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## Omic-based model of the gut microbiota

Simon Labarthe

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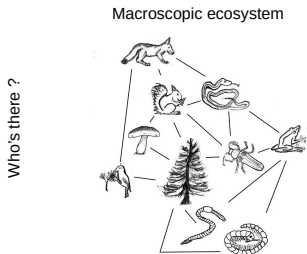
# ➤ Omic-based model of the gut microbiota



## ➤ Context

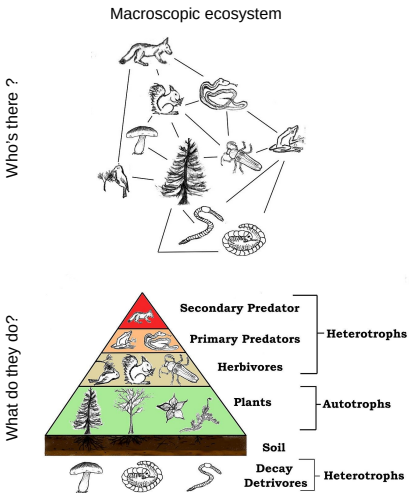
Population dynamic model in a microbial ecology context

# "Macroscopic" ecology





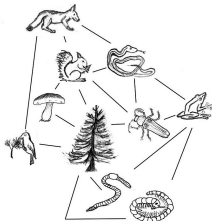
# "Macroscopic" ecology



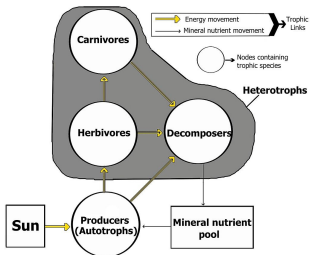
# "Macroscopic" ecology

Macroscopic ecosystem

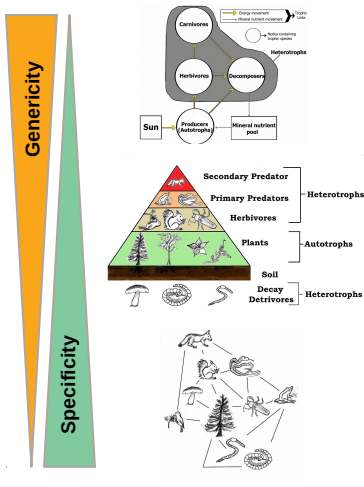
Who's there ?



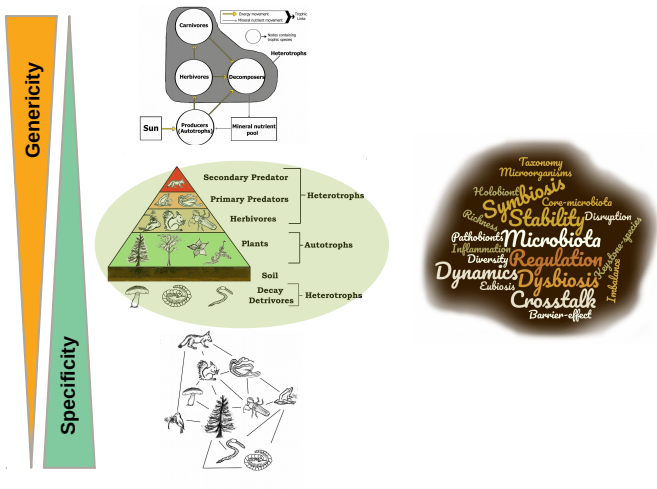
What do they do?



