizing communities ?

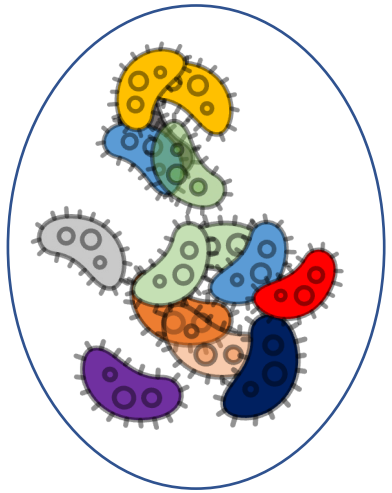
Characterizing natural communities (meta)genomics data



Community 1



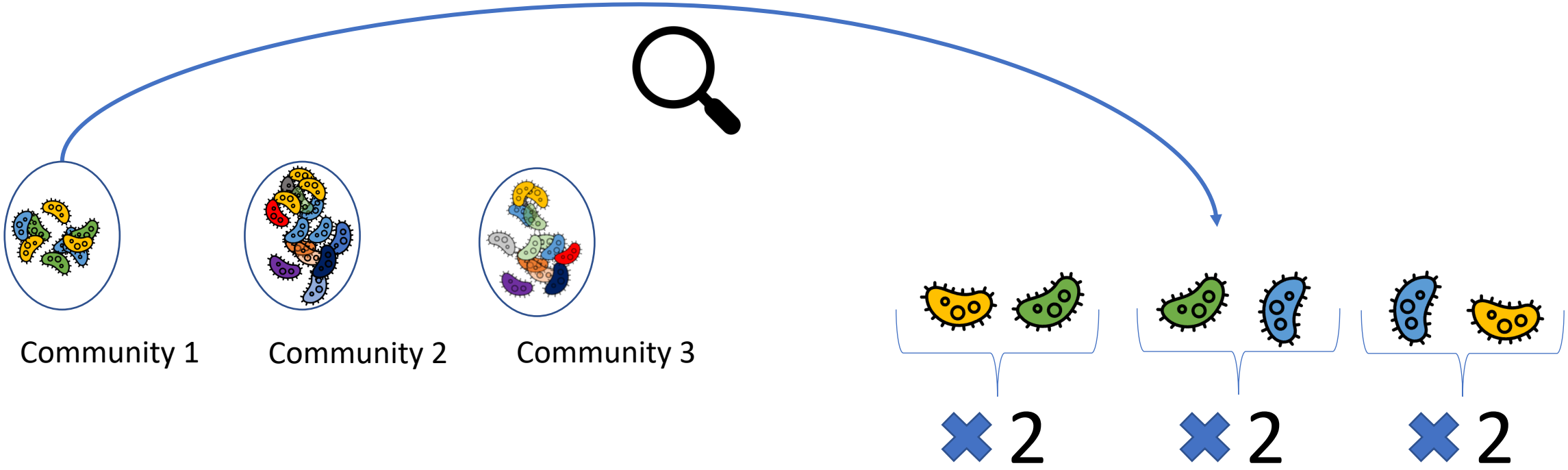
Community 2



Community 3

Calculating cooperation and competition potentials

Characterizing natural communities with (meta)genomics data



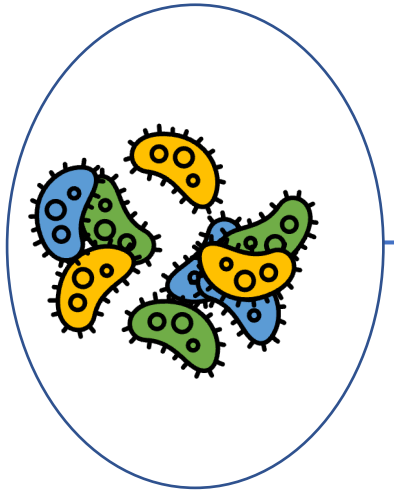
- Numerical methods
- Discrete methods

Not easily scalable

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)



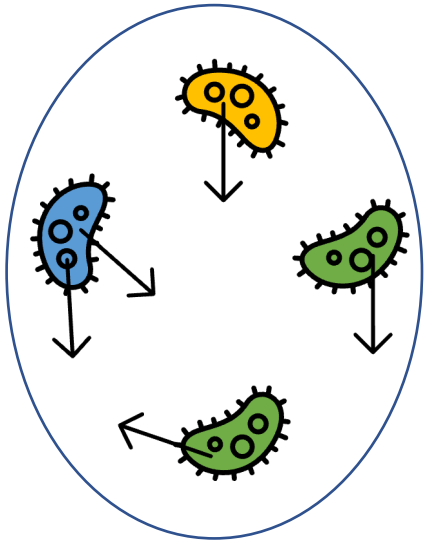
Descriptive

vocabular
using ASP

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

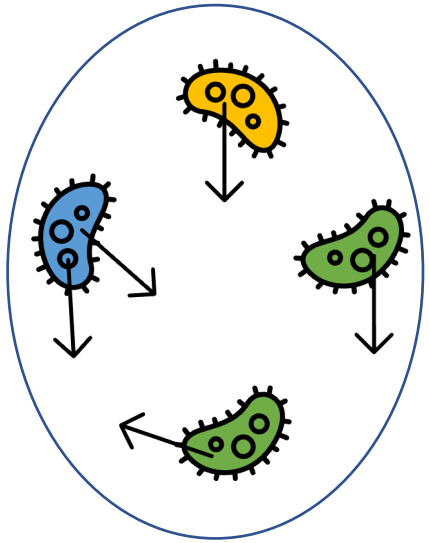
escope(M,T,S) :- pscope(M,S),
reactant(M,_,T),not product(M,_,T),S!=T.
```

Cooperation and competition metrics

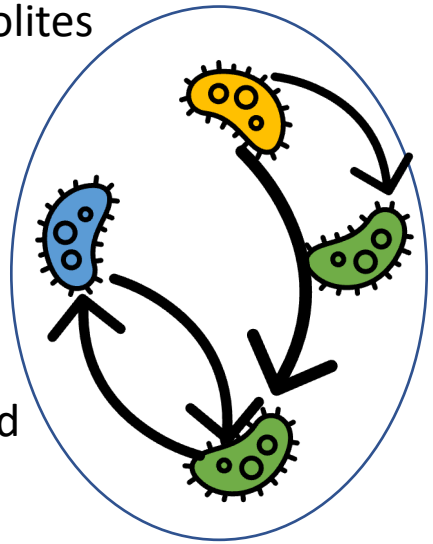


Number of metabolites produced

Cooperation and competition metrics

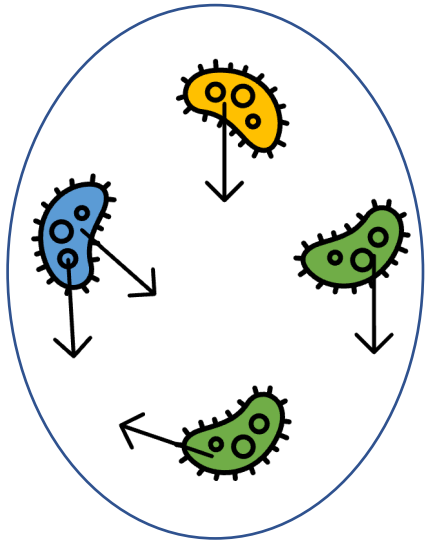


Number of metabolites produced

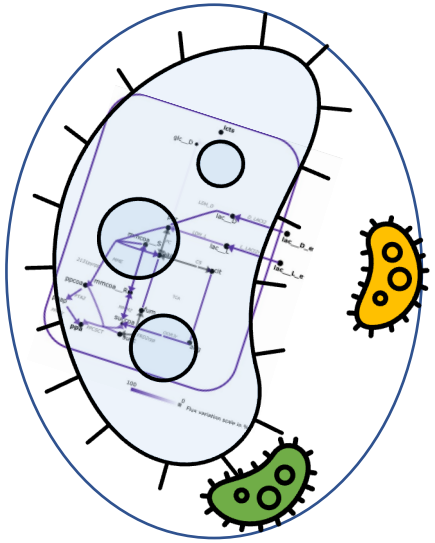