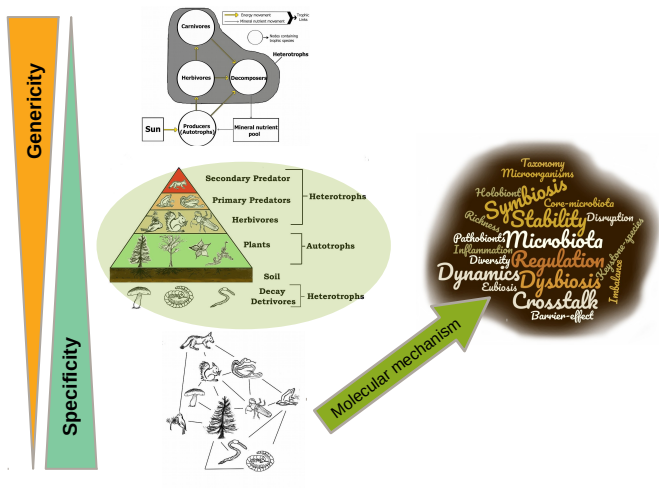
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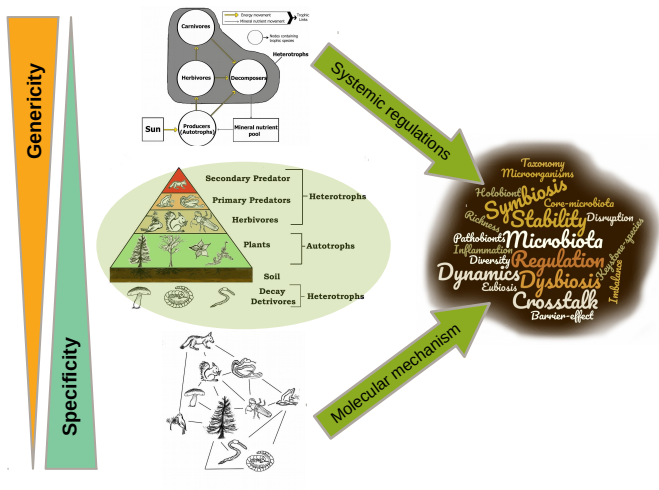
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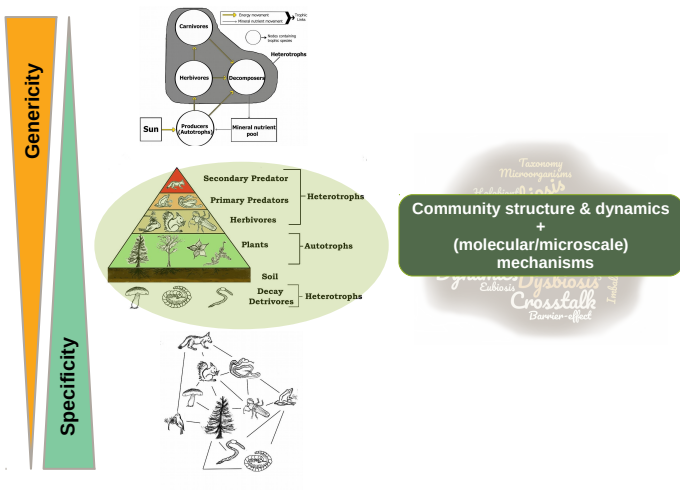
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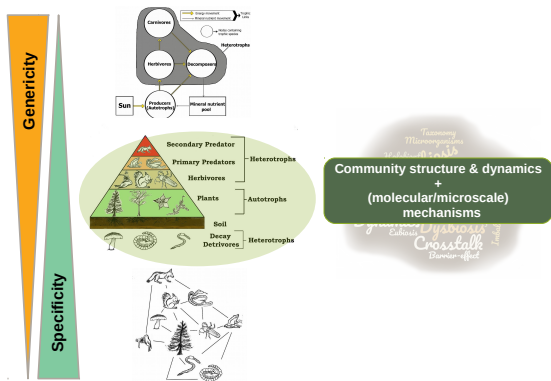
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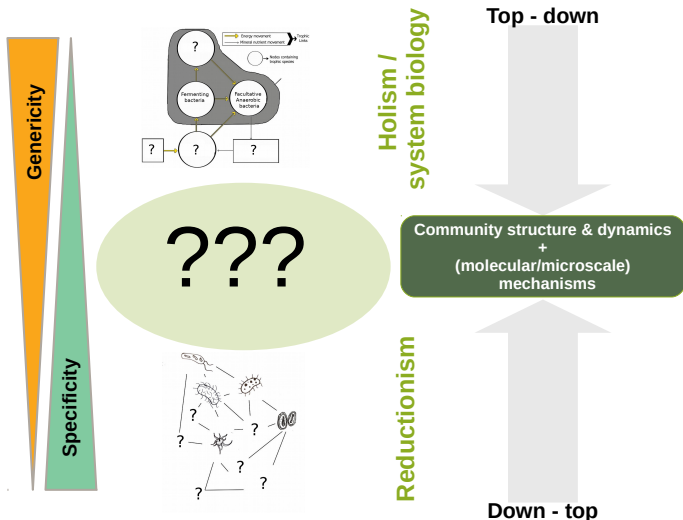
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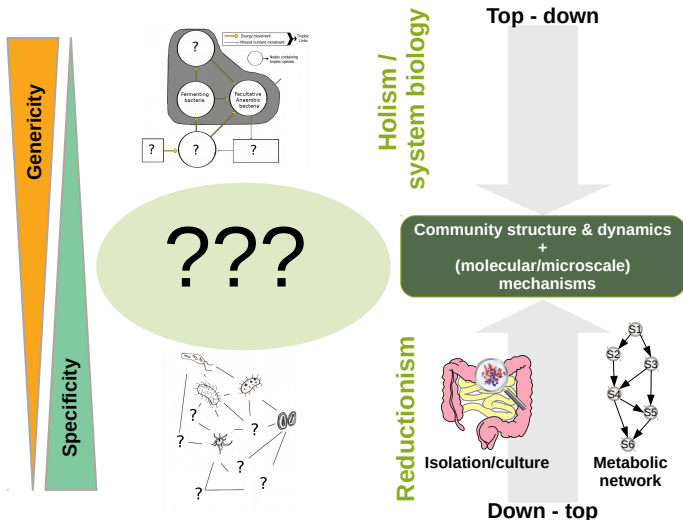
We can build a population dynamic model from the generic classes, taking into account if needed individual specificities.