Number of exchanged metabolites

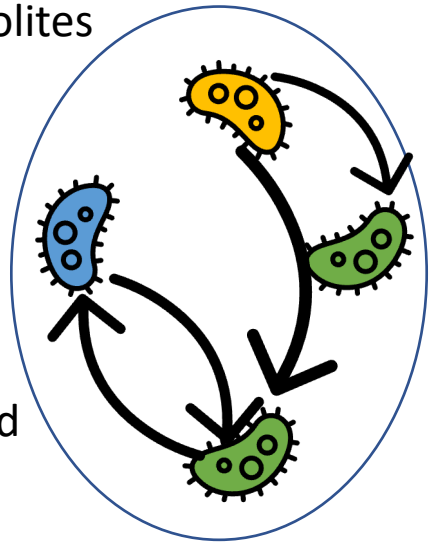
Cooperation and competition metrics



Number of metabolites produced

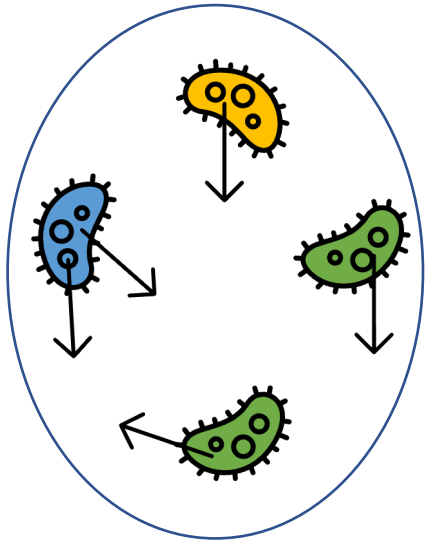


Number of activated reactions

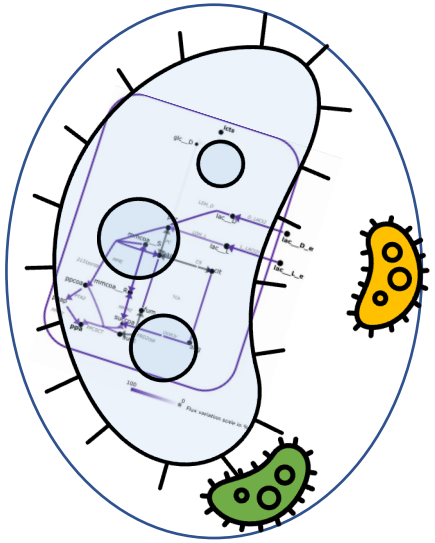


Number of exchanged metabolites

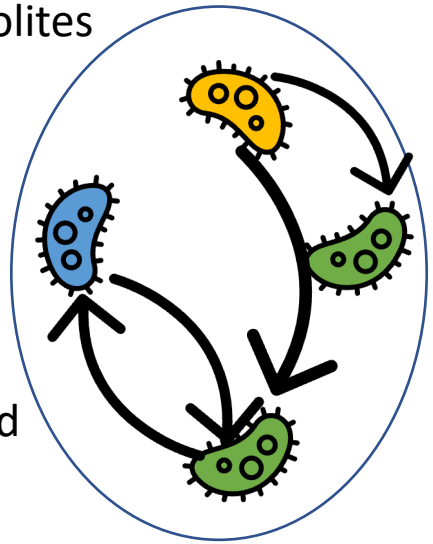
Cooperation and competition metrics



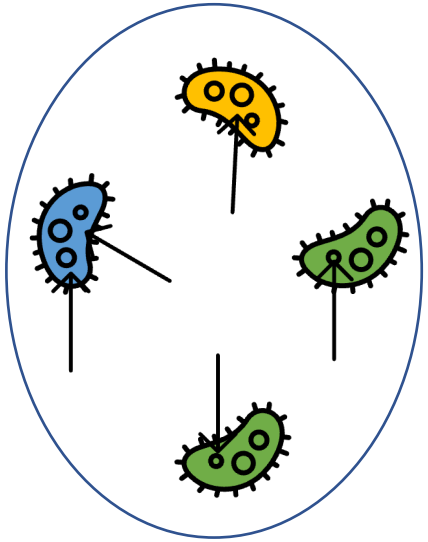
Number of metabolites produced



Number of activated reactions