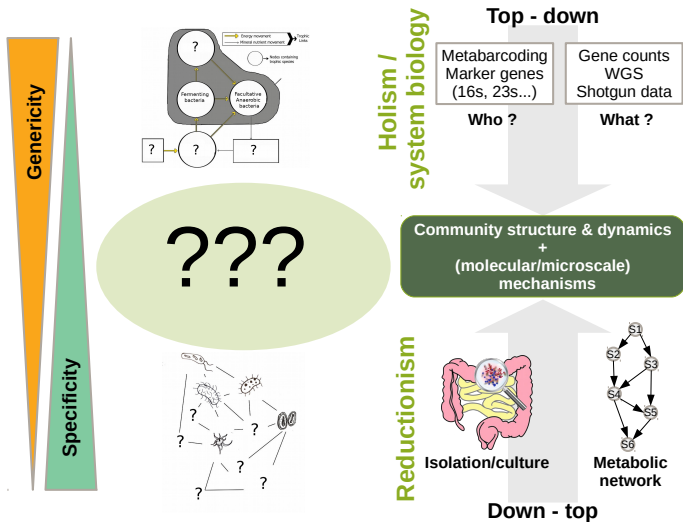
# Microbial ecology



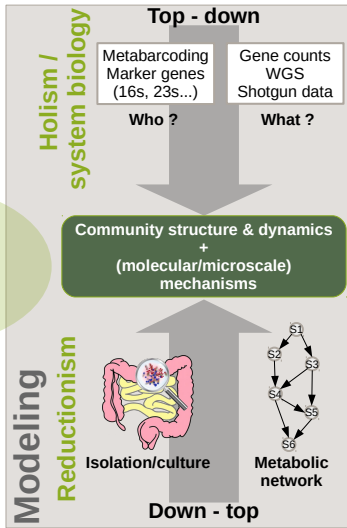
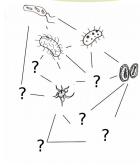
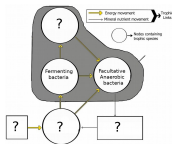
# Microbial ecology



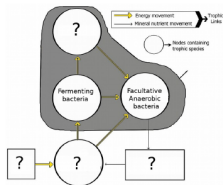
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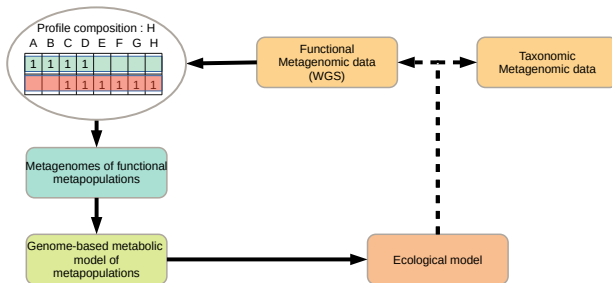
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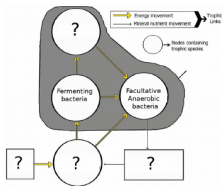
# Goal today



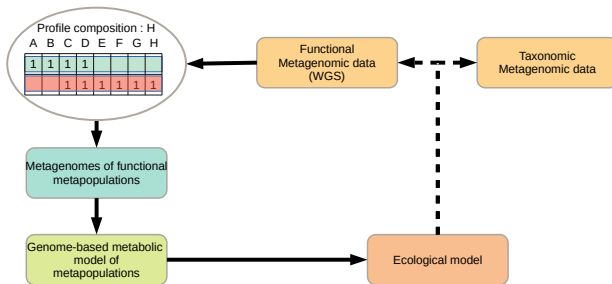
goal : Define omic-data-based "populations" to build a population dynamics model of gut microbiota



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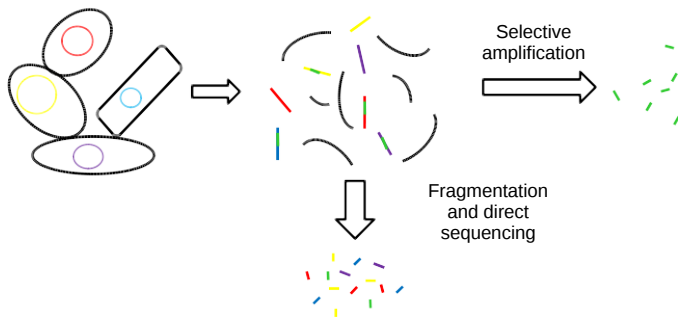


1. Model bricks
  - a- Omic-based model of bacterial metabolism
  - b- PDE model of the gut
2. Model validation : back to data

## 2 > Defining populations in the microbiota

Microbiota simplification : from omic data to generic functional 'meta-populations'

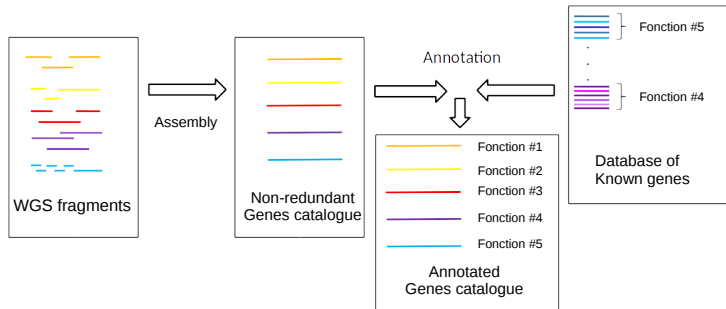
# Some bioinformatics : metagenomics



*Adapted from S.Raguideau's thesis*

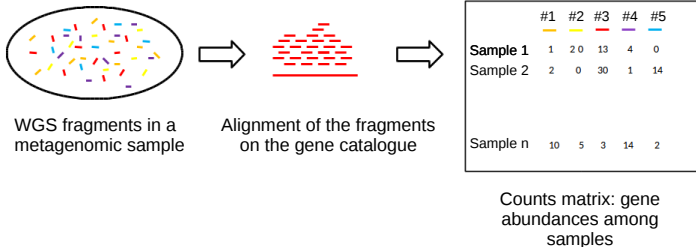


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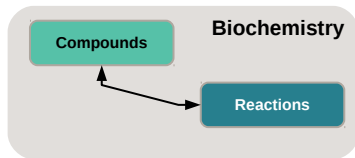
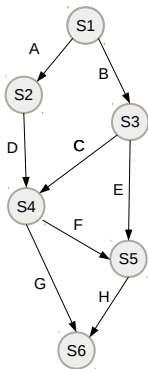
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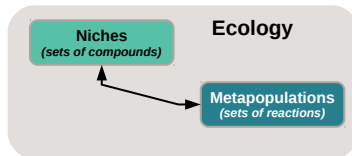
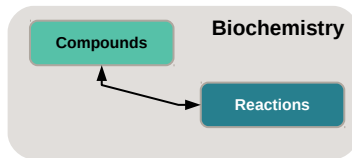
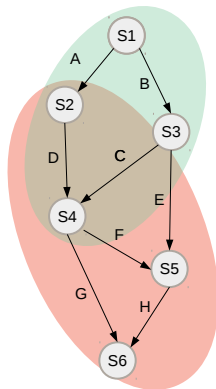