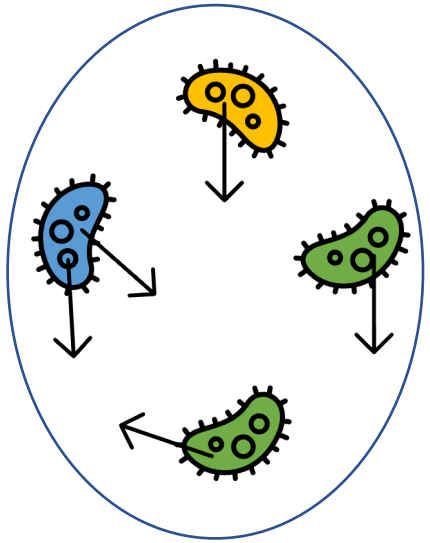


Number of exchanged metabolites

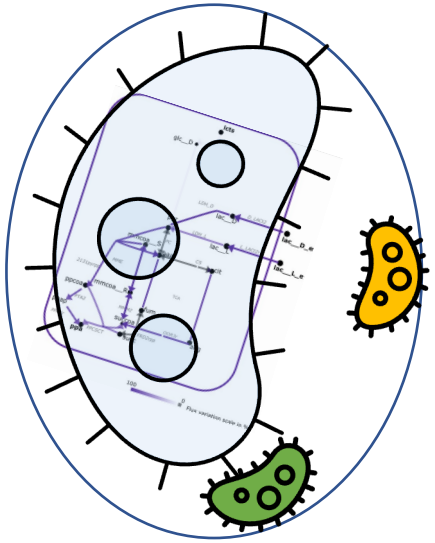


Related to limiting substrates consumed

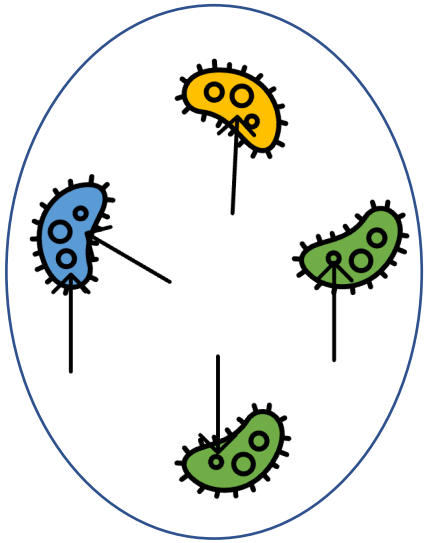
Cooperation and competition metrics



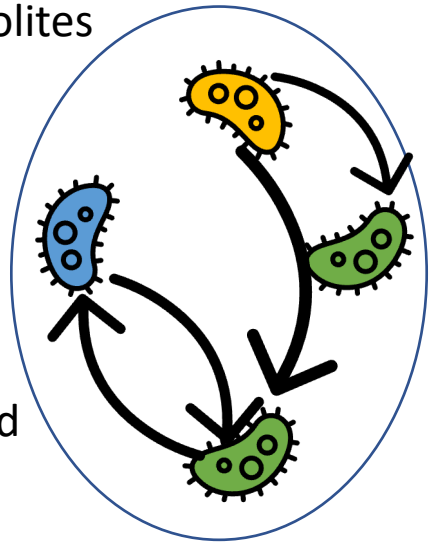
Number of metabolites produced



Number of activated reactions



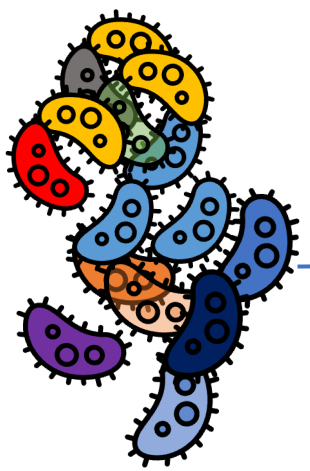
Related to limiting substrates consumed



Number of exchanged metabolites

Unify cooperation metrics to one unique score