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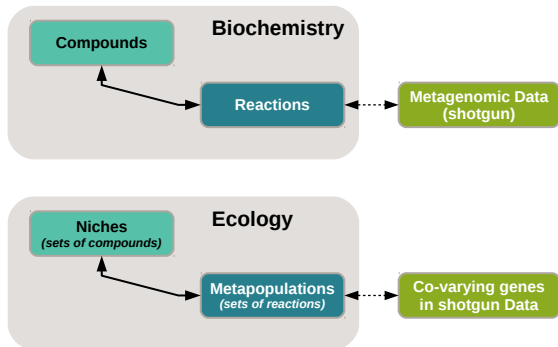
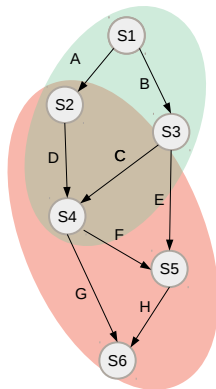
# From community-wide metabolic pathway to ecology



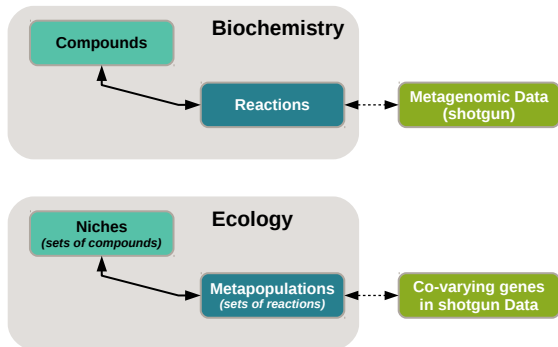
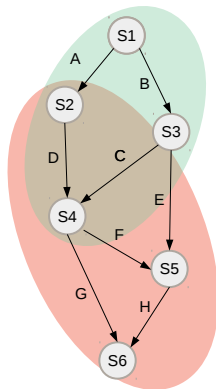
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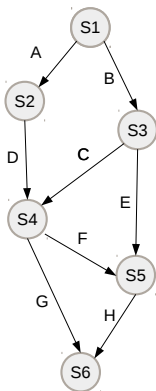
# From community-wide metabolic pathway to ecology



Statistical dimension-reduction techniques to detect co-varying genes in a gene count matrix  $\Rightarrow$  identification of metapopulations

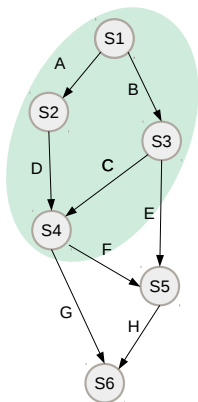
# NMF for microbiota simplification

NMF = genome-based microbiota simplification. *Raguideau et al. 2016*



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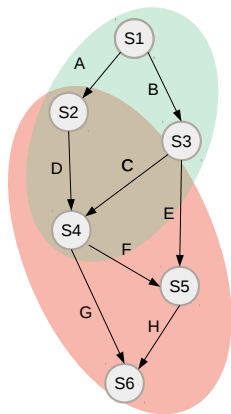
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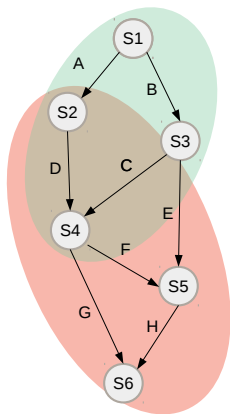
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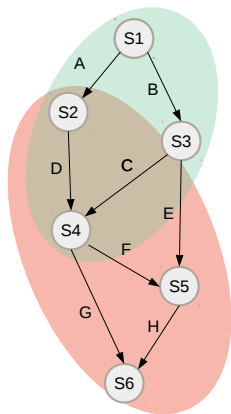


Profile composition : H

A	B	C	D	E	F	G	H
1	1	1	1				
		1	1	1	1	1	1

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Profile composition : H

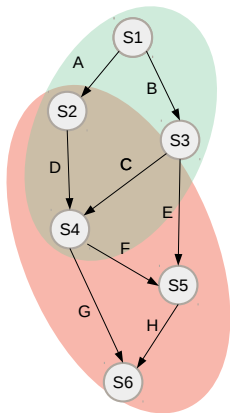
A	B	C	D	E	F	G	H
1	1	1	1				
		1	1	1	1	1	1

2	1
0	3
1	5
2	1
5	1
1	4

Profile counts: W

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Profile composition : H

A	B	C	D	E	F	G	H
1	1	1	1				
		1	1	1	1	1	1

2	1
0	3
1	5
2	1
5	1
1	4

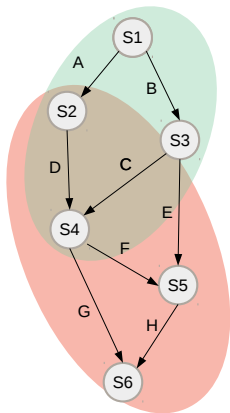
2	2	3	3	1	1	1	1
0	0	3	3	3	3	3	3
1	1	6	6	5	5	5	5
2	2	3	3	1	1	1	1
5	5	6	6	1	1	1	1
1	1	5	5	4	4	4	4

Profile counts: W

Gene counts : A

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Profile composition : H

A	B	C	D	E	F	G	H
1	1	1	1				
		1	1	1	1	1	1

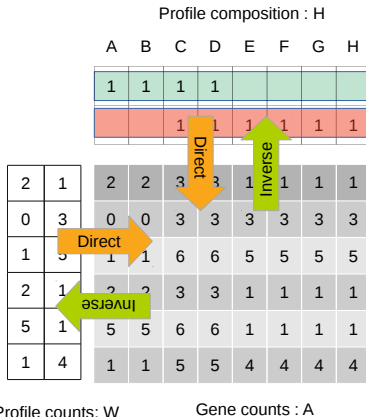
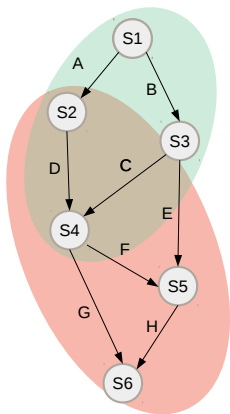
2	1	2	2	3	3	1	1	1	1
0	3	0	0	3	3	3	3	3	3
1	5	1	1	6	6	5	5	5	5
2	1	2	2	3	3	1	1	1	1
5	1	5	5	6	6	1	1	1	1
1	4	1	1	5	5	4	4	4	4

Profile counts: W

Gene counts : A

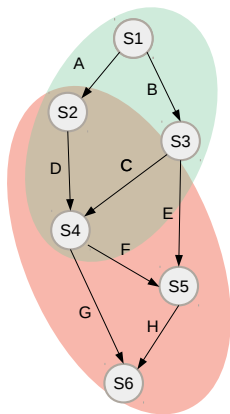
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A	B	C	D	E	F	G	H
1	1	1	1				
		1	1	1	1	1	1

2	1
0	3
1	5
2	1
5	1
1	4

2	2	3	3	1	1	1	1
0	3	0	0	0	0	0	0
1	5	1	1	1	1	1	1
2	1	2	2	2	2	2	2
5	1	5	5	5	5	5	5
1	4	1	1	5	5	4	4

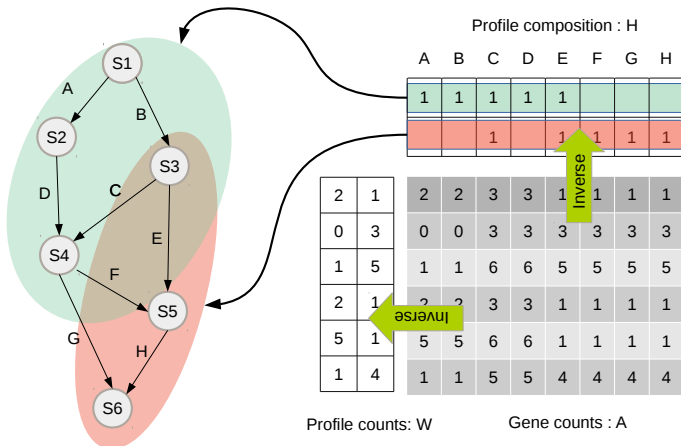
**NMF Problem :**  
 Find  $W, H$  such that  
 $[W, H] = \operatorname{argmin} \|A - WH\|$   
 Subject to positivity,  
 biological  
 and statistical constraints

Profile counts: W

Gene counts : A

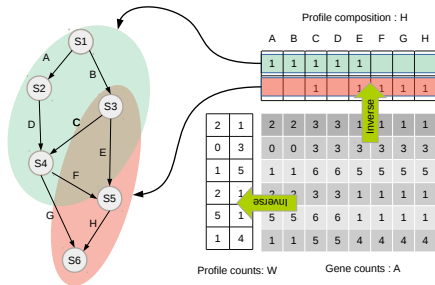
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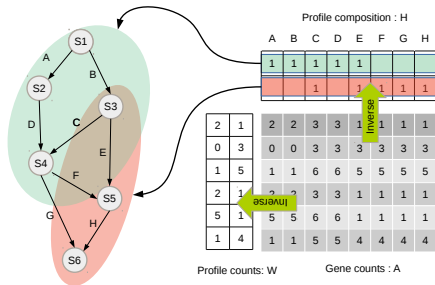
# NMF for microbiota simplification



## Result of the NMF

- H : profiles. **Functional capabilities of k metapopulations.** "Needed functions to invade a niche".

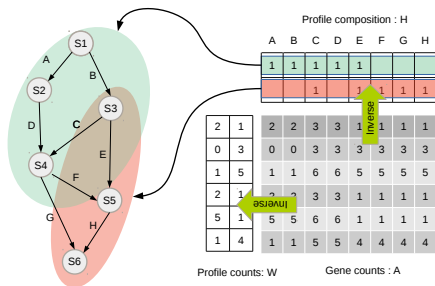
# NMF for microbiota simplification



## Result of the NMF

- H : profiles. **Functional capabilities of k metapopulations.** "Needed functions to invade a niche".
- W : microbiota/sample **composition** regarding metapopulations

# NMF for microbiota simplification



## Result of the NMF

- H : profiles. **Functional capabilities of k metapopulations.** "Needed functions to invade a niche".
- W : microbiota/sample **composition** regarding metapopulations