Model test on designed communities

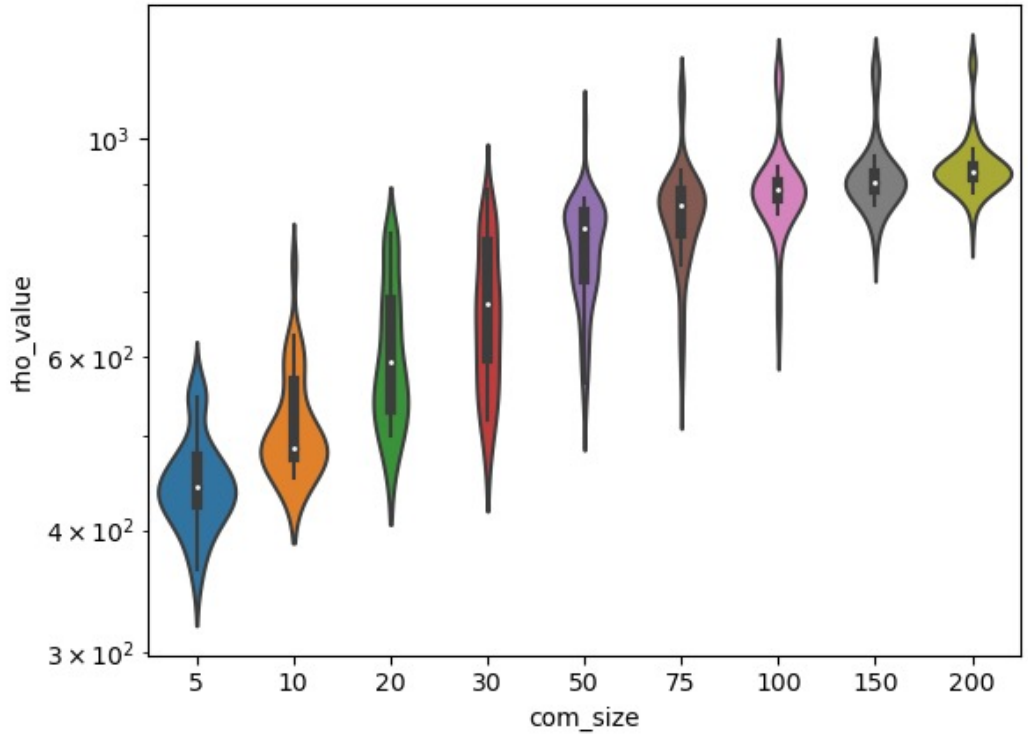


1520 bacteria



50 random communities
of size 5 to 200

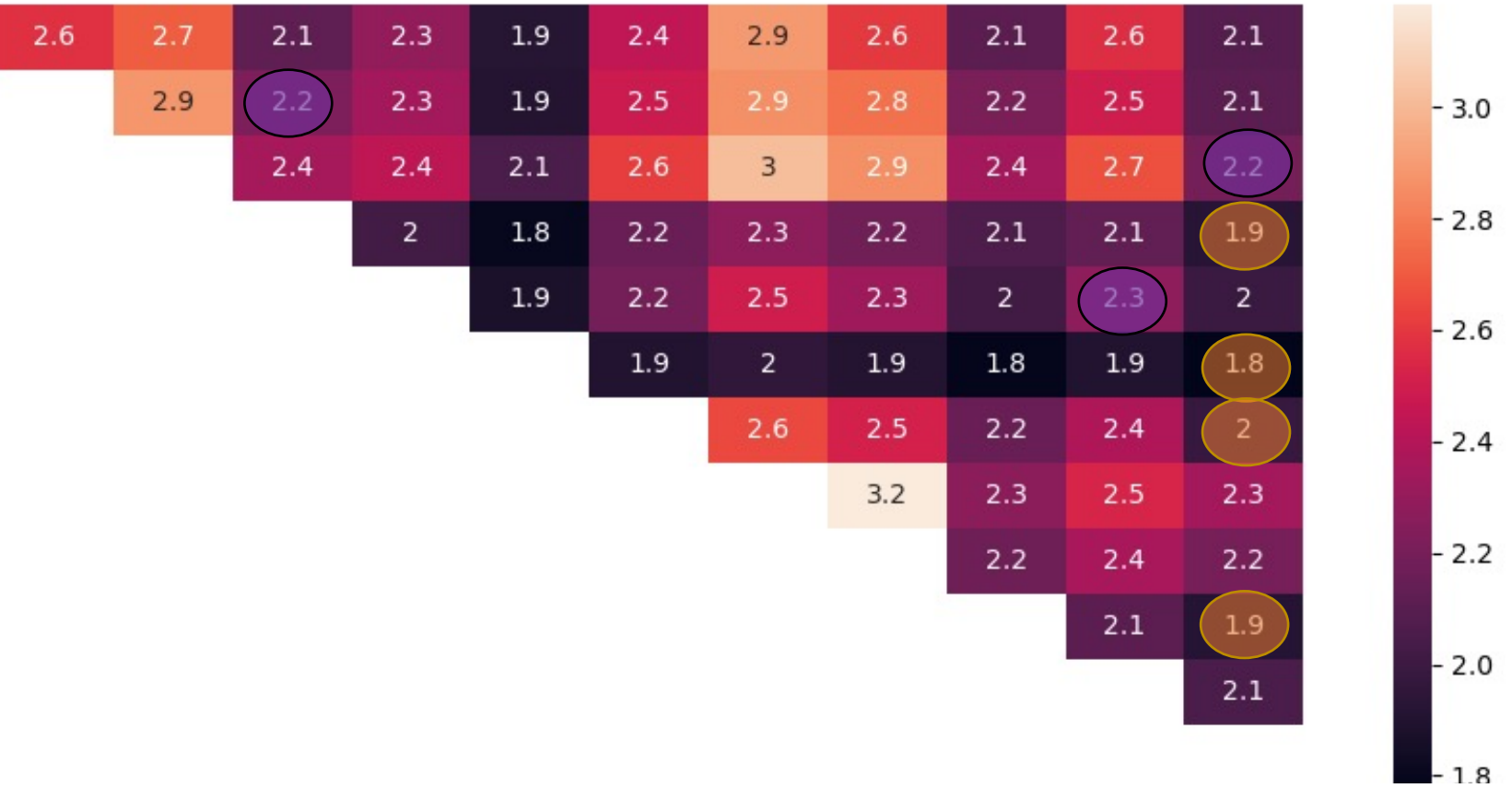
Calculation of
cooperation and
competition metrics

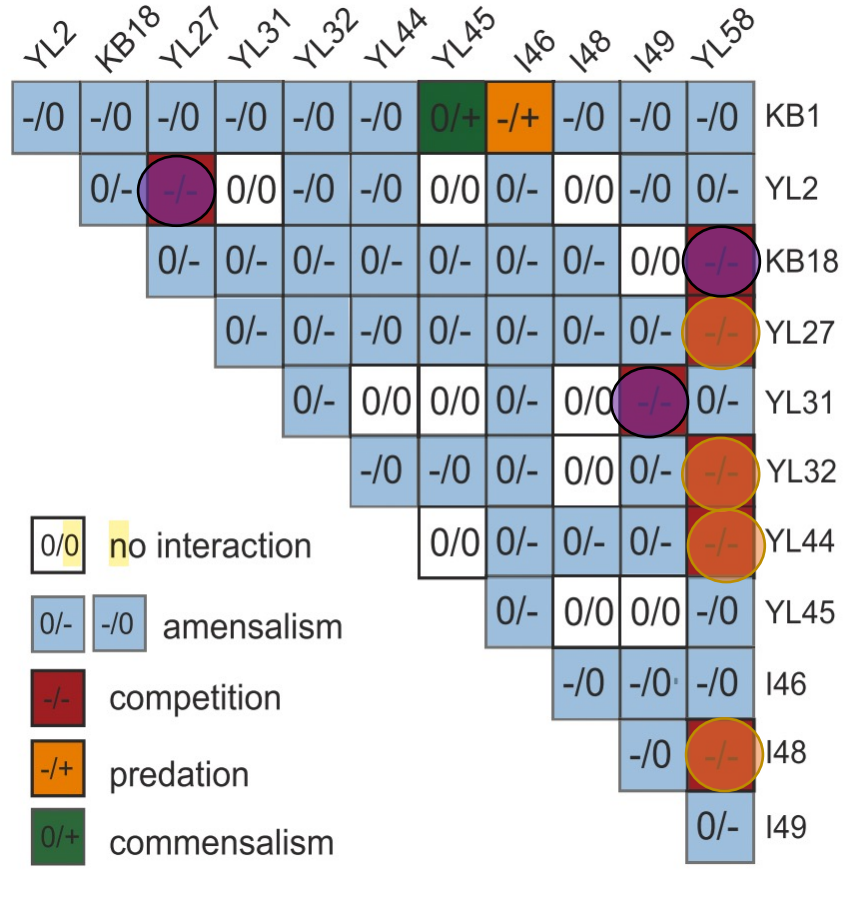


Metrics are not linearly correlate with the community size

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

Competition score test on real data





Identify some correlation between our score and the experimental data

Weiss, A. S., et al,2022, *ISME Journal*

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)









- David Sherman
- Clémence Frioux
- Simon labarthe

- Hélène Falentin

Thanks for your attention

Dynamic modeling of metabolism (dFBA)

List of pre-defined interest compounds :

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

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

Mahadevan et al, 2002, *Biophysical Journal*

Summary of the interactions in the cheese ecosystem