Data (Metahit, HMP1/2)  $\Rightarrow$  microbiota simplification

$\Rightarrow$  metapopulations for metabolic modeling

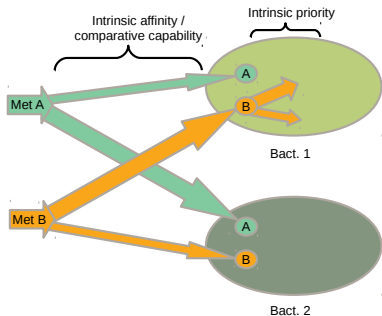
# 3 > Metabolic modeling

From metapopulation genomic profiles to metabolic flux

# Metapop. metabolic capabilities

Profile = KO frequency

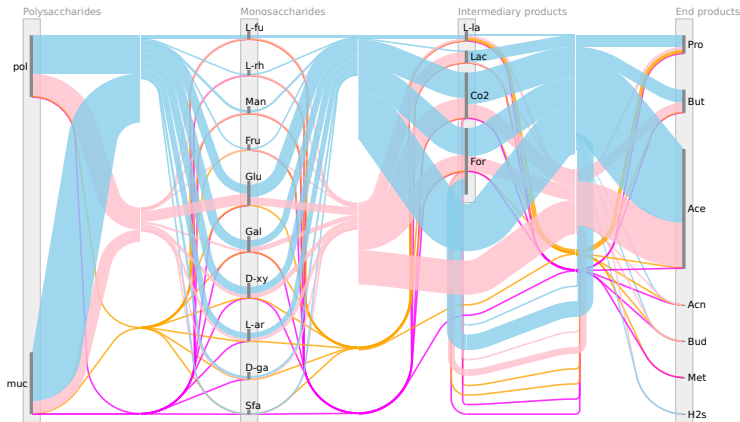
- What is the actual consumption of metabolites?
- What is the interaction with the niche?



Assumption :  
gene frequency determines

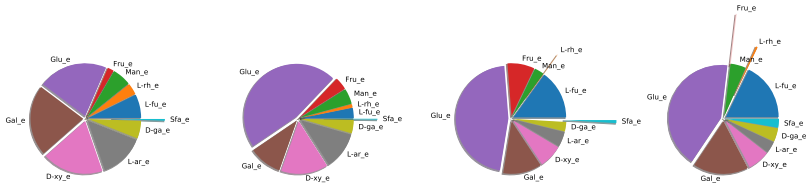
- Intrinsic affinity for a metabolite (respectively to another)
- Comparative metabolic capability (respectively to other organisms)
- Internal metabolic switch

# Metapop. metabolic capabilities

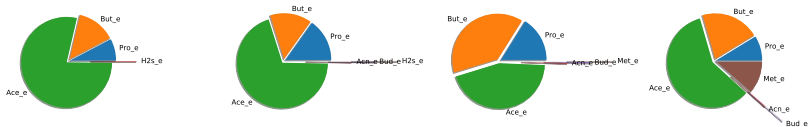


# Metapop. metabolic capabilities

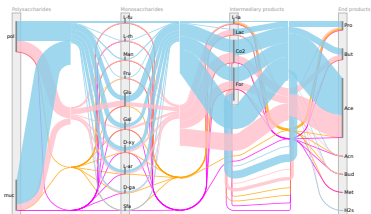
## Sugar production from fibres by profile



## End metabolite productions by profile

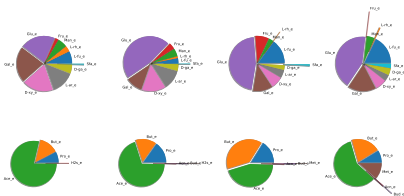


# Metapop. metabolic capabilities



## Fibre metabolism

- 2 generalist metapopulations : same SCFA but different GH
- 1 butyrate producer, 1 methane, less GH (but more L-fu)



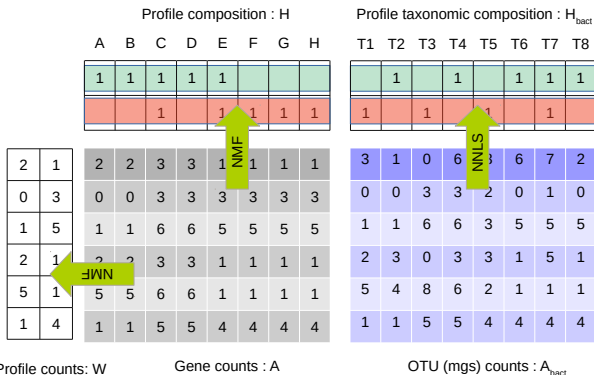


# 4 > Taxonomic composition of metapopulation

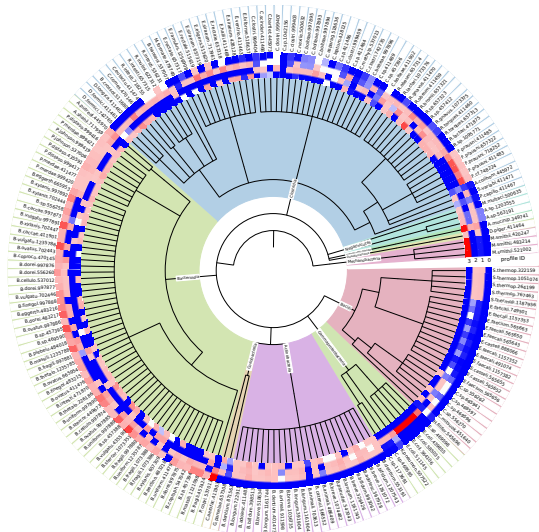
Linking functions and individuals

# Profile taxonomic composition

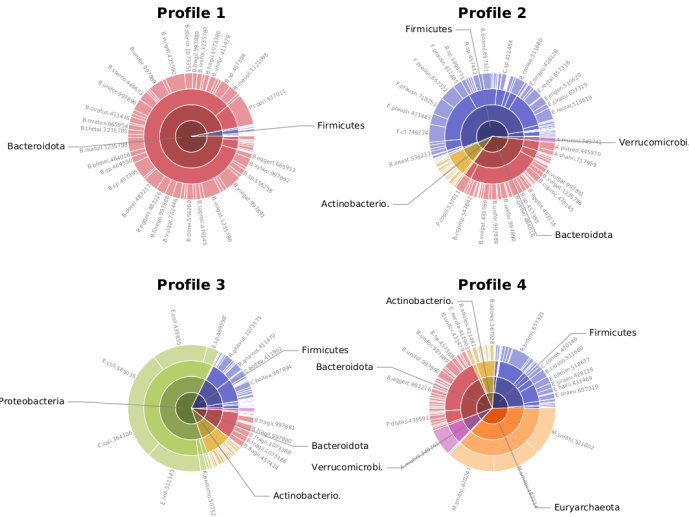
## Taxonomic composition inference : NNLS



# Profile taxonomic composition



# Profile taxonomic composition



# 5 > Host modeling

Last brick of the gut holobiont

# Host features

## Diet & nutritional environment

- nutrients influx in the gut (fibre, sugars)
- host derived nutrients (mucus)

## Mechanical environment

- Fluid mechanic of transit
- Mucus layer

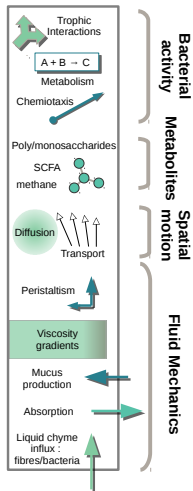
## Inter-individual specificity

- data-derived group-specific carrying capacities (proxy of immune/inflammatory specificities)

# 6 > PDE model of the gut microbiota

## Biogeography of the colon

# Model elements

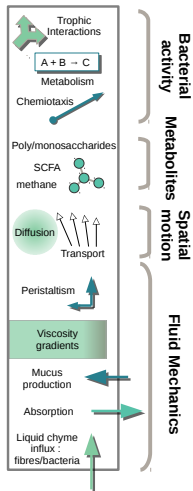


Population dynamics : mass conservation

$$\partial_t P_i = \underbrace{\mu(P, s)}_{\text{Growth}} + \underbrace{\text{div}(\sigma \nabla P_i)}_{\text{diffusion}} - \underbrace{\text{div}(u_i P_i)}_{\text{transport}}$$



# Model elements

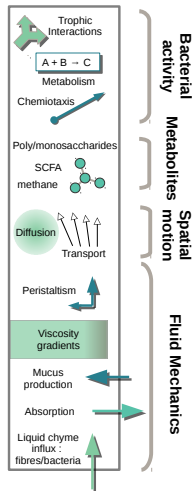


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$$\partial_t s_j = \underbrace{g(P, s)}_{\text{Consumption}} + \underbrace{\text{div}(\sigma \nabla s_j)}_{\text{diffusion}} - \underbrace{\text{div}(\tilde{u} s_j)}_{\text{transport}}$$

# Model elements



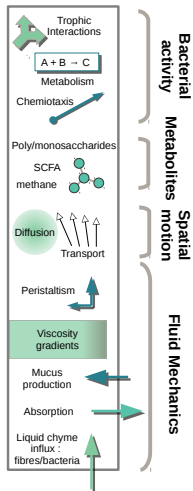
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$$u_i = u + \vartheta_{i,chem}, \quad \underbrace{\nabla p - \text{div}(\mu D(u))}_{\text{Fluid mechanic : Stokes}} = 0,$$

# Model elements



## Population dynamics : mass conservation

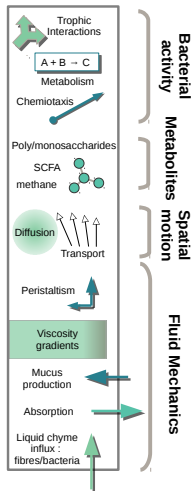
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$$u_i = u + \vartheta_{i,chem}, \quad \underbrace{\nabla p - \text{div}(\mu D(u))}_{\text{Fluid mechanic : Stokes}} = 0,$$

$$\underbrace{\vartheta_{i,chem}}_{\text{chemotactic speed}} = \lambda_{ij} \nabla \Phi_j$$

# Model elements



## Population dynamics : mass conservation

$$\partial_t P_i = \underbrace{\mu(P, s)}_{\text{Growth}} + \underbrace{\text{div}(\sigma \nabla P_i)}_{\text{diffusion}} - \underbrace{\text{div}(u_i P_i)}_{\text{transport}}$$

$$\partial_t s_j = \underbrace{g(P, s)}_{\text{Consumption}} + \underbrace{\text{div}(\sigma \nabla s_j)}_{\text{diffusion}} - \underbrace{\text{div}(\tilde{u} s_j)}_{\text{transport}}$$

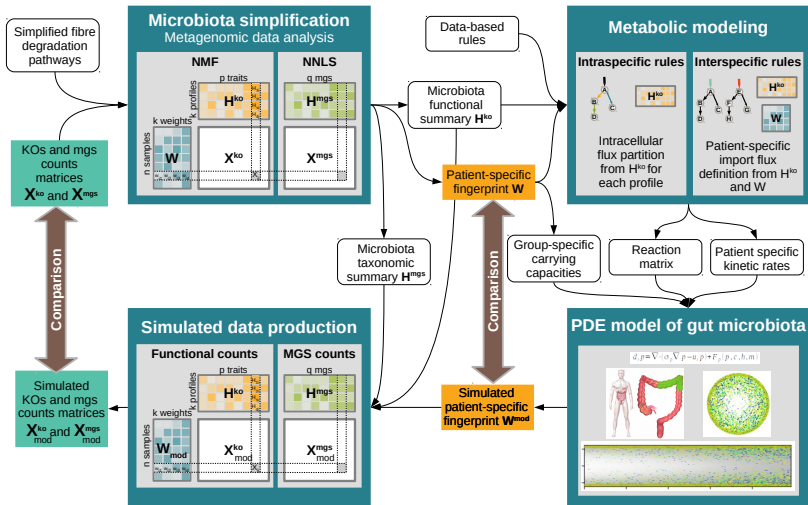
$$u_i = u + \vartheta_{i,chem}, \quad \underbrace{\nabla p - \text{div}(\mu D(u))}_{\text{Fluid mechanic : Stokes}} = 0,$$

$$\underbrace{\vartheta_{i,chem}}_{\text{chemotactic speed}} = \lambda_{ij} \nabla \Phi_j$$

B.Laroche's talk at 2pm



# All together

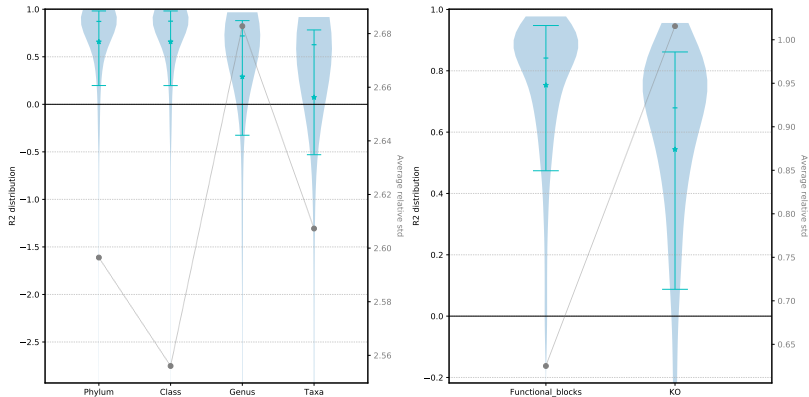




➤ **Model validation**  
Back to data

# Prediction

$R^2$



INRAE

MaIAGE S.Labarthe

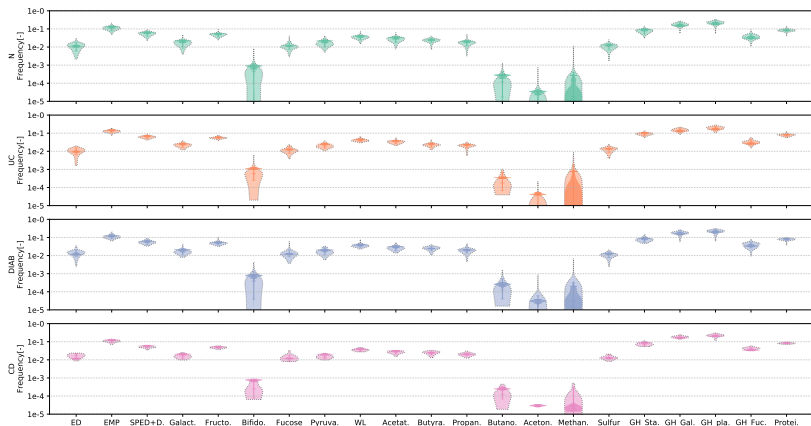
Omic-based model of the gut microbiota

10-23-2020

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# Prediction by function/class

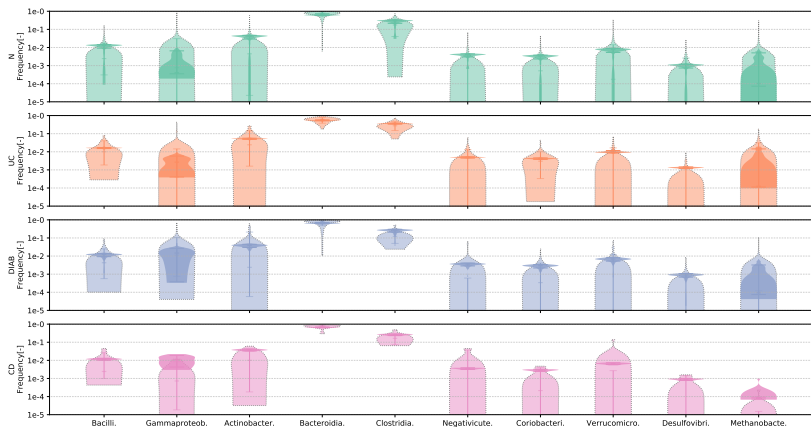
Violin plot :  $Y$  and  $\hat{Y}$  distribution





# Prediction by function/class

Violin plot :  $Y$  and  $\hat{Y}$  distribution



# 8 > Conclusion

# Conclusions

## PDE model of the gut microbiota

- Detailed mechanisms
- Biogeography

## Metabolic simplification of the microbiota

- Functional metapopulations
- Metabolic modeling

## Predictive model of the gut microbiota

- Reproducing gene & bacterial counts
- Reproducing disease stratification

## Future

- Metabolomics ?
- Exploration !



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- M.Leclerc, B.Laroche

